Current Management of Esophageal Squamous-Cell Carcinoma in Japan and Other Countries

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ABSTRACT

The incidence of adenocarcinoma of the distal esophagus or esophagogastric junction has increased considerably in Western countries during the past 3 decades, whereas the incidence of squamous-cell carcinoma has decreased slightly. In Japan, most esophageal cancers are squamous-cell carcinomas. Endoscopic examinations are more frequently performed in Japan for routine screening and diagnosis and treatment than in other countries, thereby increasing the detection rate of superficial esophageal carcinomas. In Europe and North America, many clinical trials have been conducted to assess the effectiveness of neoadjuvant chemoradiotherapy followed by surgery in patients with resectable, advanced esophageal cancer. In Japan, surgical resection had been the mainstay of treatment for esophageal cancer. Since the results of the Japan Clinical Oncology Group (JCOG) 9907 study were reported, neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil followed by surgery has emerged as a new standard treatment. As for definitive chemoradiotherapy, cisplatin, 5-fluorouracil, and concurrent radiotherapy dosed to 50.4 Gy are used as standard treatment in a randomized clinical trial performed in North America. In patients who have T4 tumors and/or M1 lymph-node metastasis, chemoradiotherapy with cisplatin and 5-fluorouracil is considered standard treatment, but docetaxel, cisplatin, and 5-fluorouracil plus concurrent radiotherapy is also being studied. Controlled studies have not shown that palliative chemotherapy is superior to best supportive care, but cisplatin plus 5-fluorouracil is still considered standard therapy. Clinical trials of targeted agents are in progress. It is hoped that targeted agents will be effective for esophageal cancer.

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Esophageal cancer is often refractory to current therapeutic approaches and has poor outcomes. Worldwide, almost 400,000 new cases of esophageal cancer are diagnosed annually — it is the eighth most common cancer and the sixth most common cause of cancer-related mortality.[1]

The incidence of esophageal cancer varies widely, according to geographic region and racial background. The incidence of adenocarcinoma of the distal esophagus or esophagogastric junction has increased considerably in Western countries over the past 3 decades, whereas the incidence of squamous-cell carcinoma (SCC) has decreased slightly.[2] Previously, adenocarcinoma of the esophagus accounted for less than 10% of all esophageal tumors, but recent studies indicate that at least 40% of esophageal tumors are now adenocarcinomas.[3]

The reasons for the rising incidence of adenocarcinomas are poorly understood, but obesity, gastroesophageal reflux, and Barrett's epithelium may be contributory factors.[4] In contrast, the risk of SCC of the esophagus and the head and neck is related to smoking and alcohol consumption.[5] Ethanol is oxidized to acetaldehyde and then to acetate by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Most of the acetaldehyde generated during alcohol metabolism in vivo is promptly eliminated by aldehyde dehydrogenase-2 (ALDH2). The gene for the homotetrameric enzyme ALDH2 has a polymorphism, and its mutant ALDH2*2 allele encodes a catalytically inactive subunit. Approximately 40% of Japanese have the mutant ALDH2*2 allele and inactive forms of ALDH2.

The distribution of the ALDH2*2 allele varies by race; it is prevalent in East Asians but has not been found in whites or Africans. In the presence of inactive ALDH2, the body fails to metabolize acetaldehyde rapidly, leading to excessive accumulation of the compound. Acetaldehyde has been established to be a carcinogen in animals and can interact with human DNA.[6]

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OVERVIEW

In Japan, 329,314 people died of malignant neoplasms in 2006; esophageal cancer was the cause of death in 11,345 cases (3.45%). Esophageal cancer is the sixth most common type of cancer in men.[7] Squamous-cell carcinoma accounts for 95% of all esophageal carcinomas. Other histologic types, including adenocarcinoma, account for the remaining 5%.[8] About 90% of all esophageal cancers arise in the thoracic esophagus, and the middle thoracic esophagus is the most frequent location. In Japan, endoscopic examinations are often performed during routine health examinations, resulting in a high detection rate of early gastrointestinal cancers. Nonetheless, clinical stage 0 or I disease accounts for only about 20% of all detected esophageal cancers. Advanced resectable esophageal cancers — ie, clinical stage II or III disease (excluding T4 tumors) — account for 35% to 40% of all cases of esophageal cancer.

