Supplementary

Title

Application of 3D reconstruction/3D printing model in pathological sampling of multifocal pulmonary nodules: a prospective single-arm study

Grant
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Principal Investigator
Shugeng Gao

Sponsor
National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

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Statement of compliance

The study will be conducted in accordance with Declaration of Helsinki, International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6) and Medical Equipment Specification for the Quality Control of Clinical Trial (State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth). All personnel involved in the conduct of this study have completed human subject protection training.

Signature page

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Principal Investigator:
Signed:_Date:_
Name: Shugeng Gao
Title: MD.

Protocol summary

Title: Application of 3D reconstruction/3D printing model in pathological sampling of multifocal pulmonary nodules: a prospective single-arm study.

Objective: To evaluate the effectiveness of 3D reconstruction/3D printing technology in the pathological collection of surgical specimens of multiple lung nodules.

Participants: Patients aged 18–79 years old; with thin-slice CT showed multiple pulmonary nodules, planning to perform lung lobe/pulmonary segment surgery; two or more nodules are present in the same lobe or segment; the largest diameter of the lung window of the main lesion is 0< d ≤20 mm; with clinical staged I (cT1N0) (UICC-TNM edition 8); ECOG scored 0–1; without history of the following operations: ipsilateral thoracotomy, ipsilateral thoracoscopic lung and esophagectomy, mediastinal surgery (except for bullae and rib fractures), contralateral thoracotomy or thoracoscopic surgery (except for bullae and rib fractures); without preoperative neoadjuvant treatment; no history of radiotherapy; all patients have complete preoperative examinations: chest and upper abdomen CT, neck ultrasound (neck, supraclavicular lymph nodes) and abdominal ultrasound (liver, gallbladder, pancreas, spleen, Both kidneys, adrenal glands) examination, cranial MRI, bone scan (PET-CT can replace ultrasound, cranial MRI and bone scan). Sign informed consent.

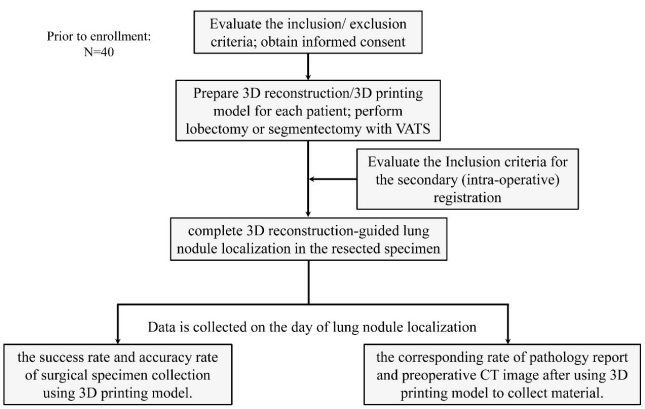
Number of site: This is a single-center trial and all participants would be recruited in National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Description of Intervention: The study will not affect the patient's surgical treatment process.

Estimated Study Duration: From 2019. 09 to 2020.09.

Estimated Time to Complete Enrollment: 2020.06

Schematic of Study Design



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List of abbreviations

3D: three-dimensional
CT: computed tomography
GGO: ground glass nodule
VATS: video assisted thoracoscopic surgery

Introduction: background information and scientific rationale

Background information

Since the middle of the 20th century, more and more evidence support tumor screening, which has made a significant contribution to the detection and treatment of early disease (1,2). With the improvement of people's awareness of cancer prevention and the clinical application of high-resolution CT (HRCT), patients with early multiple pulmonary nodules have gradually increased (3-5). The CT findings of these patients are mostly pure ground glass nodules (pGGNs) or mixed density ground glass nodules (mGGNs). Surgical treatment can not only preserve lung function to the greatest extent, but also enable most patients to receive effective radical treatment. For early multifocal pulmonary nodules, wedge resection, lobectomy or selective segmental resection should be selected according to the specific situation. In addition, surgical specimens can provide more detailed pathological and genetic characteristics for adjuvant treatment and follow-up monitoring of multiple primary lung cancers (6,7).

