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REVIEW ARTICLE

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Salvage treatment after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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Abstract

Definitive chemoradiotherapy (dCRT) for the esophageal squamous cell carcinoma (ESCC) is performed for patients with cT4 disease without distant metastasis and also for those with cStage I-III who are unable to tolerate or who refuse surgery. The rates of clinical complete response (cCR) after dCRT differ depending on the cStage, and patients who once achieved cCR frequently experience tumor recurrence. For those with residual tumor or with recurrence, salvage treatment is performed to achieve a cure. Several procedures have been reported as salvage treatments. Salvage esophagectomy is associated with high rates of morbidity and mortality, but can offer long-term survival. With R0 resection, with cCR to dCRT, pulmonary complications appear to be important prognostic factors affecting overall survival (OS). Lymphadenectomy is performed for the patients with lymph node metastasis without recurrence of primary lesions or distant metastasis, but the contribution to long-term OS is unclear. Metastasectomy is performed when distant metastasis is limited to the lung and there are few lesions, possibly contributing to long-term OS. Endoscopic resection and photodynamic therapy are indicated for cT1a and cT1-2 residual or recurrent tumors, respectively, and can yield favorable outcomes. Re-CRT and re-radiotherapy are performed for the patients with contraindications for surgery, but neither appears to contribute to long-term OS despite high incidences of esophageal fistula and perforation.

KEYWORDS

esophageal squamous cell carcinoma, definitive chemoradiotherapy, salvage surgery, salvage esophagectomy, salvage endoscopic treatment, salvage chemoradiotherapy

This review article focused on salvage treatment, i.e. esophagectomy, lymphadenectomy, metastasectomy, endoscopic resection, photodynamic therapy, and re-chemoradiotherapy/radiotherapy, after definitive chemoradiothrapy (dCRT) for esophageal squamous cell carcinoma. Among these procedures, salvage esophagectomy is associated with high mortality and morbidity, but offers long-term survival for patients with R0 resection.

1 | INTRODUCTION

In Japan, the therapeutic strategies for esophageal cancer have been based on original clinical trials considering the differences in histological types of esophageal cancer between Eastern and Western countries. The 2017 Esophageal Cancer Practice Guidelines from the Japan Esophageal Society note that definitive chemoradiotherapy (dCRT) is a standard therapeutic option aiming to cure clinical T4b esophageal squamous cell carcinoma (ESCC) patients without distant organ metastasis.[1,2] For resectable locally advanced cStage II-III ESCC, neoadjuvant chemotherapy followed by esophagectomy is the standard therapeutic strategy,[1,2] but dCRT is applied for those who refuse or are unable to tolerate surgery.[1,2] For cStage I ESCC patients, esophagectomy offers better survival than dCRT,[3] but there is strong evidence to recommend CRT for cStage I esophageal cancer patients who are unsuitable candidates for surgery or endoscopic resection.[1,2]

Previous Japanese clinical trials obtained clinical complete response (cCR) rates to dCRT of approximately 90% in cStage I,[4] 60% in cStage II/III,[5] and 15%-33% in cT4 ESCC.[6,7] In the recent JCOG0909 trial, the cCR rate was 59% in cStage II/III ESCC.[8] Despite this high cCR rate, recurrence was reported in 40%-60% of cases.[4,6] Relapse patterns of the ESCC varied among patients with stage II/III (excluding T4) who achieved cCR to dCRT.[9]

Thus, while dCRT can provide both a chance of cure and esophagus preservation simultaneously, for patients who do not achieve CR or who develop recurrence after CR, curative salvage treatment is necessary. Salvage surgery is defined as an operation for cases with residual or recurrent tumor after dCRT with more than 50 Gy radiation by Japanese Classification of Esophageal Cancer, 11th Edition.[10] Procedures include esophagectomy, lymphadenectomy, and endoscopic resection (ER). While, the term "salvage treatment" is not clearly defined, re-chemoradiotherary and re-radiotherapy are thought to be applicable to this concept. Guidelines mention that for cStage II-III patients with remnant or recurrent lesions, the practicality of surgical resection as salvage therapy should be explored,[1,2] while for cStage IVa ESCC patients with residual disease after dCRT, there is a weak recommendation not to administer the surgery.[1,2] In actual clinical practice, salvage surgery is also performed for cT4 ESCC before dCRT.

According to a meta-analysis by Faiz et al, anastomotic leakage and pulmonary disorder rates were 18.6% and 30.2%, respectively, 90 day-mortality was 8.8%, and pooled 3-year and 5-year OS were 38.7% and 24.1%, respectively.[11] Previous review articles identically noted salvage esophagectomy to potentially have high mortality and morbidity rates.[12-15] Salvage endoscopic treatment is an option if target tumors are intramural and submucosal, and there is no metastasis.[13,14,16] The roles of salvage re-chemoradiotherapy and re-radiotherapy are unclear.

Herein, we review current knowledge on salvage treatment after dCRT for ESCC by focusing on short- and long-term outcomes and prognostic factors, focusing especially on salvage esophagectomy.

2 | MATERIALS AND METHODS

We mainly searched PubMed to identify articles on salvage treatment for ESCC published from 2010 through September 2020. Duplications from the same unit or hospital were allowed. Articles with small sample sizes were excluded. Articles mainly about esophageal adenocarcinoma patients were also excluded. We reviewed the reference lists of these articles to find additional studies.

