Hyperfractionated Radiotherapy with Concomitant Boost Technique for Unresectable Non-Small Cell Carcinoma of the Lung

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Twenty five patients with unresectable non-small cell carcinoma of the lung have been treated with hyperfractionated radiotherapy with concomitant boost technique since September, 1989. Those patients with history of previous surgery or chemotherapy, pleural effusion or significant weight loss (greater than 10% of body weight) were excluded from the study. Initially, 27 Gy were delivered in 15 fractions in 3 weeks to the large field. Thereafter, large field received 1.8 Gy and cone down boost field received 1.4 Gy with twice a day fractinations up to 49.4 Gy.

After 49.4 Gy, only boost field was treated twice a day with 1.8 and 1.4 Gy. Total tumor doses were 62.2 Gy for 12 patients and 65.4 Gy for remaining 13 patients. Follow up period was ranged from 6 to 24 month. Actuarial survival rates at 6, 12, and 18 month were 88%, 62%, and 38%, respectively. Corresponding disease free survival rates were 88%, 41%, and 21%, respectively.

Actuarial cumulative local failure rates at 9, 12 and 15 month were 36%, 43%, and 59%, respectively. No significant increase of acute or late complications including radiation pneumonitis was noted with maximum follow up of 24 month. Although the longer follow up is needed, it is worthwhile to try the prospective randomized study to evaluate the efficacy of hyperfractionated radiotherapy with concomitant boost technique for unresectable non-small cell lung cancers in view of excellent tolerance of this treatment. In the future, further increase of total radiation dose might be necessary to improve local control for non-small cell lung cancer.

Key Words: Hyperfractionation, Radiotherapy, Non-small cell lung cancer

INTRODUCTION

Despite mass screening and earlier detection, lung cancer remains a highly lethal tumor. The majority of patients with this cancer are diagnosed when the disease is relatively advanced, either because of metastatic disease to regional nodes or because of distant metastases. The highest cure rate in non-smal cell lung cancer have been achieved by surgery in early stages of disease[1]. However, a substantial proportion of patients with non-small cell lung cancer who present with localized intrathoracic disease are clinically inoperable. A wide diversity of opinion exists as to whether life is prolonged by radiation therapy in this category of patients.

Roswit et al[2] reported the results of a randomized study designed to answer this question. A total of 246 patients were randomized to no treatment (placebo) and 308 patients to radiation therapy (40 ~50 Gy). This study showed a small but statistically significant influence of radiation therapy on survival (18% vs 14% at one year). Katz and Alberts[3] have summarized the results of several series reported in the literature over the past 25 years.

It is evident that the survival of definitely irradiated inoperable patients during this period has not shown any improvement, the 5 year survival ranging from 3 to 10%. In all of these reported series, doses in the range of 40 to 50 Gy have been employed. No survival advantage was demonstrated by continuous vs split course irradiation. Radiation Therapy Oncology Group study[4] showed improved local control rate with increased radiation dose.

Although significant proportion of unresectable non-small cell carcinoma patients develop distant metastases during their course of disease before they die, intrathoracic failure remains as a important cause of death for this group of patients. To gain a probability of 50% or more permanent control of non-small cell lung cancers requires higher doses than are presently given by external irradiation, and these doses would exceed the accepted tolerance levels of intrathoracic normal tissures. Therefore, we initiated hyperfractionated radiotherapy program with concomitant boost technique for unresectable non-small cell car-

cinoma of the lung in our institution since September, 1989.

It has been well documented that hyperfractionated radiation therapy has been used to treat the patients with various tumors such as locally advanced head and neck cancers, bladder tumors and inflammatory breast cancers trying to improve local control rates without increase of treatment related toxicities. We analyzed records of 25 patients who entered hyperfractionated radiation program to evaluate survival rate, local control rate and tolerance of this treatment.

