Benefits of lung modeling by high-quality three-dimensional computed tomography for thoracoscopic surgery

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Abstract: Although video-assisted thoracoscopic surgery (VATS) has become widely used as a less invasive therapeutic procedure for lung cancer, precise anatomical knowledge of each case remains crucial and greatly contributes to the safety of thoracoscopic surgery. Thus, the development of three-dimensional (3D) imaging technology is anticipated to provide surgeons with essential visualized information of anatomical structures. In this review, we evaluate the pragmatic features of 3D imaging technology for thoracoscopic lung cancer surgery, focusing on complicated surgeries and preoperative evaluation of pulmonary functions or tumor features. We also discuss 3D imaging software and the applications of the 3D image analysis system. Finally, we present our perspectives on the 3D imaging technology for thoracoscopic surgery.

Keywords: Three-dimensional computed tomography; video-assisted thoracoscopic surgery (VATS); lung cancer

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Introduction

In recent years, the development of imaging modalities and the widespread use of low-dose helical computed tomography (CT) have contributed to an increase in the detection of early stage lung cancer (1,2). At present, the standard treatment for early stage lung cancer is surgical resection. Recently, video-assisted thoracoscopic surgery (VATS) has become widely used as a less invasive procedure. In fact in the US, of 55,972 patients who underwent lobectomy for non-small-cell lung carcinoma (NSCLC) performed at 905 commission on cancer accredited hospitals over a 3-year study period between 2010 and 2012, 17,072 (30.5%) patients underwent a VATS approach (3). Moreover, the European Society of Thoracic Surgeons database showed that the number of VATS procedures for lung cancer dramatically increased to 18.8% between 2010 and 2012 (4). The Japanese Association for Thoracic Surgery Annual Report for 2016 indicated that VATS for lung cancer was performed in 64.3% of patients (26,188) in 2015, whereas the operation for lung cancer involving all procedures in general thoracic surgery was performed in 50.5% of patients (5). Minimally invasive surgeries, such as VATS lobectomy or segmentectomy, require precise anatomical knowledge of the pulmonary vessels and bronchi for each patient. Thus, preoperative information of the surgical anatomy is anticipated to substantially contribute to the safety of each operation.

The technology of three-dimensional (3D) reconstruction generated from multi-detector computed tomography (MDCT) imaging enables surgeons to recognize the anatomic structures of each patient preoperatively. Furthermore, 3D imaging reflects the actual lung structures or tumors more accurately than two-dimensional (2D) imaging that is used by conventional CT imaging. In this review, we discuss the pragmatic features of the 3D imaging technology for thoracoscopic lung cancer surgery, focusing on complicated surgeries or preoperative evaluation. We also present our perspectives on the 3D imaging technology and surgical resection for lung cancers.

Three-dimensional imaging software technology

The development of MDCT has enabled the rapid scanning of large body areas simultaneously with less artifacts from respiratory motion. Subsequently, this technology has facilitated 3D image reconstruction in general thoracic surgery using different types of software.

In 2003, Watanabe *et al.* used 3D-CT pulmonary angiography to evaluate the branch patterns of pulmonary arteries (PAs) before anatomic pulmonary resection (6). Of 14 patients with primary lung cancer who underwent anatomic pulmonary resection, 98% (84 of 86) of the PA branches were successfully identified on preoperative 3D-CT images. Fukuhara *et al.* reported 49 lung cancer patients who were examined by preoperative 3D-CT angiography before complete VATS lobectomy (7). The intraoperative findings showed that 95.2% (139 of 146) of the PA branches were precisely detected on the 3D-CT images. Some of the undetected PA branches in the studies of Watanabe *et al.* and Fukuhara *et al.* were reported to be less than 1.5 mm and 2 mm in diameter, respectively.

In 2009, Akiba *et al.* reported the 3D images of the bronchial trees of 27 lung cancer patients who underwent lobectomy or segmentectomy, as well as the 3D images of the pulmonary arteries and veins. The detected ratio of the pulmonary arteries of the patients on the 3D images was 95% (25 of 27) when compared with the actual resected pulmonary arteries. All of the resected bronchi in the patients were identified on the 3D images (8). There are also several studies that showed the 3D images of the bronchial trees and pulmonary vessels of lung cancer patients who underwent pulmonary resection (9,10).

