

Clinical efficacy of CyberKnife combined with chemotherapy and hyperthermia for advanced non-small cell lung cancer

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Abstract. Non-small cell lung cancer (NSCLC) is responsible for at least 80% of all lung tumors and has a poor prognosis, since 75% of NSCLCs are first diagnosed at an advanced stage. This study was conducted to evaluate the therapeutic efficacy of CyberKnife in combination with chemotherapy and hyperthermia for selected patients with advanced non-small cell lung cancer (NSCLC). Clinical charts, imaging and pathology reports of patients with advanced NSCLC who underwent CyberKnife therapy in our Tumor Therapy Center were retrospectively reviewed. Clinical efficacy was evaluated for local control, Karnofsky performance status scale (KPS) and toxicity analysis. A total of 119 patients with 136 target areas were evaluated. A prescribed dose of 24-51 Gy to the gross tumor volume was delivered in 3-6 fractions. The median prescription dose was 35 Gy (mean, 34.73±4.80 Gy), with an average of five fractions. Patients, who voluntarily participated in the study, were assigned to one of three groups, which were as follows: CyberKnife therapy alone, CyberKnife combined with chemotherapy and CyberKnife combined with chemotherapy and hyperthermia. The median follow-up period was 6 months and curative efficiencies were 62.16, 71.79 and 90.70%, respectively, as determined by radiographic and clinical re-examinations. Patients treated by CyberKnife combined with chemotherapy and hyperthermia achieved optimal improvement in the aspect of KPS, which was statistically different compared to the other two groups ($P<0.05$). In conclusion, our results indicated that CyberKnife combined with chemotherapy and hyperthermia achieved favorable short-term outcomes and may be a more viable option for patients with advanced NSCLC. However, further investigations are required to evaluate long-term outcomes.

Introduction

Non-small cell lung cancer (NSCLC) is responsible for at least 80% of all lung tumors and has a poor prognosis, since 75% of NSCLCs are first diagnosed at an advanced stage. Surgical treatment for advanced NSCLC is always contraindicated due to the poor condition of the patients or the presence of multiple metastatic lesions (1).

CyberKnife is a novel hypofractionated stereotactic radiosurgery system, which potentiates safe treatment of tumor lesions by delivering focused high doses of radiation in a limited number of sessions; therefore, it may be used as a first-line treatment in these patients (2). However, as a focal treatment, CyberKnife plays a limited role in controlling metastatic microscopic lesions, which have almost always developed in the majority of advanced NSCLC cases (3). Therefore, this provides a theoretical basis for CyberKnife therapy combined with chemotherapy for intermediate- to late-stage NSCLC.

Gemcitabine is an anticancer prodrug that interferes with tumor cell replication and has been proven effective in the treatment of NSCLC. Cisplatin combined with gemcitabine is currently used as a first-line regimen for advanced NSCLC. Furthermore, hyperthermia is increasingly becoming an important method for cancer treatment and numerous retrospective studies suggested that hyperthermia, chemotherapy and radiotherapy exert a synergistic effect (4,5).

Radiotherapy and chemotherapy are directly toxic to cancer cells and their combination with hyperthermia may result in enhanced cell destruction. In this study, we present preliminary data from our assessment of the clinical efficacy of these three therapeutic modalities for the management of advanced NSCLC: CyberKnife alone, CyberKnife combined with chemotherapy and the two combined with hyperthermia.

Patients and methods

Patient characteristics. Patients with advanced NSCLC who underwent CyberKnife therapy between November, 2010 and August, 2011 at the Center for Tumor Treatment of the People's Liberation Army 107th Hospital, were included in this retrospective study. The inclusion criteria were as follows: i) pathological or radiographic confirmation of stage III-IV NSCLC; ii) Karnofsky performance status scale (KPS) ≥ 50 ;

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Table I. Clinical data of CyberKnife combined with chemotherapy and hyperthermia for patients with advanced NSCLC (mean \pm SD).

