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ORIGINAL ARTICLE

Retrospective Treatment Outcomes of Concurrent Chemoradiotherapy in Patients with Stage III Non-small Cell Lung Cancer at a Single Institution: The Pre-PACIFIC Era

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ABSTRACT —— ***Objective.*** To investigate the treatment outcomes in patients with stage III non-small cell lung cancer (NSCLC) after definitive concurrent chemoradiotherapy (CCRT). ***Methods.*** We retrospectively reviewed 89 patients who received definitive CCRT for NSCLC in our hospital between April 2008 and March 2018. According to the Union for International Cancer Control system, the clinical stages were IIIA in version 7, IIIB, IIIA in version 8, IIIB, and IIIC in 44, 45, 29, 46, and 14 patients, respectively. ***Results.*** The 5-year overall survival (OS) and progression-free survival rates were 48.5% and 36.1%, respectively. Five-year OS by stage was 57.0% for stage IIIA in version 7, 41.7% for stage IIIB (p=0.14), 63.8% for stage IIIA in version 8, 45.7% for stage IIIB, and 28.6% for stage IIIC (p=0.02). ***Conclusion.*** CCRT was feasible, safe, and well tolerated in our patients and resulted in survival benefits comparable to those in the published literature. Stage IIIC NSCLC (version 8) was associated with a significantly worse prognosis. Some stage IIIC cases suggested that radiation therapy should not be omitted, even for stage IIIC, and that it is better to increase the intensity of systemic therapy, including durvalumab.

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KEY WORDS —— Lung cancer, CCRT, 3D-CRT

INTRODUCTION

Concurrent chemoradiotherapy (CCRT) has been the standard treatment for patients with locally advanced non-small cell lung cancer (NSCLC)[1]; however, the prognosis of these patients has been poor for two decades, with an estimated 5-year overall survival (OS) rate of ＜20% (range, 15-40%).[2] The treatment strategy for stage III NSCLC is complex and controversial because of the heterogeneity of these patients.[3-5] After the PACIFIC trial, durvalumab, which is a consolidation therapy for patients with stage III NSCLC with no progression after chemoradiotherapy, became the standard therapy.[6,7]

We herein present our single-institution study on the treatment of patients with NSCLC using CCRT: the pre-PACIFIC era. This retrospective study aimed to assess the outcomes of consecutive patients with locally advanced NSCLC, who were treated by only one board-certificated radiation oncologist for ten years at our institution.

The outcomes in each subgroup were also assessed. The subgroups were categorised according to the malignant tumour classification of the 8th edition of the Union for International Cancer Control (UICC), which was changed in 2017.[8,9] Determination of the therapeutic approach for stage III NSCLC was mainly based on the TNM classification system, and these outcomes will indicate the appropriate strategies for each subgroup.

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MATERIALS AND METHODS

Patient population

Patients who were treated with definitive chemoradiotherapy for locally advanced NSCLC were eligible for inclusion in this retrospective review. The exclusion criteria were as follows: treatment with radiotherapy (RT) alone, treatment with surgery after chemoradiotherapy, history of other malignancy within 5 years, and absence of follow-up because of unavailability. The diagnosis of NSCLC was confirmed by histological evaluation. All patients were staged with whole-body fluorodeoxyglucose-positron emission tomography and enhanced magnetic resonance imaging of the brain. The clinical stage at presentation was subsequently categorised according to the TNM classification of malignant tumours (in both the 7th and 8th editions).

Medical records and clinical laboratory data for the patients were retrospectively collected and anonymised to exclude personal information. The study protocol was approved by the Institutional Review Board of our hospital (19-030).

Treatment and outcomes

The patients received CCRT as initial treatment. The prescribed radiation dose was 60-66 Gy delivered in 2.0 Gy daily fractions, five times a week. Patients were treated with elective nodal irradiation therapy with three-dimensional conformal RT (3D-CRT), which prophylactically targeted the uninvolved mediastinal nodal regions. A shrinking field technique was used, with opposed anterior/posterior fields covering the primary tumour and elective mediastinal nodes, followed by the cone-down fields angle off the spinal cord. Patients were followed every 3 months for the first year and every 6 months thereafter. The toxicity of chemoradiotherapy was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

OS was defined as the time from the date of first treatment to the date of death or date of the last contact. Progression-free survival (PFS) was defined as the time from the date of first treatment to the date of disease progression or death from any cause. Patient characteristics were retrospectively obtained from the medical records.

