

S-1 Salvage Chemotherapy for Esophageal Squamous Cell Carcinoma Refractory to the Standard Chemotherapy

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Abstract

Objective: Fluorouracil, cisplatin, and taxane are widely used in the standard chemotherapy regimens for esophageal squamous cell carcinoma (ESCC). Although S-1 is expected to demonstrate considerable efficacy for ESCC, there is any clinical data. The purpose of this retrospective study was to evaluate the efficacy and safety of S-1 as salvage chemotherapy for ESCC.

Methods: From 2007 to 2014, fifteen patients with ESCC refractory or refusal to the standard chemotherapy were treated with S-1 as salvage treatment at the Kyoto University Hospital and their clinical records were reviewed retrospectively.

Results: The median age was 70 years old (range: 63-77). A complete response (CR) was achieved in 1 case (7%). A stable disease (SD) and progressive disease (PD) were seen in 9 (60%) and 5 (33%) cases, respectively. After a follow-up duration of 13.9 months, median progression free survival and overall survival was 6.2 and 10.0 months, respectively. One-year survival rate was 33.3%. Toxicities greater than CTCAE grade 3 were observed in 3 of 15 patients (20%). Two patients had grade 3 neutropenia and one patient had grade 3 diarrhea. There was no treatment related death.

Conclusions: S-1 salvage chemotherapy could be expected to be an effective and safe treatment option to improve the prognosis of patients with ESCC refractory to the standard chemotherapy.

Keywords: Esophageal cancer; Squamous cell carcinoma; Recurrent or metastatic cancer; S-1

Introduction

Esophageal cancer is the sixth most common cause of cancer deaths worldwide [1]. Neoadjuvant chemotherapy followed by esophagectomy, or chemoradiotherapy (CRT) with curative intent have been standard initial treatments for resectable esophageal squamous cell carcinoma (ESCC) in Japan. For the patients who failed those treatments (recurrent ESCC) or patients with metastatic ESCC, systemic chemotherapy is performed. Combination chemotherapy of 5-fluorouracil (5-FU) and cisplatin (FP) and single-agent chemotherapy of taxane such as docetaxel (DTX) or paclitaxel (PTX) are the most commonly prescribed as the standard chemotherapy regimen for recurrent or metastatic disease [2,3]. However, substantial numbers of patients have experienced disease progression after these treatments. There is no other established salvage chemotherapy regimen for the ESCC which is refractory for the standard chemotherapy, and then, only the best supportive care is performed. However, some cases still kept their general condition comparatively well when they failed all of standard chemotherapy. If another effective chemotherapy regimen improved their prognosis, such patients could be indicated further treatment.

S-1 is an oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate [4,5]. During the past decade, several phase II studies demonstrated the efficacy of S-1 in major solid cancers. Response rates of S-1 were 45.0% in gastric cancer [6,7], 32.6% in colorectal cancer [8,9], 18.2% in lung cancer [10,11], 41.7% in breast cancer [12], and 32.2% in pancreatic cancer [13,14]. In addition, the response rate of S-1 was 34.1% in head and neck cancer [15,16]. Similar to esophageal cancer in Japan, most of the head and neck cancer were squamous cell carcinoma. Then, S-1 is expected to have an anticancer efficacy in ESCC.

The aim of this study was to evaluate the efficacy and the safety of S-1 salvage chemotherapy for the patients with recurrent or metastatic ESCC refractory to the standard chemotherapy.

Methods

Patients

From April 2007 to December 2014, 591 patients were diagnosed as ESCC at the Kyoto University Hospital and their clinical records were reviewed retrospectively. Among them, 15 patients received S-1 monotherapy after the failure or refusal of standard chemotherapy (Figure 1). We included the patients who had synchronous head and neck cancer, gastric cancer, lung cancer and so on. The inclusion criteria of this study were as follows: (1) age over 18; (2) pathologically proven ESCC; (3) adequate medical record; (4) patients who failed or rejected all of the standard chemotherapy for ESCC. This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (Protocol Identification Number: E2085).

