Original Article

Prognosis for local radical treatment in patients with esophageal squamous cell carcinoma with low-risk oligometastatic recurrence after curative resection: a retrospective cohort study

Tingting Li[1,2#], Dongmei Ke[2#], Xiaobin Fu[1,2], Yaqing Dai[3], Jules Lin[4], Christopher J. Anker[5], Zhigang Bai[1], Jiancheng Li[2]

[1]Department of Radiation Oncology, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, China; [2]Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China; [3]Department of Radiation Oncology, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, China; [4]Section of Thoracic Surgery, University of Michigan Medical School, Ann Arbor, MI, USA; [5]Division of Radiation Oncology, The University of Vermont Cancer Center, Burlington, VT, USA

Contributions: (I) Conception and design: T Li, J Li; (II) Administrative support: J Li, Z Bai; (III) Provision of study materials or patients: J Li; (IV) Collection and assembly of data: D Ke, X Fu, Y Dai; (V) Data analysis and interpretation: T Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Jiancheng Li, MD, PhD. Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, 420 Fuma Road, Jin'an District, Fuzhou 350014, China. Email: jianchengli_jack@126.com; Zhigang Bai, MD. Department of Radiation Oncology, The Second Affiliated Hospital of Fujian Medical University, 950 Donghai Street, Fengze District, Quanzhou 362000, China. Email: drbpc65@126.com.

Background: Patients with esophageal carcinoma (EC) with recurrent disease have a poor prognosis. A limited numbers of metastases, safely treatable with curative intent, diagnosed after curative esophagectomy may be defined as oligometastatic recurrence (OLR). However, the appropriate number of metastases and metastatic organs involved remains incompletely characterized. And the role of local therapy in OLR after radical esophagectomy remains unknown. Therefore, this study aimed to more accurately define low-risk OLR in patients with esophageal squamous cell carcinoma (ESCC) treated with radical resection and investigate the role of chemotherapy combined with local treatment (CCLT) in these patients.

Methods: A total of 83 sequential patients with ESCC who underwent radical esophagectomy, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, with ability to tolerate chemotherapy (CT) and local treatment, and with newly diagnosed recurrence between January 2010 and May 2019 in our hospital were recruited. Overall survival (OS) curves after recurrence were analyzed using the Kaplan-Meier method, and a log-rank test was used to assess the OS differences. Cox proportional hazards regression analysis was performed to identify independent factors associated with 2-year OS. Regular follow-up examinations were assessed by thoracic and upper abdominal computed tomography (CT) scanning every 3 months in the first year, every 6 months over the next 2 years, and yearly thereafter.

Results: Of the 83 patients with ESCC (71 males and 12 females), the median age was 56 years (range, 37–79 years). Thirty-five patients with ESCC with ≤5 metastases safely treatable with curative intent located in a single organ had a favorable OS compared to 48 patients with metastases located in 2–3 organs with or without regional recurrence and/or regional lymph node (LN) metastases. In our study, low-risk OLR was defined as the presence of ≤5 metastases safely treatable with curative intent in a single organ and was compared to patients with 2–3 organs involved. The 2-year OS of patients with low-risk OLR with liver oligometastases was significantly worse than survival in patients with lung oligometastases (0% *vs.* 61.1%, P=0.009). Patients with ESCC in the low-risk OLR group treated with CCLT had a better 2-year OS after recurrence than those who received CT alone (66.7% *vs.* 30.4%, P=0.003). The multivariable Cox regression model identified treatment method [hazard ratio (HR) 3.920, P=0.02] as an independent factor affecting OS after recurrence for low-risk OLR.

Conclusions: Low-risk OLR was defined as ≤5 metastases safely treatable with curative intent in a single

organ. Patients with ESCC with low-risk OLR after curative resection treated with CCLT have a favorable OS compared to those treated with CT alone. CCLT is a promising treatment option for patients with ESCC and low-risk OLR.

Keywords: Esophageal squamous cell carcinoma (ESCC); oligometastatic recurrence (OLR); chemotherapy combined with local treatment (CCLT); prognosis

Submitted Mar 22, 2024. Accepted for publication May 06, 2024. Published online Jun 17, 2024.
doi: 10.21037/jgo-24-205
View this article at: https://dx.doi.org/10.21037/jgo-24-205

Introduction

The International Agency for Research on Cancer recently estimated that there were 544,000 new deaths from esophageal carcinoma (EC) and 60,400 new EC cases reported worldwide in 2020. Esophageal squamous cell carcinoma (ESCC) is the predominant subtype of EC in Southern Asia and Eastern Africa, and esophageal adenocarcinoma is the predominant subtype in Northern Europe and the United States (1). Despite the wide application of radical esophagectomy and 3-field lymph node (LN) dissection, as well as significant improvements in radiotherapy and systemic therapy in EC in recent years, the recurrence rate of advanced EC after curative treatment remains high at approximately 45% (2,3). Patients with EC with recurrent disease, including locoregional recurrence, distant metastasis, or both, have a poor prognosis with many patients dying within 4–10 months (4,5). Thus, identifying an effective treatment regimen for EC recurrence is crucial to improving survival.

