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Dosimetric comparison of nodal clinical target volume for locally advanced non-small cell lung cancer: Options for geometric expansion vs. lymph node stations

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Abstract. The purpose of the present retrospective study was to evaluate whether dosimetric differences existed in nodal clinical target volume (CTV) using options for geometric expansion and lymph node (LN) stations based on the European Society for Radiotherapy and Oncology guideline for locally advanced non-small cell lung cancer (NSCLC). In the treatment planning computed tomographic images of 17 patients with cT4N2M0 NSCLC, nodal CTVs were contoured based on the guideline options of: i) Geometric expansion, with CTV including the nodal gross tumor volume plus 5 mm margin; and ii) LN stations, with CTV including the affected LN stations. Treatment planning of 60 Gy in 30 fractions was performed using volumetric modulated arc therapy; D_{mean} was the mean irradiated dose to the structure; and V_{nGy} was the volume of the structure receiving ≥*n* Gy. Dose-volume parameters were compared between the two options. Consequently, the option of geometric expansion was associated with a significantly lower V_{60Gy} and D_{mean} of the esophagus, V_{20Gy}, V_{5Gy} and D_{mean} of the lungs, and D_{mean} of the heart than the option of LN stations in all patients (P=0.017, P<0.001, P<0.001, P<0.001, P<0.001 and P=0.029, respectively). For the V_{20Gy} of the lungs, the 8 patients (47%) with LN metastases in stations 2 or 3 had significantly larger differences in the values between the two options than the 9 patients (53%) without those metastases; the median values of the difference of V_{20Gy} of the lungs between the two options were 2.8% (range, 0.2 to 9.6%) with LN metastases in stations 2 or 3 and 0.5% (range, -0.2 to 5.0%) without these metastases (P=0.027). In conclusion, using the option for geometric expansion might help reduce the V_{60Gy} and D_{mean} of the esophagus, V_{20Gy}, V_{5Gy} and D_{mean} of the lungs, and D_{mean} of the heart in all patients, and the V_{20Gy} of the lungs in patients with LN metastases in stations 2 or 3.

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Key words: intensity-modulated radiotherapy, volumetric modulated arc therapy, radiation therapy, involved-field irradiation, selective nodal irradiation

Introduction

Lung cancer was the leading cause of globally cancer death (1). The incidence rate of non-small cell lung cancer (NSCLC) was about 85% of lung cancers (2). NSCLC was a heterogeneous disease invading the lung and adjacent tissues, eventually progressing and spreading to distant sites (3). A computed tomographic (CT) scan and a positron emission tomographic scan using ^{18}F-fluorodeoxyglucose was used for the staging of NSCLC (3,4). Whilst chances for a complete remission or a cure were highest in early-stage cancers, survival rates decreased when the cancer was locally advanced (3,5). Proper treatment of locally advanced NSCLC can result in a cure or long-term survival (3). A locally advanced lung tumor was resectable if surgery was sufficient to achieve complete tumor removal and if the patient was able to tolerate the surgery (3). For patients with unresectable locally advanced NSCLC who were medically or surgically inoperable, chemoradiotherapy (CRT) was recommended (6). Typically, the unresectable patients were managed with concurrent CRT using a platinum-based doublet with a standard radiation dose of 60 Gy (7-9). After the initial treatment, patients without disease progression were treated by consolidation durvalumab (7,10). Patients who were likely to undergo radiation therapy (RT) should be assessed for the risk of lung toxicity secondary to radiation (3,11). The mean lung dose and the volume of healthy lungs receiving ≥20 Gy radiation doses were good indicators of the risk of radiation-induced lung injury (3,11). For the treatment planning of RT, selective nodal irradiation was recommended (12). From the European Society for Radiotherapy and Oncology (ESTRO) guideline, two options were recommended for the definition of nodal clinical target volume (CTV): (a) geometric expansion, with CTV including the nodal gross tumor volume (GTV) plus 5 mm margin, and (b) lymph node (LN) stations, with CTV including the affected LN stations (13). Conventionally, the option for geometric expansion was known as involved-field irradiation (IFI). It was expected that CTVs using the option of LN stations were larger than those with the other option

