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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinical Implications of Conversion Surgery After Induction Therapy for T4b Thoracic Esophageal Squamous Cell Carcinoma

Hiroshi Miyata, MD[1], Keijirou Sugimura, MD[1], Masaaki Motoori, MD[1], Takeshi Omori, MD[1], Kazuyoshi Yamamoto, MD[1], Yoshitomo Yanagimoto, MD[1], Naoki Shinno, MD[1], Masayoshi Yasui, MD[1], Hidenori Takahashi, MD[1], Hiroshi Wada, MD[1], Masayuki Ohue, MD[1], and Masahiko Yano, MD[1]

Department of Digestive Surgery, Osaka International Cancer Institute, Osaka, Japan

ABSTRACT

Background. Definitive chemoradiation therapy or chemotherapy alone is generally recommended for patients with unresectable cT4b esophageal cancer. However, conversion surgery has emerged as a therapeutic option when downstaging is achieved by induction therapy.

Methods. We studied 169 patients with cT4 esophageal cancer who underwent induction therapy. Survival and prognostic factors were examined.

Results. Of 169 patients, 25 who achieved a clinical complete response (cCR) underwent surveillance, 72 patients underwent conversion surgery, while another 72 patients whose tumors were regarded as unresectable after induction therapy did not undergo surgery. Among 169 patients, the 3- and 5-year survival rates were 31.0% and 25.9%, respectively. Sixty-four patients who underwent curative resection showed better survival comparable with survival of 25 patients who achieved cCR (3- and 5-year survival; 56.8% and 48.6% versus 64.0% and 52.0%, respectively). However, the survival of eight patients who underwent noncurative resection was as dismal as that of patients who did not undergo conversion surgery. Multivariate analysis in 169 patients identified female sex and achieving cCR or R0 resection as independent prognostic factors. Multivariate analysis in 72 patients who underwent conversion surgery identified sex, lymph node status, and R0 resection as independent prognostic factors in patients with cT4b esophageal cancer.

Conclusions. The present study showed that conversion surgery after induction therapy can be a potentially curative treatment option for select patients with cT4b esophageal cancer. An important issue for further research is to establish a method for more accurately diagnosing tumor resectability after induction therapy for cT4b esophageal cancer.

Neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by surgery has been accepted as the standard treatment for locally advanced resectable esophageal cancer.[1–6] However, esophageal cancers sometimes invade adjacent structures such as the trachea, vertebral body, and aorta, owing to anatomical features of the esophagus, including a lack of serosa and close proximity to those organs. Unresectable T4b esophageal cancers is not generally considered as an indication for curative surgery, and definitive CRT or chemotherapy alone has been recommended for patients with T4b esophageal cancer.[7–11]

When T4b esophageal cancer responds to induction therapy, downstaging can be achieved, and, moreover, complete response (CR) becomes possible. Indeed, previous studies have shown that CR was achieved in 16–32% of patients with T4 esophageal cancer after CRT.[9,10,12,13] Thus, if T4 invasion is relieved by induction therapy, conversion surgery emerges as a therapeutic option for clinical T4b esophageal cancer. Previous studies showed that curative resection could be performed in 32–78% of patients with T4b esophageal cancer;[14–19] however, the clinical benefit of conversion surgery for cT4b esophageal

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H. Miyata, MD
e-mail: hmiyata@gesurg.med.osaka-u.ac.jp

cancer remains uncertain. In the present study, we examined the clinical implication of conversion surgery after induction therapy in patients with cT4b esophageal cancer.

MATERIALS AND METHODS

Patients

This study included 169 patients who had thoracic esophageal cancer invading adjacent structures without distant organ metastasis and who were treated at Osaka International Cancer Institute between January 2004 and December 2016. During the same period, 813 patients with esophageal cancer underwent surgery with or without neoadjuvant therapy in our institute. All 169 patients were histologically confirmed as having squamous cell carcinoma of the thoracic esophagus.

The study protocol was approved by the Human Ethics Review Committee of Osaka International Cancer Institute.

