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Quantitative evaluation of iodine and fat using dual-energy CT for assessments of the tumor aggressiveness in lung cancer

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Abstract

Background: The three-material decomposition method (3MD) of dual-energy applications can quantify iodine and fat contents of the tumor. The purpose of this study was to assess the usefulness of quantifying iodine and fat contents in the tumor grade, lymphovascular invasion, and pleural invasion to predict tumor aggressiveness in lung cancer (LC) using dual-energy computed tomography (DECT). We prospectively analyzed the cases of 32 patients with lung tumors who underwent preoperative contrast-enhanced DECT. Image data were processed with a 3MD using imaging software. Iodine and fat within the mass were quantified. In the 24 patients with cancerous lung tumors, we performed correlation analysis of iodine and fat contents with histological grade (grades 1–4), lymphovascular invasion and pleural invasion.

Results: The iodine concentration (mg/mL) and fat-volume-fraction (%) showed no significant differences among histological grades ($p = 0.514$ and $p = 0.405$, respectively) (Jonckheere–Terpstra test). Likewise, pleural invasion was not associated with either the iodine concentration or the fat-volume-fraction ($p = 0.673$ and $p = 0.251$, respectively) (Mann–Whitney test). Lymphovascular invasion, however, was significantly associated with the fat-volume-fraction ($39.3 \pm 23.4\%$ vs. $62.3 \pm 29.5\%$, $p = 0.007$), but not with the iodine concentration ($p = 0.137$). The receiver operating characteristics curve of the fat-volume-fraction between the presence and absence of lymphovascular invasion revealed an area under the curve of 0.861 at the cut-off value of 37.8%, with a sensitivity of 1.000 and specificity of 0.722.

Conclusion: The quantitative evaluation of fat within a tumor using DECT may predict lymphovascular invasion in LC.

Keywords: Lung cancer, Dual-energy computed tomography, Lymphovascular invasion, Iodine concentration, Fat-volume-fraction

Background

Lung cancer (LC) is one of the most common malignant tumors and has become the main cause of cancer mortality [1]. Pre-operative imaging is important to predict the aggressiveness of the tumors and is particularly important in the treatment of LC. ^{18}F-FDG PET/CT is useful for determining staging and therapeutic responses in LC [2]. ^{18}F-FDG PET/CT is also used to determine the tumor aggressiveness of non-small-cell lung cancer (NSCLC) [3]. The maximum standardized uptake value (SUV max) on ^{18}F-FDG PET/CT correlates with tumor aggressiveness; however, ^{18}F-FDG PET/CT has drawbacks of radiation exposure and high cost [4].

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Dual-energy computed tomography (DECT) as a spectral imaging modality with a dual-source (two types of tube voltage) technique has enabled quantification of tumor contents of both iodine and fat simultaneously. Several research groups have evaluated the iodine uptake of lung cancer using DECT [5–7]. Previous study also reported the usefulness of iodine concentrations of LC tumors revealed by DECT [5]. A correlation between iodine attenuation using DECT and the SUV max of ^{18}F-FDG PET/CT has been reported [7]. In addition, CT using a single-energy technique has been reported for the prediction of pleural invasion of LC [8]. Lymphovascular invasion was reported an adverse prognostic factor for the development of distant metastases of NSCLC and the long-term survival of patients [9]. The three-material decomposition method (3MD) of dual-energy applications can quantify iodine and fat contents of the tumor [10]. To the best of our-knowledge, no previous study has assessed the usefulness of quantifying iodine and fat contents to predict tumor aggressiveness in lung cancer.

If the usefulness of this study is revealed, it may contribute to the prediction of tumor aggressiveness in lung cancer in preoperative evaluation, and it may be useful in postoperative evaluation of treatment. The purpose of this study was to assess the usefulness of quantifying iodine and fat contents in the tumor grade, lymphovascular invasion, and pleural invasion to predict tumor aggressiveness in LC using DECT.

