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FEASIBILITY AND EFFICACY OF DEFINITIVE RADIOTHERAPY WITH 66 GY AND CONCURRENT CARBOPLATIN-PACLITAXEL CHEMOTHERAPY FOR STAGE Ⅲ NON-SMALL CELL LUNG CANCER

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Abstract : *Purpose/Objectives* : This study was conducted to assess the feasibility and efficacy of definitive radiotherapy (RT) with a total dose of 66 Gy and concurrent carboplatin-paclitaxel chemotherapy for patients (pts) with stage Ⅲ non-small cell lung cancer.

Materials/Methods : Between April 2007 and December 2013, 99 pts with non-small cell lung cancer were treated using RT with concurrent carboplatin-paclitaxel chemotherapy in our hospital. Sixty-eight of them received RT with a total dose of 66 Gy. We analyzed 46 Stage Ⅲ pts who had been treated with RT using three-dimensional radiotherapy treatment planning. The prophylactic mediastinal lymph nodes were included in the clinical target volume for RT. The survival rate after the start of RT was estimated using the Kaplan-Meier method. We estimated the cumulative local failure and distant metastasis rates with the Fine-Gray method. Adverse events were evaluated according to the CTCAE (v.4.0) .

Results : The median age of the pts was 70.9 (52.8-78.7) years old (y.o.) . The performance status (PS) of each pt was fairly good (ECOG PS 0: 25, PS 1: 20, PS3:1) , and their clinical stages (UICC 7th) were twenty-nine Ⅲ A and seventeen Ⅲ B. Diagnoses were pathologically confirmed in 32 pts. The median follow-up period was 35.7 (2.0-82.2) months among all pts, and 55.9 (40.1-82.2) months among survivors. The 3- and 5-year Kaplan-Meier overall survival rates were 52.2 and 34.0%, respectively, and the median survival time was 36.6 months. The 3- and 5-year Kaplan-Meier progression-free survival rates were 29.1 and 21.9%, respectively, and the median progression-free survival time was 9.9 months. The 5-year local failure rate was 37.6%, and the 5-year distant metastasis rate was 49.7%. Sixteen (34.8%) pts required steroid administration because of radiation pneumonitis (CTCAE Grade 2 or higher) and two of them died (Grade 5) . No other severe non-hematologic toxicity (Grade 3 or higher) was observed.

Conclusion: These results suggest that definitive RT with a total dose of 66 Gy and concurrent carboplatin-paclitaxel chemotherapy is feasible and may be promising for pts with Stage Ⅲ non-small cell lung cancer.

Key words: Non-small cell lung cancer, Concurrent chemoradiotherapy, 66 Gy, Carboplatin-paclitaxel chemotherapy

Introduction

Stage Ⅲ non-small cell lung cancer patients have a poor prognosis despite recent advances in surgery and chemoradiotherapy. According to Cancer Research UK's homepage[1], the five-year survival rates for stage Ⅲ A and Ⅲ B are 19–24 and 7–9%, respectively. The standard therapy for inoperative stage Ⅲ non-small cell lung cancer is chemoradiotherapy. The most common radiation dose in chemoradiotherapy for such patients (pts) is 60–63 Gy, given in 1.8–2.0-Gy fractions. Otherwise, the standard dose of definitive radiotherapy (RT) alone for non-small cell lung cancer is 60–70 Gy, given in 1.8–2.0-Gy fractions. A recent study[2] showed that the outcome of 74 Gy in 2-Gy fractions for concurrent chemoradiotherapy was not better than that of 60 Gy. The most suitable or optimized radiation dose in chemoradiotherapy for non-small cell lung cancer has yet to be established.

In our institution, we use definitive RT with a total dose of 66 Gy and concurrent carboplatin-paclitaxel chemotherapy for relatively elderly or impaired-status pts with stage Ⅲ non-small cell lung cancer to achieve relatively better outcomes while considering their quality of life at the same time.