A key issue of simultaneous multiple primary lung cancer is the choice of surgical methods. Due to the lack of prospective clinical trials and consistent diagnostic criteria, there is no unified consensus on the treatment criteria for multiple primary lung cancers (MPLCs). At present, there is no clear guideline for the diagnosis and treatment of simultaneous multiple primary lung cancer (sMPLC). The scope of surgical resection is mainly based on the patient's surgical risk and the surgeon's personal choice. Although some cases have been reported in the SEER database, the National Cancer Database (NCDB) of the United States, and European and Asian databases, and some treatment strategies and recommendations have been proposed, due to the controversy caused by individual differences between patients, the three major lung cancer research institutions [International Union Against Cancer (UICC), American Joint Committee on Cancer (AJCC) and International Association for the Research of Lung Cancer (IALSC)] did not agree on this consensus. The choice of surgical strategy for simultaneous multiple primary lung cancers mainly depends on the diagnosis of CT before operation.

In recent years, with the development and application of 3D reconstruction technology, treatment strategies for early lung cancer are gradually changing. For patients with early-stage lung cancer less than 2 cm, segmentectomy has become a feasible radical operation. For patients with multiple primary lung cancers, due to the influence of the number and location of the lesions, it may be difficult to plan the surgical strategy solely relying on CT judgment. Therefore, it is necessary to further evaluate the impact of three-dimensional reconstruction technology on the surgical strategy of multiple pulmonary nodules, and provide feasible suggestions and help for the surgical treatment of sMPLC. For multiple pulmonary nodules surgical specimens, the reliability of tissue specimen sampling depends on the precise positioning of each nodule. If the pathologist can accurately describe the types and characteristics of different nodules under the microscope, it will help clarify the nature of multiple lesions and this has guiding significance for tumor staging (multiple primary or lung metastasis). In addition, if the pathology report can be matched with the preoperative CT image one by one, it will help to carry out the research on the imaging and pathological characteristics of multiple primary lung cancers in the future, and benefit for the selection of appropriate treatment methods (observation, wedge resection, selection Segmental resection or lobectomy, etc.). However, in the actual operation process, due to the lack of sufficient understanding of preoperative CT images, unless the thoracic surgeon identifies all the lesions, it is difficult for the pathologist to find lesions during the process of collecting materials. At the same time, due to the lack of accurate pathological material location, the pathology report of early multiple nodules rarely corresponds to the preoperative image one-by-one, and it is difficult to retrospectively evaluate the characteristics of each nodule. Therefore, we need a method that can not only help the surgeon locate the nodules, but also help the pathologist locate all the nodules and diagnose each nodule (7).

The 3D reconstruction/3D printing model provides us with a good cross-reference method to guide surgeons and pathologists to locate multiple lesions in the specimen. This study aims to explore the application value of 3D reconstruction and 3D printing models in the surgical treatment of simultaneous multiple pulmonary nodules. It hopes to provide feasible suggestions on the selection of early multiple primary lung cancer surgery strategies and

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pathological materials, and provide evidence support for the superiority of three-dimensional reconstruction technology in the early multiple primary lung cancer surgical treatment.

Potential risk and benefits

Potential risks

The study does not affect the surgical treatment process of patients. 3D reconstruction will not affect the patient's treatment process. Therefore, complications are only related to the operation itself. 3D reconstruction does not increase potential risk of patients.

Potential Benefits

Based on our previous experience, the application of 3D reconstruction technology in multiple nodule localization in resected specimens might facilitate the process of nodule localization. For multiple nodules on the same lobe or segment, it is difficult to find all the lesions for surgeons or pathologists. In addition, due to the lack of accurate pathological material location, the pathology report of early multiple nodules rarely corresponds to the preoperative image one-by-one, thus it is difficult to retrospectively evaluate the characteristics of each nodule. Instead, the 3D reconstruction/3D printing model provides us with a good cross-reference method to guide surgeons and pathologists to locate multiple lesions in the specimen. In this way, surgeons and pathologists can locate nodules accurately on the resected specimens, which convenient for the correspondence of the nodule pathology and CT image features. At the same time, surgical procedures are performed safer under the assistant of 3D reconstruction/3D printing model.