For the univariate analysis, OS was assessed using the Kaplan-Meier method and log-rank test. P-values of < 0.05 were considered statistically significant. Statistical analyses were performed using the EZR software program (version 1.31, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria).[10]

Table 1. Patient Characteristics

Age (years)	46-79	(median 66)
Sex		
Male	69	(77.5%)
Female	20	(22.5%)
Histology		
Adenocarcinoma	37	(41.6%)
Squamous cell carcinoma	21	(23.6%)
Others	31	(34.8%)
Stage (7th ed.)		
IIIA	44	(49.4%)
IIIB	45	(50.6%)
Stage (8th ed.)		
IIIA	29	(32.6%)
IIIB	46	(51.7%)
IIIC	14	(15.7%)
Total dose of radiotherapy (Gy)	60-66	Median 60
Chemotherapy regimen		
CDDP 60 mg/m^2/VNR 25 mg/m^2	47	(52.8%)
CBDCA AUC 2/PAC 40 mg/m^2	22	(24.7%)
CBDCA AUC 6/nabPTX 100 mg/m^2	9	(10.1%)
Others	11	(12.4%)

Abbreviations: CDDP, cisplatin; CBDCA, carboplatin; VNR, vinorelbine; PAC, paclitaxel; nabPTX, nab-paclitaxel.

RESULTS

We retrospectively identified 89 consecutive patients with locally advanced NSCLC, all of whom underwent definitive chemoradiotherapy in our hospital between April 2008 and March 2018. The characteristics of the patients are shown in Table 1. Activating EGFR mutations (exon 19 deletion and exon 21 L858R point mutation) were detected in 12 of 80 patients. These patients received two cycles of platinum-based chemotherapy concurrently with definitive RT. The dose of chemotherapy is shown in Table 1. A total of 87 patients received consolidation chemotherapy with the same regimen.

The median follow-up period was 55 months (range, 3-121 months) in all patients. A total of 56 patients had disease recurrence, and 47 patients died during follow-up. The median OS and PFS were 54.7 months (95% confidence interval [CI], 36.4-79.5) and 22.7 months (95% CI: 12.2-52.8), respectively. The 5-year OS and PFS were

