Original Articles

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Efficacy of Preoperative Chemoradiation Therapy for cT4 Esophageal Cancer: a Retrospective Study

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Objective: To assess the efficacy of preoperative chemoradiation therapy (CRT) for clinical T4 (cT4) esophageal cancer.
Materials and Methods: From November 1998 to November 2008, 57 patients with cT4 esophageal cancer (any N) without distant metastases underwent preoperative CRT. All but 2 patients received a total dose of 40 Gy administered in 20 fractions over 4 weeks. Eleven patients received 5-fluorouracil and cisplatin, and 46 were treated with docetaxel. All patients underwent reassessment of their response to CRT 1 month after completion of treatment. Surgery was performed within 4 to 6 weeks of completing CRT if the tumor was diagnosed as operable.
Results: One patient discontinued preoperative treatment at 30.6 Gy, and four stopped planned chemotherapy. One patient developed grade 4 thrombocytopenia, and six developed grade 3 leukocytopenia. One patient developed a grade 3 esophagobronchial fistula. Of the 57 patients, 36 (63%) were diagnosed with operable tumors and underwent curative intent surgery. A complete pathological response (grade 3, Japanese Classification of Esophageal Cancer The 11th edition) was achieved in 3 patients. The other responses were grade 2 (The number of proliferating cells is 1/3 or less) in 16 patients, grade 1a (Proliferable cells are 2/3 or more) in 6, grade 1b (Proliferable cells are 1/3 or more and less than 2/3) in 10, and unknown in 1. The 2-year overall survival rate was 21%. The 2-year survival rates for the curative intent surgery group and the inoperable group were 46% and 0%, respectively. In the surgery group, there was no significant difference in overall survival between patients who underwent R0 (no residual tumor) resection and those who underwent R1 (microscopic residual tumor) or R2 (macroscopic residual tumor) resection.
Conclusion: Preoperative CRT for cT4 esophageal cancer was relatively safe but did not improve overall survival (OS) compared to treatment solely with CRT.

Key words: radiation therapy, preoperative CRT, esophageal cancer

Introduction

Esophageal cancer is a leading cause of cancer-related death in Japan. The Cancer Statistics in Japan estimates that 21,965 individuals developed esophageal cancer in 2012, and 11,576 died of the disease in 2014 (http://ganjoho.jp/reg_stat/statistics/stat/summary.html). Tumor resection is the best treatment option to achieve local control of the disease. However, many patients are diagnosed at advanced stages and have a poor prognosis. The 5-year overall survival (OS) rate of patients with this cancer is approximately 50% but is much worse in patients with locally advanced disease; the -

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survival rates for pathological T3 (pT3) and pT4 disease are 39% and 13%, respectively[1].

Because local recurrence and distant metastases are the main issues after surgery[2], preoperative chemotherapy with cisplatin (CDDP) plus 5-fluorouracil is the standard treatment for patients with stage II/III squamous cell carcinoma, based on the definitive results of the Japan Clinical Oncology Group (JCOG) 9907 trial in Japan[3]. In this trial, patients who received preoperative chemotherapy had a significantly higher 5-year OS rate (55%) than patients who received postoperative chemotherapy (43%). Recent meta-analyses also reported a benefit for patients who received preoperative chemoradiotherapy (CRT) compared to patients who did not[4)-6)]. Subgroup analyses of the JCOG 9907 trial revealed that preoperative CRT was less effective for stage III or T3 lesions than limited lesions[7]. For patients with T1-3 disease, preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric-junction cancer[8]. Therefore, more intensive preoperative treatments, including CRT, have been introduced to treat these advanced cases. CRT is reportedly more effective than chemotherapy alone in terms of survival benefit[9].

For patients with T4 disease, the standard treatment is definitive CRT or palliation[10]. Surgery is performed only for resectable tumors following preoperative or definitive CRT. In the present study, the effects of preoperative CRT on survival were evaluated in patients with advanced T3 or T4 disease from 1998 to 2008. We have reported the results of the treatment of patients with T3 disease elsewhere[11]. In that report, patients with lymph node metastasis exhibited a better prognosis in the DOC group than those in the FP group. Preoperative CRT for locally advanced esophageal cancer using DOC results in similar or better long-term outcomes compared with FP-based CRT. In this retrospective analysis, we assessed the efficacy of this treatment in patients with T4 stage disease.

Patients and Methods

This study was approved by the ethics board of our institution. Written informed consent from each individual patient was not required because of the retrospective nature of the study.

