Palliative Re-irradiation for In-field Recurrence after Definitive Radiotherapy in Patients with Primary Lung Cancer

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Abstract. *Aim: To evaluate the efficacy and toxicity of palliative re-irradiation for in-field recurrence of primary lung cancer after radiotherapy. Patients and Methods: Forty-four patients with locally recurrent lung cancer after radiotherapy were retreated with external beam radiation therapy. To evaluate palliative effectiveness, 31 symptoms in 25 patients were analyzed, while all patients were analyzed to evaluate pulmonary toxicity. Results: The median time between prior and secondary irradiation was 12.6 months. Prior radiation doses ranged from 50 to 70 Gy and retreatment ranged from 30 to 60 Gy. The median survival after re-irradiation was 6.5 months. After treatment 74% (23 out of 31) of the symptoms had improvement or complete resolution. After re-irradiation, acute Grade 2 and 3 pulmonary toxicity were recognized in 3 patients each. No significant factors were observed regarding pulmonary toxicity. Conclusion: Re-irradiation with moderate doses for recurrent lung cancer after definitive radiotherapy is promising in palliating the symptoms and shows acceptable toxicity.*

Many cancer patients are not candidates for resection because of regional spread or distant metastasis. The most powerful cytoreductive agent known for these patients is radiation therapy. However, in 1982, the Radiation Therapy Oncology Group reported an incidence of 34% for locoregional recurrence and 16% for locoregional plus distant failure (1).

Many patients with recurrent tumor will suffer from the symptoms of, for example, hemoptysis, cough, dyspnea and pain. Few effective treatment modalities are available to the patients at the time of recurrence. The objective response rate of second-line chemotherapy was reported as only 10% (2-3).

Brachytherapy, laser ablation, or photodynamic therapy may be considered for some patients, but will not be suitable for all. Retreatment with external beam radiotherapy should be considered as a useful option if it could be shown to relieve symptoms without causing unacceptable toxicity. However, to our knowledge, re-irradiation of locally recurrent lung cancer within the prior irradiation field has not been specifically evaluated. It is uncertain whether repeated radiotherapy of these patients is possible or useful and data regarding the efficacy and late toxicity after repeated radiotherapy are scarce. The hope of resolving these issues prompted us to review those patients receiving re-irradiation for lung cancer.

Patients and Methods

Between April 1990 and December 2004, 44 patients with locally recurrent lung cancer following previous thoracic radiotherapy were retreated with external beam radiation therapy. The indication of re-irradiation was decided at the discretion of the attending physician and radiation oncologist. All patients were informed about the possibility of severe or unexpected radiation toxicity and agreed to the re-irradiation.

Diagnosis of recurrence. Tumor recurrence was diagnosed as regrowth within the first irradiated field using chest X-ray and/or computed tomography (CT) and/or bronchoscopy and was also suggested by persistent or recurrent symptoms and increasing tumor marker levels. Histopathological proof was desirable to confirm to tumor recurrence, however, was not essential.

Evaluation of palliative effectiveness. Patients with tumor-related symptoms were analyzed in order to evaluate palliative effectiveness. Symptom relief was assessed according to scoring system created by Kramer *et al.* (4), and was defined as follows; vanished (complete resolution of the symptom); diminished (any improvement without complete resolution); stabilized (no change); or progressive (deterioration) and the best response at any time was reported. Improvement in symptoms was assessed through

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Key Words: Lung cancer, palliative re-irrradiation, radiotherapy.

Table I. *Treatment characteristics.*

Variables	Range (median)
Prior irradiation	
radiation dose (Gy)	50-70 (60)
radiation fields (cm^2)	26.0-288.0 (104)
chemotherapy (yes/no)	25/19
Interval between treatments (mo)	5.8-47.2 (12.6)
Re-irradiation	
radiation dose (Gy)	30-60 (40)
radiation fields (cm^2)	16.0-100.0 (48)
cumulative fields (cm^2)	16.0-100.0 (42)
concurrent chemotherapy	16/28
Cumulative dose (Gy)	80-130 (102)

Forty patients were treated with fractionation of 200 cGy a day. All patients but 5 were treated 5 fractions a week and one patient with accelerated hyperfractionation and the remainder 3 fractions a week with fractionation of 300 cGy a day.

written documentation and when possible, symptoms were investigated by personal communication with the patients and their families.

Evaluation of toxicity. All patients retreated with external beam radiation were analyzed. Both acute and late toxicity were assessed according to the toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research Treatment of Cancer (5). Early and late toxicity were assessed through written documentation and, when possible, symptoms were investigated by personal communication with the patients and their families.

Survival and statistic analyses. Overall survival was measured from the first day of re-irradiation. The survival rates were calculated by the Kaplan-Meier method and the differences between the curves were analyzed using the log-rank test. Cox proportional hazards regression model was used for univariate and multivariate analysis of prognostic factors affecting to toxicity. The statistical significant level was set at 0.05.