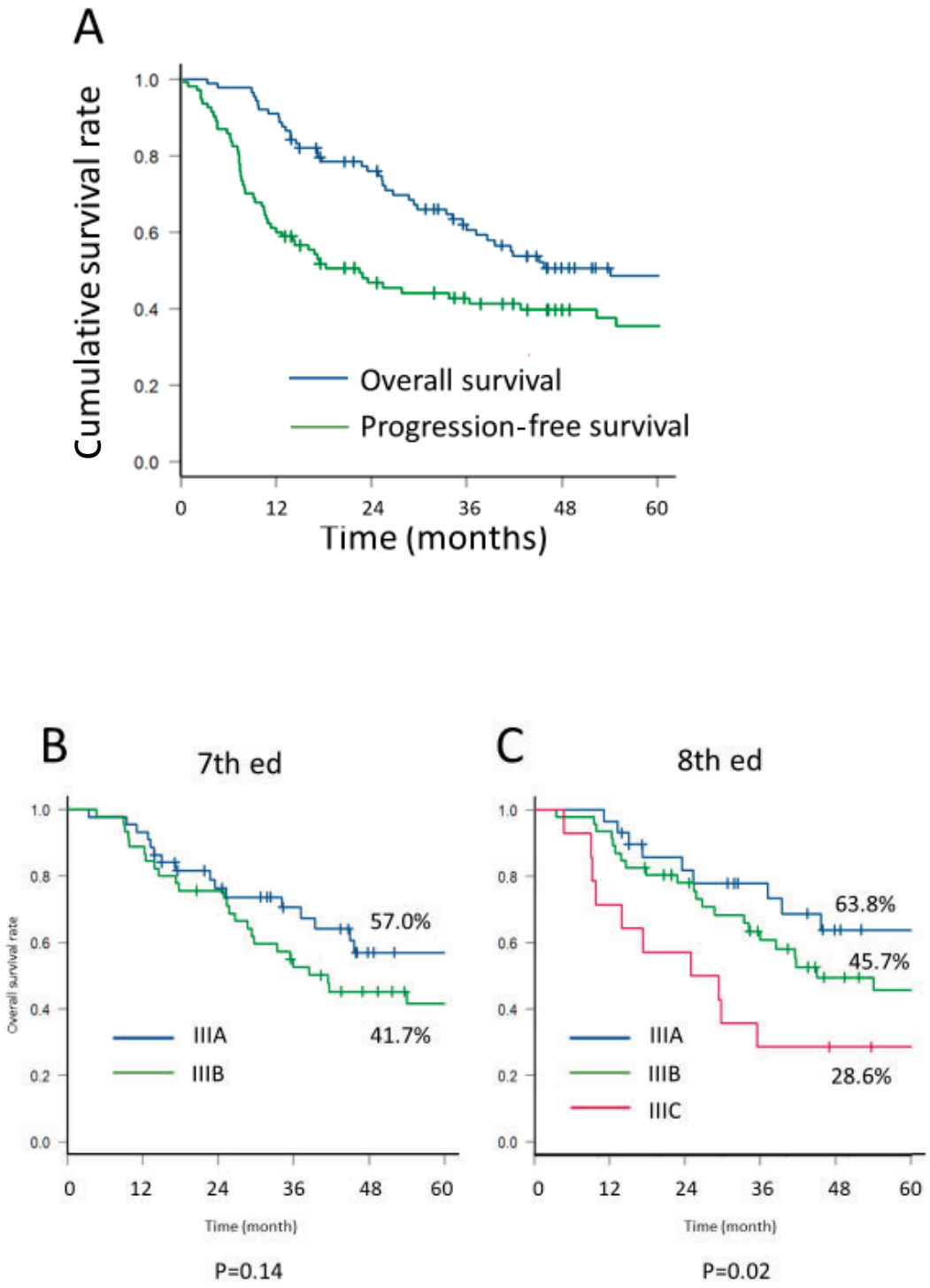

Figure 1. **A.** Kaplan-Meier curves of overall survival and progression-free survival in all patients. **B, C.** Difference in overall survival among the stages.

48.5% and 36.1%, respectively. The 5-year OS by stage was 57.0% for stage IIIA (version 7), 41.7% for stage IIIB (p=0.14), 63.8% for stage IIIA (version 8), 45.7% for stage IIIB, and 28.6% for stage IIIC (p=0.02) (Figure 1). In the subgroup analysis, there was no significant difference in 5-year OS (Table 2). OS and PFS did not differ to a statistically significant extent according to the type of chemotherapy. Grade >2 radiation pneumonitis was observed

Table 2. Subgroup Analysis

	Cut-off value	N (%)	5-year OS (%)	P-value
Age	<65 years		62.7	0.06
	>65 years	56 (62.9%)	41.0	
Sex	Male		49.4	0.91
	Female	20 (22.5%)	45.7	
Histology	Adenocarcinoma	37 (41.6%)	58.6	0.21
	Squamous cell carcinoma	21 (23.6%)	37.5	
	Others	31 (34.8%)	44.9	
T4	≤3		49.4	0.81
	4	28 (31.5%)	45.6	
N3	≤2		50.8	0.30
	3	35 (39.3%)	45.4	
Radiation pneumonitis	Grade <1		50.5	0.31
	Grade ≥2	22 (24.7%)	43.8	
V20 Gy	<25%		49.0	0.95
	≥25%	41 (46.1%)	48.4	

Table 3. Radiation Pneumonitis

V20 Gy (%)	N	G2	G5	>G2 (%)
0-15	9	1	0	11.1
15-25	40	9	0	22.5
25-35	36	9	1	27.8
35<	4	2	0	50.0
Total	89	21	1	24.7

in 24.7% of patients (Table 3). As other adverse effects of chemoradiotherapy, grade 3 and 4 bone marrow suppression was observed in 35 and 22 patients, respectively, and grade 2 esophagitis was observed in 33 patients.

RECURRENCE PATTERN

At the time of data cut-off (28 May 2019), PFS events were observed in 58 patients, and 43 patients died. Among 58 patients with recurrence, locoregional failure was observed in 28 patients. Distant metastasis was the first site of failure in 30 patients. As for stage IIIC, distant metastasis occurred at a higher rate of 72.7% (Table 4). Moreover, 44 patients received chemotherapy, 17 received palliative RT, and 16 received immunotherapy as salvage therapy (some cases overlapped).

DISCUSSION

The outcomes reported in this retrospective study suggest that CCRT is feasible, safe, and well tolerated. The results also demonstrate that CCRT was associated with a survival benefit in comparison to reports in the relevant literature. Stage IIIC (UICC 8th edition) patients showed a significantly worse prognosis.

