Simultaneous Integrated Boost of intensity modulated radiation therapy to Stage II-III Non-Small Cell Lung Cancer with metastatic lymph nodes

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Abstract

Background: Local tumor failure remains a major problem after radiation-based nonsurgical treatment for unresectable locally advanced Non-Small Cell Lung Cancer （NSCLC）and inoperable stage II NSCLC .The aim of this study was to evaluate the feasibility of Simultaneous Integrated Boos of intensity modulated radiation therapy (SIB-IMRT) to Stage II-III NSCLC with metastatic lymph nodes. Methods: Patients were diagnosed by pathology or PET-CT. PTV was divide into two parts as follow, the PTV of primary tumor (PTVp) and the PTV of metastatic lymph nodes (PTVn) .The radiation doses were simultaneously prescripted 78Gy (BED = 101.48Gy) for PTVp and 60-65Gy (BED = 73.6-81.25Gy) for PTVn, 26f/ 5.2 weeks .Response was scored according to WHO criteria. Radiotherapy toxicity was scored according to RTOG criteria .Hematology and gastrointestinal toxicity were scored according to CTCAE1.0 criteria. Results: A total of 20 patients were enrolled. 17 patients were diagnosed by pathology and 3 patients were diagnosed by PET-CT . All patients were treated with SIB-IMRT. The objective response rate (ORR) was 90%, with CR 25%, PR 65%, NC 10% and PD 0%. Although Radiation toxicitiy was common, there were no grade≥3（with Radiation pneumonitis (10 cases), esophagitis (17 cases) and dermatitis (12 cases). The local control rates at 1, 3 and 5 years were 85%, 75% and 70%, respectively. The overall survival（OS）and local progression-free survival(LPFS) rates at 1, 3 and 5 years were 90%, 42.6%, 35.5% and 84.4%, 35.5% , 28.4%, respectively. The MST was 24 months. Conclusions: SIB-IMRT can significantly improve ORR and suivival for stage II-III NSCLC with metastatic lymph nodes , with high safety and satisfactory efficacy . Keywords: cancer/non-small-cell lung cancer; radiation therapy /SIB-IMRT; efficacy; safety Retrospective Trial Registration（ (ChiCTR 2000029304)

Background

Concurrent thoracic chemoradiotherapy (CCRT) is the standard of care in patients with good performance status and inoperable stage II-III non-small-cell lung cancer(NSCLC) who have metastatic lymph nodes, especially for locally advanced NSCLC[1]. The radiation dose is one of the controversial focuses. At present, the uniform dose of radiation therapy was 60 Gy, but treatment outcomes remain poor. RTOG trials led to the conclusion that local tumor control was significantly correlated with improved survival[2]. 60 Gy may be not a reasonable dose [3–5].In this study, it is conceived that using the biological effective dose (BED) ≥ 100 Gy of large fractionated radiotherapy for stage Ⅱ-Ⅲ NSCLC can obtain more than 90% local control rate [6]and recurrence rate of mediastinal metastatic lymph nodes for locally advanced NSCLC with concurrent chemoradiotherapy (median dose 60 Gy/30f) was only 20% [7]. Different doses of radiotherapy were simultaneously prescribed for primary tumor and metastatic lymph nodes through SIB-IMRT. The aim of this study was to evaluate the safety and efficacy of (SIB-IMRT) for Stage II-III Non-Small Cell Lung Cancer(NSCLC) with metastatic lymph nodes.

Methods

Patient selection

Inclusion criteria were as follows: (1) histologically or cytologically or PET-CT confirmed NSCLC; (2) newly diagnosed stage II-III disease (staged according to the 2009 system of the American Joint Committee on Cancer); (3) KPS ≥ 70; (4) no contraindications to radiation therapy or chemotherapy; (5) Normal range of blood routine and biochemical indexes (7)good compliance with treatment and follow-up.

