

LONG TERM RESULTS OF BRONCHIAL ARTERIAL INFUSION WITH CHEMOTHERAPEUTIC AGENTS PLUS RADIATION THERAPY IN THE TREATMENT OF LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

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Abstract

Objective: To evaluate the efficacy of the bronchial arterial infusion (BAI) plus radiation therapy (RT) for locally advanced non-small-cell lung cancer (NSCLC). **Methods:** 79 patients with locally advanced NSCLC were divided randomly into two groups. In the RT group, the radiation was given by 8Mv X-ray or 18Mv X-ray with 2Gy/fraction, 5 fraction per week with a total dose of 60Gy-65Gy/6-7 weeks. In the BAI+RT group, the radiation was given as RT group. Bronchial arterial infusion was performed before RT. The regimen consisted of DDP 100 mg/m², MMC 10 mg, and 5-Fu 1000 mg. Each patient received two or three cycles. **Results:** The overall response rates were 80.5% in BAI+RT group and 50% in RT group. The 1-, 3-, 5-year survival rates in the BAI+RT group were significantly improved when compared to the RT group, being 87.8% vs 36.8%, 39.0% vs 7.9%, and 17.1% vs 2.6% respectively. The median time of radiation treatment to recurrence of primary lesion was 11 months in the BAI+RT group and 5 months in the RT group ($P<0.05$). The acute reactions were increased but acceptable in BAI+RT group, and the radiation treatments were able to be completed without any break. The late reactions were similar in both groups. **Conclusion:** The survival rates of patients with locally advanced NSCLC can be improved by BAI+RT without increasing any complication.

Key words: Lung cancer, Bronchial arterial infusion, Radiation.

Non-small-cell lung cancer (NSCLC) account for approximately 80% of all lung cancer. Only a low percentage of patients present disease susceptible to surgical resection. 30% to 40% of patients with NSCLC present with locally or regionally advanced unresectable tumors.^[1] Chest irradiation plays a critical role in the treatment of these patients. In some trials, chemotherapy had been shown to improve the survival outcome by enhancing the radiotherapy effects.^[1]

In this study, we review our experience with BAI+RT of patients with advanced NSCLC.

MATERIALS AND METHODS

Clinical Data

Between January 1990 and October 1992, 79 patients were randomized into 2 groups, the RT group and BAI+RT group. Patients required to have pathologically documented, locally advanced non-small cell lung cancers that were deemed unresectable. Stage II patients who were medically inoperable were also eligible. The other eligibility criteria included the following: (1) age less than 70 years, (2) Karnofsky performance status $\geq 70\%$, (3) measurable or assessable tumor, (4) adequate bone marrow function, (5) absence of previous chemotherapy or thoracic RT.

The pretreatment investigation consisted of a history and a physical examination, complete and differential blood cell counts, routine blood chemistry measurements, plain chest radiographs, chest computed tomographic scans (CT), whole brain CT and/or magnetic resonance imaging (MRI), abdominal ultrasound and/or CT, and an isotopic bone scan. Patients were staged according to UICC classification.

Patients characteristic are listed in Table 1.

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Table 1. Patients characteristics

Characteristic	No. (%)	
	RT	BAI+RT
Age (years)		
Median	58.2	55.3
Range	40~70	42~69
Gender		
Male	25 (65.8)	26 (63.4)
Female	13 (34.2)	15 (36.6)
Histology		
Squamous cell	23 (60.5)	22 (53.7)
Adenocarcinoma	12 (31.6)	14 (34.1)
Large cell	3 (7.9)	5 (12.2)
Clinical stage		
II	6 (15.8)	10 (24.4)
III _A	19 (50.0)	20 (48.8)
III _B	13 (34.2)	11 (26.8)
Peripheral	11 (28.9)	12 (29.3)
Central	27 (71.1)	29 (70.0)

Methods of Treatment

For the RT Group

Linear accelerator with 8Mv X-ray or 18 Mv X-ray was used. The initial opposing anterior-posterior treatment fields encompassed the primary tumor, the bilateral mediastinal lymph nodes, the subcarinal nodes, and the ipsilateral hilar nodes. The supraclavicular lymph nodes were included within the field when there was clinical evidence of their involvement. The fraction size delivered was 1.8~2.0Gy, given once per day. Five days per week. The total tumor dose was 60~65Gy in 30~36 fractions over 6~7 weeks. The spinal cord was limited to 40Gy.

For the BAI+RT Group

Chemical drugs were given through 6F tube which was inserted into the bronchial artery by way of a percutaneous puncture of the right femoral artery. Bronchial arteriography was necessary not only identify the tube in the proper ostium of the bronchial artery supplying the lung cancer but also screen for the presence of a spinal artery. The antineoplastic drugs, diluted in saline, were infused through the catheter. The regimen consisted of DDP 100 mg/m², MMC 10 mg, and 5-Fu 1000 mg. Each patient received two or three cycles of bronchial artery chemotherapy with a four weeks interval between the successive ones. RT was given after BAI, the radiation was given as RT group.

RESULTS

Follow-up Rate

Follow-up were maintained over 5 years to which 2 patients were last who were counted as deaths. The follow-up rate was 97.5%.

Tumor Responses

Table 2 shows the responses of both groups. The response rate seen in the BAI+RT group was 80.5% compared to 50% achieved in the RT group ($P<0.01$).

