

REVIEW ARTICLE

Essential Updates 2016/2017: Esophagus

Recent advancements in esophageal cancer treatment in Japan

Yoshihiro Tanaka  | Kazuhiro Yoshida  | Tomonari Suetsugu | Takeharu Imai |
Nobuhisa Matsuhashi | Kazuya Yamaguchi

Department of Surgical Oncology, Graduate School of Medicine, Gifu University, Gifu, Japan

CorrespondenceKazuhiro Yoshida, Department of Surgical Oncology, Graduate School of Medicine, Gifu University, Gifu, Japan.
Email: kyoshida@gifu-u.ac.jp**Abstract**

The 11th edition of the Japanese Classification of Esophageal Cancer (EC) was published in 2017. Some correction was made in the depth of tumor invasion to be consistent with the TNM classification by the Union for International Cancer Control (UICC). With regard to surgery, short-term safety and long-term effectiveness under thoracotomy/video-assisted thoracoscopic surgery are expected to be proven by the Japan Clinical Oncology Group (JCOG)1409 study. Results of nutritional management and countermeasures for adverse events not only during the perioperative period but also during EC chemotherapy were reported. From now on, the pursuit of low invasiveness and radicality is desired. Esophageal surgery is also expected to be safe at all institutions. To determine the optimal modality of preoperative treatment and a novel chemo(radio)therapy regimen for patients with distant metastasis, the results of the ongoing JCOG1109 and 0807 studies are being released. The effect of the addition of molecular targeted drugs on chemotherapy and concurrent chemoradiation has not yet improved overall survival. Immune checkpoint inhibitor drugs could offer a potential new treatment approach for patients with treatment-refractory advanced squamous cell carcinoma (SCC). The Cancer Genome Atlas Research Network reported the results of a comprehensive genome analysis and molecular analysis of SCC and adenocarcinoma of the esophagus. Further differentiation of SCC and adenocarcinoma by molecular characterization analysis may be useful for the development of clinical trials and targeted drug therapies as precision medicine. The era of ultimate minimally invasive surgery and personalized treatment has begun. Large, prospective studies will be required to confirm the value of these advancements.

KEYWORDS

chemoradiotherapy, chemotherapy, clinical trial, esophageal cancer, surgery

1 | INTRODUCTION

Esophageal carcinoma (EC) is the eighth most common cancer and the sixth leading cause of cancer-related deaths worldwide. Many

chemotherapy regimens for locally advanced tumors have been reported to date. Despite the availability of various chemotherapy regimens, advanced EC carries a very poor prognosis, with a mean survival time of <8.1 months with current chemotherapies used

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singly or in combination with 5-fluorouracil (FU), vindesine, mitomycin, docetaxel, paclitaxel, cisplatin (CDDP), irinotecan, vinorelbine, or capecitabine.¹ Fluorouracil and CDDP combination therapy (FP) is regarded as standard,² with median survival times reported to be 9.2 months for responders and 5.3 months for non-responders.³ The response rates reported with FP range from 35% to 40%, whereas the 2-year survival rates of patients with locally advanced EC range from 8% to 55%, with a mean of 27%.^{4,5} Preoperative chemotherapy with FP can be regarded as standard treatment for patients with stage II/III esophageal squamous cell carcinoma (ESCC).⁶ Furthermore, an antitumor effect is expected with the development of a combination therapy comprising a triplet regimen, molecular targeted drug, and immunity checkpoint inhibitor.^{7,8} Efforts to achieve individualized treatment by genetic analysis have also begun in the presence of differences in histopathological type between Caucasians and Asians. Video-assisted thoracoscopic surgery (VATS) in the pursuit of minimal invasiveness and the pursuit of safe perioperative management by the medical team are widespread in the field of esophageal surgery and treatment. In the present review article, we report recent advancements in the treatment of EC.

2 | RENEWAL OF THE JAPANESE CLASSIFICATION OF ESOPHAGEAL CANCER

The 11th edition of the Japanese Classification of EC was published in 2017, and the criteria for the diagnosis of lesions located at the gastroesophageal junction have been jointly adopted by the Japanese Gastric Cancer Association. Regarding the depth of tumor invasion, a subgroup has been added to T1, similar to that for T4, to be consistent with the Union for International Cancer Control's (UICC) TNM classification. To secure consistency with the general rules for surgical and pathological studies on gastric cancer, No. 3 has been divided into No. 3a and No. 3b.⁹

3 | TREATMENTS

3.1 | Endoscopic treatment

Endoscopic submucosal dissection (ESD) has been widely used in the resection of superficial EC. Since its use was extended to cases involving large esophageal tumors occupying nearly all or the whole circumference of the lumen, the occurrence of esophageal stricture has increased. Although endoscopic injection of triamcinolone (TA) is widely used for the prevention of postoperative stricture, a significant number of patients still develop stricture after TA injection therapy.

In 2017, Okamoto et al carried out a retrospective study to identify the clinical parameters that predispose post-ESD patients to esophageal stricture after TA injection therapy. Endoscopic TA injection is not sufficient to prevent esophageal stricture in patients bearing mucosal defects covering more than seven-eighths of the esophageal circumference after ESD.¹⁰ A randomized phase III trial started in

Japan in 2014. The purpose of this study is to confirm the superiority of giving prophylactic oral steroid following ESD in terms of stricture-free survival over endoscopic local steroid injection for patients with superficial EC.¹¹

