**Table 4** Tumor response

| Best response | Phase I ($n = 12$) | | Phase II ($n = 23$) | Total ($n = 35$) | |
|---|---|---|---|---|---|
| | 400 mg bid ($n = 9$) No. | 200 mg bid ($n = 3$) No. | 200 mg bid No. | No. | % |
| Complete response | 0 | 0 | 1 | 1 | 2.9 |
| Partial response | 0 | 0 | 2 | 2 | 5.7 |
| Stable disease | 2 | 2 | 11 | 15 | 42.8 |
| Progressive disease | 6 | 1 | 9 | 16 | 45.7 |
| Not evaluated[a] | 1 | 0 | 0 | 1 | 2.9 |

[a] This patient did not complete cycle 1

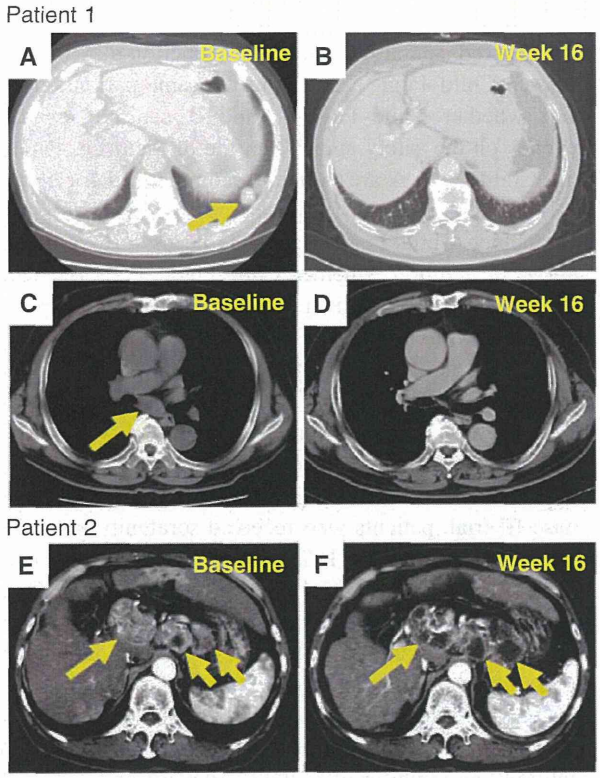


**Fig. 2** Computed tomography images of responding lesions from patient 1, who achieved a complete response. Metastatic lesions in the lung (**a**) and lymph node (**c**) disappeared after four cycles (16 weeks) of TSU-68 treatment (**b**, **d**). Representative computed tomography images of a tumor showing necrosis in patient 2. Before treatment, several abdominal lymph node metastases were apparent (**e**). After four cycles of treatment (16 weeks), the lesions demonstrated a lack of enhancement and markedly lower attenuation, consistent with tumor necrosis (**f**)

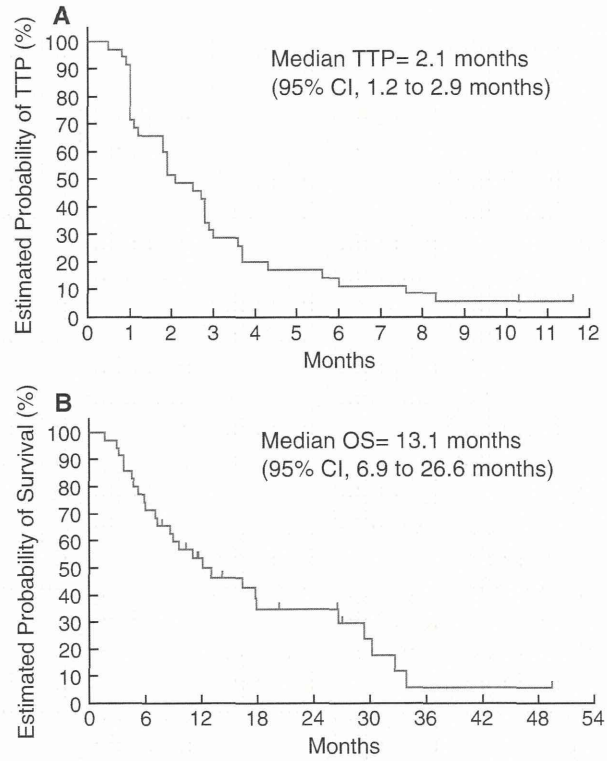


**Fig. 3** **a** The independently assessed median time to progression in all 35 patients treated with TSU-68 was 2.1 months. **b** The investigator-assessed median overall survival in all 35 patients treated with TSU-68 was 13.1 months

angiogenesis-related parameters showed any variation with treatment (as the variation of the data for PAI-1 was so large, they were not analyzed; Table 5). The mean values of sVCAM-1 for responders (patients with CR + PR + SD; 1,944 pg/ml) were higher than that for non-responders (patients with PD + NE; 1,422 pg/ml), which was statistically significant ($P = 0.026$, $t$ test).

## Discussion

In this trial, special attention was paid to patients with HCC, who often have impaired liver function and might have the potential for reduced clearance of TSU-68, which is eliminated mainly by the liver [12, 13]. This study suggests that the adverse-event profile of TSU-68 in this trial was comparable to observations in other phase I trials examining patients with solid tumors [14, 15]. Although half of the patients experienced exacerbation of pre-existing hypoalbuminemia during the treatment, this was

**Table 5** Logistic regression analysis of angiogenesis-related factors

| Variable | Evaluation variable (cut-off point) | Odds ratio | 95% CI | *P* value |
|---|---|---|---|---|
| VEGF | <47 × ≧47 | 0.480 | 0.095–2.426 | 0.375 |
| t-PA | <2.3 × ≧2.3 | 2.250 | 0.574–8.824 | 0.245 |
| VCAM-1 | <2,370 × ≧2,370 | 16.000 | 1.735–147.541 | 0.014 |
| ELAM-1 | <70 × ≧70 | 0.716 | 0.187–2.744 | 0.626 |
| IL-8 | <10.0 × ≧10.0 | 3.250 | 0.761–13.889 | 0.112 |
| PDGF | <1,450 × ≧1,450 | 3.666 | 0.907–14.813 | 0.068 |
| Factor VIII | <181 × ≧181 | 0.545 | 0.140–2.120 | 0.382 |

The *t* test was used to compare baseline levels of angiogenesis-related parameters in terms of responders. A responder means a patient who showed CR, PR and SD; non-responders showed PD and NE

not associated with a worsening of liver function. The edema, associated with hypoalbuminemia, was managed with diuretics. The lack of hypertension as a toxic effect may have been due to the difference in the inhibitory profile between TSU-68, which strongly inhibits both PDGFR and VEGFR, and other antiangiogenic compounds, which predominantly inhibit VEGFR [21, 22].

From the viewpoint of the pharmacokinetics of TSU-68, no trend was seen toward higher plasma exposure to TSU-68 with greater liver dysfunction (Levels 1–3). Furthermore, the exposure in the patients with HCC appeared to be similar to that in patients with advanced solid tumors that were not HCC in a phase I study [15]. These findings suggest that impaired liver function is unlikely to affect the pharmacokinetics of TSU-68. The present study indicated that the $C_{max}$ and AUC were reduced by the repeated administration of TSU-68, which has also been observed in previous trials [14, 15]. This decrease was found to be due to TSU-68, which caused an induction of its own metabolism in the non-clinical studies [12, 13]. Although in this study, the pharmacokinetics of TSU-68 was not examined after long-term consecutive oral administration, the AUC on day 28 has been reported to be similar to that on day 2. This suggests that the decreased exposure, which reaches steady state on day 2, is maintained throughout the therapeutic cycle. In Level 3, no obvious decrease in the AUC on day 2 was observed by reducing the dose of TSU-68 from 200 to 400 mg, although these results are based on a small amount of data. In addition, the estimated daily AUC in the patients who received 200 mg TSU-68 bid was roughly similar to the AUC data showing a 50% inhibition of human xenograft tumor growth in mice (data not shown). However, these data should be interpreted cautiously because the majority of the patients who were included as Child-Pugh B had Child-Pugh scores of 7.

In this study, we selected the fixed-dose for both Child–Pugh A and B because hepatitis or Child–Pugh A patients experienced toxicities (abdominal pain and diarrhea), although no DLT was found when 400 mg bid TSU-68 was administered, and also because liver function may fluctuate between Child–Pugh A and B in the same patients. However, whether Child–Pugh A and B can be separated depends on the safety and PK profile of the drug. Patients with Child–Pugh A are initially recommended for clinical trials in HCC research [23], whereas the design of trials that include Child–Pugh B patients needs further investigation. In addition, whether Child-Pugh score is a good system for stratifying liver function with these types of drugs is open to argument.