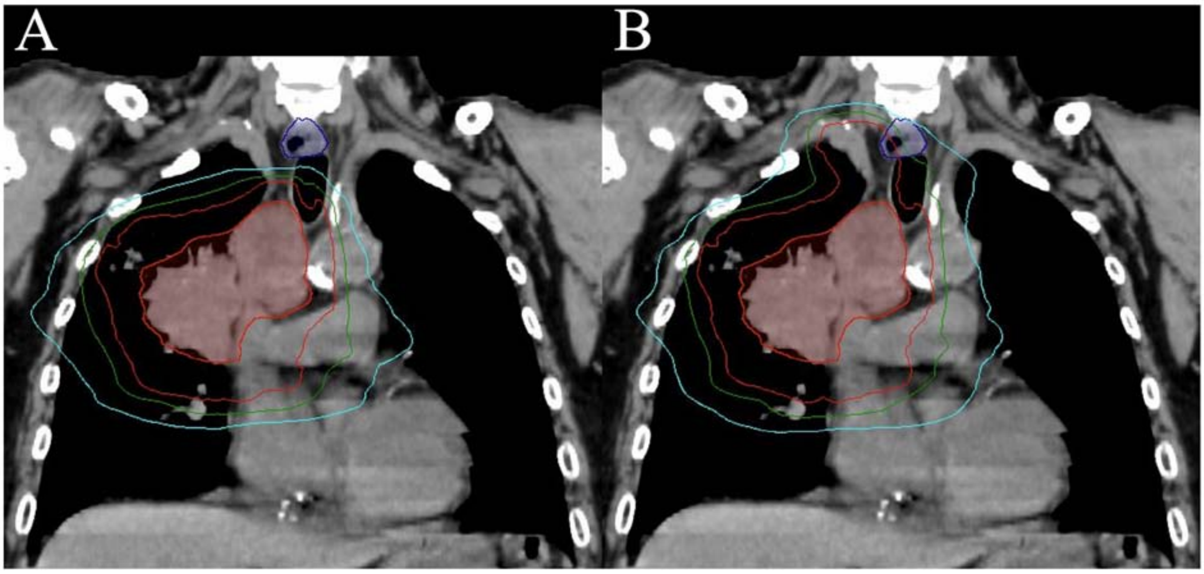

Figure 1. Dose distributions of a patient with LN metastases in station 2 based on the options of (A) geometric expansion and (B) LN stations. Contours filled with red and blue indicate the gross tumor volume and the esophagus, respectively. Red, green and cyan lines indicate 95, 70 and 30% isodose lines, respectively. LN, lymph node.

because LN stations were frequently wider than the 5 mm margin from GTVs (14). However, it was unclear which option was more advantageous for reducing the normal tissue dose to avoid radiation toxicities.

Therefore, we retrospectively evaluated whether dosimetric differences existed in the nodal CTV using the two options for locally advanced NSCLC.

Patients and methods

Type of study. This single-institutional study was retrospectively conducted at our hospital. This study was carried out in accordance with the Declaration of Helsinki. Our institutional review board (The Research Ethics Committee of Kagawa University Faculty of Medicine, Kagawa, Japan) approved this study (approval number: 2022-165). After the approval, we investigated the patients who were treated at our hospital between 2017 and 2022.

Patients. The inclusion criteria of this study were as follows: patients over 20 years old; patients who had locally advanced NSCLC with cT4N2M0 (15); patients who underwent RT; and patients who were treated between 2017 and 2022 at our department. The exclusion criteria were as follows: patients who refused to participate in this study. Written informed consent was obtained from each patient before treatment planning. The patient consent for publication in written form was obtained regarding the anonymized CT images in Fig. 1. In total, 17 patients met the selection criteria without refusal, and we used their treatment planning CT images for this study.

