Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

# Recurrence Patterns and Patient Outcomes in Resected Lung Adenocarcinoma Differ according to Ground-Glass Opacity at CT

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Conflicts of interest are listed at the end of this article.

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***Background:*** Although lung adenocarcinoma with ground-glass opacity (GGO) is known to have distinct characteristics, limited data exist on whether the recurrence pattern and outcomes in patients with resected lung adenocarcinoma differ according to GGO presence at CT.

***Purpose:*** To examine recurrence patterns and associations with outcomes in patients with resected lung adenocarcinoma according to GGO at CT.

***Materials and Methods:*** Patients who underwent CT followed by lobectomy or pneumonectomy for lung adenocarcinoma between July 2010 and December 2017 were retrospectively included. Patients were divided into two groups based on the presence of GGO: GGO adenocarcinoma and solid adenocarcinoma. Recurrence patterns at follow-up CT examinations were investigated and compared between the two groups. The effects of patient grouping on time to recurrence, postrecurrence survival (PRS), and overall survival (OS) were evaluated using Cox regression.

***Results:*** Of 1019 patients (mean age, 62 years ± 9 [SD]; 520 women), 487 had GGO adenocarcinoma and 532 had solid adenocarcinoma. Recurrences occurred more frequently in patients with solid adenocarcinoma (36.1% [192 of 532 patients]) than in those with GGO adenocarcinoma (16.2% [79 of 487 patients]). Distant metastasis was the most common mode of recurrence in the group with solid adenocarcinoma and all clinical stages. In clinical stage I GGO adenocarcinoma, all regional recurrences appeared as ipsilateral lung metastasis (39.2% [20 of 51]) without regional lymph node metastasis. Brain metastasis was more frequent in patients with clinical stage I solid adenocarcinoma (16.5% [16 of 97 patients]). The presence of GGO was associated with time to recurrence and OS (adjusted hazard ratio [HR], 0.6 [$P < .001$] for both). Recurrence pattern was an independent risk factor for PRS (adjusted HR, 2.1 for distant metastasis [$P < .001$] and 3.9 for brain metastasis [$P < .001$], with local-regional recurrence as the reference).

***Conclusion:*** Recurrence patterns, time to recurrence, and overall survival differed between patients with and without ground-glass opacity at CT, and recurrence patterns were associated with postrecurrence survival.



*Supplemental material is available for this article.*

Non–small cell lung cancer is the leading cause of cancer-related death worldwide (1). Although the main cause for its poor prognosis is that most lung cancers are diagnosed at an advanced stage, a substantial proportion of patients experience disease recurrence despite undergoing complete surgical resection with curative intent, with reported recurrence rates ranging from 30% to 75% (2–6). The majority of recurrences involve distant organs as the first recurrence site and occur within the first 2 years after surgery (7–9).

Radiologically, lung cancer can be classified according to the presence of ground-glass opacity (GGO) at CT. At pathologic analysis, GGO components correlate with lepidic growth, whereas solid components correlate with invasiveness (10). Tumors manifesting as GGO at imaging are known to have a rarer prevalence of lymph node or distant metastases and a better prognosis in their early stage than pure solid tumors (11–15). Although the eighth TNM staging system considers only the size of the solid component of a tumor with GGO for the tumor category (16), GGO is still found to be an independent favorable prognostic factor in early-stage non–small cell lung cancer (14,15,17,18). However, the recurrence patterns of tumors with GGO and their characteristics after recurrence remain unknown. When tumors with GGO recur, they may rarely metastasize to lymph nodes or distant organs, which may partially explain why tumors manifesting as GGO have a better prognosis than solid ones. In addition, information on the imaging patterns of recurrence can help radiologists know what to look for at postsurgical surveillance.

In regard to recurrence pattern, Sugimura et al (5) and Hung et al (19) reported that recurrence pattern was not a significant predictive factor for survival after recurrence. However, the two studies categorized recurrence pattern into local only, distant only, and both local and distal. Considering that the treatment modality for recurrence is

### Abbreviations

GGO = ground-glass opacity, HR = hazard ratio, OS = overall survival, PRS = postrecurrence survival


### Summary

Recurrence patterns, risk for recurrence, and overall survival in patients with resected lung adenocarcinoma differed based on the presence of ground-glass opacity at CT, and recurrence patterns were associated with postrecurrence survival.

### Key Results

- Ground-glass opacity (GGO) at CT was associated with time to recurrence and overall survival ($P < .001$).
- In clinical stage I disease, brain metastasis was more frequent in solid adenocarcinoma (16.5% [16 of 97 patients]) than in GGO adenocarcinoma (7.8% [four of 51 patients]; $P = .005$).
- Distant metastasis (adjusted hazard ratio [HR], 2.1; $P < .001$) and brain metastasis (adjusted HR, 3.9; $P < .001$), compared with local-regional recurrence, were associated with shorter postrecurrence survival.


usually determined by the presence or absence of distant metastases, the previous categorization of recurrence pattern may have underestimated the impact of distant metastases on survival. Furthermore, in the study by Sugimura et al (5), recurrence in bone, brain, or liver was associated with poorer survival compared with recurrence in the lung. In this sense, the association between recurrence pattern and survival after recurrence needs to be re-evaluated using different categorization of recurrence pattern at imaging.

Therefore, we aimed to investigate recurrence patterns at imaging and their associations with outcomes according to the presence of GGO at CT in patients with resected lung adenocarcinoma.

## Materials and Methods

This retrospective study was approved by our institutional review board, which waived the requirement for informed consent. Patient overlap with a previous study (20) is described in Appendix S1.

### Study Sample

A retrospective search of the electronic medical records at our institution identified 2019 patients who underwent lobectomy or pneumonectomy for invasive adenocarcinoma between July 2010 and December 2017. For inclusion in this study, patients needed to have undergone a chest CT examination with a section thickness of 1 mm or 1.25 mm within 30 days before surgery. The exclusion criteria were *(a)* minimally invasive adenocarcinoma, *(b)* recurrent or metastatic tumors, *(c)* synchronous lung cancer, *(d)* history of neoadjuvant chemotherapy or other primary malignant neoplasm, *(e)* incomplete survival records, and *(f)* no predominant subtype report. A total of 1019 patients were included.

