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ORIGINAL SCIENTIFIC REPORT

The Benefits of Docetaxel Plus Cisplatin and 5-Fluorouracil Induction Therapy in Conversion to Curative Treatment for Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Background Definitive chemoradiotherapy (CRT), used for treatment of patients with an initial diagnosis of unresectable locally advanced esophageal cancer, has led to unsatisfactory long-term prognosis. Moreover, CRT can lead to esophageal fistula, perforation, and strictures. Therefore, strong induction chemotherapeutic treatments are necessary to reduce the tumor volume for subsequent radical esophagectomy. This study aimed to determine the oncological utility of docetaxel plus cisplatin and 5-fluorouracil (DCF) and the technical feasibility of subsequent esophagectomy for locally advanced esophageal cancer.

Methods Eighty-seven patients with clinical borderline unresectable T3 and T4 esophageal squamous cell carcinoma without distant metastases were included in this study. There were 44 patients in primary DCF group and 43 patients in definitive CRT group, and perioperative and long-term oncological outcomes were compared between the two groups.

Results Twenty-two patients (50%) achieved R0 resection in the DCF group. Albeit not significant, the rate of curative treatment was higher in the DCF group than the definitive CRT group ($p = 0.099$). The overall survival (OS) and progression-free survival (PFS) were better with DCF than with definitive CRT (median OS, 29 vs. 17 months, $p = 0.206$; median PFS, 10 vs. 6 months, $p = 0.020$). Specifically, the OS of patients with a Charlson score of less than 3 among the DCF-treated patients tended to be better than those among the definitive CRT-treated patients.

Conclusion DCF and subsequent esophagectomy achieved R0 resection in 50% of the patients and was associated with better long-term oncological outcomes in patients with initially unresectable esophageal cancer if their systemic status is acceptable.

Introduction

In the advance stages, esophageal cancer can easily penetrate the esophageal wall and directly invade the surrounding organs including trachea, bronchi, and aorta, due to the anatomical features of esophagus including the lack

Masashi Takeuchi and Hirofumi Kawakubo have contributed equally to this study.

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of serosa and the presence of numerous organs surrounding the esophagus. Therefore, the treatment of locally advanced T3 or T4 esophageal cancer is difficult, and its prognosis is unfavorable [1–4].

Despite the use of definitive chemoradiotherapy (CRT) in patients with initially unresectable locally advanced esophageal cancer, satisfactory long-term prognosis has not yet been achieved: the complete response rates are only 15–30%, and mean survival is less than 1 year. In patients who do not receive adequate response after definitive CRT, salvage surgery is performed for tumors that are considered resectable; however, postoperative mortality is high [5, 6]. Furthermore, especially in the locally advanced cancers, definitive CRT might result in both acute and late toxicities including esophageal fistula, perforation, and strictures [7–9]. These factors can affect not only the short-term outcomes but also the long-term quality of life. Theoretically, the long-term survival can be achieved by esophagectomy if the tumor can be completely removed at any T stage [10, 11]. Therefore, strong induction chemotherapy is necessary to reduce the tumor volume and enable resection and subsequent radical esophagectomy for complete removal of the residual tumor tissue.

A multicenter prospective phase II trial conducted by a Japanese study group has indicated the efficacy and safety of docetaxel plus cisplatin and 5-fluorouracil (DCF) induction chemotherapy with subsequent conversion esophagectomy for initially unresectable T3 or T4 esophageal cancer [12]. The study results indicated that DCF might be highly efficient in achieving high curative resection and survival rates and in reducing postoperative complications in subsequent esophagectomy; however, few studies demonstrated the superiority of multimodal treatment using DCF to definitive CRT for initially unresectable locally advanced esophageal cancer.

This study was designed to determine the oncological utility of DCF and the technical feasibility of subsequent esophagectomy for locally advanced esophageal cancer.

Materials and methods

Patients

This single-institution retrospective cohort study included 87 patients with clinical borderline unresectable T3, T4a, and T4b primary esophageal cancer without distant metastases who were referred to our division between 2010 and 2016. Patients with cM1 because of clinically determined supraclavicular and celiac lymph node (LN) metastases were considered to exhibit regional lymph node in the Japanese Classification of Esophageal Cancer [13], were eligible for inclusion in this study.

Until 2009, definitive CRT as primary treatment was administered to patients with borderline unresectable T3 or T4 thoracic esophageal squamous cell carcinoma. Commencing in 2010, DCF was administered to few of these patients based on the assessment of various oncological and physical factors. In general, patients with T4b esophageal cancer and obvious infiltration of multiple organs, those with low surgical tolerance, and/or who wished to preserve esophagus underwent definitive CRT ($n = 43$). Conversely, DCF was administered in patients with tumors that did not invade multiple organs and in those with sufficient surgical tolerance such as patients younger than 75 years of age and those with a Charlson score between 0 and 3 ($n = 44$; Fig. 1). Patients who underwent palliative therapy as primary treatment or best support care were excluded from this study.

