Dosimetric comparison of four radiotherapy techniques for stage III non-small cell lung cancer

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Abstract. The present study was implemented to compare the dosimetric parameters of the target dose coverage and critical structures in the treatment planning of four radiotherapy techniques [namely, three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), hybrid IMRT (h-IMRT) and volumetric-modulated arc therapy (VMAT)] for stage III non-small cell lung cancer (NSCLC) qualified plans for medical physicists, therapists and physicians. A total of 40 patients confirmed to have stage IIIA or IIIB NSCLC were enrolled, and four plans were designed for each patient. The prescription dose to the planning target volume (PTV) was assigned as 60 Gy in 30 fractions. The conformity index (CI), heterogeneity index (HI) and parameters of organs at risk (OARs) were calculated. For the PTV, the CI for VMAT was found to be the highest of all the four techniques (P<0.05), whereas the HI for the h-IMRT technique was found to be the lowest (P<0.05). Concerning the OARs, for the percentage of lung volume receiving a dose >5 Gy (lung V_5), the highest value was obtained with VMAT (P<0.05), whereas for lung V_{30} and heart V_{30}, the VMAT and IMRT techniques were found to be better compared with 3D-CRT and h-IMRT (P<0.05). For esophagus V_{50}, the maximal dose (D_{max}) and mean dose for the IMRT technique displayed the best results (P<0.05), and in the case of the spinal cord, the D_{max} with VMAT showed a significant advantage over the other techniques (P<0.05). The treatment monitor units (MUs) in IMRT were found to be the largest (P<0.05), whereas the treatment time with VMAT was the shortest (P<0.05). For smaller PTVs, VMAT was the technique that provided the optimal dose distribution and sparing of the heart. Compared with 3D-CRT alone, adding 20% IMRT to the 3D-CRT base plan was shown to improve the plan quality, and IMRT and VMAT, as techniques, had better dose coverage and sparing of OARs. Furthermore, for patients in whom the lung V5 could be kept low enough, VMAT potentially offered a good alternative to the technique to IMRT, thereby offering additional possibilities for sparing of other OARs, and decreasing the MUs and treatment time.

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Introduction

To date, lung cancer is the tumor type that is most likely to be diagnosed, and it is also responsible for the largest proportion of cancer-associated deaths worldwide. In one single year (2020), ~200 million new cases of lung cancer and 180 million associated deaths were reported (1). Among all the new cases of lung cancer, non-small cell lung cancer (NSCLC) cases comprise the largest percentage (~85%). In the early stages, this disease may present with no symptoms, and so the majority of patients are not diagnosed until they have progressed to the advanced stages. The standard method of care for these patients is concurrent chemoradiotherapy, and when applying this method, the local control rate is typically observed to be in the order of 50-60% (2,3).

The effectiveness of radiation therapy is determined by the absorbed dose in the planning target volume (PTV) and the organ at risk (OAR). In an ideal situation, the higher the dose that is received by the PTV, and the lower the dose received by the OAR, the better. A previously published study demonstrated that a higher radiation dose intensity (>40 Gy) was associated with improved survival time for patients with metastatic disease (4). However, there is a defined limit for the dose of radiation that the OARs can receive, and these limits restrict the doses that can be applied for the PTV; therefore, it is of great importance to find an appropriate radiotherapy technique that will increase the dose associated with the PTV, while decreasing the dose for the OAR.

The effectiveness of radiation therapy has gradually improved, as the technology has shifted from two-dimensional to three-dimensional (3D) accurate radiation therapy. 3D conformal radiation therapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) now represent the two most accurate radiotherapy techniques (5,6). Numerous studies have been published that have evaluated the advantages of using IMRT over 3D-CRT, in particular with respect to: i) Improving the homogeneity index (HI) and conformity index (CI) of the PTV;

and ii) decreasing the absorbed dose in OARs (7-10). However, the disadvantages of using IMRT should be borne in mind; its increased treatment time may contribute to uncertainties in the prescribed treatment position, which may result in dose changes in PTV. For example, a 'low-dose bath' was shown to increase the risk of lethal pneumonitis (11). In 2008, a new form of IMRT was proposed by Otto (12), termed volumetric modulated arc radiotherapy (VMAT). The biggest difference from fixed-field IMRT is that, with VMAT, it is possible to coordinate the dose rate, multileaf collimator movement and gantry rotation at the same time. Apart from these advantages, VMAT has also been shown to achieve an improved dose distribution with decreasing treatment time in numerous types of cancer (e.g., in prostate, locally advanced lung carcinoma and various head and neck cancer applications) (13-17). The hybrid-IMRT (h-IMRT) technique, which is discussed in the present study, comprises a combination of 3D-CRT and IMRT, and a previous study has suggested that this technique can improve the plan quality when an appropriate ratio between the use of 3D-CRT and IMRT is set; in the study, the conventional component consisted of a nominal fraction dose of 1.8 Gy; the IMRT component consisted of a nominal 0.2 Gy per fraction, and in this ratio, compared to 3D-CRT, using the h-IMRT technique can improve the PTV coverage and avoid hot spots (18).

Although all four methods are able to achieve the necessary objectives for PTV and OAR, when it comes to considering which method is the most optimal technique for NSCLC, no unanimous consensus has been reached. Therefore, the present study performed upon a dosimetric comparison of the four techniques, aiming to determine the following: i) Whether adding 20% IMRT to the 3D-CRT base plan (3D-CRT:IMRT ratio, 4:1) leads to any improvement in the plan quality; and ii) to identify the optimal technique for patients with NSCLC (and the subgroup patients), through evaluating the dose parameters [CI, HI, dose histogram volume (DVH) of the OARs and the treatment monitor units (MUs)] of these four techniques, so as to make the best of current radiation resources.

Patients and methods

Patients' general characteristics. Between January 2017 and October 2021, 40 patients with histologically or cytologically confirmed NSCLC who were scheduled for radiotherapy were selected at our radiotherapy center (Radiotherapy Center of The First Affiliated Hospital of Yangtze University, Jingzhou, China). The inclusion criteria were as follows: i) Non-small-cell lung cancer confirmed by histology or cytology; ii) existence of measurable lesions according to the Response Evaluation Criteria in Solid Tumors (19); iii) the patients were either inoperable or did not wish to have surgery; iv) patients were in stage III based on the TNM classification (20). Exclusion criteria were as follows: i) Lung carcinoid or small cell lung cancer; ii) patients with any distant metastasis. The scheme of therapy selected for them was radical radiotherapy or combined chemoradiotherapy.

Computed tomography (CT) simulation. All patients were fixed in place with an integrated carbon fiber board and thermoplastic phantom or vacuum air cushion. Both of the patient's hands were placed on the arm-fixing device in a headfirst supine position. After intravenous injection of the contrast enhancer (100 ml iodopanol injection), all patients were scanned in free breathing mode using Philips Brilliance 16 simulation CT (Philips Medical Systems, Inc.). No special measures were taken to control the target movement caused by respiratory movement. The scanning range for each patient included the whole neck, chest and upper abdomen, and the layer thickness was 5 mm. The simulated positioning CT images obtained were subsequently transmitted to the treatment planning system used for planning design.

