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Safety and efficacy of concurrent carboplatin or cetuximab plus radiotherapy for locally advanced head and neck cancer patients ineligible for treatment with cisplatin

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Abstract

Background: Locally advanced squamous cell carcinoma of the head and neck (LASCCHN) is usually treated with cisplatin (CDDP)-based chemoradiotherapy, except when patients are elderly or have renal, cardiac, or neurogenic dysfunction. This study compared the safety and efficacy of concurrent carboplatin (CBDCA) to cetuximab (Cmab) plus radiotherapy (RT) in patients ineligible for CDDP treatment.

Methods: We retrospectively analyzed LASCCHN patients who received CBDCA plus RT (n=29) or Cmab plus RT (n=18) due to ineligibility for CDDP treatment at two Japanese institutions between August 2006 and December 2015.

Results: Patients characteristics for CBDCA plus RT and Cmab plus RT were: median age, 74 and 75 years; 0-1 performance status, 90% and 100%; main primary tumor site, hypopharynx 52% (n=15) and oropharynx 39% (n=7); and stage IV, 90% (n=26) and 50% (n=9), respectively. With a median follow-up time of 60.0 months for CBDCA plus RT and 53.6 months for Cmab plus RT,3-year loco-regional control rates was 56% versus 58%, and median progression free survival was 42.7 versus 11.6 months. CBDCA plus RT was associated with more grade 3/4 hematologic toxicities, including neutropenia and thrombocytopenia, whereas Cmab plus RT was associated with more grade 3/4 oral mucositis and radiation dermatitis.

Conclusions: CBDCA or Cmab as a concurrent systemic therapy with RT is a possible treatment option for LASCCHN patients ineligible for CDDP treatment, although attention to hematological toxicity should be paid.

Key words: head and neck cancer, carboplatin, cetuximab, chemoradiotherapy

Introduction

Cisplatin (CDDP)-based chemoradiotherapy (CRT) conferred a survival benefit over radiotherapy (RT) alone in a randomized phase III trial for patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) [1]. However, because common toxicities associated with CDDP administration—including nausea and vomiting, renal insufficiency, ototoxicity, peripheral neuropathy and cardiac overload due to large volume infusion—may cause serious adverse events for patients who are elderly or have cardiac, renal, or neurogenic dysfunction, RT alone is often still selected for LASCCHN patients despite its unfavorable outcome for them (complete response [CR] rate, 22-29%; 3-year survival, 7-45%) [1-5]. To achieve better therapeutic outcomes for these patients, RT plus a systemic chemotherapy other than CDDP is needed. To date, however, no prospective studies have evaluated alternative treatments for LASCCHN patients in whom CDDP is contraindicated.

Compared with CDDP, carboplatin (CBDCA) and cetuximab (Cmab) have lower gastrointestinal- , nephro- , and neuro-toxicity [6] and they have been concurrently used with RT for LASCCHN patients as an alternative to CDDP. Recently, in a retrospective analysis of the safety and efficacy of CBDCA plus RT for 25 consecutive LASCCHN patients who were ineligible for CDDP treatment [7], we reported a median progression-free survival (PFS) of 42.7 months, and all patients received the planned radiation dose

of 70 Gy. It is not clear, however, whether Cmab plus RT is safe and effective for LASCCHN patients ineligible for CDDP treatment or which of the two alternatives is more appropriate for them.

In this retrospective study, we analyzed the efficacy and feasibility of CBDCA or Cmab plus RT for LASCCHN patients ineligible for CDDP treatment at two institutions, by comparing most of the cohort that received CBDCA plus RT in addition to our previous study [7] with a new cohort that received Cmab plus RT.

Patients and Methods

Patients

This study involved patients with head and neck squamous cell carcinoma stage III or IV (Union for International Cancer Control Tumor, Node, Metastasis classification, 7th Edition) who were treated with CBDCA or Cmab plus RT at Shizuoka Cancer Center and Hokkaido University Hospital between August 2006 and December 2015. This study selected the patients who did not satisfy the inclusion criteria for JCOG studies [8,9] for LASCCHN. The inclusion criteria were as follows: (1) pathologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; (2) ineligibility for CDDP treatment because of the presence of ≥ 1 of the factors of age >76 years, renal impairment (creatinine clearance [CCr]<60 mL/min), cardiac

dysfunction (history of unstable angina pectoris, myocardial infarction, or chronic heart failure), neurologic impairment (peripheral neuropathy or hearing impairment),or performance status (PS) 2; (3) no distant metastatic disease; (4) no active concomitant malignancy and (5) no prior RT or surgery. The present study also included the additional criterion of no prior induction chemotherapy (ICT). The study protocol was approved by the institutional review committee of Shizuoka Cancer Center (Shizuoka, Japan) and Hokkaido University Hospital (Hokkaido, Japan), met the standards set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients in this study and we informed the contents of this study with opt-out policy.

