Clinical Research

Implications of Liver-Directed Therapy for Postoperative Hepatic Metastasis from Esophageal Cancer

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Background: Distant recurrence of esophageal cancer (EC), even after radical resection, is common, and the most frequent site of EC metastasis is the liver. However, a multidisciplinary treatment strategy for postoperative liver metastasis (LM) from EC has yet to be established; in particular, the role of liver-directed therapy (LDT) remains uncertain. We investigated the clinicopathological features and outcomes of patients undergoing post-esophagectomy LM with versus without LDT to explore its therapeutic implications.
Methods: Among 624 consecutive patients undergoing R0/R1 esophagectomy for EC, 30 were identified in whom LM had developed as the initial recurrence. Their characteristics were retrospectively reviewed.
Results: Six of the 30 subjects underwent LDT for metachronous LM. Five of those 6 also received systemic chemotherapy. A comparison between the 6 LDT and 24 non-LDT cases revealed no significant differences in major clinicopathological and operative factors, except for concurrent metastasis to extrahepatic organs (1/6 vs. 15/24, p=0.044). Twenty-nine of the 30 patients died during the study period, whereas 1 who had received multimodal treatment with LDT remained alive more than 200 months after multiple LM had been detected. Kaplan-Meier analysis for survival after LM demonstrated significantly prolonged survival in LDT cases compared to non-LDT cases treated with systemic chemotherapy alone (p=0.014). Even when the analysis was limited to patients without extrahepatic metastasis, this significant prognostic advantage of LDT was maintained (p=0.047).
Conclusion: Multimodal treatment combined with LDT might be beneficial for patients with metachronous LM from EC and should therefore be considered a potential treatment option.

Keywords: Esophageal neoplasms, Esophageal surgery, Liver-directed therapy, Liver metastasis, Recurrence

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality worldwide, accounting for 544,000 deaths in 2020 [1,2]. Despite advances in diagnostic and therapeutic modalities, the survival outcomes of patients with EC are not yet satisfactory. Although surgical resection remains the most common curative-intent treatment for EC, the postoperative recurrence rate is reportedly as high as 38% (435/1,147), with 55% of such cases developing distant metastasis [3]. The most frequent site of distant metastasis from EC is the liver, followed by the lungs, bone, and brain [4-6]. Systemic chemotherapy is generally considered to be the standard treatment for hepatic recurrence following EC resection, but its prognostic relevance is limited, with a reported median post-recurrence survival of only 7 months [6]. For other malignancies (e.g., colorectal carcinoma), liver-directed therapy (LDT), which includes surgical resection, irradiation and radiofrequency ablation (RFA), is regarded as being effective, and possibly even a curative strategy for liver recurrence [7-9]. However, the role of liver-focused management for hepatic recurrence of EC remains poorly understood [9], and thus merits further exploration.

We retrospectively assessed the characteristics and the survival outcomes of cases experiencing hepatic recurrence following surgery for EC with versus without LDT, with the aim of determining the clinical implications of LDT for this aggressive entity.

Methods

Study population

Information was obtained from a database prospectively assembled and maintained at the Department of Gastrointestinal Surgery, the University of Tokyo Hospital. We identified 624 consecutive patients, all with complete clinicopathological data available, who had undergone R0/R1 subtotal esophagectomy for histologically diagnosed EC between September 2004 and December 2018 at the University of Tokyo Hospital. Patients receiving emergency esophagectomy and those with rare malignancies (neuroendocrine carcinoma, carcinosarcoma, melanoma, salivary gland-type carcinoma, or hepatoid carcinoma) or with synchronous metastatic diseases were excluded at the start of the study. Adenocarcinomas of the esophagogastric junction (Siewert types I and II) were not regarded as EC in this study [10]. All subjects had undergone postoperative follow-up surveillance for at least 5 years after surgery or until death. Postoperative examinations routinely included a detailed physical examination, esophagogastroduodenoscopy, postcontrast computed tomography, and laboratory blood tests, in accordance with the guidelines of the Japan Esophageal Society [11]. Follow-up of all patients in the current analysis was completed in March 2022.