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Received February 17, 2017; **Accepted** March 20, 2017; **Published** March 24, 2017

Citation: Tamaoki M, Ezoe Y, Aoyama I, Horimatsu T, Morita S, et al. (2017) S-1 Salvage Chemotherapy for Esophageal Squamous Cell Carcinoma Refractory to the Standard Chemotherapy. J Cancer Sci Ther 9: 353-357. doi: [10.4172/1948-5956.1000441](https://doi.org/10.4172/1948-5956.1000441)

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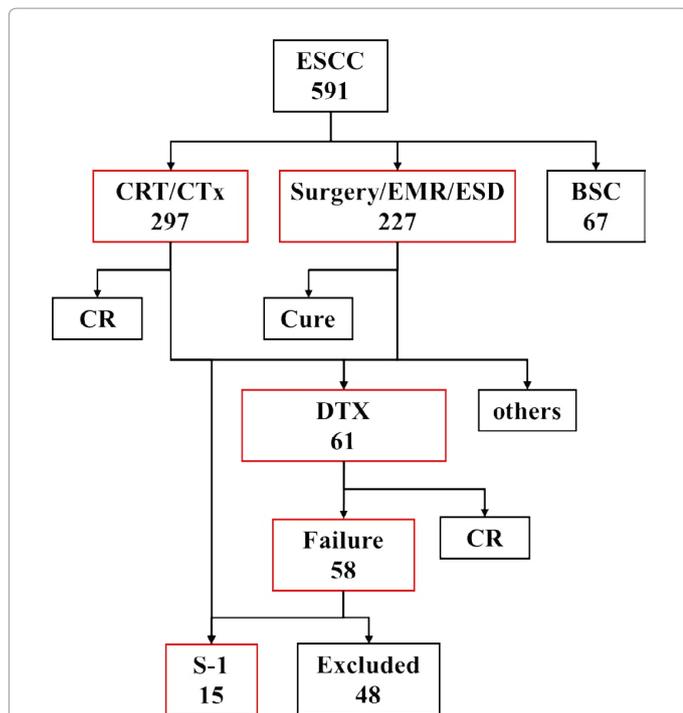


Figure 1: Patients flow. CRT chemoradiotherapy, CTx chemotherapy, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, DTX docetaxel, BSC best supportive care.

Treatment

S-1 was administered orally from day 1 to day 14, every 3 weeks. The dose of S-1 for each patient was determined according to body surface area (BSA) as follows: for BSA<1.25 m², 80 mg/day; for 1.25 m²<BSA<1.5 m², 100 mg/day; and for BSA>1.5 m², 120 mg/day divided by 2 doses. If any unacceptable adverse events appear, discontinuation or reduction of S-1 administration was carried out.

Evaluation of efficacy

Tumor response was assessed with computed tomography (CT) every 2-3 cycles. Response rate was determined by best overall response according to the response evaluation criteria in solid tumors (RECIST 1.1) [17]. Complete response (CR) was determined when the disappearance of the target tumor was confirmed. Partial response (PR) was determined when 30% reduction of the target tumor was confirmed. Stable disease (SD) was determined when neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD were confirmed. Disease control rate was defined as the percentage of patients who have achieved CR or PR or SD.

Assessment of toxicities

Toxicities were assessed according to the common terminology criteria for adverse events (CTCAE) Version 4.0.

Statistical analyses

Progression free survival (PFS) was calculated from the first day of S-1 administration to the occurrence of progression, or death from any cause. Overall survival (OS) was also measured from the first day of S-1 administration to the death from any cause or the last follow up date. Median PFS and median OS were estimated by the Kaplan-Meier

method. Correlation between the tumor response of S-1 and that of prior anticancer drugs was assessed by the Fisher's exact test. All data were analyzed using SPSS Statistics 21 (IBM, Armonk, NY).