Methods

Patients

This prospective study was approved by our hospital's institutional review board, and informed consent was obtained from all patients. Thirty-two patients with lung tumors underwent preoperative contrast-enhanced DECT at our hospital during the period from March 2018 to March 2019. We excluded patients with tumors measuring < 10 mm in diameter, those with large cystic changes, those with predominant ground-glass opacity (GGO) findings, and those with a cavity or obstructive pneumonia on DECT from the analysis. Large cystic change was defined with a solid tumor adjacent to a large cystic lesion. These cases were excluded because the region of interest (ROI) of the solid lesions of tumors could not be extracted accurately, and the boundaries of the tumors were not clear. The mean time interval between the patients' DECT imaging and their surgeries was 13.8 days with a standard deviation (SD) of (± 7.6) (range 4–32 days). Complete video-assisted thoracoscopic surgery (VATS) was performed in 19 patients, a hybrid VATS was conducted in two patients, and a thoracotomy was performed in three patients.

A total of 24 patients whose tumors were histopathologically diagnosed as lung cancer after surgery were examined. We performed an analysis based on the association between the quantified iodine and fat contents of the tumors and the patients' histological diagnoses, namely the histological grade (grades 1–4), lymphovascular invasion, and pleural invasion. Histopathological classification was based on the WHO classification 4th edition. Lymphovascular invasion was defined with or without lymphovascular invasion, and pleural invasion was defined the tumor beyond the epipleural plate.

DECT protocol, and the analysis of DECT images

DECT (SOMATOM Force, Siemens Healthcare, Erlangen, Germany) was performed in the craniocaudal direction with inspiratory apnea (scan area: 320–400 mm, tube voltage: 90 kV/Sn150kV, detector configuration: 192 × 0.6 mm, pitch factor: 0.6, rotation time: 0.28 s/rot). Iodine-enhanced DECT scans were obtained at the delayed phase 90 s after an injection with 520 mgI/kg nonionic iodinate contrast medium (370 mgI/mL). The average radiation exposure doses of iodine-enhanced DECT were 15.41 ± 2.85 (range 10.9–21.7) mGy for the computed tomography dose index volume[3]. The data were reconstructed with a slice thickness of 1.0 mm. Image data were processed with the 3MD using Syngo. via. imaging software (Liver VNC, Siemens).

The operative principle of dual-energy-source CT is that the values are affected by the different tube voltages. This application can measure the iodine and fat contents in the ROI of the tumor. The ROI of each tumor was obtained with a semi-automatic algorithm, centered on the maximum tumor cross-sectional area in three directions (Figs. 1, 2). The ROI margin was aligned with the maximum plane of the tumor margin, and was carefully enclosed while checking three directions to avoid contamination with surrounding tissue. The ROIs were measured by one 15 years experienced radiologist (M.D.), who was blinded to the subjects before surgery or pathological diagnosis.

Statistical analyses

All statistical calculations were done with PASW statistical software (ver. 23.0, SPSS, IBM, Chicago, IL). Intraobserver variability was tested with intraclass correlation coefficients (ICCs). ICCs agreement measures were considered excellent if > 0.8, good if 0.6–0.8, moderate if 0.4–0.6, moderate, and poor if < 0.4. The Jonckheere–Terpstra test was used to correlate the histological grades of the tumors (grades 1–4). The Mann–Whitney test was used for comparisons between positive and