Treatment Protocols

Induction therapy included induction CRT, induction chemotherapy, and induction chemotherapy followed by CRT (C-CRT). In the CRT treatment, a single daily fraction of 2 Gy was administered up to 40–60 Gy concurrently with cisplatin and 5-fluorouracil.[20,21] Cisplatin was administered at 70 mg/m^2 (days 1 and 29) and 5-fluorouracil was administered at 700 mg/m^2 (days 1–4 and days 29–32). The radiation field was designed to encompass the primary tumor and metastatic lymph nodes (LNs) with an ample margin. The induction chemotherapy regimen consisted of 5-fluorouracil and cisplatin plus adriamycin (ACF), or 5-fluorouracil and cisplatin plus docetaxel (DCF).[6,22] In the ACF regimen, 5-fluorouracil was administered at 700 mg/m^2 on days 1–7, with cisplatin at 70 mg/m^2 and adriamycin at 35 mg/m^2 on day 1. In the DCF regimen, 5-fluorouracil was administered at 700 mg/m^2 on days 1–5, along with cisplatin at 70 mg/m^2 and docetaxel at 70 mg/m^2 on day 1. Two courses of chemotherapy were administered, separated by a 3- to 4-week interval. In the C-CRT treatment, concurrent CRT consisting of simultaneous 40–60 Gy radiation and cisplatin and 5-fluorouracil was administered after induction of ACF or DCF.

In principle, when T4 invasion was relieved by induction therapy and complete tumor resection was considered possible, conversion surgery was performed. However, for patients who achieved clinical CR (cCR), close surveillance without surgery was proposed, and was performed if patients opted to undergo surveillance.

Our standard procedures for T4b esophageal cancer consisted of subtotal esophagectomy with mediastinal lymphadenectomy via right thoracotomy, upper abdominal lymphadenectomy, reconstruction of the gastric tube, and anastomosis in the cervical incision. Cervical lymphadenectomy was performed for patients with upper or middle thoracic esophageal cancer, although it was sometimes omitted after preoperative CRT. During the study period, three surgeons who had more than 10 years of experience as a specialized surgeon operated for patients with cT4 esophageal cancer.

Evaluation of Clinical and Pathological Response

After completion of the induction chemotherapy and/or CRT, all patients were restaged by computed tomography (CT), endoscopy, and positron emission tomography (PET). The response was categorized based on the Japanese Society for Esophageal Diseases.[23] cCR was defined as complete regression of disease based on CT scan and/or PET scan and endoscopy. The patient was not considered to achieve cCR when persistent ulceration and/or the presence of cancer cells in biopsy samples were confirmed on endoscopy.[10,24]

The degree of histopathological tumor regression was classified into five categories: grade 3, no viable residual tumor cells; grade 2, less than one-third residual tumor cells; grade 1b, one-third to two-thirds residual tumor cells; grade 1a, more than two-thirds residual tumor cells; and grade 0, no significant response to preoperative therapy.[6,22–24]

The histopathological findings were classified according to the Union for International Cancer Control (UICC) TNM classification.[25]

Follow-Up After Surgery

Following hospital discharge, patients were observed every 3 months, and CT of the neck, thorax, and upper abdomen was performed every 6 months thereafter. Upper gastrointestinal endoscopy was performed annually. When recurrence was suspected by CT scan, more selective investigations, such as PET and magnetic resonance imaging, were performed to confirm or refute recurrent disease.

RESULTS

Patient Characteristics and Treatment

Table 1 lists the characteristics of all 169 patients. The organ involved in the cT4b tumor was the trachea in 138