Target and contouring of the OARs. Experienced doctors who had positions at Deputy Director level or higher in the hospital outlined the target and OARs. The doctors outlined the tumor target volume in a Varian Eclipse™ 15.6 planning system (Varian Medical Systems), according to the requirements of the International Commission Radiological Units 83 report (21). The gross tumor volume (GTV) was defined as the primary tumor and clinical positive lymph nodes. Clinical positive lymph nodes themselves were defined as lymph nodes with a diameter ≥1 cm on the CT scan, or lymph nodes observed to have high metabolic activity on positron emission-CT. The clinical target volume (CTV) generally refers to a 1.5-cm margin in the head-foot direction and a 1-cm margin in other directions on the basis of the GTV. Considering the patient's respiratory movement during treatment and allowing for the positioning errors and other factors, 0.8 cm was used on the basis of the CTV to form a PTV. The OARs in the present study included the left lung, right lung, esophagus, heart and spinal cord.

Requirement of target volume and the constraints of OARs. A margin of 0.5 cm on the spinal cord formed the planning OAR volume (PRV) for the spinal cord. The dose limits for the bilateral lungs were as follows: Mean lung dose (MLD) <20 Gy, percentage of lung volume receiving a dose >20 Gy (V_{20}) <30%, or V_{20}<35%, V_{30}<20% and V_5<60% (22). Regarding the other OARs, the spinal cord limits were as follows: Spinal cord PRV maximal dose (D_{max}) <45 Gy (23). The esophageal limits were as follows: Mean esophagus dose (MED) <34 Gy, V_{45}<40% and D_{max}<110% prescription dose (PD). The cardiac dose limits were as follows: D_{max}<55 Gy, D_{max}<105% PD when overlapping with the target, V_{40}<30% and mean heart dose (MHD) <26 Gy (24,25). All patients were administered a PD of 60 Gy in the PTV with 2 Gy/fraction. A total of 95% of the PTV volume would receive at least 95% of the PD. The minimum dose in the target volume was no less than 90% of the PD, and no more than 115% of the PD. 'V_x' here refers to the percentage of X (Gy) dose received by the tissue in the total volume of the tissue.

Planning design. The selection of the radiation field angle in a radiotherapy plan generally follows the following principles: i) Visually, the distance from the radiation source to the PTV is the closest, and the properties of the tissue through which the radiation passes are similar; ii) the incoming ray passes through the stable tissue of the human body (avoiding loose tissue, such as fat tissue with high mobility, so as to prevent positioning errors during the implementation of the plan);

iii) avoiding direct irradiation of OARs close to the PTV; and iv) avoiding passing through substances with large atomic number (such as metal buckles or prosthetic devices). If the CI or HI of the radiotherapy plan is reduced under the above conditions, or the clinical dose requirements cannot be well met, the angle of the radiation field should be adjusted to meet the clinical requirements. In order to avoid skin toxicity, it is best to try to ensure that there is no crossing over between each field, and that the proportion of the radiation field that directly passes through the OARs is as small as possible.

All four radiotherapy plans utilized in the present study were designed by senior radiotherapy physicists utilizing the Eclipse™ Treatment Planning System (Varian Medical Systems) with 6 MV of energy. Concerning the specific arrangement of the radiation fields, the first plan design, i.e., the 3D-CRT radiotherapy plan design, usually used 3-5 radiation fields, and the angle of the radiation field was close to the tumor location. Following the above principles, it was possible to improve the CI and HI of the target volume by adjusting the weight of the radiation field while avoiding hot spots and cold spots. Concerning the second plan, the IMRT radiotherapy plan design used five radiation fields, and repeated optimization was performed through appropriate optimization conditions, so as to obtain a radiotherapy plan suitable for clinical use. The third plan included in this study was the hybrid plan of 3D-CRT and IMRT, in which the proportion of 3D-CRT was 80%, and therefore, the proportion of IMRT was 20%. After the 3D-CRT radiotherapy plan had been formulated, it was regarded as the base dose plan. On this basis, the IMRT field was arranged and optimized. Generally, in the hybrid field plan, the IMRT plan has three fields. Finally, the fourth plan was the VMAT plan with a single full arc or double half arc. The choice of arc depended on the location of the tumor. The angle of the collimator was fixed at 20 or 340˚, and the optimization conditions were consistent with those of the second plan (i.e., the IMRT radiotherapy plan). By repeating the optimization process, it was possible to finally obtain a radiotherapy plan that met all the patients' clinical needs.

Plan evaluation. The PTV and OAR parameter values were obtained from the DVH. The parameters of V_{98}, V_2 and V_{50} were selected, as the HI values could be calculated according to these indexes, and the accompanying formula was $HI=(D_{2\%}-D_{98\%})/D_{50\%}$ (26); the lower the value for HI, the better. Subsequently, the CI values were calculated. The calculation formula was as follows: $CI=(V_{ROI,PD})^2/(V_{ROI} \times V_{body,PD})$ (27), where $V_{ROI,PD}$ is the volume of PTV covered by the PD, V_{ROI} is the volume of PTV and $V_{body,PD}$ is the total volume covered by the PD. The higher the value of CI (i.e., the closer it is to 1), the better. The evaluation parameters of OARs were as follows: Total lung mean dose ($D_{mean)}$, V_5, V_{13}, V_{20} and V_{30}; ipsilateral lung D_{mean}, V_5, V_{13}, V_{20} and V_{30}; contralateral lung D_{mean}, V_5, V_{13}, V_{20} and V_{30}; spinal cord D_{max}; heart D_{mean}, V_{30}, V_{40} and V_{45}; and esophagus D_{mean}, D_{max} and $V_{50.}$

Each radiotherapy plan recorded the final treatment MUs and execution time. The execution time refers to the time from the moment when the patient's position was set up until the completion of the treatment. In the first three treatment methods, the execution time was calculated according to the following calculation method: Gantry rotation time (5.8˚/sec) plus treatment MU time (total MU/10) plus wedge changing time (60 sec for each replacement). According to the actual evaluation, the treatment time according to the VMAT plan was ~120 sec, and so all VMAT plans were fixed for 120 sec and then compared with other radiotherapy methods.

Table I. Patient characteristics.