Treatment planning. A radiation treatment planning system (Eclipse™ v16; Varian Medical Systems) was used. We contoured nodal CTVs based on the ESTRO guideline's options of: (a) geometric expansion, with CTV including the nodal GTV plus 5 mm margin, and (b) LN stations, with CTV including the affected LN stations (13). The 5 mm margins for planning target volume (PTV) were added to the nodal and primary tumors' CTVs. Treatment planning of 60 Gy in 30 fractions to the PTV $D_{50\%}$ was performed using volumetric modulated arc therapy; $D_{n\%}$ was the irradiated dose to *n*% of volumes of the structure; D_{ncc} was the irradiated dose received by the highest irradiated *n* cc volumes of the structure; D_{mean} was the mean irradiated dose to the structure; V_{nGy} was the percentage of volumes of the structure at least irradiated *n* Gy. Our goals of normal tissue dose constraints were as follows: $D_{0.1cc}$ of the spinal cord, ≤45 Gy; V_{20Gy}, V_{5Gy}, and D_{mean} of the lungs, ≤40%, ≤65%, and ≤20 Gy, respectively; V_{60Gy} and D_{mean} of the esophagus, ≤17% and ≤34 Gy, respectively; V_{50Gy} and D_{mean} of the heart, ≤25% and ≤20 Gy, respectively. Examples of the dose distribution and the dose-volume histogram (DVH) are shown in Figs. 1 and 2, respectively.

Statistical analysis. We compared DVH parameters between the two options using the Wilcoxon signed-rank test. V_{20Gy} of the lungs was the most common DVH parameter for NSCLC (11). We evaluated the difference of V_{20Gy} of the lungs between the two options in patients with or without LN metastases in stations 2 or 3 because stations 2 or 3 were wider for cranial-caudal direction than other stations (14). For the difference of V_{20Gy} of the lungs between the two options, patients with and without LN metastases in these stations were analyzed as separate groups using the Wilcoxon rank sum test. Statistical significance was defined as $P<0.05$. The software program JMP Pro 15 (SAS Institute) was used for the statistical analyses.

Results

Patient characteristics are listed in Table I. Stations 2, 3, 4, 5, 6, 7, 10, and 11 were involved in 6, 4, 11, 4, 4, 7, 12, and 12 patients, respectively (Table II). The DVH parameters between the two options are listed in Table III, and the target coverage of PTV

Table I. Patient characteristics.

Characteristics	Value
Age, years	
Median	68
Range	45-77
Sex, n (%)	
Male	14 (82)
Female	3 (18)
Histology, n (%)	
Squamous cell carcinoma	9 (53)
Adenocarcinoma	6 (35)
Non-small cell carcinoma	2 (12)
Tumor laterality, n (%)	
Right	12 (71)
Left	5 (29)
Tumor location, n (%)	
Upper lobe	13 (76)
Lower lobe	4 (24)
c-stage[a] IIIB with cT4N2M0	17 (100)
Gross tumor volume, cc	
Median	213
Range	39-812

[a]Based on the 8th edition of the Union for International Cancer Control guidelines (15).

Table II. Involved lymph node stations in each patient.

Patient no.	Involved station nos.
1	2, 6 and 10
2	4 and 7
3	4 and 11
4	2, 3, 4, 7, 10 and 11
5	2 and 4
6	4 and 10
7	7 and 11
8	4, 5, 10 and 11
9	5, 6, 10 and 11
10	4, 7, 10 and 11
11	2, 4, 10 and 11
12	7 and 11
13	3, 5, 6, 10 and 11
14	2, 4, 7, 10 and 11
15	4, 10 and 11
16	3, 5, 6 and 10
17	2, 3, 4, 7, 10 and 11

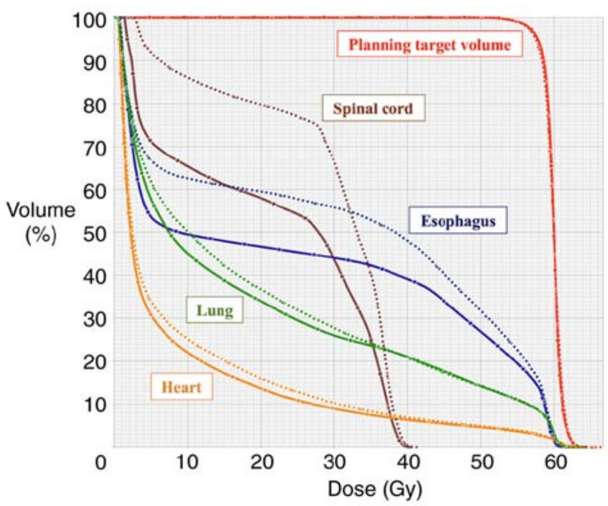

Figure 2. Dose-volume histogram of a patient with LN metastases in station 2 based on the options of geometric expansion (solid line) and LN stations (broken line). LN, lymph node.

