Impact of digital positron emission tomography/computed tomography on the delineation of clinical target volume in advanced lung cancer

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Abstract. The present study investigated the differences between digital [18F]-Fluorodeoxyglucose (FDG) positron emission tomography [PET]/computed tomography [CT] (dPET/CT) and conventional PET/CT (cPET/CT) in delineating the clinical target volume (CTV) in patients with advanced lung cancer in the involved field radiation therapy (IFRT) era. Patients with advanced lung cancer were scanned using two dual-imaging protocols (dPET/CT and cPET/CT). Two virtual delineations contoured with reference to dPET/CT and cPET/CT images were created for each patient by five radiation oncologists. Changes in the delineation of target volumes in each patient were examined. A total of 10 patients [male/female, 9/1; median age, 65 years (range, 58-80 years)] were enrolled between April 2020 and September 2020. Significant changes in the delineation of CTVs were uncommon between dPET/CT and cPET/CT. A notable increase in CTVn was observed in 10% of the patients (1/10; $P<0.05$; Smirnov-Grubbs analysis). In this patient, a node that was not assessed as lymph node metastasis when cPET/CT was used was assessed as lymph node metastasis when dPET/CT was used and was included in the CTVn by all five radiation oncologists. In patients with advanced lung cancer, notable changes in CTV delineations are uncommon, regardless of whether dPET/CT or cPET/CT is used. However, in some cases, CTVn delineation with reference to dPET/CT may improve the treatment outcomes of IFRT for advanced lung cancer.

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Introduction

Concurrent chemoradiotherapy (CCRT) is often used to prevent locoregional recurrence and improve the overall survival of patients with advanced lung cancer (1). Currently, two methods of irradiation are commonly used in the treatment planning process for CCRT in these patients: i) Elective nodal irradiation, which targets microscopic mediastinal lymph node metastases that are not evident on imaging, and ii) involved field radiation therapy (IFRT), which targets only visible lesions on imaging studies. As systemic therapies have progressed, the use of CCRT combined with IFRT has become widespread in various institutions (2,3). However, Yuan *et al* (4) demonstrated that 7% of patients with lung cancer treated with IFRT experience recurrence within the lymph node region. One possible explanation is that the clinical target volume (CTV) in IFRT planning, with reference to conventional imaging information, may have been inadequate.

Imaging information, including non-enhanced computed tomography (non-CE/CT), contrast-enhanced CT (CE/CT), and [18F]-Fluorodeoxyglucose (FDG) positron emission tomography/CT [(PET)/CT] images, is important for defining the CTV in IFRT planning. In clinical practice, the CTV is generally delineated by radiation oncologists with reference to these imaging data. Although the quality of these images can affect the CTV delineation, PET/CT images are particularly useful (5). In previous years, remarkable advances have been made in PET/CT technology (6,7). Semiconductor-based PET/CT is a new digital PET/CT (dPET/CT) technique that has demonstrated improved tumor detection than cPET/CT (8). The dPET/CT replaces the photomultiplier tube of the cPET/CT with a semiconductor optical sensor. The semiconductor optical sensor has a smaller temporal fluctuation of the electrical signal, and the time-of-flight temporal resolution is improved compared with the cPET/CT. Therefore, the signal-to-noise ratio and contrast are greatly improved, and even small lesions can be clearly visualized (9).

However, the impact of dPET/CT on CTV delineation remains unclear because radiation oncologists delineate the CTV with reference to the aforementioned clinical information

(non-CE/CT, CE/CT, and PET/CT). Therefore, in the present study, the influence of dPET/CT on CTV delineation in IFRT planning was evaluated and compared with that of cPET/CT.

Materials and methods

Study protocol and cases. In total, 26 patients with lung cancer underwent both cPET/CT and dPET/CT between April 2020 and September 2020 at Ehime University Hospital (Toon, Japan). Out of all the patients, those with early-stage lung cancer (n=15) and those with metastatic lesions in the thoracic region (n=1) were excluded. Finally, the 10 remaining patients were included in the present study. The present study was approved (approval. no. 2211016) by the Ethics Committee of Ehime University Hospital (Matsuyama, Japan).