Many agents targeting angiogenesis have been investigated in HCC [3, 4, 10, 11, 22, 24–27]. In an international phase III trial, sorafenib reduced the mortality hazard by 44% compared with placebo, with a median OS of 10.7 months (vs. 7.9 months with placebo) [3]. In an Asian phase III trial, patients who received sorafenib had a 35% disease control rate (vs. 16% with placebo), with a median TTP of 2.8 months (vs. 1.4 months) and a median OS of 6.5 months (vs. 4.2 months) [4]. The results mirrored those of the SHARP trial, although the Asia–Pacific patients had more advanced disease. In a phase I trial in Japan, sorafenib resulted in 4% PR and 83% SD, with a median TTP of 4.9 months and a median OS of 15.6 months [24]. Sunitinib, an inhibitor of VEGFR, PDGFR and c-Kit, was used against HCC in a phase II trial and produced a 3.9% PR and 38.5% SD, with a median progression-free survival of 3.9 months and a median OS of 9.8 months [22, 25]. Chemotherapy-naïve Child–Pugh A patients were enrolled in the sorafenib phase III trial [3, 4]. In our trial, eight Child–Pugh B patients were enrolled, and systemic chemotherapy had been already administered in 14 patients. The patients had been treated previously a mean of 8.2 times using various modalities. Although TTP in our trial is less than the reported data of SHARP [3] and similar to the Asian sorafenib trial in the placebo arms [4], these factors might affect the results.

The response rate (8.6%) and a median OS (13.1 months) of TSU-68 were comparable to those reported for these other agents. Some patients were

administered TSU-68 for more than 1 year after confirmed PD by independent review that was not determined by investigators, and the long-term treatment with TSU-68 might have contributed to the longer OS period. This warrants further study, but needs to be evaluated in a larger trial. Molecular-targeted agents, including TSU-68, generally show a relatively low response rate but a high disease control rate, indicating that a large proportion of patients reach SD. The treatment response assessed using RECIST may not accurately reflect the overall effect of these agents [23]. We had several cases in which necrosis was observed inside a tumor, despite the increase in tumor size. As an objective response is a weak surrogate of activity in phase II trials, a consensus conference endorsed by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommended the inclusion of TTP as the primary endpoint in phase II trials [23].

Molecular-targeted agents are being developed as systemic therapies for HCC in first- and second-line settings as monotherapy and in combination with locoregional therapies. The primary endpoint for phase III studies that assess primary HCC treatments is survival, and the control arm should be sorafenib. Comparison of single agents head to head with sorafenib might jeopardize study approval and the recruitment of patients for ethical reasons. For second-line treatments against advanced HCC, the new agents should be compared with placebo or best supportive care [23]. A phase II randomized study of TSU-68 in combination with TACE has been conducted (manuscript in preparation), and a phase III trial is being planned.

VEGF, PDGF and bFGF participate in the neovascularization of HCC [26, 27], and VEGF levels are thought to have a prognostic value [28]. IL-8 has proangiogenic activity in cancers, although its role in HCC is controversial [27]. Given that the primary target of TSU-68 is endothelial cells, we speculated that damaged vascular endothelial cells may release endothelial cell-specific markers such as sELAM-1 and sVCAM-1. As sVCAM-1 can be identified in the bloodstream, it is potentially useful as a non-invasive biomarker for the monitoring of disease progression in cancer [29]. A high level of VCAM-1 was significantly associated with an advanced disease stage and the presence of distant metastasis in gastric cancer [30] and also has been shown to be associated with angiogenesis and poor prognosis in breast cancer [31] and in HCC [32]. In this trial, we found higher baseline levels of sVCAM-1 in patients with good response (CR + PR + SD) after treatment with TSU-68. Although our data suggested that sVCAM-1 is a possible predictive marker for the response, the analysis is exploratory, and further study is necessary to confirm this possibility.

In conclusion, the step-wise study design based on hepatic function was useful in a safety assessment of TSU-68 in patients with HCC who had impaired liver function. The TSU-68 dosage of 200 mg bid has a favorable safety profile, even in patients with Child–Pugh B cirrhosis, and together with a high disease control rate, provides a rationale for its further evaluation in patients with HCC.

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**Conflict of interest statement** The author(s) have nothing to disclose.

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# A case of long-term survival of metastatic desmoplastic small round cell tumor treated with multimodal therapy

TSUBASA WATANABE[1], SHIN'ICHI MIYAMOTO[1], KOJI KITAGORI[1], TAKAHIRO HORIMATSU[1], SHUKO MORITA[1], YOKO MASHIMO[1], YASUMASA EZOE[2], MANABU MUTO[1] and TSUTOMU CHIBA[1]

Departments of [1]Gastroenterology and Hepatology, and [2]Multidisciplinary Cancer Treatment, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan

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**Abstract.** Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive and malignant tumor that predominantly affects young males. No standard therapy is currently available for patients with DSRCT and the prognosis remains extremely poor. In this study, we report a thought-provoking DSRCT case. A 24-year-old male was admitted to our hospital with a chief complaint of hematemesis. Computed tomography revealed a retrovesical mass with a splenic hilar tumor, multiple lung and liver tumors and marked lymph node swellings. The source of hematemesis was gastric varices caused by the compression of the splenic vein by a splenic hilar tumor. The patient was provided with a histological diagnosis of DSRCT based on needle biopsy from the liver tumors and the pelvic mass was thought to be the primary lesion. This is a long-term survival case of metastatic DSRCT treated with multimodal therapy including 15 courses of multiagent chemotherapy, radiation therapy for the hepatic portal region using 42.5 Gy, and four instances of therapeutic endoscopy. The prolonged progression-free survival period (15 months) obtained following chemotherapy suggests the chemosensitive feature of the disease. We used a modified P6 regimen (cyclophosphamide, pirarubicin, vincristine, ifosfamide and etoposide) and a modified PAVEP regimen (cyclophosphamide, pirarubicin, etoposide and cisplatin) to decrease severe adverse events and to improve the completion rate of chemotherapy. DSRCT is an aggressive but chemo-sensitive disease, and continuous chemotherapy using an appropriate regimen with possible supportive care is essential for long-term survival. This case report may represent a treatment option for this rare disease.

*Correspondence to:* Dr Shin'ichi Miyamoto, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
E-mail: shmiyamo@kuhp.kyoto-u.ac.jp

*Key words:* desmoplastic small round cell tumor, multimodal therapy, P6 regimen, PAVEP regimen

## Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive, malignant tumor that predominantly affects young males at a median age of 19 years (range 7-58) and with a male-to-female ratio ranging from 5:1 to 10:1 (1,2). DSRCT is a member of the small round blue cell tumor family, which includes small-cell carcinoma, Merkel cell carcinoma, synovial sarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, neuroblastoma, lymphoma, rhabdomyosarcoma and DSRCT (3). No standard therapy is currently available for patients with DSRCT and the prognosis of DSRCT remains extremely poor (2). In this study, we report a case of long-term survival of metastatic DSRCT treated with multimodal therapy, including multiagent chemotherapy, radiation therapy and therapeutic endoscopy.

## Case history

A 24-year-old male was admitted to our hospital with a chief complaint of hematemesis. The patient had neither significant medical history nor family history. Physical examination revealed only that the patient was anemic. Laboratory examination was as follows: hemoglobin, 11.4 g/dl (normal range 13.5-16.7 g/dl); white blood cell count, 6,200/dl (normal range 2,900-8,900/dl); platelet count, $13.2 \times 10^{10}$/dl (normal range, $15.9-38.9 \times 10^{10}$/dl); C-reactive protein, 0.1 mg/dl (normal value ≤0.2 mg/dl); aspartate aminotransferase, 52 IU/l (normal range 13-33 IU/l); alanine aminotransferase, 99 IU/l (normal range 8-42 IU/l); alkaline phosphatase, 588 IU/l (normal range 115-359 IU/l); γ-glutamyl transpeptidase, 380 IU/l (normal range 9-54 IU/l); and total bilirubin, 0.7 mg/dl (normal range 0.3-1.3 mg/dl). Renal function tests were normal.

Endoscopy showed oozing bleeding from varicose veins located on the greater curvature of the upper gastric body (Fig. 1A). Spontaneous hemostasis was obtained. Computed tomography (CT) demonstrated that compression of the splenic vein by the splenic hilar tumor appeared to cause the gastric varices (Fig. 1B). CT revealed the presence of a well-enhanced, bulky and lobulated mass on the pelvic floor (Fig. 1C) with a splenic hilar tumor, multiple liver and lung tumors, and marked lymph node swellings (particularly in

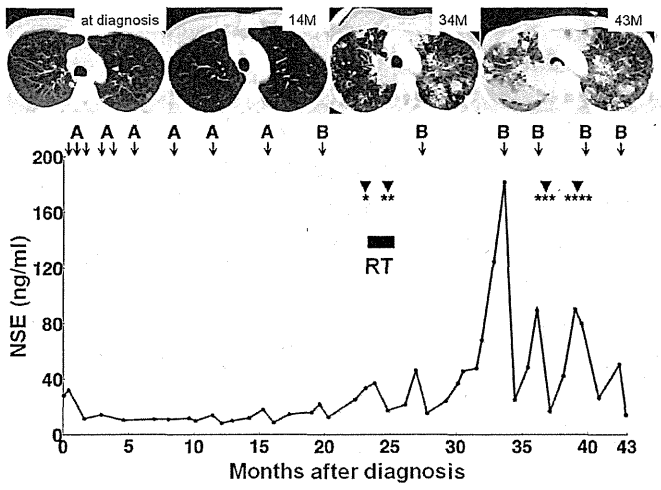


Figure 3. Clinical course of this case. Serum NSE level correlated well with clinical response. The patient received (A) nine courses of a modified P6 regimen and (B) six courses of a modified PAVEP regimen. Obstructive jaundice caused by portal lymphadenopathy was treated successfully by repeated endoscopic biliary drainage and radiation therapy (RT) to the hepatic portal region using 42.5 Gy, at 1.8 Gy per fraction. Massive hematemesis caused by active bleeding from the varicose vein was treated successfully by endoscopic hemostasis. The patient succumbed to acute pulmonary failure caused by progressive pulmonary metastases 43 months following diagnosis. Time-series CT images of pulmonary metastases are shown in parallel in the upper column (M, months after diagnosis). *Endoscopic biliary drainage using a plastic stent; **endoscopic biliary drainage using a metal stent; ***endoscopic hemostasis using metal clips for the active bleeding from a varicose vein; ****the metal stent obstruction caused by tumor ingrowth was relieved by inserting a plastic stent into the prior metal stent. NSE, neuron-specific enolase.