Results

Patient characteristics

The patients' characteristics before administration of S1 are shown in Table 1. In addition, clinical courses of each patient are shown in Figure 2. Regarding the initial Treatment, 3 cases were performed neoadjuvant chemotherapy followed by esophagectomy, 10 cases were performed CRT, and remaining 2 cases were performed chemotherapy. Previous chemotherapy regimens administered prior to the S-1 monotherapy were as follows: FP followed by DTX in 10 cases and refusal of DTX in remaining 5 cases.

Response and survival

Median duration of S-1 administration in all patients was 8 cycles (range; 1-45). Tumor best responses of S-1 are shown in Table 2. As for overall response, 1 patient (6.7%) achieved CR, 9 patients (60.0%) achieved SD, remaining 5 patients (33.3%) resulted in PD, and disease control rate was 66.7%. Disease control rate according to the tumor site were as follows; 80% (4/5) in primary lesion, 66.7% (8/12) in lymph nodes, 60.0% (3/5) in lung, 100% (1/1) in liver, and 100% (1/1) in bone.

Potential correlation between the tumor response of S-1 monotherapy and those of prior anticancer drugs was observed. Among 6 patients whose best response in prior FP treatment was CR, 5 patients achieved CR or SD by S-1 monotherapy (disease control rate; 83%). In contrast, among 9 patients who did not achieve CR in prior FP regimen, 4 patients resulted in PD by S-1 monotherapy (disease control rate; 56%). While the difference was not statistically significant, weak correlation in disease control rate was observed between the prior

	n (%)	
Age (years)	Median (Range)	70 (63-67)
sex	Male	12 (80.0)
	female	3 (20.0)
ECOG performance status	0	12 (80.0)
	1	3 (20.0)
Histological type	Squamous cell carcinoma	15 (100)
Stage at the start of TS-1	IIA	1 (6.7)
	IIA	1 (6.7)
	IV	13 (86.7)
Initial treatment status	Neoadjuvant Chemotherapy+ Esophagectomy	3 (20.0)
	chemoradiotherapy	10 (66.7)
	chemotherapy	2 (13.3)
Prior chemotherapy regimen	PF followed by DTX	10 (66.7)
	FP followed by 5-FU alone	2 (13.3)
	FP alone	3 (20.0)
Primary tumour		8 (53.3)
Metastatic tumour	Lymph nodes	12 (80.0)
	Lung	5 (33.3)
	liver	1 (6.7)
	Bone	1 (6.7)

Table 1: Patient characteristics. FP 5-fluorouracil and cisplatin, 5-FU 5-fluorouracil, DTX docetaxel.