Treatment

Patients received concurrent CBDCA or Cmab administration with conventionally fractionated RT. CBDCA was administered tri-weekly(area under the curve [AUC], 4–6 on days 1, 22, and 43) [10] or once weekly (AUC, 1.5–2 on days 1, 8, 15, 22, 29, 36, and 43) [11,12] at their physician's discretion. Cmab was delivered as a loading dose of 400 mg/m^2 at 1 week before the start of RT, followed by weekly infusions of 250 mg/m^2 during RT (days 1, 8, 15, 22, 29, 36, and 43). The planned total radiation dose was 70 Gy (2 Gy per day, 5 days per week). Three dimensional conformal RT was delivered

through a linear accelerator with a 6-MV X-ray. Patients with resectable residual disease underwent salvage surgery.

Evaluation

All clinical data were retrospectively obtained from medical records. Pretreatment evaluations included medical history, physical examination, laboratory tests, endoscopy, CT, MRI, and [18F]-fluorodeoxyglucose positron-emission tomography/CT fusion imaging. Disease assessment was performed by CT or MRI at 6-8 weeks after completing RT or when clinical signs suggested progressive disease (PD). Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Loco-regional control survival (LRCS) was calculated from the first day of RT until either disease relapse, PD at the primary site and within the radiation fields (therapeutic neck dissections allowed), death from any cause, or censored at the last follow-up visit. Loco-regional control rates (LRCR) were estimated by the Kaplan-Meier method. PFS was calculated from the first day of RT until disease relapse, PD, death from any cause, or censored at the last follow-up visit. Overall survival (OS) was calculated from the

first day of RT until death from any cause or censored at the last follow-up visit. Survival was analyzed using the Kaplan–Meier method. Statistical significance was set at $p<0.05$.

Results

Patient characteristics

During the study period, 51 LASCCHN patients who were ineligible for CDDP treatment received CBDCA (n=32) or Cmab (n=19) plus RT at two Japanese institutions (Shizuoka Cancer Center and Hokkaido University Hospital). Three patients treated with CBDCA and one patient with Cmab were excluded from this study because of prior ICT and associated with advanced esophageal cancer, respectively. This left 47 patients for analysis: 29 who received CBDCA plus RT (23 from in our previous study [7]) and 18 who received Cmab plus RT.

Table 1 shows patient characteristics at baseline according to the treatment received. Median age was 74 years for the CBDCA plus RT group and 75 years for the Cmab plus RT group (p=0.97). In the CBDCA plus RT and Cmab plus RT groups, the main primary tumor sites were the hypopharynx (52%) and oropharynx (39%), and the proportion of stage IV cases was 90% and 50% (p=0.0048), respectively. Except for five patients who received weekly CBDCA plus RT, all other patients in the CBDCA plus RT group received tri-weekly treatment.

As shown in Table 2, the main reason for choosing CBDCA plus RT or Cmab plus RT was renal impairment (median CCr of 21 patients: 48 mL/min), followed by advanced age (median age of 17 patients of advanced age: 78 years).

Treatment compliance

Forty two of 47 patients (89%) in this study received the planned total radiation dose of 70Gy. The median duration of RT in the CBDCA plus RT and Cmab plus RT groups was 50 days (range, 46-70 days) and 51 days (range, 42-63 days).A discontinuation in RT occurred in 1 patient in the CBDCA plus RT group (pneumonia) and 4 patients in the Cmab plus RT group (2 pneumonia, 1 skin infection, and 1 family affairs). An unplanned break in RT occurred for 4 patients in the CBDCA plus RT group (2 febrile neutropenia, 1 pneumonia, and 1 sepsis) and in 1 patient in the Cmab plus RT group (radiation dermatitis). Fourteen patients (48%) discontinued CBDCA (3 thrombocytopenia, 3 neutropenia, 2 febrile neutropenia, 2 pneumonia and 1 each for fatigue, oral mucositis, herpes zoster, and delirium) and 6 patients (33%) discontinued Cmab (2 neutropenia, 1 radiation dermatitis, 1 fatigue, 1 skin infection, and 1 family affairs). In terms of dose reductions, 1 patient required dose reduction in the CBDCA plus RT group, starting from the second course due to thrombocytopenia; none of the patients in the Cmab plus RT group required dose reduction.

