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Multimodality approaches to control esophageal cancer: Development of chemoradiotherapy, chemotherapy, and immunotherapy

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Short running head: Multimodality approaches for esophageal cancer

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Abstract

Esophageal cancer has a poor prognosis despite the fact that surgical techniques have been advanced and optimized, and systemic multimodality approaches have progressed recently. Adding chemotherapy, radiotherapy, and immunotherapy to the basic surgical approach have been shown to have therapeutic benefit for esophageal cancer. This review describes the latest development of chemoradiotherapy, chemotherapy, and immunotherapy, which have contributed to the reduction in esophageal cancer growth and improved the survival of patients. Chemoradiation is a treatment option for resectable esophageal cancer to preserve the esophagus for patients who cannot tolerate surgery. Moreover, a combination of chemoradiotherapy and salvage surgery could extend the survival of patients. The effects of a triplet chemotherapy regimen are currently being verified in some Phase III studies for unresectable advanced/recurrent esophageal cancer. In addition, with the great promise of immune checkpoint inhibitors, strategies that incorporate the use of immunotherapy may shift from the metastatic setting to the neoadjuvant/adjuvant setting as a result of clinical trials. More precise comprehension of the molecular biology of esophageal cancer is expected to further control disease progression using multimodality treatments in the future.

Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide [1]. Esophageal Cancer Practice Guidelines 2017, edited by the Japan Esophageal Society [2,3], provide general clinicians with information to guide them to make informed choices of the available diagnosis/treatment strategies for esophageal cancer. Surgery forms a mainstay of treatment for esophageal cancer, while chemotherapy, radiotherapy, and immunotherapy also have therapeutic effect. Tanaka et al. [4] reviewed recent advances in esophageal cancer treatment in Japan, while Seto [5] updated the field of esophageal cancer surgery by reviewing the most recent key papers. In recent years, several well-conducted randomized clinical trials have demonstrated that multidisciplinary management with chemoradiation or chemotherapy for esophageal cancer improve survival outcome. In addition, immune checkpoint inhibitors have emerged as a therapeutic option in the advanced or metastatic setting. We herein reviewed recent key evidence of multimodality treatments, which will likely support clinicians in their selection of the most appropriate treatment option for patients with esophageal cancer.

1. Chemoradiotherapy

1-1. Clinical Stage I (T1b)

In patients with cStage I (T1b) disease, the choice between surgery and chemoradiotherapy (CRT) should be made after assessing the patient's surgical tolerability [2]. The practice guidelines

recommend CRT over radiotherapy (RT) in patients with cStage I esophageal cancer who are unsuitable candidates for endoscopic resection with strong evidence [2]. Indeed, a significantly longer survival time and higher response rate have been demonstrated in patients who are administered CRT compared to those who are administered RT [2, 6]. A parallel-group controlled trial of esophagectomy versus chemoradiotherapy in patients with clinical stage I esophageal carcinoma (JCOG0502) was designed to confirm the non-inferiority of chemoradiotherapy in mortality compared to esophagectomy for Stage IA thoracic esophageal squamous cell carcinoma. If patients accepted randomization, they were randomly allocated to esophagectomy with 2-3 field lymph node dissection (arm A) or chemoradiation therapy (arm B). However, if patients had a preference and refused randomization, they were allocated to the pts preference arm, esophagectomy (arm C), or chemoradiation therapy (arm D). CRT consisted of cisplatin and 5-FU, with radiation at a dose of 60 Gy concurrently. As the primary endpoint was not calculated due to the small number of randomized arms, Kato et al. [7] reported the comparison of the non-randomized part. The 3- and 5-year overall survival (OS) were 94.7% and 86.5% in arm C (esophagectomy), and 93.1% and 85.5% in arm D (CRT, adjusted HR 1.05; 95% CI, 0.67–1.64 [< 1.78]). Moreover, the 3- and 5-year progression-free survival (PFS) rates were 84.1% and 81.7% in arm C, and 76.1% and 71.6% in arm D (adjusted HR, 1.48; 95% CI, 1.01–2.16). The PFS was better in the patients administered esophagectomy than in those did CRT. For those administered CRT, subsequent therapies were

performed by endoscopic resection (16/159) or surgery (21/159). According to the JCOG0502 protocol, metachronous development of clinical T1a esophageal squamous cell carcinoma (ESCC) which could be curatively removed by endoscopic resection was not considered to be progression. Afterall, CRT showed non-inferiority compared to esophagectomy on OS. Taken together, CRT is considered as a treatment option for stage IA esophageal squamous cell carcinoma with organ preservation.

