Treatment of Non-Small Cell Lung Cancer (NSCLC) Using CT in Combination with a PET Examination to Minimize the Clinical Target Volume of the Mediastinum

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OBJECTIVE To decrease radiation injury of the esophagus and lungs by utilizing a CT scan in combination with PET tumor imaging in order to minimize the clinical target area of locally advanced non-small cell lung cancer, without preventive radiation on the lymphatic drainage area.

METHODS Of 76 patients with locally advanced non-small cell lung cancer (NSCLC), 32 received a PET examination before radiotherapy. Preventive radiation was not conducted in the mediastinum area without lymphatic metastasis, which was confirmed by CT and PET. For the other 44 patients, preventive radiation was performed in the lymphatic drainage area. PET examinations showed that the clinical target volume of the patients was decreased on average to about one third. The radiation therapy for patients of the two groups was the same, i.e. the dose for accelerated fractional irradiation was 3 Gy/time and 5 time/week. The preventive dose was 42 to 45 Gy/time, 14 to 15 time/week, with 3-week treatment, and the therapeutic dose was 60 to 63 Gy/time, 20 to 21 time/week, with a period of 4 to 5 weeks.

RESULTS The rate of missed lymph nodes beyond the irradiation field was 6.3% and 4.5% respectively in the group with and without PET examination (P = 0.831). The incidence of acute radioactive esophagitis was 15.6% and 45.5% in the two groups respectively (P = 0.006). The incidence of acute radiation pneumonia and long-term pulmonary fibrosis in the two groups was 6.3% and 9.1%, and 68.8% and 75.0%, respectively (P = 0.982 and P = 0.547).

CONCLUSION The recurrence rate in the lymph nodes beyond the target area was not increased after minimizing the clinical target volume (CTV), whereas radioactive injury to the lungs and esophageal injury was reduced, and especially with a significant decrease in the rate of acute radioactive esophagitis. The method of CT in combination with PET for minimizing the mediastinal CTV is superior to the conventional preventive radiation of the mediastinum.

KEYWORDS: non-small cell lung cancer, three dimensional conformal radiation therapy, computerized tomography (CT), positron emission computerized tomographical scanning.

Radio-chemotherapy is the standard therapeutic regimen for treating locally advanced non-small cell lung cancer (NSCLC), but at present failure of local control remains a major cause of death. Under a prerequisite of not increasing the toxic effects of chemotherapeutic agents, enhancement of the local control rate will result in an increase in the curative effect\(^1\). Positron emission tomography (PET) in combination with CT can augment the sensitivity of detecting Stage-N-NSCLC and the negative predictive values can reach to over 95%\(^2\). For this reason, a prospective
random control study was conducted, using PET diagnostic information, based on CT localization. Preventive radiation of the lymphatic drainage area was not performed, and the clinical target volume (CTV) for conformal therapy of the NSCLC was decreased. We hoped that with the prerequisite of not decreasing the local control rate, the radioactive esophagitis and pulmonary radiation damage could still be reduced.

**MATERIALS AND METHODS**

**Selection of the cases**
From April 2000 to January 2003, 76 patients with locally advanced NSCLC received radiotherapy according to a planned therapeutic regimen. Inclusion criteria for the patients to receive radical radiotherapy included the following: a) KPS ≥ 90 scores and a decrease of body weight was less than 10\% within 2 months; b) Distant metastasis or malignant pleural fluid were not found in various auxiliary examinations of the patients, of which 32 received systemic tumor imaging by 18F-FDG-PET (Group A).

General make-up of the patients included 57 males and 19 females, with ages ranging from 36 to 81 years and a median age of 63. The results of pathologic diagnosis for 46 patients was obtained after biopsy by either bronchofibroscopy or puncturation of the intrapulmonary tumor, and by cytologic diagnosis for 30 patients using a sputum smear, bronchofibroscopic brush cytology or lavage. Of all the cases, 39 were squamous cancer, 20 adenocarcinoma, 6 large cell carcinoma, 6 undifferentiated or poorly-differentiated carcinoma (failure of cytologic grouping), 2 bronchoalveolar cell carcinoma and 3 cancers of other pathologic types. Clinical stages were determined based on the 1997 WHO NSCLC Staging, i.e. 39 in Stage IIIA and 37 in Stage IIIB. Based on Stage N standards, 10 cases were found in Stage N0, 22 in Stage N1, 30 N2 and 14 N3. For characteristics of the general condition of the patients in the two groups, see Table 1.