In 1995, Hellman *et al.* initially proposed the concept of 'oligometastases', and suggested that it represents an optimistic situation for metastatic disease (6), in contrast to that of widespread systemic recurrence. Oligometastatic disease (OMD) is defined as an intermediate phase in which systemic metastatic tumors with indolent biological behavior are limited in number and location and may theoretically be eradicated by definitive local treatment.

OMD is often encountered at the initial diagnosis or after curative treatment in clinical practice. Limited numbers of safely treatable metastases diagnosed after curative esophagectomy was defined as oligometastatic recurrence (OLR). In a retrospective study, patients with ≤5 metastases located in a single organ were defined as having OLR (4). Yamaguchi *et al.* defined EC patients with ≤3 metastases located in a single organ as OLR (7). In another study, ESCC patients with <5 recurrences in 1 organ had longer overall survival (OS) after recurrence than those with 6 or more recurrences in 1 organ, or metastases located in multiple organs (21 *vs.* 9.8 months, P=0.003) (8). There was wide variation in the number of metastases and metastatic organs involved. Radical treatment methods for primary EC have not been inconsistent. And multicenter, prospective randomized controlled trials (RCTs) are lacking. To date, there has been no consistent definition of OLR after curative esophagectomy. Moreover, the role of local therapy, including radiation, radiofrequency ablation, and resection, in OLR after radical esophagectomy remains unknown (9-12).

Thus, the primary aims of the current study were to precisely define low-risk OLR and identify independent prognostic factors in patients with ESCC with low-risk OLR after radical esophagectomy. The secondary aim was to investigate the role of chemotherapy combined with local treatment (CCLT) in patients with low-risk OLR. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-205/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of Fujian Cancer Hospital (No. YKT2021-005-01), and informed consent was taken from all the patients. We reviewed patients with ESCC who had previously undergone radical esophagectomy and 2- or 3-field lymphadenectomy and had newly diagnosed recurrence at Fujian Cancer Hospital between January 2010 and May 2019. The inclusion criteria were as follows: (I) Eastern Cooperative Oncology Group performance status score ≤2;

(II) histologically confirmed oligometastatic ESCC after radical esophagectomy and 2- or 3-field lymphadenectomy; (III) total number of metastases ≤5 and located in ≤3 organ systems with or without regional recurrence and/or regional LN metastases; (IV) no regional recurrence and/or regional LN metastases only; (V) ability to tolerate chemotherapy (CT) and local treatment; and (VI) no other history of malignant disease. The staging was re-determined according to the 8th American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system based on the clinical data (13).

Definition of low-risk and high-risk OLR

A clear consensus regarding OLR has not yet been reached. The most common definition of OLR used in clinical practice and trials is the presence of ≤5 metastases safely treatable with curative intent. However, clinical outcomes vary greatly. In this study, low-risk OLR was defined as ≤5 metastases safely treatable with curative intent located in a single organ. The presence of ≤5 metastases safely treatable with curative intent located in 2–3 organs with or without regional recurrence and/or regional LN metastases was defined as high-risk OLR.

Treatment of low-risk and high-risk OLR

OLR treatment was classified as (I) CT alone and (II) CCLT. Patients with OLR who received the best supportive care, local therapy only, or no treatment were excluded from this study. All patients with OLR were treated with 2 or more cycles of CT. The CT regimens included: (I) paclitaxel 135 mg/m^2 by intravenous (i.v.) infusion on day 1 + cisplatin 80 mg/m^2 i.v. infusion on day 2; (II) capecitabine 1,000 mg/m^2 orally twice a day on day 1–14 + cisplatin 80 mg/m^2 i.v. infusion on day 1; (III) 5-fluorouracil 750 mg/m^2 i.v. bolus on days 1–4 + oxaliplatin 75 mg/m^2 i.v. infusion on day 1; and (IV) S-1 40–60 mg orally twice a day on days 1–14 + cisplatin 80 mg/m^2 i.v. infusion on day 1. Local treatment included surgical resection, stereotactic body radiotherapy (SBRT), fractionated stereotactic radiation therapy (FSRT), conventional radiotherapy, and radiofrequency ablation. Due to the heterogeneity in tumor sites and metastatic organs, there was a variety of SBRT/FSRT schemes and conventional radiotherapy schedules applied. The range of SBRT/FSRT doses were 25–60 Gy, with 5–10 Gy per fraction in 5–10 fractions. Conventional radiotherapy was administered using medical linear accelerator with prescription radiation dose ranging from 30 to 63 Gy with 2–2.1 Gy per fraction in 10–30 fractions.