Results

The median age at the time of re-irradiation was 70.9 years (range: 49.4-86.8 years) and most patients showed good performance status (PS; 0-1=38). The distribution by histological type was as follows: squamous cell carcinoma, 19 patients; adenocarcinoma, 11 patients; small cell carcinoma, 9 patients; others, 5 patients. The time interval between the initial course of radiation and subsequent re-irradiation ranged from 5.8 to 47.2 months, with a median of 12.6 months. The tumors were centrally located in 29 patients and 15 were located peripherally. The centrally located tumor was defined to be involved the mediastinum and/or hilar region. All patients were treated with 2 dimensional anteroposterior parallel opposed fields. The initial treatment field was designed to include the primary tumor and the regional lymph nodes. On the other hand, the re-irradiation field only encompassed the detected recurrent tumor with a 5-10 mm margin. All radiation fields were conventionally defined using an X-ray simulator and precise gloss tumor volume, clinical tumor volume and etc. could not be defined. The radiation therapy characteristics are presented in Table I.

Table II. *Overview of the subjective response.*

	Symptom response					
Symptom	V	D	S	P	NA	Total
Hemoptysis	4	4	0	0	0	8
Dyspnea	0	3	3	0	0	6
Cough	1	2	3	0	1	7
Pain	2	7	2	0	0	11
Total	7	16	8	0	1	

V=vanished (complete resolution of the symptom); D=diminished (any improvement without complete resolution); S=stabilized (no change); P=progressive (deterioration); NA=not accessed. The best response at any time was scored.

Diagnosis of recurrence. Histopathological proof was desirable to confirm to tumor recurrence, but was not essential. In only 8 patients were tumor recurrences clinically evident at bronchoscopy and were confirmed by histopathological findings. In the other patients, obvious progression of tumor growth was seen on consecutive chest CT scan and 1 patient was also diagnosed by positron emission tomography.

Evaluation of palliative effectiveness. In 26 patients 32 symptoms, considered to be related with the recurrent tumor, were observed. All symptoms except 1 (cough) were evaluated after re-irradiation. Therefore, 31 symptoms in 25 patients were scored. Out of the 25 patients, 20 had only one symptom, 4 had two, and 1 had three at presentation. After treatment, 74% (23/31) of the symptoms had vanished or diminished (Table II).

Evaluation of toxicity. Six patients were scored as ≥ grade 2 pulmonary toxicity within 3 months after re-irradiation. Grade 2 and 3 were each recorded in 3 patients. No factors reached significance on univariate and multivariate analysis (Table III). There was no severe or fatal toxicity such as myelopathy, bronchoesophageal fistula, perforation, bronchial stenosis, esophageal stenosis or ulcer and severe skin toxicity.

Survival analysis. With a median follow-up of 6.5 months, a total of 37 out of 44 patients died by the time of this analysis. In the majority of patients the cause of death was lung cancer.

Table III. *Analysis of factors predicting pulmonary toxicity.*

Factors	Probability	
	Univariate	Multivariate
PreRT dose (<61 Gy *vs.* ≥61 Gy)	0.4113	0.3479
PreRT fields (<108 cm^2 *vs.* ≥108 cm^2)	0.0716	0.1260
Pre-ReRT interval (<12.7 mo *vs.* ≥12.7 mo)	0.1539	0.1638
PS (>= *vs.* =0-1)	0.5260	0.8973
Age (<71.5 *vs.* ≥71.5)	0.5410	0.6120
reRT dose (<41 Gy *vs.* ≥41 Gy)	0.8973	0.5705
reRT fields (<48 cm^2 *vs.* ≥48 cm^2)	0.3139	0.1261
Cumulative RT fields (<42 cm^2 *vs.* ≥42 cm^2)	0.3046	0.2876
Concurrent chemotherapy (yes *vs.* no)	0.0664	0.0905
Tumor location (central *vs.* peripheral)	0.8725	0.2408

PreRT=previous radiotherapy; reRT=re-radiotherapy. The thresholds used were median values.

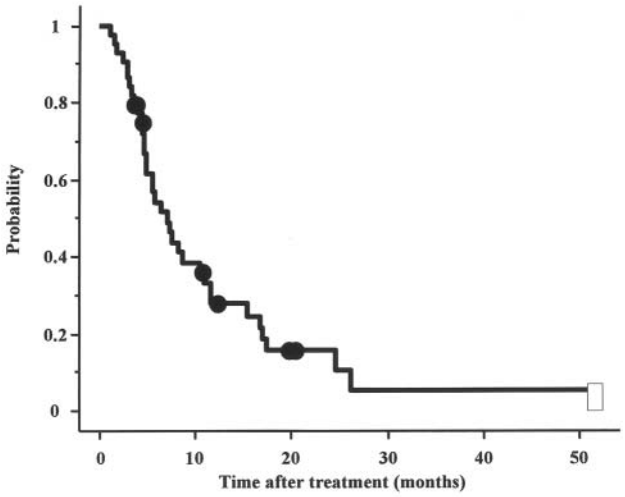

Figure 1. *The Kaplan-Meier estimates of overall survival after re-irradiation.*

The median survival was 6.5 months and the 1-year survival rate was 27.7%. The overall survival curve is shown in Figure 1. Distant metastasis at re-irradiation influenced survival. The overall survival rate in patients without distant metastasis was 31.3% at 1 year and 31.3% at 2 years, with a median survival time of 7.1 months, while in patients with distant metastasis the overall survival was 25.0% at 1-year and there were no 2-year survivors (p=0.02 by log-rank test).