Image acquisition. Whole-body PET/CT was performed using an integrated cPET/CT scanner (Discovery 600 PET/CT, GE Healthcare) and a dPET/CT scanner (Discovery MI, GE Healthcare). The patients fasted for at least 6 h and had a blood glucose level of 80-120 mg/dl before the intravenous administration of 18F-FDG (3.7 MBq/kg). The order of PET scans was randomly assigned to each patient. A total of 12 patients were first scanned using dPET followed by cPET (dPET-first), and 14 patients were first scanned using cPET followed by dPET (dPET-second). All dPET images were reconstructed using a 3-dimensional time-of-flight weighted line-of-response row-action maximum-likelihood algorithm with attenuation correction using a CT attenuation map. Integrated PET and CT images were reconstructed and reviewed using Advantage Workstations Server 3.2 (Cytiva). The display field of view was 60x60 cm and consisted of 256x256 matrices. The voxel size was 2.34x2.34x2.79 mm^3.

CTV delineation. The data of the patients with lung cancer scanned using non-CE/CT, CE/CT, cPET/CT, and dPET/CT were imported into treatment planning systems (Eclipse, Varian Medical Systems, Inc.).

Two patterns of gross tumor volume (cGTVall=cGTVp + cGTVn with reference to cPET/CT and dGTVall=dGTVp + dGTVn with reference to dPET/CT) were determined based on the primary tumor and lymph node metastases identified on PET/CT images. The CTV (cCTVall=cCTVp + cCTVn with reference to cPET/CT and dCTVall=dCTVp + dCTVn with reference to dPET/CT) was determined by expanding 0.5 cm around the GTVs and excluding normal organs in principle. Non-CE/CT and CE/CT images were referenced to delineate all plans.

In total, 20 CTVs (10 cCTVp, n, all and 10 dCTVp, n, all) were devised by five radiation oncologists as a reference for cPET/CT and dPET/CT. All patients were blinded and randomized, and one plan was created per month.

Statistical analysis. Statistical analyses were conducted using EZR version 1.61 (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (version 3.5.0; The R Foundation for Statistical Computing) (10). Extreme values (outliers) were eliminated using Smirnov-Grubbs analysis, which is a method of outlier detection that assumes the data follow a normal distribution (11).

Table I. Patient characteristics.

Characteristics	Number of patients	Percentage (%)
Age		
<65 years	5	50.0
≥65 years	5	50.0
Sex		
Male	9	90.0
Female	1	10.0
Stage		
3a	4	40.0
4a	2	20.0
4b	4	40.0
T stage		
1	2	20.0
2	4	40.0
4	4	40.0
N stage		
1	3	30.0
2	4	40.0
3	3	30.0
Metastasis		
Yes	6	60.0
No	4	40.0
Primary site		
Upper lobe	5	50.0
Middle lobe	0	0.0
Lower lobe	5	50.0

Results

Patients. After applying the exclusion criteria, 10 patients [one with small cell lung cancer and nine with non-small cell lung cancer; male/female, 9/1; age, 58-80 years (median, 65 years)] were included in the analysis (Table I). Out of all the patients only six patients had distant metastases that were not present in the thoracic area (bone, one; brain, two; bone/brain/liver, one; bone/liver, one; and adrenal/pancreas, one).

Comparison between cCTV and dCTV. In the Smirnov-Grubbs analysis of the GTVn/CTVn change ratio, one outlier was found ($P<0.05$; Fig. 1). From the results of this patient, it was found that the dGTV divided by the cGTV and the dCTVn divided by the cCTVn more than doubled (2.97 and 2.18 times, respectively). The case with GTVn/CTVn outliers is illustrated in Fig. 1. In this case, the size of the 4R lymph node was less than 1 cm, and FDG uptake was found only in the dPET/CT image. All radiation oncologists judged this lymph node as GTVn/CTVn when they contoured the GTVn/CTVn with reference to dPET/CT. By contrast, no outliers were found in the GTVp/CTVp or GTVall/CTVall change ratios.