This retrospective study was conducted to assess the feasibility and efficacy of definitive RT with a total dose of 66 Gy and concurrent carboplatin-paclitaxel chemotherapy.

Methods and Materials

Between April 2007 and December 2013, 99 pts with non-small cell lung cancer were treated using RT with concurrent carboplatin-paclitaxel chemotherapy in our hospital. The total radiation dose consisted of 48 Gy (one pt who discontinued RT because of Grade 2 radiation pneumonitis), 60 Gy (16 pts), 62 Gy (one pt), 63.4 Gy (one pt), 64 Gy (11 pts), 66 Gy (68 pts), and 70 Gy (one pt). Excluding 13 postoperative pts, 55 pts received RT with a total dose of 66 Gy: five Ⅱ A and three Ⅱ B, twenty-nine Ⅲ A, seventeen Ⅲ B, and one Ⅳ based on the UICC staging system (7th edition).

In this study, we analyzed 46 pts with stage Ⅲ who had been treated with conventional RT using three-dimensional radiotherapy treatment planning. The gross tumor volume for RT was defined as the primary tumor and regionally involved lymph nodes on CT (>1 cm short axis). Prophylactic irradiation of the mediastinal lymph nodes was performed and the radiation fields were included in the clinical target volume for RT. For most pts, we used the anterior-posterior and posterior-anterior parallel opposed (AP & PA) field technique followed by an oblique opposed field technique to reduce the dose to the spinal cord. We chose the dose of field changes (from AP & PA to oblique) after 40, 42, or 44 Gy for each pt, considering the length of the spinal cord in each radiation field and volume of the lung receiving at least 20 Gy (V20). RT was given 5 days per week in 2-Gy fractions daily using 6- or 10-MV X-rays. We prescribed 66 Gy as the planning target volume for RT.

In the concurrent carboplatin-paclitaxel chemotherapy, pts were scheduled to receive 6 cycles of carboplatin (area under curve 2) and paclitaxel (40 mg/㎡) administered intravenously once a week. The criteria for starting treatment were as follows: absolute white blood cell count of 3,000 cells per μL or higher, platelet count of 100,000 cells per μL or higher. The criteria for continuous administration were as follows: absolute white blood cell count of 3,000 cells per μL or higher, platelet count of 75,000 cells per μL or higher.

Overall and progression-free survival rates after the beginning of RT were estimated using the Kaplan-Meier method, compared with the log-rank test, and modeled with the Cox proportional hazards method. We estimated the cumulative local failure (including loco-regional failure outside the radiation field) and distant metastasis rates with the Fine-Gray method. In our analyses, dropout cases were regarded as mortality. We compared continuous data with t-tests. All analyses were done with EZR[3] on R commander (ver 01.32). Adverse events were evaluated according to the CTCAE (v. 4.0).

Results

The median age of the forty-six pts was 70.9 (52.8-78.7) years old (y.o.). The performance status (PS) of each pt was satisfactory (ECOG PS 0: 25, PS 1: 20, PS 3: 1), and the clinical stages (UICC 7th) consisted of twenty-nine Ⅲ A and seventeen Ⅲ B. Diagnoses were pathologically confirmed in 32 pts (22 squamous cell carcinomas, 8 adenocarcinomas, one large cell carcinoma, and one mucoepidermoid carcinoma) (Table 1). The other 14 pts were diagnosed radiographically and on considering other clinical factors. Other patient characteristics are also shown in Table 1.

There were four courses of the concurrent carboplatin-paclitaxel chemotherapy in 4 cases, five courses in 14, and six courses in 28.

The median follow-up period was 35.7 (2.0-82.2) months among all pts, and 55.9 (40.1-82.2) months among survivors. The 3- and 5-year Kaplan-Meier overall survival rates were 52.2 (95% CI 37.0-65.4) % and 34.0 (95% CI 20.1-48.5) %, respectively, and the median survival time was 36.6 (95% CI 18.9-50.3) months (Fig. 1). We compared the differences between each of the following pairs: aged over 71 or not, PS 0 or not, Stage Ⅲ A or Ⅲ B, and squamous cell carcinoma or not, using the log-rank test, but no significant difference was identified.