Patterns of relapse

In the CBDCA plus RT group, there were 10 patients (35%) who had locoregional (n=7) and distant tumor failure (n=3, 2 lung and 1 pituitary gland). Of the 7 patients with locoregional failure, salvage neck dissection was performed for 1 patient.

In the Cmab plus RT group, there were 8 patients (44%) who had locoregional (n=4) and distant tumor failure (n=4, 3 lung and 1 liver). Of the 4 patients with locoregional failure, salvage neck dissection was performed for 3 patients.

Survival

Median follow-up time was 60.0 months (range, 13.2-94.2 months) in the CBDCA plus RT group and 53.6 months (range, 25.5-62.5 month) in the Cmab plus RT group. The CBDCA plus RT group showed a trend toward better survival over the Cmab plus RT group with regards to median PFS (42.7 versus 11.6 months, HR [hazard ratio] 0.74; 95%CI 0.63-2.89; p=0.44) and median OS (91.9 months versus 35.5 months; HR0.69; 95%CI 0.63-3.37; p=0.38) (Figs.2, 3). There was no difference in 3-year LRCR between the CBDCA plus RT and Cmab plus RT groups (56% versus 58%) (Fig.1). As of July 2018, cause of death in 12 patients in the CBDCA plus RT group was PD (n=7), pneumonia (n=3), or aspiration (n=2) and in the11 patients in the Cmab plus RT group

was PD (n=6), pneumonia (n=2), aspiration (n=1), lung cancer (n=1), or sudden death (n=1).

Toxicity

Table 3 shows the worst grade of toxicities observed during CBDCA or Cmab plus RT. Grade 3/4 hematologic toxicities occurred in the CBDCA plus RT group (34% neutropenia, 28% anemia, and 28% thrombocytopenia), but not in the Cmab plus RT group except for 1 patient of anemia. Grade 3 non-hematologic toxicities in the CBDCA plus RT group were oral mucositis (55%), infection (17%), and febrile neutropenia (10%) and in the Cmab plus RT group were oral mucositis (78%) and radiation dermatitis (50%). No grade 4 non-hematologic toxicities were observed in either group. Two patients (8%) in the CBDCA plus RT died within 30 days of completing RT or CBDCA administration: 1 patient died of acute bacterial pneumonia 2 days after RT completion and the remaining patient died of bleeding from a primary lesion 5 days after RT completion.

Discussion

The concurrent use of CBDCA or Cmab with RT is conventionally used for LASCCHN patients who may be ineligible for CDDP due to its toxicity. However, it is

not clear whether these treatments are safe and effective because no prospective trials investigating these treatments has been conducted in this patient population. Indeed, no retrospective studies aside from our prior study on CBDCA plus RT in these patients have been conducted [7]. We demonstrated in our previous study a median PFS of 42.7 months, where all patients received the planned total radiation dose of 70 Gy [7]. These results suggested favorable adherence and efficacy of CBDCA plus RT. The present study is the first to report on the safety and efficacy of CBDCA plus RT compared with Cmab plus RT and to try to clarify which treatment is more appropriate for LASCCHN patients ineligible for CDDP treatment.

Because there is no specific consensus on the ineligibility criteria for using (high-dose) CDDP treatment, we determined ineligibility based on the toxicity of CDDP and on the inclusion and exclusion criteria of clinical trials using CDDP for head and neck cancer. In the present study, even though all patients in both treatment groups were considered ineligible for CDDP treatment according to CDDP toxicity and these criteria, most of them were able to receive the total planned dose of 70 Gy. The profiles of adverse events were different between CBDCA plus RT and Cmab plus RT. There was a higher incidence of grade 3/4 skin toxicity and oral mucositis with Cmab plus RT than with CBDCA plus RT (50% versus 7% and 78% versus 55%, respectively), but more frequent grade 3/4 hematologic toxicity, especially neutropenia and thrombocytopenia,

with CBDCA plus RT than with Cmab plus RT (34% versus 0% and 28% versus 0%, respectively). As to efficacy, CBDCA plus RT seemed to be more effective than Cmab plus RT—42.7 months versus 11.6 months for PFS and 91.9 months versus 35.5 months for OS. Regarding the patient backgrounds in both groups, patients in CBDCA plus RT had a higher occurrence of stage IV cancer (90% versus 50%) and more unresectable disease (28% versus 6%) than Cmab plus RT group. On the other hand, the proportion of oropharyngeal cancer was almost same (38% vs 39%), although HPV test were not performed in majority of oropharyngeal cancer patients. Therefore, we suppose the difference in the efficacy between two regimens may be attributed to the difference in antitumor effect between platinum-based anticancer drug and anti EGFR antibody for this population rather than the difference in the background factors.

