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Original Article

Clinical Outcome of Palliative Concurrent Chemoradiotherapy with Cisplatin/Docetaxel for Stage III Non-small Cell Lung Cancer

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Palliative concurrent chemoradiotherapy (CCRT) is often administered to patients with stage III non-small cell lung cancer (NSCLC). We investigated the clinical outcomes of patients receiving palliative CCRT for NSCLC. Data of patients with NSCLC who underwent palliative CCRT (n = 16), preoperative CCRT plus surgery (n = 97), or definitive CCRT (n = 48) were evaluated. In all groups, the concurrent chemotherapy regimens consisted of cisplatin and docetaxel. Rates of local control (LC), distant metastasis-free survival (DMFS), progression-free survival (PFS), overall survival (OS), and prognosis were compared. The 2-year rates of LC, DMFS, PFS, and OS in 16 patients who underwent palliative CCRT were 44.4%, 12.5%, 12.5%, and 18.8%, respectively. Univariate analysis showed that palliative CCRT was associated with poor LC ($p < 0.001$), DMFS ($p < 0.001$), PFS ($p < 0.001$), and OS ($p < 0.001$) outcomes in patients who completed CCRT as a preoperative treatment and poor LC ($p = 0.01$), DMFS ($p = 0.003$), PFS ($p = 0.04$), and OS ($p = 0.004$) outcomes in patients who were considered for definitive CCRT. Although there were some long-term survivors, the clinical outcomes of palliative CCRT were significantly inferior to those of the ideal treatments. Therefore, careful determination of the appropriate treatment indications and further studies are warranted.

Key words: palliative concurrent chemoradiotherapy, cisplatin/docetaxel, stage III non-small cell lung cancer

Various treatment options are available for stage III locally advanced non-small cell lung cancer (NSCLC), depending on the extent of the tumor. Surgery is recommended for resectable NSCLC, and preoperative concurrent chemoradiotherapy (CCRT) is often selected when preoperative treatment is considered necessary. Toyooka *et al.* compared clinical outcomes in patients who underwent preoperative CCRT and preoperative chemotherapy for locally advanced NSCLC and demonstrated that the former treatment group had a better prognosis [1]. In phase III trial INT0139, an exploratory analysis showed improved overall survival (OS) in patients who underwent preoperative CCRT plus lobectomy compared with that in a matched cohort who received definitive CCRT [2]. Definitive CCRT with platinum/taxanes is a standard first-line treatment option for unresectable stage III lung cancer [3, 4]. In the era of radiotherapy alone and CCRT, the total dose of definitive radiotherapy is

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defined as 54-66 Gy [5-7]. In some cases, palliative CCRT is administered when ideal treatments are not adopted for various reasons. Some patients do not undergo surgery despite completing CCRT as a preoperative treatment [2,8] or do not receive a definitive dose because of a dose constraint of the spinal cord or lungs [9,10]. Palliative CCRT for stage III NSCLC is presented as an option in the American Society for Radiation Oncology (ASTRO) guidelines [11].

Cisplatin/docetaxel is a standard regimen in Japan for concurrent administration with definitive radiotherapy. A cisplatin/docetaxel therapy group had better 2-year survival rates than a second-generation chemotherapy group [3]. To the best of our knowledge, there are no studies on palliative CCRT with cisplatin/docetaxel for stage III NSCLC.

The present study aimed to investigate the clinical outcomes of palliative CCRT with cisplatin/docetaxel as an initial treatment in comparison with the ideal treatments in patients with stage III NSCLC.

Methods

Patients. We retrospectively reviewed the medical records of patients with stage III NSCLC who underwent palliative CCRT as an initial treatment with < 50 Gy between April 2003 and March 2018 at our institution. Specifically, we reviewed patients who did not undergo surgery despite having completed CCRT as a preoperative treatment and patients who had not been administered a definitive dose although they had been considered for definitive CCRT. Patients treated with cisplatin/docetaxel as concurrent chemotherapy were included and those treated before CCRT were excluded. To compare palliative CCRT, patients who underwent preoperative CCRT plus planned surgery were evaluated, as were those who underwent definitive CCRT within the same period. Staging was performed using the UICC-TNM ver. 7. This study was approved by the Institutional Review Board of Okayama University Hospital (approval number: 1809-018). Patients were provided with the opportunity to opt out of the study at the outpatient ward or at the website. This study conformed to the Declaration of Helsinki.

