Recombinant human endostatin combined with definitive chemoradiotherapy as primary treatment for patients with unresectable but without systemic metastatic squamous cell carcinoma of the oesophagus

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Objective: The objective of this study was to review the outcomes of recombinant human endostatin combined with chemoradiotherapy (CRT) as primary treatment for patients with unresectable but without systemic metastatic squamous cell carcinoma (SCC) of the oesophagus.

Methods: A total of 38 patients with unresectable but without systemic metastatic SCC of the oesophagus (T₄ or stage IVA) were retrospectively studied. 18 patients were treated with recombinant human endostatin combined with 5-fluorouracil (5-FU)/cisplatin (CDDP)-based CRT and 20 were treated with 5-FU/CDDP-based CRT alone. Short- and long-term effects including initial treatment response, survival and treatment-related complications were assessed with a median follow-up period of 36.1 months.

Results: CRT combined with endostatin resulted in a marked improvement in complete response rates (44.4% vs 30% in the CRT-alone group), and an increase in the 1-year and 3-year overall survival rates (72% vs 50.0% and 32% vs 22.0%, respectively), while the median time to progression was extended to 11.3 months in the combination group vs 8.1 months in the CRT-alone group. There were no treatment-related toxicities that could be attributed specifically to the endostatin, and the toxicities observed across the two groups are probably due to the CRT itself.

Conclusions: The short- and long-term effects of CRT combined with endostatin were an improvement over that of CRT alone in this retrospective cohort study. This combined treatment modality may be a promising treatment modality for the patients with unresectable but without systemic metastatic oesophageal cancer. Further prospective randomised control studies are needed to confirm this finding.

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Radiology

Oesophageal cancer is the eighth most common cancer worldwide [1]. It is one of the most lethal malignancies recorded to date. Surgery is the gold standard treatment for resectable disease, but more than two-thirds of patients diagnosed with oesophageal cancer have unresectable disease and their prognosis is not favourable. There are multiple approaches in the treatment of oesophageal cancer. Definitive chemoradiotherapy (CRT) is effective for locally advanced oesophageal cancer and has improved the survival rate of patients with T1–3N0–1M0 tumours [2]. Chemotherapy alone does not provide any survival benefit compared with the best supportive care for patients with advanced oesophageal cancer, but it may improve the quality of life in patients with metastatic or unresectable oesophageal cancer [3]. Combination chemotherapy for metastatic oesophageal cancer continues to evolve, but there is a

pressing need for more effective therapies of advanced oesophageal cancer.

Oesophageal cancers are histologically classified as squamous cell carcinoma (SCC) or as adenocarcinoma. SCC is commonly seen in the endemic regions of the world (endemic meaning “high-prevalence area”, high-prevalence areas of SCC of the oesophagus include Asia, southern and eastern Africa, and northern France) and China is one of the areas with highest prevalence. The pathological node (pN) status is currently the most powerful predictor of outcome in SCC of the oesophagus [4]. Vascular endothelial growth factor (VEGF) expression is the second most important predictor of outcome after pN factor in patients with SCC of the oesophagus, and it is a useful marker for the selection of appropriate treatments in patients with more advanced oesophageal SCC [5]. Thus, VEGF might be a logical target for anticancer therapy in SCC of the oesophagus, and blockage of VEGF might be a promising tool to slow down or even stop tumour progression. However, pre-clinical and clinical trial results suggest that angiogenesis inhibitors have a delayed onset of activity and may only induce disease stabilisation for patients with advanced

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malignancy, so monotherapy with antiangiogenic agents is not sufficient for the treatment of patients with advanced cancer [6]. Antiangiogenic agents combined with other therapies have been employed for treatment of advanced cancers. A Phase II trial of bevacizumab, a neutralising anti-VEGF antibody with an irinotecan and cisplatin combination, as the first-line treatment in patients with metastatic gastric and gastroesophageal junction adenocarcinoma, has been reported [7]. It is thought that treating tumours first with angiogenesis inhibitors may sensitise the tumours to ionising radiation, allowing lower radiation doses to be used [8]. Considerable experimental and clinical evidence has indicated that radiotherapy combined with angiogenesis inhibitors could be beneficial to improving tumour response to radiotherapy [9, 10]. A Phase II study of cetuximab, paclitaxel, carboplatin and concurrent radiation for the patients with T2–T4 or nodal metastatic oesophageal cancer initially indicated that CRT combined with angiogenesis inhibitors could improve clinical response rate of advanced oesophageal cancer [11].