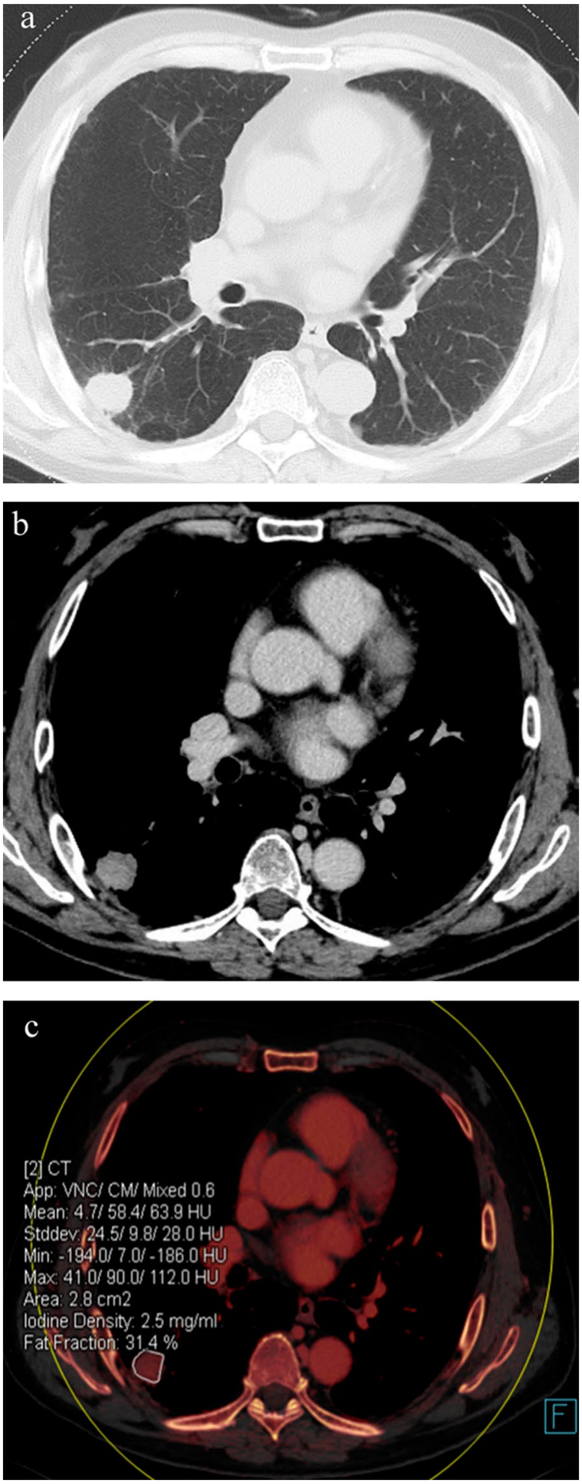

Fig. 1 The ROI of the tumor was obtained with a semi-automatic algorithm, centered on the maximum tumor cross-sectional area in three directions on an iodine-enhanced image. A 75-year-old man with adenocarcinoma of the right lower lobe. LVI was positive (**a**–**c**). (**a**) Lung window image of the tumor, (**b**) Iodine-enhanced DECT image of the tumor, (**c**) The ROI of the maximum tumor diameter on an iodine-enhanced axial image (oval ROI), FVF was 31.4%

negative lymphovascular invasion and pleural invasion. P values < 0.05 were considered to indicate statistical significance. We performed a receiver operating characteristic (ROC) analysis to assess the predictive potential of parameters for distinguishing pathological features. The cut-off value was calculated using the Youden index.

Results

We performed analysis that a total of 24 patients (24/32, 75%, age 68.9 ± 6.6 yr; female 2, males 22) whose tumors were histopathologically diagnosed as lung cancer after surgery (Fig. 3). Those data collection and demographic data are listed in Table 1. The intraobserver variability regarding iodine concentration and fat-volume-fraction values showed good to excellent agreement. The ICCs of the iodine concentration values was 0.885, and the ICCs of the fat-volume-fraction values were 0.966. The iodine concentration and fat-volume-fraction showed no significant differences among histological grades (grade 1 $n = 1$, grade 2 $n = 17$, grade 3 $n = 2$, grade 4 $n = 4$) (Jonckheere–Terpstra test) (Table 2). Likewise, pleural invasion was not associated with either the iodine concentration or the fat-volume-fraction (positive $n = 6$, negative $n = 18$) (Mann–Whitney test) (Table 3). However, lymphovascular invasion was associated with the fat-volume-fraction (positive $n = 18$: 39.3 ± 23.4% vs. negative $n = 6$: 62.3 ± 29.5%, $p = 0.007$). The iodine concentration and lymphovascular invasion were not associated (Table 3). The power calculation for the fat-volume-fraction and lymphovascular invasion was 0.462, which was attributed to the small sample size.

