



# Preoperative assessment of parietal pleural invasion/adhesion of subpleural lung cancer: advantage of software-assisted analysis of 4-dimensional dynamic-ventilation computed tomography

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## Abstract

**Objective** To evaluate the accuracy of four-dimensional (4D) dynamic-ventilation computed tomography (CT) scanning coupled with our novel image analysis software to diagnose parietal pleural invasion/adhesion of peripheral (subpleural) lung cancer.

**Methods** Eighteen patients with subpleural lung cancer underwent both 4D dynamic-ventilation CT during free breathing and conventional (static) chest CT during preoperative assessment. The absence of parietal pleural invasion/adhesion was surgically confirmed in 13 patients, while the presence of parietal pleural invasion/adhesion was confirmed in 5 patients. Two chest radiologists, who were blinded to patient status, cooperatively evaluated the presence of pleural invasion/adhesion using two different imaging modalities: (i) conventional high-resolution CT images, reconstructed in the axial, coronal, and sagittal directions, and (ii) 4D dynamic-ventilation CT images combined with a color map created by image analysis software to visualize movement differences between the lung surface and chest wall. Parameters of diagnostic accuracy were assessed, including a receiver operating characteristic analysis.

**Results** Software-assisted 4D dynamic-ventilation CT images achieved perfect diagnostic accuracy for pleural invasion/adhesion (sensitivity, 100%; specificity, 100%; area under the curve [AUC], 1.000) compared to conventional chest CT (sensitivity, 60%; specificity, 77%; AUC, 0.846).

**Conclusion** Software-assisted 4D dynamic-ventilation CT can be considered as a novel imaging approach for accurate preoperative analysis of pleural invasion/adhesion of peripheral lung cancer.

## Key Points

- 4D dynamic-ventilation CT can correctly assess parietal pleural invasion/adhesion of peripheral lung cancer.
- A unique color map clearly demonstrates parietal pleural invasion/adhesion.
- Our technique can be expanded to diagnose “benign” pleural adhesions for safer thoracoscopic surgery.

**Keywords** Lung cancer · Four-dimensional computed tomography · Computer-assisted image analysis

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## Abbreviations

AUC	Area under the curve
CT	Computed tomography
IRB	Institutional Review Board
MR	Magnetic resonance
US	Ultrasound

## Introduction

Prior to surgical resection, it is important to assess invasion and/or adhesion of peripheral (subpleural) lung cancers to the parietal pleura. If parietal pleural invasion is confirmed in advance of, or at the time of, surgery, resulting in upgrading

to clinical stage T3, more radical surgeries, including extrapleural or en-bloc resection, are usually performed [1, 2]. Even when there is no direct invasion of the parietal pleura, adhesions between the parietal and visceral pleura near the tumor can complicate thoracoscopic surgery, and lead to conversion to conventional thoracotomy [3–5]. Thus, accurate preoperative assessment of tumor invasion and/or adhesion to the parietal pleura can help thoracic surgeons prepare for longer operating times, anticipate greater blood loss, and guide appropriate informed consent.

Several imaging approaches have been shown to identify parietal pleural invasion/adhesion due to peripheral lung cancer, including conventional methods, such as static chest computed tomography (CT), cine-magnetic resonance (MR), and preoperative ultrasound (US) [6–13], as well as newer methods, such as four-dimensional (4D) dynamic-ventilation CT. Several recent studies have reported on the use of dynamic-ventilation CT to establish a preoperative diagnosis of parietal pleural invasion/adhesion [14–16].

4D CT image analysis uses registration techniques that are similar to those used with paired inspiratory and expiratory chest CT [17–21]. We have expanded these registration techniques for use with 4D dynamic-ventilation CT, in order to observe “sliding” of the lung surface towards extrapulmonary structures, such as the chest wall, diaphragm, or cardiovascular system. This technique has the potential to provide information on abnormal (fixed) regional motion of the lung surface, which would suggest pleural invasion or adhesion between subpleural lung tumors and the parietal pleura. Thus, the aim of this study was to evaluate the accuracy of 4D dynamic-ventilation CT using our novel image analysis software to diagnose parietal pleural invasion/adhesion of peripheral lung cancer.