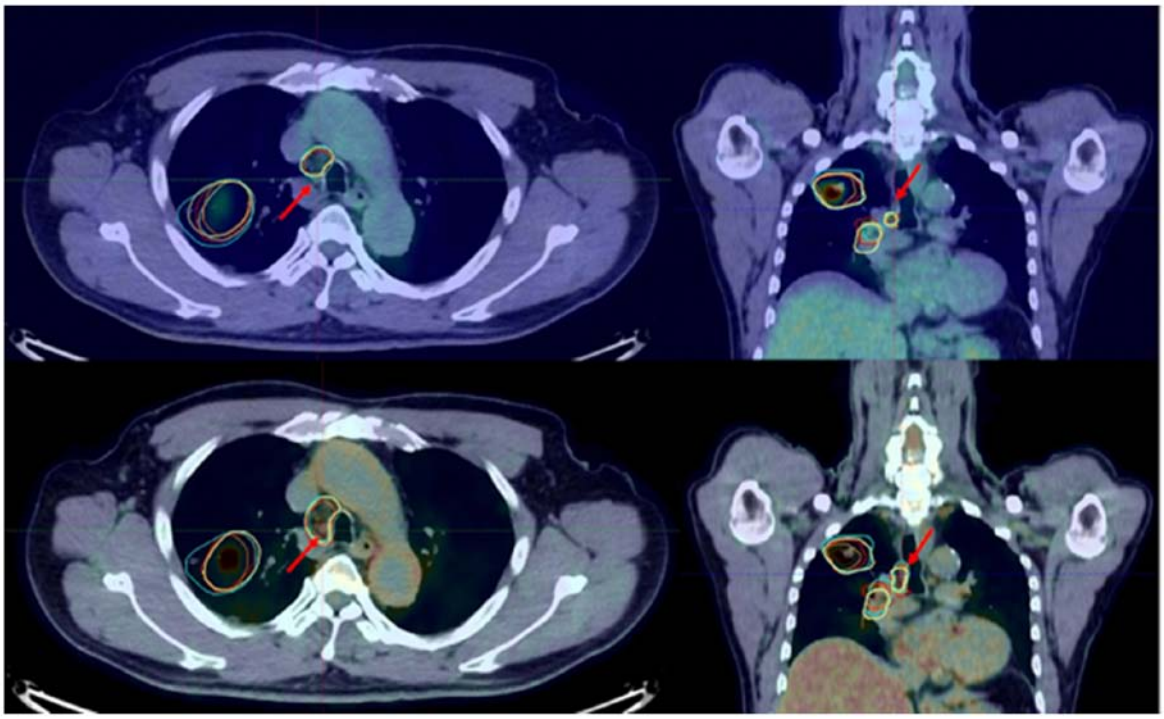

Figure 1. A case of an outlier following the Smirnov-Grubbs analysis of the GTVn/CTVn change. The red arrows indicate: GTVn/CTVn enlarged area based on the difference between cPET/CT and dPET/CT images. GTV, gross tumor volume; CTV, clinical target volume; cPET/CT, conventional positron emission tomography/computed tomography; dPET/CT, digital positron emission tomography/computed tomography.

Discussion

The present study investigated the influence of dPET/CT on GTV/CTV delineation during IFRT planning for advanced lung cancers. The results of the present study indicated that dPET/CT rarely brought about clinically significant changes in the GTV/CTV for IFRT planning for advanced lung cancer. However, it was observed that 10% (1/10) of the patients exhibited a large change that more than doubled in the GTVn/CTVn delineation with reference to the dPET/CT image compared with the cPET/CT image.

In the immune checkpoint inhibitor + intensity-modulated radiation therapy era, IFRT is commonly used for advanced lung cancer (3,12). However, some patients were treated with IFRT experience lymph node recurrence (4). The possible explanation for this, is the lack of image detection of small lymph node metastases. The lack of image detection with cPET/CT may have inhibited the GTV/CTV delineation of the true target volumes. In the present study, the GTVn/CTVn delineation with reference to dPET/CT resulted in an increased GTVn/CTVn ratio in 10% (1/10) of the patients. This suggested that the GTVn/CTVn delineation for IFRT used in previous studies may have been inadequate in some cases and that interpreting the results of previous studies using IFRT demands caution (4).

