

Chemoradiotherapy with FOLFOX for esophageal squamous cell cancer with synchronous rectal cancer: Four case reports and a literature review

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Abstract. Chemoradiotherapy (CRT) is a valuable treatment option for localized esophageal cancer. Conventional baseline chemotherapy for this type of cancer includes cisplatin and fluorouracil. Recently, CRT with leucovorin-fluorouracil-oxaliplatin (FOLFOX) has become popular due to its convenience and lower toxicity. In Japan, the use of oxaliplatin for esophageal cancer is not yet approved, so experience with this treatment is limited to cases with colorectal cancer. As such patients are not usually included in clinical trials, little is known on the efficacy and safety of this treatment for this patient subpopulation, and treatment generalization in Japan is not allowed. We herein share our experience with CRT and FOLFOX for cases with esophageal cancer and synchronous rectal cancer at our institution. The clinical data of 4 patients who were treated for esophageal cancer with CRT/FOLFOX at our hospital between 2007 and 2016, who also had synchronous rectal cancer, were retrieved and analyzed. All the patients were male and had esophageal squamous cell cancer and synchronous rectal cancer. The median patient age was 68 years (range, 65-77 years). One patient received neoadjuvant CRT followed by surgery, and the other 3 patients received definitive CRT for esophageal cancer. FOLFOX was administered biweekly during radiotherapy (41.4-60 Gy). All 4 patients completed the treatment schedule and responded to CRT. No patients experienced progression of rectal cancer during treatment. Notably, 1 patient also achieved a complete response (CR) of rectal cancer after CRT for esophageal cancer. Moreover, 2 patients without dysphagia were treated as outpatients and achieved a CR. Encephalopathy was the only

reported grade 3 adverse event. Although the present study included a limited number of cases, the findings suggest that CRT with FOLFOX may be a valuable option for the treatment of patients with esophageal squamous cell cancer and synchronous rectal cancer.

Introduction

Esophageal cancer (EC) is the ninth most common type of cancer and the sixth most common cause of cancer-related mortality globally (1). EC is associated with considerable morbidity and carries a poor prognosis in its later stages. This disease requires a multidisciplinary approach, such as neoadjuvant chemotherapy or chemoradiotherapy (CRT) plus surgery for locally advanced disease. Definitive CRT is also recognized as a curative treatment option (1-3), particularly in patients who are not surgical candidates.

A number of clinical studies of radical CRT for EC have been conducted since the 1980s, and radiotherapy (50-60 Gy) with cisplatin and fluorouracil (CF) has become the standard of care (4,5). However, CF is associated with a number of problems. It has been reported that local failure and toxicity-related deaths/other life-threatening toxicities were observed in 46 and 20% of patients with EC, respectively, who receive this CRT, and that 41% patients with EC could not complete the CRT as planned (6). CRT with CF may also cause thrombosis, sudden death, or other toxicities, and it requires hospital admission due to the requirement for prolonged intravenous hydration for cisplatin, and 5 days continuous infusion for 5FU.

Therefore, a safer and more useful regimen of CRT for EC is urgently needed. A phase II/III clinical study (PRODIGE5/ACCORD17) was conducted to investigate the superiority of leucovorin-fluorouracil-oxaliplatin (FOLFOX) to CF as the chemotherapy component of CRT, replacing cisplatin with oxaliplatin, which rarely induces kidney toxicity and does not require intravenous hydration. Although the results of the study did not meet the endpoint hypothesized, namely that FOLFOX is superior to CF, the researchers demonstrated its lower toxicity and non-inferior survival to CF; thus, CRT with FOLFOX for EC is recognized as one of the standard treatment options in Europe (7-9).

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In Japan, oxaliplatin along with several other drugs have not yet been approved for EC treatment, and CF is commonly used as the chemotherapeutic component of CRT (10-12). FOLFOX has been approved only for patients with colorectal or gastric cancer. Thus, clinical data on the feasibility of this treatment for EC in Japan are rare. We herein report the cases of 4 patients with esophageal squamous cell cancer (ESCC) and rectal cancer (RC) who were treated with CRT with FOLFOX in our hospital.

