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Original Research Article

Volumetric-modulated arc therapy as an alternative to intensity-modulated radiotherapy for primary tumors of advanced non–small-cell lung cancer: A multicenter retrospective analysis based on propensity score matching

Jie Liu[1-3], Tao Li[4], Xiaohu Wang[5], Shengfa Su[1,6], Qingsong Li[1,6], Yichao Geng[1,6], Wengang Yang[1,6], Xiaxia Chen[1,6], Weiwei Ouyang[1,6], Wei Zhang[1,2], Bing Lu[1,6]*

[1]Department of Thoracic Oncology, Affiliated Hospital, [2]Teaching and Research Section of Oncology, [3]The Fourth People's Hospital of Guiyang, Guiyang, China, [4]Sichuan Cancer Hospital and Institute, Sichuan, [5]The First Clinical Medical College of Lanzhou University, Gansu Provincial Cancer Hospital, [6]Affiliated Cancer Hospital of Guizhou Medical University, Guizhou, China

For correspondence:* ***Email:* *lbgymaaaa@163.com*

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Abstract

Purpose: *To investigate the effect of volumetric-modulated arc therapy (VMAT) versus intensity-modulated radiotherapy (IMRT) for advanced non–small-cell lung cancer (NSCLC).*
Methods: *Cases in which the primary tumors were treated with IMRT or VMAT as initial intervention in stages III and IV NSCLC patients from September 2008 to March 2020 were retrospectively analyzed. Propensity Score Matching (PSM) was used to assess the efficacy and toxicity of the two radiotherapy techniques.*
Results: *A total of 637 patients were included, out of which 483 cases were treated with IMRT, while 154 received VMAT. A total of 308 patients were selected after PSM. Patients who were having acute radiation esophagitis and pneumonia treated with VMAT had a lower percentage than those treated with IMRT ($p < 0.05$) before PSM. However, there was no significant difference in grades 3 - 4 toxicity ($\chi^2 = 2.77$, $p = 0.096$). There were also no significant differences in the primary endpoints between the two groups after PSM ($p > 0.05$), while for secondary endpoints, all lung V5, and V20, mean lung dose and heart V30, heart V40, mean heart dose in all patients and stage N2 patients in VMAT after PSM were significantly lower than those of IMRT ($p < 0.05$).*
Conclusion: *Radiation therapy of A-NSCLC primary tumors using VMAT and IMRT seem to produce similar efficacy. The volume parameters of normal tissues and organs is significantly lower in VMAT, especially in patients with stage N2. Therefore, VMAT may be more beneficial for reducing radiation damage in normal tissues and organs.*

Keywords: *Non–small-cell lung cancer, Volumetric-modulated arc therapy, Survival, Local progression-free survival, Radiation damage, Dose-volume parameter*

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INTRODUCTION

A lot of studies have shown that chemotherapy and molecular targeted therapy, combined with three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT), can prolong overall survival (OS) [1–4], especially in patients with cancer oligometastases. But two phase II prospective studies confirmed that randomization to 3D-CRT or IMRT for stage IV non–small-cell lung cancer (NSCLC) prolonged survival. The characteristics of 3D-CRT or IMRT were not analyzed [5,6].

A study showed that the cases after chemotherapy combining molecular targeted therapy with no disease progression in oligometastatic NSCLC, which then had SBRT therapy versus drug therapy alone, showed that the PFS and OS were significantly prolonged in patients treated with radiotherapy. However, which radiotherapy technique had better efficacy is still unclear, because the therapy plan was determined by the radiotherapists participating in the study, and there was no choice of radiotherapy technology or divided dose administration [7].

Iyengar *et al* [8] indicated that chemotherapy combined with radiotherapy significantly prolonged PFS in EGFR wild-type stage IV non-small cell lung cancer compared with chemotherapy alone. Although the segmented dose was described in the study, there was no analysis of the use of different three-dimensional radiotherapy modalities. A meta-analysis by Petrelli *et al* [9] confirmed that radiotherapy of primary tumors significantly prolonged OS and PFS.