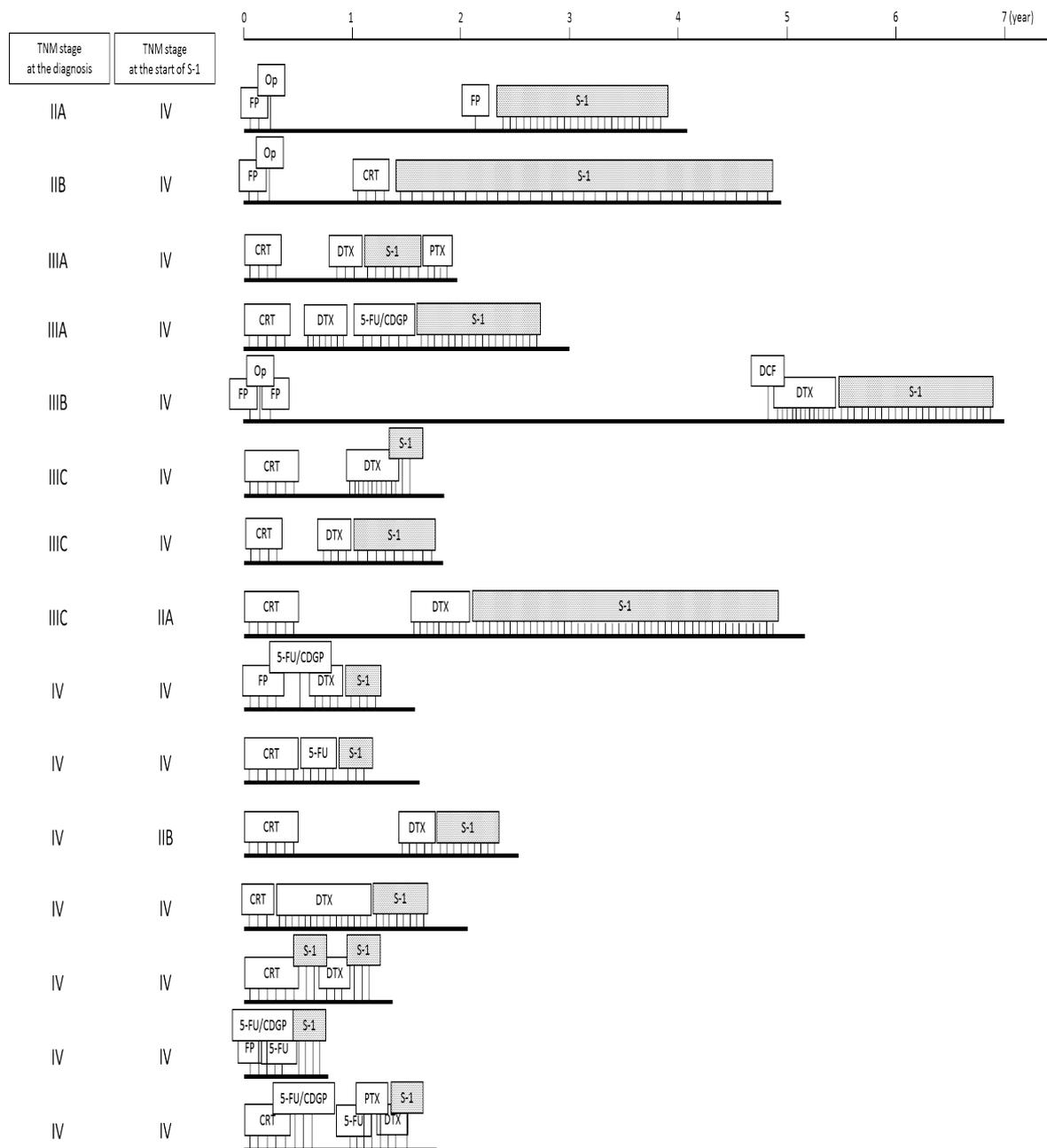


Figure 2: Clinical course of all patients. CRT chemoradiotherapy, Op operation, FP 5-fluorouracil and cisplatin, 5-FU 5-fluorouracil, CDGP nedaplatin, DTX docetaxel, PTX paclitaxel. (Clinical course of all patients).

	Overall (%)	Primary lesion (%)	Metastatic lesion (%)			
			Lymph nodes	Lung	Liver	Bone
	n=15	n=5	n=12	n=5	n=1	n=1
CR	1 (6.7)	0(0)	1(8.3)	0(0)	0(0)	0(0)
PR	0 (0)	0(0)	0(0)	0(0)	0(0)	0(0)
SD	9 (60.0)	4 (80.0)	7 (58.3)	3 (60.0)	1 (100)	1 (100)
PD	5 (33.3)	1 (20.0)	4 (33.3)	2 (40.0)	0 (0)	0 (0)

Table 2: Response to the S-1 monotherapy according to the site of lesion. CR complete response, PR partial response, SD stable disease, PD progressive disease

FP treatment and S-1 salvage chemotherapy ($p=0.29$). Among the 5 patients whose best responses in prior DTX treatment were CR or PR or SD, 4 patients (80%) achieved SD by S-1 monotherapy. Among the 5 patients who failed prior DTX treatment, 4 patients (80%) achieved SD by S-1 monotherapy. There was no significant correlation between the response of DTX and S-1 monotherapy ($p=0.78$).

The average of interval period between the last administration of prior 5-FU and the first administration of S-1 monotherapy in 10 patients who achieved CR or SD by S-1 monotherapy was 8.4 months (range: 1.4-21.3). On the other hand, the interval period in 5 patients

who resulted in PD by S-1 monotherapy was 3.8 months (range: 0.8-10.2). The interval period between the last administration of prior 5-FU and the first administration of S-1 was longer in S-1 responders, however, there was no statistical significant difference ($p=0.06$).