Table I. Chemotherapy regimens reported previously and used in this case.

| | Dose | Day |
|---|---|---|
| P6 (6) | | |
| Courses 1, 2, 3 and 6 | | |
| Cyclophosphamide | 2.1 g/m$^2$ | 1-2 |
| Doxorubicin | 25 mg/m$^2$ | 1-3 |
| Vincristine | 0.67 mg/m$^2$ | 1-3 |
| Courses 4, 5 and 7 | | |
| Ifosfamide | 1.8 g/m$^2$ | 1-5 |
| Etoposide | 100 mg/m$^2$ | 1-5 |
| PAVEP (7) | | |
| Doxorubicin | 40 mg/m$^2$ | 1 |
| Cyclophosphamide | 300 mg/m$^2$ | 1-3 |
| Etoposide | 75 mg/m$^2$ | 1-3 |
| Cisplatin | 100 mg/m$^2$ | 4 |
| Modified P6 | | |
| Courses 1, 3, 5 and 7 | | |
| Cyclophosphamide | 2 g/m$^2$ | 1-2 |
| Pirarubicin | 20 mg/m$^2$ | 1-3 |
| Vincristine | 2 mg/m$^2$ | 1 |
| Courses 2, 4 and 6 | | |
| Ifosfamide | 2.5 g/m$^2$ | 1-5 |
| Etoposide | 100 mg/m$^2$ | 1-5 |
| Modified PAVEP | | |
| Pirarubicin | 40 mg/m$^2$ | 2 |
| Cyclophosphamide | 450 mg/m$^2$ | 1-2 |
| Etoposide | 110 mg/m$^2$ | 1-2 |
| Cisplatin | 100 mg/m$^2$ | 1 |

Courses started after confirmation that the neutrophil count reached 500/$\mu$l and that the platelet count was >10,000/$\mu$l.

the hepatic portal region). $^{18}$F-fluorodeoxyglucose positron emission tomography showed multiple accumulation of a glucose analog in the same lesions detected using CT (Fig. 1D).

A needle biopsy specimen from the liver tumor revealed the presence of a poorly differentiated tumor with a variable size and shape, composed of nests of small round cells surrounded by a prominent desmoplastic stroma (Fig. 2A). Immunohistochemically, tumor cells coexpressed an epithelial marker (cytokeratin, Fig. 2B), a mesenchymal marker (desmin, Fig. 2C) and the Wilms' tumor 1 protein (Fig. 2D). Chromogranin, cluster of differentiation antigen (CD) 99 and CD56 were negative. From these findings, the patient was provided with a definite diagnosis of pelvic cavity-origin DSRCT with multiple-organ metastases (4,5).

The clinical course of this case is shown in Fig. 3. The patient was initially treated with multiagent chemotherapy using cyclophosphamide, pirarubicin, vincristine, ifosfamide and etoposide, according to the Ewing's sarcoma protocol, which is a modified protocol of the P6 regimen using pirarubicin instead of doxorubicin (modified P6 regimen) (2,6). During each course of this chemotherapy, the patient suffered from severe nausea and vomiting. The patient required frequent blood transfusions and continuous use of granulocyte colony-stimulating factor due to severe bone marrow suppression. The multiple pulmonary metastases were almost eradicated following four courses of the modified P6 regimen and the patient reached 15 months of progression-free survival after the application of this modified P6 regimen (Fig. 3). After the nine courses of treatment, second-line chemotherapy based on the PAVEP regimen (doxorubicin, cyclophosphamide, etoposide and cisplatin) (7) was introduced due to disease progression. To reduce adverse events, we modified the PAVEP regimen by using pirarubicin instead of doxorubicin and shortening the period of the regimen from five to two days (modified PAVEP regimen). The P6, modified P6, PAVEP and modified PAVEP regimens are shown in Table I.

Obstructive jaundice caused by portal lymphadenopathy developed 23 months following diagnosis. Endoscopic biliary drainage using a plastic stent was successfully performed. However, stent obstruction occurred two months after the initial placement of the plastic stent. Subsequently, we removed the stent and inserted a metal stent, which was followed by irradiation of the hepatic portal region using a total dose of 42.5 Gy, at 1.8 Gy per fraction. The patient had massive hematemesis 37 months following diagnosis caused by the active bleeding from a known varicose vein and endoscopic hemostasis using

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第３次対がん総合戦略研究事業

# 「QOLの向上をめざしたがん治療法の開発研究」に関する研究

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# Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: A phase II study

Tomonori Yano[1], Manabu Muto[2], Keiko Minashi[1], Junko Iwasaki[1], Takashi Kojima[1], Nozomu Fuse[1], Toshihiko Doi[1], Kazuhiro Kaneko[1] and Atsushi Ohtsu[1]

[1] Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

**Local failure at the primary site is a major problem after chemoradiotherapy (CRT) in patients with esophageal squamous cell carcinoma (ESCC). Salvage surgery is the only treatment option with curative intent, but it is associated with high morbidity and mortality. The aim of this study was to evaluate the efficacy and safety of salvage photodynamic therapy (PDT) after CRT. Patients with histologically proven local failure limited to the submucosal layer, and without any metastasis after definitive CRT (≥50 Gy) for ESCC were enrolled in the study. PDT began with intravenous administration of 2 mg/kg of porfimer sodium followed 48–72 hr later by excimer dye laser irradiation with a fluence of 75 J/cm$^2$. The primary endpoint was a complete response (CR) to treatment with PDT, and the secondary endpoints were toxicity related to PDT, progression-free survival (PFS) and overall survival (OS). Twenty-five patients were enrolled in the study. A CR was attained in 19 of 25 patients treated with PDT (CR rate, 76%; 95% CI, 55–91%). One treatment-related death (4%) caused by gastrointestinal hemorrhage at the irradiated site occurred 33 days after PDT. No adverse events greater than grade 3 were related to PDT in the other patients. After a median follow-up of 48 months after PDT, the PFS and OS at 3 years were 40% (95% CI, 21–59%) and 38% (95% CI, 17–60%), respectively. PDT is a potentially curative and tolerable salvage treatment after CRT for carefully selected patients with local failure without any metastasis.**

Chemoradiotherapy (CRT) is a curative treatment option for esophageal squamous cell carcinoma (ESCC). However, local failure without distant metastasis after completion of CRT remains a major problem that must be overcome to achieve a cure. Although salvage esophagectomy is now indicated for such patients, it has a higher morbidity and mortality compared with primary or planned esophagectomy.[1–4] The development of curative and safe salvage treatment options for local failure is needed to improve the survival of patients treated with CRT.

**Key words:** esophageal squamous cell carcinoma, chemoradiotherapy, photodynamic therapy, salvage treatment

**Abbreviations:** CR: complete response; CRT: chemoradiotherapy; EMR: endoscopic mucosal resection; ESCC: esophageal squamous cell carcinoma; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs: non-steroidal anti-inflammatory drugs; OS: overall survival; PDT: photodynamic therapy; PFS: progression-free survival; UMIN: University hospital Medical Information Network

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**Correspondence to:** Tomonori Yano, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East 6-5-1, Kashiwanoha, Kashiwa 277-8577 Japan, Tel.: +81-4-7133-1111, Fax: +81-4-7131-4724, E-mail: toyano@east.ncc.go.jp

After completion of CRT, a subset of ESCC patients develops local failure at the primary site without distant metastasis. In such patients, salvage surgery could be a curative treatment option, especially for those with T2 or earlier T-stage tumors or for those without lymph node metastasis.[1,2] Onozawa *et al.* reported that regional nodal failure within the field of elective lymph node irradiation is rare in patients achieving a complete response (CR) after CRT (1%; 95% CI, 0.0–5.3%).[5] These data have encouraged the use of local salvage treatment at only the primary site as a minimally invasive treatment in carefully selected patients.

We reported previously on the potentially acceptable results of endoscopic mucosal resection (EMR) or photodynamic therapy (PDT) as a salvage treatment for local failure after CRT.[6–8] PDT is a more deeply penetrating method than EMR for esophageal cancer even in the salvage setting, because, in our experience, PDT can cure patients with deep invasion of the submucosal layer or T2 local failure. In addition, PDT can be indicated both as a curative treatment for superficial esophageal cancer[9,10] and as a palliative treatment to relieve dysphagia caused by stenosis in more advanced esophageal cancer.[11] We believe that PDT might be a curative and effective treatment option for patients with local failure at the primary site after definitive CRT. We conducted a prospective study to evaluate the efficacy and safety of salvage PDT after CRT.