We previously described the usefulness of 3D-CT lung modeling using a high-speed 3D image analysis system (Synapse Vincent, Fuji Film Co., Ltd., Tokyo, Japan) and reported the ability of recent 3D imaging software to generate the segmented lung parenchyma as well as the bronchial trees and pulmonary vessels (11). The system generates 3D images using *digital imaging and communication in medicine* (DICOM) data in conventional enhanced CT scanning. This avoids exposure of patients to excessive radiation or to a leaked iodinated contrast medium in their arms. The processing time for visualizing the pulmonary vessels, tracheobronchial trees, and lung parenchyma is approximately 5 minutes. After reconstructing the 3D images, the system allows investigators to simulate each operation, evaluate the targeted tumors, or measure the surgical margins from the tumors.

Applications of 3D imaging for thoracoscopic surgery

Hagiwara *et al.* previously evaluated the short-term outcome of VATS lobectomy or segmentectomy as well as the detection ratio of the PA branches using 3D imaging analysis (12). They analyzed 179 lung cancer patients who underwent VATS anatomical lung resection. The surgical outcomes were associated with operative complications or operative time. Preoperative 3D imaging tended to reduce the occurrence of complications (risk ratio: 2.852, P=0.074). Moreover, preoperative 3D imaging was significantly associated with total operative time on multivariate analysis (risk ratio: 2.282, P=0.021).

Anomalous pulmonary veins have also been detected by preoperative 3D imaging analysis. In particular, Akiba *et al.* reported a patient who underwent VATS right lower lobectomy for lung cancer avoiding the resection of an anomalous lateral part of the middle lobe vein (V4) draining into the right inferior pulmonary vein (13). Akiba *et al.* emphasized that preoperative 3D imaging enabled them to fully comprehend the patient's vascular anatomy before the operation.

Fukuta *et al.* described 2 lung cancer patients who had anomalous veins as detected by preoperative 3D imaging and who received VATS lobectomies (14). Sumitomo *et al.* reported a lung cancer patient who had transposition of the right pulmonary artery and the V1 through V3 segments of the pulmonary vein (15). The anomalous vessels were detected by preoperative 3D imaging analysis, and VATS right upper lobectomy was performed.

Three-dimensional imaging analysis has also been reported to be useful for robot-assisted thoracic surgery. Specifically, Kajiwara *et al.* demonstrated the use of preoperative 3D imaging analysis not only for intraoperative navigation, including the detection of tumors or surrounding tissues, but also for knowing the best positioning of the robotic arms and instruments preoperatively (16).

Three-dimensional imaging and complex thoracoscopic procedures

The studies describing complex thoracoscopic procedures

Table 1 Studies of complex surgical procedures combined with 3D imaging

Authors	Year	Cases	3D imaging system	Surgical procedure	Features
Oizumi *et al.* (17)	2011	52	OsiriX	Segmentectomy	Simulation for segmental arterial branches and intersegmental veins
Shimizu *et al.* (9)	2012	42	ZioStation	Segmentectomy	3D-CT angiography and bronchography for segmentectomy
Saji *et al.* (18)	2013	4	Synapse Vincent	Segmentectomy	Assessment of the predicted surgical margins compared with the actual surgical margins
Chan *et al.* (19)	2015	51	Their own software	Segmentectomy	Assessment of the predicted surgical margins compared with the actual surgical margins
Tarumi *et al.* (20)	2014	44	Not described	Segmentectomy	3D imaging and ICG utilized for VATS segmentectomy
Mun *et al.* (21)	2017	20	Synapse Vincent	Segmentectomy	3D imaging and ICG utilized for VATS segmentectomy
Saji *et al.* (22)	2015	1	Synapse Vincent	Transmanubrial osteomuscular sparing approach for SST	3D visualization of the anterior part of the thoracic inlet

3D, three-dimensional; 3D-CT, three-dimensional computed tomography; ICG, indocyanine green; VATS, video-assisted thoracic surgery; SST, superior sulcus tumor.

combined with 3D imaging are shown in *Table 1*.

