The application of gamma stereotactic body radiation therapy in stage I/II non-small-cell lung cancer

Promising and encouraging outcome

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ABSTRACT

الأهداف: تقييم إضافي لفعالية العلاج الإشعاعي بأشعة جاما في مرضى المرحلة الأولى والثانية من سرطان الرئة ذات الخلية غير الصغيرة (NSCLC).

الطريقة: اشتملت الدراسة على 29 مريض حديث التشخيص بNSCLC في المراحل الأولى والثانية اللذين لم يخضعوا لعلاج مسبق خضعوا لنوع من قي قسم علاج الأورام بالإشعاع في مستشفى العام لسلاح الجو، بيجنج، الصين خلال الفترة من يناير 2007م حتى يوليو 2010م. تم شل حركو كل المرضى عن طريق كيس مفرغ من الهواء ثم إجراء مسح صور مقطعي بطيء دون أي حركات تنفس. تم وصف جرعة إشعاع كلية من 50% و 60% و 70% من خط حقنة تماثلية من 50، 60، 70 جراي على التوالي، بذلك يشمل 100% من حجم الهدف الإجمالي في 10 أجزاء. يتطلب CT للصدر في الشهر الأول، و3، و6، و12، و18، و24 لتقييم فعالية العلاج.

النتائج: كانت فترة المتابعة المتوسطة 24 شهر ونسبة المتابعة النهائية 96.6% ونسبة التحكم لسنة وسنتين 93.1%. كانت نسبة النجاح الخالية من التقدم مقابل نسبة النجاة الكلية لسنة واحدة هي 89.7% مقابل 96.6% وسنتين كانت 86.1% مقابل 89.4%. تم تشخيص رد فعل إشعاعي متأخر في 34.5% من المرضى.

خاتمة: ينتج عن γ–SBRT أثر علاجي جيد وتسمم بحد أدنى في علاج المرحلة الأولى والثانية من سرطان الرئة ذات الخلية غير الصغيرة.

Objectives: To further evaluate the efficacy and toxicity of the gamma-ray stereotactic body radiation therapy (γ-SBRT) in patients with stage I/II non-small-cell lung cancer (NSCLC).

Methods: Twenty-nine newly diagnosed patients with stage I/II NSCLC who had no previous treatments, underwent OUR-QGD type of the γ-SBRT at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China from January 2007 to July 2010. All patients were immobilized by vacuum bag, and then a slow CT scan was performed without any respiration gating. The total radiation dose of 50%, 60%, and 70% isodose line were prescribed in 50, 60, and 70 Grey (Gy) correspondingly, covering 100% of the planning target volume (PTV), 90% of the clinical target volume (CTV), and 80% of the gross target volume (GTV) in 10 fractions. The CT scans of the chest were required at one, 3, 6, 12, 18, and 24 months to evaluate the efficacy of the treatment.

Results: The median follow-up duration was 24 months, and the final follow-up rate is 96.6%. Local control rates of one and 2 years were all 93.1%. The progression-free survival rates versus overall survival rate of one year was 89.7% versus 96.6%, and 2 years was 86.1% versus 89.4%. Acute radiation reactions was diagnosed in 34.5%, and late radiation reactions in 37.9% of patients.

Conclusion: The γ-SBRT results in a good curative effects, and minimal toxicity in the treatment of stage I/II NSCLC.

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Lung cancer is the primary cause of death in most countries. Non-small-cell lung cancer (NSCLC), accounts for approximately 80% of the entire lung cancer, in which the stage I/II NSCLC patients is approximately 30% of all NSCLC. The past clinical effect proved that operation was the preferred surgery.[1] As referred to in other studies, local recurrences, or distant metastasis are the most important cause of treatment failure and death in malignant tumor, and the 5-year survival rate is approximately 60-80%.[2] A total of 45% new diagnosed NSCLC cases are aged patients above 65 years, and approximately 60% of patients cannot be operated due to old age, or medical reasons. For such patients, stereotactic body radiation therapy (SBRT) has now become the preferred treatment.[3] As known, SBRT is an important technique in the treatment of local and limited tumors in almost every part of the body, and the special advantages are short course, high dose of every fraction, and better local control compared with the traditional radiotherapy. Gamma knife stereotactic radiosurgery (with a single fraction) and gamma knife fractionated stereotactic radiotherapy (in which multiple fractions are given over a period of 2-4 weeks) is not familiar to most radiotherapy doctors, but it really have demonstrated the unique advantage strategy for many cancer treatments. Body gamma knife is a domestically-made stereotactic radiation therapy unit with a highly-focused dose and 3D conformal ability, which can make focusing dose in the target area layers increase to obtain the biological significance as a factor of dose escalation. We utilized this radiation technique in the treatment of early NSCLC, and obtained the same results with foreign external beam radiation.[4] In the past study, we demonstrated that 43 patients with inoperable stage I/II NSCLC underwent gamma (γ)-SBRT, which resulted in promising local control and survival with minimal toxicity. In this study, we aim to further explore the effect of radiotherapy for stage I/II NSCLC by China body gamma knife system, and provide a strong practical basis for clinically standardized treatment.

