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ORIGINAL ARTICLE

Treatment outcome for locally advanced non-small-cell lung cancer using TomoDirect plan and its characteristics compared to the TomoHelical plan

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Abstract

Introduction: TomoDirect (TD) is an intensity-modulated radiotherapy system that uses a fixed gantry angle instead of the rotational beam delivery used in the TomoHelical (TH) system. This study was performed (1) to evaluate the treatment outcome of the TD plan for locally advanced non-small-cell lung cancer (NSCLC) and (2) to compare the characteristics of TD plans with those of TH plans. **Methods:** Twenty-one patients with NSCLC were treated using the TD system. The prescribed dose was 40 Gy/20 Fx for the initial planning target volume (PTV), which included the gross tumour volume (GTV) and lymph node regions. A boost plan of 20 Gy/10 Fx was then applied, focusing on the GTV. For the planning study, matched TH plans of 40 Gy for the initial PTV were created for each patient, to meet the same dosimetric constraints specified in the TD plans. **Results:** The 2-year overall survival, progression-free survival and local control rates were 47%, 45% and 74% respectively. Grade 2 treatment-related pneumonitis occurred in three (14%) patients. The planning study comparing TD and TH showed that dose distribution to GTV and PTV were not significantly different. The lung V5 Gy was lower in the TD plans than TH plans (46.4 ± 5.4 vs. 52.3 ± 8.5), while the V20 Gy was higher (26.2 ± 4 vs. 24 ± 4.3). The TD plans had a significantly shorter treatment time than TH plans (4.5 ± 1.3 min vs. 9.8 ± 1.5 min). **Conclusions:** TD is a clinically acceptable treatment option for NSCSL. The quality of the TD and TH plans are comparable.

Introduction

The development of intensity-modulated radiation therapy (IMRT) techniques has led to improved radiation delivery with better target coverage and homogeneity. However, in the treatment of thoracic cancer, this often results in low-radiation dose exposure in an increased volume of normal lung.[1]Lung tissue is more sensitive to radiation than other structures in the chest, such as the esophagus and heart,[2,3] therefore, such an increase in the dose distribution in normal lung tissue cannot be considered negligible.

The TomoTherapy system (Accuray Inc., Sunnyvale, CA) was developed exclusively for IMRT. The TomoHelical (TH) mode is one of the delivery modalities used in the TomoTherapy system. It provides a continuous 360-degrees beam that may result in optimal dose distribution and dose conformity.[4,5] The TomoTherapy system also allows the delivery of precise image-guided IMRT (IG-IMRT) by acquiring a daily megavolt computed tomography (MVCT) scan immediately before treatment.[6]

Despite improved target coverage and the advantage of high set up accuracy, a large volume of lung tissue still

receives low doses of radiation when the radiation is delivered from 360°.[7] According to previous studies, such increases in the low-dose distribution in the lung could increase the risk of development of treatment-related pneumonitis (TRP); indeed, the TH mode has been reported to induce a somewhat higher rate of fatal TRP than other IMRT methods.[7]

The TomoDirect (TD) mode is a new modality of the TomoTherapy IMRT method; it uses a fixed gantry angle instead of a rotational beam delivery. In radiation therapy for thoracic cancer, the TD mode may reduce the low-dose spread of radiation in intact lung tissue relative to the TH methods.[8] However, few reports have addressed the benefits of a fixed-beam application using the TD for lung cancer. We have used this modality to treat patients with lung cancer in our institute. Our aim in this study was (1) to evaluate the treatment outcome of the TD plan for locally advanced non-small-cell lung cancer (NSCLC) and (2) to compare the characteristics of TD plans with those of TH plans for the treatment of this disease.