TABLE 1 Characteristics of 169 patients with T4b esophageal cancer

	Total (n = 169)	CRT (n = 109)	C (n = 29)	C-CRT (n = 31)
Age, years (mean ± SD)	64.2 ± 8.0	63.7 ± 8.7	66.2 ± 5.3	64.1 ± 7.4
Sex				
Male	136 (80)	90 (83)	23 (79)	23 (74)
Female	33 (20)	19 (17)	6 (21)	8 (26)
Tumor location				
Upper third	81 (48)	57 (52)	11 (38)	13 (42)
Middle third	84 (50)	51 (47)	15 (52)	18 (58)
Lower third	4 (2)	1 (1)	3 (10)	0 (0)
T4 organ				
Trachea	138 (82)	90 (83)	22 (76)	26 (84)
Aorta	14 (8)	9 (8)	4 (14)	1 (3)
Trachea + aorta	17 (10)	10 (9)	3 (10)	4 (13)
T4 reason				
Primary site	146 (86)	92 (84)	26 (90)	28 (90)
Lymph node	23 (14)	17 (16)	3 (10)	3 (10)
cN				
cN0	31 (18)	27 (25)	4 (14)	0 (0)
cN1	84 (50)	51 (47)	12 (41)	21 (68)
cN2-3	54 (32)	31 (28)	13 (45)	10 (32)
cM				
cM0	142 (84)	93 (85)	24 (83)	25 (81)
cM1lym	27 (16)	16 (15)	5 (17)	6 (19)
cStage				
IIIC	142 (84)	93 (85)	24 (83)	25 (81)
IV	27 (16)	16 (15)	5 (17)	6 (19)

Data are expressed as n(%) unless otherwise specified

CRT Chemoradiotherapy, *C* chemotherapy, *C-CRT* chemotherapy followed by chemoradiotherapy

patients (81.7%), aorta in 14 patients (8.3%), and the trachea plus aorta in 17 patients (10.1%). The cause for T4 invasion was the primary site in 146 patients (86.4%) and LN metastasis in 23 patients (13.6%). Among 169 patients, 109 (64.5%) underwent induction CRT, 29 (17.2%) underwent induction chemotherapy, and 31 (18.3%) underwent induction C-CRT.

After induction therapy, cCR was achieved in 26 patients, including 22 patients after CRT, 3 patients after C-CRT, and 1 patient after induction chemotherapy. The cCR rate was 20.2% in the CRT group, 9.7% in the C-CRT group, and 3.4% in the chemotherapy group. Twenty-five of these 26 patients with cCR underwent surveillance and 1 opted to undergo conversion surgery. In 72 patients, T4 invasion was not relieved and palliative therapy was performed. As a result, conversion surgery was performed for 72 patients, including 17 patients with two-field lymphadenectomy and 55 patients with three-field lymphadenectomy. Postoperative complications occurred in 28 (38.9%) of 72 patients with conversion surgery. Pulmonary complications occurred in 9 patients (12.5%), anastomotic leakage in 6 patients (8.3%), recurrent nerve palsy in 7 patients (9.7%), chylothorax in 4 patients (5.5%), arrhythmia in 4 patients (5.5%), and bleeding in 2 patients (2.8%). One patient (1.4%) died within 30 days after surgery due to postoperative bleeding.

Survival

The median length of follow-up was 15.2 months (range 1.8–174.3) for all patients. Among the 169 patients with T4b tumors, the 3- and 5-year survival rates were 31.0% and 25.9%, respectively (Fig. 1). Of the 25 patients with cCR who underwent surveillance, 14 developed recurrent disease during surveillance, 3 developed local recurrence, 7 developed LN metastasis, 2 developed distant organ metastasis, 1 developed local recurrence and LN metastasis, and 1 developed distant organ and LN metastasis. Of 9 patients with LN recurrence, 5 developed LN metastasis inside the radiation field, and 4 developed LN metastasis inside and outside the radiation field. The average time to recurrence after completion induction therapy was