In the present study, although all GTV/CTVs were contoured with reference to CE/CT and PET/CT images, the GTV/CTV changed in 10% (1/10) of the patients. Similarly, Koopman *et al* (8) revealed that dPET/CT improves the detection of small lesions and the disease in some cases [TNM upstaging with dPET/CT in 13% (4/30) of the cases]. Thus, although dPET/CT did not change the GTV/CTV in the majority of patients with advanced lung cancer, dPET/CT appeared to have an impact on GTVn/CTVn delineation in some cases, even when GTVn/CTVn was contoured with reference to multiple imaging modalities. The use of dPET/CT for GTVn/CTVn delineation may improve the outcomes of IFRT in advanced lung cancer.

The present study had several limitations. First, the sample size was small. Second, there were only a few cases of stage III lung cancer. The present study included patients with advanced lung cancer who underwent both cPET/CT and dPET/CT imaging examinations, following the upgrade of the PET/CT machines at Ehime University Hospital (Toon, Japan). The patients were randomly selected, which resulted in fewer cases of stage III lung cancer. Therefore, it was needed to include not only patients with stage III lung cancer but also those with stage IV lung cancer that did not affect the GTV/CTV delineation in the thoracic region. Third, which image was correct when the lymph node metastatic lesions depicted on dPET/CT differed from those depicted on cPET/CT was unclear. Further prospective studies are required in the future. Despite these limitations, it was considered by the authors that the present study is important because it provides a crucial perspective on the interpretation of the results of previous studies, and the use of dPET/CT can potentially improve the treatment outcomes of IFRT for advanced lung cancer. Furthermore, various treatment modalities and tumor detection techniques are currently being investigated (13-15). Still, further studies are needed because the development of these technologies may lead to more precise treatment methods for lung cancer and contribute to improved treatment outcomes.

In conclusion, most GTV/CTV delineations with reference to dPET/CT were unchanged compared with those from GTV/CTV delineations with reference to cPET/CT. However,

in some cases, the GTVn/CTVn delineation with reference to dPET/CT is larger than that of cPET/CT, which may have an impact on the treatment outcome of IFRT for advanced lung cancer.

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Availability of data and materials

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

Authors' contributions

All authors had full access to the data in the study, confirmed the authenticity of all the raw data, and take responsibility for the integrity of the data and the accuracy of the data analysis. KM designed the study. KM, YH, HK, KN, MM, NK, TO, TKi and TKo collected patient data and drafted the manuscript. KM, YH, HK, KN, MM, NK, TO, TKi and TKo collaborated on discussions. KM prepared the manuscript, and YH, KH and MM edited the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in the present study were in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments. The need for informed consent was waived due to the retrospective nature of the study. The present study was approved (approval. no. 2211016) by the Ethics Committee of Ehime University Hospital (Toon, Japan).

Patient consent for publication

The patients treated at Ehime University Hospital consented in writing for the use of their anonymous data for research. In addition, Opt-out method was applied to obtain consent in the present study.

Competing interests

TKo received an honorarium from MSD, Ono, Kyowa Hakko Kirin, AstraZeneca, Boehringer Ingelheim, Chugai, TAIHO, Eli Lilly, Bristol Myers Squibb, Pfizer, Merck Biopharma, Nippon Kayaku, Novartis, Bayer, Sawai, and AMGEN; consulting fee from Chugai, AstraZeneca, Ono, Pfizer, Daiichi-Sankyo, Bayer, and Abbvie; and received research funding from MSD, Kyowa Hakko Kirin, AstraZeneca, Eli Lilly, Pfizer, Chugai, TAIHO, Ono, Bristol-Myers, Merck Biopharma, Daiichi-Sankyo, AbbVie, AMGEN, Sanofi, Eisai, LabCorp Development, IQVIA Services, Gilead Sciences, Pfizer, and Bayer. All other authors declare that they have no competing interests.

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