Materials and Methods

Patients

From April 2011 to October 2012, 21 consecutive patients with inoperable locally advanced-stage NSCLC patients were treated using TD with curative intent at our institution. All patients were histopathologically diagnosed with NSCLC. They underwent a workup including basic laboratory studies, a CT scan of the lower neck, chest and upper abdomen, and contrast-enhanced magnetic resonance imaging of the brain. Some patients also underwent whole-body positron emission tomography/CT. This study was approved by the review board of our institution (TGE00565-024) and informed consent was obtained from all patients prior to treatment.

CT simulation

To reduce breathing motion and set up error, the patients were appropriately immobilised using Blue BAG™ and BodyFix® equipment (Medical Intelligence, Schwabmuenchen, Germany).

For radiation treatment planning, axial images with a slice thickness of 2.5-mm slice were acquired using an 8-row multi-detector CT system (GE Light Speed, GE Healthcare, Little Chalfont, UK). First, plain CT images were obtained under natural aspiration. Then contrast-enhanced CT images were acquired under natural aspiration and during different respiration phases. These images were fused to the original images using the Pinnacle^3 treatment planning system (Version 9.2, Philips Medical Systems, Fitchburg, WI, USA) to delineate the targets.

Planning for patients/clinical practice

Contours for targets and organs at risk (OARs) were drawn using the Pinnacle^3 system. The gross tumour volume (GTV) included all detectable tumours and involved lymph nodes determined using CT and positron emission tomography/CT information. The clinical target volume (CTV) was obtained by summing the GTVs from the three respiratory motion phases mentioned above. The CTV included the lymph node regions of the mediastinum and ipsilateral hilum. In patients with involved lymph nodes in the supraclavicular region or a primary tumour in the upper lobe of the lung, the CTV included this lymph node region. The planning target volume (PTV) included the CTV plus a 3 to 5-mm margin. Forty Gy in 20 fractions was delivered to the PTV as an initial plan.

The updated CT images were acquired immediately before the delivery of 40 Gy of the initial plan was completed and were used to create a boost plan. The GTV was then modified according to the updated CT images and defined as the GTV boost. The PTV for the boost (PTV boost) included the GTV boost plus a 3 to 5-mm margin. An additional dose of 20 Gy in 10 fractions was delivered focusing on the PTV boost.

Treatment plans were generated using TomoTherapy Hi-Art System tomotherapy inverse planning software based on superposition dose calculation. A TD plan was generated for the treatment of all patients as followed. Seven static ports were applied to imitate the anterior-posterior opposite portals used for conventional radiation therapy (Fig. 1). When the primary tumour was located ventral to the body, four anterior and three posterior beams were used (Fig. 1A, B). When it was located dorsally, three anterior and four posterior beams were used (Fig. 1C, D). No beams were directly opposed. A field width of 2.5 cm and a pitch of 0.25 were applied. The modulation factor was mainly in the range of 2.0–3.0.

These planning goals were as follows: (1) The prescribed dose was defined for the 50% isodoses of the PTV and PTV boost, (2) 95% of the PTV and PTV boost should receive at least 95% of the prescribed dose, (3) 80–90% of the GTV and GTV boost should receive 100% of the prescribed dose. In order of priority, the dose constraints for the OARs were: (a) a maximum dose to the spinal cord of <45 Gy, (b) a mean lung dose of <15 Gy (up to 18 Gy acceptable); lung V20 of <30% (up to 35% acceptable), a minimal dose to the contralateral lung, (c) a mean heart dose of <40 Gy, and (d) a