Objectives

Study objectives

To evaluate the effectiveness of 3D reconstruction/3D printing technology in the pathological collection of surgical specimens of multiple lung nodules.

Study outcomes

Primary outcome: the success rate and accuracy rate of surgical specimen collection using 3D printing model.

Secondary outcome: the agreement rate between the pathological results of the samples and CT images after using 3D printing model to collect material.

Study design

The basic idea

Use the univariate single-group design to clarify the success rate and accuracy of the 3D reconstruction technology assisted pathology specimen sampling.

Study population and groups

Patients enrolled in this study were performed 3D reconstruction according to preoperative CT. In this single-arm clinical trial, anatomic lobectomy or segmentectomy will be performed for all patients. To assure that the assigned surgical procedures are performed properly, the procedures will be centrally reviewed by principal investigator (SG Gao) and the lead implementer (B Qiu). The process of localizing nodules in surgical specimens will be performed by researchers of the project team. This process will be aided by 3D reconstruction image or 3D printing model.

3D printing model preparation and surgical process

(I) 3D printing model preparation: Obtain the preoperative CT data of the first enrolled patients from the workstation of the imaging department of our hospital. Import the DICOM data of thin-slice (0.625–1.25 mm) CT images into Mimics software (Materialise's interactive medical image control system) to perform three-dimensional reconstruction. Planning the resection area and cutting plane in the three-dimensional image, this process is completed by the thoracic surgeon in the research team. Subsequently, 3-Matic software is used to process the "stereolithography (STL)" format of the reconstructed image, and then print the 3D model. This process is assisted by a third-party company [Zhen Yuan (Tianjin) Medical Device Technology Co., Ltd].

(II) Surgical process: The study does not affect the surgical treatment process of patients. The patient received video-assisted thoracoscopic lobectomy or anatomical partial lobectomy, double-lumen endotracheal intubation ventilation, general anesthesia, and contralateral ventilation single-port/three-port thoracoscopic surgery. The three-hole method makes a 1.0 cm incision at the mid-axillary line of the patient's 7th and 8th intercostal

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space. The observation hole is reasonably inserted into the thoracoscope. Choose the 3.0 cm incision at the anterior axillary line between the 3th or 4th intercostals as the main operation hole, and the 2.0 cm incision at the lower line of the shoulder armor between the 7th or 8th intercostals as the auxiliary handle control operation. The single-hole method uses a 3–5 cm incision at the patient's 4th or 5th intercostal anterior axillary line as an observation/operation hole. Perform standard lobectomy or anatomical partial lobectomy on the patient. Fine thread ligation is performed for the smaller blood vessel branches, and the staple cartridge of the linear cutting stapler is selected for the thick lung tube to completely stop the bleeding and complete the operation. Observe and monitor the vital signs of patients strictly during and after surgery.

The process of localizing nodules in surgical specimens

This process is completed by surgeons and pathologists. The resected surgical specimens are compared with the preoperative 3D reconstruction/3D printing model, and the lesions are found and marked in the resected surgical specimens according to the position of the nodules identified on the 3D reconstruction. The thoracic surgeon assists the pathologist to locate the nodules, and once a lesion is found, it is marked with the corresponding Roman numeral (#1, #2, #3...) in the 3D printed model, and the pathologist performs the corresponding operation specimen mark registration. Subsequently, the pathological diagnosis process was carried out in accordance with the routine pathology procedure. After the pathology report is reported, according to the number sequence of the nodules in the pathology report, using the 3D printing model as an intermediary, the pathological diagnosis of the nodules and the location of the lesion in the CT image are one-to-one correspondence. If the nodule marked in the 3D printing model is not found in the surgical specimen, mark 'NO' on the model. Finally, calculate the success rate of all enrolled patients (the actual number of nodules * 100%/3D printing model number of nodules), and the corresponding rate of nodules and preoperative CT (the lesions in the postoperative pathology report can be Corresponding to the number of nodules on the preoperative CT*100%/total number of lesions in the postoperative pathology report).