Patients and methods

Patients. Between January 2007 and December 2016, 740 patients were registered in our hospital's database of chemotherapy for EC; that database was searched for patients who received CRT with FOLFOX, and their clinical data were investigated (Table I).

Treatment. FOLFOX was administered every 2 weeks for 3-6 cycles, with the first 3 cycles administered concurrently with radiotherapy. During each cycle, oxaliplatin (85 mg/m²) was administered as a 2 h intravenous infusion in 250-500 ml of 5% glucose on day 1, concurrently with leucovorin (200 mg/m²) as a 2 h intravenous infusion. Fluorouracil (400 mg/m²) was administered as a 10 min intravenous bolus dose on day 1, followed by continuous intravenous infusion of fluorouracil (1,600 mg/m²) over 2 days, which was based on the PRODIGE5/ACCORD17 trial (8).

Radiation therapy was delivered with megavoltage equipment (>6 MV) with anterior/posterior opposed or multi-field irradiation and continuous bilateral oblique (off-cord) portals, except for neoadjuvant cases. The patients were treated 5 days per week at 1.8-2 Gy/day to a total dose of 41.4-60 Gy. The details of the regimen for each patient are provided in the individual case report descriptions and Table II.

Response to treatment. Response was assessed by esophageal endoscopy, and neck-to-abdomen computed tomography (CT) 2-3 weeks after the completion of radiotherapy or 6 cycles of FOLFOX for each case. The response of primary tumors of the esophagus was assessed based on the criteria of the Japanese Classification of Esophageal Cancer (11th edition) (13). According to these criteria, a CR required meeting all of the following: i) No evidence of tumor except flat erosion, white exudate or a scar, ii) a negative biopsy, iii) no new lesions and iv) confirmation of i-iii with at least a 4-week interval. Progressive disease (PD) required meeting any of the following criteria: i) Tumor growth and ii) appearance of any new lesions or metastasis. If neither the criteria of CR or PD were met, the response was categorized as non-CR/non-PD. Overall response was assessed bases on RECIST version 1.1. (14).

Toxicity was assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (15) during the treatment course. The outcome and late toxicities were recorded until patient death or the final visit on the chart. Survivors were followed up by tri-monthly CT and endoscopy, and physical examination after the confirmation of CR.

The analysis was performed in April 2017. All patients provided written informed consent for treatment by CRT

with FOLFOX. Publication of this retrospective analysis was approved by the Institutional Review Board of our hospital.

Results

Four patients with EC treated by CRT with FOLFOX were selected from the database. All patients had synchronous ESCC and RC. The patient characteristics and clinical courses are summarized in Tables I and II. The details are described below.

Case 1. A 68-year-old male patient presented with dysphagia and was diagnosed with type 2 ESCC (Lt, cT3N1) and RC (Rs, cT4aN1), whereas liver metastases were synchronously diagnosed. Although liver biopsy was not performed for histological analysis, the liver metastases were clinically determined to be derived from the RC, as progression of its primary and lymph node sites was observed, with significant increases in the tumor marker carcinoembryonic antigen (CEA) level to 31.2 ng/ml (normal, <5 ng/ml). As the patient had synchronous stage IV metastatic RC, his ESCC did not fulfil the indications for radical, invasive surgery; therefore, CRT was performed. Due to the synchronous RC, FOLFOX was selected as the concurrent chemotherapy. Radiotherapy (60 Gy/30 Fr/46 days, omitting elective nodes due to the incurability of this condition) was performed with 3 cycles of FOLFOX, as described in Methods. In the following evaluation, although the response of the primary site was assessed as non-CR due to persistent severe esophagitis, the primary ESCC had regressed. The lymph nodes had also decreased in size. The overall response was assessed as non-CR/non-PD in accordance with RECIST. As regards RC, the outcome was determined as stable disease (Fig. 1).

