Oligometastatic disease in esophagogastric cancer

Tiuri E. Kroese

Oligometastatic disease in esophagogastric cancer
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Oligometastatic disease in esophagogastric cancer

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met een samenvatting in het Nederlands

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Tiuri Ewout Kroese

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Promotoren

Prof. dr. R. van Hillegersberg
Prof. dr. J.P. Ruurda
Prof. dr. H.W.M. van Laarhoven

Copromotor

Dr. P.S.N. van Rossum

Beoordelingscommissie

Prof. dr. M. Guckenberger
Prof. dr. M.P.W. Intven
Prof. dr. M.G.E.H. Lam
Prof. dr. A.M. May (voorzitter)
Prof. dr. B.P.L. Wijnhoven

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CHAPTER 1

General introduction and thesis outline

Based on *ASO Author Reflections: Role of Local Treatment for Oligometastatic Esophagogastric Cancer*

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Tiuri E. Kroese, Peter S.N. van Rossum, Richard van Hillegersberg

ESOPHAGOGASTRIC CANCER

In the Western world, the incidence of esophageal adenocarcinoma is rapidly rising, while the incidence of esophageal squamous cell carcinoma is slowly declining[1]. In 2020, the Netherlands had the highest incidence of esophageal cancer in Europe (9.11 cases per 100,000 inhabitants)[2]. In contrast, the incidence of gastric cancer (especially the intestinal type) is declining, and 3.63 cases of gastric cancer per 100,000 inhabitants were diagnosed in the Netherlands in 2020 (Figure 1)[2]. In the Netherlands, the majority of patients with esophagogastric cancer (i.e. esophageal or gastric cancer) are male (~70%) and above 60 years of age (~70%)[3,4].

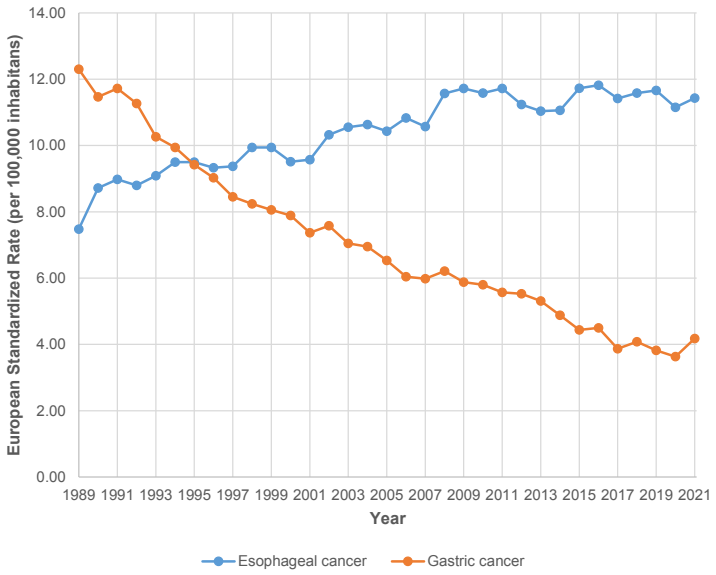


Figure 1. Incidence of esophagogastric cancer over the last 30 years in the Netherlands (Source: Netherlands Cancer Registry).

Overall survival in patients with esophagogastric cancer varies by disease stage[3,4]. The disease stage is classified using the TNM classification system of the Union for International Cancer Control (UICC)[5]. Overall 5-year survival rates in patients with esophagogastric cancer with early-stage disease (stage I) are 72-75%, as compared with 34-47% in patients with locally-advanced disease (i.e. stage II-III), and 2-3% in patients with metastatic disease (i.e. stage IV)[3,4].

METASTATIC ESOPHAGOGASTRIC CANCER

In patients with metastatic esophagogastric cancer (i.e. stage IV), palliative systemic therapy improves overall survival and quality of life compared with best supportive care alone (i.e. no tumor-directed treatment)[6]. Despite the increased use of chemotherapy for patients with metastatic esophagogastric cancer (from 24% to 33%), the overall survival in these patients has hardly improved over the last 30 years in the Netherlands. The median overall survival for esophageal cancer has improved from 4 months to 5 months, and for gastric cancer from 3 months to 4 months (Figure 2-3)[7,8].

The most common locations for metastatic disease in patients with esophageal cancer are the extra-regional lymph nodes, followed by the liver, lung, and bone[7]. The most common locations for metastatic disease in patients with gastric cancer are the peritoneum (i.e. peritoneal carcinomatosis), followed by the extra-regional lymph nodes and liver (Figure 4-5)[7].

Peritoneal metastases are usually not considered oligometastatic disease because it usually involves a diffuse type of dissemination within the peritoneal cavity through direct extension, seeding of cancer cells in the abdominal fluid (ascites), or implantation onto peritoneal surfaces[9]. Consequently, treatment approaches for peritoneal metastases vastly differ from hematogenous or lymphatic metastases (i.e. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [HIPEC] as compared with metastasectomy or stereotactic radiotherapy)[10].

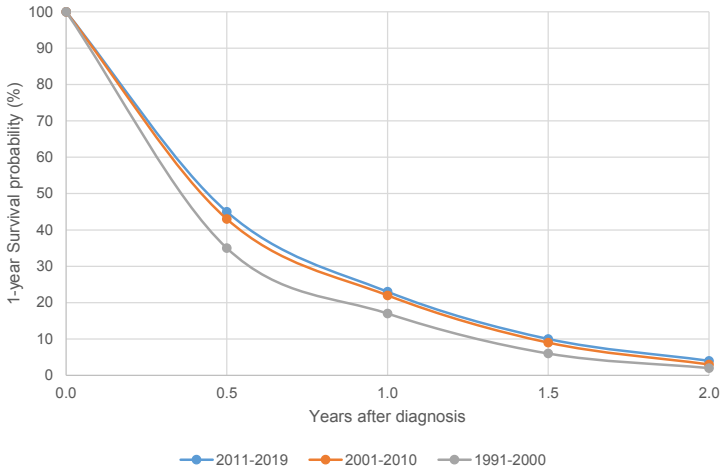


Figure 2. 1-year overall survival of patients diagnosed with metastatic (stage IV) esophageal cancer over the last 30 years in the Netherlands (Source: Netherlands Cancer Registry).

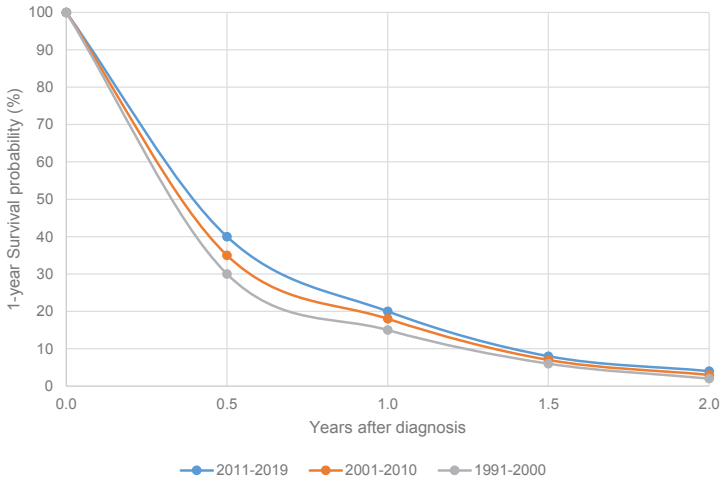
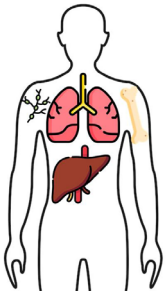
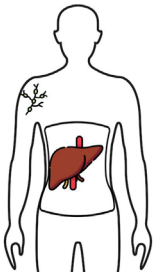


Figure 3. Overall survival of patients diagnosed with metastatic (stage IV) gastric cancer over the last 30 years in the Netherlands (Source: Netherlands Cancer Registry).



Extra-regional lymph nodes	53%
Liver	49%
Lung	25%
Bone	21%
Adrenal gland	8%
Peritoneal	8%
Other	8%
Brain	3%
Pleural	2%

Figure 4. Locations of metastatic disease (i.e. stage IV) in patients with esophageal cancer in the Netherlands (Source: Netherlands Cancer Registry[7]). Patients can have metastatic disease at multiple sites (importantly, this figure does not represent patients with oligometastatic disease and icons displayed of locations with an incidence higher than 20%).



Peritoneal	50%
Liver	40%
Extra-regional lymph nodes	34%
Lung	10%
Bone	10%
Adrenal gland	4%
Other	4%
Pleural	2%
Brain	1%

Figure 5. Locations of metastatic disease (i.e. stage IV) in patients with gastric cancer in the Netherlands (Source: Netherlands Cancer Registry[7]). Patients can have metastatic disease at multiple sites (importantly, this figure does not represent patients with oligometastatic disease and icons are displayed of locations of metastatic disease with an incidence higher than 20%).

OLIGOMETASTATIC ESOPHAGOGASTRIC CANCER

Among the described patients with metastatic disease (i.e. stage IV), there is a subgroup of patients with oligometastatic disease. Oligometastatic disease was first defined in 1995 by Hellman and Weichselbaum as an intermediate state between localized and polymetastatic disease and is characterized by a limited (oligo) number of metastases. The concept of oligometastatic disease implies that local treatment of metastasis (e.g. metastasectomy or stereotactic body radiotherapy [SBRT]) may improve the time to disease progression and, ultimately, overall survival[11].

The benefit of local treatment for oligometastatic disease might be explained by the "seed and soil hypothesis" first postulated by Paget in 1889[12]. This hypothesis suggests that the spread of cancer cells from the primary site ("seed") is not merely anatomic but rather an interaction between the cancer cells and the host organ ("soil")[12]. Metastasis only develops when the "seed" and "soil" are compatible[12]. Because of this selective compatibility, certain tumors are predisposed to metastasize to certain organs only[12]. This concept might explain why local treatment to that metastasized organ can improve progression-free and overall survival[12].

Recently, the European Society for Radiotherapy and Oncology and European Organization for Research and Treatment of Cancer (ESTRO/EORTC) have made efforts to improve the definition of oligometastatic disease by developing a comprehensive nomenclature consisting of 5 key questions[13]. First, a history of polymetastatic disease was used to differentiate between induced oligometastatic disease (i.e. previous history of polymetastatic disease) and genuine oligometastatic disease (i.e. no history of polymetastatic disease)[13]. Second, a history of oligometastatic disease was used to divide genuine oligometastatic disease into repeat oligometastatic disease (i.e. history of oligometastatic disease) and de-novo oligometastatic disease (i.e. first-time diagnosis of oligometastatic disease)[13]. Third, the detection of oligometastatic disease within 6 months after the primary tumor diagnosis was used to subclassify de-novo oligometastatic disease into synchronous (i.e. ≤6 months) and metachronous oligometastatic disease (i.e. >6 months)[13]. Fourth, a diagnosis of oligometastatic disease under active systemic therapy or a therapy-free interval was used to separate recurrence (i.e. therapy-free interval) from progression (i.e. active systemic therapy)[13]. Finally, an oligometastatic lesion progressive on imaging in a patient under active systemic therapy was used to separate progression (i.e. lesion progressive on imaging) and persistence (i.e. lesion not progressive on imaging)[13]. Figure 6 provides a classification model for oligometastatic disease (adapted from Guckenberger M et al. *Lancet Oncol.* 2020).

Although an important first step, the previously mentioned nomenclature[13] lacks specificity about metastatic disease burden to standardize inclusion criteria in future clinical trials on the benefit of local treatment and/or systemic therapy in patients with oligometastatic esophagogastric cancer. In addition, this nomenclature does not provide recommendations for treatment nor helps to guide clinical decision-making in multidisciplinary team meetings.

Up until now, 6 prospective trials have been conducted in patients with oligometastatic esophagogastric cancer (Table 1). The first prospective trial was the phase 3 randomized controlled REGATTA trial including patients with gastric cancer with synchronous oligometastatic disease limited to 1 organ (including peritoneal metastases) or 1 extra-regional lymph node station[14]. Patients were randomized to either gastrectomy plus D1 lymphadenectomy plus chemotherapy (but no resection of metastases) or chemotherapy alone[14]. Median overall survival was 14.3 months after primary tumor resection plus chemotherapy as compared with 16.6 months after chemotherapy alone (hazard ratio 1.09, 95% confidence interval: 0.78–1.52)[14]. Thus, this trial failed to show improved overall survival after primary tumor resection plus chemotherapy as compared with chemotherapy alone[14].

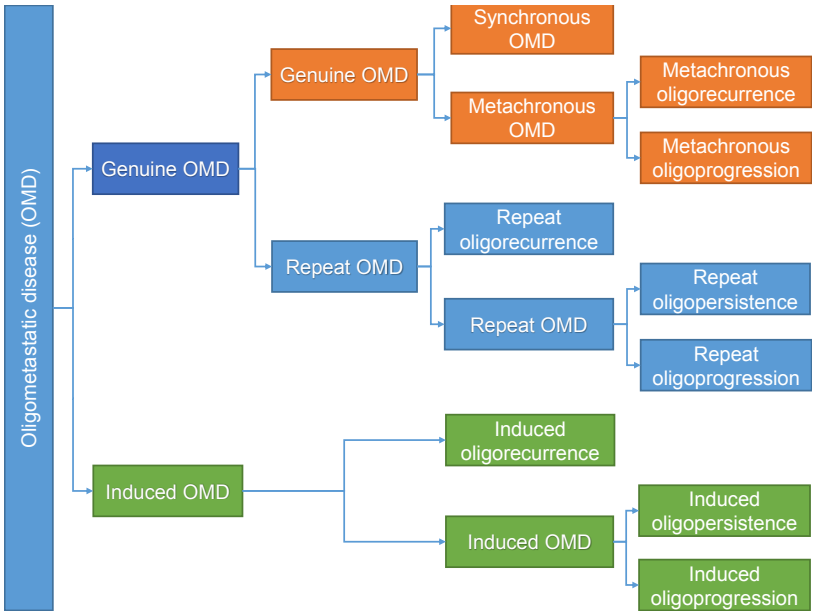


Figure 6. Classification model for oligometastatic disease (adapted from Guckenberger M. et al. *Lancet Oncol* 2020).

Table 1. Overview of completed trials in patients with oligometastatic esophagogastric cancer.

Author, year	Primary tumor	Country	Study type	Treatment	Maximum number of organs	Maximum number of metastases	Type of OMD	Staging	Median overall survival
Liu, 2023	Esophageal SCC	China	II R	ChT +/- IO+ RT versus ChT +/- IO	3	4	S+M	CT +/- ^{18}F-FDG PET	Not reached vs 18.6 months
Zhao, 2023	Esophageal SCC	China	II NR	IO+ChT+Low dose RT	ns	5	ns	ns	12.8 months
Cui, 2023	Gastric AC	China	II NR	ChT+Surgery+ChT	1	Organ-specific	S	CT or laparoscopy	Not reached
Liu, 2020	Esophageal SCC	China	II NR	SBRT +/- ChT	ns	3	M	CT or ^{18}F-FDG PET	24.6 months
Al-Batran, 2017	Gastric AC or EGJ AC	Germany	II NR	ChT+Surgery	1 + RPLN	Organ-specific	S	CT/MRI or ^{18}F-FDG PET	31.3 months
Fujitan, 2016	Gastric AC	Japan, Korea, Singapore	III	ChT+Surgery of primary tumor alone vs. ChT	1	4	S	CT	14.3 months vs 16.6 months

AC: adenocarcinoma, CT: computed tomography, ChT: chemotherapy, IO: immune-oncology, MRI: magnetic resonance imaging, M: Metachronous, NR: non-randomized, OMD: oligometastatic disease, R: randomized, RPLN: retroperitoneal lymph nodes, SCC: squamous cell carcinoma, S: Synchronous, USA: United States of America, ns: not specified, ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose position emission tomography, II: phase II, III: phase III

The second prospective trial was the phase 2 non-randomized AIO-FLOT-3 trial[15]. This trial studied the effect of chemotherapy plus resection of the primary tumor and metastases versus chemotherapy alone in patients with gastric or junction adenocarcinoma with synchronous oligometastatic disease limited to 1 organ (including peritoneal metastases) and/or the retroperitoneal lymph nodes[15]. Patients underwent 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy and patients who responded to chemotherapy underwent gastrectomy plus D2 lymphadenectomy and resection of all metastases[15]. Overall survival after FLOT chemotherapy plus resection of the primary tumor and metastases was 31.3 months as compared with 15.9 months in patients who underwent FLOT chemotherapy alone[15]. However, a selection bias was probably introduced, because only patients who responded to FLOT chemotherapy underwent resection of the primary tumor and metastases[15].

The third prospective trial was the phase 2 non-randomized trial by Liu et al[16]. This trial studied the effect of SBRT for ≤3 metachronous metastases (excluding peritoneal metastases) in patients with esophageal squamous cell carcinoma with a surgically or radiotherapy controlled primary tumor[16]. Patients underwent SBRT of all metastases, and 50% of patients underwent adjuvant chemotherapy (cisplatin plus fluorouracil, paclitaxel plus cisplatin, paclitaxel plus carboplatin, or fluorouracil plus oxaliplatin; depending on the treating physician)[16]. Overall survival across all patients was 24.6 months, and overall survival was comparable between patients with or without adjuvant chemotherapy[16]. These encouraging results let the authors to perform a subsequent phase 2 randomized trial which will be discussed at the end of this paragraph.

The fourth prospective trial was the phase II non-randomized trial by Cui et al[17]. This trial studied the effect of surgery after neoadjuvant chemotherapy in patients with gastric cancer with synchronous oligometastatic disease[17]. Patients underwent docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy, and patients without progression underwent radical resection of the primary tumor and metastases and adjuvant DOS[17]. After a median follow-up time of 30.0 months, the median progression-free survival and overall survival were not reached[17].
The fifth prospective trial was the phase II non-randomized trial by Zhao et al[18]. This trial studied the immunomodulatory effect of low dose radiotherapy plus second-line chemotherapy (irinotecan) and immunotherapy (camrelizumab) in patients with oligometastatic esophageal squamous cell carcinoma[18]. Patients with failure after first-line immunotherapy and chemotherapy were included. Median progression-free survival after low-dose radiotherapy, chemotherapy and immunotherapy was 6.9 months and overall survival were 12.8 months[18].
Finally, the sixth prospective trial was the phase II randomized trial by Liu et al.[19] This trial studied the efficacy of systemic and local therapy compared with systemic therapy alone in patients with oligometastatic esophageal squamous cell carcinoma[19]. Patients underwent 4

cycles of standard systemic therapy (57% chemotherapy, 38% immunotherapy) combined with local treatment for oligometastatic disease (mostly SBRT) compared with 4 cycles of standard systemic therapy alone[19]. The combined systemic and local therapy resulted in improved progression-free survival and overall survival as compared with systemic therapy alone[19]. After a median follow-up of 30.5 months, median progression-free and overall survival in the systemic and local therapy group was 15·3 months or median overall survival was not reached versus 6.4 months and 18.6 months in the systemic therapy alone[19].

From these 6 currently published prospective trials, 4 important conclusions can be drawn. First, resection of the primary tumor *alone* without combined resection of metastases does not improve overall survival[14]. Second, the (immunomodulatory) effect of low dose radiotherapy in patients with oligometastatic esophageal squamous cell carcinoma appears to be limited since the overall survival of this group was lower than the overall survival of patients with oligometastatic squamous cell carcinoma undergoing high dose radiotherapy (median overall survival of 12.8 months[18] versus 24.6 months[16]). Third, the overall survival after local treatment of oligometastatic disease with or without systemic therapy appear better as compared with clinical trial data including patients with metastatic disease undergoing systemic therapy alone (median overall survival of 9-11 months[6]) although this comparison is biased because patients with oligometastatic disease have a lower tumor burden and might have a better performance status, known prognostic factors for overall survival. In addition, several trials only patients with response to systemic therapy underwent local treatment for oligometastatic disease. Finally, local treatment combined with systemic therapy improves overall survival compared with systemic therapy alone in patients with oligometastatic esophageal squamous cell carcinoma[19].

These 6 currently published prospective trials have included inhomogeneous patient cohorts regarding metastatic disease burden (e.g. 3 metastases versus 1 organ with metastases), metastatic disease locations (e.g. with or without peritoneal metastases), and state of oligometastatic disease (e.g. synchronous versus metachronous)[14-18]. Furthermore, these trials have used various treatment strategies for oligometastatic disease (e.g. local treatment for oligometastatic disease with or without combined systemic therapy) and have inherent bias which makes comparison of outcomes difficult[14-18]. Thus, a multidisciplinary consensus statement for the definition, diagnosis and treatment of oligometastatic esophagogastric cancer is urgently warranted.

THESIS OUTLINE

The first aim (PART I) of this thesis was to develop a multidisciplinary European consensus statement for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer through the OligoMetastatic Esophagogastric Cancer (OMEC) project. The second aim (PART II) was to assess the incidence and treatment of oligometastatic disease in patients with esophagogastric cancer using clinical data.

RESEARCH QUESTIONS

The research questions addressed in this thesis can be summarized as follows:

PART I The OMEC project

- Which definitions of oligometastatic esophagogastric cancer are used in the current literature, and does literature suggest local treatment for oligometastatic esophagogastric cancer leads to improved overall survival?
- Which definitions and treatment strategies are used by multidisciplinary tumor boards of esophagogastric cancer expert centers in Europe for patients with oligometastatic esophagogastric cancer?
- Which statements can reach multidisciplinary European consensus regarding the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer?

PART II Oligometastatic esophagogastric cancer in clinical practice

- What is the incidence of oligometastatic disease in patients with metastatic esophagogastric cancer?
- How do different treatment strategies for oligometastatic esophagogastric cancer relate to overall survival?
- What are the incidence and overall survival outcome of oligometastatic disease in patients with gastric cancer with metastatic disease limited to the liver?

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. May 2021;71(3):209-249. doi:10.3322/caac.21660
2. IKNL. Incidentie slokdarm- en maagkanker. https://iknl.nl/kankersoorten/slokdarm-en-maagkanker/registratie/incidentie.
3. IKNL. Overlevingscijfers van maagkanker. https://www.kanker.nl/kankersoorten/maagkanker/algemeen/overlevingscijfers-van-maagkanker
4. IKNL. Overlevingscijfers van slokdarmkanker. https://www.kanker.nl/kankersoorten/slokdarmkanker/algemeen/overlevingscijfers-van-slokdarmkanker
5. O'Sullivan B, Brierley J, Byrd D, et al. The TNM classification of malignant tumours-towards common understanding and reasonable expectations. *Lancet Oncol*. Jul 2017;18(7):849-851. doi:10.1016/S1470-2045(17)30438-2
6. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*. Aug 29 2017;8(8):CD004064. doi:10.1002/14651858.CD004064.pub4
7. IKNL. Slokdarm- en maagkanker in Nederland. https://iknl.nl/slokdarm-en-maagkanker
8. Bernards N, Creemers GJ, Nieuwenhuijzen GA, Bosscha K, Pruijt JF, Lemmens VE. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. *Ann Oncol*. Dec 2013;24(12):3056-60. doi:10.1093/annonc/mdt401
9. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol*. Jul 2020;148:157-166. doi:10.1016/j.radonc.2020.04.003
10. Kerkar SP, Kemp CD, Duffy A, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. *Trials*. Dec 23 2009;10:121. doi:10.1186/1745-6215-10-121
11. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. Jan 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
12. Paget S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev*. Aug 1989;8(2):98-101.
13. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. Jan 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
14. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol*. Mar 2016;17(3):309-318. doi:10.1016/S1470-2045(15)00553-7
15. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol*. Sep 1 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
16. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. Nov 1 2020;108(3):707-715. doi:10.1016/j.ijrobp.2020.05.003
17. Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? a multicenter, prospective cohort study (Neo-REGATTA). *BMC Cancer*. Apr 4 2023;23(1):308. doi:10.1186/s12885-023-10773-x
18. Zhao W, Ke S, Cai X, et al. Radiotherapy plus camrelizumab and irinotecan for oligometastatic esophageal squamous cell carcinoma patients after first-line immunotherapy plus chemotherapy failure: An open-label, single-arm, phase II trial. *Radiother Oncol*. Jul 2023;184:109679. doi:10.1016/j.radonc.2023.109679
19. Liu Q, Chen J, Lin Y, et al. Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2023. DOI: 10.1016/S2468-1253(23)00316-3.

PART I

The OMEC project

CHAPTER 2

Study protocol for the OMEC project: a multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer

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Tiuri E. Kroese, Peter S.N. van Rossum, Magnus Nilsson, Florian Lordick, Elizabeth C. Smyth, Riccardo Rosati, Philippe Nafteux, Domenico D'Ugo, M. Asif Chaudry, Wojciech Polkowkski, Franco Roviello, Ines Gockel, Piotr Kolodziejczyk, Karin Haustermans, Matthias Guckenberger, Marianne Nordsmark, Maria A. Hawkins, Andres Cervantes, Tania Fleitas, Eric van Cutsem, Markus Moehler, Anna D. Wagner, Hanneke W.M. van Laarhoven, Richard van Hillegersberg

ABSTRACT

Background

A uniform definition and treatment for oligometastatic esophagogastric cancer is currently lacking. However, a comprehensive definition of oligometastatic esophagogastric cancer is necessary to initiate studies on local treatment strategies (e.g. metastasectomy or stereotactic radiotherapy) and new systemic therapy agents in this group of patients. For this purpose, the OligoMetastatic Esophagogastric Cancer (OMEC) project was established. The OMEC-project aims to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer and provide a framework for prospective studies to improve outcomes of these patients.

Methods

The OMEC-project consists of five studies, including 1) a systematic review on definitions and outcomes of oligometastatic esophagogastric cancer; 2) real-life clinical scenario discussions in multidisciplinary expert teams to determine the variation in the definition and treatment strategies; 3) Delphi consensus process through a starting meeting, two Delphi questionnaire rounds, and a consensus meeting; 4) publication of a multidisciplinary European consensus statement; and 5) a prospective clinical trial in patients with oligometastatic esophagogastric cancer.

Discussion

The OMEC project aims to establish a multidisciplinary European consensus statement for oligometastatic esophagogastric cancer and aims to initiate a prospective clinical trial to improve outcomes for these patients. Recommendations from OMEC can be used to update the relevant guidelines on treatment for patients with (oligometastatic) esophagogastric cancer.

INTRODUCTION

Oligometastatic disease (OMD) is defined as an intermediate state between localized and systemic metastasized disease[1]. The clinical implication of the OMD state is that local treatment for OMD (e.g. metastasectomy or stereotactic body radiotherapy [SBRT]) might improve overall survival (OS) or progression-free survival (PFS)[2]. Recently the benefit of local treatment for OMD has been demonstrated in several randomized controlled trials (RCTs) for patients with prostate, colorectal, breast, or non-small-cell lung cancer (NSCLC)[3-5]. In patients with esophagogastric cancer, several prospective non-randomized studies have shown favorable OS after local treatment for OMD[6,7]. Therefore, current German S3 gastric or gastroesophageal junction cancer guidelines recommend surgical resection of the primary tumor and metastases in a clinical trial setting in case of asymptomatic intra-operatively detected OMD when R0 resection can be reached[8]. However, the benefit of local treatment for OMD over systemic therapy alone in patients with esophagogastric cancer remains unclear due to a lack of completed RCTs, although several are currently ongoing.

The ongoing RENAISSANCE RCT by Al-Batran et al. addresses the potential benefits of systemic therapy plus surgical resection of the primary tumor and metastases over systemic therapy alone in patients with gastric or gastroesophageal junction cancer with retroperitoneal lymph node metastases with or without one incurable organ[9]. After four cycles of fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) chemotherapy, patients without progression will be randomized to either additional chemotherapy or additional chemotherapy plus surgical resection of the primary tumor and metastases[9]. In addition, the ongoing phase III RCT by the National Cancer Institute addresses the potential benefits of systemic therapy plus radiotherapy over systemic therapy alone in patients with gastric or esophageal cancer with three or less radiologically visible metastases[10]. After four cycles of oxaliplatin and capecitabine (CapOx) or FLOT chemotherapy, patients without progression will be randomized to either continuation of systemic therapy or continuation of systemic therapy plus radiotherapy of metastases[10].

These ongoing RCTs are using various definition and treatment modalities for OMD[9,10]. A comprehensive definition of oligometastatic esophagogastric cancer is desired to initiate studies on the benefit of local treatment strategies or new systemic therapy agents in this unique group of patients. Recent efforts have been made to develop a comprehensive classification system for OMD in a broader scope on all solid malignancies, but this lacks specificity for esophagogastric cancer and provides no recommendations for treatment[11,12]. Therefore, the OligoMetastatic Esophagogastric Cancer (OMEC) project was established. The OMEC project aims to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer, which will result in a prospective study in these patients.

METHODS

Ethical statement

This study protocol was written in accordance with the SPIRIT checklist and the World Medical Association for Ethical Principles for Medical Research Involving Human Subjects. The methodology of the OMEC project is comparable with the multidisciplinary consensus efforts for synchronous OMD in NSCLC by the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group[13]. The completed SPIRIT checklist is provided in Supplementary File 2.

OMEC project and consortium

The OMEC project is endorsed by EORTC, European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society for Diseases of the Esophagus (ESDE), the European chapter of the International Gastric Cancer Association (IGCA) and the Dutch Upper GI Cancer Group (DUCG). The OMEC consortium consists of 65 esophagogastric cancer experts located in 48 esophagogastric cancer expert centers across 16 countries in Europe, including Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, and the United Kingdom. Fig. 1 gives an overview of the participating countries and centers in the OMEC project. Table 1 shows the characteristics of the participating centers in the OMEC consortium.

The experts of the OMEC consortium were identified in a two-step process. First, society board members of EORTC, ESTRO, ESMO, ESSO, ESDE, IGCA, or DUCG were asked to participate in the OMEC-central working group (Supplementary File 3). Second, these society board members were asked to identify esophagogastric cancer experts in the field of OMD. These suggested experts, together with experts identified in a systemic review of first or last authors of published RCTs related to esophagogastric cancer between 2015 and 2020, were included in the OMEC-working group (Supplementary File 4). The main authors of this article represent the OMEC-core team (TK, PvR, HvL, RvH). Supplementary File 5 shows a schematic overview of the relationship between the OMEC-core group, the OMEC-central working group, and the OMEC-working group.

Study design

The OMEC project consists of 5 substudies. Fig. 2 shows a schematic overview of the OMEC project. The first study (OMEC-1) consists of a systematic review. The review protocol is prospectively registered in the online PROSPERO database for systematic reviews with registration number CRD42020205306. Reporting is performed in accordance with the PRISMA

Table 1. Characteristics of the participating centers in the OMEC consortium.

Characteristic (n=48)		(%)
Yearly volume of gastrectomies		
1-10	1	2%
11-20	2	4%
21-30	7	15%
31-50	23	48%
>50	15	31%
Yearly volume of esophagectomies		
1-10	5	10%
11-20	4	8%
21-30	4	8%
31-50	11	23%
>50	24	50%
Type of center		
Community medical center	3	6%
Comprehensive cancer center	7	15%
University medical center	38	79%

guidelines[14]. This study aims to identify definitions of oligometastatic esophagogastric cancer in the current literature. Therefore, PubMed, Embase, the Cochrane library, and clinicaltrials.gov will be systematically searched by two independent authors for studies or study protocols reporting a definition of oligometastatic esophagogastric cancer from adenocarcinoma or squamous cell carcinoma histology. Studies or study protocols reporting on <7 included patients, 'repeat OMD' or 'induced OMD', regional lymph node metastasis, hyperthermic intraperitoneal chemotherapy (HIPEC), or conversion surgery will not be included[11,12]. Studies performing local treatment for oligometastatic esophagogastric cancer without reporting on a definition of OMD (e.g. maximum number of metastases) will be excluded. Any disagreements will be resolved by consensus. The ROBINS tool will be utilized for quality assessment[15]. Finally, the references of included articles will be screened for other potentially relevant articles by cross-referencing. Furthermore, a meta-analysis will be performed of pooled adjusted hazard ratios (HRs) for OS after local treatment for OMD with or without systemic therapy versus systemic therapy alone.

The primary outcome of OMEC-1 will be the maximum number of organs or involved extra-regional lymph node stations considered OMD and the maximum number of metastases per specific organ (i.e. 'organ-specific' OMD burden). In addition, OMD in the liver will be further categorized according to unilobar or bilobar involvement, lung and adrenal gland according to unilateral or bilateral involvement and involved extra-regional lymph node stations according

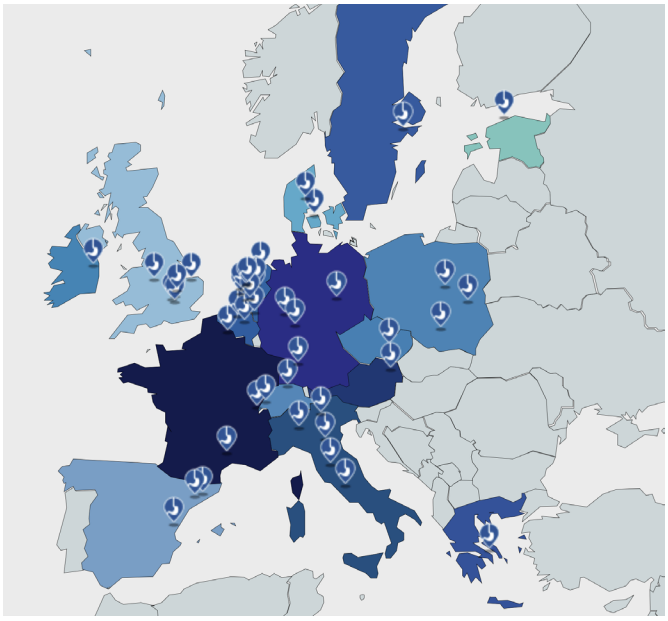

Figure 1. Overview of the participating countries and centers in the OMEC project Colors representing the different countries.

to the number of affected lymph node regions (i.e. cervical, thoracic, or abdominal/retroperitoneal extra-regional lymph node metastases) and the number of affected extra-regional lymph node stations. The secondary outcome measure will be the pooled adjusted hazard ratio (aHR) comparing OS after local treatment for OMD with or without systemic therapy to OS after systemic therapy alone.

