Trans-bronchoscopy with implantation of ^{125}I radioactive seeds in patients with pulmonary atelectasis induced by lung cancer

MINGJIAN LU[1*], DELI PU[2*], WEIDONG ZHANG[1], JIANGRONG LIAO[2], TAO ZHANG[1], GUANG YANG[1], ZHENYIN LIU[1], SRISTI SINGH[1], FEI GAO[1] and FUJUN ZHANG[1]

[1]Department of Medical Imaging & Interventional Radiology, Cancer Center and State Key Laboratory of Oncology in South China, Sun Yat-sen University, Guangzhou, Guangdong 510060; [2]Department of Oncology, Guizhou Astronautics Hospital, Zunyi, Guizhou 563003, P.R. China

Received July 15, 2014; Accepted April 14, 2015

DOI: 10.3892/ol.2015.3204

Abstract. To evaluate the role of low-dose-rate interstitial brachytherapy using trans-bronchoscope ^{125}I radioactive seeds implantation in patients with pulmonary atelectasis induced by lung cancer, in terms of feasibility, safety, quality of life (QOL), and survival time. Between April 2008 and June 2011, 15 patients from two medical institutions that had obstructive pulmonary atelectasis caused by inoperable lung cancer were assigned to receive ^{125}I implantation endoluminal brachytherapy by bronchoscopy. Subsequent to the implantation of ^{125}I seeds, the outcomes were measured in terms of procedure success rate, reopening of atelectasis, complications associated with the procedure, Karnofsky performance status (KPS) scores and survival time. The surgical procedure was successfully performed in all 15 patients. No procedure-associated mortality occurred and the complications were mild and considered acceptable. Irritable cough and temporary increase of hemoptysis occurred in 11 (73.3%) and 10 (66.7%) patients respectively, and were the most common complications. The pulmonary atelectasis reopening rate subsequent to the procedure was 86.7, 76.9, 80.0, 75.0 and 50.0% at 2, 6, 12, 18 and 24 months, respectively. The KPS score significantly improved following the implantation of ^{125}I seeds and the duration of improvement ranged between 3 and 27 months. The median and mean survival times were 15.6 and 16 months, respectively. Actuarial survival rates at 6, 12 and 24 months after the procedure were 86.7, 66.7 and 13.3%, respectively. In patients with advanced lung cancer and those presenting with obstructive pulmonary atelectasis, treatment with intraluminal implantation of ^{125}I seeds is a safe and effective therapy option with easy accessibility.

Correspondence to: Professor Fujun Zhang or Dr Fei Gao, Department of Medical Imaging & Interventional Radiology, Cancer Center and State Key Laboratory of Oncology in South China, Sun Yat-sen University, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, P.R. China
E-mail: zhangfj@sysucc.org.cn
E-mail: gaof@sysucc.org.cn

*Contributed equally

Key words: lung cancer, pulmonary atelectasis, ^{125}I radioactive seed, brachytherapy, bronchscope

Introduction

Lung cancer is one of the most frequently diagnosed types of cancer and is the leading cause of cancer-associated mortality worldwide (1). In China, the incidence and mortality rate of lung cancer have been increasing dramatically in the previous three decades and lung cancer is becoming a notable medical problem (2). Pulmonary atelectasis is a common complication in patients with lung cancer, particularly central type lung cancer. It has been reported that 30% of lung cancer patients present with obstruction of the central airway, such as the trachea or main bronchi, which manifests as symptoms of respiratory distress, bleeding or infection (3). Pulmonary atelectasis decreases quality of life (QOL) and may impair anti-tumor therapy. Due to a low possibility for resection, palliative therapy plays an important role in this condition. Currently, a variety of interventional modalities, including neodymium-doped yttrium aluminium garnet laser therapy, stenting, photo-dynamic therapy and endoluminal brachytherapy, are utilized to relieve airway obstruction, owing to the development of the flexible bronchoscope. Therapy choice depends on the presence of comorbidities, pulmonary function of the patient, previous treatment administered and life expectancy of the patient. High-dose-rate (HDR) endoluminal brachytherapy, with or without additional combined therapy, has been demonstrated to be an effective treatment modality in this condition (4,5). However, due to the high expenses of HDR endoluminal brachytherapy, the application of this technology has been tremendously restricted. As a type of novel therapy technology, ^{125}I radioactive seed implantation has been revealed as efficient in numerous types of malignant tumors (6,7).