For patients ineligible for treatment with high dose CDDP, RT alone or reduced dose of CDDP plus RT might be alternative treatment regimens. However, there are several reasons why we focused on CBDCA plus RT and cetuximab plus RT for these patients. There are consensus that RT alone is less effective than platinum-based CRT [13]. Furthermore, patients receiving cumulative dose of < 200 mg/m2 had significantly worse outcome than those receiving > 200 mg/m2 [14]. Therefore, we excluded the patients who received RT alone or reduced dose of CDDP plus RT. On the other hand, Bonner trial demonstrated that the efficacy of Cmab plus RT was superior to RT alone

[5]. Cmab plus RT has been increasingly used for elderly patients or those with comorbidity in clinical practice [15]. Furthermore, our previous retrospective study revealed that CBDCA plus RT was safe and effective for patients ineligible for treatment with CDDP according to the same criteria as this study [7]. Based on these findings, the use of sufficient amount of CBDCA or Cmab as a radiosensitizer seemed to be more appropriate treatment for this population rather than RT alone or reduced dose of CDDP plus RT.

Cmab plus RT is generally considered more appropriate for LASCCHN patients than CBDCA plus RT due to the strong evidence demonstrated by Bonner's study [5]. However, in another study, Cmab plus RT led to a greater number of cases of grade 3/4 skin toxicity compared with RT alone (35.1% versus 21.2%; $p<0.05$) [16], while there were few cases of nausea, vomiting, renal dysfunction, and neuro- or ototoxicity. Other studies also reported grade 3/4 radiation dermatitis in >30% of patients treated with Cmab plus RT [17-19]. In addition, there was a higher incidence of severe skin reaction caused by Cmab in an Asian cohort compared with a Western cohort [20]. In a study by Yokota et al. [21], Cmab plus RT caused severe oral mucositis with distinctive features. Indeed, most patients receiving Cmab plus RT needed feeding tube support due to severe mucositis, and some patients progressed to complete hypopharyngeal atresia requiring surgical treatment. In other severe adverse events caused by Cmab plus RT, Kurokawa

et al. reported gastrointestinal bleeding requiring endoscopic hemostasis and drug-induced interstitial pneumonitis requiring steroid pulse therapy [22]. Compared with hematologic toxicity, these non-hematologic toxicities caused by Cmab plus RT tend to reduce quality of life and require time for symptom improvement. On the other hand, as indicated in our results, hematologic toxicity and its associated infection caused by CBDCA often leads to CBDCA discontinuation or dose reduction and unplanned breaks in RT. A previous study reported a significant relationship between the AUC dose of CBDCA and the likelihood of thrombocytopenia and leukopenia [23]. This finding suggests that low-dose weekly CBDCA plus RT may reduce the risk of myelotoxicity, which would be in line with the results of prospective studies reporting lower grade 3/4 myelotoxicity of weekly CBDCA plus RT than tri-weekly CBDCA plus RT (10% versus 18% for leukopenia and 8% versus 27% for thrombocytopenia, respectively) [11,10].

Because Cmab plus RT and tri-weekly CDDP plus RT have never been prospectively compared in a randomized Phase III study, it is unclear whether Cmab plus RT is as effective as CDDP plus RT. In a retrospective meta-analysis comparing platinum-based CRT with Cmab plus RT for LASCCHN patients, survival— specifically, locoregional control at 2 years, disease free survival, and OS—was significantly better with CRT [24]. In a randomized phase II study comparing weekly CDDP plus RT with Cmab plus RT in LASCCHN patients, Cmab plus RT tended to have a worse outcome

than weekly CDDP plus RT with respect to locoregional control at 2 years (80% versus 53%, respectively; p=0.073) [25]. Taken together, these findings suggest that Cmab plus RT is less effective than CDDP plus RT.

As for the efficacy of CBDCA plus RT for LASCCHN patients, a randomized three-arm phase III study comparing tri-weekly CDDP plus RT, tri-weekly CBDCA plus RT (AUC=7), and RT alone (total dose 70 Gy) [10] showed significantly prolonged survival at 3 years with CDDP or CBDCA-based CRT compared with RT alone (52%, 42%, and 17.5%, respectively; $p<0.001$). Furthermore, a prospective randomized study involving patients with locally advanced nasopharyngeal carcinoma showed similar efficacy between weekly CBDCA (100 mg/m^2) plus RT and tri-weekly CDDP plus RT[11]. Additionally, meta-analysis comparing CDDP-based to CBDCA-based chemotherapy for advanced head and neck cancer showed no significant difference in OS and LRCS at 3 years [26]. Although the first two randomized trials are small underpowered and careful interpretation is needed, these findings may suggest that the efficacy of CBDCA plus RT is comparable with that of CDDP plus RT.

