Original Article

Randomized phase II trial of uracil/tegafur and cisplatin versus pemetrexed and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-squamous non-small cell lung cancer: NJLCG1001

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Background: The optimal regimen for concurrent chemoradiotherapy (CCRT) of locally advanced non-squamous non-small cell lung cancer (NSCLC) was not definitive. We conducted randomized phase II study, NJLCG0601, and chemoradiotherapy with uracil/tegafur (UFT) and cisplatin achieved promising efficacy without severe toxicities. Here, we evaluated between this regimen and pemetrexed plus cisplatin in chemoradiotherapy for stage III non-squamous NSCLC.

Methods: Patients with inoperable stage III non-squamous NSCLC were randomly assigned in a 1:1 ratio to UFT 400 mg/m^2 on days 1–14 and 29–42, and cisplatin 80 mg/m^2 on days 8 and 36 (UP), or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on days 1, 22, and 43 (PP). Involved-field radiotherapy (IFRT) underwent from day 1 to a total dose of 66 Gy in 33 fractions. Consolidation chemotherapy after CCRT was prohibited for this study. The primary endpoint was defined as 2-year overall survival (OS). This trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000003948).

Results: From November 2010 to June 2017, 86 patients were entered from 11 institutions. Median follow-up was 54 months. Of the 85 eligible patients, the 2-year OS rate was 78.6% (95% CI, 62.8–88.3%) in UP and 85.5% (95% CI, 70.5–93.2%) in PP. Median PFS and OS was 12.3 and 64.2 months in UP, 26.2 months and not reached in PP, respectively. Grade 3/4 febrile neutropenia was more frequent in the UP group (14.0% *vs.* 2.0%).

Conclusions: Both UP and PP with IFRT achieved the expected 2-year OS. PP engendered more favorable OS and PFS compared to UP in terms.

Keywords: Concurrent chemoradiotherapy (CCRT); non-squamous non-small cell lung cancer (NSCLC); uracil/tegafur (UFT); pemetrexed; involved-field radiotherapy (IFRT)

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Introduction

Inoperable stage IIIA and IIIB diseases account for 20–30% of non-small-cell lung cancer (NSCLC) patients (1). A combination of thoracic radiotherapy (TRT) and chemotherapy is regarded as the standard treatment for inoperable stage IIIA and IIIB diseases. Although the intent of treatment is curative, most patients rapidly progress, and their prognosis is poor, with 5-year overall survival (OS) rate in the 15–25% range (2). Several randomized trials have demonstrated cisplatin-based chemotherapy with concurrent TRT (c-TRT) is superior to that with sequential TRT in terms of response and survival. Although there are several candidate regimens that could be applied for concurrent chemoradiotherapy (CCRT), the best radiotherapy-containing combination regimen remains unclear. Though patients with locally advanced-NSCLC have been treated with a regimen of cisplatin-etoposide on the basis of evidence in the US (3), this regimen has not been approved in Japan. Docetaxel-cisplatin or vinorelbine-cisplatin has been developed for chemoradiotherapy in Japan (4). A phase III study showed that cisplatin-docetaxel was superior to mitomycin-vindesine-cisplatin (MVP) in the context of chemoradiotherapy with full-dose radiation (5). Although several studies of cisplatin-vinorelbine yielded poor evidence of efficacy, this combination is frequently used in Japan when selecting a cisplatin-based regimen (4,6).

We conducted a multi-institutional phase II trial of uracil-tegafur (UFT) and cisplatin (UP) with TRT for LA-NSCLC and compared it to vinorelbine-cisplatin (NP) with TRT (7). UFT is an antimetabolite that has been approved in Japan, and UFT monotherapy is considered as standard adjuvant treatment for Stage IA/IB/IIA lung cancer patients with primary tumors of more than 2-cm following resection. This study showed that the UP arm and NP arm in this study met its primary endpoint of response rate. UP showed better efficacy and safety with lower hematological toxicity compared with NP (a RR of 80.0%/71%, MST of 26.6/23.9 months, and 2-year survival rate of 54.3%/48.7%, respectively). Consequently, we decided to select a UP arm for the next step.

Treatment with platinum + pemetrexed (PEM) has been widely utilized for metastatic non-squamous NSCLC (8). We considered this regimen as the next candidate for chemoradiotherapy. A global phase III study comparing platinum + PEM (PP) to platinum + etoposide (PE) as an agent with radiotherapy for non-squamous NSCLC did not find that PP was superior to PE in terms of OS (9). The results of this phase III study were released after initiation of the study we describe below. We believe that additional studies including our current report are required in order to determine whether PP should be the chemoradiotherapy regimen of choice in this clinical context.