Among the 624 cases, 30 (4.8%) had experienced metachronous liver metastasis (LM) as an initial relapse. LM arising within a month after esophagectomy (n=1) was not taken to be an actual recurrence and such patients were thus excluded from the analysis. The diagnosis of LM was based on an evaluation by experienced radiologists, excluding the likelihood of primary hepatic malignancy, other benign lesions, and metastases of non-esophageal origin.

Detailed clinicopathological factors and therapeutic courses of these 30 cases were retrospectively reviewed. The disease staging was based on the eighth edition of the TNM (tumor-node-metastasis) classification, established by the Union for International Cancer Control [12]. This study was approved by the local ethics committee of the Faculty of Medicine at the University of Tokyo (approval no. 3962). Because this was a retrospective study, the need for informed consent from each patient was waived.

Operative procedure for esophagectomy

For resectable EC, we performed subtotal esophagectomy with 2- or 3-field lymph node dissection. Two-field lymphadenectomy was generally applied for lower thoracic and abdominal EC and 3-field lymphadenectomy for upper and middle thoracic EC. Esophagectomy was achieved through right thoracotomy by either the Ivor-Lewis or the McKeown method, or by employing a non-transthoracic technique combining transcervical video-assisted and transhiatal approaches [13]. The abdominal approach was laparoscopic surgery or open laparotomy, tailored to each individual case. Neoadjuvant therapy followed by esophagectomy is generally recommended for advanced-stage esophageal squamous cell carcinoma in Japan [11], and we accordingly introduced preoperative chemotherapy for suitable EC cases. Postoperative complications were defined as being grade III or greater according to the Clavien-Dindo classification [14].

Liver-directed local therapy

LDT was defined as local treatment targeting only hepatic tumors, not the entire liver. It included surgical metastasectomy, radiotherapy delivered by stereotactic radiation therapy (SRT), and RFA. SRT is a specialized radiotherapeutic modality employing precisely focused radiation beams directed at locoregional lesions, while minimizing the involvement of adjacent normal structures [15]. RFA is a minimally invasive technique applying heat energy in the form of radio waves to eliminate cancer cells within the liver [16]. LDT was applied to patients with LM of EC only when it was deemed to be potentially beneficial in terms of survival or palliation after multidisciplinary consultations including clinical oncologists, radiologists, gastroenterologists, and hepatic surgeons. The indications for LDT were not definitely determined, but patients of advanced age (≥80 years) and/or in poor physical condition (Eastern Cooperative Oncology Group performance status ≥2) were generally taken to have contraindications for surgical hepatectomy.

Statistical analysis

The medians and ranges of continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Pearson chi-square test or the Fisher exact test, as appropriate. The level of significance was set at $p<0.05$ for a 2-tailed test. Survival curves

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were created using the Kaplan-Meier method and were compared employing the log-rank test. All statistical analyses were carried out using JMP ver. 16.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The basic demographic variables of our 30 subjects are