Discussion

Local recurrence after radiotherapy still occurs at a high incidence, although tumor control has improved with the improvement of radiotherapy techniques and the increase in dose delivered to the tumors. There are few effective treatment modalities available to the patients at the time of recurrence. Many patients with recurrent tumor will suffer from symptoms, some of which impair the quality of life for patients and are distressing for their families. Radiation therapy is useful for such tumor-related symptom relief, thus, it was hypothesized that re-irradiation was effective for improving symptoms. The palliative effect of re-irradiation for recurrent lung cancer was reported in several studies (6-11). Symptom improvement in our patients reached 75% and was comparable to the previous reports. It is important to note the high palliating rate of hemoptysis, since of the symptoms related the lung cancer, hemoptysis is especially distressing for patient and families. Kramer *et al.* (4) reported that radiotherapy with 16 Gy in 2 fractions in 2 weeks could be very effective as palliative treatment for local complaints in non-small cell lung cancer. Hypo-fractionation is suitable for the patients with a short life expectancy.

In general, local recurrence after radiation therapy is not usually managed by radiation therapy because of the toxicity. Especially worrisome is radiation myelopathy which causes a severe decline in quality of life. Whether re-irradiation can be administered safely depends on the tolerance and volume of the structure to be treated. Our hospital did not have a CT simulation system and all treatment fields were conventionally decided using an X-ray simulator. Therefore, little information could be given on the precise cumulative normal tissue doses. However, careful simulation which shielded as much normal tissue and spinal cord as possible, by multi leaf collimator with properly angled beams, might be attributed to the low toxicity. Endobronchial brachytherapy is another means for recurrent lung cancer. However, bronchial fistula formation or fatal bleeding was reported in studies using brachytherapy (12). This particular complication was not reported with external radiotherapy, and was not observed in our patients. Although it is evident that the cumulative dose is higher than the tolerance dose for the normal tissue, the incidence of complications following re-irradiation was low in the previous reports and in the current study (6-7, 11).

After re-irradiation the cumulative dose reached a median value of 102 Gy in median, which far exceeds the threshold for tolerance dose. Hayakawa *et al.* (13) reported that of five patients with lung cancer treated with 80 Gy in 40 fractions to the hilar region, four developed marked stenosis of proximal bronchi and subsequently died of pulmonary insufficiency 1-3 years after radiotherapy. At the same time, it is commonly believed that with a longer time interval between two consecutive radiotherapy courses, a higher cumulative dose to normal tissue is tolerated, compared with a single course (14,

15). Terry *et al.* (16) reported that higher lung retreatment doses were tolerated for increased time intervals after the initial treatment in mouse lungs. On the other hands, there is a probability that the previously irradiated lung has already had fibrosis. However, the median survival after re-irradiation was only 6.5 months and was too short for assessment of true late complications.

A review of previous studies revealed that patients might live many months after re-irradiation for recurrent disease and the median survival in our group is comparable to previous reports. Dosage was usually limited to that required to relieve symptoms or to prevent critical organ involvement. The lower dose has not, however, been associated with long survival. Patients without distant metastasis at re-irradiation survived significantly longer than those with distant metastasis. Wu *et al.* (9) reported the efficacy of re-irradiation by three-dimensional conformal radiotherapy for locally recurrent lung cancer without distant metastases. The 1- and 2-year survival rate were 59% and 21%, respectively. The locoregional progression-free rates at 1 and 2 years were 51% and 42%, respectively. Okamoto *et al.* (8) reported that the overall survival rate after re-irradiation for radical treatment was 71% at 1 year and 51% at 2 years, with a median survival time of 15 months. This result was influenced by selection bias, because the candidates for radical treatment were in relatively good condition and could be expected to have a better prognosis. Recent advanced radiotherapeutic technology such as 3- or 4-dimensional conformal radiotherapy could reduce the volume of normal tissue within the treatment fields and decrease the risk of toxicity while ensuring adequate coverage of the tumor. External beam re-irradiation might be attractive modality more than expected.

Conclusion

From this retrospective study with a heterogeneous population of patients exceeding over a 14-year period, it appears that small localized fields of moderate dose irradiation in the range of 30-40 Gy in 10 to 20 fractions is safe and promising in palliating the symptoms of recurrent lung cancer following previous radiotherapy. These results encourage radiation oncologists to use re-irradiation more than before, in particular when palliative intention is pursued and severe late complications need not to be feared.

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Received October 5, 2006
Revised November 21, 2006
Accepted November 24, 2006