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Observational Study

Oesophageal cancer metastases: An observational study of a more aggressive approach

Treatment for cure in metastatic OC

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Abstract

BACKGROUND

The prognosis for oesophageal carcinoma is poor but once distant metastases emerge the prognosis is considered hopeless. There is no consistent protocol for the early identification and aggressive management of metastases.

AIM

To examine the outcome of a policy of active postoperative surveillance with aggressive treatment of confirmed metastases.

METHODS

A prospectively maintained database of 205 patients diagnosed with oesophageal carcinoma between 1998 and 2019, and treated with curative intent, was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance, and treated for cure. This cohort was compared with incomplete clinical responders to neoadjuvant chemoradiotherapy (nCRT) who subsequently underwent surgery on their primary tumour. Overall survival was estimated using The Kaplan-Meier method and the log-rank test was used to compare survival differences between groups.

RESULTS

Eleven of 205 patients (5.4%) had metastases treated for cure (82% male; median age 60 years; 9 adenocarcinoma (AC) and 2 squamous cell carcinoma (SCC). All underwent neoadjuvant chemotherapy or chemoradiotherapy, followed by surgery in all but 1 case. Of the 11 patients, 4 had metastatic disease at diagnosis, of whom 3 were successfully downstaged with neoadjuvant chemoradiotherapy (nCRT) before definitive surgery. Two of this four also developed oligometastatic recurrence and were treated with curative intent. Following definitive treatment, 7 had treatment for metachronous oligometastatic disease; 5 of whom underwent metastasectomy (adrenal x2; lung x2; liver x1). The median overall survival (MOS) was 10.9 years (95%CI: 0.7

years to 21 years) which was not statistically significantly different from incomplete clinical responders without metastatic disease undergoing surgery on the primary tumour ($n = 110$; MOS = 2.4 (95%CI: 1.2 to 3.6); $p = .080$). The cumulative proportion surviving 1, 3, and 5 years was 100%, 91%, and 61% respectively.

CONCLUSION

Metastatic oesophageal cancer represents a unique challenge, but aggressive treatment can be rewarded with impressive survival data. In view of recent advances in targeted therapies, intensive follow-up may yield a greater number of patients with curative potential and thus improved long-term survival.

Key Words: Oesophageal metastases; Oligometastases; Active surveillance; Treatment for cure: Metastasectomy; Survival

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Core Tip: Modern imaging technologies can detect oligometastatic oesophageal cancer earlier than ever before, and targeted multimodal therapies combined with innovative surgery increases the potential for cure. Unfortunately, current guidelines do not reflect these advances and all too often consign patients to palliation. This approach is incongruous with other oligometastatic cancers such as colorectal cancer. Based on the survival outcomes of patients with oligometastatic disease treated for cure at our institution we advocate for more intensive surveillance strategies to identify patients with curative potential early, and thus improve long-term survival.

INTRODUCTION

Oesophageal cancer is an aggressive disease that presents insidiously, disseminates early, and spreads rapidly in most patients. It remains a leading cause of death from cancer worldwide and fewer than 5-12% will survive 5 years^[1,2]. At least 40% of patients present with distant metastasis at initial diagnosis^[3] and only 5% of these patients will be alive at 5 years^[4]. Even when presenting with early disease, 29-59% of patients undergoing surgical resection with curative intent will develop loco-regional or distant recurrence^[5-11]. And of patients with a pT0N0M0 tumour at resection following neo-adjuvant chemoradiotherapy (nCRT), up to 17% will succumb to distant metastases^[12-14]. Because of these poor survival outcomes, the role of intensive surveillance post-oesophagectomy and treatment of metastatic disease remains controversial.

