

## Review

# Treatment of T4 Esophageal Cancer. Definitive Chemo-Radiotherapy vs Chemo-Radiotherapy Followed by Surgery

Tomoki Makino, MD, PhD and Yuichiro Doki, MD, PhD

The outcome of patients with T4 esophageal cancer, defined as a tumor that invades neighboring structures (e.g., aorta, trachea, bronchus, and lung), is extremely poor. Despite recent advances in surgical techniques, these tumors are usually considered inoperable. Two distinct therapeutic options are currently available for T4 esophageal cancers: chemo-radiotherapy followed by surgery (CRT-S), which comprises esophagectomy following down-staging of the tumor by CRT, and definitive chemo-radiotherapy (D-CRT), which is designed to avoid esophagectomy by using maximum doses of irradiation. CRT-S is superior to D-CRT with respect to local control and short-term survival although CRT-S is associated with relatively higher perioperative mortality and morbidity. On the other hand, it is sometimes difficult to achieve local control with D-CRT and the treatment often results in fistula formation, though a complete response to CRT is often associated with better prognosis. Admittedly, the difference in the survival rate between the two modalities is marginal at long-term follow-up due to operative morbidity and inadequate control of distant metastasis in CRT-S. Changes in perioperative management and intensive systemic chemotherapy may enhance the outcome. Randomized controlled trials involving large population samples are needed to define the standard treatment for T4 esophageal cancer.

**Key words:** esophageal cancer, T4, definitive chemo-radiotherapy, esophagectomy, neo-adjuvant chemo-radiotherapy

## Introduction

The lack of a serosa layer in the esophagus and the location of this conduit in a very narrow mediastinal space allows early tumor invasion into the neighboring organs such as the trachea, bronchus, lung, and aorta (T4 tumor).<sup>1)</sup> Despite advances in surgical treatment, surgery alone has not improved the prognosis of patients with T4

esophageal tumors.<sup>2–4)</sup> Furthermore, the combination of resection of neighboring organs with esophagectomy has not improved survival despite the high incidence of morbidity and mortality.<sup>4, 5)</sup> On the other hand, palliative resection (R1 or R2) followed by radiotherapy with or without chemotherapy has also failed to improve survival compared with nonsurgical treatment.<sup>6)</sup>

Multimodal therapies have been developed recently to control both local recurrence and distant metastasis of esophageal cancer and to prolong survival. The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP)<sup>7)</sup> is currently the most effective chemotherapeutic regimen against esophageal cancer due to their radio-sensitizing effects as well as the synergism between the two agents.<sup>8)</sup> Previous studies reported the effectiveness of concurrent chemo-radiotherapy (CRT) using this regimen in advanced esophageal cancer including T4 tumors.<sup>9)</sup> Thus,

*Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan*

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Corresponding author: Tomoki Makino, MD, PhD. Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2-E2, Yamada-oka, Suita, Osaka 565-0871, Japan  
Email: tmakino@gesurg.med.osaka-u.ac.jp

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**Table 1** Summary of studies on definitive chemo-radiotherapy and chemo-radiotherapy plus surgery for patients with T4 esophageal cancer