3.2 | Minimally invasive surgery

Presently, the optimal surgical technique for EC remains unclear. Dissemination of VATS has made it possible to accurately ascertain the surgical anatomy as a result of the magnification effect. In 2017, a report was published using a nationwide Japanese database. Overall, 9584 patients with thoracic EC who underwent esophagectomy at 864 hospitals in 2011-2012 were evaluated. Takeuchi et al carried out one-to-one matching between minimally invasive esophagectomy (MIE) and open esophagectomy (OE) groups on the basis of estimated propensity scores for each patient. After propensity score matching, operative time was significantly longer in the MIE group ($n = 3515$) than in the OE group ($n = 3515$) (526 ± 149 vs 461 ± 156 minutes, $P < .001$), whereas blood loss was markedly less in the MIE group than in the OE group (442 ± 612 mL vs 608 ± 591 mL, $P < .001$). The population of patients who required more than 48 hours of postoperative respiratory ventilation was also significantly less in the MIE group than in the OE group (8.9% vs 10.9%, $P = .006$); however, the reoperation rate within 30 days was significantly higher in the MIE group than in the OE group (7.0% vs 5.3%, $P = .004$). There were no significant differences between the MIE and OE groups in 30-day mortality rates (0.9% vs 1.1%) and operative mortality rates (2.5% vs 2.8%, respectively). They concluded that MIE was comparable with conventional OE in terms of short-term outcome after esophagectomy.¹²

A randomized phase III study, the Japan Clinical Oncology Group (JCOG)1409 study, started in 2015 to confirm the non-inferiority of thoracoscopic esophagectomy to open esophagectomy for clinical stage I-III EC. The primary endpoint is overall survival (OS). Secondary endpoints are relapse-free survival (RFS), proportion of patients with R0 resection, proportion of patients who undergo reoperation, adverse events, postoperative change in respiratory function, postoperative quality-of-life (QOL) score, and the proportion of patients who require conversion from thoracoscopic surgery to open surgery.¹³

The three most common techniques for thoracic esophagectomy are the transhiatal approach, Ivor Lewis esophagectomy (right thoracotomy and laparotomy), and the McKeown technique (right thoracotomy followed by laparotomy and neck incision with cervical anastomosis).¹⁴ A report comparing the operative methods for ESCC was published by Li et al who investigated whether survival is improved by using the right thoracic approach (extended lymphadenectomy) versus the left thoracic approach (limited lymphadenectomy). Disease-free survival (DFS) and OS were compared between the right ($n = 146$) and left thoracic groups ($n = 140$). They concluded that compared with the left thoracic approach, the right thoracic approach was associated with increased DFS and OS in

ESCC patients, particularly in those with lymph node involvement and/or R1-2 resection margins.¹⁵

Surgery and perioperative management for EC is not easy. Differences among institutions were reported in clinical trials conducted at multiple facilities. Kataoka et al¹⁶ reported in 2015 that interinstitutional heterogeneity as a result of complications and survival after esophagectomy are problems that merit wider consideration. A critical issue in multicenter randomized trials focusing on surgical techniques is quality control. Two randomized phase III trials (JCOG9501 and JCOG9502) were conducted to compare standard and experimental surgery for gastric and esophagogastric junction adenocarcinomas. Kurokawa et al¹⁷ concluded that there was some degree of interinstitutional variation in outcomes after standard surgery, but there was little variation in the hazard ratio (HR) for OS for experimental surgery, indicating that the final conclusions of the two randomized phase III trials can be generalized to their respective target populations. An investigation of the relationship between hospital volume and risk-adjusted mortality following esophagectomy for esophageal cancer in Japan using a nationwide web-based database was reported. The study included patients registered in the database between 2011 and 2013. Outcome measures were 30-day and operative mortality rates. In total, 16 556 esophagectomies at 988 hospitals were included for which the overall unadjusted 30-day and operative mortality rates were 1.1% and 3.0%, respectively. The unadjusted operative mortality rate in hospitals carrying out fewer than 10 procedures per year (5.1%) was more than threefold higher than that in hospitals conducting 30 or more procedures annually (1.5%). Multivariable models indicated that hospital volume had a significant effect on 30-day (odds ratio [OR] 0.88 per 10-patient increase; $P = .012$) and operative (OR 0.86 per 10-patient increase; $P < .001$) mortality.¹⁸

More than 4000 da Vinci Surgical Systems have been installed worldwide. Robotic surgery using the system has been increasingly carried out in the last decade, especially in urology and gynecology. The robotic da Vinci Ivor Lewis esophagectomy procedure now appears to be reimbursed by Japanese national health insurance. Egberts et al reported on their technique and short-term results of 75 patients undergoing Ivor Lewis esophagectomy using a fully robotic four-arm approach in the abdominal and thoracic phases with a hand-sewn intrathoracic anastomosis. Conversion to open procedure occurred in two (2.6%) patients in the abdominal and 14 patients (18.7%) in the thoracic phase. Main reasons for conversion were problems during lifting of the gastric conduit and difficulties in the construction of the esophagogastronomy.¹⁹ In Japan, however, Nakauchi et al reported on the initiation in 2009 of robotic gastrectomy and esophagectomy for patients with upper gastrointestinal cancer, and they showed potential advantages of the da Vinci Surgical System in reducing postoperative local complications after gastrectomy and recurrent laryngeal nerve palsy after esophagectomy. However, robotic surgery has the disadvantages of a longer operative time and higher costs than the conventional approach.²⁰

In 2004, Tangoku et al²¹ reported that mediastinoscope-assisted transhiatal esophagectomy is a safe and minimally invasive technique

that allows direct visualization of mediastinal structures, and lymph node sampling is feasible because of the clearly visualized mediastinum. Fujiwara et al reported an en bloc lymphadenectomy method in the upper mediastinum with a single-port mediastinoscopic cervical approach. They evaluated the safety and efficacy of single-port mediastinoscope-assisted transhiatal esophagectomy for thoracic EC. Median operation time and blood loss were 363 minutes and 235 mL, respectively, and the R0 resection rate was 95%. They concluded that this procedure is feasible in terms of perioperative outcomes as radical surgery for thoracic EC, although its safety needs to be further indicated.²²

3.3 | Chemotherapy and chemoradiotherapy

Neoadjuvant chemotherapy (NAC) or neoadjuvant chemoradiotherapy (NCRT) is considered for patients with locally advanced EC, but this is still under discussion. Preoperative chemotherapy with FP is the current standard treatment for locally advanced EC in Japan, whereas preoperative chemoradiotherapy (CRT) with FP²³ or carboplatin and paclitaxel²⁴ are the standard in Western countries. The theoretical advantages of adding chemotherapy to the treatment of EC are potential tumor downstaging prior to surgery and the targeting of micrometastases, which can decrease the risk of distant metastasis.

3.3.1 | Best preoperative therapy: Start of the JCOG1109 trial

The first major event in this area was the start in November 2012 of the three-arm phase III JCOG1109 trial, a study to determine the standard for preoperative treatment. Preoperative chemotherapy with docetaxel and cisplatin plus 5-fluorouracil (DCF) is another promising regimen. The purpose of this study is to confirm the superiority of DCF over FP and the superiority of FP with CRT over FP alone as preoperative therapy for ESCC. A total of 501 patients will be accrued from 41 Japanese institutions within 6.25 years. Primary endpoint is OS, and secondary endpoints include progression-free survival (PFS), R0 resection, response rate, pathological complete response (pCR) rate, and adverse events.²⁵

3.3.2 | Strategy for metastatic cases: JCOG0807, JCOG1314

Chemotherapy with FP is the current standard treatment for metastatic or recurrent EC. Kataoka et al developed a twice-weekly regimen of docetaxel combined with FP and conducted a phase I/II trial for metastatic or recurrent EC. Promising efficacy and safety were shown in JCOG0807, and they started a phase III trial in September 2014 to confirm the superiority of twice-weekly DCF to FP for patients with metastatic or recurrent EC. The primary end point is OS. Secondary end points are PFS, response rate, and proportion of adverse events. The results are eagerly awaited.²⁶

3.3.3 | Perioperative chemotherapy or preoperative chemotherapy?

Preoperative chemotherapy with FP can be regarded as standard treatment for patients with stage II/III ESCC in Japan.⁶ A study was reported that discussed whether preoperative treatment only is sufficient or whether it should also be given after surgery. Zhao et al assessed whether a perioperative regimen of paclitaxel, cisplatin, and 5-fluorouracil (PCF) improved outcomes among patients with curable ESCC compared with preoperative chemotherapy alone. Overall, 346 patients with resectable ESCC were randomly assigned to receive surgery plus perioperative chemotherapy or preoperative chemotherapy alone. Compared with the preoperative chemotherapy group, the perioperative chemotherapy group had a greater likelihood of 5-year relapse free survival (RFS) (HR for relapse, 0.62; 95% confidence interval [CI] 0.49-0.73; 31% vs 17%, $P < .001$) and of 5-year OS (HR for death, 0.79; 95% CI 0.59-0.95; 38% vs 22%, $P < .001$). No increase in PCF-related toxic events was detected with the addition of two postoperative cycles of PCF. They concluded that in patients with operable ESCC, a perioperative regimen of PCF can significantly improve 5-year RFS and OS compared with preoperative chemotherapy alone.²⁷

3.3.4 | CRT versus CRT plus surgery for EC

A systemic review from Cochrane Library evaluated CRT and CRT plus surgery for EC. They identified two randomized studies, in six reports, that included 431 participants. All participants were clinically staged to have at least T3 and/or node-positive thoracic EC, 93% of which was SCC. High-quality evidence found the addition of esophagectomy had little or no positive impact on OS (HR 0.99, 95% CI 0.79-1.24; $P = .92$; $I^2 = 0\%$; two trials). Moderate-quality evidence suggested that the addition of esophagectomy probably improved freedom from locoregional relapse (HR 0.55, 95% CI 0.39-0.76; $P = .0004$; $I^2 = 0\%$; two trials), but low-quality evidence suggested it may increase the risk of treatment-related mortality (RR 5.11, 95% CI 1.74-15.02; $P = .003$; $I^2 = 2\%$; two trials).²⁸

3.3.5 | Neoadjuvant chemotherapy plus surgery versus CRT for stage II/III EC

Chemoradiotherapy is the standard for unresectable EC and can also be considered an option for resectable EC.²⁹ Nomura et al conducted subgroup analysis of patients undergoing CRT to identify those with survival outcomes potentially equivalent to NAC followed by surgery (NAC-S). Pooled data from two clinical trials in patients with stage II/III ESCC, the JCOG9907 and JCOG9906 trials, were used. The analysis comprised 163 patients in the NAC-S arm and 73 patients who received CRT. OS was better in the NAC-S group than in the CRT group (adjusted HR 1.72; 95% CI 1.19-2.50). All subgroups in the NAC-S group had longer OS than those in the CRT group.³⁰

3.3.6 | Surgery after clinical failure of CRT

Long-term follow-up in the CROSS trial²⁴ confirmed the OS benefits for NCRT when added to surgery in patients with resectable esophageal or esophagogastric junctional cancer. This improvement is clinically relevant for both the SCC and adenocarcinoma subtypes. Therefore, NCRT according to the CROSS trial followed by surgical resection should be regarded as a standard of care for patients with resectable locally advanced esophageal or esophagogastric junctional cancer in Western countries. However, two randomized trials addressing thoracic EC concluded that for SCC, definitive CRT alone leads to the same OS as induction CRT followed by surgery.^{31,32}

One of these trials, FFC9102, randomized only fit, compliant, and operable responders to induction CRT, between continuation of CRT and surgery. In their analysis, Vincent et al reported that outcome in the patients not eligible for randomization was calculated to determine whether an attempt at surgery should be recommended. Eligible patients had operable thoracic EC. After initial CRT, patients with no clinical response, or with contraindication to follow any attributed treatment, were not randomized. OS was studied first in the whole population of non-randomized patients and then specifically in clinical non-responders. The impact of surgery on OS was studied in these two populations. Of the 451 registered patients, 192 were not randomized and, among them, 111 were clinical non-responders. Median OS was significantly shorter for the non-randomized patients (11.5 months) than for the randomized patients (18.9 months; $P = .0024$). However, for the 112 non-randomized patients who underwent surgery, median OS was not significantly different from that of the randomized patients: 17.3 versus 18.9 months ($P = .58$). For the clinical non-responders, median OS was longer for those who underwent surgery compared to non-operated patients: 17.0 versus 5.5 months (HR = 0.39 [0.25-0.61]; $P < .0001$) and, again, it was not different from that in responding, randomized patients ($P = .40$). In patients with locally advanced thoracic EC, OS did not differ between responders to induction CRT and patients undergoing surgery after clinical failure of CRT. This data suggested that attempting surgery after early failure of CRT is beneficial and should be considered in patients who are still operable.³²

3.3.7 | Addition of cetuximab to CRT

The role of epidermal growth factor receptor inhibition in CRT strategies in patients with EC remains uncertain. To evaluate the benefit of cetuximab added to concurrent CRT therapy for patients undergoing non-operative treatment of EC, patients were randomized to weekly concurrent cisplatin, paclitaxel, and daily radiation of 50.4 Gy with or without weekly cetuximab. No differences were seen in clinical CR between the treatment arms for either histology (esophageal adenocarcinoma [EAC] or ESCC). The addition of cetuximab to concurrent CRT did not improve OS. These phase III trial results highlighted the need for predictive biomarkers in the treatment of EC (Table 1).³³

TABLE 1 Regimens of chemoradiotherapy for esophageal cancer

Reference (first author)	Target	Chemoradiation or Chemoradiation + Surgery	Chemotherapy regimen (/m ²)	Phase	Cases, n	Median overall survival (mo)	Survival rate (%)
Herskovic ²³	Esophageal cancer (SCC, AC) Stage IIB-IIIa	Chemoradiation 50 Gy	F: 1000 (days 1-4, 29-33, 50-53, 71-74) C: 75 (weekly)	III	61	12.5	—
Shapiro ²⁴	Esophageal cancer and junctional cancer (SCC, AC) Stage IIB-IIIa	Chemoradiation + Surgery 41.4 Gy	Carboplatin (AUC 2 mg/mL/min) P: 50/days 1,8,15,22,29	III	178	48.6	5 y OS (47)
Nomura ³⁰	Esophageal cancer (SCC) Stage II, III	Chemoradiation 60 Gy	F: 400 (days 1-5, 8-12) C: 40 (day 1, 8)/5 wks	II	73	—	5 y PFS (38.3)
Bedenne ³¹	Esophageal cancer (SCC) Stage III, IV	Chemoradiation 61 Gy	F: 800 (days 1-5) C: 15 (day 1-5)/3 wks	—	130	—	2 y OS (40)
Bedenne ³¹	Esophageal cancer (SCC) Stage III, IV	Chemoradiation + Surgery for clinical response cases 46 Gy	F: 800 (days 1-5) C: 15 (day 1-5)/3 wks	—	129	—	2 y OS (34)
Vincent ³²	Esophageal cancer (SCC) Stage III, IV	Chemoradiation + Surgery for no clinical response cases 46 Gy	F: 800 (days 1-5) C: 15 (day 1-5)/3 wks	—	111	17.0	—
Suntharalingam ³³	Esophageal cancer (SCC, AC) Non-operable	Chemoradiation 50.4 Gy	P: 25 (day 1)/weekly C: 50 (day 1)/weekly Cet: 400 (day 1) 250/weekly	III	159	—	3 y OS (34)

AC, adenocarcinoma; C, cisplatin; Cet, cetuximab; F, fluorouracil; OS, overall survival; P, paclitaxel; PFS, progression free survival; SCC, squamous cell carcinoma; —, not available.

3.3.8 | Novel strategy of chemotherapy

The JCOG9407 trial using FP showed an overall response rate of 33.3% and median OS of 6.7 months.³⁴ Moreover, this trial showed a response rate of 38%, similar to those reported in previous studies of metastatic disease.⁶ As mentioned above, the combination of cisplatin (80 mg/m² on day 1) + 5-FU (800 mg/m² per day on days 1-5), repeated every 4 weeks (1 cycle), is the standard regimen used in Japanese clinical practice.³⁵ Development of the next generation of regimens to treat both distant metastasis and locally advanced cancer has already begun. Many studies have shown significant activity of taxanes in patients with locally advanced and metastatic EC.³⁶ Although a DCF regimen has been reported, it is often difficult to accomplish because of severe toxicity. Therefore, Tanaka et al developed a new biweekly-DCF (Bi-DCF) regimen and carried out a phase I/II study of Bi-DCF for advanced ESCC. After completion of the regimen, patients received esophagectomy. During chemotherapy, the most common grade 3 or 4 toxicity was neutropenia (31.3%). No treatment-related deaths were observed, and the incidence of operative morbidity was tolerable. Overall response rate (RR) after the chemotherapy was 90.3%. They concluded that this Bi-DCF regimen was well tolerated and highly active.³⁷ Tanaka et al also developed a new triplet regimen of docetaxel, nedaplatin, and S1 (DGS) for use in the outpatient setting and undertook a phase I/II study of DGS for advanced EC. After completion of chemotherapy, patients underwent esophagectomy. As with the Bi-DCF study, the most common

grade 3 or 4 toxicity during chemotherapy was neutropenia (25.0%), no treatment-related deaths were observed, and the incidence of operative morbidity was tolerable. Overall RR after chemotherapy was 83.3%. This DGS regimen was well tolerated and highly active in the outpatient setting.³⁸ Wang et al evaluated 35 patients who received gemcitabine plus vinorelbine as second-line treatment after the failure of platinum-based chemotherapy. Thirty-four of 35 patients had ESCC, and only one patient had EAC. RR was 31.3%, and the disease control rate (partial response plus stable disease) was 62.5%. PFS was 4.3 ± 0.2 months, and median OS was 7.3 ± 0.3 months. The combination of gemcitabine plus vinorelbine was well tolerated as a second-line treatment for platinum-based chemotherapy-refractory EC patients and appeared to provide enhanced clinical activity especially in patients with low expression of miRNA-214³⁹ (Table 2).

3.4 | Immune checkpoint inhibitors

3.4.1 | Nivolumab for EC

Nivolumab is a human monoclonal IgG4 antibody that inhibits the expression of programmed cell death protein 1 (PD-1) on activated T cells. In 2017, Weber et al⁴⁹ reported that among patients undergoing resection of stage IIIB, IIIC, or IV melanoma, adjuvant therapy with nivolumab resulted in significantly longer recurrence-free survival and a lower rate of grade 3 or 4 adverse events than adjuvant

therapy with ipilimumab. Kudo et al investigated the safety and activity of nivolumab in patients with treatment-refractory EC. In this phase II study, eligible patients had advanced ESCC, adenocarcinoma, or EAC of the esophagus refractory or intolerant to fluoropyrimidine-based, platinum-based, and taxane-based chemotherapy. Sixty-five patients were enrolled, all with ESCC. Median duration of OS was 10.8 months (95% CI 7.4-13.3 months). Median durations of centrally assessed and investigator-assessed PFS were 1.5 (95% CI 1.4-2.8) and 2.3 (1.5-3.0) months, respectively. Nivolumab showed promising activity with a manageable safety profile. This drug could offer a potential new treatment approach for patients with advanced treatment-refractory ESCC.⁵⁰

3.4.2 | Pembrolizumab for EC

The anti-programmed death-1 antibody pembrolizumab was evaluated in KEYNOTE-028, a multicohort phase IB study of patients with programmed death ligand-1 (PD-L1)-positive advanced solid tumors, and results from the EC cohort were reported. Eligible patients with ESCC or EAC or gastroesophageal junction carcinoma in whom standard therapy failed and who had PD-L1-positive tumors received pembrolizumab for up to 2 years or until disease progression was confirmed or intolerable toxicity occurred. Among 83 patients with EC and samples evaluable for PD-L1 expression, 37 (45%) had PD-L1-positive tumors, and 23 were enrolled, of whom 78% had squamous histology and 87% received \geq two prior therapies for advanced/metastatic disease. Overall RR was 30% (95% CI 13%-53%), and the median duration of response was 15 months (range, 6-26 months). Median PFS was 1.8 months (95% CI 1.7-2.9 months), and the 6- and 12-month PFS rates were 30% and 22%, respectively. Median OS was 7.0 (95% CI 4.3-17.7) months, and the 6- and 12-month OS rates were 60% and 40%, respectively. A six-gene interferon- γ gene expression signature analysis suggested that delayed progression and increased response occurred in the pembrolizumab-treated patients with higher interferon- γ composite scores. Pembrolizumab showed manageable toxicity and durable antitumor activity in patients with heavily pretreated, PD-L1-positive advanced EC.⁵¹

3.5 | Esophageal adenocarcinoma

3.5.1 | Reports on Barrett's esophagus

In the USA and Western Europe, the predominant histological type of EC has shifted over the past four decades from ESC to EAC, as the incidence of EAC has increased 5-6-fold whereas the incidence of ESCC has remained relatively stable.⁵²

In Japan, SCC remains the predominant type in all EC. The ratio of SCC to adenocarcinoma is 26:1. No dramatic increase in adenocarcinoma has occurred, and the absolute incidence remains low in Japan.⁵³ The incidence of Barrett's esophagus (BE)-related neoplasia in Western countries has increased in the past several decades, and

it also appears to be increasing even in Eastern countries. Therefore, it should also be noted in this area in the future.

The cost-effectiveness of surveillance in BE is still debated, and the use of biomarkers in screening and surveillance is still not recommended. Evaluation of the potential role of the determination of the immunocomplexed form of SCC antigen (SCCA-immunoglobulin [Ig] M) for the screening of BE and EAC was reported. Patients with SCCA-IgM levels above the cutoff had a 33-fold higher relative risk of harboring BE or EAC ($P = .0001$). Patients "at risk" with long or dysplastic BE had SCCA-IgM levels significantly higher than those with short non-dysplastic BE ($P = .035$), and patients with SCCA-IgM above the cutoff had an eightfold higher relative risk of their BE being "at risk." Thus, serum SCCA-IgM determination allows the identification of patients at risk for BE/EAC and the stratification of BE patients in subgroups with different cancer risk.⁵⁴

3.5.2 | Current therapy for EAC

Results of the PreOperative therapy in EAC Trial (POET) showed some benefits when including radiotherapy in the preoperative treatment. Stahl et al reported the long-term results of this phase III study. Patients with locally advanced adenocarcinomas of the esophagogastric junction (Siewert types I-III) were eligible and were randomized to receive either chemotherapy or induction chemotherapy and CRT followed by surgery. Local PFS after tumor resection was significantly improved by CRT and 20 vs 12 patients were free of local tumor progression at 5 years ($P = .03$). OS showed a trend in favor of preoperative CRT. This long-term follow-up data suggested a benefit in local PFS when radiotherapy was added to preoperative chemotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction.⁵⁵

Oxaliplatin-capecitabine (OxCap)- and carboplatin-paclitaxel (CarPac)-based NCRT have shown promising activity in EAC. A non-blinded, randomized, "pick a winner" phase II trial was reported. Both arms received induction OxCap chemotherapy. Seventy-seven patients (OxCapRT: 36; CarPacRT: 41) underwent surgery. Twelve of 41 (29.3%) and four of 36 (11.1%) patients achieved pCR in the CarPacRT and OxCapRT arms, respectively. Only CarPacRT passed the predefined pCR criteria for further investigation.⁵⁶

Perioperative chemotherapy and surgery are also a standard of care for patients with resectable EAC. A comparison of various optimal preoperative treatments for EAC was reported. The OE05 trial assessed whether increasing the duration and intensity of NAC further improved survival compared with the current standard regimen. Participants were randomly allocated to receive two cycles of FP or four cycles of epirubicin, cisplatin, and capecitabine (ECX) before surgery. Four cycles of neoadjuvant ECX compared with two cycles of FP did not increase survival and cannot be considered standard of care.⁵⁷