This study included the analysis of using 3D-CRT, IMRT, SBRT, etc., but also did not have radiotherapy techniques comparison. Advanced NSCLC is characterized by late stage (T3-4 accounts for 64 %, N2-3 accounts for 83 %), large size, spatial diversity, and high primary tumor failure rate [5,10-11].

Studies have shown that improving the primary tumor control rate can prolong survival. In order to improve the primary tumor control rate, this study compared IMRT with Volumetric Modulated Arc Therapy (VMAT), which has more optimized conformation, composite lung V20 and dose monitor unit (MU), and better radiophysical quality assurance [12-14]. The clinical value of VMAT technology was evaluated in the treatment of primary tumors of A-NSCLC by propensity score matching.

METHODS

Inclusion criteria

The case selection criteria were as follows: (1) pathologically diagnosed untreated stage Ⅲ - Ⅳ non-small cell lung cancer patients; (2) between 18 and 80 years old; (3) Karnofsky performance status (KPS) score ≥ 70 %; (4) primary tumor radiation therapy using IMRT or VMAT techniques; (5) primary tumor irradiation total dose ≥ 40 Gy, fractionated dose ≥ 2 Gy; (6) patients with no driver gene mutation received more than 2 cycles of chemotherapy; (7) patients with EGFR-sensitive mutations receive primary recommended treatment; (8) patients have accepted recent efficacy and acute radiation toxicity evaluation; (9) follow-up information is complete. In this study, oligometastases were defined as 1 - 5 distant metastases [15,16].

Approval for this study was received from the institutional ethical committee, and the study followed international guidelines for human studies.

Radiotherapy protocol

A 6-MV X-ray from Elekta Infinity linear accelerator was first selected. Computed tomography was simulated with a 5-mm-layer thickness enhancement scan. The treatment was planned using Pinnacle [14]. The gross tumor volume (GTV) was defined as primary lesion and regional lymph nodes (The single lymph node with a short diameter of ≥ 1.0 cm or at least three lymph nodes with a diameter of ≥ 0.5 cm).

The clinical target volume (CTV) was defined as a three-dimensional expansion of the GTV edge by 0.6 cm and combined with anatomical barriers, and the planning target volume (PTV) was defined as a three-dimensional expansion of the CTV edge by 0.5 to 1 cm. The Pinnacle system [14] was used to complete the radiotherapy plan design. The IMRT of the primary tumor employed four to eight coplanar or non-coplanar fields, and VMAT required two to four arcs. The plan evaluation required that the prescribed dose covered 100 % of the GTV volume; 95 % of the prescribed dose included 95 % or more of the PTV volume for stage III cases, and 90 % of the prescribed dose included 98 % or more of the PTV volume for stage IV patients. In this case mean lung dose (MLD) ≤ 20 Gy and all lung V20 ≤ 32 %. Primary tumor radiotherapy using IMRT or VMAT techniques. The first course of radiotherapy was given in 1.8 - 2 Gy fractions for 5 days a week at a total dose of 36 – 40 Gy, whereas late-course of radiotherapy was

given in 1.5 Gy fractions for 5 days a week at a total dose of 21 – 30 Gy.

Systemic therapy protocol

Platinum-based two-drug combination regimen was used in this study [17]. Platinum drugs refer to cisplatin or carboplatin, and platinum combined with docetaxel, paclitaxel, pemetrexed or vinorelbine were used, 21 - 28 days as a cycle, and 2 - 6 cycles of the treatment. Molecular targeted therapy selects drugs based on the type of sensitive mutations in driver genes.

Evaluation of therapeutic efficacy and acute toxicity

The responses of the primary tumors, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the RECIST 1.1 standard [18]. The CR + PR was defined as response rate (RR), CR + PR + SD was defined as disease control rate (DCR). Radiation damage to the lungs, esophagus, and heart was assessed according to the Radiotherapy Oncology group (RTOG) radiation damage grading criteria.