Table 1. Baseline demographics of the 30 patients

Characteristic	Total (n=30)	LDT (n=6)	Non-LDT (n=24)	p-value
Age (yr)[a]	70 (50–83)	62 (54–83)	71 (50–82)	0.84
Sex				0.54
Male	27 (90.0)	5 (83.3)	22 (91.7)	
Female	3 (10.0)	1 (16.7)	2 (8.3)	
Esophageal cancer				
Locus				0.31
Upper third	3 (10.0)	0	3 (12.5)	
Middle third	10 (33.3)	1 (16.7)	9 (37.5)	
Lower third	17 (56.7)	5 (83.3)	12 (50.0)	
Histology				0.22
Adenocarcinoma	5 (16.7)	2 (33.3)	3 (12.5)	
Squamous cell carcinoma	25 (83.3)	4 (66.7)	21 (87.5)	
Perioperative chemotherapy				0.71
Absent	12 (40.0)	2 (33.3)	10 (41.7)	
Present	18 (60.0)	4 (66.7)	14 (58.3)	
Perioperative irradiation				0.28
Absent	26 (86.7)	6 (100.0)	20 (83.3)	
Present	4 (13.3)	0	4 (16.7)	
pT category				0.67
≤T1	7 (23.3)	1 (16.7)	6 (25.0)	
≥T2	23 (76.7)	5 (83.3)	18 (75.0)	
pN category				0.54
N0	8 (26.7)	1 (16.7)	7 (29.2)	
≥N1	22 (73.3)	5 (83.3)	17 (70.8)	
Lymphovascular invasion				0.36
Absent	3 (10.0)	0	3 (12.5)	
Present	27 (90.0)	6 (100.0)	21 (87.5)	
Esophagectomy procedure				0.22
Open thoracotomy	25 (83.3)	6 (100.0)	19 (79.2)	
Thoracoscopic/robotic surgery	5 (16.7)	0	5 (20.8)	
Nodal dissection				0.19
Three-field	12 (40.0)	1 (16.7)	11 (45.8)	
Two-field or less	18 (60.0)	5 (83.3)	13 (54.2)	
Postoperative complications				0.33
Absent	20 (66.7)	5 (83.3)	15 (62.5)	
Present	10 (33.3)	1 (16.7)	9 (37.5)	
Liver recurrence				
Disease-free interval (mo)	6.5 (1.7–40.2)	8.2 (4.2–8.9)	5.5 (1.7–40.2)	0.36
Metastasis to other organs				0.044*
Absent	14 (46.7)	5 (83.3)	9 (37.5)	
Present	16 (53.3)	1 (16.7)	15 (62.5)	
No. of initial liver metastases				0.084
Single	7 (23.3)	3 (50.0)	4 (16.7)	
Multiple	23 (76.7)	3 (50.0)	20 (83.3)	

Values are presented as median (range) or number (%).
LDT, liver-directed therapy.
*p<0.05. [a] At esophagectomy.

presented in Table 1. There were 27 men and 3 women, with a median age of 70 years (range, 50–83 years) at esophagectomy. The median disease-free interval (DFI), defined as the interval between primary tumor resection and liver recurrence was 6.5 months (range, 1.7–40.2 months). Of the 30 patients, 6 had undergone LDT for metachronous LM with/without other therapeutic modalities. There were no significant intergroup differences between the LDT (n=6) and non-LDT groups (n=24) in age, sex, tumor location, histological type, perioperative chemotherapy, perioperative radiation, tumor depth (pT category), nodal metastasis (pN category) or lymphovascular involvement. Likewise, no statistically significant differences were noted with respect to operation-related factors such as esophagectomy procedure, lymph node dissection, and postoperative complications. Multiple LM tended to be less frequent (p=0.084) and concurrent metastasis to extrahepatic organs was significantly less common (p=0.044) in the LDT group.

Post-recurrence course

The median follow-up period after esophagectomy was 14.0 months (range, 3.8–213.5 months) in our 30 patients, with only 1 remaining alive to date. Fig. 1 presents the therapeutic courses following LM in these 30 cases. Among the 16 patients with both LM and extrahepatic organ metastasis, 10 underwent systemic chemotherapy alone, 5 were treated with best supportive care (BSC) without aggressive anticancer therapy, and one received both LDT

and chemotherapy. All 16 patients died of EC recurrence. Of the 14 patients with LM without extrahepatic extension, 5 received systemic chemotherapy alone and 4 received BSC. The remaining 5 patients underwent LDT, of whom 1 underwent LDT alone (hepatic metastasectomy) and 4 underwent LDT with chemotherapy. Thirteen had died and the other, who had been given multimodal treatment with LDT and chemotherapy, was still alive at the completion of follow-up of the present study.

The detailed clinicopathological characteristics and outcomes of the 6 patients who received LDT for LM are shown in Table 2. There were 5 men and 1 woman, with ages at esophagectomy ranging from 54 to 83 years. Surgical hepatectomy, RFA, and SRT were sequentially carried out in each patient. Three patients died of recurrence (lung, lymph nodes) and 2 died of other diseases (pneumonia, cerebral hemorrhage). As noted above, 1 male patient (case 5) has remained alive for more than 200 months since the initial detection of LM, apparently fulfilling the criteria for a cure of EC. His treatment course is described below.