In this study, the DCF therapy included 5-FU, docetaxel and cisplatin. Specifically, the patients were administered 70 mg/m^2 docetaxel and 70 mg/m^2 cisplatin on day 1 and 750 mg/m^2 5-FU on days 1–5, thrice weekly for two or three cycles. Computed tomography (CT) and positron emission tomography (PET) scan findings after two or three cycles were used to determine the tumor resectability. If the tumor was considered resectable, radical esophagectomy with two- or three-field LN dissection was performed. In patients with poor response to the induction treatment and unresectable tumor, additional CRT with a total radiation dose of 50–60 Gy was performed. After total irradiation, the tumor resectability was also re-evaluated by CT findings, and esophagectomy was performed for the resectable tumors.

For CRT, simulation was conducted based on the 3D-CRT techniques with a multibeam arrangement of four to five ports using a total irradiation dose of 50–60 Gy. Concurrent FP chemotherapy mostly comprised 5-FU and cisplatin (70 mg/m^2 cisplatin on day 1, 700 mg/m^2 5-FU on days 1–4 for two cycles). After two cycles, the patients without progressive disease underwent additional FP chemotherapy for two cycles. After total 2 cycles, esophagectomy was performed in patients with resectable tumors. Moreover, the patients with complete response to the treatment were considered to have completed the treatment and follow-ups. These patients as well as those with R0 resection after esophagectomy were considered to have achieved curative treatment; however, the patients with unresectable tumors, those with insufficient surgical tolerance, and those preferring esophageal preservation did not undergo surgical intervention (palliative group).

The hospital records were used to retrospectively retrieve the clinical characteristics of the patients including their age, sex, Eastern Cooperative Oncology Group performance status (PS) score, American Society of