Chemotherapy was continued focusing on the metastatic RC. Although FOLFOX was planned to continue for 6 cycles after completing radiotherapy based on the PRODIGE5/ACCORD17 trial, the subsequent treatment was changed to fluorouracil-leucovorin-irinotecan (FOLFIRI)-cetuximab, as the therapeutic efficacy of FOLFOX in RC was considered to be limited, and the RAS status of the RC was wild-type. The patient developed a fever (38-39°C) 10 days after the initiation of FOLFIRI-cetuximab. As grade 3 neutropenia was also observed (960/ μ l), the patient was hospitalized and treated with antibiotics. Although the neutrophil count had recovered to 10,910 μ l by day 12, the patient had persistent fever and developed hypoxemia on day 19. Chest computed tomography was performed and revealed interstitial pneumonia due to cetuximab. The patient did not respond to pulse steroid therapy and succumbed to aggravated interstitial pneumonia 46 days after the start of FOLFIRI-cetuximab.

Case 2. A 68-year-old male patient presented with dysphagia and was diagnosed with type 2 ESCC (Mt, cT3N1) and RC (Rs, cT3N1). As both tumors were resectable, radical surgery was planned at the same time after neoadjuvant therapy for the ESCC. For the RC, the neoadjuvant therapy adopted was CRT with FOLFOX. As this was a planned surgery, the dose of radiotherapy was adjusted to 41.4 Gy/23 Fr, which was generally administered as neoadjuvant CRT, with 3 cycles of FOLFOX administered concurrently. The response of the ESCC was evaluated as non-CR/non-PD, with slight regression of the

Table I. Patient characteristics.

Case no.	Sex/age (years)	Histology	TNM (UICC-7th)	Setting	Multiple primary cancers
1	M/68	SCC	T3/N1/M0	dCRT	RC: cT4aN1H2
2	M/68	SCC	T3/N1/M0	Neo-CRT	RC: cT3N1M0
3	M/65	SCC	T3/N2/M0	Neo→dCRT	RC: cT3N0H0
4	M/77	SCC	T2/N1/M0	dCRT	RC: preceding surgery (pStage IIIB)

M, male; F, female; SCC, squamous cell cancer; dCRT, definitive chemoradiotherapy; RC, rectal cancer; Neo-CRT, neoadjuvant chemoradiotherapy.

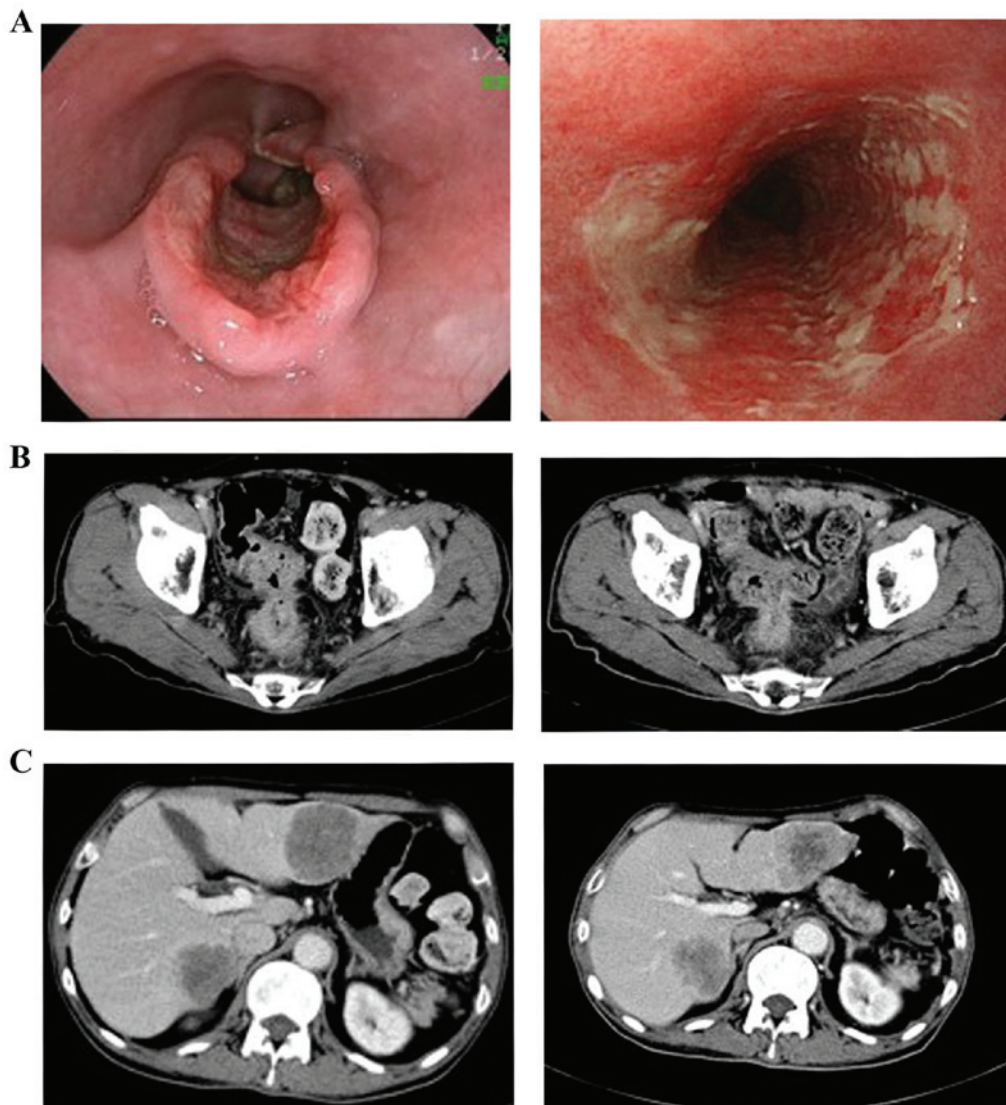


Figure 1. Case 1. (A) Esophageal cancer pre- and post-chemoradiotherapy. Despite the persistent esophagitis, the tumor has almost disappeared. (B) Rectal cancer pre- and post-chemoradiotherapy. (C) Liver metastases pre- and post-chemoradiotherapy.

lymph node metastases and tumor shrinkage, but prolonged esophagitis due to the radiation. For the RC, the outcome was also determined to be non-CR/non-PD (Fig. 2). During the 3rd cycle of FOLFOX, the patient developed 5-FU-induced encephalitis with hyperammonemia ($252 \mu\text{g/dl}$). Although

he rapidly recovered after administration of branched-chain amino acids, continuation of the remaining FOLFOX cycle, similar to PRODIGE5/ACCORD17, was considered to be harmful. At that time, both cancers were assessed as resectable, so simultaneous radical surgeries were performed.