	CK	CK+chemo	CK+chemo+hyper
Patient no.	37	39	43
Gender			
Male	27	30	35
Female	10	9	8
Age (years)	71 (66.8 \pm 11.9)	68 (65.3 \pm 13.6)	61 (63.7 \pm 11.1)
CyberKnife dose (Gy)	30 (30.62 \pm 3.88)	35 (34.64 \pm 0.78)	40 (38.35 \pm 4.80)
Curative rate	62.16% (23/37)	71.79% (28/39)	90.70% (39/43)
KPS			
Before	65.00 \pm 8.00	64.25 \pm 7.57	67.73 \pm 9.05
After	69.64 \pm 6.20	72.59 \pm 8.43	84.36 \pm 5.64

NSCLC, non-small cell lung cancer; SD, standard deviation; CK, CyberKnife; CK+chemo, CyberKnife combined with chemotherapy; CK+chemo+hyper, CyberKnife combined with chemotherapy and hyperthermia; KPS, Karnofsky performance status scale.

iii) no prior anti-tumor treatment; iv) all patients signed informed consent regarding detection and treatment. Age, gender, performance status, histological subtype, tumor stage, type of treatment and clinical response to treatment were obtained from the patient charts. Toxicity was assessed using the Common Terminology Criteria Adverse Events version 3.0. Approval for this study was obtained from the Ethics Committee of The People's Liberation Army 107th Hospital.

Treatment methods.

CyberKnife (CK) group. We used CyberKnife System (Accuray Group Co., Ltd., Sunnyvale, CA, USA) to perform highly accurate real-time tracking radiotherapy. CyberKnife treatment was delivered in 3-6 fractions and the whole treatment was completed in 1 week. Therapeutic doses were determined according to the volume, location and stage of the tumor. The gross tumor volume and planned treatment volume were determined by computed tomography (CT) scans (1.25-mm sections). The total doses ranged from 24 to 51 Gy, with a fractional dose of 4.5-11.7 Gy. During the CyberKnife therapy course, white blood cells (WBC) counts were assessed weekly and hematopoietic colony-stimulating factors were administered if the WBC count was found to be $\leq 3 \times 10^9/l$.

CyberKnife combined with chemotherapy (CK+chemo) group. Patients were treated by chemotherapy for 1 cycle, using the NP schedule: cisplatin (30 mg/m²) for the first three days and gemcitabine (25 mg/m²) on the first and eighth days. CyberKnife therapy was initiated on the ninth day, provided that the WBC count was $\geq 4 \times 10^9/l$.

CyberKnife combined with chemotherapy and hyperthermia (CK+chemo+hyper) group. Patients in this group received a treatment schedule of CyberKnife and chemotherapy as described above for the previous two groups. Additionally, hyperthermia treatment (500-800 W) was performed during the CyberKnife treatment period, once a week and for 1 h each time, using the NRL-001 Incoherent Dual RF Hyperthermia System (Morestep Science &

Technology Development Co., Ltd., Changchun, China). Two sets of high-frequency source were deployed to an operating frequency of 30.32 \pm 1.5 and 40.68 \pm 1.5 MHz. The output power was 1,100 W and the precision of thermometry was $\pm 0.1^\circ\text{C}$. There was continuous recording of the heating temperature and power curve to ensure that the surface temperature of the tumor reached 40-41 $^\circ\text{C}$.

Assessment of efficacy and statistical analysis. The efficacy was evaluated based on radiographic and clinical re-examination, KPS and toxicity responses. Comparisons between the three groups were performed in this study. The Chi-square test was used for the comparison of the rates between two samples. Comparison of KPS was performed using the Wilcoxon signed-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. The SPSS 13.0 software was used for statistical analysis.

Results

From November, 2010 to August, 2011, 119 patients (92 male and 27 female; median age, 64 years) with advanced NSCLC underwent CyberKnife therapy at the Center for Tumor Treatment of the People's Liberation Army 107th Hospital (Yantai, China). The number of tumor lesions for each patient ranged from 1 to 3. The largest tumor lesion measured 15x11x8 cm, whereas the smallest was 1.5x1.4x1.2 cm. The median prescription dose of CyberKnife was 35 Gy (mean, 34.73 \pm 4.80 Gy), with an average of five fractions at 76% isodose line (range, 68-85%). The follow-up period was 6 months. Preliminary clinical data are listed in Table I.