Resection of esophageal cancer is associated with higher surgical morbidity than in other gastrointestinal tumors, and the rate of surgery-related mortality ranges from 3% to 4%. The recent rapid growth of the elderly population is associated with an increased number of patients who are unable to tolerate surgery. Further improvement in long-term outcomes of patients with esophageal cancer will thus require the introduction of more effective multidisciplinary therapies and additional clinical trials designed to identify the most effective regimens.

In Europe and North America, the incidence of advanced cancer is higher than in Japan, resulting in an even greater dependence on multidisciplinary and nonsurgical treatment. We review the latest trends in the management of esophageal SCC according to clinical stage. All descriptions of clinical stage are in accordance with the 6th edition of the TNM Classification of Malignant Tumours.[9]

CURRENT MANAGEMENT STRATEGIES

Clinical Stage 0 (TisN0M0) and Stage I (T1N0M0)

Endoscopic Resection

In Japan, endoscopic examinations are more frequently performed for routine screening and diagnosis and treatment than in other countries. This practice has resulted in a high detection rate of superficial esophageal cancer and fostered the development of improved techniques for endoscopic treatment. Endoscopic resection is now the standard treatment for mucosal cancers.

Lesions that do not infiltrate beyond the mucosa (T1a) and those confined to the mucosal epithelium or the lamina propria mucosae are rarely accompanied by lymph-node metastasis.[10] Endoscopic resection is, therefore, a potentially curative treatment for such lesions. Because circumferential mucosal resection carries a high risk of postoperative stenosis, this procedure is indicated for lesions not exceeding two thirds of the circumference of the esophagus.[11] Lesions that reach the muscularis mucosae (MM) or infiltrate the upper submucosa (up to 200 μm: SM1) are associated with a 10% rate of lymph-node metastasis. However, mucosal resection is feasible for patients with no clinical evidence of lymph-node metastasis (relative indication).[12,13]

Lesions requiring circumferential mucosal resection also represent a relative indication. Lesions showing deep invasion (more than 200 μm) of the submucosa (SM2 or SM3) are associated with lymph-node metastasis at a frequency of about 50%, and even superficial carcinomas are treated similarly to advanced carcinomas (carcinomas invading deeper than the muscularis propria).

There are limitations in diagnosing the depth of tumor invasion before treatment. It is also difficult to estimate accurately the depth of invasion of extensive lesions. Thus, the use of resected tissue specimens is essential. There has been extensive discussion about the need for additional treatment (for example, chemoradiotherapy) after the diagnostic evaluation of resected tissue specimens. In patients with esophageal cancer invading MM or SM1, the rate of lymph-node metastasis is only about 10%. Lymphatic invasion is an established risk factor for lymph-node metastasis.[12]

Endoscopic resection includes conventional endoscopic mucosal resection (EMR), by which the affected mucosa is held or aspirated and resected with a snare,[14] and endoscopic submucosal dissection (ESD), which allows en bloc resection of an extensive lesion using a Hook knife or a Flex knife.[15,16] Other endoscopic treatments include photodynamic and argon plasma coagulation therapies.[17,18]

EMR or ESD techniques have been developed in Japan, and are used widely for SCC of the esophagus at present. In Western countries, where adenocarcinoma is more common than SCC, the detection rate of superficial esophageal carcinoma is relatively low. Thus, experiences with EMR or ESD procedures remains limited.[19–21]

Endoscopic Resection Followed by Chemoradiotherapy

Another approach to the treatment of esophageal cancer is primary EMR followed by chemoradiotherapy given as prophylactic treatment for possible lymph-node metastases. One prospective study evaluated the long-term outcomes of primary EMR followed by prophylactic chemoradiotherapy for patients with SCC of the esophagus invading the MM or SM1 compared with results in patients who underwent surgical resection alone during the same period.[22] Prophylactic chemoradiotherapy was given to 16 patients with a histopathologic diagnosis of cancer with MM or SM1 invasion confirmed by analysis of tissue specimens obtained by EMR. The treatment regimen consisted of two courses of 5-fluorouracil (5-FU) 700 mg/m^2 and cisplatin 15 mg/m^2 on days 1 to 5, given at a 3-week interval concurrently with external-beam radiation dosed to 40 to 46 Gy. Both the 5-year rates of overall and cause-specific survival were 100% in patients who received the nonsurgical regimen. The survival rates were almost equivalent to those in patients treated with surgical resection. EMR was considered effective even for the primary management of tumors with MM to SM1 invasion, provided that EMR was feasible and followed by chemoradiotherapy.