### Chest CT Protocol

Chest CT was performed with multi–detector row CT scanners from two different manufacturers (Siemens Medical Solutions [Somatom Definition and Sensation 16] and GE Medical Systems [Lightspeed 16, Lightspeed VCT, and Discovery]). The acquisition parameters were 120 kVp, 30–200 mAs, pitch of 0.875–1, and collimation of 1–1.25 mm. Intravenous contrast material (90 mL) was injected at a rate of 3 mL/sec, and scanning started after a delay of 50 seconds. Images were reconstructed using a sharp kernel with a section thickness and interval of 1 mm and 1 mm, respectively, or 1.25 mm and 1.25 mm (Appendix S1).

### Clinical Tumor Staging with Chest CT

Two radiologists (S.P. and S.M.L., with 5 and 16 years of experience in thoracic radiology, respectively) who were blinded to the pathologic results evaluated images for the presence of any GGO components and other T descriptors in consensus. After reaching a consensus, one radiologist (S.P.) measured the longest diameter of each tumor and its solid portion in the axial, coronal, and sagittal planes by using a lung window setting and electronic calipers on a picture archiving and communication system. Interobserver variability analysis for evaluation of the presence of GGO components and measurement of the solid portion size of GGO adenocarcinomas is provided in Appendix S1. Clinical T categories were determined according to the maximal solid size among the three planes, following the eighth edition of the TNM classification (21). The consolidation-to-tumor ratio was calculated as the ratio of the longest diameter of the solid portion divided by the longest tumor diameter.

### Collection of Pathologic Data

Information on the predominant histologic subtypes determined according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung adenocarcinomas (22), pathologic nodal status, and genetic information regarding *EGFR* variation status and *ALK* rearrangement of each tumor were collected from pathologic reports. These evaluations were performed upon surgical resection of tumor specimens by one of two experienced pathologists (with 32 and 15 years of experience in lung cancer pathology).

### Follow-up for Survival Analysis and Analysis of Recurrence Patterns

All follow-up chest CT scans and other imaging examinations were retrospectively reviewed by one radiologist (J.C., with 8 years of experience in thoracic radiology). The date of recurrence (defined as the date when recurrent disease first appeared at diagnostic imaging) and the initial recurrence site were recorded. Local recurrence was defined as tumor recurrence adjacent to a staple line or the bronchial stump. Regional recurrence was defined as tumor recurrence in the ipsilateral lung or lymph node stations 1–14 and bilateral supraclavicular fossa. Distant metastasis was defined as metastasis to the pleura, pericardium, contralateral lung, other lymph node stations, or extrathoracic disease. Second primary lung cancer was discriminated from recurrent disease according to the criteria of Martini and Melamed (23). Time

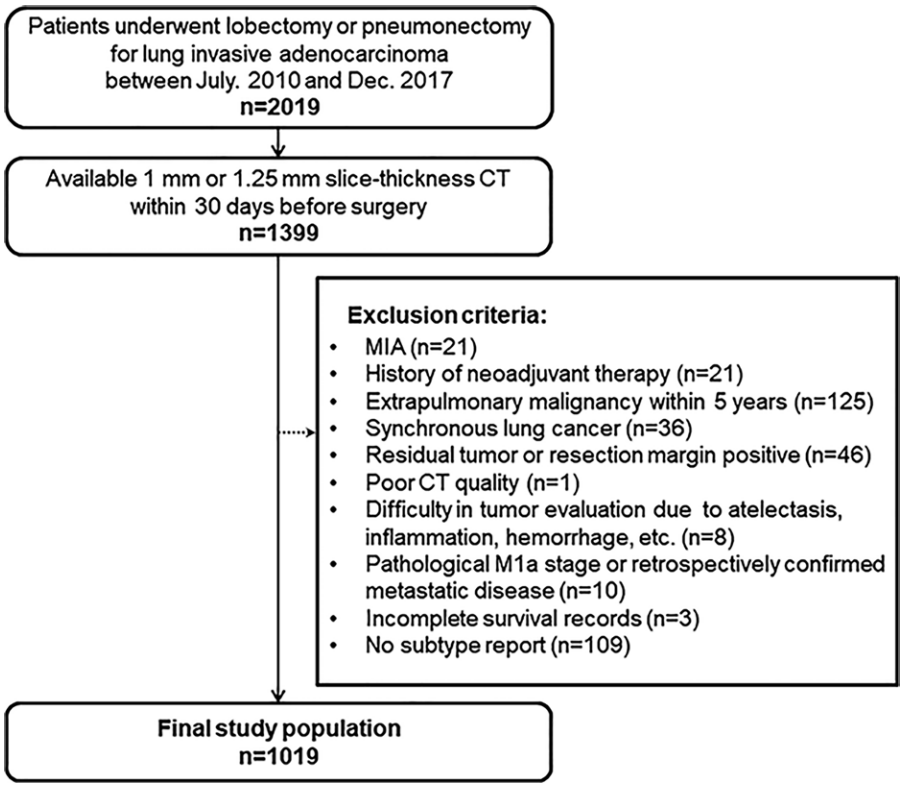


**Figure 1:** Flow diagram of patient inclusion. MIA = minimally invasive adenocarcinoma.

to recurrence, overall survival (OS), and postrecurrence survival (PRS) were the end points used for the survival analysis. The patients' follow-up data for time to recurrence were obtained from the electronic medical records at our institution, and data for OS and PRS were acquired from a database of the Ministry of the Interior and Safety. Detailed information is provided in Appendix S1.

### Statistical Analysis

Patients were classified into groups with GGO adenocarcinoma or solid adenocarcinoma according to the presence or absence of GGO components. Patient characteristics were compared between the two groups with use of the independent *t* test or $\chi^2$ test, as appropriate. Recurrence patterns were compared within patients with cancer at clinical stage I and clinical stage II or above. Time-to-event variables were calculated using the Kaplan-Meier method to describe the time to recurrence and OS rates, and these were compared between the two groups with use of the log-rank test.

Univariable and multivariable Cox proportional hazards models were used to identify potential prognostic factors for time to recurrence, OS, and PRS. For the multivariable analysis, first, all the significant clinical characteristics were included, and next, only the variables with $P < .10$ at univariable analysis were included and selected using the backward elimination process. The final model was adjusted for age and sex.

