Results of a Preliminary Study using Hypofractionated Involved Field Radiation Therapy and Concurrent Carboplatin/Paclitaxel in the Treatment of Locally Advanced Non-Small-Cell Lung Cancer

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Key words: involved field radiation therapy (IFRT), elective nodal irradiation (ENI), three-dimensional conformal radiation therapy (3DCRT), non-small-cell lung cancer (NSCLC), carboplatin (CBDCA), paclitaxel (PTX)

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ABSTRACT

Purpose

To evaluate the feasibility and efficacy of hypofractionated involved field radiation therapy (IFRT) omitting elective nodal irradiation (ENI) with concurrent chemotherapy for locally advanced non-small-cell lung cancer (NSCLC).

Patients and Methods

Between July 2004 and July 2006, 10 patients with locally advanced NSCLC were included in this study. One had stage IIIA and 9 had stage IIIB. The treatment consisted of IFRT in fractions of 2.5 Gy and weekly carboplatin (CBDCA)/paclitaxel (PTX). Hypofractionated IFRT of the median total dose of 65 Gy with the median V20 of 20.2% and chemotherapy of the median course of 5 with weekly CBDCA (area under the curve = 1.5-2.0)/PTX (30-35 mg/m^2) were given to all patients.

Results

The median survival time, the 1-, 2-, and 3-year overall survival rate were 29.5 months, 90.0%, 58.3%, and 43.8%, respectively. No elective nodal failure was encountered during the median follow-up of 18.2 months. No acute and late toxicities of Grade 3 or worse were observed. No in-field recurrence occurred in the group with a total dose of ≥67.5 Gy, but it occurred in 83.3% in a group with <67.5 Gy.

Conclusion

Hypofractionated IFRT with weekly CBDCA/PTX was a feasible treatment regimen. Hypofractionated IFRT with total dose of ≥67.5 Gy could be a promising modality to improve the treatment results.

INTRODUCTION

The standard treatment, based on evidence of patients with locally advanced non-small-cell lung cancer (NSCLC), is considered to be concurrent CHT (chemotherapy)-radiation therapy (RT) with a platinum-based regimen today.[1] This concurrent CHT-RT provides a median survival time (MST) of 16-17 months, a 1-year overall survival (OAS) rate of 60-70%, and a 2-year OAS rate of 30-40%,[2-5] but these results should be open to further improvement. In addition, there is a problem regarding the fact that Grade 3/4 radiation esophagitis occurs in 20-30% of these patients.[3-5]

Local recurrence is one reason for the poor survival rate after RT, and it has been reported that an improvement in local control leads to increased survival in locally advanced NSCLC.[6,7] Therefore, intensification of the in-field effect to improve local control has previously been attempted. However, even though an increase in the total dose and a shortening of the overall treatment time are effective for improving the local control, problems remain due to the increase in severe esophagitis and pneumonitis.

Recently, involved field radiation therapy (IFRT) omitting elective nodal irradiation

(ENI) to achieve an improved local control by high total dose irradiation without increasing toxicity for locally advanced NSCLC has been attempted, and the results of these attempt suggests that it might be possible to irradiate safely a high total dose according to IFRT.[8,9] After these results, we introduced IFRT for locally advanced NSCLC within affiliated institutions of Hiroshima University in 2001. In addition, we started a preliminary study in 2004 to evaluate the feasibility and efficacy of hypofractionated IFRT with concurrent Carboplatin/Paclitaxel. The once-daily fraction is 2.5 Gy in order to improve the in-field control due to a high total dose irradiation with a higher fraction dose and to also to shorten the overall treatment time.

PATIENTS AND METHODS

Between July 2004 and July 2006, a total of 10 patients with locally advanced NSCLC were enrolled in this preliminary study and were evaluated. Before inclusion, all patients signed a written study-specific informed consent. In addition, we explained that the treatment would be cancelled if they rejected the designed treatment of this study during the treatment period in addition to giving them the details of this study. Patients eligible criteria included those with locally advanced stage IIIA-N2 disease or

stage IIIB disease (excluding malignant pleural effusion, malignant pericardial effusion, and lymphangitic carcinomatosis), histologically or cytologically confirmed NSCLC, age between 20 and 74, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no prior therapy for this malignancy, adequate laboratory and pulmonary functions. An adequate laboratory function included a leukocyte count ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl, total bilirubin level ≤ the upper limit of normal and a creatinine clearance ≥60 mL/min. An adequate pulmonary function was defined as a forced expiratory volume in 1 second of >1.0 L and PaO_2 ≥70 torr. Any patients with previous malignancies or severe complications (obvious interstitial pneumonitis, advanced pulmonary emphysema, poorly controlled diabetes, etc) were excluded. Before therapy, all patients were evaluated clinically with a history, physical examination, laboratory examination, radiographic studies, pulmonary function test, and electrocardiogram (ECG). The laboratory examination included a complete blood cell count, liver function studies, renal function studies, and measurement of electrolytes. The radiographic studies included chest X-ray, thoracic-abdominal computed tomography (CT), head magnetic resonance imaging (MRI), and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography

(FDG-PET) scan was not routinely performed.