After a follow-up duration of 13.5 months (range: 2.6-40.8), median PFS and OS were 6.2 months (95% CI: 5.1-7.3) and 10.0 months (95% CI: 7.3-12.7), respectively (Figures 3 and 4). One-year survival rate was 33.3% (95% CI: 9.5-57.2). At the time of analysis, 14 patients died because of the disease progression.

Toxicity

Table 3 provides the toxicity profile. Toxicities greater than CTCAE grade 2 were assessed in this study. As the hematological toxicity, two patients (13.3%) developed grade 3 neutropenia. As the non-hematological toxicity, two patients (13.3%) developed grade 2 hand-foot syndrome, one patient (6.7%) developed grade 2 diarrhea and one patient (6.7%) developed grade 3 diarrhea, one patient (6.7%) developed grade 2 anorexia, and one patient (6.7%) developed grade 2 dehydration. There was no treatment related death.

Discussion

There is no sufficient evidence of S-1 salvage chemotherapy for the patients with metastatic or recurrent ESCC which is refractory to

	CTCAE Grade [n (%)]			
	Grade 2	Grade 3	Grade 4	Grade 3/4
Haematological toxicity				
Neutropenia	-	2 (13.3)	-	2 (13.3)
Non-Haematological toxicity				
Anorexia	1 (6.7)	-	-	-
Diarrhoea	1 (6.7)	1 (6.7)	-	1 (6.7)
Dehydration	1 (6.7)	-	-	-
Hand foot syndrome	2 (13.3)	-	-	-
Others	-	-	-	-

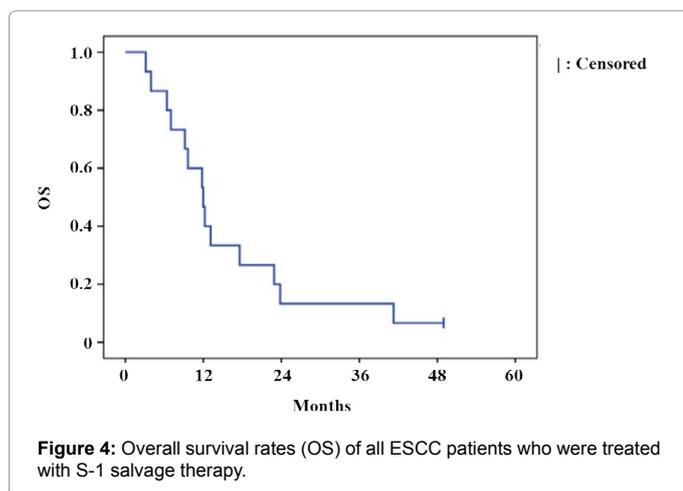
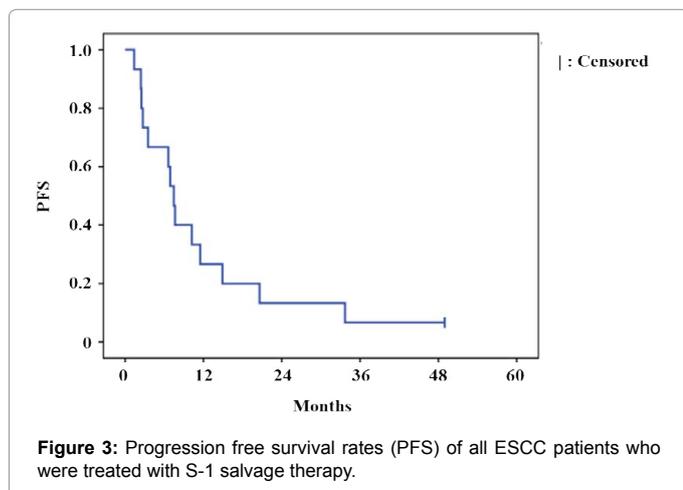
Table 3: Toxicity.

the standard chemotherapy. Two case reports showed that the residual metastatic lymph node after the definitive chemoradiotherapy for ESCC successfully treated by S-1 monotherapy [18,19]. Because S-1 is not approved to use for ESCC in Japan, we included the patients who had administered S-1 for any acceptable reason; synchronous head and neck cancer, gastric cancer, lung cancer and so on, after they failed standard chemotherapy for ESCC. Therefore, we consider that this is the valuable report about the efficacy and the safety of S-1 monotherapy as salvage chemotherapy for metastatic or recurrent ESCC.