This multidisciplinary treatment might be a more suitable approach than primary surgery or definitive chemoradiotherapy, for the following reasons: First, overtreatment can be avoided. Second, even for submucosal cancers diagnosed on pathologic examination of endoscopically resected specimens, the risk of local recurrence can

Table 1. Selected randomized trials of neoadjuvant chemotherapy or chemoradiotherapy for SCC of the esophagus

Author	Arm	n	Postoperative mortality (%)	pCR (%)	Survival	*P* value
Law[26]	S alone	73	8.7		MST: 13 mo	
	CF + S	74	8.3	6.7	MST: 16.8 mo	.17
Ancona[27]	S alone	48	4.2		5-yr OS: 22%	
	CF + S	48	4.2	12.8	5-yr OS: 34%	.55
Nygaard[28]	S alone	50	13.2		3-yr OS: 9%	
	CRT (CB + 35 Gy) + S	53	23.5	NA	3-yr OS: 17%	.3
Apinop[29]	S alone	34	14.7		5-yr OS: 10%	
	CRT (CF + 40 Gy) + S	35	14.3	20	5-yr OS: 24%	.4
Le Prise[30]	S alone	45	7		1-yr OS: 46.7%	
	CRT (CF + 20 Gy) + S	41	8.5	11.4	1-yr OS: 46.6%	.56
Bosset[31]	S alone	139	3.6		MST: 18.6 mo	
	CRT (C + 37 Gy) + S	143	12.3	25.9	MST: 18.6 mo	.78
Lee[32]	S alone	50	2.0		MST: 27.3 mo	
	CRT (CF + 45.6 Gy) + S	51	2.0	42.9	MST: 28.2 mo	.69

Abbreviations: SCC = squamous-cell carcinoma; pCR = pathologic complete response; S = surgery; CRT = chemoradiotherapy; CB = cisplatin + bleomycin; CF = cisplatin + 5-fluorouracil; C = cisplatin; NA = not available; MST = median survival time; OS = overall survival rate

be reduced by complete primary EMR. Third, the dose of radiotherapy can be reduced to 40 Gy in a prophylactic setting. This reduction in the radiation dose may decrease the risk of late toxicity, which, in addition to increased morbidity, can be fatal.[23] To evaluate the efficacy of this less invasive combined treatment, the Japan Clinical Oncology Group (JCOG) initiated a prospective multi-institutional phase II study in patients with clinically estimated stage I (T1b) esophageal SCC (JCOG 0508).[24]

Definitive Chemoradiotherapy

Surgery with radical lymph-node dissection is a standard treatment for submucosal esophageal cancer. However, such treatment usually compromises patients' quality of life, many of whom are elderly and suffer from various medical complications making them unfit for aggressive surgery. Consequently, various nonsurgical treatments have been developed to preserve the esophagus and achieve cure with fewer negative effects in such patients. Definitive radiotherapy may be a treatment option for patients with superficial esophageal cancer, particularly for those with mucosal cancers that are too wide to be resected endoscopically.

JCOG recently reported the results of a multi-institutional phase II study of definitive chemoradiotherapy for stage I SCC of the esophagus (JCOG 9708).[25] In this study, patients received two courses of chemoradiotherapy consisting of 5-FU 700 mg/m^2 on days 1 to 4 and cisplatin 70 mg/m^2 on day 1 concurrently with external-beam radiation to a total dose of 60 Gy. The complete response (CR) rate and 2-year survival rate were 96% and 93%, respectively. The survival results were similar to those after radical surgery in Japan, and JCOG has decided to conduct a randomized study comparing surgery with definitive chemoradiotherapy in patients with stage I esophageal cancer (JCOG 0502). This pivotal study will have an important role in determining the most suitable standard treatment for patients with stage I esophageal cancer and in estimating the true efficacy of definitive chemoradiotherapy.

