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Pattern of Postoperative Recurrence and Hepatic and/or Pulmonary Resection for Liver and/or Lung Metastases From Esophageal Carcinoma

Hirofumi Ichida · Hiroshi Imamura · Jiro Yoshimoto · Hiroyuki Sugo · Yoshiaki Kajiyama · Masahiko Tsurumaru · Kenji Suzuki · Yoichi Ishizaki · Seiji Kawasaki

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Abstract
Background We assessed the benefit of hepatic and pulmonary resections in patients with liver and lung recurrences, respectively, after resection of esophageal carcinoma.
Methods The study population consisted of 138 consecutive patients with recurrent esophageal carcinoma after esophagectomy conducted between 2003 and 2005. The pattern, timing of appearance, and the prognosis of these recurrences were investigated, paying particular attention to those undergoing hepatic and pulmonary resections.
Results In total, 55 and 92 patients developed locoregional and distant-organ metastases 13 and 6 months (median) after surgery, respectively, including 9 patients with both types of recurrence. The distant-organ metastases were found in the liver ($n = 26$), lung ($n = 27$), bone ($n = 21$), and other organs ($n = 29$). Patients with pulmonary recurrences had a better overall prognosis (median survival after recurrence detection 13 months) than those with hepatic metastases (5 months) or nonhepatic nonpulmonary metastases. (3 months) Hepatic and pulmonary resections were carried out in patients with oligonodular ($n = \leq 2$) isolated liver and lung metastases ($n = 5$, respectively). Although the survivals of patients with lung metastases who were treated/not treated by pulmonary resection were different (median survival: 48 vs. 10 months, $p < 0.01$), the difference in the survivals between patients with hepatic metastases who were treated/not treated by hepatic resection reached only borderline statistical significance (13 vs. 5 months, $p = 0.06$).
Conclusions Resection of pulmonary metastases yields a survival benefit in properly selected patients. The benefit of resection for hepatic metastases remains controversial.

Introduction

Although surgical resection remains the mainstay of treatment for esophageal carcinoma, the long-term outcome of patients remains poor [1]. Nearly half of the patients undergoing esophagectomy develop recurrences, and in approximately half of these cases the recurrence appears within 1 year of the surgery [2–7]. The median survival of these patients following recurrence detection is reportedly 2.7–7.0 months [2, 6–8] leading to a 5 year survival of 31.0–56.8 % after surgery [2–5, 8]. Postoperative recurrences in patients with esophageal carcinoma have been classified as locoregional and distant-organ metastases. Most distant-organ recurrences are hematogenous metastases to lung, liver, and bone [2–8]. Patients with distant-organ metastases reportedly have a poorer prognosis than those with locoregional metastases [3–5]. Chemotherapy and/or radiotherapy are usually selected as salvage treatment for patients with hematogenous recurrences [5, 7].

H. Ichida · H. Imamura (✉) · J. Yoshimoto · H. Sugo · Y. Ishizaki · S. Kawasaki
Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
e-mail: himamura-tky@umin.ac.jp

Y. Kajiyama · M. Tsurumaru
Department of Esophageal and Gastroenterological Surgery, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

K. Suzuki
Department of General Thoracic Surgery, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

The results have been disappointing, however, and these therapies can at most be considered palliative.

Liver resection is widely accepted as the only treatment modality that may lead to potential cure in patients with metastatic liver tumors from cancers of various visceral organs, including colorectal [9–11] and neuroendocrine [12, 13] carcinomas. Likewise, pulmonary resection for metastatic lung tumors has been established as a standard therapeutic procedure in properly selected patients with colorectal [11, 14] and genitourinary carcinomas and those with various types of sarcoma [15, 16]. In contrast, there are only anecdotal reports of hepatic or pulmonary resection in patients with liver and/or lung metastases from esophageal carcinoma, largely because of the poor baseline prognosis of this disease entity [17–21]. Therefore, it remains controversial whether surgical resection is an acceptable treatment offering benefit to patients with esophageal carcinoma and metastatic hepatic and/or lung tumors.

In the present study, we attempted to investigate the survival benefit of hepatic and pulmonary resection for metastatic esophageal carcinoma in the liver and lung, respectively. Toward this end, we conducted a retrospective cohort study in patients who had been treated by curative resection for primary esophageal carcinoma. We assessed the pattern and timing of the appearance of the recurrences. We also classified the postrecurrence survival according to the type of recurrence, paying particular attention to a comparison between those who were treated/not treated by hepatic and pulmonary resection.

Materials and methods

Patients

The primary cohort comprised 315 consecutive patients who had undergone curative subtotal esophagectomy with zero- to three-field lymphadenectomy for esophageal cancer between January 2003 and December 2005 at the Department of Esophageal and Gastroenterological Surgery in Juntendo University Hospital, Japan. They consisted of 272 men and 43 women with a median age of 64 years (range 38–91 years).

Squamous cell carcinoma ($n = 295$) was the predominant histologic subtype (adenocarcinoma, $n = 8$; other histologic types, $n = 12$). The locations of the tumors were as follows: cervical esophagus, 12 patients; upper thoracic esophagus, 50 patients; middle thoracic esophagus, 155 patients; lower thoracic esophagus, 92 patients; abdominal esophagus, 6 patients. The stages of the esophageal cancer in these patients at the time of the primary esophagectomy were as follows: stage 0 in 17 patients, stage I in 24 patients, stage II in 71 patients, stage III in 127 patients, stage IV in 78 patients.