The patient and tumor characteristics are shown in Table 1. The patients' median age was 68 years (range, 54-74), 9 were males, and 1 was female. Five (50.0%) presented with squamous cell carcinoma, 4 (40.0%) with adenocarcinoma, and 1 (10.0%) with large cell carcinoma. One (10.0%) had stage IIIA (T2N2: 1) and 9 (90.0%) had stage IIIB (T1N3: 1, T2N3: 5, T4N0: 1, T4N1: 1, T4N2: 1). Regarding the staging, all patients underwent thoracic-abdominal CT, head MRI, and bone scintigraphy. Whole-body FDG-PET/CT was performed on 4 patients (40.0%).

All patients were treated with three-dimensional conformal radiation therapy (3DCRT) that was planned with a three-dimensional radiation treatment planning system. All patients underwent a treatment planning CT of the chest for identification of the target and normal anatomy. The treatment planning CT was performed with continuous slices measuring 5 mm in thickness and with a long scan time of ≥3 seconds per image without breath holding throughout the whole lung and tumor. Only lymph nodes with a short-axis diameter of ≥10 mm on CT were included in the gross tumor volume (GTV-LN) without histological confirmation, in addition to the primary tumor (GTV-P). However, when lymph node involvement was suspected on

FDG-PET/CT due to diagnosis of PET specialist, lymph nodes with a short-axis of <10 mm were included in the GTV-LN. In addition, the clinical target volume (CTV) was defined as the volume of GTV-P and GTV-LN. The planning target volume (PTV) was contoured around the CTV with a 3-dimensional margin of 10-15 mm (thus making allowances for the location of the primary tumor, the respiratory mobility of the tumor, and the set up margin). In addition, a port margin of 5 mm was set around the PTV. The difference in the fields of ENI and IFRT is shown in Fig. 1. The doses were calculated at the isocenter with heterogeneity correction algorithms using both a superposition method (6 patients) and the convolution method (4 patients). The hypofractionated IFRT was delivered on a linear accelerator using a 6-10 MV photon beam. The hypofractionated IFRT was delivered in a coplanar technique or a non-coplanar technique with multiple fields to deliver a dose of 2.5 Gy once daily in 5 fractions weekly, and all radiation fields were treated every day. In the course of IFRT, field reductions according to the tumor volume reduction were permitted.

The fraction dose setting in this study was selected based on the preliminary results reported by Kimura *et al.*, which included accelerated hyperfractionated IFRT (66-75 Gy in 1.5 Gy twice-daily fractions) +/- concurrent CHT.[10] Before the induction of

IFRT, irradiation by using accelerated hyperfractionation was considered for IFRT to shorten the overall treatment time. However, we thought that twice-daily fractions might not be practical under clinical conditions, and we decided to use once-daily fractions of 2.5 Gy whose biologically effective dose (BED) Gy10 and BED Gy3 in a day were almost equivalent to that of a twice-daily fractions of 1.5 Gy. It was prescribed that the dose variation within the PTV be limited between 90% and 107% of the prescribed dose. The maximum dose of the spinal cord was kept to <40 Gy. Although the percent volume of the total lung (the volumes of both lungs minus the CTV) exceeding 20 Gy (V20) was kept to <30% in principle, as a higher volume was a predictive factor for the risk of radiation pneumonitis.[11,12] The limitation in the V20 value was considered based on the findings of a phase I study of RTOG 9311 performed by Bradley *et al.*, which included 0% of the estimated rate of Grade ≥3 lung toxicity after IFRT of 70.9 Gy in 2.15 Gy once-daily fractions for patients with <25% and ≥25%-<37% of V20.[13]

The minimal planned total dose was prescribed to 60 Gy/24 fractions (BED Gy10 is equivalent to that of 62 Gy/31 fractions). The maximum planned total dose was prescribed according to the V20 value as follows: (1) V20<15%: 70 Gy/28 fractions (BED Gy10 is almost equivalent to that of 74 Gy/37 fractions), (2) 15%≤V20<25%: 67.5

Gy/26 fractions (BED Gy10 is almost equivalent to that of 70 Gy/35 fractions), (3) 25%≤V20<30%: 65 Gy/26 fractions (BED Gy10 is almost equivalent to that of 68 Gy/34 fractions). The decision regarding the final total dose was made by the radiation oncologist under these dose settings. The details of IFRT given are shown in Table 2.

As the concurrent CHT, weekly intravenous CBDCA (area under the curve (AUC) = 1.5-2.0) and PTX (30-35 mg/m^2) during IFRT was set up in principle. This regimen and the dose setting were considered based on the findings of a phase I study performed by Ohashi *et al.*, which defined the dose level of CBDCA (AUC = 2.0) and PTX (35 mg/m^2) in combination with hyperfractionated RT (69.6 Gy in 1.2 Gy twice-daily fractions) with ENI as maximum tolerated dose.[14] Details of CHT given are shown in Table 2.