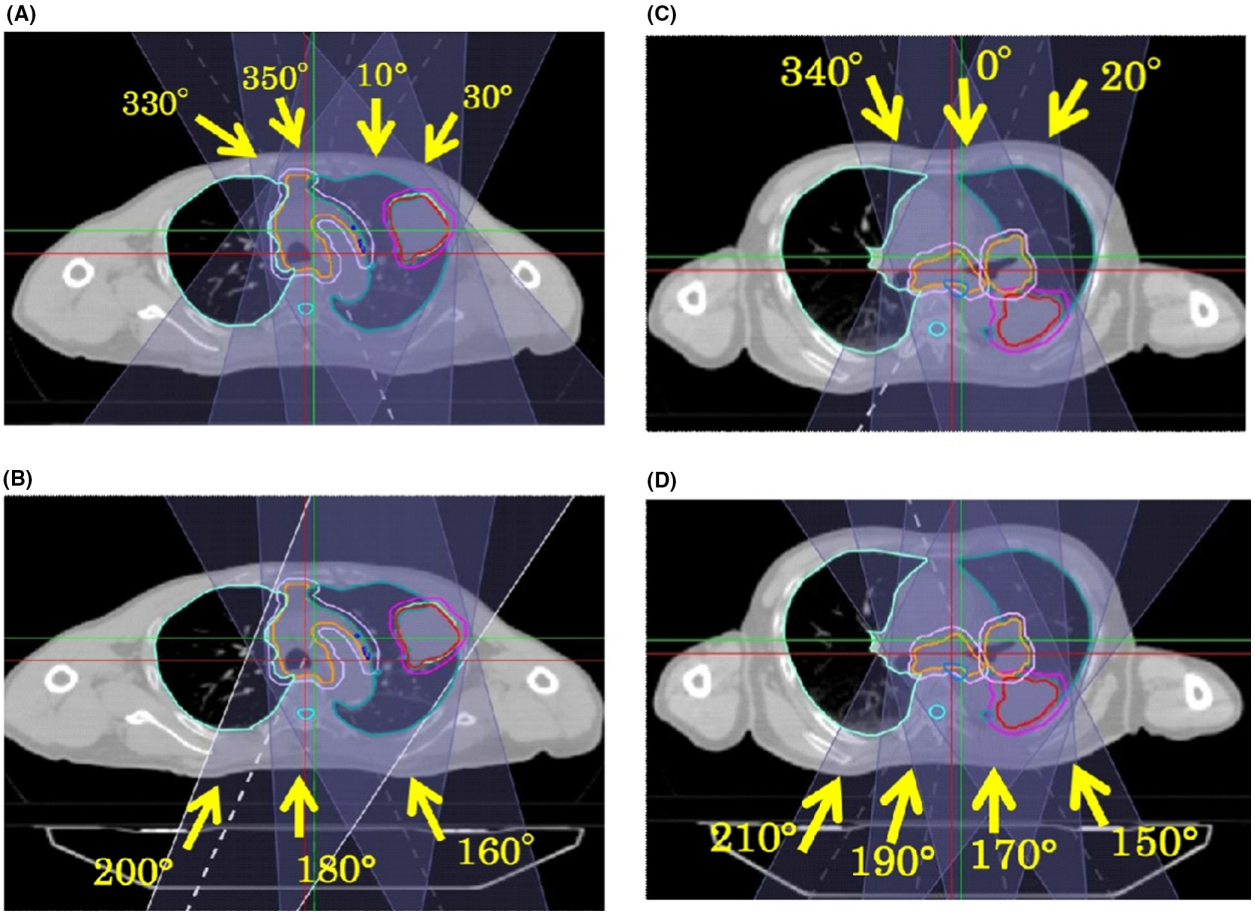

Figure 1. Tumour location and the beam angles of the two representative cases. (A–B) In cases where the primary tumour was located ventral to the body. Four anterior (A) and three posterior (B) beams were used. (C–D) In cases where the primary tumour was located dorsal to the body. Three anterior (C) and four posterior (D) beams were used.

maximum dose to the body of <110% of the prescribed dose. The planning goals for the target volumes and the dose constraints for the OARs are summarised in Table 1.

For image guidance during radiation treatment, a MVCT scan was performed daily immediately before irradiation. The chemotherapy regimen involved carboplatin (at an area under the blood concentration time curve = 2/day) and paclitaxel (at a dose of 40 mg/m^2).

Table 1. The planning goals for target volumes and the dose constraints for OARs.