Neoadjuvant chemoradiotherapy was administered in 59 patients (19 %), and neoadjuvant chemotherapy in 13 (4 %). The overall 30 day and in-hospital mortality rates were 1.6 % ($n = 5$) and 3.8 % ($n = 12$), respectively. Adjuvant chemoradiotherapy was administered in 50 patients (16 %), adjuvant chemotherapy in 87 patients (28 %), and adjuvant radiotherapy in 3 patients (1 %), at the discretion of the surgeon. Cisplatin, docetaxel, and fluorouracil were the drugs mainly used in the chemotherapy and chemoradiotherapy regimens.

Follow-up

Excluding the 12 in-hospital mortalities and 7 patients who were lost to follow-up within 3 months of discharge, complete follow-up data were available for the remaining 296 patients, who were followed up for a median period of 47 months after esophagectomy for primary esophageal carcinoma.

After discharge from the hospital, the patients were followed up monthly by an examination for tumor markers (i.e., assay for squamous cell carcinoma antigen or carcinoembryonic antigen) and every 6 months by chest and abdominal computed tomography (CT), cervical ultrasonography (US), and gastroendoscopy for the first year. Thereafter, the patients were screened by tumor marker assay every 2 months and by chest and abdominal CT, cervical US, and gastroendoscopy every 6 months.

Definition and classification of recurrence

Postoperative recurrence was diagnosed on the basis of imaging studies, usually by detecting changes from the previous imaging findings. When two metastatic sites (e.g., liver and lung metastases) were detected within a month of of the other, these recurrences were defined as simultaneous recurrences (e.g., simultaneous liver and lung metastases). The lesions were classified as locoregional (at the site of the primary tumor, at the anastomotic site, or in lymph nodes) and distant-organ metastases. Distant organs included hematogenous recurrences and "others," such as the pleura and peritoneum. Recurrences in the cervical, celiac axis, and paraaortic lymph nodes were classified as locoregional recurrences according to classifications in previous studies [3, 6].

Criteria for the resection of distant-organ recurrences

Basically, only patients with isolated hepatic or pulmonary recurrences were considered for surgery according to consistent indication criteria used throughout the study period: (1) the primary disease was controlled or controllable; (2)

metastasis was limited to a single organ, either the liver or the lung; (3) the number of metastases was limited to one or two, and it was judged that all of the detected tumors could be removed safely with a clear margin, taking into consideration the general condition of the patient after the primary esophagectomy. In the case of pulmonary recurrences, the surgical indication was not altered by the tumor distribution (i.e., unilateral or bilateral). Thoracic lymph node involvement, however, was an absolute contraindication. In principle, we considered the presence of nonhepatic, nonpulmonary recurrence a contraindication for resection, although surgery was performed in selected cases on a case-by-case basis. We conducted metastasectomy immediately after detecting resectable metastases, without administering neoadjuvant chemotherapy.

Analyses

We initially studied the pattern and timing of appearance of the recurrences in patients who had undergone esophagectomy for primary esophageal cancer. Then, we investigated the postrecurrence survival of the patients, classified according to the pattern of recurrence to examine the natural course of the patients after the development of recurrence. Finally, we scrutinized the processes by which the patients with hepatic and pulmonary recurrences had been selected for surgery. We compared the background characteristics and the survivals of the patients who were treated/not treated by hepatic and pulmonary resections to determine if there had been any selection bias. We also looked at the survival benefit of surgery performed for the recurrences. Furthermore, we investigated the survival benefit of hepatic and/or pulmonary resection, taking into account the inherent bias resulting from the selection procedure. To this end, we conducted a multiple Cox regression analysis and assessed the independent risk ratio of surgical resection adjusted for the imbalance in the distribution of the various prognostic variables between the resected and nonresected groups.

The survival times were estimated by the Kaplan–Meier method, and comparisons were made using the log-rank test. The value of $p < 0.05$ was accepted as denoting statistical significance.

Table 1 Background characteristics of the 138 patients with disease recurrence after primary esophagectomy

	Total ($n = 138$)	Patients undergoing hepatectomy ($n = 5$)	Patients not undergoing hepatectomy ($n = 21$)[a]	Patients undergoing pulmonary resection ($n = 5$)	Patients not undergoing pulmonary resection ($n = 22$)[a]
Patient-related characteristics					
Age (median (range))	63 (38–91)	62 (41–70)	63 (52–84)	61 (52–69)	66 (51–73)
Sex (male/female)	120/18	5/0	18/3	5/0	22/0
Variables related with primary esophageal cancer					
Depth of esophageal cancer (T0[b]/T1/T2/T3/T4)	2/10/14/86/26	0/1/0/3/1	0/3/2/10/6	0/1/0/4/0	1/1/3/14/3
Lymph node metastases (yes/no)	123/15	4/1	17/4	4/1	17/5
Histology (well/moderate/poor/others)[c]	52/65/15/6	3/1/0/1	6/13/2/0	0/5/0/0	7/10/5/0
Location (Ce/Ut/Mt/Lt/Ae)	6/29/65/35/3	0/0/2/3/0	0/2/10/9/0	0/4/1/0/0	0/10/11/1/0
Variables related with first recurrence					
DFI from primary esophagectomy (mo) (median (range))	8 (0–60)	6 (0–14)	6 (1–26)	6 (0–18)	6 (1–23)
No. metastases (median (range) [25–75 percentile])		1 (1–2) [1–2]	3 (1–many) [1–5]	1 (1–2) [1–1]	7.5 (1–many) [3–many]
1		3	7	4	3
2–3		2	5	1	3
4–9		0	4	0	7
>9		0	5	0	9
Maximum size of metastases (mm) (median (range) [25, 75 percentile])		70 (28–120) [41–96]	25 (9–50) [15–30]	18 (15–30) [18–18]	10 (5–50) [10–20]
Multiple organ metastases		1	9	0	6