MATERIALS AND METHODS

Between September, 1989 and April, 1991, total of twenty five patients with unresectable non-small cell carcinoma of the lung entered hyperfractionated radiation program with concomitant boost technique. All of the patients had histologically proven non-small cell carcinoma. They were diagnosed by sputum cytology, bronchoscopy or fine needle aspiration biopsy. Sixteen patients had squamous cell carcinoma. Four and 5 patients had adenocarcinoma and undifferentiated large cell carcinoma, respectively.

Those patients with history of previous surgery or chemotherapy, malignant pleural effusion or significant weight loss (greater than 10% of body weight) were excluded from the study. Patients were evaluated by careful physical examination including supraclavicular fossae, chest X-ray (CXR), Computed Tomography (CT) of the chest and upper abdomen and whole body Tc99m bone scan. CT of the brain was not performed routinely. All of the patients were staged by TNM staging system recommended by American Joint Committee on Cancer[5].

Distribution of the patients according to TNM stages is shown in table 1. Age of the patients in the study was ranged from 42 to 77 years. Male to female ratio was 22:3. Presenting symptoms were chest discomfort, shortness of breath, cough, sputum prudction, chest pain and hemoptysis in decreasing order. All of the patients in the study were treated with Linear Accelerator producing 10 MeV photons. Initially, 27 Gy were delivered in 15 fraçtions in 3 weeks to encompass primary site and regional lymphatic echelons. 1.5 cm margins were given around the primary site. Contralateral hilum and supraclavicular fossae were not routinely included in the field.

Thereafter, initial large field received 1.8 Gy in the morning and 1.4 Gy was delivered to the cone down boost field in the afternoon as a second daily treatment up to total tumor dose of 49.4 Gy including initial 27 Gy. Minimum of 4 hour interval was given between two daily treatments. Cone down boost field encompassed primary site, ipsilateral hilum and ipsilateral mediastinum to take off the spinal cord.

Total dose to the spinal cord through the large field was 39.6 Gy in 22 fractions. After 49.4 Gy, only boost field was treated twice a day with 1.8 and 1.4 Gy for morning and afternoon treatement. In twelve patients in the study, total tumor dose was 62.2 Gy in 5 weeks and 2 days. Since these patients tolerated the treatment well, we delivered one more day of treatment (1.8+1.4 Gy) for remaning 13 patients. Thus total of 65.4 Gy was delivered in 5 weeks and 3 days for these 13 patients.

All but one patients completed program without complaining of acute treatment related toxicities. One patient who developed significant generalized weakness had to stop the treatment at 52.6 Gy. Minimum follow up was 6 month. Survival time was calculated from the first day of the radiation therapy. Patients were followed in one month after completion of the treatement. CXR was routinely performed to evaluate the disease status. CT of the chest were done for only 17 patients. Thereafter patients were seen in our department or by their referring physicians in 2 or 3 month, unless they develop symptoms suggestive of local recurrence, distant metastases or treatment related complications.

Because all of the patients in the study did not have CT scan, local control was evaluated by CXR. Radiation pneumonitis was considered for patients with radiological change and significant symptoms such as dry cough or mild fever not related with local recurrence.

RESULTS

At the beginning of the study, we initiated hyperfractionated program with 1.8 and 1.6 Gy twice a day treatment instead of 1.8 and 1.4 Gy in concomitant boost schedule. Two patients were treated with 1.8 and 1.6 Gy twice a day boost. However these 2 patients complained of general weakness and moderate to severe radiation esophagitis during their treatment and both of them were not able to complete treatment. Thus, 1.8 and 1.6 Gy twice a day schedule were thought to be intolerable and we modified the treatment schedule to 1.8 and 1.4 Gy.

These two patients were excluded from the study.

As shown in Fig. 1, actuarial survival rates were 88% (22/25), 62% (13/21) and 38% (5/13) at 6, 12 and 18 month, respectively. Corresponding disease free survival rates were 88% (22/25), 41% (9/22) and 21% (4/19), respectively. Local control rate at 18 month was 60% (15/25) with total of 10 local recurrences in 2 years. Cumulative local failure rates at 9, 12 and 15 month were 36% (8/22), 43% (9/21) and 59% (10/17), respectively as shown in Fig. 2. These cumulative local failure rates are actuarial rate calculated with actual survivors.