Follow-up

Regular follow-up examinations were typically performed every 3 months in the first year, every 6 months over the next 2 years, and yearly thereafter. Routine evaluations included physical examination, blood tests, tumor markers, biochemical investigations, thoracic and upper abdominal CT scanning, and magnetic resonance imaging when recurrences in the liver, brain, or bone with suspected spinal cord compression were found. November 2022 was the last censoring date for the evaluation of survival time. The disease-free interval (DFI) was defined as the interval between the date of surgery and the date of diagnosis of recurrence. OS after recurrence was defined as the interval between the radiologic/clinical diagnosis of recurrence and death or the last follow-up. The main clinical endpoint of interest was OS after recurrence.

Statistical analysis

All recorded data were analyzed using the software SPSS 23.0 (IBM Corp., Armonk, NY, USA).

The OS curves after recurrence were analyzed using the Kaplan-Meier method, and a log-rank test was used to assess differences in OS between the groups. Cox proportional hazards regression analysis was performed to identify independent factors predictive of OS for patients with ESCC and low-risk OLR. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each factor. All tests were 2-sided, and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

We reviewed the clinical data of 990 consecutive EC patients treated with radical esophagectomy who experienced a disease recurrence. Ultimately, 83 patients with ESCC (71 males and 12 females) who met the inclusion criteria were included. Out of the entire cohort of 83 ESCC patients with OLR after curative resection, 35 patients with ≤5 metastases located in a single organ were categorized as the low-risk OLR group and 48 patients with ≤5 metastases located in 2–3 organs with or without

Table 1 Characteristics of 83 patients with ESCC

Characteristics	N (%)
Sex	
Male	71 (85.5)
Female	12 (14.5)
Age	
≤60 years	56 (67.5)
>60 years	27 (32.5)
ECOG performance status	
0	4 (4.8)
1	73 (88.0)
2	6 (7.2)
Primary tumor location	
Upper and middle third	56 (67.5)
Lower third	27 (32.5)
T stage	
T1	5 (6.0)
T2	16 (19.3)
T3	47 (56.6)
T4	15 (18.1)
N stage	
N0	27 (32.6)
N1	21 (25.3)
N2	25 (30.1)
N3	10 (12.0)
Differentiation grade	
G1	6 (7.2)
G2	59 (71.1)
G3	18 (21.7)
Surgical methods	
2-field lymphadenectomy	26 (31.3)
3-field lymphadenectomy	57 (68.7)
Neoadjuvant therapy	
No	74 (89.2)
Yes	9 (10.8)
Adjuvant therapy	
No	29 (34.9)
Yes	54 (65.1)

ECOG, Eastern Cooperative Oncology Group.

regional recurrence and/or regional LN metastases were categorized as the high-risk OLR group. The median follow-up time was 15 months (range, 1–147 months). The median age of the patients was 56 years (range, 37–79 years). The basic characteristics of all patients are summarized in the *Table 1*.

Recurrence pattern of low- and high-risk OLR

The sites of recurrence in the low-risk OLR group (n=35; 42.2%) were the lungs (n=18; 51.5%), liver (n=6; 17.1%), bones (n=4; 11.4%), and brain (n=7; 20%). The median survival times (MSTs) after recurrence for metastases located in the lung only, liver only, bone only, and brain only were 30, 13, 15, and 16 months, respectively. The 2-year OS rates after recurrence for the lung, liver, bone, and brain only were 61.1%, 0%, 50.0%, and 42.9%, respectively. The MST and 2-year OS of patients with low-risk OLR with liver oligometastases were significantly worse than those of patients with lung oligometastases (P=0.009). Statistical analysis showed no significant difference in MST and 2-year OS for brain oligometastases (P=0.056) and bone oligometastases (P=0.64) compared with lung oligometastases (*Table 2*).

Conversely, 30 patients (36.1%) in the high-risk OLR group had a recurrence in 23 organs with regional recurrence and/or regional LN metastases and 18 (21.7%) without regional recurrence and/or regional LN metastases. The MST after recurrence for patients with ESCC in the high-risk OLR group with and without regional recurrence and/or regional LN metastases was 11 and 16 months, respectively. The survival curves after recurrence in patients with ESCC with high-risk OLR according to regional recurrence and/or regional LN metastases are shown in *Figure 1A* (1- and 2-year OS of 46.3% and 14.6%, *vs.* 57.1% and 14.3%, respectively; P=0.83). In this study, regional recurrence and/or regional LN metastasis in the high-risk OLR group were not associated with long-term survival after recurrence.