## Material and Methods

This was a single-arm, open-label, single-center phase II study. The primary endpoint of this study was the CR rate at the primary site after PDT. The secondary endpoints were toxicity related to salvage PDT, progression-free survival (PFS) and overall survival (OS). All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.[12] The study protocol was approved by the institutional review board of the Japanese National Cancer Center in January 2005. The study was carried out according to the ethical principles of the Declaration of Helsinki. Before enrollment, all patients provided written informed consent. This study was registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry, and the identification number is C000000244.

### Eligibility and exclusion criteria

The eligibility criteria of this study were as follows: (*i*) local failure after definitive CRT ($\geq$50 Gy) for ESCC; (*ii*) the patient's refusal to undergo salvage surgery; (*iii*) histologically proven squamous cell carcinoma by biopsy specimen of the local failed lesions; (*iv*) local failed lesions limited to the submucosal layer; (*v*) EMR not indicated for reasons of concomitant deep ulceration, severe fibrosis caused by radiation or a lesion invading to the deep submucosal layer; (*vi*) Eastern Cooperative Oncology Group performance status $\leq$2; (*vii*) adequate bone marrow function (white blood cell count $\geq$2,000/mm,$^3$ platelet count $\geq$75,000/mm$^3$), renal function (serum creatinine level $\leq$2.0 mg/dL) and liver function (serum bilirubin level $<$2.0 mg/dL, both alanine aminotransferase and aspartate aminotransferase $<$100 IU/L) and (*viii*) provision of written informed consent. The exclusion criteria were as follows: (*i*) active malignancy other than early gastrointestinal cancer that was curable with endoscopic treatment within 1 year; (*ii*) systemic infection requiring antibiotics; (*iii*) significant cardiovascular disease (uncontrolled hypertension, myocardial infarction, unstable angina, congestive heart failure), uncontrolled diabetes mellitus, or liver cirrhosis; (*vi*) baseline stage T4 before CRT; (*v*) presence of lymph node or distant metastasis confirmed by computed tomography (CT) after CRT and (*vi*) known porphyria.

### Evaluation of baseline clinical stage and the effect of CRT

Baseline clinical stage was determined using the TNM classification of the International Union Against Cancer.[13] Clinical T stage was evaluated by endoscopy, endoscopic ultrasound (EUS) and CT of the chest. Clinical N and M stages were evaluated by EUS and CT of the neck, chest and abdomen. In this study, lymph node metastasis was diagnosed clinically if the lymph node was $\geq$10 mm in diameter on CT. After completion of CRT, all patients were followed-up with both endoscopy and CT at 1, 3, 6, 9 and 12 months, and then every 4 months after completing CRT.

### Evaluation of the local failure at the primary site after CRT

Before PDT, the depth of all failure lesions was evaluated using EUS (EU-M2000, Olympus Co. Ltd., Tokyo, Japan). We carefully observed the lesions with a high-frequency (20 MHz) miniature probe. When we detected a hetero-echoic solid component in the submucosal layer, we diagnosed it as a local failure lesion.

### PDT treatment and surveillance

All PDTs were performed as inpatient procedures. PDT began with intravenous administration of 2 mg/kg of porfimer sodium (Photofrin, Pfizer Japan Inc.) followed by excimer dye laser irradiation. Porfimer sodium was reconstituted as a 2.5 mg/mL solution in 5% glucose. It was injected within 5 min, and the injection rate was less than 12 mL/min. A 630 nm wavelength laser beam was emitted by an excimer dye laser (EDL-1, Hamamatsu Photonics, Hamamatsu, Japan), and the laser light was delivered *via* a microlens- tip fiber, without any balloon or light diffuser, through the operative channel of the scope. An attachment was fitted to the tip of the scope to keep it facing the lesion and to maintain the distance between the tip of microlens fiber and the surface of the lesion during the procedure. The laser treatment was performed 48 hr after the injection of porfimer sodium. The fluence was 75 J/cm$^2$, with a fluence rate of 160 mW/cm$^2$ (4 mJ/pulse, 40 Hz pulse frequency). If the lesions were larger than 1 cm$^2$, multiple treatment fields were overlapped to cover the entire lesion. If the effect (*e.g.*, ischemic change of mucosa) after the laser treatment change, as evaluated by endoscopic observation was insufficient, additional laser irradiation was performed at a second session, 72 hr after the injection.[8,14,15]

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of porfimer sodium to protect them from the adverse effects of skin photosensitization. Patients were discharged 2 weeks after laser irradiation, if there were no complications related to PDT. Adverse events were identified through a physical examination and endoscopic evaluation performed every 2 weeks until 2 months after PDT. One month after PDT, patients were assessed through a physical examination, measurement of haematological and biochemical variables in blood and endoscopic examination. The endoscopic examination with biopsy was repeated at least every month thereafter to evaluate the response and luminal toxicity of PDT until the response was confirmed. CT was used to evaluate distant organ or lymph node metastasis every 3 months for the first 2 years and every 6 months thereafter.

### Statistical analysis

The primary endpoint of this study was the CR rate with salvage PDT. The sample size was determined assuming a binomial distribution. A threshold CR rate was considered to be 30%, and a CR rate of 60% was considered to be of potential interest. The planned accrual was calculated as 25 patients

**Table 1.** Baseline patients' characteristics before CRT ($n = 25$)

| Characteristics | Number of patients |
|---|---|
| **Sex** | |
| Male | 23 |
| Female | 2 |
| Median age | 67 years |
| (range) | 55–82 |
| **Location** | |
| Upper | 4 |
| Middle | 19 |
| Lower | 2 |
| **Histology** | |
| W/D,SCC | 0 |
| M/D,SCC | 7 |
| P/D,SCC | 3 |
| SCC | 15 |
| **Baseline TNM stage** | |
| Stage I | 5 |
| Stage II | 11 |
| Stage III | 7 |
| Stage IVA | 2 |
| **T stage** | |
| T1 | 6 |
| T2 | 7 |
| T3 | 12 |
| **N stage** | |
| N0 | 16 |
| N1 | 9 |

Abbreviations: W/D, well differentiated; SCC, squamous cell carcinoma; M/D, moderate differentiated; P/D, poorly differentiated.

**Table 2.** Patients' characteristics before PDT ($n = 25$)

| Characteristics | Number of patients |
|---|---|
| **Regimen of chemotherapy** | |
| Cisplatin + 5FU | 23 |
| Others | 2 |
| **Radiation dose (Gy)** | |
| 50.4 | 15 |
| ≥60 | 10 |
| **Local failure pattern after CRT** | |
| Recurrent | 14 |
| Residual | 11 |
| **Lesion circumference of the lumen** | |
| <1/4 | 10 |
| 1/4–1/2 | 15 |
| **Concomitant ulceration on the lesion** | |
| Present | 6 |
| Absent | 19 |

Abbreviation: 5FU, 5-fluorouracil.

(allowing for 10% ineligibility) with $\alpha = 0.1$ and $\beta = 0.1$. If the calculated one-sided lower 95% confidence limit of the CR rate was ≥ 30%, the primary endpoint was considered to have been met. The PFS was measured from the date of enrollment to the first date of recurrence, disease progression at any site, or death. The OS was measured from the date of enrollment to the date of death for any reason or to the last follow-up visit. Survival time was calculated by the Kaplan-Meier method. Survival time was compared between variables by using the log-rank test. An alpha value of $< 0.05$ was considered significant. All statistical analyses were performed using Predictive Analysis Software Statistics 18 (SPSS Japan Inc., Tokyo, Japan).

## Results

Between April 2005 and January 2009, a total of 34 patients were recruited for this study. Nine of these patients were deemed ineligible (one with an active other malignancy within 1 year, seven with baseline stage T4 before CRT and one with a distant metastasis); thus, 25 patients were enrolled in this study. All 25 patients were treated with salvage PDT. The patients' baseline characteristics before CRT are summarized in Table 1. The patients included 23 men and two women, and the median age was 67 years (range, 55–82 years). The tumor location was the upper esophagus in four patients, middle esophagus in 19 patients and lower esophagus in two patients. The baseline clinical stages before CRT were: stage I in five, stage II in 11, stage III in seven and stage IVA in two patients, and no patient had distant organ metastasis before CRT. The patients' characteristics before PDT are summarized in Table 2. Most of the chemotherapeutic regimens of CRT comprised cisplatin and 5-fluorouracil with ≥50 Gy concomitant radiotherapy. Their failure patterns were recurrence after achieving a CR with CRT in 14 patients and residual lesions after CRT in 11 patients. All local failure lesions in this study were histologically proven T1b lesions within the radiation field. The median duration between the last day of radiation and the initiation of PDT was 192 days (range, 21–1,234 days).