Treatment. All patients underwent three-dimensional conformal radiotherapy. The total dose for palliative CCRT was defined as 40-50 Gy, and that for definitive CCRT was defined as > 54 Gy; no planned surgery was performed before recurrence. The total dose of preoperative CCRT was 40-60 Gy, and planned surgery was performed after CCRT. The details of the radiotherapy are described in previous studies [12,13]. In all groups, the concurrent chemotherapy regimens consisted of cisplatin 40 mg/m^2 and docetaxel 40 mg/m^2 [3].

Statistical analyses. The rates of local control (LC), distant metastasis-free survival (DMFS), progression-free survival (PFS), and OS after completion of CCRT were calculated. We compared the clinical outcomes of the three categories of patients. We further examined whether palliative CCRT was associated with prognosis. The Kaplan–Meier method was used to determine survival rates, the log-rank test was used for univariate analysis, and the Cox proportional hazards test was used for multivariate analysis. A p-value of < 0.05 (two-sided) was considered statistically significant. R software (version 3.5.1, R Foundation for Statistical Computing) was used for all statistical analyses.

Results

Of the 16 patients who underwent palliative CCRT, 9 completed CCRT as a preoperative treatment and 7 were considered for definitive CCRT. Of the 9 who did not undergo surgery despite completing CCRT as a preoperative treatment, 7 had distant metastasis, 1 had deterioration of their general condition, and 1 had deterioration of their general condition because of radiation pneumonitis. Moreover, 7 patients were not administered a definitive dose even though they were considered for definitive CCRT. Of these, 3 patients had a lung dose constraint, 3 had a spinal cord dose constraint, and 1 had both constraints. Table 1 shows the characteristics of all 16 patients who underwent palliative CCRT. The 2-year rates of LC, DMFS, PFS, and OS were 44.4%, 12.5%, 12.5%, and 18.8%, respectively (Fig. 1). Twelve patients died of lung cancer, 1 died of another disease, 2 were alive without recurrence, and 1 was alive with recurrence. The follow-up periods for the 2 patients who were alive without recurrence were 42.5 months and 87.5 months, respectively.

Ninety-seven patients underwent CCRT as a preoperative treatment plus planned surgery. Table 2 shows the characteristics of 106 patients, including these 97 patients and the remaining 9 patients (8.5%) who did

Table 1 Characteristics of all patients who received palliative CCRT (n = 16)

			%
Age (years)	Median (range)	64 (42–72)	–
Sex	Male	14	87
	Female	2	13
T stage	1	2	13
	2	5	31
	3	3	19
	4	6	37
N stage	0	2	13
	1	1	6
	2	7	44
	3	6	37
Clinical stage	IIIA	8	50
	IIIB	8	50
Histology	Adenocarcinoma	4	25
	Squamous cell carcinoma	8	19
	Adenosquamous carcinoma	1	6
	Non-small cell carcinoma	3	50
Lobe	Upper	10	62
	Lower	6	38
Laterality	Right	13	81
	Left	3	19
Smoking history †	Never	1	6
	Former	5	31
	Current	9	56
FEV1 (l) †	Median (range)	2.22 (1.74–3.67)	–
ECOG-PS	0	6	38
	1	10	62
Radiation dose (Gy)	Median (range)	46 (40–46)	–
X-ray energy (MV)	6	1	6
	10	15	94
Cycles of concurrent chemotherapy	1	6	38
	2	10	62
Cycles of adjuvant chemotherapy	0	14	87
	1–5	2	13

CCRT, concurrent chemoradiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 sec.
† These factors have missing values.