OS after the recurrence of low- and high-risk OLR

The MST after recurrence for patients with ESCC in the low- and high-risk OLR groups was 19 and 11 months, respectively. For patients with ESCC in the low-risk OLR group (n=35), the 1- and 2-year OS rates after recurrence were 71.4% and 42.9%, respectively. For patients with ESCC in the high-risk OLR group (n=48), the 1- and

Table 2 Number of patients and overall survival after recurrence by locations of metastases

Site	n	OS, %		MST (month)	χ^2	P value
		1-year	2-year			
Lung only	18	72.2	61.1	30		
Liver only	6	66.7	0	13	6.852	0.009
Bone only	4	75.0	50.0	15	0.213	0.64
Brain only	7	71.4	42.9	16	3.657	0.056
Single organ	35	71.4	42.9	19		
Multiple organs	48	56.2	14.6	11	4.723	0.03

OS, overall survival; MST, median survival time.

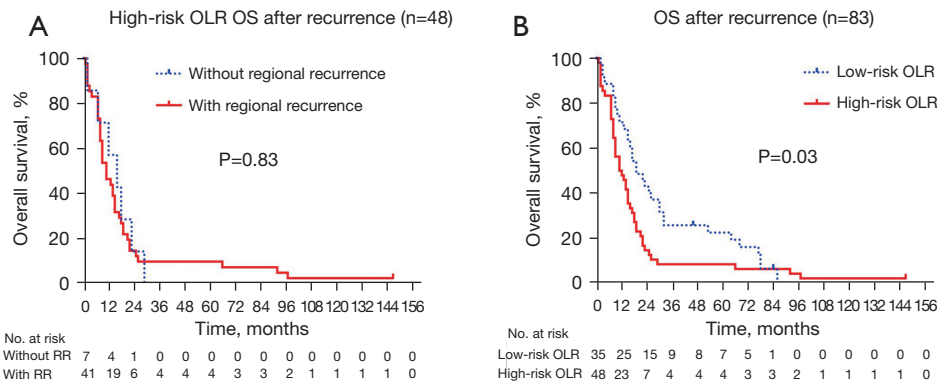

Figure 1 Kaplan-Meier survival curve for OS after recurrence for 48 patients with EC with high-risk OLR according to regional recurrence and/or regional lymph node disease (A) and 83 patients with EC according to the recurrence pattern (B). OS, overall survival; EC, esophageal carcinoma; OLR, oligometastatic recurrence; RR, regional recurrence.

2-year OS rates after recurrence were 47.9% and14.6%, respectively. Based on these results, OS after recurrence was significantly better for patients with ESCC in the low-risk OLR group than in those in the high-risk OLR group (P=0.03) (*Figure 1B*).

To identify the factors affecting long-term survival after recurrence in the entire cohort, we performed univariate analysis and demonstrated that a lower third tumor location (P=0.005), lower pathological LN (pN) stage (P<0.001), and low-risk OLR (P=0.03) were significantly associated with improved OS after recurrence. Multivariable analysis confirmed that the lower pN stage (P=0.003), low-risk OLR (P=0.003), and longer DFI (P=0.01) were independent prognostic factors for improved OS (*Table 3*).

OS after recurrence in patients with low- or high-risk OLR according to the treatment method

A total of 57 patients received ≥2 cycles of CT alone after recurrence, and 26 patients received CCLT after recurrence. The local treatment for patients with ESCC after recurrence was surgical resection (n=2, 7.7%), SBRT/FSRT or conventional radiotherapy (n=20, 76.9%), or radiofrequency ablation (n=4, 15.4%). The MST after recurrence for patients with ESCC in the low-risk OLR group treated with CT and CCLT was 17 and 32 months, respectively. For patients with ESCC in the low-risk OLR group treated with CT (n=23) *vs.* CCLT (n=12), the 1- and 2-year OS rates after recurrence were 60.9% and 30.4% versus 91.7% and 66.7%, respectively. Based on these results, OS after

Table 3 Univariate and multivariable analysis of 2-year overall survival of 83 patients with EC with recurrence after curative resection