In 2011, Oizumi *et al.* reported on complete thoracoscopic segmentectomy in 52 patients while simulating the segmental arterial branches, intersegmental veins that were to be preserved, and venous branches of the affected segment that were to be divided using 3D reconstructing software (OsiriX) (17). Oizumi *et al.* classified thoracoscopic segmentectomy into 3 categories based on technical difficulty as follows: easy, fairly difficult, and difficult. Using 3D reconstruction to identify the intersegmental veins and then dissecting along them, Oizumi *et al.* could perform segmentectomy using a complete thoracoscopic approach which can be performed even for anatomically difficult segments.

The benefits of 3D-CT angiography and bronchography for 27 hybrid VATS segmentectomies and 15 complete VATS segmentectomies have also been demonstrated by Shimizu *et al.* (9). They utilized a workstation with volume-rendering reconstruction software (Ziostation, Tokyo, Japan) to generate 3D-CT angiography images. Additionally, 3D reconstruction of the bronchial tree was performed by mathematical morphology-based 2D segmentation, and further restoration was achieved by the manual addition of segments from the 2D axial images to the 3D image. The distance between the intersegmental veins and the tumor was measured using the 3D-CT image. Shimizu *et al.* applied 3D-CT angiography and bronchography for segmentectomy to understand the positional relationship between the segmental veins and the bronchi as well as the anatomical variations of the pulmonary veins and bronchi. They described the difficulty of identifying the intrasegmental and intersegmental veins for segmentectomy using only 3D-CT angiography, because the branches of the pulmonary veins were associated with the bronchi in various patterns.

Preoperative virtual segmentectomy using a 3D imaging system (Synapse Vincent) has been shown by Saji *et al.* to contribute to making a decision regarding the appropriate anatomical segmentectomy and curative resection for thoracic malignancies (18). Their virtual segmentectomy showed a visualized segmental area based on the calculation of bronchial ventilation, the segmental surface resulting in the determination of the resected pulmonary vessels including the intersegmental veins and bronchi, and the distance of the surgical margin. The 3D imaging system could visualize the appropriate intersegmental plane which they simulated, allowing them to decide on their ideal segmentectomy procedure preoperatively with the achievement of a sufficient surgical margin. Sequentially, they assessed the actual surgical margins after

Table 2 Studies of postoperative pulmonary functions as determined by 3D imaging

Authors	Year	Cases	3D imaging system	Results
Ueda *et al.* (23)	2009	30	M900 QUADRA	Predictive postoperative FEV1.0 was estimated on 3D imaging more accurately in patients with <10% of emphysema index
Kobayashi *et al.* (24)	2017	53	Synapse Vincent	Residual pulmonary function was predicted on 3D imaging more accurately than the segment-counting method in COPD patients
Kawakami *et al.* (25)	2015	309	ZioStation	LAV% calculated by 3D imaging was significantly associated with postoperative complications
Makino *et al.* (26)	2018	504	Synapse Vincent	The Goddard score and LAA% on 3D imaging were associated with postoperative respiratory complications

3D, three-dimensional; FEV1.0, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease; LAV%, percentage of low-attenuation volume; LAA%, percentage of low attenuation area.

segmentectomy and compared them with the preoperative surgical margins generated by their 3D imaging system. The preoperative surgical margins were slightly overestimated, acknowledging this as a limitation of their preliminary study. Saji *et al.* indicated their resolve to further develop their procedure and reduce the discrepancies between the preoperative surgical margins and the actual surgical margins.

In their pilot study, Chan *et al.* described their own 3D imaging software which provided automated lung segmentation, tumor localization, and the estimated margins of surgical resection (19). Their study included 51 patients who underwent segmentectomy or lobectomy. Lung segmentation was successful in 73% of the patients using their 3D imaging system. Chan *et al.* indicated the poorly visualized fissures or poor airway visualization as the reason for the failure of lung segmentation in the other patients. Additionally, the 3D imaging software analyzed the surgical margins for segmentectomy and lobectomy. Chan *et al.* assessed the predicted surgical margins by comparing them with the actual surgical margins. They found no significant differences in the surgical margins for both segmentectomy (P=0.781) and lobectomy (P=0.681). The positive predictive value was 87% when they predicted a marginal clearance greater than 1 cm; the positive predictive value was 75% when the ratio of the surgical margin to the tumor diameter was predicted to be greater than 1.