Pretreatment evaluations

All patients underwent fiberoptic bronchoscopy and contrast-enhanced computed tomography (CT) of the chest to evaluate the extent of the primary tumor and regional lymph node status. All patients also underwent bone scintigraphy, contrast-enhanced CT of the abdominal region, and magnetic resonance imaging (MRI) of the brain to detect distant metastases. Positive findings on positron emission tomography (PET) /CT or bone scintigraphy required other additional radiologic confirmation (e.g., MRI or CT of bone). Pretreatment evaluations were to be completed within 2 weeks before treatment was begun.

Treatment methods

Thoracic radiation therapy

Using 6 MV X-ray, intensity-modulated radiotherapy(IMRT). The patient was positioned in the supine position with thermoplastic film fixation and 5-mm-thickness enhanced CT.

The target Volume of primary tumor and metastatic lymph nodes were delineated respectively. The gross tumor volume of primary tumor (GTVp) included the thoracic primary tumor in lung windows and was outlined on the treatment planning CT scan ,the clinical target volume of primary tumor (CTVp) was defined as the GTVp plus a 0.6-cm margin with anatomical correction，the planning target volume of primary tumor (PTVp) was defined as the CTVp plus another margin of 0.5 to 1.0 cm. The gross tumor volume of metastatic lymph (GTVn) included any enlarged(> 1 cm on short axis) metastatic lymph nodes and was outlined on the treatment planning CT scan，the clinical target volume of metastatic lymph (CTVn) was modified by the GTVn and expanded outward by 0.6 cm combined with anatomical correction，the planning target volume of metastatic lymph (PTVn) was defined as the CTVn plus another margin of 0.5 cm.

Different doses of radiation therapy were simultaneously prescribed for PTVp and PTVn through SIB-IMRT. The radiation doses were 78 Gy (BED = 101.48 Gy) for PTVp and 60-65Gy (BED = 73.6-81.25 Gy) for PTVn, 26f/ 5.2 weeks,, respectively. The radiotherapy plan was evaluated as 95% of the prescription dose line including 95% of PTV. The percentage of total lung volume receiving ≥ 20 Gy(V20),whole lung dose (MLD) and mean heart dose(MHD) was to be kept at ≤ 32%, ≤ 20 Gy and ≤ 30 Gy ，respectively (Fig. 1–2).

Chemotherapy

Platinum-based doublet chemotherapy (cisplatin in combination with docetaxel, paclitaxel, or pemetrexed) or Single drug given every 21 to 28. The chemotherapy regimens of all patients were as follows: 1 case of docetaxel, 1 case of pemetrexed, 1 case of cetuximab + docetaxel, 1 case of pemetrexed + cisplatin, 1 case of paclitaxel liposome + carboplatin, 1 case of pemetrexed + cisplatin, 1 case of paclitaxel liposome + carboplatin, 9 cases of docetaxel + cisplatin(2 cases of docetaxel + cisplatin + Endostar. Chemotherapy Cycles were from 2 to 4. 4 patients refused chemotherapy.

Evaluation of treatment-related toxicity and response

Response was scored according to WHO criteria as follows: complete response(CR), partial response (PR), and no change (NC), progressive response(PD). Radiotherapy toxicity was scored according to RTOG criteria .Hematology and gastrointestinal toxicity were scored according to CTCAE1.0 criteria.

Follow-up evaluations and Statistical analyses

At 1 month after completion of treatment, patients underwent CT scanning of the chest and abdominal region and MRI of the head to assess tumor response. These tests were then repeated every 3 months for 2 years and every 6 months thereafter. Primary endpoints were OS,LPFS and acute toxicity. Kaplan-Meier analyses were used for statistical analysis.