3 | SALVAGE SURGERY

3.1 | Salvage esophagectomy

Salvage esophagectomy is indicated for residual tumor or recurrence of primary lesions after dCRT, to achieve a cure when tumor invasion is deeper than the submucosal layer. Indications for salvage esophagectomy are based on a benefit-risk balance, considering the patient's general condition, comorbidities, and desires.[1,2] Salvage surgery is regarded as being difficult because of the indistinct planes between the tumor and fibrotic masses of the irradiated mediastinal tissues.[17] Table 1 lists the main results of the cited articles. Previous studies showed the right transthoracic approach to have been mainly adopted for salvage esophagectomy, though minimally invasive esophagectomy (MIE) by thoracoscpic[18-22] and transhiatal approaches[23-29] have also been reported. Notably, Taniyama et al used the thoracoscopic approach for 95% of the salvage esophagectomy cases.[22] Analyzing pooled data from a national clinical database, Yoshida et al showed MIE to be superior or equivalent to open esophagectomy in terms of most postoperative morbidities and surgery-related mortality, regardless of the type of preoperative treatment, including CRT.[30] Preoperative CRT included both neoadjuvant CRT and dCRT and mortalities in patients who received preoperative CRT were equal for MIE and open esophagectomy. However, the authors did not conclude that MIE is acceptable for salvage esophagectomy after dCRT. Recently, the safety of the transmediastinal approach was reported for salvage esophagectomy in a patient with a past history of right lung resection.[31] Transmediastinal esophagectomy is now covered by the national health insurance system in Japan, and thus has a potential as a radical option for MIE,[32] possibly being applicable to salvage esophagectomy in patients with contraindications for the transthoracic and thoracoscopic approaches. To our knowledge, robotic salvage esophagectomy has not been reported. The extents of lymph node dissection differed among studies and even among cases in the same study. Mainly two- to three-field lymph node dissection[19,20,25,27,33,34] and D2-3 lymph node dissection[20,35] have been reported, while some studies did not apply standard or prophylactic extended lymph node dissection.[23,36]

The rate of cT4 patients before dCRT varied from 8%-100% due to different patient selection criteria for each study.[19,20,22,24-26,28,29,33-41] Four articles analyzed cT4 cases only.[20,33,36,37] At present, dCRT is a standard therapeutic strategy for cT4 ESCC, but dCRT indications for cT4 patients might need to be revised because induction chemotherapy

TABLE 1 Summary of studies on esophagectomy after dCRT

First Author	Year	Study interval	N	Residual/ recurrence	cT4 (%) Before dCRT	R0 (%)	Morbidity (%)				Mortality (%)	OS (%)				MST (month)	Favorable Factor for OS (multivariate)
							leakage	Pneumonia	RLN palsy	≧CD3a		1-year	2-year	3-year	5-year		
Mitchell[18]	2020	2004-2016	35	–	–	91.4	17.1	34.3	–	54.3	17.1	68.6	–	45.7	24.2	29.6	NA
Harada[19]	2020	2009-2016	15	7/8	13.3	73.3	26.7	0.0	13.3	66.7	0	–	–	–	–	–	ycN
Sugawara[33]	2020	2006-2016	31	31/0	100.0	71.0	16.1	29.0	–	29.0	9.7	–	–	–	–	–	NA
Sugimura[34]	2020	1997-2017	73	40/33	47.9	86.3	19.2	13.7	8.2	46.6	6.8	72.1	–	44.0	42.0	–	R0, pT0-2, complication
Booka[36]	2020	2004-2016	18	15/3	100.0	77.8	38.9	5.6	44.4	–	0.0	88.9	72.2	–	51.6	90.1	NA (univariate R0, pneumonia)
Okamura[37]	2020	1998-2016	35[a]	34/1	100.0	54.3	14.3	28.6	14.3	22.9[f]	8.6	45.7	28.6	–	5.7	8.7	R0, pneumonia
Ohkura[20]	2019	2006-2018	33	21/12	100.0	42.4	12.1	–	–	33.3	0	–	–	–	–	–	(DSS; R0, cT4a)
Takeuchi[21]	2018	1994-2017	49	29/20	–	75.5	16.3	32.7	10.2	–	10.2	–	–	–	–	24.0	R0, pneumonia, pStage I
Taniyama[22]	2018	2001-2016	100	52/48	8.0	82.0	25.0	23.0	32.0	76[g]	4.0	–	–	–	–	–	NA
Kiyozumi[23]	2018	2005-2016	50	32/18	–	82.0	20.0	14	–	24.0[f]	0	–	–	–	–	–	R0, CDIIIa≦, ypStage0-II
Nakajima[24]	2018	2010-2016	16	–	–	–	6.3	12.5	–	18.8	0.0	–	–	–	–	–	NA
Sugawara[38]	2018	2006-2016	47[b]	34/13	53.2	74.5	29.8	31.9	–	–	10.6	70.0	–	31.7	–	18.0	R0, CR, GPS 0
Hayami[25]	2017	1988-2015	70	46/24	35.7	72.9	12.9	32.9	5.7	60[h]	–	–	–	–	–	–	R0, <60 Gy, CR, ypStage 0-II, pulmonary complication
Lertbutsayanukul[39]	2017	2006-2015	44	–	13.6	70.5	6.8	11.4	–	13.6	2.3	–	55.9	–	–	25.6	R0, >60 Gy
Farinella[40]	2016	2006-2014	16[c]	–	18.8	81.3	25.0	37.5	–	–	0.0	84.0	73.0	63.0	–	–	NA
Watanabe[26]	2015	1988-2013	63	43/20	33.3	73.0	15.9	36.5	6.3	44.4	7.9	–	–	29.8	15.0	–	R0, ypT1-2
Matono[41]	2014	1986-2011	20	20/5	50.0	40.0	–	–	–	–	–	–	–	–	–	–	NA
Chen[44]	2014	1996-2005	51	0/51	–	80.4	5.9	–	–	–	2.0	–	–	–	–	–	NA
Wang[46]	2014	1999-2012	104	66/38	–	79.8	–	–	–	–	0.0	74.4	–	39.8	29.5	–	R0, recurrence, LN > 15[e]
Morita[27]	2011	1994-2009	27	7/18	–	70.4	37.0	29.6[d]	–	–	7.4	70.2	–	50.6	50.6	–	R0
Takeuchi[35]	2010	1994-2008	25	–	68.0	80.0	24.0	44.0	–	–	8.0	–	–	–	43	–	R0, bacteremia/ sepsis
Tachimori[28]	2009	2000-2006	59	36/23	10.2	84.7	30.5	10.1	19.0	–	8.5	–	–	37.8	–	–	pT1-3, pM0

(Continues)

TABLE 1 (Continued)

First Author	Year	Study interval	N	Residual/ recurrence	cT4 (%) Before dCRT	R0 (%)	Morbidity (%)				Mortality (%)	OS (%)				MST (month)	Favorable Factor for OS (multivariate)
							leakage	Pneumonia	RLN palsy	≧CD3a		1-year	2-year	3-year	5-year		
Miyata[29]	2009	1994-2007	33	13/20	36.4	87.9	39.4	30.3	27.3	–	12.1	–	–	–	35	–	NA

Abbreviations: dCRT, definitive chemoradiotherapy; MST, mean survival time; NA, data not analyzed; OS, overall survival; RLN, recurrent laryngeal palsy; –, data not described.

