Am J Cancer Res 2025;15(4):1777-1789
www.ajcr.us /ISSN:2156-6976/ajcr0162690

Original Article

Effect of gamma knife stereotactic radiotherapy on the hematological system in patients with advanced lung cancer and its therapeutic effect

Chun-Guang Ling[1], Jian-Feng Chen[2], Xiao-Chen Wang[3]

[1]Department of Gamma Knife Treatment Center, Suzhou BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Suzhou 215003, Jiangsu, China; [2]Department of General Surgery, Suzhou BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Suzhou 215003, Jiangsu, China; [3]Department of Thoracic and Cardiovascular Surgery, Suzhou BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Suzhou 215003, Jiangsu, China

Received December 15, 2024; Accepted March 19, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: Objective: To evaluate the influence of Gamma Knife stereotactic body radiotherapy (SBRT) on the hematological system in patients with advanced lung cancer and to assess its clinical outcomes. Methods: A retrospective analysis was conducted on the clinical data of 192 patients with advanced lung cancer. 108 patients who received conventional radiotherapy were included in the control group, and the rest 84 patients who received Gamma Knife SBRT were included in the experimental group. Treatment outcomes, disease progression one year after radiotherapy, blood cell counts, coagulation function, quality of survival scores, and adverse reactions were compared between the two groups. Results: The experimental group exhibited a significantly higher disease control rate (DCR) and objective response rate (ORR) compared to the control group (both $P<0.05$). Radiotherapy modality was identified as an independent factor influencing disease progression within one year. Both groups experienced reductions in leukocytes, neutrophils, lymphocytes, erythrocytes, and platelets after radiotherapy, but the experimental group had less pronounced reductions ($P<0.05$). Alterations in blood cell morphology were observed in both groups, with the experimental group showing fewer alterations ($P<0.05$). Coagulation function tests indicated a rise in prothrombin time (PT), a decrease in activated partial thromboplastin time (APTT), and an increase in fibrinogen (Fib) and D-Dimer (D-D) levels in both groups, with more favorable coagulation indices observed in the experimental group. Patients in both groups showed improvement in quality of survival scores post-treatment, with the experimental group outperforming the control group ($P<0.05$). The incidence of adverse reactions was lower in the experimental group compared to the control group ($P<0.05$). Conclusion: Compared to traditional radiotherapy, Gamma Knife SBRT has a less detrimental impact on the blood cell level, morphology, and coagulation function in patients with moderate to advanced lung cancer. It also improves patients' quality of survival with fewer adverse reactions and better disease control. These findings suggest that Gamma Knife SBRT is a promising treatment option and warrants further exploration and adoption in clinical practice.

Keywords: Radiation therapy, gamma knife, middle and advanced lung cancer, hematological system, adverse effects, efficacy

Introduction

Lung cancer is a prevalent malignant tumor, typically originating from malignant cell lesions in the bronchial mucosa and glands of the lungs. Its incidence and mortality rates are notably high [1]. Early symptoms of lung cancer are often subtle and can easily be mistaken for other diseases. Additionally, many patients lack sufficient awareness, leading to diagnosis at advanced stages, with cancer metastasizing to adjacent lung tissues, lymph nodes, or other organs [2]. The treatment of lung cancer is complex, generally requiring a combination of surgery, radiation, chemotherapy, immunotherapy, and targeted therapies. Studies have shown that about 70% of patients are no longer suitable for surgical treatment at the time of diagnosis, making radiotherapy and chemotherapy the preferred treatment options. However, the

5-year survival rate for these patients is only about 19.7% [3].

Radiotherapy technology is developing rapidly, with imaging playing a crucial role in enhancing its accuracy. The emergence of new imaging technologies, such as four-dimensional computed tomography technology, has strengthened the capabilities of stereotactic body radiotherapy (SBRT) [4]. Using three-dimensional geometric localization, SBRT selectively targets the diseased tissue, delivering a large dose of gamma radiation in a focused manner to induce necrosis or functional changes in the tumor while minimizing damage to surrounding healthy tissue. SBRT offers several advantages, including a short treatment duration, high accuracy, good curative effect, and few side effects [5].

Like conventional radiotherapy, Gamma Knife radiotherapy is a non-invasive treatment that does not require anesthesia, surgery, or blood transfusion. Previous studies have shown its effectiveness in treating brain metastases from lung cancer [6]. However, radiation therapy also has adverse effects on the body, including blood system responses, such as neutropenia, which need to be closely monitored [7, 8]. This study aims to investigate the effects of Gamma Knife SBRT on the blood system and its clinical application in patients with advanced-stage lung cancer. Through retrospective analysis, we seek to provide evidence-based support for the broader application of Gamma Knife SBRT in treating intermediate and advanced-stage lung cancer.

Materials and methods

Patients and study design

This study was approved by the Ethics Committee of The Affiliated BenQ Hospital of Nanjing Medical University. A retrospective analysis was conducted on patients with middle and advanced lung cancer admitted to The Affiliated BenQ Hospital of Nanjing Medical University from January 2022 to January 2024.

Inclusion criteria: (1) Diagnosis confirmed by histopathology and imaging, with clinical staging of TNM IIIb to IV [9]; (2) Advanced lung cancer with measurable and objectively evaluable lesions; (3) First admission to the hospital; (4) Expected survival time of more than six months; (5) Complete case data available. Exclusion criteria: (1) Patients with pre-treatment liver pr kidney dysfunction or blood abnormalities; (2) Previous radiotherapy treatment; (3) Patients with other malignancies other than lung cancer; (4) Women during pregnancy.

Previous studies have shown that the incidence of lung cancer accounts for 12.4% of all cancers [10]. Sample size calculation was performed using the formula: $n = \frac{Z^2_{\alpha/2} P(1-P)}{\delta^2}$, where P is the estimated overall rate, δ is the permissible error, and α=0.05 for a bilateral confidence interval. The calculated sample size was n=166. Considering a 10% loss to follow-up and the exclusion criteria, 192 patients were finally included in the study (**Figure 1**).

Grouping

Based on patient condition, the attending physician presented available treatment options to the patient and their family, analyzed the advantages and disadvantages of each option, and provided a clear outline of the associated costs. The patients were grouped according to the treatment modalities they received. A total of 84 patients who underwent Gamma Knife SBRT were included in the experimental group, while 108 patients who received conventional radiotherapy were included in the control group. There were no significant differences in general clinical data (gender, age, body mass index (BMI), Karnofsky (KPS) score) between the two groups (all $P>0.05$), indicating that the groups were balanced and comparable. The detailed results of the analysis are shown in **Table 1**.