Methods.

Patient information and characteristics. From January 2007 to July 2010, 29 enrolled patients at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China with stage I/II NSCLC (UICC 2002 version) who were inoperable due to medical reasons, or refused operation were treated prospectively using body gamma knife radiotherapy (γ-SBRT, developed by OUR International Technology & Science Co., Ltd. Shenzhen, China). The recruited patients must attain the following enrollment criteria for inclusion: patients with stage I/II NSCLC who were inoperable or refused operation; patients receiving chemotherapy can also be arranged in group; Karnofsky performance status (KPS) score >60; pathological and cytological diagnosis; without pathological diagnosis (biopsy difficult or refused biopsy), patients must had clinical history, met the clinical imaging diagnosis, positron emission tomography (PET)/CT supported; on supine or prone for more than 30 minutes; and signed an informed consent for treatment. This research was approved by the Ethics Committee of our hospital. Patients who previously obtained chemotherapy or surgery for treatment of NSCLC, had a history of another invasive cancer, prior radiation therapy (RT) to the chest area, prior chemotherapy therapy, or the presence of any serious medical conditions were excluded from the study. All 29 cases were confirmed and staged by PET/CT diagnosis; 15 cases cannot be operated because of comorbidities, such as cardiovascular disease, chronic obstructive pulmonary disease, and diabetes or old age (≥75 years) (**Table 1**). This study was conducted according to the principles of Helsinki Declaration, and all patients who agreed to attend the research signed an informed consent.

Treatment methods. All patients were immobilized using a stereotactic body frame with a vacuum pillow to create reproducible immobilization. The CT scanning and treatment required patients with quiet breathing and not controlled breathing. Every patient underwent CT simulation ranging from the neck midline to 3 cm under the diaphragm with a CT-slide thickness of 5 mm and CT-slide interval of 5 mm. Scanning images are sent directly to the planning system through the network with a 5 second scanning speed for each level.[1,4,5] The target volume was delineated in the lung window (window width: 1500-1700 Hounsfield units (HU), window center: -300 HU), gross target volume (GTV) was the primary tumor, clinical target volume (CTV) was allowed a 5 mm margin around the GTV; planning target volume (PTV) was created using pulmonary window, which allowed a 5 mm margin around the CTV. Low-speed CT was used, and did not consider the impact of respiratory move on inside target volume (ITV).[1,4,5] The treatment planning software Unicorn

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3-D (developed by OUR International Technology & Science Co., Ltd. Shenzhen, China) with 50% isodose curve covering approximately 100% of the PTV, 60% isodose curve covering approximately 90% of the CTV, and 70% isodose curve covering approximately 80% of the GTV. The PTV, CTV and GTV prescription dose were 50 Gy, 60 Gy and 70 Gy. Radiotherapy was delivered 5 days per week for 2 weeks. Patients with poor lung function, or had hilar lymph node treatment (2 cases) was given a single dose of 3-4 Gy, a total of 13-15 fractions. The dose delivered to the critical structures, such as the main bronchi, heart, and major blood vessels were required to be below 48 Gy for one cc, 40 Gy for 10 cc, and the dose delivered to the esophagus, trachea were required to be below 40 Gy for one cc, and 36 Gy for 10 cc. Before treatment, patients were scanned by CT offline verification, then we compared the dose distribution, dose to the target volume coverage between the positioning image and validating image. The patients' posture were validated 2-3 times during the treatment, to ensure the positioning, planning, and treatment process accuracy.

Clinical staging and evaluation of therapeutic efficacy. All patients were evaluated by chest CT, brain, and bone scans.

Follow-up. The follow-up evaluations consisted of a medical history and physical examination. The CT scans of the chest was required at one, 3, 6, 12, and 24 months after treatment. The PET/CT was used for diagnosis after treatment in 3-6 months. Patient's condition, tumor control, side effects, and survival were monitored by way of visits, hospital review, telephone calls, and correspondence.