The present study aimed to evaluate the feasibility, safety and efficacy of low-dose-rate (LDR) interstitial brachytherapy trans-bronchoscopy with ^{125}I radioactive seed implantation in patients with pulmonary atelectasis induced by lung cancer. To the best of our knowledge, the present study is the first to evaluate the feasibility, safety and efficacy of LDR ^{125}I seed implantation as a palliative therapy in patients with malignant obstructive pulmonary atelectasis induced by lung cancer.

Patients and methods

Patient eligibility and characteristics. Between April 2008 and June 2011, 15 patients with central type lung cancer and secondary obstructive pulmonary atelectasis underwent interventional bronchoscopy with ^{125}I implantation for symptomatic palliation of pulmonary atelectasis at either the Department of Oncology, Guizhou Astronautics Hospital (Zunyi, Guizhou, China) or the Department of Imaging and Intervention Radiology, Cancer Center of Sun Yat-sen University (Guangzhou, Guangdong, China). All patients were diagnosed with primary lung cancer involving the central airway, which was confirmed by biopsy, and were not candidates for surgical resection. All patients had previously received chemotherapy at least four times, with a poor response rate (RR). Three patients had received prior radiation therapy at a dose between 40 and 50 Gy, at a conventional fractionation. The other patients did not undergo external beam radiation therapy due to numerous causes. Pre-operative evaluation and treatment decision making was based on the health of the patients, previous bronchoscopy exam, computed tomography (CT) scan, previous therapy and the willingness of patients. The patients consisted of 15 patients with airway obstructive atelectasis that presented with various symptoms, such as respiratory distress, cough, hemoptysis and pneumonia. All patients presented with a cough and respiratory distress, and 9 patients (60%) presented with hemoptysis. Squamous cell carcinoma was the most common histological diagnosis in 11 patients. The patient characteristics are reported in Table I. Symptoms of acute obstruction and medium to severe hemoptysis were considered unsuitable for the present study and patients exhibiting these symptoms were excluded from the study.

Pre-operative preparation and surgical procedure. The present study used 0.7 mCi ^{125}I radioactive seeds (catalog no., CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China). The dose of the radioactive seeds was determined according to the following empirical formula: Total dose (mCi) = (length + width + height) / 3 x 5. The number of seeds was calculated as follows: Number of seeds = total dose / 0.7. The prescription dose determined from this formula was expected to reach 100-130 Gy. The endoscope was obtained from Olympus (BF-IT40; Olympus Corporation, Tokyo, Japan).

Implantation of ^{125}I seeds. The technique for this therapy was, overall, the same as regular bronchoscope examination (8). All procedures were performed under airway topical anesthesia with monitoring of electrocardiogram, pulse, blood pressure and blood oxygen saturation. A unilateral nasal catheter was placed prior to the procedure for the purpose of oxygen supply. Using a specialized instrument (Endoscope with particle pusher; Innovative Medical Device Technology Co., Ltd. Jinan, Shandong, China; Fig. 1), a channel was created to implant the radioactive seeds into the tumor.

Monitoring of patients. All 15 patients that underwent this therapy were followed up clinically or by telephone, and surveillance bronchoscopy and CT scans were performed two months subsequent to the first procedure and every subsequent two months. At each follow-up, the patients were clinically evaluated through a thorough history and physical examination, and the patients were assessed to determine their Karnofsky performance status (KPS) score. Additional bronchoscopies and CT scans were performed based upon the symptoms of the patients.

