Because of the poor local control rates and survival rates for unresectable T4 esophageal tumors, a new treatment strategy is necessary.

Preoperative CRT of 20–50.4 Gy improved the 3-year overall survival for resectable esophageal cancer in some meta-analysis of clinical trials in Europe and the USA [7–12]. Based on the meta-analysis, preoperative CRT is recommended for resectable esophageal cancer in the USA, although preoperative chemotherapy is a standard treatment for resectable esophageal cancer in Japan. It has been reported that the pathological complete response (pCR) rate of preoperative CRT increased from a total dose of 30–50 Gy [10]. One the other hand, postoperative mortality was significantly increased by preoperative CRT [7].

To improve the local control rate and the overall survival rate for patients with unresectable esophageal cancer, we adopted an institutional protocol of preoperative definitive-dose 50 Gy CRT followed by surgery for locally advanced unresectable esophageal cancer. The aim of the study was to analyze clinical results of definitive-dose preoperative CRT of 50 Gy/25 fractions/5 weeks for unresectable esophageal cancer.

## Patients and methods

This institutional treatment protocol of preoperative CRT for locally advanced unresectable esophageal cancer was adopted in 2008 by our Cancer Board consisting of radiation oncologists, surgeons, medical oncologists, and gastroenterologists. Written informed consent for preoperative CRT was obtained before the protocol treatment.

### Eligibility criteria

The inclusion criteria were histologically confirmed unresectable esophageal squamous cell carcinoma with T4b or mediastinal lymph nodes (LNs) invading to the trachea or aorta. All patients underwent physical examination, upper gastrointestinal endoscopy (GIF) and computed tomography (CT) of the chest and abdomen with contrast enhancement. Positron emission tomography (PET)/CT was performed for most patients. Invasion to the aorta was diagnosed when the Picus's angle (the angle of fat plane obliteration by the tumor) exceeded 90° of the aorta on contrasted CT images [13]. The tracheal invasion was diagnosed when the floor of a tumor contacted with a deformed and irregular trachea or main bronchus on contrasted CT images. Only patients with no prior therapy, age <80 years, performance status (PS) of 0–1, and adequate bone marrow, hepatic and renal function, and N0-2 (UICC TNM Classification, 7th edition) were eligible. Patients with malignant fistula, distant metastases, N3, or positive LNs of all three LN regions (cervical, mediastinal, and abdominal areas) were excluded.

**Table 1** Patient and tumor characteristics

| | |
|---|---|
| Age (years) | |
| Range | 50–78 |
| Median | 66 |
| Gender | |
| Male:female | 26:4 |
| PS | |
| 0: 1 | 23:7 |
| Histology | |
| Squamous cell carcinoma | 30 |
| Tumor sites | |
| Ce:Ut:Mt | 9:7:14 |
| T-stage (UICC 7th, 2009) | |
| T1b:T2:T3:T4b | 1:1:4:24 |
| N-stage | |
| N0:N1:N2 | 3:25:2 |
| c-stage | |
| II:III:IV | 1:23:6 |

### Patients

From November 2008 to October 2011, 30 patients (26 males and 4 females) entered this study. Patient and tumor characteristics are shown in Table 1. The median age was 66 years (range 50–78 years). As of January 2014, the median follow-up period of the surviving patients was 35 months (range 21–57 months). Tumor sites were cervical in 9 patients, upper thoracic in 7 patients and middle thoracic in 14 patients. PS included PS0 ($n = 23$) and PS1 ($n = 7$). Primary tumor stages included T1b ($n = 1$), T2 ($n = 1$), T3 ($n = 4$) and T4b ($n = 24$). N stages included N0 ($n = 3$), N1 ($n = 25$) and N2 ($n = 2$). Clinical stages according to the UICC 7th edition included stage II ($n = 1$), stage III ($n = 23$) and stage IV ($n = 6$).

### Radiotherapy

Either 6 or 10 MV X-rays were used. The daily fractional dose of RT was 2 Gy administered for 5 days per week. The total RT dose was 50 Gy in 25 fractions. The overall treatment time was 5 weeks. CT-based treatment planning was performed for all patients. The primary tumor and involved LNs measuring ≥0.5 cm at the shortest diameter on CT represented the gross tumor volume (GTV). The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 10 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2), including the GTV with a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm).