Characteristic	Value
Sex	
Male	37 (92.5)
Female	3 (7.5)
Age, years	63 (40-81)
Histology	
SCC	28 (70.0)
AC	12 (30.0)
Tumor location	
LL	10 (25.0)
RL	30 (75.0)
T stage	
T1	0 (0.0)
T2	8 (20.0)
T3	8 (20.0)
T4	24 (60.0)
N stage	
N0	4 (10.0)
N1	7 (17.5)
N2	25 (62.5)
N3	4 (10.0)
TNM stage[a]	
IIIA	15 (37.5)
IIIB	25 (62.5)
Tumor size, cm^3	315.6 (114.2-429.1)
Lung volume, cm^3	3150.8 (1552.0-4797.0)

[a]8th edition of the American Joint Committee on Cancer. Values are expressed as n (%) or median (range). SCC, squamous cell carcinoma; AC, adenocarcinoma; LL, left lobe; RL, right lobe.

Statistical analysis. SPSS version 25 statistical software (IBM Corp.) was used for the statistical analysis, and all data are expressed as the mean ± standard deviation. One-way ANOVA was used to compare the four radiotherapy plans. When statistical significance had been reached, Tukey's Honestly Significant Difference method was used for post hoc analysis and pairwise comparisons. All P-values displayed are bidirectional. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' clinical data. Table I shows the basic characteristics of the 40 enrolled patients. The median age of the patients was 63 years (range, 40-81 years). The median value of the PTV was 315.6 cm^3 (range: 114.2-429.1 cm^3). Fig. 1 shows the DVH

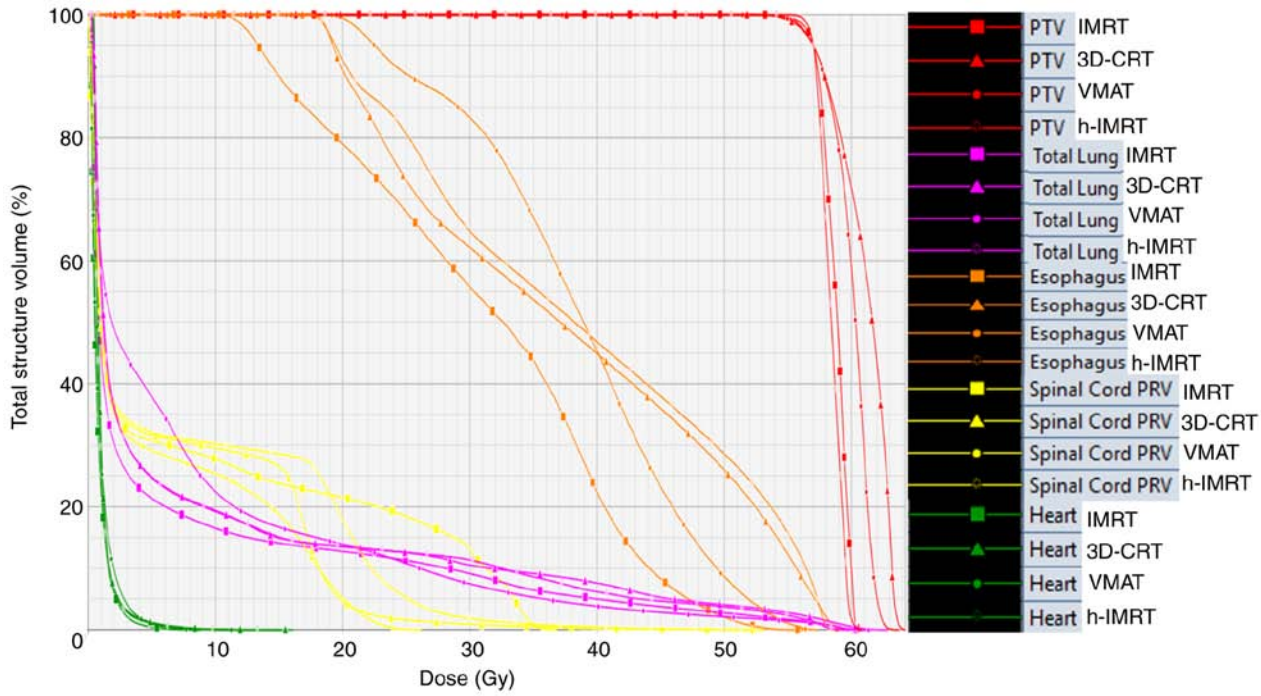

Figure 1. Dose volume histogram comparison for the target coverage and certain organs at risk, including total normal lung, heart, esophagus and spinal cord, in 3D-CRT (triangles), IMRT (squares), h-IMRT (hollow dots) and VMAT (solid dots). The prescription dose was 60 Gy in 30 fractions. 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy; PTV, planning target volume; PRV, planning organ at risk volume; A, 3D-CRT; B, IMRT; C, h-IMRT; D, VMAT.

diagram of a representative patient with stage III NSCLC when using the 3D-CRT, IMRT, h-IMRT and VMAT technologies. Fig. 2 shows the isodose range of 5, 20, 30, 57 and 60 Gy for the same patient using the 3D-CRT, IMRT, h-IMRT and VMAT technologies in cross-section, coronal plane and sagittal plane, respectively.

Comparison of the four radiotherapy plans in all patients. In terms of the average dose of PTV, the 3D-CRT radiotherapy plan had the highest value (P<0.05); those of the h-IMRT and VMAT techniques were similar (P>0.05), with IMRT ranking last (P<0.05) (Table II). However, in terms of the CI, VMAT was found to have the highest value, followed by IMRT, h-IMRT and finally 3D-CRT (Fig. 3). Significant differences in the CI value were identified among the four techniques (P<0.05), as shown in Tables II and III. With respect to the HI, h-IMRT was the technique found to have the lowest value, and the HI increased sequentially in the order IMRT, VMAT and 3D-CRT (which had the highest HI value) (Fig. 3). Similarly, as shown in Tables II and III, significant differences in the HI value were identified among the four techniques (P<0.05).

In terms of the OARs, total lung V_5 in VMAT was statistically significant compared with the other three radiotherapy plans (P<0.05). For total lung V_{30}, IMRT and VMAT were found to be better as techniques than the use of 3D-CRT and h-IMRT (P<0.05), while in terms of the mean dose to the total lung, no significant differences existed in these four techniques (P>0.05). In the comparisons of cardiac dose, the V_{30} value decreased in VMAT, and this decrease was shown to be statistically significant compared with 3D-CRT and IMRT (P<0.05). By contrast, with heart V_{40} and V_{45}, IMRT and VMAT were found to have lower values compared with 3D-CRT and h-IMRT (P<0.05); the difference between the two pairs was not found to be statistically significant (P>0.05). In terms of the mean dose, VMAT and IMRT had lower values compared with h-IMRT and 3D-CRT, although these differences did not reach the level of statistical significance (P>0.05). The difference between the two pairs was also not found to be statistically significant (P>0.05). In terms of esophageal radiotherapy, no statistically significant differences were found with regard to D_{max} and V_{50}, although VMAT was identified as the technique with higher average dose than IMRT (P<0.05). In the spinal cord, D_{max} was found to have the lowest value with the VMAT technology (P<0.05); these findings are summarized in Tables II and III.

