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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

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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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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

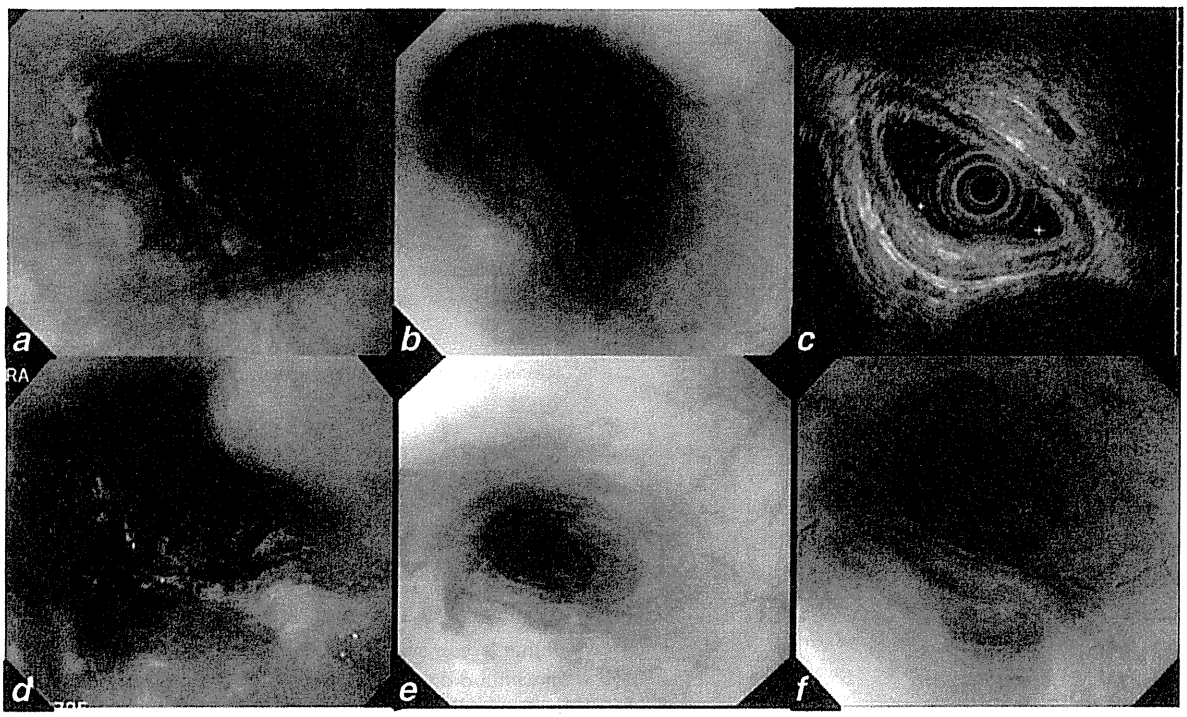

Figure 1. A patient who achieved a complete response (CR) with salvage photodynamic therapy (PDT) is presented. (*a*) Before chemoradiotherapy (CRT), the baseline stage was T2N0M0. (*b*) A local residual lesion was detected at the primary site after CRT. (*c*) The residual lesion was limited to the submucosal 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.

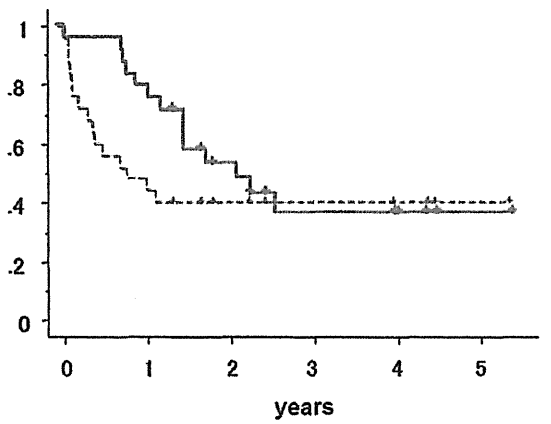

Figure 2. Progression-free survival (red dotted line) and overall survival (blue line) of 25 patients after the initiation of salvage photodynamic therapy (PDT).

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,

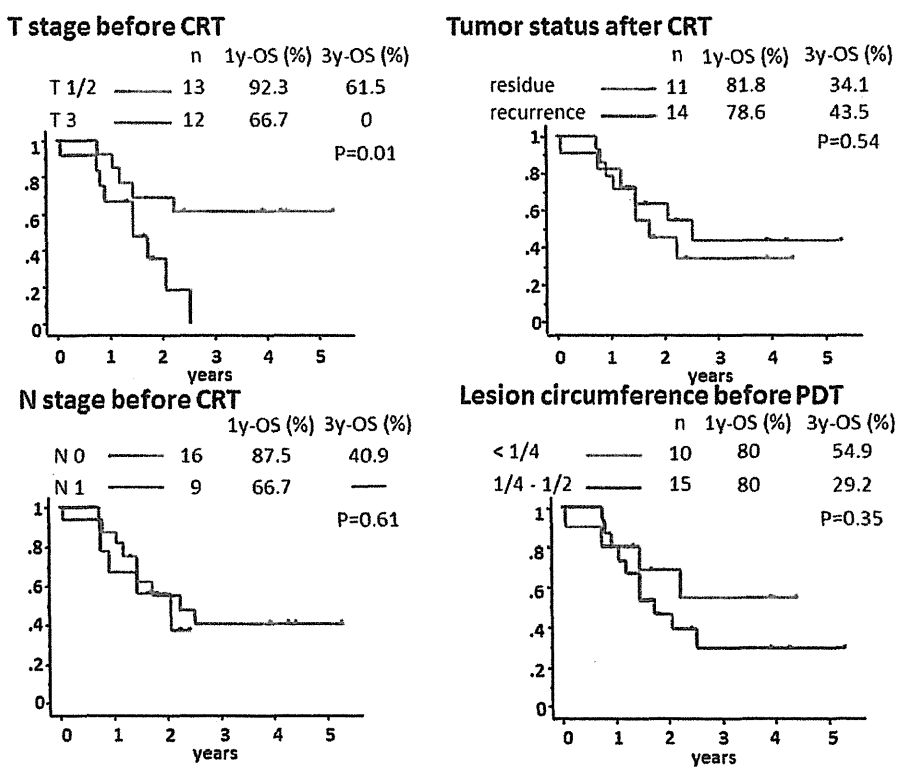

Figure 3. Comparisons of overall survival according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

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.