Clinical Stage II or III (Excluding T4 Disease)

Preoperative Therapy Followed by Surgery

Traditionally, localized esophageal SCC has been managed with surgical resection. Indeed, resection is the best treatment in terms of achieving local control. However, survival is poor, and metastatic disease or locoregional recurrence develops in many patients after surgery.

Poor outcomes after surgery alone and analyses of disease recurrence patterns have prompted the addition of adjuvant radiotherapy, chemotherapy, or chemoradiotherapy. Initial results were generally disappointing, because trials were small and lacked statistical power. Because surgery is a major intervention with a high rate of postoperative complications, attention has shifted to neoadjuvant treatment. Most randomized controlled studies of neoadjuvant chemotherapy or chemoradiotherapy vs. surgery alone lacked adequate statistical power to show a significant improvement in survival, particularly among patients with histologic subtypes of SCC (Table 1).[26–32]

Meta-analyses have been performed to increase the accuracy of comparisons and better estimate potential benefits of treatment. Recently, Gebski et al reported a meta-analysis that evaluated data from clinical trials of neoadjuvant chemotherapy and chemoradiotherapy.[33] This analysis combined the results of 10 randomized trials of neoadjuvant chemoradiotherapy vs. surgery alone and 8 randomized trials of neoadjuvant chemotherapy vs. surgery alone in patients with locally resectable esophageal carcinoma. The hazard ratio (HR) for all-cause mortality with neoadjuvant chemoradiotherapy vs. that of surgery alone was 0.81 (95% confidence interval [CI] 0.70–0.93; $P = .002$), corresponding to a 13% absolute difference in survival at 2 years, with similar results for SCC (HR 0.84; 95% CI 0.71–0.99; $P = .04$) and adenocarcinoma (HR 0.75; 95% CI 0.59–

0.95; P = .02). The HR for neoadjuvant chemotherapy was 0.90 (95% CI 0.81–1.00; P = .05), indicating a 2-year absolute survival benefit of 7%. There was no significant effect of chemotherapy on all-cause mortality in patients with SCC (HR 0.88; 95% CI 0.75–1.03; P = .12), but a significant benefit was obtained in patients with adenocarcinoma (HR 0.78; 95% CI 0.64–0.95; P = .014). In Europe and North America, many patients with stage II or III SCC receive neoadjuvant chemoradiotherapy followed by surgery.

In Japan, surgical resection has been the mainstay of treatment for clinical stage II or III esophageal cancer. Studies of the distribution of lymph-node metastases in patients with resected SCC have shown extensive metastases to lymph nodes located in the neck, chest, and abdomen.[34]

In the JCOG 9204 study, postoperative adjuvant chemotherapy with cisplatin plus 5-FU was compared with surgery alone in patients with resectable stage I or II esophageal cancer.[36] Overall survival did not differ significantly between the groups; however, disease-free survival improved significantly in the patients who received postoperative chemotherapy. This trend was most evident in patients with lymph-node metastases. On the basis of these data, postoperative chemotherapy with cisplatin and 5-FU became standard treatment in patients with a histopathologically confirmed diagnosis of lymph-node metastasis who underwent surgery.

In the JCOG 9907 study, preoperative chemotherapy with cisplatin and 5-FU was compared with postoperative chemotherapy with cisplatin and 5-FU in patients with clinical stage II or III esophageal cancer.[37] Preoperative chemotherapy with cisplatin plus 5-FU was found to be superior to postoperative chemotherapy with cisplatin plus 5-FU in overall survival. On the basis of these results, preoperative chemotherapy with cisplatin plus 5-FU followed by radical surgery became the standard treatment strategy for resectable, clinical stage II or III esophageal cancer.

Table 2. Randomized studies of adjuvant or neoadjuvant chemotherapies for SCC of the esophagus in Japan

Study	Arm	n	DFS	*P* value	5-yr OS (%)	*P* value
JCOG 9204[36]	S alone	122	45%*		52	
	S + CF	120	55%*	.037	61	.13
JCOG 9907[37]	S + CF	166	2.0 yr†		38.4	
	CF + S	164	3.0 yr†	.044‡	60.1	.013

*5-year disease-free survival rate
† Median progression-free survival
‡ This *P* value is not significant
Abbreviations: SCC = squamous-cell carcinoma; JCOG = Japan Clinical Oncology Group; DFS = disease-free survival; OS = overall survival; S = surgery; CF= cisplatin + 5-fluorouracil

In the mid-1980s, three-field dissection of cervical, thoracic, and abdominal lymph nodes was introduced, resulting in some positive results.[35] However, local control achieved by surgical resection differs considerably between Japan and Western countries. Many clinical studies of surgery alone have shown that the effect of local control after surgery alone is generally poorer in Western countries than in Japan.