Assessment of the efficacy of pulmonary atelectasis reopening. Assessment of pulmonary reopening was based on the follow-up CT scan, and the CT image was evaluated by two independent radiologists. The efficacy was defined as follows: Complete reopening (CR), lung expansion had returned to the normal size and there was no atelectasis residue; partial reopening (PR), lung expansion was partial and the maximum diameter of pulmonary atelectasis was reduced by >50%; and no reopening (NR), lung expansion was not evident, or the maximum diameter of pulmonary atelectasis reduced <50% and progressed <20%. Progressive disease (PD) was defined as the maximum diameter of pulmonary atelectasis increasing by >20%.

Assessment of QOL. Data from the assessment of the QOL of all patients was obtained using the KPS score. KPS measurements range between 0 and 100. A high score represents a high QOL. The KPS scores were determined by clinicians prior to trans-bronchoscopy with implantation of ^{125}I radioactive seeds, and again at each subsequent follow-up.

Statistical analysis. Statistical analysis was performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA). The survival time was calculated from the time between the date of the procedure and time of mortality. Survival was calculated using the Kaplan-Meier method, and KPS data were analyzed using a paired-samples *t*-test. $P<0.05$ was considered to indicate a statistically significant difference.

Ethical approval and patient consent. Ethical approval was obtained prior to the commencement of the study from the Ethical Committee of the Sun Yat-sen University Cancer Center and the Ethical Committee of Guizhou Astronautics Hospital. The present study was performed in accordance with national law and the Helsinki Declaration of 1975, in its current, revised form (9). Written informed consent was obtained from all patients prior to the commencement of the treatment procedure.

Results

Technical feasibility. The present study enrolled 15 patients, 11 male and 4 female, with a median age of 62.1 years. A total of 15 interventional bronchoscopies were performed. The procedure time ranged between 20 and 50 min, with an overall average duration of 35 min. The present study was easily performed and was well tolerated by all patients. No procedure-associated mortalities occurred and no patient required a prompt discontinuation of the surgical procedure.

Complications. No patient succumbed to disease within 30 days of the initial procedure. An irritable cough and temporary increase of hemoptysis occurred in 11 (73.3%) and 10 (66.7%) patients, respectively, and were the most common

Table I. Background characteristics of patients before ^{125}I seed implantation (n=15).

Patient characteristic	Value
Gender, n (%)	
Male	11 (73.3)
Female	4 (26.7)
Age, years	
Median	62.1
Range	43-80
Pathology type, n	
Squamous cell cancer	12
Adenocarcinoma cell cancer	3
Main clinical presentation, n	
Respiratory distress	15
Cough	15
Bleeding	9
Infection	5
Other	11
Obstructive location, n	
Right bronchus	10
Left bronchus	5
Clinical stage, n	
IIIA	2
IIIB	5
IV	8
Previous therapy, n	
Chemotherapy	15
External beam radiotherapy	3