The result of our ROC analysis of the relationship between the fat-volume-fraction and lymphovascular invasion in which the test and state variables were the fat-volume-fraction and the positivity/negativity of lymphovascular invasion, respectively; the value of the state variable was 0 if lymphovascular invasion was negative, 1 if positive, showed an area under the curve (AUC) of 0.861 at the cut-off value of 37.8%, with a sensitivity of 100% and specificity of 72.2% (Fig. 4).

Discussion

The 3MD algorithm of dual-energy applications can generate an iodine distribution map and a virtual non-contrast image [10]. With this method, it is possible to

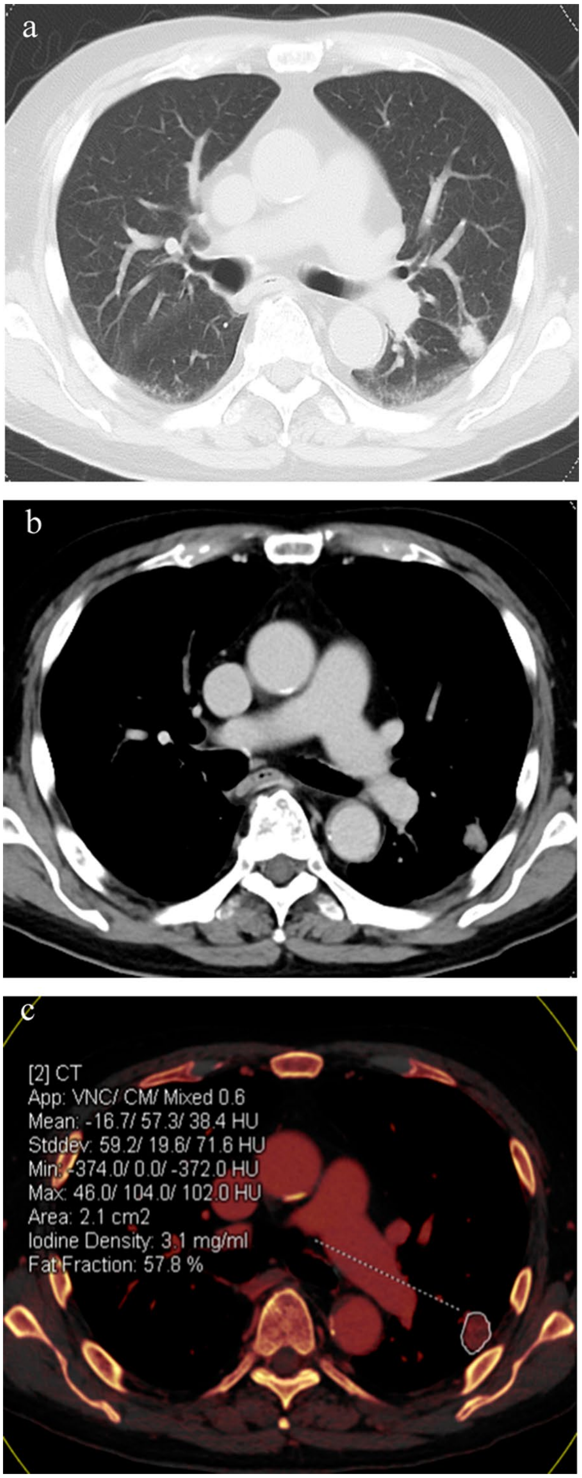

Fig. 2 Imaging of squamous cell carcinoma of the left upper lobe with negative LVI in a 73-year-old man (**a**–**c**). (**a**) Lung window image of the tumor, (**b**) Iodine-enhanced DECT image of the tumor, (**c**) The ROI of the maximum tumor diameter on an iodine-enhanced axial image (oval ROI), FVF was 57.8%

