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A meta-analysis on salvage surgery as a potentially curative procedure in patients with isolated local recurrent or persistent esophageal cancer after chemoradiotherapy

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ABSTRACT

Background: Isolated local recurrent or persistent esophageal cancer (EC) after curative intended definitive (dCRT) or neoadjuvant chemoradiotherapy (nCRT) with initially omitted surgery, is a potential indication for salvage surgery. We aimed to evaluate safety and efficacy of salvage surgery in these patients.

Material and methods: A systematic literature search following PRISMA guidelines was performed using databases of PubMed/Medline. All included studies were performed in patients with persistent or recurrent EC after initial treatment with dCRT or nCRT, between 2007 and 2017. Survival analysis was performed with an inverse-variance weighting method.

Results: Of the 278 identified studies, 28 were eligible, including a total of 1076 patients. Postoperative complications after salvage esophagectomy were significantly more common among patients with isolated persistent than in those with locoregional recurrent EC, including respiratory (36.6% versus 22.7%; difference in proportion 10.9 with 95% confidence interval (CI) [3.1; 18.7]) and cardiovascular complications (10.4% versus 4.5%; difference in proportion 5.9 with 95% CI [1.5; 10.2]). The pooled estimated 30- and 90-day mortality was 2.6% [1.6; 3.6] and 8.0% [6.3; 9.8], respectively. The pooled estimated 3-year and 5-year overall survival (OS) were 39.0% (95% CI: [35.8; 42.2]) and 19.4% [95% CI:16.5; 22.4], respectively. Patients with isolated persistent or recurrent EC after initial CRT had similar 5-year OS (14.0% versus 19.7%, difference in proportion −5.7, 95% CI [-13.7; 2.3]).

Conclusions: Salvage surgery is a potentially curative procedure in patients with locally recurrent or persistent esophageal cancer and can be performed safely after definitive or neoadjuvant chemoradiotherapy when surgery was initially omitted.

Introduction

Only half of the patients with esophageal cancer (EC) present with potentially curable disease [1]. At present, neo-adjuvant chemoradiotherapy (nCRT) followed by esophagectomy is standard care in patients with curative resectable locally advanced EC. Generally, nCRT induces downsizing and downstaging of the primary tumor and may sterilize involved lymph nodes. This improves locoregional control, while decreasing the risk of distant metastasis [2–4]. As established in the CROSS (Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study) regimen, nCRT also increases the 5-year survival with 13% compared to surgery alone [2]. This was accompanied by a high rate of microscopic radical (R0)

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resection (92%) with an overall pathologic complete response (pCR) rate of 29%. Absence of vital cancer cells at pathological examination more often occurred in esophageal squamous cell carcinoma (49%) than in adenocarcinoma (23%) [3,5–9]. Given the risk of perioperative morbidity and mortality, it is questionable whether esophagectomy is needed in all patients after nCRT, while it remains difficult to appropriate select patients who may not need the additional surgery [3]. On the other hand, when patient's current physical health is sufficient salvage surgery may even be performed in local recurrent EC after nCRT, if the presumed surgery has been deferred or omitted [3,5–9].

Moreover, definitive chemoradiotherapy (dCRT) is generally a good alternative curative treatment in patients above the age of 75 years with severe co-morbidities or those who are unfit for surgery [10,11]. Local failure after dCRT can present as local recurrent of persistent disease, which occurs in nearly 50% of the patients [5–8,12]. Salvage surgery as an attempt to cure these patients that could be offered to a subgroup of patients when non-surgical treatment has failed [2]. The variation in the rate of salvage surgery with curative intent after dCRT (4%–29%) and the reported 5-year overall survival (OS) of 0–33% stress the need for a better selection [8,9,13,14]. Moreover, the downside of salvage surgery after dCRT is the rather high rate of perioperative complications including anastomotic leakage, pneumonia with respiratory insufficiency and sepsis. This may impact on hospital stay, prolonged intensive care treatment, perioperative mortality and health-related quality of life [10].

The aim of this systematic review is to determine whether salvage surgery can be safely performed in patients with localized solitary recurrent or persistent disease after dCRT or nCRT not followed by initially planned surgery and to evaluate the efficacy of this approach.

Methods

Search strategy and study selection

A systematic literature search was performed using databases of PubMed/Medline (https://www.ncbi.nlm.nih.gov/pubmed) to retrieve all relevant studies with the following keywords 'esophageal cancer' and additive with the medical subject headings (MesH) database terms 'esophageal neoplasms', 'salvage surgery', 'salvage esophagectomy' and 'rescue esophagectomy'. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. Reference lists and reviews were additionally screened for relevant papers. Relevant published studies were selected based on the best available evidence in the period January 2007–July 2017. The starting year 2007 was chosen because in that period dCRT was a standardized treatment option and positron emission/computed tomographic (PET/CT) imaging was introduced as a standard diagnostic modality. All included studies were peer-reviewed and published in the last ten years. Duplicate publications or articles for which the full text was not available in English, or studies without PET/CT in the routine staging were excluded. Two reviewers independently assessed the methodological quality of each study by reviewing the full text. Disagreement between was resolved by discussing the paper and if necessary in consensus with the senior researcher.

Eligibility criteria and definitions

Studies were eligible if the reported analyses also included treatment-related mortality, complications, and survival after salvage surgery for regrowth persistent or recurrent localized EC after CRT. For this review, the common definitions were used. Salvage esophagectomy, designated as salvage surgery in this study, was defined as esophagectomy with curative intent for resectable locoregional recurrent or persistent tumor in a previously irradiated area. Generally, salvage esophagectomy is possible when an isolated local regrowth is clinically suspected after dCRT or nCRT without subsequent planned surgery. Persistent EC was defined as a still curable localized tumor $\leq$3 months after completion of CRT, that was still present either on endoscopic or radiologic examination (CT or PET/CT), and preferably confirmed cyto/histologically. Recurrent EC was defined as a regrowth at the primary site and/or regional area >3 months after completion of CRT with initial clinical complete response (cCR) [15,16]. Radicality of resections was designated as R0, when both longitudinal and lateral resection margins were microscopically tumor free or as R1 when incomplete (<1 mm), and as R2 in case of macroscopic residual tumor.