not undergo surgery despite having completed CCRT as a preoperative treatment. Kaplan–Meier curves for the group with preoperative CCRT plus surgery and palliative CCRT are shown in Fig. 2. The 2-year rates of LC, DMFS, PFS, and OS were 95.7%, 68.9%, 65.8%, and 89.6%, respectively, for patients with preoperative CCRT plus surgery and were 60.0%, 11.1%, 11.1%, and 22.2%, respectively, in patients receiving palliative CCRT. The 5-year rates of LC, DMFS, PFS, and OS were 92.3%, 56.9%, 53.5%, and 73.1%, respectively, in patients receiving preoperative CCRT plus surgery and 60.0% and 22.2%, respectively, for LC and OS in patients receiving palliative CCRT (rates for DMFS and PFS were not available). In the univariate analyses of the 106 patients, palliative CCRT was associated with a low rate of LC ($p < 0.001$), and palliative CCRT was associated with low rates of DMFS ($p < 0.001$), PFS ($p < 0.001$), and OS ($p < 0.001$). In the multivariate analyses, palliative CCRT ($p < 0.001$), T1-2 stage ($p = 0.002$), and location of the lower lobe ($p = 0.009$) were associated with a low rate of DMFS. Palliative CCRT ($p < 0.001$), T1-2 stage ($p < 0.001$), and location of the lower lobe ($p = 0.01$) were associated with a low rate of PFS. Palliative CCRT ($p < 0.001$) and the location of the lower

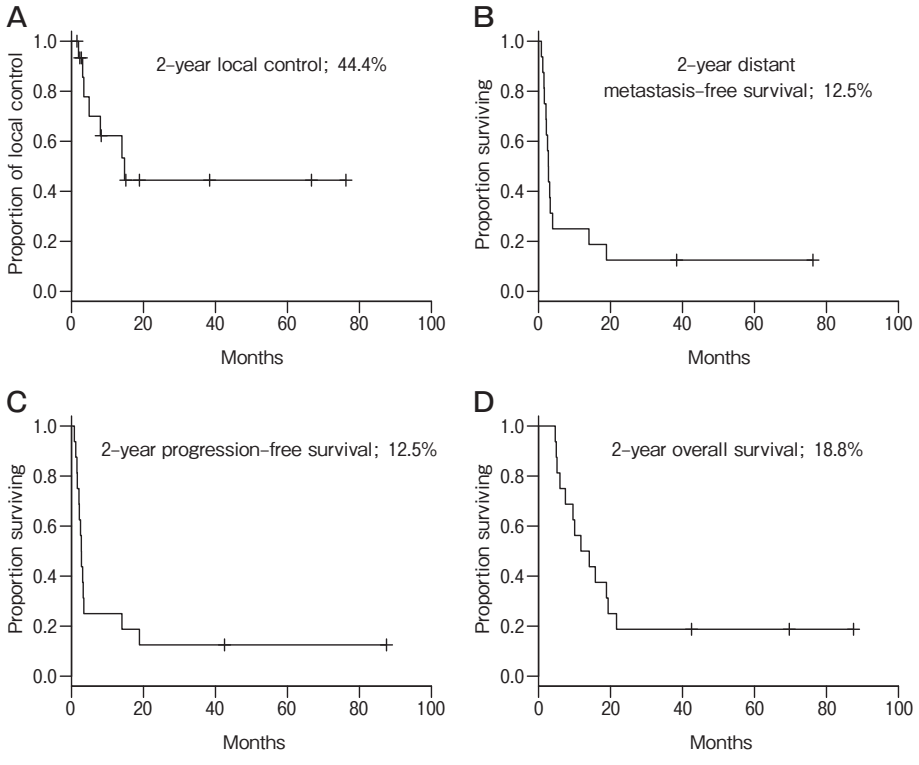

Fig. 1 Kaplan−Meier curves for all patients who underwent palliative CCRT. (**A**) Local control; (**B**) distant metastasis-free survival; (**C**) progression-free survival; (**D**) overall survival. CCRT, concurrent chemoradiotherapy.

lobe ($p=0.018$) were associated with low rates of OS.