References

1. Swisher SG, Wynn P, Putnum JB, Mosheim MB, Correa AM, Komaki RR, Ajani JA, Smythe WR, Vaporciyan AA, Roth JA, Walsh GL. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002;123:173–83.
2. Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Nishida T, Mori M, Doki Y. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. *J Surg Oncol* 2009;100: 442–6.
3. Tachimori Y, Kanamori N, Uemura N, Hosokawa N, Igaki H, Kato H. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2009;137:49–54.
4. Chao YK, Chan SC, Chang HK, Liu YH, Wu YC, Hsieh MJ, Tseng CK, Liu HP. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. *Eur J Surg Oncol* 2009;35:289–294.
5. Onozawa M, Nihei K, Ishikura S, Minashi K, Yano T, Muto M, Ohtsu A, Ogino T. Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of thoracic esophagus. *Radiother Oncol* 2009;92:266–9.
6. Hattori S, Muto M, Ohtsu A, Boku N, Manabe T, Doi T, Ishikura S, Yoshida S. EMR as salvage treatment for patients with locoregional failure of definitive chemoradiotherapy for esophageal cancer. *Gastrointest Endosc* 2003;58:65–70.
7. Yano T, Muto M, Hattori S, Minashi K, Onozawa M, Nihei K, Ishikura S, Ohtsu A, Yoshida S. Long-term results of salvage endoscopic mucosal resection in patients with local failure after definitive chemoradiotherapy for esophageal squamous cell carcinoma. *Endoscopy* 2008; 40:717–21.
8. Yano T, Muto M, Minashi K, Ohtsu A, Yoshida S. Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer. *Gastrointest Endosc* 2005;62:31–6.
9. Savary JF, Grossjean P, Monnier P, Fontolliet C, Waqnieres G, Braichotte D, van den Berqh H. Photodynamic therapy of early squamous cell carcinoma of esophagus: a review of 31 cases. *Endoscopy* 1998;30:258–65.
10. Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal cancer. *Gastroenterology* 1995;108:337–44.
11. Litle VR, Luketich JD, Christie NA, Buenaventura PO, Alvelo-Rivera M, McCaughan JS, Nguyen NT, Fernando HC. Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. *Ann Thorac Surg* 2003;76: 1687–93.
12. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003, Available at: http://ctep.cancer.gov/forms/CTCAEv3.pdf. Accessed on August 9, 2006.
13. Sobin LH, Wittekind C, eds. TNM classification of malignant tumors, 5th edn. New York: Wiley-Liss, 1997.
14. Yano T, Muto M, Minashi K, Onozawa M, Nihei K, Ishikura S, Kaneko K, Ohtsu A. Long-term results of salvage photodynamic therapy for patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma. *Endoscopy* 2011; 43:657–63.
15. Nakamura T, Fukui H, Shirakawa K, Fujii Y, Fujimori T, Terano A. Photodynamic therapy of superficial esophageal cancer with a transparent hood. *Gastrointest Endosc* 2004;60:120–4.
16. Borghesi S, Hawkins MA, Tait D. Oesophagectomy after definitive chemoradiation in patients with locally advanced esophageal cancer. *Clin Oncol* 2008;20:221–6.
17. Conroy T, Etienne PL, Adenis A, Wagener DJ, Paillot B, François E, Bedenne L, Jacob JH, Seitz JF, Bleiberg H, Van Pottelsberghe C, Van Glabbeke M, et al. Phase II trial of vinorelbine in metastatic squamous cell esophageal carcinoma. *J Clin Oncol* 1996; 14:164–70.
18. Lordick F, von Schilling C, Bernhard H, Hennig H, Bredenkamp R, Peschel C. Phase II study of irinotecan plus docetaxel in cisplatin-pretreated relapsed or refractory oesophageal cancer. *Br J Cancer* 2003;89:630–3.
19. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W, Ohtsu T. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. *Ann Oncol* 2004;15: 955–9.
20. Park BB, Im YH, Hwang IG, Lee SC, Ahn JS, Ahn MJ, Lim HY, Kang WK, Par k K. Salvage chemotherapy with mitomycin C, ifosfamide, and cisplatin (MIC) for previously treated metastatic or recurrent esophageal squamous cell carcinoma. *Invest News Drugs* 2008;26:387–92.
21. Tu CH, Muto M, Horimatsu T, Taku K, Yano T, Minashi K, Onozawa M, Nihei K, Ishikura S, Ohtsu A, Yoshida S. Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma. *Dis Esophagus* 2010;24:274–8.

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

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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).

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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 ≥ 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.