1-2. Clinical Stage II/III

The guidelines for cStage II/III weakly recommend therapy primarily consisting of surgery [2]. Neoadjuvant chemotherapy followed by surgery (NAC-S) represents the standard treatment for patients with Stage II/III ESCC in Japan. While, chemoradiotherapy (CRT) is performed in patients who refuse or have contraindications to surgery. JCOG1406-A study [8] analyzed pooled data from two clinical trials (JCOG9906 and 9907) in patients with Stage II/III ESCC to explore patient subgroups in which the survival after definite CRT was potentially similar to that after NAC-S. A Phase II trial (JCOG9906) that evaluated CRT (5-FU plus cisplatin with concurrent 60 Gy RT) demonstrated a 62.2% complete response rate and a 36.8% 5-year OS [9]. A randomized Phase III trial (JCOG9907) showed the survival benefit of NAC with cisplatin and 5-fluorouracil (CF) relative to adjuvant CF chemotherapy [10]. Comparison between NAC-S and definite CRT revealed that the

5-year OS was better in the NAC-S group than the CRT group (54.8% and 38.3%, respectively) [8]. The eligibility criteria in the two trials were almost identical, and baseline characteristics were similar between the two groups. All subgroups in the NAC-S group had longer OS compared with those in the CRT group. Furthermore, the JCOG0909 Study was designed to assess the usefulness of definitive CRT (5-FU plus cisplatin with concurrent 50.4 Gy RT) followed by positive surgical intervention as a salvage operation in an attempt to reduce the risk of adverse events, as well as the risk associated with the salvage operation that was observed in the JCOG9906 Study. Ito et al. [11] reported that a complete response was achieved in 55 (59%) of the total 94 patients included in the efficacy analysis. Salvage endoscopic resection and surgery were performed in 5 (5%) and 25 patients (27%), and R0 resection of salvage surgery was achieved in 23 (85%). Five-year OS was 64.5% and 5-year OS after salvage surgery was 31.0%. Five pts (19%) showed ≥ grade 3 operative complications and 1 treatment related death due to bronchus-pulmonary artery fistula occurred after salvage surgery. Only 9 pts (9.6%) showed grade 3 late toxicities. And no late operative complications more than grade 3 were observed. The combined modality treatment of definitive CRT with salvage treatment may represent a new standard treatment for cStage II/III esophageal cancer for patients hoping to achieve esophageal preservation. As an exploratory analysis, Hironaka et al. [12] investigated the influence of a radiation field on safety and efficacy. Grade 3–4 hematological toxicities were more frequently observed in middle thoracic (Mt) and lower thoracic

(Lt) groups than in the upper thoracic (Ut) group. In addition, a dose reduction of CDDP and 5-FU was seen more frequently in the Lt group than the Ut group, and the Lt group appeared to have a lower complete response rate and a shorter OS and PFS than the Ut group. The patterns of relapse after definitive CRT were revealed by Sudo K. et al. [13], who demonstrated that among 302 patients treated with definitive CRT, 204 achieved a complete response. The number of patients who recurred with luminal relapse, regional relapse, distant metastasis, new cancer diagnosed by esophagogastroduodenoscopy, or other new cancer were 28 (14%), 13 (6%), 39 (19%), 34 (17%), and 16 (8%), respectively. Thus, it was suggested that surveillance with esophagogastroduodenoscopy may be important in the first 3 years after definitive CRT to detect luminal relapse, and to detect new cancer beyond 3 years.