The management of oesophageal cancer has undergone major advances over the past 30 years. Specifically, both neoadjuvant chemotherapy and nCRT have been shown to increase survival over surgery alone^[15-17]. While neoadjuvant chemotherapy has achieved this increase by targeting occult micrometastases^[18], combined chemoradiotherapy has increased survival by both targeting micrometastases and sterilising locoregional disease, thus up to 50% of patients with squamous cell carcinoma (SCC) and up to 25% of patients with adenocarcinoma (AC) undergoing chemoradiotherapy have a complete pathological response in the resected specimen, depending on the regimen and the disease stage^[15,16].

Nevertheless, metastatic oesophageal cancer remains a challenge. Oligometastases ¹is defined as a state of limited metastatic disease characterised by fewer than 5 metastases^[5,19]. Synchronous oligometastases may be detected at the time of diagnosis of the primary cancer, while metachronous oligometastases are those detected during follow-up^[5,20]. Metastasectomy is well-established in the treatment of certain oligometastatic cancers such as colorectal cancer where ⁶partial hepatectomy and pulmonary resection are well established^[5], with both the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and America's National Comprehensive Cancer Network (NCCN) recommending surveillance strategies to

identify recurrence, and liver metastasectomy where possible, and the NCCN making similar recommendations for pulmonary metastasectomy^[21-23]. In contrast, NICE recommends that neither routine clinical follow-up nor radiological follow-up be offered to patients ⁴ who have no symptoms or evidence of residual disease after treatment for oesophago-gastric cancer with curative intent for the detection of recurrent disease^[24]. The NCCN recommends clinical follow-up alone for asymptomatic patients and palliation alone for patients who develop metastatic recurrence^[25].

Over the past decades, efforts have focused on the molecular and biological alterations that lead to oesophageal cancer, specifically the influence of angiogenesis on micrometastatic tumour growth^[26-28]. This has resulted in the development of novel ² molecularly targeted agents that target a variety of relevant pathways such as vascular endothelial growth factor (VEGF), ² cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR)^[29], as well as targeted radiotherapy in the form of stereotactic radiotherapy^[30]. Leading the way are HER-2 inhibitors for the treatment of HER-2 expressing metastatic adenocarcinomas^[29]. It is intuitive that aggressive treatment of oligometastatic disease would improve disease control and provide a survival benefit for patients with oesophageal cancer also. The purpose of this study is to examine survival outcomes in patients who underwent active surveillance and targeted therapy at our institution for their oligometastatic disease.

MATERIALS AND METHODS

Study design and patients

We conducted a retrospective review of a prospectively maintained database of all patients diagnosed with oesophageal carcinoma and treated with curative intent between 1998 and 2019 at Connolly Hospital Blanchardstown, Dublin, Ireland. Patients were treated with either chemoradiotherapy alone, or chemoradiotherapy followed by surgery, or surgery alone.

Patient Management and Follow-up

Over a 21-year time period, 205 patients with esophageal carcinoma underwent curative management. Following discharge patients were followed up in clinic every 3 mo for the first 3 years, with upper gastrointestinal endoscopy (EGD) performed every 3 mo and computerised tomography (CT) performed every 6 mo. Between 3 and 5 years they were followed up in clinic every 6 mo with EGD every 6 mo and CT scanning performed annually. After 5 years patients were followed up annually with endoscopy and a clinic visit (which was on the same day for patients who had to travel from a distance). In addition, patients had access to their oncology co-ordinator and were encouraged to call at any time with any concern. On receipt of a call, their co-ordinator would offer them a clinic visit or an EGD (or other imaging) depending on their symptoms or concerns.

Patient Database

A patient database was maintained over the study period, both by nursing and clinical staff. This was scrutinised for patients with synchronous and metachronous oligometastases. Only patients who underwent curative treatment of oligometastatic disease were included in this study. A second group of patients (with non-metastatic disease) who had an incomplete clinical response to nCRT and subsequently underwent surgery on the primary tumour were identified for comparison of survival outcomes.