Radiographic studies (CT or magnetic resonance imaging) were performed in all 119 cases to evaluate the short-term effectiveness. CR plus PR were considered valid. Curative efficiencies were 62.16, 71.79 and 90.70% for the three types of treatment. CyberKnife combined with chemotherapy and hyperthermia was distinctly superior to the other two treatments ($P < 0.05$).

Patients treated by CyberKnife combined with chemotherapy and hyperthermia achieved optimal improvement with regard to KPS, with alleviation of tumor oppression syndrome and evident improvement of the quality of life. The comparison of KPS scores between the three groups was performed using the Wilcoxon signed-rank test, which indicated a statistically significant difference ($P < 0.05$).

Toxicity responses included skin lesions, fever, infection, gastrointestinal reactions, bone marrow suppression and bilirubin abnormalities. Evaluation of the toxicity reactions demonstrated that, compared to the other two groups, CyberKnife combined with chemotherapy and hyperthermia increased the occurrence of toxicity. However, most of these toxicity responses were tolerable or alleviated with short-term symptomatic treatment and did not negatively affect the implementation of the whole treatment plan.

Discussion

The majority of lung cancers are diagnosed at an advanced stage and are among the leading causes of cancer-related mortality worldwide (6). The current standard of treatment for patients with advanced lung cancer is palliative surgical lobectomy and palliative chemotherapy or radiotherapy (7). However, the clinical efficacy of these treatments is unsatisfactory. Previous studies demonstrated that CyberKnife may be a highly effective treatment for advanced lung tumors, with only slight adverse reactions (8,9). However, it has not been proven as effective regarding suppression of tumor recurrence. Dose escalation alone is unlikely to enhance inhibition of recurrence and novel approaches, such as combination with other therapeutic strategies, require further investigation (10). In our study, we combined CyberKnife therapy with chemotherapy and hyperthermia in order to significantly improve its curative effects on advanced lung cancer.

The majority of lung cancer patients usually present with distant metastases at the time of diagnosis, which provides a theoretical basis for the clinical treatment schedule of radiotherapy combined with chemotherapy for these patients (11), the mechanism of which may be as follows: i) chemotherapy may eliminate the subclinical distant metastases (12); ii) chemotherapy may inhibit the damage repair of tumor cells caused by irradiation (13); iii) chemotherapy leads to tumor shrinkage, which may improve oxygenation of tumor lesions and therefore increase the sensitivity of tumor cells to radiation (14); iv) radiotherapy and chemotherapy may suppress the proliferation of tumor cells at different cycle stages, which produces a synergistic destructive effect (15). Our present study demonstrated that, compared to CyberKnife therapy alone, CyberKnife combined with chemotherapy may achieve an improved short-term curative effect in advanced lung cancer patients.

Hyperthermia is an important method for the treatment of advanced malignant tumors, which has been proven to act synergistically with radiotherapy and chemotherapy (4). Hyperthermia may enhance the cytotoxicity of certain chemotherapeutic drugs, alter the pharmacokinetics of chemicals, increase the blood flow locally around the tumor and eventually increase drug uptake of tumor lesions (5,16). Hyperthermia may also inhibit DNA polymerase-mediated damage repair,

reverse the multi-resistance to chemotherapeutic drugs, reduce the synthesis and secretion of vascular endothelial growth factor and, therefore, suppress the angiogenesis of tumor lesions (16). Furthermore, hyperthermia may improve the sensitivity of S-phase cells to radiation, as well as increase the blood supply of normal tissues surrounding the tumor; thus, radiotherapy combined with hyperthermia may be more beneficial for the recovery of normal tissues, while reducing the incidence of toxicity (17).

Although radiotherapy combined with chemotherapy increases treatment toxicity, the majority of the toxicity responses observed during our study were tolerable or alleviated with short-term symptomatic treatment and did not negatively affect the implementation of the entire treatment plan. In addition, hyperthermia may protect the bone marrow against the toxicity of radiotherapy and chemotherapy.

In conclusion, our results demonstrated that the combination of CyberKnife, chemotherapy and hyperthermia may eliminate malignant cells synergistically and may be beneficial to patients with advanced lung cancer.

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