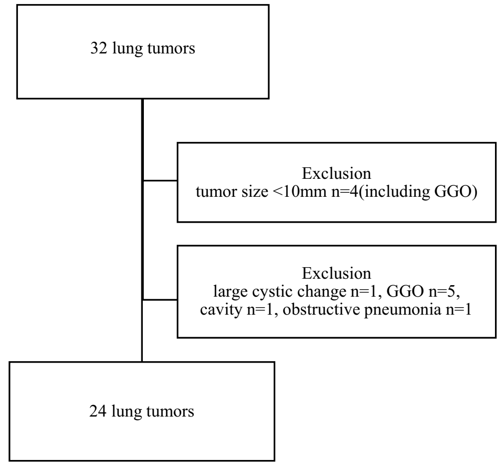

Fig. 3 Flowchart showing the patient selection process

measure the iodine concentration and the fat-volume-fraction of tumors. The results that we obtained with this method suggest that the only significant association is the difference in the fat-volume-fraction values of the lung cancer tumors with and without lymphovascular invasion [10].

We observed that the fat-volume-fraction values in the tumors with positive lymphovascular invasion were significantly lower than those of the tumors with negative lymphovascular invasion. Lymphovascular invasion has been shown to be a reliable prognostic factor for poor recurrence-free and overall survival in NSCLC [9, 11]. It was suggested that the presence of lymphovascular invasion may be helpful in the decision paradigm for adjuvant chemotherapy [9]. Indeed, lymphovascular invasion is a marker for poor prognosis not only in NSCLC but also in many other solid malignancies, including head and neck, kidney, prostate, and bladder cancers [12–15]. It can thus be expected that calculating the fat-volume-fraction using DECT is an effective method for determining the appropriate treatment for patients with lung cancer. The reason of the significant lower fat-volume-fraction in the tumor with lymphovascular invasion, although the pathological evidence was not obtained, we consider that it may be due to a decrease in the fat components within the connective tissue of lymphovascular invasion in the tumor.

Iwano et al. [5] observed that high-grade lung tumors tended to have lower iodine volumes than low-grade lung tumors. In their study, the iodine volumes were evaluated using the CT value. In our study, the iodine concentration was not associated with the histological grade, but

Table 1 Patient and tumor characteristics

Characteristics (*n* = 24)	
Age (yrs)	
Mean (± SD) (Range)	68.9 (± 6.6) (56–79)
Sex	
Male	22 (92%)
Female	2 (8%)
Tumor size (mm)	
Mean ± SD	21.0 (± 6.7)
Range	11.0–37.0
Histological type	
Squamous cell carcinoma	7 (29%)
Adenocarcinoma	14 (58%)
Large cell neuroendocrine carcinoma	3 (13%)
Pathological grade	
Grade 1	1 (4%)
2	17 (71%)
3	2 (8%)
4	4 (17%)
Lymphovascular invasion	
Positive	18 (75%)
Negative	6 (25%)
Pleural invasion	
Positive	6 (25%)
Negative	18 (75%)
pT stage	
T1a	1 (4%)
T1b	10 (42%)
T1c	8 (33%)
T2a	4 (17%)
T2b	1 (4%)
pN	
N0	19 (79%)
N1	4 (17%)
N2	1 (4%)
pM M0	24

Table 3 The iodine concentration versus FVF of pleural invasion (PI) and lymphovascular invasion (LVI) of lung cancer patients

Parameter	Positive (*n* = 18)	Negative (*n* = 6)	*p* value
PI: Iodine (mg/mL)	2.5 ± 1.1	2.2 ± 0.6	0.673
PI: Fat (%)	49.0 ± 29.1	32.9 ± 9.8	0.251
LVI: Iodine	3.0 ± 1.2	2.2 ± 0.8	0.137
LVI: Fat	39.3 ± 23.4	62.2 ± 29.5	0.007*

Data are mean ± SDs, * $p < 0.05$ (Mann–Whitney test)