Short-side effect. A CT scan was performed at 3-6 months after treatment. Complete response (CR) was defined as complete disappearance of all measurable disease; partial response (PR) was defined as a 30% reduction in the sum of the perpendicular diameters of all measurable lesions; progression disease (PD) was defined as a 20% increase in the sum of perpendicular diameters of all measurable lesions and new lesions that developed; stable disease (SD) was defined as the lesion reduced up to PR, increases not exceeding PD. Overall survival (OS), progression-free survival (PFS) and local control responses (LCR) were used to evaluate long-side effect. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (US Department of Health and Human Services, National Institutes of Health National Cancer Institute) was used to evaluate early and late radiation-induced damages.

Statistical analysis. The Statistical Package for Social Sciences software program version 13 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. Toxicity and LCR of the biological effective dose (BED) were calculated using the linear-quadratic model, assuming that the alpha/beta=10. The follow-up duration was defined as the time from the date of completion of treatment to the date of death, or to the last date of follow-up for surviving patients. The survival and local control rates were calculated from the date of treatment. The Kaplan-Meier method was used to calculate the OS and LCR. The log-rank test was used to compare the different levels of a factor. A $p<0.05$ was considered statistically significant.

Results. ***Treatment response and survival status.*** The last follow-up examination was performed on December 2011, and the final follow-up rate was 96.6%. The CR rate for 29 patients were 17.2% (one month after treatment), 44.8% (3 months after treatment), and 86.2% (6 months after treatment). The PR rate were 62.1% (one month after treatment), 44.8% (3 months after treatment), and 6% (6 months after treatment). The SD were 20.7% (one month after treatment), 10.3% (3 months after treatment), and 6.9 (6 months after treatment). None of the patients had PD. The overall response rate (CR + PR) after treatment were: LCR rates were both 93.1% (one and 2 years); OS rates were 96.6% (one year), 89.4% (2-year); and PFS rates were 89.7% (one year), 86.1% (2-year). Overall, 2 patients died (one died of hemoptysis), which might be associated with obstructive pneumonia due to left lung upper lobe atelectasis, and the other died of multiple organ failure. Two patients had a local recurrence (based on CT or PET scans), which all happened in the lower lobe of the left lung. One case (stage Ia) recurred 5 months after treatment in the site of the PTV died of multiple organ failure 13 months after treatment. The other had a recurrence 10 months after treatment (stage Ib). In addition, 5 patients had distant metastasis: one case transferred to the posterior vena cava and mediastinal lymph node on the 8-month, who received no further therapy before discharge. One died for multiple organ failure within 13 months. Treatment within 2 years; 3 cases had the appearance of distant metastases but still survived, of which 2 cases had multiple bone metastasis in 4 or 10 months, still another had single vertebral bone metastasis in 14 months.

Prognostic factors related survival. To elucidate whether the patient's age, gender, and pathological type has an impact on survival, we analyzed the prognostic factors of patients. Univariate analysis showed that age (≥75 years (n=11) versus <75 (n=18), $p=0.154$), gender (male (n=22) versus women (n=7), $p=0.342$), physical condition (cannot tolerate operation (n=14)

Table 1 - Characteristics of patient's included in a study at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China.

Characteristics	n=29	(%)
Age, year		
Median	71	
Range	55-87	
Gender		
Male	22	(75.9)
Female	7	(24.1)
Diagnostic evidence		
Squamous cell carcinoma	8	(27.6)
Adenocarcinoma	7	(24.1)
No pathology	14	(48.3)
TNM stage		
Ia	15	(51.7)
Ib	11	(37.9)
IIa	2	(6.9)
IIb	1	(3.5)
Physical state		
Cannot tolerate operation	14	(48.3)
Refuse operation	15	(51.7)
Tumor target volume diameter, cm		
Median	2.5	
Range	1-5	

TNM - tumor, lymph nodes, and metastasis

versus refused operation (n=15), p=0.563), and tumor diameter (≥3 cm (n=12) versus <3 cm (n=17), p=0.376) were not prognostic factors, which affected the survival rate in patients (**Table 2**), TNM staging (stage I (n=26) versus stage II (n=3), p<0.122), because of less stage II cases, it cannot truly reflect the statistical significance. In addition, our study found that there was no significant differences between patients who only had the clinical diagnosis (PET/CT diagnosis and so forth), without pathological diagnosis (n=14), and the group who had pathologic diagnosis (n=15) were not statistically significant (p=0.09).