Therapeutic methods

(1) Control group: The conventional segmented radiological technique was adopted using a Varian high-energy linear accelerator (6 MV photon line). After computed tomography (CT) scanning and localization, pre- and post-contralateral irradiation were performed. The treatment regimen consisted of a single radiation dose of 2 Gy, administered once daily, 5 days a week. The total radiotherapy dose was determined based on tumor size: 36-42 Gy for tumor with a diameter <3 cm, 40 Gy for tumors

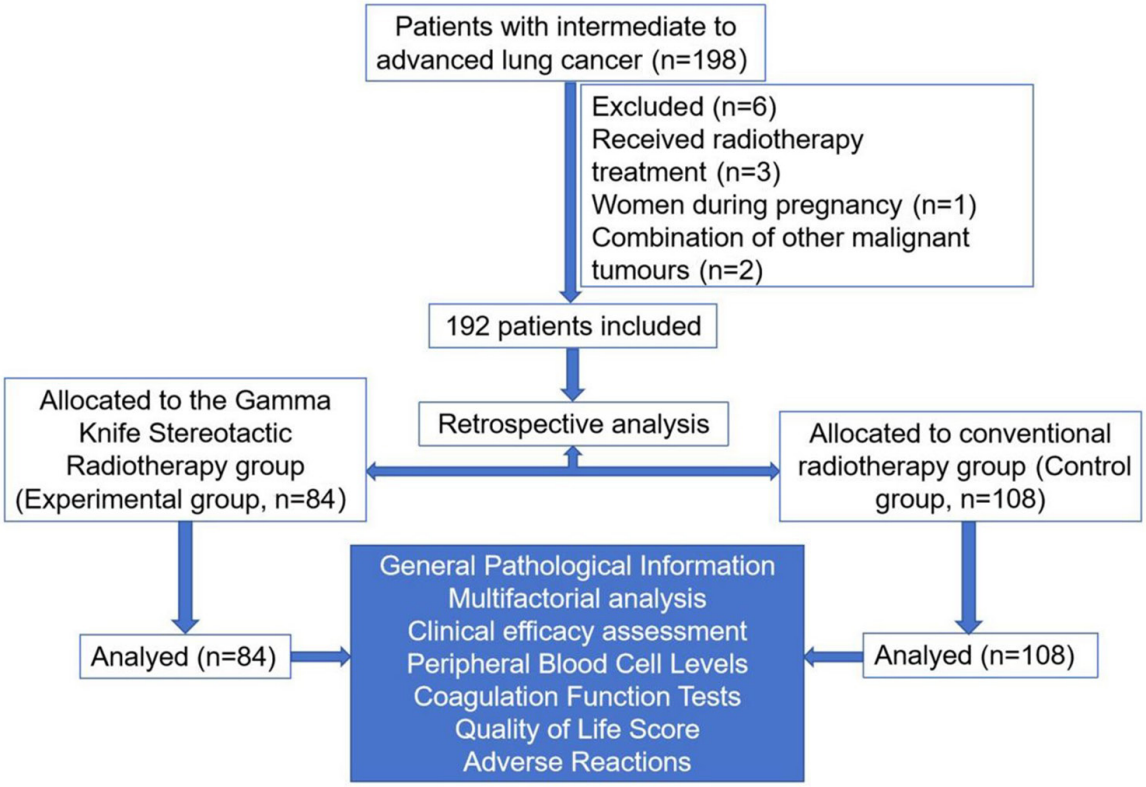

Figure 1. Flow diagram for patient inclusion.

Table 1. Comparison of general clinical data between the two groups of patients

Projects		Control group (n=108)	Experimental group (n=84)	t/x^2	*P*
Gender/n	Male	66	49	0.152	0.697
	Female	42	35		
Age		56.39±7.33	57.65±6.49	1.242	0.216
BMI (kg·m^2)		21.65±1.09	21.33±1.24	1.890	0.060
KPS Score/n	≥80	72	58	0.123	0.726
	<80	36	26		

Note: BMI: body mass index; KPS Scores: Karnofsky Score.

between 3-5 cm, and 40-42 Gy for tumors >5 cm.

(2) Experimental group: Patients were treated with Gamma Knife Stereotactic Radiotherapy with Whole Body Stereotactic Gamma Radiation Therapy System (WBSSRT). The patient was positioned supine with the assistance of a healthcare professional. A negative pressure vacuum bag was used to secure the body without restricting respiratory movement. The arms were positioned above the head, and body surface marking points were set under the positioning frame to measure the coordinates along the X-, Y-, and Z-axes. Care was taken to prevent errors in the pendulum direction and ensure the error in the Y-axis was maintained within 0.3 cm. A CT scan with contrast enhancement was performed, covering the area from the mid-neckline to 3 cm below the diaphragm to include the entire lung tissue, with a slice thickness of 5 mm. The acquired image data were input into the treatment planning system. Intrapulmonary lesions were delineated in the pulmonary window, mediastinal or hilar lesions in the mediastinal window, and organs at risk (such as bilateral lung tissue, heart, spinal cord, and esophagus) were outlined. The tumor's location and volume were used to develop a personalized treatment plan. The initial dose for Gamma Knife SBRT was generally 50-60 Gy, with an average dose of (55.26±6.67) Gy in this study. The entire focal area received 50% of the prescribed dose first,

followed by irradiation of the lesion's periphery with a total dose of 40-48 Gy, delivered in 10-12 sessions (4 Gy/session, 5 days/week).

Both groups received enhanced symptomatic support, anti-inflammatory treatment, and other supportive therapies during radiotherapy. Follow-up visits, including telephone consultations and outpatient visits, were conducted at the end of treatment to monitor disease progression within one year and determine the specific time of progression.

Data collection

The pathological diagnostic reports for each patient were retrieved from the medical record system. The pathological characteristics of both groups were recorded, including the type of lung cancer, tumor differentiation degree, tumor location, and tumor subtype.

All patients underwent disease-related examinations upon admission. Fasting venous blood samples were collected before radiotherapy, and the quality of life of the patients was assessed using a scoring system administered by healthcare staff. Adverse reactions experienced during radiotherapy were also recorded. These examinations, blood samples and scores were repeated one month after the completion of radiotherapy.

Outcome measures

Primary outcomes: Clinical efficacy: Clinical efficacy was assessed using the RECIST 1.1 criteria [11]. Complete remission (CR): complete elimination of the lesion; Partial Remission (PR): >50% reduction in lesion size; Stable Disease (SD): ≤50% reduction in lesion size or <25% increase in lesion size; Progressive Disease (PD): Lesion enlargement ≥25%. Disease control rate (DCR) was calculated as: DCR = (CR + PR + SD)/total number of cases × 100%, an objective response rate (ORR) was calculated as: ORR = (CR + PR)/total number of cases ×100%.