Subgroup analysis in the JCOG9907 Study revealed that local recurrences were observed among several patients, suggesting the necessity for more intensive local control [3, 14]. The additive effect of the currently used preoperative chemotherapy with cisplatin and 5-FU may be insufficient for improving the prognosis in patients with cStage III thoracic esophageal cancer. With the intention to determine the standard for preoperative treatment, the JCOG1109 Study [14] was designed with a three-arm Phase III trial, and started in 2012 (Table 1). The purpose of this study was to confirm the superiority of docetaxel or cisplatin + 5-FU (DCF) over cisplatin + 5-FU, and the superiority of cisplatin + 5-FU with chemoradiotherapy (41.4 Gy) over cisplatin + 5-FU as a

preoperative therapy for cStage IB/II/III (non T4) squamous cell carcinoma of the esophagus.

In Western countries, preoperative CRT with carboplatin and paclitaxel is a standard preoperative treatment for patients with potentially curable esophageal or esophagogastric-junction cancer [15]. Of the 366 patients analyzed in this CROSS trial, 275 (75%) had adenocarcinoma, 84 (23%) had squamous-cell carcinoma, and 7 (2%) had large-cell undifferentiated carcinoma. In the subgroup analysis, the adjusted hazard ratio for death in the squamous cell carcinoma group was 0.422 (P = 0.007), while that in the adenocarcinoma group was 0.741 (P = 0.07). Several randomized controlled trials are ongoing to answer the question of whether to use bimodality or trimodality therapy for patients with locally advanced esophageal cancer (Table 1). In the Neo-AEGIS trial [16], patients with adenocarcinoma of the esophagus or gastroesophageal junction were randomized between pre- and postoperative chemotherapy according to the MAGIC-regimen [17] versus neoadjuvant CRT according to the CROSS-regimen [15]. Moreover, the ESOPEC-trial [18] is a Phase III two-arm trial that randomizes patients with adenocarcinoma of the esophagus or gastroesophageal junction between perioperative chemotherapy according to the FLOT-regimen [19] followed by surgery versus neoadjuvant CRT according to the CROSS-regimen [15] followed by surgery. The TOPGEAR trial [20] is currently evaluating the perioperative MAGIC ECF regimen [17] alone versus with the addition of preoperative CRT. In addition, a Phase III RTOG-1010 trial [21] is ongoing for HER2-overexpressing esophageal and GEJ adenocarcinomas, whereby patients

are treated with the CROSS-regimen either alone or in addition to trastuzumab before surgery and postoperative trastuzumab therapy.

To identify the response to neoadjuvant multimodality treatments, an imaging technique that can accurately differentiate responders from non-responders is needed. Rossum et al. [22] reported that ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) significantly increased the predictive value of the response to trimodality treatment. This predictivity enables the treating physician to decide upfront whether to continue or discontinue preoperative chemoradiotherapy to prevent the non-responding patient from a toxic and ineffective treatment. Two prospective Phase II studies [23, 24] confirmed that FDG-PET is able to identify responders to induction chemotherapy after 2 weeks of treatment. Furthermore, The Cancer and Leukemia Group B Trial 80803 [25] used a personalized response-adapted treatment concept. In the 80803 Trial, FDG-PET based decisions were also made in relation to the choice of chemotherapy regimen used for preoperative chemotherapy. Efficacy criteria were met for an improvement in pathological complete response (pCR) rates among patients who were PET-non responders after induction chemotherapy and who received alternative chemotherapy during CRT for esophageal and GEJ adenocarcinoma [26]. In Japan, Odawara et al. [27] recommended FDG-PET to assess the tumor response to neoadjuvant chemotherapy in patients with esophageal squamous cell cancer. By using PET-guided image-based treatment algorithms, the choice of therapy, its intensity, and its

duration might become better adjusted to the individual patient's tumor biology.

1-3. Clinical Stage IVa

The standard treatment for patients with locally advanced unresectable esophageal cancer is definitive CRT [2, 28]. Recently, induction chemotherapy consisting of DCF has been shown to elicit a good response and improve outcomes in the COSMOS Trial [29], in which DCF followed by conversion surgery, showed a 1-year survival rate of 67.9%. Moreover, a multicenter randomized controlled trial, JCOG1510 [30], was started to confirm the superiority of induction DCF followed by conversion surgery or definitive CRT over definitive CRT alone for the overall survival of patients with locally advanced unresectable ESCC.