Of 205 patients treated with curative intent, 110 had an incomplete response to neoadjuvant chemoradiotherapy for non-metastatic oesophageal cancer and subsequently underwent surgery, and 11 had oligometastases treated for cure. The medical and electronic records of the oligometastatic cohort treated for cure were reviewed for demographic, clinical, and histopathologic variables. Notably, staging of the primary oesophageal cancer was prospectively assigned according to the TNM classification of the American Joint Committee for Cancer Staging, initially the 6th edition and then the 7th following its publication. Each case was assessed with respect to the use of neoadjuvant therapy, history of oesophagectomy, and timing of metastasis. Further details regarding the site and treatment of metastasis were included. Survival data was included for analysis and comparison.

Ethical Approval

As this was a retrospective audit ethical approval was not required but audit approval was sought and granted by the Connolly Hospital Ethics Committee.

Statistical Analysis

The statistical analysis of this study was performed by biostatistician Mary Dunne from St Luke's Radiation Oncology Network, Dublin D06 HH36, Ireland. Overall survival was estimated using The Kaplan-Meier method and was defined as the duration from the date of diagnosis until death from any cause or last follow-up at study endpoint on February 26th, 2020. The log-rank test was used to compare survival differences between groups (assessed for significance at the 0.05 Level). Statistical analysis was carried out using IBM SPSS Statistics 25(Chicago, IL).

RESULTS

Clinical characteristics of patients

Eleven of the 205 (5.4%) patients diagnosed with oesophageal carcinoma [146 (71%) male; 135 (65.9%) adeno; 68 (33.2%) squamous; 2 adenosquamous) between 1998 and 2019, and treated with curative intent, had metastases treated for cure. Of these, 4 had synchronous oligometastatic oesophageal cancer, 2 of which also had treatment for cure for oligometastatic recurrence. A further 7 had metachronous oligometastatic oesophageal cancer only. The median age of patients with synchronous metastasis was 65 years (range 53-71 years; AC 75%) and in patients with metachronous carcinoma only was 57 years (range 36-72 years; AC 86%) (Table 1.). The majority of both cohorts were male (75% and 86%).

Treatment of synchronous oligometastatic oesophageal cancer

The four patients that had metastatic disease at presentation were treated with nCRT, 3 of whom underwent subsequent oesophagectomy and achieved a margin free R0 resection, and 1 who declined surgery following a clinical complete response to nCRT

(Table 1). Two of these patients subsequently presented with metachronous metastases which also were treated for cure (Table 2).

Patient 1 had locally advanced SCC at diagnosis (T4N1M1). Despite a complete clinical response to definitive chemoradiotherapy, routine surveillance Positron Emission Tomography – Computed Tomography (PET-CT) almost 12 mo later (11.5 mo) revealed fluorodeoxyglucose (FDG) avid lung lesions bilaterally. These were subsequently treated with stereotactic radiotherapy. The patient survived for 3 years post metastatic recurrence (36.4 mo). Patient 2 had a 12mm short axis FDG positive lymph node lying immediately to the right of the coeliac axis on staging PET-CT (AC, T3N2M1). The patient was treated with nCRT and radical oesophago-gastrectomy for a poorly differentiated junctional/cardia AC (ypT2bN1Mx). Almost 18 mo later (17.9 mo) a radiological work-up for a pulmonary embolus revealed a 1.9cm left para-aortic node with FDG uptake on PET-CT which was subsequently treated with chemotherapy (Table 2). Follow-up CT showed reduction in tumour size and subsequent surveillance with endoscopy and CT revealed stable disease with no evidence of recurrence. The patient was alive and well at the conclusion of this study, 83.3 mo after his initial diagnosis (65.4 mo post-recurrence).

