An Analysis on Treatment Schedule of Carbon Ion Therapy to Early Stage Lung Cancer

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ABSTRACT

A total of 134 patients with stage 1 of non-small cell lung cancer treated by carbon ion beam of HIMAC NIRS were investigated for control rate and delivered dose. The delivered dose of every patient was converted to biological effective dose (BED) of LQ model using fraction number, dose per fraction and alpha beta ratio which shows the maximum correlation between BED and tumor control. The BED of every patient was classified to establish a BED response curve for control. Assuming fraction numbers, dose response curves were introduced from BED response curve. The total doses to realize several control rates were obtained for the treatment of small fraction number.

Key words: Particle therapy, Carbon ion beam, Non-small cell lung cancer, Treatment schedule, Control rate.

1. INTRODUCTION

Recently, lung cancer became the leading cause of cancer related-death in Japan. Heavy ion therapy which has the properties of excellent dose distribution and high biological effect to tumor is expected to get the survival rate similar to surgical resection to this disease. In National Institute of Radiological Sciences (NIRS) the small fraction treatment to non-small cell lung cancer (NSCLC) is being investigated to make the best use of carbon ion therapy. The advantage of small fraction treatment by high LET ion beam is the shortening of overall treatment time maintaining a specified control rate. In concurrence the increase of complication rate must be prevented.

In this study, the relationship between delivered dose and tumor control rate was investigated using the NSCLC patients' data treated with several treatment schedules, and radiobiological formula of LQ model was derived to determine the total dose necessary for small fraction treatment.

2. MATERIALS AND METHODS

2.1. Patients and Treatment Method

The subject of the present study was 134 patients with inoperable stage 1 NSCLC. They were treated with carbon ion beams which were generated by the HIMAC synchrotron of NIRS[1]. Carbon beams at the energy of 290, 350 and 400 MeV/nucleon were used for patient irradiation. The treatment schedule consisted of either 18 fractions over the course of 6 weeks or 9 fractions over 3 weeks. Only primary tumor was the target irradiated by carbon ion beams. In 18 fractions group, the starting dose was 59.6 GyE (3.3 GyE/Fr.) and the dose was escalated to 95.4 GyE. In 9 fractions group, the starting dose was 68.4 GyE (7.6 GyE/Fr.) and escalated to 79.2 GyE. Carbon beam dose was expressed by GyE (Gray equivalent). GyE was defined as the physical dose multiplied by a factor of 3 which was determined to be relative biological effectiveness at the distal region of a spread out Bragg peak[2]. Tumor response was evaluated according to WHO criteria and the control of disease was decided by the recurrence within target volume with the follow up time of 2 years or more.

2.2. Data Analysis

The delivered dose to each patient was converted to biological effective dose (BED) using LQ model formalism[3]:

$$BED = nd\left(1+\frac{d}{a}\right) \qquad (1)$$

where BED is the log cell kill from n fraction of dose d, and a is alpha beta ratio. Then the relationship between BED and control was estimated with whole patients using biserial correlation coefficient. The alpha beta ratio which showed the maximum correlation was determined by iteration method.

The whole patients were classified into several classes according to their BED. A probability distribution function (logistic curve) was derived from the control rate of every BED class (BED response curve). As the BED is calculated from equation (1), the BED response curve was converted to dose response curve (control rate vs. dose) with a certain fixed fraction number inversely.

3. RESULTS

When alpha beta ratio was 6, the biserial correlation coefficient showed the maximum value of 0.866 and the coefficient was significant statistically ($p<0.001$). Table 1 shows the patient group and their control rates which were classified according to the BED calculated with this alpha beta ratio. The dependency of control rate to BED was approximated to a BED response curve by curve fitting as follows

$$P(BED) = \frac{1}{1+\exp(BED-BED50)/s} \qquad \text{(2)}$$

where P(BED) is the control rate when the cell kill level is BED. BED50 is the 50% effective BED and s is the gradient factor of the curve. BED50 estimated from the data of Table 1 was 108.3 and s was 16.9. Assuming several fraction numbers, dose response curves were calculated from BED response curve. In the same way, total doses to attain a certain control rate were determined for each fraction number. Table 2 shows doses which are necessary for the specified tumor control rate.

Table 1. Number of patients classified by BED

BED range	Recurrence	Control	Total	Control rate
- 99	3	2	5	0.400
100 - 114	3	4	7	0.571
115 - 129	5	14	19	0.737
130 - 144	2	4	6	0.667
145 - 159	1	7	8	0.875
160 - 174	1	73	4	0.986
175 -	0	15	15	1.000
Total	15	119	134	0.888

Table 2. Total dose (GyE) necessary for tumor control

Control rate	Fraction number				
	1	2	4	9	18
0.5	22.7	30.5	41.4	54.1	66.9
0.7	24.3	32.8	43.6	58.7	73.1
0.8	25.3	34.2	45.5	61.6	76.9
0.9	26.7	36.2	48.3	65.6	82.5
0.95	27.9	38.0	50.8	69.3	87.4
0.98	29.5	40.1	53.7	73.6	93.4

4. DISSCUSION AND CONCLUSION

A BED response curve for control was estimated from the data of NSCLC patients treated by 18 or 9 fractions of carbon ion beam. From this curve, several dose response curves of the small fraction treatment were derived. The results suggest that the total doses to obtain the control rate of 95% were 28 GyE and 51 GyE for the fraction number of 1 and 4 respectively. Lung cancers are usually irradiated from 4 directions in the carbon ion beam therapy. Doses obtained here are sufficiently lower than the tolerance dose of normal lung tissue such as threshold dose to produce radiation fibrosis and to raise severe loss of pulmonary function. Therefore, the carbon ion therapy to early stage NSCLC with small fraction number is considered to be the most promising treatment.

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