The tumor response rate was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines as follows: complete response (CR)—the disappearance of all target lesions; partial response (PR)—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as a reference the baseline sum longest diameter; progressive disease (PD)—at least a 20% increase in the sum of the longest diameter of target lesions, taking as a reference the smallest sum

longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD)—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as a reference the smallest sum longest diameter since the treatment started.

Recurrences of in-field and out-field were assessed using varying combinations of radiological assessment. In-field recurrence was defined as increase in radiologic abnormality within the irradiated volume that was not considered to be radiation-induced scarring or radiation pneumonitis. Elective nodal failure (ENF) was defined by recurrence in any lymph node region that was initially uninvolved in the absence of in-field recurrence.

Acute and late toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). Acute toxicity was defined as that occurring within 90 days of treatment initiation, while late toxicity was defined as that occurring beyond 90 days after treatment initiation. During CHT-RT, CHT and RT should be interrupted for either Grade ≥3 of leukopenia or neutropenia or thrombopenia, and thereafter be resumed when that toxicity has decreased to Grade ≤2. In addition, RT should be interrupted for Grade ≥3 esophagitis or pneumonitis, and

thereafter be resumed when that toxicity has decreased to Grade ≤2. In addition, the treatment should be canceled if Grade ≥4 severe toxicity occurs.

The follow-up evaluations were performed at 2-month intervals for the first year, at 3-month intervals for the second year, and at 6-month intervals thereafter. The follow-up evaluation routinely included physical examination, chest X-ray, toxicity assessment, and blood tests. Thoracic-abdominal CT scan was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. A restaging with head MRI and bone scintigraphy was performed at 6-month intervals after the first half year. The actuarial curves of OAS and the in-field tumor control rates were calculated using the Kaplan-Meier method, with the day of treatment as the starting point.

RESULTS

Tumor response, overall survival, and in-field tumor control

Of 10 patients, 1 achieved CR (10.0%), and 9 achieved PR (90.0%) with a tumor response rate of 100%. The final analysis was performed 17 months after the registration of the last patient. At a median follow-up of 18.2 months (range, 9.6-41.9),

5 patients (50.0%) had deceased at the time of the last follow-up. The MST was 29.5 months, and the 1-, 2-, and 3-year OAS rate were 90.0%, 58.3%, and 43.8%, respectively (Fig. 2). A median time to in-field tumor progression of 18.1 months was obtained, and the 1-, 2-, and 3-year in-field tumor control rates were 60.0%, 45.0%, and 45.0%, respectively (Fig. 3).

Toxicity

The acute treatment-related toxicities are shown in Table 3. The hematological toxicities Grade 3 or worse were not observed. The acute non-hematological toxicities Grade 3 or worse including radiation esophagitis and radiation pneumonitis were not observed. With a median follow-up time of 39 months for the 4 surviving patients, Grade 1 of pneumonitis/pulmonary infiltrates in 3 patients and Grade 1 fibrosis of the subcutaneous tissue in 1 patient were only observed as late toxicities. No late Grade 2 or worse toxicities were observed. Therefore, no overall toxicity of Grade 3 or worse was observed. The relationships regarding toxicity, tumor factor, and IFRT factor according to total dose are summarized in Table 4. There was no difference in the CTV value between the patients who were irradiated with a total dose of <67.5 Gy and

67.5-70 Gy. However, the percentage of G2 esophagitis was high in the <67.5 Gy group in comparison to the group at a total dose of 67.5-70 Gy.

Patterns of failure

The patterns of failure are shown in Table 5. Of 10 patients, 3 patients (30.0%) were disease free at the last follow-up, and disease recurrences manifested in 7 patients (70.0%). In-field recurrences occurred in 5 patients (50.0%), and out-of-field recurrences were seen in 7 patients (70.0%). No ENF was observed. However, regional recurrence of out-of-field was observed in 1 patient who had an in-field recurrence and lung metastasis, this patient had a supraclavicular recurrence in a T2N3 (the primary tumor was located in the left upper lobe). The relationships regarding the patterns of failure, prognosis, tumor factor, and IFRT factor according to total dose are summarized in Table 6. No in-field recurrences occurred in 4 patients who were irradiated with a total dose of 67.5-70 Gy, and 3 have no evidence of disease (NED). On the other hand, in-field recurrences occurred in 5 (83.3%) in 6 patients who were irradiated with a total dose of <67.5 Gy, while no patients had NED, and 5 died of the disease.