These reports may provide indirect support for our finding that CBDCA plus RT is at least equally or more effective than Cmab plus RT in terms of LRCR and PFS. Furthermore, radiation dermatitis within the irradiated fields that is induced by CBDCA plus RT is less severe than that induced by Cmab plus RT. Therefore, CBDCA plus RT

appears to be more appropriate for LASCCHN patients with skin disease when they are ineligible for CDDP treatment. However, because CBDCA often causes severe myelotoxicity and results in infection, it may not be appropriate to use in patients with myelosuppression.

This study has some limitations. First, this study was conducted retrospectively at 2 institutions with a small number of patients and there were differences in patient characteristics including primary site and disease stage between the patients. Second, we cannot deny the possibility of patients' selection bias. However, the strengths of this study is the safety and efficacy of CBDCA plus RT versus Cmab plus RT for LASCCHN patients who are ineligible for CDDP treatment.

In conclusion, CBDCA or Cmab as a concurrent systemic therapy with RT is a possible treatment option for LASCCHN patients ineligible for CDDP treatment, although attention to hematological toxicity should be paid. It is necessary to select which treatment to use according to its toxicity profile. Our findings should be confirmed with a prospective investigation.

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Conflict of interest statement:

The authors declare no conflicts of interest associated with this manuscript.

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Table 1 Patient characteristics

		CBDCA plus RT (n=29)	Cmab plus RT (n=18)	p-value*
Sex				0.36
	Male	27	15	
	Female	2	3	
Median age, years (range)		74 (54-82)	75 (56-83)	0.97
PS (ECOG)				0.28
	0,1	26	18	
	2	3	0	
Primary site				0.02
	Oropharynx	11	7	
	Hypopharynx	15	5	
	Larynx	1	6	
	Oral cavity	2	0	
T stage				0.02
	T1	2	0	
	T2	8	5	
	T3	5	10	
	T4	14	3	
N stage				0.04
	N0	5	6	
	N1	1	4	
	N2	22	8	

N3	1	0	
Disease stage			0.0048
III	3	9	
IV	26	9	
Resectability[†]			0.12
Resectable	21	17	
Unresectable	8	1	
Smoking history			0.23
≥10 pack-years	26	13	
<10 pack-years	3	5	
Creatinine clearance,mL/min [median (range)] [‡]	62 (38-117)	62 (33-96)	0.97

*All p-values were obtained using Fisher's exact test except for median age and creatinine clearance, which were calculated using Wilcoxon's rank sum test.

[†]A multidisciplinary tumor board decided on tumor resectability.

[‡]Creatinine clearance was calculated according to the Cockcroft-Gault equation.

CBDCA, carboplatin; Cmab, cetuximab; ECOG, Eastern Cooperative Oncology Group; PS, performance status; RT, radiotherapy; SCC, squamous cell carcinoma

Table 2 Main reason for choosing CBDCA or Cmab plus RT

	CBDCA plus RT* (n=29)	Cmab plus RT (n=18)
	n (%)	n (%)
Renal impairment	13 (45)	8 (44)
Age ≥ 76 years	10 (35)	7 (39)
Cardiac dysfunction	6 (21)	4 (22)
PS 2	3 (10)	0 (0)
Neurologic impairment	2 (7)	3 (17)

* Partially duplicated data

CBDCA, carboplatin; Cmab, cetuximab; PS, performance status; RT, radiotherapy

Table 3 Summary of toxicity during CBDCA or Cmab plus RT

	CBDCA plus RT (n=29)				Cmab plus RT (n=18)			
	All grades		≥ Grade 3		All grades		≥ Grade 3	
	n	(%)	n	(%)	n	(%)	n	(%)
Hematologic toxicity								
Neutrophil count decreased	23	79	10	34	2	11	0	0
Anemia	28	97	8	28	8	44	1	6
Platelet count decreased	23	82	8	28	2	11	0	0
Non-hematologic toxicity								
Mucositis oral	29	100	16	55	18	100	14	78
Anorexia	20	69	2	7	15	83	4	22
Nausea	7	24	0	0	3	17	0	0
Vomiting	3	10	0	0	1	6	0	0
Fatigue	21	72	0	0	10	56	0	0