To choose a suitable phase III trial candidate for the future of LA-NSCLC treatment, we conducted a randomized phase II study comparing PP to UP with 66 Gy involved-field radiotherapy (IFRT).

We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-721).

Methods

Patient eligibility

Patients were collected by investigators in each institution belonging to North Japan Lung Cancer Study Group (NJLCG).

Eligible patients were 20–75 years, with histologically or cytologically proven stage III non-squamous NSCLC not amenable for surgical resection, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients had measurable disease with RECIST criteria, or evaluable disease on computed tomography (CT) imaging and adequate organ function.

Patients were excluded if volume irradiated at 20 Gy (V20) cannot be reduced to less than 35% volume of total lung. or if they had had prior systemic chemotherapy, chest radiotherapy, or surgery for NSCLC. Laboratory requirements included a leukocyte count of 4,000/mm^3 or

more, a neutrophil count of 2,000/mm^3 or more, a platelet count of 100,000/mm^3 or more, a hemoglobin level of 9.0 g/dL or more, a total bilirubin level of 1.5 mg/dL or less, an AST/ALT value of twice the upper normal limit or less, a creatinine level of 1.5 mg/dL or less, a creatinine clearance of 60 mL/min or more, and partial pressure of arterial oxygen of 70 torr or more, or SpO_2 of 95% or more.

Patients were ineligible if they had concomitant malignancies, malignant pleural or pericardial effusion, or malignant ascites, interstitial pneumonitis or pulmonary fibrosis overt with chest CT, serious complications (uncontrolled diabetes mellitus, heart failure, respiratory failure, renal failure, or hepatic failure).

For staging, all patients underwent CT of the thorax and abdomen, and either brain CT or brain magnetic resonance imaging. An ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) was also performed on all patients.

This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the participating institution's Institutional review board (approval number 2010-016). All patients provided written informed consent before enrollment.

Treatment schedules

In this open-label study, eligible patients were stratified by age (59>/60–64/65–69/70–75), sex (female *vs.* male), disease stage [IIIA *vs.* IIIB (TNM 7th edition)], and EGFR mutation status (positive/wild type/unknown) and were randomly assigned (1:1) to one of two arms by NJLCG staffs with dynamic allocation. The PP arm received pemetrexed 500 mg/m^2 intravenously (IV) plus cisplatin 75 mg/m^2 IV every 3 weeks for three cycles with c-TRT. PP arm received daily folic acid, beginning at least 1 week before the first dose of pemetrexed, and continuing daily until 3 weeks after the last dose of pemetrexed. Intramuscular vitamin B12 was begun at least 1 week before the first dose of pemetrexed and continued every 9 weeks until 3 weeks after the last dose of pemetrexed. UP arm received oral UFT 400 mg/m^2/day twice daily from days 1 to 14 and cisplatin 80 mg/m^2 IV on day 8 every 3 weeks for three cycles and c-TRT. Consolidation was not allowed in either arm. Chemotherapy was terminated after 3 cycles of chemotherapy with radiotherapy (Figure S1).

Radiotherapy

All patients were treated using a linear accelerator photon beam of 4 MV or more from day 1. The primary tumor and involved nodal disease received 66 Gy in 33 fractions. In this protocol, a four-dimensional (D) treatment planning system was allowed. To determine the target volume, we used FDG-PET with all patients and delineated the primary tumor and lymph nodes that were more than 1 cm in the short axis or were PET-positive as the gross tumor volume (GTV) or internal target volumes (ITV).

A clinical target volume (CTV) margin of 5–10 mm was usually added to the GTV according to the pathology. A planning target volume margin of 10 mm was usually added, which included the reproducibility of respiratory motion and setup error to CTV. Elective nodal irradiation was prohibited in principal to overcome dose limitation by pulmonary and esophageal toxicities.

Involved field irradiation was chosen in this study, and it is recommended that 66 Gy is administered in a common irradiation field using this approach. However, irradiation field reduction was permitted at the radiologist's discretion. For example, when the target lymph node is distant from the primary lesion, split-field irradiation was permitted. The maximum dose that can be received by the spinal cord was 45 Gy or less. It was also recommended that V20 should be 35% or less.