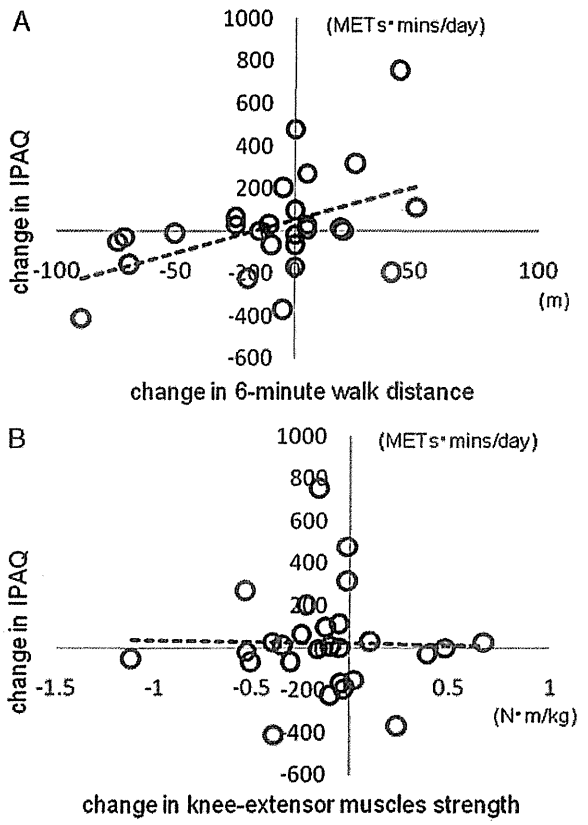

FIGURE 1. Relationship between changes in physical activity and changes in physical fitness. The change in 6-minute walking distance was correlated positively with the change in International Physical Activity Questionnaire (IPAQ) ($r=0.45$, $P=0.02$) (A), whereas the change in knee extensor muscle strength 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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REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127: 2893–2917.
2. Altorki N, Kent M, Ferrara C, et al. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg.* 2002;236:177–183.
3. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med.* 1998;339:1979–1984.
4. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med.* 1997;337:161–167.
5. Igaki H, Kato H, Ando N, et al. A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG 9907). ASCO Annual Meeting, 2008.
6. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol.* 2003;21: 4592–4596.
7. Safieddine N, Xu W, Quadri S, et al. Health-related quality of life in esophageal cancer: effect of neoadjuvant chemoradiotherapy followed by surgical intervention. *J Thorac Cardiovasc Surg.* 2009;137:36–42.
8. Blazeby JM, Sanford E, Falk SJ, et al. Health-related quality of life during neoadjuvant treatment and surgery for localized esophageal carcinoma. *Cancer.* 2005;103:1791–1799.
9. van Meerten E, van der Gaast A, Looman CW, et al. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. *Int J Radiat Oncol Biol Phys.* 2008;71:160–166.
10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166:111–117.
11. Craig CL, Marshall AL, Sjöström M, et al. International Physical Activity Questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* 2003;35:1381–1395.
12. Murase N, Katsumura T, Ueda C, et al. Validity and reliability of Japanese version of International Physical Activity Questionnaire. *Jpn J Health Welf Stat.* 2002;1–9.
13. Aaronson NK, Admedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;365–376.
14. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* 1998;139–144.
15. Redelmeier DA, Bayoumi AM, Goldstein RS, et al. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *Am J Respir Crit Care Med.* 1997;155:1278–1282.
16. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J.* 1999;14:270–274.
17. Steffen TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: six-minute walk test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. *Phys Ther.* 2002;82:128–137.
18. Kervio G, Carre F, Ville NS. Reliability and intensity of the six-minute walk test in healthy elderly subjects. *Med Sci Sports Exerc.* 2003;35:169–174.
19. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer.* 2003;97: 1746–1757.
20. Courneya KS, Friedenreich CM. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *J Altern Complement Med.* 1997;3:215–226.
21. Nagamatsu Y, Shima I, Yamana H, et al. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. *J Thorac Cardiovasc Surg.* 2001;121: 1064–1068.
22. de Bruin ED, Hartmann A, Uebelhart D, et al. Wearable systems for monitoring mobility-related activities in older people: a systematic review. *Clin Rehabil.* 2008;22(10–11):878–895.
23. Bravata DM, Smith-Spangler C, Sundaram V, et al. Using pedometers to increase physical activity and improve health: a systematic review. *JAMA.* 2007;298:2296–2304.

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SHORT COMMUNICATION

Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy

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Abstract
Purpose To establish an appropriate administration schedule for oxaliplatin in FOLFOX plus bevacizumab therapy for a hemodialytic patient.
Methods A 50-year-old man on chronic hemodialysis was treated for colon cancer and synchronous hepatic metastasis with modified FOLFOX-6 plus bevacizumab therapy every 3 weeks. The plasma concentration of free platinum was measured at eight points, before and within the first 50 h after oxaliplatin administration. A dose escalation study of oxaliplatin was performed at doses of 60, 70, and 85 mg/m^2. A 4-h dialysis session was begun at the end of the oxaliplatin treatment.
Results The pharmacokinetics of free platinum showed a bimodal pattern at each dose: The serum concentration decreased rapidly soon after dialysis, then increased, and remained at a high level for 24 h. The areas under the curves (AUC) for free platinum were 17.6, 23.6, and 32.6 μg h/mL after doses of 60, 70, and 85 mg/m^2 oxaliplatin, respectively. These exceeded the AUC when 90 mg/m^2 was given to a patient with normal renal function (7.9 μg h/mL). Treatment was safely continued for 6 months without severe toxicity.
Conclusion FOLFOX plus bevacizumab therapy can be given safely to hemodialytic patients with no reduction in the dose of oxaliplatin if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks.

Keywords Colorectal cancer · Renal failure · Hemodialysis · FOLFOX plus bevacizumab · Oxaliplatin

Introduction

The number of long-lived hemodialytic patients has been increasing with improvements in dialysis treatments. However, hemodialytic patients are potentially at increased risk of cancer for several reasons, including the presence of chronic infection, a weakened immune system, nutritional deficiencies, and altered DNA repair [1].

Colorectal cancer is the third leading cause of cancer deaths, and its incidence is also increasing yearly in Japan [2]. FOLFOX plus bevacizumab is a chemotherapeutic regimen consisting of oxaliplatin and infusional 5-Fluorouracil (5-FU)/levofolinate plus bevacizumab and is accepted widely as an initial treatment for unresectable colorectal cancer, with an objective response in up to 50% of patients treated [3]. However, there have been few reports of the use of oxaliplatin in hemodialytic patients [4–6], and little is known about the safety/efficacy of FOLFOX plus bevacizumab therapy or its optimum dosage in this patient population. Here, we report the case of a hemodialytic patient with metastatic colon cancer, successfully treated with modified FOLFOX-6 plus bevacizumab therapy.

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Materials and methods

A 50-year-old Japanese man with gouty nephropathy had been maintained on hemodialysis since 2006. A computed tomography (CT) scan showed more than 20 metastases (up to 3 cm in diameter) scattered throughout both lobes of his liver. A colonoscopy showed a protuberant type of tumor located on the sigmoid colon. After the surgical resection of the primary tumor to prevent intestinal obstruction and bleeding, the patient received systemic chemotherapy. Chemotherapy was initiated with the modified FOLFOX-6 (mFOLFOX-6) regimen plus bevacizumab, given every 3 weeks. After bevacizumab was administered by infusion over 90 min, oxaliplatin and levofolinate were administered simultaneously for 2 h. 5-FU was then administered as a bolus injection, followed by its continuous infusion for 46 h with a pump after a 4-h dialysis session (Fig. 1). The starting dose of oxaliplatin was 60 mg/m^2 (70% of the standard dose of 85 mg/m^2) because oxaliplatin is known to be primarily excreted in the urine and was expected to be eliminated by hemodialysis alone in this patient [7]. The dose of oxaliplatin was increased to 70 and 85 mg/m^2, while possible adverse events were monitored. The starting dose of 5-FU was set at the standard dose, because 5-FU is largely (80%) eliminated by the hepatic metabolism and secreted into the bile [8]. Many previous reports have shown that there is no need to adjust its dose in dialysis patients [9]. During each course of mFOLFOX-6 plus bevacizumab therapy, a 4-h dialysis session was begun immediately after the administration of oxaliplatin, using a polysulfonate hollow-fiber dialyzer (APS-21SA) and acetic acid-free dialysate (Carbostar P). The blood flow rate was set at 250 mL/min and the dialysate flow rate at 600 mL/min. The patient's free platinum levels were measured. Blood samples were collected at the following eight points: before the start of oxaliplatin administration, 2 (just before dialysis), 2.25, 2.5, 3, 6, 26, and 50 h after oxaliplatin administration (the last collection was just before the second dialysis session). The blood samples were immediately centrifuged at 1,700×g for 10 min, and the serum thus obtained was further centrifuged at 1,700×g for 20 min in an ultrafiltration tube. The ultrafiltrate sample was then stored in a freezer until the platinum concentration was assayed by flameless atomic absorption spectrometry (NAC Co., Ltd, Tokyo, Japan). The area under the curve (AUC) for platinum in the ultrafiltrate was calculated from time 0 to 50 h after the start of oxaliplatin administration, using the trapezoidal method.