Endostatin is a 20-kDa internal fragment of the c-terminal of collagen XVIII. It has been reported as one of the most potent endothelial cell inhibitors of angiogenesis and tumour growth without displaying toxic side effects and drug resistance [12]. In a Phase III clinical study, it has been demonstrated that recombinant human endostatin (Endostar) significantly improved overall and progression-free survival when used in combination with the first-line chemotherapy regime in patients with advanced non-small-cell lung cancer [13]. As a result, it was approved by the State Food and Drug Administration in China in September 2005 for the treatment of non-small-cell lung cancer. It has also been reported that endostatin can block tumour revascularisation after radiation therapy of A431 human epidermoid carcinomas growing intramuscularly in the legs of mice, and can thereby augment radioresponse [14]. Another study has indicated that Endostar significantly sensitised the function of radiation in antitumour and antiangiogenesis in human nasopharyngeal carcinoma and human lung adenocarcinoma xenografts by increasing the apoptosis of the endothelial cell and tumour cell, improving the hypoxia of the tumour cell and changing the proangiogenic factors [15]. Therefore, we conducted this retrospective study in a single institution to clarify the effect of CRT combined with endostatin and evaluate the radioresponse enhancing effect of endostatin combined with CRT in patients with unresectable but without systemic metastatic SCC of the oesophagus.

Methods and materials

Patients

The retrospective study involved 38 patients with unresectable but without systemic metastatic SCC of the oesophagus who were medically unfit for surgery, had technically unresectable cancer, chose to be free from surgery and were able to tolerate CRT between September 2005 and December 2008 in the Research Institute of Surgery and Daping Hospital, Third Military Medical University. All patients underwent endoscopic

evaluation with biopsy. Endoscopic ultrasonography (EUS) was performed on patients with the use of a 7.5-MHz radial array probe to assess the depth of tumour penetration and the presence of regional lymphadenopathy. CT of the chest and abdomen was performed to evaluate for metastatic disease. Bone scintigraphy was additionally performed if indicated for the determination of individual staging. The tumour stages were based on the tumour/node/metastasis (TNM) classification developed by the American Joint Committee on Cancer in 2002 [16]. The patients' tumours consisted of T4 tumours with involvement of heart, great vessels, trachea or adjacent organs (including liver, pancreas, lung and spleen)—Stage IVA tumours with non-regional lymph node involvement but without systemic metastases. 29 (76.3%) patients in our study were male and their median age was 68 years. 20 patients had carcinomas of the upper thoracic oesophagus, 14 had carcinomas of the middle thoracic oesophagus and the remaining 4 patients had carcinomas of the lower thoracic oesophagus. The patients did not receive prior treatment. These patients were discussed by a multidisciplinary team including surgical oncology, medical oncology, radiation oncology and radiology. If the experts recommended definitive CRT with one accord, the opinions of the patients were inquired. Of these patients, 18 were treated with recombinant human endostatin in combination with CRT on the basis of their own opinions. The remaining 20 patients were treated with CRT alone according to their wills. All patients provided written informed consent before treatment. Table 1 summarises the baseline characteristics of the patients in this study. There was no significant difference in gender, age, location, pre-treatment status or clinical stage between patients in the CRT-alone group and CRT-combined-with-endostatin group.

Chemoradiotherapy

Radiotherapy was performed using a precise 8-MV linear accelerator (Precise Treatment SystemTM Medical Linear Accelerator; ELEKTA, Stockholm, Sweden) at a dose rate of 2 Gy min⁻¹ with standard fractionation (2.0 Gy fraction⁻¹, 5 days per week). CT-based radiotherapy treatment planning was used in all patients. The

Table 1. Pre-treatment patient characteristics

Characteristics	Definitive CRT	CRT combined with endostatin	p-value
Gender (male/female)	15/5	15/3	ns
Median age (range)	68 (58–76)	65 (56–73)	ns
Location			
Upper	12	8	ns
Middle	6	8	
Lower	2	2	
cStage			
T4	9	8	ns
IVA	11	10	

CRT, chemoradiotherapy; cStage, clinical stage; ns, not significant.