All statistical analyses were performed using SPSS (version 19.0, IBM), and $P < .05$ was considered to indicate a statistically significant difference.

## Results

### Patient Demographic and Clinical Characteristics

Of 2019 patients who underwent lobectomy or pneumonectomy for invasive lung adenocarcinoma, 1019 patients (mean age, 62 years ± 9 [SD]; 520 women) were included in the final study sample (Fig 1). The mean tumor size was 32 mm ± 16. Of the included patients, 487 were classified into the GGO adenocarcinoma group, and 532 were classified into the solid adenocarcinoma group. All collected clinical characteristics, except for age and surgical method, were significantly different between the two groups (Table 1). Clinical T1 category and overall stage I accounted for the most patients, both in the group with GGO adenocarcinoma (72.5% [353 of 487 patients] and 81.5% [397 of 487], respectively) and the group with solid adenocarcinoma (47.2% [251 of 532 patients] and 63.0% [335 of 532], respectively).

### Comparison of Recurrence Patterns according to the Presence of GGO

Of the 1019 patients, 271 experienced tumor recurrence; recurrence was diagnosed in 99 patients (36.5%) with pathologic confirmation and in 172 patients (63.5%) with a clinical-radiologic consensus. Sixty-one patients were reported to have died due to other cancer or noncancer-related causes without recurrence. A second primary lung cancer was detected in 1.0% of patients (10 of 1019). Four of these cancers occurred in patients with GGO adenocarcinoma, and the other six occurred in patients with solid ad-

**Table 1: Demographic and Clinical Characteristics of the Total Study Sample**

| Characteristic | All Patients ($n$ = 1019) | Patients with GGO Adenocarcinoma ($n$ = 487) | Patients with Solid Adenocarcinoma ($n$ = 532) | $P$ Value |
|---|---|---|---|---|
| Age (y)* | 62 ± 9 | 62 ± 9 | 63 ± 10 | .19† |
| Sex | | | | <.001‡ |
| M | 499 (49.0) | 206 (42.3) | 293 (55.1) | |
| F | 520 (51.0) | 281 (57.7) | 239 (44.9) | |
| Tumor size (mm)*§ | 32 ± 16 | 30 ± 15 | 34 ± 17 | .001† |
| Solid component size (mm)*§ | 29 ± 17 | 23 ± 14 | 34 ± 17 | <.001† |
| Smoking history | | | | <.001‡ |
| Currently smokes or formerly smoked | 432 (42.4) | 166 (34.1) | 266 (50.0) | |
| Never smoked | 587 (57.6) | 321 (65.9) | 266 (50.0) | |
| Smoking amount (pack-year)* | 13.3 ± 21.5 | 9.0 ± 17.6 | 17.2 ± 23.9 | <.001† |
| Clinical T stage | | | | <.001‡ |
| T1 | 604 (59.3) | 353 (72.5) | 251 (47.2) | |
| T1a | 66 (6.5) | 60 (12.3) | 6 (1.1) | |
| T1b | 241 (23.7) | 152 (31.2) | 89 (16.7) | |
| T1c | 297 (29.1) | 141 (29.0) | 156 (29.3) | |
| T2 | 280 (27.5) | 88 (18.1) | 192 (36.1) | |
| T2a | 199 (19.5) | 65 (13.3) | 134 (25.2) | |
| T2b | 81 (7.9) | 23 (4.7) | 58 (10.9) | |
| T3 | 90 (8.8) | 34 (7.0) | 56 (10.5) | |
| T4 | 45 (4.4) | 12 (2.5) | 33 (6.2) | |
| Overall clinical stage | | | | <.001‡ |
| IA | 567 (55.6) | 340 (69.8) | 227 (42.7) | |
| IB | 165 (16.2) | 57 (11.7) | 108 (20.3) | |
| IIA | 67 (6.6) | 20 (4.1) | 47 (8.8) | |
| IIB | 125 (12.3) | 47 (9.7) | 78 (14.7) | |
| IIIA | 86 (8.4) | 21 (4.3) | 65 (12.2) | |
| IIIB‖ | 9 (0.9) | 2 (0.4) | 7 (1.3) | |
| Pathologic N stage | | | | <.001‡ |
| N0 | 771 (75.7) | 411 (84.4) | 360 (67.7) | |
| N1 | 102 (10.0) | 38 (7.8) | 64 (12.0) | |
| N2 | 146 (14.3) | 38 (7.8) | 108 (20.3) | |
| Histologic subtype | | | | <.001‡ |
| Lepidic | 100 (9.8) | 100 (20.5) | 0 (0) | |
| Acinar | 320 (31.4) | 135 (27.7) | 185 (34.8) | |
| Papillary | 451 (44.3) | 242 (49.7) | 209 (39.3) | |
| Micropapillary | 18 (1.8) | 4 (0.8) | 14 (2.6) | |
| Solid | 130 (12.8) | 6 (1.2) | 124 (23.3) | |
| Surgical method | | | | .21‡ |
| Lobectomy | 1014 (99.5) | 486 (99.8) | 528 (99.2) | |
| Pneumonectomy | 5 (0.5) | 1 (0.2) | 4 (0.8) | |
| *EGFR* variation | | | | |
| Positive# | 265 (26.0) | 131 (26.9) | 134 (25.2) | |
| Negative | 240 (23.6) | 76 (15.6) | 164 (30.8) | |
| Unknown | 514 (50.4) | 280 (57.5) | 234 (44.0) | |

***(Table 1 continues)***

enocarcinoma. Six pathologically confirmed metachronous cancers included three adenocarcinomas, two small cell lung cancers, and one squamous cell carcinoma. The median follow-up time for time to recurrence was 50.2 months (range, 1.1–123.1 months) for the group with GGO adenocarcinoma and 42.2 months (range, 0.8–119.3 months) for the group with solid adenocarcinoma.

In patients with clinical stage I disease, recurrences occurred more frequently in the group with solid adenocarcinoma (29.0% [97 of 335 patients]) than in the group with GGO adenocarcinoma (12.8% [51 of 397 patients]; $P$ < .001) (Table 2). The most frequent recurrences were distant metastases, occurring in 69.1% of patients (67 of 97) with solid adenocarcinoma and 54.9% (28 of 51) with GGO adenocarcinoma ($P$ = .09).

