



# Benefits of Metastasectomy in Esophagogastric Cancer

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## Abstract

**Background:** Esophagogastric cancer is the second most common cause of cancer related deaths worldwide and often presents late with approximately 32% of US patients presenting with distant metastases. The current guidelines for metastases of gastric cancer involve palliative chemotherapy and supportive measures. However, the median overall survival with these guidelines is less than 1 year. Performing a gastrectomy, along with metastasectomy and chemotherapy shows the highest median overall survival of 28.0 months for metastatic gastric cancer. The aim of this systematic review is to determine whether performing metastasectomies increases overall, 1-year and 3-year survival in metastatic esophagogastric carcinoma.

**Methods:** A systematic review was performed. Inclusion and exclusion criteria were developed, specific outcomes were identified (overall, 1 and 3 year survival for esophagogastric cancer with and without metastasectomies) and a search strategy with key words for Embase and Google Scholar was employed.

**Results:** 37 articles were found through the Embase database search and 20 additional sources were identified via independent Google Scholar searches. After careful review of the titles, abstracts and full texts by 2 separate reviewers, 6 articles were included for systematic review. The median overall survival, 1-year survival and 3-year survival were greater for patients who received gastrectomy with metastasectomy compared to gastrectomy without metastasectomy, with the exception of study that did not concur with a greater 1-year survival in metastasectomy patients.

**Conclusions:** This systematic review, suggests that surgery for resection of oligometastases improves prognosis. However, randomized, larger scale studies are recommended.

## Case Report

JSM, a 54 year-old male, presented in 2006 with dysphagia. Endoscopy demonstrated a tumour at the gastro esophageal junction. Biopsy was positive for adenocarcinoma. He underwent resection for a high grade, transmural tumour, with 4 of 11 resected para-gastric lymph nodes positive for metastatic disease. Post-operatively he was treated with combined chemotherapy (5-FU and Folinic Acid) and radiation as per the Intergroup protocol [1]. One year after completion of chemotherapy and radiation he presented with two growing pulmonary nodules. A PET scan was positive only in these two nodules. Subsequently the patient had a thoracotomy for resection of these nodules. Pathology confirmed that this was an adenocarcinoma with similar morphologic and staining characteristics as his primary lesion. He was treated post operatively with adjuvant Epirubicin, Oxaliplatin, and Capecitabine chemotherapy for 4 cycles. He has been followed since then and as of December, 2015, remains in remission.

As resection of oligometastases for esophagogastric cancer is not considered standard therapy, we performed a systematic review to determine the prognostic benefits of this therapeutic approach.

## Introduction

Esophagogastric cancer encompasses all forms of esophageal and gastric cancer. Gastric cancer is the second most common cause of cancer related deaths worldwide [2]. Since early gastric cancer is frequently asymptomatic, patients often present late with locally advanced disease and distant metastases [3]. In the United States, 32% of patients have metastatic disease at the time of diagnosis of gastric cancer [4]. The most common sites of gastric carcinoma metastases are liver, lung, bone, and peritoneum [5]. For regional gastric carcinoma without metastases, the gold standard of treatment is a radical gastrectomy to remove all malignant tissue, with or without neoadjuvant chemotherapy and postoperative radiotherapy, resulting in improved prognosis and potential cure [1,6]. When metastases are present, the role and extent of surgery is controversial. The current standard treatment for metastases is palliative chemotherapy and best supportive care, including

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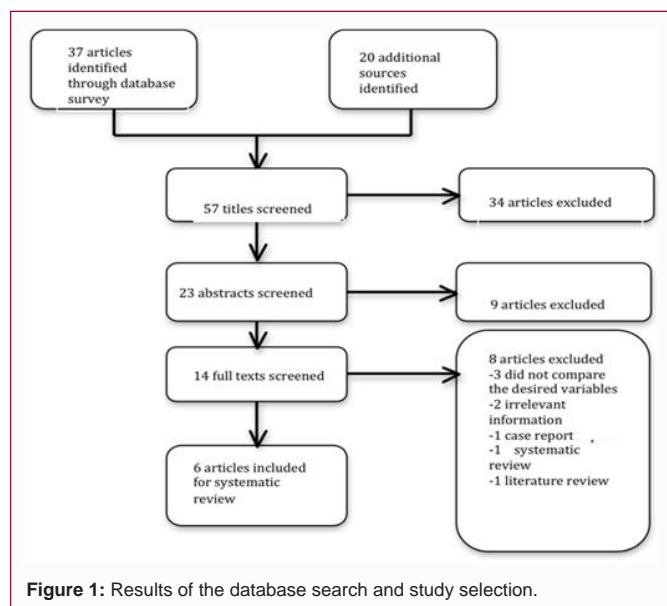
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radiotherapy, in order to prolong survival and alleviate symptoms [7]. However, standard practice reveals very poor prognosis with median overall survival being less than 1 year [8]. The benefit of surgical removal of metastases in gastric carcinoma is not widely accepted [7]. However, it has been suggested that performing a gastrectomy, along with metastasectomy and chemotherapy shows the highest median overall survival of 28.0 months [9]. When compared to other treatment regimens with median overall survival of less than 1 year and standard practice guidelines as demonstrated by Wagner et al. [8]. Esophageal cancer is the 6th most fatal cancer worldwide [10]. The current treatment options for patients with esophageal carcinoma include esophagectomy, three-field lymph node dissection, radiotherapy, and chemotherapy [11]. However, recurrence rates are still around 30-50% [12]. Therefore, similar to gastric cancer, there is a need to investigate the potential use of metastasectomies in metastatic esophageal cancer to decrease the rates of recurrence and decrease mortality. The aim of this systematic review is to determine whether performing metastasectomies increases overall, 1 year and 3 year survival in metastatic esophagogastric carcinoma.

**Methods**

**Inclusion and exclusion criteria**

Studies published in English between the years 2002 and 2013 were included in this systematic review. Retrospective, prospective, randomized, non-randomized and controlled studies were included if the patient population were adults with a confirmed diagnosis of esophagogastric carcinoma and metastases. Moreover, studies were

included if patients had synchronous or met asynchronous hepatic metastases. Studies were excluded if a comparative approach was not taken between metastasectomy and non-metastasectomy. Publication types including case reports, systematic reviews, and conference proceedings were also excluded.

**Outcome**

The aim of this review is to determine the benefit of metastasectomies with respect to overall, 1 year and 3 year survival in metastatic esophagogastric carcinoma.

**A. Search Strategy** Embase, a comprehensive, international biomedical database, was utilized in the search methodology. The search strategy involved a key word search, as shown in the appendix below

**B.** A Google scholar search was also performed with the following key terms: “oesophagogastric metastasectomy”, “esophagogastric metastasectomy”, “metastasectomy” and “gastric”, “metastasectomy and “oesphagus”, “metastasectomy” and “esophagus”

**Study selection**

Initial searches were conducted by 4 reviewers on Embase and Google Scholar. Repeat articles were excluded. At least two reviewers were responsible for independently identifying pertinent articles by title and subsequently by abstract. The full text of the remaining articles was reviewed and the relevant data was extracted. Third and fourth members of the team were sought if discrepancies amongst the first 2 reviewers arose.

**Data extraction and quality assessment**

Data recovered from reviewers include population cohort total, mean age, gender distribution, the number of patients receiving a gastrectomy with metastasectomy, the number of patients receiving gastrectomy/palliative care without metastasectomy, median overall survival, 1 and 3 year survival, follow up duration, complications and prognostic factors while undergoing metastasectomy.

**Results**

In total, the literature search revealed 6 relevant articles with comparable data (Figure 1). Note that only one selected article with complete data involved esophageal cancer. Figure 1 (Found in section 11.1 found at end of paper). The data extracted from the articles is represented in Tables 1,2,3 and 4. The number of patients receiving primary gastrectomy and metastasectomy were compared to the number of patients receiving only gastrectomy/palliative care (Table 1). Also, the median overall survival (Table 2), 3 year survival (Table 3), and 1 year survival (Table 4) were all compared between the two groups when the relevant information was available.

**Table 1:** General Description and characteristics of the studies used in the literature review, including patient numbers.

Author	Year	Type of Study	Number of Patients with Metastasectomy	Number of Patients without Metastasectomy
Okanu et al. [13]	2002	Retrospective Cohort Study	19	9
Ueda et al. [14]	2008	Retrospective Cohort Study	15	11
Kim et al. [9]	2010	Prospective Cohort Study	42	47
Takemura et al. [15]	2012	Retrospective Cohort Study	5	20
Yang et al. [16]	2013	Retrospective Cohort Study	30	59
Mohri et al. [17]	2014	Retrospective Cohort Study	28	58
Total			139	204

**Table 2:** The median overall survival of patients who received primary gastrectomy and metastasectomy vs. patients who received gastrectomy only.