Outcomes

The primary endpoints were response, local control rate (LCR), local-regional progress-free survival (LRPFS) of primary tumor, acute radiation pneumonitis (RP) and esophagitis (RE). The secondary endpoints were all lung (V5, V20) MLD; heart (V30, V40) MHD; V50 of esophagus, two-years overall survival (OS) and other dose-volume parameters.

Statistical analysis

Statistical tests were done with Statistical Package for the Social Sciences version 26.0 software (Chicago, IL). The PSM characteristics including sex, age, pathological type, T/N/M staging, GTV, primary lesion location, clinical stage, metastasis status, targeted therapy, chemotherapy cycle, prescription dose, and other factors for IMRT and VMAT and the matching tolerance was 0.02. Survival analysis used Kaplan–Meier and log-rank methods; local control rate was calculated by the life table method; and recent measurements, radiation injury, and dose-volume parameters were determined using chi-squared test. *P*-value of 0.05 or less was considered statistically significant.

RESULTS

Clinical characteristics

From September 2008 to March 2020, 637 cases met the case selection criteria. In the study population, the male to female ratio was 2.5:1; the median age was 58 years (range 22 – 79 years); and there were 51, 91, 68, and 427 patients in stages IIIA, IIIB, IIIC, and IV, respectively. Of the 637 cases, 102 cases of driver gene–sensitive mutations were detected before treatment (including 83 cases of *EGFR* mutations and 19 cases of *ALK* mutations), and only 10.20 % of patients received molecular targeted therapy (including Gefitinib in 28 cases, Icotinib in 22 cases, Ositinib in two cases, and Crizotinib in 13 cases), while chemotherapy was used in 89.80 % of the total 637 cases. Before PSM, the proportions of N2–3 and IV stages among IMRT patients was higher than that in VMAT ($p < 0.05$), the radiation therapy dose and GTV were also similar before PSM ($p > 0.05$). After PSM, there were 308 patients (154 pairs) with a median age of 58 years. The clinical baseline conditions of the two groups were similar ($p > 0.05$) Table 1.

Response to radiotherapy with different techniques for primary tumors

Before PSM, the response of treatment with IMRT showed that CR, PR, SD, and PD were 1.7, 69.4, 18.2, and 10.8 %, respectively. The response of treatment with VMAT showed CR, PR, SD, and PD were 1.3, 72.1, 21.4, and 5.2 %, respectively. The RR of IMRT was 71.01 % and RR of VMAT was 73.37 % ($\chi^2 = 1.037$, $P = 0.309$), the DCR of IMRT was 89.23 % and of VMAT was 94.08 % ($\chi^2 = 2.781$, $P = 0.427$). After PSM, the response of treatment with IMRT showed that CR, PR, SD, and PD were 1.3, 72.7, 19.5, and 6.5 %, respectively. The response of treatment with VMAT showed CR, PR, SD, and PD were 1.3, 72.1, 21.4, and 5.2 %, respectively. The RR of IMRT was 72.72% and RR of VMAT was 73.37% (χ^2=1.662, P=0.197), the DCR of IMRT was 93.5% and of VMAT was 94.80% (χ^2=0.370, P=0.197) (Table 2). Before PSM, the 1- year local control rates with IMRT and VMAT were 93.2 % vs. 93.3 %, and the 2-year local control rates with IMRT and VMAT were 76.2 % vs. 86.1 % ($\chi^2 = 0.292$, $P = 0.589$). After PSM, the 1- year local control rates with IMRT and VMAT were 93.50 vs. 93.3 %, and the 2-year local control rates with IMRT and VMAT were 76.1 vs. 86.1 % ($\chi^2 = 0.467$, $P = 0.490$).