Two further patients (Patient 3 and Patient 4) had treatment for cure of synchronous oligometastatic disease only (Table 1, Table 2). Patient 3 had liver metastasis on staging PET-CT (AC, T3N1M1). Restaging CT post nCRT was negative for liver metastasis and the patient subsequently underwent oesophagectomy (ypT3N0M0). Patient 4 had a 1cm FDG avid right supraclavicular node on staging PET-CT (AC, T3N2M0) and underwent nCRT and subsequent oesophagectomy for a moderate to poorly differentiated adenocarcinoma at the oesophago-gastric junction (OGJ) (ypT2N0Mx). The patient was alive and well at the conclusion of this study, 8.5 years after his initial diagnosis (102.8 mo).

Treatment of metachronous oligometastatic oesophageal cancer

The remaining 7 patients did not have clinical evidence of metastatic oesophageal cancer at diagnosis. These patients had mostly T3 disease with or without nodal

involvement (Table 1; Patient 5-11). All underwent nCRT or neoadjuvant chemotherapy followed by surgery for their primary cancer. Of this cohort ($n = 7$), 3 developed pulmonary recurrence, 2 adrenal, 1 Liver, and 1 patient had biopsy proven retroperitoneal nodal recurrence. All 7 patients underwent targeted treatment for metastatic recurrence with intent to cure, the details of which are summarized in Table 2. The median time from diagnosis to recurrence was 19.2 mo (range 15.7 - 33 mo) and the median survival post recurrence was 97.4 mo (95%CI: 0-204 mo). The MOS was 130 mo (95%CI: 3 to 258 mo), or the MOS was 10.9 years (95%CI: 0.2 to 21.5 years).

Survival Outcomes

The MOS of the 11 patients who underwent curative treatment for synchronous or metachronous metastatic disease, or both was 10.9 years (95%CI: 0.7 to 21) which was not statistically significantly different from patients with an incomplete clinical response following nCRT undergoing surgery ($n = 110$; MOS = 2.4 years (95%CI: 1.2 to 3.6); $p = .080$). The cumulative proportion of patients with metastatic disease treated for cure surviving 1, 3, and 5 years was 100%, 91%, and 61% respectively, with 6 patients still alive at the end of the study period.

Patients that underwent surgical resection for their recurrence ($n = 5$) had a MOS of 10.9 years (95%CI: 0.6 to 21.2) from date of diagnosis and 8.1 years (95%CI: 0 to 16.8 years) post recurrence, and a 5-year survival of 80% from date of diagnosis.

DISCUSSION

Patients with metastatic oesophageal cancer present a unique challenge. Although solitary metastases of oesophageal cancer are uncommon^[31] the evolution of imaging will ensure ever-earlier detection, challenging oncologists and surgeons to detect and deal with them. Treatment of oligometastatic oesophageal cancer is controversial and to date formal guidelines are lacking. There are no large randomized multicentre trials and thus case series, such as ours, remain an important source of information for clinicians managing these challenging patients.

Those patients treated surgically for recurrence in our study had a MOS of 10.9 years, or 130.3 mo, and a 5-year survival of 80%. Depypere and colleagues^[32] conducted a large retrospective study comparing different treatment options for different subtypes of recurrence following curative resection, including single solid organ metastasis and single metastasis at another location. Of 1754 patients that had curative resection, 43.7% had recurrence; 14.4% of whom had clinical solitary solid organ recurrence (liver, lung, brain, or adrenal)^[32]. Only 20 patients (1.14%) had their recurrence resected with or without systemic therapy and had a significantly better median and 5-year survival, than 63 non-surgically treated patients (54.8 months, (5-year survival 43.9%) v. 11.6 months, (5-year survival 4.6%))^[31,32]. Arguably those suitable for resection self-select but the survival statistics for metastatic resection in a disease as aggressive as oesophageal cancer are impressive.