Furthermore, 48 patients underwent definitive CCRT. Table 3 shows the characteristics of 55 patients, including these 48 patients and 7 others who were not administered a definitive dose although they were considered for definitive CCRT. Kaplan–Meier curves for the groups with definitive CCRT and palliative CCRT are shown in Fig. 3. The 2-year rates of LC, PFS, and OS were 64.3%, 39.2%, 37.2%, and 59.7%, respectively, in patients receiving definitive CCRT and 20.8%, 14.3%, 14.3%, and 14.3%, respectively, in patients receiving palliative CCRT. The 5-year rates of LC, DMFS, PFS, and OS were 53.4%, 22.3%, 24.4%, and 37.3%, respectively, in those receiving definitive CCRT and 20.8%, 14.3%, 14.3%, and 14.3%, respectively, in those receiving palliative CCRT. In the univariate analysis of 55 patients, palliative CCRT was associated with low rates of LC ($p=0.01$), DMFS ($p=0.03$), and PFS ($p=0.04$), and palliative CCRT was associated with a low rate of OS ($p=0.004$). In the multivariate analysis, palliative CCRT was associated with a low rate of OS ($p=0.049$).

Discussion

In this study, we examined the clinical outcomes of palliative CCRT with cisplatin/docetaxel in patients with stage III NSCLC. Palliative CCRT was associated with poor outcomes in univariate and multivariate analyses, as demonstrated by four parameters (LC, DMFS, PFS, and OS), compared with preoperative CCRT plus surgery or definitive.

The 2-year OS rate was low (22.2%) in patients in the palliative CCRT group. As demonstrated by the rates of LC, DMFS, PFS, and OS, patients who underwent CCRT alone had significantly worse outcomes than those who underwent planned surgery. Analysis of the Phase III trial of INT0139 showed improved OS in patients receiving preoperative CCRT plus lobectomy compared to patients receiving definitive CCRT. According to OS, this study failed to show the superiority of the preoperative CCRT group over the definitive CCRT group. After randomization, 18.8% of patients could not undergo surgery and 7.7% could not undergo definitive CCRT. This may be a reason why there was no difference in OS between the 2 groups. Therefore, it is highly advisable to avoid situations in which the ini-

Table 2 Characteristics of patients who completed CCRT as preoperative treatment

		Preoperative CCRT plus surgery (n=97)	Palliative CCRT (n=9)
Age (years)	Median (range)	61 (33–78)	64 (42–71)
Sex	Male	75	8
	Female	22	1
T stage	1	17	1
	2	28	2
	3	18	3
	4	34	3
N stage	0	9	0
	1	14	1
	2	66	7
	3	8	1
Clinical stage	IIIA	65	7
	IIIB	32	2
Histology	Adenocarcinoma	48	2
	Squamous cell carcinoma	34	6
	Adenosquamous carcinoma	1	0
	Undifferentiated carcinoma	1	0
	Non-small cell carcinoma	13	1
Lobe	Upper	69	5
	Middle	6	0
	Lower	17	4
	Upper and lower	1	0
	Middle and lower	4	0
Laterality	Right	43	7
	Left	54	2
Smoking history †	Never	11	0
	Former	16	4
	Current	35	5
FEV1 (l) †	Median (range)	2.55 (1.40–4.17)	2.29 (1.74–3.67)
ECOG-PS †	0	59	5
	1	37	4
	2	1	0
Radiation dose (Gy)	Median (range)	46 (40–60)	46 (40–46)

CCRT, concurrent chemoradiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 sec.
† These factors have missing values.

tial treatment terminates with palliative CCRT without surgery. Only 8.5% of patients who underwent preoperative CCRT were unsuitable for surgery; this was lower than the 18.8% in INT0139, suggesting that the determination of the indication for treatment at our institution was appropriate. However, in our study, 7 of 9 patients who underwent palliative CCRT did not undergo surgery because of distant metastases. Estimation of the group in which surgery is unlikely to be performed using volumetric positron emission tomography [14] and carefully determining the indications for preoperative CCRT may help to avoid termination of the initial treatment with palliative CCRT. Similar to the results of previous reports, in our study the location of the lower lobe was a poor prognostic factor in the preoperative CCRT group [15]. A possible explanation for this association, mentioned by Shien *et al.*, could be that patients with tumors located in the lower lobes may have a wider spread of potential disease than an imaging-based diagnosis would indicate.