There were, however, significant differences identified in terms of the MUs and treatment times (P<0.05). IMRT was found to have the highest value in terms of the MU (P<0.05), followed sequentially (in decreasing order) by h-IMRT, VMAT and 3D-CRT (the technique with the lowest MU) (P<0.05). In terms of the treatment time, VMAT was the technique with the shortest time (P<0.05), followed by IMRT, 3D-CRT and h-IMRT (with the longest treatment time) (P<0.05). These data are summarized in Table IV.

Comparison of the radiotherapy plans in their respective subgroups. The radiotherapy plans were subsequently divided into three subgroups, according to the type, volume and location of the primary tumors. When the tumor was located on the left, the total lung V_5 was still observed to be the highest when using VMAT as the technique (with the lowest V_{30} value and the highest CI value) (P<0.05), whereas the advantage of using h-IMRT as the technique was seen most clearly in terms of the HI value (P<0.05). VMAT also was advantageous from

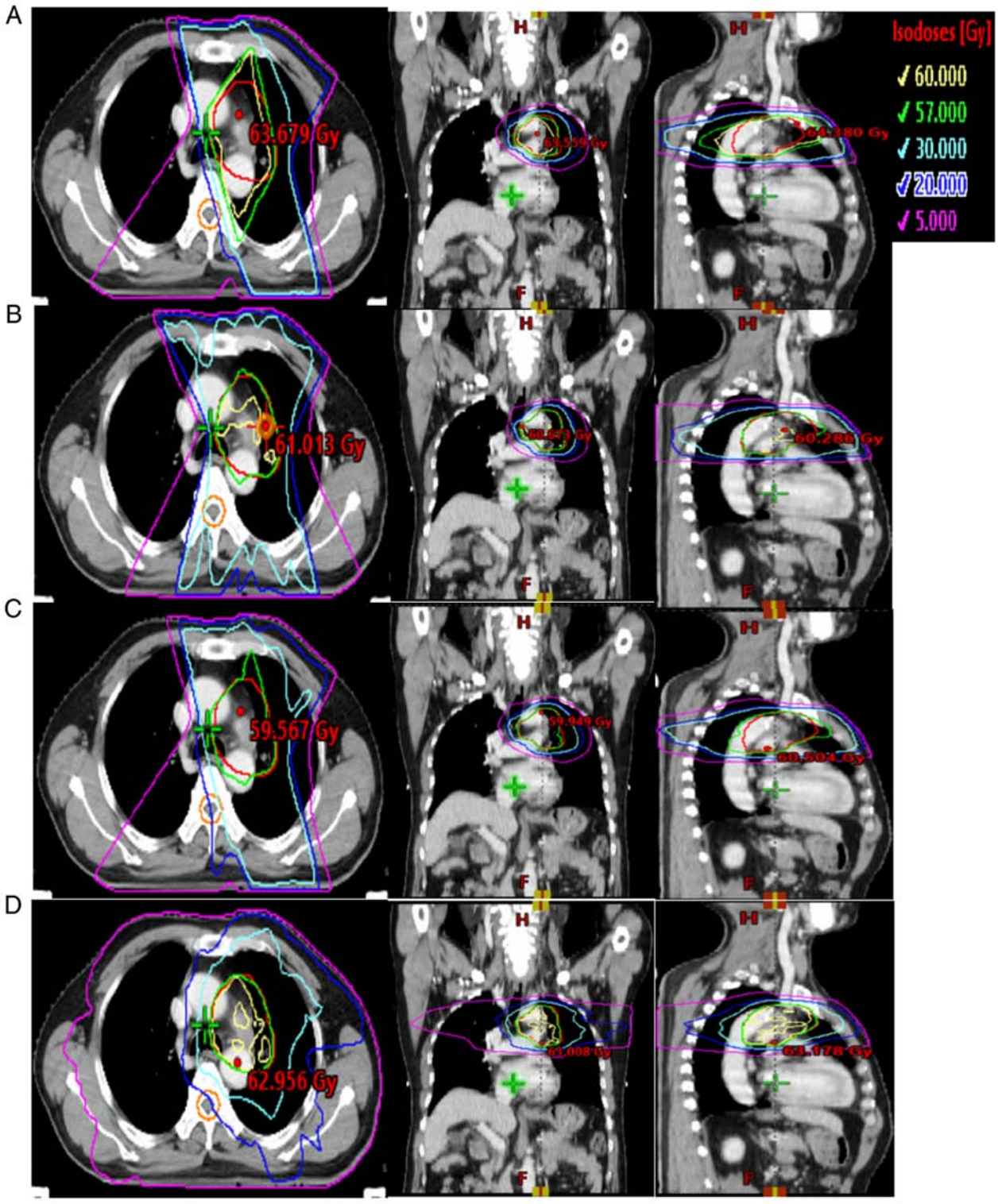

Figure 2. Typical isodose distributions for the four plans for a patient in the same computed tomography slice. (A) Three-dimensional conformal radiation therapy, (B) intensity-modulated radiation therapy, (C) hybrid intensity-modulated radiation therapy and (D) volumetric-modulated arc therapy. The red, blue, cyan, green and yellow lines represent the dose curves of 5, 20, 30, 57 and 60 Gy (i.e., the prescription doses), respectively.

the perspective of the V_{40} and V_{45} parameters in the heart. When the tumor was located on the right side, the MLD was higher for the 3D-CRT and h-IMRT techniques, although not statistically significant (P>0.05), while the lowest V_{30} value was identified for VMAT (P<0.05). In terms of cardiac dose, the V_{30} value was also found to be advantageous with VMAT (P<0.05), as shown in Table V.

In central lung cancer, for the spinal cord, VMAT was the technique associated with the lowest D_{max} value (P<0.05). No significant differences in D_{max} were identified in the esophagus (P>0.05), although VMAT was the technique that had the highest mean dose (P<0.05). In peripheral lung cancer, no significant differences were identified comparing between VMAT and IMRT in terms of CI (P>0.05), although this

Table II. Dose-volume histogram parameters for PTV and OARs according to the radiotherapy techniques applied for all the patients with non-small cell lung cancer.