Three-dimensional reconstructed imaging and indocyanine green (ICG) have also been used for VATS segmentectomy by Tarumi *et al.* (20) and Mun *et al.* (20,21). During the preoperative evaluation, dominant pulmonary arteries for a targeted segmental lung were identified. After the dominant pulmonary arteries and segmental bronchus were divided in the operation, ICG was injected into a peripheral vein. Under infrared light, the appearance of the lung in the areas with blood flow gradually changed, whereas the appearance of the lung in the areas without blood supply remained pale. This method allowed surgeons to recognize the segmental fissures easily for anatomical segmentectomy even with a limited surgical view such as in VATS. Moreover, Tarumi *et al.* identified the intersegmental lines in 84% of their patients (20). Mun *et al.* demarcated a border between the targeted segments and preserved lung clarity, and marked the resected line on the lung surface in 95% of their patients (21). Moreover, Mun *et al.* evaluated the time it took for the demarcation lines to appear after ICG injection and the time the lines lasted, namely, 20 s (10–100 s) and 180 s (90–300 s), respectively.

Preoperative 3D-CT imaging analysis has also been applied to a patient with superior sulcus tumor which invaded the anterior part of the thoracic inlet including the clavicle, sternoclavicular joint, first rib, subclavian vessels, and brachial plexus (22). The patient underwent a transmanubrial osteomuscular-sparing approach and an additional third anterolateral thoracotomy with a hemi-clamshell incision to achieve complete tumor resection.

Prediction of postoperative pulmonary function by 3D imaging

Several studies on the prediction of postoperative pulmonary function by 3D-CT imaging have been conducted (*Table 2*).

Ueda *et al.* compared postoperative ground glass opacity (GGO) (FEV1.0) calculated by 3D-CT imaging analysis with postoperative FEV1.0 measured by the actual pulmonary function test in 30 patients who underwent pulmonary resection (23). They initially demonstrated a high correlation coefficient of predictive postoperative FEV1.0 between the conventional segment-counting method and the 3D-CT imaging analysis (correlation coefficient =0.984, P<0.001). Subsequently, they showed that the measured postoperative FEV1.0 was higher than the predictive postoperative FEV1.0 by 3D-CT imaging analysis with an average difference of 16.9% in patients with ≥10% of the emphysema index. The measured FEV1.0 value was similar to the values analyzed by 3D-CT with an average difference of 2.3% in patients with <10% of the emphysema index (P=0.042). Their results suggested that the predictive postoperative pulmonary function was underestimated in patients with ≥10% of the emphysema index.

Similarly, Kobayashi *et al.* evaluated the predictive residual pulmonary function by the 3D-CT volumetry method in 53 patients who underwent anatomical pulmonary resection for primary lung cancer, and thereafter compared this pulmonary function with that evaluated by the conventional segment counting method (24). After analyzing their 2 methods, they investigated the differences between the predictive values and the actual values shown in the results of the postoperative pulmonary function tests. Although there was no significant difference between the conventional segment counting method and the 3D-CT imaging analysis, the linear correlation coefficients between the values of predictive postoperative pulmonary function and those of the actual measured pulmonary function were 0.57–0.78 in patients with chronic obstructive pulmonary disease (COPD) based on the Global initiative of Obstructive Pulmonary Disease (GOLD) classification; the correlation coefficients were approximately 0.9 or more in patients without COPD. Furthermore, the correlation coefficients of the 3D-CT volumetry method tended to be higher than those of the segment-counting methods in the patients with COPD. Kobayashi *et al.* concluded that the 3D-CT volumetry method enabled the prediction of a more accurate residual pulmonary function than the conventional segment counting method, particularly in patients with COPD.

Importantly, there are also some studies on the relationship between 3D-CT imaging analysis and postoperative complications, particularly in patients with emphysema. Kawakami *et al.* evaluated the association between preoperative 3D-CT volumetry and postoperative complications in 309 patients who underwent lobectomy for primary lung cancer (25). The percentage of low attenuation volume (LAV%) was defined as the proportion of the volume of voxels with attenuation values less than –950 HU of thresholds against the total lung volume. Their cohort included 133 patients with COPD based on the GOLD classification. Their results showed that LAV% was significantly associated with postoperative complications on multivariate analysis (P=0.006), whereas FEV1.0 was not significantly associated with postoperative complications

Makino *et al.* illustrated the relationship between postoperative respiratory complications and 3D-CT imaging analysis (26). Their analysis included the percentage of low attenuation area (LAA%), which was the same as the above-mentioned LAV%, and the Goddard score. The Goddard score was evaluated from 6 axial images which were provided from 3 specific slices of each patient. The Goddard score and predictive postoperative FEV1.0 were significantly associated with postoperative respiratory complications and gender. The results also demonstrated that the Goddard score and LAA% were strongly correlated with each other (q=0.713, P<0.001).