Peripheral blood cell level: Before and after radiotherapy, 2 mL of fasting venous blood was collected into anticoagulant tubes, and the levels of leukocytes, neutrophils, lymphocytes, erythrocytes and platelets were measured using an automated whole blood cell analyzer.

Blood cell morphology: Before and after radiotherapy, venous blood was collected from patients, mixed, and smeared for Rachel-Giemsa staining. Approximately 0.5-0.8 mL of Giemsa staining solution (A) was applied to the smear and stained for 0.5-1.0 min. Phosphate buffer PH=6.8 (B liquid) was then added, and the smear was stained for an additional 6-8 minutes before rinsing and drying. The slide was examined microscopically.

Coagulation function: Coagulation function was assessed using the Sysmcx CS-500 automatic coagulation analyzer to measure prothrombin time (PT) and activated partial thromboplastin time (APTT). Additionally, the levels of D-D dimer (D-D) and fibrinogen (Fib) were detected by ELISA kits.

Secondary outcomes: Quality of Survival Score: Before treatment and after 5 cycles of treatment, the quality of life of patients in both groups was evaluated using the World Health Organization quality of life brief scale (WHOQOL-BREF) [12], including four domains of physical health, psychological health, social relationships, and environmental factors. Each domain is scored out of 100, physical health, psychological health, social relationships, and environmental factors.

Adverse reactions: The occurrence of adverse reactions in both groups was observed and recorded, including radiation pneumonitis, radiation esophagitis, bone marrow suppression, skin reactions and gastrointestinal reactions. The frequency of adverse reactions was calculated for both groups.

Statistical analysis

Data were analyzed using SPSS 19.0 statistical software. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), with comparisons made using t-test or analysis of variance (ANOVA) with a repeated-measures design. Count data were expressed as frequencies (%), and comparisons were made by the x^2 test. Multifactorial COX regression analysis was conducted to identify risk factors affecting disease progression. *A P-value of <0.05 was considered statistically significant*.

Table 2. Comparison of clinical outcomes between the two groups of patients

Group	n	CR	PR	SD	PD	DCR	ORR
Control group (n=108)	108	9	50	25	24	77.78%	54.63%
Experimental group (n=84)	84	12	47	16	9	89.29%	70.24%
x^2	-	-	-	-	-	4.396	5.382
P	-	-	-	-	-	0.036	0.020

Note: CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Progression Disease; DCR: Disease Control Rate; ORR: Objective Response Rate.

Table 3. Comparison of pathological features of lung cancer between the two groups of patients

Projects		Control group (n=108)	Experimental group (n=84)	t/x^2	*P*
Pathological staging	Squamous carcinoma	54	43	0.027	0.870
	Adenocarcinoma	32	25	0.004	0.984
	Small cell carcinoma	15	10	0.164	0.685
	Others	7	6	0.033	0.857
Degree of differentiation	Middle ground	44	36	0.087	0.768
	Low ground	64	48		
Tumor location	Left lung	60	32	5.772	0.016
	Right lung	48	52		
Tumor type	Central type	50	52	4.623	0.032
	Peripheral	58	32		
Tumor size	≤5 cm	47	51	5.591	0.018
	>5 cm	61	33		

Results

Comparison of tumor characteristics between the two groups

Table 3 illustrates the tumor characteristics of patients in the two groups. A comparison revealed that the experimental group had a higher prevalence of tumors located on the left side (*P*=0.016), a lower incidence of central tumors (*P*=0.032), and more tumors smaller than 5 cm (P=0.018). However, no significant differences were observed between the two groups in the distribution of tumor types and the degree of tumor differentiation (*P*>0.05).

Comparison of short-term outcomes between the two groups

In the control group (n=108), 9 cases achieved CR, 58 cases had PR, 25 cases had SD, and 24 cases had PD after conventional radiotherapy, with an ORR of 54.63% and a DCR of 77.78%. In the experimental group (n=84) treated with gamma knife SBRT, there were 12 cases of CR, 47 cases of PR, 16 cases of SD, and 9 cases of PD, yielding an ORR of 70.24% and a DCR of 89.29%. The DCR and ORR in the experimental group were significantly higher compared to the control group (both *P*<0.05, **Table 2**).

COX univariate and multivariate analyses

The results of the univariate COX analysis revealed that treatment method and tumor size were the primary factors influencing disease progression in patients. Among these, the treatment method (gamma knife SBRT) was identified as a protective factor, while a tumor size >5 cm was recognized as a risk factor (*P*<0.05). Furthermore, factors with statistical difference were incorporated into the multivariate COX analysis, which demonstrated that treatment method (gamma knife SBRT) was an independent protective factor influencing disease progression within one year (*P*<0.05). The detailed results of the analysis are presented in **Table 4**.

Table 4. COX regression analysis of factors affecting patients with intermediate and advanced lung cancer

Variables	Univariate analysis					Multivariate analysis				
	β	S.E	Wald x^2	P	HR (95% CI)	β	S.E	Wald x^2	P	HR (95% CI)
Tumor location										
0					1.00 (Reference)					
1	0.23	0.15	2.27	0.13	0.80 (0.59-1.07)					
Tumor type										
0					1.00 (Reference)					
1	-0.16	0.15	1.06	0.30	0.86 (0.64-1.15)					
Modality of radiotherapy										
0					1.00 (Reference)					1.00 (Reference)
1	-1.04	0.161	41.818	<0.001	2.83 (2.06-3.87)	-1.00	0.17	36.51	<0.001	2.72 (1.97-3.77)
Tumor size										
0					1.00 (Reference)					
1	0.33	0.15	4.90	0.027	1.40 (1.04-1.88)					

Note: HR: Hazard Ratio; CI: Confidence Interval.

Table 5. Comparison of blood cell levels between the two groups

Index \ Group		Control group (n=108)	Experimental group (n=84)	*t*	*P*
Leucocyte ($\times10^9$/L)	Before radiotherapy	6.25±1.41	6.17±1.43	0.388	0.699
	After radiotherapy	3.88±0.84*	4.21±1.09*	2.370	0.019
neutrophil ($\times10^9$/L)	Before radiotherapy	4.59±1.06	4.56±0.91	0.207	0.837
	After radiotherapy	2.88±0.61*	3.15±0.53*	3.220	0.002
Lymphocyte ($\times10^9$/L)	Before radiotherapy	1.73±0.35	1.76±0.42	0.540	0.590
	After radiotherapy	0.92±0.26*	1.03±0.21*	3.158	0.002
Red blood cell ($\times10^{12}$/L)	Before radiotherapy	4.92±1.17	4.88±1.22	0.231	0.818
	After radiotherapy	2.85±1.09*	3.24±0.88*	2.671	0.008
Blood platelet ($\times10^9$/L)	Before radiotherapy	240.15±10.26	238.31±11.25	1.182	0.239
	After radiotherapy	195.29±8.79*	199.42±9.25*	3.157	0.002

Note: Compared with the same group before radiotherapy, *P<0.05.