Authors (year)	n	Histology (SCC/AC/other)	Treatment (n)		Total radiation dose /chemotherapy regimen		1/3/5-year overall survival rate (%)	
			CRT	CRT + S	CRT	CRT + S	CRT	CRT + S
Seto et al. (2007)	88	88/0/0	29	59	60 Gy/FP	40 Gy/FP	35/7/7	68/38/20
Fujita et al. (2005)	53	53/0/0	23	30	60 Gy/FP	36 Gy (+24 Gy*)/FP	44/13/13	73/28/17
Miyoshi et al. (2009)	42	42/0/0	-	42	-	40 Gy FP or FAP	-	66/45/38
Manzoni et al. (2007)	51	51/0/0	-	51	-	50–60 Gy/FP	-	NA/9/6
Noguchi et al. (2003)	41	41/0/0	-	41	-	40 Gy/FP	-	24/5/0
Ikeda et al. (2001)	37	37/0/0	-	37	-	60 Gy/FP	-	45/23/23
Yano et al. (1999)	45	45/0/0	-	45	-	40 Gy/FP	-	48/35/25
Nishimura et al. (2002)	28	28/0/0	23	-	60 Gy/FP	-	30/NA/NA	-
Font et al. (2007)	19	NA/NA/NA	19	-	66 Gy/docetaxel	-	26/0/0	-
Crosby et al. (2004)	27	NA/NA/NA	27	-	50 Gy/FP	-	45/23/NA	-
Kaneko et al. (2003)	35	35/0/0	35	-	60 Gy/FP	-	45/8/NA	-
Itoh et al. (2001)	35	33/1/1	35	-	60 Gy/FP	-	38/10/10	-
Ohtsu et al. (1999)	36	36/0/0	36	-	60 Gy/FP	-	41/14/14	-

SCC, squamous cell carcinoma; AC, adenocarcinoma; CRT, chemo-radiotherapy; S, surgery; FP, 5-fluorouracil and cisplatin;

FAP, 5-fluorouracil, doxorubicin and cisplatin; NA, data not available

\*postoperative dose

two modalities are currently in use for the treatment of esophageal tumors<sup>10, 11</sup>; chemo-radiotherapy followed by surgery (CRT-S)<sup>10–16</sup> and definitive chemo-radiotherapy (D-CRT).<sup>17–22</sup> To the best of our knowledge, there is little or no information on the differences in clinical outcome of patients with T4 esophageal tumors who undergo D-CRT and those who receive CRT-S. In this review, we discuss these two treatment modalities.

## Definitive Chemo-radiotherapy (D-CRT)

### Regimen

As listed in **Tables 1** and **Table 2**, eight studies examined the outcome of patients with T4 esophageal cancer after D-CRT. Seven<sup>10, 11, 18–22</sup> out of 8 studies used 5-FU plus CDDP; at standard-doses (5-FU 300–700 mg/m<sup>2</sup>, CDDP 40–60 mg/m<sup>2</sup>) in 4 studies,<sup>10, 18, 19, 21</sup> low-dose CRT (5-FU 200–500 mg/m<sup>2</sup>, CDDP 3–10 mg/m<sup>2</sup>) in two studies,<sup>11, 22</sup> and both in one study.<sup>20</sup> Recently, Font et al.<sup>17</sup> used weekly docetaxel regimen (20 mg/m<sup>2</sup>). Concurrent radiotherapy was applied to all studies using total external radiation dose of 50–66 Gy.

### Toxicity, morbidity and mortality

The most commonly reported hematotoxicities during and after D-CRT, as assessed by the NCI-CTC criteria,<sup>23</sup> are leukocytopenia, anemia, and thrombocytopenia (**Table 2**). On the other hand, inflammation of the

mucosa including esophagitis, buccal mucositis, and esophageal dysphagia are the most common non-hematological toxicities (**Table 2**).

Fistula formation occurred in 9%–18%<sup>19, 21, 22</sup> of patients with T4 diseases during or after D-CRT. Nishimura et al.<sup>22</sup> studied 28 patients with T4 esophageal squamous cell carcinoma (ESCC) who underwent D-CRT (60 Gy/5-FU + CDDP), and reported worsening or development of esophageal fistulas in 5 (18%) of their patients and 2 (7%) treatment-related deaths. Otsu et al.<sup>21</sup> reported that 5 (14%) of their 36 patients with T4 disease developed treatment-related perforation of the esophageal wall (including esophagobronchial fistula in 2, mediastinal fistula in 2, and aortic fistula in 1). Itoh et al.<sup>20</sup> followed 35 patients with T4 tumors and reported 27 deaths, fistula formation in the airways (n = 6), esophageal bleeding (n = 3), perforation into the pericardial cavity (n = 2), and bleeding from the aorta (n = 2), although the exact proportion of patients who developed fistula was not clear in that study. On the other hand, Otsu et al.<sup>21</sup> reported that 3 of the 5 cases with esophageal perforation were successfully closed with additional CRT after improvement of the inflammatory changes and that the patients achieved clinical complete response (cCR). Nishimura et al.<sup>22</sup> also reported that CRT resulted in closure of 2 of the 5 T4 tumors with fistula.