Eight patients developed distant metastases during their course of disease and one patient developed contralateral supraclavicular recurrence for which palliative radiotherapy was given since that was not included in original field. Radiation pneumonitis was noted in 5 patients and none of those patients had continuous medically intrac-

Table 1. Distribution of Patients According to TNM Staging System

Stage	Number of patients
T3N2M0	9
T4N0M0	3
T4N1M0	2
T4N2M0	10
T4N3M0	1

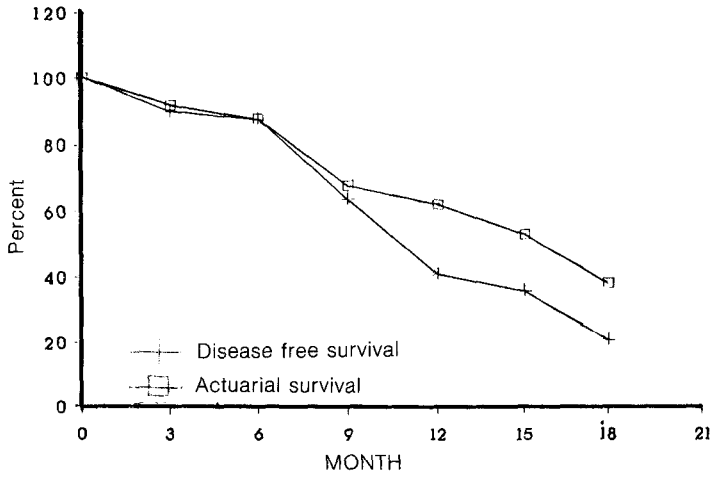

Fig. 1. survival curve.

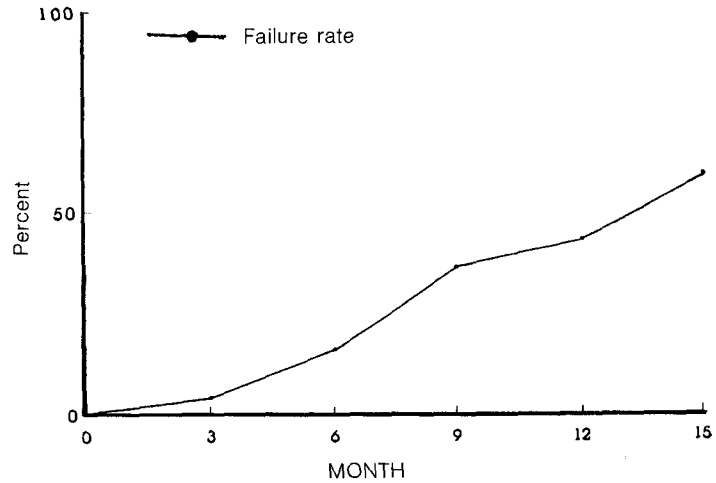

Fig. 2. Cumaulative local lallure rate.

table cough. All pneumonitis was developed between 2 and 6 month after the completion of radiotherapy. Except for symptomatic radiation pneumonitis, no other late complications related with soft tissue or bone damage were noted with maximun follow up of 24 month.

DISCUSSION

Perez[4] et al reported the results of the Radiation Therapy Oncology Group randomized study in 378 patients with medically inoperable or unresectable non-small cell carcinoma of the lung, treated by definitive radiation therapy. This study was designed to test the effect of four treatment regimens on tumor control and survival. The doses tested were: 40 Gy split course (20 Gy in one week, followed by two week rest and additional 20 Gy in one week). and 40, 50, and 50 Gy continuous conventional treatment.

The intrathoracic failure rate was lower in the patients with lesions smaller than 6 cm receiving 50 to 60 Gy as compared with those receiving 40 Gy (30% for 60 Gy; 41% for 50 Gy; and 52% for the 40 Gy groups). Survival was not correlated with tumor size, however. Also final report of a randomized trial conducted by the VA Lung Cancer Study Group[6] was published by Petrovich et al. In it 343 patients with unresectable or inoperable lung cancers were randomized to a short course of 42 Gy in 3 weeks and to an intermediate course of 50 Gy in five weeks. No significant difference in median survival, response, local control, and complications could be demonstrated. These studies suggest that the higher the total irradiation, the better the tumor response, local control and survival.