The second study (OMEC-2) will consist of a discussion of real-life clinical cases by multidisciplinary tumor boards of esophagogastric cancer expert centers. The methodology of this study is comparable with a simulated multidisciplinary expert opinion study on OMD in NSCLC by the EORTC Lung Cancer Group[16]. In total, 48 European esophagogastric cancer expert centers have agreed to discuss 15 real-life anonymized clinical cases in their multidisciplinary tumor board meeting. Each center will host a multidisciplinary tumor board meeting with at least a surgical oncologist, medical oncologist, and radiation oncologist present to ask for the multidisciplinary team responses on whether the case is considered OMD and what the proposed treatment should be. These 15 real-life anonymized clinical cases will be varying in terms of 1) location of metastatic lesion; 2) number of metastatic lesions; 3) timing of detection (synchronous or metachronous); 4) primary tumor treatment status; 5) histology;

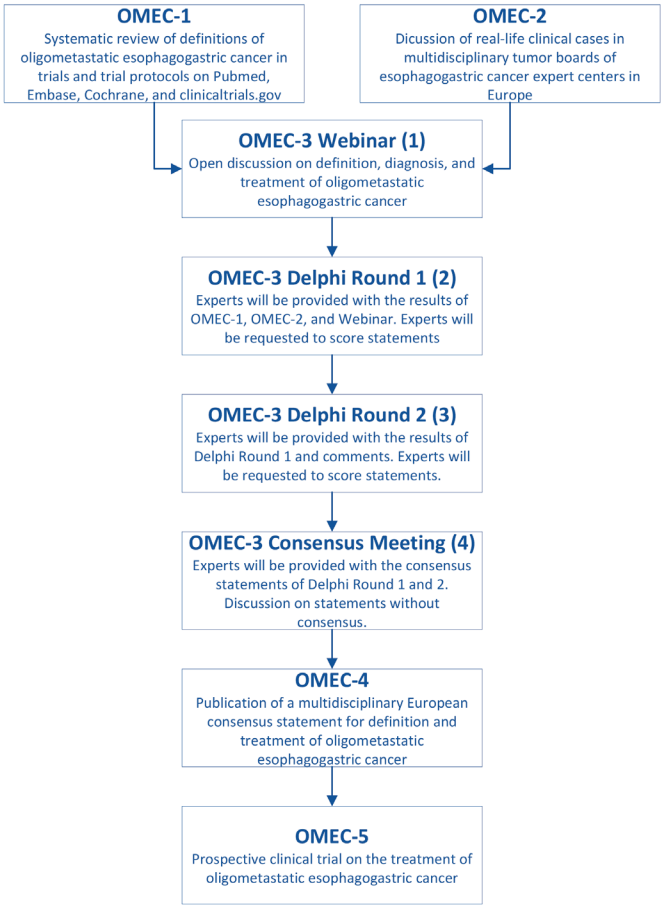

Figure 2. Schematic overview of the OMEC project.

and 6) response to systemic therapy at restaging. The clinical cases will be provided to the experts using an online tool (Castor EDC, Amsterdam, The Netherlands).

The clinical case information of OMEC-2 will consist of 1) the patient history (including primary tumor stage and treatment); 2) the current problem (including location and size of metastases); 3) pathology of the primary tumor and metastases (including histology, Her2Neu positivity, and microsatellite stability status); and 4) imaging of the primary tumor and metastases (^{18}F-fluorodeoxyglucose positron emission tomography [^{18}F-FDG PET], computed tomography [CT], or magnetic resonance imaging [MRI]). The experts will be unaware of the actual diagnosis or treatment of the real-life clinical cases. The primary outcome of this study will be the

agreement across tumor boards in Europe on the definition of oligometastatic esophagogastric cancer ("not OMD" versus "OMD"). The secondary outcome of this study will be the agreement across tumor boards on treatment strategies for oligometastatic esophagogastric cancer. Treatment strategies for OMD will be categorized into upfront local treatment (metastasectomy, SBRT, or other local treatment for OMD), systemic therapy followed by restaging to consider local treatment for OMD, or systemic therapy alone (without considering local treatment for OMD later).

In the third study (OMEC-3) multidisciplinary consensus will be sought on the definition, diagnosis, and treatment strategy of esophagogastric OMD using the Delphi consensus methodology [17]. The Delphi consensus process will consist of four steps, including a starting meeting, 2 online Delphi questionnaire rounds using Google Forms (Google Ireland Limited, Dublin, Ireland), and finally an online Delphi consensus meeting using Zoom (Zoom Video Communications Inc., San Jose, California, USA). A total of 65 OMEC experts have agreed to participate in this Delphi consensus study.

In the OMEC starting meeting (Step 1 of OMEC-3) the results of the systematic review (OMEC-1) and clinical cases discussions by multidisciplinary tumor boards (OMEC-2) will be presented to the experts, and an open discussion on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer will be initiated. The discussion will be recorded, and the discussion will be used for Delphi questionnaire round 1 (Step 2 of OMEC-3).

In the first Delphi questionnaire round (Step 2 of OMEC-3), experts will be provided with the results of the systematic review (OMEC-1), the clinical case discussions (OMEC-2), and the discussion of the webinar (Step 1 of OMEC-3). Experts will be asked to score statements on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer on a 5-point Likert scale (1 strongly disagree; 3 neither disagree nor agree; 5 strongly agree) using Google Forms. After each statement, experts are allowed to comment on the statements.
In the second Delphi questionnaire round (Step 3 of OMEC-3), experts will be provided with the agreement and comments on the statements of the first Delphi questionnaire round (Step 2 of OMEC-3). Subsequently, experts will be asked to score updated statements on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer on a 5-point Likert scale using Google Forms. Statements without consensus will be updated by lowering the number of metastases or based on comments on the statements from the experts. For example, if no consensus was reached in the first Delphi questionnaire round that 'bilateral liver involvement with 3 lesions in total' was considered OMD. In that case, this statement will be updated for the second Delphi questionnaire round to 'bilateral involvement with 2 lesions in total' (i.e. 1 metastasis less) to determine if consensus could be reached for the latter statement instead.

During the online consensus meeting (Step 4 of OMEC-3), statements with a consensus in the first and second Delphi questionnaire round will be presented. Domains without consensus will be discussed until consensus is reached. The online consensus meeting will be hosted using Zoom and the meeting will be recorded.

In the fourth study (OMEC-4) a multidisciplinary European consensus statement will be formulated and published for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer. This study incorporates the results of OMEC-1, OMEC-2, OMEC-3, and will include a flow diagram with a proposed work-up and treatment strategy.

The final study (OMEC-5) will consist of a prospective international multicenter clinical trial for oligometastatic esophagogastric cancer. This study will be a collaborative effort within the OMEC consortium. Only patients with esophagogastric OMD according to the OMEC definition are included. The treatment arms will be determined in a later stage, depending on the OMEC consensus findings and on what will become the most promising and urgent comparison of treatment strategies at the time of designing the study. The trial will aim to improve OS or PFS.

Study population

The OMEC project applies to patients with esophageal or gastric cancer with adenocarcinoma or squamous cell carcinoma histology with OMD in organs and/or extra-regional lymph nodes. Patients with peritoneal carcinomatosis are not included in the OMEC project as this is not considered OMD, but rather polymetastatic disease with cytoreductive surgery and HIPEC as the primary treatment[18]. In addition, the OMEC project applies to patients with synchronous and metachronous de-novo OMD only (i.e. patients with induced OMD [i.e. history of polymetastatic disease] or repeat OMD [i.e. previous history of OMD] will not be included)[11]. Synchronous OMD is defined as OMD detected at diagnosis or during primary tumor treatment (e.g. at restaging after neoadjuvant treatment). Metachronous OMD is defined as OMD detected after completion of primary tumor treatment. The disease-free interval (DFI) is defined as the time interval between the completion of treatment of the primary tumor and metachronous OMD. The DFI will be categorized into short (<1 year), intermediate (1–2 years), or long (>2 years).

Outcome measures

The aim of the OMEC project is to develop a multidisciplinary European consensus statement for the definition, diagnosis, treatment for oligometastatic esophagogastric cancer. The pre-specified outcomes of the definition of oligometastatic esophagogastric cancer are of the maximum number of locations with metastases (organs and/or involved extra-regional lymph

node stations) and the maximum number of metastases per specific location (i.e. "organ-specific" OMD burden). The pre-specified outcome of the diagnosis of oligometastatic esophagogastric cancer is the imaging modality used for baseline staging and restaging of OMD (e.g. PET, CT, or MRI). Finally, the pre-specified outcomes for the treatment of oligometastatic esophagogastric cancer are the indications for either upfront local treatment for OMD or systemic therapy followed by restaging to consider local treatment for OMD, and the minimum duration and the response to systemic therapy to consider local treatment for OMD. Fig. 3 gives an overview of the outcomes of the OMEC project.

Statistical analyses

The agreement across definitions in literature or statements in the Delphi process will be either scored as absent/poor (<50% agreement), fair (50%–75% agreement), or consensus (≥75% agreement) comparable with recent studies on the definition of OMD for other tumors[11.13.19].

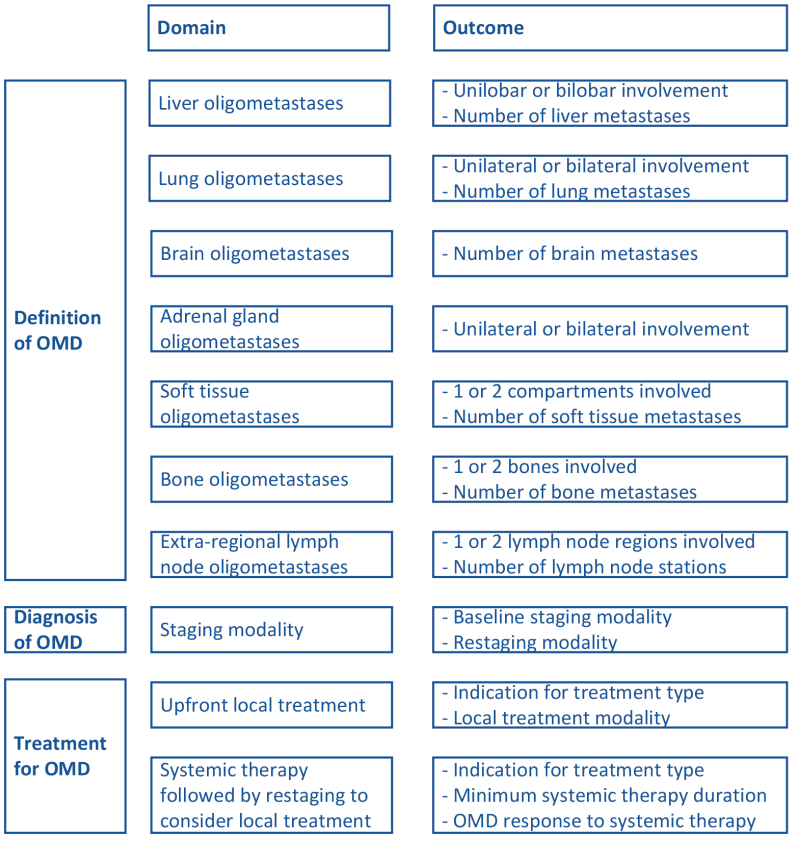

Figure 3. Schematic overview of the outcomes of the OMEC project.

Moreover, this choice was also in accordance with a recent systemic review wherein it was reported that the most common definition for consensus in Delphi studies was percent agreement, with 75% being the median threshold to define consensus among 25 Delphi studies[20].

DISCUSSION

The OMEC projects will result in the first multidisciplinary European consensus statement on the definition and treatment of oligometastatic esophagogastric cancer. The OMEC project consists of 5 substudies, including a systematic review (OMEC-1) and real-life clinical case discussions (OMEC-2) which will be used as input for Delphi consensus rounds (OMEC-3). This Delphi consensus study will lay the foundation for a multidisciplinary European consensus statement for the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer (OMEC-4) resulting in a prospective study on treatment for oligometastatic esophagogastric cancer (OMEC-5). This multidisciplinary European consensus statement is needed to standardize inclusion criteria in future clinical trials and guide treatment decision-making in multidisciplinary tumor board meetings which ultimately may outcomes of these patients.

Systemic therapy alone has been the gold standard for treatment in patients with systemic metastasized esophagogastric cancer and is currently being recommended by the National Comprehensive Cancer Network (NCCN)[21] and ESMO guidelines[22]. However, in patients with oligometastatic esophagogastric cancer, it is hypothesized that local treatment for OMD (e.g. metastasectomy or SBRT) results in improved OS as compared with systemic therapy alone. Accordingly, surgical resection of the primary tumor and metastases is currently recommended in a clinical trial setting by German S3 gastric or gastroesophageal junction cancer guidelines in patients with asymptomatic intra-operatively detected OMD when R0 resection can be reached[8]. Furthermore, German S3 guidelines recommend referral to a high-volume center for gastric cancer patients with synchronous OMD[8]. This benefit of local treatment for OMD might be explained by the 'seed and soil' hypothesis, first introduced by Paget in 1889[23]. This hypothesis suggests that metastatic spread is not random and does not solely depend on circulatory patterns but rather is an interaction between tumor cells and the target organ[23]. In this concept, certain tumors have a predisposition for a particular organ only that supports secondary growth from the primary tumor[23]. This selective process might explain why certain patients develop a limited number of metastases in a certain organ only and why local treatment to that organ improves OS. If this hypothesis is confirmed, the results of this study can be used to update the relevant guidelines on treatment for patients with (oligometastatic) esophagogastric cancer[21,22].

Up until now, no biomarkers have been discovered that accurately define or predict OMD[24]. However, recent advances in imaging have made it possible to discriminate OMD from polymetastatic disease. For example, ^{18}F-FDG PET/CT has shown to improve the selection of patients with a low tumor burden in colorectal cancer who might benefit the most from local treatment for OMD[25]. Accordingly, EORTC has proposed recommendations for the staging of OMD which currently includes ^{18}F-FDG PET/CT, PET/CT with tumour-specific radiotracers (e.g. choline or prostate-specific membrane antigen ligand), or whole-body MRI with diffusion-weighted imaging[24]. Therefore, seeking consensus on the ideal imaging modality at baseline and for restaging after systemic therapy will be one of the aims of the OMEC project.

Strengths of this OMEC project include the structured study design. If no high-level evidence on the diagnosis or treatment of oligometastatic esophagogastric cancer can be identified, a structured Delphi process is followed to formulate this consensus. The EORTC Lung Cancer Group has demonstrated that this study design is feasible and results in a multidisciplinary European consensus statement for OMD in NSCLC[13]. Another strength is multidisciplinary and inclusive approach of the OMEC project as only surgical oncologist, radiation oncologist, and medical oncologist identified in a systemic review or by medical societies as experts in the field of oligometastatic esophagogastric cancer were included. A potential limitation of the OMEC project is that this consensus definition represents the view of European esophagogastric cancer experts only, which might not match with the view of esophagogastric cancer experts outside of Europe. In addition, another limitation could be that the definition of oligometastatic esophagogastric cancer could become absolute in the future, as new data on these patients is published. Finally, implementation of the OMEC treatment protocol could be hampered by cost increases, which could be especially challenging in low-income countries, or by increased travel distance to reach esophagogastric cancer expert centers.

CONCLUSION

A comprehensive definition of oligometastatic esophagogastric cancer is desired to initiate studies on the benefit of local treatment strategies (e.g. metastasectomy or SBRT) or new systemic agents in these patients. The OMEC project will take into account the results of a systematic review, real-life clinical case discussions, and Delphi consensus rounds to formulate a multidisciplinary European consensus statement on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer. This multidisciplinary European consensus statement will provide the basis for a prospective European study aiming to improve the treatment and outcomes for these patients.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
2. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378-382. doi:10.1038/nrclinonc.2011.44
3. Gomez DR, Blumenschein GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672-1682. doi:10.1016/S1470-2045(16)30532-0
4. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet Oncol. 2019;393(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5
5. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. JAMA Oncol. 2018;4(1). doi:10.1001/jamaoncol.2017.3501
6. Al-Batran S-EE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. JAMA Oncol. 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
7. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys. 2020;108(3):707-715. doi:10.1016/j.ijrobp.2020.05.003
8. Moehler M, Al-Batran SE, Andus T, et al. S3-Leitlinie Magenkarzinom-Diagnostik und Therapie der Adenokarzinome des Magens und des ösophagogastralen Übergangs. Z Gastroenterol. 2019;57(12):1517-1632. doi:10.1055/a-1018-2516
9. Al-Batran S-EE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. BMC Cancer. 2017;17(1):893. doi:10.1186/s12885-017-3918-9
10. ECOG-ACRIN Cancer Research. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. clinicaltrials.gov/NCT04248452. 2020. doi:10.31525/ct1-nct04248452
11. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
12. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157-166. doi:10.1016/j.radonc.2020.04.003
13. Dingemans AMC, Hendriks LEL, Berghmans T, et al. Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. J Thorac Oncol. 2019;14(12):2109-2119. doi:10.1016/j.jtho.2019.07.025
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700. http://www.ncbi.nlm.nih.gov/pubmed/19622552. Accessed October 10, 2016.
15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016. doi:10.1136/bmj.i4919
16. Hendriks L, Dooms C, Berghmans T, et al. MA25.03 Defining Oligometastatic Non-Small Cell Lung Cancer (NSCLC): An Evolving Multidisciplinary Expert Opinion. J Thorac Oncol. 2018;13(10):S446-S447. doi:10.1016/j.jtho.2018.08.531
17. Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. J Clin Epidemiol. 2003;56(12):1150-1156. doi:10.1016/S0895-4356(03)00211-7

18. Rudloff U, Langan RC, Mullinax JE, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: Results of the GYMSSA trial. J Surg Oncol. 2014;110(3):275-284. doi:10.1002/jso.23633
19. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. Eur Urol Oncol. 2019:1-8. doi:10.1016/j.euo.2019.07.010
20. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401-409. doi:10.1016/j.jclinepi.2013.12.002
21. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2019. doi:10.6004/jnccn.2019.0033
22. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v50-v57. doi:10.1093/annonc/mdw329
23. Paget S. THE DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST. Lancet. 1889;133(3421):571-573. doi:10.1016/S0140-6736(00)49915-0
24. deSouza NM, Liu Y, Chiti A, et al. Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer. 2018;91:153-163. doi:10.1016/j.ejca.2017.12.012
25. Samim M, Molenaar IQ, Seesing MFJ, et al. The diagnostic performance of 18F-FDG PET/CT, CT and MRI in the treatment evaluation of ablation therapy for colorectal liver metastases: A systematic review and meta-analysis. Surg Oncol. 2017;26(1):37-45. doi:10.1016/j.suronc.2016.12.006

2

CHAPTER 3

Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis

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Tiuri E. Kroese, Hanneke W.M. van Laarhoven, Magnus Nilsson, Florian Lordick, Matthias Guckenberger, Jelle P. Ruurda, Domenico D'Ugo, Karin Haustermans, Eric van Cutsem, Richard van Hillegersberg, Peter S.N. van Rossum

ABSTRACT

Background

Local treatment (metastasectomy or stereotactic radiotherapy) for oligometastatic disease (OMD) in patients with esophagogastric cancer may improve overall survival (OS). The primary aim was to identify definitions of esophagogastric OMD. A secondary aim was to perform a meta-analysis of OS after local treatment versus systemic therapy alone for OMD.

Methods

Studies and study protocols reporting on definitions or OS after local treatment for esophagogastric OMD were included. The primary outcome was the maximum number of organs/lesions considered OMD and the maximum number of lesions per organ (i.e. 'organ-specific' OMD burden). Agreement was considered to be either absent/poor (<50%), fair (50%-75%), or consensus (≥75%). The secondary outcome was the pooled adjusted hazard ratio (aHR) for OS after local treatment versus systemic therapy alone. The ROBINS tool was used for quality assessment.

Results

A total of 97 studies, including 7 study protocols, and 2 prospective studies, were included. OMD was considered in 1 organ with ≤3 metastases (consensus). 'Organ-specific' OMD burden could involve bilobar ≤3 liver metastases, unilateral ≤2 lung metastases, 1 extra-regional lymph node station, ≤2 brain metastases, or bilateral adrenal gland metastases (consensus). Local treatment for OMD was associated with improved OS compared with systemic therapy alone based on 6 non-randomized studies (pooled aHR 0.47, 95% CI: 0.30-0.74) and for liver oligometastases based on 5 non-randomized studies (pooled aHR 0.39, 95% CI: 0.22-0.59). All studies scored serious risk of bias.

Conclusions

Current literature considers esophagogastric cancer spread limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station to be OMD. Local treatment for OMD appeared associated with improved OS compared with systemic therapy alone. Prospective randomized trials are warranted.

INTRODUCTION

The general concept of oligometastatic cancer (OMD) was first introduced in 1995 and described a clinical state between locally confined and systemic metastasized disease[1]. OMD reflects distinct tumor biology and implies that local treatment for OMD (e.g. metastasectomy or stereotactic body radiation therapy [SBRT]) could provide long-term disease control or even be curative in a proportion of patients[2]. In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) proposed a classification system of OMD[3]. The first question differentiates between "genuine OMD" and "induced OMD" by analyzing whether or not the patient has had polymetastatic disease before the current diagnosis of OMD ("no" versus "yes", respectively). The second question differentiates between "de-novo OMD" and "repeat OMD" by analyzing whether or not the patient with "genuine OMD" has had OMD before the current diagnosis of OMD ("no" versus "yes", respectively)[3].

In patients with oligometastatic esophagogastric cancer, no RCTs have yet been completed, but several non-randomized trials[4,5] suggested improved OS after local treatment for OMD compared to systemic therapy alone. In the phase II trial by Al-Batran et al. the benefit of surgical resection of the primary tumor and metastases plus systemic therapy for patients with gastric or gastroesophageal junction cancer and synchronous OMD limited to the retroperitoneal lymph nodes and/or one organ was assessed[5]. After 4 cycles of FLOT chemotherapy, patients without progression underwent surgical resection of the primary tumor and metastases, which resulted in a median OS of 31.3 months[5]. In addition, the phase II of Liu et al. assessed the benefit of SBRT in patients with esophageal squamous cell carcinoma with ≤ 3 metachronous oligometastases[4]. All patients underwent SBRT and 50% underwent systemic therapy after SBRT, which resulted in a median OS of 24.6 months[4]. However, interpretation of these individual studies and translation to clinical practice is hampered by varying definitions of OMD.

A population-based study of autopsy reports of 3,876 patients with esophageal or gastric adenocarcinoma or squamous cell carcinoma between 1990 and 2017 in the Netherlands revealed that the most common metastatic location for esophageal cancer were liver (56%), extra-regional lymph nodes (53%), and lung (50%) and for gastric cancer were extra-regional lymph nodes (56%), liver (53%), and peritoneum (51%)[6]. Esophageal adenocarcinoma more frequently metastasizes to the peritoneum and bone as compared with esophageal squamous cell carcinoma[6]. In addition, diffuse type gastric cancer more frequently metastasizes to the peritoneum as compared with intestinal type gastric cancer[6]. However, for both esophageal and gastric cancer (all histological subtypes) the liver was the most common metastatic site[6].

Peritoneal disease was considered to fall outside the scope of this systematic review and meta-analysis because this reflects a polymetastatic disease state, which requires a different treatment modality (hyperthermic intraperitoneal chemotherapy [HIPEC]) as opposed to OMD (metastasectomy or SBRT)[7,8]. After exclusion of peritoneal disease, we consider esophageal adenocarcinoma and squamous cell carcinoma and diffuse and intestinal gastric cancer as well as patients with cancer of the gastroesophageal junction comparable for this study aim.
The primary aim of this study was to summarize the applied definitions of de-novo oligometastatic esophagogastric cancer in literature and ongoing studies. To this end, the OMEC study group performed a systematic review of studies and study protocols reporting on a definition of oligometastatic esophagogastric cancer or on patients undergoing local treatment for oligometastatic esophagogastric cancer. The secondary aim was to compare local treatment with systemic therapy alone for oligometastatic esophagogastric cancer by performing a meta-analysis of reported hazard ratios (HRs) for OS.

MATERIALS AND METHODS

This study was prospectively registered in the online PROSPERO database for systematic reviews with registration number CRD42020205306. Reporting is performed in accordance with the PRISMA guidelines (Supplementary File A)[9].

Search strategy

A systematic search was performed and last updated April 1, 2021, in Medline (via Pubmed), Embase, and ClinicalTrials.gov with the keywords “esophageal cancer” or “gastric cancer” and “oligometastasis” or “SBRT” or “metastasectomy” (and synonyms). Studies or study protocols published after January 1, 2010, that report on a definition of oligometastatic esophagogastric cancer or the local treatment for oligometastatic esophagogastric cancer were identified (Supplementary File B). OMD could be located in a distant organ or the extra-regional lymph nodes (according to the AJCC/UICC 8th edition)[10].

Study selection

After removing duplicates, 2 authors (PR and TK) independently screened titles and abstracts for eligibility. Studies or study protocols reporting a definition or local treatment of “de-novo OMD” in patients with esophagogastric cancer of adenocarcinoma or squamous cell carcinoma histology were eligible for inclusion. Studies or study protocols reporting on <7 included patients, “repeat OMD”, “induced OMD”, regional lymph node metastasis, HIPEC, or conversion surgery were not included. Studies performing local treatment for metastases of esophagogastric cancer without reporting on a definition of OMD (i.e. maximum number of

organs and metastases) were excluded. Any disagreements were resolved by consensus. Finally, the references of included articles were screened for other potentially relevant articles by cross-referencing. The inter-rater reliability was not assessed.

Data extraction

From the selected studies, data were extracted on first author, year of publication, country of origin, inclusion years, type of study (i.e. retrospective or prospective, single- or multi-center), location, and histology of the primary tumor, number of patients treated with local treatment and/or systemic therapy, the timing of detection of OMD (i.e. synchronous versus metachronous), the maximum number of organs and/or metastases considered OMD, and the modality of imaging for detecting OMD (i.e. computed tomography [CT], ^{18}F-fluorodeoxyglucose positron emission tomography [^{18}F-FDG PET], or magnetic resonance imaging [MRI]). The disease-free interval was extracted from studies on metachronous OMD (i.e. time interval between definitive treatment of the primary tumor and detection of OMD). Finally, survival outcomes in terms of median OS, 1-year and 5-year OS rates, and the HR comparing OS after local treatment with systemic therapy alone for oligometastatic esophagogastric cancer were retrieved.

Outcomes

The primary outcome was the maximum number of organs and metastases considered OMD and the maximum number of metastases per specific organ (i.e. 'organ-specific' OMD burden). In addition, liver oligometastases were further categorized according to unilobar or bilobar involvement, lung and adrenal gland oligometastases according to unilateral or bilateral involvement, and extra-regional lymph node oligometastases according to the number of affected lymph node regions (i.e. cervical, thoracic or abdominal/retroperitoneal) and the number of extra-regional lymph node stations (according to the AJCC/UICC 8th edition)[11]. The secondary outcome measure was the pooled aHR comparing OS after local treatment to OS after systemic therapy alone for oligometastatic esophagogastric cancer.

Quality assessment

Quality assessment of comparative studies eligible for inclusion in the quantitative synthesis (meta-analysis) was assessed by 2 authors using the ROBINS tool[12]. "Confounding" was considered a serious risk of bias if studies did not measure or control for important baseline confounders such as performance status and number and distribution of metastases. 'Selection bias' was considered at serious risk if studies selected patients retrospectively without a pre-specified study protocol. "Classification of intervention bias" was considered at serious risk if studies did not clearly define treatment in both groups. "Assignment to intervention bias" was considered at serious risk if studies reported substantial deviations from the intervention and

this was not controlled for. “Missing data bias” was considered at serious risk if >10% of subjects had missing data. Publication bias was checked by visual assessment of funnel plots.

Statistical analysis

The agreement between studies was scored to be either absent/poor (<50%), fair (50%–75%), or consensus (≥75%)[3,13]. According to a recent systemic review, the most common definition for consensus was percent agreement, with 75% being the median threshold to define consensus[14]. From each study, the median OS, 1-year and 5-year OS rates after local treatment for OMD and systemic therapy alone was extracted as well as the adjusted and unadjusted HRs of OS with 95% confidence intervals (CIs) comparing local treatment for OMD with systemic therapy alone.

For meta-analysis of the data, a funnel and forest plot of the adjusted and unadjusted HRs for OS were made. A random-effects model was used to pool the data. Subgroup analyses were only performed in case 3 or more studies were available in each subgroup. Heterogeneity was assessed with the I^2 test. Substantial and considerable heterogeneity were defined as $I^2 \geq 50\%$ and $I^2 \geq 75\%$, respectively[14,15]. A p-value <0.05 was considered statistically significant. R version 4.1.1 with “Rcurl”, “metaphor”, and “meta” packages were used for statistical analysis.

RESULTS

Study selection

After the removal of duplicates, 7,782 articles were screened on title and abstract for eligibility. Subsequently, the full-text of 236 potentially relevant articles were assessed, of which 72 studies were excluded because no definition of OMD was reported, 47 liver-related studies because no definition of liver oligometastasis was reported, 16 studies because of complete overlap in study population with another (larger) included study, 3 lung-related studies because no definition of lung oligometastasis was reported and 1 lymph node-related study because no definition of extra-regional lymph node oligometastasis was reported. Consequently, 97 studies or study protocols were included in this systemic review, of which 15 studies were included in the meta-analysis (Fig. 1).

Oligometastatic esophagogastric cancer

A definition of oligometastatic esophagogastric cancer was provided by 21 studies[7,8,15-33] and 7 study protocols[35-41]. The studies were predominantly retrospective (95%) and included a total of 1,439 patients. The median disease-free interval for patients with metachronous OMD was 13 months (interquartile range [IQR] 10–19). Most patients were diagnosed with esophageal

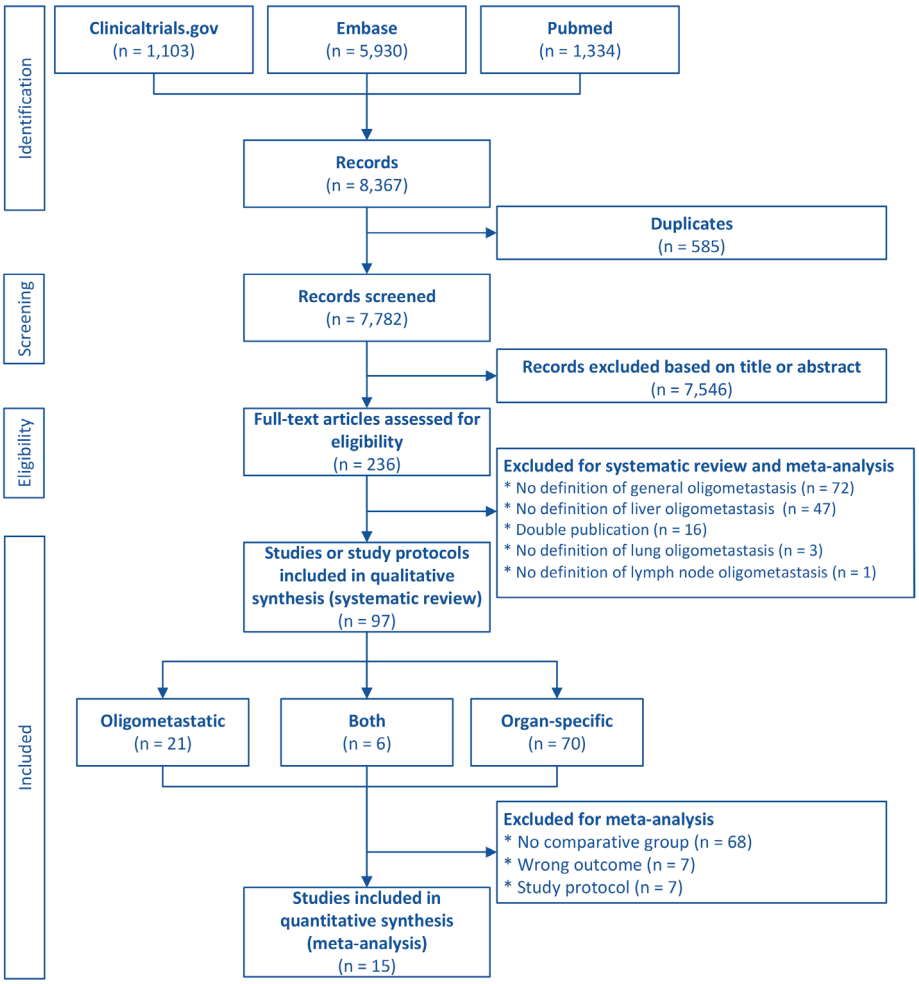

Figure 1. Flowchart of study selection.

cancer (82%) with squamous cell carcinoma histology (53%) and underwent metastasectomy (69%) for metachronous OMD (51%). In addition, 7 study protocols which include patients with synchronous gastric cancer[38-41], synchronous or metachronous esophageal cancer[37], or synchronous esophagogastric cancer[35,36] were included. The imaging modality for detecting OMD was specified by 23 out of 28 studies or study protocols and was CT (100%), and/or ^{18}F-FDG PET (35%) and/or MRI (26%, Table 1).

Table 1. Study characteristics of oligometastatic esophagogastric cancer.

Study, year or clinicaltrial#	Country	Inclusion			Included patients / estimated enrollment	Treatment	Primary tumor	
		Type	Center	Period			Esophagus	
							(n=)	(%)
Nobel, 2021	USA	RNR	Single	1995-2016	104	M / SBRT	104	100%
Li, 2021	China	RNR	Single	2009-2018	55	SBRT	55	100%
Ohkura, 2020	Japan	RNR	Multi	2011-2017	119	M	119	100%
Li, 2020	China	RNR	Single	ns	163	M / SBRT	163	100%
Yamashita, 2020	Japan	RNR	Single	2012-2017	18	SBRT	18	100%
Hilal 2020	USA	RNR	Single	2008-2018	197	SBRT	197	100%
Morinaga, 2020	Japan	RNR	Single	2005-2019	43	M / SBRT	43	100%
Liu, 2020	China	II NR	Single	2015-2018	34	SBRT	34	100%
Omari, 2019	Poland	RNR	Single	2010-2016	12	B	0	0%
Chen, 2019	China	RNR	Multi	2012-2015	196	SBRT	196	100%
Iwatsuki, 2019	USA	RNR	Multi	2002-2016	85	ns	85	100%
Depypere, 2018	Belgium	RNR	Single	2002-2015	10	M	10	100%
CarmonaBayonas, 2018	Spain	RNR	Multi	2008-2017	92	M	12	13%
Hamai, 2018	Japan	RNR	Single	1990-2013	13	M	13	100%
Ghaly, 2018	USA	RNR	Multi	1988-2015	26	M / SBRT	26	100%
Depypere, 2017	Belgium	RNR	Single	1990-2012	25	M / SBRT	25	100%
Al-Batran, 2017	Germany	II NR	Multi	2009-2010	36	M	0	0%
Schmidt, 2015	Germany	RNR	Single	2002-2012	123	M	70	57%
Xu, 2014	China	RNR	Single	2008-2011	19	SBRT	0	0%
Port, 2012	USA	RNR	Single	1988-2011	27	M / SBRT	27	100%
Kim, 2011	Korea	RNR	Single	2003-2008	42	M	0	0%
Pooled (%)					**1,439**		**1,197**	**83%**
NCT04510064	China	II NR	Multi	2021-2022	40	M	0	0%
NCT04248452	USA	III R	Multi	2020-2023	314	SBRT	ns	ns
NCT04263870	China	II NR	Single	2020-2021	36	M	0	0%
NCT03904927	China	II NR	Single	2019-2022	102	SBRT	102	100%
NCT03161522	USA	II R	Single	2018-2023	100	M	ns	ns
NCT03399253	China	III R	Single	2017-2022	120	M	0	0%
NCT02578368	Germany	III R	Multi	2016-2021	271	M	0	0%
Pooled (%)					**983**		**102**	**17%**

RNR = retrospective non-randomized; II NR = Phase II non-randomized trial; II R = Phase II randomized trial; III R = Phase III randomized trial; B = brachytherapy; SBRT = stereotactic body radiation therapy; M = metastasectomy; AC = adenocarcinoma; SCC = squamous cell carcinoma; ns = not specified; NA = not applicable; DFI = disease-free interval; * = CT, MRI, PET/CT, bone scan

		Histology				Type of oligometastasis				Median DFI (months)	Imaging modality
Gastric		AC (%)		SCC (%)		Synchronous		Metachronous			
(n=)	(%)	(n=)	(%)	(n=)	(%)	(n=)	(%)	(n=)	(%)		
0	0%	94	90%	10	10%	0	0%	104	100%	8.8	CT
0	0%	4	7%	51	93%	0	0%	55	100%	ns	ns
0	0%	ns	ns	ns	ns	0	0%	119	100%	13.2	CT
0	0%	0	0%	163	100%	163	100%	0	0%	ns	ns*
0	0%	ns	ns	ns	ns	0	0%	18	100%	ns	PET or CT
0	0%	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
0	0%	0	0%	43	100%	0	0%	43	100%	12.6	PET/CT or CT
0	0%	0	0%	34	100%	0	0%	34	100%	ns	PET or CT
12	100%	12	100%	0	0%	4	33%	8	67%	ns	MRI or CT
0	0%	6	3%	190	97%	ns	ns	ns	ns	ns	CT
0	0%	85	100%	0	0%	85	100%	0	0%	NA	ns
0	0%	8	80%	2	20%	10	100%	0	0%	NA	PET/CT
80	87%	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
0	0%	0	0%	13	100%	0	0%	13	100%	9.1	(PET)CT
0	0%	ns	ns	ns	ns	0	0%	26	100%	19	CT
0	0%	ns	ns	ns	ns	0	0%	25	100%	9.9	PET/CT or CT
36	100%	36	100%	0	0%	36	100%	0	0%	NA	CT or MRI
53	43%	123	100%	0	0%	123	100%	0	0%	NA	CT
19	100%	19	100%	0	0%	0	0%	19	100%	ns	CT
	0%	21	78%	6	22%	0	0%	27	100%	26	CT
42	100%	42	100%	0	0%	42	100%	0	0%	NA	CT
242	**17%**	**450**	**47%**	**512**	**53%**	**463**	**49%**	**491**	**51%**	**12.6**	
40	100%	40	100%	0	0%	40	100%	0	0%	NA	CT or MRI
ns	ns	314	100%	0	0%	314	100%	0	0%	NA	CT or MRI
36	100%	36	100%	0	0%	36	100%	0	0%	NA	CT or MRI
0	0%	0	0%	102	100%	0	0%	102	100%		CT
ns	ns	100	100%	0	0%	100	100%	0	0%	NA	PET/CT
120	100%	120	100%	0	0%	120	100%	0	0%	NA	CT
271	100%	271	100%	0	0%	271	100%	0	0%	NA	CT/MRI or PET
467	**83%**	**881**	**90%**	**102**	**10%**	**881**	**90%**	**102**	**10%**	**NA**	

The maximum number of involved organs considered OMD was specified by 26 out of 28 studies or study protocols. Solitary organ involvement was considered OMD by 26 out of 26 (100%, consensus), of which 10 (38%) allowed 1 additional involved organ. Also, 4 studies or study protocols (15%) allowed limited extra-regional lymph node metastases in addition to solitary organ involvement[5,20,38,40]. The maximum number of metastases considered OMD was specified by 17 out of 28 studies or study protocols. A total of ≤3 metastases were considered OMD by 17 out of 17 (100%, consensus), of which 11 also allowed ≤4 metastases (65%, fair agreement). In 5 studies or study protocols[5,38-41], the maximum number of metastases to be considered OMD depended on the specific organ affected, and these studies or study protocols were included in the 'organ-specific' definition of OMD (Table 2). Fig. 2 shows a summary of definitions of oligometastatic esophagogastric cancer according to literature and study protocols.

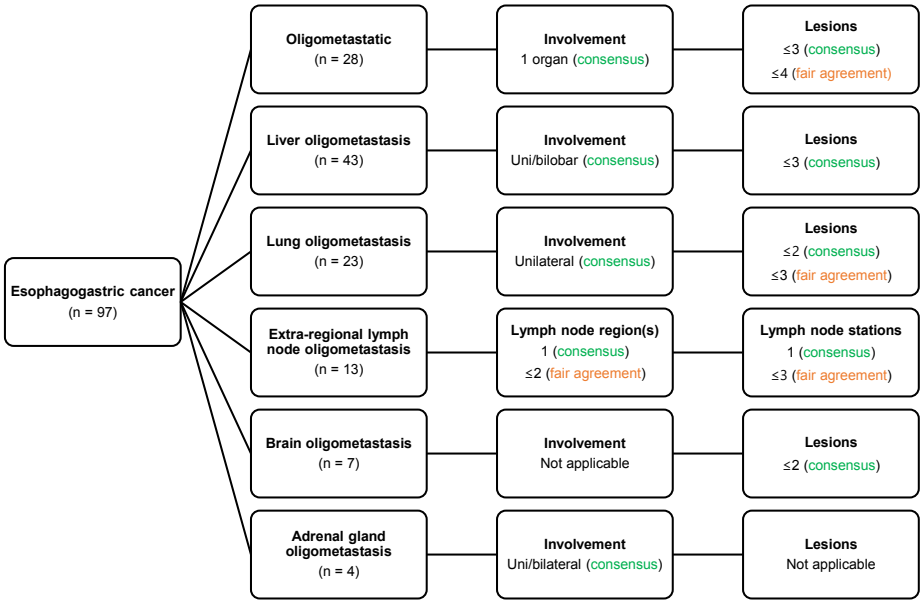

Figure 2. Summary of definition of oligometastatic esophagogastric cancer according to literature and study protocols.

Liver oligometastasis

A definition of liver oligometastasis from esophagogastric cancer was provided by 39 studies[8,31,41-77] and 4 study protocols[38-41]. The studies were predominantly retrospective (97%) and included a total of 1,383 patients. The median disease-free interval for metachronous

Table 2. A definition of oligometastatic esophagogastric cancer.

Study, year or clinicaltrials.gov ID	Definition		Patients							
	Organ	Lesions	Organ				Lesions			
	Maximum	Maximum	Solitary		Multiple		Solitary		Multiple	
Nobel, 2021	1	5	98	100%	0	0%	51	52%	47	48%
Li, 2021	2	5	50	91%	5	9%	31	56%	24	44%
Ohkura, 2020	1	5	119	100%	0	0%	ns	ns	ns	ns
Li, 2020	3	5	ns	ns	ns	ns	ns	ns	ns	ns
Hilal, 2020	1 + LN	5	ns	ns	ns	ns	ns	ns	ns	ns
Yamashita, 2020	1	3	18	100%	0	0%	ns	ns	ns	ns
Morinaga, 2020	1	5	ns	ns	ns	ns	ns	ns	ns	ns
Omari, 2019	2	5	11	92%	1	8%	ns	ns	ns	ns
Chen, 2019	ns	3	ns	ns	ns	ns	225	49%	236	51%
Liu, 2019	2	3	32	94%	2	6%	28	82%	6	18%
Iwatsuki, 2019	1	4	85	100%	0	0%	ns	ns	ns	ns
Depypere, 2018	1	4	10	100%	0	0%	ns	ns	ns	ns
Carmona-Bayonas, 2018	2	4	54	59%	38	41%	ns	ns	ns	ns
Hamai, 2018	1	ns	13	100%	0	0%	ns	ns	ns	ns
Ghaly, 2018	1	ns	26	100%	0	0%	ns	ns	ns	ns
Depypere, 2017	1 + RPLN	ns	25	100%	0	0%	ns	ns	ns	ns
Al-Batran, 2017	1	Organ-specific	36	100%	0	0%	ns	ns	ns	ns
Schmidt, 2015	2	ns	102	83%	21	17%	ns	ns	ns	ns
Xu, 2014	2	3	14	74%	5	26%	8	42%	11	58%
Port, 2012	1	ns	27	100%	0	0%	ns	ns	ns	ns
Kim, 2011	2	ns	33	79%	9	21%	ns	ns	ns	ns
NCT04510064	1	Organ-specific	na	na	na	na	na	na	na	na
NCT04248452	ns	3	na	na	na	na	na	na	na	na
NCT04263870	1 + RPLN	Organ-specific	na	na	na	na	na	na	na	na
NCT03904927	2	4	na	na	na	na	na	na	na	na
NCT03161522	1	3	na	na	na	na	na	na	na	na
NCT03399253	2	Organ-specific	na	na	na	na	na	na	na	na
NCT02578368	1 + RPLN	Organ-specific	na	na	na	na	na	na	na	na

LN = limited extra-regional lymph node involved in addition to organ metastasis; RPLN = limited retroperitoneal lymph node involvement in addition to organ metastasis; ns = not specified; NA = not applicable

OMD was 12 months (IQR 10–12). Most patients were diagnosed with gastric cancer (97%) with adenocarcinoma histology (97%) and underwent surgery or radiofrequency ablation (99%) for synchronous (65%) liver oligometastasis. In addition, 4 study protocols which all include

patients with synchronous gastric cancer[38-41] were included. The imaging modality for detecting liver oligometastasis was specified by 28 out of 43 studies or study protocols and was predominantly CT (86%) and/or MRI (61%, Supplementary File C1).

The maximum number of liver lobes was specified by 26 out of 43 studies or study protocols. Liver oligometastasis could be present in both liver lobes (i.e. bilobar) according to 23 out of 26 (88%, consensus). The maximum number of liver metastases was specified by 32 out of 43 studies or study protocols. A total of ≤3 metastases were considered OMD by 25 out of 32 (78%, consensus; Supplementary File C2).

Lung oligometastasis

A definition of lung oligometastasis from esophagogastric cancer was provided by 22 studies[8,31,76,78-97] and 1 study protocol[38]. The studies were predominantly retrospective (95%) and included a total of 444 patients. The median disease-free interval for metachronous OMD was 17 months (IQR 15–25). Most patients were diagnosed with esophageal cancer (74%) with squamous cell carcinoma histology (72%), and all underwent surgery or radiofrequency ablation (100%) for predominantly metachronous (87%) lung oligometastasis. In addition, 1 study protocol which includes patients with synchronous gastric cancer was included[38]. The imaging modality for detecting lung oligometastasis was specified by 15 out of 23 studies or study protocols and was predominantly CT (80%, Supplementary File D1).

Unilateral or bilateral lung involvement was specified by 16 out of 23 studies or study protocols. Unilateral lung metastasis was considered OMD according to 16 out of 16 (100%, fair agreement), of which 7 (44%) also allowed bilateral involvement. The maximum number of lung metastases was specified by 18 out of 23 studies or study protocols. A total of ≤2 metastases were considered OMD by 14 out of 18 (78%, consensus), of which 12 also allowed ≤3 metastases (66%, fair agreement; Supplementary File D2).

Extra-regional lymph node oligometastasis

A definition of extra-regional lymph node oligometastasis from esophagogastric cancer was provided by 6 studies[5,98-102] and 7 study protocols[35-41]. The studies were mainly retrospective (83%) and included a total of 217 patients. The median disease-free interval for metachronous OMD was 12 months (IQR 11–13). Most patients were diagnosed with gastric cancer (59%) with adenocarcinoma histology (70%) and underwent surgery (56%) for synchronous (56%) extra-regional lymph node oligometastasis. In addition, 6 study protocols which include patients with synchronous gastric cancer[38-41], synchronous or metachronous esophageal cancer[37], or synchronous esophagogastric cancer[35,36] were included. The imaging modality for detecting extra-regional lymph node oligometastasis was specified by 11 out of 12 studies or study protocols and was predominantly CT (73%, Supplementary File E1).

The number of extra-regional lymph node regions was specified by 12 out of 12 studies or study protocols. A solitary extra-regional lymph node region with metastases (e.g., cervical, thoracic or retroperitoneal/abdominal) was considered OMD according to 12 out of 12 (100%, consensus), of which 7 allowed 1 additional extra-regional lymph node region (58%, fair agreement). The maximum number of AJCC/UICC lymph node stations was specified by 5 of 12 studies or study protocols. A total of 1 AJCC/UICC extra-regional lymph node station with metastases was considered OMD according to 5 out of 5 (100%, consensus), of which 3 also allowed ≤3 AJCC/UICC extra-regional lymph node stations (60%, fair agreement; Supplementary File E2).

Brain oligometastasis

A definition of brain oligometastasis from esophagogastric cancer was provided by 7 studies[103-109]. All studies were retrospective and included a total of 82 patients. The median disease-free interval for metachronous OMD was 8 months (IQR 7–11). Most patients were diagnosed with esophageal cancer (73%) with adenocarcinoma histology (72%) and underwent radiosurgery (82%) for metachronous (88%) brain oligometastasis. The imaging modality for detecting brain oligometastasis was specified by 5 out of 7 studies or study protocols and was predominantly MRI (100%) and/or CT (75%, supplementary File F1). The maximum number of brain metastases was specified by 7 of 7 studies. A total of ≤2 metastases were considered OMD according to 6 out of 7 (86%, consensus; Supplementary File F2).

Adrenal gland oligometastasis

A definition of adrenal gland oligometastasis was provided by 1 retrospective study[110], 1 prospective non-randomized study[5], and 2 study protocols[5,40]. Studies included a total of 6 patients. The median disease-free interval for metachronous OMD was 11 months (range 8–15). Most patients were diagnosed with esophageal cancer (83%), and all patients underwent surgery for predominantly metachronous (80%) unilateral (100%) adrenal gland oligometastasis. The imaging modality for detecting adrenal gland oligometastasis was specified by 4 out of 4 studies or study protocols and was predominantly CT (100%) or MRI (75%, Supplementary File G1). The unilateral or bilateral involvement was specified by 4 of 4 studies or study protocols. Adrenal gland oligometastasis could be present in both adrenal glands (bilateral) according to 3 out of 4 studies or study protocols (75%, consensus; Supplementary File G2).

Other sites of oligometastasis

Studies providing a definition of bone, soft tissue, or other oligometastatic sites were not identified.

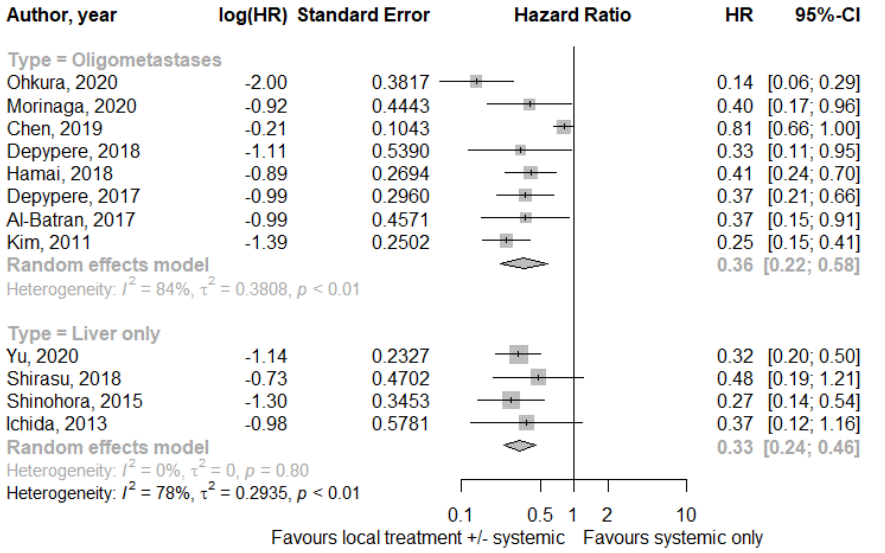

Figure 3A. Forest plot of reported unadjusted hazard ratios for overall survival after local metastasis-directed treatment versus systemic therapy alone in oligometastatic esophagogastric cancer.

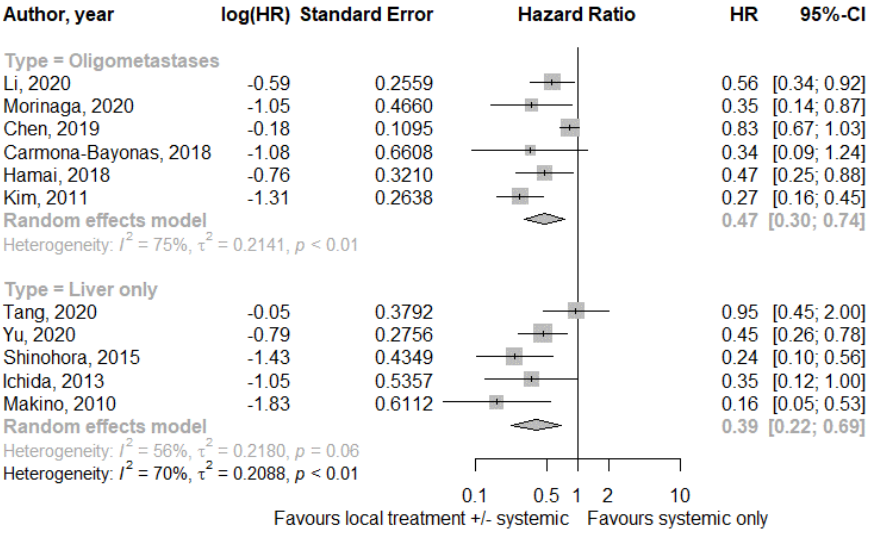

Figure 3B. Forest plot of reported adjusted hazard ratios for overall survival after local metastasis-directed treatment versus systemic therapy alone in oligometastatic esophagogastric cancer.

OS after local treatment for oligometastasis

The median OS after local treatment for OMD was specified by 16 studies including 740 patients in total. The median OS was 25 months (IQR 21–27), and the median 1-year and 5-year OS rates were 75% and 44%, respectively. The median OS after local treatment for different organ-specific oligometastasis as well as systemic therapy alone are presented in Table 3.

Meta-analysis comparing OS

A total of 16 non-randomized studies[5,18,19,21,22,25,27-29,32,34,43,45,50] compared OS after local treatment to systemic therapy alone for oligometastatic esophagogastric cancer. The overall risk of bias was considered serious. Studies were generally considered at serious risk for confounding bias because of the non-randomized study design and because studies did not adjust for potentially important confounding domains such as performance status[111] or HER2neu[112] and microsatellite instability (MSI) status[113] (Supplementary File H).

Local treatment was associated with improved OS as compared with systemic therapy alone for OMD based on 8 studies without multivariable adjustment (pooled HR for OS 0.36, 95% CI: 0.22–0.58) and 6 studies with multivariable adjustment (pooled aHR for OS 0.47, 95% CI: 0.30–0.74). There was considerable heterogeneity among these studies (I^2 = 84% and I^2 = 75%, respectively). In addition, local treatment was associated with improved OS as compared with systemic therapy alone for liver oligometastasis based on 4 studies without multivariable adjustment (pooled HR for OS 0.33, 95% CI: 0.24–0.46) and 5 studies with multivariable adjustment (pooled aHR for OS 0.39, 95% CI: 0.22–0.69). There was no substantial heterogeneity among these studies (I^2=0% and I^2=56%, respectively). No comparative studies were identified for other sites of OMD from esophagogastric cancer. The forest plots of HRs for OS with and without multivariable adjustment are presented in Fig. 3. In addition, the funnel plots of unadjusted and adjusted HRs for OS after local metastasis-directed treatment versus systemic therapy alone for OMD are presented in Supplementary Files I and J. Both funnel plots reveal an asymmetrical appearance with a gap in the right corner, suggesting that studies with HRs closer to 1 (indicating less or no benefit of local metastasis-directed treatment) more often remained unpublished. This points to a certain extent of publication bias with a tendency towards overestimating the effect of local metastasis-directed treatment in the current meta-analysis.

DISCUSSION

The primary aim of this systemic review and meta-analysis was to identify applied definitions of oligometastatic esophagogastric cancer from the available literature and compare local treatment versus systemic therapy alone for oligometastatic esophagogastric cancer. In literature, consensus (i.e. ≥75% agreement) among 28 available studies and study protocols was observed on considering 1 organ with ≤3 metastases or 1 extra-regional lymph node station with metastases as OMD. Moreover, fair agreement (i.e. 50%–75% agreement) was observed on considering 1 organ with ≤4 metastases or ≤2 extra-regional lymph node stations with metastases as OMD. Furthermore, local treatment for oligometastatic esophagogastric cancer appeared associated with improved OS compared with systemic therapy alone, but the included non-randomized studies generally did not adjust for or report on potentially important confounding domains such as performance status[111], HER2neu[112] or MSI status[113]. Therefore, prospective randomized trials are warranted.

A universal consensus definition of OMD in esophagogastric cancer could aid in the standardization of inclusion criteria in future clinical trials and prospective data collection. In addition, such a definition could guide the treatment decision-making process in multidisciplinary tumor board meetings. The current review is the first step in our joint aim within the OligoMetastatic Esophagogastric Cancer (OMEC) consortium to achieve consensus on the definition of oligometastatic esophagogastric cancer (www.OMECproject.eu). OMEC is a consortium of 50 cancer expert centers in Europe and aims to develop a multidisciplinary European consensus statement for oligometastatic esophagogastric cancer. OMEC has been endorsed by ESDE, ESMO, ESSO, EORTC, ESTRO, IGCA, and DUCG. Subsequent steps of the OMEC-project include real-life clinical case discussions by multidisciplinary teams of esophagogastric cancer expert centers in Europe asking for multidisciplinary team responses on definition and treatment (OMEC-2)[114], Delphi consensus rounds among upper gastrointestinal experts to establish consensus about the definition and treatment of oligometastatic esophagogastric cancer (OMEC-3) and the publication of a consensus statement on this topic (OMEC-4). This consensus statement will result in a prospective study for oligometastatic esophagogastric cancer (OMEC-5).

The definition of oligometastatic esophagogastric cancer identified in the current literature (1 organ with ≤3 metastases or 1 extra-regional lymph node station with metastasis) was more restrictive than the definition of oligometastatic NSCLC (≤3 organs with ≤5 metastases)[115]. This difference might be explained by the more aggressive tumor biology and lower OS of oligometastatic esophagogastric cancer as compared with oligometastatic NSCLC (i.e. median OS of 25 months versus 41 months)[116].

The observed favorable OS after local treatment for oligometastatic esophagogastric cancer and the apparent survival benefit for local treatment as compared with systemic therapy alone in the current meta-analysis represents supportive evidence for an OMD state in esophagogastric cancer. However, these results could be confounded by publication bias or the response to systemic therapy since patients who respond to systemic therapy are offered subsequent local treatment for OMD and these responders already have an improved OS, irrespective of local treatment for oligometastasis[111]. Therefore, RCTs are warranted to confirm the benefit of local treatment for OMD over systemic therapy alone. Currently, the Renaissance trial by Al-Batran et al. addresses the benefit of surgical resection of the primary tumor and metastases plus systemic therapy over systemic therapy alone in patients with gastric or gastroesophageal junction cancer with synchronous OMD[38]. After 4 cycles of FLOT chemotherapy, patients without progression will be randomized to either surgical resection of the primary tumor and metastases plus continuation of systemic therapy or continuation of systemic therapy alone[38]. In addition, the ECOG trial by National Cancer Institute addresses the benefit of radiotherapy plus systemic therapy over systemic therapy alone in patients with esophageal or gastric cancer with metachronous OMD[35]. After 4 cycles of CapOx or FLOT chemotherapy, patients without progression will be randomized to either radiotherapy of metastases plus continuation of systemic therapy or continuation of systemic therapy alone[35]. Furthermore, the REGATTA trial has previously shown that systemic therapy plus local treatment for the primary tumor only (i.e. no local treatment for metastases) does not improve OS as compared with systemic therapy alone in patients with gastric cancer with one organ with metastases[117]. Therefore, future prospective studies for oligometastasis should always incorporate systemic therapy plus local treatment for primary tumor and metastases.

The studies included in this systematic review represent the currently best available evidence but have certain limitations that warrant consideration for the interpretation of results. First, all studies scored a serious risk of bias because of the retrospective study design or because studies did not measure or control for important baseline confounders such as performance status. Second, considerable heterogeneity in the HR for OS was identified, but this study could not determine the cause of this heterogeneity due to the limited number of studies. Third, no pooling of studies for other oligometastasis sites from esophagogastric cancer was possible. Fourth, the studies included in this systematic review mainly used CT as the imaging modality for detecting OMD. However, CT has a lower sensitivity for detecting distant metastasis than PET/CT, which might have overestimated the proportion of patients with OMD[118]. Fifth, there were not enough studies on SBRT only to evaluate the potential different impacts of local treatment strategies. Sixth, there were too few studies comparing outcomes after local treatment versus systemic therapy alone for OMD in patients with esophageal adenocarcinoma versus squamous cell carcinoma to differentiate the outcomes on histology. Seventh, both

funnel plots pointed to a certain extent of publication bias with a tendency towards overestimating the effect of local metastasis-directed treatment in the current meta-analysis. Finally, the evidence on oligometastatic esophagogastric cancer could change over time as new (prospective) studies in this field become available, potentially requiring an update of this review in the (near) future. However, the current study is strengthened by the variety of studies and treatment modalities included. Prospective and retrospective, Asian and Western studies were included, and patients with either synchronous or metachronous oligometastatic esophageal or gastric cancer who were treated with metastasectomy or SBRT. Therefore, we believe this study has excellent multidisciplinary applicability and generalizability.

CONCLUSION

In conclusion, a consensus was found in the available literature (including predominantly retrospective studies) and ongoing trials that a disease burden of 1 extra-regional lymph node station or 1 organ with ≤3 metastases could be considered OMD in esophagogastric cancer. These findings will be confirmed or updated in subsequent steps of the OMEC project. An apparent survival benefit was observed for local treatment with or without systemic therapy compared to systemic therapy alone for oligometastatic esophagogastric cancer in non-randomized studies, which supports the idea of an actual OMD state in esophagogastric cancer. As such, improvement in the definition and management of oligometastatic esophagogastric cancer is warranted in prospective randomized studies.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011;8(6):378-382. doi:10.1038/nrclinonc.2011.44
3. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
4. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019. doi:10.1016/S0140-6736(18)32487-5
5. Ruers T, Van Coevorden F, Punt CJA, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *J Natl Cancer Inst*. 2017. doi:10.1093/jnci/djx015
6. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. Maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019. doi:10.1200/JCO.19.00201
7. Liu QQ, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients With Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. May 2020. doi:10.1016/j.ijrobp.2020.05.003
8. Al-Batran S-EE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. *JAMA Oncol*. 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. http://www.ncbi.nlm.nih.gov/pubmed/19622552. Accessed October 10, 2016.
10. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. *Ann Cardiothorac Surg*. 2017. doi:10.21037/acs.2017.03.14
11. Rice TW, Ishwaran H, Blackstone EH, et al. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016. doi:10.1111/dote.12540
12. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016. doi:10.1136/bmj.i4919
13. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. *Eur Urol Oncol*. 2019:1-8. doi:10.1016/j.euo.2019.07.010
14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J*. 2003. doi:10.1136/bmj.327.7414.557
15. Li J, Wen Y, Xiang Z, et al. Radical radiotherapy for metachronous oligometastasis after initial treatment of esophageal cancer. *Radiother Oncol*. 2021;154:201-206. doi:10.1016/j.radonc.2020.09.042
16. Yamashita H, Ogita M, Aoki S, Abe O, Nakagawa K. Linear accelerator-based stereotactic body radiation therapy in the treatment of oligometastatic disease. *Mol Clin Oncol*. 2020;13(2):109-114. doi:10.3892/mco.2020.2065
17. Li B, Li W, Fan B, et al. Efficacy of Radiotherapy In Oligometastatic Esophageal Squamous Cell Cancer Patients: New Evidence From A Retrospective Study. *Int J Radiat Oncol*. 2020. doi:10.1016/j.ijrobp.2020.07.1857
18. Ohkura Y, Shindoh J, Ueno M, Iizuka T, Udagawa H. Clinicopathologic Characteristics of Oligometastases from Esophageal Cancer and Long-Term Outcomes of Resection. *Ann Surg Oncol*. 2020;27(3):651-659. doi:10.1245/s10434-019-08175-0
19. Hilal L, Ku G, Molena D, et al. Survival and Patterns of Failure in Oligometastatic Esophagogastric Cancer. *Int J Radiat Oncol*. 2020;108(3):e623. doi:10.1016/j.ijrobp.2020.07.1886

20. Morinaga T, Iwatsuki M, Yamashita K, et al. Oligometastatic recurrence as a prognostic factor after curative resection of esophageal squamous cell carcinoma. *Surg Today*. 2020;(0123456789). doi:10.1007/s00595-020-02173-6
21. Chen Y, Cheng X, Song H, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for esophageal squamous cell cancer patients presenting with oligometastases. *J Thorac Dis*. 2019;11(4):1536-1545. doi:10.21037/jtd.2019.03.10
22. Omari J, Drewes R, Othmer M, Hass P, Pech M, Powerski M. Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy. *Diagnostic Interv Radiol*. 2019;25(5):360-367. doi:10.5152/dir.2019.18390
23. Iwatsuki M, Harada K, Wang X, et al. The prognostic factors associated with long-term survival in the patients with synchronous oligometastatic esophageal adenocarcinoma. *J Clin Oncol*. 2019;37(15_suppl):e15523-e15523. doi:10.1200/jco.2019.37.15_suppl.e15523
24. Carmona-Bayonas A, Jiménez-Fonseca P, Echavarria I, et al. Surgery for metastases for esophageal-gastric cancer in the real world: Data from the AGAMENON national registry. *Eur J Surg Oncol*. 2018;44(8):1191-1198. doi:10.1016/j.ejso.2018.03.019
25. Ghaly G, Harrison S, Kamel MK, et al. Predictors of Survival After Treatment of Oligometastases After Esophagectomy. *Ann Thorac Surg*. 2018;105(2):357-362. doi:10.1016/j.athoracsur.2017.10.039
26. Hamai Y, Hihara J, Emi M, et al. Treatment Outcomes and Prognostic Factors After Recurrence of Esophageal Squamous Cell carcinoma. *World J Surg*. 2018;42(7):2190-2198. doi:10.1007/s00268-017-4430-8
27. Depypere LP, Moons J, Lerut TE, Coosemans W, Van Veer H, Nafteux PR. Palliative esophagectomy in unexpected metastatic disease: sense or nonsense? *Asian Cardiovasc Thorac Ann*. 2018;26(7):552-557. doi:10.1177/0218492318797228
28. Depypere L, Lerut T, Moons J, et al. Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. *Dis Esophagus*. 2017;30(1):1-8. doi:10.1111/dote.12508
29. Schmidt T, Alldinger I, Blank S, et al. Surgery in oesophago-gastric cancer with metastatic disease: Treatment, prognosis and preoperative patient selection. *Eur J Surg Oncol*. 2015;41(10):1340-1347. doi:10.1016/j.ejso.2015.05.005
30. Xu C, Xie J, Liang N, et al. Concurrent involved-field radiotherapy and XELOX in gastric cancer patients with postoperative oligometastatic recurrence. *J Cancer Res Ther*. 2014;10(8):C267-C271. doi:10.4103/0973-1482.151487
31. Ichida H, Imamura H, Yoshimoto J, et al. Pattern of postoperative recurrence and hepatic and/or pulmonary resection for liver and/or lung metastases from esophageal carcinoma. *World J Surg*. 2013;37(2):398-407. doi:10.1007/s00268-012-1830-7
32. Port JL, Nasar A, Lee PC, et al. Definitive therapy for isolated esophageal metastases prolongs survival. *Ann Thorac Surg*. 2012;94(2):413-420. doi:10.1016/j.athoracsur.2012.03.075
33. Kim KH, Lee KW, Baek SK, et al. Survival benefit of gastrectomy ± metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. *Gastric Cancer*. 2011;14(2):130-138. doi:10.1007/s10120-011-0015-7
34. ECOG-ACRIN Cancer Research. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. *clinicaltrials.gov/NCT04248452*. 2020. doi:10.31525/ct1-nct04248452
35. Nguyen Q-N. Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03161522. Published 2020. Accessed July 11, 2019.
36. Zhao K Le. Local Therapy for Oligorecurrent and Oligometastatic Esophageal Squamous Cell Carcinoma. *clinicaltrial.gov/NCT03904927*. 2021;(Cdc):1-9.
37. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. *BMC Cancer*. 2017;17(1). doi:10.1186/s12885-017-3918-9
38. Xu D. Chemotherapy Alone Versus Surgery Plus Chemotherapy for Distal Gastric Cancer With One

Non-curable Factor. *Clinicaltrials.gov/NCT03399253*. 2020:1-7. https://clinicaltrials.gov/ct2/show/study/NCT03399253. Accessed August 13, 2020.
39. Zhen-Yu Ding. Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction. *Case Med Res*. 2020. doi:10.31525/ct1-nct04263870
40. Guo W. PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment ofUnresectable Locally Advanced or Limited Metastatic Gastric Cancer. *clinicaltrials.gov/NCT04510064*. 2021.
41. Lee JW, Choi MH, Lee YJ, et al. Radiofrequency ablation for liver metastases in patients with gastric cancer as an alternative to hepatic resection. *BMC Cancer*. 2017;17(1):1-8. doi:10.1186/s12885-017-3156-1
42. Shirasu H, Tsushima T, Kawahira M, et al. Role of hepatectomy in gastric cancer with multiple liver-limited metastases. *Gastric Cancer*. 2018;21(2):338-344. doi:10.1007/s10120-017-0730-9
43. Song A, Zhang X, Yu F, Li D, Shao W, Zhou Y. Surgical resection for hepatic metastasis from gastric cancer: A multi- institution study. *Oncotarget*. 2017;8(41):71147-71153. doi:10.18632/oncotarget.16705
44. Makino H, Kunisaki C, Izumisawa Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. *Anticancer Res*. 2010;30(6):2367-2376.
45. Tang K, Zhang B, Dong L, Wang L, Tang Z. Radiofrequency ablation versus traditional liver resection and chemotherapy for liver metastases from gastric cancer. *J Int Med Res*. 2020. doi:10.1177/0300060520940509
46. Qiu JL, Deng MG, Li W, et al. Hepatic resection for synchronous hepatic metastasis from gastric cancer. *Eur J Surg Oncol*. 2013;39(7):694-700. doi:10.1016/j.ejso.2013.03.006
47. Yazawa T, Hori T, Yamamoto H, et al. Do liver metastases from gastric cancer contraindicate aggressive surgical resection? A 14-year single-center experience. *World J Gastrointest Pharmacol Ther*. 2020;11(5):110-122. doi:10.4292/wjgpt.v11.i5.110
48. Ministrini S, Solaini L, Cipollari C, et al. Surgical treatment of hepatic metastases from gastric cancer. *Updates Surg*. 2018;70(2):273-278. doi:10.1007/s13304-018-0536-2
49. Shinohara T, Maeda Y, Hamada T, Futakawa N. Survival Benefit of Surgical Treatment for Liver Metastases from Gastric Cancer. *J Gastrointest Surg*. 2015;19(6):1043-1051. doi:10.1007/s11605-015-2775-6
50. Wang W, Liang H, Zhang H, Wang X, Xue Q, Zhang R. Prognostic significance of radical surgical treatment for gastric cancer patients with synchronous liver metastases. *Med Oncol*. 2014;31(11):1-8. doi:10.1007/s12032-014-0258-3
51. Wang YN, Shen KT, Ling JQ, et al. Prognostic analysis of combined curative resection of the stomach and liver lesions in 30 gastric cancer patients with synchronous liver metastases. *BMC Surg*. 2012;12(1):1. doi:10.1186/1471-2482-12-20
52. Jagric T, Horvat M. Surgical resection of synchronous liver metastases in gastric cancer patients. A propensity score-matched study. *Radiol Oncol*. 2020;55(1):57-65. doi:10.2478/raon-2020-0067
53. Garancini M, Uggeri FFFFFF, Degrate L, et al. Surgical treatment of liver metastases of gastric cancer: Is local treatment in a systemic disease worthwhile? *Hpb*. 2012;14(3):209-215. doi:10.1111/j.1477-2574.2011.00428.x
54. Ryu T, Takami Y, Wada Y, et al. Oncological outcomes after hepatic resection and/or surgical microwave ablation for liver metastasis from gastric cancer. *Asian J Surg*. 2019;42(1):100-105. doi:10.1016/j.asjsur.2017.09.005
55. Djuraev F, Atakhanova N. Approaches for optimal choice in treatment of gastric cancer with liver metastases. *Eur J Cancer*. 2017;72(January):S74. doi:10.1016/s0959-8049(17)30320-9
56. Chen L, Song MQ, Lin HZ, et al. Chemotherapy and resection for gastric cancer with synchronous liver metastases. *World J Gastroenterol*. 2013;19(13):2097-2103. doi:10.3748/wjg.v19.i13.2097
57. Guner A, Son T, Cho I, et al. Liver-directed treatments for liver metastasis from gastric adenocarcinoma: comparison between liver resection and radiofrequency ablation. *Gastric Cancer*. 2016;19(3):951-960. doi:10.1007/s10120-015-0522-z
58. Oguro S, Imamura H, Yoshimoto J, Ishizaki Y, Kawasaki S. Liver metastases from gastric cancer represent systemic disease in comparison with those from colorectal cancer. *J Hepatobiliary Pancreat Sci*. 2016;23(6):324-332. doi:10.1002/jhbp.343

59. Zhang W, Yu Y, Fang Y, et al. Systemic chemotherapy as a main strategy for liver metastases from gastric cancer. *Clin Transl Oncol*. 2015;17(11):888-894. doi:10.1007/s12094-015-1321-z
60. Liu J, Wei Z, Wang Y, Xia Z, Zhao G. Hepatic resection for post-operative solitary liver metastasis from oesophageal squamous cell carcinoma. *ANZ J Surg*. 2018;88(4):E252-E256. doi:10.1111/ans.13810
61. Nonaka Y, Hiramatsu K, Kato T, et al. Evaluation of Hepatic Resection in Liver Metastasis of Gastric Cancer. *Indian J Surg Oncol*. 2019;10(1):204-209. doi:10.1007/s13193-018-0827-6
62. Ito D, Kawaguchi Y, Yamashita H, et al. Intestinal-type histology is associated with better prognosis in patients undergoing liver resection for gastric/esophagogastric-junction liver metastasis. *Glob Heal Med*. 2019;1(2):101-109. doi:10.35772/ghm.2019.01012
63. Oki E, Tokunaga S, Emi Y, et al. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). *Gastric Cancer*. 2016;19(3):968-976. doi:10.1007/s10120-015-0530-z
64. Yao GL, Fan YG, Zhai JM, Lu BS, Liu KL. Radical gastrectomy with hepatoarterial catheter implantation for late-stage gastric cancer. *World J Gastroenterol*. 2015;21(9):2754-2758. doi:10.3748/wjg.v21.i9.2754
65. Baek HU, Kim SB, Cho EH, et al. Hepatic resection for hepatic metastases from gastric adenocarcinoma. *J Gastric Cancer*. 2013;13(2):86-92. doi:10.5230/jgc.2013.13.2.86
66. Liu Q, Bi JJ, Tian YT, Feng Q, Zheng ZX, Wang Z. Outcome after simultaneous resection of gastric primary tumour and synchronous liver metastases: Survival analysis of a single-center experience in China. *Asian Pacific J Cancer Prev*. 2015;16(4):1665-1669. doi:10.7314/APJCP.2015.16.4.1665
67. Yang XW, Li Z, Liu K, Fu XH, Yang JH, Wu MC. Correlation between the survival rate of the patients with synchronous hepatic metastases from gastric carcinoma after surgical resection and patient's index. *Chin Med J (Engl)*. 2012;125(5):747-751. doi:10.3760/cma.j.issn.0366-6999.2012.05.005
68. Li J, Zhang K, Gao Y, et al. Evaluation of hepatectomy and palliative local treatments for gastric cancer patients with liver metastases: A propensity score matching analysis. *Oncotarget*. 2017;8(37):61861-61875. doi:10.18632/oncotarget.18709
69. Tsujimoto H, Ichikura T, Ono S, et al. Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer. *Hepatol Int*. 2010;4(1):406-413. doi:10.1007/s12072-009-9161-y
70. Yu P, Zhang Y, Ye Z, et al. Treatment of synchronous liver metastases from gastric cancer: A single-center study. *Cancer Manag Res*. 2020;12:7905-7911. doi:10.2147/CMAR.S261353
71. Ohkura Y, Shinohara H, Haruta S, et al. Hepatectomy Offers Superior Survival Compared with Non-surgical Treatment for ≤3 Metastatic Tumors with Diameters < 3 cm from Gastric Cancer: A Retrospective Study. *World J Surg*. 2015;39(11):2757-2763. doi:10.1007/s00268-015-3151-0
72. Saiura A., Koga R., Yoshioka R., Oyama S., Arita J., Sano T. YT. Efficacy and indication of liver resection for liver metastases from gastric cancer. *Ann Oncol*. 2011;22 SUPPL. doi:10.1093/annonc/mdr287
73. Komeda K, Hayashi M, Kubo S, et al. High Survival in Patients Operated for Small Isolated Liver Metastases from Gastric Cancer: A Multi-institutional Study. *World J Surg*. 2015;38(10):2692-2697. doi:10.1007/s00268-014-2608-x
74. Tatsubayashi T, Tanizawa Y, Miki Y, et al. Treatment outcomes of hepatectomy for liver metastases of gastric cancer diagnosed using contrast-enhanced magnetic resonance imaging. *Gastric Cancer*. 2017;20(2):387-393. doi:10.1007/s10120-016-0611-7
75. Dittmar Y, Altendorf-Hofmann A, Rauchfuss F, et al. Resection of liver metastases is beneficial in patients with gastric cancer: Report on 15 cases and review of literature. *Gastric Cancer*. 2012;15(2):131-136. doi:10.1007/s10120-011-0080-y
76. Seesing MFJ, Van Der Veen A, Brenkman HJF, et al. Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: A nationwide study. *Dis Esophagus*. 2020;32(12):1-8. doi:10.1093/dote/doz034
77. Nakajima K, Iwata H, Hattori Y, et al. Image-guided Proton Therapy (IGPT) for Oligometastatic Liver Tumors from Gastric/Colorectal Cancer. *Int J Radiat Oncol*. 2019;105(1):E224-E225. doi:10.1016/j.ijrobp.2019.06.1982
78. Shigaki H, Kosumi K, Tokunaga R, et al. Radiofrequency ablation for pulmonary metastases from esophageal squamous cell carcinoma. *J Clin Oncol*. 2016;34(4). doi:10.1200/jco.2016.34.4_suppl.138
79. M. H, H. O, K. T, et al. Pulmonary metastasectomy for metachronous metastasis of esophageal cancer after esophagectomy. Esophagus. 2016;13(2):163-166. doi:10.1007/s10388-015-0506-4 LK - https://

utrechtuniversity.on.worldcat.org/atoztitles/link?sid=EMBASE&sid=EMBASE&issn=16129067&id=doi:10.1007%2Fs10388-015-0506-4&atitle=Pulmonary+metastasectomy+for+metachronous+metastasis+of+esophageal+cancer+after+esophagectomy&stitle=Esophagus&title=Esophagus&volume=13&issue=2&spage=163&epage=166&aulast=Hirao&aufirst=Motohiro&auinit=M.&aufull=Hirao+M.&coden=&isbn=&pages=163-166&date=2016&auinit1=M&auinitm=

80. Yamanashi K, Hamaji M, Tsunoda S, et al. Survival outcomes of resection for pulmonary malignancies including non-small cell lung cancer and pulmonary metastasis after esophagectomy for esophageal carcinoma. *Gen Thorac Cardiovasc Surg*. 2020;68(10):1179-1186. doi:10.1007/s11748-020-01373-8
81. Yamamoto T, Niibe Y, Matsumoto Y, et al. Stereotactic body radiotherapy for pulmonary oligometastases from esophageal cancer: Results and prognostic factors. *Anticancer Res*. 2020;40(4):2065-2072. doi:10.21873/anticanres.14164
82. Ichikawa H, Kosugi SI, Nakagawa S, et al. Operative treatment for metachronous pulmonary metastasis from esophageal carcinoma. *Surgery*. 2011;149(2):164-170. doi:10.1016/j.surg.2010.07.047
83. Iijima Y, Akiyama H, Atari M, et al. Pulmonary resection for metastatic gastric cancer. *Ann Thorac Cardiovasc Surg*. 2016;22(4):230-236. doi:10.5761/atcs.oa.16-00049
84. Kanai R, Tane K, Ishii G, et al. Clinical prediction of solitary pulmonary nodule after a curative resection for gastric cancer. *Jpn J Clin Oncol*. 2018;48(12):1083-1087. doi:10.1093/jjco/hyy146
85. Kanamori J, Aokage K, Hishida T, et al. The role of pulmonary resection in tumors metastatic from esophageal carcinoma. *Jpn J Clin Oncol*. 2017;47(1):25-31. doi:10.1093/jjco/hyw141
86. Kobayashi Y, Fukui T, Ito S, et al. Pulmonary metastasectomy for gastric cancer: A 13-year single-institution experience. *Surg Today*. 2013;43(12):1382-1389. doi:10.1007/s00595-012-0432-1
87. Matsui Y, Hiraki T, Gobara H, et al. Percutaneous radiofrequency ablation for pulmonary metastases from esophageal cancer: Retrospective evaluation of 21 patients. *J Vasc Interv Radiol*. 2014;25(10):1566-1572. doi:10.1016/j.jvir.2014.06.030
88. Kanzaki R, Kimura T, Kawamura T, et al. Surgery for malignant pulmonary nodules in patients with a history of oesophageal cancer. *Interact Cardiovasc Thorac Surg*. 2017;24(3):418-424. doi:10.1093/icvts/ivw358
89. Kozu Y, Oh S, Takamochi K, Suzuki K. Surgical outcomes of pulmonary metastases from esophageal carcinoma diagnosed by both pathological and clinical criteria. *Surg Today*. 2015;45(9):1127-1133. doi:10.1007/s00595-014-1036-8
90. Komatsu H, Izumi N, Tsukioka T, Inoue H, Miyamoto H, Nishiyama N. Impact of perioperative chemotherapy on prognosis of patients with esophageal carcinoma undergoing pulmonary metastasectomy. *Ann Thorac Cardiovasc Surg*. 2019;25(5):253-259. doi:10.5761/atcs.oa.19-00075
91. Kobayashi N, Kohno T, Haruta S, et al. Pulmonary metastasectomy secondary to esophageal carcinoma: Long-term survival and prognostic factors. *Ann Surg Oncol*. 2014;21(SUPPL. 3):365-369. doi:10.1245/s10434-014-3677-7
92. Omae K, Hiraki T, Gobara H, et al. Long-Term Survival after Radiofrequency Ablation of Lung Oligometastases from Five Types of Primary Lesions: A Retrospective Evaluation. *J Vasc Interv Radiol*. 2016;27(9):1362-1370. doi:10.1016/j.jvir.2016.05.017
93. Oguri Y, Okui M, Yamamichi T, Asakawa A, Harada M, Horio H. The impact of pulmonary metastasectomy from gastric cancer. *Mol Clin Oncol*. 2019;11(4):401-404. doi:10.3892/mco.2019.1910
94. Takemura M, Sakurai K, Takii M, Yoshida K. Metachronous pulmonary metastasis after radical esophagectomy for esophageal cancer: prognosis and outcome. *J Cardiothorac Surg*. 2012;7(1):1-5. doi:10.1186/1749-8090-7-103
95. Shiono S, Sato T, Horio H, et al. Outcomes and prognostic factors of survival after pulmonary resection for metastatic gastric cancer. *Eur J Cardiothorac Surg*. 2013;43(1):13-16. doi:10.1093/ejcts/ezs574
96. Yoshida Y, Imakiire T, Yoneda S, Obuchi T, Inada K, Iwasaki A. Ten cases of resected solitary pulmonary metastases arising from gastric cancer. *Asian Cardiovasc Thorac Ann*. 2014;22(5):578-582. doi:10.1177/0218492313513777
97. Kato F, Monma S, Koyanagi K, et al. Long-term outcome after resection for recurrent oesophageal cancer. *J Thorac Dis*. 2018;10(5):2691-2699. doi:10.21037/jtd.2018.05.17
98. Maruyama K, Motoyama S, Anbai A, et al. Therapeutic strategy for the treatment of postoperative recurrence of esophageal squamous cell carcinoma: Clinical efficacy of radiotherapy. *Dis Esophagus*.

2011;24(3):166-171. doi:10.1111/j.1442-2050.2010.01119.x
99. Matsumoto T, Nishina T, Kajiwara T, et al. P-050 The role of radiotherapy or chemoradiotherapy for oligo-recurrence of esophageal cancer after curative resection or chemoradiotherapy. *Ann Oncol*. 2015;26(Supplement 4):iv14. doi:10.1093/annonc/mdv233.50
100. Park IH, Kim SY, Kim YW, et al. Clinical characteristics and treatment outcomes of gastric cancer patients with isolated para-aortic lymph node involvement. *Cancer Chemother Pharmacol*. 2011;67(1):127-136. doi:10.1007/s00280-010-1296-y
101. Sato Y, Motoyama S, Wada Y, et al. Neoadjuvant chemoradiotherapy followed by esophagectomy with three-field lymph node dissection for thoracic esophageal squamous cell carcinoma patients with clinical stage iii and with supraclavicular lymph node metastasis. *Cancers (Basel)*. 2021;13(5):1-14. doi:10.3390/cancers13050983
102. Song Z, Lin B, Shao L, Zhang Y. Brain metastases from esophageal cancer: Clinical review of 26 cases. *World Neurosurg*. 2014;81(1):131-135. doi:10.1016/j.wneu.2013.02.058
103. Bowden G, Kano H, Tempel ZJ, et al. Gamma knife radiosurgery for management of cerebral metastases from esophageal carcinoma. *J Neurooncol*. 2014;118(1):141-146. doi:10.1007/s11060-014-1408-3
104. Welch G, Ross HJ, Patel NP, et al. Incidence of brain metastasis from esophageal cancer. *Dis Esophagus*. 2017;30(9):1-6. doi:10.1093/dote/dox071
105. Han JH, Kim DG, Chung HT, et al. Radiosurgery for brain metastasis from advanced gastric cancer. *Acta Neurochir (Wien)*. 2010;152(4):605-610. doi:10.1007/s00701-009-0554-4
106. Park YS, Chang JH, Chang JW, Park YG. The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases. *J Neurooncol*. 2011;103(3):513-521. doi:10.1007/s11060-010-0405-4
107. Li Q, Deng M, Xi M, Zhu Y, Hu Y. Characteristics and treatment of brain metastases from esophageal squamous cell carcinoma. *J Cancer*. 2018;9(5):901-905. doi:10.7150/jca.21511
108. Onal C, Akkus Yildirim B, Guler OC. Outcomes of aggressive treatment in esophageal cancer patients with synchronous solitary brain metastasis. *Mol Clin Oncol*. 2017;7(1):107-112. doi:10.3892/mco.2017.1263
109. Fumagalli U, De Carli S, De Pascale S, Rimassa L, Bignardi M, Rosati R. Adrenal metastases from adenocarcinoma of the esophagogastric junction: Adrenalectomy and long-term survival. *Updates Surg*. 2010;62(1):63-67. doi:10.1007/s13304-010-0012-0
110. Dingemans AMC, Hendriks LEL, Berghmans T, et al. Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. *J Thorac Oncol*. 2019;14(12):2109-2119. doi:10.1016/j.jtho.2019.07.025
111. Gomez DR, Blumenschein GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016. doi:10.1016/S1470-2045(16)30532-0
112. Noble F, Bailey D, SWCIS Upper Gastrointestinal Tumour Panel, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer-a UK population-based cohort study. *Clin Radiol*. 2009. doi:10.1016/j.crad.2009.03.003

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CHAPTER 4

Definitions and treatment of oligometastatic esophagogastric cancer according to multidisciplinary tumor boards in Europe

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Tiuri E. Kroese, Richard van Hillegersberg, Sebastian Schoppmann, Pieter R.A.J. Deseyne, Philippe Nafteux, Radka Obermannova, Marianne Nordsmark, Per Pfeiffer, Maria A. Hawkins, Elizabeth Smyth, Sheraz Markar, George B. Hanna, Edward Cheong, Asif Chaudry, Anneli Elme, Antoine Adenis, Guillaume Piessen, Cihan Gani, Christiane J. Bruns, Markus Moehler, Theodore Liakakos, John Reynolds, Alessio Morganti, Riccardo Rosati, Carlo Castoro, Domenico D'Ugo, Franco Roviello, Maria Bencivenga, Giovanni de Manzoni, Paul Jeene, Johanna W. van Sandick, Christel Muijs, Marije Slingerland, Grard Nieuwenhuijzen, Bas Wijnhoven, Laurens V. Beerepoot, Piotr Kolodziejczyk, Wojciech P. Polkowski, Maria Alsina, Manuel Pera, Tania F. Kanonnikoff, Magnus Nilsson, Matthias Guckenberger, Stefan Monig, Dorethea Wagner, Lucjan Wyrwicz, Maaike Berbee, Ines Gockel, Florian Lordick, Ewen A Griffiths, Marcel Verheij, Peter S.N. van Rossum, Hanneke W.M. van Laarhoven, OMEC working group

ABSTRACT

Background

Consensus about the definition and treatment of oligometastatic esophagogastric cancer is lacking.

Objective

To assess the definition and treatment of oligometastatic esophagogastric cancer across multidisciplinary tumor boards (MDTs) in Europe.

Material and methods

European expert centers (n = 49) were requested to discuss 15 real-life cases in their MDT with at least a medical oncologist, surgical oncologist, and radiation oncologist present. The cases varied in terms of location and number of metastases, histology, timing of detection (i.e. synchronous versus metachronous), primary tumor treatment status, and response to systemic therapy. The primary outcome was the agreement in the definition of oligometastatic disease at diagnosis and after systemic therapy. The secondary outcome was the agreement in treatment strategies. Treatment strategies for oligometastatic disease were categorized into upfront local treatment (i.e. metastasectomy or stereotactic radiotherapy), systemic therapy followed by restaging to consider local treatment, or systemic therapy alone. The agreement across MDTs was scored to be either absent/poor (<50%), fair (50%-75%), or consensus (≥75%).

Results

A total of 47 MDTs across 16 countries fully discussed the cases (96%). Oligometastatic disease was considered in patients with 1-2 metastases in either the liver, lung, retroperitoneal lymph nodes, adrenal gland, soft tissue, or bone (consensus). At follow-up, oligometastatic disease was considered after a median of 18 weeks of systemic therapy when no progression or progression in size only of the oligometastatic lesion(s) was seen (consensus). If at restaging after a median of 18 weeks of systemic therapy the number of lesions progressed, this was not considered as oligometastatic disease (fair agreement). There was no consensus on treatment strategies for oligometastatic disease.

Conclusion

A broad consensus on definitions of oligometastatic esophagogastric cancer was found among MDTs of esophagogastric cancer expert centers in Europe. However, high practice variability in treatment strategies exists.

INTRODUCTION

Oligometastatic disease is defined as an intermediate state between loco-regional and systemic disease and reflects a potentially distinct and favorable tumor biology[1]. Consequently, local treatment for oligometastatic disease (e.g. metastasectomy or stereotactic body radiation therapy [SBRT]) could improve overall survival (OS)[1]. A recent randomized controlled trial (RCT) has shown improved OS after SBRT for oligometastatic prostate-, lung- or colorectal cancer as compared with systemic therapy alone or observation[2]. In addition, another recent RCT has shown improved OS after SBRT plus palliative standard-of-care treatment for oligometastatic non-small cell lung cancer (NSCLC) as compared with palliative standard-of-care treatment alone[3]. In patients with esophagogastric cancer, RCTs for oligometastatic disease are ongoing[4-10] while non-randomized trials have suggested improved OS after local treatment for oligometastasis as compared with systemic therapy alone[11,12]. However, interpretation and comparison of individual studies are hampered by different clinical definitions of oligometastatic disease, heterogeneity in case mix, selection bias, and various treatment strategies probably due to a lack of international consensus and guidelines.

A comprehensive definition of oligometastatic disease is necessary to initiate studies on the benefit of treatment strategies in this group of patients. For this purpose, the OligoMetastatic Esophagogastric Cancer (OMEC) consortium was established. OMEC is a consortium of 50 esophagogastric cancer expert centers in Europe and is endorsed by the European Organization for Research and Treatment of Cancer (EORTC), European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society for Diseases of the Esophagus (ESDE), the European chapter of the International Gastric Cancer Association (IGCA) and the Dutch Upper GI Cancer Group (DUCG). The OMEC project aims to develop a European consensus definition for oligometastatic esophagogastric cancer in organs, as well as extra-regional lymph nodes. Peritoneal disease was not included in the OMEC project, as this is a distinct entity that has already received much attention with hyperthermic intraperitoneal chemotherapy (HIPEC) as the main treatment[13-15]. The OMEC-project consists of 5 studies and includes a systematic review and meta-analysis on oligometastatic esophagogastric cancer (OMEC-1), the distribution of real-life clinical cases to multidisciplinary tumor boards (OMEC-2), Delphi consensus questionnaire rounds with experts (OMEC-3), the publication of a multidisciplinary European consensus statement on oligometastatic esophagogastric cancer (OMEC-4) and, finally, a prospective study for oligometastatic esophagogastric cancer (OMEC-5).

The current study (OMEC-2) was conducted to assess the definitions and treatment strategies for oligometastatic disease used in daily practice across multidisciplinary tumor boards (MDTs) in Europe. Decision-making on definition and treatment is based on various variables, such as

the organ involved, extra-regional lymph node metastases[11,16], the number of metastases[17], synchronous versus metachronous metastases[18], treatment status of the primary tumor[19], HER2Neu status[20,21], and response to systemic therapy at restaging[5,11]. The assessment of (dis) agreement in definition and management can be used to define oligometastatic esophagogastric cancer and to identify the currently used treatment options[22]. Therefore, esophagogastric cancer expert centers were requested to discuss 15 real-life clinical cases in their MDT to assess the agreement in definition and treatment strategies for oligometastatic esophagogastric cancer across MDTs in Europe.

MATERIAL AND METHODS

This study was approved by the institutional review board of the UMC Utrecht, and the need for informed consent was waived for this study. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. The methodology of this study was comparable with a simulated multidisciplinary expert opinion study on oligometastatic non-small cell lung cancer by the EORTC Lung Cancer Group[23].

Identification of cases

A search was performed of real-life patients with distant metastases from esophagogastric cancer with adenocarcinoma or squamous cell carcinoma histology. Distant metastasis was limited to either a distant organ or 1–2 extra-regional lymph node stations (according to TNM 8th edition)[24]. All patients were in good clinical condition with few to no comorbidities and were discussed at the MDT of the UMC Utrecht or Amsterdam UMC, both in The Netherlands, between 2015 and 2020. The cases varied in terms of 1. location of metastatic lesions (e.g. liver or lung); 2. number of metastatic lesions (one or two); 3. timing of detection (synchronous, interval [i.e. detected at restaging after neoadjuvant treatment before surgery], or metachronous); 4. primary tumor treatment status (surgery with or without neoadjuvant chemoradiotherapy, definitive chemoradiotherapy, or no primary tumor treatment); 5. histology (adenocarcinoma or squamous cell carcinoma), HER2 Neu status (positive, negative or mixed [i.e. the difference in the HER2 Neu status between the metastasis and the primary tumor]) and microsatellite stability; and 6. response to systemic therapy at restaging. The response to systemic therapy at restaging was categorized into no progression (i.e. complete or partial response, or stable disease), progression in size only of the metastatic lesion(s) (i.e. ≥20% growth in size), or progression in the number of lesions. The response to systemic therapy at restaging was classified according to response evaluation criteria in solid tumors (RECIST 1.1)[25]. Table 1 shows the characteristics of the presented cases.

Table 1. Characteristics of the real-life clinical cases included in the survey.

Case	1. Location of oligometastasis	2. Number of lesions	3. Timing of detection	4. Primary tumor treatment	5. Histology and HER2neu	6. Response to systemic therapy
1.	Liver (unilobar)	1	Metachronous (12 months)	cT3N1 distal esophagus treated with dCRT	AC HER2: – MSS	Progression in size only
2.	Liver (unilobar)	2	Metachronous (4 months)	cT2N1 distal esophagus treated with nCRT + surgery	ypT2N0 AC HER2: + MSS	Progression in size only
3.	Liver (bilobar)	2	Synchronous	cT3N2 distal esophagus	AC HER2: – MSS	Progression in number of lesions
4.	Retroperitoneal lymph node (right)	1	Interval	cT3N3 distal esophagus treated with nCRT	SCC	Stable disease
5.	Retroperitoneal lymph node (left)	1	Synchronous	cT3N1 cardia	AC HER2: – MSS	Complete response
6.	Neck lymph node (level IV)	1	Interval	cT3N1 mid esophagus treated with nCRT	SCC	Progression in number of lesions
7.	Neck lymph node (level III + IV)	2	Synchronous	cT3N2 distal esophagus	SCC	Complete response
8.	Lung unilateral (left upper lobe)	1	Metachronous (24 months)	cT4b(aorta)N2 mid esophagus treated with nCRT + surgery	ypT0N1 SCC	Progression in number of lesions
9.	Lung bilateral (right and middle lobe)	2	Synchronous	cT2N0 proximal esophagus	SCC	Stable disease
10.	Adrenal gland	1	Metachronous (12 months)	cT3N3 distal esophagus treated with nCRT + surgery	ypT3N0 AC HER2: – MSS	Partial response
11.	Adrenal gland	1	Synchronous	cT3N2M1 cardia	HER2: – MSS	Partial response
12.	Soft tissue (skin)	1	Metachronous (4 months)	pT1sm2N0 treated with surgery	pT2N0 AC HER2: – MSS	Stable disease
13.	Soft tissue (muscle)	1	Metachronous (24 months)	cT2N0 distal esophagus treated with nCRT + surgery	ypT3N1 HER2:-; MSS	Progression in number of lesions
14.	Bone (arm)	1	Metachronous (1 month)	cT3N3 distal esophagus treated with nCRT + surgery	ypT3N0 SCC	Progression in number of lesions
15.	Bone (clavicula)	1	Synchronous	cT3N1 distal esophagus	AC HER2: mixed MSS	Complete response

dCRT = definitive chemoradiotherapy; nCRT = neoadjuvant chemoradiotherapy; AC = adenocarcinoma; SCC = squamous cell carcinoma; MSS = microsatellite stable

MDT case discussion

The 15 real-life clinical cases were provided to 49 European esophagogastric cancer experts on March 23rd, 2020, using an online tool (Castor EDC). These experts were either identified by EORTC, ESTRO, ESMO, ESSO, ESDE, IGCA, or DUCG or identified by a systemic review of first or last authors of published RCTs related to esophagogastric cancer between 2015 and 2020.

Discussion of clinical cases

The experts were required to host a local MDT with at least a surgical oncologist, medical oncologist, and radiation oncologist present to discuss the 15 real-life clinical cases before 1st of August 2020. The case information consisted of 1. the patient history (including primary tumor stage and treatment), 2. the current problem (including location and size of distant metastasis), 3. pathology of the primary tumor and metastasis (including histology, HER2Neu status, and microsatellite stability), and 4. imaging of the primary tumor and metastasis (^{18}F-fluorodeoxyglucose positron emission tomography [^{18}F-FDG PET], computed tomography [CT], or magnetic resonance imaging [MRI]). The experts were not aware of the actual diagnosis or treatment of the real-life clinical cases.

Fig. 1 shows an example of a real-life clinical case provided to the expert. The first question for this case was: 'Does the MDT consider this patient to have oligometastatic disease?' If the answer was 'no', the questions for this specific case stopped. If the answer was 'yes', subsequent questions were asked regarding the treatment for the oligometastasis. The case continued only if the answer was 'systemic therapy followed by restaging to consider local treatment' (Fig. 2). At restaging, the case information consisted of 1. the current problem at restaging (including the response of the primary tumor and metastasis to systemic therapy) and 2. restaging imaging of the primary tumor and metastasis (^{18}F-FDG PET/CT, MRI, or CT). Next, the following question was asked: 'Does the MDT consider this patient to have oligometastatic disease at restaging?' If the answer was 'no', questions for this specific case stopped. If the answer was 'yes', subsequent questions were asked regarding the treatment for the oligometastasis. If all the questions were completed, the next case was presented (built-in data verification tool).

Outcome measure

The primary outcome of this study was the agreement across MDTs in Europe on the definition of oligometastatic esophagogastric cancer at diagnosis and after systemic therapy ('not oligometastatic disease' versus 'oligometastatic disease'). The secondary outcome of this study was the agreement across MDTs in Europe on treatment strategies for oligometastatic esophagogastric cancer. Treatment strategies for oligometastatic disease were categorized into upfront local treatment (e.g. metastasectomy, SBRT, or other local oligometastasis-directed

Case 3: Synchronous hepatic metastases

First presentation case 3

Synchronous hepatic metastases

Current problem (now):

- Primary tumor: cT3N2M1 adenocarcinoma of the distal esophagus (at 32-35 cm from the incisors)
- Liver:
  - Metastasis segment IV, diameter 45 mm with FDG-uptake.
  - Metastasis segment VI/VII, diameter 34 mm with FDG-uptake.
- Rest of the body: no evidence of metastases.

Pathology:

- Primary tumor: adenocarcinoma, Her2/neu –, microsatellite stable (MSS).
- Liver metastasis segment VI/VII: adenocarcinoma, Her2/neu –, origin upper gastrointestinal.

Conclusion:

- cT3N2M1 adenocarcinoma of the distal esophagus.
- Synchronous liver metastases (2) in segment IV and VI/VII.

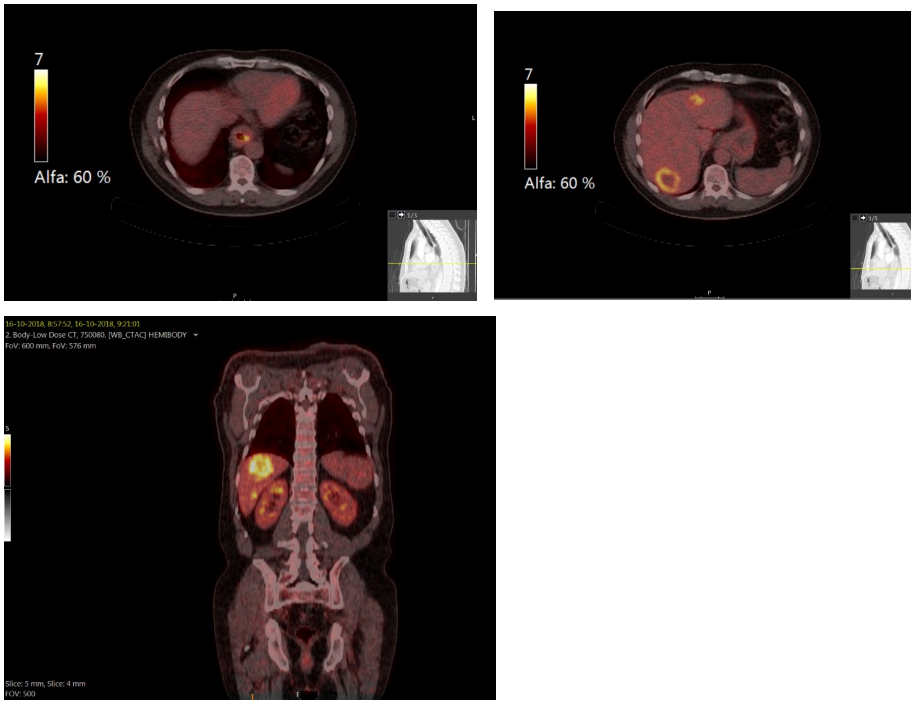

Figure 1. Baseline information of real-life clinical case #3 included in this survey.

treatment), systemic therapy followed by restaging to consider local treatment for oligometastatic disease, or systemic therapy alone (without considering local treatment for oligometastasis later).

Follow-up case 3

Current problem (at follow-up):

- Primary tumor: residual disease (confirmed by endoscopy with bite-on-bite biopsy).
- Liver:
  - Metastasis segment VI/VII: reduction in size, diameter 15 mm (previously 45 mm) and no more FDG-uptake.
  - Metastasis segment IV: no longer visible on imaging (previously diameter 34 mm).
- New right supraclavicular lymph node metastasis
- Rest of the body: no evidence of metastases.

Pathology (right supraclavicular lymph node)

- Adenocarcinoma, Her2/neu –, origin upper gastrointestinal.

Conclusion:

- Primary tumor: residual disease at follow-up (distal esophageal adenocarcinoma).
- Liver:
  - Metastasis segment VI/VII, reduction in size.
  - Metastasis segment IV, no longer visible on imaging at follow-up.
- New right supraclavicular lymph node metastasis.

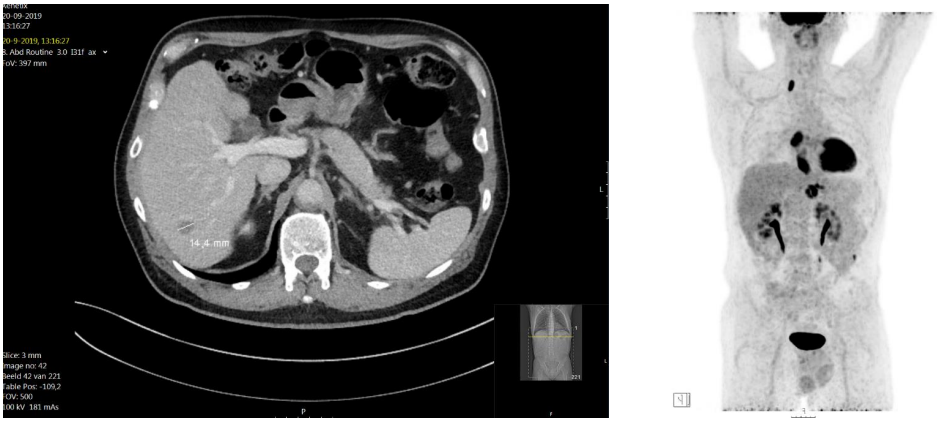

Figure 2. Follow-up information of real-life clinical case #3 included in this survey.

Statistical analysis

Regarding the primary and secondary outcome, the agreement across MDTs was either scored as absent/poor (<50% agreement), fair (50%–75% agreement) or consensus (≥75% agreement), comparable with recent studies on the definition of oligometastatic disease for other tumors[26-28]. According to a recent systemic review, the most common definition for consensus was per cent agreement, with 75% being the median threshold to define consensus among 25 studies[29].

RESULTS

Participant characteristics

A total of 47 MDTs across 16 countries in Europe fully discussed the cases (response rate: 96%). The hospital type was university medical center in 79%, comprehensive cancer center in 15%, and community medical center in 6%. Centers were generally high-volume (i.e. 91% of centers performed >30 esophagectomies or gastrectomies per year). Besides a medical oncologist, surgical oncologist, and radiation oncologist, the following specialities were present at the MDT meetings: a radiologist in 60%, a gastroenterologist in 49%, a pathologist in 40%, and a nuclear medicine physician in 28%. Table 2 shows the characteristics of the participating MDTs.
3.2 Definition of oligometastatic disease

Oligometastatic disease was considered when one or two metastases in either liver, lung, retroperitoneal lymph nodes, adrenal gland, soft tissue, or bone were present (consensus). In addition, oligometastatic disease was considered at restaging after median 18 weeks of systemic therapy when no progression or progression in size only of the oligometastatic lesion(s) was seen (consensus). If at restaging after systemic therapy the number of lesions increased, this was not considered as oligometastatic disease (fair agreement).

The definition of oligometastatic disease was not limited to one lesion, as one lesion or two lesions were considered oligometastatic disease (consensus). Moreover, the definition of oligometastatic disease was not limited to a specific primary tumor treatment status, as a resected or definitively irradiated primary tumor with a subsequent complete response was considered oligometastatic (consensus). Also, the definition of oligometastatic disease was not limited to a specific histology or HER2Neu status, as either HER2Neu positive, HER2Neu mixed, or HER2Neu negative tumor, or with squamous cell carcinoma histology were considered oligometastatic disease (consensus). Finally, the definition of oligometastatic disease was not limited to a particular timing of detection, as synchronous, interval, or metachronous metastasis were considered oligometastatic disease (consensus). Table 3 shows the agreement across MDTs on the definition of oligometastatic esophagogastric cancer.

Restaging of oligometastatic disease

^{18}F-FDG PET/CT imaging was used for restaging after systemic therapy in patients with either lung, retroperitoneal lymph node, adrenal gland, soft tissue, or bone oligometastasis (consensus). For patients with liver oligometastasis, either MRI or ^{18}F-FDG PET/CT imaging was used for restaging after systemic therapy (fair agreement). Table 4 shows the agreement in restaging modalities for oligometastatic esophagogastric cancer.

Table 2. Characteristics of the participating multidisciplinary tumor boards.

Characteristic	n = 47 (%)
Yearly volume of gastrectomies	
1-10	1 (2.1)
11-20	2 (4.3)
21-30	9 (19.1)
31-50	21 (44.7)
>50	14 (29.8)
Yearly volume of esophagectomies	
1-10	5 (10.6)
11-20	4 (8.5)
21-30	4 (8.5)
31-50	11 (23.4)
>50	23 (48.9)
Type of center	
University medical center	37 (78.7)
Comprehensive cancer center	7 (14.9)
Community medical center	3 (6.4)
Work experience >10 years	
Surgical oncologist	45 (95.7)
Medical oncologist	37 (78.7)
Radiation oncologist	35 (74.5)
Additional specialties present at MDT meetings	
Radiologist	28 (59.6)
Gastroenterologist	23 (48.9)
Pathologist	19 (40.4)
Nuclear medicine physician	13 (27.7)
Clinical geneticist	2 (4.3)

Treatment strategies for oligometastatic disease

No consensus on treatment strategies for oligometastatic esophagogastric cancer was identified across presented cases. However, if the number of lesions increased at restaging after a median of 18 weeks of systemic therapy, consensus was reached that systemic therapy should be continued (rather than local treatment for oligometastasis). Upfront local treatment for oligometastatic disease was recommended with a fair agreement for soft tissue oligometastasis, a resected or definitively irradiated primary tumor, or with interval or metachronous HER2Neu negative oligometastasis. Systemic therapy followed by restaging to consider local treatment for oligometastatic disease was recommended with fair agreement for HER2Neu positive or HER2Neu mixed tumors. Local treatment for oligometastatic disease after a median of 18 weeks of systemic therapy was recommended with a fair agreement when no progression (i.e. partial or complete response or stable disease) or progression in size only of the oligometastatic lesion(s) was seen at restaging. Table 5 shows the agreement in treatment strategies for oligometastatic esophagogastric cancer across MDTs.

Table 3. Agreement in definitions of oligometastatic esophagogastric cancer.

Factor	Number of cases	Agreement	Conclusion
Location of oligometastasis			
Liver	3	83 - 100%	Consensus
Lung	2	81 - 100%	Consensus
Retroperitoneal lymph nodes	2	79 - 94%	Consensus
Adrenal gland	2	94 - 100%	Consensus
Soft tissue	2	98 - 100%	Consensus
Bone	2	83 - 89%	Consensus
Neck lymph nodes	2	62 - 72%	Fair agreement
Number of lesions			
One	10	79 - 100%	Consensus
Two	3	81 - 100%	Consensus
Primary tumor treatment			
nCRT and surgery	5	83 - 100%	Consensus
Surgery alone	1	98%	Consensus
Definitive chemoradiotherapy	1	100%	Consensus
Histology and HER2 status			
Her2 positive adenocarcinoma	1	100%	Consensus
Her2 negative adenocarcinoma	7	83-100%	Consensus
Her2 mixed adenocarcinoma*	1	89%	Consensus
Squamous cell carcinoma	4	79-100%	Consensus
Timing of detection			
Synchronous	5	83-94%	Consensus
Interval**	1	79%	Consensus
Metachronous	7	83-100%	Consensus
Restaging after systemic therapy			
No progression***	7	75-100%	Consensus
Progression in size only****	2	97-100%	Consensus
Progression in number of lesions	2	59-60%	Fair agreement

nCRT = neoadjuvant chemoradiotherapy * = difference in HER2neu status of the primary tumor and the metastasis; ** = detected after nCRT before surgery; *** = <20% growth in size and no new lesions; **** = ≥20% growth in size and no new lesions

Table 4. Agreement in restaging modalities for oligometastatic esophagogastric cancer.

Factor	Number of cases	18F-FDG PET/CT	CT	MRI	Agreement
Organ					
Liver	3	67-80%	35-58%	50-70%	Fair agreement
Lung	2	92%	31-36%	0-8%	Consensus
Retroperitoneal lymph nodes	2	83-87%	50-53%	0-33%	Consensus
Adrenal gland	2	100%	40-42%	0%	Consensus
Soft tissue	2	85-97%	31-52%	5-6%	Consensus
Bone	2	85-90%	33-46%	43%	Consensus

^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging

Table 5. Agreement in treatment strategies for oligometastatic disease.

Factor	Number of cases	Upfront local treatment	Systemic therapy to consider local treatment	Systemic therapy	Conclusion
Location of oligometastasis					
Liver	3	0-45%	40-74%	4-26%	No agreement
Lung	2	31-89%	6-47%	0-18%	No agreement
Retroperitoneal lymph nodes	2	2-51%	27-86%	11-14%	No agreement
Adrenal gland	2	2-57%	36-77%	5-20%	No agreement
Soft tissue	2	55-63%	28-43%	0-2%	Fair agreement
Bone	2	33-87%	13-50%	0-14%	No agreement
Number of lesions					
One	10	2-89%	6-86%	0-20%	No agreement
Two	3	8-32%	45-74%	3-26%	No agreement
Primary tumor treatment					
nCRT and surgery	5	8-89%	6-68%	0-21%	No agreement
Surgery alone	1	63%	28%	9%	Fair agreement
Definitive CRT	1	54%	40%	6%	Fair agreement
Histology and HER2 status					
Adenocarcinoma (overall)	9	0-63%	28-70%	0-22%	No agreement
Her2: positive adenocarcinoma	1	8%	70%	22%	Fair agreement
Her2: negative adenocarcinoma	7	0-63%	28-86%	0-26%	No agreement
Her2: mixed adenocarcinoma	1	33%	50%	16%	Fair agreement
Squamous cell carcinoma	4	29-89%	6-45%	0-18%	No agreement
Timing of detection					
Synchronous	5	0-33%	45-86%	11-26%	No agreement
Interval	1	51%	27%	17%	Fair agreement
Metachronous	7	8-89%	6-70%	0-21%	No agreement
Metachronous HER2-	6	54-89%	7-70%	0-21%	Fair agreement
Restaging after systemic therapy					
No progression	7	59-100%	NA	0-14%	Fair agreement
Progression in size only*	2	59-95%	NA	5-41%	Fair agreement
Progression in number of lesions	3	0-21%	NA	79-100%	Consensus

nCRT = neoadjuvant chemoradiotherapy; CRT = chemoradiotherapy; * = i.e. ≥20% growth in size but no new lesions;

DISCUSSION

This is the first study investigating the agreement in the definition and treatment of oligometastatic esophagogastric cancer in European expert centers. Consensus (i.e. ≥75% agreement) across MDTs was reached that the term oligometastatic disease was appropriate across presented cases with esophagogastric cancer with one or two metastases in either liver, lung, retroperitoneal lymph nodes, adrenal gland, soft tissue, or bone. In addition, the term oligometastatic disease remained appropriate at restaging after a median of 18 weeks of systemic therapy when no progression or progression in size only of the oligometastatic lesion(s) was seen. However, in contrast to the consensus on the definition of oligometastatic disease, we found no consensus (i.e. <75% agreement) across MDTs regarding the treatment strategies that should be followed in the case of oligometastatic disease. In fact, a considerable variation in treatment approaches for oligometastatic esophagogastric cancer across European esophagogastric cancer expert centers was exposed. This lack of consensus on treatment strategies can partly be explained by the lack of evidence-based guidelines to guide treatment decision-making and the lack of completed RCTs for oligometastatic esophagogastric cancer.

If oligometastatic disease was no longer considered at restaging after systemic therapy (i.e. the number of lesions increased), a consensus was reached that presented cases should not receive local treatment for oligometastatic disease but rather subsequent systemic therapy. The administration of systemic therapy followed by restaging allows for the identification of patients with (suspected) oligometastatic disease at baseline but with an actual biologically aggressive tumor who might not benefit from local treatment for oligometastatic disease[12]. This treatment protocol is currently being investigated in 2 ongoing phase III RCTs by the Arbeitsgemeinschaft fur Internistische Onkologie (AIO)[5] and the Eastern Cooperative Oncology Group (ECOG)[6]. In both trials, including patients with synchronous oligometastatic gastric or esophagogastric cancer, local treatment for the primary tumor and metastases will be performed at restaging in patients with a partial or complete response after systemic therapy. However, this study identified a fair agreement (i.e. 50-75% agreement) across MDTs that local treatment for oligometastatic disease was also appropriate at restaging after median 18 weeks of systemic therapy when progression in size only of the oligometastatic lesion(s) was seen.

Despite the potential advantage of the administration of systemic therapy first to identify patients who benefit the most from local treatment for oligometastatic disease, which is incorporated in several ongoing RCTs for oligometastatic esophagogastric cancer and German S3 guidelines[5,6,10,15,30], upfront local treatment for oligometastatic disease was recommended with a fair agreement across MDTs for presented cases with soft tissue oligometastasis, a resected or a definitively irradiated primary tumor, metachronous or interval HER2neu negative

tumours. The use of upfront local treatment for oligometastatic disease in these presented cases might be explained by the timing of detection of the oligometastasis (metachronous) and thus after previous systemic therapy for the primary tumor.

A consensus statement for the definition and treatment strategies of oligometastatic esophagogastric cancer could reduce practice variability, increase the quality of care, and offer all patients the optimal treatment approach for oligometastatic disease [31]. The findings of this study (OMEC-2), together with a systematic review on the definition of oligometastatic esophagogastric cancer (OMEC-1), will be used for a multidisciplinary consensus statement on the definition and treatment of oligometastatic esophagogastric cancer (OMEC-4). This consensus statement will result in a prospective study for oligometastatic esophagogastric cancer (OMEC-5).

Strengths of this study include the excellent response rate of 96%, the use of real-life clinical cases, and the distribution of these real-life clinical cases to MDTs of esophagogastric cancer expert centers in Europe, resulting in real-life multidisciplinary (dis)agreement. Therefore, this study provides a largely unbiased reflection of clinical practice and excellent generalizability. However, a limitation was that this study could not address the causes of (dis)agreement, and these causes will be investigated in subsequent steps of the OMEC project.

CONCLUSION

In conclusion, 47 multidisciplinary tumor boards of European esophagogastric cancer expert centers fully discussed 15 real-life clinical cases. A multidisciplinary consensus was identified on the definition of oligometastatic esophagogastric cancer at diagnosis and after systemic therapy. However, no consensus and even high practice variability in treatment decision-making for oligometastatic disease was established. This practice variability could potentially impact on quality of care. The findings of this study and a systematic review on the definition of oligometastatic esophagogastric cancer will be used for a consensus statement on the diagnosis and treatment of oligometastatic esophagogastric cancer in the OMEC project.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8–10. https://doi.org/10.1200/JCO.1995.13.1.8.
2. Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016. https://doi.org/10.1016/S1470-2045(16)30532-0.
3. Palma DA, Olson R, Harrow S, Gaede S, Louie A V., Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019. https://doi.org/10.1016/S0140-6736(18)32487-5.
4. Nguyen Q-N. Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer. ClinicalTrialsGov 2020:1–10. https://clinicaltrials.gov/ct2/show/NCT03161522 (accessed July 11, 2019).
5. Al-Batran S-EE, Goetze TO, Mueller DW, Vogel A, Winkler M, Lorenzen S, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. BMC Cancer 2017;17:893. https://doi.org/10.1186/s12885-017-3918-9.
6. ECOG-ACRIN Cancer Research. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. ClinicaltrialsGov/NCT04248452 2020. https://doi.org/10.31525/ct1-nct04248452.
7. Liu Q, Chen J, Li B, Ye J, Wei S, Wang Y, et al. Local therapy for oligometastatic esophageal squamous cell carcinoma: a prospective, randomized, Phase II clinical trial. Futur Oncol 2021. https://doi.org/10.2217/fon-2020-0873.
8. Xu D. Chemotherapy Alone Versus Surgery Plus Chemotherapy for Distal Gastric Cancer With One Non-curable Factor. ClinicaltrialsGov/NCT03399253 2020:1–7.
9. Zhen-Yu Ding. Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction. Case Med Res 2020. https://doi.org/10.31525/ct1-nct04263870.
10. Guo W. PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment ofUnresectable Locally Advanced or Limited Metastatic Gastric Cancer. ClinicaltrialsGov/NCT04510064 2021.
11. Al-Batran S-EE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. JAMA Oncol 2017;3:1237–44. https://doi.org/10.1001/jamaoncol.2017.0515.
12. Chen Y, Cheng X, Song H, Wu AJ, Ku GY, Lee P, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for esophageal squamous cell cancer patients presenting with oligometastases. J Thorac Dis 2019;11:1536–45. https://doi.org/10.21037/jtd.2019.03.10.
13. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: Final results of a phase III randomized clinical trial. Ann Surg Oncol 2011;18:1575–81. https://doi.org/10.1245/s10434-011-1631-5.
14. Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, et al. Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is Cure a Possibility? Ann Surg Oncol 2016;23:1971–9. https://doi.org/10.1245/s10434-015-5081-3.
15. Moehler M, Al-Batran SE, Andus T, Arends J, Arnold D, Baretton G, et al. S3-Leitlinie Magenkarzinom-Diagnostik und Therapie der Adenokarzinome des Magens und des ösophagogastralen Übergangs. Z Gastroenterol 2019;57:1517–632. https://doi.org/10.1055/a-1018-2516.
16. Wang W, Liang H, Zhang H, Wang X, Xue Q, Zhang R. Prognostic significance of radical surgical treatment for gastric cancer patients with synchronous liver metastases. Med Oncol 2014;31:1–8. https://doi.org/10.1007/s12032-014-0258-3.

17 Wu SG, Zhang WW, He ZY, Sun JY, Chen YX, Guo L. Sites of metastasis and overall survival in esophageal cancer: A population-based study. Cancer Manag Res 2017;9:781–8. https://doi.org/10.2147/CMAR.S150350.
18 Kim JH, Rha SY, Kim C, Kim GM, Yoon SH, Kim KH, et al. Clinicopathologic Features of Metachronous or Synchronous Gastric Cancer Patients with Three or More Primary Sites. Cancer Res Treat 2010;42:217. https://doi.org/10.4143/crt.2010.42.4.217.
19. Goense L, van Rossum PSN, Xi M, Maru DM, Carter BW, Meijer GJ, et al. Preoperative Nomogram to Risk Stratify Patients for the Benefit of Trimodality Therapy in Esophageal Adenocarcinoma. Ann Surg Oncol 2018. https://doi.org/10.1245/s10434-018-6435-4.
20. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–97. https://doi.org/10.1016/S0140-6736(10)61121-X.
21. Plum PS, Gebauer F, Krämer M, Alakus H, Berlth F, Chon SH, et al. HER2/neu (ERBB2) expression and gene amplification correlates with better survival in esophageal adenocarcinoma 11 Medical and Health Sciences 1112 Oncology and Carcinogenesis. BMC Cancer 2019;19:38. https://doi.org/10.1186/s12885-018-5242-4.
22. Tomson CRV, Van Der Veer SN. Learning from practice variation to improve the quality of care. Clin Med J R Coll Physicians London 2013. https://doi.org/10.7861/clinmedicine.13-1-19.
23. Hendriks LEL, Dooms C, Berghmans T, Novello S, Levy A, De Ruysscher D, et al. Defining oligometastatic non-small cell lung cancer: A simulated multidisciplinary expert opinion. Eur J Cancer 2019;123:28–35. https://doi.org/10.1016/j.ejca.2019.09.013.
24. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. Ann Cardiothorac Surg 2017. https://doi.org/10.21037/acs.2017.03.14.
25. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009. https://doi.org/10.1016/j.ejca.2008.10.026.
26. Aluwini SS, Mehra N, Lolkema MP, Oprea-Lager DE, Yakar D, Stoevelaar H, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. Eur Urol Oncol 2019:1–8. https://doi.org/10.1016/j.euo.2019.07.010.
27. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020;21:e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1.
28. Dingemans AMC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. J Thorac Oncol 2019;14:2109–19. https://doi.org/10.1016/j.jtho.2019.07.025.
29. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401–9. https://doi.org/10.1016/j.jclinepi.2013.12.002.
30. Hellingman T, Swart ME d., Meijerink MR, Schreurs WH, Zonderhuis BM, Kazemier G. Optimization of transmural care by implementation of an online expert panel to assess treatment strategy in patients suffering from colorectal cancer liver metastases: A prospective analysis. J Telemed Telecare 2020. https://doi.org/10.1177/1357633X20957136.

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CHAPTER 5

Definition, diagnosis and treatment of oligometastatic esophagogastric cancer: A Delphi consensus study in Europe

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Tiuri E. Kroese, Hanneke W.M. van Laarhoven, Sebastian F. Schoppman, Pieter R.A.J. Deseyne, Eric van Cutsem, Karin Haustermans, Philippe Nafteux, Melissa Thomas, Radka Obermannova, Hanna R. Mortensen, Marianne Nordsmark, Per Pfeiffer, Anneli Elme, Antoine Adenis, Guillaume Piessen, Christiane J. Bruns, Florian Lordick, Ines Gockel, Markus Moehler, Cihan Gani, Theodore Liakakos, John Reynolds, Alessio G. Morganti, Riccardo Rosati, Carlo Castoro, Francesco Cellini, Domenico D'Ugo, Franco Roviello, Maria Bencivenga, Giovanni de Manzoni, Mark I. van Berge Henegouwen, Maarten C.C.M. Hulshof, Jolanda van Dieren, Marieke Vollebergh, Johanna W. van Sandick, Paul Jeene, Christel T. Muijs, Marije Slingerland, Francine E.M. Voncken, Henk Hartgrink, Geert-Jan Creemers, Maurice J.C. van der Sangen, Grard Nieuwenhuijzen, Maaike Berbee, Marcel Verheij, Bas Wijnhoven, Laurens V. Beerepoot, Nadia H. Mohammad, Stella Mook, Jelle P. Ruurda, Piotr Kolodziejczyk, Wojciech P. Polkowski, Lucjan Wyrwicz, Maria Alsina, Manuel Pera, Tania F. Kanonnikoff, Andrés Cervantes, Magnus Nilsson, Stefan Monig, Anna D. Wagner, Matthias Guckenberger, Ewen A. Griffiths, Elizabeth Smyth, George B. Hanna, Sheraz Markar, M Asif Chaudry, Maria A Hawkins, Edward Cheong, Richard van Hillegersberg, Peter S.N. van Rossum, OMEC collaborators

ABSTRACT

Background

Local treatment improves the outcomes for oligometastatic disease (OMD, i.e. an intermediate state between locoregional and widespread disseminated disease). However, consensus about the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer is lacking. The aim of this study was to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer.

Methods

In total, 65 specialists in the multidisciplinary treatment for esophagogastric cancer from 49 expert centers across 16 European countries were requested to participate in this Delphi study. The consensus finding process consisted of a starting meeting, 2 online Delphi questionnaire rounds, and an online consensus meeting. Input for Delphi questionnaires consisted of (1) a systematic review on definitions of oligometastatic esophagogastric cancer and (2) a discussion of real-life clinical cases by multidisciplinary teams. Experts were asked to score each statement on a 5-point Likert scale (1: fully disagree, 5: fully agree). The agreement was scored to be either absent/poor (<50%), fair (50%-75%) or consensus (≥75%).

Results

A total of 48 experts participated in the starting meeting, both Delphi questionnaire rounds, and the consensus meeting (overall response rate: 71%). OMD was considered in patients with metastatic esophagogastric cancer limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station (consensus). In addition, OMD was considered in patients without progression at restaging after systemic therapy (consensus). For patients with synchronous or metachronous OMD with a disease-free interval ≤2 years, systemic therapy followed by restaging to consider local treatment was recommended (consensus). For metachronous OMD with a disease-free interval >2 years, either upfront local treatment or systemic treatment followed by restaging was recommended (fair agreement).

Conclusion

The OMEC project has resulted in a multidisciplinary European consensus statement for the definition, diagnosis, and treatment of oligometastatic esophagogastric adenocarcinoma and squamous cell cancer. This can be used to standardize inclusion criteria for future clinical trials.

INTRODUCTION

Oligometastatic disease (OMD) is defined as an intermediate state between locoregional and widespread systemically metastasized disease[1]. The concept of OMD implies that local treatment for OMD could improve survival outcomes[1,2]. Recently, 2 phase II randomized controlled trials (RCTs) have shown improved overall survival (OS) or progression-free survival (PFS) after local treatment for OMD compared with systemic therapy alone in patients with non-small cell lung cancer (NSCLC)[3,4]. In addition, the phase II stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET) RCT has shown improved OS after local treatment for OMD compared with systemic therapy alone or observation in patients with either NSCLC, prostate, breast or colorectal cancer[5]. Importantly, the results of the SABR-COMET study were confounded by unbalanced key prognostic factors[6]. In the SABR group, more patients had solitary metastasis (46% versus 36%) and prostate cancer (21% versus 6%) than the control group, in which colorectal cancer was more common (27% versus 14%)[5]. Post-hoc sensitivity analysis that excluded patients with prostate cancer was consistent with a treatment benefit for SABR, with 5-year OS rates of 16% versus 33%, respectively (stratified log-rank test p-value = 0.085)[7]. Furthermore, the applicability of the SABR-COMET RCT is unclear because only patients with a disease-free interval >2 years were included, who might form a unique subset of a patients with more favorable characteristics.

RCTs on local treatment for OMD in patients with esophagogastric cancer are ongoing[8-15] and non-randomized trials have suggested improved OS after combining systemic therapy with local treatment for OMD[16-18]. Important to note is that in the prospective fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT-)3 trial[16], the potential benefit of resection of metastases was predominantly demonstrated in patients with gastric or esophagogastric junction adenocarcinoma with retroperitoneal lymph node involvement only whereas patients with liver metastases showed less favorable OS (median OS not reached versus 13.6 months, respectively). Furthermore, interpretation and comparison of individual studies are hampered by different definitions of OMD as well as different treatment strategies. A comprehensive definition of oligometastatic esophagogastric cancer would help to initiate a prospective European clinical trial on the value of local treatment strategies for OMD and/or new systemic agents (e.g. immunotherapy) in this group of patients.

For this purpose, the OligoMetastatic Esophagogastric Cancer (OMEC) project was initiated[19], consisting of five pre-specified subprojects. The current subproject (OMEC-3) builds on the results of a systematic review on the definitions of oligometastatic esophagogastric cancer in the current literature (OMEC-1)[20], and discussion of real-life clinical cases by multidisciplinary

teams of European esophagogastric cancer expert centers (OMEC-2)[21]. The aim of OMEC-3 was to achieve consensus among European esophagogastric cancer experts on the definition, diagnosis, and treatment for oligometastatic esophagogastric cancer using the Delphi consensus methodology.

METHODS

This Delphi consensus study was conducted between 1st of May, 2021, and 30th of April, 2022, to establish consensus on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer. Delphi methodology is a consensus-based technique that systematically collects and aggregates opinions from a group of experts via multiple rounds of questionnaires[22]. This approach has previously been described in the development of a comprehensive nomenclature for OMD[23], as well as for OMD in NSCLC[24]. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. This study was approved by the institutional review board of the UMC Utrecht and the need for informed consent was waived.

Definition of metastatic disease

Distant metastases and extra-regional lymph node metastases were defined according to the American Joint Committee/Union for International Cancer Control (AJCC/UICC) 8th edition staging system[25]. In case extra-regional lymph node stations were not defined according to AJCC/UICC staging system (e.g. extra-regional lymph node metastases along the abdominal aorta)[26], the Japanese lymph node station classification system was used (i.e. lymph node stations 16A1, 16A2, 16B1, or 16B2)[27]. Patients with peritoneal or pleural metastases were not included because these patients were considered to have polymetastatic disease requiring specific treatment (e.g. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy)[35]. Also, patients with brain metastases are not included because these patients often require immediate local treatment[36,37].

Participants

An international European study was conducted as a collaborative project among various European specialists in the treatment of esophagogastric cancer. The consortium consisted of 65 esophagogastric cancer experts from 49 esophagogastric cancer expert centers across 16 European countries, including Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland and the United Kingdom (Table 1).

Table 1. Characteristics of the participating experts in the OMEC consortium.

Characteristic	(n = 65)	(%)
Type of hospital		
Community medical center	5	7.7%
Comprehensive cancer center	8	12.3%
Academic medical center	52	80.0%
Specialty		
Surgical oncology	30	46.2%
Medical oncology	19	29.2%
Radiation oncology	16	24.6%
Work experience		
≤10 years	5	7.7%
>10 years	60	92.3%
Esophagectomies per year per hospital		
<30	12	18.5%
30-50	16	24.6%
>50	37	56.9%
Gastrectomies per year per hospital		
<30	12	18.5%
30-50	30	46.2%
>50	23	35.3%

The esophagogastric cancer experts were suggested by the board members of the European Organisation for Research and Treatment of Cancer (EORTC), European SocieTy for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society for Diseases of the Esophagus (ESDE), the European chapter of the International Gastric Cancer Association (IGCA) and the Dutch Upper GI Cancer Group (DUCG). Additional experts were identified by a systematic review on first or last authors of published RCTs related to esophagogastric cancer between 2015 and 2020.

Input for Delphi consensus rounds

Factors for the definition of OMD in esophagogastric cancer were defined in a two-step process. First, a systematic review on the definitions of oligometastatic esophagogastric cancer was performed in Embase, PubMed and clinicaltrials.gov[20]. This systematic review (OMEC-1) was prospectively registered in the PROSPERO database with the registration number CRD42020205306, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. In this study, it was found that OMD was considered to be limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station in patients with metastatic esophagogastric cancer[20]. In addition, 'organ-specific' OMD burden

could involve bilobar ≤3 liver metastases, unilateral ≤2 lung metastases, 1 extra-regional lymph node station with metastases, ≤2 brain metastases, or bilateral adrenal gland metastases[20].

Second, 15 real-life anonymized clinical cases with metastatic esophagogastric cancer were provided to multidisciplinary tumor boards of esophagogastric cancer expert centers using an online survey tool (Castor EDC, Amsterdam, the Netherlands). The request was to discuss the cases in the local multidisciplinary team (with at least a surgical oncologist, medical oncologist, and radiation oncologist present) to ask for multidisciplinary team responses on whether the case was considered OMD and what the proposed treatment should be[21]. This study (OMEC-2) found a broad consensus among multidisciplinary tumor boards on the definition and diagnosis of OMD[21]. However, no consensus and rather high practice variability was exposed in the treatment strategies to be recommended in the case of OMD[21].

Consensus finding process

The Delphi consensus finding process consisted of a starting meeting following the presentation of the results of OMEC-1[20] and OMEC-2[21] subprojects, 2 online Delphi questionnaire rounds and an online consensus meeting.

OMEC starting meeting (December 2020)

An online starting meeting was hosted for the participants of the OMEC project using Zoom (Zoom Video Communications Inc., San Jose, California, USA). The aim of this starting meeting was (1) to present the results of the OMEC-1[20] and OMEC-2[21] subprojects and (2) to initiate an open discussion to suggest items needed for a multidisciplinary European consensus statement on the definition, diagnosis and treatment for oligometastatic esophagogastric cancer. The discussion was recorded and used to construct the first online Delphi questionnaire.

Delphi questionnaire round 1 (May 2021)

Experts were asked to score 35 statements online on the definition, diagnosis, and treatment for OMD on a 5-point Likert scale (1 fully disagree; 2 disagree; 3 neither disagree nor agree; 4 agree; 5 fully agree) using Google Forms (Google Ireland Limited, Dublin, Ireland). The experts were provided with the results of the OMEC-1 and OMEC-2 subprojects[20,21], and the open discussion of the OMEC starting meeting. Experts could comment on each statement.

Delphi questionnaire round 2 (November 2021)

Experts were asked to score 32 new statements online on the definition and treatment for OMD on a 5-point Likert scale using Google Forms. Consensus was achieved on the diagnosis of OMD in the first Delphi questionnaire round. Experts were provided with the agreements and comments on the statements of the first Delphi questionnaire round and could comment on each statement.

After each Delphi round, 2 authors independently analyzed all collated items. Statements not reaching consensus on the definition of OMD were updated based on the comments of participants or by lowering the number of metastases. For example, if no consensus was reached in the first Delphi questionnaire round that '4 bilobar liver metastases' was OMD. In that case, this statement was updated for the second Delphi questionnaire round to '3 bilobar liver metastases' (i.e. 1 metastasis less). If this updated statement also did not result in consensus, this statement was updated for the Delphi consensus meeting to '2 bilobar liver metastases' (i.e. 1 metastasis less). After each Delphi questionnaire round invitation, a reminder was sent at 2, 4 and 6 weeks, and the Delphi questionnaire round was closed at 8 weeks following the initial invitation.

Delphi consensus meeting (April 2022)

An online consensus meeting was hosted to discuss areas without consensus using Zoom (Zoom Video Communications, San Jose, California, USA). After an extensive discussion, experts were asked to score 11 statements on the definition and treatment for OMD on a 5-point Likert scale. The experts were provided with the agreements and comments on the statements of the second Delphi questionnaire round. The meeting was video recorded.

Statistical analysis

The disease-free interval was defined as the time interval between the completion of primary tumor treatment (surgery or radiotherapy) and the diagnosis of metachronous OMD and was categorized into short (<1 year), intermediate (1–2 years) or long (>2 years). The agreement across each statement was either scored as absent/poor (<50% agreement), fair (50%–75% agreement; demonstrated with ?) or consensus (≥75% agreement; demonstrated with ??), comparable with recent studies on the definition of OMD for other tumors[23,24,28]. This choice was in accordance with a recent systemic review wherein it was reported that the most common definition for consensus in literature was percent agreement, with 75% being the median threshold to define consensus among 25 studies[29]. Response to systemic therapy was analyzed according to the RECIST v1.1 criteria[30].

RESULTS

Participant characteristics

A total of 62 experts participated in the OMEC starting meeting (response rate: 95%), 61 experts in both Delphi questionnaire rounds (response rate: 94%), and 51 experts in the online consensus meeting (response rate: 78%). A total of 48 experts participated in all the steps of this study (overall response rate: 71%). Fig. 1 demonstrates a schematic overview of the Delphi consensus finding process.

Definition of oligometastatic esophagogastric cancer

A consensus (i.e. ≥75% agreement) was reached that OMD in patients with metastatic esophagogastric cancer was limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station. In addition, OMD was considered at restaging after systemic therapy in patients without progression (i.e. stable disease, partial response or complete response[30]; consensus). Finally, organ-specific OMD burden could be limited to bilobar ≤2 liver metastases, unilobar ≤3 liver metastases, unilateral ≤3 lung metastases, unilateral adrenal gland involvement, or 1 metastasis in either soft tissue or bone (consensus).

A fair agreement (i.e. 50–75% agreement) was reached that OMD in patients with metastatic esophagogastric cancer was limited to 1 organ with ≤4 metastases or 2 extra-regional lymph node stations in 1 lymph node compartment (i.e. cervical, thoracic, or abdominal). In addition, OMD was considered at restaging after systemic therapy in patients with progression in size of the existing OMD lesion(s) only (fair agreement). Finally, organ-specific OMD burden could be limited to bilobar ≤3 liver metastases, bilateral ≤2 lung metastases, 2 soft tissue metastases in 1 compartment, or 2 bone metastases in 1 bone (fair agreement). Fig. 2 outlines statements on the definition of oligometastatic esophagogastric cancer with consensus or fair agreement.

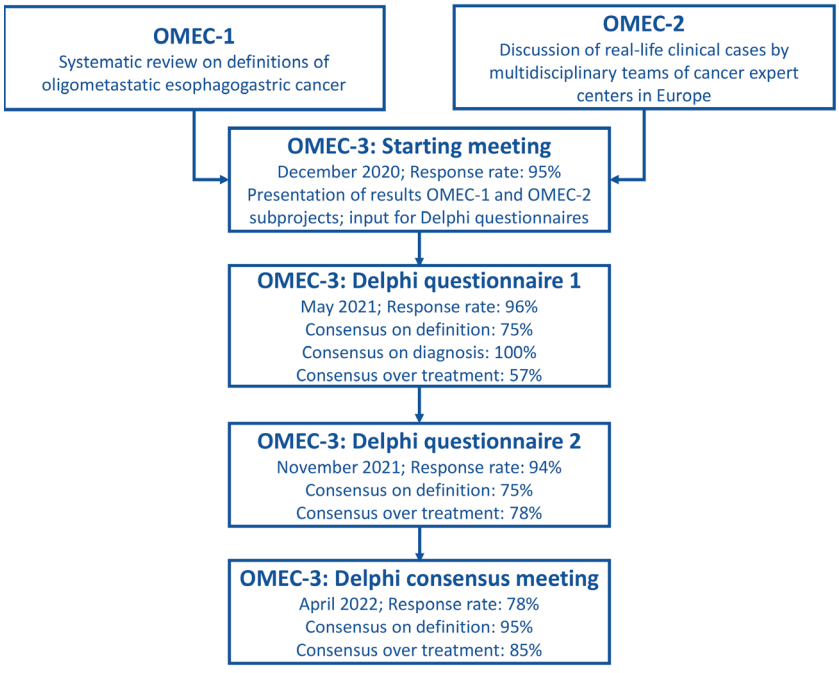

Figure 1. Schematic overview of the Delphi consensus formation.

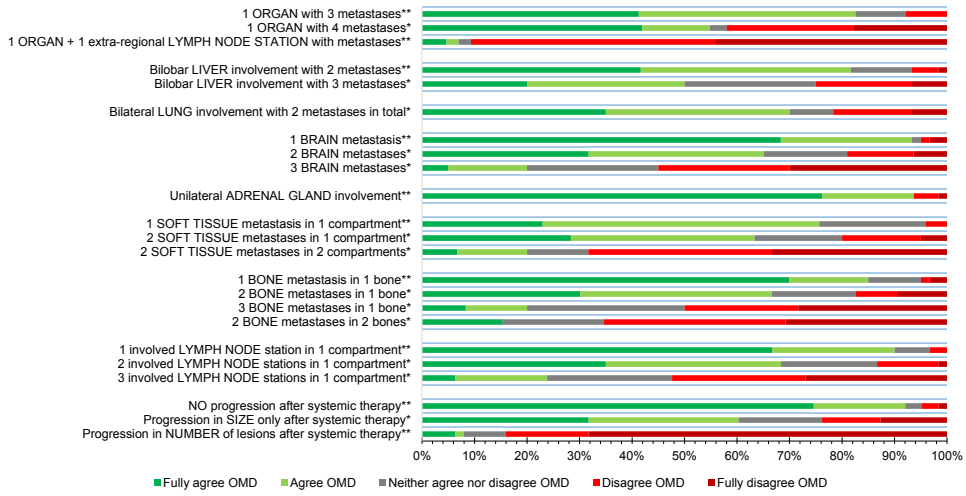

Figure 2. Statements on the definition of oligometastatic esophagogastric cancer with consensus or fair agreement. OMD: Oligometastatic disease.

Diagnosis and treatment of oligometastatic esophagogastric cancer

In patients with metastatic esophagogastric cancer with (suspected) OMD, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging was considered for baseline staging and for restaging after systemic therapy to consider local treatment for OMD (consensus). For patients with synchronous or metachronous OMD with a short or intermediate disease-free interval (i.e. ≤2 years), systemic therapy followed by restaging to consider local treatment for OMD could be considered as treatment (consensus). The type of local treatment modality (e.g. surgery, stereotactic radiotherapy, radiofrequency ablation, or cryoablation) should be decided by the local multidisciplinary team (consensus).

For patients with metachronous OMD with a long disease-free interval (i.e. >2 years), either upfront local treatment for OMD or systemic therapy followed by restaging to consider local treatment for OMD could be considered as suitable treatment approaches (fair agreement). In addition, no consensus on the minimum duration and type of systemic therapy was achieved, although minimum 3 months of triplet chemotherapy could be considered as systemic therapy for patients with oligometastatic esophagogastric cancer (fair agreement). Finally, no consensus on the timing of checkpoint inhibition was achieved, although checkpoint inhibition could be considered after systemic therapy and local treatment for OMD (fair agreement). Fig. 3 outlines statements on the diagnosis and treatment of oligometastatic esophagogastric cancer with consensus or fair agreement.

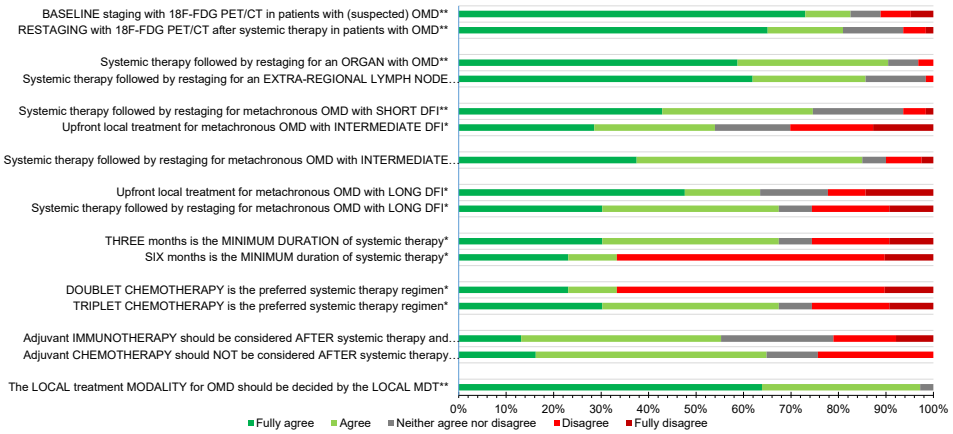

Figure 3. Statements on the diagnosis and treatment of oligometastatic esophagogastric cancer with consensus or fair agreement. OMD: Oligometastatic disease; DFI: disease-free interval; MDT: multidisciplinary team.

DISCUSSION

In this OMEC project, a first multidisciplinary European consensus on the definition, diagnosis, and treatment of oligometastatic esophagogastric adenocarcinoma and squamous cell cancer was developed using the Delphi consensus methodology. The OMEC project has pursued to be as inclusive as possible by creating a consortium of medical oncologists, surgical oncologists, and radiation oncologists from different geographical locations, healthcare systems (i.e. academic centers, comprehensive cancer centers, and community medical centers), work experience and institutional volumes. As these experts were suggested by the medical European oncological societies or were identified by a literature review of published RCTs in patients with esophagogastric cancer, we believe these experts are a good representation of the expert opinions in this field across Europe. The consensus established in this study resulted from a rigorous Delphi formation process. Input for the online Delphi questionnaire rounds consisted of a systematic review on the current literature on definitions of oligometastatic esophagogastric cancer as well as real-life clinical case discussions[20,21]. Furthermore, the Delphi consensus finding process consisted of a starting meeting with an open discussion, 2 online Delphi questionnaire rounds, and an online consensus meeting with an extensive discussion. As such, we believe this consensus formulated by the OMEC group will have good general applicability and generalizability across Europe. This definition and treatment algorithm can be used to carefully design a RCT for patients with oligometastatic esophagogastric cancer in which the control arm could be to continue systemic therapy alone. We acknowledge that for patients with squamous cell carcinoma with the associated higher response rates to

chemoradiotherapy, different choices regarding treatment decision-making could be made (e.g. upfront chemoradiotherapy rather than systemic therapy followed by restaging).

Formerly, esophagogastric oligometastatic esophagogastric cancer was defined case-by-case to argue for individualized treatment. Herein the OMEC project clearly formulated and settled on a clinically relevant consensus (i.e. ≥75% agreement between experts) thus avoiding controversial extremes. The aim of the OMEC project was to identify patients with metastatic esophagogastric cancer for whom the term OMD *should* be considered and who might benefit the most from local treatment of metastases. In addition, the OMEC project identified patients for whom the term OMD *could* be considered (i.e. fair agreement, which was defined as 50–75% agreement). These patients would potentially benefit from local treatment of metastases, but the expected benefit from local treatment for metastases in these patients was considered to be less. This hypothesis is currently being evaluated in the SABR-COMET-10 trial[29]. In this ongoing RCT, patients with 4–10 metastases from various cancers (e.g. prostate, colorectal or renal) are being randomized to either stereotactic body radiotherapy (SBRT) plus standard care palliative treatment or standard of care palliative treatment alone (i.e. no SBRT)[29].

Furthermore, the OMEC project aimed to identify a potential treatment algorithm that could be followed in the case of OMD since the current high practice variability could potentially impact on quality of care[21]. For patients with synchronous or metachronous OMD with disease-free interval ≤2 years, systemic therapy followed by restaging with ^{18}F- FDG PET/CT could be a treatment strategy. These patients with a short or intermediate disease-free interval are a heterogeneous group. Therefore, the so-called 'test-of-time' (i.e. systemic therapy followed by restaging and local treatment in case of response to systemic therapy only) is considered to be necessary for the tumor to show its true biological behavior[38]. For patients with metachronous OMD with a disease-free interval >2 years, either upfront local treatment for OMD or systemic therapy followed by restaging could be a suitable treatment approach. These patients with a disease-free interval >2 years form a less heterogeneous group. Therefore, the 'test-of-time' with systemic therapy is not considered essential for the tumor to show its true biologically behavior. If a patient with OMD who undergoes systemic therapy and at restaging does not develop progression (i.e. stable disease, partial response, or complete response, according to RECIST criteria[30]), local treatment for OMD could be considered. In this light, it is important to note that surveillance protocols after curative primary tumor treatment vary and are inconsistent across Europe[39]. A minority of European centers performs intensive surveillance after surgery (defined as annual CT for 3 years postoperatively) while the majority of centers perform imaging on clinical indication only[39]. Therefore, trials are needed to link the various surveillance strategies to both (metachronous) OMD detection rates and survival outcomes.

Primary tumor treatment was not specified in the OMEC project, which could potentially affect treatment outcomes and result in heterogeneity when comparing results. For primary tumor treatment, we propose to follow the international guidelines on locally advanced esophagogastric cancer which recommends for esophagogastric adenocarcinoma neoadjuvant chemoradiotherapy or perioperative chemotherapy, and for esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy followed by resection or definitive chemoradiotherapy[31-34].

Importantly, ongoing trials in esophagogastric oligometastatic esophagogastric cancer do not include checkpoint inhibition in the treatment algorithm[9,10]. Recent studies have shown that checkpoint inhibition improves OS in the first-line metastatic setting compared with chemotherapy alone[40,41] and disease-free survival (DFS) in the adjuvant setting after an incomplete pathologic response after neoadjuvant chemoradiotherapy plus surgery for locally advanced esophageal cancer[42]. The more effective combinations of chemotherapy with checkpoint inhibition are making secondary local treatment for OMD more likely, even more so in specific patient subpopulations, such as patients with microsatellite instability–high/mismatch repair–deficient[43], and human epidermal growth factor receptor 2 positive tumors[44,45]. Although no consensus on the timing of checkpoint inhibition for OMD was achieved, checkpoint inhibition could be considered after systemic therapy and local treatment for OMD (fair agreement).

Also, on the type and duration of systemic therapy for OMD, no consensus was achieved. Although several studies have demonstrated no benefit for triplet compared with doublet chemotherapy in the metastatic setting[46-49], minimum 3 months of triplet chemotherapy could be considered for patients with oligometastatic esophagogastric cancer (fair agreement), in line with the published FLOT-3 trial[16], the recruiting RENAISSANCE (FLOT-5) trial[9], and the recruiting phase III trial by the Eastern Cooperative Oncology Group (NCT04248452). The RENAISSANCE phase III trial currently evaluates the effect of chemotherapy alone versus chemotherapy followed by surgical resection of the primary tumor and metastases on survival and adverse events in patients with adenocarcinoma of the stomach or esophagogastric junction[9]. Patients without disease progression after 4 FLOT cycles are randomized 1:1 to receive additional chemotherapy or surgical resection of the primary tumor and metastases followed by subsequent chemotherapy[9]. The phase III trial by the Eastern Cooperative Oncology Group currently evaluates the effect of chemotherapy alone versus chemotherapy followed by stereotactic radiotherapy on survival and quality of life in patients with esophagogastric adenocarcinoma in the OMD setting[9]. Patients without disease progression after 4 months of FOLFOX or CapOx cycles are randomized 1:1 to receive additional chemotherapy cycles or radiotherapy to metastases (and the primary tumor) followed by subsequent chemotherapy[10].

The limitations of this study include the lack of evidence (as demonstrated by the systematic review and heterogeneity in multidisciplinary team responses on real-life clinical case discussions[20,21]) and the inclusion of European esophagogastric cancer experts only. Other limitations include the lack of stratification of results for adenocarcinoma versus squamous cell carcinoma histology and esophageal versus gastric cancer, although the differences in management for the metastatic setting appear to be limited since current guidelines recommend first-line systemic therapy for all these patients. Furthermore, the experts of the OMEC project have mainly experience and expertise in Western patients (i.e. patients with esophageal adenocarcinoma, rather than patients with gastric cancer or esophageal squamous cell carcinoma as more often seen in Asia)[50]. Therefore, the consensus statement formulated by the OMEC project might not reflect the view of esophagogastric cancer experts outside of Europe. However, this can also be seen as strength because the consensus statement applies to a well-defined population of European patients. Other strengths include the inclusive and multidisciplinary approach with an endorsement of several European societies in the field of esophagogastric cancer and the structured study protocol.

CONCLUSION

In this OMEC project, a first multidisciplinary European consensus on the definition, diagnosis, and treatment of oligometastatic esophagogastric adenocarcinoma and squamous cell cancer was developed using the Delphi consensus methodology. The aim of the OMEC project was to identify patients for whom OMD could be considered and who might benefit from local treatment of metastases. In addition, the OMEC project identified a promising treatment algorithm that could be followed in the case of OMD. This definition and treatment algorithm can be used to carefully design a RCT for patients with oligometastatic esophagogastric cancer. We acknowledge that for patients with squamous cell carcinoma different choices regarding treatment decision-making may be made.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011;8(6):378-382. doi:10.1038/nrclinonc.2011.44
3. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. Maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol*. 2019. doi:10.1200/JCO.19.00201
4. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4(1). doi:10.1001/jamaoncol.2017.3501
5. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet Oncol*. 2019;393(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5
6. Nguyen Q-N. Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03161522. Published 2020. Accessed July 11, 2019.
7. Al-Batran S-EE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. *BMC Cancer*. 2017;17(1):893. doi:10.1186/s12885-017-3918-9
8. ECOG-ACRIN Cancer Research. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. *clinicaltrials.gov/NCT04248452*. 2020. doi:10.31525/ct1-nct04248452
9. Liu Q, Chen J, Li B, et al. Local therapy for oligometastatic esophageal squamous cell carcinoma: a prospective, randomized, Phase II clinical trial. *Futur Oncol*. 2021. doi:10.2217/fon-2020-0873
10. Xu D. Chemotherapy Alone Versus Surgery Plus Chemotherapy for Distal Gastric Cancer With One Non-curable Factor. *Clinicaltrials.gov/NCT03399253*. 2020:1-7. https://clinicaltrials.gov/ct2/show/study/NCT03399253. Accessed August 13, 2020.
11. Zhen-Yu Ding. Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction. *Case Med Res*. 2020. doi:10.31525/ct1-nct04263870
12. Guo W. PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment ofUnresectable Locally Advanced or Limited Metastatic Gastric Cancer. *clinicaltrials.gov/NCT04510064*. 2021.
13. Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03042169. Accessed August 11, 2022.
14. Al-Batran S-EE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. *JAMA Oncol*. 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
15. Chen Y, Cheng X, Song H, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for esophageal squamous cell cancer patients presenting with oligometastases. *J Thorac Dis*. 2019;11(4):1536-1545. doi:10.21037/jtd.2019.03.10
16. Kroese TE, Buijs GS, Burger MDL, et al. Metastasectomy or Stereotactic Body Radiation Therapy With or Without Systemic Therapy for Oligometastatic Esophagogastric Cancer. *Ann Surg Oncol*. April 2022. doi:10.1245/S10434-022-11541-0
17. Kroese TE, Rossum PSN Van, Nilsson M, et al. European Journal of Surgical Oncology Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project : A multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer. *Eur J Surg Oncol*. 2022. doi:10.1016/j.ejso.2022.09.012

18. Kroese TE, Laarhoven HWM Van, Nilsson M, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment : A systematic review and meta-analysis. *Eur J Cancer*. 2022;166:254-269. doi:10.1016/j.ejca.2022.02.018
19. Kroese TE, van Hillegersberg R, Schoppmann S, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *Eur J Cancer*. 2022;164:18-29. doi:10.1016/j.ejca.2021.11.032
20. Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. *J Clin Epidemiol*. 2003;56(12):1150-1156. doi:10.1016/S0895-4356(03)00211-7
21. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
22. Dingemans AMC, Hendriks LEL, Berghmans T, et al. Definition of Synchronous Oligometastatic Non–Small Cell Lung Cancer—A Consensus Report. *J Thorac Oncol*. 2019;14(12):2109-2119. doi:10.1016/j.jtho.2019.07.025
23. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. *Ann Cardiothorac Surg*. 2017. doi:10.21037/acs.2017.03.14
24. Schuring N, Matsuda S, Hagens ERC, et al. A proposal for uniformity in classification of lymph node stations in esophageal cancer. *Dis Esophagus*. 2021;34(10):1-8. doi:10.1093/dote/doab009
25. Japan Esophageal Society. *Japanese Classification of Esophageal Cancer, 11th Edition: Part II and III*. Vol 14.; 2017. doi:10.1007/s10388-016-0556-2
26. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. *Eur Urol Oncol*. 2019:1-8. doi:10.1016/j.euo.2019.07.010
27. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: A systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. 2014;67(4):401-409. doi:10.1016/j.jclinepi.2013.12.002
28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009. doi:10.1016/j.ejca.2008.10.026
29. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): Study protocol for a randomized phase III trial. *BMC Cancer*. 2019;19(1):1-15. doi:10.1186/s12885-019-5977-6
30. Elliott JA, Markar SR, Klevebro F, et al. An International Multicenter Study Exploring Whether Surveillance After Esophageal Cancer Surgery Impacts Oncological and Quality of Life Outcomes (ENSURE). *Ann Surg*. 2022;Publish Ah. doi:10.1097/sla.0000000000005378
31. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2
32. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398(10302):759-771. doi:10.1016/S0140-6736(21)01234-4
33. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384(13):1191-1203. doi:10.1056/nejmoa2032125
34. Andre T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma (OGA): The GERCOR NEONIPIGA phase II study. *https://doi.org/101200/JCO2022404_suppl244*. 2022;40(4_suppl):244-244. doi:10.1200/JCO.2022.40.4_SUPPL.244
35. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2018;19(10):1372-1384. doi:10.1016/S1470-2045(18)30481-9

36. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature*. 2021;600(7890):727-730. doi:10.1038/s41586-021-04161-3
37. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021. doi:10.3322/caac.21660

CHAPTER 6

European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4)

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Tiuri E. Kroese, Sebastiaan Bronzwaer, Peter S.N. van Rossum, Sebastian F. Schoppman, Pieter R.A.J. Deseyne, Eric van Cutsem, Karin Haustermans, Philippe Nafteux, Melissa Thomas, Radka Obermannova, Hanna R. Mortensen, Marianne Nordsmark, Per Pfeiffer, Anneli Elme, Antoine Adenis, Guillaume Piessen, Christiane J. Bruns, Florian Lordick, Ines Gockel, Markus Moehler, Cihan Gani, Theodore Liakakos, John V. Reynolds, Alessio G. Morganti, Riccardo Rosati, Carlo Castoro, Francesco Cellini, Domenico D'Ugo, Franco Roviello, Maria Bencivenga, Giovanni de Manzoni, Mark I. van Berge Henegouwen, Maarten C.C.M Hulshoff, Jolanda van Dieren, Marieke Vollebergh, Johanna W. van Sandick, Paul Jeene, Christel Muijs, Marije Slingerland, Francine E.M. Voncken, Henk Hartgrink, Geert-Jan Creemers, Maurice J.C. van der Sangen, Grard A.P. Nieuwenhuijzen, Maaike Berbee, Marcel Verheij, Bas Wijnhoven, Laurens V. Beerepoot, Nadia Haj Mohammad, Stella Mook, Jelle P. Ruurda, Piotr Kolodziejczyk, Wojciech P. Polkowski, Lucjan Wyrwicz, Maria Alsina, Josep Tabernero, Manuel Pera, Tania F. Kanonnikoff, Andrés Cervantes, Magnus Nilsson, Stefan Monig, Anna D. Wagner, Matthias Guckenberger, Ewen A. Griffiths, Elizabeth Smyth, George B. Hanna, Sheraz Markar, M. Asif Chaudry, Maria A. Hawkins, Edward Cheong, Hanneke W.M. van Laarhoven, Richard van Hillegersberg

ABSTRACT

Introduction

The OligoMetastatic Esophagogastric Cancer (OMEC) project aims to provide clinical practice guidelines for the definition, diagnosis, and treatment of esophagogastric oligometastatic disease (OMD).

Methods

Guidelines were developed according to AGREE II and GRADE principles. Guidelines were based on a systematic review (OMEC-1), clinical case discussions (OMEC-2), and a Delphi consensus study (OMEC-3) by 49 European expert centers for esophagogastric cancer. The disease-free interval (DFI) was defined as the time between primary tumor treatment and detection of OMD.

Results

Moderate to high quality of evidence was found (i.e. 1 randomized and 4 non-randomized phase II trials) resulting in moderate recommendations. OMD is considered in esophagogastric cancer patients with 1 organ with ≤3 metastases or 1 involved extra-regional lymph node station. In addition, OMD continues to be considered in patients with OMD without progression in number of metastatic sites after systemic therapy. ^{18}F-FDG PET/CT imaging is recommended for baseline staging and for restaging after systemic therapy when local treatment is considered. For patients with synchronous OMD or metachronous OMD and a DFI ≤2 years, recommended treatment consists of systemic therapy followed by restaging to assess suitability for local treatment. For patients with metachronous OMD and DFI >2 years, upfront local treatment is additionally recommended.

Discussion

These multidisciplinary European clinical practice guidelines for the uniform definition, diagnosis, and treatment of esophagogastric OMD can be used to standardize inclusion criteria in future clinical trials and to reduce variation in treatment.

INTRODUCTION

Overall survival in patients with esophagogastric (esophageal or gastric) cancer varies by disease stage[3,4]. Esophagogastric cancer patients with early-stage disease (stage I) have a 72%-75% 5-year survival rate, compared to 18%-47% for those with locally-advanced disease (stage II-III), and 2%-3% for patients with distant metastatic disease (stage IV)[3,4]. Approximately half of esophagogastric cancer patients present with (synchronous) distant metastatic disease at the time of initial presentation[3,4]. In addition, one third of patients develop (metachronous) distant metastatic disease during follow-up after treatment with curative intent[3,4].

A subset of patients with stage IV disease have a limited number of distant metastases, so-called "oligometastatic disease"[11]. The concept of oligometastatic disease was introduced in 1995 by Hellman and Weichselbaum to describe a biological state between localized and polymetastatic disease[11]. The concept of oligometastatic disease suggests that local treatment, for instance through metastasectomy or stereotactic body radiotherapy (SBRT), may prolong time to disease progression and, possibly, overall survival[11]. In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) provided a consensus recommendation on the characterization and classification of oligometastatic disease[20]. In this definition, de-novo oligometastatic disease is defined as the first-time diagnosis of oligometastatic disease without a previous history of polymetastatic disease)[20], and patients with peritoneal or pleural metastases are excluded, as they are considered to have a distinct entity of metastatic disease which may require specific treatment (e.g. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [HIPEC])[9,10,21]. In addition, patients with brain metastases are outside the scope of oligometastatic disease since these patients often require immediate local treatment[22].

Oligometastatic esophagogastric cancer appears to be a significant healthcare burden worldwide. A multicenter retrospective cohort study suggested that the incidence of oligometastatic disease (defined in that study as ≤5 lesions) was 24% among patients with metastatic esophagogastric cancer[23]. Combining local treatment and systemic therapy appears to improve survival outcomes in patients with oligometastatic squamous cell carcinoma[19]. In the ESO-Shanghai 13 randomized controlled trial, patients were randomized to 4 cycles of standard systemic therapy combined with local treatment of oligometastatic disease or systemic therapy alone[19]. The combined treatment resulted in improved progression-free and overall survival[19]. In addition, four non-randomized trials have shown favorable survival after local therapy for oligometastatic disease in patients with esophagogastric cancer[15-19]. Two Chinese studies in patients with esophageal squamous cell carcinoma investigated the value of SBRT for oligometastatic disease[16,18,19]. Median overall survival for patients with esophageal

squamous cell carcinoma who underwent SBRT was 12.8 months[8] and 24.6 months[7], respectively. In addition, 1 German study[5] and 1 Chinese study[6] included patients with gastric adenocarcinoma investigating the value of metastasectomy for oligometastatic disease. The median overall survival in this group was 31.3 months[5] or the median overall survival was not reached after a median follow-up time of 30.0 months[6]. Finally, some studies are still underway[24-32].

The ability to compare and apply findings from published and ongoing trials regarding oligometastatic disease is hindered due to differences in patient characteristics, staging methods, and definition of oligometastatic disease. This study provides clinical practice guidelines on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer following the literature and expert consensus findings of the OligoMetastatic Esophagogastric Cancer (OMEC) project.

METHODS

These clinical practice guidelines were developed in accordance with the AGREE II and GRADE principles for clinical practice guidelines (Supplementary file A)[33,20]. This guideline will be updated in 5 years using the same methodology.

To date, OMEC comprised of three completed subprojects, each detailed in the OMEC study protocol[34]. Firstly, a systematic review of the existing literature was performed on definitions of oligometastatic esophagogastric cancer, and a meta-analysis of survival outcomes following local treatment for oligometastatic esophagogastric cancer (OMEC-1)[35]. Secondly, multidisciplinary teams held discussions of real-life clinical cases from European expert centers, focusing on defining and treating oligometastatic esophagogastric cancer (OMEC-2)[36]. Thirdly, a Delphi consensus study was carried out among the same expert centers, with an initial meeting, 2 Delphi questionnaire rounds, and a final consensus meeting (OMEC-3)[37]. A visual representation of the OMEC subprojects is portrayed in Figure 1. For these clinical practice guidelines, two investigators (TK, SB) performed an updated systematic search independently on November 28, 2023. The search encompassed clinicaltrials.gov and Medline (via PubMed) to identify ongoing trials (i.e. trial protocols) and published phase II-III trials involving patients with oligometastatic esophagogastric cancer. Keywords for this search were ‘esophageal or gastric cancer’, ‘oligometastatic disease’, and synonyms.

The objective of the OMEC definition of oligometastatic disease was twofold. Firstly, it aimed to identify patients for whom the term oligometastatic disease *should be* considered and where a *substantial* benefit from local treatment of oligometastatic disease is expected (as categorized

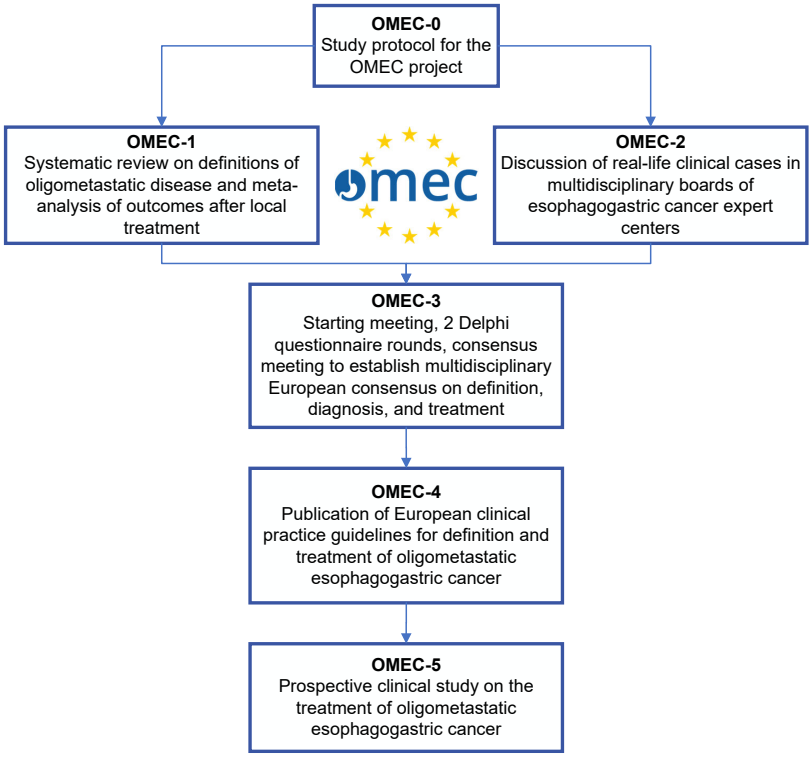

Figure 1. Schematic overview of the OMEC project.

by *consensus* in Delphi rounds). Secondly, it sought to identify patients for whom oligometastatic disease *could* be considered and where *modest* benefit from local treatment of oligometastatic disease is expected (as categorized by *fair agreement* in Delphi rounds)[34].

OMEC is endorsed by the European Societies of Surgical Oncology (ESSO), Medical Oncology (ESMO), and Radiation Oncology (ESTRO), the European Organization for Research and Treatment of Cancer (EORTC), the European Chapter of the International Gastric Cancer Association (IGCA), and the Dutch Upper GI Cancer Group (DUCG)[34].

The OMEC consortium consisted of 69 esophagogastric cancer experts, located in 49 expert centers from 16 countries across Europe[34]. These experts were identified by the European medical oncological societies as experts in the field of oligometastatic esophagogastric cancer or were identified by reviewing first and last authors of randomized trials in the field of esophagogastric cancer[34]. The roles of the various members in the guideline development group are provided in the study protocol[34].

In both the OMEC-2 and OMEC-3 studies, experts were requested to evaluate each statement using a 5-point Likert scale. The level of agreement was scored as either absent/poor (<50%), fair agreement (50%-75%) or consensus (≥75%)[13,38,39]. This threshold for consensus was determined based on a recent systematic review, which indicated that a 75 percent agreement was the median threshold used for defininining consensus in 25 Delphi studies[40].

The disease-free interval (DFI) for metachronous oligometastatic disease was characterized as the duration between the conclusion of primary tumor treatment and the occurrence of metachronous oligometastatic disease. Overall survival was determined as the time between the identification of (oligo)metastatic disease and either death or the last follow-up, whereas progression-free survival was defined as the time between the detection of (oligo)metastatic disease and first progression or last follow-up. Response to systemic therapy was analyzed according to the RECIST v1.1 criteria[41].

RESULTS

Quality of evidence

A total of 1 randomized and 4 non-randomized phase II clinical trials were identified (Table 1). The quality of evidence was scored as high for the randomized controlled trial and as moderate for the 4 non-randomized controlled trials. Therefore, moderate recommendations for the definition, diagnosis and treatment of oligometastatic esophagogastric cancer are provided (according to GRADE-criteria)[20].

Definition of oligometastatic disease

Oligometastatic disease is defined as patients with esophagogastric cancer with 1 organ affected by ≤3 metastases or 1 involved extra-regional lymph node station[23]. In addition, patients with oligometastatic disease at baseline without disease progression in the number of sites after systemic therapy (i.e. stable disease, partial response, or complete response) may continue to be regarded as having oligometastatic disease[37].

The disease is not classified as oligometastatic disease in patients with esophagogastric cancer with both organ and extra-regional lymph node metastases, or in patients with oligometastatic disease at baseline who develop progression in the number of metastases after systemic therapy[37]. Disease progression in size only after ≥3 months of systemic therapy could be considered oligometastatic disease. An organ-specific definition of oligometastatic disease includes ≤3 unilobar liver metastases, ≤3 unilateral lung metastases, unilateral adrenal gland involvement, or 1 bone or soft tissue metastasis.

Recommendations for the definition of oligometastatic esophagogastric cancer

	Oligometastatic disease	Not oligometastatic disease
omec	1 organ with ≤3 metastases (consensus) or 1 involved extra-regional lymph node station (consensus)	Organ metastases and extra-regional lymph node metastases (consensus)
	No progression in number of metastases after ≥3 months of systemic therapy (consensus)	Progression in number of metastases after ≥3 months of systemic therapy (consensus)
	≤3 unilobar liver metastases (consensus)	
	≤3 unilateral lung metastases (consensus)	
	Unilateral adrenal gland involvement (consensus)	
	1 bone metastasis or 1 soft tissue metastasis (consensus)	

Diagnosis of oligometastatic disease

Currently, the primary method for identifying oligometastatic disease and selecting patients for local treatment both at baseline and after systemic therapy involves imaging[42]. Modern imaging modalities, such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) with integrated computed tomography (CT), can detect small metastases, and can therefore assist in distinguishing oligometastatic disease from polymetastatic disease[42].

^{18}F-FDG PET/CT imaging is recommended at baseline for patients with (suspected) oligometastatic disease and ^{18}F-FDG PET-positive tumors to exclude polymetastatic disease[37]. In addition, ^{18}F-FDG PET/CT imaging is recommended at restaging after systemic therapy in patients with ^{18}F-FDG PET-positive tumors to consider local treatment for oligometastatic disease[37].

An important limitation of ^{18}F-FDG PET-staging is that a substantial portion of patients with gastric cancer (especially those with poorly cohesive disease) has ^{18}F-FDG PET-negative disease[43].

Recommendations for the diagnosis of oligometastatic esophagogastric cancer

Baseline staging and restaging after systemic therapy of patients with (suspected) oligometastatic disease and ^{18}F-FDG PET-positive tumor
^{18}F-FDG PET/CT imaging (consensus)

Table 1. Overview of completed and ongoing trials in patients with oligometastatic esophagogastric cancer.

	Author or clinicaltrials.gov ID, year	Primary tumor	Country	Study type	Max organs	Max metastases	OMD type	Staging	Treatment	Median overall survival	GRADE
Completed	Liu. et al., 2023	Esophageal SCC	China	II R	3	4	S+M	CT	ChT +/- IO+ RT/ Surgery vs ChT +/- IO	Not reached after 30 months follow-up vs 18.6 months	High
	Zhao et al., 2023	Esophageal SCC	China	II NR	ns	5	S+M	ns	IO+ChT+ SBRT	12.8 months	Moderate
	Cui et al., 2023	Gastric AC	China	II NR	1	Organ-specific	S	CT or laparoscopy	ChT+Surgery+ChT	Not reached	Moderate
	Liu et al., 2020	Esophageal SCC	Chins	II NR	ns	3	M	CT or ^{18}F-FDG PET	SBRT +/- ChT	24.6 months	Moderate
	Al-Batran et al., 2017	Gastric AC or EGJ AC	Germany	II NR	1 + RPLN	Organ-specific	S	CT/MRI or ^{18}F-FDG PET	ChT+ Surgery	31.3 months	Moderate
Ongoing	NCT04510064	Gastric AC or EGJ AC	China	II NR	1	Organ-specific	S	CT or MRI	IO+ChT+ Surgery	NA	NA
	NCT04248452	Esophageal AC and Gastric	USA	III R	ns	3	S	CT or MRI	ChT + SBRT vs ChT	NA	NA
	NCT03904927	Esophageal SCC	China	II R	2	4	S	CT	ChT + SBRT/ Surgery	NA	NA
	NCT03161522	Esophageal AC	USA	II NR	1	3	S	^{18}F-FDG PET/CT	ChT+ SBRT/Surgery	NA	NA
	NCT03399253	Gastric AC	China	II-III R	2	Organ-specific	S	CT	ChT+Surgery	NA	NA
	NCT02578368	Gastric AC or EGJ AC	Germany	III R	1 + RPLN	Organ-specific	S	CT/MRI or ^{18}F-FDG PET	ChT+Surgery	NA	NA
	NCT04512417	Esophageal SCC or AC	China	II R	ns	4	S+M	ns	IO+ChT+ SBRT	NA	NA
	NCT03042169	Gastric AC or EGJ AC	France	III R	1 + RPLN	Organ-specific	S	CT/MRI or ^{18}F-FDG PET	ChT+ Surgery	NA	NA

AC: adenocarcinoma, CT: computed tomography, ChT: chemotherapy, IO: immune-oncology, M: Metachronous, MRI: magnetic resonance imaging, NA: not applicable, NR: non-randomized, OMD: oligometastatic disease, R: randomized, RPLN: retroperitoneal lymph nodes, S: synchronous, SBRT: stereotactic body radiotherapy, SCC: squamous cell carcinoma, USA: United States of America, ns: not specified, ^{18}F FDG PET: fluorodeoxyglucose position emission tomography, II: phase II, III: phase III.

Treatment of oligometastatic disease

In patients with synchronous oligometastatic disease or patients with metachronous oligometastatic disease and DFI ≤2 years, treatment starts with systemic therapy[37]. In the absence of progression in the number of metastatic sites after systemic therapy after systemic therapy, local treatment is considered for oligometastatic disease and the primary tumor[37]. The local multidisciplinary team decides the type of local treatment for oligometastatic disease (e.g. metastasectomy, radiofrequency, radiofrequency ablation, or SBRT) or has the option to refer the patient to an expertise center for local treatment[28].

Patients with metachronous oligometastatic disease with DFI >2 years may either undergo upfront local treatment for oligometastatic disease, or systemic therapy followed by restaging to consider local treatment for oligometastatic disease[37].

At least 3 months of systemic therapy is recommended for patients with oligometastatic disease before considering local treatment for oligometastatic disease. In addition, after systemic therapy and local treatment for oligometastatic disease, consolidating checkpoint inhibition could be considered[37].

Importantly, these recommendations were not broken down for the histology of the primary tumor (e.g. adenocarcinoma or squamous cell carcinoma, human epidermal growth factor receptor 2 [HER2] positivity, microsatellite instability [MSI], or combined positive score [CPS]). In general, patients should receive the most optimal treatment for metastatic disease as defined in ESMO guidelines[44,45]. Of note, triplet chemotherapy (e.g. fluorouracil, leucovorin, oxaliplatin, and docetaxel [FLOT]) may be considered as a chemotherapy backbone, but no consensus was reached among the experts regarding doublet versus triplet chemotherapy in this setting[37].

Recommendations for the treatment of oligometastatic esophagogastric cancer

Treatment for synchronous or metachronous oligometastatic disease and disease-free interval ≤2 years	Treatment for metachronous oligometastatic disease and disease-free interval >2 years
Systemic therapy followed by restaging to consider local treatment for oligometastatic disease (consensus)	Systemic therapy followed by restaging to consider local treatment for oligometastatic disease (fair agreement)
	or Upfront local treatment for oligometastatic disease (fair agreement)

DISCUSSION

These clinical practice guidelines provide practical recommendations for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer based on moderate to high quality of evidence (1 phase II randomized controlled trial[19], 4 non-randomized trial[15-18]) as well as a systematic review[35], clinical case discussions[36], and Delphi consensus study of European expert centers[37]. These guidelines can be used to identify patients with OMD and to standardize inclusion criteria in future clinical trials. In addition, these guidelines could be an important step into the use of a uniform treatment approach in these patients, addressing the significant variation in treatment approaches that was observed across Europe[36]. However, the guidelines largely reflect the view of European experts and may therefore be more applicable to Western patients (with esophageal or gastric adenocarcinoma) than Asian patients (with esophageal squamous cell carcinoma)[34]. In addition, these guidelines are only applicable to patients with de-novo oligometastatic disease[9,13]. Accordingly, these guidelines are not applicable to patients with repeat oligometastatic disease or induced oligometastatic disease (i.e. patients who underwent systemic therapy for polymetastatic disease and were found to have oligometastatic disease after restaging).

These guidelines are in line with completed or ongoing trials in the field of oligometastatic esophagogastric cancer. The definition of oligometastatic esophagogastric cancer used in the current guideline is in agreement with the literature defining oligometastatic disease as 1 organ affected by ≤3 metastases or 1 involved extra-regional lymph node station[35]. Furthermore, in line with these guidelines, ongoing trials for patients with oligometastatic esophagogastric cancer are predominantly using ^{18}F-FDG PET/CT imaging for baseline staging and for restaging after systemic therapy to consider local treatment for oligometastatic disease[25,29,32]. Regarding the treatment of patients with synchronous oligometastatic disease or those with metachronous oligometastatic disease and DFI ≤2 years, phase III trials are also using systemic therapy followed by restaging to consider local treatment for oligometastatic disease[24,25,32]. Regarding treatment of patients with metachronous oligometastatic disease with DFI >2 years**,** the SABR-COMET trial (in multiple cancer sites) also used upfront combined local treatment (SBRT) and systemic therapy[46].

In the context of oligometastatic disease, it is important to consider 1) primary tumor treatment, 2) local oligometastasis-directed treatment, 3) systemic therapy, and 4) harms or risk. The phase III REGATTA trial, including gastric cancer patients with synchronous oligometastatic disease, has shown that primary tumor resection plus systemic therapy does not improve overall survival compared with systemic therapy alone[14]. Importantly, in this trial a gastrectomy plus D1-lymphadenectomy was performed[14], which is not considered an

adequate lymphadenectomy for gastric cancer patients in the curative setting, and metastases were not locally treated[45]. The negative result of this trial presumably suggests that in case of oligometastatic disease, the primary tumor and all (oligo)metastases may require adequate local treatment. Accordingly, the non-randomized FLOT-3 phase II trial including gastric cancer patients with synchronous oligometastatic disease has shown favorable overall survival in carefully selected patients who underwent gastrectomy with D2 lymphadenectomy and resection of all metastases (i.e. cytoreductive surgery) after responding to ≥4 cycles of FLOT chemotherapy[15]. A single-arm, phase 2 clinical trial found that the incidence of grade ≥3 toxicity after SBRT for oligometastatic prostate, colorectal, breast, or lung cancer was less than 5%[47], suggesting that local treatment for oligometastatic disease can be performed with limited morbidity. Finally, it is important that clinicians and patients discuss potential harms and benefits of treatment and that a shared decision is made.

Up until now, 1 randomized controlled trial in patients with oligometastatic esophagogastric squamous cell cancer has demonstrated a benefit of combined local treatment and systemic as compared with systemic therapy alone for oligometastatic disease[19]. The applicability of this trial for patients with esophagogastric adenocarcinoma is currently unclear because of the higher expected response rates to (chemo)radiotherapy of esophageal squamous cell cancer compared to adenocarcinoma. Therefore, the results of the FLOT-5 (RENAISSANCE) trial including patients with oligometastatic gastric and gastroesophageal junction adenocarcinoma are eagerly awaited[25].

Implementation of these guidelines can pose significant challenges, particularly in low- or middle-income countries. These challenges are primarily attributed to elevated costs and the extended travel distances required for accessing specialized esophagogastric cancer treatment centers. The incremental costs stem from the intensified ^{18}F-FDG PET/CT imaging and additional local treatment (e.g. SBRT or metastasectomy). It is important to note that we have not conducted a formal cost assessment for this guideline, which would have enabled us to evaluate the incremental financial burdens associated with these recommendations when compared to conventional metastatic treatment approaches. However, a recent study from the United States suggested that local treatment with SBRT adds quality-adjusted life years for patients with oligometastatic prostate, colorectal, breast, or lung cancer and represents an intermediate- and long-term cost-effective treatment strategy as compared with standard-of-care alone[48].

In our guidelines, primary tumor treatment was not specified but it is recommended to follow the contemporary ESMO treatment guidelines for locally advanced esophagogastric cancer. These guidelines recommend gastrectomy with D2 lymphadenectomy for patients with gastric

cancer[44] and a transthoracic esophagectomy with adequate two-field lymphadenectomy for patients with esophageal cancer[45].

A growing body of evidence demonstrates an important role for immunotherapy in esophagogastric cancer patients with locally-advanced[49] or metastatic disease[50,51]. The relative benefit and best sequence of immunotherapy and local ablative treatments for different biomarker-defined subgroups of patients needs to be determined by future studies. In addition, future studies should evaluate new methods to select patients for local treatment for oligometastatic disease. Some studies have shown an additional prognostic value of the clearance of circulating tumor DNA[52]. For example, an ongoing phase III trial including patients with oligometastatic disease and esophageal, gastroesophageal junction, gastric, duodenal, or ampullary adenocarcinoma with circulating DNA clearance after systemic therapy, is evaluating the benefit of adding local treatment to systemic therapy for oligometastatic disease compared with continuation of systemic therapy only[53]. For patients who achieve a clinical complete response, local treatment would only take place in case if a biopsy confirmed metastatic disease.

In conclusion, multidisciplinary European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer are presented using the results of OMEC-1[35], OMEC-2[36], and OMEC-3[37]. A consensus was reached that oligometastatic disease is considered in patients with 1 organ affected by ≤3 metastases or 1 involved extra-regional lymph node station and in those with oligometastatic disease at baseline who do not develop progression of disease at restaging after systemic therapy. Patients with synchronous oligometastatic disease or those with metachronous oligometastatic disease and DFI ≤2 years treatment consists of systemic therapy followed by restaging to consider local treatment of oligometastatic disease. Results of randomized controlled trials are warranted to assess the exact value of local treatment for oligometastatic esophagogastric cancer. Patients with metachronous oligometastatic disease and DFI>2 years could also undergo upfront local treatment for oligometastatic disease. ^{18}F-FDG PET/CT imaging is recommended for baseline staging and for restaging after systemic therapy to consider local treatment. This clinical practice guideline requires validation in a clinical study (OMEC-5).

REFFERENCES

1. IKNL. Overlevingscijfers van slokdarmkanker. https://www.kanker.nl/kankersoorten/slokdarmkanker/algemeen/overlevingscijfers-van-slokdarmkanker
2. IKNL. Overlevingscijfers van maagkanker. https://www.kanker.nl/kankersoorten/maagkanker/algemeen/overlevingscijfers-van-maagkanker
3. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. Jan 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
4. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. Jan 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
5. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol*. Jul 2020;148:157-166. doi:10.1016/j.radonc.2020.04.003
6. Kerkar SP, Kemp CD, Duffy A, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. *Trials*. Dec 23 2009;10:121. doi:10.1186/1745-6215-10-121
7. Koemans WJ, van der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). *BMC Cancer*. May 6 2019;19(1):420. doi:10.1186/s12885-019-5640-2
8. Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study. *Radiother Oncol*. Aug 2022;173:269-276. doi:10.1016/j.radonc.2022.06.012
9. Liu Q, Chen J, Lin Y, et al. Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. Nov 16 2023;doi:10.1016/S2468-1253(23)00316-3
10. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol*. Sep 1 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
11. Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? a multicenter, prospective cohort study (Neo-REGATTA). *BMC Cancer*. Apr 4 2023;23(1):308. doi:10.1186/s12885-023-10773-x
12. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. Nov 1 2020;108(3):707-715. doi:10.1016/j.ijrobp.2020.05.003
13. Zhao W, Ke S, Cai X, et al. Radiotherapy plus camrelizumab and irinotecan for oligometastatic esophageal squamous cell carcinoma patients after first-line immunotherapy plus chemotherapy failure: An open-label, single-arm, phase II trial. *Radiother Oncol*. Jul 2023;184:109679. doi:10.1016/j.radonc.2023.109679
14. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. https://classic.clinicaltrials.gov/ct2/show/NCT04248452
15. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer*. Dec 28 2017;17(1):893. doi:10.1186/s12885-017-3918-9
16. PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment of Unresectable Locally Advanced or Limited Metastatic Gastric Cancer. *https://classicclinicaltrialsgov/ct2/show/NCT04510064*. 2020;

17. Local Therapy for Oligorecurrent and Oligometastatic Esophageal Squamous Cell Carcinoma. *https://classicclinicaltrialsgov/ct2/show/NCT03904927*. 2019;
18. Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction (CTSCAPOXSEA). *https://classicclinicaltrialsgov/ct2/show/NCT04263870*. 2020;
19. Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer.
20. Chemotherapy Alone Versus Surgery Plus Chemotherapy for Distal Gastric Cancer With One Non-curable Factor. *https://classicclinicaltrialsgov/ct2/show/NCT03399253*. 2018;
21. A Clinical Study Of Camrelizumab With Or Without Radiotherapy In The Treatment Of Esophageal Cancer. *https://classicclinicaltrialsgov/ct2/show/NCT04512417*. 2020;
22. Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer (SURGIGAST). *https://classicclinicaltrialsgov/ct2/show/NCT03042169*. 2017;
23. Brouwers MC, Kerkvliet K, Spithoff K, Consortium ANS. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ*. Mar 8 2016;352:i1152. doi:10.1136/bmj.i1152
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. Apr 26 2008;336(7650):924-6. doi:10.1136/bmj.39489.470347.AD
25. Kroese TE, van Rossum PSN, Nilsson M, et al. Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project: A multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer. *Eur J Surg Oncol*. Jan 2023;49(1):21-28. doi:10.1016/j.ejso.2022.09.012
26. Kroese TE, van Laarhoven HWM, Nilsson M, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis. *Eur J Cancer*. May 2022;166:254-269. doi:10.1016/j.ejca.2022.02.018
27. Kroese TE, van Hillegersberg R, Schoppmann S, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *Eur J Cancer*. Mar 2022;164:18-29. doi:10.1016/j.ejca.2021.11.032
28. Kroese TE, van Laarhoven HWM, Schoppman SF, et al. Definition, diagnosis and treatment of oligometastatic oesophagogastric cancer: A Delphi consensus study in Europe. *Eur J Cancer*. May 2023;185:28-39. doi:10.1016/j.ejca.2023.02.015
29. Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. *J Thorac Oncol*. Dec 2019;14(12):2109-2119. doi:10.1016/j.jtho.2019.07.025
30. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. *Eur Urol Oncol*. Apr 2020;3(2):231-238. doi:10.1016/j.euo.2019.07.010
31. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol*. Apr 2014;67(4):401-9. doi:10.1016/j.jclinepi.2013.12.002
32. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. Jan 2009;45(2):228-47. doi:10.1016/j.ejca.2008.10.026
33. Lecouvet FE, Oprea-Lager DE, Liu Y, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. *Lancet Oncol*. Oct 2018;19(10):e534-e545. doi:10.1016/S1470-2045(18)30571-0
34. Gertsen EC, Brenkman HJF, van Hillegersberg R, et al. 18F-Fludeoxyglucose-Positron Emission Tomography/Computed Tomography and Laparoscopy for Staging of Locally Advanced Gastric Cancer: A Multicenter Prospective Dutch Cohort Study (PLASTIC). *JAMA Surg*. Dec 1 2021;156(12):e215340. doi:10.1001/jamasurg.2021.5340
35. Obermannova R, Alsina M, Cervantes A, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2022;33(10):992-1004. doi:10.1016/j.annonc.2022.07.003

36. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2022;33(10):1005-1020. doi:10.1016/j.annonc.2022.07.004
37. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol*. Mar 2016;17(3):309-318. doi:10.1016/S1470-2045(15)00553-7
38. Olson R, Jiang W, Liu M, et al. Treatment With Stereotactic Ablative Radiotherapy for Up to 5 Oligometastases in Patients With Cancer: Primary Toxic Effect Results of the Nonrandomized Phase 2 SABR-5 Clinical Trial. *JAMA Oncol*. Nov 1 2022;8(11):1644-1650. doi:10.1001/jamaoncol.2022.4394
39. Mehrens D, Unterrainer M, Corradini S, et al. Cost-Effectiveness Analysis of Local Treatment in Oligometastatic Disease. *Front Oncol*. 2021;11:667993. doi:10.3389/fonc.2021.667993
40. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. Apr 1 2021;384(13):1191-1203. doi:10.1056/NEJMoa2032125
41. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. Aug 28 2021;398(10302):759-771. doi:10.1016/S0140-6736(21)01234-4
42. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. Jul 3 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2
43. Cohen SA, Liu MC, Aleshin A. Practical recommendations for using ctDNA in clinical decision making. *Nature*. Jul 2023;619(7969):259-268. doi:10.1038/s41586-023-06225-y
44. Dhiman A, Vining CC, Witmer HDD, et al. Phase II Prospective, Open-Label Randomized Controlled Trial Comparing Standard of Care Chemotherapy With and Without Sequential Cytoreductive Interventions for Patients with Oligometastatic Foregut Adenocarcinoma and Undetectable Circulating Tumor Deoxyribose Nucleic Acid (ctDNA) Levels. *Ann Surg Oncol*. Jan 5 2022;29(7):4583-92. doi:10.1245/s10434-021-11249-7

PART II

Oligometastatic esophagogastric cancer in clinical practice

CHAPTER 7

Incidence and survival of patients with oligometastatic esophagogastric cancer: a multicenter cohort study

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Tiuri E. Kroese, Sebastian M. Christ, Peter S.N. van Rossum, Matthijs D.L. Burger, George S. Buijs, Urs Mühlematter, Nicolaus Andratschke, Jelle P. Ruurda, Martin Hüllner, Christian A. Gutschow, Richard van Hillegersberg, Matthias Guckenberger

ABSTRACT

Purpose/objective

This multicenter study assessed the incidence and survival of patients with esophagogastric cancer and oligometastatic disease (OMD) in two tertiary referral cancer centers in the Netherlands and Switzerland.

Materials/methods

Between 2010 and 2021, patients with metastatic esophagogastric cancer were identified. Patients with de-novo OMD were included (first-time diagnosis of ≤5 distant metastases on ^{18}F-FDG-PET/CT). Control of the primary tumor was considered in patients who underwent primary tumor resection or definitive chemoradiotherapy without locoregional recurrence. Treatment of OMD was categorized into 1) systemic therapy, 2) local treatment (stereotactic radiotherapy or metastasectomy), 3) local plus systemic therapy, or 4) best supportive care. The primary outcomes were overall survival (OS) and independent prognostic factors for OS. Independent prognostic factors for OS were analyzed using multivariable Cox proportional hazard models.

Results

In total, 830 patients with metastatic esophagogastric cancer were identified of whom 200 patients with de-novo OMD were included (24%). The majority of included patients had esophageal cancer (73%) with adenocarcinoma histology (79%) and metachronous OMD (52%). The primary tumor was controlled in 68%. Treatment of OMD was systemic therapy (25%), local treatment (43%), local plus systemic therapy (13%), or best supportive care (18%). Median follow-up was 14 months (interquartile range: 7-27). Median OS was 16 months (95% confidence interval [CI]: 13-21). Improved OS was independently associated with local plus systemic therapy compared with systemic therapy alone (hazard ratio [HR] 0.47, 95% confidence interval [CI]: 0.25-0.87). Worse OS was independently associated with squamous cell carcinoma (HR 1.70, 95% CI: 1.07-2.74), bone oligometastasis (HR 2.44, 95% CI: 1.28-4.68), brain oligometastasis (HR 1.98, 95% CI: 1.05-4.69), and two metastatic locations (HR 2.07, 95% CI: 1.04-4.12). Median OS after local plus systemic therapy was 35 months (95% CI: 22-NA) as compared with 13 months (95% CI: 9-21, p <0.001) after systemic therapy alone for OMD.

Conclusion

Patients with metastatic esophagogastric cancer present in 24% with de-novo OMD. Local treatment of OMD plus systemic therapy was independently associated with long-term OS and independently improved OS when compared with systemic therapy alone. Randomized controlled trials are warranted to confirm these results.

INTRODUCTION

Oligometastatic disease (OMD) implies that radical local treatment of OMD (e.g., stereotactic body radiotherapy [SBRT] or metastasectomy) could slow down disease progression and improve overall survival (OS)[1]. Indeed, recent randomized controlled trials (RCTs) have demonstrated that local treatment of OMD when compared with systemic therapy alone may improve OS for patients with non-small-cell-lung cancer (NSCLC)[2,3]. In addition, another RCT has shown that local treatment of OMD improves OS when compared with systemic therapy alone or observation in patients with colorectal, breast, prostate, or NSCLC[4].

Up until recently, a consistent definition of OMD did not exist. Therefore, these RCTs included quite inhomogeneous patient cohorts with regards to the number of metastases, metastatic organs involved, and the disease trajectories[2-4]. Recent advances in the characterization of OMD have been made by the European Society for Radiotherapy (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) by developing a consensus classification and nomenclature of OMD[5]. In addition, ESTRO and the American Society for Radiotherapy (ASTRO) convened a committee to establish consensus guidelines regarding the definition of OMD[6]. Currently, de-novo OMD can be defined as the first-time diagnosis of ≤5 safely treatable metastases, without a previous history of polymetastatic disease, and with a controlled primary tumor regarded as optional[6].

For esophagogastric cancer, no consensus has been reached regarding the definition or treatment of OMD. Therefore, the OligoMetastatic Esophagogastric Cancer (OMEC) consortium has initiated the OMEC project to come to a uniform definition. In the OMEC-1 study, the reporting on definitions of oligometastatic esophagogastric cancer in the literature was assessed[7], and in the OMEC-2 study the multidisciplinary tumor boards of 50 esophagogastric cancer expert centers were asked to judge several real-life cases on the definition and treatment of OMD[8]. These results will be used for input into Delphi consensus rounds (OMEC-3) to establish a multidisciplinary European consensus statement on the definition and treatment of oligometastatic esophagogastric cancer (OMEC-4). The lack of a definition might be explained by a lack of RCTs, although a few prospective non-randomized studies have suggested improved OS after local treatment of OMD[9,10]. However, because of the exclusion of OMD patients who underwent systemic therapy alone, these studies do not enable to compare different treatment strategies of OMD[9,10]. In addition, the incidence of de-novo OMD among patients with metastatic esophagogastric cancer remains unclear from both studies[9,10].

Therefore, the primary aims of this European multicenter study were to assess OS and identify independent prognostic factors for OS in patients with esophagogastric cancer and de-novo OMD. Secondary aims were to determine progression-free survival (PFS) and the incidence of de-novo OMD among patients with metastatic esophagogastric cancer.

METHODS

Ethical statement

The institutional review boards of the UMC Utrecht and University Hospital Zurich approved this multicenter study and waived the need for informed consent. This study was performed in accordance with the World Medical Association International Code of Medical Ethics, the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, and the STROBE checklist. The completed STROBE checklist is provided in Supplementary File 1.

Patient inclusion

Between 2010 and 2021, consecutive patients diagnosed at the UMC Utrecht or University Hospital Zurich with metastatic esophagogastric cancer were eligible for inclusion in this European multicenter retrospective cohort study. Patients with synchronous or metachronous de-novo OMD were included. De-novo OMD was defined as the first-time diagnosis of ≤5 safely treatable distant metastases on ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG-PET/CT) without a previous history of polymetastases (i.e. >5 distant metastases, peritoneal or pleural carcinomatosis) in accordance with recommendations by ESTRO, ASTRO, and EORTC[5,6].

Treatment of primary tumor and OMD

Control of the primary tumor was considered in patients who underwent primary tumor resection or definitive chemoradiotherapy without locoregional recurrence. Treatment of OMD was classified into (1) systemic therapy alone, (2) local treatment alone, (3) local plus systemic therapy (concomitant or sequential within 6 months between both treatments), or (4) best supportive care. Systemic therapy comprised immunotherapy, targeted therapy, chemotherapy, or combinations thereof. Local treatment was defined as SBRT, metastasectomy, radiofrequency ablation (RFA), or combinations thereof. Common SBRT schemes were ≥10 Gy per fraction with ≥1 fraction(s), ≥7Gy per fraction with ≥5 fractions, or ≥5 Gy per fraction with ≥10 fractions. Best supportive care could include no treatment of OMD or palliative (e.g., analgesic) radiotherapy only.

Staging

Patients with esophageal cancer underwent baseline staging with ^{18}F-FDG-PET/CT and patients with gastric cancer patients underwent baseline staging with CT and diagnostic laparoscopy in case of clinical advanced disease stage (i.e. ≥cT3 and/or cN+)[11-15]. Follow-up in the Netherlands was performed without standardized imaging and/or endoscopy protocol according to Dutch national guidelines[14,15]. Follow-up in Switzerland was done with standardized

imaging and endoscopy protocol, consisting of contrast-enhanced ^{18}F-FDG-PET/CT or contrast-enhanced CT every 6 months during the first 3 years after primary tumor treatment and subsequently annually ^{18}F-FDG-PET/CT or CT as well as standard annually endoscopies. Clinical and pathological staging was according to TNM 8th edition[16]. Patients with peri-esophageal cervical lymph node metastases were not included because this was considered to be locoregional lymph node metastases (and not extra-regional lymph node metastases) according to TNM 8th edition[16].

OMD characteristics

The location of OMD was classified into an extra-regional lymph node, liver, lung, bone, brain, other solitary organ (i.e. adrenal gland, soft tissue, or appendix), or 2 metastatic locations. The state of OMD was categorized into synchronous (i.e. OMD detected before completion of primary tumor treatment) or metachronous (i.e. OMD detected after completion of primary tumor treatment). The disease-free interval was defined as the time interval between the treatment of the primary tumor and metachronous OMD. The disease-free interval was categorized into ≤24 months, or >24 months[17].

Outcomes

The primary outcomes of this study were OS and prognostic factors for OS. OS was defined as the time interval between the first-time diagnosis of de-novo OMD and death or last follow-up. Prognostic factors for OS were analyzed using multivariable Cox proportional hazard models and expressed with hazard ratios (HRs) with 95% confidence intervals (CIs). Secondary outcomes were PFS and the incidence of de-novo OMD among patients with metastatic esophagogastric cancer. PFS was defined as the time interval between the first-time diagnosis of de-novo OMD and disease progression, death, or last follow-up.

Statistical analyses

Categorical variables were described using frequencies with proportions and compared using Fisher's exact test. Parametric data were described using mean with standard deviation (SD) and were compared using Student's T-test. Non-parametric data were described using median with interquartile range (IQR) and were compared using the Mann-Whitney U test. OS and PFS were determined using Kaplan-Meier curves. Prognostic factors included in the univariable and multivariable Cox proportional hazard model for OS were based on a systemic review on prognostic factors for OS in patients with metastatic esophagogastric cancer[18]. They included age, performance status, histology (adenocarcinoma or squamous cell carcinoma), number of OMD lesions, location of OMD lesions (extra-regional lymph node, lung, liver, bone, brain, other solitary organ [i.e. adrenal gland, soft tissue, or appendix], or 2 metastatic locations), OMD treatment (systemic therapy, local treatment, local plus systemic therapy, or best

supportive care), OMD state (synchronous vs. metachronous), and primary tumor treatment (controlled vs. not controlled)[18]. Complete case analyses were performed. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patient selection

Between 2010 and 2021, 1,607 patients with esophagogastric cancer were screened, of whom 830 patients with metastatic esophagogastric cancer were identified. A total of 200 patients with synchronous or metachronous de-novo OMD were eligible for inclusion. Thus, the incidence of de-novo OMD among patients with metastatic esophagogastric cancer was 24.7%. The incidence of de-novo OMD was 25.7% in the Netherlands and 23.1% in Switzerland and was comparable between hospitals (p = 0.185). A total of five patients with de-novo OMD were lost to follow-up. Consequently, 200 patients were included. Fig. 1 shows the patient inclusion process.

Patients characteristics

Most patients had only 1 organ or 1 extra-regional lymph node station involved (89%). The most common involved solitary organs were liver (n=51), lung (n=23), bone (n=20), brain (n=17), adrenal gland (n=9), soft tissue (n=9), or appendix (n=2). The most common solitary extra-regional lymph node stations involved were retroperitoneal (n=20), supraclavicular (n=14), para-aortic (n=11), or axilla (n=1). Among patients with 2 locations with OMD involved (n=23), most patients had 1 organ and 1 extra-regional lymph node station (n=14) or 2 organs involved (n=9).