Treatment modifications

The administration of cisplatin was suspended on either arm under the following conditions: if there was a decrease in the neutrophil count to under 1,500/mm^3, or the platelet count to less than 100,000/mm^3, if creatinine concentration was more than 1.5 mg/dL, or if grade 2 or more nonhematological toxicities (with the exception of hyponatremia) were observed. Cisplatin treatment could not be restarted until resolution of toxicity to grade 0 or 1. In the UP arm, in the event of grade 4 hematologic toxicity or grade 3 non-hematologic toxicity except for alopecia, anorexia, or malaise, the administration of UFT was stopped and then reduced in subsequent cycles from 600 mg or 500 to 400 mg or 300 mg, respectively. UFT was reduced whenever grade 2 diarrhea or stomatitis occurred. In the PP arm, pemetrexed was stopped and then reduced from 500 to 400 to 350 mg/m^2, respectively if any grade 4 hematologic toxicity, or creatinine concentration more than

1.5 mg/dL, or grade 3 non-hematologic toxicity except for hyponatremia, were observed. TRT was withheld on either arm in cases of any grade 4 hematologic toxicity, grade 3 esophagitis or dermatitis, grade 1 fever, or any sign of pneumonitis. Patients who did not receive the next cycle within 7 days, discontinued the study treatment.

Treatment assessment and toxicity evaluation

Baseline evaluations included medical history, a physical examination, electrocardiogram, tumor status, ECOG performance status, and clinical laboratory tests. Blood cell counts and biochemistry tests were performed once a week during the treatment period. Thoracic CT was performed every 4 weeks during and after the treatment period until progressive disease was recognized.

During the extramural review, tumor response was evaluated according to criteria in RECIST version 1.1. Progression-free survival (PFS) was defined as the period from the date of randomization to the date when disease progression was first observed or death occurred. These events were confirmed by several experienced physicians in the periodic extramural review. OS was defined as the period between randomization and death from any cause. Toxicities were assessed on the basis of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

The primary end point was 2-year OS, and secondary end points including objective response rate (ORR), PFS, OS, toxicity profile. Assuming a 2-year OS of 55% in eligible patients would indicate potential usefulness, while a 2-year OS of 35% would be the lower limit of interest, with alpha = 0.05 and beta = 0.20, the estimated accrual was 39 patients in each arm. Allowing for a certain number of dropouts, the accrual goal was determined to be 42 patients in each arm.

In this study, 3 cycles of chemotherapy and 66 Gy of radiation therapy were combined. Therefore, when 10 patients were registered, the safety assessment committee evaluated risks and determined whether it was safe for each patient to continue. The analysis of the primary end point was performed 2 years after the last patient was enrolled in this study.

Fisher's exact test was used to estimate the correlation among different variables between arms. Survival estimation was performed according to the Kaplan-Meier method and evaluated with the log-rank test. This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000003948).

Results

Patient characteristics

Between November 2010 and June 2017, 86 patients were enrolled from 11 institutions and were allocated to the UP arm (n=43) and PP arm (n=43). Of the 86 patients enrolled, 1 patient was excluded from final analysis due to ineligibility (V20 35% <). Therefore, 85 patients (UP arm, n=43 and PP arm, n=42) were evaluable for efficacy and safety (*Figure 1*). Baseline patient and disease characteristics were well balanced in terms of age, gender, stage, and EGFR mutation (*Table 1*); these characteristics were used as stratification factors. Regarding performance state, the PP arm was slightly biased toward PS1 when compared to the UP arm.

Treatment administered

As shown in *Table 2*, the median number of treatment cycles was 3 (range, 1–3) in both arms. In the UP and PP arms, 74.0% and 85.0% of patients underwent the three cycles of chemotherapy with radiotherapy, respectively. The slightly lower completion rates of the three cycles of the UP arm may be related to myelosuppression and the schedule, in which UFT started on day 1 and cisplatin chemotherapy started on day 8. TRT at 66 Gy was completed in 39 of the 43 patients (91%) in the UP arm and 38 of 42 patients (90%) in the PP arm.

Efficacy

The ORR was 76.7% (95% CI, 61.0–87.7%) versus 81.0% (95% CI, 65.4–90.9%), and the disease control rates (DCR) were 90.7% (95% CI, 76.9–97.0%) versus 100% (95% CI, 89.6–100%), for the UP arm versus PP arm, respectively (*Table 3*). The response rate of the PP group was better than that of the UP group, but the difference between the two groups was not statistically significant (P=0.7916).