1. Patients

From November 1998 to November 2008, 57 patients with cT4 esophageal (any N) without distant metastases underwent preoperative CRT. All patients were reclassified according to the International Union Against Cancer (UICC) TNM classification, seventh edition[12]. The patient characteristics are presented in Table-1. There were 50 male and 7 female patients. The median age was 64 years. Twelve patients had concomitant malignancies: 5 with hypopharyngeal cancer, 2 with gastric cancer, and 1 each with larynx, sigmoid colon, lung, prostate, or uterine cervical cancer. All tumors were early stage and treatable. All patients provided informed consent for treatment. The patients' general condition was relatively good.

The routine pretreatment evaluation included barium esophagography, esophagoscopy, endoscopic ultrasonography, cervical node ultrasonography, and cervical, chest, and abdominal computed tomog-

Table-1 Patient characteristics

Sex	
Male	50
Female	7
Age (years)	64 (39-82)
Performance status *	
0	48
1	5
2	4
cN	
0	1
1	12
2	23
3	18
X	3
Site **	
Ce	7
Ut	17
Mt	27
Lt	3
Unknown	2
Tumor size (mm)	80 (15-143)

Data are presented as n or the median (range).
Data are presented as the number of patients.
* Common Toxicity Criteria, Version2.0 Publish Date April 30, 1999.
** Ce: cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus.

raphy (CT) scan. ^{18}F-Fluorodeoxyglucose positron emission scanning and bronchoscopy were optional.

Clinical stage T4 was defined according to Hironaka, *et al.*[13] as follows: 1) a tumor that extends into the lumen or causes deformity of the tracheobronchial tree or 2) a tumor that is attached to organs at a contact angle of ≥90° in the thoracic aorta, as observed on a CT scan.

The last follow-up was performed in November 2014. Complete follow-up was obtained for 44 patients. Among them, 6 were alive with no evidence of disease, 26 died of disease or treatment-related diseases. Twelve died of non-related disease (median: 44 months, range: 8-94 months). The median follow-up period for the six survivors was 73 months. Thirteen were lost for follow-up: 9 with diseases were treated as died of disease, and 4 without disease were censored at the last visit day in the follow-up analyses.

2. Chemotherapy regimen

In this study, 11 patients received 5-fluorouracil and cisplatin (FP group), and 46 were treated with docetaxel (DOC). The details of chemotherapy have been described elsewhere[10]. Briefly, the FP group received continuous infusion of 5-FU (500 mg/m^2) daily for five days and intravenous infusion of cisplatin (10 mg/m^2) on days 1 to 5, repeated every 4 weeks. The DOC group received DOC (10 mg/m^2) by intravenous infusion on day 1, repeated weekly.

3. Radiation methods

All but two patients received a total dose of 40 Gy administered in 20 fractions over 4 weeks. One patient received 41.4 Gy in 22 fractions. The other patient was treated with 30.6 Gy in 17 fractions. Radiation therapy was administered by a linear accelerator (Mevatrone KDX77; Siemens AG, Erlangen, Germany or Clinac 21EX; Varian Medical Systems, Palo Alto, CA, USA) using two opposing anterior-posterior and posterior-anterior 10-MV X-ray beams. One or two additional subfields were added if necessary to maintain the dose distribution from 95% to 107% of the prescribed dose within the target volume.

The clinical target volumes included the primary tumors and bilateral supraclavicular and mediastinal lymph nodal regions (T-field) in 46 patients; primary lesions and mediastinum (I-field) in 4 patients; and primary lesions, mediastinum, and pericardiac regions (L-field) in 7 patients.

4. Surgery

The response to CRT was assessed in all patients 1 month after completion of treatment using barium esophagography, esophagoscopy, endoscopic ultrasonography, cervical node ultrasonography, and cervical, chest, and abdominal CT scans. Surgery was performed within 4 to 6 weeks of completion of CRT for operable tumors. Additional irradiation of 20 to 26 Gy and/or combination chemotherapy was administered for inoperable tumors.

The pathological response to treatment was judged using the Rules for Classification of Esophageal Cancer in Japan of the Japan Esophageal Society[14]. Adverse effects were scored according to the National Cancer Institute Common Toxicity Criteria, v4.0[15].

5. Statistical evaluation

Overall survival (OS) rates were calculated from the first day of treatment using the Kaplan-Meier method. Differences between curves were analyzed by the log-rank test appropriate when assessing the differences in OS, because the number of samples was not large, and it was difficult to assume a normal distribution. Differences in the incidence of factors between the two groups were compared using Fisher's exact test or the Mann-Whitney U test. The threshold of statistical significance was $p < 0.05$. These analyses were performed using HALBAU statistical software (http://halbau.jp/index.htm) and BellCurve for Execel ver.2.0.