The 3- and 5-year Kaplan-Meier progression-free survival rates were 29.1 (95% CI 16.8-42.7) % and 21.9 (95% CI 10.2-36.3) %, respectively, and the median progression-free survival time was 9.9 (95% CI 4.9-15.4) months (Fig. 2). The 5-year local failure rate was 37.6 (95% CI 22.5-52.7) % (Fig. 3), and the 5-year distant metastasis rate was 49.7 (95% CI 33.8-63.7) % (Fig. 4).

As for adverse events, sixteen (34.8%) pts required steroid administration because of radiation pneumonitis (CTCAE Grade 2 or higher) and two (4.3%) pts died (CTCAE Grade 5). No other severe non-hematologic toxicity (Grade 3 or higher) was observed.

We analyzed only 15 pts' dose-volume histograms because the radiation treatment planning system in our institute was being changed. The median lung volume receiving at least 5 Gy (V5), V20, and mean lung dose were 32.3 (20.7-43.8) %, 26.4 (15.8-37.0) %, and 15.9 (9.9-21.1)

Table 1. Patient Characteristics

Age	
Median (range)	70.9 (52.8–78.7)
Sex	
Men	42 (91%)
Women	4 (9%)
ECOG performance status	
0	25 (54%)
1	20 (44%)
2	0 (0%)
3	1 (2%)
Smoking history	
Non-smoker	3 (7%)
Former smoker	25 (54%)
Current	14 (30%)
Unknown	4 (9%)
Histology (32 pts)	
Squamous cell carcinoma	22 (69%)
Adenocarcinoma	8 (25%)
Large cell carcinoma	1 (3%)
Mucoepidermoid carcinoma	1 (3%)
Stage (UICC 7th)	
Ⅲ A	29 (63%)
Ⅲ B	17 (37%)
T (UICC 7th)	
1	8 (17%)
2	14 (30%)
3	9 (20%)
4	15 (33%)
N (UICC 7th)	
0	1 (2%)
1	5 (11%)
2	28 (61%)
3	12 (26%)

Table 2. Summary of the outcomes

Overall survival	
Dead	29
3-year	52.2% (37.0–65.4)
5-year	34.0% (20.1–48.5)
Median (months)	36.6 (18.9–50.3)
Progression-free survival	
Fail	34
3-year	29.1% (16.8–42.7)
5-year	21.9% (10.2–36.3)
Median (months)	9.9 (4.9–15.4)
Local failure	
Fail	16
2-year	24.5% (13.0–37.9)
3-year	31.2% (18.2–45.1)
5-year	37.6% (22.5–52.7)
Distant metastasis	
Occurrence	22
2-year	42.2% (27.5–56.2)
3-year	46.7% (31.5–60.6)
5-year	49.7% (33.8–63.7)

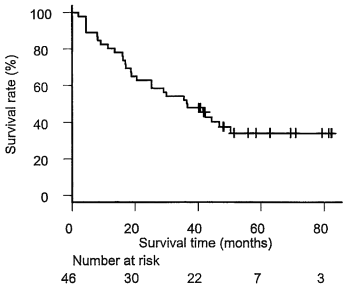

Fig.1 Overall survival
The 3- and 5-year Kaplan-Meier overall survival rates were 52.2% and 34.0 %, respectively.