Variables	Univariate				Multivariable		
	n	MST (month)	χ^2	P value	HR	95% CI	P value
Age			0.000	0.99			
≤60 years	56	10			1		0.15
>60 years	27	14			1.492	0.865–2.573	
ECOG			1.241	0.54			
0	4	19			1		0.84
1	73	15			0.757	0.186–3.072	0.70
2	6	11			1.048	0.412–2.666	0.92
Primary tumor location			8.034	0.005			
Upper and middle third	56	16			1		0.82
Lower third	27	11			1.079	0.556–2.092	
T stage			0.497	0.48			
T1–2	21	13			1		0.65
T3–4	62	15			0.881	0.487–1.574	
N stage			15.399	<0.001			
N0–1	48	18			1		0.003
N2–3	35	13			2.503	1.363–4.601	
Differentiation grade			0.703	0.40			
G1/2	65	15			1		0.89
G3	18	15			0.957	0.509–1.799	
Surgical methods			1.873	0.17			
2-field lymphadenectomy	26	9			1		0.27
3-field lymphadenectomy	57	16			0.725	0.410–1.283	
Neoadjuvant and/or adjuvant therapy			0.788	0.38			
No	24	19			1		0.14
Yes	59	14			0.652	0.372–1.144	
OLR state			4.723	0.03			
A single organ	35	19			1		0.003
2–3 organs	48	11			2.359	1.339–4.262	
DFI			3.932	0.047			
≤12 months	47	13			1		0.01
>12 months	36	18			0.469	0.258–0.853	

EC, esophageal carcinoma; MST, median survival time; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OLR, oligometastatic recurrence; DFI, disease-free interval.

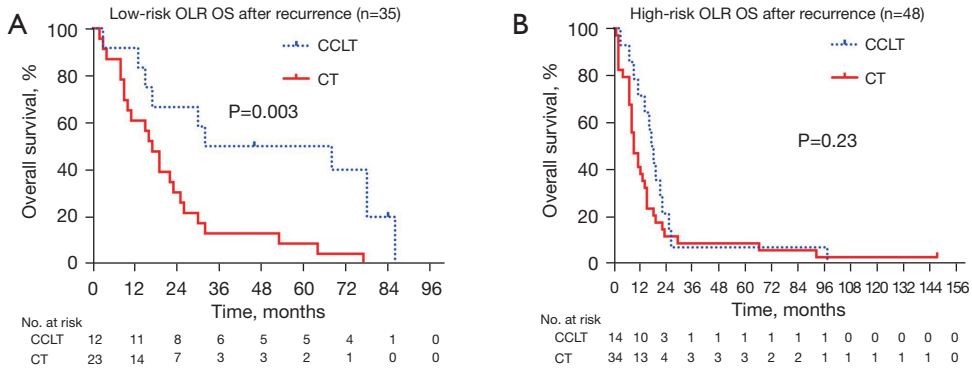

Figure 2 Kaplan-Meier survival curve for OS after recurrence in 35 patients with low-risk OLR (A) and 48 patients with high-risk OLR (B) according to treatment type. OS, overall survival; OLR, oligometastatic recurrence; CCLT, chemotherapy combined with local treatment; CT, chemotherapy.

recurrence was significantly better for patients with ESCC in the low-risk OLR group treated with CCLT than in those treated with CT (P=0.003) (*Figure 2A*). For patients with ESCC in the high-risk OLR group treated with CT (n=34) or CCLT (n=14), the 1- and 2-year OS rates after recurrence were 38.2% and 11.8% versus 71.4% and 21.4%, respectively. From these results, the OS after recurrence was not significantly different between patients with ESCC in the high-risk OLR group treated with CT and those treated with CCLT (P=0.23) (*Figure 2B*).

To identify the factors affecting OS after recurrence in patients with low-risk OLR, we performed univariate analysis and demonstrated that treatment method with CCLT (P=0.003) and lower pN stage (P<0.001) were significantly associated with improved OS after recurrence. Multivariable analysis confirmed that a higher degree of differentiation (lower grade) (P=0.01), CCLT treatment (P=0.02), and lower pN stage (P=0.006) were independent prognostic factors for improved OS (*Table 4*).

Discussion

In this study, 83 patients with ESCC who underwent radical esophagectomy and newly diagnosed OLR were analyzed. Patients with ≤5 metastases safely treatable with curative intent located in 2–3 organs with or without regional recurrence and/or regional LN metastases had worse 2-year OS after recurrence than those with ≤5 metastases safely treatable with curative intent located in a single organ (2-year OS, 14.6% *vs.* 42.9%, P=0.03). Multivariable analysis confirmed that ESCC with ≤5 metastases safely treatable with curative intent located in a single organ was an independent prognostic factor. Thus, low-risk OLR was defined as ≤5 metastases safely treatable with curative intent located in a single organ in our study. We also established that CCLT with local treatment, including surgical resection, SBRT/FSRT, conventional radiotherapy, and radiofrequency ablation, was the main prognostic factor for patients with ESCC with low-risk OLR after radical esophagectomy and 2- or 3-field LN dissection. For patients with ESCC in the low-risk OLR group treated with CT and CCLT, the 2-year OS rates after recurrence were 30.4% versus 66.7% (P=0.003), respectively. Further multivariable analysis demonstrated that treatment method was an independent prognostic factor affecting OS after recurrence in patients with low-risk OLR. These findings suggest that CCLT is a promising treatment option for patients with ESCC and low-risk OLR.