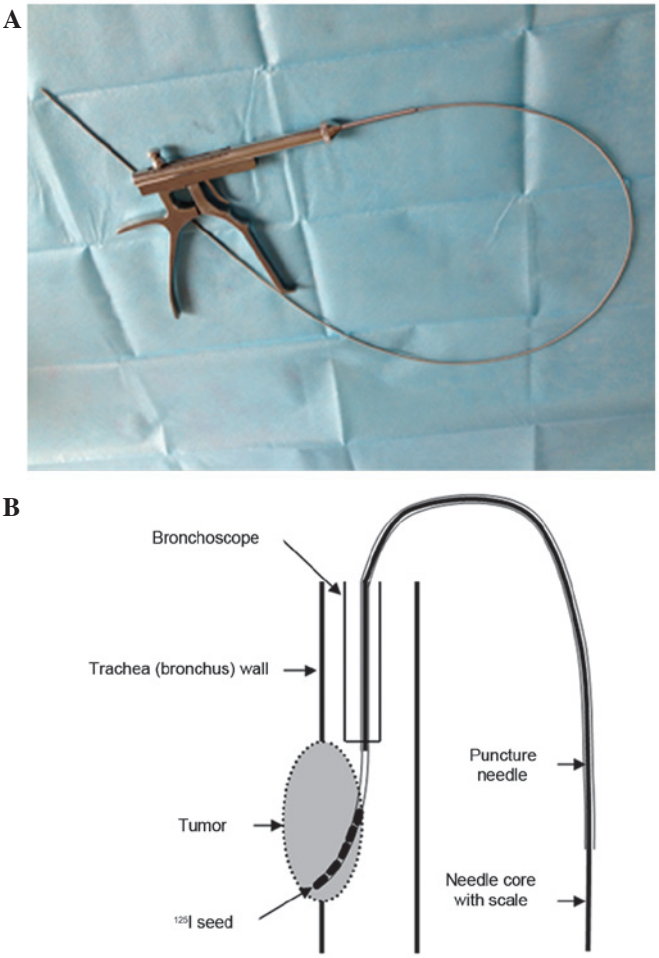

Figure 1. Instrument used for the surgical procedure and a schematic diagram of the procedure. (A) The instrument used for the implantation of radioactive seeds. The front of the instrument is sharp and can penetrate tumor tissue. The ^{125}I seeds were loaded into the instrument prior to the procedure. (B) When the puncture needle was in the tumor, the ^{125}I seeds were pushed into tumor by the needle core. The needle core had a scale incorporated on the end, so that the ^{125}I seeds were implanted accurately into the tumor.

Table II. The effect of trans-bronchoscope ^{125}I radioactive seeds implantation for the treatment of atelectasis in 15 patients with central type lung cancer.

Follow-up time, months	Patients, n	Reopening of atelectasis				Reopening rate, %
		CR	PR	NR	PD	
2	15	5	8	2	0	86.7
6	13	3	7	2	1	76.9
12	10	2	6	1	1	80.0
18	8	2	4	1	1	75.0
24	4	1	1	2	0	50.0

Reopening rate was calculated from the sum of the CR and PR. CR, complete reopening; PR, partial reopening; NR, no reopening.

complications. Other complications, including chest pain and fever, were mild and considered acceptable. No patients required additional emergency bronchoscopic treatment subsequent to the initial intervention.

Pulmonary atelectasis control. Overall, lung reopening was observed in the majority of patients between the procedure and the last follow-up. The reopening rate, calculated as the sum of the CR and PR, was 86.7, 76.9, 80.0, 75.0 and 50.0% in patients at 2, 6, 12, 18 and 24 months, respectively. The pulmonary atelectasis control rate is reported in Table II. A typical case is illustrated in Fig. 2.

QOL response. The majority of the patients demonstrated an improvement in KPS scores subsequent to the surgery, particularly in those with a lower KPS score prior to the procedure. The improvement in symptoms and feeling of well-being was observed 2-3 weeks subsequent to the procedure and was maintained until the final follow-up in the majority of patients. In addition, there was a significant improvement in the pre- and post-operative KPS scores. The mean KPS score was 72.3±5.6 prior to the procedure and was improved to 84.7±4.8 one month later (P=0.004; Table III).

Survival analysis. The median follow-up time was 20.8 months (range, 5-27). The median survival time was 15.6 months, and

Table III. KPS scores for the 15 patients pre- and post-implantation of ^{125}I radioactive seeds.

Patient number	Gender	Age, years	KPS score					
			Pre-implantation	1-month follow-up	2-month follow-up	6-month follow-up	1-year follow-up	2-year follow-up
1	M	65	65	75	80	80	-	
2	M	64	70	80	80	85	80	-
3	M	60	60	85	85	85	80	85
4	M	63	70	80	80	80	75	
5	M	46	75	85	80	80	80	-
6	M	72	80	90	90	-		
7	M	69	75	90	90	85	80	-
8	M	80	75	90	85	-		
9	M	60	70	80	85	80	-	
10	M	43	70	85	90	80	80	-
11	F	57	70	85	90	90	80	-
12	F	63	75	85	85	85	85	80
13	F	67	80	90	85	85	80	-
14	F	54	80	90	90	80	-	
15	F	68	70	80	85	80	80	-
Mean ± SD		62.1±9.5	72.3±5.6	84.7±4.8	85.4±4.0	82.7±4.3	80.0±2.4	82.5±3.5

KPS, Karnofsky performance status; SD, standard deviation.