The patients in our study who underwent adrenalectomy were alive at 62.1 and 118.9 mo post recurrence. The oesophagus is the third most frequent site of origin of adrenal metastasis^[33] and there are only a few reports of adrenalectomy for recurrence with survival ranging from 28 mo to over 5 years^[33-36]. These findings confirm that adrenalectomy for isolated adrenal metastases from oesophageal carcinoma is worthwhile. A disease-free interval of over six months and an AC subtype, are reported as predictors of improved survival and should be considered in patient selection^[37,38]. As adrenal metastases are clinically silent, intensive surveillance imaging is indicated if they are to be identified early enough for curative resection.

The remaining patients who underwent metastasectomy in our case series had either lung or liver metastases. All had metachronous oligometastases, had received nCRT and had undergone resection of their primary tumours. Those who underwent pulmonary metastasectomy lived for 26.1 and 97.4 mo post recurrence. While the patient who underwent liver metastasectomy was alive and disease-free at 51.9 mo post recurrence. While hepatectomy and pulmonary resection are universally recommended for colorectal cancer metastases^[21-23] they are not recommended for oesophageal cancer^[24,25]. A nationwide study by Van Der Veen *et al* of the Dutch national registry for

histopathology and cytopathology identified 32,057 patients who underwent resection for gastro-oesophageal cancer between 1991 and 2016 and reported that 34 (0.11%) underwent resection for pulmonary ($n = 15$) or hepatic ($n = 19$) metastases across 21 hospitals and had an overall 5-year survival of 53% and 31% respectively^[39]. Liu *et al* reported that 26 SCC patients with solitary hepatic metastasis, who underwent liver resection, had 1- and 2-years survival rates of 50.8% and 21.2% respectively which was significantly higher than the 31.0% and 7.1% survival rates for the 43 non-surgically treated patients^[40].

Oesophageal cancer patients very frequently present with metastases, which almost inevitably consigns them to palliative management. Until recently primary cancer resection in these circumstances was rarely considered. Of the 4 patients who presented with metastatic oesophageal in our case series, 3 underwent surgery to the primary cancer. All 3 had nCRT and all achieved an R0 resection, with a cumulative proportion surviving 2 years of 67%. Zhang *et al* analysed a large population-based cohort of 4367 metastatic oesophageal cancer patients (M1b-stage) from the SEER database^[41] and found a significant survival benefit for surgery for the primary tumour with a median survival for the surgery group – 14 compared with 9 mo for the no-surgery AC group, and a similar significant survival advantage for surgery (11 mo) compared with the no-surgery SCC group (7 mo)^[41]. Of note, patients who had not received neoadjuvant chemotherapy failed to benefit from resection for either tumour subtype^[41]. Thus, when combined with neoadjuvant chemotherapy, surgery for the primary tumour is associated with improved survival in a select group of patients with metastatic oesophageal cancer^[41].

Three of the patients in our series received chemotherapy alone for recurrent oligometastatic oesophageal cancer (patients 2, 6, and 11). Although chemotherapy is commonly considered as merely palliative in recurrent metastatic cancer it also has the potential to cure^[42]. Taxanes as single agents have a slightly higher response rate in patients with AC (34%) than in patients with SCC (28%), resulting in an overall survival rate of 13.2 mo^[43]. Parry *et al* reported complete tumour regression in 2 patients after

chemotherapy alone, with both patients alive at last follow-up (35 and 112 mo)^[44]. Developments in proton beam therapy and stereotactic ablative radiation increases its conformality and reduces radiation-toxicity^[45]. Sachdeva *et al* recently reported on the use of external beam radiotherapy for the treatment of oligometastatic sacral metastases in a 46-year-old male with a rare case of primary oesophageal lymphoma^[46]. Moreover, one-year and 2-year progression-free survival and overall survival rates have been reported at 62% and 48%, and 90% and 72%, respectively following stereotactic ablative therapy for pulmonary metastases^[47].