Target volume	
50% isodoses of the PTV	Prescribed dose
95% of the PTV volume	95% of the prescribed dose
80–90% of the GTV	Prescribed dose
Constrains for OARs	
Maximum dose to the spinal cord	<45 Gy
Mean lung dose	<15 Gy (acceptable up to 18 Gy)
Lung V20	<30% (acceptable up to 35%)
Contralateral lung dose	Minimised
Mean heart dose	<40 Gy
Maximum dose to the body	<110% of the prescribed dose

Evaluation criteria and statistical analysis

The overall survival rate and progression-free survival rate from the beginning of treatment were calculated using the Kaplan–Meier method. Toxicities associated with radiation therapy were evaluated using the Common Terminology Criteria for Adverse Events v4.0. TRP was defined as grade 1 pneumonitis (asymptomatic radiographic findings), and grade 2 pneumonitis (clinical symptoms that needed medical intervention).[9]

Planning study

The initial plan up to 40 Gy was used for the planning study to compare TH and TD. For the planning study, TH plans were created for each patient to meet the same dosimetric constraints specified for the TD plans that were used for

their actual treatments. Following the same approach as used for the TD plans, a field width of 2.5-cm was applied and the modulation factor was mainly in the range of 2.0–3.0. A pitch of 0.43 was used. Figure 2 illustrates a representative case of a TH plan. In the TH plan, dose-limiting volumes (DLVs) were added to both sides of the mediastinum to reduce the dose to the lung. The DLVs covered the 2-cm outside aspect of the PTV and consisted of nested structures. The outer and inner structures were defined as 'blocking' the beam on only the entrance side (a directional block) and blocking the beams at both the entrance and exit sides (a complete block) respectively.

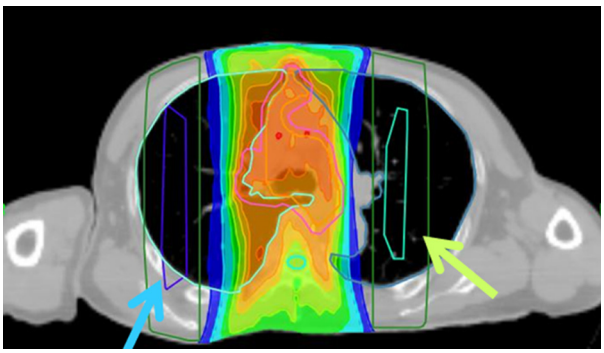

Figure 2. The outer and inner 'blocking' structures for TH planning for dose-limiting volumes (DLVs). The outer structure (green arrow) and inner structures (blue arrow) were defined as 'blocking' the beam on only the entrance side (a directional block), or the beams on both the entrance and exit sides (a complete block) respectively.

Treatment plan evaluation

The dose distribution and dose volume parameters for the PTV and OARs were compared between the TD and TH plans for the initial treatment fields at a dose of 40 Gy. To characterise the dose distributions to the targets, the various types of heterogeneity index (HI) were defined as follows: PTV D5-D95/prescribed dose; GTV D5-D95/prescribed dose; PTV D99-D1; and PTV D50/D90.[10] The V5, V10 and V20 of the total lung and the mean dose were evaluated. The maximum dose to the body and spinal cord were also assessed.

The Wilcoxon signed-rank test was used to compare the dose parameters of the TD and TH plans. All *P*-values of <0.05 were considered statistically significant.

Results

Patients and disease characteristics

The disease characteristics of the 21 patients are summarised in Table 2. The median age at the start of

Table 2. Disease characteristics of the 21 non-small-cell lung cancer patients.