### Efficacy

In this study, the range of esophageal surface areas that were treated was 3–9 $cm^2$.CR was attained in 19 of 25 patients with PDT, resulting in a CR rate of 76% (95% CI, 55–91%). A representative case of a patient who achieved CR is shown in Figure 1. There was no dose-response relationship in this study. The median esophageal surface area was 6 $cm^2$ in 19 patients who achieved CR and in six patients who did not achieve CR with PDT. The relationship between the degree of baseline lymph node metastasis and CR rate was as

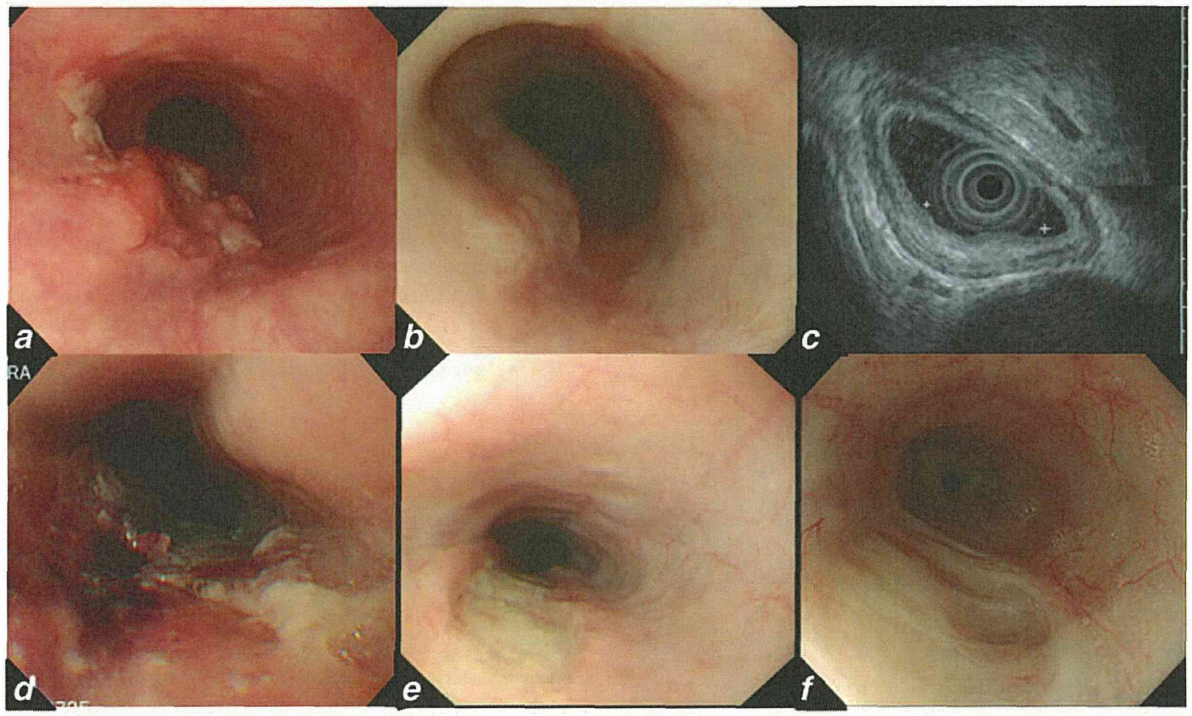


**Figure 1.** A patient who achieved a complete response (CR) with salvage photodynamic therapy (PDT) is presented. (*a*) Before chemoradiotherapy (CRT), the baseline stage was T2N0M0. (*b*) A local residual lesion was detected at the primary site after CRT. (*c*) The residual lesion was limited to the submucosal layer. (*d*) Two days after PDT, an ischemic change was observed at the laser-irradiated site. (*e*) One month after PDT, deep ulceration was observed at the laser-irradiated site. (*f*) A CR was achieved, and there was no recurrence at the primary site 3 years after PDT.

**Table 3.** Adverse events after PDT ($n = 25$)

| | Grade (no. of patients) | | | | | |
|---|---|---|---|---|---|---|
| **Adverse events** | **1** | **2** | **3** | **4** | **5** | **% (any)** |
| Pain-Pharynx | 3 | 1 | 0 | 0 | 0 | 17 |
| Pain-Chest | 11 | 3 | 0 | 0 | 0 | 61 |
| Anorexia | 1 | 0 | 0 | 0 | 0 | 4 |
| Dysphagia | 7 | 2 | 0 | 0 | 0 | 39 |
| Nausea | 1 | 0 | 0 | 0 | 0 | 4 |
| Vomiting | 1 | 0 | 0 | 0 | 0 | 4 |
| Fever | 11 | 0 | 0 | 0 | 0 | 48 |
| Photosensitivity | 7 | 1 | 0 | 0 | 0 | 32 |
| Hemorrhage-GI | 0 | 0 | 0 | 0 | 1 | 4 |

Abbreviation: GI, gastrointestinal.

follows: the CR rate of 16 N0 patients was 75% (12/16), whereas the CR rate of 9 N1 patients was 78% (7/9). The relationship between the baseline T stage before CRT and CR rate was as follows: the CR rate with baseline T1 or T2 was 85% (11/13, 95% CI, 55–98%), whereas that with baseline T3 before CRT was 67% (8/12, [95% CI, 35–90%]). Furthermore, the 1-year local control rate of patients with baseline T1 or T2 was significantly higher compared with that of patients with baseline T3 (T1 or 2 *vs.* T3 = 77% [95% CI, 54–100%] *vs.* 42% [95% CI, 14–70%], $p = 0.04$).

### Safety

The safety of PDT in all 25 patients is shown in Table 3. Common adverse events after PDT were chest pain (61%), pharyngeal pain (17%), dysphagia (39%) and fever (48%). Photosensitivity was observed in eight (32%) patients. All patients' fevers were grade 1 with NCI-CTCAE, and most patients recovered within a day. Predose nonsteroidal anti-inflammatory drugs (NSAIDs) might not have been necessary based on the results of this study, because patients' fevers were not severe nor prolonged. Severe complications (≥grade 3) related to PDT limited to one patient death due to gastrointestinal hemorrhage 33 days after PDT. His baseline stage before CRT was T3N0M0, and a histologically confirmed local residual lesion was detected after CRT. After enrollment in this study, he was treated with a fluence of 75 J/cm$^2$ and a fluence rate of 160 mW/cm$^2$ for the treatment area of 9 cm$^2$. He received the maximum treatment field with the largest light dose in this study. He complained of continuous chest pain (grade 2) after PDT, but his pain was controlled with

oral administration of a NSAID. Although we could not confirm the origin of the hemorrhage with endoscopic observation or autopsy, deep ulceration was observed endoscopically at the PDT-irradiated site 1 week before his death. We thought that the hemorrhage was caused by an aortic-esophageal fistula at the laser-irradiated site. The death of this patient gave a 4% (1/25) rate of treatment-related death. No other patient developed an esophageal fistula. Six patients (24%) developed esophageal stenosis requiring balloon dilatation.

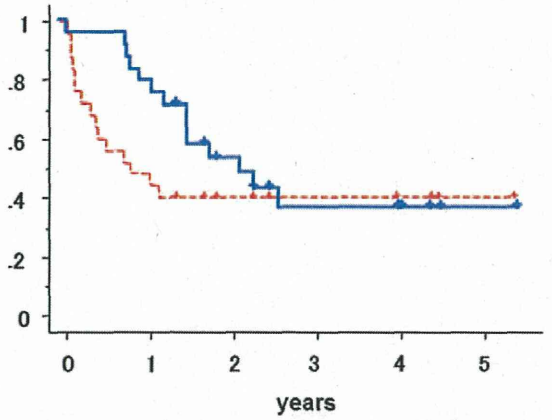


**Figure 2.** Progression-free survival (red dotted line) and overall survival (blue line) of 25 patients after the initiation of salvage photodynamic therapy (PDT).

### Survival

The median follow-up was 48 months (range, 17–64 months). The clinical courses of the 19 patients who had achieved a CR with PDT were as follows. Of the 11 patients who did not develop recurrence, ten are still alive and one died of multiple liver metastases from a prior gastric adenocarcinoma without any esophageal cancer recurrence. Among the remaining eight patients, three developed local recurrence, and all three were treated with salvage esophagectomy, but none survived. Local recurrence was detected within a year (range, 5–10 months) after achieving CR in all three patients, and therefore, the local control rate at 1 year was 64% (16/25, [95% CI, 43–82%]). Lymph node metastasis without local recurrence was detected in three patients; one underwent surgery and the other two were treated with systemic chemotherapy, but all died of cancer progression. Two patients developed liver metastasis and were treated with systemic chemotherapy; one died because of disease progression,