We reported the clinical outcome of palliative CCRT in patients who were considered for definitive CCRT but did not receive a definitive dose. The ASTRO guidelines recommend the concurrent use of 2 platinum-containing chemotherapy agents in combination with low-fraction, moderate-dose palliative radiotherapy over either

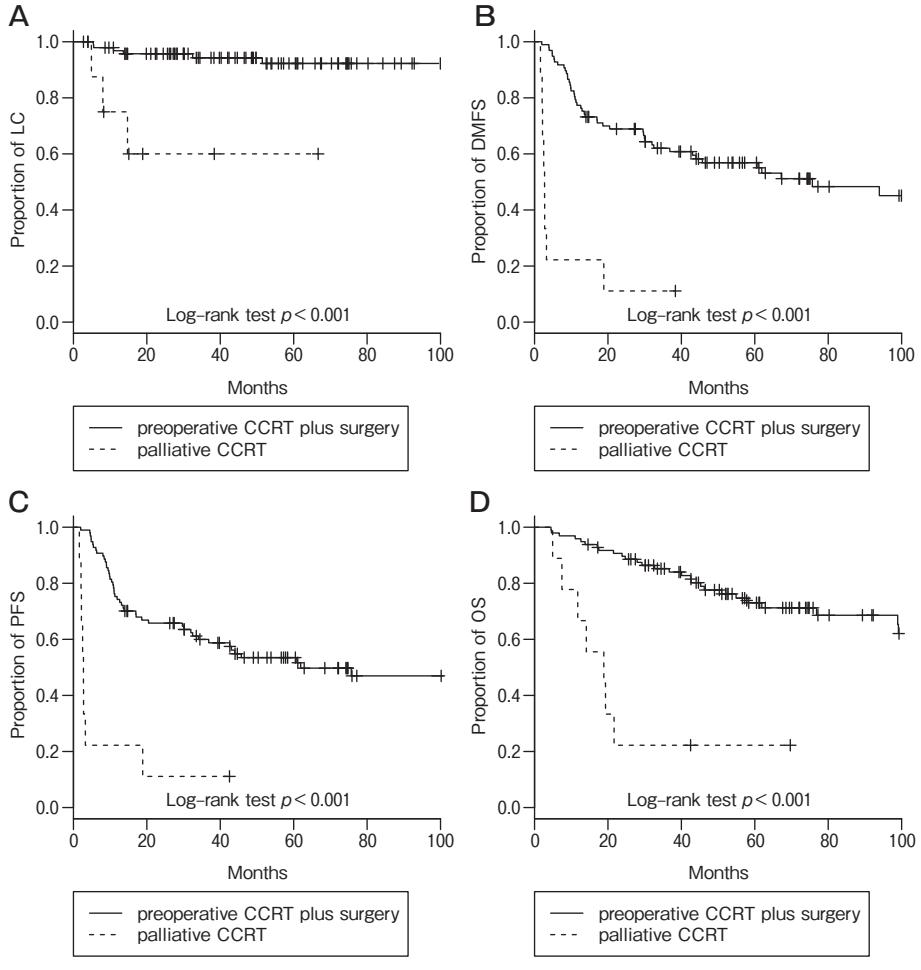

Fig. 2 Kaplan−Meier curves for preoperative CCRT plus surgery (n = 97) and palliative CCRT (n = 9). (**A**) Local control; (**B**) distant metastasis-free survival; (**C**) progression-free survival; (**D**) overall survival.
CCRT, concurrent chemoradiotherapy.