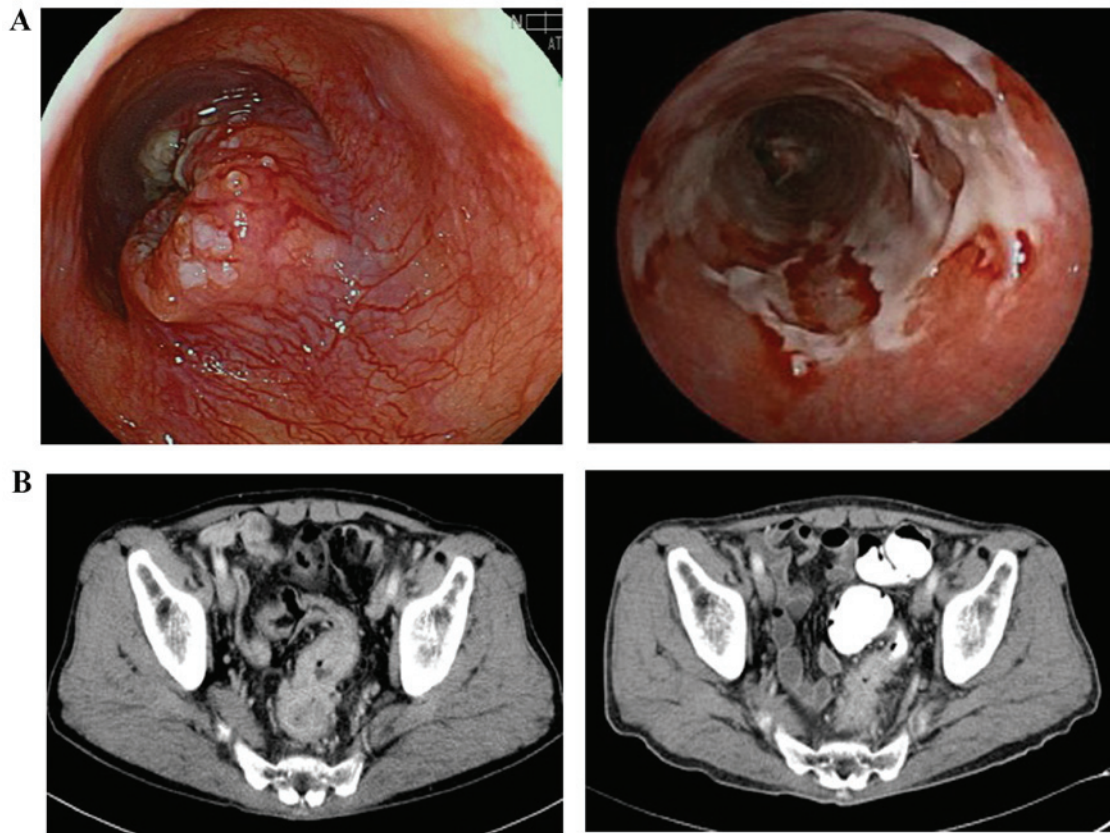


Figure 2. Case 2. (A) Esophageal cancer pre- and post-chemoradiotherapy. Despite the persistent esophagitis, the tumor has almost disappeared. (B) Rectal cancer pre- and post-chemoradiotherapy.

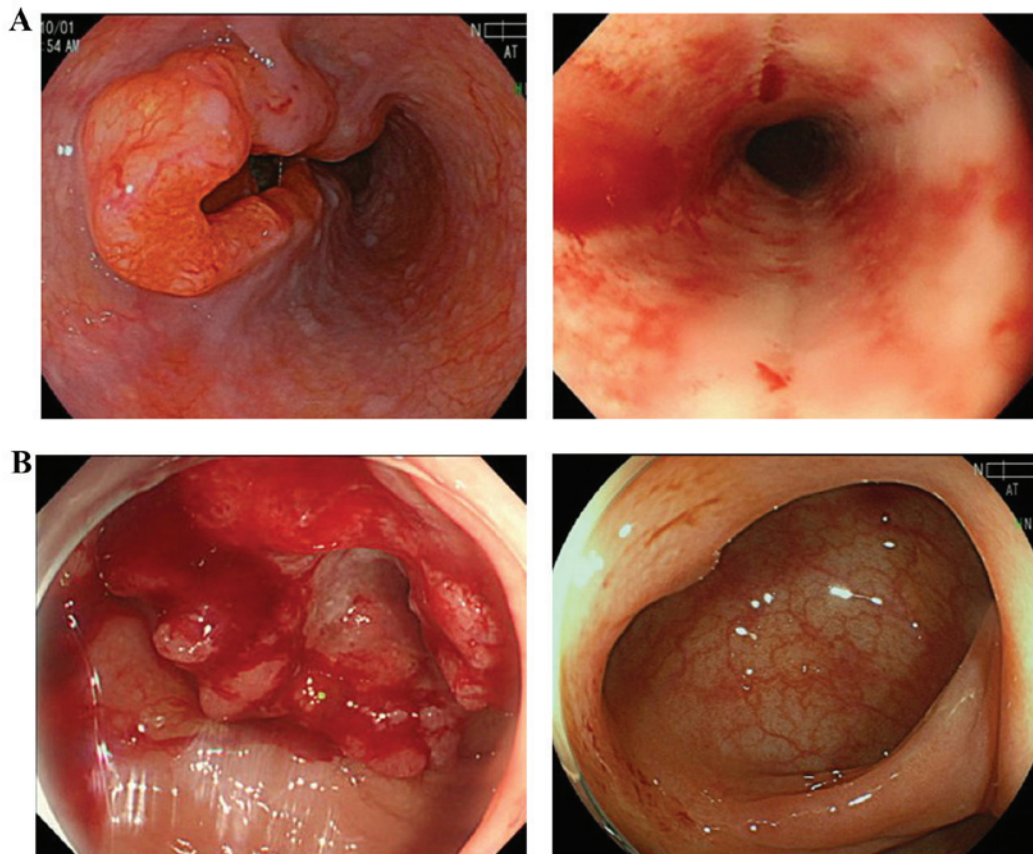


Figure 3. Case 3. (A) Esophageal cancer pre- and post-chemoradiotherapy. Despite the persistent esophagitis, the tumor has almost disappeared. (B) Rectal cancer pre- and post-chemoradiotherapy. The rectal cancer exhibits complete response.