Results

Table 1 shows the C_{max} and AUC data for free platinum in the serum of a hemodialytic patient receiving mFOLFOX-6 plus bevacizumab therapy. Figure 2 shows the time course of the free platinum concentration. The level of free platinum, which is related to the antitumor activity and toxicity of oxaliplatin, decreased soon after dialysis. It subsequently increased for 26 h after the administration of oxaliplatin and thereafter remained at the same level for 24 h. These findings differ considerably from those previously reported for patients with normal renal function who received 90 mg/m^2

Table 1 Pharmacokinetic parameters of platinum in plasma ultrafiltrate

	60 mg/m^2 $n = 1$	70 mg/m^2 $n = 1$	85 mg/m^2 $n = 3$	90 mg/m^2 ($n = 3$*)
C_{max} (ng/mL)	500	600	863	963.3
AUC_{0-50} (μg h/mL)	17.6	23.6	32.6	7.9

AUC area under the plasma concentration–time curve

* Shirao et al. [10]

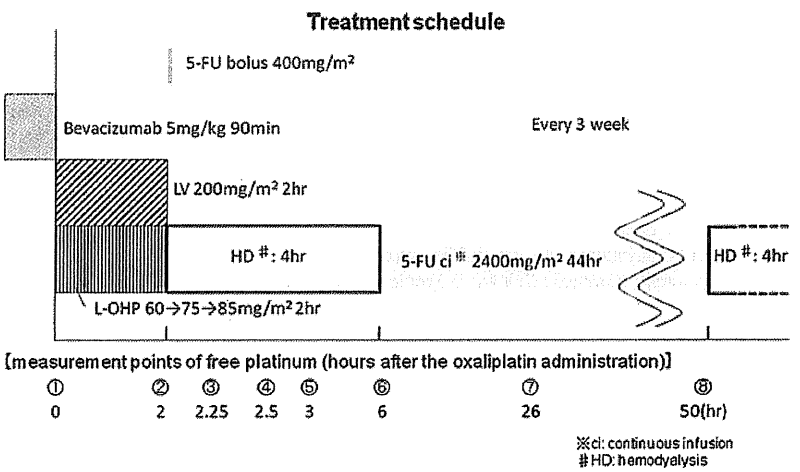

Fig. 1 Treatment schedule

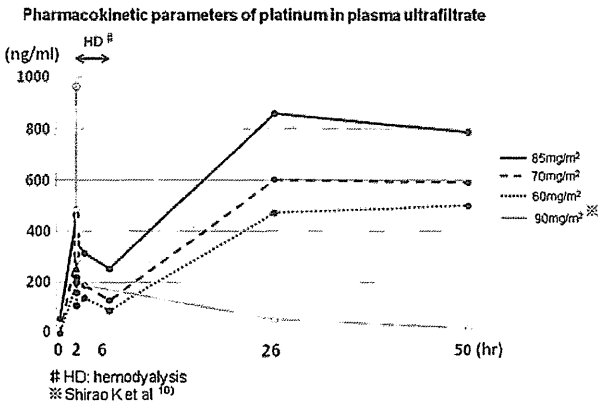

Fig. 2 Concentration of platinum in plasma ultrafiltrate

oxaliplatin (free platinum C_{max} was 963.3 ng/mL and AUC was 7.9 μg h/mL) [10]. The tolerability data and pharmacokinetic profiles obtained during each cycle were used to optimize the dose of each drug and the dosing intervals for the subsequent cycles. The free platinum AUCs were 17.6, 23.6, and 32.6 μg h/mL at doses of 60, 70, and 85 mg/m^2, respectively, which are about 2–4 times greater than that obtained with 90 mg/m^2 oxaliplatin in patients with normal renal function [11]. Therefore, a longer dose interval of 3 weeks was set for the subsequent cycles, instead of the standard interval of 2 weeks for mFOLFOX-6 plus bevacizumab therapy. The free platinum C_{max} values measured in this patient were 500, 600, and 863 ng/mL at oxaliplatin doses of 60, 70, and 85 mg/m^2, respectively, which are about 50–90% of that obtained with a dose of 90 mg/m^2 oxaliplatin in patients with normal renal function [10]. Therefore, a standard dose of 85 mg/m^2 was given during the subsequent five cycles. In all, eight courses of mFOLFOX-6 plus bevacizumab therapy (a total of 815 mg/m^2 oxaliplatin) were completed, although grade 1 peripheral neuropathy by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3) criteria was observed. A CT scan showed no changes in the number or sizes of the metastatic liver tumors.

Discussion

To the best of our knowledge, this is the first report of a hemodialytic patient with metastatic colon cancer successfully treated with mFOLFOX-6 plus bevacizumab therapy. In the patient reported here, the free platinum level showed a bimodal pattern, with peaks appearing at 2 and 26 h after the start of oxaliplatin administration. The second peak was as high as the first peak. In patients treated with oxaliplatin, the serum-free platinum concentration reflects the biological activity of the drug, i.e., it determines both its antitumor activity and its toxicity [11, 12]. Previous studies have shown that most circulating platinum molecules derived from oxaliplatin are immediately bound to plasma proteins (primarily albumin) and irreversibly inactivated [13, 14]. The free platinum in the blood is serially excreted by the kidneys, and its excretion is delayed in patients with impaired renal function [15]. A second peak in the free platinum concentration between hemodialyses has also been observed in hemodialytic patients treated with cisplatin [16]. This might be caused by the dissociation of the platinum bound to plasma proteins and blood cells or by platinum in the tissues returning to the blood [17]. In patients with normal renal function, it is likely that free platinum is rapidly eliminated by renal excretion, so no second peak is observed [10].

