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## Detection and management of oligometastatic disease in oesophageal cancer and identification of prognostic factors: A systematic review

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### Abstract

#### BACKGROUND

Oesophageal cancer is the eighth most common cancer worldwide. The prognosis of oesophageal cancer patients still remains poor. The 5-year survival rate rarely exceeds 5% in case of metastatic disease. Some patients may however present with oligometastasis which can be treated with loco-regional therapy.

#### AIM

To assess the current practice regarding the management of patients with oligometastatic oesophageal cancer and identify prognostic factors affecting survival following treatment for oligometastasis.

#### METHODS

A systematic search of the literature was performed in Cochrane Library, MEDLINE and EMBASE databases from September 1950 to January 2019. Relevant electronic databases were searched for studies assessing the clinical outcome of oligometastasis.

#### RESULTS

A total of 14 publications were included, of which 12 studies assessing metachronous oligometastasis and 2 on synchronous oligometastasis. All included articles evaluated the specific outcomes of metastasis, management modality and survival outcomes. The majority of the patients presented with oesophageal squamous cell carcinoma. The median disease free interval (time to recurrence) in patients was 19.6 mo and the overall survival reached 30.8 months. Unfavourable prognostic factors were assessed in eight studies and included time to recurrence < 12 mo, large diameter pulmonary lesions (> 20 mm), disease free interval (DFI) < 12 mo, extra-pulmonary metastasis, primary tumour pathological

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## CONCLUSION

Oligometastatic oesophageal cancer in selected patients is amenable to loco-regional treatment, and the overall survival of this patient cohort may be improved with patient and tumour-specific treatments.

**Key words:** Oligometastasis; Oesophageal cancer; Neoplasm; Liver; Pulmonary

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**Core tip:** Oesophageal cancer often presents with early metastatic spread, which carries a poor prognosis. Some patients may have limited metastatic disease that can be treated with loco-regional therapy. The guidelines for the management of oligometastasis in oesophageal cancer are however not clearly established and survival outcomes remain unclear. The aims of this review were to assess the current practice for the treatment of oligometastatic oesophageal cancer and factors affecting survival following treatment of oligometastasis. A total of 14 publications were included assessing the management and survival outcomes and the majority of these studies opted for aggressive treatment in appropriate patient selection.

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## INTRODUCTION

Oesophageal cancer is the eight most common cancer and the sixth leading cause of death from cancer with 400200 deaths<sup>[1-3]</sup>. Metastatic spread can occur early, and symptoms often only become apparent in the later stage of the disease. Hence, the prognosis of oesophageal cancer still remains poor with an overall 5-year survival rate of 18%<sup>[4]</sup>. Surgical resection is the standard treatment for patients presenting with early stage cancer. However, the survival is still low due to high incidence of either loco-regional or distant recurrence, ranging from 29% to 59%<sup>[5-11]</sup>. Moreover, approximately half of the patients present primarily with distant metastasis at the time of diagnosis with a 5-year survival of less than 5%<sup>[6]</sup>. Combined treatment modalities are used for the management of locally advanced disease, consisting of neoadjuvant chemotherapy with or without radiotherapy followed by surgery<sup>[12]</sup>. Meanwhile, patients with recurrent or metastatic disease most commonly undergo systemic palliative therapy<sup>[13-15]</sup>.