2. Chemotherapy

Combined therapy with cisplatin + 5-FU (FP) is used as the standard therapy for unresectable advanced/recurrent esophageal cancer, while taxanes are used as the second-line therapy [3]. A biweekly DCF regimen in which docetaxel is administered twice every 4 weeks (days 1 and 15) has been developed, and a randomized controlled Phase III trial (JOCG1314) confirming the superiority of biweekly DCF to FP has been conducted [31]. Contrary to expectations, molecular-targeting agents, mainly anti-epidermal growth factor receptor (EGFR) inhibitors such as gefitinib,

panitumumab, and nimotuzumab, have not contributed to the prolongation of survival in Phase 3 trials thus far [32]. Furthermore, negative results from Phase 3 trials testing gefitinib and panitumumab suggest the importance of identifying predictive biomarkers of responses to molecular-targeting agents, such as EGFR gene copy number aberrations [33], or soluble EGFR [34].

Many patients suffer from chemotherapy-induced nausea and vomiting (CINV) during chemotherapy treatment. Triplet-combination therapy with a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, neurokinin-1 (NK1) receptor antagonist, and dexamethasone, is a standard antiemetic therapy for the prevention of CINV in patients receiving cisplatin-based chemotherapy. Olanzapine is an antipsychotic drug that targets multiple receptors and acts as an antagonist against various substances, including dopamine, serotonin, adrenaline, histamine, and muscarine [35]. A randomized double-blind, placebo-controlled, Phase 3 study [36] which included 154 patients with esophageal cancer in a total of 701 patients, has been conducted in Japan in order to evaluate the efficacy of olanzapine 5 mg with triplet-combination antiemetic therapy. Olanzapine was administered in the evening, because somnolence which is one of the adverse events should be prevented. In the delayed phase (24–120 h), the proportion of patients who achieved a complete response (defined as absence of vomiting and no use of rescue medications) was significantly higher in the olanzapine group than in the placebo group (79% vs. 66%, $p < 0.0001$). Thus, olanzapine with

triplet-combination could represent a new standard antiemetic therapy for patients undergoing cisplatin-based chemotherapy.

3. Immunotherapy

Inhibitors of immune checkpoint protein programmed death (PD)-1 have been shown to enhance antitumor activity of T cells in several types of cancer including esophageal cancer [37, 38]. In the randomized, open-label, Phase 3 ATTRACTION-3 Trial, Kato et al. [39] compared nivolumab with chemotherapy (paclitaxel or docetaxel) in patients with unresectable advanced or recurrent esophageal squamous cell carcinoma who were refractory or intolerant to one previous fluoropyrimidine-based and platinum-based chemotherapy. Overall survival was significantly improved in the nivolumab group compared to the chemotherapy group (median, 10.9 months vs 8.4 months; HR for death, 0.77; P = 0.019); thus, nivolumab might represent a new standard second-line treatment option. In addition, Keynote-181 [40, 41] is a randomized, open-label, Phase 3 study comparing pembrolizumab and chemotherapy as second-line therapy for patients with advanced/metastatic squamous cell carcinoma (SCC) and adenocarcinoma (ACC) of the esophagus. In patients with tumors that had combined positive score (CPS) ≥ 10, median OS was superior with pembrolizumab vs chemotherapy (median, 9.3 months vs 6.7 months; HR, 0.69; 95% CI, 0.52-0.93; P=0.0074). Of patients with CPS≥10, median OS was 10.3 months vs 6.7 months in those with SCC

and 6.3 months vs 6.9 months in those with ACC. These data also support pembrolizumab as a new second-line standard of care for esophageal cancer with PD-L1 and a CPS ≥ 10. In addition, both anti PD-1 antibodies showed more favorable safety profiles than anticancer drugs.