The patient received subtotal esophagectomy with right thoracotomy for EC (squamous cell carcinoma, pT3N0M0) without any preoperative therapeutic interventions. Post-contrast computed tomography performed for monitoring purposes approximately 9 months after surgery revealed 4 sporadic LM lesions in S2/3, S3, S7, and S8 (Fig. 2A–C). He was given 4 courses of DCF (docetaxel, cisplatin, and 5-fluorouracil) chemotherapy, which diminished the S2/3 and S3 lesions. RFA was subsequently administered for the remaining S7 and S8 lesions. Thereafter, the
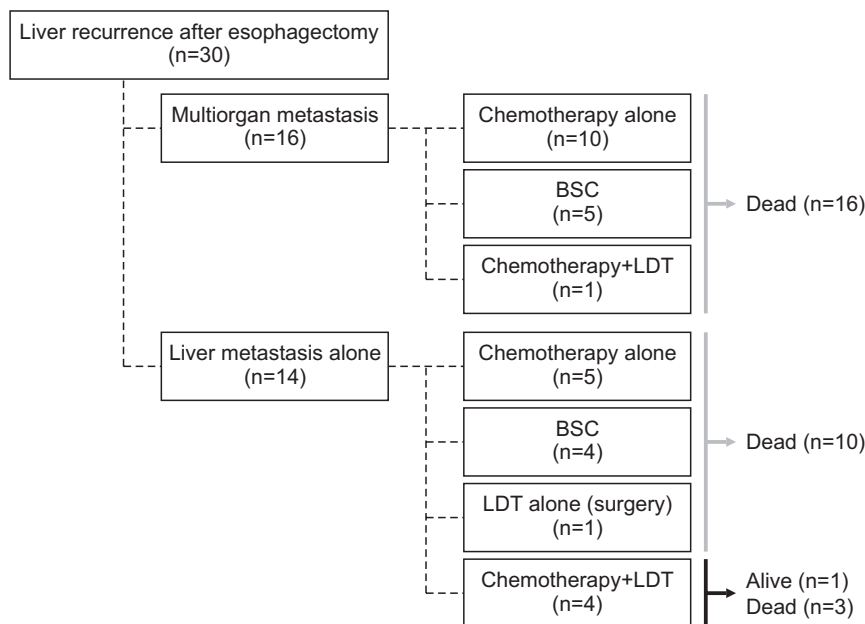

Fig. 1. Treatment courses following liver recurrence. BSC, best supportive care; LDT, liver-directed therapy.

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Table 2. Clinicopathological characteristics and outcomes of the 6 patients who underwent liver-directed local therapy

| Case | Age (yr)/ sex | Esophageal cancer | | | Disease-free interval (mo) | Liver recurrence | | | Survival after recurrence |
		Histology	pTNM	Perioperative therapy		Extrahepatic metastasis	No. of LM	Post-recurrence treatment	
#1	54/M	AD	T3N3M0	Adjuvant CT (FP)	6.4	Absent	Multiple (S1, S7)	CT (DCF); SRT; RFA	Dead (pulmonary recurrence); 16.8 mo
#2	60/M	SCC	T3N2M0	Neoadjuvant CT (DCF); adjuvant CT (S-1)	8.1	Absent	Solitary (S4)	SRT; CT (DCF)	Dead (nodal recurrence); 21.4 mo
#3	62/M	SCC	T4N1M0	None	4.2	Absent	Solitary (S5)	SRT; hepatectomy	Dead (cerebral hemorrhage); 9.9 mo
#4	83/F	AD	T3N2M0	Adjuvant CT (FP)	8.2	Absent	Multiple (S4, S8)	CT (DCF); RFA; CT (DCF, PTX)	Dead (pulmonary recurrence); 32.1 mo
#5	61/M	SCC	T3N0M0	None	8.9	Absent	Multiple (S2, S3, S7, S8)	CT (DCF); RFA; hepatectomy	Alive; 204.7 mo
#6	78/M	SCC	T1N3M0	Adjuvant CT (FP)	8.3	Present (LN)	Solitary (S4)	CT (PTX); SRT; ICI (NIV)	Dead (pneumonia); 16.7 mo