Results

Patient characteristics

From December 2009 to March 2019,20 patients were enrolled in this study. There were 3 patients with stage Ⅰ A ,1 patient with stage Ⅰ B ,12 patients with stage Ⅱ A and 4 patients with stage ⅡB .The patients with stage II refused operation Because of old-aged patients (3 cases) and pulmonary dysfunction (1 case).There were 17 males and 3 females. Median age of patients was 75 years (range, 44–82 years). 50% of patients (10/20) were older than 70 years. Age of 8 patients were ≥ 77 years (range,77–82 years). There were 4 adenocarcinomas, 10 squamous cell carcinomas, 3 non-small cell lung carcinoma and 3 clinically diagnosed lung cancers. Median long axis of primary tumor was 4.55 cm(range Ⅰ1.2 -11cm). Median number of metastatic lymph nodes was 1(range Ⅰ1–5). Median volume of GTVp was 69.99 cm3 (range Ⅰ8.74-530.07 cm3). Median volume of PTVp was 189.22 cm3 (rangeⅠ83.85-886.71 cm3); Median volume of GTVn was 35.96 cm3(range Ⅰ4.37 -139.05 cm3). Median volume of PTVn was 148.37 cm3 (range Ⅰ35.79-405.68 cm3). The number of patients with V 20 ≤ 20%, 21%-25%, 25%-30% and > 30% were 4, 7, 7 and 2 (rangeⅠ12.1%-32%, median 24.6%),respectively. The number of with MLD ≤ 20 Gy and > 20 Gy were 17 and 3 (range 8.57–21.23 Gy, median MLD16.67 Gy), respectively. The number of patients mean heart doseⅠMHD)≤ 26 Gy and > 26 Gy were 16 and 4 (range 1.83–32.41 Gy, median 7.65 Gy), respectivelyⅠTable1Ⅰ.

Table 1
Clinical characteristics, treatment data and survival of 20 patients of stage II-III NSCLC

No	Sex	A	B	C	D	stage	metastatic lymph node		GTV_P (cm^3)	PTV_P (cm^3)	GTV_N (cm^3)	PTV_N (cm^3)	V20 (%)	MLD(Gy)	MHD(Gy
							Drainage area	Number							
1	Male	+	-	-	-	T2aN2M0	4R + 10R	2	79.13	290.08	46.93	169.93	24.9	18.32	11.91
2	Male	+	-	-	-	T3N2M0	4L + 7	2	465.91	886.71	37.28	137.57	31.3	20.43	32.41
3	Male	-	-	-	-	T1aN2M0	5 + 7	5	94.85	360.35	72.14	281.72	24.3	13.73	6.3
4	Male	+	-	-	-	T2aN1M0	10L	1	26.13	123.83	61.65	239.53	32	21.19	30.86
5	Male	-	-	+	+	T2bN1M0	10R	1	49.2	163.01	16.03	63.07	19.9	14.96	2.35
6	Male	-	+	+	-	T3N1M0	10L	1	93.83	234.75	71.32	201.32	25.5	17.92	22.79
7	Male	-	-	+	-	T2aN1M0	10L	1	27.53	83.85	22.37	84.38	16.1	10.96	9.04
8	Female	-	+	-	-	T3N2M0	4R	1	398.47	711.64	32.44	123.93	26.5	16.96	19.39
9	Male	+	-	-	-	T3N2M0	4R	1	76.35	204.29	62.72	159.16	23.9	21.23	7.58
10	Male	+	-	-	-	T3N2M0	2R	1	70.11	211.57	10.1	72.11	22.5	14.32	4.1
11	Male	+	-	-	-	T3N1M0	10L(fusion)	Fusion	530.07	868.64	107.51	261.05	22.8	17.7	26.92
12	Male	+	+	-	-	T3N3M0	4L	1	69.87	174.15	21.56	74.76	27.3	16.49	7.7
13	Male	-	-	-	-	T2N2M0	4R	1	26.22	111.72	4.37	44.54	12.11	8.57	6.84
14	Female	-	+	-	-	TN1N1M0	10L	1	8.74	84.70	58.20	227.79	28.00	14.17	30.9
15	Male	-	+	-	-	T3N2M0	4R	2	46.28	133.98	7.68	35.79	17.9	18.32	1.83
16	Male	-	-	-	-	T4N3M0	4R/L/7/10R	5	231.13	475.15	34.01	188.11	25.28	16.96	8.48
17	Female	-	+	-	+	T2N3M0	4R/L/5/6	6	52.12	96.08	12.15	76.36	20.49	12.78	1.98
18	Male	+	-	-	-	T4N2M0	6/7	5	261.14	472.17	34.63	132.15	21.92	13.82	4.74
19	Male	-	-	-	-	T3N2M0	2R/3A/4R/5/10R	5	35.24	118.53	80.61	245.22	27.43	16.85	5.94
20	Male	-	-	-	-	T2N2M0	2R/3A/4R(fusion),7	3	23.9	87.08	139.05	405.68	25.80	15.34	7.60