In Japan, three-field lymph-node dissection improved outcomes slightly in patients with SCC of the thoracic esophagus; however, the 5-year survival rate did not reach 70%. The introduction of multidisciplinary treatment was therefore considered necessary to improve outcomes in esophageal cancer. JCOG has conducted randomized, controlled trials to assess potential benefits of adding adjuvant therapy to surgery (Table 2).

To our knowledge, no randomized, controlled study has evaluated the clinical significance of preoperative chemoradiotherapy in Japan. This is attributed to the fact that Japanese surgeons have attempted to improve treatment outcomes by meticulous resection and lymph-node dissection in patients with resectable esophageal cancer, owing to the lack of clear-cut evidence showing that preoperative radiotherapy improves local control. Differences in the perceived role of surgery in achieving local control may thus differ between Western and Japanese surgeons, leading to the considerable differences in the use of multidisciplinary therapy.

Definitive Chemoradiotherapy

Because esophageal SCC is generally sensitive to radiation, definitive chemoradiotherapy, which allows the esophagus to be preserved, was expected to be useful therapeutically. Evidence supporting the use of radiotherapy in Europe and North America has been actively introduced to Japan. The Radiation Therapy Oncology Group (RTOG) in the United States conducted a randomized controlled trial to compare the effect of radiotherapy alone (64 Gy) with that of concurrent chemoradiotherapy (cisplatin, 5-FU, and radiotherapy 50 Gy) in patients with SCC or adenocarcinoma of the esophagus (RTOG 8501 study). This study confirmed that concurrent chemoradiotherapy produced significantly better outcomes than radiotherapy alone, and the former was designated a standard, nonsurgical treatment.[38]

In Japan, a phase II study was conducted to assess the effectiveness of definitive chemoradiotherapy (cisplatin, 5-FU, and classic portal radiation 60 Gy) in patients with stage II or III esophageal SCC (JCOG 9906). The CR rate was 68%, and the 3-year survival rate was 46%.[39] These results were not superior to those obtained with conventional surgical resection with or without chemotherapy, but the study focused attention on the role of definitive chemoradiotherapy in preserving the esophagus. To improve upon long-term outcomes of this treatment, a reduction in late adverse events and the active introduction of safe salvage surgery are required.

RTOG and other study groups conducted a randomized trial to evaluate the optimal dose of radiotherapy (standard dose of 50.4 Gy vs. high dose of 64.8 Gy) in the Intergroup 0123 study and concluded that the standard dose of radiation for patients who receive concurrent chemotherapy with cisplatin and 5-FU is 50.4 Gy.[40]

In Japan, a phase II clinical study is ongoing to evaluate the effectiveness of the international standard RTOG regimen (cisplatin, 5-FU, conformal radiation 50.4 Gy). In Western countries, many studies have

Table 3. Definitive chemoradiotherapy vs. chemoradiotherapy followed by surgery for SCC of the esophagus

Author	Arm	n	TRM (%)	2-yr LCR (%)	*P* value	2-yr survival (%)	*P* value
Stahl[42]	CT (FLEP) + CRT (PE + 40 Gy) + S	86	12.8	64.3		39.9	
	CT (FLEP) + CRT (PE + 50–60 Gy)	86	3.5	40.7	.003	35.4	NS (.007*)
FFCD[43]	CRT (CF + 30–46 Gy) + S	129	9.3	66.4		33.6	
	CRT (CF + 45–66 Gy)	130	0.8	57.0	.0014	39.8	NS (.03*)

*Test for noninferiority.
Abbreviations: SCC = squamous-cell carcinoma; TRM = treatment-related mortality; LCR = local control rate; CT = chemotherapy; CRT = chemoradiotherapy; S = surgery; FLEP = 5-fluorouracil + leucovorin + etoposide + cisplatin; PE = cisplatin + etoposide; CF = cisplatin + 5-fluorouracil; NS = not significant; FFCD = Fédération Francophone de la Cancérologie Digestive