Treatment delivery

Nine of 10 patients (90%) received a higher dose than the minimum planned total dose of 60 Gy which was prescribed in protocol. One patient No. 3 who received <60 Gy of IFRT had T2N3 disease with multiple contralateral mediastinal nodes. In the course of therapy, this patient had Grade 2 esophagitis, and volunteered to stop the treatment when the total dose reached 55 Gy. In 3 patients (Nos. 4,8,9) IFRT was completed with a smaller dose than the maximum planned dose according to the judgment of the radiation oncologist. Incidentally, patients Nos. 4 and 8 had N3 disease which had a wide regional spread of the mediastinum, and patient No. 9 had T4N1 disease whose primary tumor lay adjacent to the esophagus widely. In these 3 patients, Grade 2 esophagitis developed during the treatment period. Therefore, the radiation oncologist worried that the esophagitis would worsen, and they completed treatment at a smaller dose than the maximum planned dose.

DISCUSSION

The treatment results of conventional RT for NSCLC were not satisfactory,

therefore many therapeutic challenges to improve the treatment results have been attempted so far. In stage I NSCLC, stereotactic body radiotherapy (SBRT) has been recently performed, and those excellent local control rates of >90 % and OAS of 70-80% that matched results from a surgical resection are reported.[15, 16, 17] In addition, SBRT is going to be recognized as a choice of alternative treatment of stage I NSCLC. In contrast, in locally advanced NSCLC, the standard treatment has changed dramatically to obtain better result in the past 20 years. The current standard treatment for locally advanced NSCLC is recognized to be concurrent CHT-RT, but the results which are provided by concurrent CHT-RT are not entirely satisfactory. Moreover, the optimal details of RT such as CTV delineation, irradiated field remain unclear. For many years, it has been thought that standard RT typically entails delivering 40 Gy of ENI to the ipsilateral hilum, the whole mediastinum, and occasionally supraclavicular fossa even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV.[18] However, it is never easy to irradiate a high total dose using this irradiation technique with ENI because incidence of severe radiation esophagitis and pneumonitis increases with an increase of total dose and ENI has not been shown to be effective.

Recently, IFRT omitting ENI to achieve an improvement in the local control by

high dose irradiation without increasing the toxicity for locally advanced NSCLC has been attempted[8-10,13,19-24]. As a result, the possibility of prolongation of MST and reduction in severe toxicity has been reported, and in addition a low incidence of ENF after IFRT has been also shown. Table 7 lists the results of IFRT. At present, 74 Gy in 2 Gy fractions is considered to be the recommended dose setting for IFRT with concurrent weekly CBDCA/PTX for locally advanced NSCLC according to the results of several phase I and II studies, and it was reported that this treatment provides MST of 22-37 months[22-25]. Furthermore, the RTOG 0617 trial of randomized phase III study, comparison of standard dose (60 Gy) versus high dose (74 Gy) 3DCRT or intensity modulated radiation therapy (IMRT) without ENI with concurrent and consolidation CBDCA/PTX for locally advanced NSCLC, is currently underway. In this way, many radiation oncologists are interested in the efficacy of IFRT with concurrent CBDCA/PTX. However, in Japan the clinical trial of this treatment has not been performed. Therefore, we consider that feasibility study of IFRT with concurrent CBDCA/PTX is worth performing in Japan.

In this preliminary study, MST, the 1-, 2-, and 3-year OAS in 10 subject patients who were treated with hypofractionated IFRT in once daily fractions of 2.5 Gy with

concurrent weekly CBDCA/PTX were 29.5 M, 90.0%, 58.3% and 43.8%, respectively. In addition, no ENF and no Grade 3 or worse radiation esophagitis was observed. Moreover, no Grade 3 or worse radiation pneumonitis was observed, although primary site on 70% of patients were located in the upper lobe whose risk of pneumonitis was lower than that of the lower lobe. Considering these results, hypofractionated IFRT in once-daily fractions of 2.5 Gy with concurrent weekly CBDCA/PTX is therefore considered to be a feasible and safe irradiation method to increase the total dose without increasing the occurrence of either severe radiation esophagitis or pneumonitis, while also demonstrating a low rate of ENF. In addition, hypofractionated IFRT with high total dose of ≥67.5 Gy might be a promising modality for improving the in-field tumor control and prolonging the OAS. However, we think that small CTV in the mediastinum may be one of the conditions that will allow us to irradiate patients safely at a high dose. Though the irradiated field is certainly small in IFRT in comparison to the general RT field with ENI, the irradiated volume of the esophagus is never small in N2-3 cases which have a wide and long spread of lymph node metastasis in the mediastinum. In these cases, due to the large irradiated volume of the esophagus, V20 increases. Therefore, in this study we determined the total irradiated dose according to

the value of V20, it seems that patients with a narrow spread of mediastinal lymph node metastases could therefore receive a high total dose. As a result, a good in-field control and low rate of esophagitis were obtained in the patients who received a total dose of 67.5-70 Gy.