Dosimetric parameter	3D-CRT	IMRT	h-IMRT	VMAT	P-value
PTV					
CI	0.480±0.099	0.805±0.057	0.565±0.113	0.876±0.030	<0.001
HI	0.130±0.020	0.085±0.025	0.058±0.016	0.093±0.019	<0.001
D_{98}, Gy	55.73±0.33	55.94±0.69	57.38±0.85	55.99±0.27	<0.001
D_2, Gy	63.65±1.17	61.00±1.15	60.82±0.78	61.56±1.00	<0.001
D_{mean}, Gy	60.65±0.82	59.16±0.74	59.50±0.62	59.54±0.65	<0.001
OAR					
Normal lung					
V_5, %	36.13±9.35	35.10±9.23	36.69±9.27	51.64±10.78	<0.001
V_{13}, %	25.82±7.57	25.33±6.98	25.89±7.45	27.70±6.99	0.346
V_{20}, %	21.21±7.30	20.97±6.04	21.09±7.28	20.27±6.02	0.887
V_{30}, %	17.59±6.53	14.57±5.17	17.70±6.45	12.82±4.75	<0.001
MLD, Gy	12.38±3.75	10.77±2.94	14.14±14.29	11.81±2.92	0.142
Heart					
V_{30}, %	17.45±14.89	14.31±12.31	17.67±14.72	9.88±11.52	0.009
V_{40}, %	14.65±12.97	7.35±7.30	13.57±11.82	4.90±5.32	<0.001
V_{45}, %	11.37±9.97	5.24±5.74	9.78±9.33	3.50±3.87	<0.001
MHD, Gy	13.57±8.61	10.59±7.09	12.74±8.61	10.23±6.57	0.072
Esophagus					
V_{50}, %	16.62±23.81	8.56±16.05	15.93±23.08	11.71±18.20	0.143
D_{max}, Gy	45.25±19.90	42.43±20.45	44.62±19.36	47.35±15.05	0.600
MED, Gy	21.70±15.14	19.28±13.19	22.35±14.60	26.64±10.68	0.042
Spinal cord					
D_{max}, Gy	38.85±12.90	36.02±9.51	38.63±11.95	32.79±9.97	0.017

Values are expressed as the mean ± standard deviation. PTV, planning target volume; OAR, organ at risk; CI, conformity index; HI, heterogeneity index; D_{98}, radiation doses delivered to 98% of the PTV; D_2, radiation doses delivered to 2% of the PTV; D_{mean}, mean dose; MLD, mean lung dose; MHD, mean heart dose; D_{max}, maximum dose; MED, mean esophagus dose; V_x, percentage of X (Gy) dose received by the tissue in the total volume of the tissue; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy.

pair of techniques was better compared with the other two radiotherapy methods (P<0.05). VMAT and IMRT showed great advantages in terms of the cardiac dose, as shown in Table VI. When the tumor volume was large, the value for lung V_5 was highest for VMAT (P<0.05), although the V_{13} value was found not to be statistically significant (P>0.05). In terms of the cardiac dose, for V_{40}, VMAT and IMRT were shown to be more effective as techniques compared with the others (P<0.05). When the tumor volume was small, the lung V_{30} was found to be the lowest with VMAT (P<0.05), although no statistically significant differences were identified in terms of the MLD (P>0.05). For the spinal cord, the D_{max} values for the VMAT technique were lower compared with those for 3D-CRT and h-IMRT, (P<0.05), as shown in Table VII.

Discussion

The present study compared the dosimetric characteristics and treatment efficiencies of four radiotherapy techniques in patients with stage III NSCLC (and its subgroups). To date, and to the best of our knowledge, this study is the first to have examined the application of 3D-CRT, IMRT, h-IMRT and VMAT in stage III NSCLC and its subgroups. Based on the findings of the study, it was clear that all four techniques were capable of meeting their clinical objectives, although each technique had its own specific characteristics. The main findings to be derived from the dosimetric comparisons among these four radiotherapy techniques were as follows: i) Compared with 3D-CRT alone, adding 20% IMRT to the 3D-CRT base plan led to an improvement in both CI and HI, with increased MUs and treatment time as a tradeoff; ii) compared with 3D-CRT and h-IMRT, additional OAR sparing was possible with IMRT and VMAT; and iii) VMAT is comparable with IMRT in numerous respects, although it possessed an improved conformal coverage, with lower MUs and a shorter treatment time.

Guillemin *et al* (28) found that, in NSCLC radiotherapy treatment, compared with 3D-CRT as a technique, IMRT could improve the coverage of PTV without increasing the dose to OARs, and when the numbers of patients with dysphagia were counted following radiotherapy, that in the IMRT arm was significantly decreased. The present results were found

Table III. Comparison of the P-values of the dose-volume histogram parameters for the PTV according to the four radiotherapy techniques for all the patients with non-small cell lung cancer.

	P-values of subgroup comparisons[a]					
Dosimetric parameters	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
PTV						
CI	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HI	<0.001	<0.001	<0.001	<0.001	0.161	<0.001
D_{98}, Gy	0.249	<0.001	0.048	<0.001	0.967	<0.001
D_2, Gy	<0.001	<0.001	<0.001	0.804	0.025	0.001
D_{mean}, Gy	<0.001	<0.001	<0.001	0.061	0.030	0.993
OAR						
Normal lung						
V_5, %	0.945	0.990	<0.001	0.827	<0.001	<0.001
V_{13}, %	0.985	>0.999	0.536	0.977	0.326	0.567
V_{20}, %	0.998	>0.999	0.885	>0.999	0.949	0.920
V_{30}, %	0.036	>0.999	<0.001	0.027	0.394	0.015
MLD, Gy	0.694	0.631	0.980	0.480	0.895	0.391
Heart						
V_{30}, %	0.618	>0.999	0.020	0.564	0.321	0.015
V_{40}, %	0.001	0.941	<0.001	0.007	0.572	<0.001
V_{45}, %	<0.001	0.702	<0.001	0.012	0.638	<0.001
MHD, Gy	0.194	0.946	0.045	0.475	0.995	0.337
Esophagus						
V_{50}, %	0.178	0.998	0.602	0.247	0.856	0.710
D_{max}, Gy	0.864	0.998	0.939	0.930	0.528	0.876
MED, Gy	0.789	0.994	0.231	0.639	0.026	0.355
Spinal cord						
D_{max}, Gy	0.556	>0.999	0.027	0.620	0.438	0.036

[a]The three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, hybrid intensity-modulated radiation therapy and volumetric-modulated arc therapy groups are represented by numbers 1-4, respectively, in the subgroup analysis. PTV, planning target volume; OAR, organ at risk; CI, conformity index; HI, heterogeneity index; D_{98}, radiation doses delivered to 98% of the PTV; D_2, radiation doses delivered to v% of the PTV; D_{mean}, mean dose; MLD, mean lung dose; MHD, mean heart dose; D_{max}, max dose; MED, mean esophagus dose; V_x, percentage of X (Gy) dose received by the tissue in the total volume of the tissue.