With respect to late toxicities caused by D-CRT, although there are only two studies with relevant data,<sup>10, 19</sup>

**Table 2 Summary of outcomes in definitive chemo-radiotherapy group**

Author	n	Grade 3/4 toxicities		Fistula formation (%)	Mortality (%)	Response rate (%)	cCR rate (%)	1/3/5-year overall survival rates (%)	
		Acute (%)	Late (%)					cCR	non-cCR
Seto et al.	29	NA	(0)	NA	0	NA	24	83/33/33	23/0/0
Fujita et al.	23	leukocytopenia (30 <sup>a</sup> ), anemia (13 <sup>a</sup> )	NA	NA	NA	57	39	NA	NA
Nishimura et al.	23	leukocytopenia (50), dysphagia (32), anemia (21), thrombocytopenia (11)	NA	18	7	88	32	NA	NA
Font et al.	19	esophagitis (17 <sup>b</sup> )	NA	NA	6 <sup>b</sup>	NA	NA	NA	NA
Crosby et al.	27	oral mucositis (12 <sup>b</sup> ), leukocytopenia (10 <sup>b</sup> )	NA	NA	0	NA	NA	NA	NA
Kaneko et al.	35	anemia (33 <sup>b</sup> ), leukocytopenia (30 <sup>b</sup> ), esophagitis (25 <sup>b</sup> )	(0)	9	6	NA	29	NA	NA
Itoh et al.	35	NA	NA	NA	NA	68	17	83/25/25	26/7/0
Ohtsu et al.	36	anemia (28 <sup>c</sup> ), leukocytopenia (24 <sup>c</sup> ), thrombocytopenia (17 <sup>c</sup> ), esophagitis (15 <sup>c</sup> )	NA	14	7 <sup>c</sup>	81	25	NA	NA

NA, data not available; CR, complete response

Data of patients of the <sup>a</sup>CRT and CRT plus surgery group,

<sup>b</sup>T3/4 tumors, or <sup>c</sup>T4/M1 lym tumors

CRT, chemo-radiotherapy

Keneko et al.<sup>19)</sup> reported no serious late toxicity (grade 3 or higher) in their patients. Seto et al.<sup>10)</sup> followed nine patients who survived more than 1 year from the initiation of D-CRT and reported grade 2 pericardial effusion and radiation pneumonitis in 4 and 2 patients, respectively, while no late toxicity-related deaths were noted. Analysis of data of 6 studies<sup>10, 17–19, 21, 22)</sup> with relevant data indicated that the mortality rate related to D-CRT ranges from 0% to 7%. The main causes of D-CRT-related deaths were esophageal fistula with massive bleeding<sup>19, 21, 22)</sup> and peumonitis.<sup>17)</sup>

### Tumor response and survival rate

The data listed in **Table 2** show a cCR of 17%–39% and overall response rate (complete and partial response rate) of 57%–88% for patients with T4 tumors. On the other hand, the 1-, 3-, and 5-year overall survival (OS) rates of patients with T4 esophageal cancer who received D-CRT were 26%–45%, 0%–23%, and 0%–14%, respectively. Notably, the 5-year OS was much low regardless of the cCR rate (17%–39%). Seto et al.<sup>10)</sup> examined prognosis according to the response to CRT and reported that the 1-, 3-, and 5-year survival rates of patients showing cCR and non-cCR were 83%, 33%, 33%, and 23%, 0%, 0%, respectively. Ito et al.<sup>20)</sup> also reported that the prognosis of patients who achieved cCR was significantly better than those of the non-cCR group (1-, 3-, 5-year overall survival rate; 83%, 25%, 25% vs 26%, 7%, 0%  $p = 0.0317$ ).