CTV1 for cervical esophageal cancer (Ce) included GTV and LN areas from the middle deep cervical in the subcarinal area (short T-shape fields). CTV1 for upper thoracic esophageal cancer (Ut) included GTV and LN areas from the supraclavicular to the middle thoracic paraesophageal area (T-shape fields). CTV1 for the middle thoracic esophagus (Mt) included GTV and LN areas from the recurrent nerve area to the lower thoracic paraesophageal area (I shape fields). Although no patient with lower thoracic esophageal cancer (Lt) were included in this series, CTV1 for Lt should include GTV and LN areas from the recurrent nerve area to the perigastric LN areas.

For both CTV1 and CTV2, a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm) was added to make planning target volume 1 and 2 (PTV1, 2). In addition, leaf margins for PTV1, 2 of 0.5–0.8 cm were added. RT doses were specified in the center of the target volume and calculated with lung inhomogeneous correction. The initial RT for PTV1 was given with an anterior/posterior RT field. At 40 Gy, the RT field was reduced to PTV2. The total RT dose to the spinal cord was limited to 40 Gy, usually by using oblique opposed fields. Second CT simulation was performed before 40 Gy. Intensity modulated radiation therapy was used for one patient because of difficulty in reducing the spinal cord dose by conformal RT.

### Chemotherapy

Two cycles of chemotherapy (FP therapy) were delivered concurrently with RT. Cisplatin (CDDP) 70 mg/m$^2$ (days 1 and 29) was delivered via 2 h intravenous (IV) infusion, and 5-FU 700 mg/m$^2$/day for 5 days was administered as a continuous IV infusion (days 1–5 and days 29–33).

### Evaluation of response and toxicity

Tumor response was evaluated by GIF and CT at 4 weeks after completion of RT. In the present study, tumor response was categorized as resectable, unresectable, or progressive disease (PD) based on contrasted CT findings. When the Picus's angle of the aorta invasion decreased to $<90°$ [13], or the deformity and/or irregularity of the trachea invasion diminished, the tumors were regarded as resectable. When distant metastasis was detected, the disease was regarded as PD. Acute toxicities encountered within 6 weeks of completion of CRT were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 4.0).

### Surgery and adjuvant chemotherapy

Esophagectomy was planned for 6–8 weeks after completion of RT for patients with good tumor regression. Most patients underwent right thoracotomy, laparotomy, and cervicotomy to perform esophagectomy with 2- or 3-field lymphadenectomy, and gastroesophageal anastomosis at the left side of the neck. Surgical complications were evaluated from the day of surgery until the time to discharge.

For patients with poor tumor response and for those whose tumors remained unresectable, a further 2–3 courses of DCF therapy were performed (docetaxel 60 mg/m$^2$, CDDP 70 mg/m$^2$, 5-FU 700 mg/m$^2$/d $\times$ 5 days).

### Follow-up

Loco-regional recurrence and distant metastasis were evaluated by upper GIF and thoracic-abdominal CT scans at 3- to 6-month intervals after initial evaluation of tumor response. When tumor progression or recurrence was noted, salvage treatment was mandatory for the attending physicians.

Late toxicities observed 3 months after the start of treatment were graded once a year according to the NCI-CTC (version 4.0). Late toxicities in the surgery group were evaluated after discharge. The maximum grade scored in the follow-up period was recorded for each patient.

### Endpoints and statistical analysis

In-field local control rate, overall and progression-free survival rates, acute and late toxicities, surgical complications, and the compliance rate of the protocol were evaluated. When 2 cycles of FP therapy and 50 Gy of RT could be given, the patient was regarded as in full compliance with the protocol.

The probability of survival and local control was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Overall survival considered deaths due to any cause. In-field local control considered any local or regional tumor progression within CTV1 which received $\geq$40 Gy as events. When patients died of distant metastasis or other disease without in-field progression, local control was censored.