Time schedule

The trail is planned to start in October 2019 and complete before September 2020.

Statistical analysis

Sample size estimation: α (inspection level) is set to 0.05, 1-β (inspection power) is set to 0.8, the experimental group rate value is set to 0.95, the reference rate value is based on the previous multiple nodules surgery specimens in our department The accuracy rate and the corresponding rate of the preoperative CT image were set to 0.7, and the Δ (cutoff value) was set to 0.1. The algorithm uses Z-pooled approximate estimation method to perform high-quality estimation, and the calculated sample size is n=32. Because there may be unqualified cases due to various reasons, the sample size increases by 10–20%, and the final sample size N=40 cases.

Study enrollment and withdraw

Inclusion criteria for the first (pre-operative) registration

For inclusion in the first (pre-operative) registration, patients will be required to fulfill all of the following criteria: (I) patients aged 18–79 years old; (II) with thin-slice CT showed multiple pulmonary nodules, planning to perform lung lobe/pulmonary segment surgery; (III) the largest diameter of the lung window of the main lesion is $0< d \leq 20$ mm; (IV) two or more nodules are present in the same lobe or segment; (V) with clinical staged I (cT1N0) (UICC-TNM edition 8); (VI) ECOG scored 0–1; (VII) without history of the following operations: ipsilateral thoracotomy, ipsilateral thoracoscopic lung and esophagectomy, mediastinal surgery (except for bullae and rib fractures), contralateral thoracotomy or thoracoscopic surgery (except for bullae and rib fractures); (VIII) without preoperative neoadjuvant treatment; (IX) no history of radiotherapy; (X) all patients have complete preoperative examinations: chest and upper abdomen CT, neck ultrasound (neck, supraclavicular lymph nodes) and abdominal ultrasound (liver, gallbladder, pancreas, spleen, Both kidneys, adrenal glands) examination, cranial MRI, bone scan (PET-CT can replace ultrasound, cranial MRI and bone scan); (XI) sign informed consent.

Exclusion criteria

(I) Taking other experimental drugs at the same time or in other clinical trials; (II) preoperative examination results

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are considered as metastatic lesions; (III) pregnant/lactating female patients; (IV) people without legal capacity, medical or ethical the cause affects those who continue the study.

Inclusion criteria for the secondary (intra-operative) registration

(I) The patient underwent lobectomy or segmentectomy; (II) the patient prepared 3D reconstruction/printing model.

Exclusion criteria for the secondary (intra-operative) registration

(I) Conversion to wedge resection during the operation.

Shedding standard

(I) The patient does not follow-up the study according to the procedure after he/she signed the informed consent; (II) after the patient was enrolled, the operation was performed in other hospital.

Rejection criteria

(I) The data of the enrolled patients are missing or incorrect due to human/objective reasons; (II) after registration, the research group found that the patient concealed illness.

Study intervention

This trial is mainly designed to confirm that 3D reconstruction can be benefit to pathological sampling in resected specimens which contains multiple lesions. Therefore, all nodule localization procedures in resected specimens are performed under the auxiliary of 3D reconstruction images and 3D printing models [Zhen Yuan (Tianjin) Medical Device Technology Co., Ltd]. After successful nodule localization, the nodule will be signed by silk thread. Then the signed nodule is marked with the corresponding Roman numeral (#1, #2, #3...) in the 3D printed model.

Ethics and protection of human subjects

Ethical standard

The investigator will ensure that this study is conducted in full conformity with the rules set by the Medical Equipment Specification for the Quality Control of Clinical Trial (*State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth*). All personnel involved in the conduct of this study have completed human subject protection training.

Institutional review board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB (*National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital*, *Chinese Academy of Medical Sciences and Peking Union Medical College*) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

Informed consent process

Before the participants agree to participate into the trial, Informed consent is obtained in the study and continues throughout study participation. A consent form describing in detail the study procedures and related risks would be given to the subject before participation. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study in detail to the participants and answer any questions that may arise. Subjects will sign the informed consent document before any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely compromised if they refuse to participate in this trial. The consent process will be documented in the clinical or research record.