Data collection processes and definition, clinical end–point and study selection

Titles and abstracts were screened, and data, including first author, year of publication, sample size, patient and tumor characteristics (age, sex, co-morbidity, physical status, stage of tumor, staging modality, histology (esophageal squamous cell carcinoma: ESCC or esophageal adenocarcinoma: EAC), prior initial treatment dCRT or nCRT, and survival (overall and disease-free) were extracted from relevant studies using a predefined form. Primary outcomes were treatment-related morbidities and mortality (safety), defined as death caused by peri-operative complications associated with salvage surgery and postoperative mortality was defined as 30-day or 90-day mortality after salvage surgery. Pulmonary complications were pneumonia, atelectasis, or hypoxia that required re-intubation. Cardiovascular complications included myocardial infarction, dysrhythmias, cardiac failure, and stroke. Secondary outcomes were overall survival (OS) defined as the time from the date of salvage surgery until date of death from any cause, or end of follow-up. As only 2 studies described disease-free survival (DFS) we decided to evaluate OS alone. The quality of the individual studies was assessed using the Newcastle-Ottawa Scale (NOS) score for risk of bias developed as an assessment tool for non-randomized studies in meta-analyses or systematic reviews (http://www.ohri.ca/programs/clinical epidemiology/oxford. asp), which has been validated in other systematic reviews. The NOS score for cohort studies contains eight items that focus on the following three aspects depending on study type: selection, comparability, and outcome. The risk of bias assessment, including low, medium and high risk was performed by two independent reviewers.

Follow-up

In most studies ($N = 24$), the minimal follow-up consisted of CT thorax/abdomen, every 3 months during the first year and every 6 months thereafter, to detect tumor re-growth. The more recently reported follow-up studies also added periodic PET or PET-CT to rule out metastatic disease. Based on the detected suspicious lesions further examination i.e EUS/cytological and/or histological examination was performed.

Statistical analysis

Continuous variables were expressed as mean or median and range. Categorical variables were expressed as number and percentage. We assessed estimates and standard errors of overall survival (OS) using the fixed-effects inverse variance-weighting

(IVW) approach, and of mortality and complications using proportions and standard errors. The fixed effects model assumes that the included studies share a single true effect size, whereas IVW summarizes effect sizes from multiple independent studies by calculating the weighted mean of the effect sizes using the inverse variance of individual studies, as weights. The 95%-confidence intervals for the differences between the group proportions were calculated. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.).

Results

Study population

In this systematic review 28 of the 278 identified studies, including 1076 patients were eligible for further analyses (Fig. 1). Twenty-five studies included only patients treated with dCRT and 2 studies reported on patients after nCRT who underwent delayed surgery. In one study, salvage esophagectomy was performed in patients after both dCRT ($N = 10$; mean 54.7 Gy) and nCRT ($N = 2$; mean 42.7 Gy) [17]. These twelve patients were only included in the whole group analyses (Fig. 1 and Table 1).

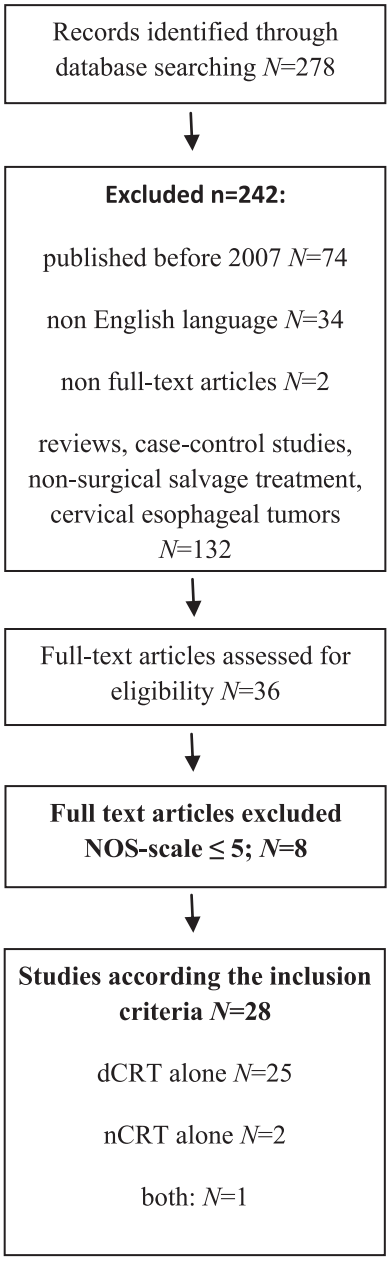

Fig. 1. Flowchart of studies assessed during the selection process.
dCRT = definitive chemoradiotherapy; nCRT = neoadjuvant chemoradiotherapy.

The majority of patients were males (88.1%) and the mean age was 62.4 (range 50.9–73.9) years in the dCRT and 62.5 (range 49.5–75.5) years in the nCRT group (Table 1). Most patients had an ESCC (76.7%) and had stage III disease (52.5%). The indication for surgery, i.e. persistent or recurrent disease, was unknown in 73.6%. Persistent or recurrent disease was reported in 17.5% and 8.9%, respectively. A radical (R0) resection was achieved in 80.7% of the patients, which was higher after dCRT compared to nCRT (Table 1).

Surgery after dCRT and nCRT

Salvage resections were more frequently reported after dCRT, including 3 studies with isolated locoregional recurrent (LR) EC, 4 studies with persistent and 18 studies with recurrent or persistent EC (Table 2a). In the dCRT-setting, chemotherapy consisted of 5-fluorouracil (5-FU) plus cisplatin and/or taxane ($N = 21$) or was not reported ($N = 4$). The median radiotherapy dose was 57.0 (range 30–62.5) Gy. Only two studies reported delayed surgery after >6 months in patients after nCRT for regrowth during a wait and see approach after refusing the initially planned surgical procedure (Table 2b). Taketa et al. showed the outcome of salvage resection in patients with LR disease after declining primary surgery because of cCR, whereas Piessen et al. reported the results of persistent EC in non-complete responders after initially nCRT. The median time to salvage resection were 9.3 and 14.3 months, respectively (Table 2b) [17–20].

Morbidity and mortality

Pulmonary complications were seen in 29.3% of patients, anastomotic leak in 17.2%, and cardiovascular complications in 6.7% of the patients (Table 3). In patients treated with salvage surgery after dCRT, pulmonary disorders, anastomotic leaks, infections and cardiovascular complications occurred in 30.2%, 18.6%, 12.5% and 7.6%, respectively (Table 4).

The overall 30- and 90-day mortality were 2.6% and 8.0%, respectively. The estimated 30-day mortality was similar for patients with both type of regrowth (1.7%) and comparable in both the primary dCRT and nCRT groups (Tables 3 and 4). The estimated 90-day mortality was slightly lower after nCRT versus dCRT (3.1% versus 8.8%) and after recurrent disease (3.7% versus 7.3%) versus persistent tumor.