## Results

### Compliance and tumor response

All 30 patients completed RT of 50 Gy/25 fractions. Twenty-three patients (77 %) completed two courses of FP therapy. The remaining seven patients could not be given a second course of FP therapy because of prolonged leukopenia for four patients, serum creatine increase for two and hyponatremia for one. Tumor responses to preoperative

**Table 2** Acute toxicities of preoperative CRT ($n = 30$)

| $n = 30$ | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Leukopenia | 3 | 13 | 14 | 0 |
| Anemia | 21 | 4 | 1 | 0 |
| Thrombocytopenia | 14 | 0 | 0 | 0 |
| Hyponatremia | 3 | 0 | 1 | 1 |
| Hypoalbuminemia | 0 | 1 | 0 | 0 |
| Anorexia | 8 | 2 | 2 | 0 |
| Malaise | 5 | 0 | 1 | 0 |
| Nausea | 8 | 2 | 2 | 0 |
| Vomiting | 5 | 1 | 1 | 0 |
| Pharyngitis | 12 | 5 | 0 | 0 |
| Mucositis | 10 | 5 | 0 | 0 |
| Dermatitis | 4 | 4 | 0 | 0 |
| Diarrhea | 3 | 5 | 0 | 0 |
| Creatinine increase | 3 | 1 | 0 | 0 |

CRT were 21 patients with resectable disease, 7 with unresectable disease, and 2 with PD (pleural dissemination and bone metastasis).

### Acute toxicities

Although the treatment regimen was intensive, acute toxicities were manageable in most patients and none died of treatment-related toxicities. Only one patient showed Grade 4 hyponatremia. Hematological toxicities of Grade 3 consisted of leukopenia ($n = 14$) and anemia ($n = 1$). Non-hematological toxicities of Grade 3 included hyponatremia ($n = 1$), anorexia ($n = 2$), malaise ($n = 1$), nausea ($n = 2$), vomiting ($n = 2$) (Table 2).

### Resectable disease

Of the 21 patients with resectable disease after CRT, esophagectomy was performed in 18 (60 % of the 30 enrolled patients); three of the 21 patients with resectable disease refused surgery. Although no further treatment, including adjuvant chemotherapy, was performed for the three patients, no recurrence or metastasis was noted for two patients in the follow-up at 41 and 61 months. Curative resection (R0) was achieved in all 18 patients (100 %). In addition, five (28 %) of the 18 patients showed pCR.

Postoperative complications after esophagectomy are shown in Table 3. No patient with operative death died within 30 days of surgery. There were two patients with hospitalization death who died 2–3 months after surgery (11 %). Both of these patients died of aspiration pneumonia.

**Table 3** Postoperative complications after esophagectomy

| Surgical complication | $n = 18$ |
|---|---|
| Pneumonia | 6 |
| Wound infection | 4 |
| Pleural effusion | 4 |
| Recurrent nerve paralysis | 3 |
| Dysrhythmia | 2 |
| Diarrhea | 2 |
| Pneumothorax | 2 |
| Air leak | 2 |
| Atelectasis | 1 |
| Anastomotic leak | 1 |
| Low blood pressure | 1 |
| Hypokalemia | 1 |
| Heart failure | 1 |
| Phlebothrombosis | 1 |
| Liver function failure | 1 |
| Dysphagia | 1 |

**Table 4** Late toxicities associated with CRT for the surgery and non-surgery groups

| | Surgery ($n = 18$) | | Non-surgery ($n = 12$) | |
|---|---|---|---|---|
| | G1 | G2 | G1 | G2 |
| Pneumonia | 4 | 1 | 3 | 2 |
| Pleural effusion | 6 | 2 | 2 | 0 |
| Pericardial effusion | 3 | 1 | 3 | 0 |
| Hypothyroidism | 0 | 6 | 0 | 2 |
| Dysphagia | 3 | 1 | 1 | 0 |
| Skin hardening | 1 | 0 | 0 | 0 |

### Unresectable diseases and PD

Six of the seven patients with unresectable disease were treated with 1–3 courses of DCF therapy, but all six patients died of the disease within 2 years. The remaining patient with interstitial pneumonia received no further treatment, but this patient showed no evidence of the disease at follow-up at 42 months. Two PD patients with poor PS received no further treatment.