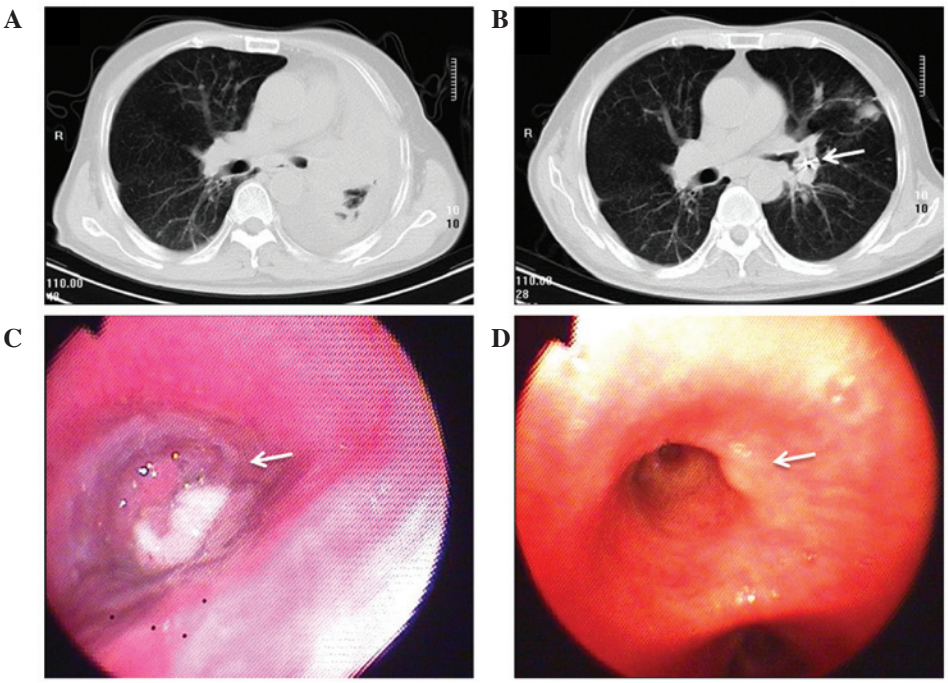

Figure 2. A 69-year-old man with pulmonary atelectasis induced by lung cancer treated with trans-bronchoscopy with implantation of ^{125}I radioactive seeds. (A) Pre-operative CT image revealing almost complete pulmonary atelectasis in the left lung. (B) Post-operative CT image revealing the complete reopening of the atelectasis, and high density ^{125}I seeds can be observed in the tumor (white arrow). (C) Pre-operative bronchoscope image revealing the tumor in the bronchus (white arrow). (D) Post-operative image revealing that the tumor had almost completely disappeared (white arrow). CT, computed tomography.

the survival rate was 86.7% at 6 months, 66.7% at 12 months and 13.3 at 24 months subsequent to the procedure (Fig. 3).

At the time of analysis, 13 patients had succumbed. Nine patients had succumbed to progressive disease, including locoregional progression and brain metastasis, two patients had succumbed to a brain-vascular accident, one of which possessed a history of hypertension, one patient with a history of coronary artery disease succumbed to sudden cardiac arrest, and one

Table IV. Characteristics of the patients that underwent ^{125}I seed implantation and the outcome of the treatment.

			Treatment and follow-up result						
Patient number	Gender	Age, years	Pathology	Clinical stage	Seeds, n	Alive	Survival time, months	Cause of mortality	Medical history
1	M	65	SC	IV	10	No	9	Heart failure	COPD
2	M	64	SC	IV	9	No	16	Brain metastases	Diabetes
3	M	60	SC	IIIA	6	Yes	>26	-	
4	M	63	SC	IV	8	No	13	CVD	Coronary disease
5	M	46	SC	IIIB	8	No	21	Tumor progression	
6	M	72	SC	IV	8	No	6	Brain metastases	COPD
7	M	69	SC	IV	10	No	15	Brain metastases	Diabetes
8	M	80	SC	IV	10	No	5	AMI	COPD, diabetes
9	M	60	SC	IIIB	9	No	15	Tumor progression	
10	M	43	SC	IV	12	No	11	Brain metastases	
11	F	57	SC	IIIA	10	No	20	Tumor progression	Diabetes
12	F	63	AC	IIIB	7	Yes	>27	-	
13	F	67	AC	IIIB	11	No	17	Tumor progression	Hypertension
14	F	54	SC	IV	13	No	12	Brain metastases	
15	F	68	AC	IIIB	14	No	20	Tumor progression	

SC, squamous cancer; AC, adenocarcinoma; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; AMI, acute myocardial infarction.