Table II. Summary of cases.

Case no.	Chemotherapy regimen: Dose (mg/m ²) x cycles (Ox/bolus/civ FU)	Radiation dose (Gy/fr)	Response	Later treatment	Status during CRT	Outcome	Cause of death	Survival (days)
1	85/400/1,600 x 3	60/30	Non-CR/Non-PD	FOLFIRI + cetuximab	Inpatient	Deceased	IP	105
2	85/400/1,600 x 3	41.4/23	Non-CR/Non-PD	Planned surgery	Inpatient	Deceased	Cause-specific	194
3	85/400/1,600 x 3 (followed by 3 cycles)	60/30	PR (→CRu s/o)	Watchful waiting	Outpatient	No progression	-	465
4	85/400/1,600 x 3 (followed by 3 cycles)	60/30	CR	Additional capecitabine as adjuvant→surveillance	Outpatient	No progression	-	450

OX, oxaliplatin; IP, interstitial pneumonia; PR, partial response; CRu, complete response unconfirmed.

Table III. Adverse events (n=4).

Adverse events ^a	Grade, n (%)	
	All	≥ 3
Hematological		
Neutropenia	3 (75)	0
Anemia	3 (75)	0
Thrombocytopenia	2 (50)	0
Febrile neutropenia	0	0
Anorexia	3 (75)	0
Esophagitis	3 (75)	0
Constipation	3 (75)	0
Dysphagia	3 (75)	0
Non-hematological		
Erythema	2 (50)	0
Diarrhea	2 (50)	0
Hypokalemia	2 (50)	0
Nausea	2 (50)	0
Paresthesia	2 (50)	0
Encephalopathy	1 (25)	1 (25)
Vomiting	1 (25)	0
Hiccups	1 (25)	0
Pneumonia	1 (25)	0
Mucositis	0	0
Thrombocytopenia	0	0
Renal insufficiency	0	0

^aCommon Terminology Criteria for Adverse Events (version 4).

Unexpectedly, the resection of the ESCC was classified as R2. As the patient did not achieve recovery of his performance status, additional treatment for ESCC was not feasible, so close follow-up was planned. The patient developed recurrence of mediastinal lymph node metastasis 84 days after surgery. His performance status at the time was poor, and he succumbed to ESCC 112 days after surgery.

Case 3. A 65-year-old male patient presented with dysphagia and was diagnosed with type 2 ESCC (Mt, cT3N2) and RC (Rs, cT3N0). Due to mediastinal lymph node metastases (no. 112) invading the aorta, they were deemed to be unresectable. Therefore, the treatment selected for the ESCC was definitive CRT with FOLFOX, followed by radical surgery for the RC. Three cycles of FOLFOX were administered with definitive radiotherapy (60 Gy/30 Fr/46 days), followed by another 3 cycles of FOLFOX. The response of the ESCC was evaluated after all 6 cycles of chemotherapy as non-CR/non-PD, with regression of lymph node metastases and prolonged radiation esophagitis, but the primary tumor had shrank notably. On the other hand, the outcome of FOLFOX for RC was CR (Fig. 3). Considering a delayed CR of the ESCC, the patient was closely followed up to avoid invasive salvage surgery. To date, neither the ESCC nor the RC have progressed. The progression-free survival (PFS) for both cancers has been >2 years since CRT, without surgery.