gross tumour volume (GTV) included the primary oesophageal tumour and the involved regional lymph nodes. The planning target volume included the tumour plus 5.0 cm cephalad–caudal margin, 1.0 cm radial margin in the other direction and regional lymph nodes. Initial anteroposterior opposed radiation field for carcinoma of the upper thoracic oesophagus encompassed the primary tumour, and the bilateral supraclavicular and upper-to-middle mediastinal lymph nodes. The initial field for carcinoma of the middle or lower thoracic oesophagus encompassed the primary tumour, and all of the mediastinal, perigastric and celiac lymph nodes. After a dose of 45–46 Gy to the initial field, the radiation field was reduced to a booster field limited to the GTV with an adequate margin. An oblique-opposed technique and three-dimensional conformal radiotherapy were used to reduce margins adjacent to the lung, heart, liver and spinal cord so that the volumes of these organs receiving high radiotherapy doses were limited. Patients were regularly monitored during therapy. The spinal cord dose was not allowed to exceed 45 Gy. The volumes of the lung receiving 20 and 30 Gy were limited to 30% and 20%, respectively. 30% of the heart was limited to 50 Gy and 60% of liver tissue was limited to 30 Gy. All patients of two groups completed radiotherapy with a total dose of 52–60 Gy.

Concurrent chemotherapy consisted of a 96-h continuous infusion of 5-fluorouracil (5-FU) at a dose of 4000 mg m⁻² in combination with a 1-h bolus infusion of cisplatin (CDDP) at a dose of 75 mg m⁻². Minor modifications of chemotherapy dose were allowed according to the physician's decision depending on individual patients. The course of treatment took place over 3 weeks, administered twice within the period of radiotherapy, followed by two courses of 5-FU and CDDP.

Recombinant human endostatin was used with 3–4 h continuous infusion at a dose of 15 mg once daily for 14 days, with a second course repeated after a 1-week interval. The first course began on the first day of concurrent chemotherapy.

Result assessment and follow-up

The initial response was assessed 1 month after completion of the CRT by oesophagography or endoscopy for the primary tumour, by CT or ultrasonography scanning for lymph node metastasis and by chest radiography or CT and abdomen CT for metastatic disease in accordance with the criteria of the World Health Organization (WHO) [17]. In brief, the responses were classified as follows: complete response (CR), the disappearance of all measurable and assessable disease for a minimum of 4 weeks; partial response (PR), 50% or more decrease in total tumour load or no appearance of new lesions or progression of any lesions for a minimum of 4 weeks; progressive disease (PD), 25% or more increase in the total tumour load of measurable disease or the appearance of new lesions; stable disease (SD), the failure to observe a PR, CR or PD for at least 4 weeks. Acute toxicities were assessed according to Common Terminology Criteria for Adverse Events v. 3.0 guidelines [18]. Late toxicity was defined as that occurring more than 3 months after the initiation of treatment.

All patients received a follow-up systematically. For asymptomatic patients, follow-up included a complete history and physical examination every 3 months for 1 year, then every 6 months for 2 years, and annually thereafter. Complete blood count (CBC), multichannel serum chemistry evaluation, oesophagography or endoscopy and chest radiography, ultrasonography or CT scanning were performed at least every 6 months to detect possible recurrent disease. The median follow-up period of surviving patients was 36.1 months (range 12.5–52.0 months).

Statistical analysis

Statistical analysis was performed using the χ^2 test or Fisher's exact probability test for two-proportion comparisons. Survival rates were calculated from the date of the initiation of treatment until death or the last follow-up for surviving patients using the Kaplan–Meier method. Differences between the survival curves were assessed using the Breslow test. A *p*-value of <0.05 was considered significant. All analyses were performed with SPSS® for Windows v. 13.0 (SPSS Inc., Chicago, IL).

Results

The patients completed radiotherapy with the standard fractionation initially planned and received concurrent chemotherapy of 5-FU and CDDP. The median radiation dose was 56 Gy (range 52–60 Gy) in the CRT-alone group as in the CRT/endostatin group. All patients of the CRT-combined-with-endostatin group received endostatin that was initially planned. There was no salvage treatment including oesophagectomy or endoscopic resection for locoregional failure.

The initial responses of the patients receiving CRT included 30% (6/20) obtaining complete response, and 45% (9/20) a partial response. The overall response rate in this group was 75% (15/20). At the median follow-up period of 38.3 months (range 15.7–50.1 months), 3 patients showed no evidence of disease, 2 had developed cancer and 15 had died of cancer and cancer-related complications, though no patients died of treatment-related complications. The 1- and 3-year overall survival (OS) rates were 50.0% and 22.0%, respectively, with a median survival time (MST) of 11.6 months. Median time to progression (TTP) was 8.1 months.