Table 1: Clinical characteristics of 637 patients for A-NSCLC with IMRT or VMAT before and after PSM

Variable	Before PSM		*P*-value	After PSM		*P*-value
	IMRT (n = 483)	VMAT (n = 154)		IMRT (n = 154)	VMAT (n = 154)	
Sex (Male/female)	344/139	113/41	0.606	113/41	113/41	1.000
Age (years)	22–79	28–78	0.717	30–77	28–78	0.680
Median age (years)	58	58		58	58	
Pathological type			0.179			0.426
Squamous cell carcinoma	180	64		73	64	
Adenocarcinoma	273	84		74	84	
Other	30	6		7	6	
Primary lesion site			0.404			0.458
Right upper lung	125	43		48	43	
Right middle lung	50	12		17	12	
Right lower lung	87	39		29	39	
Upper left lung	129	34		38	34	
Lower left lung	92	26		22	26	
Gene mutation	54	48	0.857	47	48	0.727
Targeted therapy	50	15	0.827	20	15	0.547
Chemotherapy	433	139	0.260	134	139	0.827
Transfer situation			0.058			0.831
Oligotransfer	302	63		69	63	
Non-oligo transfer	45	17		19	17	
T stage			0.998			0.324
T1–2	160	51		43	51	
T3–4	323	103		111	103	
N stage			0.035			0.874
N0–1	61	10		10	10	
N2	157	53		51	53	
N3	265	91		93	91	
M stage			0.000			0.437
M0	136	74		66	74	
M1a	57	20		17	20	
M1b	203	23		36	23	
M1c	87	37		35	37	
Stage (III/IV)	136/347	74/80	0.000	66/88	74/80	0.491
GTV (cm^3)			0.335			0.104
III	205 ± 185	212 ± 193		216 ± 190	212 ± 193	
IV	224 ± 179	194 ± 169		239 ± 151	194 ± 169	
III+IV	216 ± 181	200 ± 175		228 ± 167	200 ± 175	
Prescribed dose/ median (Gy)	40–76.5/63	40–71/64	0.056	40–76/63	40–71/64	0.190

Table 2: The recent results of IMRT and VMAT before and after PSM in the treatment of primary tumors

Group	Technology	Cases	CR	PR	SD	PD	RR (%)	χ^2	*P*-value	DCR (%)	χ^2	*P*-value
Before PSM	IMRT	483	8	335	88	52	71.01	1.037	0.309	89.23	2.781	0.427
	VMAT	154	2	111	33	8	73.37			94.8		
After PSM	IMRT	154	2	112	30	10	72.72	1.662	0.197	93.50	0.370	0.946
	VMAT	154	2	111	33	8	73.37			94.80		

LRPFS after PSM

The 1- year LPFS with IMRT and VMAT radiotherapy were 67.5 vs. 68.8 %. The 2-year LPFS with IMRT and VMAT radiotherapy were 29.9 vs. 51.2 %, and the median LPFS of IMRT and VMAT was 19 months vs. 29 months respectively (χ^2 = 1.525, *P* = 0.217). Stratified analysis showed that stage III patients under the 1- year LPFS with IMRT and VMAT radiotherapy were 80.3 vs. 73.4 %. The 2-year LPFS with IMRT and VMAT radiotherapy were 42.9 vs. 63.1 % (χ^2 = 0.023, P = 0.880). In stage IV patients, the 1- year LPFS with IMRT and VMAT radiotherapy were 57.9 vs. 65.0 %. The 2-year LPFS with IMRT and VMAT radiotherapy were 20.4 vs. 41.8 % (χ^2 = 2.242, *P* = 0.119), and the median LPFS of IMRT and VMAT was 14 months vs. 18 months, respectively (χ^2 = 2.242, *P* = 0.119) Figure 1 A – C.