Efficacy: overall survival

The pooled 3- and 5-year OS were 39.0% and 19.4%, respectively. Patients with R0 resection had a higher 3- and 5-year OS of 48.8% and 25.6%, respectively. The 3-and 5-year OS were not statistically significant different following salvage surgery for persistent and recurrent EC (Table 3). Patients treated with salvage surgery after dCRT had a pooled 3-year OS of 38.7% and a pooled 5-year OS of 24.1%. After nCRT, which was performed only in two studies, the 5-year OS among patients with recurrent EC was 75% (Table 4).

Discussion

This systematic review shows that salvage surgery is feasible and potentially curative in a selective group of EC patients with

Table 1
Clinicopathological characteristics of patients.

Characteristics	Total $N = 1076$[b] N (%)	dCRT $N = 954$ N (%)	nCRT $N = 110$ N (%)
Sex			
Male	907 (88.1)	785 (86.5)	110 (100)
Female	122 (11.9)	122 (13.5)	
Unknown	47	47	0 (0)
Mean age/range (years)[a]	62.4 (49.4–75.4)	62.4 (50.9–73.9)	62.5 (49.5–75.5)
Histology			
Adenocarcinoma	232 (23.3)	214 (24.5)	18 (16.4)
Squamous cell carcinoma	762 (76.7)	658 (75.5)	92 (83.6)
Unknown	82	82	0
Stage (clinical or pathological[&])			
I	62 (7.2)	62 (7.2)	–
IIA	244 (28.2)	243 (28.5)	–
IIB	39 (4.5)	37 (4.3)	–
III	454 (52.5)	447 (52.4)	–
IVA	66 (7.6)	64 (7.5)	–
Unknown	211	101	110
M1a	11 (1.0)	11 (1.2)	0 (0.0)
Salvage indication			
Persistent cancer	188 (17.5)	90 (9.4)	98 (89.1)
Recurrent cancer	96 (8.9)	84 (8.8)	12 (10.9)
Persistent or recurrent cancer[c]	792 (73.6)	780 (81.8)	–
R0 after salvage surgery[d]	806 (80.7)	725 (87.7)	73 (66.4)

[a] Age was not reported in 339 patients in the dCRT group.
[b] Including the group of Yoo et al. [17] with patients after nCRT ($N = 2$) and dCRT ($N = 10$).
[c] The patients in whom it is unclear whether it was persistent or recurrent cancer.
[d] Radicality of the operation not reported in 77 patients in the dCRT group & Tachimori et al. [55] and Smithers et al. [56].

locoregional regrowth (residual or recurrent) after initial treatment with dCRT or nCRT not followed by surgery. The novelty of this review is that we reported the commonly presented complications i.e. respiratory and cardiovascular complications with the impact among EC patients after salvage esophagectomy in both isolated recurrent and persistent disease after dCRT and nCRT when surgery was initially omitted for >3 months.

As shown in Tables 3 and 4, salvage esophagectomy following dCRT is also associated with a high rate of anastomotic leak (17.2%–18.6%). This relatively high rate of anastomotic leak may be related to the common high doses of radiotherapy (50.4–60Gy) and a subsequently reduced microcirculation and conduit perfusion with even areas of patchy necrosis, especially after unintended surgical micro-injuries [15]. Although correlated with a high incidence of postoperative morbidity, salvage surgery can be performed with acceptable risks in selected patients with isolated locoregional failure. In a subset of these patients, the outcome seems even comparable to the results of patients who underwent planned surgery as reported in some studies (Table 5a/b) [3,5,21–23]. Moreover, salvage surgery with curative intent may offer a significant survival benefit with a 5-year OS rate of 35% and 5-year DFS rate of 21% [5–8,24]. After initial curative treatment, approximately 50–75% of the EC patients develop recurrent disease usually within the first two to three years [6,12,25]. Nearly 19–25% are isolated locoregional recurrences (LR's) which are more often seen after dCRT [26–28].

Although salvage resection is a potential option, the surgical management of LR's or persistent remnants after dCRT remains controversial for several reasons. Most salvage procedures are performed in SCC (76.7%) compared to 23.3% with EAC (Table 1). The study of Marks et al. [16] is the only one that described salvage surgery after failed dCRT in patients with EAC into more detail. The incidence of major event (35%), including major pulmonary complications (23.1%) and anastomotic leak (18.5%), 30-day mortality (3.1%) and 3-year overall survival (48%) were comparable with patients after planned resection. The results were more or less comparable with those after dCRT in all patients in this review (Tables 3 and 4) suggesting that salvage esophagectomy also should be considered in recurrent EAC after CRT. Another issue is the timing of salvage esophagectomy, which generally depends upon the time of diagnosis of regrowth isolated recurrences or persistent disease. This stresses the importance of follow-up schedules. Moreover, timing of surgery is directly associated with patients condition and severe co-morbidities. Exact timing is therefore difficult to give. Of great importance is whether the resection will be radical (R0) as shown on preoperative PET-CT and preferably combined with magnetic resonance imaging (MRI) and EUS [15,16,29–34]. As in this review, Sudo et al. stressed the importance of R0 resection in salvage surgery with a median OS of 58.6 months compared to 9.5 months when surgery was refused. Besides, the achievement of complete R0 resection after salvage surgery, the presence of early ($cT \leq 2/N0$) recurrent EC is the most favorable prognostic factor in patients with isolated regrowth after dCRT [9,35]. Also in clinical non-responders with still surgically curable residual disease, Stahl et al. found a 3-year survival rate of 32% in those with a R0 resection vs. 9.4% after the initial dCRT [11]. Recently, Swisher et al. described even more encouraging long-term survival rates in clinical non-responders, with a 5- and 7-year survival of 41% and 35%, respectively [32].

These results stress the importance of better locoregional control through improved chemoradiation strategies in dCRT (combined cisplatin/5-FU or paclitaxel/carboplatin) and adequate staging with sophisticated imaging methods to ensure complete salvage resection with an increased probability of R0 resection [32,36]. Moreover, to select candidates for surgery with curative intent, a standard surveillance protocol should be used during the first 2–3 years after initial dCRT in localized tumors [2,9,28,35].

Currently there are no widely accepted follow-up protocols for early detection of LR's, which might result in a better outcome after salvage resection. A recently proposed follow-up scheme by the RTOG 0246 consists of serial endoscopies with ultrasound (EUS), CT scans or PET-CTs every 3 months twice and every 6 months three times for the first 2 years, and yearly thereafter. The results should be discussed in a specialized multidisciplinary team and could eventually result in salvage surgery in patients with isolated recurrent or persistent cancer [23].

Table 2
a: Characteristics of the studies on salvage surgery after dCRT.

Study	Chemotherapy regime	$N = 954$	Mean age	Male (%)	Histology SCC/AC (*N*)	R0 (%)	Indication for salvage surgery	Median dose RT (Gy) Radiation techniques	Median time from CRT to surgery (months)
Lertbutsayanukul [13]	5-FU + cisplatin/carboplatin	44	60	81.8	44/0	70.4	Persistent	60; IMRT VMAT 3DRT	4
Farinella [61]	5-FU + cisplatin	16	61	62.5	14/2	81.3	Persistent or recurrent	57.7	8.4
Swisher [23]	5-FU + cisplatin + paclitaxel	21	–	–	–	–	Persistent or recurrent	50.4	–
Okumura [62]	–	10	–	–	–	–	Persistent or recurrent	50	–
Markar [15]	–	308	–	84.1	193/109	87.3	Persistent or recurrent	50	5.5
Watanabe [9]	5-FU + cisplatin	63	63	92.1	63/0	73.0	Persistent or recurrent	60	–
Chen [37]	5-FU + cisplatin	51	58	84.3	51/0	80.4	Recurrent	54 IMRT	8.0
Sudo [28]	5-FU + cisplatin/taxane	23	67	91.3	5/18	91.3	Recurrent	50.4; IMRT or proton beam	21
Akutsu [63]	5-FU + cisplatin	12	62	100	12/0	–	Persistent	53.2	–
Aquino [64]	–	18	67.5	88.9	18/0	–	Persistent	–	7.5
Adenis [65]	5-FU + cisplatin	16	60	–	–/–	–	Persistent	50.4; Multiple field technique	–
Saeki [66]	5-FU + cisplatin	10	64.7	80.0	10/0	75.0	Persistent or recurrent	60.2; parallel oblique fields or multiple fields	10.3
Marks [16]	–	65	63	90.8	0/65	90.8	Persistent or recurrent	50	–
Morita [67]	5-FU + cisplatin	5	61.8	100	5/0	60.0	Persistent or recurrent	60.2; parallel oblique fields or multiple fields	–
Morita [29]	5-FU + cisplatin	27	63	85.2	–/–	70.4	Persistent or recurrent	>60.2; parallel oblique fields or multiple fields	9
Takeuchi [57]	5-FU + cisplatin	25	61	100	25/0	80.0	Persistent or recurrent		3.6
Ariga [68]	5-FU + cisplatin	13	65.5	100	13/0	92.3	Persistent or recurrent	60	8.3
Miyata [30]	5-FU + cisplatin	33	63.4	84.9	33/0	87.9	Persistent or recurrent	59.8	–
Tachimori [69]	5-FU + cisplatin	59	63	96.6	59/0	87.7	Persistent or recurrent	60	–
Chao [58]	5-FU + cisplatin	27	62.4	96.3	27/0	65.4	Persistent or recurrent	30[#]	2.5
D'Journo [24]	5-FU + cisplatin	24	59	75.0	16/8	87.5	Persistent or recurrent	62.5	5
Borghesi [70]	5-FU + cisplatin	10	64.5	60.0	7/3	30.0	Recurrent	57; 1 or 2-phase technique	
Nishimura [71]	5-FU + cisplatin	46	61	91.3	46/0	100	Persistent or recurrent	50	12
Smithers [72]	5-FU + cisplatin	14	66	50.0	5/9	85.7	Persistent or recurrent	60	25
Oki [73]	5-FU + cisplatin	14	56	92.9	14/0	50.0	Persistent or recurrent	75.2; parallel oblique fields or multiple fields	–

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; dCRT = definitive chemoradiotherapy [#] Radiation with a total dose of 30 Gy in 2 Gy daily fractions, 5 days a week. IMRT = intensity-modulated radiation therapy VMAT = volumetric modulated arc therapy, 3DRT = three-dimensional radiation therapy.

b: Characteristics in studies with salvage surgery after nCRT

Study	Chemotherapy regimen	$N = 110$	Mean age (yrs)	Sex/male (%)	Histology: SCC/AC (*N*)	R0 (%)	Indication of salvage surgery	Median RT dose (Gy)	Median time CRT to surgery (months)
Taketa [18]	5-FU + platinum/taxane	12	69	100	3/9	100	Recurrent disease	50.4 (39–66)	9.3
Piessen [20]	5-FU + cisplatin	98	56	100	89/9	61.0	Persistent disease	38 (30–46)	14.2

c: Mortality and morbidity in studies on salvage surgery after dCRT

Study	Histology: SCC/AC (*N*)	Indication for salvage surgery	Median dose RT (Gy) Radiation techniques	Mortality % 30/90 days	Pulmonary complications[a]	Cardiovascular complications[b]
Lertbutsayanukul 13]	44/0	Persistent	60 IMRT VMAT 3DRT	2.3/-	6.8	15.9
Farinella [61]	14/2	Persistent or recurrent	57.7	0/0	37.5	0
Swisher [23]	–	Persistent or recurrent	50.4	-/-	0	0
Okumura [62]	–	Persistent or recurrent	50	-/10.0	-	–
Markar [15]	193/109	Persistent or recurrent	50	-/8.4	42.9	13.6

(*continued on next page*)

Table 2 (*continued*)

c: Mortality and morbidity in studies on salvage surgery after dCRT

Study	Histology: SCC/AC (*N*)	Indication for salvage surgery	Median dose RT (Gy) Radiation techniques	Mortality % 30/90 days	Pulmonary complications[a]	Cardiovascular complications[b]
Watanabe [9]	63/0	Persistent or recurrent	60	0/0	-	–
Chen [37]	51/0	Recurrent	54 IMRT	2.0/-	3.8	0
Sudo [28]	5/18	Recurrent	50.4 IMRT or proton beam	0/9.0	17.0	0
Akutsu [63]	12/0	Persistent	53.2	-/-	-	–
Aquino [64]	18/0	Persistent	–	-/-	38.9	0
Adenis [65]	–/–	Persistent	50.4 Multiple field technique	-/-	-	–
Saeki [66]	10/0	Persistent or recurrent	60 2 parallel oblique or multiple fields	-/20.0	50.0	0
Marks [16]	0/65	Persistent or recurrent	50	3.1/4.6	23.1	0
Morita [67]	5/0	Persistent or recurrent	60 2 parallel oblique or multiple fields	0/0	20.0	0
Morita [29]	?/?	Persistent or recurrent	>60 2 parallel oblique or multiple fields	-/7.4	29.6	0
Takeuchi [57]	25/0	Persistent or recurrent	60 2 parallel oblique or multiple fields	0/8.0	44.0	0
Ariga [68]	13/0	Persistent or recurrent	60	0/-	0	0
Miyata [30]	33/0	Persistent or recurrent	59.8	3.0/12.0	30.0	24.0
Tachimori [69]	59/0	Persistent or recurrent	60	-/8.0	32.0	0
Chao [58]	27/0	Persistent or recurrent	30[&]	-/22.2	27.0	0
D'Journo [24]	16/8	Persistent or recurrent	62.5	20.8/25.0	41.6	12.5
Borghesi [70]	7/3	Recurrent	57 1 or 2-phase technique	10.0/10.0	10.0	0
Nishimura [71]	46/0	Persistent or recurrent	50	9.0/15.0	9.0	2.0
Smithers [30]	5/9	Persistent or recurrent	60	7.0/7.0	57.0	29.0
Oki [73]	14/0	Persistent or recurrent	75 2 parallel oblique fields or multiple fields	0/7.1	21.4	7.1

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy; dCRT = definitive chemoradiotherapy [&] Radiation with a total dose of 30 Gy in 200 cGy daily fractions, 5 days a week. IMRT=Intensity-modulated radiation therapy, VMAT=Volumetric modulated arc therapy = VMAT, 3DRT = three-dimensional radiation therapy.

[a] Pneumonia, airway congestion, atelectasis, acute lung injury, and acute respiratory distress syndrome.

[b] Myocardial infarction, dysrhythmias, cardiac failure, and stroke.

Table 3
Pooled outcome after salvage according to persistent or recurrent disease.

Outcome	Total $N = 1076$ (persistent and recurrent or both) % (95% Cl)	Persistent $N = 482$% (95% Cl)	Recurrence $N = 211$% (95% Cl)	Difference in proportion (persistent − recurrence) (95% Cl)
Radical (R0)-resection	806 80.7 [78.2; 83.1]	300 77.5 [73.3; 81.7]	160 83.8 [78.8; 89.2]	−6.5 [-13.2; 0.2]
Anastomotic leak	168 17.2 [14.8; 19.6]	50 12.6 [9.4; 15.9]	26 14.8 [9.6; 20.0]	−2.2 [-8.4; 4.0]
Pulmonary complication	286 29.3 [24.0; 34.6]	133 33.6 [29.0; 38.2]	40 22.7 [16.5; 28.9]	10.9 [3.1; 18.7]
Cardiovascular complication	65 6.7 [5.1; 8.2]	41 10.4 [7.4; 13.4]	8 4.5 [1.4; 7.6]	5.9 [1.5; 10.2]
Infection	110 11.3 [9.3; 13.3]	42 10.6 [7.6; 13.6]	26 14.7 [9.6; 20.0]	−4.1 [-10.2; 1.9]
Hemorrhage	7 0.7 [0.2; 1.2]	1 0.2 [0; 0.7]	0 0	0.2 [-0.2; 0.7]
Chylothorax	19 1.9 [1.1; 2.8]	9 2.3 [0.8; 3.7]	1 0.6 [0.5; 1.7]	1.7 [-0.1; 3.6]
Conduit necrosis	8 0.8 [0.2; 1.4]	3 0.8 [0; 1.6]	1 0.6 [0.5; 1.7]	0.2 [-1.0; 1.3]
Recurrent nerve paralysis	29 3.0 [1.9; 4.0]	6 1.5 [0.3; 2.7]	1 0.6 [0.5; 1.7]	0.9 [-0.7; 2.6]
30-day mortality	24 2.6 [1.6; 3.6]	7 1.7 [0.4; 3.0]	3 1.7 [0.0; 3.6]	0.0 [-3.8; 3.8]
90-day mortality	76 8.0 [6.3; 9.8]	24 7.2 [4.4; 9.9]	6 3.7 [0.8; 6.6]	3.5 [-0.6; 11.1]
3-year OS	819 39.0 [35.8; 42.2]	325 44.0 [38.7; 49.3]	158 40.1 [33.9; 48.1.]	3.9 [-4.8; 12.8]
3-year OS R0-resection	320 48.8 [43.5; 54.0]	44 71.0 [-]	74 31.0 [21.0; 41.0]	–
5-year OS	588 19.4 [16.5; 22.4]	184 14.0 [9.3; 18.7]	104 19.7 [13.6; 25.7]	−5.7 [2.3; −13.7]
5-year OS R0-resection	286 25.6 [21.3; 29.9]	-	86 15.8 [9.1; 22.5]	–

Table 4
Outcome of delayed surgery for recurrent or persistent cancer after nCRT.

Outcome	dCRT total[a] % [95% Cl]	nCRT-recurrent: Taketa 2012, $N = 12$ *N*, %	nCRT-persistent: Piessen 2007, $N = 98$ *N*, %
R0-resection	725/877 82.7 [80.2; 85.2]		
Anastomotic leak	159/853 18.6 [16.0; 21.2]	1, 8.3	7, 7.1
Pulmonary complication	258/853 30.2 [27.2; 33.3]	2, 16.7	21, 21.4
Cardiovascular complication	65/853 7.6 [5.8; 9.4]	0,0	0, 0
Infection	107/853 12.5 [10.3; 14.8]	1, 8.3	0, 0
Hemorrhage	6/853 0.7 [0.1; 1.3]	0, 0	0, 0
Chylothorax	18/853 2.1 [1.1; 3.1]	0, 0	0, 0
Conduit necrosis	8/853 0.9 [0.3; 1.6]	0, 0	0, 0
Recurrent nerve paralysis	26/853 3.0 [1.9; 4.2]	0, 0	0, 0
30-day mortality	26/817 3.2 [2.0; 4.4]	1, 8.3	2, 2
90-day mortality	73/833 8.8 [6.8; 10.7]	-	3, 3.1
3-year OS	807 38.7 [35.4; 42.0]	-	-
5-year OS	610 24.1 [20.4; 27.8]	75	8
3-year OS R0-resection	308 48.8 [43.5; 54.1]		
5-year OS R0-resection	274 24.4 (19.4; 28.4)		

[a] Excluding the group of patients with nCRT ($N = 2$) and dCRT ($N = 10$) in the group of Yoo [15].

Table 5
a: Complications after esophagectomy compared with Esophageal Multimodality Trials.

Trial	Treatment	Pulmonary complications %	Cardiac complications %	Anastomotic leakage %	30-day mortality %	90-day mortality %
CROSS [3]	nCRT + S	46	21	22	4	2
CALGB 9781 [21]	nCRT + S	33	0	8.3	0	-
Urba [22]	nCRT + S	-	-	14.9	2	-
RTOG 0246 [23]	dCRT + SS	-	-	4.7	-	-
This study	dCRT + SS	30.2	7.6	18.6	3.2	8.8

S = surgery; SS = salvage surgery; dCRT = definitive chemoradiotherapy; nCRT = neoadjuvant chemoradiotherapy.

b: Survival results of salvage surgery compared with Esophageal Multimodality Trials

Trial	Treatment	3-year OS %	5-years OS %	7-years OS %
CROSS [3]	nCRT + S	60	39	-
CALGB 9781 [21]	nCRT + S	63	39	-
Urba [22]	nCRT + S	30	20	20
RTOG 0246 [23]	dCRT + SS	44	37	32
This study	SS after CRT (total group)	38.7	24.1	32#
	R0 only group	48.8	24.4	

S = surgery; SS = salvage surgery # RTOG 0246 [43].

Depending on follow-up strategies, approximately one-third of these patients may eventually benefit or able to undergo a salvage resection [28]. However, in the detection of persistent disease the accuracy of restaging by EUS remains limited due to obliterated fibrous tissue planes [32,33,37–39]. Whereas, both ^{18}F-FDG-PET/CT and the more recently applied diffuse weighted magnetic resonance imaging (DWI-MRI) seem to be promising in the post-CRT setting [32–34].

Surgery more than 3 months after dCRT is challenging due to difficulties in the dissection of friable and obliterated fibrous tissue planes with healing disorders and increased local complications based on hypovascularity and microvasculature injuries. If performed for regrowth in recurrent or persistent EC, it may lead to poorer local disease control, as was observed in the R0 resection rate of 80.7% (range 30–100) in Table 3. It is obvious that selection bias plays a role, as salvage resection is the only chance of cure in patients with potentially resectable recurrent and persistent EC, especially if the probability of R0 resection is disputable (in ≥ cT3 tumors). This is reflected in the reported lower percentages of complete resections compared to studies on planned surgery after nCRT (up to 95%) [9,35,40].

The performance of salvage surgery and even the initial choice of treatment is frequently limited by poor condition due to coexisting severe co-morbidities in a subgroup of patients with isolated LR EC. As shown in this study, pulmonary and cardiovascular complications often occur after salvage esophagectomy in patients with regrowth of persistent EC, probably due to earlier surgery in biologically more aggressive tumors with inadequate response after dCRT [9,25,32,41–43]. Since salvage surgery after dCRT is more challenging to perform than surgery after nCRT, complications develop more frequently after dCRT. In previous irradiated mediastinal tissues salvage surgery commonly carries substantial morbidity with increased blood transfusion, length of surgery, IC and hospital stay and overall mortality compared with standard surgical resection after nCRT [5,6,15,44]. This is not surprisingly, as the given radiation dose is commonly higher (≥50.4–60 Gy) with subsequently more fibrotic tissues, hampering adequate identification and dissection of recurrent tumor mass [2,15,25]. In the study of Markar et al. patients who had salvage surgery after a total radiation dose >55 Gy revealed a significant increase of in-hospital mortality (27.8% v 4.3%) and overall morbidity (75.9% v 61%) compared with those who received <55 Gy [15]. Moreover, it was accompanied by a higher rate of anastomotic leaks (27.8% vs. 15%), surgical infections (29.6% vs. 16.1%), and pulmonary complications (55.6% vs. 40.2%). However, in our study the pooled 30-day mortality and 90 day-mortality after surgery were comparable with the postoperative mortality in patients after nCRT and planned surgery (2.8% and 8.1% vs. 2–4% vs. 5–10%) [3,4,21,22,45,46]. With this in mind the performance of salvage esophagectomy should be well considered in patients with isolated persistent EC after dCRT. This procedure can be performed depending on the grade of preexistent respiratory, and cardiovascular co-morbidities. To prevent the common cardiopulmonary related complications pre, peri and postoperative measures should be taken into account.

More recent studies showed that postoperative pulmonary complications also have a great impact on overall survival [47–49]. Several factors may decrease the associated risk of morbidity and mortality after salvage resection. The use of modern radiotherapy techniques, like modulated radiation therapy and or volumetric arc therapy (IMRT/VMAT) may decrease the risk of cardiac and pulmonary toxicities by lowering the radiation dose to normal tissue during the initial treatment (Table 2c) [51,52]. In the near future, proton radiotherapy allows an even larger reduction of the dose to normal tissues [53]. In addition, lower toxic profiles of new chemotherapeutic schemes contribute to decrease these complications [50,51,54]. However, one of the most important factors in lowering the risk of morbidity and mortality, is the concentration of salvage and delayed surgery in specialized high-volume centers. Although the operative approach is commonly not described into detail in most reported articles, salvage esophagectomy should be performed only when potential curability is achievable, preferably with wide margins through a transthoracic approach with two-field lymphadenectomy and cervical anastomosis. Meticulous preserving of the gastroepiploic vascularization and if possible even the right gastric artery may avoid conduit necrosis with subsequent anastomotic leak. Moreover, specialized centers have the disposal of special adaptive surgical techniques, including a two-staged procedure with retrosternal gastric tube reconstruction and the use of long-pedicle omental flaps or colon interposition occasionally even with cervical microvascular anastomosis when the viability of the stomach is disputable. Moreover, caution should be taken to preserve bronchial arteries in preventing tracheabronchial necrosis [23,55–58]. Isolated recurrences in the upper thoracic part are even more difficult to treat. They are correlated with less favorable outcomes, limited rescue options after initial dCRT and additional side effects including strictures and fistulas, which should be treated by an experienced team [59,60].

In conclusion, in this systematic review we have shown that salvage surgery is a feasible high-risk curative approach in patients with isolated local recurrent or persistent EC after dCRT or nCRT

alone. In patients with a high probability of complete (R0) resection, the prognosis after salvage surgery is more or less equivalent to that after planned surgery following nCRT. Careful surveillance is important to define the position of salvage surgery in isolated recurrent disease after previous CRT, which can be performed with acceptable results when performed in high-volume institutes.

Key message

Salvage surgery is a feasible and potentially curative treatment in patients with isolated recurrent or persistent EC after definitive CRT or when surgery was deferred or omitted after neoadjuvant CRT. Major pulmonary and cardiovascular complications were less frequent after salvage esophagectomy among patients with recurrent disease compared to those with persistent disease.

Conflicts of Interest

No Conflicts of Interest

References

[1] D'Journo XB1, Thomas PA. Current management of esophageal cancer. J Thorac Dis 2014 May;6(Suppl 2):S253–64.
[2] Tachimori Y. Role of salvage esophagectomy after definitive chemoradiotherapy. Gen Thorac Cardiovasc Surg 2009;57:71–8.
[3] van Hagen P, Hulshof M, van Lanschot J, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012 May 31;366(22):2074–84.
[4] Wang D, Smit JK, Zwaan E, et al. Neoadjuvant therapy reduces the incidence of nodal micrometastases in esophageal adenocarcinoma. Am J Surg 2013 Nov;206(5):732–8. Epub 2013 Aug 12.
[5] Hofstetter WL. Salvage esophagectomy. J Thorac Dis 2014;6:S341–9.
[6] Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–74.
[7] Button MR, Morgan CA, Croydon ES, Roberts SA, Crosby TD. Study to determine adequate margins in radiotherapy planning for esophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009 Mar 1;73(3):818–23.
[8] Kato H, Nakajima M. Treatments for esophageal cancer: a review. Gen Thorac Cardiovasc Surg 2013 Jun;61(6):330–5.
[9] Watanabe M, Mine S, Nishida K, 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;22:4438–44.
[10] Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160–8.
[11] Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310–7.
[12] Cooper JS1, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. J Am Med Assoc 1999 May 5;281(17):1623–7.
[13] Lertbutsayanukul C, Tharavej C, Klaikeaw N, et al. High dose radiation with chemotherapy followed by salvage esophagectomy among patients with locally advanced esophageal squamous cell carcinoma. Thorac Cancer 2017 May;8(3):219–28.
[14] D1 Moher, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009 Jul 21;339:b2535.
[15] Markar S, Gronnier C, Duhamel A, et al. Salvage surgery after chemoradiotherapy in the management of esophageal cancer: is it a viable therapeutic option? J Clin Oncol 2015 Nov 20;33(33):3866–73.
[16] Marks JL, Hofstetter W, Correa AM, et al. Salvage esophagectomy after failed definitive chemoradiation for esophageal adenocarcinoma. Ann Thorac Surg 2012 Oct;94(4):1126–32. discussion 1132-3.
[17] Yoo C, Park JH, Yoon DH, et al. Salvage esophagectomy for locoregional failure after chemoradiotherapy in patients with advanced esophageal cancer. Ann Thorac Surg 2012 Dec;94(6):1862–8.
[18] Taketa T, Correa AM, Suzuki A, et al. Outcome of trimodality-eligible esophagogastric cancer patients who declined surgery after preoperative chemoradiation. Oncology 2012;83(5):300–4.
[19] Taketa T, Xiao L, Sudo K, et al. Propensity-based matching between esophagogastric cancer patients who had surgery and who declined surgery after preoperative chemoradiation. Oncology 2013;85(2):95–9.
[20] Piessen G, Briez N, Triboulet JP, Mariette C. Patients with locally advanced esophageal carcinoma nonresponder to radiochemotherapy: who will benefit from surgery? Ann Surg Oncol 2007 Jul;14(7):2036–44.
[21] Tepper J, Krasn MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086–92.
[22] Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.
[23] Swisher SG, Moughan J, Komaki RU, et al. Final results of NRG oncology RTOG 0246: an organ-preserving selective resection strategy in esophageal cancer patients treated with definitive chemoradiation. J Thorac Oncol 2017;12:368–74.
[24] D'Journo XB, Michelet P, Dahan L, et al. Indications and outcome of salvage surgery for oesophageal cancer. Eur J Cardio Thorac Surg 2008 Jun;33(6):1117–23.
[25] 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 Mar;21(3):922–31.
[26] Smit JK, Pultrum BB, van Dullemen HM, et al. Prognostic factors and patterns of recurrence in esophageal cancer assert arguments for extended two-field transthoracic esophagectomy. Am J Surg 2010 Oct;200(4):446–53.
[27] Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol 2013 Dec;8(12):1558–62.
[28] Sudo K, Xiao L, Wadhwa R, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol 2014 Oct 20;32(30):3400–5.
[29] Morita M, Kumashiro R, Hisamatsu Y, et al. Clinical significance of salvage esophagectomy for remnant or recurrent cancer following definitive chemoradiotherapy. J Gastroenterol 2011 Nov;46(11):1284–91.
[30] Miyata H, Yamasaki M, Takiguchi S, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. J Surg Oncol 2009;100:442–6.
[31] Taniyama Y, Sakurai T, Heishi T, et al. Different strategy of salvage esophagectomy between residual and recurrent esophageal cancer after definitive chemoradiotherapy. J Thorac Dis 2018 Mar;10(3):1554–62.
[32] Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg 2004;78:1152–60.
[33] Amini A, Ajani J, Komaki R, et al. Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. Ann Surg Oncol 2014;21:306–14.
[34] Beukinga RJ, Hulshoff JB, van Dijk LV, et al. Predicting response to neoadjuvant chemoradiotherapy in esophageal cancer with textural features derived from pretreatment 18F-FDG PET/CT imaging. J Nucl Med 2017 May;58(5):723–9.
[35] Wang S, Tachimori Y, Hokamura N, et al. Prognostic analysis of salvage esophagectomy after definitive chemoradiotherapy for esophageal squamous cell carcinoma: the importance of lymphadenectomy. J Thorac Cardiovasc Surg 2014;147. 1805–181.
[36] Sugimura K, Miyata H, Yano M, et al. Is 18F-FDG-PET useful for predicting R0 resection after induction therapy for initially unresectable locally advanced esophageal carcinoma? Gen Thorac Cardiovasc Surg 2017;65:455–62.
[37] Chen Y, Lu Y, Wang Y, et al. Comparison of salvage chemoradiation versus salvage surgery for recurrent esophageal squamous cell carcinoma after definitive radiochemotherapy or radiotherapy alone. Dis Esophagus 2014 Feb-Mar;27(2):134–40.
[38] Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Organ-sparing treatment in oesophagus cancer: feasible and safe? Ned Tijdschr Geneeskd 2017;161(0):D1818.
[39] Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Active surveillance in clinically complete responders after neoadjuvant chemoradiotherapy for esophageal or junctional cancer. Dis Esophagus 2017 Dec 1;30(12):1–8.
[40] Busweiler LA, Wijnhoven BP, van Berge Henegouwen MI, et al. Early outcomes from the Dutch upper gastrointestinal cancer audit. Br J Surg 2016 Dec;103(13):1855–63.
[41] Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123:175–83.
[42] Meunier B, Raoul J, Le Prise E, Lakehal M, Launois B. Salvage esophagectomy after unsuccessful curative chemoradiotherapy for squamous cell cancer of the esophagus. Dig Surg 1998;15:224–6.
[43] Heidecke CD, Weighardt H, Feith M, et al. Neoadjuvant treatment of esophageal cancer: immunosuppression following combined radiochemotherapy. Surgery 2002;132:495–501.
[44] Donnellan E, Masri A, Johnston DR, et al. Long-Term outcomes of patients with mediastinal radiation-associated severe aortic stenosis and subsequent surgical aortic valve replacement: a matched cohort study. J Am Heart Assoc 2017 May 5;6(5).
[45] Wang DB, Sun ZY, Deng LM, et al. Neoadjuvant chemoradiotherapy improving survival outcomes for esophageal carcinoma: an updated meta-analysis. Chin Med J (Engl). 2016 20th Dec;129(24):2974–82.
[46] Ku GY, Ilson DH. Long-term survival with salvage surgery for recurrent esophageal adenocarcinoma after chemoradiotherapy. J Clin Oncol 2015 Nov

20;33(33):3854–7.
[47] Takeuchi M, Kawakubo H, Mayanagi S, 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 Jul 6. https://doi.org/10.1007/s11605-018-3857-z.
[48] Hayami M, Watanabe M, Ishizuka N, et al. Prognostic impact of postoperative pulmonary complications following salvage esophagectomy after definitive chemoradiotherapy. J Surg Oncol 2018 May;117(6):1251–9.
[49] Sohda M, Kumakura Y, Saito H, et al. Clinical significance of salvage esophagectomy for patients with esophageal cancer and factors of influencing long-term survival. Anticancer Res 2017 Sep;37(9):5045–51.
[50] Kole TP, Aghayere O, Kwah J, Yorke ED, Goodman KA. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys 2012 Aug 1;83(5):1580–6.
[51] Welsh J, Gomez D, Palmer MB et al Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumours: a dosimetric study.
[52] Langendijk JA, Lambin P, De Ruysscher D, et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013;107:267–73.
[53] Lin SH, Komaki R, Liao Z, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2012 Jul 1;83(3):e345–51.
[54] Honing J, Smit JK, Muijs CT, et al. A comparison of carboplatin and paclitaxel with cisplatin and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol 2014;25:638–43.
[55] Swisher SG, Marks J, Rice D. Salvage esophagectomy for persistent or recurrent disease after definitive chemoradiation. Ann Cardiothorac Surg 2017 Mar;6(2):144–51.
[56] Marks J, Rice DC, Switcher SG. Salvage esophagectomy in the management of recurrent or persistent esophageal carcinoma. Thorac Surg Clin 2013;23(4):559–67.
[57] Takeuchi H, Saikawa Y, Oyama T, et al. Factors influencing the long-term survival in patients with esophageal cancer who underwent esophagectomy after chemoradiotherapy. World J Surg 2010 Feb;34(2):277–84.
[58] Chao YK, Chan SC, Chang HK, et al. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. Eur J Surg Oncol 2009 Mar;35(3):289–94.
[59] Wang S, Liao Z, Chen Y, et al. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. Thorac Oncol 2006 Mar;1(3):252–9.
[60] Tu Lingli, Sun Lan, Xu Yong, et al. Paclitaxel and cisplatin combined with intensity-modulated radiotherapy for upper esophageal carcinoma. Radiat Oncol 2013;8:75.
[61] Farinella E, Safar A, Nasser HA, et al. Salvage esophagectomy after failure of definitive radiochemotherapy for esophageal cancer. J Surg Oncol 2016 Dec;114(7):833–7.
[62] Okumura H, Mori N, Tanaka T, et al. Clinical features and treatment of patients with esophageal cancer and a history of gastrectomy: a multicenter, questionnaire survey in Kyushu, Japan. Dis Esophagus 2016 Nov;29(8):1135–43.
[63] Y1 Akutsu, Kono T, Uesato M, et al. Is the outcome of a salvage surgery for T4 thoracic esophageal squamous cell carcinoma really poor? World J Surg 2014 Nov;38(11):2891–7.
[64] Aquino JL, Said MM, Pereira DA, Cecchino GN, Leandro-Merhi VA. Complications of the rescue esophagectomy in advanced esophageal cancer. Arq Bras Cir Dig 2013 Jul-Sep;26(3):173–8.
[65] Adenis A1, Tresch E, Dewas S, et al. Clinical complete responders to definite chemoradiation or radiation therapy for oesophageal cancer: predictors of outcome. BMC Canc 2013 Sep 6;13:413.
[66] Saeki H1, Morita M, Tsuda Y, et al. Multimodal treatment strategy for clinical T3 thoracic esophageal cancer. Ann Surg Oncol 2013 Dec;20(13):4267–73.
[67] Morita M, Toh Y, Saeki H, et al. Clinical significance of chemoradiotherapy and surgical resection for cT4 esophageal cancer. Anticancer Res 2012 Aug;32(8):3275–82.
[68] Ariga H, Nemoto K, Miyazaki S, et al. Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 2009 Oct 1;75(2):348–56.
[69] Tachimori Y, Kanamori N, Uemura N, et al. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg 2009;137:49–54.
[70] Borghesi S, Hawkins MA, Tait D. Oesophagectomy after definitive chemoradiation in patients with locally advanced oesophageal cancer. Clin Oncol (R Coll Radiol). 2008 Apr;20(3):221–6.
[71] Nishimura M, Daiko H, Yoshida J, Nagai K. Salvage esophagectomy following definitive chemoradiotherapy. Gen Thorac Cardiovasc Surg 2007 Nov;55(11):461–4. discussion 464-5.
[72] Smithers BM1, Cullinan M, Thomas JM, et al. Outcomes from salvage esophagectomy post definitive chemoradiotherapy compared with resection following preoperative neoadjuvant chemoradiotherapy. Dis Esophagus 2007;20(6):471–7.
[73] Oki E, Morita M, Yet al Kakeji. Salvage esophagectomy after definitive chemoradiotherapy for esophageal cancer. Dis Esophagus 2007;20(4):301–4.