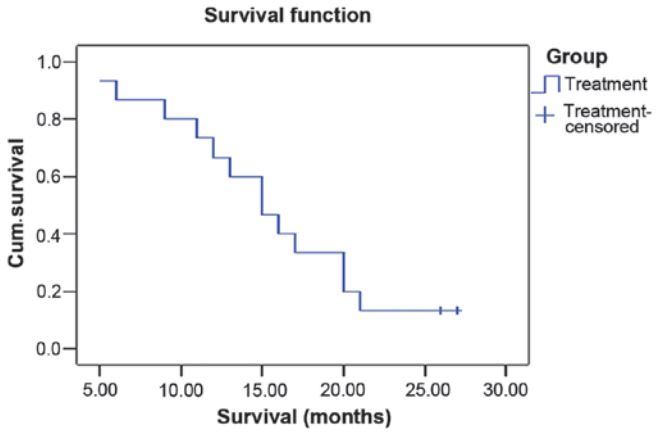

Figure 3. Kaplan-Meier estimates of overall survival. The median survival was calculated to be 15.6 months. The 6-month, 1-year and 2-year survival rates were 86.7, 66.7 and 13.3%, respectively.

patient with a history of COPD experienced heart failure. The characteristics of the ^{125}I seed implantation and outcome of the treatment with ^{125}I seed implantation is reported in Table IV.

Discussion

Lung cancer remains the leading cause of cancer mortality worldwide, and only 25-30% of patients with non-small cell lung cancer present with locally-advanced disease on initial diagnosis, whereas 40-50% present with metastatic disease (1,10). Although the majority of the patients with inoperable lesions experience clinical benefit subsequent to receiving chemotherapy, radiotherapy and even targeted therapy, the overall survival (OS) rate remains suboptimal, with a five-year survival rate of <1% (11). The overall survival time was 8-10 months and the one-year survival rate was 30-35% (12). The majority of patients with lung cancer eventually require palliative treatment (13). Obstruction of the central airway is frequently encountered in patients with inoperable lung cancer, and may be caused by an intraluminal tumor growth, extrinsic compression or weakness of the bronchial wall. A variety of bronchoscopic techniques are currently available for the management of malignant obstruction of the central airway (14). For all these bronchoscopic techniques, several studies have reported excellent palliation with varying rates of complications in patients treated with endobronchial brachytherapy (15,16).

For locally advanced lung cancer, there are several studies (17-19) that have demonstrated the effectiveness of ^{125}I radioactive seeds implantation in the local control and improvement of OS time and rate. However, for central type lung cancer, the technique of percutaneous puncture means great risk of hemorrhage and pneumothorax. However, the development of the technology used in interventional bronchoscopy makes the trans-bronchoscopy procedure with ^{125}I radioactive seed implantation possible and flexible. In the present study, all 15 patients completed this therapy safely. The procedure time was 20-50 min, with an average duration of 35 min in all patients, and there was no procedure-associated mortality. The present result revealed that this technique is safe and flexible.

Complications of HDR intraluminal brachytherapy are mild and infrequently reported in the majority of previous studies, while severe complications, such as fatal

hemoptysis and broncho-esophageal fistula, were occasionally observed (15,20,21). Therefore, the adverse effects of HDR brachytherapy on the airways are more thoroughly considered. Compared with HDR, LDR demonstrates an improved relative biological effect (RBE) (22,23). The present results revealed that the treatment complications were mild and acceptable, mainly presenting as a transient increase in hemoptysis, chest pain and fever. However, the duration of the complications was short and the majority of patients did not require additional therapy. There were no severe complications compared with those reported for HDR intraluminal brachytherapy. Probable explanations include that LDR has more excellent radiation biology characteristics compared with that of HDR. LDR brachytherapy is a type of continuous therapy with reduced peak dose. In addition, HDR intracavitary therapy requires several surgical procedures, and this increases the risk of complications. Notably, in the current study, one patient expelled two radioactive seeds two weeks subsequent to the procedure. This case resulted in certain requirements for radiological safety. Therefore, a small lead bottle was prepared for each patient in the present study to store any seeds that were coughed out so that the radioactive seeds would not harm the environment or other individuals.