The 1- and 2-year OS after PSM

The 1- year OS with IMRT and VMAT radiotherapy were 70.1 vs. 69.9 %, the 2-year OS with IMRT and VMAT radiotherapy were 31.3 vs. 50.1 %, respectively (χ^2 = 1.543, *P* = 0.214). Stratified analysis showed that in stage III patients, the 1- year OS with IMRT and VMAT radiotherapy were 81.8 vs. 74.1 %. The 2-year OS with IMRT and VMAT radiotherapy were 44.7 vs. 67.5 % (χ^2 = 0.076, *P* = 0.782). In stage IV patients, the 1- year OS with IMRT and VMAT radiotherapy were 61.3 vs. 66.4 %, and the 2-year OS with IMRT and VMAT radiotherapy were 21.4 vs. 37.1%, respectively (χ^2 = 2.023, *P* = 0.155) Figure 2 A – C.

RP and RE treated with different techniques

There was no grade 5 damage in the all patients. Before PSM, the incidences of RE and RP in IMRT were 73.70% and 36.02%, which were significantly higher than those in VMAT (P<0.05), but the incidence of grade III-IV RE in IMRT and VMAT were 8.28% vs. 7.14%, RP in IMRT and VMAT were 7.03% vs. 7.79% (χ^2=2.77 P=0.096). There was no significant difference after PSM (Table 3).

IMRT and VMAT dose-volume parameters after PSM

After PSM, the all lung V5, V20, MLD, heart V30, V40 and MHD of patients with N2 stage treated with IMRT technology were higher than those of VMAT ($p < 0.05$). The all lung V5 of patients with IMRT technique was much higher ($p < 0.05$). There was no significant difference in the esophageal V50 of all patients ($p > 0.05$) Table 4.

Table 3: IMRT or VMAT before and after PSM for acute radiation damage

Group	Acute toxicity	IMRT					VMAT					χ^2	*p*-value
		0	*I*	*II*	*III*	*IV*	*0*	*I*	*II*	*III*	*IV*		
Before PSM	RE	127	172	144	40	0	61	54	28	11	0	13.04	.005
	RP	309	110	30	33	1	115	17	10	12	0	10.75	.029
After PSM	RE	60	50	26	18	0	61	54	28	11	0	1.336	.721
	RP	109	21	14	10	0	115	17	10	12	0	0.533	.912

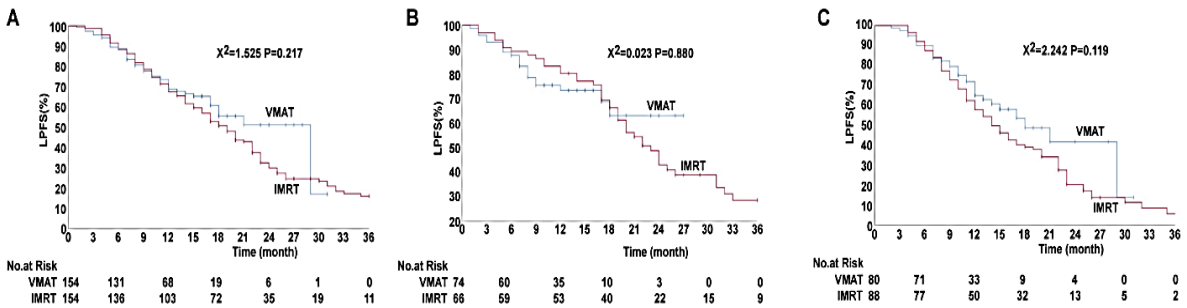

Figure 1: IMRT or VMAT radiotherapy for primary tumor LPFS after PSM. (A) Stages III through IV, (B) stage III, and (C) stage IV