Data storage policy

The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation

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of data. The investigators need to maintain adequate case histories of study subjects, including accurate case report forms (CRFs) and source documentation.

Data collection and accurate documentation are the responsibilities of the study staff under the supervision of the primary investigator. All source documents, laboratory results and CT images must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the primary investigator.

All the study documents and records should be stored for a minimum of 2 years after trial completion, which is required by the Medical Equipment Specification for the Quality Control of Clinical Trial (State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth). No trial documents should be deliberately destroyed or damaged without consent of the IRB.

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Table S1 Patients' detailed information

Patient no.	Age (years)/sex	No. of lesions	Size (mm)	CT finding	Treatment	Pathologic finding	Lymph node	Distance from the visceral pleura to the nodule* (mm)
1	58/M	1	14	pGGO	RS1a + S2b + S3ai	MIS	0	9
		2	18	PSN		Adenocarcinoma		11
		3	3	pGGO		AIS		4
2	62/F	1	13	pGGO	RS3b	MIS	0	3
		2	4	pGGO		AIS		6
3	51/F	1	8	pGGO	LS6 + S9a + S10a	Adenocarcinoma	0	5
		2	4	pGGO		AIS		6
4	43/F	1	18	PSN	RUL	Adenocarcinoma	0	12
		2	7	pGGO		AIS		9
5	52/F	1	5	pGGO	RS3	MIS	0	4
		2	5	pGGO		MIS		7
6	43/F	1	5	pGGO	RS4 + RS1 + S6	AIS	0	6
		2	6	pGGO		AIS		9
		3	8	pGGO		MIS		2
7	55/M	1	15	PSN	LLL	Adenocarcinoma	0	7
		2	8	pGGO		Adenocarcinoma		11
8	50/F	1	4	pGGO	S2b + S3aii	AAH	0	4
		2	5	pGGO		AAH		6
9	65/F	1	17	PSN	LS6	Adenocarcinoma	0	7
		2	4	PSN		granuloma		12
10	50/M	1	5	pGGO	RS1	AAH	0	8
		2	20	Pure solid nodule		Reactive lymph node hyperplasia		1
11	54/F	1	10	pGGO	LS10	Adenocarcinoma	0	3
		2	5	pGGO		MIS		11
12	45/F	1	10	PSN	RS1 + S2	Adenocarcinoma	0	14
		2	4	pGGO		AIS		7
		3	4	pGGO		AIS		8
13	57/F	1	9	Pure Solid Nodule	LLL	Adenocarcinoma	0	4
		2	4	pGGO		Adenocarcinoma		8
14	47/M	1	9	PSN	RUL + S6	Adenocarcinoma	0	9
		2	4	pGGO		MIS		13
		3	3	pGGO		AIS		11
		4	4	pGGO		AIS		3
15	70/M	1	11	PSN	RS8	Adenocarcinoma	0	15
		2	3	Pure solid nodule		AAH		2
16	67/M	1	13	PSN	LS3 + S4 + S5	Adenocarcinoma	0	17
		2	4	pGGO		AAH		11
		3	3	pGGO		AAH		9
17	33/F	1	7	pGGO	RS9b + S3a	MIS	0	14
		2	4	pGGO		AAH		11
		3	4	pGGO		AAH		4
18	47/F	1	6	pGGO	LS6b + 8a	MIS	0	3
		2	2	pGGO		AIS		8
		3	4	pGGO		AIS		2
		4	3	pGGO		AIS		5
		5	6	pGGO		AIS		7
		6	4	pGGO		AIS		5
19	48/F	1	8	pGGO	LS1 + 2	MIS	0	22