Cunningham et al aimed to assess the safety and efficacy of adding bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), to perioperative chemotherapy in patients with resectable gastric, esophagogastric junction, or lower EAC. They

TABLE 2 Regimens of chemotherapy for esophageal cancer

Reference (first author)	Target	Regimen (/m ²)	Phase	Cases, n	Grade 3/4 leukopenia (%)	Grade 3/4 neutropenia (%)	Febrile neutropenia (%)	Response rate (%)	Histopathological response rate (>Grade 2) (%)	Histopathological complete response rate (Grade 3) (%)	Dose reduction rate in the second cycle (%)	Protocol completion rate (%)
Ando ⁶	Esophageal cancer (SCC) Stage II, III	F: 800 (days 1-5) C: 80 (day 1)/3 wks	III	Post 166 Pre 164	Post 5 Pre 4	—	—	Pre 38	—	—	—	—
Takahashi ⁴⁰	Esophageal cancer (SCC) Stage III, IV	D: 50 (day 1) C: 70 (day 1) F: 700 (days 1-5)/3 wks	I/II	39	53.8	43.6	12.8	66.6	—	—	—	—
Osaka ⁴¹	Esophageal cancer (SCC) Stage III, IV	D: 60 (day 1) C: 60 (day 1) F: 800 (days 1-5)/3-4 wks × 2 courses	II	30	33.3	—	—	83.3 (primary lesion)	—	—	—	96.7
Yamasaki ⁴²	Esophageal cancer (SCC) Stage III, IV	D: 70 (day 1) C: 70 (day 1) F: 700 (days 1-5)/3 wks × 2 courses	I/II	9/40	72.5	90	10	72.5	40	25	—	82.5
Tamura ⁴³	Esophageal cancer (SCC) Stage IV	D: 60 (day 1) C: 70 (day 1) F: 600 (days 1-5)/4 wks × 2 courses	II	29	52	76	21	34.5 (confirmed cases)	—	—	13.8	—
Hara ⁷	Esophageal cancer (SCC) Stage II, IIB, III	D: 70 (day 1) C: 70 (day 1) F: 750 (days 1-5) D: 75 (day 1) C: 75 (day 1) F: 750 (days 1-5)/3 wks × 3 courses	II	42	45.2	83.3	2.4	64.3	51	17	64.3	95.2
Watanabe ⁴⁴	Esophageal cancer (SCC, AD) Stage IIB, III, IVA, IVB (TNM6)	D: 60 (day 1) C: 6 (days 1-5) F: 350 (days 1-5)/3 wks × 2 courses	Prospective intension-to-treat	50	—	78.2	14.5	53.7	26	12	—	—

(Continues)

TABLE 2 (Continued)

Reference (first author)	Target	Regimen (m^2)	Phase	Cases, n	Grade 3/4 leukopenia (%)	Grade 3/4 neutropenia (%)	Febrile neutropenia (%)	Response rate (%)	Histopathological response rate (>Grade 2) (%)	Histopathological complete response rate (Grade 3) (%)	Dose reduction rate in the second cycle (%)	Protocol completion rate (%)
Hironaka ⁴⁵	Esophageal cancer (SCC, AS, B) Stage IV	D: 30 (days 1, 15) C: 80 (day 1) F: 800 (days 1-5)/4 wks	I/II	10/52	9.1	25.5	0	62	—	—	—	—
Tanaka ³⁸	Esophageal cancer (SCC) Stage II, III	D: 35 (day 8) CDGP: 40 (day 8) S1: 80 (days 1-14)/4 wks × 2	II	32	18.8	25.0	3.1	83.3	43.7	15.6	18.8	96.9
Tanaka ³⁷	Esophageal cancer (SCC) Stage IB, II, III	D: 35 (days 1, 8) C: (days 1, 8) F: 400 (days 1-5, 15-19)/4 wks × 2	II	32	12.5	31.3	0	90.3	53.2	21.9	0	100
Kato ⁴⁶	Esophageal cancer (SCC, AD) Advanced or recurrent	P: 100 (days 1, 8, 15, 22, 29, 36)/7 wks	II	53	45.3	52.8	3.8	44.2	—	—	—	—
Shirakawa ⁴⁷	Esophageal cancer (SCC) Advanced or recurrent	D: 70 (day 1)/3 wks or P: 100 (days 1, 8, 15, 22, 29, 36)/7 wks	Retrospective	D: 132 P: 31	—	D: 32.6 P: 16.1	D: 6.1 P: 0	D: 5.3 P: 19.4	—	—	—	—
Huang ⁴⁸	Esophageal cancer (SCC) recurrent or metastatic	G: 1000 (days 1, 8) C: 40 (days 1, 2)/3 wks	II	38	44.7	28.9	—	41.2	—	—	—	—
Wang ³⁹	Esophageal cancer (SCC, AD) 2nd line	G: 1000 (days 1, 8, 21) V: 25 (days 1, 8, 21)/3 wks	2nd line	32	—	31.2	3.1	31.3	—	—	—	—

AD, adenocarcinoma; AS, adenosquamous carcinoma; B, basaloid carcinoma; C, cisplatin; D, docetaxel; F, fluorouracil; G, gemcitabine; P, paclitaxel; SCC, squamous cell carcinoma; V, vinorelbine; —, not available.

randomly assigned patients 1:1 to receive perioperative epirubicin, cisplatin, and capecitabine chemotherapy or chemotherapy plus bevacizumab, in addition to surgery. The 3-year OS was 50.3% (95% CI 45.5%-54.9%) in the chemotherapy-alone group and 48.1% (43.2%-52.7%) in the chemotherapy plus bevacizumab group (HR 1.08, 95% CI 0.91-1.29; $P = .36$). Wound healing complications and postoperative anastomotic leakage were more prevalent in the bevacizumab group; therefore, recruitment of patients with lower esophageal or junctional tumors planned for an esophagogastric resection was stopped toward the end of the trial. The results of this trial did not provide any evidence for the use of bevacizumab in combination with perioperative epirubicin, cisplatin, and capecitabine chemotherapy for patients with resectable gastric, esophagogastric junction, or lower EAC.⁵⁸

Hecht et al evaluated the efficacy of adding lapatinib, a tyrosine kinase receptor inhibitor, to capecitabine and oxaliplatin (CapeOx) in patients with previously untreated human epidermal growth factor receptor 2 (HER2)-amplified advanced gastroesophageal adenocarcinoma. These patients were randomly assigned in a 1:1 ratio to CapeOx plus lapatinib or placebo daily. Median OS in the primary efficacy population was 12.2 (95% CI 10.6-14.2) months in the lapatinib arm and 10.5 (95% CI 9.0-11.3) months in the placebo arm, which was not statistically significant (HR, 0.91; 95% CI 0.73-1.12; $P = .3492$). Thus, the addition of lapatinib to CapeOx did not increase OS in patients with HER2-amplified gastroesophageal adenocarcinoma.⁵⁹

Ramucirumab, an antivascular endothelial growth factor receptor-2 monoclonal antibody, plus paclitaxel significantly improved PFS and RR, resulting in a prolonged median OS and an acceptable safety profile in East Asians with advanced gastric cancer.⁶⁰ Yoon et al reported the first randomized, phase II trial of ramucirumab as front-line therapy for patients with advanced esophageal, gastric, or gastroesophageal junction adenocarcinoma who randomly received mFOLFOX6 plus ramucirumab or mFOLFOX6 plus placebo. Objective response rates were similar between the two arms. The authors concluded that the addition of ramucirumab to front-line mFOLFOX6 did not improve PFS in the intent-to-treat population.⁶¹

4 | MULTIDISCIPLINARY THERAPY

4.1 | Perioperative management

Treatment teams have been recommended so that all medical staff can exercise their expertise and treat EC in a patient-centered way and on an equal basis. EC patients experience a clinically relevant deterioration in both short- and long-term health-related QOL. Thus, the PERFECT study was started in The Netherlands with the aim of investigating effects of physical exercise on health-related QOL in EC patients following surgery. The patients were randomly allocated to an exercise group or a usual care group. The primary outcome is health-related QOL. Because the design of the exercise program closely resembles daily practice, this study is expected to contribute both to evidence on the effects of exercise in EC patients and to

potential implementation strategies.⁶² An examination of how we should invasively treat elderly EC patients was also reported by Vlatic et al. Patients ≥ 70 years old with clinical stage II and III EC diagnosed between 1998 and 2012 were identified from the National Cancer Database and stratified based on treatment type. Age ≥ 80 years (OR 0.73), female gender (OR 0.81), Charlson-Deyo comorbidity score ≥ 2 (OR 0.82), and high-volume centers (OR 0.83) were associated with a decreased likelihood of palliative therapy versus no treatment. Age ≥ 80 years and clinical stage III were associated with a decreased likelihood, whereas adenocarcinoma histology and non-academic cancer centers were associated with an increased likelihood of esophagectomy alone compared to definitive CRT. Age ≥ 80 years, female gender, and non-Caucasian race were associated with a decreased likelihood, whereas adenocarcinoma histology and high-volume centers were associated with an increased likelihood of trimodality therapy compared to definitive CRT. The authors concluded that care should be taken not to unnecessarily deprive these individuals of treatment that may improve their survival.⁶³ Pulmonary infections are the most frequent non-surgical complication. Thoracic epidural anesthesia and perfusion-orientated fluid management can reduce the rate of pulmonary complications.⁶⁴ Perioperative oral care can reduce the risk of postoperative pneumonia in patients undergoing EC surgery.⁶⁵

4.2 | Nutritional management

Patients with EC can potentially be compromised by their postoperative nutritional status while in a vulnerable state and also by powerful chemotherapy or CRT. Many reports have addressed the necessity for nutritional management from the preoperative and early postoperative days. Changes in nutritional parameters reported by 18 studies indicated a weight loss of 5%-12% at 6 months postoperatively. More than half of patients lost $>10\%$ of body weight at 12 months.⁶⁶ A retrospective study investigated the relationship between sarcopenia and clinical outcome in ESCC patients treated by surgical resection or definitive CRT. Sarcopenia in ESCC patients without lymph node involvement was associated with poor prognosis (log rank $P = .035$), indicating sarcopenia as a potential biomarker for identifying patients likely to experience an inferior outcome. Moreover, sarcopenia was associated with anastomosis leakage ($P = .032$).⁶⁷ Nakashima et al⁶⁸ also reported that the incidence of anastomotic leakage and in-hospital death was significantly higher in the elderly sarcopenia group than in the elderly non-sarcopenia group (31.5% vs 15.2%, $P = .015$, 6.8% vs 0.0%, $P = .037$, respectively), and the OS rate in patients with sarcopenia correlated with a significantly poor prognosis in the elderly group ($P < .001$). Thus, it is shown that nutrition management is important. Takesue et al⁶⁹ have reported that postoperative enteral nutrition suppressed weight loss and reduced the incidence of pneumonia in patients after thoracoscopic esophagectomy as a less invasive surgery. Although studies describing the use of an additional nutritional intervention in patients with EC receiving neoadjuvant therapy prior to esophagectomy were summarized, the review indicates the uncertainty of the optimal nutritional approach. Among