In our patient, who was given 60 mg/m^2 oxaliplatin, the AUC of free platinum was about twofold greater than that observed after an oxaliplatin dose of 90 mg/m^2 in patients with normal renal function. Although the relationship between the AUC of free platinum and the antitumor activity of oxaliplatin is poorly understood, it has been reported that the antitumor activities of cisplatin and carboplatin correlate with the AUC of free platinum [12]. Takimoto et al. [9] reported that reductions in the dose of single-agent oxaliplatin are unnecessary, even in patients with impaired renal function, suggesting that the AUC of free platinum does not correlate with the toxicity of oxaliplatin, regardless of the patient's renal function. They proposed the hypothesis that after the administration of oxaliplatin, the majority of free platinum is in the inactive form in low molecular weight conjugates, which are cleared by glomerular filtration. Therefore, the increase in systemic platinum exposure associated with renal impairment does not increase the drug-related toxicity [18].

Giacchetti et al. [19] compared the antitumor activity and hematological toxicity of oxaliplatin in two regimens: four daily doses versus continuous infusion for 48 h. They reported that hematological toxicity was three times more frequent with the former regimen than with the latter regimen, whereas a similar tumor response was achieved with both regimens. These findings suggest that the antitumor activity of oxaliplatin does not correlate with the AUC of free platinum, whereas its hematological toxicity correlates with its C_{max}.

In our patient, treatment with the standard dose of oxaliplatin in the mFOLFOX-6 plus bevacizumab regimen resulted in a larger AUC with a lower C_{max} for free platinum than those observed with the standard dose of oxaliplatin in patients with normal renal function. This pharmacokinetic profile might explain the significant tumor response achieved with relatively mild toxicity.

Recently, Kawazoe et al. reported that long-term FOLFOX-6 therapy given every 2 weeks with the standard dose of oxaliplatin in patients with mild renal dysfunction led to

accumulated renal toxicity, and the patients were forced to undergo dialysis [20]. However, in the patient reported here, the concentration of free platinum before the administration of oxaliplatin increased gradually (<30, 40, 50, and 80 ng/mL in the second, third, fifth, and seventh courses, respectively). The 3-week dosing interval set for this patient may have been optimal, but it is essential to monitor the serum concentration of free platinum before the administration of oxaliplatin in each course.

In contrast, it has been reported that the clearance rate of bevacizumab by hemodialysis was 0 mL/min and that the pharmacokinetic parameters in hemodialytic patients were similar to those in patients with normal renal function [21].

In conclusion, mFOLFOX6 plus bevacizumab therapy can be used safely for hemodialytic patients, with no dose reduction in oxaliplatin, if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks. The cumulative toxicities and long-term outcomes remain to be established. Larger studies of hemodialytic patients with longer follow-up periods are required.

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References

1. Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354:93–99
2. Hyodo I, Suzuki H, Takahashi K et al (2010) Present status and perspectives of colorectal cancer in Asia: colorectal cancer working group report at the 30th Asia-Pacific cancer conference. Jpn J Clin Oncol 40(Suppl 1):i38–i43
3. Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 26:3523–3529
4. Shitara K, Munakata M, Muto O et al (2007) Hepatic arterial infusion of oxaliplatin for a patient with hepatic metastases from colon cancer undergoing hemodialysis. Jpn J Clin Oncol 37:540–543
5. Matoba S, Sawada T, Toda S et al (2008) Modified FOLFOX6 in a patient on hemodialysis with metastatic colorectal cancer. Gan To Kagaku Ryoho 35:673–675 (in Japanese)
6. Watayo Y, Kuramochi H, Hayashi K et al (2010) Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. Jpn J Clin Oncol 40:360–364
7. Takimoto CH, Remick SC, Sharma S et al (2003) Administration of oxaliplatin to patients with renal dysfunction: a preliminary report of the National Cancer Institute Organ Dysfunction Working Group. Semin Oncol 30:20–25
8. Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB (1987) Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res 47:2203–2206
9. Takimoto CH, Remick SC, Sharma S et al (2003) Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J Clin Oncol 21:2664–2672
10. Shirao K, Matsumura Y, Yamada Y et al (2006) Phase I study of single-dose oxaliplatin in Japanese patients with malignant tumors. Jpn J Clin Oncol 36:295–300
11. Schellens JHM, Ma J, Planting AST et al (1996) Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer 73:1569–1575
12. Jodrell DI, Egorin MJ, Canetta RM et al (1992) Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520–528
13. Graham MA, Lockwood GF, Greenslade D et al (2000) Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Cancer Res 6:1205–1218
14. Calvert H, Judson I, van der Vijgh WJ (1993) Platinum complexes in cancer medicine: pharmacokinetics and pharmacodynamics in relation to toxicity and therapeutic activity. Cancer Surv 17:189–217
15. Massari C, Brienza S, Rotarski M et al (2000) Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. Cancer Chemother Pharmacol 45:157–164
16. Watanabe R, Takiguchi Y, Moriya T et al (2003) Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. Br J Cancer 88:25–30
17. Levi F, Metzger G, Massari C, Milano G (2000) Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clin Pharmacokinet 38:1–21
18. Takimoto CH, Graham MA, Lockwood G et al (2007) Oxaliplatin pharmacokinetics and pharmacodynamics in adult cancer patients with impaired renal function. Clin Cancer Res 13:4832–4839
19. Giacchetti S, Bjarnason G, Garufi C et al (2006) Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy group. J Clin Oncol 24:3562–3569
20. Kawazoe H, Sugishita H, Watanabe S et al (2010) Nephrotoxicity induced by repeated cycles of oxaliplatin in a Japanese colorectal cancer patient with moderate renal impairment. Gan To Kagaku Ryoho 37:1153–1157
21. Garnier-Viougeat N, Rixe O, Paintaud G et al (2007) Pharmacokinetics of bevacizumab in haemodialysis. Nephrol Dial Transplant 22:975

Successful Endoscopic Submucosal Dissection for Esophageal Squamous Cell Carcinoma together with a Lipoma

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SUMMARY

Superficial carcinomas over submucosal tumors of the esophagus have seldom been detected. Esophageal lipomas are very rare and only a few cases have been reported. We describe the case of a 73-year-old man with superficial squamous cell carcinoma overlying a lipoma. We successfully performed *en bloc* resection by endoscopic submucosal dissection (ESD) using the IT-knife. Histological examination showed curative resections. In such cases, ESD may be a promising tool to perform less invasive treatment.

KEY WORDS: Esophageal squamous cell carcinoma; Lipoma; Endoscopic submucosal dissection

INTRODUCTION

A superficial squamous cell carcinoma coexisting with a lipoma is quite rare in the esophagus (1-3). Such tumors show an elevated form and this makes it difficult to diagnose the depth of invasion. Among the several procedures for endoscopic resection, endoscopic submucosal dissection (ESD) method is now considered to be useful in achieving en bloc resection (4-6). Here we reported a case of superficial squamous cell carcinoma located just over an esophageal lipoma that was successfully resected together with the lipoma by the ESD method.