Comparison of blood cell levels between the two groups

Before radiotherapy, there were no significant differences between the two groups in terms of white blood cell counts, neutrophils, lymphocytes, erythrocytes, or platelets (all P>0.05); After radiotherapy, the levels of these parameters decreased (P<0.05), with the experimental group showing higher values compared to the control group (P<0.05), the details are shown in **Table 5**.

Comparison of morphological changes in blood cells between the two groups

In the control group, there were 7 cases of immature granulocyte (IG), 1 case of nucleated red blood cells (NRBC), 2 cases of Hemoglobin concentration variability (HC VAR), 4 cases of left shift (LS), 10 micro cells (Micro), and 5 cases of macro cells (Macro) before radiotherapy; During radiotherapy, there were 31 cases of IG, 18 cases of atypical lymphocytes (ATYPS), 25 cases of NRBC, 17 cases of HC VAR, 32 cases of LS, 27 cases of Micro, 18 cases of Macro and 15 cases of Large PLT; After radiotherapy, there were 9 cases of IG, 4 cases of ATYPS, 3 cases of NRBC, 4 cases of HC VAR, 7 cases of LS, 8 cases of Micro, 6 cases of Macro and 3 cases of Large platelet (Large PLT).

In the experimental group, there were 4 cases of IG, 2 cases of ATYPS, 1 case of NRBC, 3 cases of HC VAR, 5 cases of LS, 9 cases of

Table 6. Comparison of the number of morphological changes in blood cells between the two groups

Group		IG	ATYPS	NRBC	HC VAR	LS	Micro	Macro	Large PLT
Control group (n=96)	Before radiotherapy	7	0	1	2	4	10	5	0
	During radiotherapy	33**	18**	25**	17**	32**	27**	18**	18**
	After radiotherapy	9##	4##	3##	4##	7##	8##	6##	3##
Experimental group (n=96)	Before radiotherapy	4	2	1	3	5	9	4	1
	During radiotherapy	20**	8	11**	9	17**	17	9	8*
	After radiotherapy	6##	2	2##	4	7##	5##	4	2

Note: Compared with the same group before radiotherapy, *P<0.05, **P<0.01; Compared with the same group during radiotherapy, ##P<0.01; IG: immature granulocyte; NRBC: nucleated red blood cells; HC VAR: Hemoglobin Concentration Variability; LS: left shift; Micro: micro cells; Macro: macro cells; ATYPS: atypical lymphocytes.

Table 7. Comparison of coagulation function between the two groups

Index \ Group		Control group (n=108)	Experimental group (n=84)	*t*	*P*
PT (s)	Before radiotherapy	13.21±0.67	13.35±0.74	1.372	0.172
	After radiotherapy	18.01±1.21*	17.44±1.09*	3.380	<0.001
APTT (s)	Before radiotherapy	34.10±3.14	35.09±3.88	1.95	0.052
	After radiotherapy	26.68±3.13*	28.32±3.39*	3.473	<0.001
Fib (g/L)	Before radiotherapy	3.61±0.71	3.58±0.77	0.280	0.780
	After radiotherapy	4.25±0.95*	3.75±0.92*	3.668	<0.001
D-D (mg/L)	Before radiotherapy	0.55±0.12	0.54±0.11	0.594	0.553
	After radiotherapy	0.80±0.11*	0.72±0.13*	4.615	<0.001

Note: PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; Fib: Fibrinogen; D-D: D-Dimer. Compared with the same group before radiotherapy, *P<0.05.

Micro, 4 cases of Macro and 1 case of Large PLT before radiotherapy. During radiotherapy, there were 20 cases of IG, 8 cases of ATYPS, 11 cases of NRBC, 9 cases of HC VAR, 17 cases of LS, 19 cases of Micro, 9 cases of Macro and 8 cases of Large PLT. After radiotherapy, there were 6 cases of IG, 2 cases of ATYPS, 2 cases of NRBC, 4 cases of HC VAR, 7 cases of LS, 5 cases of Micro, 4 cases of Macro, and 2 cases of Large PLT.

The morphological changes of all types of blood cells in both groups were higher after radiotherapy. However, the control group exhibited more IG, ATYPS, HC VAR, LS, Micro and Large PLT than the experimental group (P<0.05, **Table 6**).

Comparison of coagulation function between the two groups

Compared to the pre-radiotherapy period, both groups exhibited significant changes in coagulation parameters, including prolonged PT, shortened APTT, and increases in Fib and D-D levels (all P<0.05). Notably, the coagulation function-related indices in the experimental group demonstrated less variation compared to the control group (P<0.05). The details are presented in **Table 7**.

Comparison of quality-of-life scores between the two groups

There was no significant difference in the quality-of-life scores between the experimental group and the control group across all four domains (all P>0.05). After radiotherapy, these scores improved in the both groups (P<0.05), with patients in the experimental group showing higher scores across all four domains compared to the control group (all P<0.05). The details are presented in **Table 8** and **Figure 2**.

Comparison of the incidence of adverse reactions

Both groups experienced some adverse effects after radiotherapy, including radiation pneumonitis, radiation esophagitis, bone marrow

Table 8. Comparison of quality of life between the two groups

Group	Before radiotherapy			
	Physiological	Psychosocial	Society	Environment
Control group (n=108)	52.01±5.63	52.5±5.79	51.62±6.33	53.43±5.74
Experimental group (n=84)	51.23±7.78	52.66±7.49	50.25±5.16	53.96±6.95
t	0.80	0.167	1.610	0.588
P	0.422	0.868	0.109	0.564
Group	After radiotherapy			
	Physiological	Psychosocial	Society	Environment
Control group (n=108)	63.02±5.31*	65.12±4.50*	64.46±5.66*	63.38±5.85*
Experimental group (n=84)	65.34±6.09*	67.81±6.06*	67.83±5.69*	65.82±5.65*
t	2.816	3.530	4.083	2.910
P	0.005	<0.001	<0.001	0.004

Note: Compared with the same group before radiotherapy, *P<0.05.