Author	Median Overall Survival with Metastectomy (months)	Median Overall Survival without Metastectomy (months)	Difference in Median Overall Survival (months)	Significance
Okanu et al. [13]	21	6	15	P <0.05
Kim et al. [9]	28	15.5	12.5	P = 0.001
Takemura et al. [15]	80% still alive*	12	NA	NA
Mohri et al. [17]	21.9	12.5	6.4	P <0.001

\*4 patients still alive at the time of paper publication without signs of metastatic disease (124, 65, 48, and 32 months after initial metastasectomy, respectively)

**Table 3:** The 3 year survival of patients who received primary gastrectomy and metastasectomy.

Author	3 Year Survival with Metastectomy	3 Year Survival without Metastectomy
Okanu et al. [13]	34%	0%
Ueda et al. [14]	60%	0%
Kim et al. [9]	42.8%	8.1%
Yang et al. [16]	23.3%	8.5%
Mohri et al. [17]	25.3%	10.1%

**Table 4:** The 1 year survival of patients who received primary gastrectomy and metastasectomy vs. patients who received gastrectomy only.

Author	1 Year Survival with Metastectomy	1 Year Survival without Metastectomy
Okanu et al. [13]	34%	43%*
Ueda et al. [14]	80%	36.4%
Takemura et al. [15]	100%	50%
Yang et al. [16]	70%	57.6%

\*9 patients of the 71 non-resectable metastases cohort were included in the 1-year survival rate. These 9 patients were the only eligible patients to potentially undergo metastases resection from the non-resection group.

## Discussion

The characteristics of the six studies meeting the inclusion conditions are shown in Table 1. All papers reviewed were retrospective cohort studies with small patient populations,  $\leq 90$  patients. Due to the retrospective nature of these studies, and chosen criteria to undergo metastasectomy, the studies were neither randomized nor blinded. The median overall survival (Table 2), 1-year survival (Table 4) and 3-year survival (Table 3) were greater for patients who received gastrectomy with metastasectomy compared to gastrectomy without metastasectomy, with the exception. Study demonstrated a greater 1-year survival for the non-metastatic resection cohort [13]. The 9 patients used to calculate the non-resectable cohort's 1-year survival rate are not based on the whole cohort population of 71. These 9 patients met the inclusion criteria for metastasis resection but only received a gastrectomy. Seven of these nine patients died from cancer post-gastrectomy within 31 months, presumably due to lack of complete metastatic resection. Therefore [14] concluded that the 1-year survival was actually greater in the metastasectomy group than the non-metastasectomy group if all eligible patients were taken into account. All four articles reporting overall median survival demonstrated an improved overall survival of at least 6 months when undergoing metastasectomy compared no metastases resection [9,13,15,16]. More over the smallest improvement in 3-year survival between cohorts undergoing metastasectomy and non-metastasectomy was 14.8%, [17] while the largest was 60% [18]. All studies included in the systematic review demonstrated survival benefits for performing a metastasectomy with synchronous or met asynchronous gastric carcinoma. However, patient cohorts were selected based on specific criteria resulting in a potential selection bias towards fit, healthier patients for those undergoing metastasectomy. More advanced disease; worsening symptoms and poor state of health are negative prognostic factors and also acted as exclusion criteria for the resection procedures. Metastectomy was not performed unless there was a reasonable expectation of cure [18], or complete tumour resection [9,17]. In addition, patients with peritoneal dissemination [13,14,17], recurring met asynchronous metastases [13], multiple tumour metastases across liver lobes [14,16,17], and severe symptoms [9,17], such as bleeding or obstruction were excluded from metastases resection in certain studies. These exclusion criteria ensure a certain level of fitness, wellness and overall better prognosis for those undergoing metastasectomy versus those deemed unfit

for metastases resection. An objective, definitive recommendation for metastasectomies in esophagogastric carcinoma is difficult to obtain from this review as each study created a different set of biased inclusion/exclusion criteria. However, given that all studies demonstrated significant survival benefits for patients undergoing metastasectomies, there may be benefits for patients with particular prognostic characteristics. For example, Okano et al. [13] found the clinicopathological factors of the primary gastric cancer, the number and distribution of metastases, the timing of metastasectomy and the surgical margin were important prognostic factors. Further controlled and randomized studies must be performed to definitively demonstrate metastasectomy survival benefits in esophagogastric carcinoma patients.

## Conclusion

In conclusion, this review has demonstrated survival benefits for performing metastasectomies on esophagogastric cancer patients. However, these results could be due to selection bias and favourable patient characteristics that ensure a higher level of fitness for those undergoing the metastasis resection compared to non-resection patients. Moreover, only one article [15], addressed esophageal cancer. Therefore, further controlled and randomized studies are recommended to provide objective evidence for the beneficial use of metastasectomies in esophagogastric cancer. However, the use of randomized control studies provides an ethical dilemma that is difficult to overcome. Either patients are unknowingly receiving a treatment that is less beneficial than the alternative, or some patients are receiving a superior treatment than others based entirely on chance, not on autonomy or beneficence. The current evidence based recommendation of the NCCN does not include resection of metastases [7]. However, this systematic review, suggests that surgery for resection of oligometastases improves prognosis.

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