**Table 1 *(continued)*: Demographic and Clinical Characteristics of the Total Study Sample**

| Characteristic | All Patients ($n$ = 1019) | Patients with GGO Adenocarcinoma ($n$ = 487) | Patients with Solid Adenocarcinoma ($n$ = 532) | $P$ Value |
|---|---|---|---|---|
| *ALK* variation | | | | |
| Positive** | 45 (4.4) | 9 (1.8) | 36 (6.8) | |
| Negative | 619 (60.7) | 291 (59.8) | 328 (61.7) | |
| Unknown | 355 (34.8) | 187 (38.4) | 168 (31.6) | |

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. Percentages may not add up to 100 because of rounding. GGO = ground-glass opacity.

* Data are means ± SDs.

† Derived with the independent $t$ test.

‡ Derived with the Pearson $\chi^2$ test.

§ The longest diameter among the axial, coronal, and sagittal planes.

‖ Eighteen patients underwent upfront surgery because the overall clinical stage was IIIA based on the seventh edition of TNM staging system applied at the time of surgery.

# *EGFR* variation positivity was determined by means of polymerase chain reaction–based assay.

** *ALK* variation positivity was determined by means of fluorescence in situ hybridization analysis.

**Table 2: Recurrence Patterns according to the Presence of GGO and Histologic Subtype in Clinical Stage I**

| Recurrence Pattern | All Patients ($n$ = 148) | Patients with GGO Adenocarcinoma ($n$ = 51) | Patients with Solid Adenocarcinoma ($n$ = 97) | $P$ Value |
|---|---|---|---|---|
| Overall recurrence | 148/732 (20.2) | 51/397 (12.8) | 97/335 (29.0) | <.001 |
| Local recurrence* | 7 (4.7) | 3 (5.9) | 4 (4.1) | .63 |
| Regional recurrence* | 46 (31.1) | 20 (39.2) | 26 (26.8) | .12 |
| Ipsilateral hila or mediastinum | 13 (8.8) | 0 (0) | 13 (13.4) | .006 |
| Contralateral hila or mediastinum, or ipsilateral or contralateral supraclavicular fossae | 6 (4.1) | 0 (0) | 6 (6.2) | .07 |
| Ipsilateral lung | 32 (21.6) | 20 (39.2) | 12 (12.4) | <.001 |
| Distant metastasis* | 95 (64.2) | 28 (54.9) | 67 (69.1) | .09 |
| Brain | 20 (13.5) | 4 (7.8) | 16 (16.5) | .005 |
| Bone | 14 (9.5) | 4 (7.8) | 10 (10.3) | .63 |
| Contralateral lung | 37 (25.0) | 16 (31.4) | 21 (21.6) | .20 |
| Other lymph node | 8 (5.4) | 3 (5.9) | 5 (5.2) | .85 |
| Chest wall or pleura | 27 (18.2) | 5 (9.8) | 22 (22.7) | .054 |
| Other | 3 (2.0) | 2 (3.9) | 1 (1.0) | .24 |

Note.—Data are numbers of patients with recurrence, with percentages in parentheses. GGO = ground-glass opacity.

* If two or more patterns of recurrence appeared at the same time on the date of recurrence, the higher grade of recurrence was selected (distant, regional, then local). If there were two or more initial recurrence sites within each recurrence pattern, they were all recorded.

There was a higher incidence of brain metastasis in the group with solid adenocarcinoma (16.5% [16 of 97]) than in the group with GGO adenocarcinoma (7.8% [four of 51]; $P$ = .005) (Fig 2). Of note, all regional recurrences in the group with GGO adenocarcinoma were ipsilateral lung metastasis (39.2% [20 of 51 patients]) (Table 2) without regional lymph node metastasis (Fig 3).

In patients with clinical stage II disease or above, recurrences also occurred more frequently in the group with solid adenocarcinoma (48.2% [95 of 197 patients]) than in the group with GGO adenocarcinoma (31.1% [28 of 90 patients]; $P$ = .006) (Table 3). Distant metastasis was the most common form of occurrence in the group with solid adenocarcinoma (62.1% [59 of 95 patients]) but was less frequent in the group with GGO adenocarcinoma (42.9% [12 of 28 patients] vs 46.4% [13 of 28] for regional recurrence). Brain metastasis occurred in 13.7% of patients (13 of 95) with solid adenocarcinoma and 7.1% of patients (two of 28) with GGO adenocarcinoma, but no evidence of a difference was observed between the two groups ($P$ = .07). By contrast, the incidence of contralateral lung metastasis in the group with solid adenocarcinoma (18.9% [18 of 95 patients]) was higher than that in the group with GGO adenocarcinoma (3.6% [one of 28 patients]; $P$ < .001). Some patients with GGO adenocarcinoma showed regional lymph node metastases (10.7% [three of 28] for ipsilateral hila or mediastinum, 10.7% [three of 28] for contralateral hila or mediastinum or for

supraclavicular fossae), which was not the observed in those with clinical stage I disease (Fig 4).

### Predictors for Time to Recurrence

The median follow-up time for time to recurrence was 45.9 months (range, 0.8–123.1 months), and most of the recurrences occurred within the first 2 years after surgery (73.1% [198 of 271 patients]). The 2-year time to recurrence was 88.3% in the group with GGO adenocarcinoma and 71.5% in the group with solid adenocarcinoma. The Kaplan-Meier curves showed that patients in the solid adenocarcinoma group had the shorter time to recurrence compared with those in the GGO adenocarcinoma group ($P < .001$) (Fig S3).

Univariable analysis revealed that time to recurrence was associated with the presence of GGO in addition to tumor size, solid component size, consolidation-to-tumor ratio, clinical T category, overall clinical stage, pathologic N category, and histologic subtype ($P < .001$ for all). In the multivariable analysis with adjustments for all the significant clinical characteristics, the presence of GGO ($P = .001$) was significantly associated with longer time to recurrence in addition to lower clinical T category ($P = .048$) and pathologic N0 category ($P < .001$) (Table 4). In the final model, the presence of GGO (adjusted hazard ratio [HR], 0.6 [95% CI: 0.4, 0.8]; $P < .001$), lower clinical T category ($P < .001$), and pathologic N0 category ($P < .001$) remained independent predictors of time to recurrence.

### Predictors for PRS

In 271 patients with recurrence, the median follow-up time for PRS was 36.6 months (range, 0.1–115.2 months), and 48.0% (130 of 271) died during follow-up. Univariable analysis revealed that shorter time to recurrence (≤12 months) and recurrence pattern were associated with poor PRS ($P < .001$ for both). When recurrence pattern divided into two categories (local-regional vs distant) was included in the multivariable analysis, recurrence with distant metastasis was an independent predictor of poor prognosis, with shorter PRS (adjusted HR, 2.1 [95% CI: 1.4, 3.1]; $P < .001$) after adjustment for age, sex, number of pack-years smoked, solid component size, and pathologic N category (Table S1). When the recurrence patterns were divided into three categories (local-regional vs brain metastasis vs nonbrain distant metastases), brain metastasis was also an independent factor for shorter PRS (adjusted HR, 3.9 [95% CI: 2.2, 6.8]; $P < .001$, with local-regional recurrence serving as the reference group).

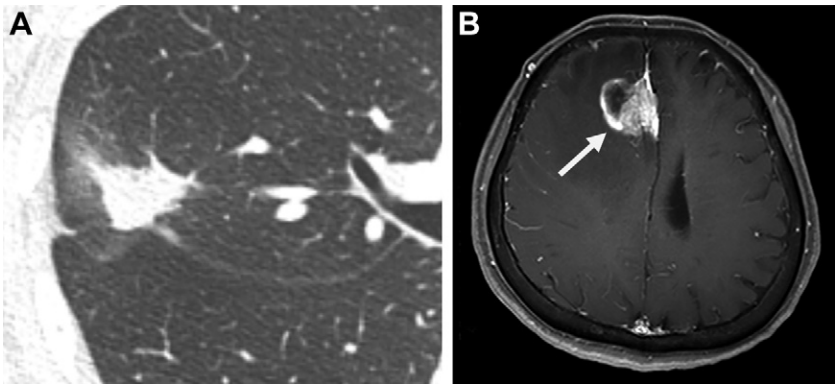


**Figure 2:** Images in a 58-year-old woman with brain metastasis after surgical resection of solid lung adenocarcinoma in clinical stage I. **(A)** Axial contrast-enhanced CT image with a lung window setting shows a 22-mm spiculated solid nodule in the right upper lobe. Because neither enlarged lymph nodes nor evidence of distant metastases were found at staging chest CT or PET/CT (not shown), the clinical staging of the patient was T1cN0M0, with an overall stage of IA3. At pathologic assessment of the surgical resection specimens, acinar-predominant histologic subtype and pathologic N0 stage were confirmed. Two years after the surgery, the patient reported new-onset headache. **(B)** Axial contrast-enhanced T1-weighted brain MRI scan acquired in the emergency department shows an enhancing lesion at the right anterior falx (arrow) with perilesional edema, indicating brain metastasis. Metastatic carcinoma was confirmed at cerebrospinal fluid analysis, and the patient was treated with whole-brain radiation therapy and chemotherapy.

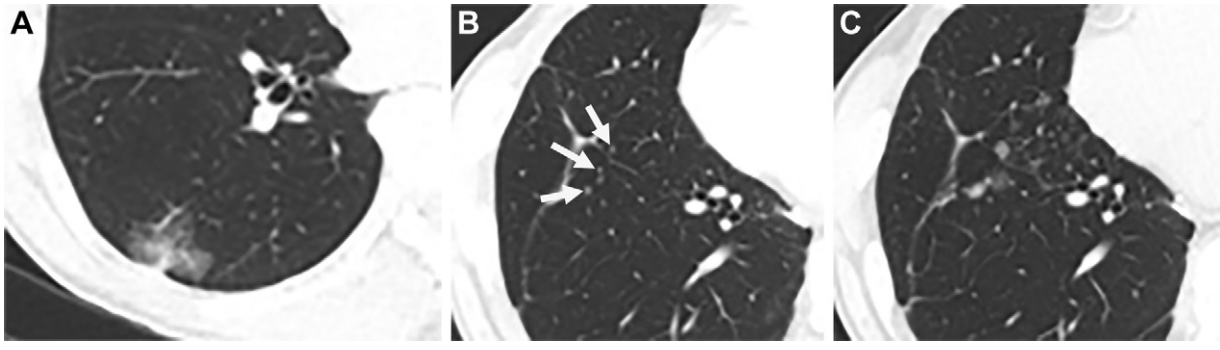


**Figure 3:** Axial contrast-enhanced CT images in a 58-year-old man with ipsilateral lung metastases after surgical resection of lung adenocarcinoma with ground-glass opacity in clinical stage I. **(A)** CT image with a lung window setting shows a 34-mm part-solid mass with an 18-mm solid component in the right lower lobe. No enlarged lymph nodes or distant metastases were found at staging chest CT or PET/CT (not shown). The clinical staging of the patient was T1bN0M0, with an overall stage of IA2. At pathologic assessment of the surgical resection specimens, acinar-predominant histologic subtype and pathologic N0 stage were confirmed. **(B)** CT image acquired 1 year after surgery at routine postoperative follow-up shows several tiny nodules in the rearranged right middle lobe (arrows) that had newly appeared and increased in size and number on the **(C)** CT image acquired 2 years 7 months after the surgery, indicating ipsilateral lung metastases. There were no enlarged regional lymph nodes suggestive of metastasis (image not shown). The patient was treated with chemotherapy.