[a]Included 28 dCRT and seven RT cases.

[b]Included one adenocarcinoma patient.

[c]Included two adenocarcinoma patients.

[d]Pneumonia, atelectasis and hypoxia required reintubation.

[e]LN > 15 total mediastinal dissection with 15 or more dissected lymph nodes.

[f]≧CD3b.

[g]Defined according to the Esophageal Complications Consensus Group definitions.

[h]≧CD2.

for cT4 patients has recently come to be regarded as an option,[42] and a phase III trial for cT4 ESCC and JCOG1510, comparing triple induction regimens with docetaxel, cisplatin, and 5-fluorouracil plus radical surgery to dCRT is ongoing.[43]

Anastomotic leakage occurred in 6.3%-39.4% of the cases.[18-29,33-40,44] Pulmonary complication rates ranged from 15.9%-44%.[18,19,21-29,33-40] Recurrent nerve palsy rates ranged from 5.7% to 44.4%.[19,21,22,25,26,28,29,34,36,37] Chylothorax reportedly occurred in 0%-13.3% of the cases.[18-20,22,23,33,35,38-40] Broncho-tracheal necrosis or leakage/fistula, potentially a fatal general condition, reportedly occurred in 3%,[20] 4%,[22] 7%,[28] and 4%,[34] of the cases. Postoperative complications more severe than Clavien-Dindo (CD)[45] Grade≧3a were seen in 18.8%-66.7% of cases,[18,19,21,23,25,33,34,40] and CD Grade≧3b in 24.0%[20] to 22.9% of cases.[36] CD Grade 5 complications, i.e. in-hospital death, reportedly occurred in 0% to 17.1% of cases.[18-24,26-29,33-40,44,46] In efforts to reduce postoperative morbidities and mortality, novel surgical interventions have been advocated. Swisher et al suggested alternative vascularized conduit and omentum transposition to be useful for preventing leakage.[47] Tachimori et al suggested the preservation of the right bronchial artery and the omission of cervical lymph node dissection to preserve the inferior thyroid artery, thereby avoiding tracheal and bronchial necrosis.[28] Morita et al suggested a two-stage operation when salvage surgery was required for patients with some general risks.[48] Swisher also suggested a two-stage procedure to decrease potential morbidity.[47]

R0 resection was performed in 42.4%-86.9% of cases.[18-29,33-41,44,46] One-year, 3-year, and 5-year OS rates were 45.7%-84%,[18,27,34,36-38,40,46] 29.8%-63%, [18,26-28,34,38,40,46] and 5.7%-51.6%,[18,26,27,34-37,46] respectively. Multivariate analysis revealed the following independent prognostic factors: R0 resection,[21,23-27,34,35,37-39,46] CR to dCRT,[25,38,46] pneumonia or pulmonary complications,[21,25,37] morbidity,[34] complications ≦CD Grade3a,[23] ycN,[19] pT0-2,[34] ypStage 0-II,[23,25] Glasgow prognostic score 0,[38] pStage I,[21] radiation dose > 60 Gy,[39] radiation dose < 60 Gy,[25] total mediastinal dissection with 15 or more dissected lymph nodes,[46] bacteremia/sepsis,[35] and pT1-3.[28] Notably, 12 out of 15 studies applying multivariate analysis showed R0 resection to be an independent risk factor for OS, and three studies found CR to dCRT and pulmonary complications to be independent factors associated with outcomes. Considering that CR to dCRT and R0 resection are important prognostic factors in salvage esophagectomy, identification of residual tumors, i.e. assessment of "true" CR, is clinically meaningful. It is, in fact, difficult to judge whether or not curative resection is possible, despite extensive diagnostic imaging.[14] A multi-institutional study promoted by the Japan Esophageal Society to evaluate true CR after dCRT is currently underway.[49] These results obtained may facilitate confirming CR, as well as identifying patients with "false" CR, for whom the follow-up examination interval is critical for promptly detecting recurrent tumors.

The 5-year OS of R0 patients was 90.9%,[20] 44.4%,[23] 74.3%,[27] 8.5%,[44] and 36.9%,[46] while the reported 5-year OS of R1/2 patients was consistently 0%.[20,23,27,38,44,46] Watanabe et al reported that ycT1-2, cT1-2, CR to dCRT, and resectability before dCRT predicted R0 resection on univariate analysis, but no independent factors predicting R0 resection were identified. Hayami et al reported

pulmonary complications to be an independent prognostic factor, and factors significantly predictive of pulmonary complications were body mass index <20 kg/m^2, ASA-PS 2-3, and radiation dose >60 Gy.[25] Sugimura et al reported postoperative complications to be one of the independent prognostic factors for OS, and that univariate analysis factors correlating with postoperative complications included low albumin, cT4 disease, non-CR to dCRT, and radiation dose ≧60 Gy.[34] Ohkura reported that R0 resection and cT4b were independent prognostic factors for disease-free survival in their analysis of cT4 patients. There have been reports emphasizing the importance of radical lymph node dissection,[20,46] but the clinical significance of prophylactic lymph node dissection remains unclear.

To summarize, salvage esophagectomy is associated with high mortality and morbidity, but offers long-term survival for patients with R0 resection.

3.2 | Salvage lymphadenectomy

Regional recurrence was reported in 6% of cStage II-III ESCC patients with CR to dCRT.[9] Salvage lymphadenectomy, i.e. lymphadenectomy without esophagectomy, is performed when apparent disease other than lymph node recurrence or metastasis is detected. Cited articles are listed in Table 2. Watanabe et al reported the R0 resection rate to be 57.1%, the median progression-free survival to be 2 months, OS to be 15 months, and 5-year OS to be 0%. Their lymphadenectomy candidates were patients with solitary lymph node metastasis or metastases limited to a single lymphatic station.[50] Kato et al reported 30 cases of salvage lymphadenectomy cases. The 5-year OS was 18.7%, and salvage lymphadenectomy for lymph node recurrence was significantly better than for lymph nodes with residual disease (21.7% vs 0.0%, respectively). The 5-year OS of patients who underwent salvage lymphadenectomy outside, as compared to within, the radiation field was significantly better (47.6% vs 8.9%, respectively).[51] In these studies, the only severe surgical complication was recurrent laryngeal nerve palsy (one case).[50] Yuan et al concluded in their review article that salvage lymphadenectomy in patients with dCRT for thoracic ESCC was unlikely to control locoregional disease.[52] Salvage lymphadenectomy is thus a less invasive esophagus-preserving surgery and the complication rate is low, but its contribution to OS is unclear.