**RADIOThERAPEUTIC METHODS**

**Main radiotherapy equipment**
A negative-pressure moulding pad method was used for localization of the patient’s body position. A PICKER PQS-2000 systemic spiral CT (US) was employed for scanning localization, a Leibinger STP3 (Germany) or AQSIM/PLAN (US) 3-dimensional treatment planning system was used for simulating the treatment plan and Varian 600C/D or Varian 2100C linear accelerator used for carrying out the plan.

| Table 1. Statistical table for general condition of the patients of the two groups. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Item                           | Group A (n = 32) | Group B (n = 44) | Test          | P value       |
| Age                            |                 |                 |               |               |
| <40                            | 3(9.4)          | 3(6.8)          |               |               |
| 40-49                          | 7(21.9)         | 8(18.2)         |               |               |
| 50-59                          | 6(18.8)         | 9(20.5)         |               |               |
| 60-69                          | 7(21.9)         | 14(31.8)        |               |               |
| 70-79                          | 8(25.0)         | 10(22.7)        | Z=0.135       | 0.893         |
| ≥80                            | 1(3.1)          | 0               |               |               |
| Sex                            |                 |                 |               |               |
| Male                           | 25(78.1)        | 32(72.7)        |               |               |
| Female                         | 7(21.9)         | 12(27.3)        | χ²=0.288      | 0.592         |
| Lymph node stages              |                 |                 |               |               |
| N 0                            | 4(12.5)         | 6(13.6)         |               |               |
| N 1                            | 9(28.1)         | 13(29.5)        |               |               |
| N 2                            | 14(43.8)        | 16(36.4)        |               |               |
| N 3                            | 5(15.6)         | 9(20.5)         | Z=0.044       | 0.965         |
| Pathologic classification      |                 |                 |               |               |
| Squamous carcinoma             | 16(50.0)        | 23(52.3)        |               |               |
| Adenocarcinoma                 | 8(25.0)         | 12(27.3)        |               |               |
| Large cell carcinoma           | 3(9.4)          | 3(6.8)          |               |               |
| Other pathologic types         | 5(15.6)         | 6(13.6)         | χ²=0.259      | 0.968         |
| Tumor site                     |                 |                 |               |               |
| Central type                   | 28(87.5)        | 37(84.1)        |               |               |
| Peripheral type                | 4(12.5)         | 7(15.9)         | χ²=0.174      | 0.667         |

*P* = Mann Whitney test and Pearson Chi-Square test.

Group A, had a PET examination; Group B, no PET examination.
Grouping
The patients were divided into the two groups: Group A received a PET examination and Group B had no PET examination. The 32 patients with a pre-radiotherapeutic systemic $^{18}$F-FDG-PET tumor imaging were classified to the group A with a diminution of the scope of the irradiation field. Detailed information such as an introduction of the patient’s condition and radiotherapy method, as well as a guarantee for exactness of the PET examination and an indication of not conducting the preventive radiation at the lymphatic drainage area, was explained to the patients and their relatives to provide informed consent. In Group B, preventive radiation at the lymphatic drainage area for the patients was conducted, based on the conventional method. Since the cost of a PET examination is expensive, whether or not to perform a PET scan was mainly related to the economic status of the patients, but not related to the age, sex, patient’s condition and other human factors. For comparison of the general condition, pathological and clinical stages between the patients of the two groups, see Table 1.

Delimitation of the target area treated
The image of the patients in the two groups indicated that the focus, i.e. the gross tumor volume (GTV), was the primary focus of the lesion and the metastasized lymph nodes proven by CT/PET scan. The scope for the GTV of the patients in Group A was 0.5 cm wider than usual to form the clinical target volume (CTV). If skipped lymphatic metastasis occurred, a metastatic pathway was included in the CTV, and scope of the CTV was 0.5 cm wider outwards to form the planning target volume (PTV). In group B, the CTV of patients included the GTV, and the hilum of the lung and total mediastinum in the diseased site. The lower edge of the CTV reached to 3 to 4 cm below the bronchial eminence, and the upper edge at the entrance of the thoracic cavity. If the Troisier sign (N3) occurred, a boost irradiation was given in the involved area. The CTV for the patients with peripheral lung cancer of Stage-N0 included those with the hilum of the lung in the diseased site only, and the CTV was 0.5 cm wider outwards to form the PTV.

The mean CTV of the patients in the two groups was as follows, i.e. CTV of Group A: 254.57 ± 45.73 cm$^3$, and CTV of Group B: 387.76 ± 75.71 cm$^3$, t’ =9.523, P = 0.0001. The difference between the mean target area was approximately one third.

Irradiation method and dosage
A regimen with 3 to 5 conformal exposure fields for an iso-center focusing irradiation of the PTV was performed, with reference to a dose-volume histogram for optimizing the treatment plan, and the optimal principles of the irradiation treatment to meet the following 3 requirements: a) The exposure dose of the spinal cord at the segment corresponding to the PTV was less than 45 Gy; b) The lung volume (V[20]) with an exposure dose of over 20 Gy did not exceed 25% of the unilateral lung volume, and the average exposure dose of the unilateral lung did not exceed 25 Gy; c) The esophagus (V[50]) with an exposure dose of over 50 Gy did not exceed 1/4 of the length of the total esophagus.