In the CRT/endostatin group, the initial responses of the patients fulfilling the complete response to treatment criteria were significantly higher than the CRT-alone group, at 44.4% (8/18), while 7 (38.9%) patients experienced partial responses to treatment. The overall response rate increased from 75% to 83.3% (15/18). At the median follow-up period of 35.6 months (range 14.5–51.0 months), 4 patients had no evidence of disease, 1 patient was suffering from cancer and 12 had died of cancer and cancer-related complications, but no patients died from treatment-related complications. One patient died of complications arising from a cerebrovascular accident. The 1- and 3-year OS rates were 72.0% and 32.0%, respectively, with an MST of 18.2 months also a considerable improvement over the CRT-alone group. TTP was

11.3 months. The overall survival curves for patients for each treatment modality are shown in Figure 1. The patients receiving CRT in combination with endostatin have an overall survival rate and a median survival rate that is significantly higher than that for patients receiving CRT alone (1-year OS rates of 72% *vs* 50%; 3-year OS rates of 32% *vs* 22%; median survival of 18.2 months *vs* 11.6 months; Breslow χ^2 statistic: $p=0.044$). In addition, the combination therapy extends the time of progression to disease considerably by 3 months.

Treatment-related complications of each modality

Patients were monitored for acute and late toxicities to treatment. The results for the acute reactions are summarised in Table 2, measured in grades of severity ranging from 0 to 4, with 4 being the most severe. There was no significant difference between treatment groups in any of the indices measured. There was no observable adverse liver toxicity (aspartate aminotransferase/alanine aminotransferase) nor blood toxicity and the combination treatment did not result in an increase in symptoms affecting appetite or additional nausea/vomiting.

Late toxicities observed among the two groups are summarised in Table 3. There was one incidence of pneumonia 4.5 months post CRT/endostatin combination treatment and a single incidence of oesophageal stenosis in the CRT-alone group 14.5 months post treatment. No patients developed secondary cancers in either group, and death as a result of late toxicities did not occur.

Discussion

There have been many studies evaluating the benefits of CRT for the treatment of advanced oesophageal carcinoma. Some of these have demonstrated that CRT was of significant benefit to the patients with unresectable but without systemic metastatic SCC of the oesophagus (T4 or Stage IVA) and concluded that these

patients should not be excluded from potentially definitive and curative treatment [19–25]. For these patients a definitive 5-FU/CDDP-based CRT is one of the most promising ways to achieve a complete therapeutic response. In the studies of chemoradiotherapy with 5-FU, CDDP and 60 Gy of radiotherapy, the CR rate ranged from 15.0% to 37.5%, with an MST of 9–12 months [20–24], but with significant toxicity. The differences in treatment outcomes are probably due to different doses of chemotherapeutic agents. In the current study, the CR rate of 30% (6/20) in the CRT-alone group was lower than 37.5%, and MST of 11.6 months in the CRT-alone group was also slightly lower than 12 months. The difference can be explained by a higher plasma concentration of 5-FU because the latter study modified the treatment schedule and increased the dose of 5-FU [22]. To improve both local and distant control in patients with unresectable but without systemic metastatic SCC of the oesophagus (T4 or Stage IVA), new regimens must be developed. Besides modification of the treatment schedule and dose escalation, the treatment might be improved further through addition of new agents and replacement of 5-FU and CDDP. A study about the replacement of 5-FU with paclitaxel demonstrated that the CR rate was 29%, and the 2-year cancer progression-free and overall survival rates were 40% and 42%, respectively [25]. A Phase I clinical trial of docetaxel added to CDDP plus 5-FU with concurrent radiotherapy (DCF-R) (KDOG0501) for advanced thoracic oesophageal cancer with T4 tumours and/or M1 lymph node metastasis was conducted [19]. The overall response rate was 89.5%, including a CR rate of 42.1%, and MST was 20.0 months. But the incidence of adverse events related to haematologic toxicity and oesophagitis was higher than that in previous studies of 5-FU/CDDP-based CRT [21, 23, 24]. Therapies that block aberrant growth factor signal transduction pathways have substantial promise in human malignancies, including oesophageal cancer. A Phase II study of cetuximab, paclitaxel, carboplatin and concurrent radiation for the patients with T2–T4 or nodal disease was therefore

Figure 1. Overall survival curves for patients of each treatment modality. Patients were monitored for a total of 3 years. The combination chemoradiotherapy (CRT)/endostatin treatment significantly increased total lifespan of patients following treatment ($p<0.05$) by 7 months on average (median lifespan 18.2 months *vs* 11.6 months for the CRT-alone group). Comparisons based on Breslow χ^2 statistic: $p=0.044$.