It remains unclear whether patients with OLR benefit from local treatment. For breast cancer patients with OMD, the role of local treatment was not formally recommended by guidelines and clear-cut reference literature. However, some selecting patients with OMD would increase the chance of long-term local control by appropriate local treatments (14). In a review article by Saeed *et al.*, locally ablative therapies (LAT) including primarily surgery and SBRT had a positive impact on oligometastatic breast cancer compared with standard of care treatments. A recent study demonstrates the local treatments play crucial roles in ESCC with OLR (15). A multicenter cohort study by Kroese *et al.* retrospectively evaluated 205 patients with esophagogastric cancer with synchronous and metachronous OMD who underwent (I) systemic therapy, (II) local treatment, (III) CCLT, or (IV) best supportive care

Table 4 Univariate and multivariable analysis of 2-year overall survival of 35 patients with EC with low-risk OLR after curative resection

Variables	Univariate				Multivariable		
	n	MST (months)	χ^2	P value	HR	95% CI	P value
Age			0.006	0.94			
≤60 years	26	17			1		0.21
>60 years	9	30			0.486	0.158–1.497	
ECOG			1.793	0.41			
0	2	19			1		0.33
1	32	17			0.455	0.017–12.144	0.64
2	1	23			2.168	0.241–19.414	0.49
Primary tumor location			0.406	0.52			
Upper and middle third	28	22			1		0.99
Lower third	7	19			0.986	0.276–3.528	
T stage			0.114	0.74			0.14
T1–2	7	26			1		
T3–4	28	19			0.391	0.111–1.373	
N stage			16.518	<0.001			0.006
N0–1	20	32			1		
N2–3	15	15			5.857	1.655–20.733	
Differentiation grade			2.921	0.09			0.01
G1/2	23	23			1		
G3	12	16			3.354	1.284–8.757	
Surgical methods			0.775	0.38			0.56
2-field lymphadenectomy	9	19			1		
3-field lymphadenectomy	26	17			0.640	0.144–2.853	
Neoadjuvant and/or adjuvant therapy			1.023	0.31			0.60
No	8	15			1		
Yes	27	19			0.761	0.272–2.127	
Treatment of low-risk OLR			8.631	0.003			0.02
CCLT	12	32			1		
Systemic therapy alone	23	17			3.920	1.239–12.403	
DFI			3.573	0.06			0.87
≤12 months	27	17			1		
>12 months	8	53			0.913	0.301–2.773	

EC, esophageal carcinoma; OLR, oligometastatic recurrence; MST, median survival time; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CCLT, chemotherapy combined with local treatment; DFI, disease-free interval.

and found that the median OS was significantly increased for local plus systemic therapy compared with systemic therapy alone (35 *vs.* 13 months, P<0.001). Moreover, CCLT was an independent factor for improved OS. The local treatment performed in the study included SBRT and metastasectomy (16). In another study by Morinaga *et al.* with 97 ESCC patients with OLR, systemic therapy combined with local therapy after recurrence was the only prognostic factor for OS after recurrence (8). Kanamori *et al.* retrospectively analyzed 33 patients with EC who had undergone metastasectomy for lung metastases after definitive treatment and found that the 5-year OS and MST were 43% and 17.9 months, respectively. Surgical resection is safe and effective in patients with EC with metastatic pulmonary tumors (17). In a prospective, single-arm phase II trial by Liu *et al.*, 34 patients with ESCC and ≤3 metastases were enrolled to receive radical treatment with SBRT to all metastatic lesions and at least 4 cycles of CT. The results showed that the median disease-free interval was 13.3 months. The 2-year progression-free survival (PFS) and OS rates were 33.8% and 58%, respectively. SBRT with systemic therapy was well-tolerated and effective for patients with lung metastases (18). In a retrospective analysis of real-world data, Duan *et al.* investigated 86 oligometastatic ESCCs treated with local radiotherapy plus programmed cell death protein 1 (PD-L1) inhibitors and found that the 1- and 2-year PFS rates were 61.4% and 26.7%, respectively. The objective response rate and disease control rate were 91.3% and 57.3%, respectively. Only 1 patient was observed as having a grade 5 treatment-related adverse event. Local therapy plus PD-L1 was shown to be a safe and effective treatment option (19). Our study focused on OS after ESCC recurrence in patients with low-risk OLR and found that CCLT was associated with a better 2-year OS after recurrence than CT (66.7% *vs.* 30.4%, P=0.003). Moreover, CCLT was a significant independent predictor of a favorable OS after recurrence. A select subgroup of patients with ESCC with low-risk OLR benefited from CCLT.

The lack of consensus regarding the definition of OLR and OMD makes identification of prognostic factors in patients with EC more challenging. Several studies have investigated the factors that could be utilized in daily clinical practice for better patient selection. DFI, defined as the phase between the date of surgery and the date of diagnosis of recurrence, has been treated as a prognostic factor in many studies. Ohkura *et al.* studied 206 patients with EC with recurrence after radical therapy and found that a DFI ≥12 months had a better OS than a DFI <12 months (4). Ghaly *et al.* (20) found that DFI was an independent prognostic factor for isolated recurrence in patients with EC treated with definitive treatment, which is similar to the findings of Shiono who found that in 57 patients with EC with pulmonary metastases who underwent resection, patients with a DFI ≤12 months had a worse OS than those with a DFI >12 months. Moreover, the DFI is an independent factor for OS (21). In our study, a DFI >12 months was also a clinical factor significantly related to 2-year OS in patients with ESCC with recurrence.

In some studies, the location of the metastasis was treated as a prognostic factor for EC recurrence. Nobel *et al.* studied 104 EC cases with isolated solid organ recurrence in the liver, lung, and brain and found that patients with lung oligometastases had longer median OS than those with brain or liver oligometastases (P<0.001) (22). Depypere *et al.* studied 766 patients with EC with recurrence and found that patients with solitary LN recurrence located in one region had a superior OS than those with metastasis in single organs, including the liver, brain, lung, and adrenal glands (16.8 *vs.* 9.9 months, P=0.0074) (23). Grou-Boileau *et al.* studied 755 esophageal cancer patients and found that 27 patients (3.6%) exhibited locoregional recurrence after esophagectomy following neoadjuvant therapy. Locoregional recurrence in that study was defined as pathologically confirmed recurrences at the anastomosis or radiologically confirmed mediastinal and celiac LN metastasis. Local therapy including radiotherapy and surgery were the main modality used in this study and the 2- and 5-year OS were 61.1% and 22.2%, respectively (24). In our study, the 2-year OS rates after recurrence in patients with EC with isolated solid organ recurrence in the lung, liver, bone, and brain were 61.1%, 0%, 50%, and 42.9%, respectively. The OS rate of patients with low-risk OLR with liver oligometastases was significantly worse than that of those with lung oligometastases (P=0.009). Yokoyama *et al.* found that rectal cancer patients with isolated lung metastases had a more indolent course and should be treated with surgery, which leads to a better prognosis compared with that of patients with liver and brain metastases. Moreover, the wide application of magnetic resonance imaging could enable the earlier detection of small lesions in the brain and liver to achieve better results (25). The OS after EC recurrence in patients with high-risk OLR according to the presence of regional recurrence and/or regional LN metastases was not statistically significant in the current study (2-year OS 14.6% *vs.* 14.3%; P=0.83).

The strengths of our study include that we precisely defined low-risk OLR and reported that CCLT is a particularly promising treatment method for EC with low-risk OLR according to our data. In addition, our study further analyzed the OS difference among patients with low-risk OLR with isolated solid organ recurrence in the lung, liver, bone, and brain and demonstrated that patients with lung oligometastases had longer OS than those with liver oligometastases. These results will help oncologists to define low-risk OLR and select optimal treatment methods for ESCC patients with low-risk OLR after curative resection in real-world settings. However, this study had some limitations. First, the number of low and high-risk OLR cases included was limited to a single institution, and more data will be required to verify our results. Additionally, the number of patients with low-risk OLR treated with CCLT was also limited, and the role of CCLT in these patients needs to be elucidated in further studies. Second, selection bias inherent in retrospective studies may have reduced the overall validity of our results. Third, owing to the lack of data on progression-free survival and cause-specific survival, these factors were not included in the assessment.

Conclusions

Our results showed that low-risk OLR is reasonably defined as ≤5 metastases safely treatable with curative intent in a single organ. Patients with ESCC who experience low-risk OLR after curative resection treated with CCLT had a favorable OS compared to those treated with CT alone in multivariable analysis. Thus, CCLT is a promising treatment option for patients with ESCC and low-risk OLR. Prospective randomized studies to verify our results are warranted.