CASE REPORT

A 73-year-old man with a tumor in the middle thoracic esophagus was referred to our hospital. He had smoked one pack of cigarettes a day for 20 years and drank a glass of alcohol per day for more than 50 years. He had no significant medical history and no symptoms. The results of the peripheral blood and blood chemistry examinations were within normal limits. Esophagoscopy revealed a whitish lesion in the middle thoracic esophagus. This lesion showed a yellowish color underneath and the top of the lesion showed uneven surface and was partially coated in white (**Figure 1A**). Lugol chromoendosco-

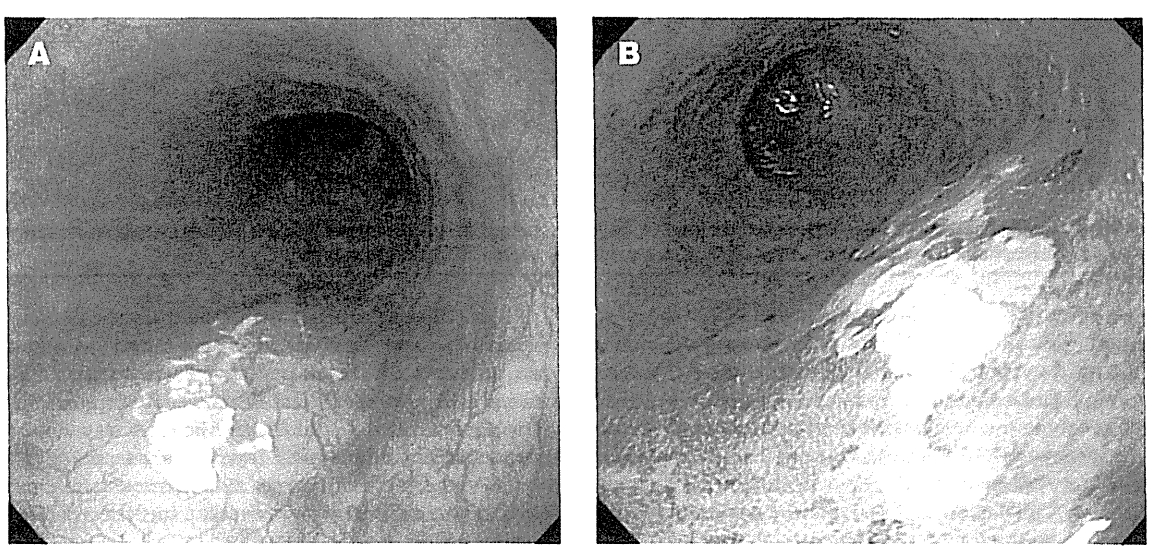

FIGURE 1 (A) White light endoscopy, revealing a whitish coated mucosa with erosion and uneven surface. This lesion is slightly raised by a yellowish component underneath. **(B)** Lugol chromoendoscopy, revealing a non-staining pattern coinciding with depressed area.

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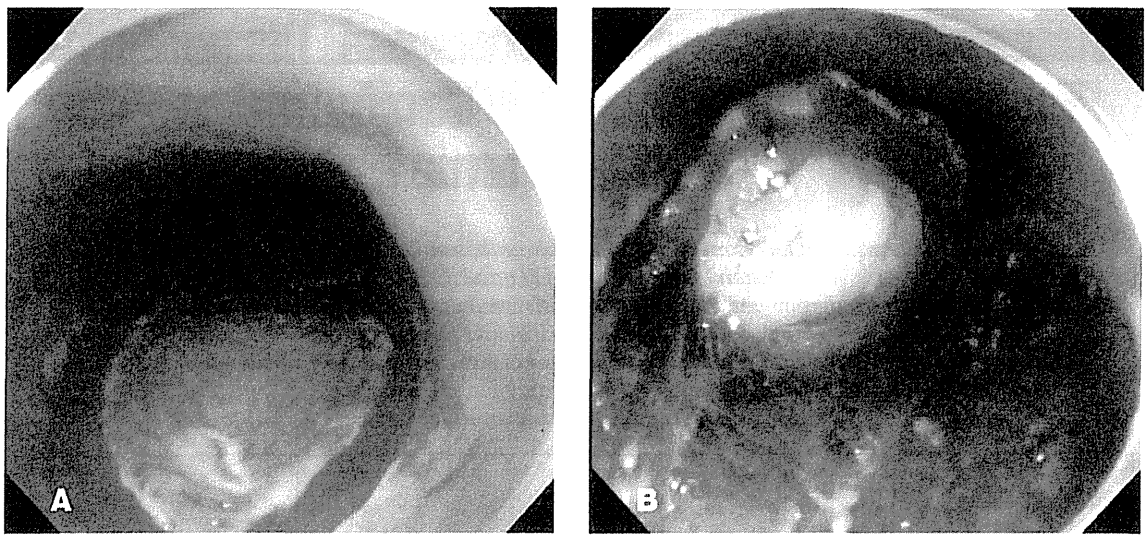

FIGURE 2 (A) Circumferential incision during ESD. **(B)** During submucosal dissection, a lipomatous component was clearly revealed.