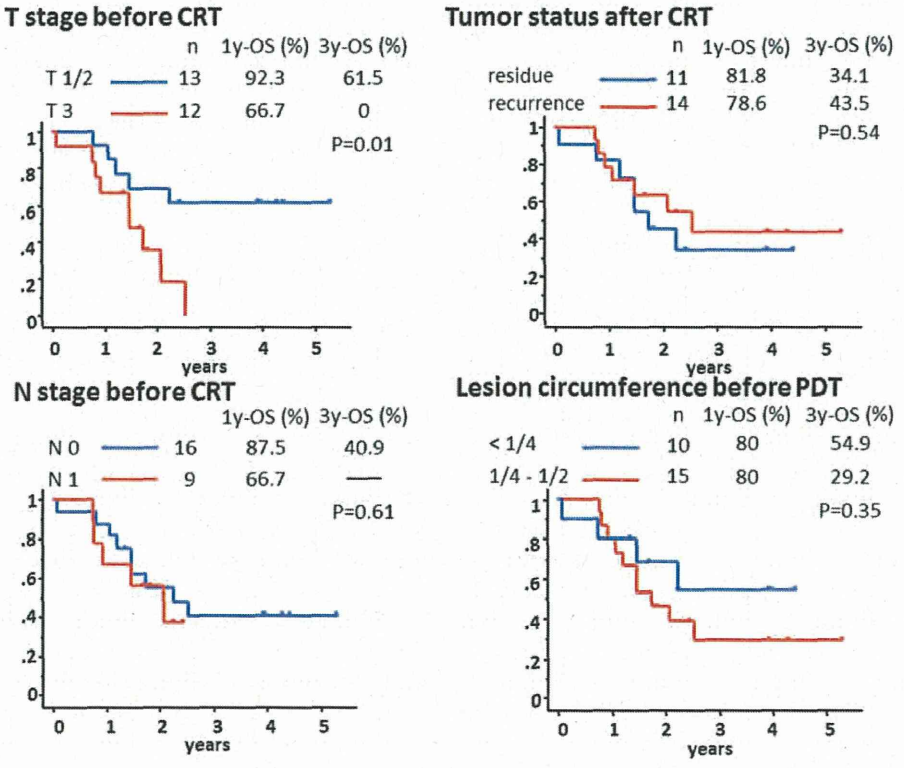


**Figure 3.** Comparisons of overall survival according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

and the other is still alive about 2 years after detection of liver metastasis. Six patients could not achieve a CR with PDT. Two were treated with systemic chemotherapy, two received salvage surgery and one was treated with a second PDT; all died because of disease progression. The remaining patient's death was classified as a treatment-related death, as described earlier. The PFS rates of all 25 patients at 1 and 3 years were 48% (95% CI, 28–68%) and 40% (95% CI, 21–59%), respectively, and the OS rates at 1 and 3 years were 80% (95% CI, 64–96%) and 38.4% (95% CI, 17–60%), respectively (Fig. 2). Comparisons of OS according to various clinical variables before CRT and before PDT are presented in Figure 3. Patients with clinical T1 or T2 before CRT had significantly higher OS than those with clinical T3 before CRT (T1 or T2 *vs.* T3: 1-year OS = 92.3% [95% CI, 77.8–106.8%] *vs.* 66.7% [95% CI, 40–93.3%], 3-year OS = 61.5% [35.1–88%] *vs.* 0%, $p = 0.01$), whereas there was no significant difference between patients with clinical N0 and N1 before CRT (N0 *vs.* N1: 1-year OS = 87.5% [95% CI, 71.3–103.7%] *vs.* 66.7% [95% CI, 35.9–97.5%], 3-year OS = 40.9% [95%CI, 16–65.8%] *vs.* not reached, $p = 0.61$). There was no difference in OS between patients with a residual lesion after CRT and a recurrent lesion after achieving CR (residual *vs.* recurrent: 1-year OS = 81.8% [95% CI, 59.0–104.6%] *vs.* 78.6% [95% CI, 57.1–100%], 3-year OS = 34.1% [95% CI, 4.8–63.4%] *vs.* 43.5% [95% CI, 14.4–72.6%], $p = 0.54$). Patients with a local failure lesion less than 1/4 the circumference of the lumen had a better OS than those with 1/4 to 1/2 circumference lesions; however, the difference was not statistically significant (<1/4 *vs.* 1/4-1/2: 1-year OS = 80% [95% CI, 55.2–104.8%] *vs.* 80% [95% CI, 59.8–100%], 3-year OS = 54.9% [95% CI, 21.1–88.7%] *vs.* 29.2 [95% CI, 4.1–54.3%], $p = 0.35$).

## Discussion

To our knowledge, this is the first prospective study of salvage treatment for local failure after definitive CRT in patients with ESCC. In this study, the primary endpoint (CR rate) was met, and the results exceeded our expectations. The CR rate at the primary site was 76% (95% CI, 54.9–90.6%), suggesting that salvage PDT could be a curative treatment option for carefully selected patients with local failure at only a primary site after CRT. The 3-year survival rate of salvage PDT was 38.4%. This result indicates that salvage PDT can cure a subset of patients with local failure after CRT.

If the failure lesions are tiny and superficial, EMR could be a salvage treatment option for local failure after CRT. We have reported the long-term results for salvage EMR, and the 5-year survival rate was 49.1%.[7] In our report, more than half of the patients had baseline clinical T1 lesions before CRT, and all their local failure lesions were within the submucosal layer before EMR.[7] By contrast, in this study about half of the patients (12/25) had baseline clinical T3 lesions before CRT. Salvage EMR is technically difficult if the failure lesion is severely fibrotic after CRT or there is deep invasion of the submucosal layer. PDT could be a treatment option if local failure after CRT is limited to the submucosal layer without lymph node metastasis and in patients for whom surgery would be intolerable because of physical limitations. Therefore, PDT has a niche role between EMR and surgery in the salvage setting after CRT.

In general, salvage surgery is indicated for patients with local failure after CRT. However, the most serious problems with salvage surgery are the high rates of complications and treatment-related mortality. Compared with esophagectomy without CRT or esophagectomy after planned neoadjuvant CRT, salvage surgery is associated with several complications, such as a longer hospital stay and higher anastomotic leak rate. The treatment-related mortality rate ranges from 8 to 22%.[1–4,16] Therefore, the indications for salvage surgery should be carefully considered. Although treatment-related death occurred in one patient in this study, the incidence rate (4%) was lower than that for salvage surgery. This suggests that salvage PDT is a less morbid treatment option than salvage surgery for carefully selected patients with local failure at the primary site after CRT.

In this study, five patients received salvage surgery for local failure after PDT. Although their physical condition was evaluated as tolerable for salvage surgery, they refused surgery before enrollment in this study. When the failure after PDT was detected, we informed them that their failure lesions were unlikely to be cured with reapplication of PDT because their lesions were suspected to be progressive refractory tumors; they then accepted salvage surgery. None of these patients achieved cure with salvage esophagectomy after PDT, and their median survival time after esophagectomy was 13 months (range: 4–18 months).

At present, nine patients remain alive without disease and one patient is alive with liver metastasis and is being treated with systemic chemotherapy. All of these patients survived with esophagus preservation. Second-line chemotherapy is one treatment option for patients with residual ESCC after CRT, although it is not curative and has a limited effect; that is, the overall response rate of second-line chemotherapy is low (0–16%), and a CR is difficult to achieve (0–6%).[17–20] This suggests that second-line systemic chemotherapy is a palliative treatment.

From the results of a comparison of OS according to various clinical variables, patients with T1 or T2 stage before CRT had a significantly higher survival rate than those with T3 lesions before CRT. All failure lesions in this study were determined before PDT to be within the submucosal layer; however, more advanced failure lesions might be included in the T3 group because of the difficulty of EUS evaluation after CRT, especially in advanced cases. However, N stage before CRT did not affect the survival after PDT. Patients with earlier T stage before CRT tend to be cured with salvage PDT, and these data demonstrate the reproducibility of our retrospective analysis.[14]

Before this phase II study, we did not perform the laser dose escalation study for local failure after CRT for

esophageal cancer. The fluence of 75 J/cm$^2$ with a fluence rate of 160 mW/cm$^2$ in this phase II study was determined from the results of our preliminary experience.[8,14] The variable of total fluence depends on the lesion size. In this study, the range of esophageal surface areas that were treated was 3–9 cm$^2$, and multiple treatment fields were overlapped to cover large lesions. From the results of this study, the fluence of 75J/cm$^2$ is effective with tolerable toxicity for local failure after CRT. However, because of the risk of esophageal perforation, we should treat carefully if the lesion requires a large treatment field.

Salvage PDT provided an effective treatment for local failure at the primary site. To achieve CR by salvage PDT, early detection of local failure is critical. We reported previously that a submucosal tumor-like appearance is closely associated with local failure at the primary site.[21] Our previous report led us to believe that careful and close surveillance by endoscopy is needed to provide early detection of residual tumor at the primary site after completion of CRT. Although repeated endoscopic surveillance can be complicated, these efforts allow for early detection and provide a minimally invasive curative treatment with organ preservation.

In conclusion, salvage PDT is an effective and tolerable salvage treatment option for local failure after CRT for ESCC in patients whose failure lesion is limited to the submucosal layer without any metastasis.

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# Impact of Neoadjuvant Chemotherapy on Physical Fitness, Physical Activity, and Health-related Quality of Life of Patients With Resectable Esophageal Cancer

*Noriatsu Tatematsu, RPT,* Yasumasa Ezoe, MD,† Eiji Tanaka, MD,‡ Manabu Muto, MD,§ Yoshiharu Sakai, MD,‡ and Tadao Tsuboyama, MD**

**Objective:** Neoadjuvant chemotherapy (NAC) followed by radical surgery is the standard treatment for patients with resectable esophageal squamous cell carcinoma (ESCC) in Japan. However, some adverse events associated with NAC may result in a decrease in physical fitness that may influence the patient's ability to tolerate surgery. The purpose of this study was to evaluate the impact of NAC on physical fitness, physical activity, and health-related quality of life (HRQOL) of patients with ESCC.