Regimens of CT/ICI: DCF, FP, PTX, NIV, and S-1.
LM, liver metastasis; M, male; F, female; AD, adenocarcinoma; CT, chemotherapy; FP, 5-fluorouracil and cisplatin; DCF, docetaxel, cisplatin and 5-fluorouracil; SRT, stereotactic radiation therapy; RFA, radiofrequency ablation; SCC, squamous cell carcinoma; S-1, oral 5-fluorouracil; PTX, paclitaxel; LN, lymph node; ICI, immune checkpoint inhibitor; NIV, nivolumab.

Fig. 2. Postoperative monitoring with computed tomography detected liver metastases in S2/3 (A), S3 (B), and S7 and S8 (C) (arrows).

S3 lesion showed gradual regrowth. Administration of RFA for this S3 lesion was deemed to not be feasible, due to its location just behind the retrosternal gastric conduit (Fig. 2B). After consulting with liver surgeons, S3 partial hepatectomy was carried out 34 months after the initial LM diagnosis. No additional treatments have been administered, to date, and the patient has remained free of recurrent disease for 170 months since the hepatectomy.

Survival analysis

We carried out a post hoc Kaplan-Meier analysis for survival time after liver recurrence. In all LM cases, except 9 patients who received BSC only (n=21), the LDT group (n=6) showed significantly better survival than the non-LDT group treated with systemic chemotherapy alone (n=15) (p=0.014) (Fig. 3A). Even when the cohort was limited to those without extrahepatic metastasis (n=10), the significant survival superiority of the LDT group persisted (p=0.047) (Fig. 3B).

Discussion

The prognostic relevance of LDT for LM from certain malignancies, such as colorectal cancer, has already been established [7-9]. In such tumors, LDT can achieve good
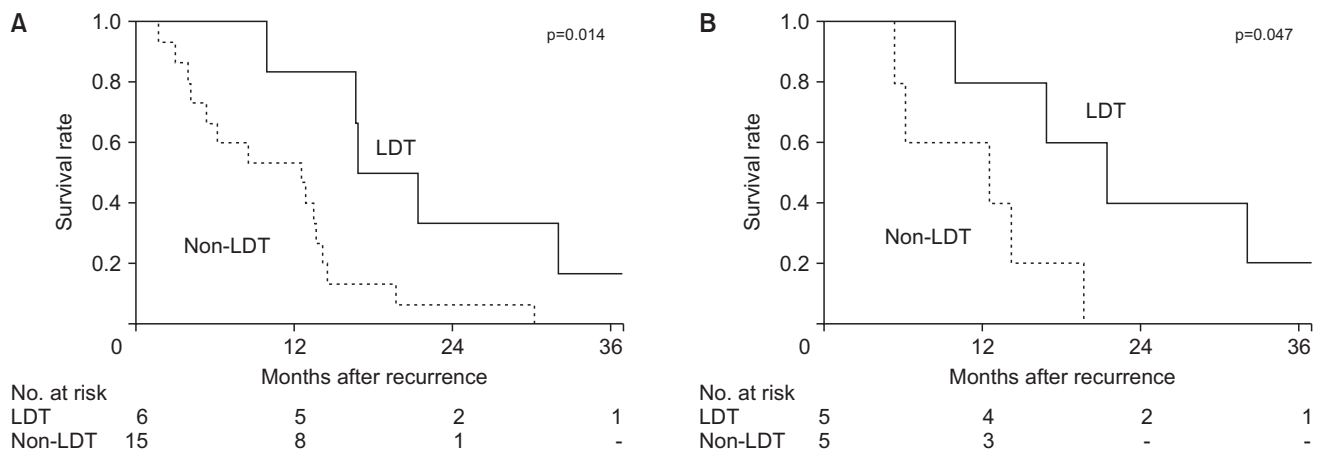
Fig. 3. Kaplan-Meier survival curves of the groups with versus without liver-directed local therapy (LDT). (A) All 21 cases with liver recurrence (excluding those who received only best supportive care); (B) 10 cases with liver recurrence, but no metastases to other organs.