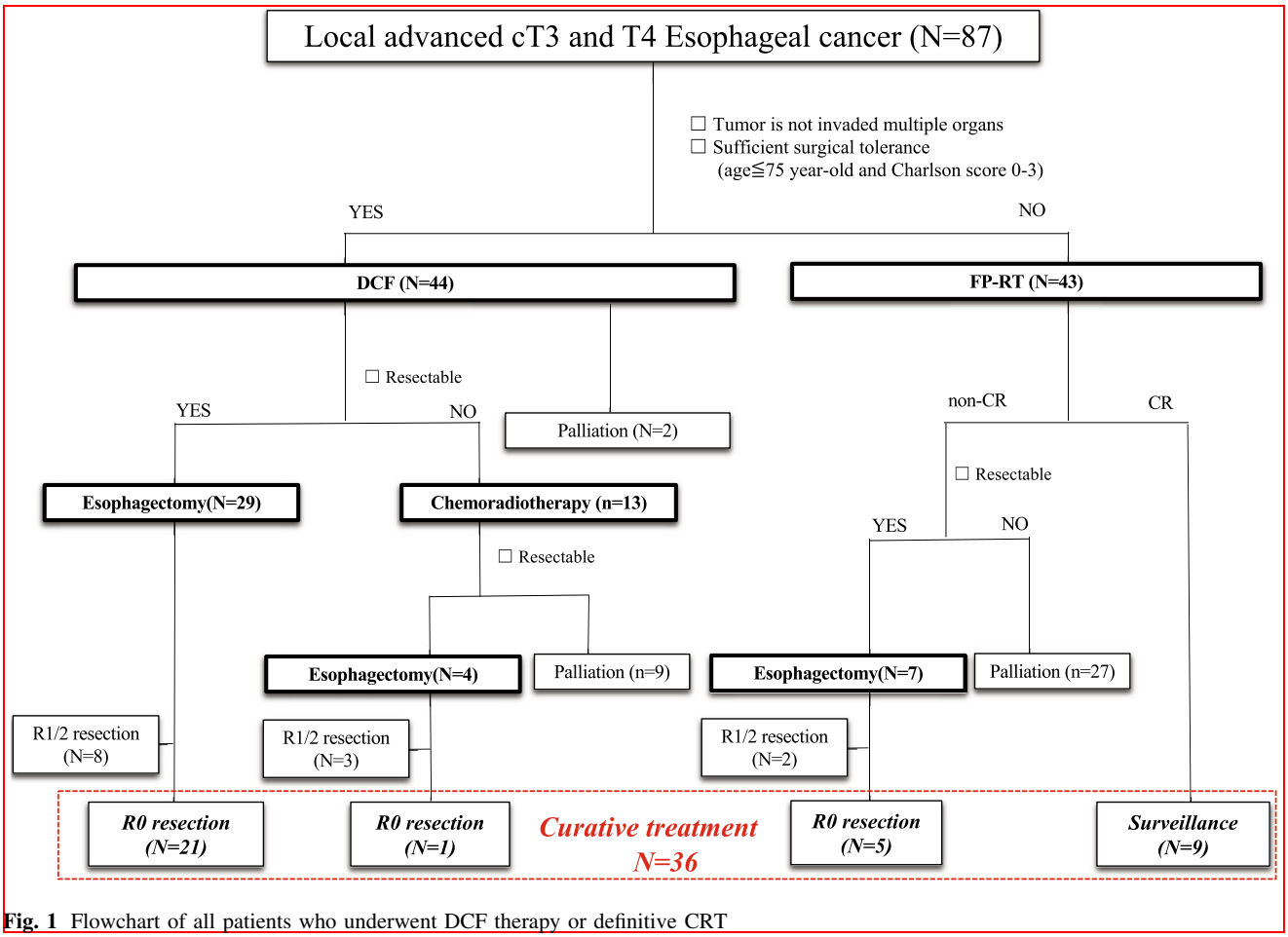

Fig. 1 Flowchart of all patients who underwent DCF therapy or definitive CRT

Anesthesiologists (ASA) classification score, and updated Charlson comorbidity index score [14]. The Charlson comorbidity index score, which comprises all 12 comorbidities, such as congestive heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, and HIV exhibited a good performance in discriminating the long-term outcomes including hospital mortality [14], oncological findings, and prognosis. Overall survival (OS) was defined as the time interval from the treatment initiation until death regardless of cause, and progression-free survival (PFS) was defined as the shortest time interval from the treatment initiation to progressive disease, disease recurrence, or death [13]. Clinical cancer stage was determined according to the Union Against Cancer, 7th edition [15]. Responses to the treatment were evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines [16]. The diagnosis of complete response (CR) based on CT scan, PET scan, and deep biopsy, and these results were confirmed in medical panel among the expert surgeons, oncologists, and radiotherapists. The histological efficacy of chemotherapy and/or radiotherapy were graded as follows: grade 0, no recognizable cytological or histological therapeutic effect; grade 1, viable cancer cells account more than 1/3 of tumor tissue; grade 2, viable cancer cells account less than 1/3 of tumor tissue; and grade 3, no viable cancer cells are evident [13]. Residual tumor status was classified as follows: pR0, no residual tumor; pR1, microscopic residual tumor; and pR2, macroscopic residual tumor [13]. According to pathologic criteria of college of American Pathologists, positive circumferential margin was assessed based on true margin involvement.

This study was conducted with the approval of the ethics committee of Keio University School of Medicine in accordance with the principals of the Declaration of Helsinki.

Diagnosis of clinical T4 and borderline unresectable T3 tumors

The diagnosis criteria for T4 tumors were as follows: tumor protrusion into the lumen of the trachea or bronchus and obliteration of the fat plane in the triangular space between

the aorta, esophagus, and spine in the CT images [17]. Moreover, tumors with more than 90 degrees of direct contact with the aorta and tumors with evident invasion to the adjacent organ/s were diagnosed as T4 stage [18]. Borderline unresectable T3 tumors were defined as locally advanced esophageal cancer with suspected invasion of the adjacent organs that could not be definitively diagnosed as T4 disease [19]. We included patients with metastatic LN invades surrounding organ other than esophagus in this study. Upper gastrointestinal endoscopy, esophagography, and PET scan were used to obtain clinical information, and some patients underwent bronchoscopy. All diagnoses were confirmed by an agreement among the expert surgeons, oncologists, and radiotherapists at a medical panel prior to therapy initiation.

Surgical procedures

At our institution, the thoracic procedures were performed through a right thoracic incision or video-assisted thoracic surgery (VATS) in a hybrid position combining the left decubitus and prone positions [20, 21]. Considering the alimentary tract reconstruction, gastric conduit through the posterior mediastinal route was generally used; however, antesternal route was mainly chosen in patients after definitive CRT or in patients who had high risk of anastomotic leakage, such as low nutrition. An ileocolic conduit via the antesternal route was also used in patients with synchronous dual gastric cancer or a history of gastrectomy. The Clavien–Dindo classification was used to evaluate the perioperative complications [22]. Briefly, grade II indicated the requirement of pharmacological treatment; grade III indicated the requirement of surgical, endoscopic, or radiological intervention; grade IV indicated the presence of life-threatening complications requiring intensive care unit management; and grade V indicated death of the patient. Patients with major complications were defined as those with Clavien–Dindo grade III or more complications. Pneumonia was defined as the presence of a fever greater than 38 °C with an abnormal shadow on chest X-ray and positive sputum and/or a white blood cell count greater than 12,000/mm^3 [23]. Anastomotic leakage was diagnosed based on CT imaging or esophagography and/or the characteristics of the anastomotic drain fluid. Hospitalized death was defined as the death occurring during hospitalization.

Statistical analysis

Statistical analyses were performed using Stata/SE 12.1 for Mac (StataCorp, College Station, TX, USA) and R (version 3.1.2; R Foundation Statistical Computing, Vienna, Austria). Categorical variables were analyzed using the Chi-square test for univariate analyses, and continuous variables were analyzed using the Mann–Whitney *U* test. The prognosis was assessed using the Kaplan–Meier method, and the log-rank test and the significant variables with p values <0.05 were entered into a Cox hazards regression model for multivariate analyses. Interactions were evaluated to determine whether DCF was superior to CRT for predicting OS in the subgroups including age; sex; PS; Charlson scores; tumor location; clinical stage; and curative resection. p values for interaction were significant at the 5% level [24]. The R package "forestplot" was used.