them, only one comparative study was included that compared esophageal stents to jejunostomy. This study reported no significant difference between the two groups with respect to complication rates (stents 22% vs jejunostomy 4%, $P = .11$) or increase in weight (stents 4.4 kg vs jejunostomy 4.2 kg, $P = .59$).⁷⁰ Naranjo et al have compiled and presented the most up-to-date nutritional evidence available regarding the provision of immune-enhancing formulas containing Arg, omega-3, and RNA to help clinicians develop an evidence-based nutrition care plan, identify available evidence of whether an esophagectomy patient should receive immune-enhancing formulas, and determine both the cost-effectiveness and safety of such nutrition and the appropriate quantity and timing of dosage (pre-, peri-, or post-esophagectomy). The first results are expected in 2018.⁷¹ Despite recent advances in chemotherapy for gastrointestinal cancer, a crucial factor related to poor prognosis is reduced tolerance to chemotherapy induced by cancer cachexia. Shirai et al systemically analyzed chronological changes in biochemical and physiological status using bioelectrical impedance analysis in 128 gastrointestinal cancer patients provided with or without fish oil-enriched nutrition during chemotherapy. They concluded that fish oil-enriched nutrition may improve the prognosis of patients with cancer cachexia and systemic inflammation (ie, those with a modified Glasgow prognostic score of 1 or 2).⁷² Optimal timing for the first postoperative oral feeding was also investigated. Sun et al evaluated the impact of early oral feeding (EOF) on postoperative cardiac, respiratory, and gastrointestinal complications after McKeown minimally invasive esophagectomy for EC. Patients were randomly allocated to receive oral feeding on the first postoperative day (EOF group) or late oral feeding (LOF group) 7 days after surgery. Compared with the LOF group, the EOF group showed significantly shorter times to first flatus and bowel movement. Two weeks after the operation, the EOF patients reported higher global QOL and function scores and lower symptom scores than the LOF patients.⁷³ A cohort study concerning long-term differences between patients in the oral feeding group and patients with early enteral jejunostomy feeding but delayed oral intake undergoing minimal invasive Ivor-Lewis esophagectomy was reported. One year after surgery, median body mass index (BMI) was 22.8 kg/m² and weight loss was 7.0 kg (9.5%) in 114 patients. Patients in the early oral feeding group lost more weight during the first postoperative month ($P = .004$). However, in the months thereafter this difference was no longer observed. Direct start of oral intake following esophagectomy seems to have no impact on early nutritional reinterventions and long-term weight loss.⁷⁴

4.3 | Venous thromboembolism

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), which was established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. Extended prophylaxis (4 weeks) with low molecular weight heparin for the prevention of VTE in patients with cancer undergoing laparoscopic surgery is recommended, as it is

for laparotomy.⁷⁵ VTE can often be the first clinical manifestation of an underlying malignancy. Raskob et al randomly assigned patients with cancer who had acute symptomatic or incidental VTE to receive either low molecular weight heparin for at least 5 days followed by oral edoxaban or subcutaneous dalteparin. They concluded that oral edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent VTE or major bleeding.⁷⁶ Perioperative VTE measures are important in any cancer type. Hachey et al retrospectively evaluated the Caprini VTE risk assessment model (RAM) in postoperative lung and EC patients to survey adherence, safety, and VTE outcomes. Per the RAM protocol, patients with high-risk scores were prescribed 30 days of postoperative daily enoxaparin prophylaxis, whereas patients at moderate risk received 10 postoperative days of treatment. Implementation of a VTE risk assessment protocol with extended course prophylaxis in high-risk patients was safe and feasible for providers and thoracic surgical patients.⁷⁷

4.4 | Biomarkers

4.4.1 | Integrated genomic characterization of EC

The Cancer Genome Atlas Research Network carried out a comprehensive molecular analysis of 164 EC derived from Western and Eastern populations. Their analyses identified three molecular subclasses of ESCC, but none showed evidence for an etiological role in human papillomavirus. SCC showed frequent genomic amplifications of CCND1 and SOX2 and/or TP63, whereas ERBB2, VEGFA, and GATA4 and GATA6 were more commonly amplified in adenocarcinoma. EAC strongly resembled the chromosomally unstable variant of gastric adenocarcinoma, suggesting that these cancers could be considered as a single disease entity. However, some molecular features, including DNA hypermethylation, occurred disproportionately in EAC. These data provide a framework to facilitate more rational categorization of these tumors and a foundation for new therapies.⁷⁸

4.4.2 | Biomarkers for chemo(radio)therapy

Research into predictive biomarkers of response of EC treated with chemo(radio)therapy are in progress. P53 for predicting EC response has been reported.⁷⁹ Li et al carried out a systematic review and meta-analysis to summarize and evaluate the biomarkers for predicting response to chemo(radio)therapy. Their results indicated that low expression of COX2, miR-200c, ERCC1, and TS, or high expression of CDC25B and p16 can be potential biomarkers for predicting the response of EC patients treated with chemo(radio)therapy.⁸⁰

4.5 | Risk factors

Alcohol consumption is strongly associated with an increased risk of ESCC but is not associated with EAC. Smoking can cause EC, and Dong and Thrift emphasized the importance of focusing efforts on controlling the worldwide burden of EC by reducing alcohol and tobacco use.⁸¹ Xu et al investigated the association and quantified

the correlation between diabetes mellitus (DM) and EC by a meta-analysis. Their results showed a positive correlation between type 2 DM and EC risk (relative risk = 1.28, 95% CI 1.12-1.47, $P < .001$). Subgroup analysis based on gender showed that male gender was an important risk factor for EC whereas female gender was not. In addition, subgroup analysis based on ethnicity showed that DM correlated significantly with EC in North American and European subjects, but no correlation was found in Asian subjects. Furthermore, DM correlated significantly with an increased risk of EAC.⁸²

5 | CONCLUSION

Esophageal cancer remains a major public health problem worldwide. Chemo(radio)therapy including novel molecular targeted drugs and immune checkpoint inhibitors will be a new therapeutic approach for patients with EC in the near future. Precision oncology and minimally invasive surgery might be new innovative approaches, but large randomized controlled trials will be required to establish global standards of care.

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ORCID

Yoshihiro Tanaka  <http://orcid.org/0000-0002-0300-7924>

Kazuhiro Yoshida  <http://orcid.org/0000-0003-1408-0104>

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