Radiation dermatitis	29	100	2	7	18	100	9	50
Dry mouth	28	97	0	0	16	89	0	0
Dysgeusia	20	69	-	-	16	89	-	-
Dysphagia	19	66	3	10	14	78	6	33
Hearing impaired	1	3	0	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	0	0
Infection	5	17	5	17	4	22	4	22
Febrile Neutropenia	3	10	3	10	0	0	0	0
AST increase	15	52	0	0	7	39	0	0
ALT increase	15	52	1	3	7	39	0	0
Creatinine increase	11	38	0	0	1	6	0	0
Acneiform rash	0	0	0	0	18	100	1	6
Paronychia	0	0	0	0	6	33	0	0

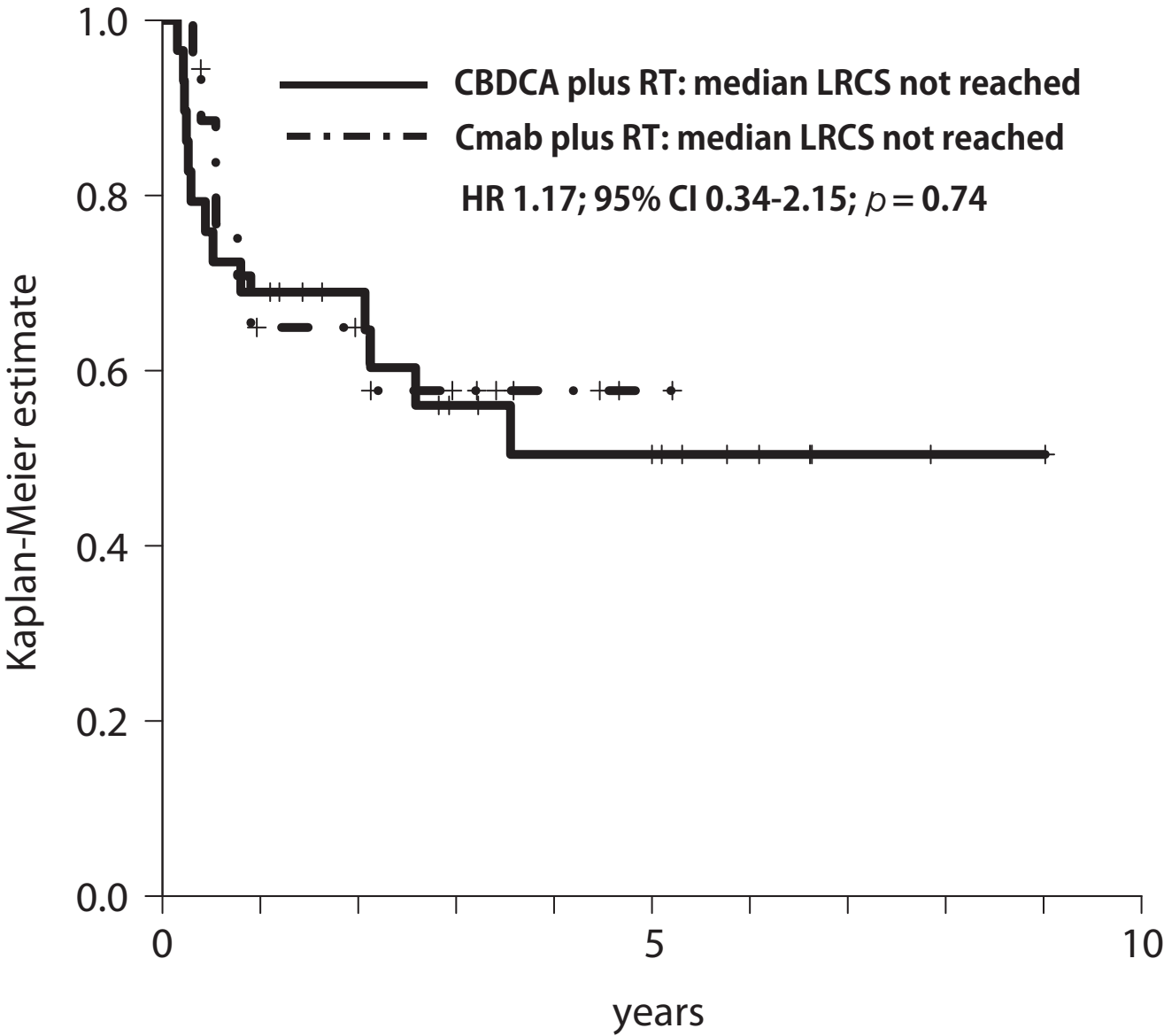
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBDCA, carboplatin; Cmab, cetuximab; RT, radiotherapy