A: chronic obstructive pulmonary disease,B: hypertension,C: coronary heart disease,D: diabetes mellitus,L = local recurrence, M = distant metastasis

Response

The CR, PR and SD rate was 25%(5cases), 65% （13cases）and 10%（2cases）,respectively. The CR, PR and SD rate of primary tumor was 30%（6 cases）（55%（11 cases）（15%（3 cases）respectively. The CR, PR and SD rate of metastatic lymph nodes was 25%（5cases）（60%（12cases）（15%（3cases）. The clinical benefit rate was 100%.

Progress, cause of death and survival

During follow-up, there were local recurrence and / or metastasis progressed in 7 patients (2 patients with local recurrence and bone metastasis, 1 patient with local recurrence and pulmonary metastasis, 1 patient with local recurrence ,1 patient with local recurrence and hemoptysis （1 patient with alone lung metastasis, 1 patient with malignant pleural effusion). By the last follow-up, 12 patients died .The cause of death in 9 patients was not related to tumor (3 died of cardiogenic death, 5 died of pulmonary infection and 1 died of respiratory failure). The cause of death in 3 patients was related to tumor(1 died of local recurrence with metastasis, 1 died of local recurrent hemoptysis and 1 died of local recurrence). The local control rates at 1, 3 and 5 years were 85%, 75% and 70%, respectively. The OS and LPFS rates at 1, 3 and 5 years were 90%, 42.6%, 35.5% and 84.4%, 35.5%, 28.4%, respectively. The MST was 24 months(Fig. 3–4).

Toxicity

No patient experienced grade 3 + acute radiation toxicity. Grade Ⅱ radiation pneumonitis was observed in 9 patients (7 in concurrent chemoradiotherapy, 2 in radiotherapy alone) and grade Ⅲ in 1 patient (concurrent chemoradiotherapy). Grade Ⅱ radiation dermatitis was observed in 9 patients (8 in concurrent chemoradiotherapy, 1 in radiotherapy alone) and grade Ⅲ in 3 patients (all in concurrent chemoradiotherapy). Grade Ⅱ radiation esophagitis was observed in 7 patients (3 in concurrent chemoradiotherapy, 4 in radiotherapy alone) and grade Ⅲ in 10 patients (all in concurrent chemoradiotherapy). Chronic radiation-induced lung injury was observed in 1 patients, which occurred 3 months after radiotherapy (the serial number 12, lung V20 was 27%, MLD was 16.49 Gy). Grade Ⅰ, Ⅱ, Ⅲ and Ⅳ of gastrointestinal and hematological toxicity were 6, 8, 1, 0 and 1, 6, 5, 4 cases, respectively, all of which occurred in concurrent chemoradiotherapy. There was no radiomyelitis or heart injury observed in all patients.

Discussion

At present,,the radiation dose ≥ 60 Gy/30f is needed for concurrent chemoradio- therapy to locally advanced NSCLC[8]，but the local control rates at 1, 3 and 5 years were about 70%, 50%, 40% [9]，and the OS rate at 5 years was about 15% [8, 10].The local recurrence rates of stage Ⅱ-Ⅲ NSCLC with concurrent chemoradiotherapy at 1, 2, 3 and 5 years were 23% [11]，30.8% -37.1%[12]，28.1%，28.9[10].Uncontrolled local tumors may be a potential source of distant metastasis [13].Although the RTOG0617 study showed that 60 Gy may be more reasonable than other radiation dose [3], further analysis of the study showed that the result was affected by many other factors [12].There is still debate about that increasing the dose of radiation therapy can reduce recurrence and prolong survival. A phase II clinical study by KongFM et al showed that the local control rate was 82% at 2 years and 30% at 5 years because of the high radiation therapy (86Gy/30day) with adaptive radiotherapy guided by PET/CT[4].Many studies still supported the idea that high dose of radiation therapy was necessary [14–17].After the report of RTOG0617 study in 2012, MachtayM et al conducted a meta-analysis, which included 7 prospective randomized concurrent chemoradiotherapy studies about locally advanced NSCLC. The study[18] showed that BED ≥ 74.67 Gy (conventional fractionated dose 62-64Gy) was more beneficial to improve the local control and survival, increasing the tBED of 1 Gy can increase the local control by 3%, and the BED of 1 Gy can increase OS by 4%.After conventional fractionated radiotherapy, dose escalation for local tumor may improve local control and survival [19].