The Kaplan-Meier curves of OS and PFS are shown in *Figure 2*. Most of the patients were observed for more than 2 years and median follow-up time for the censored patients was 54 months; survival events occurred in 31 patients. The median survival time was 64.2 months for the UP arm and not reached for the PP arm. However, there was no statistically significant difference between the two arms in

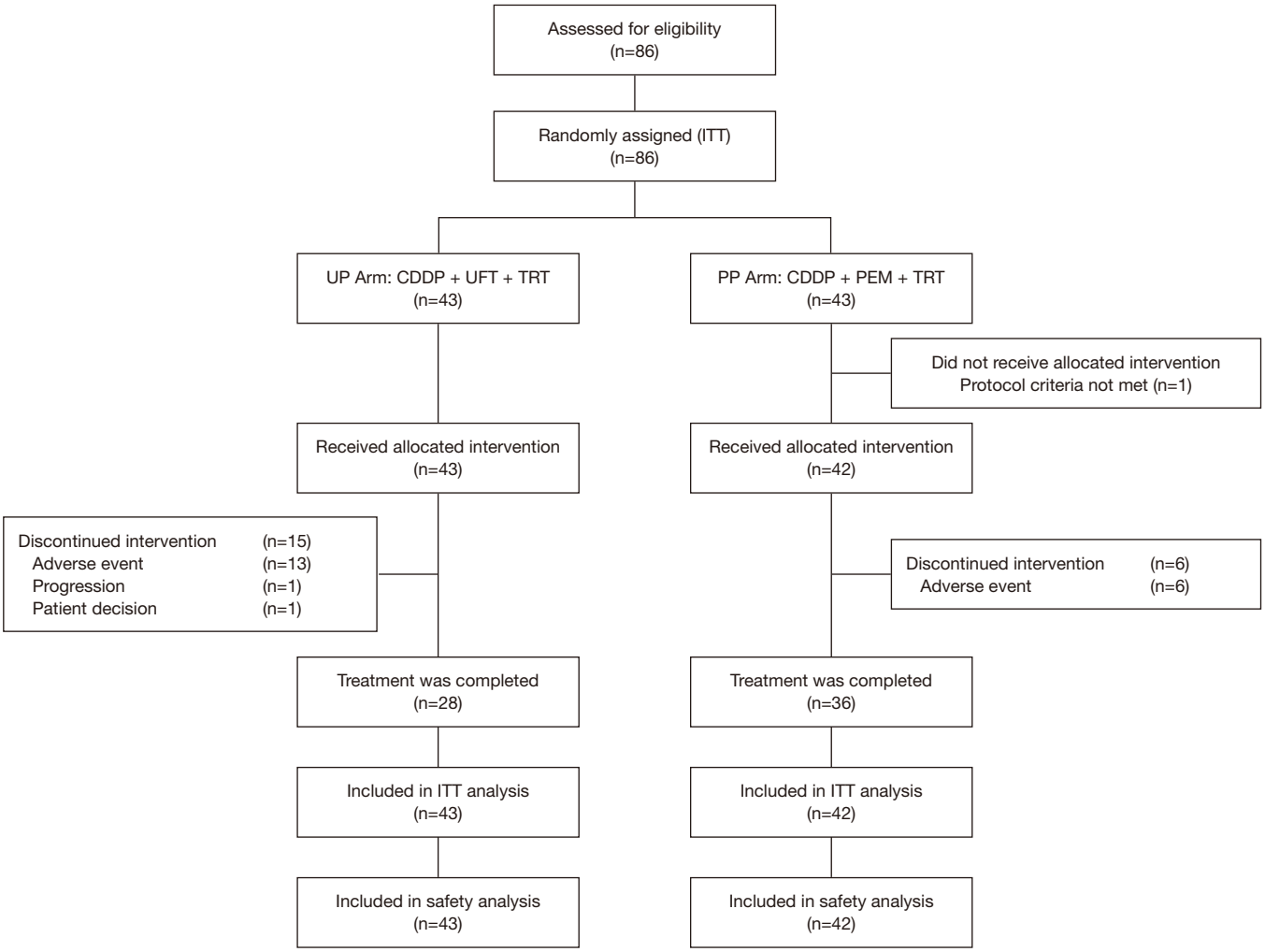

Figure 1 CONSORT diagram. 86 patients were enrolled from11 institutions. Finally 85 patients were evaluable for efficacy and safety.

terms of OS (HR =0.612; 95% CI, 0.30–1.27; P=0.18). The median PFS was 12.3 months (95% CI, 9.2–19.2 months) for the UP arm and 26.2 months (95% CI, 17.6–69.3 months) for the PP arm. PFS in the PP arm was more than twice as long as in the UP arm, but there was also no statistically significant difference in PFS between the arms (HR =0.605; 95% CI, 0.36–1.02; P=0.06). The 2-year OS rates were 78.6% (95% CI, 62.8–88.3%) and 85.5% (95% CI, 70.5–93.2%) with the UP arm and the PP arm, respectively. The lower limit of the CI for 2-year OS in both arms exceeded the threshold of 50%. Subset analyses showed that OS was not significantly different when various factors were taken into consideration (*Figure 3*).

Disease recurrences were found in 31 patients in the UP arm and 28 patients in the PP arm. In-field relapse was observed in 4 patients (12.9%) in the UP arm and 2 patients (8.7%) in the PP arm. Distant metastases were observed in 27 patients (87.1%) in the UP arm and 21 patients (91.3%) in the PP arm.

Safety

Treatment-emergent AEs possibly related to study treatment are listed in *Table 4*. Grade 3/4 neutropenia occurred in 34.9% and 31.0% of patients in UP and PP arms, respectively.

Grade 3/4 febrile neutropenia was more frequent in the UP arm than in the PP arm (14.0% and 2.0%, respectively). Grade 3/4 pneumonitis was present in 7.0% of the UP arm and 4.8% of the PP arm. Grade 3 or higher anorexia

Table 1 Patient characteristics

Characteristics	UP arm, n=43 (%)	PP arm, n=42 (%)
Age		
≤59	17 (39.5)	15 (35.7)
60–64	10 (23.3)	12 (28.6)
65–69	7 (16.3)	6 (14.3)
70–75	9 (20.9)	9 (21.4)
Median	62.0	62.5
Gender		
Male	32 (74.4)	34 (81.0)
Female	11 (25.6)	8 (19.0)
PS (ECOG)		
0	29 (67.4)	33 (78.6)
1	14 (32.6)	9 (21.4)
Stage		
IIIA	23 (53.5)	24 (57.1)
IIIB	20 (46.5)	18 (42.9)
Smoking history		
Current/former	39 (90.7)	36 (85.7)
Never	4 (9.3)	6 (14.3)
EGFR mutation		
Positive	7 (16.3)	9 (21.4)
Wild type	32 (74.4)	32 (76.2)
Unknown	4 (9.3)	1 (2.4)

UP, UFT and cisplatin; PP, pemetrexed and cisplatin; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 2 Treatment delivery

Characteristics	UP arm, n=43 (%)	PP arm, n=42 (%)
Cycle number		
1	6 (14.0)	4 (9.5)
2	5 (11.6)	2 (4.8)
3	32 (74.4)	36 (85.7)
Median	3	3
Radiation dose (Gy)		
66	39 (90.7)	38 (90.5)
60–65	1 (2.3)	0 (0.0)
50–59	1 (2.3)	0 (0.0)
40–49	0 (0.0)	1 (2.4)
<40	2 (4.7)	3 (7.1)
Median	66	66

UP, UFT and cisplatin; PP, pemetrexed and cisplatin.

and diarrhea were more common in the UP arm. No one had skin disorders of grade 3 or worse in either arm. No treatment-related deaths occurred during the study period.

Discussion

In this study, both groups met the primary endpoints of 2-year OS, with 78.6% (95% CI, 62.8–88.3%) in the UP group and 85.5% (95% CI, 70.5–93.2%) in the PP group. The median PFS was significantly longer in the PP group than in the UP group. The improved PFS did not translate to a significant effect on OS. These results are consistent with a previously reported association between PFS and OS in lung cancer patients, where long post-progression survival counteracts the effects of first-line treatment (10-12).

Our study revealed a significant efficacy of PFS and OS in both arms. We suggest that this efficacy can be attributed to the design of radiotherapy schedule. Although the standard radiation dose was 60 Gy in practice and in most trials, we selected a 66-Gy dose in this trial (5,13). In the RTOG 0617 trial, the efficacy of radiotherapy at either 60 or 74 Gy with chemotherapy ± cetuximab was evaluated (14). The results showed that 74 Gy treatment was associated with poorer survival when compared with 60 Gy; the toxicities were not significantly different in either radiation dose cohort, regardless of cetuximab treatment. There have been no studies comparing 66 and 60 Gy, and we selected 66 Gy as the feasible high dose radiotherapy. Another difference between our study and those carried out previously is the method by which radiotherapy was administered. In this study, IFRT was performed instead of conventional radiotherapy that includes elective nodal irradiation. Involved-field RT can decrease the number of radiation fields required while providing an increased radiation dose. Previous studies did not observe statistically significant differences in efficacy in patients treated with IF-RT versus those treated with conventional RT (15,16). Next, we excluded consolidation of chemotherapy from the chemo-radiotherapy schedule. During the development of this protocol, severe radiation pneumonitis was observed during

Table 3 Responses in treated patients

	UP arm, n=43 (%)	PP arm, n=42 (%)
CR	3 (7.0)	1 (2.4)
PR	30 (69.8)	33 (78.6)
SD	6 (14.0)	8 (19.0)
PD	2 (4.7)	0 (0.0)
Not evaluable	2 (4.7)	0 (0.0)
ORR, [95% CI]	33 (76.7), [61.0–87.7]	34 (81.0), [65.4–90.9]
DCR, [95% CI]	39 (90.7), [76.9–97.0]	42 (100), [89.6–100]

UP, UFT and cisplatin; PP, pemetrexed and cisplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; CI, Confidence interval.

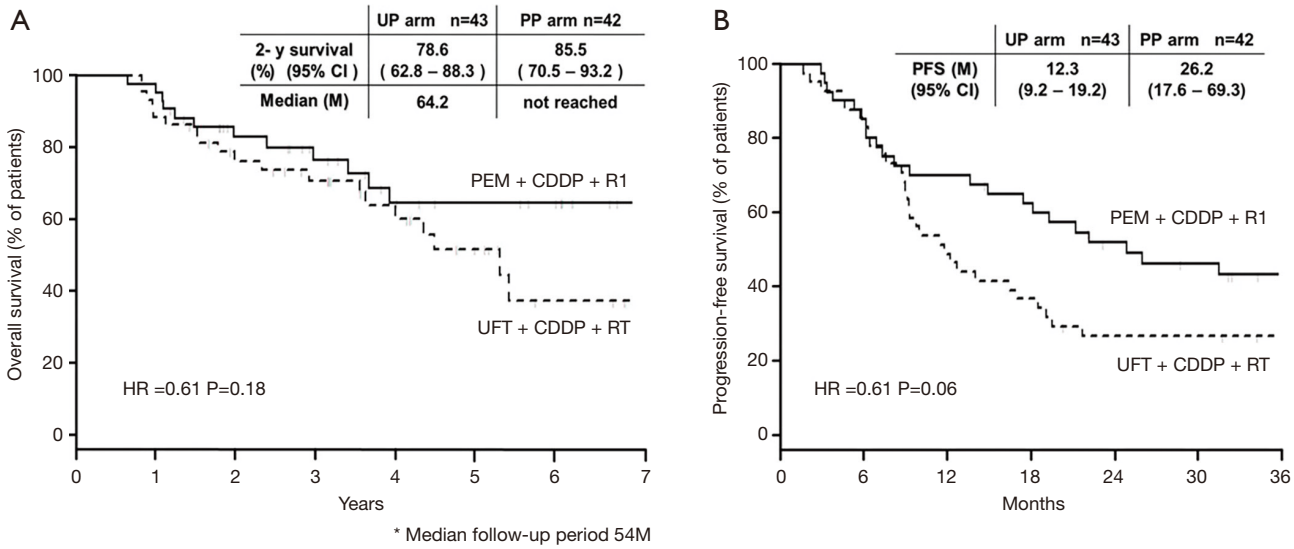

Figure 2 Kaplan–Meier curves. (A) Overall survival and (B) progression-free survival for the randomly assigned treatment arms.

the consolidation phase in a phase 1 study in Japan (17). Generally, the evidence that consolidation after chemoradiotherapy is efficacious and safe is poor according to the JCO guidelines and a pooled analysis (18).

The use of consolidation chemotherapy remains controversial. After chemoradiation, consolidation chemotherapy did not improve OS and is not currently recommended. A pooled analysis of forty-two studies comparing consolidation chemotherapy after CCRT with best supportive care showed no difference in median OS (P=0.4). Consequently, in this study three cycles of chemotherapy were administered during 66-Gy radiation without consolidation chemotherapy.

Our current study demonstrated that, when compared to cisplatin plus UFT, a regimen of cisplatin plus pemetrexed achieved superior PFS and improved OS, although both PFS and OS was not statistically significant. Our study revealed a longer PFS and OS than those reported by PROCLAIM phase III study comparing cisplatin plus pemetrexed to cisplatin plus etoposide (9). PROCLAIM study could not achieve the primary endpoint to validate OS benefit. (2 year-OS: 52%, PFS: 17.4). One of the differences between this study and the PROCLAIM study were whether consolidation was a feature. We note that various consolidation treatments were accepted in the PROCLAIM study, but not accepted in our study. Another difference is race. Specifically, although the 23% of patients in the PROCLAIM study included East Asians (but not