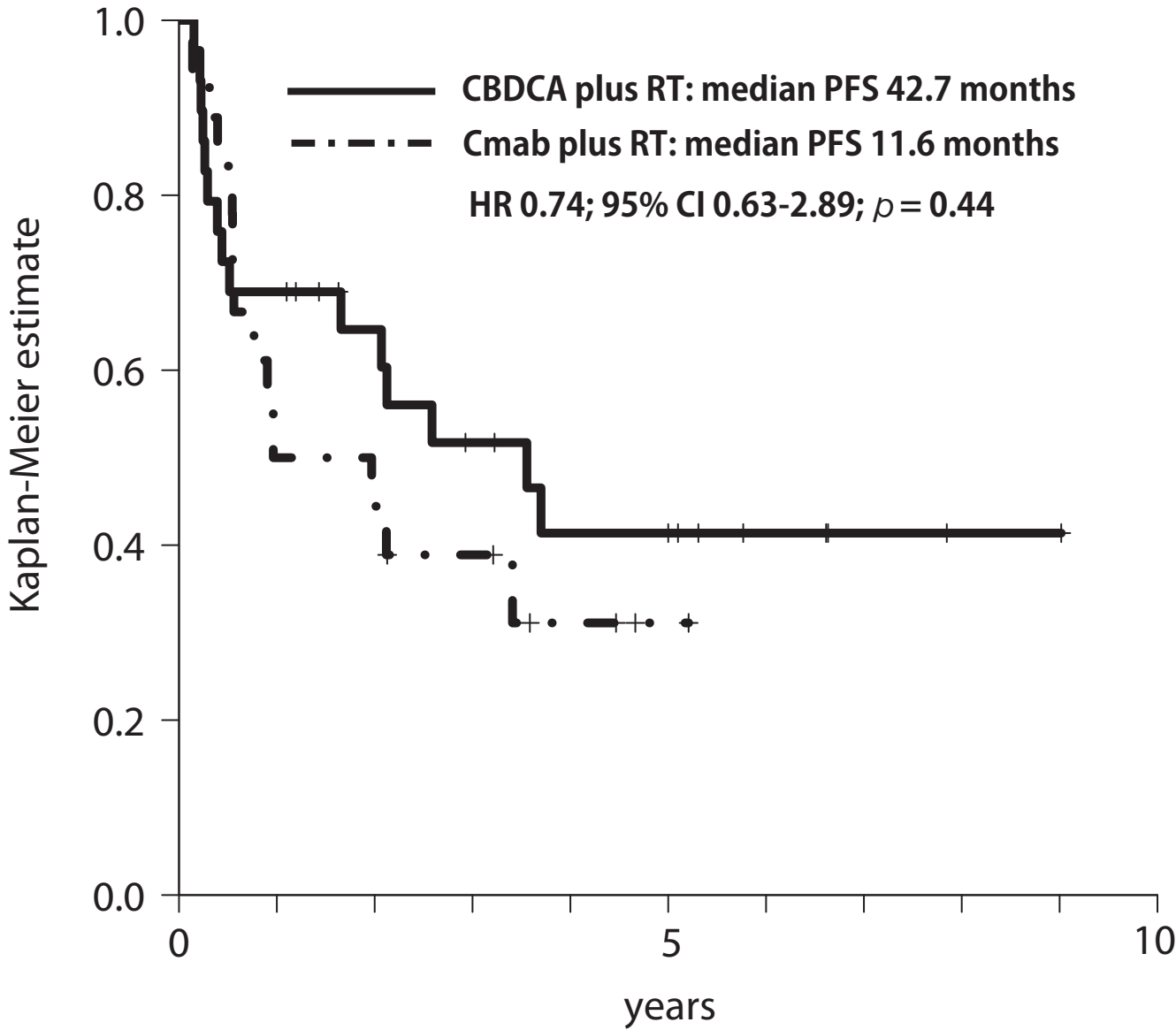
Figure captions

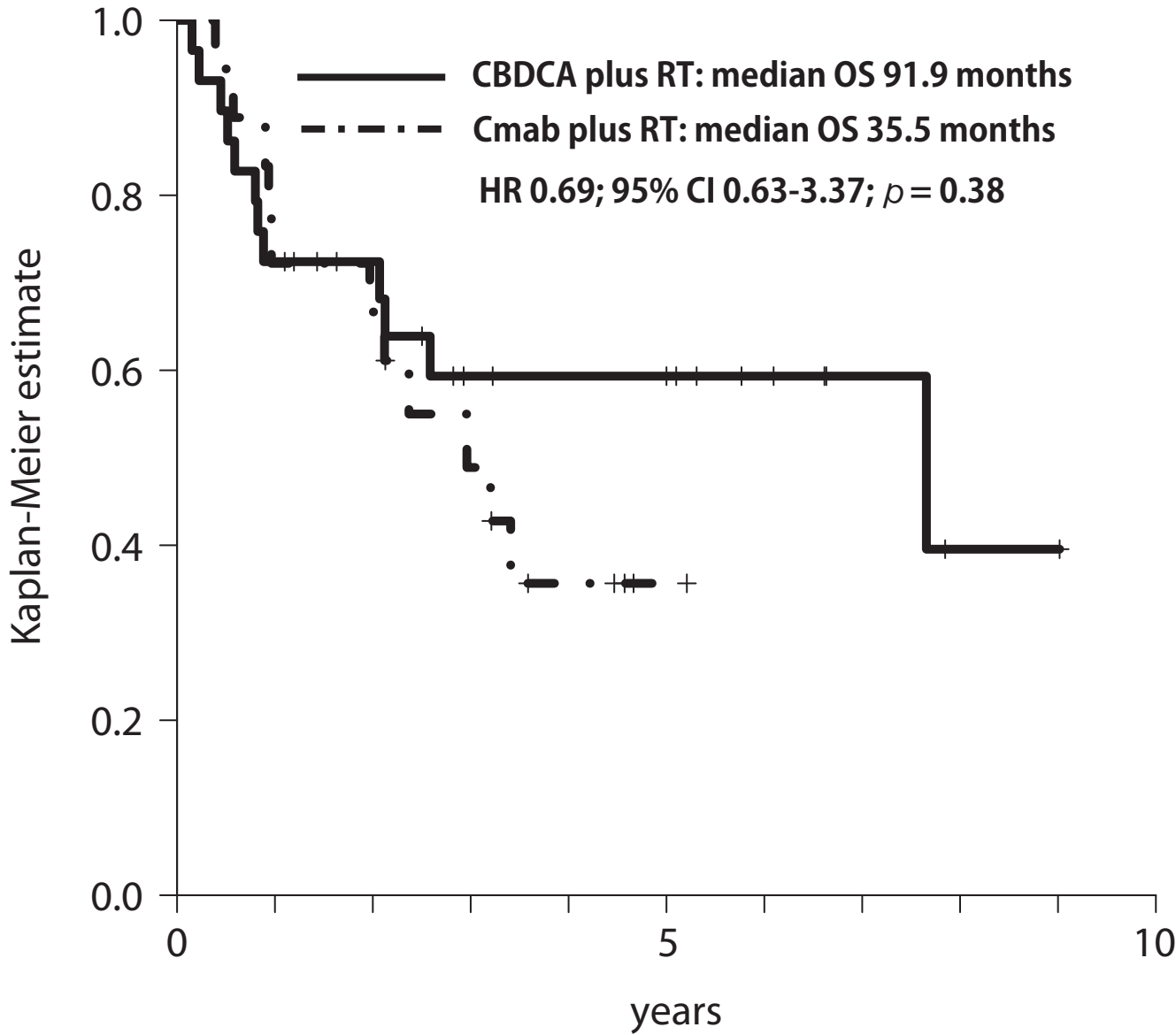
Fig. 1 Kaplan–Meier plot showing loco-regional control survival with carboplatin (CBDCA) plus radiation therapy (RT) (n=29) and cetuximab (Cmab) plus RT (n=18)

Fig. 2 Kaplan–Meier plot showing progression-free survival with CBDCA plus RT (n=29) and Cmab plus RT (n=18)

Fig. 3 Kaplan–Meier plot showing overall survival with CBDCA plus RT (n=29) and Cmab plus RT (n=18)


CBDCA plus RT: median LRCS not reached
Cmab plus RT: median LRCS not reached
HR 1.17; 95% CI 0.34-2.15; p = 0.74
Kaplan-Meier estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
years


1.0
0.8
0.6
0.4
0.2
0.0
Kaplan-Meier estimate
CBDCA plus RT: median PFS 42.7 months
Cmab plus RT: median PFS 11.6 months
HR 0.74; 95% CI 0.63-2.89; p = 0.44
0
5
10
years


CBDCA plus RT: median OS 91.9 months
Cmab plus RT: median OS 35.5 months
HR 0.69; 95% CI 0.63-3.37; p = 0.38
Kaplan-Meier estimate
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
years