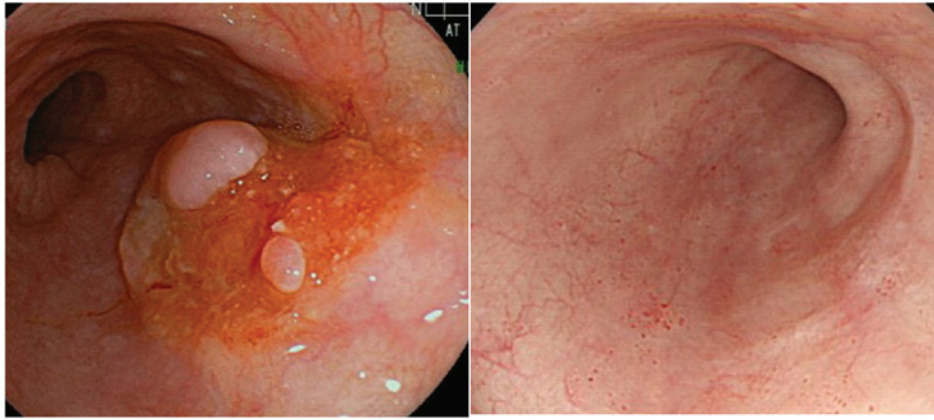


Figure 4. Case 4. Esophageal cancer pre- and post-chemoradiotherapy. The esophageal cancer exhibits complete response.

Case 4. A 77-year-old male patient presented with defecation problems. Type 2 circumferential RC (Rsa, cT3N0) and ESCC (Lt, cT2N1) were diagnosed. The RC caused severe stenosis, and there was a risk of ileus, so radical surgery was performed. Subsequently, it was decided to treat the ESCC with definitive CRT due to an anatomic anomaly (a right aortic arch) that would make the surgery for the ESCC difficult. As the pathological stage of the RC after resection was pStage IIIB (pT3N1), adjuvant chemotherapy with FOLFOX was scheduled for 6 months. Therefore, CRT with FOLFOX was selected for this ESCC case according to the PRODIGE5/ACCORD17 trial, as described in Methods. After completion of 6 cycles of FOLFOX with definitive radiation (60 Gy/30 fr/46 days), the patient developed grade 2 peripheral sensory neuropathy due to treatment with oxaliplatin. Therefore, his chemotherapy was switched to capecitabine monotherapy for the remaining 3 months of adjuvant chemotherapy for the RC. The outcome for the ESCC was determined as CR (Fig. 4). The patient has survived without progression for >1 year and 9 months since the completion of FOLFOX chemotherapy.

The encephalitis in patient 2 was the only grade ≥ 3 adverse event observed among the 4 patients, whereas the other AEs were common events caused by CRT with CF (Table III).

Discussion

In the RTOG 85-01 study, CRT was found to be notably superior to radiotherapy alone in terms of survival prolongation for esophageal cancer. In that study, CF was concurrently administered (1,000 mg/m² 5-FU on days 1-4; 75 mg/m² cisplatin every 28 days) (4). In the RTOG 94-05 study, which was a randomized controlled trial comparing radiation doses of 50.4 vs. 64.8 Gy, with concurrent CF, no survival benefit was achieved with the increased radiation dose (5). Therefore, in the US and Europe, CF in combination with a radiation dose of 50.4 Gy is commonly used for EC, as in the RTOG 85-01 study. However, CF is associated with renal and gastrointestinal toxicity, thrombosis, and other AEs linked to cisplatin, and hospital admission is required for continuous 5-FU infusion.

FOLFOX is one of the global standard treatments for colorectal cancer (16,17). In the US and Europe, oxaliplatin may be used for treatment of EC (2). FOLFOX is expected to contribute to a reduction in toxicity and to increase outpatient

treatment through replacement of cisplatin with oxaliplatin in CRT for EC. The results of phase I and II clinical studies of CRT with FOLFOX for EC have been promising (18-20). Conroy *et al* conducted phase I and II clinical trials of FOLFOX with CRT for EC and obtained favorable results (7). Consequently, randomized phase II and III studies comparing FOLFOX with CF have been conducted, including PRODIGE5/ACCORD17 (8). The results of the phase II study were promising but, unexpectedly, the primary endpoint was not met in the phase III study, as FOLFOX was not found to be superior in terms of PFS with statistical significance [9.7 months for the FOLFOX group vs. 9.4 months for the CF group; hazard ratio (HR)=0.93; 95% confidence interval (CI): 0.7-1.24; P=0.64]. However, due to the lower rates of nephrotoxicity, treatment-related death/sudden death, and other toxicities, and due to the fact that it can be administered on an outpatient basis, CRT with FOLFOX is commonly used in clinical practice in western countries.