Stage III NSCLC includes a highly heterogeneous group of patients with differences in the extent and localisation of the disease. Many aspects of the treatment of stage III disease are controversial. These patients are at high risk for both local and distant recurrence. Even with major improvements in therapy, including the use of more active chemotherapy agents and refinements in radiation, the prognosis for these patients has remained poor for two decades. RTOG0617 revealed that the delivery of 74 Gy with concurrent carboplatin and paclitaxel resulted in worse median OS (20 months versus 29 months) in comparison to the delivery of 60 Gy.[11,12] This study was a two-by-two phase 3 randomised trial to compare a standard dose of 60 Gy and a high dose of 74 Gy and concurrent chemotherapy with or without cetuximab in patients with inoperable stage III NSCLC. As a result, high-dose RT was associated with shorter survival and increased risk of death in comparison to conventional-dose RT. A multivariate analysis suggested that poorer survival may be related to a higher dose of radiation to the heart. However, higher doses of RT will be beneficial when chemotherapy cannot be indicated. Recently, a paradigm shift has occurred. The PACIFIC trial results showed that the administration of durvalumab, an anti-programmed death ligand 1 monoclonal antibody, after CRT in patients with unresectable stage III significantly prolonged PFS and OS in compari-

Table 4. Recurrence Pattern

Recurrence pattern	IIIA	IIIB	IIIC	All patients
Local recurrence	6 (37.5%)	11 (35.5%)	2 (18.2%)	19 (33.9%)
Regional lymph node	4 (25.0%)	4 (12.9%)	1 (9.1%)	9 (16.1%)
Metastasis	6 (37.5%)	16 (51.6%)	8 (72.7%)	30 (57.1%)
Lung	4	6	2	12
Brain	1	4	4	9
Bone	1	4	0	5
Liver	0	1	2	3
Adrenal gland	0	1	0	1
Total	16/29	31/46	11/14	58/89

son to placebo.[6,7] In the subgroup analysis, the contribution of durvalumab was higher in the stage IIIA (7th edition) than in stage IIIB (7th edition), which included stage IIIC (8th edition). This therapy has become the standard therapy for all stage III NSCLC. Durvalumab also had a favourable effect on the frequency of new distant metastasis, and was associated with a lower incidence of new brain metastasis.

The UICC staging system changed in 2017. The new dataset of the UICC 8th edition contains a higher proportion of clinical cases from Asia, mostly from Japan, which contributed to 41% of the total cases.[13] A new stage group was created for the most advanced local disease categories, T3 and T4 associated with N3 disease, but category M0. Such cases are presently classified as stage IIIC, reflecting their worse outcomes in comparison to cases involving tumours that remain in stage IIIB. The prognosis for stage IIIC cases is similar to that of stage IVA cases, but the separation is justified by the different treatment approaches used in such cases. Due to the changes in T category, despite the association of N2 or N3 disease, the change in stage classification, which has been proposed in the 8th edition, resulted in the shift from IIIA to IIIB and from IIIB to IIIC. In our study, the classification of the 8th edition was well reflected in the prognosis. As the feature of stage IIIC, a higher rate of metastatic recurrence leads to a worse prognosis. The post-treatment outcomes of some stage IIIC cases suggested that RT should not be omitted, even in stage IIIC; thus, this may be a better strategy to increase the intensity of systemic therapy, including durvalumab.

The present study was associated with some limitations. First, because this was a retrospective study in a single institution, an information bias was inevitable, and the sample size was small. Second, patients with recurrence had the benefit of immunotherapy after nivolumab was approved for clinical use in 2014. A larger, multicentre analysis is warranted to discuss the strategy for unresectable stage III NSCLC. One merit of this study was that the RT policy had not changed for ten years. Furthermore, at the time of data cut-off (28 May 2019), only three patients were lost to follow-up, and these data were considered to reflect the real world setting.

CONCLUSION

CCRT was feasible, safe, and well tolerated in our patients and resulted in survival benefits that were comparable to those reported in the relevant literature. Stage IIIC (UICC 8th edition) was associated with a significantly worse prognosis. A few stage IIIC cases suggested that radiation therapy should not be omitted, even in stage IIIC, and that it is a better strategy for increasing the intensity of systemic therapy, including durvalumab.

本論文内容に関連する著者の利益相反：なし

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Ethical statement: This study was approved by the local ethics committee of the National Hospital Organization Kyoto Medical Center of 19-030.

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