Several factors are believed to influence the long-term survival in patients undergoing curative treatment. One study found that presence of regional lymph node metastasis and chemoradiation, compared to surgery, were associated with poor 5-year survival, whilst female gender and patients receiving neoadjuvant therapy had better outcomes<sup>[16]</sup>. Nevertheless, the specific prognostic factors in patients treated loco-regionally for oligometastatic disease in oesophageal cancer remain unclear. Type and extent of recurrence may also affect survival as distant recurrence and more than three recurrent locations were associated with worse post-recurrence survival compared to loco-regional and solitary recurrence respectively<sup>[17]</sup>. Most recurrences occur in the first postoperative year, and approximately 90% develop by the end of the third year<sup>[9]</sup>. Metastatic oesophageal cancer has been regarded as end-stage disease with the most commonly affected sites for metastasis being the distant lymph nodes, liver, brain, lung and bone<sup>[18]</sup>. However, some of these patients may present with oligometastatic cancer. Oligometastasis is defined as a state of limited metastatic disease characterised by fewer than 5 metastasis<sup>[19]</sup>. Oligometastasis can be synchronous oligometastasis, which are detected at the time of primary cancer diagnosis or metachronous, which occur following treated primary cancer site<sup>[20]</sup>. The clinical implication of oligometastasis lies largely in the possible improvement in disease control and survival when patients with oligometastatic disease are treated

with definitive loco-regional therapy. Early detection of oligometastasis enables early intervention and may thus potentially improve survival. Careful surveillance is therefore one of the key components in the management of oesophageal cancer. However, to date there is a lack in specific guidelines regarding optimal management of patients presenting with oligometastatic oesophageal cancer.

For the purposes of our study, we defined oligometastasis as a single solid organ recurrence. This systematic review focuses on the current practice regarding treatment of oligometastatic oesophageal cancer and factors affecting survival following treatment of oligometastasis.

## MATERIALS AND METHODS

### **Search strategy and study selection**

A systematic literature search of MEDLINE (January 1950 to September 2018), EMBASE (January 1974 to September 2018), Web of Science (January 1990 to September 2018), and the Cochrane Library databases was performed. The following search terms were used “(o)esophageal cancer”, “oligometastasis” and “oligo-recurrence” and the Medical Subject Headings (MeSH) term “esophageal neoplasms”. The search was expanded by identifying synonyms or closely related terms and a manual search of the references of included studies was performed to identify any missing articles. The full search strategy is shown in [Supplementary Table 1](#). Two reviewers (SJ and KT) independently assessed titles and abstracts for inclusion of relevant references, followed by screening of the full text. Articles were included if the following elements were evaluated: (1) Assessment of survival outcomes and/or prognostic factors in patients presenting with solid organ metastasis following treatment for oesophageal cancer; and (2) Synchronous or metachronous oligometastasis. Only articles published in English were included. Review articles were excluded. Articles focusing on solely lymph node recurrence without solid organ metastasis were excluded. The following data was extracted: study design, sample size, mean age, diagnostic tool, type of treatment modality, histological subtype, site of metastatic lesion, disease free survival and overall survival for synchronous oligometastasis and metachronous oligometastasis.

### **Quality assessment**

The methodological quality of included studies was assessed by means of the Newcastle-Ottawa scales for cohort and case-control studies. The quality is rated by awarding stars in each domain with three domains in total (selection, comparability and exposure)<sup>[21]</sup>. Articles are graded as “good quality” if 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain, “fair quality” if 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain or “poor quality” if 0 or 1 star in the selection domain OR 0 stars in comparability domain OR 0 or 1 stars in the outcome/exposure domain. The methodological quality assessment of the case series was reported using a novel tool based on modifications of the Newcastle-Ottawa, Pierson and Bradford Hills scales<sup>[22]</sup>. Eight items are categorised into four domains (selection, ascertainment, causality and reporting). A total score on these 8 items can be created by adding up the binary response to a sum score.

## RESULTS

### **Literature search**

The systematic search yielded 399 initial results. After removal of duplicates, 235 references were screened on title and abstract. Subsequent assessment of full text resulted in inclusion of 14 articles. A graphical representation of the review process is demonstrated in a PRISMA flow chart ([Figure 1](#))<sup>[23]</sup>.