Case No.	Age	Gender	TNM	Stage	Location	Total dose (Gy)	Radiation pneumonitis	Follow-up time (month)	Treatment outcome
1	80	M	T3N0M0	IIIA	L-LL	60	G1	18	PD
2	77	M	T3N3M0	IIIB	L-UL	60	–	35	DOD
3	71	M	T3N2M0	IIIA	R-UL	60	–	12	PD
4	74	M	T4N0M0	IIIA	L-UL	60	G2	42	CR
5	69	M	T3N3M0	IIIB	L-UL	60	–	2	DOD
6	61	F	T4N2M0	IIIB	R-UL	60	–	13	DOD
7	82	F	T2N2M0	IIIA	R-LL	60	–	7	DOD
8	78	M	T2N3M0	IIIB	R-UL	60	–	24	DOD
9	71	M	T4N2M0	IIIB	L-UL	60	–	2	SD
10	64	M	T4N2M0	IIIB	R-UL	60	G2	24	DOD
11	68	M	T4N3M0	IIIB	R-UL	60	–	45	CR
12	43	M	T4N2M0	IIIB	R-UL	60	–	2	DOD
13	77	M	T2N2M0	IIIA	L-LL	60	–	18	PD
14	66	F	T3N3M0	IIIB	R-UL	60	G1	15	PD
15	58	M	T1N2M0	IIIA	R-UL	60	–	26	DOD
16	66	F	T1N2M0	IIIA	R-LL	60	G1	13	DOD
17	73	M	T3N3M1	IV	L-UL	60	–	2	SD
18	76	F	T4N1M0	IIIA	R-UL	48	–	4	SD
19	59	M	T3N2M0	IIIA	R-UL	60	–	4	DOD
20	89	F	T1N2M1	IV	R-ML	56	G1	43	CR
21	52	F	T3N3M1	IV	L-UL	54	G2	21	PD

The patients were classified according to the staging system of the 2002 International Union Against Cancer staging system. M, male; F, female; L, left lobe; R, right lobe; UL, upper lobe; LL, lower lobe; G1, Grade1; G2, Grade2; CR, complete response; PD, partial response disease; SD, stable disease; DOD, death of disease.

Table 3. Plan parameters of the TomoHelical and TomoDirect plans in the 21 patients.

	TomoDirect	TomoHelical	*P*-value
GTV mean (Gy)	40.4 ± 0.3	40.3 ± 0.2	0.07
GTV minimum dose (Gy)	38.2 ± 1.7	38.22 ± 1.7	0.31
PTV mean (Gy)	39.9 ± 0.7	40.0 ± 0.2	0.72
PTV D95 (Gy)	38.19 ± 0.7	38.06 ± 0.6	0.64
PTV D5-D95/ prescribed dose	0.073 ± 0.042	0.068 ± 0.021	0.96
GTV D5-D95/ prescribed dose	0.033 ± 0.01	0.034 ± 0.01	0.87
PTV D99-D1 (Gy)	6.2 ± 2.4	5.7 ± 2.2	0.313
PTV D50/D90	1.06 ± 0.02	1.07 ± 0.02	0.375
Lung V5 (%)	46.41 ± 5.4	52.31 ± 8.5	**0.00073 < 0.05**
Lung V10 (%)	36.7 ± 4.7	35.8 ± 5.4	0.24
Lung V20 (%)	26.27 ± 4.1	24.0 ± 4.3	**0.00028 < 0.05**
Mean lung dose (Gy)	11.96 ± 11.6	12.16 ± 2.0	0.94
Maximum dose of body (Gy)	43.49 ± 1.4	43.49 ± 0.36	0.54
Maximum dose of spinal cord (Gy)	35.2 ± 4.1	34.7 ± 3.6	0.77
Treatment time (min)	4.5 ± 1.3	9.8 ± 1.5	**0.00006 < 0.05**

Treatment time refers to beam on time.
Bold values indicate significant difference.

radiation therapy was 71 years (range, 43–89 years). Fourteen (66.7%) patients were male and seven (33.3%) were female. According to the staging system of the 2002 International Union Against Cancer staging system, nine (42.8%), nine (42.8%), and three (14.3%) patients had Stage IIIA, IIIB and IV disease respectively. The ECOG status for these patients are: performance status (PS) of 0 $n = 14$, PS of 1 $n = 6$ and PS of 2 $n = 1$. As shown in Table 2, most of patients received a total dose of 60 Gy (median 60 Gy, range 48–60 Gy). The median duration of radiation therapy was 42 days (range, 31–54 days). All patients received carboplatin and paclitaxel intravenously once every week.