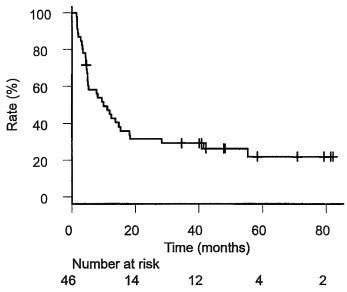

Fig. 2. Progression-free survival
The 3- and 5-year Kaplan-Meier progression-free survival rates were 29.1 % and 21.9%, respectively,

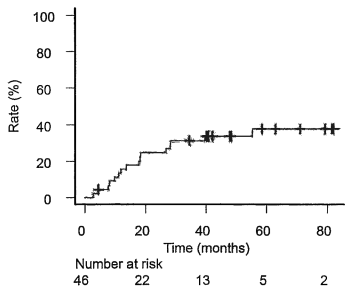

Fig. 3. Local failure
The 5-year local failure rate was 37.6 %.

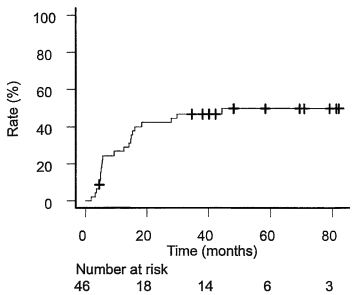

Fig. 4. Distant metastasis
The 5-year distant metastasis rate was 49.7%.

Gy, respectively. Those pts included one with Grade 5 radiation pneumonitis. This pt had the largest V5 (43.8%), V20 (37.0%), and mean lung dose (21.1 Gy). We analyzed V5, V20, and the mean lung dose of the cases with and without radiation pneumonitis with t-tests, but no significant difference was identified.

Discussion

A previous randomized phase 3 study[2] showed a median overall survival of 28.7 months (95% CI 24.1-36.9) for patients who received 60-Gy radiotherapy with concurrent carboplatin-paclitaxel chemotherapy. Another phase 2 study[4] indicated a median overall survival of 110 weeks (95% CI 90-184) for patients who received 60-Gy radiotherapy with concurrent weekly paclitaxel plus carboplatin. Our results showed a median overall survival of 36.6 months (95% CI 18.9-50.3) for patients who received 66-Gy radiotherapy with the same concurrent regimen of chemotherapy.

Regarding progression-free survival, a randomized phase 3 study[2] showed that median survival was 11.8 months (95% CI 10.2-14.3) for patients who received 60 Gy and a phase 2 study[4] indicated 46 weeks (95% CI 31-64). Our result was 9.9 months (95% CI 4.9-15.4).

Concerning local failure and distant metastasis, the randomized phase 3 study above[2] used the same Fine-Gray method for statistical analysis, and showed a 2-year local failure rate of 30.7% (95% CI 24.5-36.9) and 2-year distant metastasis rate of 46.6% (95% CI 39.9-53.4) for patients who had received 60 Gy. Our results show a local failure rate of 24.5% (95%CI 13.0-37.9) and distant metastasis rate of 42.2% (95%CI 27.5-56.2) in the same years (Table 2).

Our results suggest better overall survival and local control rates, and slightly better distant metastasis control, although our study was retrospective and observational and several biases may have affected the outcomes; however, most of the pts were elderly. A dose increase within the normal clinical dose range may improve the outcome of chemoradiotherapy for Stage Ⅲ non-small cell lung cancer. Two phase 2 studies[5) 6)] on definitive radiotherapy with concurrent nab-paclitaxel plus carboplatin for Stage Ⅲ non-small cell lung cancer were reported. One study[5)]'s dose was 60 Gy, and the other study[6)]'s was 66 Gy. These two studies' mature data may provide useful references.