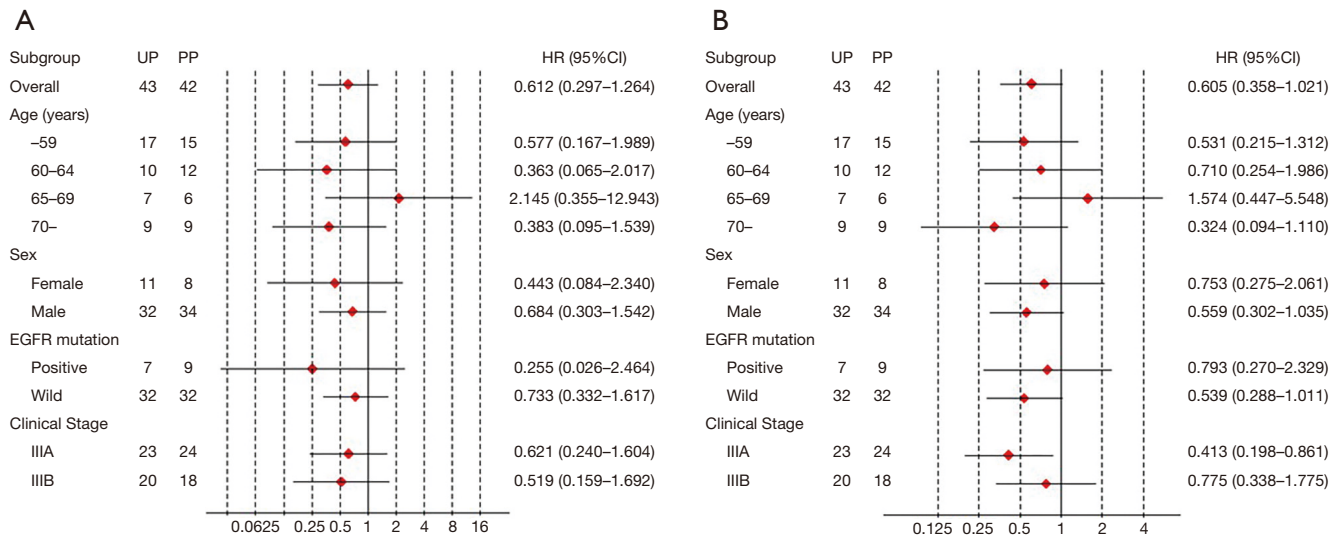

Figure 3 Subgroup analysis. Overall survival (A) and progression-free survival (B) hazard ratio in subgroups according to baseline characteristics.

Table 4 Toxicity profiles

	UP arm, n=43 (%)		PP arm, n=42 (%)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Leukopenia	40 (93.0)	20 (46.5)	29 (69.0)	15 (35.7)
Neutropenia	35 (81.4)	15 (34.9)	27 (64.3)	13 (31.0)
Anemia	27 (62.8))	3 (7.0)	22 (52.4)	0 (0.0)
Thrombocytopenia	19 (44.2)	4 (9.3)	14 (33.3)	2 (4.8)
Febrile neutropenia	6 (14.0)	6 (14.0)	1 (2.4)	1 (2.4)
Anorexia	25 (58.1)	8 (18.6)	23 (54.8)	1 (2.4)
Nausea/Vomiting	3 (7.0)	0 (0.0)	2 (4.8)	0 (0.0)
Diarrhea	9 (20.9)	5 (11.6)	1 (2.4)	0 (0.0)
Constipation	11 (25.6)	0 (0.0)	15 (35.7)	0 (0.0)
Infection	2 (4.7)	2 (4.7)	5 (11.9)	3 (7.1)
AST/ALT increased	17 (39.5)	2(4.7)	5 (11.9)	0 (0.0)
Pneumonitis	33 (76.7)	3 (7.0)	36 (85.7)	2 (4.8)
Esophagitis	22 (51.2)	2 (4.7)	16 (38.1)	2 (4.8
Dermatitis	12 (27.9)	0 (0.0)	20 (47.6)	1 (2.4)

UP, UFT and cisplatin; PP, pemetrexed and cisplatin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

the Japanese), our current study was entirely composed of Japanese individuals. The Japanese studies of lung cancer have often revealed longer PFS and OS compared to studies of Western populations. This difference can be explained by both racial differences and a Japanese insurance system that supports the provision of the most appropriate line of cancer treatment according to the individual's clinical characteristics. Actually, 87% of patients in this study received second-line or later therapies after conclusion of the study treatment, whereas this figure was only 42.5% in the PROCLAIM study. Other differences among two studies are rate of PET test. Approximately 80% of patients underwent PET in the PROCLAIM study, but in our study all cases were examined using PET, which helps with correct staging (19,20). The staging may therefore have been more accurate in this study.

In terms of toxicity, more hematological toxicity was observed in the UFT group than in the PEM group; this was a major reason for failure to complete 3 cycles in the UFT group. Diarrhea was more common in the UFT group and skin disorders were more common in the PEM group. Although pneumonitis was a concern in the PEM group before initiation of the study, the percentage of grade 3 or higher pneumonitis cases was 7.0% in the UFT group and 4.8% in the PEM group. Taken together, toxicities in both regimens were expected and manageable.