### **Methodological quality assessment**

The results of the quality assessment of the studies included are summarised in the [Supplementary Tables 1, 2 and 3](#) respectively. The majority of included studies were cohort studies. For all studies, both the case and control population consisted of patients treated for oesophageal cancer and data was retrospectively obtained from existing hospital databases. Furthermore, patients in the control group were not obtained as a random sample in the population and were selected from the same source as the cases. However, no information was given in the methodology of the

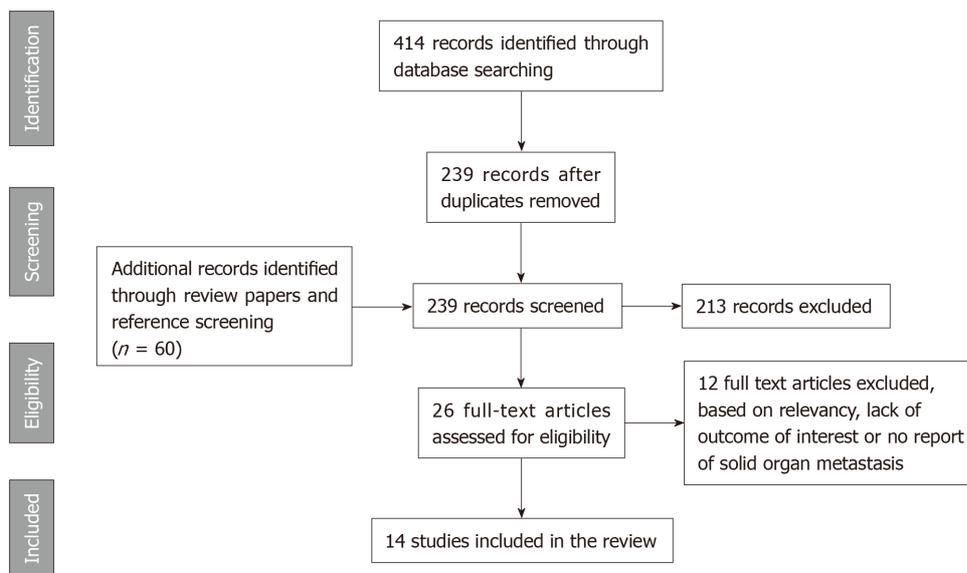


Figure 1 PRISMA flow chart of the selection process.

studies regarding matching of both groups. The remaining articles had a retrospective cohort design or were case series. Again, the study population consisted of a selected group of patients. The comparability of the cohorts was well established, but the outcome of interest was already present at the start across all studies due to retrospective design.

### Management of metachronous oligometastasis

Twelve studies included<sup>[24-35]</sup>, eight of those assessed the survival outcomes of patients treated with resection of pulmonary metastases, three included multiple oligometastasis sites and one study only on liver oligometastasis (Supplementary Tables 4 and 5). The histological subtype of primary oesophageal cancer was squamous cell carcinoma (75.2%), adenocarcinoma (23.0%) and sarcoma/basaloid tumour (1.8%). The mean age was 63.3 years across all studies. The majority of patients has undergone resection for the primary oesophageal cancer with either chemotherapy or radiotherapy or a combination. In only one study patients were managed with definitive chemotherapy<sup>[27]</sup>. The Disease-Free Interval (DFI) was reported in 8 of the studies and the mean DFI was 19.6 months. The DFI duration was established as a prognostic factor in four studies. A disease-free survival (DFS) of less than 12 mo resulted in a 5-year survival rate of 15.7%, which was much lower than for patients with a DFI exceeding 12 months (39.2%,  $P = 0.048$ )<sup>[25]</sup>.

Patients were investigated with various imaging modalities including Chest X-ray (CXR), computed tomography (CT) and positron emission tomography (PET) scan. However, the follow-up regimes were not specified in the studies included to assess variation in clinical practice and impact on detection. The management of oligometastasis involved surgery and mostly either chemotherapy or chemoradiotherapy. The main reported outcomes were overall survival (OS) and the mean was 30.8 mo across all studies. Oligometastasis recurrence occurred in 32.1% of cases. Time to recurrence was identified as a predictor of survival and patients presenting with recurrence within 12 mo of definitive therapy for the primary tumour, had worse survival ( $P = 0.034$ )<sup>[35]</sup>.