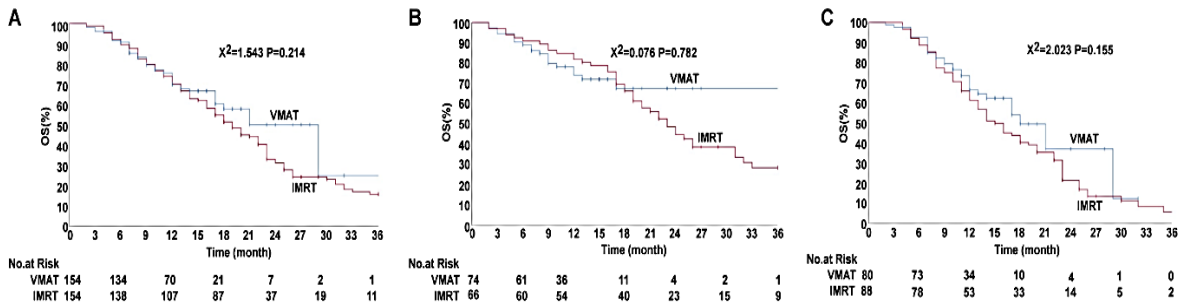

Figure 2: (A) The OS of IMRT or VMAT primary tumor radiotherapy after PSM. All patients; (B) The OS of IMRT or VMAT primary tumor radiotherapy after PSM. stage III, and (c) stage IV. (C) The OS of IMRT or VMAT primary tumor radiotherapy after PSM. stage IV

Table 4: Normal tissue dose-volume parameters of IMRT and VMAT radiotherapy for primary tumor after PSM

Variable	Staging	IMRT	VMAT	*P*-value
All lungV5	All patients	67.06 ± 13.36	56.90 ± 16.28	0.000
	N2	63.74 ± 14.41	48.22 ± 15.84	0.000
	N3	70.55 ± 13.66	62.50 ± 13.72	0.000
All lungV20	All patients	28.10 ± 6.17	25.71 ± 6.88	0.001
	N2	27.02 ± 6.30	22.36 ± 7.76	0.000
	N3	29.29 ± 4.95	28.39 ± 4.84	0.154
MLD	All patients	17.82 ± 3.54	16.21 ± 4.34	0.001
	N2	17.30 ± 4.18	14.30 ± 4.95	0.000
	N3	18.30 ± 3.27	17.88 ± 3.20	0.312
Heart	All patients	25.36 ± 12.88	21.58 ± 11.80	0.010
V30	N2	25.29 ± 13.44	17.04 ± 11.91	0.000
	N3	26.99 ± 14.73	24.89 ± 10.82	0.230
Heart	All patients	17.09 ± 9.77	14.71 ± 8.99	0.017
V40	N2	17.52 ± 10.85	11.98 ± 8.41	0.001
	N3	17.82 ± 10.91	16.85 ± 8.90	0.463
MHD	All patients	19.77 ± 8.65	17.22 ± 8.09	0.019
	N2	19.63 ± 8.62	13.74 ± 8.23	0.000
	N3	20.36 ± 8.77	19.66 ± 7.38	0.515
Esophagus	All patients	32.95 ± 20.03	32.37 ± 19.99	0.800
V50	N2	34.84 ± 18.33	28.60 ± 18.02	0.046
	N3	36.80 ± 20.05	35.22 ± 21.05	0.545

DISCUSSION

The results of this study showed that male to female ratio was 2.5 vs.1, the median age was 58 years. This research also found adenocarcinoma and squamous cell carcinoma cases to be about 94.3 % of the study population, which is similar to the epidemiological characteristics of the incidence of NSCLC [19]. The T3–4 and N2–3 cases were 67 and 88.9 %, respectively. The average volume of GTV was 200 cm^3. There was no significant difference in the distribution of primary lesions between patients who received VMAT or IMRT, respectively. The disease stage was late, and mediastinal lymph node metastasis was obvious [5,20]. The proportions of N2–3 and stage IV patients in the pre-PSM IMRT group were relatively high, regardless of stage III or oligometastasis of more than 50 % among stage IV NSCLC patients. Research by Yang Y *et al* [21]. also indicated that when the primary tumor is large in size, it is difficult to obtain the local control rate by increasing the dose under the premise of controlling the damage. It is necessary to use the physical characteristics of different three-dimensional radiotherapy techniques to explore the clinical value.