An accelerated fractionated irradiation was used in both groups, with a dose of 3 Gy/t, 5 t/w. The PTV dose of first treatment was 42 to 45 Gy, 14 to 15 t and 3 w. The target area was minimized after the first treatment of the patients. Of these patients, 17 received a second CT localization, but 59 still used the former CT localization parameter. As concerning the field reduction, GTV was extended outwards for 0.5 cm to form a PTV-2, and the PTV-2 was employed for the sequential irradiation, with a dose of 15 to 18 Gy /5 to 6 t and 1 to 2 w, allowing the total dose of GTV to amount to 60 to 63 Gy /20 to 21 t and 4 to 5w.

Combined therapy
Before and after radiotherapy, the patients received 3 to 4 cycles of combined chemotherapy. During the follow-up, distant metastasis occurred in 31 patients, among which 23 received palliative radiotherapy of the metastasis, and a hypo-fractionated, and multiple-field focus irradiation, a dose similar to a radical treatment, was administered on the metastasis. On average, the treatment was conducted on 3 metastases for each patient, and at most on 12.

Observation of the curative effect
Follow-up of over 2 years was performed for all the patients, with a median of 27 months. A comparative observation of the survival rate, local recurrence and distant metastasis of the patients in both the groups was conducted. Based on the standards for classifications of the radiation therapy oncology group (RTOG), USA, the incidence of acute radiation pneumonia and advanced radioactive injury to the lungs, and of the acute radio-induction of esophagitis or advanced esophageal injury were compared. No chemotherapeutic factor was included in the statistical analysis.

Statistical analysis
Statistical analysis was carried out using SPSS13.0.
RESULTS

Survival statistics and distant metastasis
Survivals were calculated from the date of a definite diagnosis. The overall median survival of patients in the two groups was 19 months (95% confidence interval [CI], 15.4 to 22.6 months). Among the patients, 27 died of distant metastasis, 22 died of progression into the hilum of the lung and the mediastinum, and 8 died of other causes. Loss of follow-up occurred in 8 patients and 11 are still surviving to date. None of them died of a radioactive complication. There was no statistical difference between the survival rates of the patients in the groups A and B (P = 0.59) (Fig.1).

The incidence of distant metastasis for patients of groups A and B was 25.0% (8/32) and 52.3% (23/44) respectively, $\chi^2 = 5.706$, $P = 0.0174$. Distant metastases were significantly higher in group B compared to group A. See Fig. 1 for statistics of the survival rate.

Analysis of the local therapeutic effect
Within 2 years, the failure rate of radiotherapy of the hilum of the lungs and of the mediastinal septum was 23.7% (18/76) in the patients of the two groups, and the median recurrence time 8.5 months, i.e. 21.9% (7/32) and 25.0% (11/44) in groups A and B respectively, $\chi^2 = 0.100$, $P = 0.752$. There was no statistical difference between the two groups.

The rate of missed lymph nodes beyond the exposure field for the patients of groups A and B was 6.3% (2/32) and 4.5% (2/44) respectively, $\chi^2 = 0.037$, $P = 0.831$. In other words, diminution of the target area did not bring about an increase in the recurrence in the lymph node-draining area.

Statistics of acute and advanced radioactive injury to the lungs
The overall incidence of acute radiation pneumonia for the patients was 7.9% (6/76). Among the cases, grade-1 to 2 radioactive pneumonia occurred in 4 patients, grade-3 radioactive pneumonia in 2, and the incidence of radioactive pneumonia with a grade higher than 3 was zero. The incidence of pneumonia in the groups A and B was 6.3% (2/32) and 4/44) respectively, $\chi^2 = 0.001$, $P = 0.982$. There was no significant difference between the two groups.

The incidence of the long-term metastasis of the pulmonary hilum and the pulmonary fibrosis around the mediastinum was 72.4% (55/76). The CT scans revealed there was a callosal change in the hilum of the lung, which was in accordance with the target area. The bronchofibroscopy showed a tracheostenosis or a scarring. Chronic cough was found in most patients, with symptoms of pneumonia caused by infection in a few patients. The incidence of pulmonary fibrosis around the mediastinum and hilum of the lung in the patients of groups A and B was 68.8% (22/32) and 75.0% (33/44) respectively, $\chi^2 = 0.362$, $P = 0.547$, and with no significant difference between the two groups. Atelectasis in the lesion-side pulmonary lobes and segment was found in 14 patients (18.4%), which was related to the tumor invasion, the lobular and segmental bronchial stenosis or imperforation after radiotherapy. The patients with atelectasis following the radiotherapy, amounted to 5 in group A and 9 in group B, with an incidence of 15.6% and 20.5%, respectively, $\chi^2 = 0.322$, $P = 0.571$. No significant difference was found.