Based on results of these studies, we initiated hyperfractionated radiotherapy with concomitant boost technique to deliver the higher total dose of irradiation in relatively short treatment time. Compared with 60 Gy in 6 weeks in conventional radiation regimen, we delivered 65.4 Gy in 5 weeks and 3 days. One could expect increased acute or late complications with higher doses in shorter treatment time.

However, the patients in our study did not show any increased toxicities except for more severe radiation esophagitis than conventional radiation. More importantly, unexpected increase of late complications was not noted thus far. Suh and Rhee[7] reported the incidence of occurrence of radiation peumonitis for patients treated with irradiation. Seventeen out of 40 patients developed radiological changes and 9 out of those 17 patients showed clinical features of radiation pneumonitis. This result (9/40) is comparable to that of our study (5/25).

Recently published RTOG study[8] showed that 69.6 Gy hyperfractionated results were significantly better than results with standard fractionation in comparable patients from earlier RTOG trials (58% and 20% versus 30% and 7% survival rates at 1 and 3 year). Thus, they are undergoing a prospective randomized Phase III comparison of 60 Gy standard fractionation versus hyperfractionation with 69.6 Gy. This result may indicate the need to increase the total dose to improve the survival for non-small cell carcinoma of the lung. Our institution[9] did report 23.5% of two year survival rate for non-small cell lung cancer patients treated with conventional irradiation.

In this hyperfractionated radiation regimen, we obtained 38% of 18 month actuarial survival rate. Because of small number of patients in the study, comparison of treatment results between two regimens might be inappropriate. Therefore, accumulation of more number of patients in the future and long term follow up would make it possible to compare each treatment.

CONCLUSION

In conclusion, Hyperfractinated radiation therapy with concomitant boost technique for locally advanced unresectable non-small cell carcinoma of the lung has been tolerated well without increase of significant acute and late complications. Although the longer folow up is needed, it is worthwhile to try randomized study to evaluate the efficacy of hyperfractionated radiotherapy in view of acceptable toxicity. Also further increase of total tumor dose might be necessary to improve local control as well as survival with good tolerance.

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= 국문초록 =

절제 불가능한 비소세포 폐암의 다분할조사 방사선 치료

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전 하 정 · 이 명 자

25예의 절제 불가능한 비소세포폐암 환자를 다불할조사 방사선 치료 및 추가 조사 기술로 치료하였다. 전에 수술이나 항암제 치료를 받았거나 늑막삼출 및 심한 체중 감소(체중의 10%이상)가 있는 환자는 이 연구에서 제외했다. 처음 3주에 걸쳐 27 Gy를 15번에 나누어 large field에 조사하였다. 그 후에 large field에 1.8 Gy를 준 후 cone down boost field에 1.4 Gy를 하루에 두번 주어 총 49.4 Gy를 주었다. 49.4 Gy를 준 후 추가조사 영역에 하루에 두번 1.8 Gy와 1.4 Gy를 주었다. 총 조사량은 12명의 환자에서는 62.2 Gy , 13명의 환자에서는 65.4 Gy였다. 추적관찰 기간은 6개월에서 24개월 사이였다. 실질적인 생존율은 6, 12, 18개월에 각각 88%, 62%, 38%였다. 무병 생존율은 88%, 41%, 21%였다. 집합적 국소 재발율은 9, 12, 15개월에 각각 36%, 43%, 59%이었다. 24개월간 추적관찰한 결과 급성 합병증이나 후기 합병증의 증가는 없었다. 더 긴 기간의 추적관찰이 필요하지만, 절제 불가능한 비소세포 폐암의 다분할조사 방사선 치료 및 추가 조사기술의 효과를 판정하는데는 무작위 추출법을 사용하여 prospective 연구를 시행함이 필요하리라 생각된다.