Local control and survival

As shown in Table 2, the median follow-up time was 15 months (range, 2–45 months). The 2-year overall survival rate was 47.0%, and the 2-year progression-free survival rate was 45.4%. Two patients (Nos. 10 and 15) had marginal recurrence within the radiation field. One of them (No. 10) had simultaneous distance metastases. The 2-year local control rate was 74%.

TRP and mortality

As shown in Table 2, grade 1 and 2 TRP developed in four (19%) and three (14%) patients respectively in this cohort. No other severe adverse effects were observed. No treatment-related deaths occurred.

Planning study; differences in dosimetric indexes between the TD and TH plans

The dose distribution and dose volume parameters for the PTV and OARs were compared between the TD and TH plans for the initial treatment fields at a dose of 40 Gy. Table 3 summarises the plan parameters for the TD and TH plans in the 21 patients. Figure 3 compares the isodose curve distributions in the transverse view, and the dose-volume histograms (DVHs) of the paired TD and TH plans for a representative patient (patient No. 3).

As shown in Table 3, none of the parameters regarding the dose distributions in the GTV and PTV (GTV mean, GTV minimum, PTV mean and PTV D95) were significantly different between the TD and TH plans. The HI including PTV D5-D95/prescribed dose, GTV D5-D95/ prescribed dose, PTV D99-D1 and PTV D50/D90 also showed no significant differences between the two plans. The lung V5 in the TD plans was significantly lower than that in the TH plans (TD, 46.41 ± 5.4 vs. TH, 52.31 ± 8.5 respectively; $P = 0.00073 < 0.05$). Conversely, the lung V20 in the TD plans was significantly higher than that in the TH plans (TD, 26.27 ± 4.1, vs. TH, 24.0 ± 4.3 respectively; $P = 0.00028 < 0.05$). The lung V10 and mean lung dose did not differ significantly between the two plans (V10, TD, 36.7 ± 4.7 vs. TH, 35.8 ± 5.4; $P = 0.24$; mean lung dose, TD, 11.96 ± 11.6 vs. TH, 12.16 ± 2.0; $P = 0.94$). The maximum dose to the body and spinal cord did not differ significantly between the two plans. (Maximum dose to body, TD, 43.49 ± 1.4 vs. TH, 43.49 ± 0.36; $P = 0.54$; maximum dose to spinal cord, TD, 35.2 ± 4.1 vs. TH, 34.7 ± 3.6; $P = 0.77$). The mean treatment time, referring to the 'beam on time' shown in the treatment planning system, was significantly shorter with the TD plans than with the TH plans (TD, 4.5 ± 1.3 vs. TH, 9.8 ± 1.5 respectively; $P = 0.00006 < 0.05$).

Discussion

In this study, we investigated the clinical outcomes of 21 patients with locally advanced NSCLC treated with IMRT using the TD system in our institute. The 2-year overall survival, progression-free survival and local control rates were 47%, 45% and 74% respectively. Among 21 patients, grade 2 TRP was found in 3 (14%), an incidence that is comparable with previous studies using three-dimensional