Table 4. Definitive chemoradiotherapy for SCC of the esophagus with T4 and/or M1 lymph node in Japan

Study	Regimen	N	cCR rate (%)	MST	Leukopenia (%) (≥ grade 3)	Esophagitis (%) (≥ grade 3)
Ohtsu[44]	CF + 60 Gy	54	33.3	9 mo	24.1	14.8
JCOG 9516[45]	CF + 60 Gy	60	15.0	10 mo	33.3	3.3
JCOG 9908[46]	NF + 60 Gy	26	12.0	12 mo	34.6	15.4
KDOG 0501[47]	DCF + 61.2 Gy	19	41.2	20 mo	73.7	31.6

Abbreviations: SCC = squamous-cell carcinoma; cCR = clinical complete response; MST = median survival time; CF = cisplatin + 5-fluorouracil; NF = nedaplatin + 5-fluorouracil; DCF = docetaxel + cisplatin + 5-fluorouracil

raised concern about the potential risks vs. benefits of salvage surgery after definitive chemoradiotherapy.[41] In Japan, attempts are under way to improve treatment outcomes by safely performing salvage surgery, previously considered high risk, at an appropriate time.

Definitive Chemoradiotherapy vs. Chemoradiotherapy Followed by Surgery

Two large randomized trials were conducted to compare definitive chemoradiotherapy with preoperative chemoradiotherapy in esophageal SCC (Table 3). In a study performed by the German Esophageal Cancer Study Group, all patients were randomly assigned to receive the same induction chemotherapy: 5-FU, leucovorin, etoposide, and cisplatin.[42] Patients in the surgery arm received neoadjuvant cisplatin and etoposide with concurrent radiotherapy to a total dose of 40 Gy followed by surgery, whereas patients in the nonsurgery arm continued concomitant chemoradiotherapy to a minimum total dose of 50 Gy. The 2-year overall survival results were similar in the surgery (39.9%) and nonsurgery (35.4%) treatment groups. A disadvantage of trimodality therapy in the surgery group was early postoperative mortality, while the definitive chemoradiotherapy in the nonsurgery group was associated with more local relapses.

These results were confirmed in another large randomized study performed by the Fédération Francophone de la Cancérologie Digestive (FFCD).[43] The FFCD 9102 study assessed induction chemotherapy with radiation administered in either a split-course or continuous fashion and randomly assigned patients who responded to either complete chemoradiotherapy or to proceed to surgery. Once again, surgery improved local control, but did not improve survival, because trimodality therapy was associated with increased early mortality.

Clinical Stage III (T4), IVa (M1 Lymph-Node Metastasis)

Patients with T4 tumors and/or M1 lymph-node metastasis are usually treated with definitive chemoradiotherapy because survival outcomes of surgical treatment are poor. In Japan, clinical trials of definitive chemoradiotherapy have been performed in an attempt to improve outcomes (Table 4).[44–47] The standard regimen for chemoradiotherapy combines cisplatin plus 5-FU with radiation to achieve good clinical outcomes and a radiosensitizing effect. In phase II studies of chemoradiotherapy with cisplatin, 5-FU, and 60 Gy of radiotherapy in advanced thoracic esophageal cancer with T4 tumors and/or M1 lymph-node metastasis, the CR rate ranged from 15% to 33%, with a median survival time (MST) of 9 to 10 months.[44,45]

To improve both local and distant control in patients with esophageal cancer, new regimens must be developed. There has been considerable interest in the use of taxanes. Many studies have demonstrated that taxanes are effective in patients with locally advanced and metastatic esophageal cancer. Taxanes promote tubulin conjugation and stabilize microtubule formation, thereby inhibiting mitosis. In addition to cytotoxic activity, taxanes also act as excellent radiosensitizers, arresting the cell cycle in the G_2/M phase. In Japan, docetaxel was approved for the indication of esophageal cancer in January 2004.

The addition of docetaxel to cisplatin plus 5-FU with concurrent radiotherapy (DCF-R) is expected to improve treatment outcomes for patients with esophageal cancer. We therefore conducted a clinical phase I trial of DCF-R (KDOG0501) in patients with advanced thoracic esophageal cancer with T4 tumors and/or M1 lymph-node metasasis.[47] The incidence of adverse events related to hematologic toxicity and esophagitis was higher than that in previous studies of chemoradiotherapy with cisplatin plus 5-FU.[44,45] The overall response rate was 89.5%, including a CR rate of 42.1%. The MST was 20.0 months, indicating good outcomes. The results of an ongoing phase II study with CR rate as the primary end point are awaited.