Prognostic factors of lung cancer as determined by preoperative 3D imaging

The studies on the prognostic factors of lung cancer as determined by 3D imaging are summarized in *Table 3*.

Yu *et al.* previously assessed the association between tumor invasiveness and parameters generated by 3D-CT imaging analysis (27). They analyzed 99 patients who underwent complete resection for stage IA lung adenocarcinoma. Tumor invasiveness was defined as invasive adenocarcinoma based on the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification, which is based on the World Health Organization (WHO) classification 4th edition. After 3D reconstruction of CT images, 3D solid tumor size and 3D GGO ratio were calculated, as well as one-dimensional (1D) or two-dimensional (2D) size and ratio. The cut-off values were detected by receiver operating characteristic (ROC) analysis, and the sensitivities of the 3D GGO ratio and 3D solid size were 89.7% and 85.3%, respectively; the specificities of the 3D GGO ratio and 3D solid size were 93.5% and 87.1%, respectively. Yu *et al.* concluded that the 3D GGO ratio was more strongly correlated with pathologic invasiveness than the 3D solid size.

Similarly, Shikuma *et al.* investigated the relationship between tumor invasiveness and parameters obtained by 3D-CT imaging analysis (28). Their analysis of tumor

Table 3 Studies of prognostic factors of lung cancer as determined by 3D imaging

Authors	Year	Cases	3D imaging system	Results
Yu *et al.* (27)	2016	99	Aquarius Intuition	The 3D GGO ratio was more strongly correlated with pathologic invasiveness
Shikuma *et al.* (28)	2016	211	AZE Virtual Place	Evaluation of the solid tumor ratio on 3D imaging was a more accurate method for assessing tumor invasiveness and was associated with the subtypes of adenocarcinoma (WHO classification 4th edition)
Su *et al.* (29)	2017	274; stage I NSCLC	PHILIPS IntelliSpace Portal	The tumor volume was associated with the prognosis of OS and DFS
Takenaka *et al.* (30)	2016	255; clinical stage IA NSCLC	Synapse Vincent	The solid part volume was better for predicting the prognosis than the tumor size, whole tumor volume, and CTR
Furumoto *et al.* (31)	2018	170; clinical stage IA adenocarcinoma	Synapse Vincent	The solid-part volume and SUV max on 3D imaging were critical predictors of prognosis as well as the solid-part size
Eriguch *et al.* (32)	2018	225; stage 0/I lung adenocarcinoma	Synapse Vincent	The parameters of quantitative CT histogram and PET/CT could predict lepidic growth adenocarcinoma

3D, three-dimensional; GGO, ground glass opacity; WHO, World Health Organization; OS, overall survival; DFS, disease-free survival; CTR, consolidation tumor ratio; SUVmax, maximum standardized uptake value; CT, computed tomography; PET/CT, positron emission tomography computed tomography.

invasiveness included pathological lymph node metastases, macroscopic pleural invasion, vessel invasion, and lymphatic invasion. The parameters were evaluated by ROC analysis using the 3D solid tumor side and 3D solid tumor ratio, and compared with the 1D/2D solid tumor size and solid tumor ratio. Interestingly, the accuracy of the 3D solid tumor size was equal to that of the 1D solid tumor size on ROC analysis for each tumor invasive factor. However, the accuracy of the 3D solid tumor ratio was higher than those of the 1D and 2D solid tumor ratios on the ROC analysis. Therefore, Shikuma *et al.* indicated that the 3D evaluation of the solid tumor ratio was a more accurate method for assessing tumor invasiveness, whereas the 1D evaluation was more appropriate for the evaluation of the solid tumor size. Furthermore, Shikuma *et al.* analyzed the correlations between the 3D solid tumor ratio and the subtypes of adenocarcinoma based on the WHO classification 4th edition. Their results showed significant differences in the 3D solid tumor ratio for adenocarcinoma *in situ* (AIS)/minimally invasive adenocarcinoma (MIA) versus lepidic adenocarcinoma, lepidic adenocarcinoma versus papillary adenocarcinoma, and lepidic adenocarcinoma versus acinar adenocarcinoma ($P=0.011$, $P<0.0001$, $P<0.0001$, and $P<0.0001$, respectively).