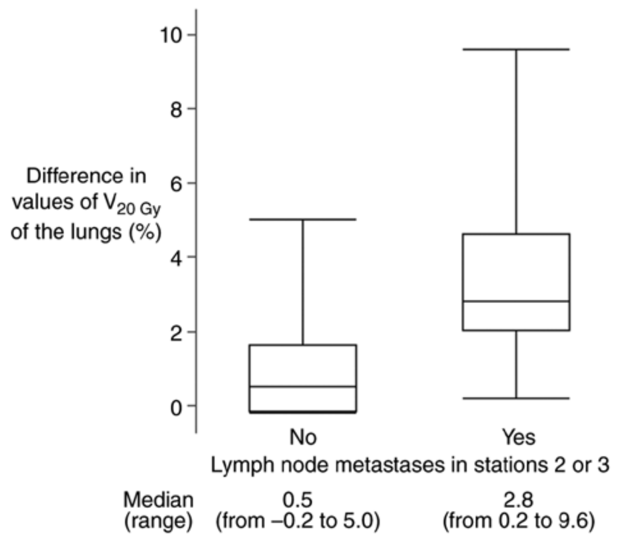

Figure 3. Difference in values of V_{20Gy} of the lungs between the two options with and without lymph node metastases in stations 2 or 3. V_{20Gy} is the volume of the structure receiving ≥20 Gy. Center lines, boxes and error bars indicate the median, interquartile range, and maximum or minimum, respectively.

$D_{95\%}$ was comparable between the two options. The normal tissue dose constraints of the spinal cord, lungs, esophagus, and heart were fulfilled in both options. The option of geometric expansion was associated with a significantly lower V_{60Gy} and D_{mean} of the esophagus, V_{20Gy}, V_{5Gy} and D_{mean} of the lungs, and D_{mean} of the heart than the option of LN stations (P=0.017, P<0.001, P<0.001, P<0.001, P<0.001 and P=0.029, respectively).

For the V_{20Gy} of the lungs, the eight patients (47%) with LN metastases in stations 2 or 3 had significantly larger difference values between the two options than the nine patients (53%) without those metastases (Fig. 3); median values of the difference were 2.8% (range, from 0.2 to 9.6%) and 0.5% (range, from -0.2 to 5.0%) with and without LN metastases in stations 2 or 3, respectively (P=0.027).

Discussion

In this study, we identified the merits of the option for geometric expansion to reduce the irradiated dose to the

Table III. Comparison of dose-volume histogram parameters between the two options in all patients.

Parameter	Geometric expansion (n=17)	Lymph node stations (n=17)	P-value
PTV, volume (cc)	569 (149-2005)	635 (184-2109)	<0.001
PTV, $D_{95\%}$ (Gy)	58.2 (57.5-58.7)	58.1 (57.5-58.7)	0.260
Spinal cord, $D_{0.1cc}$ (Gy)	39.1 (30.2-40.3)	39.1 (32.8-40.5)	0.998
Lung, V_{20Gy} (%)	20.5 (14.8-33.9)	24.0 (15.1-36.7)	<0.001
Lung, V_{5Gy} (%)	40.4 (25.8-57.6)	45.4 (32.6-61.7)	<0.001
Lung, D_{mean} (Gy)	12.2 (8.7-18.4)	13.5 (9.5-19.4)	<0.001
Esophagus, V_{60Gy} (%)	0.0 (0.0-1.4)	0.2 (0.0-2.6)	0.017
Esophagus, D_{mean} (Gy)	12.2 (6.6-24.9)	16.1 (13.6-30.5)	<0.001
Heart, V_{50Gy} (%)	0.7 (0.0-11.4)	0.8 (0.0-11.5)	0.284
Heart, D_{mean} (Gy)	3.3 (0.6-19.1)	4.6 (0.7-18.9)	0.029

Data are presented as the median (range). PTV, planning target volume; $D_{n\%}$, the highest dose to n% of the structure; D_{ncc}, the highest dose received by n cc of the structure; V_{nGy}, the volume of the structure receiving ≥n Gy; D_{mean}, the mean irradiated dose to the structure.

esophagus, lungs and heart in all patients with locally advanced NSCLC as compared with the option for LN stations. In daily clinical practice, if the dose constraints of the esophagus, lungs and heart were not fulfilled with the options for LN stations, we should try using the option for geometric expansion.