Results are expressed as the median and range or the number. Numbers in brackets are the 25–75 percentiles

DFI disease-free interval, *Ce* cervical, *Ut* upper thoracic, *Mt* middle thoracic, *Lt* lower thoracic, *Ae* abdominal esophageal

[a] Two patients were included into patients not undergoing hepatectomy and patients not undergoing pulmonary resection because they had concomitant hepatic and pulmonary recurrences

[b] The cancer disappeared after neoadjuvant chemoradiotherapy

[c] Well, Moderate and Poor indicates differentiation of squamous cell carcinoma, Others includes adenocarcinoma, basaloid carcinoma and undifferentiated carcinoma

Results

Pattern and timing of appearance of recurrences after primary esophagectomy for esophageal cancer

Among the 296 patients undergoing esophagectomy for primary esophageal carcinoma, 138 (47 %) had disease recurrence (Table 1, Fig. 1) at the time of the data collection for this study. Figure 1 shows the pattern of metastases/recurrences in these patients. In total, 55 (40 %) and 92 (67 %) patients developed locoregional and distant-organ recurrences, respectively, including 9 (7 %) who developed both types of recurrences (Fig. 1a). Of the 92 patients with distant-organ recurrences, 27 (20 %) had pulmonary recurrence, 26 (19 %) had hepatic recurrence, 21 (15 %) had bone recurrence, and 29 (21 %) had recurrence in other solid organs, including the patients who developed metastases at multiple sites (Fig. 1b). The background characteristics of these 138 patients are shown in Table 1.

In the cases of the primary cancer in the cervical or upper thoracic esophagus, pulmonary recurrences occurred more frequently than hepatic recurrences, with the case being vice versa for those with the primary cancer in the lower thoracic or abdominal esophagus ($p < 0.0001$) (Table 2).

Figure 2 shows the timing of recurrence detection. More than half of all the recurrences were detected within 9 months after the primary cancer surgery. Distant-organ recurrences developed earlier during the postoperative period than the locoregional recurrences: More than half of the distant-organ recurrences developed within 6 months of the primary cancer surgery. There was no significant difference in the temporal profiles of development between the hepatic and pulmonary recurrences.

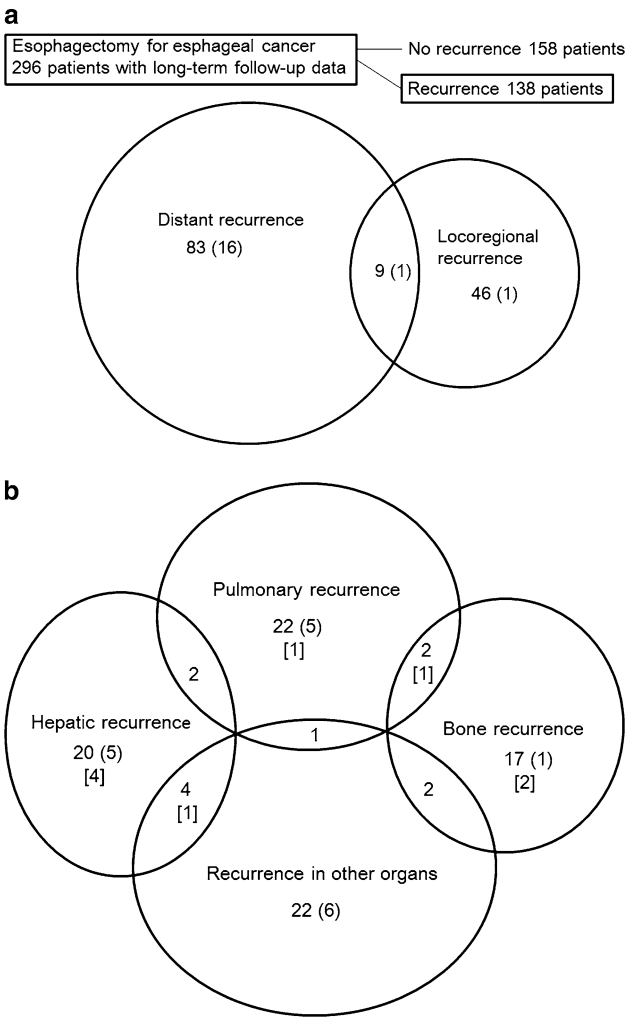

Fig. 1 Venn diagram of the pattern of recurrence/metastases in patients who had undergone primary esophagectomy for esophageal cancer. **a** All of the patients, in whom the recurrence sites were classified into distant organ or locoregional. *Overlapping circles* signify patients with both kinds of metastases. **b** Patients with distant-organ recurrences according to the respective sites of metastases. *Overlapping circles* signify patients with metastases in multiple organs. Other organ metastases include those to the pleura ($n = 9$), brain ($n = 5$), adrenal gland ($n = 5$), kidney ($n = 3$), skin ($n = 3$), peritoneum, pericardium, pancreas ($n = 1$), and rectum ($n = 1$). *Numbers in parentheses* represent the patients who underwent metastasectomy. *Numbers in brackets* represent the number of patients with concomitant locoregional metastases

Patient survival after the detection of recurrences in cases of esophageal cancer

Figure 3 shows the overall survival of the patients after recurrence detection following primary esophagectomy for primary esophageal carcinoma. The median survival time after recurrence detection in the 138 patients, including the patient who died within 2 weeks of detection, was 6 moonths (0–70 months). The estimated 1-, 3-, and 5-year survival rates were 24.6, 4.3, and 1.4, respectively.

Table 2 Incidence of recurrence in relation to the site of primary esophageal cancer

Site of primary esophageal cancer	Distant recurrence ($n = 92$)	Isolated hepatic recurrence ($n = 20$)	Isolated pulmonary recurrence ($n = 22$)
Cervical esophagus, upper thoracic esophagus	22	1 (5 %)	12 (55 %)
Middle thoracic esophagus	48	11 (23 %)	10 (21 %)
Lower thoracic esophagus, abdominal esophagus	22	8 (36 %)	0

$p < 0.0001$, Cochran-Armitage test

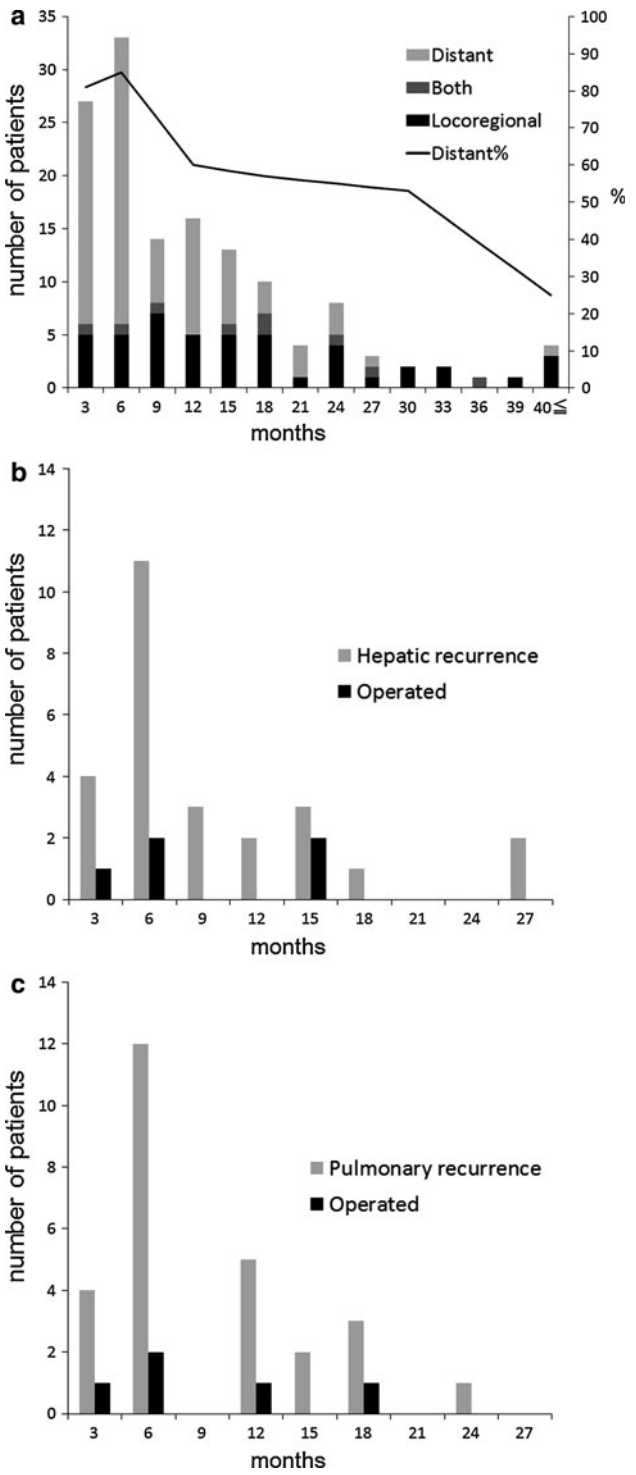

Fig. 2 Timing of appearance of the recurrence following primary esophagectomy. **a** Overall timing of the onset of recurrences classified by distant-organ and locoregional metastases. *Line* represents the ratio of distant-organ/total number of recurrences at the respective time points. Patients who had both distant-organ and locoregional recurrences were counted as having a distant-organ recurrence. **b** Timing of the onset of hepatic recurrence and the number of these patients undergoing hepatectomy. **c** Timing of the onset of pulmonary recurrence and the number of these patients undergoing pulmonary resection

Resection of hepatic, pulmonary, and other solid organ recurrences in cases of esophageal cancer

Figure 4 shows the patient selection process for resection of hepatic and pulmonary recurrences. Of the 26 patients with hepatic recurrences, 5 (19 %) underwent hepatectomy, including one patient who underwent concomitant paraaortic lymph node resection for metastases to this group of lymph nodes detected at the time of hepatectomy. Surgical treatment was not undertaken in the remaining 21 patients for oncologic reasons (17 patients), poor performance status (3 patients), or performance of radiofrequency ablation (RFA) therapy at another hospital (1 patient). Of the 27 patients with pulmonary recurrences, 5 (19 %) underwent resection. Surgical treatment was not undertaken in the remaining 22 patients for oncologic reasons (17 patients) or poor performance status (5 patients). Furthermore, seven patients with nonhepatic nonpulmonary distant-organ metastases underwent resection, as follows: two patients for skin recurrences and one each for pancreatic, kidney, brain, pericardial, or bone recurrence. In addition to these 17 patients who underwent resection for distant-organ recurrences, another patient underwent resection for a locoregional (i.e., isolated lymph node) recurrence, resulting in a total of 18 (13 %) patients in whom resection was undertaken for metastases with curative intent.

The background characteristics of the 10 and 41 patients who were treated or not treated by metastasectomy for hepatic or pulmonary recurrences are summarized in Table 1.

Long-term outcomes after resection of hepatic, pulmonary, and nonhepatic nonpulmonary recurrences of esophageal cancer

Figure 5 shows the overall survival curves for the patients who were treated/not treated by resection of the distant-organ metastases calculated after recurrence detection. There were no in-hospital deaths.

The median survival times of the patients with hepatic recurrences who were treated ($n = 5$) or not treated ($n = 21$) by resection were 13 months (2–70 months) and 5 months (1–16 months), respectively ($p = 0.061$). Of the five patients undergoing resection for hepatic recurrence, one patient was still alive without disease at the time of the data collection for this study (70 months after recurrence detection). The other four patients developed re-recurrence either in the liver (3 patients) or in the lymph nodes (2 patients). All four of these patients died of the disease 2–15 months after recurrence detection.

The median survival times of the patients with pulmonary recurrences who were treated ($n = 5$) or not treated ($n = 22$) by resection were 48 months (10–63 months)

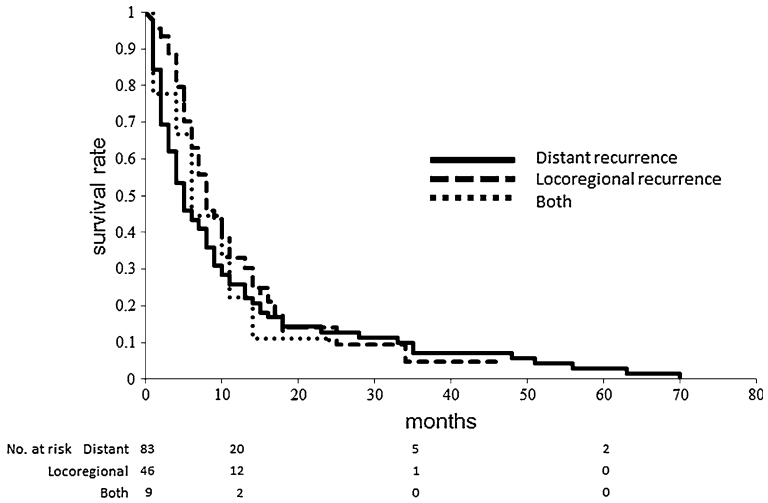

Fig. 3 Survival curves for patients after recurrence detection following primary esophagectomy for esophageal cancer. Patients were classified as having a distant-organ recurrence ($n = 83$), locoregional recurrence ($n = 46$), or both ($n = 9$). The median survival time was 5 months (0–70 months) for the group with distant-organ recurrence, 8 months (0–46 months) for those with locoregional recurrence, and 6 months (1–24 months) for those with both types of recurrence. There was no statistically significant difference in the median survival times between the patients with distant organ recurrence and those with locoregional recurrence ($p = 0.18$)

and 10 months (1–51 months), respectively ($p = 0.009$). Of the 5 patients who underwent pulmonary metastasectomy, 2 patients died of pneumonia 56 and 63 months, respectively, after recurrence detection. They were both recurrence-free at the time of their deaths. The other 3 patients developed re-recurrence: 2 patients with locoregional re-recurrence and one each with pulmonary re-recurrence and lymphatic carcinomatosis. All died of the disease 10–48 months after the detection of their respective recurrences.

All of the seven patients who underwent resection for nonhepatic nonpulmonary recurrences developed re-recurrence and eventually died. Of the 75 patients who did not undergo surgical resection for distant recurrence, chemotherapy was administered to 26 (35 %) patients, chemoradiotherapy to 11 (15 %) patients, radiotherapy to 11 (15 %) patients, and RFA to 1 (1 %) patient with hepatic metastasis. Cisplatin, docetaxel, and fluorouracil were the drugs mainly used for the chemotherapy and chemoradiotherapy regimens. Radiotherapy was carried out for bone metastases, except in two patients with brain metastases.

Among the patients who did not undergo resectional therapy ($n = 75$), all died of disease recurrence, irrespective of the site of the distant organ metastases (Fig. 5).

A multivariate Cox regression analysis was conducted for the patients who developed hepatic and/or pulmonary metastases. During this analysis, we assumed that the baseline hazards for death were different among patients with hepatic, pulmonary, and hepatic/pulmonary metastases but that the effects of resections were equal for hepatectomy and pulmonary resection. These assumptions allowed us to set a common covariate. Other variables that were included in the analysis were the existence/absence of nonhepatic nonpulmonary metastases, the stage of the primary cancer, disease-free interval from the primary resection, and the number and the maximum size of the metastases. The results are shown in Table 3. The independent risk ratio attributable to resection of hepatic and/or pulmonary metastases with the 95 % confidence interval (CI) was 0.35 (0.12–0.98) ($p = 0.046$).

Discussion

Although, theoretically, a distant-organ metastasis denotes hematogenous dissemination of tumor cells, hepatic and/or pulmonary resections are carried out with curative intent for metastatic tumors from solid organ malignancies (e.g., colorectal [9, 10, 14], neuroendocrine [12, 13], and genitourinary carcinomas) and various types of sarcoma [15, 16]. The rationale for such surgical resection can be summarized into two considerations.

The first is the cascade-spreading process [22]. That is, the liver or the lung acts as a filter for tumor cells before they escape into the systemic circulation because of their anatomic relations with the organs affected by the primary malignancy. Accordingly, the tumor spread is limited to the liver or the lung during the presystemic stage. The second relates to the selection of tumors with favorable biologic behavior either by the type of the original tumor or the metastatic lesion(s) [17–19, 23–26]. The oncologic benefit of metastasectomy of a hepatic and/or pulmonary recurrence in cases of esophageal cancer has been viewed with skepticism because of the multidirectional tumor spread considered to be

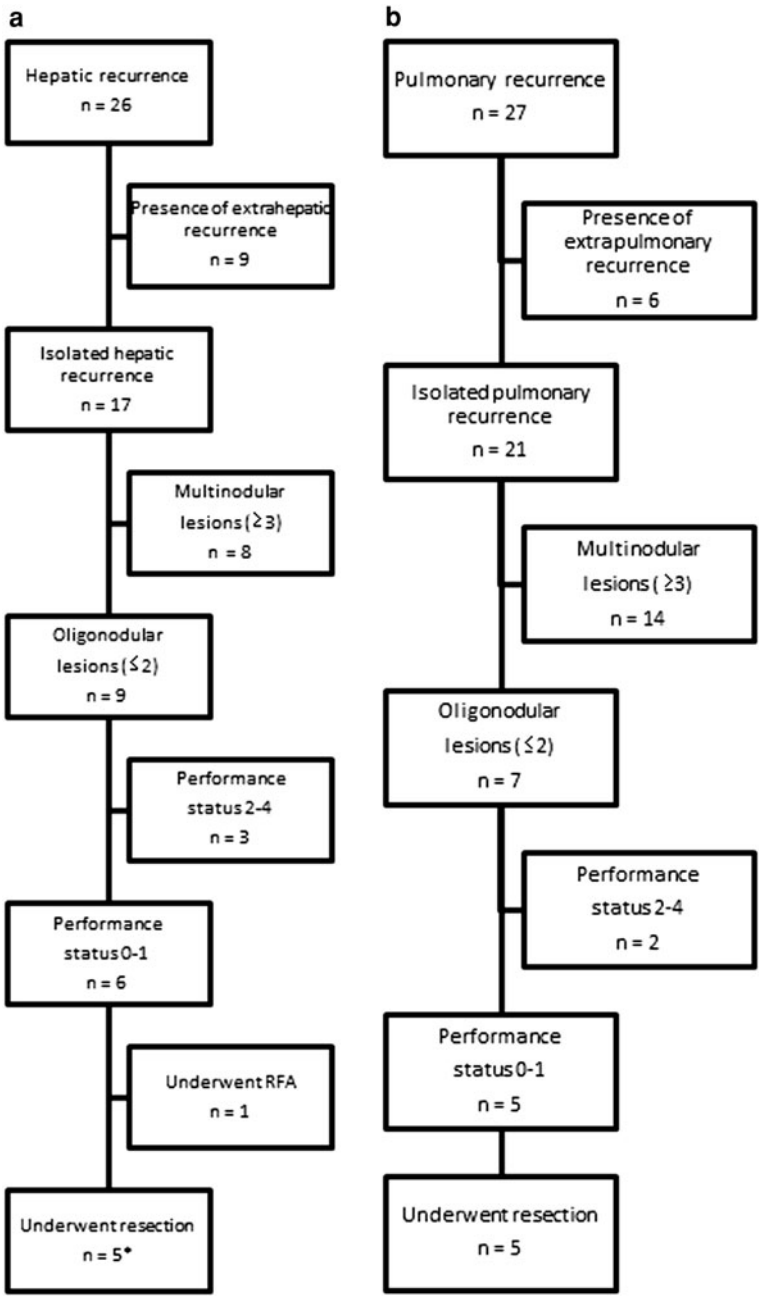

Fig. 4 Flow charts show the selection process of patients with **a** hepatic and **b** pulmonary recurrences for surgical resection. *One patient underwent concomitant resection of a paraaortic lymph node metastasis that was detected at the time of hepatectomy. *RFA* radiofrequency ablation

associated with the anatomic location of the primary tumor and the poor tumor biology of esophageal carcinoma [17–19]. Consequently, only sporadic cases undergoing metastasectomy have been reported [17–21] and the results were thought to be greatly affected by a selection bias. Taking these issues into account, we conducted a comprehensive study to clarify the survival benefit of hepatic and/or lung resection for metastatic tumors from esophageal carcinoma.

In the present series, 47 % (138/296) of the patients undergoing esophagectomy for primary esophageal carcinoma developed a recurrence during a median follow-up of 4 years, a result consistent with previous reports (37–52 %) [2–8]. The median survival of the 138 patients after recurrence detection was 6 months (Fig. 3), which is also in accordance with the results (2.7–7.0 months) reported previously [2, 6–8].

Whereas the dominant pattern (i.e., distant-organ vs. locoregional recurrence) varied in previous studies [2–8], distant-organ recurrences developed more frequently than locoregional recurrences in the present series (Fig. 1a). The distant-organ recurrences also tended to occur earlier during the postoperative period than locoregional recurrences (Fig. 2a), consistent with previous reports [3–5, 8] and reflective of the poorer biologic behavior of the distant-

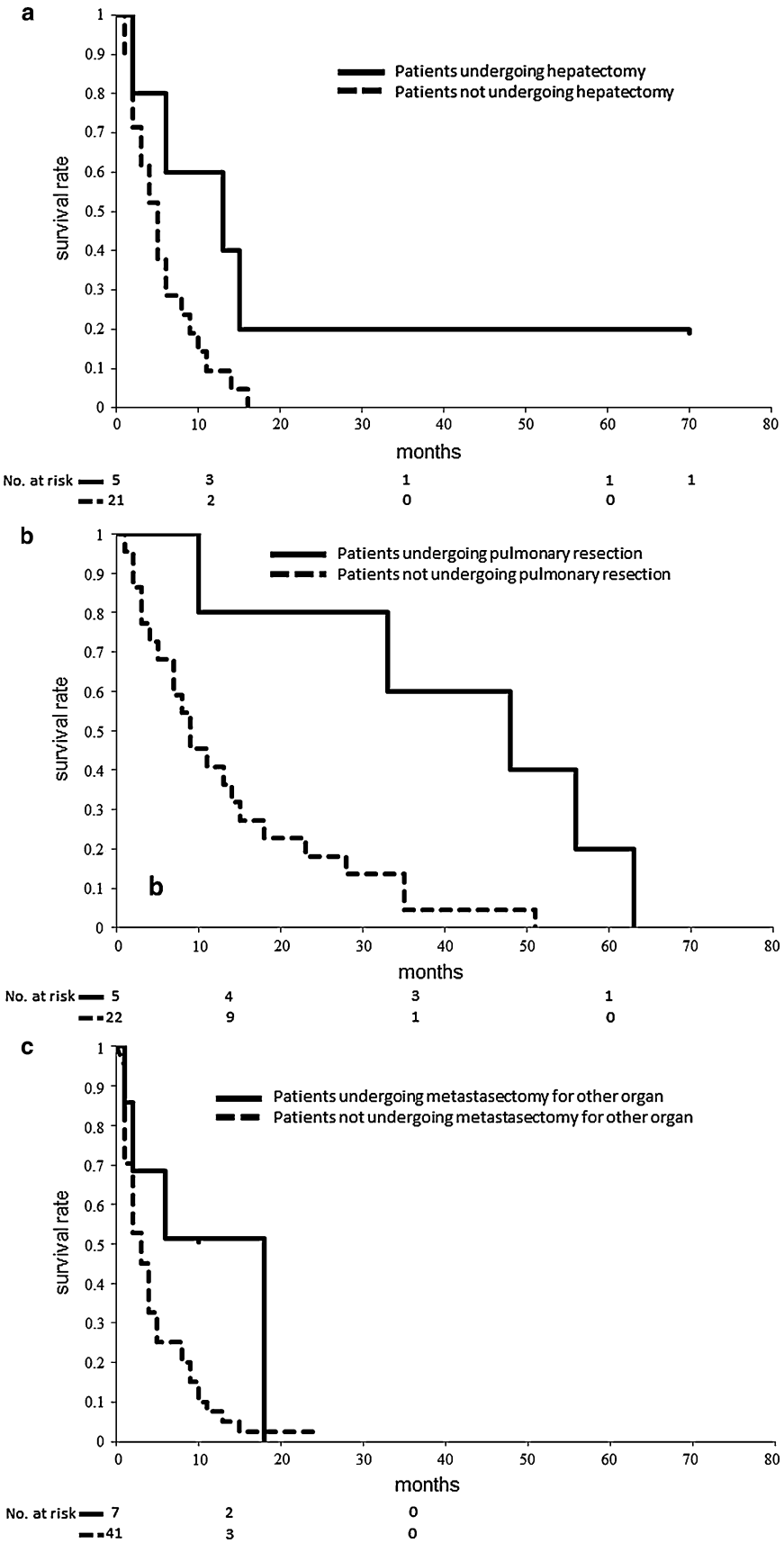

Fig. 5 Survival curves of patients who were treated/not treated by resection of **a** hepatic, **b** pulmonary, and **c** nonhepatic nonpulmonary recurrences. Survival duration was calculated from the time at which the recurrence was detected. $p = 0.06$, $p = 0.009$, and $p = 0.16$ between those undergoing and not undergoing resections for (**a**), (**b**) and (**c**), respectively

Table 3 Multivariate analysis to identify the predictors of survival in patients with hepatic and/or pulmonary metastases

Variable	Risk ratio	95 % CI	*p*
Resection/no resection	0.35	0.12–0.98	0.046
Multiple organ metastases			
No	1		
Yes	1.91	0.82–4.24	0.130
Stage of primary cancer			
0–II	1		
III–IV	1.09	0.51–2.39	1.095
DFI (months)			
≥7	1		
≤6	1.66	0.89–3.16	0.110
No. of metastases			
≤2	1		
≥3	1.32	0.59–3.10	0.504
Maximum size of metastases (mm)			
≤20	1		
≥21	2.39	1.10–5.18	0.029
Site of metastasis			
Lung	1		
Liver	1.46	0.67–3.27	0.346
Lung and liver	4.75	0.68–21.07	0.105

CI Confidence interval

organ recurrences. Although the results of previous studies that compared the survivals of patients with distant-organ and locoregionl recurrences lent support to this notion [3–5], the survival functions in the two groups were similar in the present study (Fig. 3).

In the present cohort, although the hepatic, bone, and other-organ metastases occurred at almost equal frequencies (Fig. 1b), the likelihood of a hepatic metastasis compared with that of a pulmonary metastasis was clearly associated with the location of the primary tumor. These results signify the multidirectional spread of esophageal carcinoma as a whole. In summary, the pattern of development and timing of a recurrence and the prognosis for the patients appear to be similar irrespective of the histologic type of the primary cancer. The dominant histologic type was squamous cell carcinoma (SCC) in the present series, whereas it differed among previous reports, being SCC in some studies and adenocarcinoma in others [2–8].

Many investigators have insisted that in addition to the primary tumor type the length of the disease-free interval is a surrogate marker of tumor biology. In fact, this parameter is one of the criteria that has been used to assess the suitability of patients for resection of hepatic and/or pulmonary metastases [16, 19, 20, 23–26]. Although esophageal carcinoma is classified as a tumor that has unfavorable biology [17–19], we did not use the disease-free interval or the depth/nodal status of the primary tumor when assessing the patient for surgical indication. Accordingly, patients undergoing hepatic/pulmonary resection were distributed randomly during the postoperative period (Fig. 2b, c), and the primary tumor stage and largest diameter of the metastatic nodules were comparable in those undergoing and not undergoing metastasectomy (Table 1). We abided by the criteria relating to the number (≤2 nodules) and localization of the metastatic recurrences (i.e., single-organ recurrence of metastatic nodules) when assessing the indications for surgery. Consequently, approximately one-fourth of the patients with hepatic and/or pulmonary metastases were considered suitable candidates for surgical resection of their metastatic tumors. Of note, nearly 10 % of the patients were found to be poor-risk candidates for resection because of poor performance status after the primary esophageal resection, in clear contrast to the case for recurrences from other primary tumors such as colorectal [9–11, 14] and neuroendocrine [12, 13] carcinomas (Fig. 4).

Overall, patients with pulmonary metastases appeared to have a more favorable prognosis than those with hepatic metastases or nonhepatic nonpulmonary metastases (Fig. 5a, b). Also, patients treated by pulmonary metastasectomy showed more prolonged survival than those who were found to be unsuitable candidates and therefore did not undergo resectional therapy. The results were inevitably affected by a selection bias, however, and there was only a single 5 year survivor (1/5) in the present cohort (Fig. 5b). On the other hand, the survival benefit of surgical resection of hepatic metastases appeared more doubtful despite the fact that there was one long-term (6 years) survivor (1/5), and the survival for those who were treated/not treated by hepatectomy tended to be different (Fig. 5a). The subsequent multivariate Cox regression analysis revealed that the independent risk ratio attributable to resection of hepatic and/or pulmonary metastases (95 % CI) was 0.35 (0.12–0.98). This figure corresponds to 3 year survival rates of 45 and 57 %, respectively, for patients undergoing resection when we assume that the 3 year survival rates for nonresected patients were 10 and 20 %, respectively. Nevertheless, a definitive conclusion on the survival benefit of hepatic and/or pulmonary resection could not be drawn because various prognostic variables—e.g., the number of metastases or the existence/absence of nonhepatic nonpulmonary metastases—were unevenly distributed among the resected and nonresected groups. In any event, pulmonary and hepatic resection for metastatic recurrences associated with esophageal carcinoma could serve as a useful adjuvant therapy to other nonsurgical therapies, including systemic chemotherapy. Finally, patients with nonhepatic and nonpulmonary metastases

showed a poor prognosis, and metastasectomy in these cases did not modify the natural course of the disease.

Conclusions

Nearly half of the patients undergoing curative surgery for esophageal carcinoma developed recurrence, with distant-organ recurrences being more frequent than locoregional recurrences. More than half of the distant-organ recurrences developed within 6 months of the resection. They included hepatic, pulmonary, bone, and other-organ metastases, which occurred at almost equal frequency. Patients with a pulmonary recurrence had a better prognosis than those with hepatic or nonhepatic nonpulmonary metastases. Resection of pulmonary metastases was associated with probable survival benefit in properly selected patients. The benefit of resection of hepatic metastases was more doubtful, although there were occasional long-term survivors. There was no place for surgical resection of metastases in patients with nonhepatic and nonpulmonary metastases.

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