3.3 | Salvage metastasectomy

Lung, liver, brain, and bone are frequent sites of metastases after radical esophagectomy.[1,2] Distant metastasis reportedly occurred in 19% of cStage II-III ESCC patients with CR to dCRT.[9] Guidelines notes that long-term survival and complete cure have also been reported, and recommended considering active treatment for recurrent lesions.[1,2] Cited articles are listed in Table 2. Kanamori et al reported 5-year OS of those who underwent lung resection to be 43%, but their study included patients initially given treatment

TABLE 2 Summary of studies on lymphadenectomy and metastasectomy after dCRT

First Author	year	Study interval	N	L/M	Residual/ recurrence	Radiation Field in /out	Dissected LN site Ce/ Med/Abd	Metastasectomized site	R0 (%)	Morbidity	OS (%)				MST (month)
											1-year	2-year	3-year	5-year	
Harada[19]	2020	2009-2016	9	L	3/6	–	–	–	–	–	–	–	–	–	–
Nakajima[24]	2018	2010-2016	6	L	–	–	–	–	–	all CD 0-I	100	–	50	–	–
Kato[51]	2018	2004-2016	30	L	4/26	23/7	11/10/9	–	93.3	none (severe)	–	–	–	18.7	–
Matono[41]	2014	1986-2011	5	L	2/3	4/1	2/1/2	–	40	none (severe)	–	–	–	–	–
Watanabe[50]	2014	2004-2013	7	L	3/4	5/2	3/1/3	–	57.1	RLN palsy 1	–	–	–	0	15
Harada[19]	2020	2009-2016	3	M	–	–	–	Lung 2, brain 1	–	–	–	–	–	–	–
Kato[51]	2018	2004-2016	3	M	–	–	–	Lung 3	–	none (severe)	–	–	–	–	–
Kanamori[53]	2017	1992-2013	14	M	–	–	–	Lung 14	90.9[a]	15.2[a]	79.4[a]	–	47.8[a]	43.0[a]	17.9[a]

Abbreviations: Abd, abdominal; Ce, cervical; dCRT, definitive chemoradiotherapy; L, lymphadenectomy; M, metastasectomy; Med, mediastinal; MST, mean survival time, OS, overall survival; RLN, recurrent laryngeal nerve; –, not described.

[a]Analyzed pulmonary resection cases including 14 cases after dCRT, 16 cases after esophagectomy, and three cases after endoscopic resection.

other than dCRT.[53] Kato et al reported their three cases undergoing pulmonary resection to have one or two pulmonary recurrent tumors.[51] Harada et al reported that two lung resection cases showed long-term survival (59 and 42 months, respectively), and one case undergoing brain metastasis resection followed by whole brain radiation therapy survived more than 5 years without recurrence.[19] Based on these reports with small sample sizes, when metastases are limited to the lung and few in number, salvage lung metastasectomy might improve outcome. Furthermore, our literature search yielded no reports of metastatic liver resection after dCRT.

4 | SALVAGE ENDOSCOPIC TREATMENT

4.1 | Salvage endoscopic resection (ER)

Luminal recurrence and new lesions after CR to dCRT reportedly occurred in 14% and 7%, respectively, of patients with cStage II-III ESCC.[9] Salvage endoscopic resection, which includes endoscopic mucosal resection, endoscopic submucosal resection, and strip biopsy, is an esophagus-preserving treatment and less invasive than salvage esophagectomy, and is performed for patients with local recurrence or residual or metachronous tumors limited to the mucosal layer with neither lymph node metastasis nor distant metastasis. Cited articles are listed in Table 3. ER was chosen when target lesions were limited to mucosal layer even if tumor invasion was T2 or deeper prior to dCRT.[54-57] The en bloc resection rates ranged from 46%-100%.[54-62] Major complications were stricture and perforation, the former occurred in 0%-16.7%,[54-58,60-64] the latter in 0%-2.7%.[54-58,60-64] The 5-year OS rates ranged from 29.7%-55%.[57,59,62] Kondo et al identified cT1-2 and cN0 as independent prognostic factors by analyzing 37 patients with 49 nonmetachronous lesions.[57] Hatogai et al reported cT3-4 and uT2 (depth evaluated by endoscopic ultrasonography) to be significant predictors of a poor OS by univariate analysis of 39 patients.[59] Taking these observations together, considering the low complication rate and relatively long OS, salvage ER appears to be a safe and feasible treatment option for patients when residual or recurrent lesions are limited to the luminal layer. Yamamoto et al, examining luminal recurrence, reported that submucosal tumor-like lesions or erosions may indicate local recurrence after CR to dCRT and advocated that follow-up endoscopy be performed within 1-2 months if findings suggestive of local recurrence are observed on prior endoscopy, even when biopsy results are negative.[65]

4.2 | Salvage photodynamic treatment (PDT)

Photodynamic treatment is based on the accumulation of photosensitizers in dysplastic or malignant cells,[16] and is associated with phototoxicity requiring prolonged avoidance of sunlight.[59,66-68] PDT is applied for residual or recurrent lesions in cases with suspected invasion of the submucosa or muscularis propria without lymph node or distant metastasis. Reported CR rates by treating for lesions were 65.8%,[59] 89.3%,[66] 58.4%,[67] and 83.3%.[68] Esophageal fistula is a severe complication of PDT, which developed in 4.4%[67] and 8.3% of the cases.[68] Ishida et al reported an esophageal stricture rate of 41.7%.[68] Treatment-related death rates were 2.6%[59] and 1.8%.[67] Hatogai reported 5-year OS rates of 41.6%[59] and 36.9%,[67] and that cN status before dCRT was the only factor significantly associated with OS on multivariate analysis.[67] Ishida et al reported 2-year OS to be 80.0% and that the progression-free survival rate was 72.7%.[68] Correctively, these result indicate that, despite the relatively high rate of esophageal fistula/perforation formation, PDT is considered as one of the potentially useful treatment options when recurrent lesions are no more advanced than T1-2.