treatment alone for stage III NSCLC in situations where resection or definitive dose administration is not possible [11]. Strøm *et al.* conducted a phase III trial that compared palliative CCRT to chemotherapy alone [16]. Treatment consisted of chemotherapy of carboplatin/vinorelbine and radiotherapy of 42 Gy/15 fractions; 2-year OS rates were 27.7% and 7.4% in the palliative CCRT and chemotherapy-alone groups, respectively, showing a significant difference between the groups. Nawrocki *et al.* also conducted a randomized phase II trial [17]. Treatment consisted of chemotherapy with cisplatin/vinorelbine and radiotherapy of 30 Gy/10 fractions; 2-year OS rates were 24% and 6% in the palliative CCRT and chemotherapy-alone groups, respectively, indicating a significant difference. Palliative CCRT is a meaningful treatment for the palliation of symptoms and the prolongation of survival. To the best of our knowledge, our report is the first to show that palliative CCRT with cisplatin/docetaxel resulted in a 2-year OS rate of 14.3%, slightly lower than those shown in previous studies. Our study is retrospective and included a small number of cases, which may have caused this difference. Sundstrøm *et al.* conducted a phase III study comparing three groups of radiotherapy regimens: the 3-year OS rate tended to be better in the 42 Gy/15 and 50 Gy/25 fraction groups than in the 17 Gy/2 fraction group, according to the subgroup analyses of stage III patients with good performance status [18]. Further evidence on the total dose and fractions for palliative CCRT for prolonging prognosis is needed. Patients in the definitive CCRT group who received palliative CCRT had a 2-year survival rate of 14.3%, higher than the 7.4% 2-year survival rate of the chemotherapy-alone group in the study conducted by Strøm *et al.* [16]. Palliative CCRT with cisplatin/docetaxel seems to be a more frequently recommended

Table 3 Characteristics of patients who were considered for definitive CCRT

		Definitive CCRT (n=48)	Palliative CCRT (n=7)
Age (years)	Median (range)	62 (35–84)	60 (49–72)
Sex	Male	43	6
	Female	5	1
T stage	1	7	1
	2	9	3
	3	4	0
	4	25	3
	x	3	0
N stage	0	1	2
	1	6	0
	2	19	5
	3	22	0
Clinical stage	IIIA	8	1
	IIIB	40	6
Histology	Adenocarcinoma	16	2
	Squamous cell carcinoma	28	2
	Adenosquamous carcinoma	0	1
	Non-small cell carcinoma	4	2
Lobe †	Upper	36	5
	Lower	10	2
Laterality †	Right	26	6
	Left	20	1
Smoking history †	Never	1	1
	Former	21	1
	Current	25	4
FEV1 (l) †	Median (range)	2.34 (0.48–4.11)	2.28 (2.17–2.49)
ECOG-PS †	0	18	1
	1	29	6
Radiation dose (Gy)	Median (range)	60 (54–60)	44 (40–46)

CCRT, concurrent chemoradiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; FEV1, forced expiratory volume in 1 sec.
† These factors have missing values.

treatment than chemotherapy alone, although there are no data comparing the use of the two treatments at our institution. In recent years, molecular targeted drugs and immune checkpoint inhibitors have dramatically improved treatment outcomes of advanced NSCLC [19, 20]. In case a patient with stage III NSCLC is not suitable for surgery and definitive CCRT, the attending physician may have difficulty in determining the treatment. Hence, our study could assist in the choice of the best treatment strategy.

Radiation can activate immune-related signals [21], and the addition of durvalumab after definitive CCRT can prolong OS in stage III lung cancer [22]. Improved prognosis may be expected if an immune checkpoint inhibitor is administered. Levy *et al.* treated patients with palliative radiotherapy and durvalumab [23]; however, further studies are needed to address this issue.