**Methods:** In this prospective study, we investigated 27 consecutive patients with newly diagnosed resectable ESCC who were scheduled to receive NAC followed by surgery between January 2009 and November 2010. Primary endpoints were change from baseline in physical fitness (knee extensor muscle strength and 6-min walking distance) and physical activity after NAC. A secondary endpoint was change from baseline in HRQOL.

**Results:** Physical fitness and physical activity level after NAC did not differ significantly from those before NAC. With regard to HRQOL, only social functioning was significantly different ($P=0.04$). The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance ($r=0.45$, $P=0.02$).

**Conclusions:** NAC had no impact on physical fitness and physical activity in patients with ESCC. This result indicated that there was no need for a physiotherapy intervention during NAC to prevent a decline in these parameters.

**Key Words:** esophageal cancer, HRQOL, neoadjuvant chemotherapy, physical activity, physical fitness

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Esophageal cancer was the eighth most common malignancy (482,000 cases, 3.8% of all cancers) and the sixth leading cause of cancer death (406,000 deaths, 5.4% of all cancers) worldwide in 2008.[1] Despite optimal treatment, median survival for advanced disease remains <1 year. Even in patients with resectable disease, the prognosis is relatively poor after surgery alone.[2–4] This fact has prompted many investigators to explore perioperative systemic treatment, such as chemotherapy or chemoradiotherapy, to improve survival. In Japan, on the basis of the results of several studies, such as Japan Clinical Oncology Group 9204 and Japan Clinical Oncology Group 9907, neoadjuvant chemotherapy (NAC) with cisplatin combined with 5-fluorouracil followed by radical surgery has become the standard treatment strategy for resectable esophageal squamous cell carcinoma (ESCC).[5,6]

Although NAC is a well-established treatment for improving the outcomes of surgery, several side effects may result in the deterioration of physical fitness, physical activity, and health-related quality of life (HRQOL). Recently, several studies reported the impact of neoadjuvant treatment (chemotherapy or chemoradiotherapy) on HRQOL.[7–9] However, there are no reports on the impact of NAC on physical fitness or physical activity. It is important to clarify whether these parameters will be decreased by NAC, because the compromise of physical fitness by NAC may negatively influence the tolerability and outcome of surgery. In addition, the results of this study will be useful to determine whether a physiotherapy intervention is necessary during the neoadjuvant treatment period to improve these parameters.

The objectives of this study were to evaluate the impact of NAC on physical fitness, physical activity, and HRQOL in patients with ESCC and to determine whether physiotherapy is needed during the NAC period.

## MATERIALS AND METHODS

### Study Design and Subjects

This was a single-center, prospective study conducted to evaluate the impact of NAC on the physical fitness, physical activity, and HRQOL of patients with resectable ESCC. The Institutional Review Board of Kyoto University Graduate School of Medicine approved the protocol and consent form for this study, and written informed consent was obtained from all patients. Between January 2009 and November 2010, patients with newly diagnosed ESCC who were scheduled to receive NAC followed by surgery were asked to participate in this study. All the patients who were scheduled to receive NAC followed by surgery were eligible. Patients with gait disturbances or cognitive impairment were excluded. Preoperative chemotherapy consisted of 2 cycles of cisplatin (80 mg/m$^2$, intravenously) on day 1 and 5-fluorouracil (800 mg/m$^2$/d in a continuous infusion) on days 1 through 5 at 3-week intervals. Primary outcomes were physical fitness (knee extensor muscle strength and 3-min walking distance) and physical activity. The secondary outcome was HRQOL. We assessed these outcomes before the initiation of NAC (pre-NAC) and after the completion of NAC (post-NAC).

From the *Departments of Human Health Sciences; †Multidisciplinary Cancer Treatment; ‡Surgery; and §Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

The authors declare no conflicts of interest.

Reprints: Noriatsu Tatematsu, RPT, Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: noriatsu.t@ay4.ecs.kyoto-u.ac.jp.



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### Demographic and Treatment Information

Information regarding age, sex, weight, clinical stage, histologic tumor type, and side effects was obtained from electronic medical records. Side effects were assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. The National Cancer Institute Common Terminology Criteria for Adverse Events measure toxicities as grades 1 through 5 (1 is mild, 2 is moderate, 3 is severe, 4 is life threatening or disabling, and 5 is death associated with the adverse event).

### Physical Fitness

To assess physical fitness, we tested the knee extensor muscle strength and 6-minute walking distance. Knee extensor muscle strength was assessed with an isometric knee extensor muscle strength machine (IsoForce GT-330, OG GIKEN, Japan). The subject was in the sitting position, and the hip and knee were kept at 90-degree angle. The maximal isometric strength was measured after adequate premeasurement trials. The 6-minute walking distance was measured with the 6-minute walk test, as described by the American Thoracic Society.[10] Subjects walked as far and as fast as they could for 6 minutes. (Subjects were allowed to rest if and as necessary during the 6-min period.) These tests were conducted by physiotherapists who had been trained in the proper techniques for conducting them.

### Physical Activity

Physical activity status was assessed using the last 7-day short version of the International Physical Activity Questionnaire (IPAQ) Japanese version.[11,12] This measure assessed total vigorous intensity physical activity, total moderate intensity physical activity, total time walking, and time spent sitting during the last 7 days. Each activity type and intensity score is provided a metabolic equivalent (MET) value according to the published protocol (eg, MET for walking = 3.3, cycling = 6.0, moderate intensity = 4.0, vigorous intensity leisure = 8.0) (Craig, IPAQ. At a glance: IPAQ scoring protocol, http://www.ipaq.ki.se/scoring.htm, accessed March 20, 2006). According to the published IPAQ scoring protocol, we calculated the average daily physical activity (METs min/d).

### Health-related Quality of Life

HRQOL was measured with the European Organization for the Research and Treatment of Cancer Quality of Life (QOL) Core Questionnaire with 30 items.[13] This QOL scale includes a global health status/QOL scale, 5 functional scales (physical, role, emotional, cognitive, and social functioning), and symptom scales (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems). Calculation of scores was carried out according to the European Organization for the Research and Treatment of Cancer QOL Core Questionnaire with 30 items manual. A difference of $\geq 10$ points in each scale indicates a clinically important change.[14]

### Sample Size Calculation and Statistical Analysis

Sample size calculation was based on the difference in the 6-minute walk test; primary outcome in this study. As the walking distance of 54 m (SD = 93) was thought to be clinically an important difference,[15–18] the estimated sample sizes required to achieve a power of the test of 80% and a 2-sided level of significance of 5% were calculated as 27 patients.

Demographic and treatment variables were described using means and SD, medians and ranges, and percentages, where appropriate. All variables were tested for distribution normality using the Shapiro-Wilks normality test. Differences over the course of NAC (pretreatment to posttreatment) were analyzed using paired-sample $t$-test for continuous variables with normal distribution (weight, knee extensor muscle strength, and 6-min walking distance) and the Wilcoxon signed-rank test for non-normally distributed variables (IPAQ score and HRQOL scores). Spearman rank correlation coefficient was used to evaluate the relationship between changes in physical activity and changes in physical fitness. All statistical analyses were performed with the R statistical package (www.r-project.org). All hypothesis testing was 2-tailed, and $P$ values $< 0.05$ were considered to indicate statistical significance.

## RESULTS

During the study period, 33 patients with ESCC underwent NAC before surgery. Among them, 6 were excluded because of gait disturbances (n = 2), cognitive impairment (n = 1), and declined participation (n = 3), so the remaining 27 patients were properly registered and underwent NAC. Patient demographic and treatment data are presented in Table 1. The mean age was 63 years, and 81% were men. The baseline clinical stage (UICC-TNM stage 6th edition) at enrollment was IIA in 11 (41%) patients, IIB in 10 (37%) patients, III in 5 (18%) patients, and IVA in 1 (4%) patient. The histologic type was squamous cell carcinoma in all patients. The occurrence of side effects was as follows: grade 1 in 23 (85%) patients, grade 2 in 16 (59%) patients, grade 3 in 3 (11%) patients, and grade 4 in 1 (4%) patient. The grade 3 chemotherapy-related toxicities were mucositis, abdominal pain, and thrombocytopenia. The grade 4 chemotherapy-related toxicity was hyponatremia. Most patients underwent 2 cycles of preoperative chemotherapy, although 5 (19%) patients underwent only 1 cycle because of severe adverse events (n = 2) and progression of disease (n = 3).

Table 2 shows changes in weight, physical fitness data, and physical activity over the course of NAC. Post-NAC variables did not differ significantly from pre-NAC variables. With regard to the global health status/QOL scale, functional scales, and symptom scales, there was a statistically significant difference only in terms of social functioning ($P = 0.04$; Table 3).