Acknowledgments

The authors thank all patients who participated in the study. *Funding:* This research was funded by the National Clinical Key Specialty Construction Program, 2021 and Fujian Provincial Clinical Research Center for Cancer Radiotherapy and Immunotherapy (No. 2020Y2012).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-205/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-205/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-205/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-205/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of Fujian Cancer Hospital (No. YKT2021-005-01), and informed consent was taken from all the patients.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Liu S, Wen J, Yang H, et al. Recurrence patterns after neoadjuvant chemoradiotherapy compared with surgery alone in oesophageal squamous cell carcinoma: results from the multicenter phase III trial NEOCRTEC5010. Eur J Cancer 2020;138:113-21.
3. Xi M, Hallemeier CL, Merrell KW, et al. Recurrence Risk Stratification After Preoperative Chemoradiation of Esophageal Adenocarcinoma. Ann Surg 2018;268:289-95.
4. Ohkura Y, Shindoh J, Ueno M, et al. Clinicopathologic Characteristics of Oligometastases from Esophageal Cancer and Long-Term Outcomes of Resection. Ann Surg

Oncol 2020;27:651-9.
5. Miyata H, Yamasaki M, Kurokawa Y, et al. Survival factors in patients with recurrence after curative resection of esophageal squamous cell carcinomas. Ann Surg Oncol 2011;18:3353-61.
6. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
7. Yamaguchi H, Kato T, Honda M, et al. Effectiveness of proton beam therapy for liver oligometastatic recurrence in patients with postoperative esophagus cancer. J Radiat Res 2023;64:582-9.
8. Morinaga T, Iwatsuki M, Yamashita K, et al. Oligometastatic recurrence as a prognostic factor after curative resection of esophageal squamous cell carcinoma. Surg Today 2021;51:798-806.
9. Fode MM, Høyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases. Radiother Oncol 2015;114:155-60.
10. Franceschini D, De Rose F, Franzese C, et al. Predictive Factors for Response and Survival in a Cohort of Oligometastatic Patients Treated With Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys 2019;104:111-21.
11. Klement RJ, Hoerner-Rieber J, Adebahr S, et al. Stereotactic body radiotherapy (SBRT) for multiple pulmonary oligometastases: Analysis of number and timing of repeat SBRT as impact factors on treatment safety and efficacy. Radiother Oncol 2018;127:246-52.
12. Phillips R, Shi WY, Deek M, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol 2020;6:650-9.
13. Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. J Thorac Oncol 2017;12:36-42.
14. Lonardi S, Guarneri V. To resect or not to resect?-the dilemma in oligometastatic breast cancer. Hepatobiliary Surg Nutr 2022;11:623-5.
15. Saeed H, Kirby AM. Local therapies for managing oligometastatic breast cancer: a review. Ann Breast Surg 2022;6:4.
16. Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study. Radiother Oncol 2022;173:269-76.
17. Kanamori J, Aokage K, Hishida T, et al. The role of pulmonary resection in tumors metastatic from esophageal carcinoma. Jpn J Clin Oncol 2017;47:25-31.
18. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys 2020;108:707-15.
19. Duan Y, Qin W, Yang L, et al. Safety and Efficacy of Concurrent or Sequential Radiotherapy Plus (PD-1) Inhibitors in Oligometastatic Esophageal Cancer. Cancer Manag Res 2023;15:55-65.
20. Ghaly G, Harrison S, Kamel MK, et al. Predictors of Survival After Treatment of Oligometastases After Esophagectomy. Ann Thorac Surg 2018;105:357-62.
21. Shiono S, Kawamura M, Sato T, et al. Disease-free interval length correlates to prognosis of patients who underwent metastasectomy for esophageal lung metastases. J Thorac Oncol 2008;3:1046-9.
22. Nobel TB, Sihag S, Xing X, et al. Oligometastases After Curative Esophagectomy Are Not One Size Fits All. Ann Thorac Surg 2021;112:1775-81.
23. Depypere L, Lerut T, Moons J, et al. Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. Dis Esophagus 2017;30:1-8.
24. Grou-Boileau F, Tankel J, Nevo Y, et al. Locoregional Recurrence of Esophageal Cancer Treated with Curative Intent Local Salvage Therapy: A Single Center Experience. J Gastrointest Cancer 2023;54:1292-9.
25. Yokoyama S, Mitsuoka M, Kinugasa T, et al. Survival after initial lung metastasectomy for metastatic colorectal cancer in the modern chemotherapeutic era. BMC Surg 2017;17:54.

Cite this article as: Li T, Ke D, Fu X, Dai Y, Lin J, Anker CJ, Bai Z, Li J. Prognosis for local radical treatment in patients with esophageal squamous cell carcinoma with low-risk oligometastatic recurrence after curative resection: a retrospective cohort study. J Gastrointest Oncol 2024;15(3):807-817. doi: 10.21037/jgo-24-205