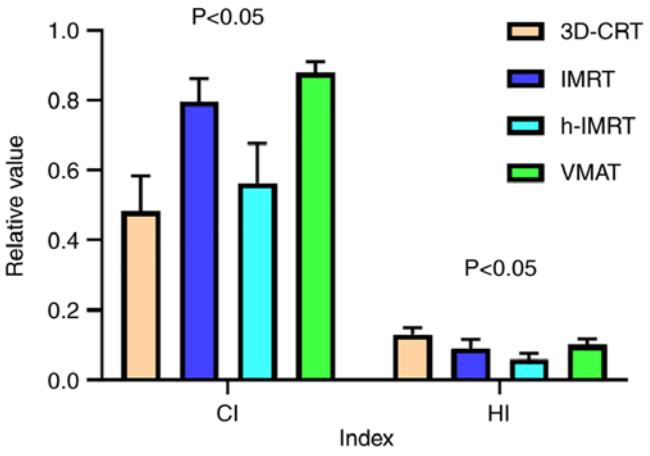

Figure 3. Comparison of CI and HI of planning target volume among the four radiation techniques in all the patients with stage III non-small cell lung cancer. CI, conformal index; HI, homogeneity index; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy.

to be similar to this previous study, as in the present study, compared with those for 3D-CRT, the CI and HI values in the PTV of IMRT were improved, and the lung V_{30}, heart V_{40} and MHD parameters were significantly decreased. This led to the conclusion that, at our radiotherapy center, IMRT was superior to 3D-CRT as a technique in terms of decreasing the risk of developing dysphagia. Peng *et al* (29) conducted a clinical trial in 3,872 patients with stage III NSCLC to compare their survival outcomes when using 3D-CRT, IMRT and VMAT, and it was concluded that: i) Survival is not compromised in patients using IMRT or VMAT; and ii) given their dosimetric advantages (e.g., in improving the conformality of high-dose regions), IMRT and VMAT would be recommended for treating patients with stage III NSCLC. According to these findings, the present study attempted to identify the optimal technique for performing optimal dosimetrics in patients with stage III NSCLC at our radiotherapy center.

Jang *et al* (30) conducted dosimetric comparisons between 3D-CRT and IMRT in 31 lung tumors, and found that lung dose

Table IV. Treatment time and MU comparison according to the radiotherapy techniques in all the patients with non-small cell lung cancer.

			P-values of MUs/treatment time comparisons[a]				
Technology	MUs	Treatment time, sec	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
3D-CRT	367.62±47.73	216.56±4.77	<0.001/<0.001	<0.001/<0.001	0.002/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001
IMRT	658.76±163.39	201.12±16.34	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001
h-IMRT	533.36±51.95	258.92±5.19	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001
VMAT	433.19±59.31	120.00±0.00	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001	<0.001/<0.001

[a]The 3D-CRT, IMRT, h-IMRT and VMAT groups are represented by numbers 1-4, respectively, in the subgroup analysis. Values are expressed as the mean ± standard deviation. MUs, monitor units; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy

differences between these two techniques were mainly associated with the size of the PTV, rather than location-associated parameters. In the present study, all the patients were divided into 3 subgroups according to the size of the PTV, the location of the tumors and the tumor type. Livingston *et al* (31) found that, among 15 patients with larger PTVs (mean PTV size, 501 cm^3) compared with 3D-CRT, V_{20} and V_5 were reduced by IMRT to 3.3 and 6.4%, respectively. The MLD could be reduced by 1.4 Gy, whereas in 15 patients with smaller PTV (mean PTV size, 168 cm^3), the differences in the dosimetric parameters were not found to be significant. In the present study, in the group with a larger PTV, it was found that when comparing IMRT with 3D-CRT, a decrease of only 1.7% was observed for lung V_{20} with IMRT, while V_5 only decreased by 1.1%. The MLD was reduced by 1.77 Gy, which was different from the results identified in previous studies. The main reason for this difference may be the different definitions of larger and smaller tumors; for example, Livingston *et al* (31) set 501 cm^3 for the cutoff, whereas the cutoff was set to 310.5 cm^3 in the present study. In a study by Xu *et al* (7), all the patients were divided into several groups according to the patients' characteristics. The study found that VMAT had improved CI and HI values compared with IMRT when the tumor was located in the center; however, when the tumor was peripherally located, no statistically significant differences in the OARs (lung, heart, spinal cord and esophagus) were observed among the three techniques, although VMAT was still slightly better than IMRT in terms of the CI and HI. In the present study, in central lung cancer, VMAT was shown to be better than IMRT in terms of the CI, but it was not as good as IMRT with respect to HI. In peripheral lung cancer, VMAT was also better than IMRT in terms of CI, but no statistically significant differences were identified between the two techniques in terms of HI. The reason for these differences, when comparing the present study with that by Xu *et al* (7), may be that the proportions of patients with peripheral lung cancer and central lung cancer were different. Among the patients enrolled in the present study, there were 8 patients with peripheral lung cancer and 32 with central lung cancer, whereas in the study by Xu *et al* (7), the total number of patients enrolled was only 30, and the proportions with peripheral lung cancer or central lung cancer were unknown. Li *et al* (13), when studying the application of VMAT and IMRT in peripheral lung cancer and central lung cancer, respectively, found that different types of patients required different radiotherapy techniques. In peripheral lung cancer, the V_5 value was found to be lower in half-arc VMAT compared with that in IMRT, and the V_{30} in IMRT was lower compared with that in VMAT. In central lung cancer with a PTV that did not include the mediastinum, increased values for CI and HI were observed with single-arc VMAT compared with the values with IMRT, and V_{30} and V_5 were found to be lower with VMAT compared with those with IMRT. In central lung cancer with PTV including the mediastinum, the CI and HI parameters were improved when using two-half-arc VMAT, but when using double-half-arc VMAT, the V_{30} and V_5 values were higher compared with those when using IMRT. The results from the present study showed that there were no significant differences in the V_{30} value comparing between the two radiotherapy techniques (VMAT and IMRT) whether central or peripheral lung cancer was under consideration,

Table V. Organs-at-risk dose parameters according to the radiotherapy techniques in the left lung and right lung of patients with non-small cell lung cancer.

A, Left

Dosimetric parameter	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
PTV										
CI	0.499±0.104	0.797±0.060	0.585±0.112	0.869±0.022	<0.001	0.020	<0.001	<0.001	0.045	<0.001
HI	0.129±0.015	0.090±0.027	0.055±0.016	0.092±0.019	<0.001	<0.001	<0.001	<0.001	0.993	<0.001
Lung										
V_5, %	32.25±7.60	30.05±7.85	33.15±7.82	47.62±10.44	0.875	0.990	<0.001	0.712	<0.001	<0.001
V_{30}, %	15.60±4.99	13.31±4.37	15.74±4.89	11.73±4.63	0.496	>0.999	0.043	0.446	0.763	0.043
Heart										
V_{40}, %	14.88±16.26	8.89±10.19	14.21±15.57	5.15±6.08	0.286	0.999	0.048	0.618	0.827	0.126
V_{45}, %	11.58±13.23	6.78±8.42	11.36±12.84	3.64±4.08	0.254	0.950	0.038	0.501	0.579	0.084

