

Clinical Outcomes and Prognostic Factors of Patients With Esophageal Squamous Cell Carcinoma With Oligo-recurrence Treated With Radical Re-irradiation

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Abstract. *Background:* For patients with esophageal squamous cell carcinoma (ESCC) with oligo-recurrence (OR) after previous curative radiotherapy and not eligible for radical resection, the role of radical re-irradiation was not clear. Therefore, we aimed to investigate the outcome and prognostic factors of such patients. *Patients and Methods:* We identified patients with OR of ESCC after previous curative radiotherapy and were treated with radical re-irradiation within 2012-2018 via an in-house prospectively established database. The characteristics of patients, disease, treatment, and outcome were retrospectively obtained via chart review. The first day of re-irradiation was defined as the index date. Overall survival was calculated via the Kaplan–Meier method. Log-rank test was used for univariate analysis and Cox regression method was used for multivariable analysis. *Results:* We identified thirty patients for analyses. After a median follow-up of 9 (range=2-76) months, the 5-year

overall survival rate was 21%. Four patients with possible radiotherapy-related complication in need of inpatient care were identified. Gross tumor volume was the only significant prognostic factor in both univariate and multivariable analyses. *Conclusion:* We found that radical definitive re-irradiation may lead to one-fifth long-term survivors of patients with OR after previous curative radiotherapy for ESCC, and the gross tumor volume was the only significant prognostic factor for these patients. Randomized controlled trials should be considered to compare radical re-irradiation with the current standard of care (systemic therapy) for this population.

Esophageal cancer is a common cancer worldwide (1). Common histology differs for eastern (squamous cell carcinoma) and western (adenocarcinoma) populations (1, 2), and radiotherapy is a common treatment modalities (3-5). The prognosis of esophageal cancer is poor, and the recurrence rate high (1). At the time of recurrence, treatment options are often limited and palliative (1, 5). For patients who have persistent/recurrent esophageal squamous cell carcinoma (ESCC) after previous curative radiotherapy which is not amenable to radical resection, systemic therapy or best supportive care are the current standard of care (3).

However, for those with oligo-recurrence (OR), the optimal treatment is less clear. Radical local treatment was advocated for oligo-metastatic disease in several randomized controlled trials (RCT) (6-8). For ESCC, surgery is the

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Key Words: Esophageal squamous cell carcinoma, oligo-recurrence, radical re-irradiation.

Table I. Patient characteristics (n=30, all male).

Characteristic		Value
Age at re-irradiation, years	Median (range)	59 (45-82)
Before re-irradiation		
Clinical stage, n	I	2
	II	4
	III	22
	IV	2
RT dose, Gy	Median (range)	50 (41.4-70)
RT fractions, n	Median (range)	28 (18-39)
RT setting, n	Definitive	18
	Neoadjuvant or adjuvant	12
CTx regimen in CCRT, n	Preferred [‡]	17
	Non-preferred	12
	Missing data (other institute)	1
At re-irradiation		
Interval from prior RT, months	Median (range)	11 (1-67)
ECOG PS, n	1	24
	2	6
OR site, n	Neck	2
	Chest	18
	Abdomen	4
	Neck + abdomen	1
	Neck + chest	4
	Neck, abdomen + chest	1
Solitary OR, n	Yes	23
	No	7
Mucosa involved (alimentary tract or airway), n	Yes	16
	No	14
Pathological proof, n	Yes	17
	No	13
SUVmax	Median (range)	6.7 (2.1-18)
GTV volume, ml	Median (range)	13 (2-152)
Use of CTV, n	Yes	25
	No	5
RT dose, Gy	Median (range)	50.4 (48.6-60.4)
RT fractions, n	Median (range)	28 (25-33)
At summed RT plan		
RT dose max, Gy	Median (range)	107 (95-137)*
Spinal cord dose max, Gy	Median (range)	59 (35-66)*
Mean lung dose, Gy	Median (range)	15 (4-27)**
IGRT, n	Yes	24
	No	6
CCRT, n	Yes	25
	No	5

CCRT: Concurrent chemoradiotherapy; CTV: clinical target volume; CTx: chemotherapy; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IGRT: image-guided radiotherapy; OR: oligo-recurrence; PS: performance status; RT: radiotherapy; SUVmax: maximal standardized uptake value in positron-emission tomography. [‡]Preferred regimen to be at least two-drug combination of platinum, taxane, or fluorouracil as modified from the current treatment guideline (3); other regimens were classified as non-preferred. *Excluding missing data for two patients whose initial RT was at another institute. **Excluding missing data for five whose initial RT at other institute or incomplete lung scanning during simulation for re-RT.

preferred modality as reported in a systemic review published in 2016 and suggested in the 2019 Japanese guideline (5, 9). On the other hand, the role of radical re-irradiation is usually less certain (10, 11). In the four studies included in the above-mentioned systemic review (12-15),

three reported no 2-year survivors for the non-surgical group, whereas the 3-year overall survival rate 12% was reported in the fourth study (14). However, the case number in the non-surgery group was small in all four studies in this systematic review, ranging from 13-36 patients.

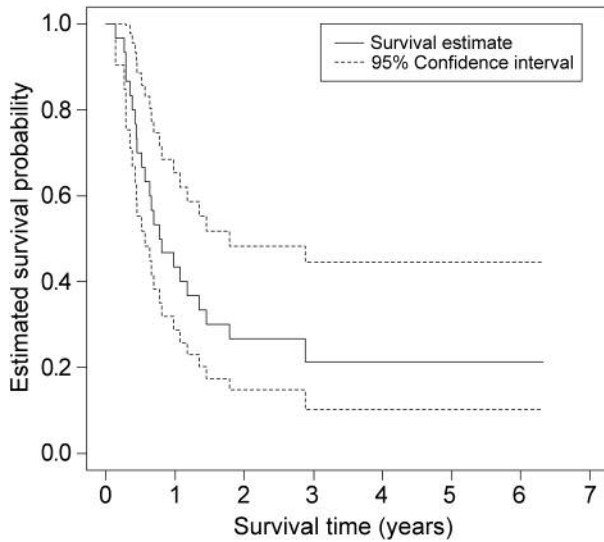


Figure 1. Kaplan–Meier overall survival curve with 95% confidence interval.

Due to these drawbacks in the literature, we aimed to investigate the outcome and prognostic factors of patients with OR of ESCC after previous radiation and treated with radical re-irradiation *via* retrospective review of patients treated at our Institute.

Patients and Methods

Study population. We identified patients with OR of ESCC after previous curative radiotherapy and who were treated with radical re-irradiation within 2012-2018 *via* an in-house prospectively established database. Our inclusion criteria included: (i) History of histological confirmation of ESCC; (ii) OR [by restaging positron-emission tomography (PET)] after previous curative concurrent chemoradiotherapy (CCRT); (iii) unsuitable for surgery and treated with radical re-irradiation. Radical re-irradiation was defined as at least 45 Gy at 1.8-2 Gy/fraction (90% of the recommended minimal 50 Gy in the treatment guideline) (3). The characteristics of patients, disease status, treatment, and outcome were retrospectively obtained *via* chart review and confirmed with the referring physicians. This study was approved by the Ethics Committee of our institute [CMUH106-REC3-119 (CR2)].

Re-irradiation. Patients were treated with 6- or 10-MV linear accelerators. Generally, a thermoplastic cast was used for immobilization then simulations with computed tomography (CT) were carried out in the treatment position. The gross target volume (GTV) was defined as the region of OR in the simulation CT image with the information from the restaging PET/endoscopic examination or diagnostic CT. At least 5 mm margin with editing was added to form the clinical target volume for most patients. We then added a 6-10 mm margin for the planning target volume to be used in intensity-modulated radiotherapy (IMRT) planning. Dose distribution and doses to the organs at risk in the summed

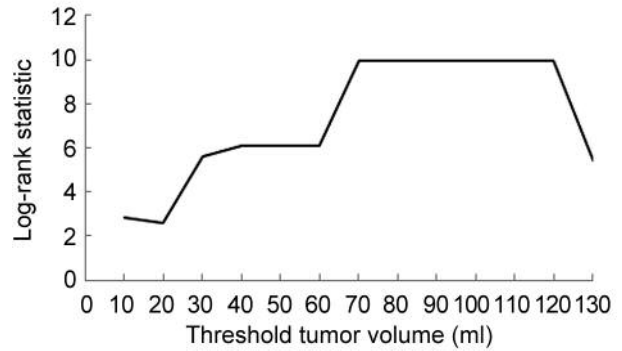


Figure 2. Running log-rank test for different tumor volume cut-off points.

plan *via* rigid fusion with previous radiation were evaluated whenever possible. Image-guided radiotherapy was used in the setup due to patient preference (in need of out-of-pocket payment).

Statistical analysis. The first day of re-irradiation was defined as the index date. Overall survival was calculated from the index date to the last date of contact or death *via* the Kaplan–Meier method. Log-rank test was used for univariate analysis and Cox regression method was used for multivariable analyses to adjust for covariables before or at the time of re-irradiation. The inclusion and classification of these covariables were based on our clinical experience. Statistical analysis was performed using software R package "survival".

Results

Study population and treatment. We identified 30 eligible patients (all male). The median age at re-irradiation was 59 (range=45-82) years. Most patients had locally advanced [clinical stage II-III by American Joint Committee on Cancer (AJCC) seventh edition staging (16)] at diagnosis and were treated with definitive CCRT with median 50 Gy radiotherapy dose (Table I). At the time of re-irradiation, after a median interval of 11 months from the previous radiotherapy, most patients had good performance status [Eastern Cooperative Oncology Group performance status (ECOG PS) 1] and had pathological proof of OR located in the chest with median re-irradiation dose of 50.4 Gy, mostly concurrently with chemotherapy.

Subsequent treatment and clinical outcomes. Nineteen patients received subsequent systemic therapy after re-irradiation but only four patients received additional radical local treatment during follow-up. At the time of analysis, after a median follow-up of 9 (range=2-76) months, 23 had died. The median (range) follow-up for the survivors was 51 (22-76) months. The 5-year overall survival rate was 21% as estimated *via* the Kaplan–Meier method (Figure 1). Twenty-two patients had radiologic or symptomatic improvement after re-irradiation recorded in their medical charts. Four patients without disease

Table II. Univariate analysis.

		Reference	HR	95% CI	p-Value
Age	Per year increase		1.008	0.970-1.048	0.7
Clinical stage	4	1-3	1.400	0.325-6.029	0.7
Initial RT dose	Per Gy increase		0.989	0.940-1.039	0.7
Initial RT setting	Neoadjuvant/adjuvant	Definitive	0.610	0.250-1.487	0.3
CTx regimen during initial CCRT	Preferred	Non-preferred	1.369	0.584-3.214	0.5
Interval from prior RT	Per month increase		0.993	0.971-1.017	0.6
ECOG PS	2	1	1.102	0.407-2.979	0.8
OR site	Abdominal	Neck or chest	0.445	0.131-1.507	0.2
Solitary OR	Yes	No	0.711	0.279-1.811	0.5
Mucosa involved*	Yes	No	1.611	0.696-3.730	0.3
Pathologically proven	Yes	No	1.040	0.448-2.412	0.9
SUVmax	Per unit increase		1.070	0.967-1.184	0.2
GTV volume	Per ml increase		1.019	1.007-1.031	<0.001
Use of CTV	With	Without	0.564	0.188-1.692	0.3
Re-RT dose	Per Gy increase		0.953	0.844-1.076	0.4
IGRT	With	Without	0.795	0.270-2.348	0.7
CCRT (at re-irradiation)	With	Without	0.854	0.289-2.525	0.8

CCRT: Concurrent chemoradiotherapy; CTV: clinical target volume; CTx: chemotherapy; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IGRT: image-guided radiotherapy; OR: oligo-recurrence; PS: performance status; RT: radiotherapy; SUVmax: maximal standardized uptake value in positron-emission tomography. *Alimentary tract or airway. Bold value shows significance.

Table III. Multivariable analyses.