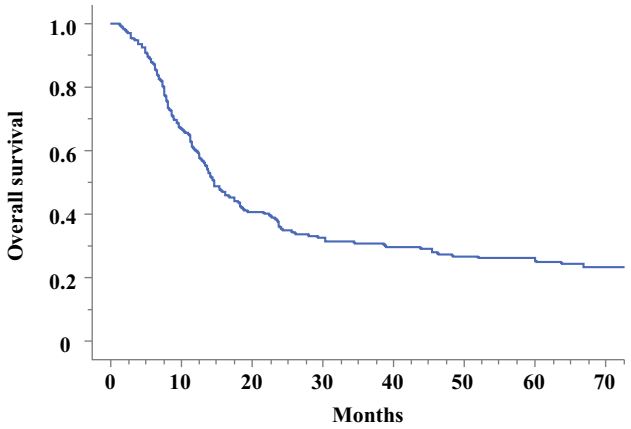

FIG. 1 Overall survival rate of 169 patients with cT4b esophageal cancer

413 days in 14 patients who developed recurrence after achieving cCR. Of these 14 patients, 1 patient with local recurrence and 2 patients with LN recurrence underwent salvage surgery. The survival of patients who underwent surgical resection was significantly better than that of patients who did not undergo surgical resection (3- and 5-year survival: 50.4% and 43.1% vs. 0% and 0%, respectively; $P < 0.001$) (Fig. 2a). However, there was no significant difference in survival between patients who underwent conversion surgery and patients with cCR and surveillance (3- and 5-year survival: 50.4% and 43.1% vs. 64.0% and 52.0%, respectively; $P = 0.227$) (Fig. 2a). In subclass analysis according to curability, 64 patients who underwent curative resection (R0) showed better survival comparable to the survival of patients with cCR (3- and 5-year survival: 56.8% and 48.6%, respectively) (Fig. 2b). However, the survival of 8 patients with noncurative resection (R1/2), including 7 patients whose tumors invaded the trachea and 1 patient whose tumor invaded the aorta, was nearly as dismal as that of patients who did not undergo conversion surgery.

Of 64 patients with R0 resection, recurrence was observed in 35 patients. Local recurrence was observed in 7 patients, lymphatic recurrence in 18 patients (cervical in 8 patients, thoracic in 12 patients, distant abdominal in 2 patients), and distant organ metastasis in 17 patients (sites were lung in 10 patients, liver in 1 patient, pleura or peritoneum in 6 patients, bone in 5 patients, and brain in 1 patient). The average time to recurrence was 11.0 months. There was no significant difference in the recurrence rate and failure patterns after surgery between the types of induction therapy. Of 64 patients with R0 resection, deaths due to other diseases were observed in 7 patients (due to other cancers in 2 patients, heart failure in 2 patients, suicide in 1 patient, bleeding after surgery in 1 patient, and unknown reason in 1 patient). The cause-specific survival (electronic supplementary figure) had almost the same tendency as the overall survival shown in Fig. 2b.

Factors Associated with Survival

Univariate analysis showed that female sex and achieving cCR or R0 resection, which seemed to be synonymous with actual T4 relief, was significantly associated with better prognosis of patients with cT4b esophageal cancer. Multivariate analysis identified these two factors as independent prognostic factors (Table 2).

In 72 patients who underwent conversion surgery, pathological CR (grade 3) was observed in 13 patients (18.1%). Univariate analysis showed that sex, tumor depth, LN status, histopathological response, and R0 resection were significantly associated with patient survival, while multivariate analysis identified sex, LN status, and R0 resection as independent prognostic factors in patients with