In Japan and worldwide, cisplatin has been replaced with oxaliplatin for gastric cancer treatment, as it reduces gastrointestinal toxicity and enables outpatient treatment (3,21-24). However, the use of oxaliplatin for EC has not been approved. Therefore, clinical data of FOLFOX for EC in Japan were available only from patients with multiple primary cancers, for which oxaliplatin is approved. Watanabe *et al* administered CRT with FOLFOX to a patient who had both locally advanced ESCC and synchronous metastatic colon cancer (25). Unlike the ACCORD17 study, an 80% dose of 5-FU-oxaliplatin-leucovorin (mFOLFOX6) (26), which is commonly used for colorectal cancer, was used. Although a tracheoesophageal fistula developed at the end of treatment, the patient was able to complete CRT with FOLFOX, and the tumor size was reduced. The only other grade 3 adverse event was leukocytopenia (25). However, such cases are usually excluded from clinical trials, and little is known on the feasibility of this treatment for Japanese EC patients.

The 4 patients in the present study had both ESCC and advanced RC. As patients 3 and 4 were able to ingest food and did not require hydration, they were treated as outpatients and they achieved a CR for ESCC. Moreover, patient 3 also achieved a CR for RC and was able to avoid surgery. Patient 4 underwent CRT with FOLFOX as postoperative adjuvant

chemotherapy for RC and achieved a satisfactory progression-free period. Although neither patient 1 nor patient 2 achieved a CR for ESCC, the primary lesions were reduced in size, and progression of RC was arrested. In other words, both ESCC and RC were well controlled, and the patients were able to complete CRT with FOLFOX for ESCC. These experiences suggest that CRT with FOLFOX may be a useful therapeutic option for such patients, at least in Japan.

We should be careful regarding the extrapolation of this regimen to ESCC in our country due to the differences in clinical practice between Japan and other countries. First, the major histological type of EC is adenocarcinoma in western countries and SCC in Asia. However, although evidence of this regimen has been verified in US and Europe, several trials include a non-negligible ESCC population. Chiarion *et al* reported that their study included 85% cases of ESCC, and PRODIGE5/ACCORD17 consists of 85-86% of cases of ESCC (8,19). Therefore, CRT with FOLFOX for ESCC may be acceptable. Another point is the difference in the radiation dose. Although a radiation dose of 50.4 Gy was used in an overseas phase III clinical study (5), a dose of 60 Gy/30 Fr is the standard in Japan (10,11). Following a discussion, we decided to use full-dose radiation as the domestic standard in cases 1, 3 and 4, as salvage surgery was unlikely, in an attempt to avoid non-CR. Despite the high-dose radiation, neither acute nor late toxicity was observed. Thus, 50.4 Gy will be adopted as it is estimated to be an acceptable dose for ESCC in Japan.

Patient 2 was scheduled to receive neoadjuvant CRT; therefore, an exposure dose of 41.4 Gy was used, and he also did not experience any clinically significant toxicity. He developed an AE of grade ≥ 3 (5-FU-induced encephalitis), but this toxicity was predictable and it was quickly treated as reported in the literature (27).

Unlike CRT with CF, CRT with FOLFOX did not cause any specific or serious AEs in the 4 reported cases. Although attention should be paid to variations in chemotherapy cycles or irradiation dose and fields in each case, which is the limitation of retrospective case studies, the safety and efficacy of radiation with 3 cycles of FOLFOX may be discussed in approximation.

In conclusion, the present study suggests that CRT with FOLFOX may be well tolerated and feasible in patients with ESCC and synchronous RC, although the retrospective nature of the study and the small number of patients in Japan constitute major limitations. As the antitumor activity of this treatment was found to be highly promising, further investigation with more subjects is required.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

TY, HH, MA, YK, SM, NT, TM and SS and YS contributed to the treatment and follow-up examinations, and TY wrote the manuscript. All the authors have read and approved the final version of this manuscript for publication.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Saitama Cancer Center.

Patient consent for publication

The requirement for the patients' written consent was waived with removal of all identifying information in this retrospective study under the approval of the Ethics Committee of Saitama Cancer Center.

Competing interests

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