It is reported that chemotherapy provides a survival benefit over BSC for patients with ESCC who cannot tolerate or whose tumor is refractory to the standard chemotherapy including 5FU, platinating agent and taxane; OS in patients who received BSC or chemotherapy were 4.3 and 7.9 months, respectively [20]. It is impossible to compare the PFS and OS of S-1 in this study and those of BSC in the previous report because of many differences in study settings and in patient characteristics that can influence PFS/OS such as performance status, propriety of oral ingestion, and the presence or absence of 2nd line failure. However, S-1 monotherapy demonstrated a sufficient efficacy and safety as salvage chemotherapy for ESCC, although S-1 monotherapy in this study was performed as 2nd or 3rd line treatment. Although the response rate was relatively low (7%: CR/PR were 1/0 cases), disease control rate (67%: CR/PR/SD were 1/0/9 cases), one year survival (33%), PFS (6.2 months), and OS (10.0 months) was impressive.

As for the safety, we think it is a significant result that there were no patients who experienced any serious adverse events in our study. In our practice, S-1 was administered orally from day 1 to day 14, every 3 weeks based on the patients' body surface area (BSA). It is possible that the safety of S-1 in this study was due to the relatively low dose intensity of S-1. However, it seemed reasonable dose because the efficacy of S-1 was sufficient as mentioned above. Considering the poor prognosis of the patients with metastatic or recurrent ESCC who failed the standard chemotherapy, the 2nd or 3rd line S-1 monotherapy is expected to improve the prognosis of those patients. We believe that the results of our study will bring hope to those patients.

It is interesting that S-1 showed apparent efficacy for the patients who had failed the 5-FU containing prior chemotherapy. In our study, 67% of them achieved CR or SD and their prognosis was clearly prolonged. One of the possible reason for it is that S-1 might show an enhanced therapeutic effect because S-1 contains 5-chloro-2,4-dihydropyridine which is recognized to enhance the anticancer effect. The interval period between the last medication of prior 5-FU and S-1 monotherapy might also be one of the reasons for it. Actually, retreatment with anthracyclines and taxanes has been reported to be an effective treatment option in metastatic breast cancer [21]. In this



study, 83% (5/6) of patients who had completely responded to prior FP regimen achieved CR/SD by S-1 monotherapy. The treatment interval between the last administration of prior 5-FU and S-1 monotherapy in 10 patients who achieved CR/SD by S-1 monotherapy was longer than 5 patients who failed S-1 monotherapy. S-1 monotherapy should be considered especially in patients who had responded to a prior 5-FU containing chemotherapy with an enough interval period.

This study had limitations of selection bias, small number of the patients, and the heterogeneity of patients' clinical stage (II and IV) at the beginning of S-1 treatment. However, the analysis of the selected patients (n=13) whose clinical stage limited to IV showed a similar tendency compared to the analysis of all patients. The potentially high disease control rate of S-1 treatment might provide a valuable treatment option for the carefully selected patients with relatively well general condition, because there is no available treatment option for the ESCC patients refractory for 5FU, platinating agent and taxanes at this time. To confirm the effect and the safety of S-1 monotherapy as salvage chemotherapy for ESCC, a prospective study with a large number of patients is required.

In conclusion, S-1 monotherapy could be an effective and safe treatment option to improve the prognosis of patients with ESCC refractory to the standard chemotherapy.

Ethical Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

Conflict of Interest

All authors declare no financial conflict of interest.

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