Esophagitis was one of the major toxicities after RT for locally advanced NSCLC. In a large phase 3 trial using CRT for locally advanced NSCLC, grades 2 and 3 esophagitis after a radiation dose of 60 Gy in 30 fractions occurred in 24% and 7% of patients, respectively (8). In long-term results of the trial, the maximum grade of esophagitis was one of the factors that affected overall survival (OS) on a multivariable analysis (9). Therefore, our finding might be important for prolonging OS through reducing the irradiated dose to the esophagus in all patients.

Pneumonitis was also one of the major adverse events after thoracic RT. As the V_{20Gy} increased, the incidence rate of fatal pneumonitis rose in proportion in an international individual patient data meta-analysis: V_{20Gy} <20%, 0.0% fatal rate; 20-29.99%, 1.0%; 30-39.99%, 2.9%, respectively (11). In the meta-analysis, the V_{20Gy} was one of the predictors of fatal pneumonitis (11). Therefore, our finding might be important for avoiding fatal pneumonitis through reducing the irradiated dose to the lungs in all patients and especially in patients with LN metastases in stations 2 or 3. Stations 2 or 3 were wider for cranial-caudal direction than other stations (14). In stations 2 or 3, a 5 mm margin might be more advantageous to reduce the irradiated dose to the lungs than including the affected LN stations.

Recently, cardiac toxicities after RT for locally advanced NSCLC has been a topic. Pooled analysis of six prospective trials showed that the heart dose was associated with symptomatic cardiac events in multivariate analysis (16). The article concluded that heart doses should be minimized (16). Therefore, the present finding might be important for avoiding symptomatic cardiac events through reducing the irradiated dose to the heart in all patients.

To the best of our knowledge, no other study has compared the options for geometric expansion and LN stations, to date. For a somewhat modified comparison, a randomized phase 2 trial was conducted for no geometric expansion without CTV margins vs. LN stations (17). The trial showed that the option without CTV margins had significantly lower DVH parameters for the esophagus, lung, and heart than the option of LN stations (17). However, this CTV definition without margins was not mentioned in the ESTRO guideline (13). Therefore, it was difficult to compare the previous knowledge with our findings. Conventionally, the option for geometric expansion was known as IFI. Compared to elective nodal irradiation that irradiated mediastinal LN stations without LN metastases, IFI reduced the dose to the lungs and the incidence rate of pneumonitis (18). It was our new finding that IFI in all patients reduced the lung dose compared to the option of LN stations.

Due to its retrospective nature, our study has certain limitations, such as the small number of samples analyzed and its single-institutional design. A multi-center study was preferable to a single-center study to enhance the reliability and generalizability of our findings.

In conclusion, using the option for geometric expansion might help reduce the V_{60Gy} and D_{mean} of the esophagus, V_{20Gy}, V_{5Gy} and D_{mean} of the lungs, and D_{mean} of the heart in all patients, and the V_{20Gy} of the lungs in patients with LN metastases in stations 2 or 3. A further large-scale study is needed to support our findings. Moreover, further research is necessary whether the option for geometric expansion reduces the incidence of esophagitis, pneumonitis and symptomatic cardiac events compared with the option for LN stations.

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Availability of data and materials

The data generated in the present study are not publicly available due to the restricted permission for the current study by the institutional review board (Research Ethics Committee of Kagawa University Faculty of Medicine, Kagawa, Japan) but may be requested from the corresponding author.

Authors' contributions

ST conceived and designed the study. ST, MA, TK and TN acquired data. ST and MA confirmed the authenticity of all the raw data. ST analyzed the data. ST, MA, TK, TN and TS interpreted the data. ST drafted the manuscript. Article revision was critically done by all authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Research Ethics Committee of Kagawa University Faculty of Medicine (Kagawa, Japan) approved the present retrospective study (approval no. 2022-165). Written informed consent for participation was obtained before treatment planning.

Patient consent for publication

Written patient consent for publication was obtained for the anonymized CT images.

Competing interests

The authors declare that they have no competing interests.

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