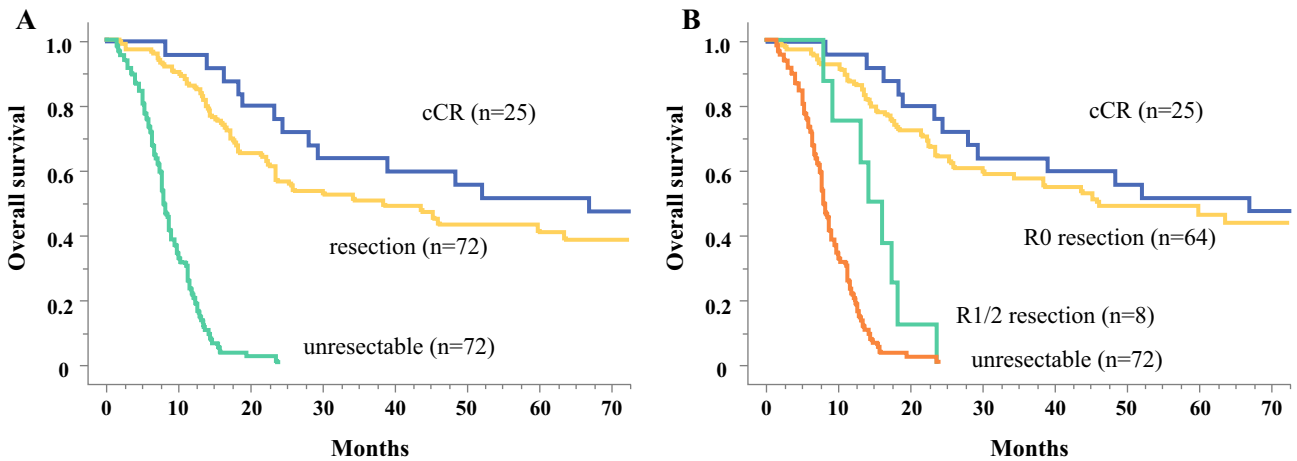

FIG. 2 Overall survival rate of 169 patients with cT4b esophageal cancer according to **a** surgical resection, and **b** curative resection. *cCR* clinical complete response

TABLE 2 Univariate and multivariate analyses of 169 patients with T4b esophageal cancers

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (> 70 years)	1.42	0.97–2.08	0.070	1.11	0.76–1.63	0.593
Sex (female)	0.50	0.30–0.82	0.006	0.59	0.36–0.98	0.042
Tumor location (upper third)	0.88	0.62–1.24	0.459			
T4 organ (aorta)	1.36	0.89–2.11	0.168			
T4 by LN metastasis (present)	1.44	0.90–2.313	0.127			
cN (cN2-3)	1.06	0.73–1.53	0.772			
M1lym (present)	1.18	0.74–1.89	0.477			
Initial therapy (CRT)	1.16	0.80–1.67	0.437			
CR or R0 resection (achieved)	0.09	0.05–0.14	<0.001	0.17	0.06–0.15	<0.001

LN Lymph node, *CRT* chemoradiotherapy, *CR* complete response, *HR* hazard ratio, *CI* confidence interval

cT4b esophageal cancer who underwent conversion surgery (Table 3).

DISCUSSION

In an era when definitive CRT or chemotherapy alone are generally recommended for patients with cT4b esophageal cancer, the clinical implication of conversion surgery after induction therapy in those patients is uncertain. The present study showed that the prognosis of patients who underwent curative resection was as favorable as that of patients who achieved cCR after induction therapy. However, the prognosis of patients who underwent noncurative resection was as dismal as that of patients whose tumors remained unresectable after induction therapy.

The survival of patients in this study with cT4b esophageal cancer who underwent R0 resection seems to be better than in previous studies (3- and 5-year survival: 56.8% and 48.6%, respectively).[17,26–28] The study by de Manzoni et al.[17] reported that 20 of 51 patients (39.2%) who received induction CRT underwent R0 resection, and the 3-year survival of patients with R0 resection was < 30%. Ancona et al.[26] also reported that the 5-year survival rate of 52 patients with R0 resection after induction chemotherapy was 29.0%. A more recent study by Ishikawa et al.[27] showed that 18 of 30 patients (60%) with cT4b esophageal cancer who received induction CRT underwent R0 resection, and the 3-year survival rate of those patients was 50.0%. Our favorable prognosis of patients with cT4b esophageal cancer who underwent R0 resection suggests that conversion surgery may offer a survival benefit for select patients.

In this study, there was no significant difference in survival between patients who achieved cCR after induction therapy and then underwent surveillance without surgery and patients who underwent conversion surgery. It remains unclear whether there is a role for additional surgery for patients who achieved cCR after CRT. To our knowledge, there has only been one study comparing planned surgery with surveillance without surgery after cCR to CRT. In their intention-to-treat case–control study

TABLE 3 Univariate and multivariate analyses of 72 patients with surgical resection