		Reference	HR	95%CI	p-Value
Age	Per year increase		0.948	0.872-1.031	0.2
Clinical stage	4	Stage 1-3	0.188	0.006-5.701	0.3
Initial RT dose	Per Gy increase		0.940	0.850-1.040	0.2
Initial RT setting	Neoadjuvant/adjuvant	Definitive	0.529	0.072-3.894	0.5
CTx regimen during initial CCRT	Preferred	Non-preferred	0.269	0.065-1.107	0.1
Interval from prior RT	Per month increase		0.972	0.922-1.024	0.3
ECOG PS	2	ECOG PS 1	0.660	0.087-5.005	0.7
OR site	Abdominal	Neck or chest	0.123	0.012-1.223	0.1
Solitary OR	Yes	No	1.439	0.091-22.844	0.8
Mucosa involved*	Yes	No	9.802	0.666-144.209	0.1
Pathologically proven	Yes	No	0.137	0.011-1.664	0.1
SUVmax	Per unit increase		1.210	0.901-1.625	0.2
GTV volume	Per ml increase		1.028	1.001-1.055	<0.05
Use of CTV	With	Without	1.823	0.261-12.742	0.5
Re-RT dose	Per Gy increase		0.817	0.631-1.057	0.1
IGRT	With	Without	4.230	0.684-26.141	0.1
CCRT (at re-irradiation)	With	Without	0.197	0.012-3.211	0.3

CCRT: Concurrent chemoradiotherapy; CTV: clinical target volume; CTx: chemotherapy; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; IGRT: image-guided radiotherapy; OR: oligo-recurrence; PS: performance status; RT: radiotherapy; SUVmax: maximal standardized uptake value in positron-emission tomography. *Alimentary tract or airway. Bold value shows significance.

progression had possible radiotherapy-related complications in need of inpatient care. Among these four patients, one developed esophageal stricture and was treated with incision but was complicated by mediastinitis, which improved after in-patient supportive care. Three patients developed fistula which led to death in two of them.

Prognostic factors. In univariate analysis (Table II), none of the included covariables were significantly associated with overall survival except GTV volume [hazard ratio (HR) of death per milliliter increase=1.019, 95% confidence interval (95% CI)=1.007-1.031, $p<0.001$], it remained the only statistically significant prognostic factor

with adjusted HR of death of 1.028 (95% CI=1.001-1.055) (Table III). We found a GTV volume of approximately 70 ml may be used as a threshold for prognosis classification *via* running log-rank test using incremental volume of 10 ml (Figure 2).

Discussion

In this single-institute retrospective analysis, we found that radical definitive re-irradiation may lead to one-fifth long-term survivors for patients with OR of ESCC after previous curative radiotherapy, and GTV was the only significant prognostic factor for these patients.

Our results were somehow better than those reported in the recent systemic review, in which the highest overall survival rate reported was 12% at 3 years and 3% at 5 years (9, 14). Because this systematic review included articles up to June 2014, we searched PubMed using key words “((salvage radiotherapy) OR (salvage radiation therapy) OR (re-irradiation)) AND (esophageal cancer)” in Nov 2019 and identified four subsequent studies with sample sizes ranging from six to 55 (17-20). However, our 5-year overall survival rate was still higher than those of these four studies.

However, our results cannot be interpreted as definitive evidence to support the use of radical re-irradiation for patients after previous curative radiotherapy for ESCC because of potential bias due to our retrospective design. For example, PET was required to confirm OR in our study as used in a previous study (21), whereas PET was not mandatory in the above-mentioned studies (17-20). Furthermore, the advanced RT technology IMRT (22) was used in our study but not mandatory in the above-mentioned studies (17-20). These factors (use of PET and IMRT) may partly explain the impressive results seen in our study. However, our study was obviously not large enough for firm conclusions to be drawn. Furthermore, due to the lack for comparison group, RCT should be considered to compare radical re-irradiation with the current standard of care [systemic therapy] for this population. Other prospective studies such as ChiCTR1900020609 (23) or larger retrospective studies may also be helpful.

In conclusion, we found that radical definitive re-irradiation may lead to improved long-term survival rates for patients who have OR after previous curative radiotherapy for ESCC, and GTV was the only significant prognostic factor for these patients. Randomized controlled trials should be considered to compare radical re-irradiation with the current standard of care (systemic therapy) for this population.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Lin CY, Fang HY, Lein MY, Lin CC, Bai LY, Tsai MH, Chen CC, Hsieh TC, Wang YC, Liang JA and Li CC participated in the conception and design of study, interpreted data, and drafted the article. Chien CR participated in the conception and design of study, collected the related researches, analyzed and interpreted data, and drafted the article.

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