## Materials and methods

This retrospective study was approved by the Institutional Review Board (IRB) of Ohara General Hospital. Written informed consent was waived by the IRB since all dynamic-ventilation CT scans were performed as part of routine clinical care (preoperative assessment) for lung cancer.

### Subjects

From October 2013 to November 2016, 26 consecutive patients were initially identified for the study. The inclusion criteria were the following: (1) patients who were suspected to have peripheral lung cancer (the center of the cancer located within 10 mm of the pleura); (2) patients who underwent dynamic-ventilation CT at Ohara Medical Center, a part of Ohara General Hospital, to assess cancer invasion or adhesion to the parietal pleura; (3) patients who were planned to receive

subsequent operation to remove the lung cancer. Patients who met the following exclusion criteria were excluded from the study: (1) patients who could not complete the dynamic-ventilation CT due to severe respiratory failure ( $n = 1$ ); (2) patients whose surgical record did not mention presence/absence of parietal pleural invasion or adhesion around the cancer ( $n = 1$ ); (3) patients who eventually canceled subsequent surgical operation and were followed up ( $n = 5$ ); (4) patients whose lung lesion was confirmed as a benign lung nodule ( $n = 1$ ). Eventually, 18 patients included 8 females and 10 males (median age 75 years, range 56–81 years) were analyzed in this study. All the enrolled patients underwent surgical resection of the cancer after dynamic CT imaging. Among the 18 subjects, 13 had previously been included in a different research study using a completely different diagnostic approach [14]. Thus, the results presented here do not overlap with the results presented in the previous report.

### Dynamic-ventilation CT

All patients were scanned on a 320-row CT scanner (Aquilion ONE, Canon Medical Systems). Dynamic scanning was performed at a fixed point without bed movement (non-helical mode), providing fluoroscopic images of 160 mm in length. The detailed information of the scanning and reconstruction parameters are described in Appendix 1 of the online-only Supplementary Materials.

### Conventional (static) high-resolution CT

A conventional, static chest CT was also performed using helical scanning to image the entire thorax. The parameters for conventional chest CT were as follows: tube currents, automatic exposure control; tube voltage, 120 kVp; rotation time, 0.35 s; beam pitch, 0.828; imaging field-of-view, 320 mm; collimation, 0.5 mm  $\times$  80; slice thickness, 1 mm; reconstruction kernel, FC17 (for mediastinum); iterative reconstruction, Adaptive Iterative Dose Reduction Using Three-Dimensional Processing (AIDR3D) (“mild” setting). Intravenous contrast medium was used in all patients (2 ml/kg, iomeprol [Iomeron<sup>®</sup> 350], Bracco-Eisai).

### Research software

We developed a package of image analysis software that could visualize lung surface sliding based on 4D CT data. In brief, the software registered all voxels throughout the dynamic-ventilation CT as pairs within two continuous frames, and calculated the movement distances of the lung surface and surrounding structures (at 10 mm outside the lung surface). A three-dimensional (3D) color map was created to visualize lung surface motion compared to the motion of surrounding extrapulmonary structures (Fig. 1). If the lung surface was

judged to be sliding primarily towards the surrounding structures, the surface was colored red. In contrast, if the software judged that the lung surface was less mobile than, or fixed to, the surrounding structures, the region was colored blue. Software details are shown in Appendix 2 in the online-only Supplementary Materials.

## Image analysis

Two chest radiologists (T.Y. and M.T., 15 and 10 years of experience in thoracic radiology, respectively) were blinded to patient status and cooperatively evaluated the presence of pleural invasion/adhesion on chest CT images by two different methods: (i) reviewing conventional high-resolution CT images, reconstructed in the axial, coronal, and sagittal directions; and (ii) reviewing 4D dynamic-ventilation CT images combined with a 3D color map created by the analysis software. The 4D dynamic-ventilation CT images were presented in cine mode in the axial, coronal, and sagittal directions (Movies S1–S2 as Supplementary Materials), and the 3D color maps were viewed on a different monitor. The probability of parietal pleural invasion/adhesion was scored using a 1–100 confidence scale (1, no invasion/adhesion; 100, definite invasion/adhesion). The conventional CT and dynamic-ventilation CT reading sessions were held separately, with an interval of 2 weeks. All CT scans were randomly presented to the reviewers at each reading session. If the two observers disagreed on the interpretation, additional discussion was made by the observers to make a final decision from multiple views of the cancer on CT scans.

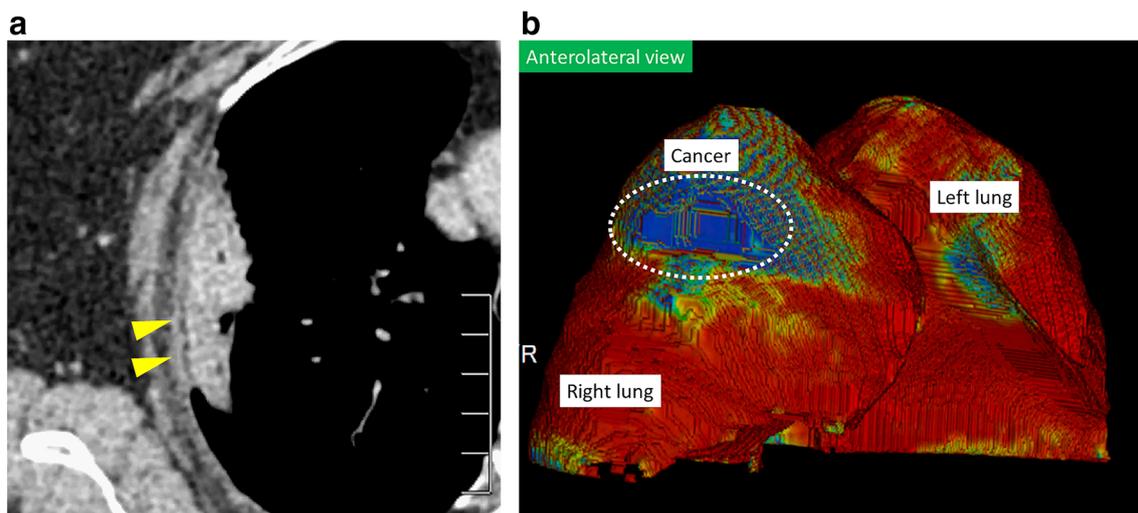
## Statistical analysis

Surgical findings of pleural invasion/adhesion were defined as the gold standard. The diagnostic accuracy of CT assessment was evaluated, including sensitivity, specificity, positive predictive value, and negative predictive value. A receiver operating characteristic analysis was also performed. Statistical analyses were performed using JMP 12.0 software (SAS Institute). Since this was a pilot study to examine the effectiveness of 4D dynamic ventilation CT in assessing parietal pleural invasion/adhesion preoperatively, the sample size was determined based on similar previous studies that evaluated malignant neoplasms' invasion to the chest wall or aorta [12–14].

## Results

### Patient characteristics

Pleural invasion or tumor adhesion was identified in 5 patients during surgical resection (parietal pleural adhesion without tumor invasion,  $n = 4$ ; minimum parietal pleural invasion,  $n = 1$ ). The remaining 13 patients did not have pleural invasion or adhesions observed during surgical resection. Final histopathological examination after surgery revealed adenocarcinoma ( $n = 13$ ), squamous cell carcinoma ( $n = 3$ ), large cell neuroendocrine carcinoma ( $n = 1$ ), and metastatic lung cancer (a single lesion) from resected rectal cancer ( $n = 1$ ). Tumors were located in the right upper lobe ( $n = 3$ ), right



**Fig. 1** A 77-year-old female with adenocarcinoma in the right upper lobe. Although slight pleural thickening is observed (arrowheads) on the axial CT image, it is unclear whether the cancer invades or adheres to the parietal pleura (a). A color-coded map, generated by the analysis software and based on 4D CT images, demonstrates that the tumor is

fixed to the surrounding structures (b). Severe pleural adhesions were observed around the tumor during surgical resection. 4D dynamic-ventilation CT images are available online in the Supplementary Material (Movie 1)

**Table 1** Comparison of the accuracy of 4-dimensional dynamic-ventilation CT and conventional chest CT in the diagnosis of parietal pleural invasion/adhesion of subpleural lung cancer

	4-dimensional dynamic-ventilation CT <sup>2</sup>	Conventional (static) chest CT
Binary classification test		
Sensitivity (%)	100	60
Specificity (%)	100	77
Positive predictive value (%)	100	50
Negative predictive value (%)	100	83
ROC analysis <sup>1</sup>		
Area under the curve	1.000	0.846

CT, computed tomography; ROC, receiver operating characteristic

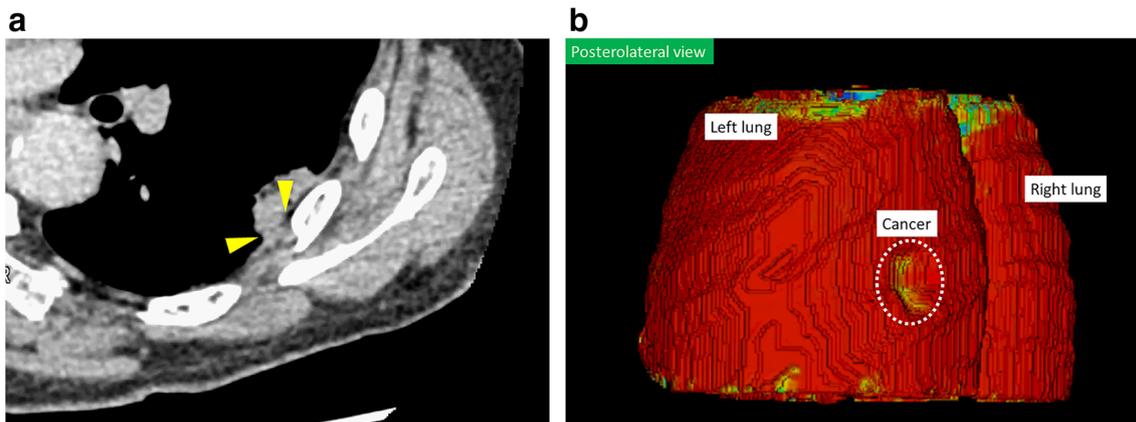
<sup>1</sup> The ROC analysis was performed using a 1–100 confidence scale

<sup>2</sup> 4-dimensional dynamic-ventilation CT was interpreted with the help of a color-coded map created by novel image analysis software

middle lobe ( $n = 1$ ), right lower lobe ( $n = 6$ ), left upper lobe ( $n = 5$ ), and left lower lobe ( $n = 3$ ). The maximum tumor diameter ranged from 13 to 60 mm (mean 25 mm) on axial CT imaging.

### Radiation exposure of dynamic-ventilation CT

For a single gantry rotation of 160 mm (0.35 s), the CT dose index volume was 0.71 (20 mA, “large” scanning FOV), 1.28 (40 mA, “medium”), or 1.41 (40 mA, “large”) mGy. The dose-length product value for a single rotation was 11.3, 20.4, or 22.5 mGy cm. The total estimated radiation exposure for the dynamic-ventilation CT for 4.5–6.5 s varied from 3.0 to 6.1 mSv (mean 5.1 mSv) [22].



**Fig. 2** A 75-year-old male with adenocarcinoma in the left lower lobe. On a conventional CT axial image (a), the tumor appears to protrude into the subpleural fat layer, which is connected to the intercostal muscle layer (arrowheads). However, a color-coded map (b), generated by the analysis software and based on 4D CT images, demonstrates no clear pleural

### Image analysis

Analysis of the 4D dynamic-ventilation CT images combined with the color map achieved perfect diagnostic accuracy (sensitivity, 100%; specificity, 100%; area under the curve [AUC], 1.000). In contrast, analysis of the conventional chest CT resulted in lower diagnostic accuracy (sensitivity, 60%; specificity, 77%; AUC, 0.846) (Table 1, Figs. 1 and 2, Movies S1–S2 as Supplementary Materials).

### Discussion

In this preliminary study, we demonstrated that the combination of 4D dynamic-ventilation CT images and a unique color map of lung sliding movement led to the correct diagnosis of parietal pleural invasion/adhesion caused by peripheral lung cancer. Although our methodology should be evaluated in a larger cohort of patients, we believe this novel technique can be used as part of the preoperative assessment during lung cancer treatment.