B, Right

Dosimetric parameter	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Lung										
MLD, Gy	12.98±3.89	11.34±2.90	15.56±17.02	12.22±2.87	0.859	0.605	0.983	0.183	0.975	0.379
V_{30}, %	18.50±7.00	15.15±5.45	18.61±6.92	13.32±4.78	0.048	>0.999	0.002	0.038	0.572	0.002
Heart										
V_{30}, %	17.09±12.97	13.64±10.44	17.36±12.62	10.09±12.43	0.614	0.554	0.048	0.554	0.592	0.040

[a]The 3D-CRT, IMRT, h-IMRT and VMAT groups are represented by numbers 1-4, respectively, in the subgroup analysis. Values are expressed as the mean ± standard deviation. CI, conformity index; HI, heterogeneity index; MLD, mean lung dose; PTV, planning target volume; V_x, percentage of X (Gy) dose received by the tissue in the total volume of the tissue; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy.

whereas VMAT was always found to be better than IMRT in terms of the V_5 value. The study by Li *et al* (13) did classify central lung cancer again, i.e., i) a PTV that did not include the mediastinum; ii) a PTV that included the mediastinum, which may provide the reason for the different results.

In the RTOG 0617 trial, albeit with some caveats, the survival benefits were offset by the toxicities associated with the chemoradiation. In the trial, a dose of 60 Gy was found to be superior to 74 Gy in terms of the survival rate (32). Cardiac injury, pneumonia, esophagitis and myelitis caused by radiation therapy may be the most important causes underlying this phenomenon.

Radiation pneumonia is an important factor that threatens the prognosis of patients with stage III NSCLC. Patients with severe radiation pneumonia are not usually responsive to strict antibacterial treatment, respiratory support treatment or high-dose corticosteroid treatment. Pneumonia-associated deaths may provide the main reason for the poor efficacy of radiotherapy in patients with stage III lung cancer (33). In conventional fractionated radiotherapy, dosimetric parameters have been used to predict the probability of pneumonia to a certain extent. In order to limit the incidence of pneumonia, a number of researchers have put forward their own views on the lung dose limit for radiotherapy (34-36). Grambozov *et al* (37) found that radiotherapy for stage III NSCLC led to a decline in pulmonary function (PF). The study concluded that patients with a total lung V_{20} <21% were at a low risk of PF decrease after high-dose irradiation treatment.

Based on the above studies, the parameters of lung V_5, V_{13}, V_{20}, V_{30} and MLD were selected as the criteria for evaluating the lung dose in the present study. Zhang *et al* (8) found that the lung V_5 and V_{10} values obtained using VMAT were significantly higher compared with those found when using IMRT as the technique. In the present study, lung V_5 was found to be the highest with VMAT, especially for patients with a central tumor type and larger PTV (53.59±10.51 and 55.43±10.8, respectively); however, in peripherally located cancer, this parameter was small (46.06±9.88). Although V_5 was still larger with VMAT than that with the other techniques, its value remained within an acceptable range. Therefore, the actual probability of radiation pneumonia caused by use of the VMAT technique in peripheral lung cancer may be lower than that associated

Table VI. Dose-volume histogram parameters for PTV according to radiotherapy techniques in patients with centrally located and peripherally located non-small cell lung cancer.

A, Central

Dosimetric parameter	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Spinal cord										
D_{max}, Gy	42.12±9.69	38.34±6.74	41.96±8.83	34.93±8.72	0.201	>0.999	0.001	0.237	0.288	0.002
Esophagus										
D_{max}, Gy	51.89±13.86	49.00±16.52	51.09±13.57	52.35±11.50	0.792	0.994	0.999	0.909	0.706	0.977
MED, Gy	24.88±14.51	22.18±13.10	24.75±14.16	29.21±10.31	0.794	>0.999	0.455	0.818	0.038	0.428

B, Peripheral

Dosimetric parameter	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
PTV										
CI	0.508±0.108	0.814±0.050	0.597±0.133	0.873±0.025	<0.001	0.048	<0.001	<0.001	0.324	<0.001
Heart										
V_{30}, %	16.85±13.99	9.55±8.55	16.86±13.68	6.21±6.35	0.217	>0.999	0.042	0.315	0.858	0.042
V_{40}, %	14.24±11.85	4.47±4.91	12.31±9.32	3.14±3.42	0.013	0.922	0.004	0.048	0.972	0.021

[a]The 3D-CRT, IMRT, h-IMRT and VMAT groups are represented by numbers 1-4, respectively, in the subgroup analysis. Values are expressed as the mean ± standard deviation. CI, conformity index; D_{max}, max dose; MED, mean esophagus dose; PTV, planning target volume; V_x, percentage of X (Gy) dose received by the tissue in the total volume of the tissue; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy.

with central tumor type and larger PTV. The advantage of using VMAT over the other three techniques is focused on the medium and high (V_{30}) dose values associated with the total lung and ipsilateral lung, although it must be considered whether it is reasonable to reduce the medium- and high-dose areas in the lung at the expense of increasing the low-dose area in the lung. This question requires further research and discussion. In certain study, it has been shown that the use of IMRT as the technique also leads to an increase in the low-dose area (38). However, in the present study, IMRT, as a technique, was not shown to differ significantly from 3D-CRT or h-IMRT in terms of the total lung V_5. The possible reason for this finding was that the IMRT technology in the present study used the 5-field technique. The more radiation fields that are used, the larger the irradiation area will be. In this way, the low-dose area will inevitably increase; moreover, the present study also aimed to avoid lung tissue while selecting the field angle. At the same time, it was found that, for the total patients, the MLD for h-IMRT was higher compared with that for the other techniques, although not statistically significant, this suggests that the selection of h-IMRT should be made with certain caution in these patients.

In the process of considering the most appropriate radiotherapy treatment for patients with NSCLC, the heart is an organ that requires special attention. Due to the short survival time of patients with stage III lung cancer and the late occurrence of radiation cardiotoxicity, there is a scarcity of data, and few published studies are available on the cardiotoxicity of radiotherapy in such patients. A previous study by Atkins *et al* (39) did find that the mortality of patients increased with an increase of the mean cardiac dose above 10 Gy in patients without statin, but no association between patient mortality and an increase of the mean cardiac dose above 10 Gy was identified in patients who were taking statin. The mean cardiac dose of patients in the present study was >10 Gy in the whole group and in all subgroups, and the mean dose was the highest when using 3D-CRT for the total patients, but lower when using the VMAT and IMRT techniques. Further analysis of each subgroup found that this trend also existed in the subgroup with central lung cancer. Therefore, in terms of the mean cardiac dose, either the VMAT or the IMRT technique appears to be the better option for selection for patients with poor cardiac function. Moreover, in the smaller PTV subgroup, the use of VMAT had a greater potential for reducing the parameter of cardiac V_{30}, suggesting that it may be advantageous to use VMAT in the subgroup with a smaller PTV for the purpose of protecting the heart. Therefore, we consider that if patients have poor cardiac function (such as myocardial infarction and ischemic heart disease), it would be advisable to use VMAT instead of 3D-CRT and h-IMRT, especially for patients with a smaller PTV.