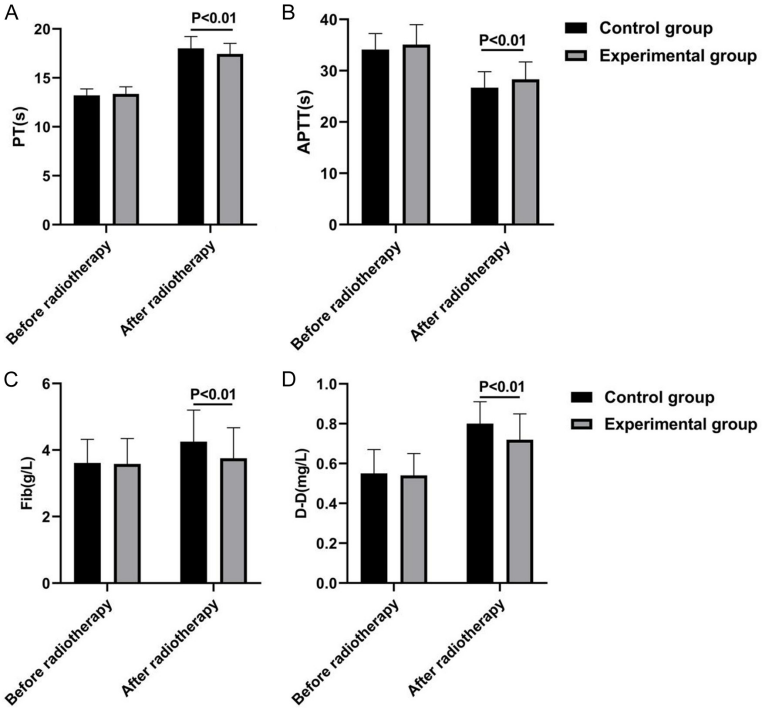

Figure 2. Comparison of coagulation function parameters between the two groups before and after radiotherapy. Note: A: PT; B: APTT; C: Level of Fib; D: Level of D-D. PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; Fib: Fibrinogen; D-D: D-Dimer.

suppression, skin reactions, and gastrointestinal reactions. The control group had 35 cases of radiation pneumonitis, 27 cases of radiation esophagitis, 25 cases of bone marrow suppression, 28 cases of skin reactions, and 27 cases of gastrointestinal reactions. In comparison, the experimental group reported significantly fewer cases: 15, 11, 9, 12, and 11 cases, respectively (P<0.05). The detailed results are presented in **Table 9** and **Figure 3**.

Discussion

Lung cancer currently holds the position of having the highest incidence and mortality rates among malignancies globally [13]. It can be classified into small cell lung cancer and non-small cell lung cancer based on histology, with non-small cell lung cancer accounting for more than 85% of cases [14]. Although surgical resection remains the mainstay of treatment for lung cancer to date [15], the Gamma Knife is considered one of the most effective palliative treatments for patients in the middle to advanced stages of the disease. This is especially true for those who are inoperable, cannot tolerate surgery or chemotherapy, cannot afford targeted therapies, and have a strong desire to be treated with radiotherapy [16].

Both body gamma knife and conventional radiotherapy use radiation to destroy diseased tissues; however, they differ in treatment principles and techniques. Conventional radiotherapy primarily functions therapeutically by exploiting the differential sensitivity of tumor

Table 9. Comparison of the incidence of adverse reactions between the two groups of patients

Group	n	Radiation pneumonitis	Radiation esophagitis	Bone marrow depression	Skin reaction	Gastrointestinal reaction
Control group	108	35	27	25	28	27
Experimental group	84	15	11	9	12	11
x^2	-	5.194	4.218	5.013	3.882	4.218
P	-	0.023	0.040	0.025	0.049	0.040

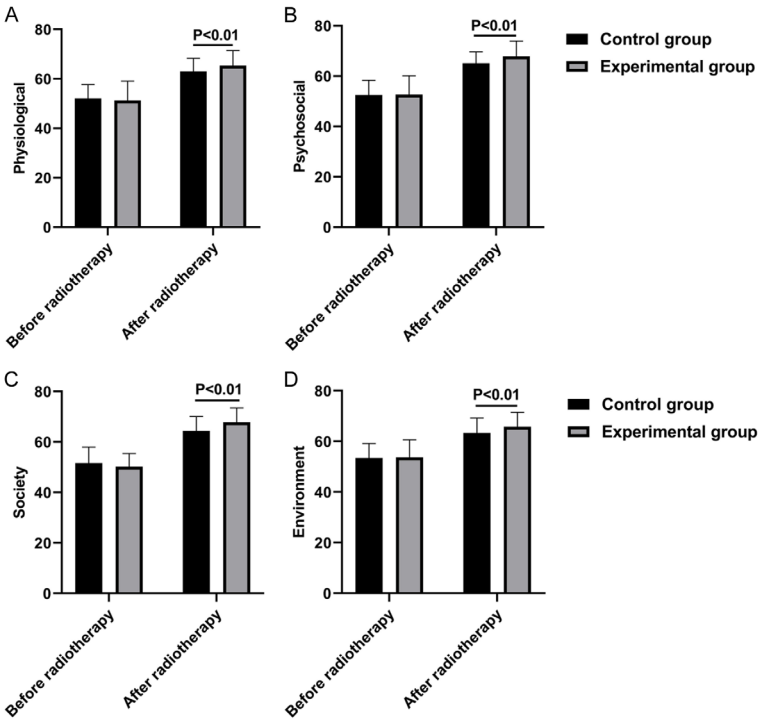

Figure 3. Comparison of quality of life between the two groups before and after radiotherapy. A: Physiological dimension; B: Psychosocial dimension; C: Society dimension; D: Environment dimension.

tissue to radiation compared to normal tissue, which inevitably leads to some degree of damage to the surrounding healthy tissues [17]. In contrast, gamma knife represents a high-precision form of radiotherapy that can be administered multiple times or even perform non-invasive ablation of both primary and secondary lung cancer in a single outpatient session. This technique involves irradiating the target area with a large dose to induce radiation necrosis. Consequently, previous studies have demonstrated the efficacy of the Gamma Knife in treating tumor lesions [5, 18]. The findings of this study suggest a notable distinction in outcomes between the experimental group and the control group. Specifically, patients who underwent the intervention demonstrated a significantly higher DCR, indicating that a greater proportion of these patients achieved effective disease control. Additionally, the ORR was also significantly higher in the experimental group, suggesting that more patients experienced either complete or partial alleviation of their symptoms compared to those in the control group. This further confirming that gamma knife SBRT for patients with intermediate and advanced lung cancer.