Results of the correlational analysis are presented in Figures 1A, B. The change in physical activity demonstrated a significant correlation with the change in 6-minute walking distance ($r = 0.45$, $P = 0.02$), but not with the change in knee extensor muscle strength ($r = -0.01$, $P = 0.95$).

## DISCUSSION

This is the first report regarding the impact of NAC on physical fitness and physical activity. Results of this prospective study suggested that NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. We hypothesized that physical activity would decrease because of adverse events, leading to a deterioration in physical fitness. Several studies have reported that treatment (surgery and/or chemotherapy and/or radiation) had a significant negative effect on physical activity.[19,20] In our study, however, physical fitness and physical activity levels did not decrease over the course of NAC. In addition, the change in physical activity demonstrated a significant positive correlation with the change in 6-minute walking distance. These results indicated that patients who maintained their pretreatment physical activity levels could maintain physical fitness, especially the 6-minute walking distance. Although most patients in this study experienced some kind of adverse event,

**TABLE 1.** Characteristics of Subjects

| | N = 27 (%) |
|---|---|
| Age (mean ± SD) | 63.4 ± 6.8 |
| Sex | |
| Male | 22 (81%) |
| Female | 5 (19%) |
| Clinical stage | |
| IIA | 11 (48%) |
| IIB | 10 (37%) |
| III | 5 (18%) |
| IVA | 1 (4%) |
| Histologic tumor type | |
| Adenocarcinoma | 0 (0%) |
| Squamous cell carcinoma | 27 (100%) |
| Side effects | |
| Grade 1 | 23 (85%) |
| Grade 2 | 16 (59%) |
| Grade 3 | 3 (11%) |
| Grade 4 | 1 (4%) |
| Grade 5 | 0 (0%) |

**TABLE 3.** Changes in EORTC QLQ-C30 Over the Course of NAC Treatment

| | Pre-NAC | Post-NAC | *P* |
|---|---|---|---|
| Global health status (QOL score) | 66.7 (16.7-100) | 66.7 (16.7-91.7) | NS |
| Functional scales | | | |
| Physical | 93.3 (66.7-100) | 93.3 (60-100) | NS |
| Role | 100 (33.3-100) | 100 (33.3-100) | NS |
| Emotional | 75 (41.7-100) | 83.3 (50-100) | NS |
| Cognitive | 83.3 (50-100) | 83.3 (33.3-100) | NS |
| Social | 100 (33.3-100) | 83.3 (0-100) | 0.04 |
| Symptom scales | | | |
| Fatigue | 22.2 (0-55.6) | 22.2 (0-66.7) | NS |
| Nausea and vomiting | 0 (0-33.3) | 0 (0-66.7) | NS |
| Pain | 0 (0-50) | 0 (0-33.3) | NS |
| Dyspnea | 0 (0-66.7) | 0 (0-33.3) | NS |
| Insomnia | 0 (0-66.7) | 0 (0-66.7) | NS |
| Appetite loss | 0 (0-66.7) | 0 (0-100) | NS |
| Constipation | 0 (0-100) | 0 (0-100) | NS |
| Diarrhea | 0 (0-33.3) | 0 (0-33.3) | NS |
| Financial difficulties | 0 (0-100) | 0 (0-100) | NS |

Values expressed as median (range).
EORTC QLQ-C30 indicates European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire with 30 items, NAC, neoadjuvant chemotherapy; NS, not significant; QOL, quality of life.

the severity of these adverse events was relatively mild. This seemed to be one of the reasons that most patients could maintain their physical activity levels. Similarly, HRQOL scores did not deteriorate significantly over the course of NAC, except for social functioning. Our findings are similar to previous work by Safieddine et al, who reported that the impact of NAC on HRQOL in patients with operable esophageal cancer was transient because HRQOL scores returned to baseline levels before surgical intervention.[7]

It was important to understand the impact of NAC on physical fitness, physical activity, and HRQOL in patients with ESCC to determine the need for a physiotherapy intervention to improve these parameters during NAC. The results of the present study indicated that there was no need for a physiotherapy intervention during NAC. However, Nagamatsu et al reported that esophagectomy can be safely performed in patients with a $Vo^2 max/m^2$ of at least 800 mL/m$^2$.[21] Thus, physiotherapy may be important before surgery to reduce the risk of postoperative cardiopulmonary complications. Further studies are needed to examine the role of physiotherapy in the treatment of ESCC comprehensively.

This study has some limitations. First, our study was conducted with small sample size, which might not have had enough power to detect significant differences in outcomes. It was possible that each outcome might reach statistical significance with more patients. However, even so, they might not be clinically significant; such as 1 kg weight loss, minimal difference in knee strength, or 2% difference in walk distance. Although only the 17% difference in IPAQ might be a clinically significant difference with more patients, the conclusion of this study might not be changed, because IPAQ was the secondary outcome. In addition, the small sample size precluded subgroup analyses stratified by the demographic and treatment characteristics of the patients. Second, we evaluated the impact of chemotherapy alone as a neoadjuvant treatment, because NAC followed by surgery is the standard treatment for the patients with resectable disease in Japan. However, the standard neoadjuvant treatment for the esophageal cancer in Western countries, such as in United States or in Europe, is chemotherapy with more strong combination regimen or chemoradiotherapy. Although it might be possible that inclusion of patients who received neoadjuvant chemoradiotherapy or different regimen of NAC might have changed the results of this study, we could not discuss about it from the results of this study. Third, the frequency of the excluded patients [6 patients (18.2%)] was relatively high in this study with the small sample size. Moreover, among them, 2 patients were excluded because of gait disturbances. This might introduce a potential of selection bias, because the finally analyzed patients were limited to the patients with relatively better condition. The fourth limitation was the assessment of physical activity. The Japanese short version of IPAQ is validated and reliable. However, it is not a direct assessment tool of real physical activity, such as daily walking steps.[22,23] Thus, it should be noted that the IPAQ data alone were

**TABLE 2.** Changes in Weight, Physical Fitness Data, and Physical Activity Over the Course of NAC Treatment

| | Pre-NAC | Post-NAC | *P* |
|---|---|---|---|
| Weight (kg) | 57.5 ± 11.8 | 56.5 ± 11.6 | NS |
| Physical fitness | | | |
| Knee extensor muscles strength (N m/kg) | 2.5 ± 0.6 | 2.4 ± 0.5 | NS |
| 6-min walk distance (m) | 574.9 ± 77.8 | 565.1 ± 75.3 | NS |
| Physical activity | | | |
| IPAQ (METs min/d) | 119.1 (0-605.6) | 99 (0-819) | NS |

Weight and physical fitness values expressed as mean ± SD. IPAQ values expressed as median (range).
IPAQ, indicates International Physical Activity Questionnaire; MET, metabolic equivalent; NAC, neoadjuvant chemotherapy; NS, not significant.

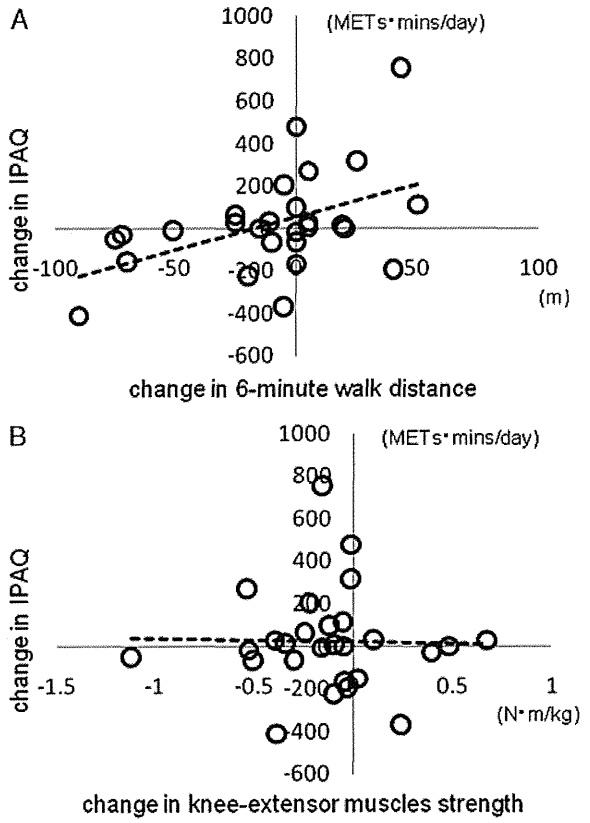


**FIGURE 1.** Relationship between changes in physical activity and changes in physical fitness. The change in 6-minute walking distance was correlated positively with the change in International Physical Activity Questionnaire (IPAQ) ($r=0.45$, $P=0.02$) (A), whereas the change in knee extensor muscle strength had no correlation ($r=-0.01$, $P=0.95$) (B). METs indicate metabolic equivalent.

probably insufficient to draw definitive conclusions that patients maintained their physical activity levels during NAC.

In conclusion, NAC had no impact on physical fitness, physical activity, and HRQOL in patients with ESCC. The results of this study indicated that there was no need to implement a physiotherapy intervention during NAC to prevent a decline in these parameters. As the number of patients was rather small, and the assessment tool used was insufficient, further study of a larger number of cases with more quantitative assessment tools is required to confirm the impact of NAC on physical fitness, physical activity, and HRQOL.

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