Through changing the fractionated radiotherapy dose of 2.5-6Gy with concurrent chemoradiotherapy for locally advanced NSCLC ,the CR ,PR,1, 2, 3 years OS rates and mean suivival time(MST) were 26.5%, 42.9%,63.3%, 40.8%, 20.4% and 22 months, respectively [20]. A fraction dose of 3 Gy and total dose of 65-68Gy were given after initially 50 Gy/20 fractions，the 3-years OS and PFS rates were 32.1% and 29.8% respectively，and the 1 -, 2-and 3-years LRPFS rates were 69.6%, 60.9% and 60.9%, respectively[21]. Based on the characteristics of IMRT, the dose of the PTV was kept at 60 Gy and the dose of GTV was 72–78 Gy synchronously，the result showed that MST was 25.3 months [13]. 63-103Gy was the recommended radiation therapy dose to improve the local control rate [22]. The commonness of these studies was that the primary tumor and drainage lymph nodes were defined as the same target. The ways to increase dose of physical or BED were as follows: dose escalation after conventional fractionated radiotherapy，different doses were simultaneously prescribed to GTV and PTV. The aim was to improve the tumor local control and survival. The way of increasing the dose of radiotherapy in our study was different from the above studies. The primary tumor and drainage lymph nodes were defined as different targets，GTVp and GTVn，. Different doses of radiation therapy were simultaneously prescribed for primary tumor and metastatic lymph nodes through SIB-IMRT. One principle is that the BED ≥ 100 Gy for stage I NSCLC can obtain a local control rate of > 90% [23], significantly reduce the local recurrence rate and improve the survival rate at 3-years [24]. Another principle is that the long-term local control rate is more than 50% through conventional fractionated radiotherapy dose （60-66Gy） for mediastinal metastatic lymph nodes [25]. Through SIB-IMRT, the radiation doses were simultaneously prescripted 78 Gy (BED = 101.48 Gy) for primary tumor and 60-65Gy / 26f (BED = 73.6-81.25 Gy) for metastatic lymph nodes .The result showed that the ORR was 90% (18 / 20), and the SD was only observed in 2 patients (primary tumor reduced by 14%, 30%, metastatic lymph node reduced by 44%, 32%).The ORR of primary tumor and metastatic lymph node was both 85% and there was no PD. The local control rates at 1, 3 and 5 years were 85%, 75% and 70%, respectively. Only 4 patients were diagnosed as local recurrence confirmed by imaging and / or pathology and 3 of them died from the following causes: myelosuppression grade IV, sudden cardiac death, hemoptysis. The result showed that the ORR was kept at 90% by SIB-IMRT ，which was superior to the result of chemotherapy and conventional fractionated radiotherapy for local advanced NSCLC[26]. It may be due to the increase of ORR, the proportion of tumor shrinkage and regression increased ,which was beneficial to reduce the recurrence and mortality rate and positively correlated with the prolongation of survival rate [4]，The OS and LPFS rates at 1, 3 and 5 years were 90%, 42.6%, 35.5% and 84.4%, 35.5%, 28.4%, respectively. The MST was 24 months.