The atelectasis reopening rate, calculated from the sum of the CR and PR, was revealed to be 86.7, 76.9, 80.0, 75.0 and 50.0% in patients at 2, 6, 12, 18 and 24 months subsequent to the procedure, respectively. Compared with a previous study (20), the atelectasis recanalization effect was good, and the effect was similar between the two studies, but demonstrated a longer duration in the present study. A possible reason is that the implantation of ^{125}I radioactive seeds by intraluminal brachytherapy has a longer therapeutic effect compared with HDR intraluminal brachytherapy. The majority of patients in the present study demonstrated an improved KPS score subsequent to the surgical procedure. The mean KPS score was 72.3±5.6 prior to the procedure and improved to 84.7±4.8 one month later (P=0.004). Intraluminal brachytherapy with ^{125}I radioactive seed implantation has a longer therapeutic effect, which may be an explanation for the comparatively long duration of the improvement in KPS.

In the present study, the long-term survival of lung cancer was the ultimate treatment goal. The median survival was 15.6 and the survival rate was 86.7% at 6 months subsequent to the procedure, 66.7% at 12 months and 13.3% at 24 months. The two-year survival rate was lower in the current study compared with certain studies of HDR intraluminal brachytherapy (5,24). This difference may be a result of patient selection or additional therapy, as numerous intraluminal brachytherapy procedures were combined with external radiation treatment. In the present study, eight patients presented with stage IV disease. Therefore, a two-year survival rate of 13.3% is a favorable outcome. However, the present study also demonstrated certain limitations. Firstly, accurate measurement of the dosimetry of the irradiation was not possible due to the lack of sophisticated measuring techniques dedicated to this condition. Therefore, no quantitative data associated with radiation therapy could be provided. Secondly, pulmonary atelectasis is occasionally challenging to differentiate from the tumor, so the present study cannot supply accurate data for local tumor control. Thirdly the current study was not a randomized trial and, as a pilot study, only 15 patients were approved to receive the therapy.

Management of malignant tumor complicated with pulmonary atelectasis is a challenging issue. Interventional bronchoscopy with a multimodality approach may improve symptom control and survival. This study demonstrated that trans-bronchoscopy with ^{125}I radioactive seed implantation is a feasible procedure that demonstrates good symptom control, minimal complications and improvement in survival and QOL. Physicians treating such patients should recognize the limitation of single modality therapy and become skilled in utilizing alternative complementary treatment approaches in order to achieve optimal outcome.

Acknowledgements

This study was supported by the Provincial & Ministry of Education Research Project of Guangdong (grant no., 2012B091100458), Major Project of Science and Technology of Guangzhou (grant no., 132400027) and National Natural Science Foundation of China (grant no., 81371654). The authors thank Dr. Marcin Bednarz and Dr. Zou Fang for their kind help with the English language.