**Table 3: Recurrence Patterns according to Histologic Subtype and the Presence of GGO in Clinical Stage II or Above**

| Recurrence Pattern | All Patients ($n$ = 123) | Patients with GGO Adenocarcinoma ($n$ = 28) | Patients with Solid Adenocarcinoma ($n$ = 95) | $P$ Value |
|---|---|---|---|---|
| Overall recurrence | 123/287 (42.9) | 28/90 (31.1) | 95/197 (48.2) | .006 |
| Local recurrence* | 5 (4.1) | 3 (10.7) | 2 (2.1) | .04 |
| Regional recurrence* | 47 (38.2) | 13 (46.4) | 34 (35.8) | .31 |
| Ipsilateral hila or mediastinum | 14 (11.4) | 3 (10.7) | 11 (11.6) | .90 |
| Contralateral hila or mediastinum, or ipsilateral or contralateral supraclavicular fossae | 14 (11.4) | 3 (10.7) | 11 (11.6) | .90 |
| Ipsilateral lung | 25 (20.3) | 9 (32.1) | 16 (16.8) | .08 |
| Distant metastasis* | 71 (57.7) | 12 (42.9) | 59 (62.1) | <.001 |
| Brain | 15 (12.2) | 2 (7.1) | 13 (13.7) | .07 |
| Bone | 9 (7.3) | 1 (3.6) | 8 (8.4) | .39 |
| Contralateral lung | 19 (15.4) | 1 (3.6) | 18 (18.9) | <.001 |
| Other lymph node | 8 (6.5) | 3 (10.7) | 5 (5.3) | .31 |
| Chest wall or pleura | 22 (17.9) | 6 (21.4) | 16 (16.8) | .58 |
| Others | 7 (5.7) | 0 (0) | 7 (7.4) | .14 |

Note.—Data are numbers of patients with recurrence, with percentages in parentheses. GGO = ground-glass opacity.

* If two or more patterns of recurrence appeared at the same time on the date of recurrence, the higher grade of recurrence was selected (distant, regional, then local). If there were two or more initial recurrence sites within each recurrence pattern, they were all recorded.

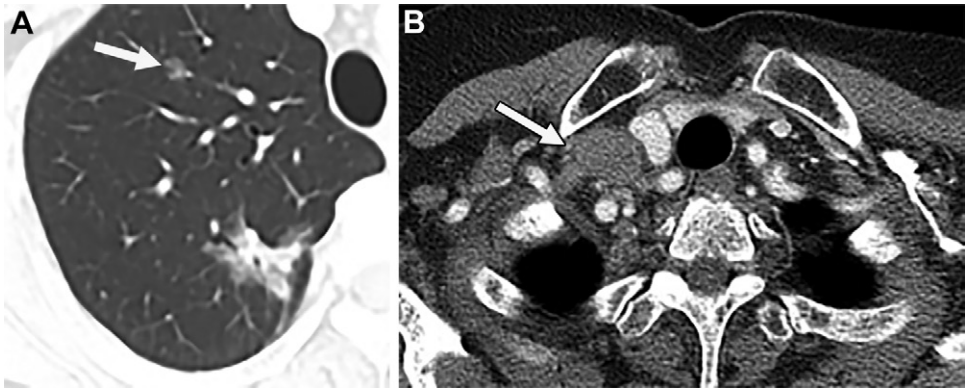


**Figure 4:** Axial contrast-enhanced CT images in a 68-year-old woman with regional lymph node metastasis after surgical resection of lung adenocarcinoma in clinical stage IIB. **(A)** CT image with a lung window setting shows a 46-mm part-solid mass with a 28-mm solid component and a separate nodule (arrow) in the right upper lobe. No enlarged lymph nodes or distant metastases were found at staging chest CT or PET/CT (not shown). The clinical staging of the patient was T3N0M0, with an overall stage of IIB. At pathologic assessment of the surgical resection specimens, multiple tumors of papillary-predominant histologic subtype and pathologic N1 stage were confirmed. **(B)** CT image with a mediastinal setting from routine postoperative follow-up 1 year after the surgery shows newly enlarged lymph nodes in the right supraclavicular area (arrow) and ipsilateral mediastinum (not shown), indicating regional lymph node metastasis. PET/CT findings supported the diagnosis of recurrence (not shown), and the patient was treated with chemotherapy.

The presence of GGO did not show a significant association with PRS ($P$ = .11 and .14 for the two and three recurrence categories, respectively) (Tables S1, S2).

## Predictors for OS

The median follow-up time for OS was 62.5 months (range, 1.1–132.1 months), and 191 of 1019 patients (18.7%) died during the follow-up period. The 5-year OS rates were 92.3% in the group with GGO adenocarcinoma and 77.8% in the group with solid adenocarcinoma. The Kaplan-Meier curves showed that OS was significantly shorter in the group with solid adenocarcinoma ($P$ < .001) (Fig S4). In the multivariable analysis, the presence of GGO was independently associated with reduced hazards for death (adjusted HR for OS, 0.6 [95% CI: 0.4, 0.8]; $P$ < .001) after adjustment for other predictors of OS, including older age (HR, 1.06; $P$ < .001), higher number of pack-years of smoking (HR, 1.8 for ≤20 pack-years and 2.2 for >20 pack-years; $P$ = .01), larger solid component size (HR, 1.2; $P$ < .001), and pathologic N1 or N2 category (HR, 3.7; $P$ < .001) (Table S3).