Several large Phase III studies are ongoing in the US in the adjuvant setting (CheckMate-577 [42, 43]), as well as first-line, advanced, or metastatic disease with combination immunotherapy or immunochemotherapy (CheckMate-648 [44, 45], Keynote-590 [46, 47]) (Table 2). Of note, immunotherapy may be more effective in esophageal squamous cell cancer (ESCC) with approximately 44% PD-L1 positive rate [48] than in adenocarcinoma with an 18% PD-L1 positive rate [49]. Collectively, ESCC has biological characteristics suitable for immunotherapy, such as high frequency of neoantigens, radio-sensitive tumors, and the identification of several immunogenic cancer antigens [50]. Some cytotoxic drugs or molecular target drugs are also thought to induce immunogenic tumor cell death, resulting in the induction of cytotoxic T lymphocytes [51,52]. Indeed, chemoradiation has been shown to induce cancer antigen-specific cytotoxic T lymphocytes in ESCC patients [53]. After chemoradiation in esophageal adenocarcinoma, it has been shown that PD-L1 is significantly upregulated on immune cells from 45.16% to 77.42% (P = 0.001) [54].

In addition to nivolumab and pembrolizumab, camrelizumab and tislelizumab are anti-PD-1 antibodies those were developed for ESCC in China. The randomized Phase III ESCORT trial that compared camrelizumab with investigator's choice regimen (docetaxel or irinotecan) as second-line

chemotherapy showed superior OS (8.3 vs 6.2 months; HR: 0.71; 95% CI: 0.57–0.87; p = 0.001) [55]. Several phase III studies [56-60] are ongoing using camrelizumab or tislelizumab (Table 2).

Mamdani et al. [61] conducted a Phase II trial evaluating the safety and efficacy of durvalumab, an anti-PD-L1 antibody, in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma who had residual disease in surgical specimens after neoadjuvant CRT and R0 resection. The 1-year relapse free survival and OS were 79.2% and 95.5%, respectively. Adjuvant durvalumab following trimodality therapy for esophageal adenocarcinoma is considered safe, with an improvement in the 1-yr RFS to 79.2% compared to the historical rate of 50%.

Trastuzumab stimulates HER2-specific T cell responses and increases tumor PD-L1 expression, while use of an anti-PD-1 antibody can enhance the T cell-specific immunity of trastuzumab [62, 63]. A Phase II trial of pembrolizumab with chemotherapy (capecitabine and oxaliplatin) plus trastuzumab has been conducted for patients with previously untreated HER2 IHC 3+ or FISH+ tumors [64]. All the 24 evaluable patients had tumor regression, the overall response rate was 83%, and the median progression-free survival was 11.4 months. These promising Phase II safety and efficacy results led to the initiation of a definitive Phase III Keynote 811 Trial involving pembrolizumab/trastuzumab/chemotherapy vs. placebo/trastuzumab/chemotherapy [65, 66] (Table 2).

Conclusions

The treatment options for esophageal cancer are steadily increasing as a result of the recent advances in chemoradiation, chemotherapy, and immunotherapy. These multimodalities open up possibilities for new combinations with both traditional and novel agents to optimize outcomes. The most appropriate approach should be chosen by a multidisciplinary team assessment and following consideration of patient factors including the margin of benefit, quality of life, and best practice for each patient. It is important to identify predictive biomarkers of response and outcome in order to achieve these goals. Although PET imaging is close to being able to assess the response during chemotherapy, we are still several steps away from identifying targetable, differentially expressed pathways that yield higher response rates and result in significant improvements in overall survival. A deeper knowledge of specific molecular subtypes and genomic alterations may allow for more precision in the application of novel therapies in the near future.

Conflict of Interest

None of the authors have any commercial sponsorship to disclose regarding this research.

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Table 1. Current ongoing phase III trials for the patients with locally advanced esophageal cancer.