### Late toxicities associated with CRT

There were no Grade 3 or higher late toxicities for any patients (Table 4). Pneumonia and pleural effusion were frequently observed. Hypothyroidism was seen in patients with Ce and Ut carcinomas.

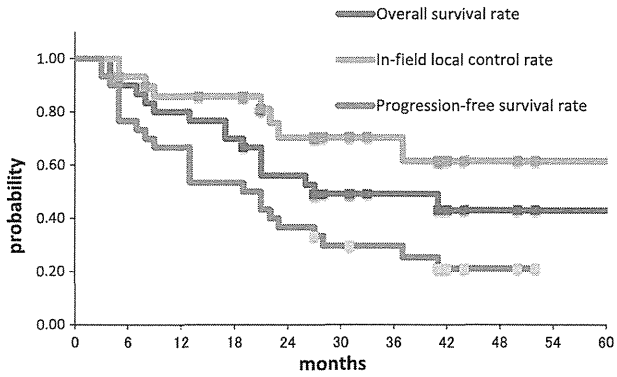


**Fig. 1** In-field local control rate, progression-free survival rate and overall survival rate for all 30 patients

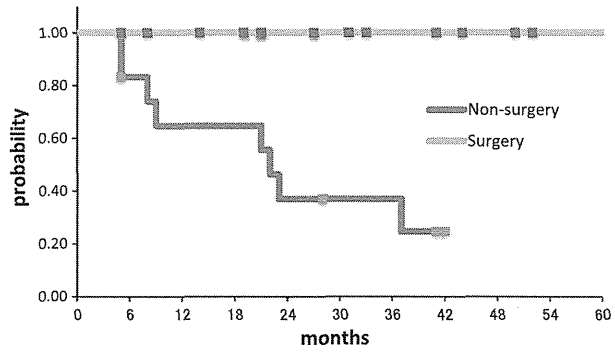


**Fig. 2** In-field local control rate for the surgery and non-surgery groups

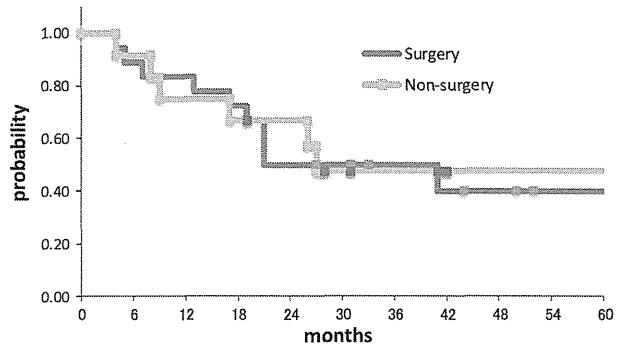


**Fig. 3** Overall survival rate for the surgery and non-surgery groups

## In-field local control and survival rates

The 3-year in-field local control rate for the 30 patients was 70 %. The 3-year overall and progression-free survival rates were 49 and 30 %, respectively (Fig. 1). In the surgery group ($n = 18$), the 3-year local control rate, overall survival rate and progression-free survival rate were 100, 50 and 32 %, respectively. In the non- surgery group ($n = 12$), the corresponding values were 40, 47 and 25 % (Figs. 2–4). In terms of failure pattern, no patients showed local recurrence and seven patients showed distant failure alone in the surgery group. In the non-surgery group, eight patients showed local recurrence alone, and the other three patients developed distant failure. In terms of the in-field local control rate, the difference between the two groups was statistically significant ($p < 0.00002$).