The motivation for developing our image analysis software was to allow thoracic surgeons to visualize 3D surface-motion prior to surgery. Evaluating a 4D dynamic-ventilation CT in cine mode requires extensive time and knowledge of tumor and chest wall movements. We thus attempted to create new software to visualize lung surface motion at a glance and from any direction. Furthermore, evaluating dynamic-ventilation CT images in three directions (axial, sagittal, and coronal views) is not always appropriate for tracing tumor motion, as tumors may occasionally move in all three directions during ventilation (resulting in the targeted tumor being out of the plane of all three views). Although our analysis software cannot currently show the exact location of the targeted lung

adhesion/invasion by the tumor. Absence of adhesion/invasion was confirmed during surgical resection. The 4D CT images show the tumor sliding against the inner surface of the chest wall (available online in the Supplementary Material as Movie 2)

tumor on the color map, we are working to merge information from 4D CTs and conventional CTs to better correlate tumor location and lung surface motion.

The usefulness of cine-MR for identifying tumor invasion to the parietal pleura or other extrapulmonary structures has been described in several reports [8–12], but the indications for cine-MR in lung cancer remain limited, perhaps due to excessive cost. Chest CT is routinely performed as part of the preoperative assessment of lung cancer; it is reasonable to add a dynamic-ventilation CT to the conventional helical CT, thereby providing valuable and economical information on parietal pleural invasion/adhesion.

In this study, we reported our observations regarding peripheral lung cancer. In addition, the color map created by our analysis software has the potential to visualize “non-cancerous” inflammatory adhesions between the parietal and visceral pleura. Since the software evaluates motion differences between the lung surface and surrounding structures, severe “benign” pleural adhesions are also visualized on the 3D color map. Severe pleural adhesions often cause thoroscopic procedures to be terminated and converted to conventional thoracotomy [4, 5]; hence, accurate preoperative assessment would be helpful to thoracic surgeons. We are rigorously upgrading the image analysis software using a deep learning method, by inputting multiple 4D CTs, with and without surgically confirmed pleural adhesions.

Our study has several limitations. First, the study included a small number of patients. Since this study was considered technical development of the methodology, we prioritized promptness of the publication. More detailed studies, with an increased number of patients enrolled, and including different affected lung areas, are needed to confirm the reproducibility of the current findings. Second, the conventional CT scans were only viewed in two dimensions. Third, extraradiation exposure was needed, particularly at a tube current setting of 40 mA. Thus, we investigated a 20-mA setting for some patients and confirmed that the 20-mA setting was more appropriate for future use (3.0 mSv for 6.5 s). However, an even greater reduction in radiation exposure, such as a 10-mA setting, may be tried in the future to increase the clinical utility of the 4D CT evaluation, particularly with a combination of novel iterative reconstruction techniques. Fourth, since it has been reported that the lung surface around the lung apex or in patients with severe obstructive diseases does not show much movement during ventilation [23], our approach should be reevaluated in a larger population including cancers in the apex and patients with obstructive diseases. Finally, our study included only two radiologists.

In conclusion, software-assisted, 4D dynamic-ventilation CT can be considered as a novel imaging method for accurate preoperative assessment of parietal pleural invasion/adhesion of peripheral lung cancer. Future studies with a larger number

of enrolled patients are needed to verify the clinical utility of this imaging technique.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Dr. Yamashiro (first author).

**Conflict of interest** University of the Ryukyus, Ohara General Hospital, and Shiga University of Medical Science received a research grant from Canon Medical Systems. Mr. Kimoto is an employee of Canon Medical Systems.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was waived by the Institutional Review Board of Ohara General Hospital.

**Ethical approval** Institutional Review Board approval was obtained at Ohara General Hospital.

**Study subjects or cohorts overlap** Among the 18 subjects analyzed in this study, 13 had previously been included in a different research study using a completely different diagnostic approach. Thus, the results presented here do not overlap with the results presented in the previous report. Please refer to the following paper that has been attached with the manuscript as a PDF file.

Sakuma K, et al Parietal pleural invasion/adhesion of subpleural lung cancer: quantitative four-dimensional CT analysis using dynamic-ventilatory scanning. *Eur J Radiol.* 2017; 86(2): 36–44. doi: <https://doi.org/10.1016/j.ejrad.2016.12.004>.

### Methodology

- Retrospective
- Observational
- Performed at one institution

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