Univariate and multivariate analysis showed that there were some differences in the location and type of tumors between the two groups, with more tumors located on the left side of the lungs in the control group than in the experimental group, while the central type of tumors was lower than in the experimental group. Further, the factors with differences and the effect of radiotherapy modality on the patients' progression-free survival within one year were analyzed by COX regression multivariate analysis, and it was found that the radiotherapy modality was an independent influencing factor affecting the prognosis of the patients, which is basically in line with the results of the previous. This is basically consistent with the results of the study, and gamma knife SBRT has a crucial role in prolonging the survival of patients.

The results of this study indicated that after radiotherapy, the levels of white blood cells, neutrophils, lymphocytes, red blood cells, and platelets in both the control and radiation

groups showed a reduction when compared to their levels before radiotherapy. Notably, the decrease in cell counts was significantly greater in the control group. The reduction in these cell types was more pronounced in the control group than in the experimental group. This is consistent with the research of Juliana Matiello et al. [19] and Sophia Kastle et al. [20] which indicates that radiotherapy can have a significant impact on the levels of blood cells in patients. This phenomenon may be attributed to the impact of radiotherapy, where radiation passing through bone tissue affects the division and reproduction of various types of progenitor blood cells in the bone marrow, leading to a decline in the counts of these cells in the bloodstream [21]. Among these, the white blood cell count is a reliable indicator of the body's inflammatory and immune status [22]. An increase in white blood cell count typically occurs during infection. Research indicates that over 50% of lung cancer patients experience a decrease in white blood cell counts post-radiotherapy. This outcome not only prolongs the duration of radiotherapy for patients but may also increase the risk of infection, potentially endangering their lives [23]. Neutrophils, which constitute 40% to 75% of total white blood cells, serve as the first line of defense against infections and are crucial in tumor progression [24]. Platelets exhibit similar behavior; when stimulated by tumors, the body can exhibit symptoms akin to inflammatory responses. The aggregation of platelets and the release of platelet-derived pro-angiogenic mediators contribute to tumor growth [25, 26]. Additionally, lymphocytes and red blood cells are vital for both cellular and humoral immunity. During radiotherapy, radiation can suppress the body's immune function. Therefore, in clinical practice, it is essential to avoid excessive irradiation doses to mitigate the immunosuppressive effects of radiotherapy. Moreover, Microscopy can be used to observe the size and morphology of red blood cells, as well as changes in the abnormal structures of the cells. It also allows for the detection of changes in the number of white blood cells and neutrophils, such as whether there is a left or right shift in the nucleus, toxicity changes, or the presence of immature cells. The study indicates that changes in blood cell morphology after radiation therapy are fewer in the experimental group compared to the control group. By directly observing changes in the morphology of peripheral blood cells, the recovery pf patients with myelosuppression can be monitored more effectively [10].

According to statistics, more than half of tumor patients exhibit coagulation abnormalities, with PT reflecting the activity of various coagulation factors and providing insight into the exogenous coagulation function. APTT, on the other hand, reflects to the activity of endogenous coagulation factors and the level of prothrombin [27]. In addition, Fib, a key factor in the coagulation system, plays an indispensable role in the coagulation system, and changes in its level are closely related to the occurrence and development of various diseases [28]. Mayne et al. [29] found that Fib participates in the blood coagulation process and promotes the formation of thrombus, which acts as a protective barrier for tumor cells, facilitating their survival and metastasis in the bloodstream; It also interacts with inflammatory cells around the tumor, promoting the formation of an inflammatory response and tumor microenvironment, creating favorable conditions for tumor growth and metastasis. D-D is a fibrinolytic products in the blood, and its level reflects the balance between the body's coagulation and fibrinolytic systems [30, 31]. The findings of our research indicated that both groups experienced an increase in PT after radiotherapy, with a more significant prolongation observed in the control group compared to the experimental group. Similarly, APTT decreased in both groups, with a more pronounced shortening in the control group than in the experimental group. Moreover, both groups showed elevated levels of Fib and D-D, with the rise in these markers being more substantial in the control group than in the experimental group. This suggests that the coagulation function of patients with advanced lung cancer patients is abnormal, and both radiotherapy modalities can exacerbate this abnormal coagulation state. However, Gamma Knife Stereotactic Radiotherapy appears to cause less damage to vascular endothelial cells and coagulation function, effectively reduces the incidence of thromboembolic disease. The results obtained are largely consistent with those reported by Bentsen KK et al. [32] in their study on stereotactic radiosurgery for patients with local non-small cell lung can-

cer. In blood samples collected before and after SBRT treatment, platelet aggregation levels were reduced compared to those prior to treatment yet remained within the reference range. This finding suggests that SBRT does not impact thrombin production in vivo or in vitro, nor does it affect platelet aggregation.

In this study, it was found that both groups of patients experienced radiation pneumonitis, radiation esophagitis, bone marrow suppression, varying degrees of skin reactions, and gastrointestinal reactions; however, the frequency of these adverse events was lower in the experimental group compared to the control group. Adverse radiation reactions, or radiation damage, following radiotherapy represent unnecessary radiological changes and thus warrant significant clinical attention [33]. Currently, there is no definitive conclusion regarding the actual incidence of adverse radiation reactions in gamma knife SBRT. However, research indicates that patients undergoing this treatment may begin to exhibit symptoms within 18 months, with over 75% of lesions developing within the same period. These lesions generally resolve within 22 months, with only a small proportion remaining as permanent lesions [34, 35]. Moreover, these changes are not disease-specific, suggesting that despite the high doses of radiation used in gamma knife SBRT for targeted irradiation, there is no corresponding increase in adverse reactions among patients' post-treatment.

A comparison of the WHOQOL-BERF scores across various dimensions after radiotherapy revealed that the experimental group scored higher than the control group. This finding suggests that Gamma Knife SBRT can enhance the quality of survival for patients with intermediate and advanced lung cancer. This improvement may be attributed to the precise three-dimensional distribution of the high-dose radiation delivered by Gamma Knife SBRT, which effectively minimizes the irradiated dose and volume to surrounding healthy tissues. By controlling the dose and volume of radiation to adjacent normal tissues, the treatment reduces the adverse effects of irradiation, facilitates quicker recovery post-treatment and ultimately improves the overall quality of survival for these patients.

This study has several limitations. Firstly, as a retrospective analysis, there may be selection bias in the sample selection. Secondly, due to the limited sample size, we were unable to include additional radiation parameters for analysis. Finally, the follow-up period after radiotherapy was relatively short; therefore, longer follow-up is required to confirm the long-term effects of Gamma Knife SBRT in future studies.