**Table 4: Univariable and Multivariable Cox Proportional Hazards Model Analyses of Time to Recurrence**

| | Univariable Analysis | | Multivariable Analysis* | | Multivariable Analysis (Final Model) | |
|---|---|---|---|---|---|---|
| Variable | HR | *P* Value | HR | *P* Value | HR | *P* Value |
| Age (per year increase) | 1.00 (0.99, 1.02) | .69 | 1.00 (0.99, 1.01) | .87 | 1.00 (0.99, 1.02) | .72 |
| Sex | | | | | | |
| F | Reference | | Reference | | Reference | |
| M | 0.9 (0.7, 1.1) | .38 | 0.8 (0.5, 1.2) | .27 | 0.8 (0.7, 1.1) | .14 |
| Ground-glass opacity | | | | | | |
| Absence | Reference | | Reference | | Reference | |
| Presence | 0.4 (0.3, 0.5) | <.001 | 0.6 (0.5, 0.8) | .001 | 0.6 (0.4, 0.8) | <.001 |
| Smoking amount | | .77 | | .61 | | |
| Never smoked | Reference | | Reference | | | |
| ≤20 pack-years | 1.1 (0.8, 1.5) | .47 | 1.2 (0.7, 1.8) | .46 | | |
| >20 pack-years | 1.0 (0.8, 1.4) | .77 | 1.0 (0.6, 1.5) | .95 | | |
| Tumor size (per 1-cm increase) | 1.3 (1.2, 1.3) | <.001 | | | | |
| Solid component size (per 1-cm increase) | 1.3 (1.2, 1.4) | <.001 | 1.1 (0.9, 1.2) | .20 | | |
| CTR (per 0.1 increase) | 1.6 (1.4, 1.8) | <.001 | | | | |
| Clinical T category | | <.001 | | .048 | | <.001 |
| T1a | Reference | | Reference | | Reference | |
| T1b | 4.4 (1.1, 18.4) | .04 | 2.5 (0.6, 10.8) | .21 | 3.1 (0.7, 13.1) | .12 |
| T1c | 10.3 (2.5, 42.0) | .001 | 4.4 (1.0, 18.4) | .045 | 5.8 (1.4, 24.0) | .01 |
| T2a | 15.4 (3.8, 62.9) | <.001 | 6.6 (1.3, 33.3) | .02 | 6.8 (1.7, 28.3) | .008 |
| T2b | 19.7 (4.8, 82.0) | <.001 | 5.7 (1.0, 32.0) | .047 | 7.5 (1.8, 31.8) | .006 |
| T3 | 19.2 (4.6, 80.0) | <.001 | 8.7 (1.7, 45.3) | .01 | 10.3 (2.4, 43.6) | .002 |
| T4 | 23.2 (5.4, 99.8) | <.001 | 5.6 (0.9, 33.4) | .06 | 10.1 (2.3, 44.0) | .002 |
| Overall clinical stage | | <.001 | | .35 | | |
| IA | Reference | | Reference | | | |
| IB | 2.0 (1.4, 2.8) | <.001 | 0.6 (0.3, 1.4) | .28 | | |
| IIA | 2.8 (1.8, 4.3) | <.001 | 0.8 (0.3, 2.2) | .70 | | |
| IIB | 3.2 (2.3, 4.4) | <.001 | 0.8 (0.4, 1.7) | .60 | | |
| IIIA | 4.4 (3.1, 6.3) | <.001 | 1.0 (0.5, 1.9) | .98 | | |
| IIIB | 2.3 (0.6, 9.3) | .03 | 0.2 (0.0, 1.1) | .06 | | |
| Pathologic N category | | | | | | |
| N0 | Reference | | Reference | | Reference | |
| N1 or N2 | 5.1 (4.0, 6.4) | <.001 | 3.6 (2.7, 4.7) | <.001 | 3.7 (2.9, 4.8) | <.001 |
| Histologic subtype | | <.001 | | .31 | | |
| Lepidic | Reference | | Reference | | | |
| Acinar or papillary | 6.3 (2.6, 15.2) | <.001 | 2.0 (0.8, 5.2) | .13 | | |
| Solid or micropapillary | 11.8 (4.8, 29.4) | <.001 | 1.9 (0.7, 5.2) | .19 | | |
| Surgical method | | | | | | |
| Lobectomy | Reference | | | | | |
| Pneumonectomy | 0.9 (0.1, 6.4) | .92 | | | | |

Note.—Unless otherwise specified, data are hazard ratios (HRs), with 95% CIs in parentheses. CTR = consolidation-to-tumor ratio.

* Tumor size was excluded because it was correlated with solid component size (Spearman correlation $r = 0.902$; $P < .001$) and was the same as the solid component size in the group with solid adenocarcinoma. Consolidation-to-tumor ratio was excluded because it was correlated with solid component size (Spearman correlation $r = 0.496$; $P < .001$), being defined as the ratio of solid component size to total size, and it provides no prognostic information about solid adenocarcinomas, as all consolidation-to-tumor ratios are 1.0 in the group with solid adenocarcinoma.

## Discussion

Little is known about the recurrence pattern and outcomes in patients with resected lung adenocarcinoma according to the presence of ground-glass opacity (GGO) at CT. Our study showed that recurrence patterns differed based on the presence of GGO: higher incidence of ipsilateral lung metastasis (39.2% [20 of 51 patients]) with no regional lymph node metastasis in patients with GGO adenocarcinoma and higher incidence of brain metastasis (16.5% [16 of 97 patients]) in patients with solid adenocarcinoma in clinical stage I. Distant metastasis compared

with local-regional recurrence (adjusted hazard ratio [HR], 2.1; $P < .001$) and brain metastasis (adjusted HR, 3.9; $P < .001$) compared with local-regional recurrence were associated with poor postrecurrence survival. In addition, GGO at CT was associated with time to recurrence and overall survival ($P < .001$).

In our study, recurrence patterns in patients with and without GGO differed according to clinical stage. In clinical stage I, patients with GGO adenocarcinoma only had regional recurrence in the ipsilateral lung and no incidences of regional lymph node metastasis. It appeared that the recurrent tumor of GGO adenocarcinoma retains the characteristics of the primary tumor, which is known to have a low frequency of lymph node metastasis. However, in clinical stage II or above, patients in the GGO adenocarcinoma group showed a rate of 10.7% (three of 28) for both ipsilateral hilar or mediastinal lymph node metastases and contralateral hilar or mediastinal or supraclavicular lymph node metastases. There was no evidence of a difference between the two groups ($P = .90$ for both). This is in line with a previous investigation that showed that the presence of GGO was associated with better disease-free survival only for patients with pathologic N0 category and clinical T1 category disease (20).

In keeping with several previous studies (7–9), distant metastasis was the most common pattern of recurrence in our study sample (64.2% [95 of 148 patients] with clinical stage I disease and 57.7% [71 of 123 patients] with clinical stage II disease or above). However, the association between recurrence pattern and survival was not clear in previous studies. In the study by Sugimura et al (5), local and distant recurrence showed similar 2-year PRS rates ($P = .42$), and in the study by Hung et al (19), recurrence pattern was not associated with PRS, even in the univariable analysis ($P = .18$). Because these previous studies collected information about recurrence from medical records and not from imaging reviews, the very first time points and sites of recurrence might not have been accurate. In our study, with meticulous retrospective reviews of all postoperative imaging examination findings, distant metastasis (adjusted HR, 2.1; $P < .001$) and brain metastasis (adjusted HR, 3.9; $P < .001$), relative to local-regional recurrence, were associated with shorter PRS. Additionally, we found that brain metastases were more common in the group with solid adenocarcinoma (16.5% [16 of 97 patients]) than in the group with GGO adenocarcinoma (7.8% [four of 51 patients]; $P = .005$) among patients with clinical stage I disease.