Treatment-associated esophagitis is also a common disease in radiotherapy for lung cancer. Grade 3 and higher

Table VII. Organs at risk dose parameters according to radiotherapy techniques in patients with non-small cell lung cancer of smaller and larger PTV.

A, PTV ≥315.6 cm^3

Dosimetric parameters	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Lung										
V_5, %	38.56±9.71	38.13±10.23	38.92±9.54	55.43±10.83	0.999	0.999	<0.001	0.999	<0.001	<0.001
V_{13}, %	27.95±7.34	27.37±6.98	27.87±7.19	29.99±6.38	0.990	>0.999	0.706	0.993	0.515	0.681
Heart										
V_{40}, %	15.65±14.33	9.04±8.65	14.69±13.50	6.76±6.62	0.048	0.989	0.020	0.257	0.879	0.048

B, PTV <315.6 cm^3

Dosimetric parameters	3D-CRT	IMRT	h-IMRT	VMAT	P-values of subgroup comparisons[a]					
					1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Lung										
V_{30}, %	15.25±6.47	12.56±5.10	15.47±6.60	10.69±4.38	0.315	0.999	0.021	0.247	0.627	0.014
MLD, Gy	12.51±7.61	9.98±6.07	11.87±7.36	9.20±5.53	0.168	0.727	0.072	0.302	0.670	0.146
Heart										
V_{30}, %	16.85±13.33	12.38±10.21	16.91±13.20	6.23±5.42	0.446	>0.999	0.003	0.454	0.089	0.003
Spinal cord										
D_{max}, Gy	38.51±12.56	35.48±9.30	38.28±11.72	31.34±9.95	0.741	>0.999	0.042	0.783	0.511	0.049

[a]The 3D-CRT, IMRT, h-IMRT and VMAT groups are represented by numbers 1-4, respectively, in the subgroup analysis. Values are expressed as the mean ± standard deviation. D_{max}, max dose; PTV, planning target volume; V_x, percentage of X (Gy) dose received by the tissue in the total volume of the tissue; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; h-IMRT, hybrid IMRT; VMAT, volumetric-modulated arc therapy.

radiation-induced esophagitis will have a negative effect on the patients' long-term survival (40). In order to predict the probability of radiation esophagitis, the three parameters of esophageal V_{50}, D_{max} and D_{mean} were selected as the prediction reference values in the present study. Compared with the other techniques, IMRT was associated with a significant reduction in the esophageal V_{50} value. This trend existed in the subgroup with large PTV volume, although no statistically significant differences were identified in the other subgroups. The dose parameter of D_{mean} was found to be the highest with the VMAT technique. This trend was also reflected in the subgroups where the tumor was the central type, and for the larger PTV. Therefore, when considering the treatment strategy for esophageal injury, using IMRT would be the preferred option.

In determining which radiotherapy option would be most suitable for patients with lung cancer, the probability of spinal cord-associated side effects occurring is small; however, spinal cord injuries caused by radiotherapy can be serious. Since the spinal cord is a serial organ, if any part of the spinal cord is irradiated beyond the dose limit, the function of the whole spinal cord will be lost, thereby leading to paralysis (41). On this basis, in the present study, only the parameter D_{max} was selected in order to evaluate the spinal cord dose. None of the four radiotherapy techniques exceeded the maximum dose limit of the spinal cord. Therefore, at least from this analysis, it was possible to conclude that the four radiotherapy techniques were essentially safe to use. On the basis of meeting the spinal cord dose limits, it was found that the VMAT technology was capable of sustaining a reduced spinal cord dose compared with the other techniques for the total patients; looking at the subgroup analysis more specifically, this trend was also found to exist in patients with the tumor located on the right, in those with centrally located lung cancer and in patients with a smaller PTV.

A previous study (42) reported that a significant reduction in the number of MUs helps to minimize the systemic integrated dose, thereby reducing the risk of radiation-induced carcinogenesis and secondary cancer, especially in patients with long-term survival times. In the present study, it was found that IMRT was the technique that was associated with the highest number of MUs, whereas 3D-CRT had the lowest number. Therefore, it is preferable to select a plan featuring a lower number of MUs during radiotherapy for younger patients. However, if other aspects can meet the dose limit, then a plan with fewer MUs would be preferred in order to reduce the probability of a secondary tumor. Treatment time is also an index that is of concern for patients and medical practitioners. Reducing the treatment time would not only improve

the patients' comfort and satisfaction, but it would also reduce the positioning error in treatment. In the present study, it was calculated that the treatment time using the VMAT technique was the shortest, whereas the treatment time using h-IMRT was the longest. Therefore, we consider that, if the patient's physical condition is not good and they cannot tolerate being treated over a long period of time, then VMAT, with its relatively short treatment time and fewer MUs, should be preferred as the treatment option.

However, the present study did have certain limitations. Firstly, this study was only a retrospective study. Secondly, our patient population was relatively small, which may have resulted in an inability to determine efficacies with a high degree of confidence. Finally, in the present study, the planning strategies, optimization algorithms and field angles would all have affected the final dose parameter results. In the process of implementing the aforementioned radiation therapy techniques, if auxiliary equipment could be integrated into the procedures, then the resultant values for the radiation therapy parameters may be improved. For example, during the implementation of chest radiation therapy, deep inspiration breath hold (DIBH) has been shown to have dosimetric advantages in terms of reducing excessive lung exposure and lung risk factors. This method can also reduce cardiac exposure, although, at the same time, it incurs additional costs and is difficult to implement for the patients (43,44). Due to the lack of such equipment at our radiation therapy center, this technology could not be used. Future studies should ideally analyze the application of DIBH in these four radiotherapy techniques.

In conclusion, the present study showed that, compared with use of 3D-CRT alone, adding 20% IMRT to the 3D-CRT base plan can improve the quality of the plan. Compared with 3D-CRT and h-IMRT, using IMRT and VMAT as the treatment options provided better dose coverage and sparing of OARs; moreover, for patients in whom the lung V_5 can be kept low enough, VMAT is a good alternative, offering more possibilities for sparing of other OARs and decreasing the treatment time and MUs.

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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

CL and ZC were responsible for the design and conception of the study. CL, HL, WS, YH and JL collected patient data, analyzed and interpreted the data and collaborated in the discussion. CL prepared the manuscript and ZC revised it critically for important intellectual content. ZC supervised the study. All authors have read and approved the final manuscript. CL, ZC and HL confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

The Ethics Committee of the First Affiliated Hospital of Yangtze University (Jingzhou, China) approved the study (approval no. KY202018). Since this is a retrospective analysis, written consent for participation was not required. All the data relating to the patients was anonymized to protect their privacy. All the methods used were in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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