The difference between VMAT and IMRT is that, during the accelerator irradiation process of VMAT, the rotating irradiation is realized by continuous changes in the gantry speed, collimator angle, and dose rate, it has the characteristic of a short irradiation time. Studies on head and neck tumors in elderly patients over 80 years old with irregular target volume and need more protection of organs at risk showed that because VMAT has better conformal degree, when using the same target dose-volume as IMRT, it can significantly reduce the dose of organs at risk and obtain the same disease-free survival rate as young patients. A small sample of A-NSCLC radiation therapy plan dose-volume parameter study showed that VMAT increased the $V_{95\%}$ and conformity of the planned target area, and reduced the average dose to the lungs, esophagus, and heart as well. Therefore, in this multicenter and retrospective analysis of VMAT and IMRT treatment, results through PSM showed that the RR, DCR, and LCR were similar both before and after PSM ($p > 0.05$), suggesting that when VMAT and IMRT have similar primary tumor volume and radiation dose, the efficacy of VMAT in A-NSCLC patients is not lower than that of IMRT. There was no significant difference in LRPFS in the whole group nor during stratified analysis under the premise of the same baseline conditions after PSM, indicating that VMAT combined with drugs can be used in the first-line treatment of A-NSCLC with a long-term efficacy similar to that of IMRT. Moreover, the 1-, and 2-year OS rates of VMAT combined with chemotherapy in the first-line treatment of stage IV NSCLC patients were 66.4 and 37.1 %, respectively, which it is higher than the 1- , and 2-year OS rates of 35 and 10 %, respectively. This is associated with platinum-containing two-drug regimen first-line chemotherapy, suggesting a prolonged survival rate [4].

In summary, the effect of VMAT in the treatment of A-NSCLC was similar to that of IMRT, which can improve recent efficacy and OS. The

proportion of primary tumor volume shrinkage is also negatively correlated with the risk of progression failure, and OS is prolonged through radiotherapy, as well as an increased dose and local control rate [5].

It is well known that acute radiation injury caused by the dose-limiting toxicity of radiotherapy, RE and RP over grade 3 are unfavorable factors for the prognosis of NSCLC, and the volume of normal lung low-dose radiation is related to the occurrence of RP. VMAT irradiation needs to be performed through a rotating arc of the gantry, but the low dose volume of normal tissues does not necessarily increase. This study showed that the incidence rates of RP and RE of primary A-NSCLC tumors with a median dose of 64 Gy and an average volume of more than 200 cm^3 after VMAT treatment were lower than that of IMRT before PSM. There was no significant difference in grades 3 and 4 acute radiation damage between groups and no significant difference after PSM.

There were suggestions that the rotating irradiation mode of VMAT did not increase the acute radiation injury which was caused by the low dose volume of normal tissue in clinical practice. This study analyzed MHD and the important indicators of RE and RP (esophageal V50 and all lung V5, V20, MLD), showing that VMAT has more advantages. After PSM, the dose-volume parameters of VMAT technology were more advantageous, especially for N2 cases in stratified analysis, suggesting that radiotherapy with VMAT technology may be a better choice for N2 patients. While N3 patients with only normal whole-lung V5 had parameters significantly lower than IMRT group (p = 0.000), further suggesting that the VMAT rotary irradiation method has a more reasonable dose distribution and maintains the low dose volume to reduce radiation damage.

The VMAT rotary irradiation method has the advantage of a more reasonable dose distribution and better control of low dose volume to reduce radiation damage, especially in patients with mediastinal lymph node metastasis only on the same side. More importantly, the reduction in dose volume may reduce the damage to normal tissues, especially heart tissue damage.

CONCLUSION

The application of VMAT for primary tumor radiotherapy in A-NSCLC achieves similar efficacy to IMRT, but it may be more advantageous to use this approach to reduce acute radiation injury, especially for late cardiac damage. Further research will be required to establish this.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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