In our study, the presence of GGO was a consistently favorable prognostic factor in terms of both time to recurrence (HR, 0.6; $P < .001$) and OS (HR, 0.6; $P < .001$), which aligned with the findings of previous studies (11–15). Notably, the lower rates of distant metastasis and brain metastasis in GGO adenocarcinomas may explain the better prognosis of GGO adenocarcinomas compared with that of solid adenocarcinomas. Knowing the common sites of recurrence according to GGO presence and clinical stage may help radiologists read imaging examinations without missing lesions in patients under surveillance for recurrence and facilitate the establishment of personalized surveillance strategies or selection of candidates for adjuvant therapy based on the risk of specific recurrence patterns. For example, brain surveillance or adjuvant therapy may be considered after resection of solid adenocarcinoma if the patient has additional risk factors for brain metastasis, such as *EGFR* variation or *ALK* rearrangement (24–26), pathologic N2 stage, or imaging predictors, such as the presence of spiculation or absence of air bronchogram (27). Additionally, follow-up with contrast-enhanced CT may be recommended until 2 years after surgery in high-risk groups because most of the recurrences occurred within the first 2 years after surgery (73.1% [198 of 271 patients]).

There are several limitations to our study. First, this study was conducted using single-center data in a single ethnic group with a high frequency of *EGFR* variation (28) and a relatively favorable prognosis (29). Therefore, our results need to be validated in larger, multicenter studies. Second, the variation status of *EGFR* and *ALK* was unknown in a high number of patients; therefore, its association with recurrence patterns could not be analyzed. Third, there were only a small number of patients for each of the different sites of recurrence. Fourth, there is still controversy over the definition of second primary lung cancer, although the criteria of Martini and Melamed (23) are the most widely used. Validation and modification of the criteria for application to a contemporary population may be needed in future studies. Last, the presence of the GGO component was evaluated by two radiologists in consensus, and the size measurement of each tumor and analysis of recurrence patterns were performed by one observer, although interobserver variability of size measurements was provided.

In conclusion, recurrence patterns, time to recurrence, and overall survival differed according to the presence of ground-glass opacity (GGO) at CT. Patients with GGO adenocarcinomas had a lower incidence of brain metastasis in stage I compared with those with solid adenocarcinomas. Distant metastasis, particularly brain metastasis, was associated with shorter postrecurrence survival. Further validation is warranted to apply our results to personalized surveillance strategies and patient selection for adjuvant therapy.

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## References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–249.

2. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109(1):120–129.
3. al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. Eur J Cardiothorac Surg 1997;12(3):380–384.
4. Martin J, Ginsberg RJ, Venkatraman ES, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. J Clin Oncol 2002;20(8):1989–1995.
5. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg 2007;83(2):409–417; discussion 417–418.
6. Westeel V, Choma D, Clément F, et al. Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. Ann Thorac Surg 2000;70(4):1185–1190.
7. Hung JJ, Jeng WJ, Hsu WH, et al. Prognostic factors of postrecurrence survival in completely resected stage I non-small cell lung cancer with distant metastasis. Thorax 2010;65(3):241–245.
8. Alberts WM. Follow up and surveillance of the patient with lung cancer: what do you do after surgery? Respirology 2007;12(1):16–21.
9. Lou F, Sima CS, Rusch VW, Jones DR, Huang J. Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung cancer. Ann Thorac Surg 2014;98(5):1755–1760; discussion 1760–1761.
10. Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol 2011;6(4):751–756.
11. Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. AJR Am J Roentgenol 2000;174(3):763–768.
12. Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. Ann Thorac Surg 2006;81(2):413–419.
13. Aoki T, Tomoda Y, Watanabe H, et al. Peripheral lung adenocarcinoma: correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 2001;220(3):803–809.
14. Kim H, Goo JM, Kim YT, Park CM. Validation of the eighth edition clinical T categorization system for clinical stage IA, resected lung adenocarcinomas: prognostic implications of the ground-glass opacity component. J Thorac Oncol 2020;15(4):580–588.
15. Hattori A, Hirayama S, Matsunaga T, et al. Distinct clinicopathologic characteristics and prognosis based on the presence of ground glass opacity component in clinical stage IA lung adenocarcinoma. J Thorac Oncol 2019;14(2):265–275.
16. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2016;11(8):1204–1223.
17. Fu F, Zhang Y, Wen Z, et al. Distinct prognostic factors in patients with stage I non-small cell lung cancer with radiologic part-solid or solid lesions. J Thorac Oncol 2019;14(12):2133–2142.
18. Aokage K, Miyoshi T, Ishii G, et al. Influence of ground glass opacity and the corresponding pathological findings on survival in patients with clinical stage I non-small cell lung cancer. J Thorac Oncol 2018;13(4):533–542.
19. Hung JJ, Yeh YC, Jeng WJ, et al. Prognostic factors of survival after recurrence in patients with resected lung adenocarcinoma. J Thorac Oncol 2015;10(9):1328–1336.
20. Park S, Lee SM, Choe J, et al. Differences in the prognostic implication of ground-glass opacity on CT according to pathological nodal status in lung cancers treated with lobectomy or pneumonectomy. Eur Radiol 2022;32(7):4405–4413.
21. Amin MB, Edge S, Greene F, et al. eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer, 2017. https://link.springer.com/book/9783319406176.
22. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6(2):244–285.
23. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70(4):606–612.
24. Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol 2014;9(2):195–199.
25. Mitra D, Chen YH, Li R, et al. EGFR mutant locally advanced non-small cell lung cancer is at increased risk of brain metastasis. Clin Transl Radiat Oncol 2019;18:32–38.
26. Wang H, Wang Z, Zhang G, et al. Driver genes as predictive indicators of brain metastasis in patients with advanced NSCLC: EGFR, ALK, and RET gene mutations. Cancer Med 2020;9(2):487–495.
27. Park S, Lee SM, Ahn Y, et al. Identification of predictors for brain metastasis in newly diagnosed non-small cell lung cancer: a single-center cohort study. Eur Radiol 2022;32(2):990–1001.
28. Liu W, Innocenti F, Chen P, Das S, Cook EH Jr, Ratain MJ. Interethnic difference in the allelic distribution of human epidermal growth factor receptor intron 1 polymorphism. Clin Cancer Res 2003;9(3):1009–1012.
29. Ou S-HI, Ziogas A, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. J Thorac Oncol 2009;4(9):1083–1093.