This study has some limitations. It was a retrospective analysis and included a small number of patients. Because palliative CCRT was not performed to control symptoms, symptomatic relief was not evaluated. Palliative CCRT was associated with worse outcomes than in ideal treatments; this result represents the tumor factor in addition to the treatment factor. This study included a palliative CCRT patient group that completed CCRT as a preoperative treatment but did not undergo surgery, and another palliative CCRT patient group that was considered for definitive CCRT but did not receive a definitive dose. Since the palliative CCRT patient group that completed CCRT as a preoperative treatment was not operated upon, mainly

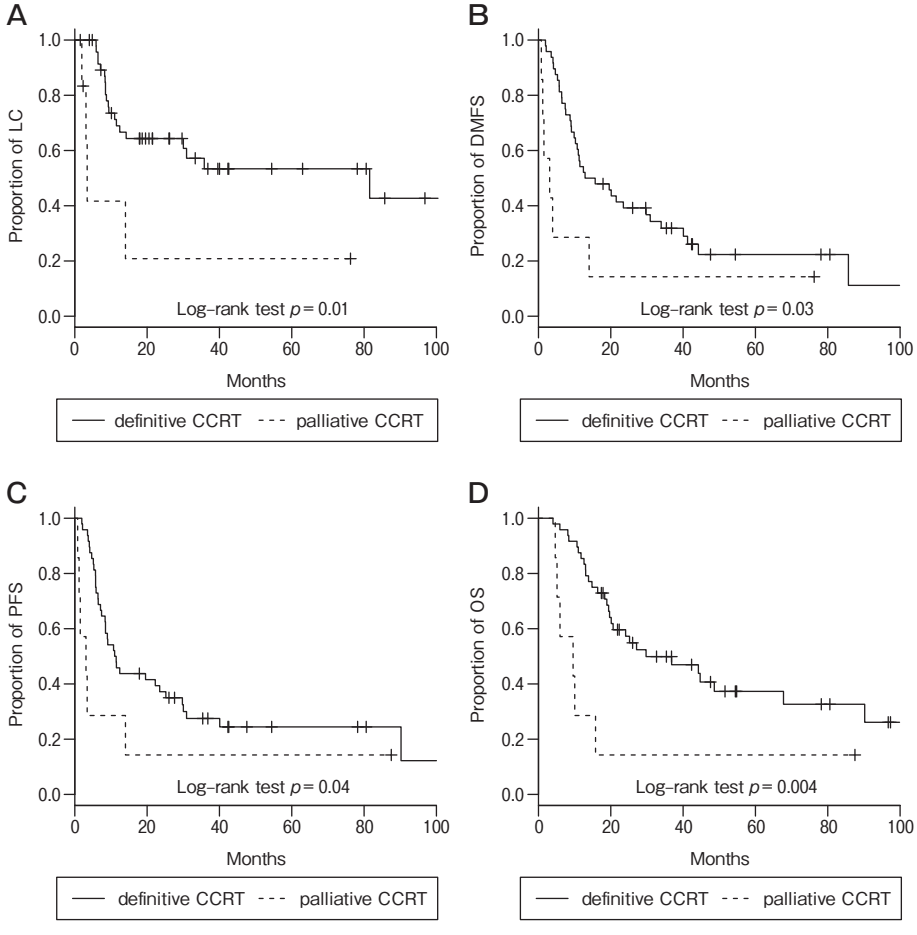

Fig. 3 Kaplan—Meier curves for definitive CCRT (n = 49) and palliative CCRT (n = 7). (**A**) Local control; (**B**) distant metastasis-free survival; (**C**) progression-free survival; (**D**) overall survival. CCRT, concurrent chemoradiotherapy.

because of the appearance of distant metastases, it is not surprising that the DMFS and PFS of this group were lower than those of patient group that underwent surgery. This retrospective study has these two biases and thus its results should be interpreted with caution.

In conclusion, the clinical outcomes of palliative CCRT were significantly inferior to those of the ideal treatments, although there were some long-term survivors. Therefore, careful determination of the appropriate treatment indication and further studies are warranted.

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