### Recurrence pattern

Ito et al.<sup>20)</sup> reported that 4 of 6 (67%) cCR patients who received D-CRT showed good local control. Among them, 2 survived without tumors, 1 died of lymph node and bone metastases, and the fourth died of brain metastasis. Of the two deaths, the recurrence status was not clear in one and the other patient died of local recurrence.

### Chemo-radiotherapy Followed by Surgery (CRT-S)

#### Regimen

As shown in **Tables 1** and **Table 3**, seven studies<sup>10–16)</sup> have analyzed the outcome of patients with T4 esophageal cancer who underwent CRT-S. Basically, the combination of 5-FU (200–1000 mg/m<sup>2</sup>) and CDDP (5–100 mg/m<sup>2</sup>) was used in all the studies as the primary chemotherapeutic regimen. Although the doses of concurrent radiation varied across studies (36–60 Gy), all CRT in the series were performed as a “planned” treatment before surgical resection. The interval between the completion of CRT and surgery was 4–6 weeks in all studies with available related data (**Table 3**).<sup>11, 13, 14, 16)</sup>

#### Toxicity and mortality due to CRT

Yano et al.<sup>16)</sup> reported that the major toxicities equal to or greater than grade 3 due to CRT (40 Gy/5FU + CDDP)

**Table 3 Summary of outcomes after chemo-radiotherapy plus surgery**

Author	n	Interval <sup>*</sup> (week)	Combined resection rate (%)	Postoperative complications (%)	Mortality (%)	Resection rate <sup>**</sup> (%)	Curative resection rate <sup>**</sup> (%)	Clinical response rate (%)	pCR rate (%)		1/3/5-year overall survival rate (%)	
									main	all	Grade 3	Grade 0–2
Seto et al.	59	NA	respiratory tract (17), lung (10), pericardium (10)	NA	5	NA	NA	68	14	7	NA	NA
Fujita et al.	30	4–6	0	total (87): recurrent nerve palsy (50), respiratory (35), tracheal ischemia (23), pyothorax (23)	7	57	34	63	15	7	NA	NA
Miyoshi et al.	42	4	NA	NA	NA	NA	NA	83	21	21	90/78/78	58/30/30
Manzoni et al.	51	NA	NA	NA	10	78	39	20	NA	13	NA	NA
Noguchi et al.	41	4–6	0	total 29: anastomotic leak (17)	21	59	NA	59	17	17	100/75/25	20/0/0
Ikeda et al.	37	NA	0	NA	0	35	32	76	8	8	NA	NA
Yano et al.	45	4	NA	total (62): respiratory (43), delirium (25), recurrent nerve palsy (21)	0	62	44	64	29	25	86/86/86	65/35/20

\* Interval from completion of chemo-radiotherapy to surgery.

\*\*Calculated by intention to treat analysis

NA, data not available; CR, complete response

were leukocytopenia in 49% of the patients, gastrointestinal toxicities in 47%. Furthermore, 1 (2%) patient died of treatment-related cause (pancytopenia). Ikeda et al.<sup>15)</sup> reported that during and after CRT (60 Gy/5FU + CDDP), grade 3 toxicity included anemia (14% of patients) and leukocytopenia (14% of patients). In addition, 2 patients developed esophago-bronchial fistula, 2 esophago-vascular fistula, and 1 developed esophago-mediastinal fistula. Furthermore, they reported 1 (3%) case of toxicity-related death.