The injury control index used in the evaluation of radiotherapy plan was based on the standard of conventional fractionated radiotherapy of locally advanced NSCLC Acute radiation pneumonitis, radiation esophagitis and radiation dermatitis were all grade 1–2. Further analysis showed that grade 2 toxicity mainly occurred in concurrent chemoradiotherapy, which increased acute radiotoxicity[10]. Compared with the conventional radiotherapy, there was no increase in radiotoxicity despite the increase in fractionated dose(3Gy/f) and BED [27].The main systemic toxicity was gastrointestinal toxicity (grade 1 in 6 patients, grade 2 in 8 patients, grade 3 in 1 patient) and hematological toxicity (grade 2 in 6 patients, grade 3 in 5 patients, grade 4 in 4 patients). All of them occurred in concurrent chemoradiotherapy. Radiotherapy alone had no obvious systemic toxicity. It showed that systemic toxicity was mainly related to cytotoxic drugs.

A total of 12 patients died. 5 patients died of pulmonary infection (ages: 55, 71, 78, 79, 85 years;V20: 26. 5%, 25.8%, 24.3%, 27.3%, 17.9%， RP grade:2, 0, 0, 2, 0， MLD < 20Gy). 3 patients died of cardiogenic diseases (age 79, 78, 80 years， accompanied by hypertension and diabetes, coronary heart disease with coronary stent implantation, paroxysmal atrial fibrillation， MHD: 2.35 Gy, 22.79 Gy, 9.04 Gy).4 patients died of local recurrence,local recurrence along with metastasis, local recurrence with massive hemoptysis and respiratory failure，respectively.

Conclusions

SIB-IMRT can significantly improve ORR and survival for stage II-III NSCLC with metastatic lymph nodes. This treatment approach has high safety and satisfactory efficacy .

Abbreviations

SIB-IMRT：Simultaneous Integrated Boos of intensity modulated radiation therapy; PTV： planning target volume ； PTVp： PTV of primary tumor；PTVn ：PTV of metastatic lymph ORR：objective response rate；CR: Complete response; PR: Partial response; NC：no change；PD: Progressive disease; MST：mean survival time； KPS: Karnofsky Performance Status; NSCLC: Non-small cell lung cancer; LPFS：local progression free survival; BED：biological effective dose.

Declarations

None of the authors have any financial disclosures or conflicts of interest to declare.

No actual or potential conflicts of interest exist.

Ethics approval and consent to participate

This study was reviewed by the ethical review boards in China (Ethics Committee of Guizhou Cancer Hospital, GuiYang, China). Informed consent for treatment was obtained from patients.

Consent for publication

Not applicable

Availability of data and material

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

All authors have read and approved the final manuscript

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Authors' contributions

BL designed the study. QSL，NL，WWO，SFS,ZM,YCG，WGY，YXH,HQL collected the data. BL and QSL undertook the data analysis and interpretation, and wrote the report. BL and QSL carried out the statistical analysis. All authors read and approved the final manuscript.