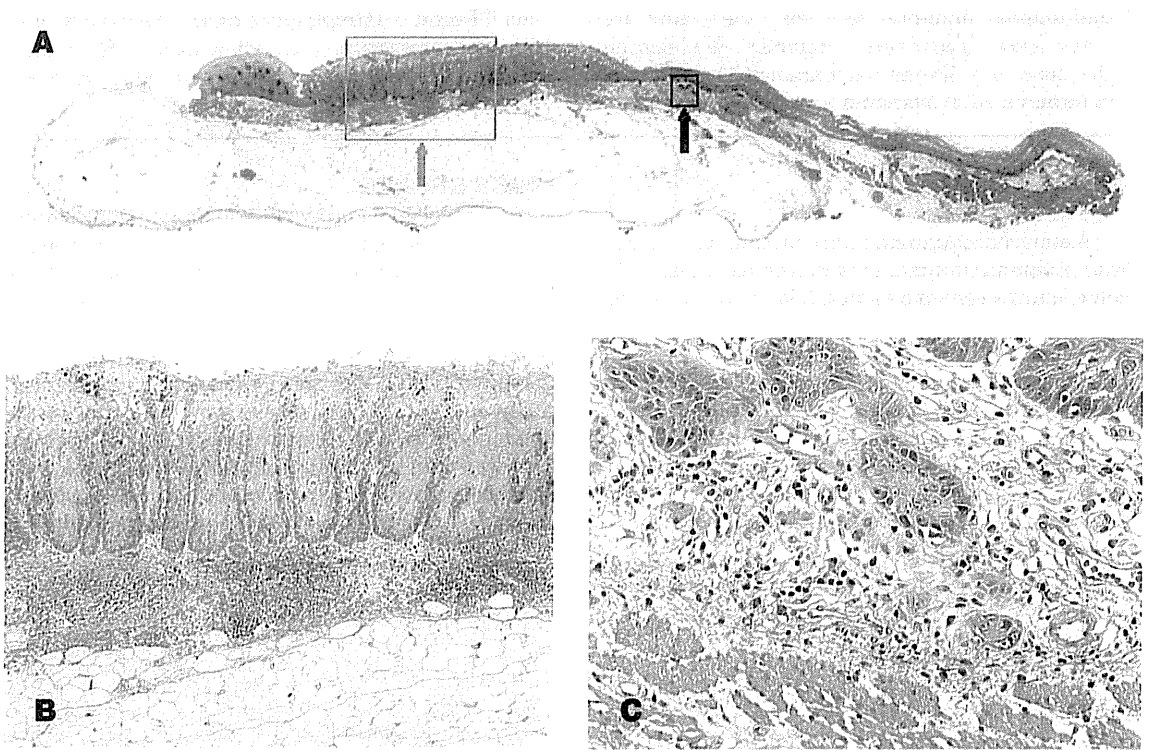

FIGURE 3 Histopathology from the ESD of the target lesion, revealing a squamous cell carcinoma in the mucosal layer and a lipoma in the submucosal layer just beneath the cancerous lesion. **(A)** Low power view. **(B)** Squamous cell carcinoma *in situ*. **(C)** The invasive area.

py disclosed a non-staining pattern coinciding with the depressed area (**Figure 1B**). Biopsy specimens taken from the lesion revealed squamous cell carcinoma. Endoscopic ultrasonography demonstrated a hyperechoic mass localized within the submucosal layer, which had a homogenous inner echoic pattern with a well demarcated smooth outline and a clear margin. The lesion of superficial carcinoma could not be detected by endoscopic ultrasonography. The CT examination of the chest and abdomen showed no evidence of metastasis.

From these findings, we made a diagnosis of superficial squamous cell carcinoma overlying a lipoma, and endoscopic treatment was scheduled. ESD was performed using the IT-knife. After marginal cutting with the IT knife, the lipoma was clearly bared and the submucosal layer was dissected (**Figure 2A** and **B**). The lipoma and squamous cell carcinoma were successfully resected together without complications.

The resected specimen was 30×20mm in size and histological examination showed squamous

cell carcinoma overlying a submucosal tumor (**Figure 3A** and **B**). The submucosal tumor consisted of mature adipocytes, was well-defined and encapsulated with a fibrovascular septa. The invasion depth of the squamous cell carcinoma was limited to within the mucosal layer (**Figure 3C**). There was no lymphovascular invasion of carcinoma cell. The patient's postoperative course was uneventful. At endoscopy one month later there was no evidence of recurrence.

DISCUSSION

In the alimentary tract, lipomas are relatively uncommon (7-8) and account for 4% of benign neoplasms (9). Among them, esophageal lipomas are very rare and their incidence is only 0.4% of all lipomas in the gastrointestinal tract (7). Therefore the coexistence of superficial squamous cell carcinoma with lipoma has only been reported in 3 cases previously.

Wehrmann *et al.* reported that endoscopic resection of esophageal submucosal tumors (SMTs) is safe and effective, if the tumors are small in size (<4cm) (10). Endoscopic removal using snare electrocautery is favored for smaller, pedunculated lesions, while large submucosal tumors cannot be extracted by the polypectomy method. Recently, the ESD method has been developed for en bloc resection of gastric neoplasm, which has resulted in high complete resection rates and contributed to correct histological diagnosis (11). Therefore, we introduced ESD for our case and successfully performed en bloc resection together with superficial squamous cell carcinoma and lipoma.

In conclusion, we have described a rare case of esophageal lipoma concomitant with an early esophageal carcinoma. An increased detection of superficial squamous cell carcinoma can lead to a better chance of finding out if the lesion coexists with SMT. In such cases, the ESD method should be considered as a minimally invasive treatment.

REFERENCES

1. **Marcial-Rojas RA:** Epidermoid carcinoma in mucosa overlying a pedunculated lipoma of the esophagus. J Thorac Surg 1959; 37:427-34.
2. **Kuwano H, Sadanaga N, Watanabe M, et al.:** Esophageal squamous cell carcinoma occurring in the surface epithelium over a benign tumor. J Surg Oncol 1995; 59:268-72.
3. **Usui S, Inoue H, Yoshida T, et al.:** Endoscopically managed superficial carcinoma overlying esophageal lipoma. Digestive Endoscopy 2004; 16:50- 53.
4. **Ohkuwa M, Hosokawa K, Boku N, et al.:** New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001; 33:271-275.
5. **Miyamoto S, Muto M, Hamamoto Y, et al.:** A new technique for endoscopic mucosal resection with an insulated-tip electrosurgical knife improves the completeness of resection of intramucosal gastric neoplasms. Gastrointest Endosc 2002; 55:576-581.
6. **Muto M, Miyamoto S, Hosokawa A, et al.:** Endoscopic mucosal resection in the stomach using the insulated-tip needle-knife. Endoscopy 2005; 37:178-182.
7. **Mayo CW, Pagtalunan RJ, Brown DJ:** Lipoma of the alimentary tract. Surgery 1963 ; 53:598-603.
8. **Sossai P, De Bernardin M, Bissoli E, et al.:** Lipomas of the esophagus: a new case. Digestion 1996; 57:210-2.
9. **Ackerman NB, Chughtai SQ:** Symptomatic lipomas of the gastrointestinal tract. Surg Gynecol Obstet 1975; 141:565-8.
10. **Wehrmann T, Martchenko K, Nakamura M, et al.:** Endoscopic resection of submucosal esophageal tumors: a prospective case series. Endoscopy 2004; 36:802-7.
11. **Ono H, Kondo H, Gotoda T, et al.:** Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48:151-2.

ORIGINAL ARTICLE: Clinical Endoscopy

Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer

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Background: Early detection of pharyngeal cancer has been difficult. We reported that narrow-band imaging (NBI) endoscopy can detect superficial pharyngeal cancer, and these lesions can be treated endoscopically.

Objective: To assess the safety and long-term efficacy of transoral organ-preserving pharyngeal endoscopic resection (TOPER) for superficial pharyngeal cancer.