local disease control, and even a cure in some cases. Its rationale lies in the liver having a role in filtering tumor cells before their spread into the systemic circulation, and tumor dissemination is therefore considered to be kept within the liver at the pre-systemic phase [17]. Although this stepwise pattern of progression is also theoretically applicable to EC, extrahepatic extension is more common in LM of EC and the responsiveness of recurrent EC to chemotherapy or chemoradiotherapy is low, with complete remissions being quite rare [18]. The 3-year overall survival for patients with LM from EC is reportedly as low as 12%–32% [19] and very few cases survive beyond 5 years, according to a Surveillance, Epidemiology, and End Results program dataset [5]. The therapeutic role of LDT has yet to be fully ascertained in liver recurrence of EC, presumably due to the dismal prognosis and tendency for extrahepatic spread of this disease entity.

Hepatic relapse of EC is considered to have a multifactorial etiology, and a few studies have suggested prognostic factors associated with liver recurrence of EC such as adenocarcinoma histology [20], oligometastatic presentation [21] and longer DFI [22,23]. Two prior investigations also demonstrated that liver surgery may yield a survival benefit for selected patients with LM from squamous cell carcinoma, including EC [24,25]. Unfortunately, however, these data did not focus specifically on EC; therefore, the clinical implications of hepatectomy for metachronous LM of EC remain uncertain. In fact, another group, analyzing 5 patients who underwent hepatectomy for hepatic recurrence from EC, suggested that the prognostic value of surgical intervention remained a matter of debate [26]. Our results, implying that LDT, including hepatic metastasectomy, may provide a prognostic advantage, would thus serve as a valu-

able reference for oncological care providers. It is noteworthy that, in our cohort, 1 patient achieved exceedingly long-term survival after metachronous multifocal LM, which appeared to have been eradicated by successive systemic, ablative, and surgical treatments. This clinical experience allows us to speculate that a multimodal combination of systemic chemotherapy and LDT may provide a chance of cure, even with multiple LM or a short DFI (<12 months).

Advances in therapeutic technology have enhanced the safety and feasibility of local treatments such as hepatectomy, RFA and SRT, and these modalities have become more readily available [7]. Therefore, these components of LDT are options for liver relapse even in EC, providing hope and possibly even optimism, especially for patients without extrahepatic metastasis, with well-maintained performance status and who can tolerate LDT. Our results suggest that neither multifocal LM nor short DFI is an absolute contraindication for LDT. Given that establishing concrete criteria for selecting candidates for LDT remains an unresolved issue, more research is needed. Moreover, it is difficult to ascertain which LDT modality is the most relevant to the outcomes of patients with EC-LM. At present, we can assert that the multidisciplinary team approach, especially one including gastroenterologists and liver surgeons, is essential for providing optimal treatments tailored to each individual post-esophagectomy LM patient [27].

The current study has limitations. Although the present analysis was based on a prospectively collected database, indication selection bias is inherent and inevitable due to the retrospective nature of the study. For instance, information on the performance status of each patient was not fully available and thus was lacking in the current investi-

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gation. The relatively limited number of patients from a single center and the consequent lack of multivariate estimations are also concerns, though essentially complete follow-up data were available for all cases. In particular, survival analysis for cases with solitary LM was potentially associated with a type I error due to the small number of the subjects (n=10). A cumulative multi-center analysis with adequate statistical methods (e.g., propensity-score adjustment analysis) is warranted for further assessment of the actual survival outcomes and prognostic factors associated with LDT.

In conclusion, we conducted a comprehensive review of our clinical experience with 30 cases of liver recurrence after EC surgery. Patients who underwent LDT had significantly better survival outcomes than those without LDT. Multimodal treatment combined with LDT might have a prognostic benefit, possibly even providing a chance for cure, in some patients with metachronous LM from EC. LDT should thus be considered an option for suitable candidates.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

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