Other previous reports[7) 8)] suggested that definitive radiotherapy with concurrent carboplatin-paclitaxel chemotherapy caused more frequent radiation pneumonitis than the cisplatin-etoposide regimen. Another recent research[9)] showed Grade 3-4 (CTCAE v3.0) and Grade 5 radiation pneumonitis was 9% and 1% among 107 pts with concurrent carboplatin-paclitaxel chemotherapy (60-66 Gy) for Stage Ⅲ non-small cell lung cancer, respectively. In our study, sixteen (34.8%) pts required steroid administration because of radiation pneumonitis (grade 2 or higher) and two (4.3%) pts died (Grade 5). No other severe non-hematologic toxicity (Grade 3 or higher) was observed. Fatal radiation pneumonitis may have been slightly more frequent, but adverse events may be acceptable in general. International individual patient data meta-analysis[7)] showed an overall rate of symptomatic pneumonitis of 29.8%, with fatal pneumonitis of 1.9%, and V20 (OR 1.09 per 1% increase, p=0.044) was found to be associated with fatal pneumonitis. One pt with a fatal outcome among 15 pts subjected to dose-volume

histogram analysis had the largest V20. In radiotherapy with concurrent carboplatin-paclitaxel chemotherapy, we need to take particular care to minimize the dose to the normal lung.

In conclusion, this study suggests that definitive radiotherapy with a total dose of 66 Gy and concurrent carboplatin-paclitaxel chemotherapy is feasible and might be promising for pts with Stage Ⅲ non-small cell lung cancer. A prospective study is needed to confirm our results.

Ethical Statement

This study was approved by the institutional ethics committee of Nara Medical University.

References

1) http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/treatment/statistics-and-outlook-for-lung-cancer (date: 10/15/2015)
2) Bradley J.D., Paulus R., Komaki R., Masters G., Blumenschein G., Schild S., Bogart J., Hu C., Forster K., Magliocco A., Kavadi V., Garces Y.I., Narayan S., Iyengar P., Robinson C., Wynn R.B., Koprowski C., Meng J., Beitler J., Gaur R., Curran W. Jr, Choy H.: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617) : a randomised, two-by-two factorial phase 3 study. Lancet Oncol, **16**:187-199, 2015.
3) Kanda, Y.: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant, **48**: 452-458, 2013.
4) Takayama K., Inoue K., Tokunaga S., Matsumoto T., Oshima T., Kawasaki M., Imanaga T., Kuba M., Takeshita M., Harada T., Shioyama Y., Nakanishi Y.: Phase II study of concurrent thoracic radiotherapy in combination with weekly paclitaxel plus carboplatin in locally advanced non-small cell lung cancer: LOGIK0401. Cancer Chemother Pharmacol, **72**:1353-1359, 2013.
5) Hasegawa T., Futamura Y., Horiba A., Yoshida T., Suzuki T., Kato T., Kaito D., OhnoY., Iida T., Hayashi S., Sawa T.: A phase II study of nab-paclitaxel plus carboplatin in combination with thoracic radiation in patients with locally advanced non-small-cell lung cancer. J Radiat Res, **57**:50-54, 2016.
6) Lammers P.E., Lu B., Horn L., Shyr Y., Keedy V.: Nab-paclitaxel in combination with weekly carboplatin with concurrent radiotherapy in stage III non-small cell lung cancer. Oncologist, **20**:491-492, 2015.
7) Palma D.A., Senan S., Tsujino K., Barriger R.B., Rengan R., Moreno M., Bradley J.D., Kim T.H., Ramella S., Marks L.B., De Petris L., Stitt L., Rodrigues G.: Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys, **85**:444-450, 2013.
8) Liew M.S., Sia J., Starmans M.H., Tafreshi A., Harris S., Feigen M., White S., Zimet A., Lambin P., Boutros P.C., Mitchell P., John T.: Comparison of toxicity and outcomes of concurrent radiotherapy with carboplatin/paclitaxel or cisplatin/etoposide in stage III non-small cell lung cancer. Cancer Med, **2**:916-924, 2013.
9) Trinh H., Pinkham M.B., Lehman M., Zarate D., Dauth M., McGrath M., McCaffrey E., Mai G.T., Horwood K.: Outcomes treating stage III non-small cell lung carcinoma with curative-intent radiotherapy and concurrent carboplatin-paclitaxel chemotherapy. Clin Respir J, **10**:428-434, 2016.