Design and Setting: Retrospective 2-center cohort study.

Patients: The study included 104 consecutive patients with superficial pharyngeal cancer.

Intervention: TOPER with the patients under general anesthesia.

Main Outcome Measurements: Safety of the procedure, long-term survival, clinical outcome.

Results: A total of 148 consecutive lesions were resected in 104 patients. There was no severe adverse event. Temporary tracheostomy was required in 17 patients (16%) to prevent airway obstruction. The median fasting period and hospital stay after TOPER were 2 days (range 1-20 days) and 8 days (range 3-58 days), respectively. Ninety-six patients (92%) had no local recurrence or distant metastases. Local recurrence at the primary site developed in 6 patients, but all were resolved by repeat TOPER. With a median follow-up period of 43 months (range 3-96 months), the overall survival rate at 5 years was 71% (95% CI, 59-82). Cause-specific survival rate at 5 years was 97% (95% CI, 93-100). The cumulative development rate of multiple cancers in pharyngeal mucosal sites at 5 years was 22% (95% CI, 12-33). The pharynx was preserved in all patients, and they experienced no loss of function.

Limitation: Retrospective design.

Conclusions: Peroral endoscopic resection of superficial pharyngeal cancer is a feasible and effective treatment with curative intent. (Gastrointest Endosc 2011;74:477-84.)

Pharyngeal cancer other than nasopharyngeal cancer (130,000 new cases and 83,000 deaths worldwide in 2002) is predominantly a cancer of men.[1] Smoking and alcoholic beverages are the class I carcinogens for these cancers.[2] Furthermore, acetaldehyde-associated alcoholic beverages were reclassified as a class I carcinogen in 2009 by the International Agency for Research on Cancer.[2]

Abbreviations: EMR-C, EMR with a cap; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging; TOPER, transoral organ-preserving pharyngeal endoscopic resection.

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Although the definite risk factors are well known, it has been quite difficult to detect pharyngeal cancer at an early stage. Thus, most of the cases are diagnosed at an advanced stage and have a poor prognosis. In addition, the standard treatments of surgical resection and/or chemoradiotherapy worsen the patients' quality of life, resulting in speech defects, swallowing disorders, salivary disorders, and cosmetic deformities of the neck.

We previously reported that a new image-enhanced endoscopic technology,[3] narrow-band imaging (NBI), was very useful for detecting these cancers at an early stage and that these superficial cancers could be treated with peroral endoscopic resection with minimal invasiveness.[4-6] Shimizu et al[7] and Iizuka et al[8] also reported the usefulness of endoscopic resection for oropharyngeal and hypopharyngeal cancer. However, these reports included small numbers of patients, and their long-term outcome has not been reported. In addition, it seems to be premature to conduct a prospective study of peroral endoscopic resection for superficial pharyngeal cancer because its feasibility and safety have not been fully evaluated. In this study, we assess a large number of patients with a longer follow-up time to address the feasibility and usefulness of peroral organ-preserving endoscopic resection for superficial pharyngeal cancers.

Take-home Message

- **Peroral endoscopic laryngopharyngeal mucosal resection is a feasible and effective method for superficial pharyngeal cancer. This minimally invasive procedure can preserve the organ itself and is expected to improve the patient's quality of life and survival.**

PATIENTS AND METHODS

During the period from June 2002 to April 2008, 148 consecutive superficial oropharyngeal and hypopharyngeal cancers in 104 patients were treated by transoral organ-preserving pharyngeal endoscopic resection (TOPER) while under general anesthesia at National Cancer Center Hospital East and Kyoto University Hospital. Written informed consent for the treatment was obtained from all patients, and this study was approved by the local ethics committee.

Histological diagnosis of the lesions was made according to the World Health Organization classification of the tumor (head and neck tumors).[9] Evaluation of the invasion of the tumor was also made according to the general rules for clinical studies of head and neck cancer by the Japanese Society for Head and Neck Cancer and the Japanese classification of esophageal cancer by Japan Esophageal Society.[10] According to these guidelines, carcinoma in situ and subepithelial cancers are defined as a superficial cancer regardless of lymph node or distant organ metastasis. To date, there is no generally accepted definition of superficial cancer in this field. Thus, a cancer limited to the subepithelial layer of the pharynx is defined as superficial cancer in this study.

If the lesion was evaluated as carcinoma in situ or carcinoma with invasion to the subepithelial layer (not to the muscular layer), TOPER was indicated as a minimally invasive treatment (Fig. 1). Patients who received radiotherapy to the head and neck region previously were not indicated. All patients refused radical surgical resection or chemotherapy or chemoradiotherapy. All lesions were detected by NBI with a magnifying endoscope and histologically confirmed by biopsy specimen as severe dysplasia/carcinoma in situ or squamous cell carcinoma.

TOPER was based on the methods of EMR using a cap (EMR-C)[11] or endoscopic submucosal dissection (ESD),[12] and the procedures were performed as previously reported[11,12] by using a high-definition endoscope (Q240Z, Q260J, or H260Z; Olympus Medical Systems, Tokyo, Japan). For EMR-C, a soft food attachment (D-206-06; Olympus Medical Systems) to the tip of the endoscope was used. For ESD, an insulated-tip electrosurgical knife (IT knife; Olympus Medical Systems) was used. In both methods, the lesion was removed after inserting a needle beside the lesion and injecting an adequate volume of saline solution or glycerol containing diluted epinephrine (0.02 mg/mL) beneath the epithelium to lift it above the surrounding mucosa. We used a rigid laryngoscope (Nagashima, Tokyo, Japan) to obtain a sufficient working space by lifting the larynx. Iodine staining was used both to delineate the exact margin of the cancer lesion before resection and to detect residual lesion after resection. If a small residual lesion was endoscopically identified after EMR or ESD, argon plasma coagulation was done to prevent local recurrence. To check whether the larynx was swollen after resection, an endoscopic examination was performed on the day after resection with the patient under conscious sedation by periodic intravenous administration of pethidine hydrochloride (in total 0.5 mg/body weight). If the movement of the pharynx and larynx was unimpaired, the patient was encouraged to start eating semisolid food. If the larynx was swollen, the patient continued fasting until the swelling disappeared.

All resected specimens were cut into longitudinal slices measuring 2 mm in width. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated by 3 pathologists (S.F., A.Y., A. Ochiai) according to the World Health Organization classification.[9]

Follow-up endoscopy was performed after 1 to 3 months to check the healing of the mucosal defect and local residue after TOPER, and thereafter every 6 months to detect metachronous superficial cancer in