Conclusion

Gamma Knife SBRT is an effective and relatively safe treatment option for patients with intermediate and advanced lung cancer. This efficacy is demonstrated by the high DCR and ORR, minimal damage to peripheral blood cell levels and morphology, as well as coagulation function, and a low incidence of adverse effects. Furthermore, this treatment contributes to the improvement of patients' quality of life following therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Xiao-Chen Wang, Department of Thoracic and Cardiovascular Surgery, Suzhou BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, No. 181 Zhuyuan Road, Huqiu District, Suzhou 215003, Jiangsu, China. Tel: +86-0512-80838800; E-mail: 15852666837@126.com

References

[1] Huang T, Ren K, Ding G, Yang L, Wen Y, Peng B, Wang G and Wang Z. miR-10a increases the cisplatin resistance of lung adenocarcinoma circulating tumor cells via targeting PIK3CA in the PI3K/Akt pathway. Oncol Rep 2020; 43: 1906-1914.

[2] Tsiouda T, Sardeli C, Porpodis K, Pilikidou M, Apostolidis G, Kyrka K, Miziou A, Kyrka K, Tsingerlioti Z, Papadopoulou S, Heva A, Koulouris C, Giannakidis D, Boniou K, Kesisoglou I, Vagionas A, Kosmidis C, Sevva C, Papazisis G, Goganau AM, Sapalidis K, Tsakiridis K, Tryfon S, Platanas M, Baka S, Zaric B, Perin B, Petanidis S and Zarogoulidis P. Sex differences and adverse effects between chemotherapy and immunotherapy for non-small cell lung cancer. J Cancer 2020; 11: 3407-3415.

[3] Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, Xia C, Sun K, Yang Z, Li H, Wang N, Han R,

Liu S, Li H, Mu H, He Y, Xu Y, Fu Z, Zhou Y, Jiang J, Yang Y, Chen J, Wei K, Fan D, Wang J, Fu F, Zhao D, Song G, Chen J, Jiang C, Zhou X, Gu X, Jin F, Li Q, Li Y, Wu T, Yan C, Dong J, Hua Z, Baade P, Bray F, Jemal A, Yu XQ and He J. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018; 6: e555-e567.

[4] Qi Y, Li J, Zhang Y, Shao Q, Liu X, Li F, Wang J, Li Z and Wang W. Effect of abdominal compression on target movement and extension of the external boundary of peripheral lung tumors treated with stereotactic radiotherapy based on four-dimensional computed tomography. Radiat Oncol 2021; 16: 173.

[5] Xie Q, Xie B, Ou L, Wang M, Tang Z, He Y, Yang X, Hong J, Lyu Z and Wei R. Clinical outcomes and prognostic analysis of 101 patients of central neurocytoma: a 10-year treatment experience at a single institution. Front Oncol 2022; 12: 881460.

[6] Zhao X, Ding S, Zhang M and Wang C. Gamma knife radiosurgery for patients with brain metastases from non-small cell lung cancer: comparison of survival between <5 and ≥5 metastases. Thorac Cancer 2022; 13: 2152-2157.

[7] Vera P, Thureau S, Le Tinier F, Chaumet-Riffaud P, Hapdey S, Kolesnikov-Gauthier H, Martin E, Berriolo-Riedinger A, Pourel N, Broglia JM, Boissellier P, Guillemard S, Salem N, Brenot-Rossi I, Le Péchoux C, Berthold C, Giroux-Leprieur E, Moreau D, Guillerm S, Benali K, Tessonnier L, Audigier-Valette C, Lerouge D, Quak E, Massabeau C, Courbon F, Moisson P, Larrouy A, Modzelewski R, Gouel P, Ghazzar N, Langlais A, Amour E, Zalcman G and Giraud P. Adaptive radiotherapy (up to 74 Gy) or standard radiotherapy (66 Gy) for patients with stage III non-small-cell lung cancer, according to [18F]FDG-PET tumour residual uptake at 42 Gy (RTEP7-IFCT-1402): a multicentre, randomised, controlled phase 2 trial. Lancet Oncol 2024; 25: 1176-1187.

[8] Akcay M, Etiz D, Celik O and Ozen A. Evaluation of acute hematological toxicity by machine learning in gynecologic cancers using postoperative radiotherapy. Indian J Cancer 2022; 59: 178-186.

[9] Fong KM, Rosenthal A, Giroux DJ, Nishimura KK, Erasmus J, Lievens Y, Marino M, Marom EM, Putora PM, Singh N, Suárez F, Rami-Porta R, Detterbeck F, Eberhardt WEE and Asamura H; Members of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Members of the Advisory Boards, and Participating Institutions of the Lung Cancer Domain. The international association for the study of lung cancer staging project for lung cancer: proposals for the revision of the M descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. J Thorac Oncol 2024; 19: 786-802.

[10] Tian S, Huang P, Gu Y, Yang J, Wu R, Zhao J, Liu AJ and Zhang W. Systems biology analysis of the effect and mechanism of Qi-Jing-Sheng-Bai granule on leucopenia in mice. Front Pharmacol 2019; 10: 408.

[11] Kim DW, Tan E, Zhou JM, Schell MJ, Martinez M, Yu J, Carballido E, Mehta R, Strosberg J, Imanirad I and Kim RD. A phase 1/2 trial of ibrutinib in combination with pembrolizumab in patients with mismatch repair proficient metastatic colorectal cancer. Br J Cancer 2021; 124: 1803-1808.

[12] Sirey JA, Solomonov N, Guillod A, Zanotti P, Lee J, Soliman M and Alexopoulos GS. PROTECT: a novel psychotherapy for late-life depression in elder abuse victims. Int Psychogeriatr 2021; 33: 521-525.

[13] Zhao J, Li G, Zhao G, Wang W, Shen Z, Yang Y, Huang Y and Ye L. Prognostic signature of lipid metabolism associated LncRNAs predict prognosis and treatment of lung adenocarcinoma. Front Oncol 2022; 12: 986367.

[14] Cong S, Di X, Li R, Cao Y, Jin X, Tian C, Zhao M and Wang K. RBM10 regulates alternative splicing of lncRNA Neat1 to inhibit the invasion and metastasis of NSCLC. Cancer Cell Int 2022; 22: 338.

[15] Li W, Feng SS, Wu H, Deng J, Zhou WY, Jia MX, Shi Y, Ma L, Zeng XX, Zuberi Z, Fu D, Liu X and Chen Z. Comprehensive analysis of CDK1-associated ceRNA network revealing the key pathways LINC00460/LINC00525-Hsa-Mir-338-FAM111/ZWINT as prognostic biomarkers in lung adenocarcinoma combined with experiments. Cells 2022; 11: 1220.

[16] Khorfan R, Kruser TJ, Coughlin JM, Bharat A, Bilimoria KY and Odell DD. Survival of primary stereotactic body radiation therapy compared with surgery for operable stage I/II non-small cell lung cancer. Ann Thorac Surg 2020; 110: 228-234.