Statistics of acute and advanced radioactive esophageal injury
During the treatment, or 3 months after it, the overall incidence of grade-1 and 2 acute radiation esophagitis of the patients in the two groups was 32.9% (25/76), and in groups A and B, 15.6% (5/32) and 45.5% (20/44) respectively, $\chi^2 = 7.468$, $P = 0.006$. The incidence of esophagitis was significantly higher in the patients of group B compared to those in group A. No grade-3 or esophagitis of a higher grade occurred in patients of the two groups. The incidence of grade-2 and 3 radioactive esophageal stricture of the later stage in patients of the two groups was 9.2% (7/76), and no grade-4 esophageal injury developed. Among these patients, 5 were required to insert an esophageal endoprosthesis. The incidence of grade-2 and 3 radioactive esophageal stricture in patients of groups A and B was 6.3% (2/32) and 11.4% (5/44), $\chi^2 = 0.129$, $P = 0.719$. 

Fig.1. Statistics of the survival rate in patients of groups A and B.

![Graph showing survival rates in groups A and B](image)
DISCUSSION

The three dimensional conformal radiation therapy treatment plan is designed based on the CT scanning data. Enhancement of the resolution of the treatment target area and normal tissue was a prerequisite for optimizing the treatment plan. Of course, a safe therapeutic borderline for limiting the target area and increasing the target area dose could improve the local control rate. ¹⁸F-FDG-PET produced an exact diagnosis of the non-small cell lung cancers, and especially it was superior over the conventional examinations such as CT, allowing for the sensitivity, specificity and positive and negative predictive values, etc., when evaluating the mediastinal lymph nodes. However, the efficiency of CT-PET diagnosis was even higher. It surely would be helpful to enhance the precision of the radiation field, if the diagnostic information from PET could be employed for ascertainment of the radiotherapeutic target area.

In this study, we took the data from CT and PET scans to minimize the preventive radiation scope of the lymph node-drainage area. After diminishing the irradiation dose, the local control rate of the patients was not decreased, and lymphatic recurrence beyond the therapeutic target area also was not frequently seen. The recurrence in lymph nodes beyond the target area was 6.3% and 4.5%, respectively in the patients of groups A and B, P = 0.831, without a statistical difference between the groups. There was a marked increase in the incidence of the distant metastasis in the patients without receiving the PET examination (52.3% and 25% respectively, P = 0.0174), with an increased relative risk of lethal metastasis. This is mainly because of a high selectivity of the PET, which can identify an insidious metastasis which is often difficult to find by routine examinations. There was no overt difference between the survival rates in the patients of the two groups.

Although the CTV dose was the same in the patients of the two groups, the incidence of acute radio-induced esophagitis (45.5%) was significantly higher in group B than in group A (15.6%) (P = 0.006), because of a larger target volume and a longer length of the exposed esophagus in group B compared to group A. These results suggest that a preventive dose ranging from 42 to 45 Gy and 13 to 15 Gy resulted in acute radioactive esophagitis, which had a positive correlation with the length of the exposed esophagus. The GTV dose was the same in both groups, and there was no statistical difference in the incidence of a long-term radioactive esophageal stricture between the groups, indicating a considerable correlation between the long-term esophageal strictures and exposure dose. Esophageal injury was a key factor for restriction of the radiation dose, because irradiation on the hilum of the lungs and mediastinum failed to exempt the esophagus. This was especially true in treatment of the left central-type lung cancer. After receiving a preventive dose, the exposed field of the patients was reduced to the GTV, and it still failed to exclude the esophagus in most instances. Therefore, diminution of the irradiation scope to the esophagus is extremely important.

The incidence of acute and advanced radioactive-induced pneumonia was not very high in the two groups, mainly owing to the multiple-field conformal radiation technology, allowing the utilization of a major difference of dose gradients between the target area and normal tissue. This methodology allowed implementing therapeutic gain by radiological technology to better achieve our goal of not exceeding 25% of the unilateral lung volume with an exposure dose beyond 20 Gy (V(20)<111). The incidence of grade-3 radioactive pneumonia was mainly related to injuries of the lobar and segmental bronchus, because there was edema, stenosis or obstruction in the bronchus and lobular bronchus, resulting in atelectasis or consolidation of the lungs. Therefore radioactive injury to the bronchus is another key reason for limiting the irradiation dose. Although there was no significant difference between the incidence of radioactive injury of the lungs in the two groups, the exposed volume of lung became smaller after a diminution of the clinical target area, and the size of pulmonary fibrosis was relatively downsized after radiotherapy.

REFERENCES