Trial	Target Population	Study Arms	Primary Endpoint
NeXT [14]	Squamous cell carcinoma	・CF → Surgery (cisplatin + 5-fluorouracil) ・DCF → Surgery (docetaxel + cisplatin + 5-fluorouracil) ・CRT → Surgery (cisplatin + 5-fluorouracil + radiation 41.4 Gy)	3-y Overall Survival
Neo-AEGIS [16]	Adenocarcinoma	・Modified MAGIC → Surgery → Modified MAGIC (epirubicin + cisplatin/oxaliplatin + 5-fluorouracil/capecitabine) ・CROSS → Surgery (paclitaxel + carboplatin + radiation 41.4 Gy)	3-y Overall Survival
ESOPEC [18]	Adenocarcinoma	・FLOT → Surgery → FLOT (5-fluorouracil + leucovorin + oxaliplatin + docetaxel) ・CROSS → Surgery (paclitaxel + carboplatin + radiation 41.4 Gy)	3-y Overall Survival
TOPGEAR [20]	Adenocarcinoma of the stomach or gastroesophageal junction (GEJ) (Siewert type II and III)	・MAGIC ECF + CRT → Surgery → ECF (epirubicin + cisplatin + 5-fluorouracil) (5-fluorouracil/capecitabine + radiation 45 Gy) ・MAGIC ECF → Surgery → ECF (epirubicin + cisplatin + 5-fluorouracil)	Overall Survival
RTOG 1010 [21]	HER2-overexpressing adenocarcinoma	・CROSS + trastuzumab → Surgery → trastuzumab (paclitaxel + carboplatin + trastuzumab + radiation 50.4 Gy) ・CROSS → Surgery (paclitaxel + carboplatin + radiation 50.4 Gy)	Disease-Free Survival

Table 2. Current ongoing phase III trials of immune checkpoint inhibitors for the patients with esophageal or gastroesophageal junction cancer.

Trial	Target Population	Study Arms	Primary Endpoint
CheckMate-577 [42, 43]	Stage II/III carcinoma of the esophagus or GEJ	・CRT → Surgery (R0) → Nivolumab ・CRT → Surgery (R0) → Placebo	Disease-Free Survival Overall Survival
CheckMate-648 [44, 45]	unresectable advanced, recurrent, or metastatic SCC 1st line	・Nivolumab + ipilimumab ・Nivolumab + 5-FU + cisplatin ・5-FU + cisplatin	Progression-Free Survival Overall Survival In patients with PD-L1+ tumors
Keynote-590 [46, 47]	unresectable or metastatic ADC or SCC of the esophagus or advanced Siewert Type 1 ADC of the GEJ 1st line	・Pembrolizumab + 5-FU + cisplatin ・Placebo + 5-FU + cisplatin	Progression-Free Survival Overall Survival in all patients and in the subgroup of patients with a PD-L1 combined positive score (CPS) ≥10.
Keynote-811 [65, 66]	HER2+ advanced gastric or GEJ ADC 1st line	・Pembrolizumab +Trastuzumab + Chemotherapy* ・Placebo +Trastuzumab + Chemotherapy* (*FP or CAPOX (Global Cohort) or SOX (Japan cohort))	Progression-Free Survival Overall Survival
NCT04426955 [56]	locally advanced SCC	・Camrelizumab + CRT ・Placebo + CRT	Progression-Free Survival
NCT03691090 [57]	unresectable local advanced/recurrent or metastatic SCC 1st line	・Camrelizumab + paclitaxel + cisplatin ・Placebo + paclitaxel + cisplatin	Progression-Free Survival Overall Survival

NCT03957590 [58]	localized SCC for whom cCRT is suitable and surgery is unsuitable/declined	・Tislelizumab + CRT ・Placebo + CRT	Progression-Free Survival
Rationale-302 (NCT03430843) [59]	advanced unresectable / metastatic SCC 2nd line	・Tislelizumab ・Investigator chosen chemotherapy (paclitaxel or docetaxel or irinotecan)	Overall Survival
Rationale-306 (NCT03783442) [60]	unresectable, locally advanced recurrent or metastatic SCC 1st line	・Tislelizumab + Platinum (cisplatin or oxaliplatin) + Fluorouracil (5-FU or capecitabine) or paclitaxel ・Placebo + Platinum (cisplatin or oxaliplatin) + Fluorouracil (5-FU or capecitabine) or paclitaxel	Progression-Free Survival Overall Survival

GEJ: Gastroesophageal junction, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma