Review Article

Surgery for metachronic metastasized esophageal cancer

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Abstract: Esophageal cancer (EC) is an aggressive type of malignancy which is nowadays responsible for 16,000 deaths solely in the USA region and 400,200 deaths in Western countries. Despite the fact that there have been significant improvements in multimodality therapies, operative and perioperative management, the overall 5-year survival rate ranges from 25–50%, and a significant proportion (30–50%) of patients will develop recurrence within months or few years after esophagectomy. The aim of this article is to review the current evidence on the role of surgical treatment for metachronous oligometastases from EC. A literature search about surgical management of metachronous EC metastases was conducted and the results from the most relevant studies are presented. The types and locations of recurrence considerably differ among individual patients mainly categorized as locoregional at the site of anastomosis, lymphatic and hematogenic metastasis, or a combination of these. The standard treatment for EC patients experiencing recurrence is currently based on systemic chemotherapy and/or radiotherapy. Recent literature shows that in highly selected individuals, surgical resection of oligometastatic disease might lead to improved outcomes as far as survival rates are concerned over medical management alone. Nowadays, only few retrospective studies with small number of patients report the results of surgical treatment in oligometastatic disease. Thus, the low quality of existing scientific data is not yet possible to define the role of surgery as a part of multimodality treatment in patients with isolated distant recurrence in solid organs. However, a well-selected group of patients, especially those with a disease-free interval of more than 12 months with isolated one-field lymph node (LN) metastasis or solitary lesions in organs, might benefit from surgical management.

Keywords: Cancer; esophageal cancer (EC); metachronous; metastasis; oligometastatic; surgery

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Background

Esophageal cancer (EC) is considered the sixth most common cause of cancer related mortality worldwide based on recent medical literature data, accounting for 400,200 deaths in Western countries (1,2). Neoadjuvant chemotherapy with or without radiotherapy and surgical resection along with lymph node (LN) dissection is considered the mainstay of treatment for EC. Despite the fact that there have been significant improvements in multimodality therapies, operative and perioperative management, the overall 5-year survival rate remains moderate; reaching 25–50%, meaning that almost a half of EC patients will develop recurrence after esophagectomy mostly within months or few years (3). The group of patients with a recurrence are candidates for systemic chemotherapy but median survival is still poor (6.0–8.2 months) (4).

The most common sites of recurrence are distant LNs, liver, brain, lung, and bone. The types and locations of recurrence considerably differ among individual patients mainly categorized as locoregional at the site of

anastomosis, lymphatic and hematogenic metastasis, or a combination of these. The majority of patients present with metastases at multiple sites (5,6). The concept of oligometastases, which was initially proposed by Hellman (7) as a limited number (up to five lesions) of metastatic lesions in a single organ or domain of LNs for which local therapies may be implemented, is currently thought to represent a variant of disease more indolent in biological behavior. Oligometastasis is considered synchronous, when detected at the time of initial diagnosis of EC, or metachronous, which becomes apparent following definite treatment of primary cancer site (8).

While, non-small cell lung cancer and colorectal cancer metastasis patients represent a group of patients showing favorable results after surgical treatment of oligometastatic disease, recent evidence suggest that this strategy may be applicable for EC patients experiencing oligo-recurrence (9-12). Despite the fact that there is a lack of best treatment strategy options and robust scientific data for patients with oligo-recurrence of EC, many specialized institutions have adopted such strategies for this type of recurrence on a case-by-case basis (13). This article aims to review the current evidence on the role of surgical treatment for metachronous oligometastasis after surgery for EC.

Methods

A literature search about surgical management of metachronous EC metastases was conducted and the results from the most relevant studies are presented. Identification of eligible studies was performed through a systematic search of the MEDLINE (through PubMed) and Cochrane database until June 30th, 2020. We used the following keywords: “surgery”, “surgical treatment”, “cancer”, “esophageal”, “oesophageal”, “metastasis”, “metastases”, “metastasectomy”, “recurrence”.

Results

LNs

Based on aforementioned concept of oligometastatic disease, solitary LN recurrence may represent disease with more favorable biological behavior, in which aggressive surgical treatment may be justified (14). Wang *et al.* (15) in their study assessed a total of 66 patients with solitary cervical LN recurrence or multiple LN involvement, reporting that patients who followed radical salvage lymphadenectomy had better overall survival than patients who underwent reduction surgery. Ma *et al.* (16) in their study reported on 79 patients with cervical LN disease recurrence, comparing survival rates of those who underwent surgery with salvage radiotherapy and/or chemotherapy. Five-year survival rates were 50.1% and 12.6%, respectively. Similarly, Watanabe *et al.* (17) reported overall survival rates for 17 EC patients who underwent lymphadenectomy for LN recurrence after EC surgery reaching 75.5%. Likewise, Motoyama *et al.* (18) have reported the results after lymphadenectomy followed by radiotherapy and/or chemotherapy in 10 patients and demonstrated a median survival of 20 months after initial diagnosis of cervical LN recurrence.

Liver

The liver is one of the most common sites of recurrence and the first recurrence site in 6–25% of EC patients (19). While these patients are usually referred for palliative chemotherapy (20), low response rates to chemotherapeutic regimens, initiated new strategies which combine chemotherapy with liver resection for individuals with a low-tumor burden (21). Most data are derived from case reports and case series with no prospective cohort studies or randomized control trials available (*Table 1*).

Resection of metachronous liver metastases from EC has been performed in a group of patients with good performance status and low-tumor burden on a patient-by-patient basis after multidisciplinary team consultation. One of the largest studies was published in 2018 by Liu *et al.* (22) who compared surgically and non-surgically treated patients (26 versus 43 patients) with solitary hepatic metastasis who had undergone esophagectomy. Patients in the surgical group had 1- and 2-year cumulative survival rates of 50.8% and 21.2%, respectively, which were superior compared to the 31.0% and 7.1% survival rates of patients in the non-surgical group. In the same study, the authors concluded that patients with a longer disease-free interval (>12 months after esophagectomy) had a better survival rate than those with a disease-free interval of less than 12 months ($P<0.05$). Adam *et al.* (23) reviewed a total of 1,452 patients to determine the role of hepatic resection in the treatment of patients with non-colorectal nonendocrine liver metastases. Twenty patients with metastases from EC and 25 patients with metastases from gastroesophageal junction cancer were included, reporting a 3-year survival rate of 32% and 12%, respectively. This implies that in a carefully selected group of patients surgery is associated with a moderate survival. Similarly, Ichida *et al.* (24), assessed the benefit of

Table 1 Most relevant data of patients with recurrent liver and lung disease treated with resection

First author	Study type	Year of publication	Pathology	No of liver or lung OEC patients	DFI (months)	Survival
Liu *et al.* (22)	RS	2018	SCC	26 liver	14.15±9.68	2-year OS 21.2%
Adam *et al.* (23)	RS	2006	NR	45 liver (20 EC, 25 GEJ)	NR	3-year 32%, 3-year, 12% respectively
Ichida *et al.* (24)	RS	2013	Adeno	5 liver	0–14	OS 13 months
Ohkura *et al.* (25)	RS	2020	NR	53 lung	16.9	3-year survival 60.6%
Shiono *et al.* (26)	RS	2008	Miscellaneous	49 lung	14	Median OS 27 months
Kanamori *et al.* (27)	RS	2017	SCC (1 case basaloid carcinoma)	33 lung	15.5	Median OS 17.9 months
Kobayashi *et al.* (28)	RS	2014	SCC (1 case carcinosarcoma)	23 lung	23.8	Median OS 37.4 months

RS, retrospective study; NR, not reported; DFI, disease-free interval; EC, esophageal cancer; OEC, esophageal cancer oligometastatic disease; GEJ, gastroesophageal cancer; OS, overall survival; SCC, squamous cell carcinoma; Adeno, adenocarcinoma.

hepatic and pulmonary resections in patients with liver and lung recurrences after resection of esophageal carcinoma, reporting a median overall survival of 13 months in 5 surgically treated patients with liver metastases.

Lung

Numerous studies published in the last decade have reported favorable outcomes for patients with lung oligo-recurrence who underwent lung metastasectomy in metachronous lesions from EC (*Table 1*). Ohkura *et al.* (25) published the outcome of 53 of 119 patients with metachronous oligometastases treated by surgical resection. The 3- and 5-year survival rates were 64.3% and 55.6%, respectively for patients undergoing metastasectomy. Moreover, Shiono *et al.* (26), reviewed the records of 49 patients who underwent resection of metachronous pulmonary metastases from primary EC mostly SCC. The authors reported a 5-year survival rate of 29.6% after pulmonary metastasectomy, also emphasizing a worse prognosis for patients with a disease-free interval of less than 12 months (26). Kanamori *et al.* (27), assessed in their study the outcomes of 33 patients who had undergone resection of pulmonary metastatic tumors from EC after definitive treatment reporting overall median survival time of 17.9 months. Lastly, Kobayashi *et al.* (28) reviewed 23 patients with EC who underwent pulmonary metastasectomy for metachronous lesions and investigated their long-term prognosis and prognostic factors. Thirty patients after curative metastasectomies were reported: 26 cases of wedge resection, two cases of segmentectomy, and two cases of lobectomy. The mean survival time was 37.4 months (range, 1–114 months), with five patients treated with repeated metastasectomy for recurrent pulmonary metastases surviving a mean of 58 months (range, 24–114 months). In the same study, it was identified that history of extrapulmonary metastases before pulmonary recurrence, poorly differentiated carcinoma, and short disease-free interval were negative prognostic factors (28).

Brain

Brain metastasis from EC remains a rare event with approximately 100 cases reported in the literature. Its incidence is estimated to be around 2% (29). Ogawa *et al.* (30) reviewed the records of 36 patients with brain metastases from EC who were treated between 1986 and 2000. Twelve patients (33%) were treated with surgical resection followed by radiation therapy and the remaining 24 patients were treated with radiation therapy alone. The longest median survival observed after the diagnosis of brain metastasis (9.6 months) occurred in patients with a single brain lesion who underwent resection and received whole brain radiotherapy (WBRT), while the corresponding figure was 1.8 months for radiotherapy only group (30). Song *et al.* (31) retrospectively reviewed medical files of 26 consecutive patients with central nervous system involvement (4 patients with adenocarcinoma and 22 with

SCC). Twelve patients presented with a single cerebral metastasis, while 14 had multiple brain lesions. Five patients underwent surgery followed by WBRT, five underwent stereotactic radiosurgery, 13 received WBRT only, and three received chemotherapy. The median survival by treatment modality was 7 months for the surgical group, 4 months for the WBRT group and 1.8 months for the chemotherapy group (31). Similarly, Weinberg *et al.* (32) tried to assess the frequency of brain metastasis from EC, to determine factors associated with survival, and to describe treatment modalities and their outcomes. They reported the outcomes of 27 patients with brain metastases (adenocarcinoma in 22 patients, unclassified carcinoma in 3 patients, and squamous cell carcinoma in 2 patients). WBRT was applied in 15 patients, surgery in 10 patients (four of whom also received WBRT), and two patients underwent stereotactic radiosurgery. The longest survival was seen in patients with single brain metastasis who underwent surgery followed by WBRT (median survival of 9.6 months), while the median survival for patients with a single brain lesion who underwent surgery only was 3.8 months (32).

Adrenal glands

Surgical resection of adrenal metastases has been studied widely and is justified for malignancies such as lung cancer. However, there is no clear indication in EC patients experiencing metachronous recurrence (33). Fumagalli *et al.* (34) reported the clinical outcome of one patient with isolated adrenal metastasis who underwent adrenalectomy and eventually died 15 months postoperatively. Abate *et al.* (35) reported the outcome of 2 patients who underwent resection with or without adjuvant chemoradiotherapy with isolated adrenal metachronous lesions, reporting a median survival of 18 months. Additionally, Bui *et al.* (36) described three esophageal adenocarcinoma patients with a resected metachronous adrenal metastasis; the first two patients were still alive and disease-free at 20 months and 5 years postoperatively, while the third patient experienced mediastinal LN recurrence 3 months postoperatively.

Discussion

Despite radical surgery for EC patients and novel chemotherapeutic regimens and treatment modalities, about half of the patients experience recurrence within 1–3 years postoperatively (19,37). Studies with a retrospective design and including small patient numbers have reported the results of surgical treatment for oligometastatic recurrence. In some studies the addition of surgical management strategies has shown promising results as far as survival rates are concerned. However, these patients are often selected form a larger cohort of patients with metastases. In general, surgery for metachronous metastases is still experimental and chemoradiotherapy) therapy is often the first line of treatment given the lower morbidity/mortality.

Several potential pathways have been described as culprits for the development of such metastases. Longitudinal spread along the submucosa to LN basins has been implicated in LN recurrence, while invasion of neoplastic cells through the muscularis propria and perpendicular spread through the muscularis mucosa to the thoracic duct and venous system account for the rest of distant organ recurrences (5). There have also been rare sites of recurrence such as soft tissue, gallbladder, renal, spleen, skin, eyes, heart, and pancreas, reported in small case series or case reports (33).

A newly established system for the comprehensive characterization of oligometastatic disease has recently been proposed in a study published by Guckenberger *et al.* (38). Based on this novel nomenclature, a history of polymetastatic disease before diagnosis of oligometastatic disease was used as the criterion to differentiate between induced oligometastatic disease and genuine oligometastatic disease. Furthermore, the same group subclassified genuine oligometastatic disease into repeat oligometastatic disease (previous history of oligometastatic disease) and *de-novo* oligometastatic disease (first time diagnosis of oligometastatic disease). In *de-novo* oligometastatic disease, there has been differentiation between synchronous (first time diagnosis of primary site and oligometastases within 6 months) and metachronous oligometastatic disease (first time diagnosis >6 months after diagnosis of cancer). A final subclassification was also suggested into oligo-recurrence, oligoprogression, and oligopersistence, considering whether oligometastatic disease is diagnosed during a treatment-free interval or during active systemic therapy and whether or not an oligometastatic lesion is progressing on current imaging (38). Adopting this nomenclature worldwide is important for the comparison of studies and may enhance progress in this field.

Although recurrence usually correlates with widespread metastatic disease in various distant sites, a subset of EC patients presents with localized oligometastatic disease. Depypere *et al.* (37) evaluated survival of a number of different subgroups of patients with recurrent disease after esophagectomy for EC with an emphasis on the effect of

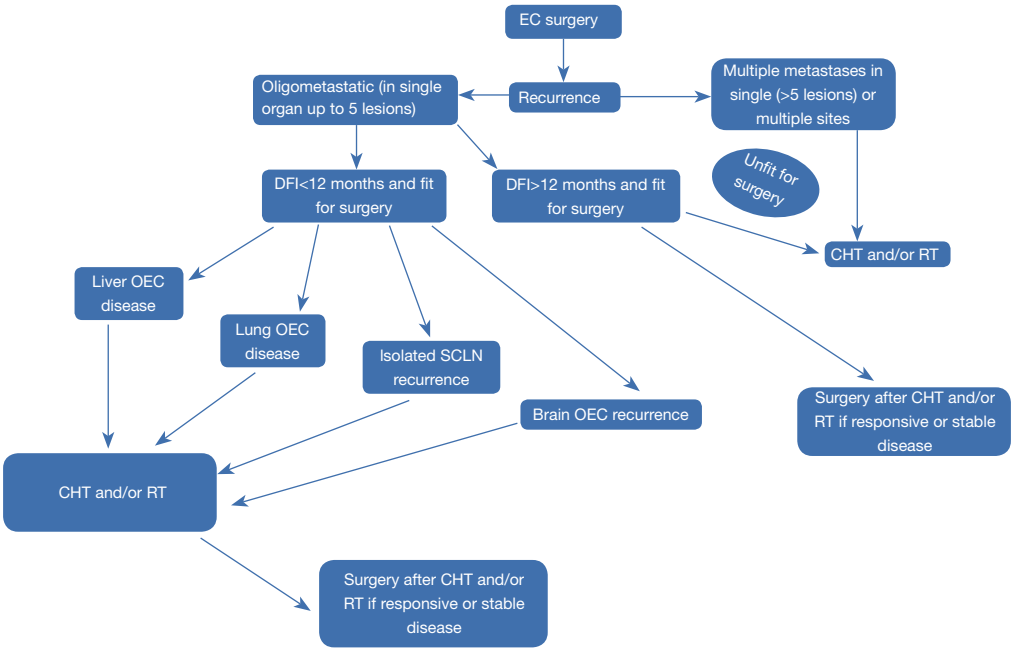

Figure 1 Proposed treatment algorithm for metachronous oligometastatic esophageal cancer.

surgical and nonsurgical salvage strategies. They analyzed 766 consecutive patients with recurrence after curative resection for EC. In the group of patients with a solitary organ recurrence, surgical extirpation was associated with statistically significant superior survival rates when compared to no surgery group, with a median survival after diagnosis of recurrence of 54.8 versus 11.6 months, respectively (37).

Recent studies have tried to identify factors that may be associated with specific group of patients, in whom surgical treatment of metachronous oligometastatic disease might be of benefit. A disease-free interval lasting more than 12 months is a prognostic criterion to select patients who will benefit more following this strategy (2,20,27,28,39-41). Additionally, TNM stage has also been reported as another factor associated with survival after surgery for EC recurrence (6,39). Good response to chemotherapeutic regimens after liver recurrence was also identified as a predictive factor of biologically favorable disease and potential selection criterion for curative liver resection (42). The primary location of the tumor has also been reported to be a prognostic factor in patients with recurrent disease (13), while in patients treated surgically for metastatic disease from gastroesophageal carcinomas, the presence of a HER2-positive tumor treated with trastuzumab was another factor predictive of superior survival (43).

Most studies however have serious limitations since they are retrospective, with a limited number of patients included and significant heterogeneity of the baseline characteristics of the study populations. Selection bias is apparent in many of these studies, due to the fact that patients with poor performance status and/or bulky disease were generally excluded from any surgical treatment. Moreover, systemic chemotherapy regimens are different among these studies and based on the fact that recently new regimens have been linked to improved outcomes, non-statistically significant conclusions can be reported.

Conclusions

It is well-known that a uniform recommended management strategy for EC patients suffering from metachronous oligometastatic lesions is still lacking. However, it becomes apparent that a well-selected group of patients, especially those with a disease-free interval of more than 12 months with isolated one-field LN metastasis or solitary lesions in organs, may benefit from surgical management. Thus, prospective studies and registries are needed to get a better estimate on the role of surgery for metachronous metastatic disease and how to select patients that may benefit. A treatment algorithm proposed by our group is illustrated in *Figure 1*. We conclude that patients, with good

performance status presenting with oligometastatic disease, should follow systemic therapy regimens (chemotherapy and/or radiotherapy) in order to assess the response and biology of the recurrence. Thus, surgical treatment could be implemented in well selected cases, when there is no progression of disease while on systemic therapy.

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Footnote

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