[17] Kwak SY, Park S, Kim H, Lee SJ, Jang WS, Kim MJ, Lee S, Jang WI, Kim AR, Kim EH, Shim S and Jang H. Atorvastatin inhibits endothelial PAI-1-mediated monocyte migration and alleviates radiation-induced enteropathy. Int J Mol Sci 2021; 22: 1828.

[18] Lee WJ, Lee JI, Choi JW, Kong DS, Nam DH, Cho YS, Shin HJ and Seol HJ. Optimal volume of the residual tumor to predict long-term tumor control using stereotactic radiosurgery after facial nerve-preserving surgery for vestibular schwannomas. J Korean Med Sci 2021; 36: e102.

[19] Matiello J, Dal Pra A, Zardo L, Silva R and Berton DC. Impacts of post-radiotherapy lymphocyte count on progression-free and overall sur-

vival in patients with stage III lung cancer. Thorac Cancer 2020; 11: 3139-3144.
[20] Kästle S, Stechele MR, Richter L, Schinner R, Öcal E, Alunni-Fabbroni M, De Toni E, Corradini S, Seidensticker M, Goldberg SN, Ricke J, Wildgruber M and Kimm MA. Peripheral blood-based cell signature indicates response to interstitial brachytherapy in primary liver cancer. J Cancer Res Clin Oncol 2023; 149: 9777-9786.
[21] Chugh RM, Bhanja P, Olea XD, Tao F, Schroeder K, Zitter R, Arora T, Pathak H, Kimler BF, Godwin AK, Perry JM and Saha S. Human peripheral blood mononucleocyte derived myeloid committed progenitor cells mitigate H-ARS by exosomal paracrine signal. Int J Mol Sci 2022; 23: 5498.
[22] Zhu J, Duan Y, Duo D, Yang J, Bai X, Liu G, Wang Q, Wang X, Qu N, Zhou Y and Li X. High-altitude hypoxia influences the activities of the drug-metabolizing enzyme CYP3A1 and the pharmacokinetics of four cardiovascular system drugs. Pharmaceuticals (Basel) 2022; 15: 1303.
[23] Li F, Wang L, Cai Y, Luo Y and Shi X. Safety assessment of desaminotyrosine: acute, subchronic oral toxicity, and its effects on intestinal microbiota in rats. Toxicol Appl Pharmacol 2021; 417: 115464.
[24] Qu Z, Wang Q, Wang H, Jiao Y, Li M, Wei W, Lei Y, Zhao Z, Zhang T, Zhang Y and Gu K. The effect of inflammatory markers on the survival of advanced gastric cancer patients who underwent anti-programmed death 1 therapy. Front Oncol 2022; 12: 783197.
[25] Shen F, Liu C, Zhang W, He S, Wang F, Wang J, Li Q and Zhou F. Serum levels of IL-6 and CRP can predict the efficacy of mFOLFIRINOX in patients with advanced pancreatic cancer. Front Oncol 2022; 12: 964115.
[26] Huong PT, Nguyen LT, Nguyen XB, Lee SK and Bach DH. The role of platelets in the tumor-microenvironment and the drug resistance of cancer cells. Cancers (Basel) 2019; 11: 240.
[27] Kotál J, Polderdijk SGI, Langhansová H, Ederová M, Martins LA, Beránková Z, Chlastáková A, Hajdušek O, Kotsyfakis M, Huntington JA and Chmelař J. Ixodes ricinus salivary serpin iripin-8 inhibits the intrinsic pathway of coagulation and complement. Int J Mol Sci 2021; 22: 9480.
[28] Kalyvas A, Gutierrez-Valencia E, Lau R, Ye XY, O'Halloran PJ, Mohan N, Wong C, Millar BA, Laperriere N, Conrad T, Berlin A, Bernstein M, Zadeh G, Shultz DB and Kongkham P. Anatomical and surgical characteristics correlate with pachymeningeal failure in patients with brain metastases after neurosurgical resection and adjuvant stereotactic radiosurgery. J Neurooncol 2023; 163: 269-279.
[29] Mayne NR, Lin BK, Darling AJ, Raman V, Patel DC, Liou DZ, D'Amico TA and Yang CJ. Stereotactic body radiotherapy versus delayed surgery for early-stage non-small-cell lung cancer. Ann Surg 2020; 272: 925-929.
[30] Bodensohn R, Kaempfel AL, Fleischmann DF, Hadi I, Hofmaier J, Garny S, Reiner M, Forbrig R, Corradini S, Thon N, Belka C and Niyazi M. Simultaneous stereotactic radiosurgery of multiple brain metastases using single-isocenter dynamic conformal arc therapy: a prospective monocentric registry trial. Strahlenther Onkol 2021; 197: 601-613.
[31] Stankiewicz M, Tomasik B and Blamek S. A new prognostic score for predicting survival in patients treated with robotic stereotactic radiotherapy for brain metastases. Sci Rep 2021; 11: 20347.
[32] Bentsen KK, Hojbjerg JA, Vinholt PJ, Hansen O, Hvas AM and Jeppesen SS. Impact of stereotactic body radiotherapy on thrombin generation and platelet aggregation in patients with non-small cell lung cancer. Clin Appl Thromb Hemost 2023; 29: 10760296231216962.
[33] van der Werf LR, Cords C, Arntz I, Belt EJT, Cherepanin IM, Coene PLO, van der Harst E, Heisterkamp J, Langenhoff BS, Lamme B, van Berge Henegouwen MI, Lagarde SM and Wijnhoven BPL. Population-based study on risk factors for tumor-positive resection margins in patients with gastric cancer. Ann Surg Oncol 2019; 26: 2222-2233.
[34] Qu Q, Zhang Z, Guo X, Yang J, Cao C, Li C, Zhang H, Xu P, Hu Z and Tian J. Novel multifunctional NIR-II aggregation-induced emission nanoparticles-assisted intraoperative identification and elimination of residual tumor. J Nanobiotechnology 2022; 20: 143.
[35] Klement RJ, Sonke JJ, Allgäuer M, Andratschke N, Appold S, Belderbos J, Belka C, Blanck O, Dieckmann K, Eich HT, Mantel F, Eble M, Hope A, Grosu AL, Nevinny-Stickel M, Semrau S, Sweeney RA, Hörner-Rieber J, Werner-Wasik M, Engenhart-Cabillic R, Ye H, Grills I and Guckenberger M. Correlating dose variables with local tumor control in stereotactic body radiation therapy for early-stage non-small cell lung cancer: a modeling study on 1500 individual treatments. Int J Radiat Oncol Biol Phys 2020; 107: 579-586.