Table 2. Acute toxicities in CRT-alone vs CRT-and-endostatin treatment groups

Adverse events	Group	Grade				
		0	1	2	3	4
Neutropaenia	CRT-alone	2	8	5	3	2
	CRT combined with endostatin	1	6	6	2	3
Anaemia	CRT-alone	10	5	3	2	0
	CRT combined with endostatin	9	5	2	1	1
Thrombocytopaenia	CRT-alone	11	6	2	1	0
	CRT combined with endostatin	10	3	4	0	1
AST/ALT	CRT-alone	13	3	3	1	0
	CRT combined with endostatin	14	1	2	1	0
Oesophagitis	CRT-alone	4	8	5	1	2
	CRT combined with endostatin	3	7	5	2	1
Lack of appetite	CRT-alone	1	10	4	3	2
	CRT combined with endostatin	2	8	4	2	2
Nausea/vomiting	CRT-alone	4	8	5	2	1
	CRT combined with endostatin	3	7	6	2	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRT, chemoradiotherapy.

initiated [11]. The clinical CR rate in this trial was 75%. However, cutaneous toxicities and hypersensitivity reactions were increased with the addition of cetuximab. In this retrospective study, we expected to improve treatment outcomes for patients with unresectable but without systemic metastatic SCC of the oesophagus (T4 or Stage IVA) through the addition of recombinant human endostatin to 5-FU/CDDP-based CRT. In this study, the CR rate of 44.4% (8/18) in the CRT-combined-with-endostatin group was higher than the 30% (6/20) in the CRT-alone group, but this difference was not statistically significant ($p=0.503$), probably owing to the limited number of patients. The median survival time of 18.2 months in the CRT/endostatin group was significantly higher than the 11.6 months in the CRT-alone group, and the 1- and 3-year OS rates of 72.0% and 32.0%, respectively, in the CRT/endostatin group were also significantly higher than in the CRT-alone group. Endostatin did not increase treatment-related complications, including acute toxicities and late toxicities. The major acute toxicities reported were leukocytopenia and oesophagitis. In the studies of 5-FU/CDDP-based CRT, the rate of grade 3 and 4 leukopaenia ranged from 24% to 50% [20–24]. In this study, the rates of grade 3 and 4 leukopaenia in two groups were 25.0% (5/20) and 27.8% (5/18), respectively ($p=0.568$), a significant improvement over earlier studies [20–24]. In the reports evaluating the effect of 5-FU/CDDP-based CRT, the rate of oesophagitis ranged from 10.0% to 37.5%. In this study, the rates of grade 3 and 4 oesophagitis in two groups were significantly lower at 15.0% (3/20) and 16.7% (3/18),

respectively ($p=0.616$). No significant differences were observed in the incidence of grade 3 and 4 leukopaenia and oesophagitis in the two groups with or without endostatin. Late toxicities including cardiopulmonary complications after definitive CRT are a critical issue to be resolved. To address this issue, we applied three-dimensional conformal radiotherapy to reduce the dose to the heart and the lungs in this study. There were also no apparent increases in the late toxicities as compared with CRT without endostatin. Treatment-related deaths caused by late toxicities were not observed. Standard-dose definitive CRT combined with endostatin in this study seems tolerable for the patients with unresectable but without systemic metastatic SCC of the oesophagus (T4 or Stage IVA), with similar toxicities and almost identical impact on survival. The toxicities observed were mainly associated with CRT. The patient population in this study was heterogeneous, and included patients with upper, middle and lower oesophageal cancers. These findings can probably be utilised for other patients with oesophageal cancer treated with this chemoradiation regimen and endostatin. A multi-institutional prospective randomised controlled study is needed to compare the two modalities.

Conclusions

We conclude that combining endostatin with CRT in treating primary unresectable carcinoma of the oesophagus may be a promising treatment modality for patients with

Table 3. Late toxicities in CRT-alone vs CRT-and-endostatin treatment groups

Adverse events	Group	Number of patients (%)
Pneumonia	CRT-alone	0 (0.00)
	CRT combined with endostatin	1 (5.56)
Pulmonary embolism	CRT-alone	0 (0.00)
	CRT combined with endostatin	0 (0.00)
Cardiac infarction	CRT-alone	0 (0.00)
	CRT combined with endostatin	0 (0.00)
Secondary cancer	CRT-alone	0 (0.00)
	CRT combined with endostatin	0 (0.00)
Oesophageal stenosis	CRT-alone	1 (5.56)
	CRT combined with endostatin	0 (0.00)

CRT, chemoradiotherapy.

unresectable but without systemic metastatic oesophageal cancer, with no observable increase in adverse effects and tolerable toxicity. Further prospective randomised controlled studies are needed to confirm this finding.

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