### Resection rate and curative resection rate

The intention to treat (ITT) analysis showed a median resection rate and curative resection (R0) rate of T4 diseases of 59% (range, 35%–78%) and 36.5% (range, 32%–44%), respectively, (Table 3). Seto et al.<sup>10)</sup> analyzed the data of 59 T4 patients who underwent CRT-S and reported that 10 (17%), 6 (10%), and 6 (10%) of their patients underwent combined resection of the major respiratory tract, lung, or pericardium, respectively. However, no combination resection was used in the other three studies (Table 3).<sup>11, 14, 15)</sup>

### Perioperative morbidity and mortality

The reported median perioperative morbidity and mortality rates are 62%<sup>11, 14, 16)</sup> (range, 29%–87%) and

6%<sup>10–12, 14–16)</sup> (range, 0%–21%), respectively. Fujita et al.<sup>11)</sup> reported overall postoperative mortality rate of 7% (2/30), and postoperative complications in 87% (26/30) of their patients with T4 tumors who underwent CRT-S (36 Gy/5-FU + CDDP), including 50% of patients who developed recurrent nerve palsy, 35% respiratory complications, 23% tracheal ischemia, and 23% pyothorax. Noguchi et al.<sup>14)</sup> indicated a morbidity rate of 29% (7/24) in their study of patients who received CRT-S (40 Gy/5-FU + CDDP) had and that anastomotic leakage was the most frequent complication (17%). The overall postoperative mortality rate after surgical resection was 21% (5/24): of 5 deaths, 2 were from postoperative complications involving anastomotic leak; 1, from postoperative pneumonia; 1, from liver failure; and 1, from catheter sepsis. Yano et al.<sup>16)</sup> analyzed 45 patients who received CRT-S (40 Gy/5-FU + CDDP) and reported respiratory complications, delirium, and recurrent nerve palsy in 43%, 25%, and 21% of their patients, respectively, with an overall morbidity rate of 62% (28/45).

### Tumor response and survival

As described in Table 3, 20%–83% of patients with T4 esophageal cancer who received CRT-S achieved clinical response to CRT. However, pathological complete response (pCR) was observed in only 8%–29% of cases

for the main tumor and 7%–25% for all involved lesions. The 1-, 3-, and 5-year overall survival rates of T4 patients who underwent CRT-S were 24%–73%, 5%–45%, and 0%–38%, respectively. Data of the three studies<sup>13, 14, 16)</sup> with prognosis classified according to the pathological response to CRT showed the 1-, 3-, and 5-year OS rates of 86%–100%, 75%–86%, and 25%–86%, respectively, in patients with grade 3 and 20%–65%, 0%–35%, and 0%–30% for grade 0–2 (**Table 3**).

In the survival analysis according to infiltrated organs on pre-treatment staging, Manzoni et al.<sup>12)</sup> reported that curative resections were possible after CRT (50–60 Gy/FP) in patients with tumor invasion of the aorta and no long survivors were observed in other categories; the 3-year survival time of patients with invasion of the aorta, airway, and others were 31.3, 4.5, and 0 months, respectively.<sup>12)</sup> Furthermore, the median survival time was 22.3 and 9 months for patients with R0 and R1-2 resection, respectively ( $p < 0.001$ ). In another study, prognosis of patients who underwent CRT (40 Gy/5-FU + CDDP) combined with resection of the trachea was poor even after R0 resection; all 6 patients who received R0 resection after CRT died and their median survival time was 7 months.<sup>10)</sup>

### Recurrence pattern

Only one of the 7 studies discussed the recurrence pattern after curative resection of T4 tumors. Yano et al.<sup>16)</sup> reported that among 17 of 27 patients (63%) who showed recurrence after curative resection, the recurrence was local in 8 (30%), distant in 6 (22%), local plus distant in 2 (7%), and unknown recurrence pattern in 1 (4%) cancer death.

### Comments

The reported incidence of stage T4 is 12%–34%<sup>24–27)</sup> among thoracic esophageal cancer and the depth of invasion is usually diagnosed by computed tomography (CT) or endoscopic ultrasonography (EUS). However, it is often difficult to obtain an accurate preoperative diagnosis of organ invasion.<sup>12)</sup> Matsubara et al.<sup>28)</sup> indicated that clinical and radiographic criteria correctly diagnose organ infiltration in 51% of the cases with a false positive rate of approximately 40%. Moreover, the accuracy of clinical staging after induction treatment is even worse, mainly because EUS and CT hardly differentiate between tumors and inflammation. In the reports reviewed here, the disparity between resection rates and

curative resection rates might be due to under-staging of the primary tumor after CRT, which only resulted in exploratory thoracotomy or palliative resection. Furthermore, clinical over-staging may also lead to a reduced chance of cure in a number of patients, in which the diagnosis of T4 was made in error. Our previous studies<sup>29)</sup> as well as recent reports<sup>30)</sup> have shown that the metabolic response of esophageal cancers to preoperative CRT as assessed by FDG-PET more accurately reflects tumor regression and predicts prognosis, compared with that by conventional imaging including CT. Therefore, accurate initial staging and response evaluation by using multi-modal diagnostic tools including FDG-PET is no doubt necessary to provide appropriate treatments and also to improve prognosis of esophageal cancer patients with T4 tumors.

Most of the CRT trials excluded tumors with fistulas, due to the high incidence of esophageal perforation after radiotherapy for T4 tumors.<sup>31–34)</sup> In studies with available related data,<sup>19, 21, 22)</sup> fistula formation occurred in 9%–18% of patients with T4 disease after D-CRT. Furthermore, Ishida et al.<sup>34)</sup> reported that 6 (13%) of 45 patients with T4 tumors and/or M1 lymph disease developed esophago-bronchial fistula before or during D-CRT, necessitating withdrawal of CRT in these patients. Roussel et al.<sup>35)</sup> reported fistula formation in 29% of patients with esophagobronchial involvement treated palliatively with irradiation. Thus, the risk of esophageal perforation seems inevitable when T4 esophageal tumors are treated with radiation or CRT. On the other hand, however, the Japan Clinical Oncology Trial (JCOG) 9516 study<sup>36)</sup> reported only one toxicity-related death due to bleeding from the tumor in patients with T4 or M1 lymph (n = 60) after D-CRT (60 Gy/5-FU + CDDP) although patients with esophagomediastinal fistula at initial diagnosis were included in that study. In addition, some cases<sup>21, 22)</sup> showed closure of the fistula following CRT and good local control even after CRT, suggesting that CRT is not a contraindication for T4 tumors with fistula<sup>37, 38)</sup> although a high incidence of esophageal perforation must be kept in mind. Generally, compared with D-CRT, there seems less incidence of fistula formation during/after CRT in the CRT-S group although accurate comparison is not available due to the lack of data, especially on CRT-S. This might be due, at least in part, to the difference in the total radiation dose between the two groups. In this context, 50.4 Gy is currently the standard dose of definitive radiation<sup>39)</sup> after the abandonment of the higher dose (60–66 Gy) following the publication of the results of the

Radiation Therapy Oncology Group (RTOG) 9405.<sup>40)</sup> One might expect this dose to reduce some of the complications associated with D-CRT such as fistula formation, however, at the same time, the number of “salvage” resection surgeries after CRT has increased due to the relatively lower dose used to eradicate T4 tumors. Since most of studies on D-CRT reviewed here used a high-dose regimen (60 Gy-), future trials are urgently required to decide on the most appropriate dose of definitive CRT for T4 tumors.

It is obvious that R0 resection provides longer survival compared with R1/2 resection.<sup>16, 28, 41)</sup> However, for T4 tumors, surgeons need also to resect the invaded organ(s) to achieve R0 surgery. Few studies<sup>28, 41)</sup> examined the effect of this kind of extended surgery for T4 esophageal cancer; and the available results indicate that the combined resections of the trachea, bronchus, and lung did not prolong survival, although most of these cases did not receive neo-adjuvant therapy. New and alternative anti-cancer therapeutic modalities have been described recently.<sup>14, 42)</sup> For locally-advanced esophageal cancer, CRT is frequently performed before surgery to achieve tumor down-staging.<sup>16, 43)</sup> Such achievement should allow complete cure after R0 resection in distant metastasis-free patients with T4 esophageal cancer. ITT analysis showed median overall resection rate and curative resection (R0) rate for T4 disease of 59% (range, 35%–78%) and 36.5% (range, 32%–44%) respectively; the main reason for the variability is the response to CRT. However, analysis of survival of 51 patients with T4 esophageal tumors according to the infiltrated organ by Manzoni et al.<sup>12)</sup> indicated that long-term survival might be limited to some, rather than all, patients with T4 tumors who had undergone R0 resection; only patients with infiltration of the thoracic aorta on pre-treatment staging or patients with major response to CRT had a chance of achieving favorable survival. On the other hand, Seto et al.<sup>10)</sup> showed little benefit for resection of the trachea after CRT (40 Gy/5-FU + CDDP), which is associated with serious complications, even when R0 resection was performed. These findings are also supported by other groups; Yano et al.,<sup>44)</sup> in another study of patients with T4 esophageal cancer who underwent CRT-S (40 Gy/5-FU + CDDP), reported that the prognosis was significantly poorer in patients with tumors infiltrating the respiratory tract (T) or aorta plus respiratory tract (A + T) than patients with tumors infiltrating the aorta alone (A) or other organs (Oth). Patients positive for respiratory tract invasion (T, T + A), compared with those negative for

respiratory tract invasion (A, Oth), showed a poorer clinical response to chemoradiotherapy [3.0%, 45.5%, 39.4%, and 9.1% *versus* 4.3%, 82.6%, 4.3%, and 8.7% in complete responders (CR), partial responders (PR), non-responders (NC) and those with progressive disease (PD), respectively,  $p = 0.0156$ ] and surgical resectability (36.4% *vs* 87.0%,  $p = 0.0003$ ).

Analysis of the available data suggests that CRT-S offers a favorable short-term survival compared with D-CRT (median 1-year OS in relevant reports 57.0% *vs* 39.5%) although direct comparison of prognosis between the two groups was available only in a few reports.<sup>10, 11)</sup> On the other hand, the difference in long-term survival between the two groups is marginal due to operative morbidity and inadequate control of distant metastasis (median 5-year OS in relevant reports, 20% *vs* 10%). Then, what population of patients with T4 tumors would achieve survival benefit by undergoing resection after CRT? In the review just mentioned, pathological non-responders (grades 0–2) of the CRT-S group showed a favorable prognosis compared with non-cCR of the D-CRT group (median 1-, 3-, 5-year OS 58%, 30%, and 20% *vs* 24.5%, 3.5%, and 0%). Fujita et al.<sup>11)</sup> also concluded that in patients with T4N0-1M0 esophageal cancer, survival after D-CRT was similar to that achieved by surgery for responders but not for non-responders; among responders to first CRT cycle (36 Gy), there was no difference in long-term (5-year) survival rate between patients who underwent subsequent resection and those who did not (23% *vs* 23%). On the other hand, among non-responders, patients who underwent surgery after first CRT tended to show longer survival than those without subsequent surgery (1- and 2-year survival rates; 64% and 33% *vs* 20% and 20%, respectively). In a randomized phase III trial from France that compared CRT *vs* CRT followed by surgery for patients with locally-advanced but operable (T3N0-1M0) esophageal squamous cell carcinoma, Bedenne et al.<sup>45)</sup> showed no survival benefit for surgery in responder to CRT, compared with additional course of CRT (2-year survival rate; 34% *vs* 40%). These results suggest that surgical resection after CRT adds survival benefits particularly in patients resistant to CRT since in responders to CRT, distant metastasis is the only determinant of prognosis (similar between D-CRT and CRT-S groups). However, further evaluation of large cohorts of T4 tumors in a prospective randomized trial is necessary to determine the survival benefits of each of the above treatment modalities.

## Conclusion

CRT-S seems superior to D-CRT as treatment for T4 esophageal cancer, with respect to local control and short-term prognosis despite relatively high perioperative morbidities. On the other hand, although local control is sometimes difficult in D-CRT, a complete response to CRT might lead to a better prognosis. However, the survival difference in long-term follow-up is marginal due to operative morbidity and inadequate control of distant metastasis. Randomized controlled trials involving large population samples are needed to define the standard treatment for T4 esophageal cancer.

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