Toxicity. The side effects were mild during the treatment: the main symptom was intermittent cough, chest discomfort, and leukocyte reduction. Acute radiation-induced within 3 months, and late radiation-induced more than 3 months are shown in **Table 3**. Acute radiation-induced mainly for pneumonia (Grade I: 6, Grade III: 2), upper gastrointestinal reaction (Grade II: 1), blood reaction (Grade II: 1), and no Grade IV acute radiation reaction occurs. Late pulmonary toxicity side effects were expressed as asymptomatic pulmonary fibrosis and cough (Grade I: 9), late bone radiation-induced was mainly expressed as pain (Grade I+II: 1), no Grade III or above late radiation-induced occurs, and no treatment related deaths.

Table 2 - Clinical features and single factor analysis of prognosis with stage I/II NSCLC patients included in a study at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China.

Prognostic factors	Patient		one-year LCR	2-year LCR	1-year OS	2-year OS	χ^2	*P*-value
	N			(%)				
Patients								
Age, year							2.030	0.154
≥75	11	(37.9)	(100.0)	(100.0)	(100.0)	(100.0)		
<75	18	(62.1)	(88.9)	(88.9)	(94.4)	(82.6)		
Gender							0.904	0.342
Male	22	(75.9)	(90.9)	(90.9)	(95.5)	(86.4)		
Female	7	(24.1)	(100.0)	(100.0)	(100.0)	(100.0)		
TNM stage							2.392	0.122
I	26	(89.7)	(92.3)	(92.3)	(100.0)	(92.0)		
II	3	(10.3)	(100.0)	(100.0)	(66.7)	(66.7)		
Diagnostic evidence							2.861	0.091
Pathological	15	(51.7)	(86.7)	(86.7)	(93.3)	(80.0)		
No pathological	14	(48.3)	(100.0)	(100.0)	(100.0)	(100.0)		
Physical state							0.335	0.563
Cannot tolerate operation	14	(48.3)	(92.9)	(92.9)	(100.0)	(92.9)		
Refuse operation	15	(51.7)	(93.3)	(93.3)	(93.3)	(86.2)		
Tumor diameter, cm							0.784	0.376
≥3	12	(41.4)	(91.7)	(91.7)	(91.7)	(83.3)		
<3	17	(58.6)	(94.1)	(94.1)	(100.0)	(93.8)		

NSCLC - non-small cell lung cancer, TNM - tumor, lymph nodes, and metastasis, LCR - local control responses, OS - overall survival

Table 3 - Acute and late radiation side effects 3 months and more than 3 months after treatment in stage I/II NSCLC patients included in a study at the Radiation Oncology Department, People's Liberation Army Airforce General Hospital, Beijing, China.

Organs	stage 0	stage 1	stage 2	stage 3	stage 4
			N (%)		
Acute and late radiation side effects 3 months					
Upper GI tract	28	0	1 (3.5)	0 -	0 -
Lung	21	6 (20.7)	0 -	2 (6.9)	0 -
Blood	28	0 -	1 (3.5)	0 -	0 -
Total	-	**6 (20.7)**	**2 (6.9)**	**2 (6.9)**	**0 -**
Late radiation side effects more than 3 months					
Lung	20	9 (31.0)	0 -	0 -	0 -
Bone	27	1 (3.4)	1 (3.4)	0 -	0 -
Total	-	**10 (34.5)**	**1 (3.4)**	**0 -**	**0 -**

NSCLC - non-small cell lung cancer, GI - gastrointestinal

Discussion. Recently, several long-term follow-up studies showed that SBRT achieved good effect in treating with inoperable stage I/II NSCLC patients. A 3-year LCR rates were more than 90%, and 3-year OS rates were approximately 70%. The SBRT has high accuracy, high dose, and highly conformal dose distribution with less fraction.[5] Our self-developed body gamma knife is one of the typical representative technologies in SBRT. Our preliminary study result showed a 95% 3-year LCR rate, 78% 3-year OS rate with minimal toxicity in ≤5 cm in stage I/II NSCLC using the γ-SBRT.[1,2] On this basis, we carried out this prospective study. In this paper, we systematically analyzed local control responses, survival rates, and radiation toxicity, in order to prove the safe and effective use of γ-SBRT in the treatment of stage I/II NSCLC. A radiation dose of 50 Gy was prescribed to the 50% isodose line in our study. The total dose of PTV was 50 Gy, CTV - 60 Gy, and GTV edges - 70 Gy. When we calculated the BED using the formula: BED=nd (1+d/α/β), α/β=10]: the BED of PTV was 75 Gy, CTV - 96 Gy, and GTV - 117 Gy. This unique dose distribution and treatment patterns can improve enough dose to GTV, on the other hand, can be effective to PTV, while the surrounding normal tissue can be tolerated, which can make focusing dose in the target area layers increase to obtain the biological significance as a factor of dose escalation. In present study, the 2-year LCR rate was 93.1% and 2-year OS rate was 89.40%, which was similar to our preliminary results, and other SBRT in the treatment of stage I NSCLC.[3] It is important to note that even with the big differences superficially between our study using 50 Gy/10 f, and a broad research using 48-60 Gy/3-5 f, actually, the equivalent biological doses of GTV were all greater than 100 Gy. The LCR rates were all greater than 90%.[6-8] When a radiation dose of 50 Gy was prescribed to the 50% isodose line in γ-SBRT, the dose of normal tissue surrounding was low and decreased fast, so the radiation reaction and damage is slight. Basing on primary experiences, the results show that γ-SBRT is a safe and effective treatment in dealing with periphery tumors (<5 cm) using a total dose of 50 Gy of PTV, and 70 Gy of GTV 10 times. However, for centrally located lung tumors that are close to critical structures, such as the main bronchi, trachea, esophagus, and spinal cord, individualized fraction sizes and numbers should be considered.[9]

We did not carry out prophylactic mediastinal lymph node radiotherapy in patients with early-stage NSCLC as other studies reported.[3] Existing clinical data showed that omitting prophylactic lymph node irradiation does not reduce the LCR for patients receiving definitive radiotherapy, with isolated outside-field (field of radiotherapy) local recurrence rates less than 8%, particularly in patients with stage I who undergo PET scanning for staging.[10] The occurrence rate of radiation-induced lung injury is much higher than the purely local tumor radiotherapy when the tumor is large at the same time make radiotherapy of mediastinal region.[11,12] A total 29 patients in our study were diagnosed and staged by PET/CT. We did not perform prophylactic irradiation if there was no clinical indication of lymph node involvement. Two patients received irradiation of lymph nodes staged N1. One patient staged IIb had mediastinal lymph node surrounding the inferior vena cava recurrence only after the eighth month. Other cases showed no hilar or mediastinal lymph node recurrence and metastasis. Therefore, the results further indicate that no lymph node preventive radiotherapy in patients with N O diagnosed by PET/CT not only makes any increase regional failure, but also improves local control rate and reduces the radiation damage.

In our study, patients had good tolerance and compliance with radiotherapy. All the patients completed the established treatment options, and there were no treatment-related deaths. A single dose of GTV is 7 Gy with a total dose of 70 Gy (BED=119 Gy), which is lower single dose, and longer progress than abroad. Furthermore, it is higher and shorter than the conventional radiotherapy significantly, and there is no apparent early or late response organs serious injury.[13,14]

The acute radiation-induced were mild during the treatment, which did not affect the completion. Acute and late radiation-induced reaction is acceptable. None of the patients had Grade 4 radioactive toxicity. So it reflects obvious advantages of dose distribution and decreased steeply the radiation response, and the radiation injury are slight at the same time.

There are also some limitations of γ-SBRT in our study. First, as the γ-SBRT dose curve distribution is ellipsoidal, it is difficult to obtain the excellent dose distribution if the tumor is irregular, or its transverse horizontal direction is too long.[15] Second, the dose decreases steeply requiring more reliable fix and verification system. It may be highly accurate to use online verification system other than CT offline verification. Third, clinical treatment results showed that γ-SBRT in the state of natural breathing and slow CT scan can accurately irradiate, but positioning treatment will help to narrow the scope and further improve the dose by 4D-CT.

Our study is a clinical prospective study in treating stage I/II NSCLC using γ-SBRT. The findings proved once again that the 2-year local control and overall survival rates of γ-SBRT seem to be much better than the conventional radiotherapy in those for treatment of inoperable or refuses to surgery stage I/II NSCLC. Like other advanced radiotherapy, it is comparable with surgical resection, which is a safe and effective treatment with slight toxicity. In future research, we want to explore the reason of local control failure and technology of verification. With improved confirmed dose distribution, further dose escalation, better tumor-motion-tracking techniques, real-time image verification technology, and online correction may further improve clinical outcomes in the future.

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