Clinical Stage IVb or Recurrent Disease

Palliative Chemotherapy

Chemotherapy for patients with metastatic or recurrent esophageal cancer is designed to improve quality of life and survival. For palliation of local symptoms such as dysphagia, pain, and bleeding, local treatments with expandable stents and radiotherapy are recommended.

Monotherapy with cytotoxic drugs such as 5-FU, vindesine, cisplatin, mitomycin, nedaplatin, vinorelbine, and taxanes induced a partial response in 15% to 52% of patients with SCC of the esophagus (Table 5).[48–54] Weekly administration of paclitaxel 100 mg/m^2 has demonstrated promising activity with acceptable toxicity when used as second-line treatment after platinum-based chemotherapy.[54] Several combinations of cytotoxic drugs have induced a partial response in 16% to 60% of patients; cisplatin was included in most regimens (Table 6).[55–66] Cisplatin plus 5-FU is the most commonly used regimen for combination chemotherapy in various phase II and III trials.

New combination regimens, such as cisplatin plus capecitabine and docetaxel plus vinorelbine, have shown promising activity with tolerable toxicity profiles.[64,66] An advantage of these new treatment combinations is greater convenience (ie, ease of administration) compared with cisplatin/5-FU. Cisplatin/capecitabine appears to be particularly promising and may replace cisplatin/5-FU. However, the potential benefits of these new regimens in the treatment of advanced esophageal cancer have to be confirmed in randomized trials.

Only two randomized trials have compared combination chemotherapy with best supportive care in patients with esophageal SCC (Table 7).[67,68] These trials did not demonstrate a survival advantage for chemotherapy. However, it is important to realize that these trials were performed with inferior chemotherapy schedules in small numbers of patients.

Only two studies have compared different combinations of chemotherapy.[69,70] In a randomized phase II study, 88 patients received cisplatin plus 5-FU (CF) or cisplatin alone.[69] No difference in survival was demonstrated, whereas treatment-related mortality in the CF arm was 16% as compared with 0% in the cisplatin arm.

Targeted Agents

Attention has focused on the role of targeted agents in the treatment of various types of cancer. A few studies have evaluated targeted agents in patients with SCC of the esophagus (Table 8).[70–73] Epidermal growth factor receptor (EGFR) is overexpressed in 30% to 90% of patients with esophageal cancer. EGFR expression is higher in SCC than in adenocarcinoma and may correlate with outcomes. Agents targeting EGFR include gefitinib, a tyrosine kinase inhibitor, and cetuximab, an EGFR antibody. A phase II study of gefitinib alone in patients with previously treated esophageal cancer reported a response rate of 3% and a disease control rate of 28%.[71]

In a randomized phase II study, 62 patients received CF with or without cetuximab.[70] The primary end point was tumor response. Unfortunately, this study did not have sufficient power to demonstrate a significant

Table 5. Selected trials of monotherapy for SCC of the esophagus

Author	Regimen	N	Line	Response rate (%)
Ezdinli[48]	5-FU	26	1st	15
Kelsen[49]	Vindesine	23	1st / 2nd	18
Engstrom[50]	Cisplatin	24	1st / 2nd	25
Engstrom[50]	Mitomycin	24	1st / 2nd	42
Taguchi[51]	Nedaplatin	29	1st / 2nd	52
Conroy[52]	Vinorelbine	46	1st / 2nd	15 (2nd line: 6)
Muro[53]	Docetaxel	49	1st / 2nd	20 (2nd line: 18)
Tahara[54]	Paclitaxel (weekly)	56	2nd	44 (CR: 7)