Results

Background characteristics

A total of 87 patients were included in this retrospective cohort study, 44 patients in the primary DCF group and 43 patients in the definitive CRT group. The clinicopathological characteristics of all study patients are listed in Table 1. Significant between-group differences were observed in the PS score ($p < 0.001$), ASA score ($p < 0.001$), tumor location ($p = 0.011$), and esophagectomy ($p < 0.001$). In the DCF and CRT groups, respectively, 2 and 11 patients were aged above 75 years. Among the patients with T4 disease ($n = 52$), invasion into at least two or more organs was recognized in 11 patients. Of the 11 patients, six had airway and aorta invasion, three had airway and pericardium, and two had pericardium and pulmonary vein. In these 11 patients, curative treatment was obtained in 5 patients in the CRT group and none of the patients in the DCF group.

Short-term outcomes

Although complete response was diagnosed only in nine patients in the CRT group, clinical response (CR + PR) tended to be higher as identified in the DCF group than those of the CRT group (26 patients vs. 17 patients, $p = 0.068$) (Table 2). Albeit not significant, the rate of curative treatment was higher in the DCF group than that in the CRT group (22 vs. 14 patients, $p = 0.099$). Moreover, several remaining patients ($n = 27$) in the CRT group underwent palliative therapy or best supportive care (Fig. 1). In the patients who had T4b invaded to the airway, four patients who were developed to fistula after CRT were also included in palliative group.

In the entire cohort, a total of 40 patients underwent esophagectomy, including 29, and 7 patients who received DCF, and CRT, respectively (Table 3). Four patients received DCF followed by CRT. We compared between the DCF followed by surgery group ($n = 29$) and CRT

Table 1 Clinicopathological characteristics of the study patients

	All (n = 87)	DCF (n = 44)	CRT (n = 43)	p
Sex—male/female	69/18	38/6	31/12	0.100
Age—median (min, max)	66 (35–85)	65 (35–78)	67 (50–85)	0.143
PS score 0/1/2/3	69/9/8/1	43/1/0/0	26/8/8/1	<0.001
ASA score 1/2/3	5/68/14	5/39/0	0/29/14	<0.001
Charlson score (2/3/4/5)	66/12/8/1	35/8/1/0	31/4/7/1	0.070
Tumor location (Ut/Mt/Lt)	24/50/13	6/31/7	18/19/6	0.011
cT				0.060
T3	35 (40%)	23 (52%)	12 (28%)	
T4a	6 (7%)	3 (7%)	3 (7%)	
T4b	46 (53%)	18 (41%)	28 (65%)	
Invaded organ (cT4; n = 52)				0.250
Aorta	6 (12%)	3 (14%)	3 (10%)	
Airway	27 (52%)	11 (52%)	16 (51%)	
Others	8 (15%)	5 (24%)	3 (10%)	
Multiple	11 (21%)	2 (10%)	9 (29%)	
cN 0/1/2/3	3/32/41/11	1/16/22/5	2/16/19/6	0.889
cM 0/1	61/26	32/12	29/14	0.590
Esophagectomy	40 (46%)	33 (75%)	7 (16%)	<0.001

ASA American Society of Anesthesiologists, *c* clinical, *CRT* chemoradiotherapy, *DCF* docetaxel plus cisplatin and 5-fluorouracil, *Lt* lower thoracic esophagus, *Mt* middle thoracic esophagus, *PS* Eastern Cooperative Oncology Group performance status, *SCC* squamous cell carcinoma, *Ut* upper thoracic esophagus

Table 2 Overall response

	All (n = 87)	DCF (n = 44)	CRT (n = 43)
Overall response			
CR	9 (10%)	0	9 (22%)
PR	34 (40%)	26 (59%)	8 (19%)
SD	22 (26%)	11 (25%)	11 (26%)
PD	21 (24%)	7 (16%)	14 (33%)

CR complete response, *CRT* chemoradiotherapy, *DCF* docetaxel plus cisplatin and 5-fluorouracil, *PD* progressive disease, *PR* partial response, *SD* stable disease

followed by surgery group (n = 7) in surgical outcomes, VATS could be performed in 23 patients (79%) in the DCF group that had a high rate of three-field LN dissection (28 patients [97%]). Eight patients were diagnosed as R1. Of these patients, five patients had positive circumferential margins and two had positive proximal margin in the DCF group, whereas one had positive circumferential margins in the CRT group.

In general, 20 patients developed adverse events classified as Clavien–Dindo grade II or greater. The most common adverse event was anastomotic leakage (7 patients [19%]), which tended to be higher in the CRT group (3 patients [43%], p = 0.081).

R0 resection was achieved in 21, 1, and 5 patients who received DCF, DCF followed by CRT and CRT, respectively. Thirteen patients in the DCF group underwent subsequent CRT due to tumors that could not be determined as resectable after DCF. R1/2 resection was the most frequent approach (three [75%]) among four patients who could undergo esophagectomy after DCF followed by CRT. The patients who refused adjuvant therapy or exhibited poor general condition after surgery did not undergo adjuvant chemotherapy after R1/2 resection. In the DCF group, three patients (38%) achieved adjuvant therapy including irradiation after R1/2 resection. Only one patient (33%) who received DCF following CRT, and no patients in the CRT group with R1/R2 resection received adjuvant chemotherapy.

Long-term oncologic outcomes

In the entire study cohort, the 3-year OS rate was 36.4%, and the PFS rate was 21.6%. The OS and PFS were better with the DCF group than those with the CRT group (median OS, 29 vs. 17 months, p = 0.206; median PFS, 10 vs. 6 months, p = 0.020; Fig. 2). Thirty-sex patients (41%) received curative treatment including 22 and 14 patients in the DCF and the CRT groups. In those 36 patients, there were no significant differences in the OS and PFS rates (Fig. 3). No significant difference in OS was also observed between the DCF and CRT; however, there were significant differences in the PFS rates among patients who underwent R1/2 resection (p = 0.028; Suppl. Fig. 1).

Table 3 Surgical outcomes

	All (n = 36)	DCF followed by surgery (n = 29)	CRT followed by surgery (n = 7)	p
VATS	23 (64%)	23 (79%)	0	<0.001
Reconstructive route				<0.001
Posterior mediastinal	26 (70%)	25 (86%)	1 (14%)	
Antesternal	10 (30%)	4 (14%)	6 (86%)	
FD 2/3	4/32	1/28	3/4	0.003
Operating time (min); median (range)	533 (441–730)	545 (441–730)	505 (442–593)	0.617
Amount of bleeding (ml); median(range)	202 (0–1225)	200 (0–920)	330 (0–1225)	0.412
ypT 0/1/2/3/4	2/6/2/23/3	1/4/2/21/1	1/2/0/2/2	0.079
ypN 0/1/2/3	12/11/8/5	9/8/8/4	3/3/0/1	0.458
ypM 0/1	29/7	25/4	4/3	0.081
Residual cancer R0/R1/R2	26/8/2	21/7/1	5/1/1	0.487
Chemo/CRT effect				0.675
Grade0	6 (17%)	5 (18%)	1 (14%)	
Grade1a	11 (31%)	10 (36%)	1 (14%)	
Grade1b	7 (20%)	5 (18%)	2 (29%)	
Grade2	9 (26%)	7 (25%)	2 (29%)	
Grade3	2 (6%)	1 (4%)	1 (14%)	
Hospitalized death	0	0	0	NA
Major complication (≥CDIII)	14 (39%)	11 (38%)	3 (43%)	0.810
Complication (≥CDII)	20 (56%)	17 (59%)	3 (43%)	0.451
Pneumonia	4 (11%)	3 (10%)	1 (14%)	0.766
Anastomotic leakage (including conduit necrosis)	7 (19%)	4 (14%)	3 (43%)	0.081
RLNP	5 (14%)	5 (17%)	0	0.236

CD Clavien–Dindo, *CRT* chemoradiotherapy, *DCF* docetaxel plus cisplatin and 5-fluorouracil, *FD* field dissection, *p* pathological, *R0* resection with negative margins, *R1* resection with microscopically positive margins, *R2* resection with macroscopically positive margins, *RLNP* recurrent laryngeal nerve paralysis, *VATS* video-assisted thoracic surgery

Sixty-two patients (71%) experienced progression or recurrence at one or more regions during the follow-up period. Although there were no differences in the rate of distant metastases between the two groups, local recurrence was less frequent in the DCF group than in the CRT group (6 vs. 13 patients, $p = 0.061$; Table 4).

Univariate analyses revealed that definitive CRT was not a risk factor for death; however, several factors including cT4b stage and noncurative treatment were identified as significant risk factors. By multivariate analysis using the Cox hazards regression model that included these factors, both cT4b (hazard ratio [HR] 2.18; 95% confidence interval [CI] 1.18–4.04; $p = 0.013$) and noncurative treatment (HR 4.24; 95% CI 2.16–8.26; $p < 0.001$) were identified as predictors of death. These two factors were also the significant risk factors of progression, and definitive CRT tended to be the risk factor of disease progression (HR 1.48; 95% CI 0.89–2.48; $p = 0.134$) in multivariate analysis.

Subgroup analysis for overall survival

We investigated the utility of DCF for OS in subgroups according to sex, age, PS score, Charlson score, tumor location, clinical stage, and curability. In the DCF group, the OS tended to be better in patients with a Charlson score of less than 3 ($p = 0.076$), which also tended to have an interaction for OS, which was not statistically significant (Fig. 4).

Discussion

The present study demonstrated the oncological utility of DCF and the technical feasibility subsequent esophagectomy for the patients with locally advanced esophageal cancer if their performance status is acceptable. To the best of our knowledge, this is the first report demonstrating the significance of decision-making during the initial treatment of unresectable locally advanced esophageal cancer.

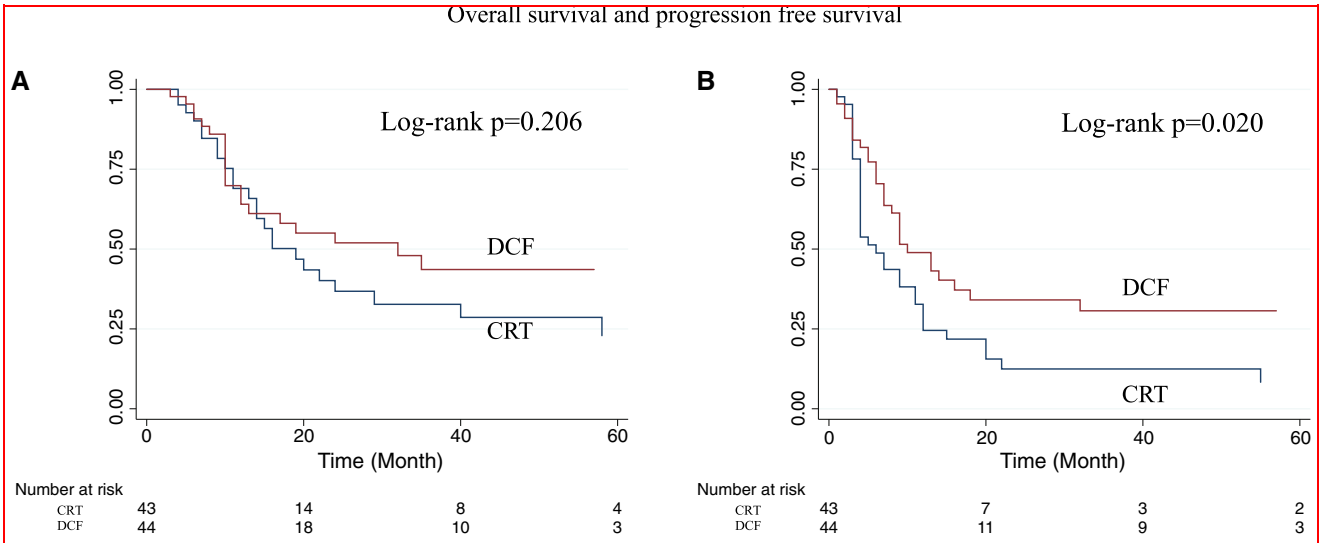

Fig. 2 **a** Kaplan–Meier curves for overall survival. **b** Kaplan–Meier curves for progression-free survival. Red and blue lines indicate the DCF and definitive CRT groups, respectively

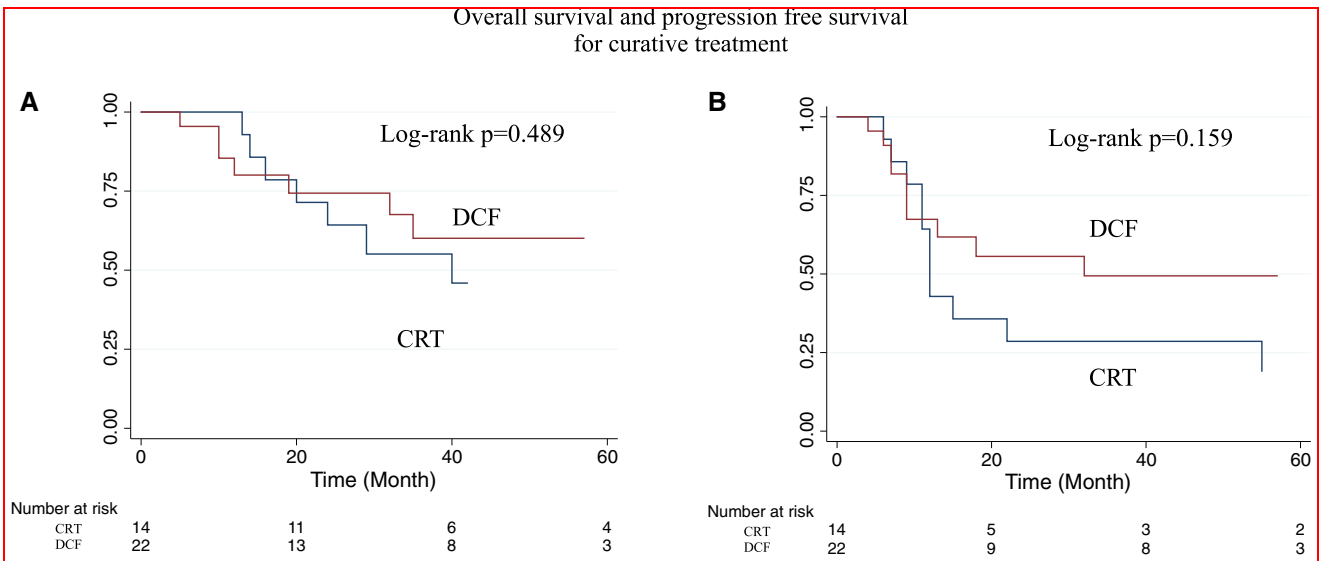

Fig. 3 **a** Kaplan–Meier curves for overall survival with curative resection. **b** Kaplan–Meier curves for progression-free survival with curative resection. Red and blue lines indicate the DCF and definitive CRT groups, respectively

Table 4 Patterns of recurrence

Patterns of recurrence	All (n = 87)	DCF (n = 44)	CRT (n = 43)	p
Lymph node	31 (36%)	17 (39%)	14 (33%)	0.554
Local	19 (22%)	6 (14%)	13 (30%)	0.061
Distant organ	32 (37%)	17 (39%)	15 (35%)	0.717

CRT chemoradiotherapy, *DCF* docetaxel plus cisplatin and 5-fluorouracil

Although several studies reported the efficacy of DCF [12, 19, 25, 26], few studies compared DCF with definitive CRT as an initial treatment suitable for locally advanced esophageal cancer. Makino *et al.* reported that DCF could achieve a reduction in the incidence of esophageal perforation and an increase in the overall resectability compared to definitive CRT [27]. The authors of that important study [27], which suggested the utility of DCF as an induction

treatment option, acknowledged the historical bias between the DCF and the CRT groups. Therefore, the present study compared the patients treated during the same time period according to the same indications to reveal three major findings.

First, our findings clearly suggested that DCF contributed to the high rate of R0 resection and the achievement of acceptable long-term prognosis for the patients with good systemic status. In the present study, curative treatment rate was 50% in the DCF group, closely comparable with the results of a phase II study in Japan, which revealed a complete response rate of 47.9% [12]. Shimoji *et al*. indicated that good long-term prognosis could be obtained by performing R0 resection, even in patients with T4 stage disease [10]. Thus, better long-term outcomes could be obtained by high rate of R0 resection in the DCF group. Another reason for achievement of acceptable outcomes in DCF group is that even among patients who could not undergo R0 resection, those who received DCF as primary treatment could undergo adjuvant therapy including irradiation. This might be involved in the results that good PFS for R1/2 resection in the DCF group. However, the forest plot in the present study revealed that the long-term outcomes of patients with comorbidities (specifically those with a Charlson score over 3) in the DCF group were worse, compared to patients who had comorbidities in the definitive CRT group. Our previous studies indicated that certain comorbidities, such as pneumonia and chronic obstructive pulmonary disease, were associated with worse short-term and long-term outcomes [28, 29]. Therefore, careful decision-making is warranted for all patients receiving treatments such as DCF that are followed by surgical intervention. The results of the present study indicated that older patients as well as those with high Charlson scores should be considered for definitive CRT without surgery. Moreover, our analysis revealed that the outcomes were poor with DCF and subsequent surgery in patients with tumor invasion to multiple organs. Although no studies investigated the role of tumor invasion to multiple organs in the outcomes of these patients, definitive CRT without planned surgery might be considered for patients with large tumors, which might more likely invade the surrounding structures both in anterior and posterior directions.

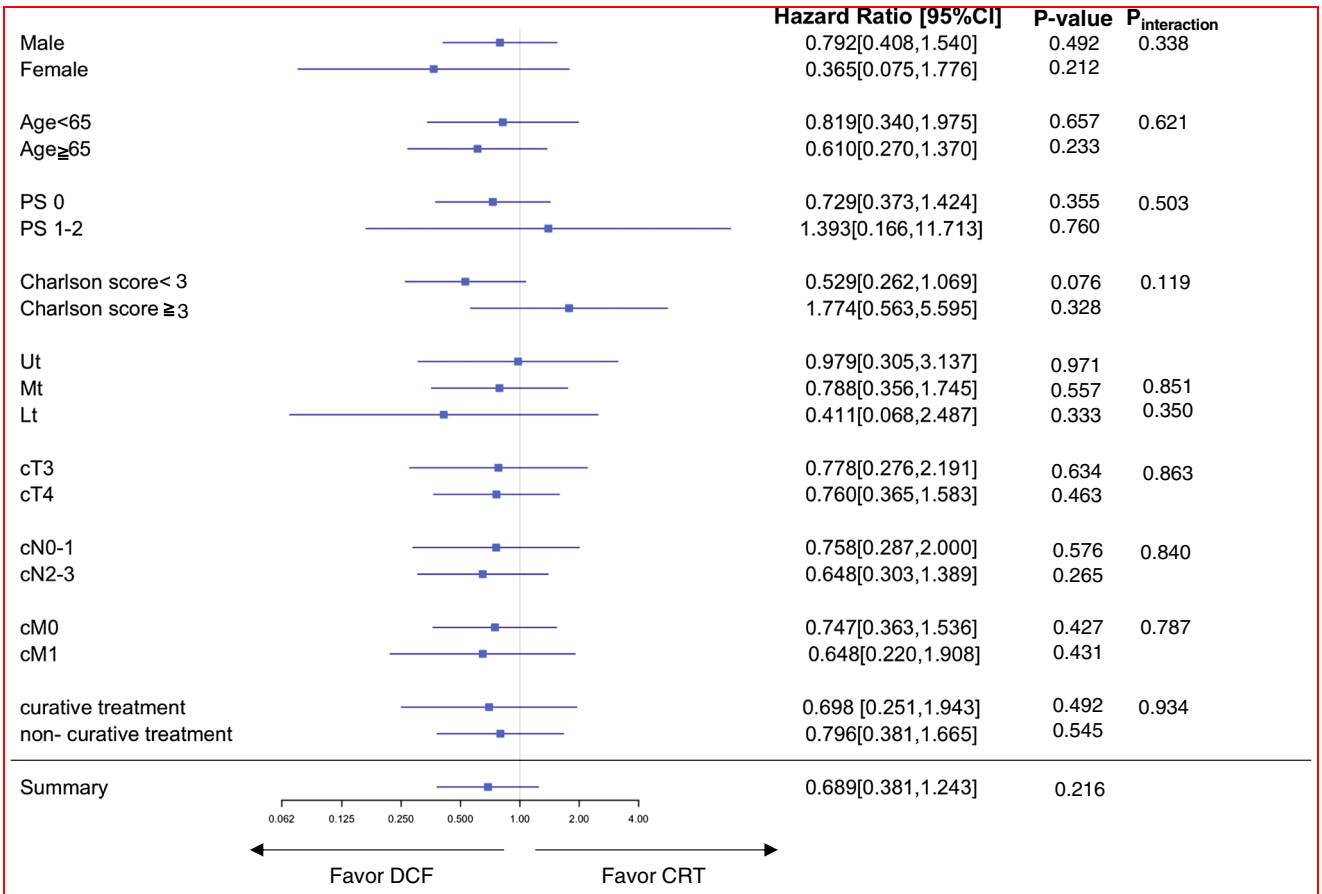

Fig. 4 Hazard ratio of primary treatment for overall survival according to the clinicopathological characteristics. Interaction *p* value indicated the evidence of whether the reliability of the primary treatment differed among the subgroups

The second major finding of the study was the demonstration that esophagectomy after DCF was relatively more safe than salvage surgery after definitive CRT, as we have previously shown [30]. In the present study, there were no hospitalized deaths, and the rates of other complications were comparable to those of the planned surgery [31]. Moreover, esophagectomy with three-field LN dissection could be performed using VATS, as surgical difficulty could be mitigated by the absence of radiotherapy-associated adverse effects. Therefore, subsequent esophagectomy after DCF is feasible.

Third, the present study revealed that DCF therapy might have suppressed local recurrence compared to definitive CRT. Since DCF acts on the entire body, improvement of distant control is predicted due to its suppression of micrometastases; however, DCF therapy did not suppress distant metastasis in this study. It might be more difficult to control than resectable T1–T3 tumors because locally advanced tumors are highly malignant. This possibility should be further explored in future studies involving larger number of patients with recurrence.

This study has several limitations. First, there is a major selection bias, as patients with higher ASA classification and poor performance status, and higher T stages (mainly T4b) were selected for the definitive CRT group. Hence, it is not surprising that these patients had a more limited long-term outcome. Moreover, this was a retrospective single-center study limited to a Japanese patient cohort. Analyses with the low number of patients, particularly concerning the subgroup analyses, could also be limitation. Second, there was interevaluator heterogeneity in the clinical diagnosis of T4 [32, 33]. Several criteria of T4, first reported over 20 years ago, are still in use and were included in the present study. Therefore, the decision of resectability differs among the institutions and evaluators. To overcome this bias, we utilized a medical panel; to reach an agreement among the expert surgeons, oncologists, and radiotherapists prior to the therapy initiation. Furthermore, several studies reported the reliability of endoscopic ultrasonography and endobronchial ultrasonography to determine the depth of tumor [32], and these additional modalities can be incorporated in future studies. Third, the diagnosis of invasion to the airway, including trachea and bronchus, was not routinely proved by biopsy. We mainly diagnosed it using the CT and PET scans. Fourth, the results of surgical treatment, especially high-risk operations, such as esophagectomy, can be affected by hospital volume and training status. The recently initiated Japan Clinical Oncology Group (JCOG) 1510 trial, a phase III prospective study comparing induction DCF therapy with definitive CRT for the patients with locally advanced esophageal cancer, should provide clearer evidence for the utility and feasibility of this approach.

Conclusion

In conclusion, the present study demonstrated the oncological utility and technical feasibility of DCF and subsequent esophagectomy compared to definitive CRT for the patients with locally advanced esophageal cancer if their performance status is acceptable. DCF and subsequent esophagectomy achieved R0 resection in the 50% of the patients with initially unresectable esophageal cancer.

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Compliance with ethical standards

Conflict of interest Yuko Kitagawa have personal fees from sanofi K.K, personal fees from ETHICON PART OF JOHNSON AND JOHNSON FAMILY OF COMPANIES, personal fees from Medtronic Japan Co., Ltd., grants from KYOWA HAKKO KIRIN CO., LTD, outside the submitted work.

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