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Figures

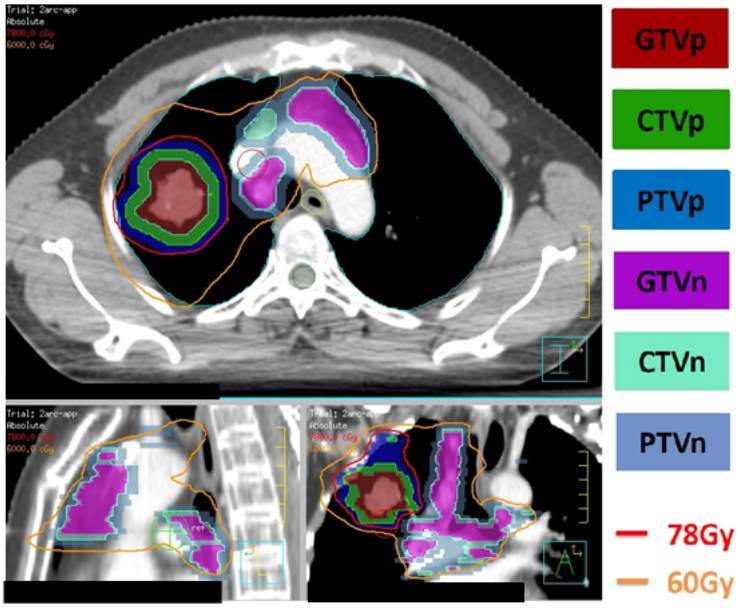

Figure 1

PTVp and PTVn were given different prescription

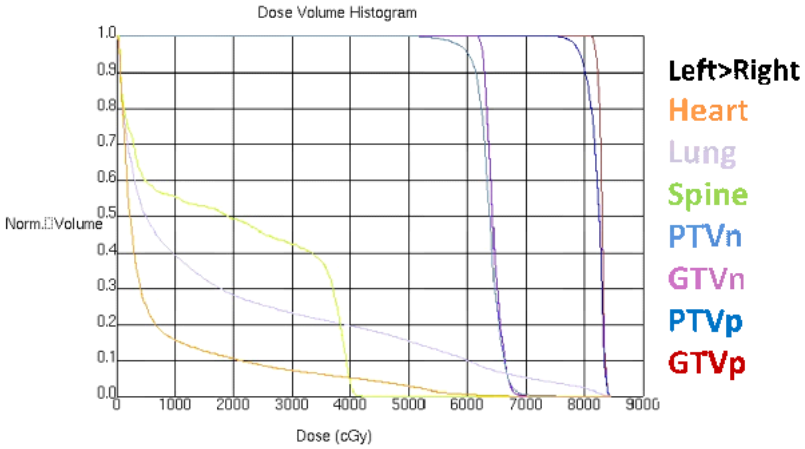

Figure 2

dose volume histogram

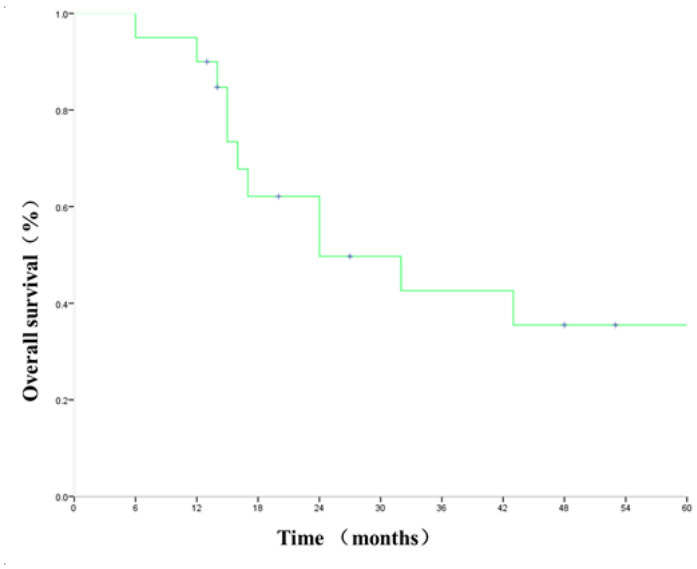

Figure 3

overall survival for all patients

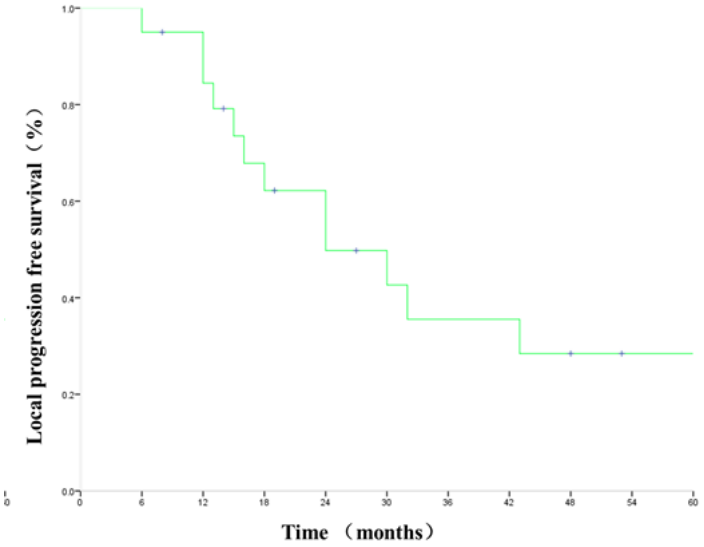

Figure 4

Local progression free survival for all patients

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