In phase I study of RTOG 0117, 3 of the initial 8 patients treated to 75.25 Gy in daily 2.15 Gy fractions with weekly CBDCA/PTX developed dose-limiting pulmonary toxicity. Therefore, it was concluded that toxicity of high total dose with high fraction dose and concurrent CHT exceeded the safety limit. In addition, now the phase II portion of RTOG 0117 is underway to accrue at the de-escalated dose level of 74 Gy in 2 Gy daily fractions. However we nevertheless consider that 75.25 Gy in 2.15 Gy fractions might still be a safe dose fractionation with concurrent CHT, if the total lung V20 values are set at <25%, instead of ≤30%, in regard to eligibility for such patients to undergo the RTOG 0117 trial. And in the near future we are planning to design a dose escalation study of hypofractionated IFRT in 2.5 Gy fractions with concurrent weekly CBDCA/PTX for patients with total lung V20 values of <25%.

References

1. Pfister DG, Johson DH, Azzoli CG, et al. (2004) American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22:330-353.
2. Curran WJ, Scott CB, Langer CJ, et al. (2003) Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 22:621 (abstr 2499)
3. Zatloukal P, Petruzelka L, Zemanova M, et al. (2004) Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non–small-cell lung cancer. A randomized study. Lung Cancer 46:87-98
4. Belani CP, Choy H, Bonomi P, et al. (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non–small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23:5883-5891
5. Pierre F, Gilles R, Pascal T, et al. (2005) Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie

Thoracique-Groupe Français de Pneumo-Cancérologie NPC 95-01 Study. J Clin Oncol 25:5910-5917

6. Saunders M, Dische S, Barrett A, et al. (1999) Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: Mature data from a randomised multicentre trial. Radiother Oncol 52:137-148
7. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. (1992) Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 326:524-530
8. Senan S, Burgers S, Samson MJ, et al. (2002) Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. Int J Radiat Oncol Biol Phys 54:999-1006
9. Rosenzweig KE, Sim SE, Mychalczak B, et al. (2001) Elective nodal irradiation in the treatment of non–small-cell lung cancer with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 50:681-685
10. Kimura T, Hirokawa Y, Murakami Y, et al. (2004) The preliminary results of

accelerated hyperfractionated radiotherapy with involved-field omitted elective nodal irradiation (ENI) for inoperable advanced non-small cell lung cancer (in Japanese with English abstract). J Jpn Soc Ther Radiol Oncol 16:79-84

11. Graham MV, Purdy JA, Emami B et al. (1999) Clinical dose–volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 45:323-329
12. Tsujino K, Hirota S, Endo M, et al. (2003) Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 55:110-115
13. Bradley JD, Graham MV, Winter KW, et al. (2003) Acute and late toxicity results of RTOG 9311: a dose escalation study using 3D conformal radiation therapy in patients with inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 57:137-138 (abstr 23)
14. Ohashi N, Arita K, Daga H, et al. (2003) Sequential phase I studies of paclitaxel +/- carboplatin and hyperfractionated radiation therapy (HFX RT) for advanced

non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 22:680 (abstr 2736).

15. Uematsu M, Shioda A, Suda A, et al. (2001) Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 51:666-670
16. Onishi H, Araki T, Shirato H, et al. (2004) Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 101:1623-1631
17. Nagata Y, Takayama K, Matsuo Y, et al. (2005) Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 63:1427-1431
18. Chang JY, Bradley JD, Govindan R, et al. (2008) Thoracic tumors. In: Halperin EC, Perez CA, Brady LW(eds) Perez & Brady's Principles and Practice of Radiation Oncology 5th edn. Lippincott Williams & Wilkins, Philadelphia, PA, pp 1076-1108
19. Rosenzweig KE, Sura S, Jackson A, et al. (2007) Involved-field radiation therapy for in operable non-small-cell lung cancer. J Clin Oncol 35:5557-5561
20. Yuan S, Sun X, Li M, et al. (2007) A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for

inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol 30:239-244

21. Bradley JD, Graham MV, Winter K, et al. (2005) Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 61:318-328
22. Bradley JD, Graham M, Suzanne S, et al. (2005) Phase I results of RTOG L-0117; a phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with Inoperable NSCLC. J Clin Oncol 23:636 (abstr 7063)
23. Schild SE, McGinnis WL, Graham D, et al. (2006) Results of a phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 15:1106-1111
24. Socinski MA, Blackstock AW, Bogart JA, et al. (2008) Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 26:2457-2463
25. Blackstock AW, Govindan R. (2007) Definitive chemoradiation for the treatment of locally advanced non-small-cell lung cancer. J Clin Oncol 25:4146-4152

Figure legends

Fig. 1: Digitally reconstructed radiographs (DRR) demonstrating the typical elective nodal irradiation (ENI) field and the involved field radiation therapy (IFRT) for a patient with stage IIIA NSCLC. The primary tumor is displayed in red; metastatic lymph nodes are displayed in green; the esophagus is displayed in orange. On DRR of IFRT, the esophagus is outside of the radiation field.

Figure 2: Overall survival of patients with locally advanced non-small cell lung cancer after hypofractionated involved field radiation therapy with concurrent CBDCA/PTX.

Figure 3: In-field tumor control of patients with locally advanced non-small cell lung cancer after hypofractionated involved field radiation therapy with concurrent CBDCA/PTX.

Fig 1

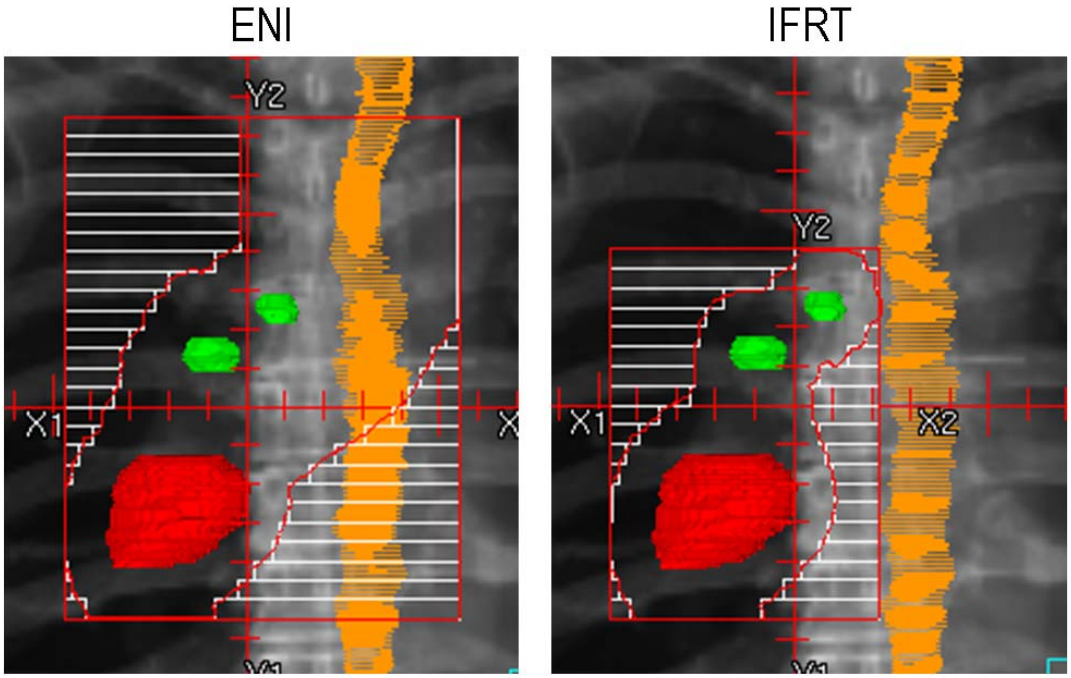

Fig 2

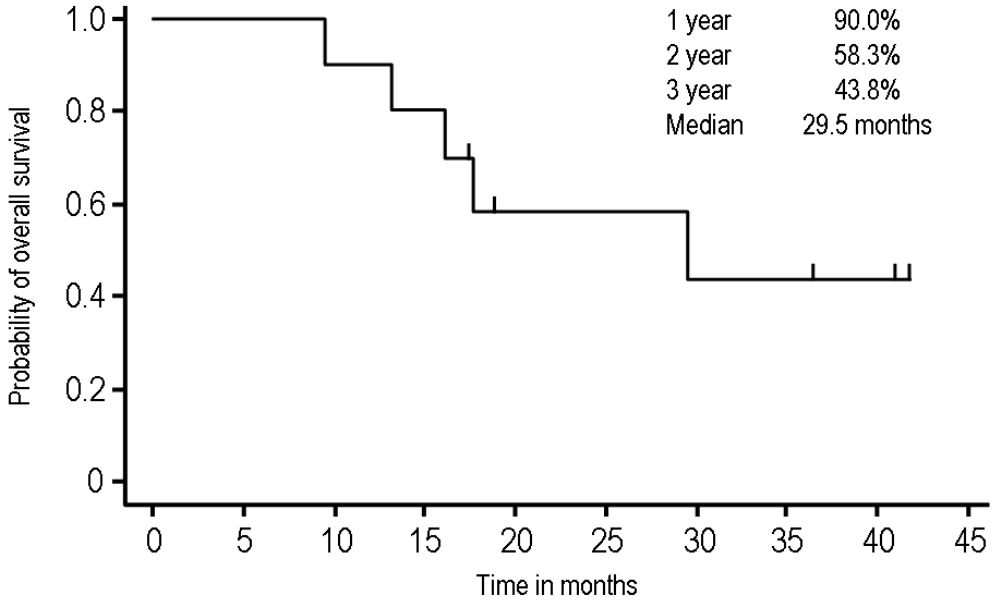
1 year 90.0%
2 year 58.3%
3 year 43.8%
Median 29.5 months
Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0
0 5 10 15 20 25 30 35 40 45
Time in months

Fig 3

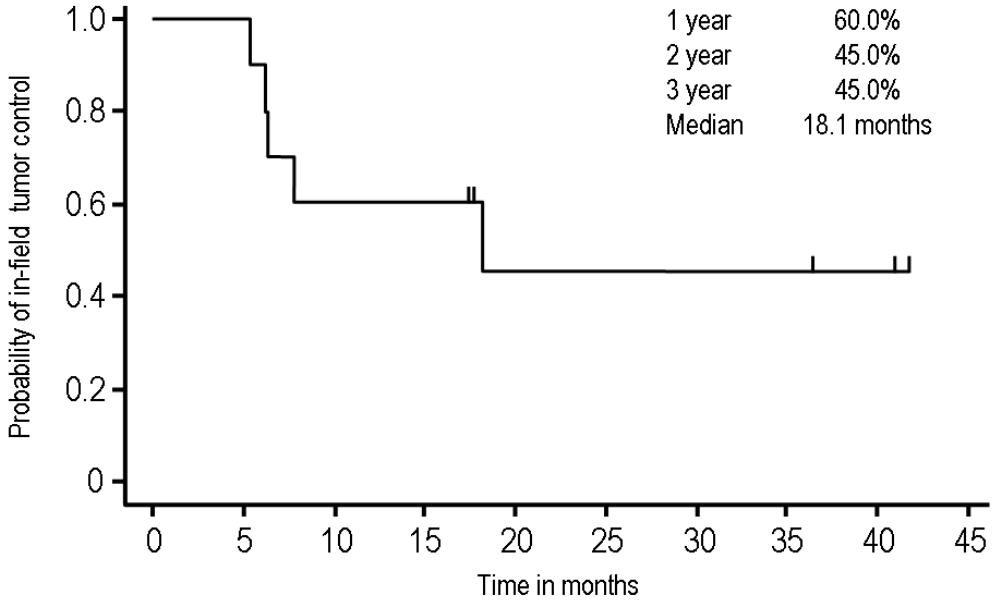
1 year 60.0%
2 year 45.0%
3 year 45.0%
Median 18.1 months
Probability of in-field tumor control
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
45
Time in months

Table 1. Characteristics of patients and tumor

Pt. No.	Age	Sex	PS	Histology	T	N	M	Stage	Location of primary tumor
1	57	M	0	SQ	2	3	0	IIIB	Rt. LL
2	60	M	0	AD	1	3	0	IIIB	Rt. UL
3	65	F	0	AD	2	3	0	IIIB	Lt. UL
4	74	M	0	SQ	2	3	0	IIIB	Lt. UL
5	72	M	0	SQ	4	2	0	IIIB	Rt. LL
6	70	M	0	SQ	2	2	0	IIIA	Lt. LL
7	73	M	0	SQ	4	0	0	IIIB	Lt. UL
8	72	M	1	LC	2	3	0	IIIB	Rt. UL
9	58	M	1	AD	4	1	0	IIIB	Lt. UL
10	54	M	0	AD	2	3	0	IIIB	Rt. UL

Abbreviations: M, male; F, female; PS, performance status; SQ, squamous cell carcinoma; AD, adenocarcinoma; LC, large cell carcinoma; LL, lower lobe; UL, upper lobe

Table 2. Details of treatment for each patient

		Involved Field Radiation Therapy				Concurrent Chemotherapy		
Pt. No.	Location of primary tumor	CTV (cc)	V20 (%)	OTT (days)	TD (Gy)	CBDCA (AUC)	PTX (mg/m^2)	Total Course
1	Rt. LL	47.4	28.0	37	65	2	35	6
2	Rt. UL	65.5	21.4	37	67.5	1.5	30	6
3	Lt. UL	28.3	29.0	36	55	2	35	5
4	Lt. UL	37.1	19.0	37	65	2	30	4
5	Rt. LL	77.7	8.0	40	70	2	30	6
6	Lt. LL	86.7	28.0	37	65	2	35	4
7	Lt. UL	33.4	8.4	40	70	2	30	5
8	Rt. UL	64.2	18.8	33	62.5	1.5	30	5
9	Lt. UL	137.3	16.1	37	65	1.5	30	6
10	Rt. UL	52.6	26.7	38	70	1.5	30	5
Median	-	58.4	20.2	37	65	-	-	5

Abbreviations: CTV, clinical target volume; TD, total dose; OTT, overall treatment time; CBDCA, carboplatin; AUC, area under the curve; PTX, paclitaxel

Table 3. Acute treatment-related toxicities

Toxicity	Grade*				
	1	2	3	4	5
Hematologic					
Leukocytopenia	1	5	0	0	0
Neutropenia	3	3	0	0	0
Thrombocytopenia	1	1	0	0	0
Anemia	4	1	0	0	0
Non-hematologic					
Esophagitis	3	4	0	0	0
Pneumonitis	2	0	0	0	0
Dermatitis	1	0	0	0	0
Fever	1	0	0	0	0
Fatigue	1	0	0	0	0

*Common Terminology Criteria for Adverse Events, version 3.0

Table 4. Relationship of acute toxicity, tumor factor and IFRT factor according to total dose

Total dose		67.5-70 Gy (n = 4)		<67.5 Gy (n = 6)	
		No.	(%)	No.	(%)
Toxicity					
	Esophagitis Grade 1	1	(25.0)	2	(33.3)
	Esophagitis Grade 2	0	(0.0)	4	(66.7)
	Pneumonitis Grade 1	1	(25.0)	1	(16.7)
Tumor factor					
	T1-2	2	(50.0)	5	(83.3)
	T3	0	(0.0)	0	(0.0)
	T4	2	(50.0)	1	(16.7)
	N0-1	1	(25.0)	1	(16.7)
	N2	1	(25.0)	1	(16.7)
	N3	2	(50.0)	4	(66.7)
IFRT factor		Median		Median	
	Clinical target volume (CTV)	59.1 cc		55.8 cc	
	V20	14.9%		23.5%	

Table 5. Patterns of failure

	Patients (n = 10)	
Recurrences	No.	(%)
None	3	(30.0)
Exclusively in-field	0	(0.0)
In-field and elective nodes	0	(0.0)
In-field and distant	4	(40.0)
In-field, elective nodes and distant	1	(10.0)
Elective nodes only without in-field (ENF)	0	(0.0)
Distant only without in-field	2	(20.0)

Table 6. Relationship of patterns of failure, prognosis, tumor factor, esophagitis and IFRT factor according to Total Dose

Total dose	67.5-70 Gy (n = 4)		<67.5 Gy (n = 6)	
	No.	(%)	No.	(%)
Patterns of failure				
In-field recurrence	0	(0.0)	5	(83.3)
Elective nodal failure (ENF)	0	(0.0)	0	(0.0)
Distant metastasis	1	(25.0)	6	(66.7)
Prognosis				
No evidence of disease (NED)	3	(75.0)	0	(0.0)
Alive with disease (AWD)	1	(25.0)	1	(16.7)
Dead of disease (DOD)	0	(0.0)	5	(83.3)
Tumor factor				
T1-2	2	(50.0)	5	(83.3)
T3	0	(0.0)	0	(0.0)
T4	2	(50.0)	1	(16.7)
N0-1	1	(25.0)	1	(16.7)
N2	1	(25.0)	1	(16.7)
N3	2	(50.0)	4	(66.7)
IFRT factor	Median		Median	
Clinical target volume (CTV)	59.1 cc		55.8 cc	
V20	14.9%		23.5%	

Table 7. Summary of involved field radiation therapy for non-small-cell lung cancer

Author/Trial (year)	Trial type	No. of patients	Stage	CHT Regimen	Timing of CHT	Fraction size (Gy)	Radiation dose (Gy)	MST (months)	% Acute Grade 3/4		% ENF
									Esophagitis	Pneumonitis	
Rosensweig[19] (2007)	-	524	I-III (III: 65%)	CDDP -based	SEQ/CON (41%/15%)	1.8-2	66	21	NR	NR	6
Yuan[20] (2007)	PRT	98	III	CDDP ETP	CON (100%)	2	68-74	20	4	1	7
DDHK 97-11[8] (2002)	PII	50	III	CBDCA PTX	SEQ (100%)	2	70	18	2	0	0
RTOG 9311[21] (2005)	PI/I	177	I-III (III: 47%)	NR	SEQ (14%)	2.15	(V20<25%) 70.9-83.8 90.3 (25%≤V20<37%) 70.9 77.4	NR NR	0 0 0 0	0 9 0 8	7
RTOG 0117[22] (2005)	PI	17 9	I-III	CBDCA PTX	CON (100%)	2.15 2	(V20≤30%) 75.25 74	NR	0 11	12 0	NR
	PII	24				2	74	22[b]			
NCCTG 0028[23] (2006)	PII	13	I-III (III: 69%)	CBDCA PTX	CON (100%)	2	(V20<40%) 70 74 78	NR	0 0 0	0 17 50	0
						2	74	37[b]			
CALGB 30105[24] (2008)	PII	42	III	CBDCA PTX	CON (93%)	2	74[a]	24	16	16	NR

Abbreviations: DDHK, Daniel den Hoed Kliniek; RTOG, Radiation Therapy Oncology Group; NCCTG, North Central Cancer Treatment Group; CALGB, Cancer and Leukemia Group B; PRT, prospective randomized trial; CHT, chemotherapy; CDDP, cisplatin; ETP: etoposide; NR, not reported; CBDCA, carboplatin; PTX, paclitaxel; SEQ, sequential; CON, concurrent; MST, median survival time; ENF, elective nodal failure

[a] Slightly wide involved field radiation therapy with limited elective nodal irradiation, [b] Data from reference (25)