Abbreviations: SCC = squamous-cell carcinoma; CR = complete response

Table 6. Selected trials of combined chemotherapy for SCC of the esophagus

Author	Regimen	Pathology	N (SCC)	Line	Response rate (%)
Iizuka[55]	Cisplatin + vindesine	SCC	31	1st	16
Iizuka[56]	Cisplatin + 5-FU	SCC	39	1st	36
Hayashi[57]	Cisplatin (5 days) + 5-FU	SCC	36	1st	33
Bleiberg[58]	Cisplatin + 5-FU	SCC	44	1st	35
Ilson[59]	Cisplatin + 5-FU + paclitaxel	SCC/adeno	61 (31)	1st	48 (SCC: 50)
Ilson[60]	Cisplatin + irinotecan	SCC/adeno	35 (12)	1st	57 (SCC: 66)
Conroy[61]	Cisplatin + vinorelbine	SCC	71	1st	33
Millar[62]	Cisplatin + gemcitabine	SCC/adeno	42 (14)	1st	45 (SCC: 71)
Laack[63]	Cisplatin + docetaxel	SCC/adeno	16 (10)	1st	31 (SCC: 40)
Lee[64]	Cisplatin + capecitabine	SCC	45	1st	57
Muro[65]	Nedaplatin + 5-FU	SCC	38	1st	40
Airoldi[66]	Docetaxel + vinorelbine	SCC	20	1st / 2nd	60 (CR: 15)

Abbreviations: SCC = squamous-cell carcinoma; adeno = adenocarcinoma; CR = complete response

Table 7. Randomized trials of palliative chemotherapy for advanced esophageal SCC

Author	Arm	n	RR (%)	TTP	MST	*P* value
Schmid[67]	BSC	46			15 wk	
	RT 40 Gy	41	22	NA	13 wk	
	CT	40	20	NA	11 wk	NS
Levard[68]	BSC	84			12 mo	
	CF	72	NA	NA	12 mo	NS
Bleiberg[69]	C	44	19	18 wk	28 wk	
	CF	44	35	27 wk	33 wk	NS
Lordick[70]	CF	30	13	3.6 mo	5.5 mo	
	CF + cetuximab	32	19	5.9 mo	9.5 mo	NS

Abbreviations: SCC = squamous-cell carcinoma; BSC = best supportive care; RT = radiotherapy; CT = chemotherapy (trimetrexate or ifosfamide + mesna, 5-fluorouracil + leucovorin); CF = cisplatin + 5-fluorouracil; C = cisplatin; TTP = median time to progression; MST = median survival time; NA = not available; NS = not significant

Table 8. Selected trials of targeted agents for SCC of the esophagus

Author	Regimen	Pathology	N (SCC)	Line	Response rate (%)
Janmaat[71]	Gefitinib	SCC/adeno	36 (9)	2nd	3
Ku[72]	Cetuximab + cisplatin + irinotecan	SCC/adeno	8 (1)	2nd*	11
Lordick[70]	Cetuximab + cisplatin + 5-FU	SCC	32	1st	19
Safran[73]	Cetuximab + paclitaxel + carboplatin + RT 50.4 Gy	SCC/adeno	60 (12)	1st	cCR 70

*Cisplatin + irinotecan failure
Abbreviations: SCC = squamous-cell carcinoma; adeno = adenocarcinoma; RT = radiotherapy; cCR = clinical complete response

difference in response rate, progression-free survival, or overall survival (Table 7).

Cetuximab has been shown to prolong survival in patients with advanced SCC of the head and neck who receive concurrent radiotherapy.[74] Safran et al conducted a phase II study of a combination of cetuximab and radiotherapy in patients with esophageal cancer and obtained a clinical complete response rate of 70%, with an excellent tolerability profile.[73] Cetuximab is also expected to enhance the effect of chemoradiotherapy in patients with esophageal cancer.

Studies of targeted agents have just begun. At present, no positive data are available. However, these agents are expected to be effective for esophageal cancer, as well as for colorectal cancer and SCC of the head and neck.

DISCUSSION

Squamous-cell carcinoma of the esophagus can be treated with various techniques, such as endoscopy, surgery, radiotherapy, and chemotherapy. However, the effect of any one therapy is limited. To achieve improved outcomes, the development of new combination regimens and new drugs, including targeted agents, that are effective for the treatment of esophageal SCC is essential. In Western countries, clinical trials are now primarily focusing on the treatment of adenocarcinoma, owing to the recent increase in the prevalence of this type of esophageal cancer. In Japan and other Asian countries, SCC is the main type of esophageal cancer. The development of new treatment strategies for SCC is awaited.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.