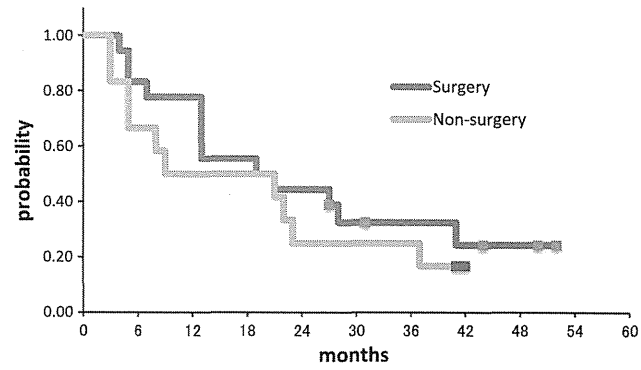


**Fig. 4** Progression-free survival rates for the surgery and non-surgery groups

## Discussion

To improve the local control rate and the overall survival rate for patients with unresectable esophageal cancer, we adopted a protocol of preoperative definitive-dose 50 Gy CRT followed by surgery for locally advanced unresectable esophageal cancer. All 30 patients completed RT of 50 Gy/25 fractions. Twenty-three patients (77 %) completed two courses of FP therapy. Although the preoperative treatment regimen was intensive, acute toxicities were manageable in most patients and none died of treatment-related toxicities.

There were two patients with hospitalization death after surgery (11 %). However, significantly higher operative mortality rates (6–15 %) were reported for preoperative CRT compared with surgery alone [7–9, 14–16]. Pneumonia is the most common postoperative complication. Respiratory complications occurred in 42–48 % of patients after standard dose (40 Gy) preoperative CRT [15, 17] One retrospective analysis of high-dose (median 66 Gy) preoperative CRT followed by surgery revealed a postoperative pulmonary complication rate as high as 63 % [18]. In the present study, pulmonary complications were noted in 33 % of the patients. Thus, our protocol was safe and feasible.

Esophagectomy was performed in 18 (60 %) of the 30 patients. Curative R0 resection was achieved in all 18 patients (100 %). Five (28 %) of the 18 patients showed pCR. For unresectable esophageal cancer, resectable rates, R0 rates, and pCR rates by preoperative CRT have been reported as 62–78, 39–71 and 13–25 %, respectively [19–21]. In our series, the resectable rate and pCR rate were similar to other reports, but the R0 rate was as high as 100 %. The overall survival rate is closely related to the R0 status [22].

The 3-year overall survival rate of the 30 patients was 49 %. In prospective studies of definitive CRT for unresectable esophageal cancer, 3-year overall survival rates of approximately 20 % have been reported [3–5]. A retrospective survey of 9 major Japanese institutions revealed median 3-year overall survival rates of 21 % (range 10–36 %), for unresectable stage III-IVA tumors by definitive CRT [6]. Thus, the 3-year overall survival rate of 49 % seems favorable for unresectable esophageal cancer.

The in-field local control rate of the surgery group was significantly better than the non-surgery group (Fig. 2, $p < 0.00002$). As the pCR rate in the surgery group was 28 %, surgical removal of the tumors was necessary to obtain local control for the remaining 72 % of patients. pCR rates in resectable esophageal cancer with preoperative CRT of 20–40 Gy have been reported as 13–33 % [7–9, 23]. The pathological effect of high-dose preoperative CRT for unresectable esophageal cancer may be similar to standard preoperative CRT for resectable esophageal cancer.

On the other hand, the overall survival rate of the surgery group was not significantly different from the non-surgery group. The 3-year overall survival rates for the surgery group and the non-surgery group were 50 and 47 %, respectively (Fig. 3); this may be attributable to hospitalization deaths or aspiration pneumonia in the surgery group. On the other hand, there were three patients treated with 50 Gy CRT alone who showed long-term survival in the non-surgical group. As we adopted a definitive total dose of 50 Gy for preoperative CRT, some patients with unresectable esophageal cancer could be cured by CRT alone without surgery. At present, pCR cannot be determined accurately by clinical examinations including CT, PET/CT, and GIF with biopsy. To select patients who do not need surgery after definitive dose preoperative CRT, more accurate imaging methods on pCR are warranted.

## Conclusions

Definitive-dose (50 Gy) preoperative CRT for unresectable esophageal cancer could be performed safely and the 3-year overall survival rate of 49 % was promising. Definitive-dose preoperative CRT is a promising treatment strategy for unresectable esophageal cancer.

**Conflict of interest** The authors declare that they have no conflict of interest.

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