5 | SALVAGE RE-CRT/RT

Re-irradiation following previous dCRT is thought to generally be contraindicated considering the radiation tolerance of the organs at risk, including the lung, trachea, esophagus, and spinal cord.[69] Moreover, Kumagai reviewed salvage esophagectomy and recognized significant gains in long-term survival as compared with second-line CRT, although salvage surgery carries a risk.[70] However, re-CRT/RT for relapse after dCRT has been performed for the patients refusing surgery or with contraindications. Cited articles are listed in Table 4. Reported oncological indications for re-CRT/RT were reported as follows, locoregional recurrence including regional recurrence only or primary failure with or without regional lymph node recurrence,[71] local recurrence without simultaneous local lymph node metastasis,[72] in field recurrence with no distant metastasis,[73] one to five lymph nodes with no other forms of recurrence.[74] The median re-irradiation doses ranged from 50.4-60 Gy.[44,71-75] Cisplatin-based regimens were commonly used as a concurrent chemotherapy.[44,69] Esophago-tracheal, esophago-bronchial fistula and esophageal perforation were identified as severe lethal comorbidities of re-CRT/RT, occurring in 19.4%,[44] 20.0%,[72] 8.5%,[73] 30.0%,[75] and 0%[69,74] of the cases, respectively. In-hospital death rates were 2.8%,[44] 3.9%,[74] 6.4%,[75] 30.0%,[75] and 0%,[69] respectively. The 5-year survival rates were 0%-3.1%.[44,73-75] Chen et al reported that there was no survival difference between R0 resection for salvage esophagectomy and re-CRT,[44] but their 5-year OS rate for esophagectomized patients was low. Considering the high morbidities and unsatisfactory OS rate, salvage-CRT/RT should only be offered to patients with contraindications for salvage surgery.

6 | CONCLUSION

We reviewed salvage treatment after dCRT for ESCC according to the treatment procedures, i.e. esophagectomy, lymphadenectomy, metastasectomy, endoscopic resection, PDT, and re-CRT/RT. Indication and outcomes differ among the procedures, and the optimal treatment procedure for achieving a cure should be given.

TABLE 3 Summary of studies on endoscopic treatment after dCRT

First Author	year	Study interval	N (lesion)	Types of Endoscopic treatment	Residual/Recurrence/ metachronous	cT before dCRT cT1/2/3/4	en-bloc resection rate (%)	CR rate (%)	Morbidity	OS (%)			
										1-year	2-year	3-year	5-year
Nagai[63]	2020	—	13	ESD	3/10/0	13/0/0/0	—	—	stricture1 (7.7%)	—	—	72	—
Ego[56]	2020	2000-2017[a]	45	EMR-C 23, ESD 2, Strip 20	6/39/0	36/3/6/0	46	—	stricture1 (2.2%)	—	—	72	—
Kagawa[60]	2018	2010-2016[a]	8(10)	ESD	3/3/4	7/1/0/0	100	—	none	—	—	—	—
Nakajo[58]	2018	2009-2017	33(35)	ESD	35[c]/0	17/5/7/1[b]	86	—	perforation 0 bleeding 0	95.8	—	—	—
Nakajo[58]	2018	2009-2017	25(34)	ESD	0/0/34	8/1/9/6	100	—	perforation 0 bleeding 0	94.1	—	—	—
Hombu[54]	2018	1998-2013[a]	72	EMR 67, ESD 5	19/53/0	37/8/23/4	51	—	none (≧Grade 3) [d]	—	—	61.2	—
Kondo[57]	2016	2000-2010	37(49)	EMR-C 44, ESD 3, Strip 2,	14/35/0	28/1/3/5	81.6	—	stricture 4 (10.8%) bleeding 1 (2.7%) perforation 1 (2.7%), pneumonia 1 (2.7%)	—	—	72.9	53.3
Nakamura[64]	2016	2001-2012	37(78)	EMR/ESD 67, APC 11	51[c]/27	29/1/3/4	—	—	none (serious)	—	—	—	—
Hatogai[59]	2016	1998-2008[a]	39	EMR	0/39/0	21/4/11/3	—	—	—	—	—	—	55.0
Koizumi[56]	2014	2004-2011[a]	12	ESD	0/12/0	—	91.7	—	stenosis 2 (16.7%)	—	—	—	—
Makazu[62]	2014	2000-2008[a]	11(13)	EMR	2/9/0	6/2/3/0	46	—	none (severe)	—	81.3	62.3	41.6
Takeuchi[55]	2013	2005-2013	19	ESD	4/15/0	12/4/3/0	100	—	none	—	—	74	—
Ishida[68]	2020	2016-2020	12	PDT	2/10/0	—	—	83.3	fistula 1 (8.3%), stricture5 (41.6%)	—	80	—	—
Yano[66]	2017	2012-2013	26(28)	PDT	6/22/0	14/6/6/0	—	89.3	lymphopenia (grade3) 2 (7.7%)	91.4	—	—	—
Hatogai[59]	2016	1998-2008	38	PDT	0/38/0	12/6/16/4	—	65.8	in-hospital death 1 (2.6%)	—	—	—	41.6
Hatogai[67]	2016	2002-2009	113	PDT	63/50/0	18/18/60/17	—	58.4	in-hospital death 1 (1.8%) fistula 5 (4.4%)	—	—	—	35.9

Abbreviations: APC, argon plasma coagulation; CR, complete response; dCRT, definitive CRT; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal resection; OS, overall survival; PDT, photodynamic therapy; —, data not described.

[a]dCRT interval.

[b]Three cases unknown

[c]Total of residual and recurrent lesions.

[d]Defined by NCI-CTCAE; National Cancer Institute-Common Toxicity Criteria of Adverse Events ver. 4.0.

TABLE 4 Summary of studies on re-CRT or re-RT after dCRT

First Author	year	Study interval	N	cT before dCRT cT1/2/3/4	Re-CRT/ re-RT	Re-Radiation Dose (Gy)	Complication Fistula/ perforation (%)	Mortality (%)	OS (%) 1-year	2-year	3-year	5-year	MST
Xu[73]	2019	2012-2014	47	–	13/34	58(26-64)	8.5	2.1	72.3	25.5	17	2.1	17
Hong[71]	2018	2000-2014	39	–	19/20	60(24.4-84.9)	–	–	–	–	–	–	10
Katano[69]	2017	2011-2016	6	1/1/1/2[b],	5/1	30-50.4	0	0	–	–	–	–	13.6
Jingu[74]	2017	2000-2015	33	–	29/4	60(18-70)	0	3.9	–	–	17.8	0	16.0
Zhou[72]	2015	2003-2012	55	–	0/55	54(18-66)	20.0	–	83.6	41.8	21.8	–	20
Chen[44]	2014	1996-2005[a]	36	–	36/0	50.4	19.4	2.8	51.7	21.4	12.2	3.1	–
Kim[75]	2012	2007-2011	10	1/3/4/2	3/7	44-50.4	30.0	30.0	–	–	–	0	5.8

Abbreviations: CRT, chemoradiotherapy; MST, mean survival time; OS, overall survival; RT, radiotherapy; –, data not described.

[a]Interval of dCRT.

[b]One case unknown.

DISCLOSURE

Conflict of Interest: The authors have no conflicts of interest regarding this article to declare.

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REFERENCES

1. Kitagawa Y, Uno T, Oyama T, Kato K, kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. Esophagus. 2019;16(1):1–24.
2. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus. 2019;16(1):25–43.
3. Nomura M, Kato K, Ando N, Ohtsu A, Muro K, Igaki H, et al. Comparison between neoadjuvant chemotherapy followed by surgery and definitive chemoradiotherapy for overall survival in patients with clinical Stage II/III esophageal squamous cell carcinoma (JCOG1406-A). Jpn J Clin Oncol. 2017;47(6):480–6.
4. Kato H, Sato A, Fukuda H, Kagami Y, Udagawa H, Togo A, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol. 2009;39(10):638–43.
5. Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys. 2011;81(3):684–90.
6. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol. 1999;17(9):2915–21.
7. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol. 2004;34(10):615–9.
8. Ito Y, Takeuchi H, Ogawa G, Kato K, Onozawa M, Minashi K, et al. A single-arm confirmatory study of definitive chemoradiotherapy (dCRT) including salvage treatment in patients (pts) with clinical (c) stage II/III esophageal carcinoma (EC) (JCOG0909). J Clin Oncol. 2018;36(15_suppl):4051.
9. Sudo K, Kato K, Kuwabara H, Sasaki Y, Takahashi N, Shoji H, et al. Patterns of relapse after definitive chemoradiotherapy in stage II/III (Non-T4) esophageal squamous cell carcinoma. Oncology. 2018;94(1):47–54.
10. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part I. Esophagus. 2017;14(1):1–36.
11. Faiz Z, Dijksterhuis WPM, Burgerhof JGM, Muijs CT, Mul VEM, Wijnhoven BPL, et al. A meta-analysis on salvage surgery as a potentially curative procedure in patients with isolated local recurrent or persistent esophageal cancer after chemoradiotherapy. Eur J Surg Oncol. 2019;45(6):931–40.
12. Watanabe M, Otake R, Kozuki R, Toihata T, Takahashi K, Okamura A, et al. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Surg Today. 2020;50(1):12–20.
13. Saeki H, Sohda M, Sakai M, Sano A, Shirabe K. Role of surgery in multidisciplinary treatment strategies for locally advanced esophageal squamous cell carcinoma. Ann Gastroenterol Surg. 2020;4(5):490–7.
14. Sohda M, Kuwano H. Current status and future prospects for esophageal cancer treatment. Ann Thorac Cardiovasc Surg. 2017;23(1):1–11.
15. Markar SR, Karthikesalingam A, Penna M, Low DE. Assessment of short-term clinical outcomes following salvage esophagectomy for

the treatment of esophageal malignancy: systematic review and pooled analysis. Ann Surg Oncol. 2014;21(3):922–31.
16. Khangura SK, Greenwald BD. Endoscopic management of esophageal cancer after definitive chemoradiotherapy. Dig Dis Sci. 2013;58(6):1477–85.
17. Gardner-Thorpe J, Hardwick RH, Dwerryhouse SJ. Salvage oesophagectomy after local failure of definitive chemoradiotherapy. Br J Surg. 2007;94(9):1059–66.
18. Mitchell KG, Nelson DB, Corsini EM, Vaporciyan AA, Antonoff MB, Mehran RJ, et al. Morbidity following salvage esophagectomy for squamous cell carcinoma: the MD Anderson experience. Dis Esophagus. 2020;33(3).1–8.
19. Harada H, Yamashita K, Katada C, Ishiyama H, Soeno T, Washio M, et al. Patient selection for salvage surgery after definitive chemoradiotherapy in esophageal squamous cell carcinoma. Langenbecks Arch Surg. 2020;405(6):767–76.
20. Ohkura Y, Ueno M, Iizuka T, Udagawa H. Prognostic factors and appropriate lymph node dissection in salvage esophagectomy for locally advanced T4 esophageal cancer. Ann Surg Oncol. 2019;26(1):209–16.
21. Takeuchi M, Kawakubo H, Mayanagi S, Yoshida K, Fukuda K, Nakamura R, et al. Postoperative pneumonia is associated with long-term oncologic outcomes of definitive chemoradiotherapy followed by salvage esophagectomy for esophageal cancer. J Gastrointest Surg. 2018;22(11):1881–9.
22. Taniyama Y, Sakurai T, Heishi T, Okamoto H, Sato C, Maruyama S, et al. Different strategy of salvage esophagectomy between residual and recurrent esophageal cancer after definitive chemoradiotherapy. J Thorac Dis. 2018;10(3):1554–62.
23. Kiyozumi Y, Yoshida N, Ishimoto T, Yagi T, Koga Y, Uchihara T, et al. Prognostic factors of salvage esophagectomy for residual or recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy. World J Surg. 2018;42(9):2887–93.
24. Nakajima M, Kato H, Muroi H, Kikuchi M, Takahashi M, Yamaguchi S, et al. Minimally invasive salvage operations for esophageal cancer after definitive chemoradiotherapy. Digestion. 2018;97(1):64–9.
25. Hayami M, Watanabe M, Ishizuka N, Mine S, Imamura Y, Okamura A, et al. Prognostic impact of postoperative pulmonary complications following salvage esophagectomy after definitive chemoradiotherapy. J Surg Oncol. 2018;117(6):1251–9.
26. Watanabe M, Mine S, Nishida K, Yamada K, Shigaki H, Matsumoto A, et al. Salvage esophagectomy after definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma: who really benefits from this high-risk surgery? Ann Surg Oncol. 2015;22(13):4438–44.
27. Morita M, Kumashiro R, Hisamatsu Y, Nakanishi R, Egashira A, Saeki H, et al. Clinical significance of salvage esophagectomy for remnant or recurrent cancer following definitive chemoradiotherapy. J Gastroenterol. 2011;46(11):1284–91.
28. Tachimori Y, Kanamori N, Uemura N, Hokamura N, Igaki K, Kato H. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2009;137(1):49–54.
29. Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Nishida T, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. J Surg Oncol. 2009;100(6):442–6.
30. Yoshida N, Yamamoto H, Baba H, Miyata H, Watanabe M, Toh Y, et al. Can minimally invasive esophagectomy replace open esophagectomy for esophageal cancer? Latest analysis of 24,233 esophagectomies from the Japanese National Clinical Database. Ann Surg. 2020;272(1):118–24.
31. Okumura T, Seto Y, Aikou S, Moriyama M, Sekine S, Hashimoto I, et al. Mediastinoscopic salvage esophagectomy for recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy in a previously pneumonectomized patient. Asian J Endosc Surg. 2019;12(4):452–6.
32. Seto Y. Essential updates 2018/2019: essential updates for esophageal cancer surgery. Ann Gastroenterol Surg. 2020;4(3):190–4.
33. Sugawara K, Yagi K, Okumura Y, Nishida M, Aikou S, Yamashita H, et al. Long-term outcomes of multimodal therapy combining definitive chemoradiotherapy and salvage surgery for T4 esophageal squamous cell carcinoma. Int J Clin Oncol. 2020;25(4):552–60.
34. Sugimura K, Miyata H, Shinno N, Ushigome H, Asukai K, Hara H, et al. Prognostic impact of postoperative complications following salvage esophagectomy for esophageal cancer after definitive chemoradiotherapy. Oncology. 2020;98(5):280–8.
35. Takeuchi H, Saikawa Y, Oyama T, Ozawa S, Suda K, Wada N, et al. Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. World J Surg. 2010;34(2):277–84.
36. Booka E, Haneda R, Ishii K, Kawakami T, Tsushima T, Yasui H, et al. Appropriate candidates for salvage esophagectomy of initially unresectable locally advanced T4 esophageal squamous cell carcinoma. Ann Surg Oncol. 2020;27(9):3163–70.
37. Okamura A, Hayami M, Kozuki R, Takahashi K, Toihata T, Imamura Y, et al. Salvage esophagectomy for initially unresectable locally advanced T4 esophageal squamous cell carcinoma. Esophagus. 2020;17(1):59–66.
38. Sugawara K, Mori K, Yagi K, Aikou S, Uemura Y, Yamashita H, et al. Association of preoperative inflammation-based prognostic score with survival in patients undergoing salvage esophagectomy. Dis Esophagus. 2019;32(4).1–7.
39. Lertbutsayanukul C, Tharavej C, Klaikeaw N, Prayongrat A, Lowanitchai C, Sriuranpong V. High dose radiation with chemotherapy followed by salvage esophagectomy among patients with locally advanced esophageal squamous cell carcinoma. Thorac Cancer. 2017;8(3):219–28.
40. Farinella E, Safar A, Nasser HA, Bouazza F, Liberale G, Paesmans M, et al. Salvage esophagectomy after failure of definitive radiochemotherapy for esophageal cancer. J Surg Oncol. 2016;114(7):833–7.
41. Matono S, Fujita H, Tanaka T, Mori N, Nagano T, Nishimura K, et al. Salvage lymphadenectomy without esophagectomy is an option for recurrent or residual lymph nodes after definitive chemoradiotherapy for esophageal cancer. Esophagus. 2014;11(3):197–203.
42. Makino T, Yamasaki M, Tanaka K, Miyazaki Y, Takahashi T, Kurokawa Y, et al. Treatment and clinical outcome of clinical T4 esophageal cancer: a systematic review. Ann Gastroenterol Surg. 2019;3(2):169–80.
43. Terada M, Hara H, Daiko H, Mizusawa J, Kadota T, Hori K, et al. Phase III study of tri-modality combination therapy with induction docetaxel plus cisplatin and 5-fluorouracil versus definitive chemoradiotherapy for locally advanced unresectable squamous-cell carcinoma of the thoracic esophagus (JCOG1510: TRIANgLE). Jpn J Clin Oncol. 2019;49(11):1055–60.
44. Chen Y, Lu Y, Wang Y, Yang H, Xia Y, Chen M, et al. Comparison of salvage chemoradiation versus salvage surgery for recurrent esophageal squamous cell carcinoma after definitive radiochemotherapy or radiotherapy alone. Dis Esophagus. 2014;27(2):134–40.
45. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
46. Wang S, Tachimori Y, Hokamura N, Igaki H, Nakazato H, Kishino T. Prognostic analysis of salvage esophagectomy after definitive chemoradiotherapy for esophageal squamous cell carcinoma: the importance of lymphadenectomy. J Thorac Cardiovasc Surg. 2014;147(6):1805–11.
47. Swisher SG, Marks J, Rice D. Salvage esophagectomy for persistent or recurrent disease after definitive chemoradiation. Ann Cardiothorac Surg. 2017;6(2):144–51.

48. Morita M, Nakanoko T, Kubo N, Fujinaka Y, Ikeda K, Egashira A, et al. Two-stage operation for high-risk patients with thoracic esophageal cancer: an old operation revisited. Ann Surg Oncol. 2011;18(9):2613–21.
49. https://www.esophagus.jp/private/research_task/
50. Watanabe M, Mine S, Yamada K, Shigaki H, Baba Y, Yoshida N, et al. Outcomes of lymphadenectomy for lymph node recurrence after esophagectomy or definitive chemoradiotherapy for squamous cell carcinoma of the esophagus. Gen Thorac Cardiovasc Surg. 2014;62(11):685–92.
51. Kato F, Monma S, Koyanagi K, Kanamori J, Daiko H, Igaki H, et al. Long-term outcome after resection for recurrent oesophageal cancer. J Thorac Dis. 2018;10(5):2691–9.
52. Yuan X, Lv J, Dong H, Wang J. Does cervical lymph node recurrence after oesophagectomy or definitive chemoradiotherapy for thoracic oesophageal squamous cell carcinoma benefit from salvage treatment? Interact Cardiovasc Thorac Surg. 2017;24(5):792–5.
53. Kanamori J, Aokage K, Hishida T, Yoshida J, Tsuboi M, Fujita T, et al. The role of pulmonary resection in tumors metastatic from esophageal carcinoma. Jpn J Clin Oncol. 2017;47(1):25–31.
54. Hombu T, Yano T, Hatogai K, Kojima T, Kadota T, Onozawa M, et al. Salvage endoscopic resection (ER) after chemoradiotherapy for esophageal squamous cell carcinoma: what are the risk factors for recurrence after salvage ER? Dig Endosc. 2018;30(3):338–46.
55. Takeuchi M, Kobayashi M, Hashimoto S, Mizuno K, Kawaguchi G, Sasamoto R, et al. Salvage endoscopic submucosal dissection in patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma. Scand J Gastroenterol. 2013;48(9):1095–101.
56. Ego M, Abe S, Nakatani Y, Nonaka S, Suzuki H, Yoshinaga S, et al. Long-term outcomes of patients with recurrent squamous cell carcinoma of the esophagus undergoing salvage endoscopic resection after definitive chemoradiotherapy. Surg Endosc. 2020. May 13. https://doi.org/10.1007/s00464-020-07632-2. Online ahead of print.
57. Kondo S, Tajika M, Tanaka T, Kodaira T, Mizuno N, Hara K, et al. Prognostic factors for salvage endoscopic resection for esophageal squamous cell carcinoma after chemoradiotherapy or radiotherapy alone. Endosc Int Open. 2016;4(8):E841–8.
58. Nakajo K, Yoda Y, Hori K, Takashima K, Sinmura K, Oono Y, et al. Technical feasibility of endoscopic submucosal dissection for local failure after chemoradiotherapy or radiotherapy for esophageal squamous cell carcinoma. Gastrointest Endosc. 2018;88(4):637–46.
59. Hatogai K, Yano T, Kojima T, Onozawa M, Fujii S, Daiko H, et al. Local efficacy and survival outcome of salvage endoscopic therapy for local recurrent lesions after definitive chemoradiotherapy for esophageal cancer. Radiat Oncol. 2016;11:31.
60. Kagawa T, Ishikawa S, Inaba T, Colvin M, Toyosawa J, Aoyama Y, et al. Clinicopathological examination of ESD as salvage therapy for esophageal cancer after definitive chemo-radiation therapy. Endosc Int Open. 2018;6(4):E450–61.
61. Koizumi S, Jin M, Matsuhashi T, Tawaraya S, Watanabe N, Sawaguchi M, et al. Salvage endoscopic submucosal dissection for the esophagus-localized recurrence of esophageal squamous cell cancer after definitive chemoradiotherapy. Gastrointest Endosc. 2014;79(2):348–53.
62. Makazu M, Kato K, Takisawa H, Yoshinaga S, Oda I, Saito Y, et al. Feasibility of endoscopic mucosal resection as salvage treatment for patients with local failure after definitive chemoradiotherapy for stage IB, II, and III esophageal squamous cell cancer. Dis Esophagus. 2014;27(1):42–9.
63. Nagai Y, Yoshida N, Baba H. Salvage treatment for superficial local failure after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Dig Endosc. 2020;32(1):146.
64. Nakamura R, Omori T, Takeuchi H, Kawakubo H, Takahashi T, Wada N, et al. Salvage endoscopic resection as a treatment for locoregional failure or recurrence following chemoradiotherapy or radiotherapy for esophageal cancer. Oncol Lett. 2016;11(6):3631–6.
65. Yamamoto Y, Kadota T, Yoda Y, Hori K, Hatogai K, Kojima T, et al. Review of early endoscopic findings in patients with local recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Esophagus. 2020;17(4):433–9.
66. Yano T, Kasai H, Horimatsu T, Yoshimura K, Teramukai S, Morita S, et al. A multicenter phase II study of salvage photodynamic therapy using talaporfin sodium (ME2906) and a diode laser (PNL6405EPG) for local failure after chemoradiotherapy or radiotherapy for esophageal cancer. Oncotarget. 2017;8(13):22135–44.
67. Hatogai K, Yano T, Kojima T, Onozawa M, Daiko H, Nomura S, et al. Salvage photodynamic therapy for local failure after chemoradiotherapy for esophageal squamous cell carcinoma. Gastrointest Endosc. 2016;83(6):1130–1139.e3.
68. Ishida N, Osawa S, Miyazu T, Kaneko M, Tamura S, Tani S, et al. Photodynamic therapy using talaporfin sodium for local failure after chemoradiotherapy or radiotherapy for esophageal cancer: a single center experience. J Clin Med. 2020;9(5):1509.
69. Katano A, Yamashita H, Nakagawa K. Re-irradiation of locoregional esophageal cancer recurrence following definitive chemoradiotherapy: a report of 6 cases. Mol Clin Oncol. 2017;7(4):681–6.
70. Kumagai K, Mariosa D, Tsai JA, Nilsson M, Ye W, Lundell L, et al. Systematic review and meta-analysis on the significance of salvage esophagectomy for persistent or recurrent esophageal squamous cell carcinoma after definitive chemoradiotherapy. Dis Esophagus. 2016;29(7):734–9.
71. Hong L, Huang YX, Zhuang QY, Zhang XQ, Tang LR, Du KX, et al. Survival benefit of re-irradiation in esophageal Cancer patients with Locoregional recurrence: a propensity score-matched analysis. Radiat Oncol. 2018;13(1):171.
72. Zhou ZG, Zhen CJ, Bai WW, Zhang P, Qiao XY, Liang JL, et al. Salvage radiotherapy in patients with local recurrent esophageal cancer after radical radiochemotherapy. Radiat Oncol. 2015;10:54.
73. Xu X, Wang Z, Jiang S, Shang Y, Wu Y. Evaluating the optimal re-irradiation dose for locally recurrent esophageal squamous cell carcinoma after definitive radiotherapy. Radiat Oncol. 2019;14(1):191.
74. Jingu K, Niibe Y, Yamashita H, Katsui K, Matsumoto T, Nishina T, et al. Re-irradiation for oligo-recurrence from esophageal cancer with radiotherapy history: a multi-institutional study. Radiat Oncol. 2017;12(1):146.
75. Kim YS, Lee CG, Kim KH, Kim T, Lee J, Cho Y, et al. Re-irradiation of recurrent esophageal cancer after primary definitive radiotherapy. Radiat Oncol J. 2012;30(4):182–8.

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