Results

1. Treatment sequelae

Treatment sequelae are presented in Table-2. All but one patient completed radiation therapy. One patient discontinued treatment at 30.6 Gy in 17 fractions due to deteriorating pulmonary symptoms. Four patients discontinued chemotherapy because of anaphylaxis in response to DOC (n=1), skin reactions (n=1), mucositis (n=1), and bone marrow suppression (n=1, WBC: 1,200/mm^3). Bone marrow suppression was a common acute adverse effect of CRT. One patient developed grade 4 thrombocytopenia, and six patients developed grade 3 leukocytopenia. One patient developed a

grade 3 esophagobronchial fistula.

2. Responses to CRT 1 month after completion of treatment

Based on the imaging results, the clinical responses were partial response in 19 patients, stable disease in 34, and progressive disease in 4. Of the 57 patients, 36 (63%) were deemed to have operable tumors and underwent curative intent surgery. A total of 27 patients underwent right thoracotomy and total extirpation of the thoracoabdominal esophagus combined with lymph node dissection in the cervical, thoracic, and abdominal regions. Another 2 patients underwent the same resection only in the lymph node regions of the mediastinum and abdomen. A total of 7 patients underwent other surgeries.

Table-3 presents the pathological evaluation results of the resected lesions in 36 patients. A complete pathological response (grade 3)[13] was achieved in 3 patients. The other responses were grade 2 (The number of proliferating cells is 1/3 or less) in 16 patients, grade 1a (Proliferable cells are 2/3 or more) in 6 patients, grade 1b (Proliferable cells are 1/3 or more and less than 2/3) in 10 patients, and unknown in 1 patient. Thirty patients had a stage pT3 or lower tumor at the time of surgery, whereas six had pT4 tumors. Twenty-four patients underwent R0 (no residual tumor)[13] resection, and 12 underwent R1 (microscopic residual tumor) or R2 (macroscopic residual tumor) resection.

Of the 21 patients who were not designated to undergo curative intent surgery, 4 were treated with palliative surgery, 2 with additional CRT, 8 with radiation therapy only, 2 with chemotherapy only, and 1 with esophageal stent placement. Another 4 patients received no further treatment.

3. Survival

The OS rates for all patients were 39% and 21% 1 year and 2 years after the commencement of treatment, respectively. The median survival time was 9 months (Figure-1). Between curative intent surgery group and inoperable group, the 2-years survival rates were 31% vs 0%, median survival time were 10.5 months vs 6 months,respectively. The difference in OS between these two groups was significant.

In the surgery group, there was no significant

Table-2 Acute adverse effects of preoperative chemoradiation therapy

Grade	2	3	4
Leukopenia	5	6	0
Thrombocytopenia	1	0	1
Anemia	3	0	0
Esophagitis	1	0	0
Dermatitis	1	0	0
Esophagobronchial fistula	1	1	0

Data are presented as the number of patients.

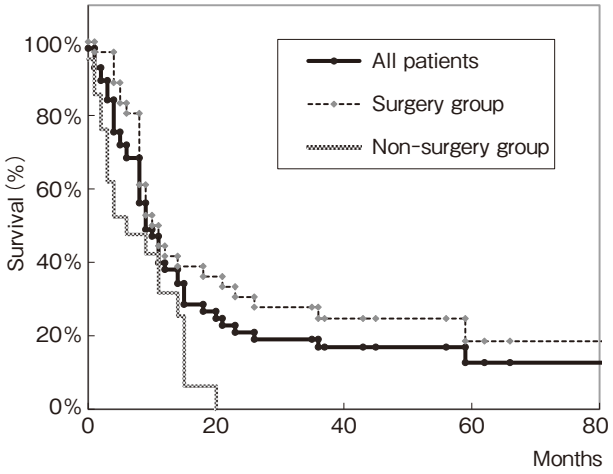

Figure-1
Kaplan-Meier curve of overall survival for 57 patients with cT4 stage III esophageal cancer who received preoperative CRT according to operability.
Median Survival Time: All patients 9 months, Surgery group 11 months, Non-surgery group 6 months

Table-3 Histopathological findings of resected specimens from 36 patients

pT stage	pT1b	pT2	pT3	pT4
	2	4	24 *	6
pN stage	pN0	pN1	pN2	pN3
	9	9	7	11

Data are presented as number of patients.
* Among these 24 patients, tumor cells were observed at the surgical margins in 6 patients.

(p=0.011). Difference in OS between patients who underwent R0 resection and those who underwent R1 or R2 resection (Figure-2). In the nonsurgery group, there was no significant difference in OS between patients who received additional radiation and patients who did not (p=0.19).

Discussion

Preoperative CRT for cT4 esophageal cancer was performed relatively safely in 56 (98%) of 57 patients. The 2-year OS for the 36 patients who underwent resection with curative intent was 31%. Nishimura, *et al.*[16] reported a 2-year OS of 27% for 11 patients with cT4 stage III esophageal cancer treated with CRT; in that study, only one of the five patients who underwent resection after CRT (30-60 Gy) was still alive after 2 years.

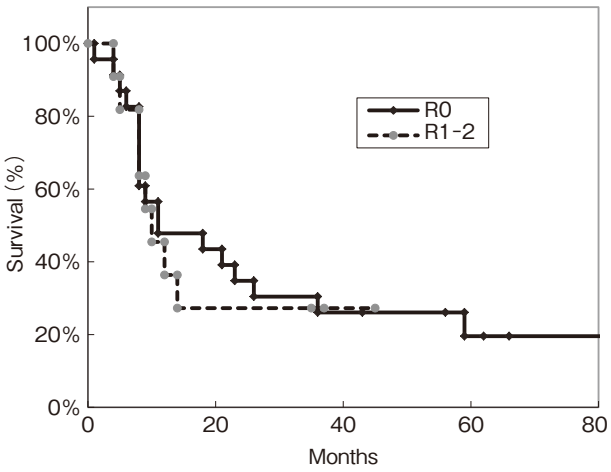

Figure-2
Kaplan-Meier curve of overall survival for 36 patients with cT4 stage III esophageal cancer who received preoperative CRT and resection according to pathological stage. (p=0.82)
R0: no residual tumor, R1: microscopic residual tumor, R2: macroscopic residual tumor
Median Survival Time: R0 group 11M, R1-2 group 10M

Table-4 summarizes the treatment results for the patients with cT4 disease who received CRT[16)-20)]. Overall, there was no difference in OS between patients who underwent CRT alone and patients who underwent resection after CRT. Fujita[10] has proposed that the standard treatment should be definitive CRT or palliation. Our results and those reported by others support this recommendation. In our study, survival rates were higher in the surgery group than in the nonsurgery group, but this result was likely influenced by a strong selection bias.

Among all patients with cT4 disease at diagnosis, 36 (63%) had stage T3 or lower disease after CRT as confirmed by imaging examination, and 30 (53%) had pathological T3 or lower disease at the time of surgery. These findings indicate either that CRT is effective in reducing tumor size or that patients were overdiagnosed during the pretreatment examinations. Moreover, 12 patients who underwent surgery did not achieve complete resection, indicating that one-third of tumors were misdiagnosed as operable by imaging examination after CRT. Uncertainties about the extent of tumor invasion based on imaging findings should be considered when selecting a treatment plan for individual patients. The extent of tumor infiltration into adjacent organs is usually diagnosed using the CT criteria described above[13], but adequately judging tumor invasion to other structures can be difficult. More accurate diagnostic methods are needed to improve the outcomes of esophageal cancer treatment.

Table-4 Clinical results of CRT for T4 and/or M1 esophageal cancer

Reference	Cx	Dose	MST	OS (%)		
		(Gy)	(mo)	2-y	3-y	5-y
Ishikura S[18)]	PF *	60	11	-	22	13
Ishida K[19)]	PF	60	10	31.5		
Nishimura Y[17)]	PF	60	12	27		
Higuchi K[20)]	DCF **	50.4 ***	29		43.9	
Ishikura S[21)]	nedaplatin + 5-FU	60	12	31		
Present study	DOC (+S)	40	10.5	31	25	
	Total	40-60	9	21	17	

* CDDP+5-FU, ** Docetaxel+CDDP+5-FU, *** 50.4 Gy, 30 patients; 61.2 Gy, 12 patients
MST: median survival time; OS: overall survival

A total of 46 patients were treated with DOC in this study. In our previous study of T3 disease, pathological evaluation of the resected lesions revealed a significant curative effect in the FP group but a higher survival rate in the DOC group than in the FP group[11]. The intensity of the FP treatment in this study was lower than the protocol used in standard induction chemotherapy or in definitive CRT for esophageal cancer. This is one possible reason for the insufficient effect of induction CRT in this study.

Stahl, *et al*.[8] demonstrated that in patients who received neoadjuvant CRT, continuation of CRT resulted in OS equivalent to that of surgery. However, in the nonsurgery group in the present study, there was no difference in OS between the patients who did and did not receive additional radiation. This suggests that additional treatment of patients who did not respond to preoperative CRT had no effect, and palliative therapy should instead be considered for these patients.

Conclusions

Preoperative CRT for cT4 esophageal cancer was performed relatively safely but did not improve OS compared to the reported results of patients treated with CRT alone.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1) Tachimori Y, Ozawa S, Fujishiro M, *et al*: Comprehensive registry of esophageal cancer in Japan, 2005. Esophagus, 2014; 11: 1–20.
2) Kim MK, Kim SB, Ahn JH, *et al*: Treatment outcome and recursive partitioning analysis–based prognostic factors in patients with esophageal squamous cell carcinoma receiving preoperative chemoradiotherapy. Int J Radiat Oncol Biol Phys, 2008; 71: 725–734.
3) Ando N, Kato H, Igaki H, *et al*: A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5–fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol, 2012; 19: 68–74.
4) Gebski V, Burmeister B, *et al*; Australasian Gastro–Intestinal Trials Group: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta–analysis. Lancet Oncol, 2007; 8: 226–234.
5) Kranzfelder M, Schuster T, Geinitz H, Friess H, Buchler P: Meta–analysis of neoadjuvant treatment modalities and definitive non–surgical therapy for oesophageal squamous cell cancer. Brit J Surgery, 2011; 98: 768–783.
6) Sjoquist KM, Burmeister BH, Smithers BM, *et al*: Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta–analysis. Lancet Oncol, 2011; 12: 681–692.
7) Ando N: Progress in multidisciplinary treatment for esophageal cancer in Japan as reflected in JCOG studies. Esophagus, 2011; 8: 151–157.
8) Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D; ESMO Guidelines Working Group: Oesophageal cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow–up. Ann Oncol, 2013; 24 S4: vi51–vi56.
9) van Hagen P, Hulshof MCCM, van Lanschot JJB, *et al*: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med, 2012; 366: 2074–2084.
10) Fujita H: A history of surgery for locally–advanced (T4) cancer of the thoracic esophagus in Japan and a personal perspective. Ann Thorac Cardiovasc Surg, 2013; 19: 409–415.
11) Kushida T, Nohara S, Yoshino K, *et al*: Utility of weekly docetaxel combined with preoperative radiotherapy for locally advanced esophageal cancer from pathological analysis. Dis Esophagus, 2014; 27: 368–373.
12) In: Sobin LH, Gosoidarowicz MK, Wittekind C, eds. TNM Classification of Malignant Tumours, 7th edition. New York: Wiley–Blackwell Inc, 2009.
13) Hironaka S, Ohtsu A, Boku N, *et al*: Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T2–3Nany M0 squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys, 2003; 57: 425–433.
14) Japan Esophageal Society: Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus, 2017; 14: 1–36.
15) U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. (https://evs. nci. nih. gov/ftp1/CTCAE/CTCAE_4.03_2010–06–14_QuickReference_5x7.pdf)
16) Nishimura Y, Suzuki M, Nakamatsu K, Kanamori S, Yagyu Y, Shigeoka H: Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5–fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys, 2002; 53: 134–139.
17) Ishikura S, Nihei K, Ohtsu A, *et al*: Long–term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol, 2003; 21: 2697–2702.
18) Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M: Phase II study of cisplatin and 5–fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan esophageal oncology group (JEOG)/Japan clinical oncology group trial (JCOG9516). Jpn J Clin Oncol, 2004; 34: 615–619.
19) Higuchi K, Komori S, Tanabe S, *et al*; Kitasato Digestive Disease and Oncology Group: Definitive chemoradiation therapy with docetaxel, cisplatin, and 5–fluorouracil (DCF–R) in advanced esophageal cancer: a phase 2 trial (KDOG 0501–P2). Int J Radiat Oncol Biol Phys, 2014; 89: 872–879.
20) Ishikura S, Ohtsu A, Shirao K, *et al*: A phase I/II study of nedaplatin and 5–fluorouracil with concurrent radiotherapy in patients with T4 esophageal cancer: Japan clinical oncology group trial (JCOG 9908). Esophagus, 2005; 2: 133–137.