Three-dimensional tumor size has also been reported as a prognostic factor in patients with surgically resected lung cancer. In particular, Su *et al.* evaluated the prognostic impact of tumor volume on 274 patients who underwent surgical resection for stage I NSCLC (29). They performed 3D-CT analysis to calculate tumor volume and the greatest tumor diameter. The cut-off values of the tumor volume for disease-free survival (DFS) and overall survival (OS) were determined using their ROC curves. Based on the cut-off values, a larger tumor volume was found to be a significant poor prognostic factor for OS and DFS. Notably, similar results were observed in the tumors whose greatest tumor diameter was less than 3 cm.

Takenaka *et al.* investigated the solid part volume and whole tumor volume in 255 patients who underwent surgical curative resection for clinical stage IA NSCLC by 3D volumetric analysis (30). They determined each parameter for recurrence using ROC curves, the whole tumor size, consolidation tumor ratio (CTR), the whole tumor volume, and the solid part volume. Their results showed that the whole tumor volume and solid part volume stratified by the above threshold were significantly associated with DFS in the patients ($P=0.02$ and $P<0.01$, respectively). Additionally, the solid part volume was better for predicting the prognosis of clinical stage IA NSCLC than the tumor size, whole tumor volume, and CTR on the multivariate analysis.

The combination of 3D-CT imaging with WHO (PET/CT) for lung cancer surgery has also been recently reported. Furumoto *et al.* in particular showed that the maximum standardized uptake values (SUVmax), solid part size on high-resolution CT (HRCT), and solid part volume on 3D imaging were critical predictors of prognosis and pathological invasiveness in patients with clinical stage IA adenocarcinoma (31). Their 170 patients underwent PET/CT, HRCT, and 3D reconstruction imaging before the complete resection of lung cancer. The ROC curve allowed them to determine the cut-off values of each parameter, and the prognosis of the patients stratified by those values obviously reflected better or worse. The solid part volume was an independent predictor of DFS on multivariate analysis, whereas the volumetric quantification of the solid part and SUVmax were the most powerful predictors.

On the other hand, Eriguchi *et al.* assessed the parameters of 3D-CT imaging and PET/CT to predict lepidic growth adenocarcinoma, including AIS, MIA, and lepidic-predominant adenocarcinoma (32). Their study included 225 patients with clinical stage 0 or stage I lung adenocarcinoma. When the quantitative CT histograms and PET/CT assessment of the tumors were utilized, the SUVmax, maximum CT attenuation value, and 75th percentile CT attenuation value enabled them to distinguish lepidic growth adenocarcinoma from other tumors.

Conclusions and future perspectives

The development of 3D imaging technologies has led to the preoperative evaluation of lung functions or tumors, as well as to obtaining more precise information of anatomical structures for lung cancer surgery. The unique visualization of anatomical structures generated by 3D imaging software has enabled surgeons to perform safer and more accurate operations despite performing minimally invasive surgery with a limited field of vision. Moreover, 3D imaging requires no additional examination for patients, and the process of reconstructing 3D images is simple and takes only a few minutes. Additionally, the visualization technology can predict the risk of postoperative complications while it analyzes factors associated with lung functions. Moreover, 3D imaging can predict histopathological features (e.g., lepidic growth pattern) or prognostic factors with/without the combination of PET/CT examination.

Importantly, the preoperative data and feedback from the 3D imaging may be used for developing different types of real-time navigation software, such as a global positioning system. This will enable surgeons or robots to more accurately recognize anatomical structures and perform operation easier. On the other hand, considerable efforts must be exerted to identify parameters for the prediction of histopathological features, tumor invasiveness, or prognostic factors by 3D imaging.

In the future, we anticipate that the 3D imaging technology will enable the prediction of the molecular features of lung cancer in combination with other examination devices without the need for pathological examination.

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