Chen *et al*<sup>[24]</sup> showed that patients with multiple pulmonary metastasis developed recurrence in comparison to those with solitary lesions, however, this was a small study of 5 patients. Regarding pulmonary metastasis, a larger diameter of the lesion (> 20 mm) was marginally associated with worse outcomes ( $P = 0.087$ )<sup>[27]</sup>. Presence of extra pulmonary metastases was established as unfavourable prognostic factor in five of the studies and Ichikawa *et al*<sup>[28]</sup> showed that none of the patients with extrapulmonary metastasis survived beyond 3 years, compared to 54.7% for patients presenting with a solitary pulmonary lesion ( $P = 0.0411$ ).

A 2013 retrospective cohort study assessed survival following resection of liver and lung metastases. Patients with pulmonary recurrences had better outcomes (median survival of 13 mo) than metastases in the liver (median survival of 5 mo) or other sites (median survival of 3 mo) and a surgical approach of these pulmonary lesions also seemed to be beneficial with a median survival of 48 mo compared to 10 mo if not

treated with resection ( $P = 0.009$ ). Hepatic metastasectomy failed to establish a significant survival benefit ( $P = 0.06$ )<sup>[32]</sup>. The latter results were similar to the findings of Huddy *et al*<sup>[33]</sup> who assessed the outcomes of 4 patients treated with liver resection and to Hiyoshi *et al*<sup>[34]</sup>. In addition, the latter author could not demonstrate an improvement in survival following resection of lesions in the brain and bone. However, patients treated with pulmonary metastasectomy (solitary, bilateral or multiple lesions) showed a trend towards better outcomes. A recent study conducted by Ghaly *et al*<sup>[35]</sup> evaluated prognostic factors for survival of 56 patients following multimodal therapy of oligometastasis in the liver, bone, brain or adrenal glands. The median survival was not significantly different between both groups ( $P = 0.661$ ). Time to recurrence was identified as a predictor of survival and patients presenting with recurrence within 12 mo of definitive therapy for the primary tumour, had worse survival ( $P = 0.034$ )<sup>[35]</sup>.

### **Management of synchronous oligometastasis**

Two studies assessed survival in oesophageal cancer patients presenting with synchronous oligometastasis<sup>[36,37]</sup> (Supplementary Tables 4 and 5). Onal *et al*<sup>[36]</sup> assessed the impact of an aggressive treatment approach of both primary tumour and solitary brain metastasis. Patients underwent definitive CRT of the primary tumour locally ablative treatment of the brain metastasis, consisting of radiotherapy, surgery or radiosurgery. The median time to progression was 8 mo and median survival was 18.9 mo, suggesting that this approach might improve survival in selected patients. A more recent study investigated the impact of suspicious lesions on pre-treatment imaging on the survival of patients undergoing oesophagectomy. The presence of suspected liver metastases had a 5-year survival rate of only 9.9% compared to 26.1% in patients with suspicious lesions at other sites or with no evidence of metastases on pre-treatment imaging ( $P = 0.014$ )<sup>[37]</sup>.

## **DISCUSSION**

Despite advances in diagnostic tools and treatment modalities, loco-regional and distant recurrences still occur frequently in oesophageal cancer. Survival rate is worse in the presence of haematogenous metastases (16 mo) compared to loco-regional recurrence (25.5 mo)<sup>[38]</sup>. Standard treatment modality for recurrences in oesophageal cancer often consists of systemic therapy. Patients presenting with oligometastatic disease may however benefit from aggressive local therapy with improvement in survival rates. To date, there is no guideline on the management of distant oligometastasis in oesophageal cancer and currently resection of distant metastases is mostly a personalised treatment.

The lungs are amongst the most common affected sites for metastasis in oesophageal cancer. Patients often present with multiple lesions and might have metastases at other sites as well. Furthermore, primary lung tumours commonly coexist with oesophageal cancer as smoking is a known risk factor in both malignancies<sup>[39,40]</sup>. Distinguishing metastases from second primary lung cancer requires genetic analysis, which was not performed in the included studies. Kanamori *et al*<sup>[31]</sup> excluded lesions suggestive of second primary lung cancer based on histological findings and Kozu *et al*<sup>[27]</sup> applied several clinical criteria. The latter author found poor long-term survival in these patients, confirming the aggressive nature of metastatic disease in oesophageal cancer. Consequently, survival rates could be affected in the other included studies as the number of patients with pulmonary metastases might be fewer than reported<sup>[41]</sup>. Pulmonary metastasectomy has proven its efficacy in other types of cancer, including colorectal, renal and head and neck malignancies. Both initial as repeated resections were encouraged in colorectal cancer as it could significantly improve survival rates<sup>[42]</sup>. This is consistent with the findings in the studies included in our review as the vast majority of the papers believed that pulmonary metastasectomy was a promising treatment option for improvement in survival following resection of a solitary pulmonary lesion. Ichikawa *et al*<sup>[28]</sup> has shown that it was a safe and feasible approach as the incidence of pulmonary complications remained low and no in-hospital mortality occurred. Hiyoshi *et al*<sup>[34]</sup> suggested that not only patients with a solitary lesion are good candidates for metastasectomy, but resection of bilateral and metachronous pulmonary multiple lesions might improve the prognosis as well. However, the study population only consisted of 9 patients with a solid organ metastasis. Furthermore, resection of pulmonary metastasis may have an improved prognostic value in metastatic gastric cancer<sup>[43]</sup>.

Resection of liver metastases is common practice in colorectal cancer with a 5-year

survival rates of more than 50% compared to patients receiving palliative treatment<sup>[44,45]</sup>. None of our included studies demonstrate a survival benefit of resection of liver metastasis, however, it is important to note that patient numbers were small. In addition, there is contrary evidence to survival benefit in patients undergoing resection for brain metastasis. Hiyoshi *et al.*<sup>[34]</sup> did not show any benefit in the resection of lesions in the brain or bone. In contrast with this, Onal *et al.*<sup>[36]</sup> suggested an improvement in survival outcome in patients with oligometastatic brain metastasis when treated with an aggressive approach of both the primary tumour and the metastatic lesion.

Recently, Kanamori *et al.*<sup>[31]</sup> showed that the risk of re-recurrence of metastasis was 70% in those undergoing pulmonary metastectomy. However, smaller studies had lower recurrence rates of 22% Kobayashi *et al.*<sup>[30]</sup>, 50% Huddy *et al.*<sup>[33]</sup> and 60% in Chen *et al.*<sup>[24]</sup>. The rate of recurrence following treatment of oligometastasis was not reported in other studies. In all the included reports patients had surgical resection of their oligometastasis and either chemotherapy or chemoradiotherapy. It is thus unclear whether these patients significantly benefit from resection of metastases.

Hsu *et al.*<sup>[9]</sup> showed that patients with more risk factors such as liver recurrence, early recurrence, and no treatment for recurrence would suffer from poorer post-recurrence survival. Therefore, patients with isolated, oligometastasis of EC after multimodality therapy may represent a subset of patients who will benefit from aggressive treatment of their metastatic disease and survival might be extended in this patient population. The majority of patients included had oesophageal squamous cell carcinoma (OSCC). The pattern of metastasis is different as OSCC has a higher incidence rate of lung metastasis in comparison to oesophageal adenocarcinoma which had a higher incidence rate of liver metastasis. The median disease free interval in patients was 18.6 months. The overall survival was 31.1 months. Furthermore, to our knowledge, there are currently no commonly accepted prognostic factors of metastatic oesophageal cancer indicating an improved prognosis. Several reports have reported favourable prognostic factors depending on their patient cohort, this included solitary metastasis, absence of extrapulmonary metastases and lack of nodal involvement and greater disease free interval > 12 months. In addition, the concept of the “test of time” is a convincing indicator of a more favourable biological cancer behaviour. However, there is an increasing shift toward individualized, multidisciplinary management of oligometastasis because it is difficult to conduct randomized controlled trials due to the variety of presentations<sup>[7]</sup>. The multicenter FLOT3 study with metastatic tumours of the oesophagogastric junction and gastric cancer suggests that well-selected patients may benefit from surgery following chemotherapy at the stage of limited metastases<sup>[46]</sup>. The results of the FLOT5 study is still awaiting to be published, assessing the effect of chemotherapy alone versus chemotherapy followed by surgical resection on survival and quality of life in patients with limited metastatic adenocarcinoma of the stomach or oesophagogastric junction. Only two papers assessed the presence of synchronous oligometastasis in patients with oesophageal cancer<sup>[36,37]</sup>. Hence, no comparison in the difference of between the presence of synchronous or metachronous oligometastatic disease could be made regarding survival outcomes.

The main limitation to this review is that all the studies included were retrospective observational studies. The majority of patients were OSCC and therefore not representing the other major oesophageal cancer subtype of adenocarcinoma. Therefore, there was clinical heterogeneity was present due to majority of patients being of Asian-predominant studies. Most of the studies included the proportion of patients receiving metastasectomy in their assessment. Hence, the sample size in the majority of the studies was small, which may introduce selection bias. Another limitation is that only papers published in English were included.

Aggressive treatment of oligometastatic disease in oesophageal cancer is performed on an individual basis. The lung and liver are amongst the most common sites of metastasis in oesophageal cancer. Several factors have been identified which might influence survival and should be taken into consideration in the management of oligometastasis. Most studies advocate a personalised approach to patient management until there are more studies to guide future decision making.

## ARTICLE HIGHLIGHTS

### Research background

Oesophageal cancer is the eighth most common cancer worldwide with an associated poor prognosis. The 5-year survival rate rarely exceeds 5% in case of metastatic disease. Combined treatment modalities are used for the management of locally advanced disease, consisting of neoadjuvant chemotherapy with or without radiotherapy followed by surgery. Meanwhile,

patients with recurrent or metastatic disease most commonly undergo systemic palliative therapy. However, to date there is a lack in specific guidelines regarding optimal management of patients presenting with oligometastatic oesophageal cancer. The European Society for Medical Oncology, suggests that patients with metastasis can be considered for different options of treatment depending on the clinical case. It is unclear for current studies whether resection improves the overall survival and what is the optimal management.

### Research motivation

This systematic review focuses on the current practice regarding treatment of oligometastatic oesophageal cancer and factors affecting survival following treatment of oligometastasis.

### Research objectives

This review aims to assess the current practice regarding the management of patients with oligometastatic oesophageal cancer and identify prognostic factors affecting survival following treatment for oligometastasis.

### Research methods

An extensive systematic search of the literature was performed in Cochrane Library, MEDLINE and EMBASE databases on January 4th, 2019. Relevant electronic databases were searched for studies assessing the clinical outcome of oligometastasis.

### Research results

The main finding of this systematic review is that Oligometastatic oesophageal cancer in selected patients is amenable to loco-regional treatment, and the overall survival of this patient cohort may be improved with patient and tumour-specific treatments. However, there is an increasing shift toward individualized, multidisciplinary management of oligometastasis because it is difficult to conduct randomized controlled trials due to the variety of presentations.

### Research conclusions

The lung and liver are amongst the most common sites of metastasis in oesophageal cancer. Most studies advocate a personalised approach to patient management until there are more studies to guide future decision making. Aggressive treatment of oligometastatic disease in oesophageal cancer is performed on an individual basis. Several factors have been identified which might influence survival and should be taken into consideration in the management of oligometastasis. Most studies advocate a personalised approach in the management of oligometastatic oesophageal cancer.

### Research perspectives

The current management advocated by most studies is based on a personalised approach to patient management until there are more studies to guide future decision making. Larger scale future studies or randomised controlled trials to assess optimal management plan for oligometastatic disease is required to guide management of this patient cohort.

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