Table 2. Response to the therapy

	CR	PR	NC	PD	CR+PR (%)
RT	4	15	14	5	50% (19/38)
HRI+RT	11	22	8	0	80.5% (33/41)

Survival Rates

The survival rates are given in Table 3. The 1-year, 3-year survival rates in the BAI+RT group were superior to those of the RT group ($P<0.01$). The 5-year survival rate increased in the BAI+RT group compared that in the RT group, the difference was significant ($P<0.01$).

Recurrence Time

The recurrence time was calculated from the end day of the radiation to the last day of the recurrences. Included the local persistent diseases. The median recurrence time was 11 months in BAI+RT group and 5 months in RT group ($P<0.05$).

The Cause of Death

RT Group

One patient was lost. One patient survived with supraclavicular lymph node metastasis. 13 patients died of local persistent disease. 10 patients died of local recurrences. 5 patients died of local persistent diseases and distant metastases. 6 patients died of distant metastases. One patient died of local persistent disease and haemoptysis. One patient died of other disease.

BAI+RT Group

One patient was lost. 4 patients survived with disease free. One patient survived with supraclavicular lymph node metastasis. One patient survived with distant metastasis. One patient developed local recurrence after BAI+RT with 2 years. He received operation and survived over 3 years after operation. 8

patients died of local persistent disease. 6 patients died of recurrences. 5 patients died of local recurrences and distant metastases. 8 patients died of

distant metastases. 3 patients died of other diseases. 2 patients died of radiational pneumonia and haemoptysis. The detail is given in Table 4.

Table 3. Survival rates of each year

	1-year	2-year	3-year	5-year
RT	36.8% (14/38)	21.1% (8/38)	7.9% (3/38)	2.6% (1/38)
BAI+RT	87.8% (36/41)	68.3% (28/41)	39.0% (16/41)	17.1% (7/41)
<i>P</i>	<i>P</i> <0.01	<i>P</i> <0.01	<i>P</i> <0.01	<i>P</i> <0.01

Reaction and Complication

Acute Reaction

Radiational pneumonia was the principal reaction in 2 group. It occurring in both groups were 15.8% and 24.3% respectively. Radiation esophagitis was another main reaction. It occurred 18.4% in RT group, and 31.7% in BAI+RT group.

Hematologic Toxicities Occurred in BAI+RT Group

Leukopenia and neutropenia was observed in BAI+RT group. None of the patients suffered from severe complications due to hematologic toxicity. Digestive symptoms did not significantly interfere with treatment.

Late Reaction

RT Group

One patient developed esophageal stricture after radiotherapy with 2 years. She received esophageal dilation. But she dies of massive

haemorrhage. Pulmonary fibrosis was found in 15 patients, 2 of them developed bronchial obstruction.

Table 4. The cause of death (No. patients)

	RT	BAI+RT
Local recurrence	10	9
Recurrence+matestasis	0	5
Matestasis	6	8
Persistent disease	13	8
Persistent disease+matestasis	5	0
Persistent disease+complication	1	0
Complication	0	1
Other disease	1	3
Total	36	34

BAI+RT Group

Pulmonary fibrosis was found in 22 of 41 patients in this group. Only 4 patients developed bronchial obstruction, and 2 of them died of haemoptysis. No incidence of radiation myelopathy was noted. The detail is shown in Table 5.

Table 5. Reaction and complication

	No. patient (%)		<i>P</i>
	RT	BAI+RT	
Acute radiation reaction			
Esophagitis	12/38 (18.4%)	13/41 (31.7%)	>0.05
Pneumonitis	6/38 (15.8%)	10/41 (24.3%)	>0.05
Reaction of BAI			
Neutropenia	9	14	
Thrombocytopenia	6	10	
Anemia	6	10	
Alimentary tract	4	8	
Complication			
Esophageal stricture	1	0	
Pulmonary fibrosis	15	22	>0.05
Bronchial obstruction	2	4	
Bronchial obstruction+haemoptysis	0	2	

DISCUSSION

The treatment for lung cancer patients with BAI has been widely performed in China. It is well known that the short time effect by this method is higher than using systemic venous infusion, and bronchial artery chemotherapy not only produce a regional treatment but also has a systemic effect.^[2,3] To infuse the drugs directly into the artery supplying the tumor can increase the concentration of the drugs in the tumor.

Qian et al.^[4] reported that the results of BAI+RT on advanced lung cancer showing the response rate was 89.2%. The results of Den et al.^[5] randomized trial show the BAI with hyperfractionated RT can improve survival when compared with RT alone. Miyaji^[6] reported a 11.3% 5-year survival rate of NSCLC by BAI with RT in 138 patients. They considered that BAI caused the cytostasis and increased radiosensitivity from RT.^[5,6] Murakami^[7] treated 35 patients with BAI and unevenly fractionated RT. Survival rates were 71% at 1-year, 27% at 3-years, and 5-years, including 3 survivors without recurrence. In this study, the short-term effect of the BAI+RT group was superior to that from the RT group, which was of statistical significance. BAI+RT could raise the local control rate. The long-term survival rate of the BAI+RT group was higher than that of the RT group with statistical significant in the 1-year and 3-year survival rates. The 5-year survival rate was 17.1% in BAI+RT group, which is higher than that of the RT group, and 3 patients survived without recurrence. The rate of distant metastasis of the BAI+RT group was not higher than that of the RT group.

Radiation pneumonitis was the fatal side effect of the BAI+RT group.^[7] In our study, pneumonitis was the main side reaction. Although the incidence of

acute toxicities was slight high in BAI+RT group, the treatment was tolerated. All patients recovered well from the acute toxicity of the treatment. The late radiation reaction increased in BAI+RT group, but has no significance in both groups.

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