		2	11	pGGO		MIS		10
20	54/F	1	9	PSN	RML	Adenocarcinoma	0	4
		2	3	pGGO		MIS		2
		3	2	pGGO		AAH		3
		4	2	Pure solid nodule		AAH		1
21	61/F	1	18	PSN	LS1 + 2c + S3a	Adenocarcinoma	0	12
		2	10	pGGO		Adenocarcinoma		8
		3	3	pGGO		AIS		6
		4	3	pGGO		AIS		9
22	42/F	1	5	pGGO	LS10	AIS	0	13
		2	6	pGGO		AIS		2
23	57/F	1	7	pGGO	RS3 + S5 + S6	Adenocarcinoma	0	1
		2	5	pGGO		AIS		23
		3	3	pGGO		AIS		5
		4	2	Pure solid nodule		AIS		4
		5	8	pGGO		MIS		3
24	44/F	1	18	PSN	RUL	squamous cell carcinoma	0	23
		2	4	pGGO		squamous cell carcinoma		3
		3	3	pGGO		squamous cell carcinoma		5
		4	5	pGGO		squamous cell carcinoma		5
25	55/F	1	5	pGGO	LS8a + 9a	AIS	0	4
		2	6	pGGO		AIS		8
26	49/F	1	17	PSN	RUL	Adenocarcinoma	0	23
		2	10	pGGO		Adenocarcinoma		12
27	46/M	1	5	pGGO	RS3	MIS	0	10
		2	4	pGGO		MIS		2
28	60/F	1	7	PSN	LS6	Adenocarcinoma	0	7
		2	4	pGGO		AIS		5
29	58/F	1	8	pGGO	RLL	Adenocarcinoma	N1	2
		2	12	pGGO		Adenocarcinoma		5
		3	6	pGGO		Adenocarcinoma		3
		4	20	Pure solid nodule		Adenocarcinoma		18
		5	3	Pure solid nodule		Benign		0
		6	5.8	pGGO		Not found		
30	66/M	1	5	pGGO	RUL	AIS		8
		2	4	pGGO		AIS		14
		3	16	Pure solid nodule		Benign		17
		4	8	pGGO		AIS		9
		5	14	pGGO		Adenocarcinoma		3
		6	6	pGGO		MIS		6
		7	5	pGGO		MIS		6
31	44/F	1	10	pGGO	RS6b + S1 + S3b	MIS	0	8
		2	2	pGGO		AIS		8
		3	4	pGGO		AIS		10
		4	4	pGGO		AIS		16
		5	5	pGGO		AIS		7
		6	5	pGGO		AIS		3
		7	3	pGGO		AIS		8
32	67/F	1	10	pGGO	RUL	Adenocarcinoma	0	32
		2	4	Pure solid nodule		MIS		2
		3	12	pGGO		MIS		8
		4	14	PSN		Adenocarcinoma		5
		5	9	pGGO		Adenocarcinoma		9
		6	4.2	pGGO		Not found		
33	56/M	1	8	pGGO	RS3 + 1b	AIS	0	7
		2	3	pGGO		AIS		10
34	61/F	1	15	pGGO	RML + S6	MIS	0	8
		2	17	PSN		Adenocarcinoma		12
		3	5	pGGO		AIS		6
35	64/F	1	18	PSN	RUL	Adenocarcinoma	0	24
		2	7	pGGO		AIS		13
		3	4	pGGO		AAH		3
36	56/F	1	8	pGGO	RS6b + S8a + S9a	AIS	0	5
		2	4	pGGO		AIS		8
37	50/F	1	8	pGGO	LS4 + S5	Adenocarcinoma	0	6
		2	10	Pure solid nodule		granuloma		14
38	50/F	1	8	PSN	RML	Adenocarcinoma	0	22
		2	2	pGGO		MIS		6
		3	4	pGGO		MIS		8
		4	4	pGGO		AIS		5
39	59/F	1	4	pGGO	LS6c + S9 + S10	AIS	0	9
		2	5	pGGO		AIS		9
		3	5	pGGO		AIS		6
		4	6	pGGO		AIS		8
		5	13	pGGO		AIS		9
40	42/F	1	5	pGGO	RS1 + S2 + S6	AIS	0	13
		2	5	pGGO		MIS		15
		3	6	pGGO		MIS		8

*, distance from the visceral pleura to the nodule: measured on specimens. pGGO, pure ground-glass opacity; PSN, partial solid nodule; RUL, right upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; LLL, left lower lobectomy; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIS, microinvasive adenocarcinoma.

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