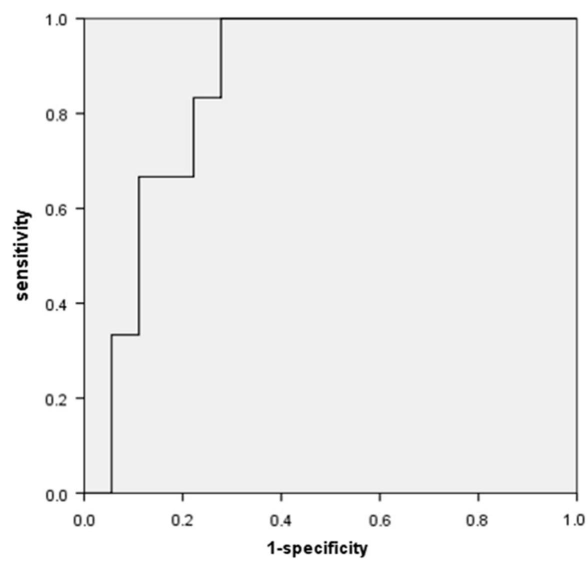

Fig. 4 The ROC curves of the FVF in predicting lymphovascular invasion. The AUC was 0.861 at the cut-off value of 37.8%, with a sensitivity of 100% and specificity of 72.2%.

we did not evaluate the iodine-containing CT value. We speculate that the lack of a significant association of iodine contents with pathological factors in our results was due to intracellular micronecrosis or degeneration. CT values may decrease due to liquefaction inside intracellular micronecrosis or degeneration of the tumor. Baxa et al. [16] demonstrated the benefit of identifying the quantitative ratio of the early and late post-contrast iodine contents using dual-energy CT of lymph nodes for predicting the response of lung cancer to treatment. They did not evaluate the treatment response using the quantification of iodine in the tumors. To the best of our knowledge, our study is the first quantitative evaluation in lung cancer tumors using the 3MD algorithm of DECT.

Table 2 The iodine concentration vs fat-volume-fraction (FVF) of the histological grades of lung cancer

Parameter	Grade 1 (*n* = 1)	Grade 2 (*n* = 17)	Grade 3 (*n* = 2)	Grade 3 (*n* = 4)	*p* value
Iodine (mg/mL)	2.1	2.5 ± 1.0	1.9 ± 0.6	2.2 ± 1.4	0.514
Fat (%)	37.7	45.0 ± 22.6	28.0 ± 1.6	55.1 ± 47.4	0.405

Data are means ± SDs

Limitations

There are some study limitations to consider, however. [1] The study population was very small, with a small statistical power at 0.462. It is necessary to increase the number of cases in the future. [2] Selection bias was present. Our study excluded patients with predominant GGO findings. The iodine content of GGO could not be measured due to poor visualization under the mediastinal window.

Conclusion

The quantitative evaluation of tumor fat content using delayed-phase DECT may have the potential to predict lymphovascular invasion in LC.

Abbreviations

3MD: Three-material decomposition method; ADC: Apparent diffusion coefficient; AUC: Area under the curve; DECT: Dual-energy computed tomography; FVF: Fat-volume-fraction; GGO: Ground-glass opacity; ICCs: Interclass correlation coefficients; LC: Lung cancer; LVI: Lymphovascular invasion; NSCLC: Non-small-cell lung cancer; PI: Pleural invasion; R^2: Coefficient of determination; ROC: Receiver operating characteristic; ROI: Region of interest; SDs: Standard deviations; VATS: Video-assisted thoracoscopic surgery.

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Author contributions

MD and HT conceived of the idea for the study. MD and NT, collected the data. MD, NT, YN, and HN contributed data or analysis tools. MD and KU verified the analytical methods. MD, YN and HN performed the statistical analysis. MD and NT wrote the paper. All authors discussed the results and contributed to the final manuscript. HT, HU and MM supervised the work. All authors read and approved the final manuscript.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent participate

Institutional Review Board approval was obtained, medical research ethics review committee, Kanazawa Medical University (Number: I279).

Consent for publication

An informed consent was obtained for every individual person's data included in the study.

Competing interests

The authors declare that they have no competing interests.

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