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (> 70 years)	1.24	0.62–2.46	0.545			
Gender (female)	0.33	0.14–0.79	0.012	0.36	0.14–0.93	0.035
Tumor location (upper)	0.97	0.53–1.77	0.918			
T4 organ (aorta)	1.13	0.54–2.37	0.749			
T4 by LN metastasis (present)	2.16	0.95–4.89	0.067	1.54	0.62–3.83	0.354
pT (T3-4)	2.31	1.13–4.69	0.021	1.01	0.39–2.60	0.998
pN (N2-3)	2.59	1.36–4.93	0.004	2.69	1.43–5.95	0.015
Pathological response (path CR)	0.47	0.25–0.88	0.018	0.91	0.41–2.04	0.820
Number of resected LNs (< 60)	1.37	0.75–2.53	0.297			
R0 resection (achieved)	0.21	0.09–0.47	0.002	0.15	0.06–0.39	0.001

LN Lymph node, *path CR* pathological complete response, *HR* hazard ratio, *CI* confidence interval

including 177 patients who achieved cCR to CRT, Piessen et al.[29] showed that the survival of patients with cCR after CRT was better after planned surgery than after surveillance without surgery. They assumed that this result was partly due to inherent limitations of clinical response assessment, finding that pathologically residual tumors remained in 34.6% of patients who achieved cCR. In our study, among 25 patients who achieved cCR after induction therapy and underwent surveillance, 14 patients developed recurrent disease. Our results suggest that cCR after induction therapy for cT4b esophageal cancer does not necessarily mean being cured. Considering the previously reported low rate of pathological CR (2.7–16.7%) in patients with cT4 esophageal cancer who underwent induction CRT,[14–18] even in patients who respond well to induction therapy, additional surgery can add survival benefit to induction therapy for cT4b esophageal cancer.

In this study, prognosis of patients who underwent noncurative resection was as dismal as that of patients who had unresectable tumors after induction therapy. This result suggests that accurate determination of the resectability of cT4b esophageal cancer after induction therapy is vitally important in the decision-making process for conversion surgery in patients with cT4b cancer. However, only a few studies have assessed resectability after induction therapy for patients with cT4b esophageal cancer.[21,30] In their study, in which 30 of 48 patients with cT4 esophageal cancer who received induction therapy underwent R0 resection, Karimata et al.[30] reported that clinical major response and improvement in dysphagia were independent factors associated with R0 resection. Our previous study showed that a post-treatment maximum standardized uptake value (SUV_{max}) of < 4.7 by ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG-PET) and the volume reduction rate of $\geq$ 44% based on CT scans were independent predictors of R0 resection after induction therapy in patients with cT4b tumors. The sensitivity and specificity for predicting R0 resection in that study were 94.2% and 61.5% in volume reduction rate by CT, and 62.9% and 92.3% in post-treatment SUV_{max} by ^{18}F-FDG-PET, respectively.[21] Further studies are needed to explore the method to accurately diagnose the resectability of cT4b esophageal cancer after induction therapy.

Our study has several limitations. First, the study was retrospective in design and was conducted in only one institution. The second limitation was that the indication for surgical resection depended not only on respectability but also on patient selection. When cCR was achieved by induction treatment, almost all patients excluding one opted to undergo surveillance without surgery rather than surgical resection. Third, the cCR rate of 15.9% (26 of 169 patients) in this study seems to be relatively low compared with that in previous studies, with the reported cCR rate being 16–32% of patients with T4 esophageal cancer.[9,10,12,13] This result may be caused by the difference in timing when patients were restaged after induction therapy. Several studies showed that a longer interval between neoadjuvant CRT and surgery was associated with a higher probability of pathological CR.[31,32] In this study, patients were restaged relatively early after completing induction therapy, in many cases within 3–4 weeks after induction therapy. This relatively shorter interval between induction therapy and restaging may result in a relatively low cCR rate.

CONCLUSIONS

The present study showed that the prognosis of patients who underwent curative resection was as favorable as that of patients who achieved cCR after induction therapy. We think that conversion surgery can be recommended if tumor is resectable after induction therapy in patients with cT4b esophageal cancer. However, further studies are needed to determine whether surgical resection should be performed for patients who achieve cCR. Another important issue is to establish a method for more accurately diagnosing resectability after induction therapy for cT4b esophageal cancer.

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