With few predictive factors for survival of metastatic oesophageal cancer in the literature^[9,48] it is unclear which patients or which tumour characteristics predict the best survival outcomes. The current approach to metastatic disease all too often consigns the patient to palliative care and a dismal outcome. We have previously reported that bone marrow positivity for micrometastases at the time of oesophagectomy is a predictor of increased risk of cancer-related death and can identify patients requiring intensive surveillance for early detection of metastases with intent to treat^[49]. Our current findings suggest that a more optimistic approach can be rewarded with impressive survival data. It is intuitive that aggressive treatment can improve survival, but it implies a need for more intensive surveillance strategies, especially in the first three years post-resection, to identify salvageable patients and consider curative intent. In an era of molecularly targeted agents, the identification of such patients is more important than ever as identified by the CheckMate 557 trial where the addition of nivolumab for patients with residual disease following chemoradiotherapy provided a median disease-free survival of 22.4 mo *vs* 11.0 mo in the placebo arm, which was significant^[50].

The obvious limitation of our study is the small sample size of patients with metastatic oesophageal cancer treated for cure. Moreover, the survival data reported in our study reflects a policy of aggressive treatment of confirmed limited metastases only. Such patients self-select and our survival data cannot be applied to all patients with metastatic oesophageal cancer.

CONCLUSION

In conclusion, as advances in imaging facilitate earlier metastatic disease detection and advances in multimodal and targeted treatments improve survival outcomes, surveillance strategies must be intensified to diagnose metastatic disease earlier in the recurrence process in order to institute medical or surgical measures with a greater possibility of success. Future studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma in the context of today's imaging technologies in order to update surveillance and treatment guidelines in line with those for cancers of the lower gastrointestinal tract.

ARTICLE HIGHLIGHTS

Research background

The prognosis of metastatic oesophageal cancer is poor. The rate of oligometastatic oesophageal cancer is not well established, nor is the survival benefit of intervention. As a result, current guidelines advocate against a proactive approach which is incongruent with other oligometastatic cancers such as colorectal cancer. Based on a policy of active postoperative surveillance and survival outcomes of patients with oligometastatic disease treated with curative intent at our institution, we advocate for more intensive surveillance strategies to identify patients with curative potential early and thus improve long-term survival.

Research motivation

To evaluate the impact of a policy of active surveillance and aggressive management of confirmed metastases on long-term survival.

Research objectives

To examine survival outcomes in patients who underwent active surveillance and targeted therapy of their oligometastatic disease, either at diagnosis or on follow-up

surveillance, at our institution. When compared to incomplete clinical responders to neoadjuvant chemoradiotherapy for non-metastatic oesophageal cancer who subsequently underwent surgery on their primary tumour, the median overall survival of the oligometastatic cohort was not statistically significantly different. These findings suggest that aggressive treatment of confirmed metastases can be rewarded with impressive survival data and that a more proactive approach to oesophageal oligometastases should be considered.

Research methods

A prospectively maintained database of patients diagnosed with oesophageal carcinoma and treated with curative intent in a single institution was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance, and treated for cure. This cohort was compared with incomplete clinical responders to neoadjuvant chemoradiotherapy who subsequently underwent surgery on their primary tumour. Overall survival was estimated using The Kaplan-Meier method and the log-rank test was used to compare survival differences between groups.

Research results

The overall survival of patients with oligometastatic disease who were treated for cure at our institution is impressive and not statistically significantly different from incomplete clinical responders without metastatic disease who subsequently underwent surgery on their primary tumour. These results suggest that intensive follow-up and aggressive management of confirmed metastases may improve long-term survival. Further studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma and evaluate the cost-benefit ratio of a policy of active surveillance and aggressive management of confirmed oligometastatic disease.

Research conclusions

In view of recent diagnostic and therapeutic advances, intensive follow-up and aggressive treatment of confirmed metastases may improve long-term survival in patients with oligometastatic oesophageal carcinoma.

Research perspectives

Further research should prospectively establish the rate of oligometastatic recurrence in oesophageal carcinoma in order to evaluate the cost-benefit ratio of active surveillance and aggressive management, and inform future clinical guidelines.

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