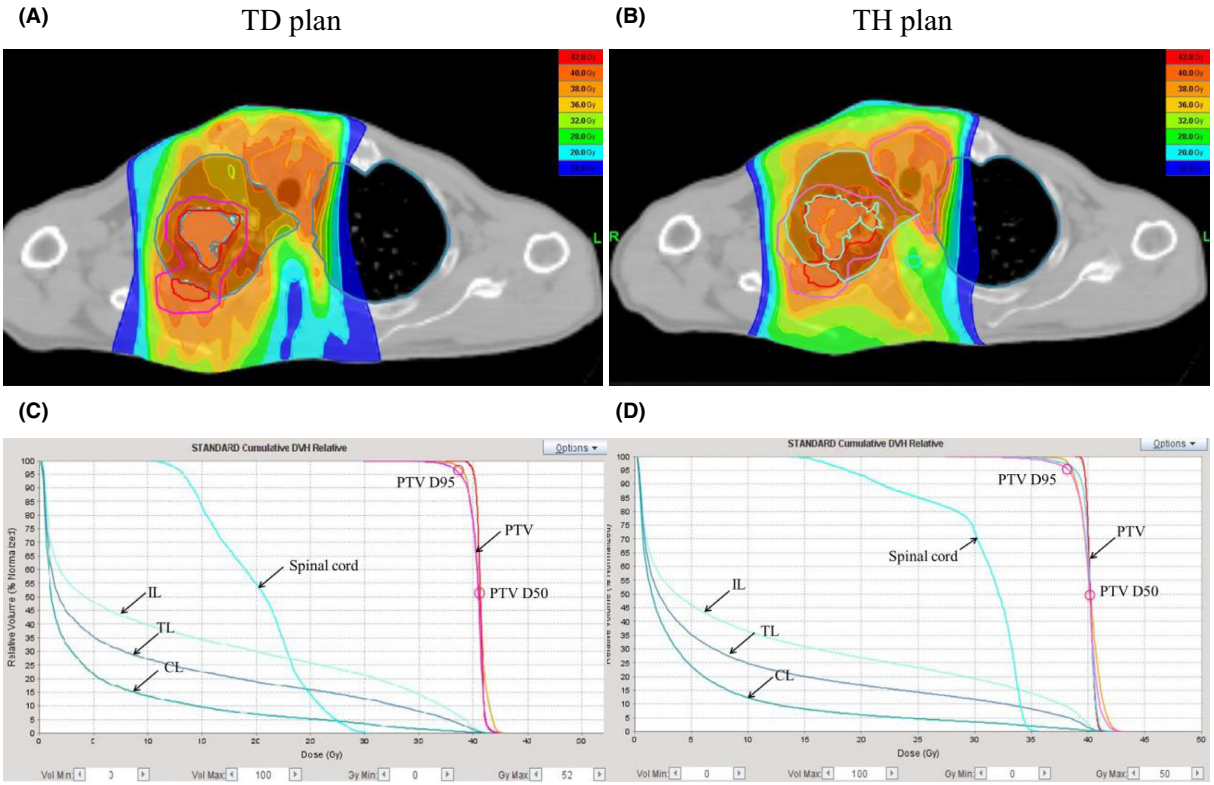

Figure 3. The isodose curve distributions of the paired plan for patient No. 3. (A) TD and (B) TH plans. The dose-volume histograms (DVH) of the TD (C) and TH (D) plans are shown. TL, total lung; IL, ipsilateral lung; CL, contralateral lung.

conformal radiotherapy (3DCRT).[11–13] In previous IMRT studies involving lung cancer, the reported incidences of grade ≥3 TRP ranged from 8% to 13%.[1,14,15] In contrast, we found no grade ≥3 TRP in this study. This is also the first study to show the feasibility of TD plans for locally advanced NSCLC. We consider that our results are clinically acceptable.

We evaluated the characteristics of the TD plans relative to the TH plans for locally advanced NSCLC. For this purpose, a planning study was performed for the initial PTV including the GTV and the lymph node regions at a dose of 40 Gy. Notably, the TD plans were applied to the patients as actual treatments, while the TH plans were created for each patient to meet the same dosimetric constraints specified for the TD plans. We found that both the TD and TH plans achieved comparable dose coverage and homogeneity in the target while sparing critical structures.

In the TD plans, the lower dose area (V5) of the lung was reduced, while the higher dose area (V20) was increased relative to the TH plans. The treatment time required for the TD plans was almost half that required for the TH plans, indicating a benefit for clinical use. To the best of our knowledge, few studies have compared treatment planning using TD versus TH plans in lung cancer.