Recently, the PACIFIC trial, a phase III study of chemoradiation with consolidation using durvalumab inhibiting PD-L1 compared to without consolidation in patients with stage III unresectable NSCLC, demonstrated statistically significant increases in OS and PFS (21,22). Consolidation with durvalumab following CCRT became a new standard of care for patients with locally advanced NSCLC. Important things in this situation are to select efficacious and safety chemoradiation methods to connect successfully to consolidation with durvalumab. This CCRT of 66 Gy IF-RT with cisplatin plus pemetrexed may thus have therapeutic potential as an appropriate CCRT followed by durvalumab for inoperable stage III non-squamous NSCLC.

This study has several limitations. First, the study is a phase II randomized trial to select candidates for a phase III trial and thus has no confirmatory meaning. Second, the study required nine years of recruitment and observation. During this period, the parameters related to some standard treatment regimens and TNM classification have changed. However, studies with a small number of locally advanced patients compared to studies with metastatic patients are always faced with challenges in recruitment.

In conclusion, PP was safer and more efficacious than UP. Thus, in a future phase III study, PP should be considered as the experimental arm for comparison to the standard regimen with c-TRT for non-squamous NSCLC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the participating institution's Institutional review board (approval number 2010-016). All patients provided written informed consent before enrollment.

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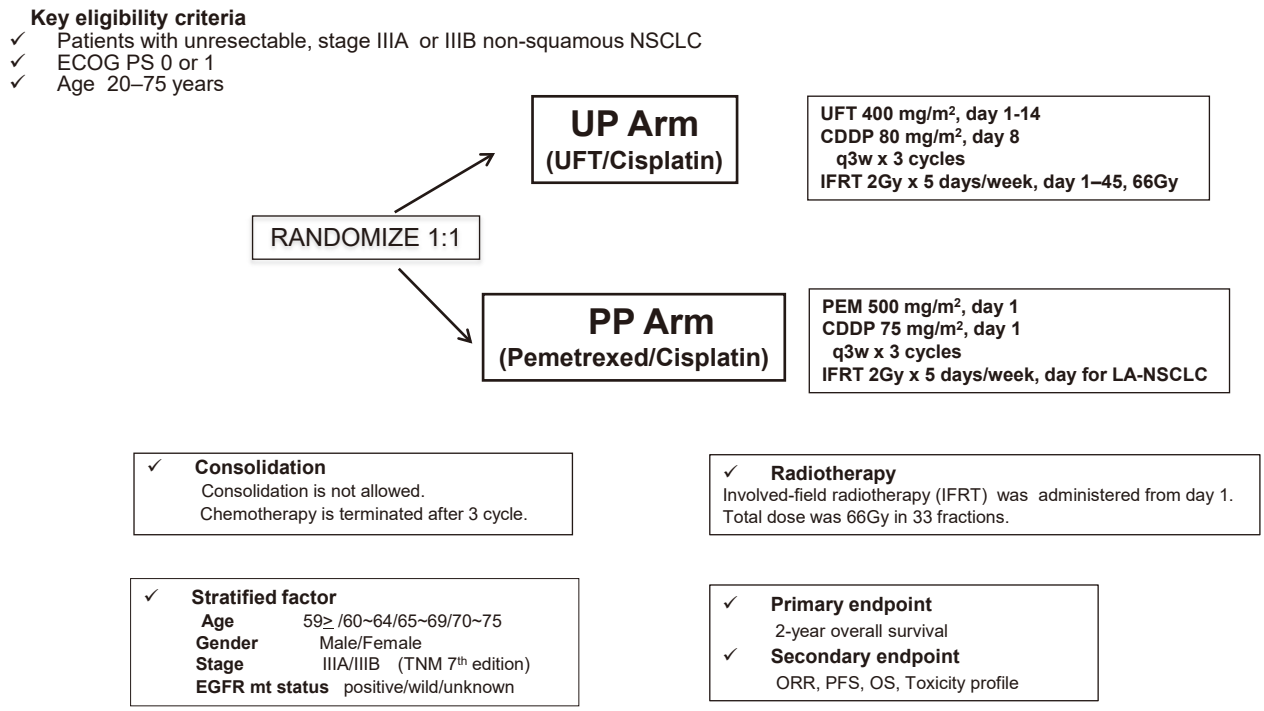

Figure S1 Treatment schedule of each arm. This figure shows key eligibility criteria and dose of each treatment.

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