References

1. Jemal A, Bray F, Center MM, *et al*: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
2. Au WW, Su D and Yuan J: Cigarette smoking in China: Public health, science, and policy. Rev Environ Health 27: 43-49, 2012.
3. Cavaliere S, Venuta F, Foccoli P, *et al*: Endoscopic treatment of malignant airway obstructions in 2,008 patients. Chest 110: 1536-1542, 1996.
4. Niemoeller OM, Pöllinger B, Niyazi M, *et al*: Mature results of a randomized trial comparing two fractionation schedules of high dose rate endoluminal brachytherapy for the treatment of endobronchial tumors. Radiat Oncol 8: 8, 2013.
5. Aumont-le Guilcher M, Prevost B, Sunyach MP, *et al*: High-dose-rate brachytherapy for non-small-cell lung carcinoma: A retrospective study of 226 patients. Int J Radiat Oncol Biol Phys 79: 1112-1116, 2011.
6. Taira AV, Merrick GS, Galbreath RW, *et al*: Long-term outcomes of prostate cancer patients with Gleason pattern 5 treated with combined brachytherapy and external beam radiotherapy. Brachytherapy 12: 408-414, 2013.
7. Guo JH, Teng GJ, Zhu GY, *et al*: Self-expandable esophageal stent loaded with ^{125}I seeds: Initial experience in patients with advanced esophageal cancer. Radiology 247: 574-581, 2008.
8. British Thoracic Society Bronchoscopy Guidelines Committee, a Subcommittee of Standards of Care Committee of British Thoracic Society: British Thoracic Society guidelines on flexible bronchoscopy. Thorax 56 (Suppl 1): i1-i21, 2001.
9. World Medical Association: World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 310: 2191-2194, 2013.
10. Novello S and Le Chevalier T: Chemotherapy for non-small-cell lung cancer. Part 1: Early-stage disease. Oncology (Williston Park) 17: 357-364, 2003.
11. Jemal A, Siegel R, Xu J and Ward E: Cancer statistics, 2010. CA Cancer J Clin 60: 277-300, 2010.
12. Schiller JH, Harrington D, Belani CP, *et al*; Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346: 92-98,2002.
13. Tishelman C, Petersson LM, Degner LF and Sprangers MA: Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. J Clin Oncol 25: 5381-5389, 2007.
14. Gorden JA and Ernst A: Endoscopic management of central airway obstruction. Semin Thorac Cardiovasc Surg 21: 263-273, 2009.
15. Mallick I, Sharma SC and Behera D: Endobronchial brachytherapy for symptom palliation in non-small cell lung cancer - analysis of symptom response, endoscopic improvement and quality of life. Lung Cancer 55: 313-318, 2007.

16. Escobar-Sacristán JA, Granda-Orive JI, Gutiérrez Jiménez T, *et al*: Endobronchial brachytherapy in the treatment of malignant lung tumours. Eur Respir J 24: 348-352, 2004.
17. Niu L, Zhou L, Xu K and Mu F: Combination of cryosurgery and Iodine-125 seeds brachytherapy for lung cancer. J Thorac Dis 4: 504-507, 2012.
18. Zhang S, Zheng Y, Yu P, *et al*: The combined treatment of CT-guided percutaneous ^{125}I seed implantation and chemotherapy for non-small-cell lung cancer. J Cancer Res Clin Oncol 137: 1813-1822, 2011.
19. Wang ZM, Lu J, Liu T, *et al*: CT-guided interstitial brachytherapy of inoperable non-small cell lung cancer. Lung Cancer 74: 253-257, 2011.
20. Kubaszewska M, Skowronek J, Chicheł A and Kanikowski M: The use of high dose rate endobronchial brachytherapy to palliate symptomatic recurrence of previously irriadiated lung cancer. Neoplasma 55: 239-245, 2008.
21. Ozkok S, Karakoyun-Celik O, Goksel T, *et al*: High dose rate endobronchial brachytherapy in the management of lung cancer: response and toxicity evaluation in 158 patients. Lung Cancer 62: 326-333, 2008.
22. Wang J, Wang J, Liao A, *et al*: The direct biologic effects of radioactive ^{125}I seeds on pancreatic cancer cells PANC-1, at continuous low-dose rates. Cancer Biother Radiopharm 24: 409-416, 2009.
23. Liao A, Wang J, Wang J, *et al*: Relative biological effectiveness and cell-killing efficacy of continuous low-dose-rate ^{125}I seeds on prostate carcinoma cells in vitro. Integr Cancer Ther 9: 59-65, 2010.
24. Hennequin C, Bleichner O, Trédaniel J, Quero L, Sergent G, Zalcman G and Maylin C: Long-term results of endobronchial brachytherapy: A curative treatment? Int J Radiat Oncol Biol Phys 67: 425-430, 2007.