In 3DCRT, it is well known that the V20 is the most reliable predictor of the incidence and grade of TRP in radiation therapy of lung cancer.[16–19] As IMRT has become more generally applied, several reports have suggested that the volume of lung receiving a dose of ≤20 Gy may be more predictive of the incidence of TRP.[20,21] Some studies have reported unexpected fatal pulmonary toxicity when lung cancer patients were treated using TH.[7,22] It was suspected that this toxicity was related to increased lung volumes exposed to low-dose (≤20 Gy) radiation because the radiation beam of this modality was delivered in 360°. Indeed, Zhang et al.,[23] reported that grade ≥2 acute and late pneumonitis occurred more frequently in patients treated with TH than in those treated with TD. Our findings also suggested that TD may effectively reduce low-dose areas than TH, an indication that TD may have the potential to become one of the options for lung cancer radiation therapy.

We evaluated the paired plan for each patient and found a possible relationship between tumour characteristics and the superiority of the TH or TD plans.

For example, when the primary tumour size was ≤200 cm^3, the V5, V10, and mean lung dose were clearly lower in the TD plan than TH plan. In the TD plan, the beam entry was set based on the anterioposterior-posterioanterior direction. When the target sizes were smaller, the beams passed through a lower lung volume. Therefore, for these cases, the TD plan may be superior to the TH plan in clinical practice. In contrast, when the primary tumour was ≥200 cm^3, the V20 and even the V5 were obviously lower in the TH plan than TD plan. The possible reasons for this are discussed as follows. The TH plan has the advantage of using a high number of independent beams from directions encompassing 360°. Therefore, the TH plan could provide greater flexibility for intensity modulation of dose delivery using multiple beams, a better dose conformity in the targets, and better dose sparing of critical structures. In this study, DLVs were added on both sides of the mediastinum in the same manner in all of the TH plans. This limited the beam entry, reducing the dose to the lung. When the tumour size was small and the beam entry was tightly limited, the unique advantages of the TH plans mentioned above were diminished. In contrast, as the tumour size increased, the beam entry increased, close to 360°, and the advantages of the TH plans were enhanced. In addition, when the tumour was located close to the spinal canal, the TH plan provided obviously superior spinal cord sparing than did he TD plan. Taken together, the findings indicate that the clinical application of the TD plan for lung cancer may be acceptable in general cases, while the TH plan may be recommended according to the tumour location and volume.

In the three patients who developed grade 2 TRP, their lung V10 and V20 in the TD plan tended to be higher than in the matched TH plan, which was created later for this planning study. For these patients, we should have considered applying the TH plan instead of the TD plan. It is essential to establish both TD and TH plans, and then to evaluate the lung DVH for both of the plans.

The treatment time was significantly shorter using the TD than TH plans. The radiation therapy using the TomoTherapy system requires MVCT imaging immediately before every treatment hence patients must remain at rest for considerably longer than when other modalities are used. In addition, most of the patients with locally advanced NSCLC are elderly (as was also true in this study), sometimes their respiratory function is not always well preserved and they may have difficulty remaining at rest during a longer treatment. Therefore, a reduction in the treatment time would be of benefit to these patients.

In this study, the number of patients and the follow-up time were limited. Furthermore studies are required to evaluate long-term efficacy and late toxicities using the TD system. In particular, it remains essential to establish the clear evidence regarding which technique, TD or TH, is suitable for each tumour according to its location and size.

Conclusions

Our results suggested that IMRT using TD plans is the feasible for locally advanced NSCLC. In the planning study to compare the TD and TH plans for treating NSCLC, the quality of the TD treatment plans was equivalent to that of the TH plans. The TD plans were superior with respect to the volume of lung tissue that received a low dose, and resulted in a treatment time that was almost half that of the TH plans. TD can be considered as a treatment option for NSCLC.

Conflict of Interest

The authors declare no conflict of interest.

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