The primary tumor was controlled in 66.5%, either after upfront primary tumor resection (9.5%), chemoradiotherapy (10.5%), or neoadjuvant treatment followed by resection (46.5%). In patients with metachronous OMD, the disease-free interval was 10 months (IQR: 5–19). In patients with metachronous OMD, 16.3% of patients had no controlled primary tumor because they did not want to proceed to surgery after neoadjuvant treatment or developed recurrence of the primary tumor. Supplementary File 2 lists the patient characteristics stratified by OMD state (metachronous versus synchronous).

Treatment characteristics

Treatment of OMD was local treatment alone (43.5%), systemic therapy alone (25.0%), local plus systemic (13.5%), or best supportive care (18.0%). Local treatment of OMD consisted of patients undergoing SBRT (21.0% of total), metastasectomy (16.5%), metastasectomy plus

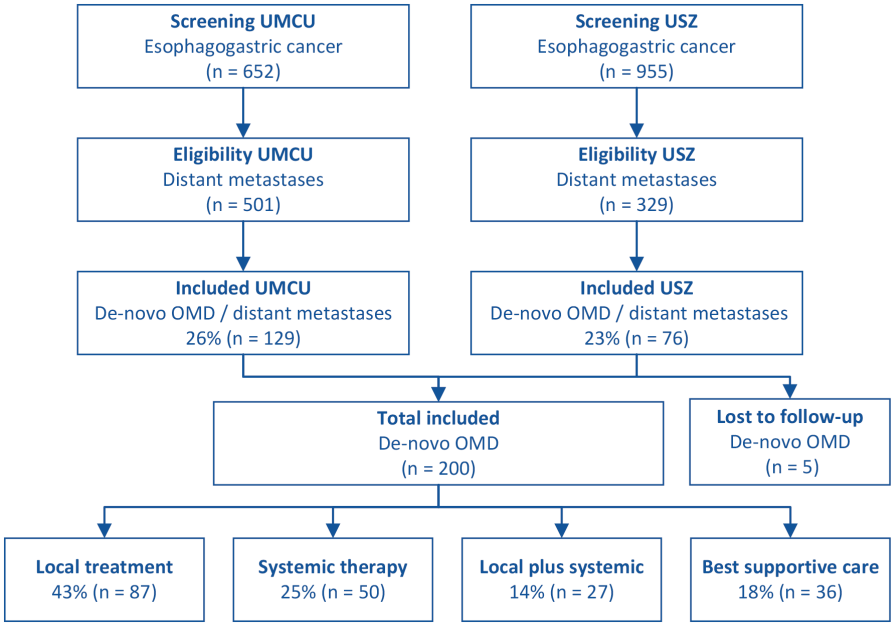

Figure 1. Overview of patient inclusion.

SBRT (4.5%), or RFA (1.5%). Systemic therapy alone consisted of patients undergoing chemotherapy (18.0%) or chemotherapy plus targeted therapy (7.0%). Local treatment plus systemic therapy consisted of patients undergoing systemic therapy plus SBRT (5.0%), metastasectomy (5.0%), or definitive chemoradiotherapy (3.5%). The sequencing of systemic therapy in these patients was before local treatment (8.0%), concomitant (3.5%) or after local treatment (2.0%). Table 2 outlines the treatment characteristics.

Histology, control of primary tumor, and the number of OMD locations were associated with treatment of OMD. Squamous cell carcinoma histology was more common among patients who underwent local treatment of OMD alone as compared with patients undergoing systemic therapy alone or local plus systemic therapy (32.2% versus 10.0% and 7.4%, respectively). Control of the primary tumor was more common among patients who underwent local treatment of OMD, or local plus systemic therapy as compared with patients undergoing systemic therapy alone (90.1% and 81.5% versus 34.0%, respectively). Two metastatic locations were more common among patients who underwent systemic therapy alone as compared with patients who underwent local treatment of OMD alone or local plus systemic therapy (24.0% versus 1.1% or 7.4%, respectively). Supplementary File 3 shows patient characteristics

Table 1. Patient characteristics

		Overall (n = 200)	Missing
Mean age		64 (SD: 10)	
Sex	Male	153 (76.5)	0 (0.0)
	Female	47 (23.5)	
Performance score	WHO 0-1	177 (88.5)	1 (0.5)
	WHO >1	22 (11.0)	
Primary tumor location	Esophagus	146 (73.0)	0 (0.0)
	Cardia	32 (16.0)	
	Stomach	22 (11.0)	
Clinical T stage	T1	13 (6.5)	11 (5.5)
	T2	30 (15.0)	
	T3	127 (63.5)	
	T4	19 (9.5)	
Clinical N stage	N0	53 (26.5)	7 (3.5)
	N1	85 (42.5)	
	N2	36 (18.0)	
	N3	19 (9.5)	
Pathological T stage*	T0	20 (15.2)	1 (0.5)
	pT1	18 (13.6)	
	pT2	17 (12.9)	
	pT3	66 (50.0)	
	pT4	11 (8.3)	
Pathological N stage*	pN0	51 (38.6)	0 (0.0)
	pN1	41 (31.1)	
	pN2	24 (18.2)	
	pN3	15 (11.4)	
Histology	AC	158 (79.0)	0 (0.0)
	SCC	42 (21.0)	
Signet ring cell carcinoma		14 (7.0)	0 (0.0)
Her2Neu positivity		31 (15.5)	0 (0.0)
Differentiation grade	Well	16 (8.0)	52 (26.0)
	Moderate	33 (16.5)	
	Poor	99 (49.5)	
Controlled primary tumor	Yes	136 (68.0)	0 (0.0)
	No	54 (32.0)	
Timing of detection	Synchronous	96 (48.0)	0 (0.0)
	Metachronous	104 (52.0)	
Number of OMD lesions	1	105 (52.5)	0 (0.0)
	2	61 (30.5)	
	3	19 (9.5)	
	4	7 (3.5)	
	5	8 (4.0)	
Number of OMD locations	1	177 (88.5)	0 (0.0)
	2	23 (11.5)	

AC = adenocarcinoma; OMD = oligometastatic disease; SCC = squamous cell carcinoma; * = among patients who had primary tumor resection

stratified by treatment of OMD. Finally, patients undergoing best supportive care had worse performance scores (30.6% versus 6.7%), less often a controlled primary tumor (50.0% versus 72.0%), and more OMD lesions (i.e. ≥3 in 30.5% versus 14.0%) as compared with patients undergoing treatment of OMD. Supplementary File 4 outlines the patient characteristics stratified by best supportive care.

Table 2. Treatment characteristics

Primary tumor treatment	Overall (n = 200)	(%)
Controlled	133	68%
Upfront resection	19	10%
CRT	21	11%
CRT + resection	93	47%
Not controlled	64	32%
Treatment for OMD		
Systemic therapy	50	50
Chemotherapy	36	18%
CapOx	17	9%
FLOT	7	4%
EOX/ECC	6	3%
Other	2	1%
Chemotherapy + targeted therapy	5	3%
CapOx + Trastuzumab	7	1%
FLOT + Trastuzumab	3	2%
Other + Trastuzumab	4	2%
Local treatment	87	43%
Metastasectomy	33	17%
SBRT	42	21%
RFA	3	2%
Metastasectomy + SBRT	9	5%
Local plus systemic	27	14%
Metastasectomy	10	5%
SBRT	10	5%
CRT	7	4%
BSC	36	18%

BSC = best supportive care; CRT = chemoradiotherapy; CapOx = capecitabine and oxaliplatin; FLOT = docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; CROSS = carboplatin and paclitaxel; EOX/ECC = epirubicin, oxaliplatin/ cisplatin, and capecitabine; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy

Table 3. Univariable and multivariable Cox proportional hazard model analyses for overall survival.

	(n=)	Univariable		Multivariable	
WHO performance score		HR (95% CI)	p-value	HR (95% CI)	p-value
0-1	177	reference	reference	reference	reference
>1	22	2.47 (1.54-3.99)	<0.001	1.92 (1.08-3.40)	0.027
Histology					
Adenocarcinoma	158	reference	reference	reference	reference
Squamous cell carcinoma	42	1.31 (0.88-1.97)	0.179	1.60 (1.01-2.52)	0.041
Number of OMD lesions					
1	105	reference	reference	reference	reference
2-3	80	1.18 (0.83-1.67)	0.344	0.86 (0.57-1.29)	0.467
4-5	15	1.06 (1.62-5.19)	<0.001	1.65 (0.88-3.09)	0.119
Location of OMD					
One location					
Extra-regional lymph node	46	reference	reference	reference	reference
Lung or liver	74	1.17 (0.74-1.86)	0.495	1.38 (0.82-2.31)	0.227
Bone or brain	37	1.48 (0.89-2.48)	0.133	2.29 (1.30-4.01)	0.003
Other organ	20	1.27 (0.68-2.37)	0.459	2.11 (1.07-4.16)	0.030
Two separate locations	23	2.12 (1.20-3.73)	0.001	2.08 (1.06-4.10)	0.032
Treatment for OMD					
Systemic therapy	50	reference	reference	reference	reference
Local treatment	87	0.56 (0.37-0.86)	0.007	0.60 (0.35-1.04)	0.070
Local plus systemic	27	0.44 (0.25-0.79)	0.005	0.44 (0.24-0.83)	0.010
Best supportive care	36	2.87 (1.79-4.60)	<0.001	2.27 (1.57-4.75)	<0.001
Disease-free interval					
≤24 months	173	reference	reference	reference	reference
>24 months	27	0.74 (0.48-1.32)	0.376	1.06 (0.62-1.83)	0.833
Primary tumor controlled					
No	64	reference	reference	reference	reference
Yes	136	0.59 (0.42-0.83)	0.003	0.75 (0.48-1.17)	0.212

HR = hazard ratio; 95% CI = 95% confidence interval; OMD = oligometastatic disease

Location of OMD

The location of OMD was either the liver (25.5%), extra-regional lymph nodes (23.0%), lung (11.5%), bone (10.0%), brain (8.5%), or 2 metastatic locations (11.5%). Systemic therapy alone was mostly used for patients with liver metastases (43.1%). Local treatment of OMD alone was predominantly used as treatment of OMD in extra-regional lymph nodes (56.5%), brain (76.5%), bone (50.0%), or lung (60.8%). Finally, local plus systemic therapy was relatively often used for treatment of adrenal gland OMD (44.4%). Supplementary File 5 shows treatment modalities stratified by the location of OMD and Supplementary File 6 shows the applied SBRT schedules with biologically effective dosage using EQD2.

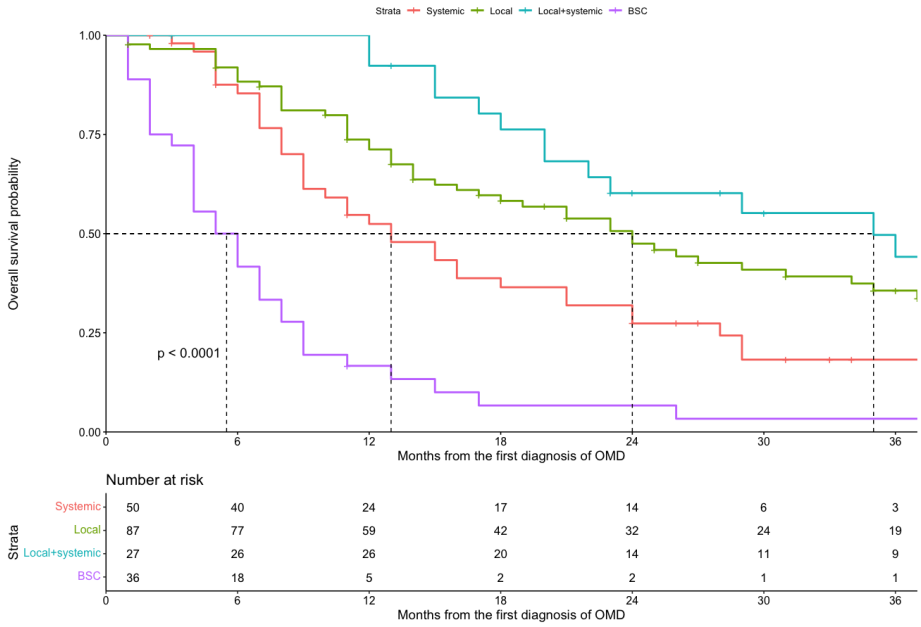

Figure 2. Overall survival stratified by treatment of OMD.

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Overall survival

The median follow-up time was 14 months (IQR: 7–27), and 28% of patients were alive at the end of follow-up. Median follow-up for surviving patients was 25 months (IQR: 13–39). Median OS across all included patients was 16 months (95% CI: 13–21). Supplementary File 7 shows the OS curve of included patients.

In multivariable Cox regression analyses, improved OS was independently associated with local plus systemic therapy as compared with systemic therapy alone of OMD (HR 0.46, 95% CI: 0.25–0.87). Worse OS was independently associated with squamous cell carcinoma histology (HR 1.70, 95% CI: 1.06–2.73), bone oligometastasis (HR 2.65, 95% CI: 1.39–5.06), brain oligometastasis (HR 1.98, 95% CI: 1.05–4.69), 2 metastatic locations (HR 2.24, 95% CI: 1.15–4.35), and best supportive care (HR 2.27 95% CI: 1.57–4.75). Table 3 demonstrates the results of the univariable and multivariable Cox regression analyses for prognostic factors for OS.
Median OS in patients undergoing systemic therapy alone was 13 months (95% CI: 9–21), local treatment 24 months (95% CI: 17–35), local plus systemic therapy 35 months (95% CI: 22-NA), and best supportive care 6 months (95% CI: 4–8; p = <0.001). Fig. 2 represents the OS curve stratified by treatment strategy of OMD.

Median OS in patients with adenocarcinoma was 18 months (95% CI: 15–24) as compared with 13 months (95% CI: 11–29) in patients with squamous cell carcinoma (p = 0.180; Supplementary File 7). Median OS in patients with extra-regional lymph node oligometastasis was 15 months (95% CI: 12–46) as compared with 13 months (95% CI: 9–29) in patients with bone oligometastasis and 11 months (95% CI: 6-NA) in patients with brain oligometastasis (p=0.087, Supplementary File 8).

Finally, median PFS across all patients was 18 months (95% CI: 14–28). Median PFS in patients undergoing systemic therapy alone was 11 months (95% CI: 7-NA), local treatment 16 months (95% CI: 12–28), and local plus systemic 28 months (95% CI: 9-NA; p = 0.56). Fig. 3 shows the PFS stratified by treatment of OMD.

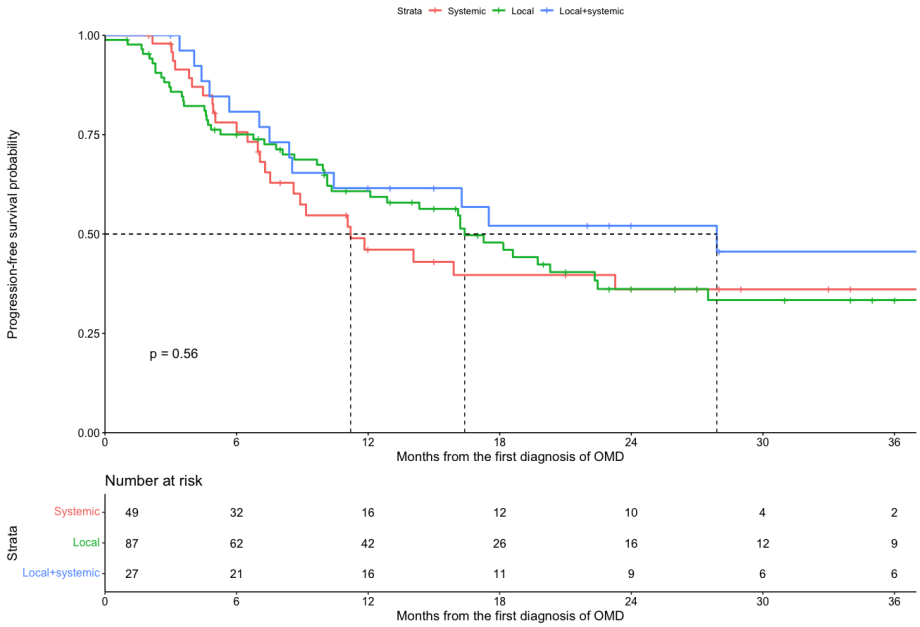

Figure 3. Progression-free survival stratified by treatment.

DISCUSSION

This multicenter study showed that approximately 25% of patients with metastatic esophagogastric cancer had de-novo OMD. This portion was comparable between the two tertiary referral cancer centers in the Netherlands and Switzerland (26% versus 23%), despite

differences in indications for ^{18}F-FDG-PET/CT imaging (i.e., with or without standardized imaging and endoscopy protocol during follow-up, respectively) and referral criteria (i.e., with or without centralization of esophagogastric cancer surgery, respectively). In addition, this study shows that local treatment of OMD plus systemic therapy resulted in long-term PFS and OS and was independently associated with improved OS as compared with systemic therapy alone, after correction for performance status, histology, number and location of OMD lesions, and primary tumor treatment. In fact, local treatment of OMD plus systemic therapy appeared independently associated with a 56% lower chance of death over time as compared with systemic therapy alone. This benefit of the addition of local treatment over systemic therapy alone must be interpreted with caution because the independently improved OS could also be the effect of confounding-by-indication, or the result of unadjusted confounders in multivariable regression analyses. Therefore, randomized trials are warranted to verify these findings.

Despite the favorable OS associated with local treatment plus systemic therapy, only 13% of patients underwent this treatment in our study. This low portion might be explained by the location of oligometastasis since patients with extra-regional lymph node metastases (22% of the total study population) more often underwent local treatment alone than local treatment plus systemic therapy (44% versus 11%). In addition, the low portion of patients who underwent local treatment plus systemic therapy might be explained by the low tumor burden of the patients included in our study since patients with 1 oligometastasis (53% of the total study population) more often underwent local treatment alone than local treatment plus systemic therapy (74% versus 56%) while patients with >1 oligometastases more often underwent local treatment plus systemic therapy than local treatment alone (44% versus 26%). With the knowledge of the current study, more patients will be offered a local treatment for OMD plus systemic therapy, to improve the chances of survival.

The OS of patients included in our study who underwent local treatment of OMD plus systemic therapy (35 months) was comparable with the phase II trial by Al-Batran et al. (median OS 31 months)[9]. In this phase II trial, patients with gastric cancer with OMD with response to fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy underwent resection of the primary tumor and oligometastases[9]. In addition, the results of our study are comparable with the phase II trial by Liu et al. (median OS 25 months)[19]. In this phase II trial, patients with esophageal squamous cell carcinoma with OMD underwent SBRT of oligometastases[19]. The benefit of local treatment of OMD plus systemic therapy over systemic therapy alone could be confirmed in the ongoing RENAISSANCE trial[20]. In this phase III trial, patients with gastric cancer and OMD with response to FLOT chemotherapy will be randomized to either resection of the primary tumor and oligometastases plus FLOT chemotherapy or FLOT chemotherapy alone[20].

Besides the type of treatment of OMD, independent prognostic factors for worse OS identified in the current study were squamous cell carcinoma histology, bone or brain oligometastases, and 2 metastatic locations. Besides squamous cell carcinoma histology, these prognostic factors for worse OS are line with a recent systematic review and meta-analysis on prognostic factors for OS in patients with metastatic esophagogastric cancer[18]. The worse OS in patients with OMD with squamous cell carcinoma as compared with adenocarcinoma histology was in line with an American retrospective cohort study by Nobel et al. on patients with lung, brain, or lung oligometastases after R0 esophagectomy[21]. This study also found that squamous cell carcinoma histology was independently associated with worse OS as compared with adenocarcinoma in the OMD setting (HR 2.63, 95% CI: 1.06–6.52)[21]. This suggests that the improved OS associated with esophageal squamous cell carcinoma as compared with adenocarcinoma histology observed in the locally advanced setting after multimodality treatment (i.e. neoadjuvant chemoradiotherapy plus esophagectomy) is not applicable to the OMD setting[22]. We do not have an explanation for the worse of patients with OMD with squamous cell carcinoma, nor do the authors of the study by Nobel et al.[21]. Future studies are warranted to confirm these results. Furthermore, this study shows that the number of OMD locations (e.g. 1 or 2 organs with metastases) was more important than the total number of OMD lesions, since bone or brain oligometastases or 2 metastatic locations (e.g. 2 organs with metastases) were independently associated with worse OS, while a higher total number of OMD lesions was not.

The results of our study are predominantly applicable to Western countries, since 79% of included patients had an adenocarcinoma while in Eastern countries squamous cell carcinoma histology is more common[23]. Furthermore, the results of our study are applicable to patients with OMD in distant lymph nodes and organs only, since patients with peritoneal or pleural carcinomatosis were not included. Such diffuse lesions were not considered OMD, but rather polymetastatic disease[6], requiring a very specific treatment (e.g. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [HIPEC][24]), which is not comparable to treatment of OMD in distant lymph nodes or organs.

Strengths of our study include its multicenter study design. In addition, our study uniquely not only included patients who underwent local treatment of OMD but also systemic therapy alone or best supportive care, enabling us to compare different current management strategies of OMD. Another strength is the size of the study population, currently representing the largest multicenter study on oligometastatic esophagogastric cancer (to the best of our knowledge). A limitation includes selection bias caused by confounding-by-indication, which could result in an overestimation of OS after treatment of OMD. Another potential limitation is the heterogeneity in the study population, since patients with esophageal or gastric cancer with

synchronous or metachronous OMD were included as well as patients with adenocarcinoma or squamous cell carcinoma histology. However, these differences have been addressed and additional data on these differences are provided in the Supplementary Files.

CONCLUSION

In conclusion, 25% of patients with metastatic esophagogastric cancer with adenocarcinoma or squamous cell carcinoma histology had de-novo OMD. Local treatment of OMD (SBRT or metastasectomy) plus systemic therapy was associated with long-term OS and appeared to improve OS compared with systemic therapy alone in multivariable analyses. However, these results could be confounded by unadjusted confounders in multivariable analyses, or selection bias. Therefore, prospective randomized studies are warranted to confirm these results.

REFERENCES

1. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8:378–82. https://doi.org/10.1038/nrclinonc.2011.44.
2. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. JAMA Oncol 2018;4. https://doi.org/10.1001/jamaoncol.2017.3501.
3. Gomez DR, Tang C, Zhang J, Blumenschein GR, Hernandez M, Jack Lee J, et al. Local consolidative therapy vs. Maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. J Clin Oncol 2019. https://doi.org/10.1200/JCO.19.00201.
4. Palma DA, Olson R, Harrow S, Gaede S, Louie A V., Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet Oncol 2019;393:2051–8. https://doi.org/10.1016/S0140-6736(18)32487-5.
5. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020;21:e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1.
6. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol 2020;148:157–66. https://doi.org/10.1016/j.radonc.2020.04.003.
7. Kroese TE, van Laarhoven HWM, Nilsson M, Lordick F, Guckenberger M, Ruurda JP, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis. Eur J Cancer 2022;166:254–69. https://doi.org/10.1016/j.ejca.2022.02.018.
8. Kroese TE, van Hillegersberg R, Schoppmann S, Deseyne PRAJ, Nafteux P, Obermannova R, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. Eur J Cancer 2022;164:18–29. https://doi.org/10.1016/j.ejca.2021.11.032.
9. Al-Batran S-EE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. JAMA Oncol 2017;3:1237–44. https://doi.org/10.1001/jamaoncol.2017.0515.
10. Liu Q, Zhao K, Chen Y, Lu S. Stereotactic Body Radiotherapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma: Preliminary Results of a Phase 2 Clinical Trial. Int J Radiat Oncol 2019;105:S129. https://doi.org/10.1016/j.ijrobp.2019.06.112.
11. NCCN. NCCN Guidelines: Gastric cancer. Natl Compr Cancer Netw 2019.
12. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 2019. https://doi.org/10.6004/jnccn.2019.0033.
13. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D, Smyth EC, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50–7. https://doi.org/10.1093/annonc/mdw329.
14. Netherlands Cancer Registry. Richtlijn Oesofaguscarcinoom 2017.
15. Netherlands Cancer Registry. Richtlijn Maagcarcinoom 2017.
16. Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. Ann Cardiothorac Surg 2017. https://doi.org/10.21037/acs.2017.03.14.
17. Seesing MFJ, Van Der Veen A, Brenkman HJF, Stockmann HBAC, Nieuwenhuijzen GAP, Rosman C, et al. Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: A nationwide study. Dis Esophagus 2020;32:1–8. https://doi.org/10.1093/dote/doz034.

18. ter Veer E, van Kleef JJ, Schokker S, van der Woude SO, Laarman M, Haj Mohammad N, et al. Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis. Eur J Cancer 2018. https://doi.org/10.1016/j.ejca.2018.07.132.
19. Liu Q, Zhu Z, Chen Y, Deng J, Ai D, Liu Q, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys 2020;108:707–15. https://doi.org/10.1016/j.ijrobp.2020.05.003.
20. Al-Batran S-EE, Goetze TO, Mueller DW, Vogel A, Winkler M, Lorenzen S, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. BMC Cancer 2017;17:893. https://doi.org/10.1186/s12885-017-3918-9.
21. Nobel TB, Sihag S, Xing XX, Eljalby M, Hsu M, Tan KS, et al. Oligometastases After Curative Esophagectomy Are Not One-Size-Fits-All. Ann Thorac Surg 2021. https://doi.org/10.1016/j.athoracsur.2021.03.002.
22. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090–8. https://doi.org/10.1016/S1470-2045(15)00040-6.
23. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021. https://doi.org/10.3322/caac.21660.
24. Rudloff U, Langan RC, Mullinax JE, Beane JD, Steinberg SM, Beresnev T, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: Results of the GYMSSA trial. J Surg Oncol 2014;110:275–84. https://doi.org/10.1002/jso.23633.

CHAPTER 8

Metastasectomy or stereotactic radiotherapy for oligometastatic esophagogastric cancer: a nationwide population-based cohort study

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Tiuri E. Kroese, Nikita K.N. Jorritsma, Hanneke W.M. van Laarhoven, Rob H.A. Verhoeven, Stella Mook, Nadia Haj Mohammad, Jelle P. Ruurda, Peter S.N. van Rossum, Richard van Hillegersberg

ABSTRACT

Background and purpose

This nationwide population-based study analyzed the outcomes of local treatment (i.e. stereotactic body radiotherapy [SBRT] or metastasectomy) or systemic therapy for oligometastatic disease (OMD) in patients with esophagogastric cancer in the Netherlands.

Materials and methods

Between 2015 and 2016, all patients in the Netherlands with esophagogastric cancer and synchronous or metachronous OMD were eligible for inclusion. Patients who underwent local treatment of OMD (SBRT or metastasectomy) and/or systemic therapy were included. OMD was defined as distant metastases in 1 organ or 1 extra-regional lymph node region. The primary outcomes were overall survival (OS) and independent prognostic factors for OS. OS was calculated from diagnosis of OMD. Prognostic factors for OS were analyzed using a multivariable Cox proportional hazard model.

Results

A total of 594 patients were included, of whom 83 underwent local treatment for OMD alone, 22 local treatment plus systemic therapy, and 489 systemic therapy alone. Median OS after local treatment for OMD alone was 16.0 months, local treatment plus systemic therapy 22.7 months, and after systemic therapy alone 8.5 months. Improved OS was independently associated with local treatment for OMD alone or combined with systemic therapy as compared with systemic therapy alone (hazard ratio [HR] 0.52, 95% CI: 0.31–0.90 and HR 0.42, 95% CI: 0.22-0.82, respectively) and a controlled primary tumor (HR 0.48, 95% CI: 0.27–0.86). Worse OS was independently associated with worse performance scores (HR 1.41, 95%: 1.32-1.75), poorly or undifferentiated tumor as compared with good or moderately differentiated tumor (HR 1.37, 95% CI: 1.06-1.76), and peritoneal as compared with lymph mode metastases (HR 1.39, 95% CI: 1.00-1.93).

Conclusion

Local treatment of OMD alone or combined with systemic therapy was independently associated with improved OS as compared with systemic therapy alone in this population-based cohort study in the Netherlands. Randomized controlled trials are warranted to confirm these results.

INTRODUCTION

Gastric and esophageal cancer are the 5th and 7th most common cancers worldwide and the incidence of esophageal cancer is rapidly rising[1]. Approximately 30–50% of patients with esophagogastric cancer (i.e. esophageal or gastric cancer) have metastatic disease at the time of initial diagnosis (i.e. synchronous)[2]. In addition, >30% of patients develop metastatic disease during follow-up after initial primary tumor treatment with curative intent (i.e. metachronous)[3,4]. Patients with metastatic esophagogastric cancer have a poor prognosis, with a median overall survival (OS) between 3 and 9 months[4-6] and are usually treated with systemic therapy or best supportive care[7-10].

In a small portion of metastatic patients, distant metastases are limited in number and distribution, so-called oligometastatic disease (OMD)[11]. OMD reflects a disease state between locoregional and widespread metastatic disease[11]. Randomized controlled trials (RCTs) have shown that local treatment (e.g. metastasectomy or stereotactic body radiotherapy [SBRT]) improves OS as compared with systemic therapy alone in patients with breast, prostate, colorectal, or lung cancer[12,13]. For esophagogastric cancer, phase II trials have suggested improved OS after local treatment of OMD[14,15], which is currently being investigated in RCTs[16-18].

However, the applicability and generalizability of the currently available data from the literature is unclear since clinical trial results cannot always be reproduced in the real-world setting due to strict selection criteria[19]. Therefore, real-world population-based data are a valuable addition to trial results because they deepen the understanding of the outcome of therapies in patients encountered on a day-to-day basis, making results better interpretable in clinical practice[20]. Furthermore, population-based studies enable us to analyze a relatively large population considering the proportion of patients receiving local treatment for OMD is relatively small[21]. Finally, the adoption of local treatment of OMD varies and knowledge on outcomes on a population-based level is currently lacking. Therefore, this study aimed to determine OS and independent prognostic factors for OS after local treatment or systemic therapy for OMD in patients with esophagogastric cancer on a nationwide population-based level.

METHODS AND MATERIALS

Study design

This study included patients registered in the Netherlands Cancer Registry (NCR). The NCR is the only national oncological registry in the Netherlands and provides cancer statistics among all 17.4 million residents. According to the Central Committee on Research involving Human

Subjects, this study did not need approval by an institutional review board in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the scientific committee of the Dutch Upper GI Cancer Group (DUCG). The study was reported according to the guidelines of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary File A)[22].

Patient inclusion

Consecutive patients with synchronous or metachronous metastatic esophagogastric cancer were identified from the NCR between 2015 and 2016 (i.e. according to UICC/AJCC 7th edition as Tx-4b, Nx-N3, M1[18] and according to ICD-10as 15.3–15.5, 15.8, 15.9, and 16.0–16.9)[23]. The years 2015 and 2016 were selected because the NCR registered additional data on metachronous metastases for these years only. OMD was defined as distant metastases in 1 organ or 1 extra-regional lymph node region comparable with a recent systemic review on definitions of oligometastatic esophagogastric cancer in current literature[24]. OMD was not defined by a maximum number of lesions per organ/extra-regional lymph node station because this was not recorded by the NCR. Patients undergoing local treatment of OMD (i.e. SBRT or metastasectomy) or systemic therapy were included. SBRT was defined as radiotherapy according to one of the following radiotherapy schemes: ≥10 Gy per fraction with ≥1 fraction, ≥5 Gy per fraction with ≤12 fractions, or ≥7 Gy per fraction with ≤5 fractions. All other radiotherapy schemes were considered palliative radiotherapy. Patients undergoing palliative radiotherapy were not included. Metastasectomy was defined as surgery, which could include radiofrequency ablation.

Variables

From the NCR patient characteristics were extracted, including sex, age, and WHO performance score. WHO performance score was determined at the time of treatment of OMD. Collected disease characteristics included clinical and pathological disease stage (according to UICC 7th edition[25], histology, tumor differentiation grade, and morphology (i.e. signet ring cell carcinoma). The OMD state was categorized into synchronous or metachronous (defined as before or after completion of primary tumor treatment, respectively[26]. The location of OMD lesions was categorized into a distant organ (e.g. lung, liver, or brain), an extra-regional lymph node region (i.e. head and neck, intra-thoracic, intra-abdominal, axilla, pelvic, multiple locations, or not specified[23], or peritoneal (i.e. peritoneum, ovary, or omentum). Finally, treatment characteristics were extracted, including treatment of the primary tumor and OMD and the type of hospital where this treatment was performed. Hospitals were categorized into ‘academic’, or ‘non-academic’.

Treatment of primary tumor and oligometastasis

The primary tumor was considered controlled in patients who underwent primary tumor resection or definitive chemoradiotherapy (radiotherapy to dose ≥50 Gy with concurrent chemotherapy) without evidence of locoregional recurrence at the time of OMD detection. Treatment of OMD was categorized into 1) local treatment alone (i.e. stereotactic radiotherapy and/or metastasectomy); 2) local treatment plus systemic therapy (i.e. chemotherapy or targeted therapy); 3) systemic therapy alone. The administration of systemic therapy was divided into before or after local treatment of OMD. The first-line systemic therapy regimen administrated after the diagnosis of current OMD was analyzed (i.e. second-line systemic therapy for recurrent or progressive disease was not analyzed).

Outcome

The primary outcomes of this study were OS and prognostic factors for OS. OS was defined as the time interval between the diagnosis of OMD and death or end of follow-up. Vital status was obtained through annual linkage with the municipal population registers and was last updated on January 31, 2021. Prognostic factors for OS were expressed using hazard ratios (HRs) with 95% confidence intervals (CIs). Kaplan-Meier curves were constructed for OS and independent prognostic factors for OS and were compared using log-rank test.

Statistical analysis

Parametric data were presented as mean with standard deviation (SD) and were compared using Student's T test. Non-parametric data were presented as median with interquartile range (IQR) and compared using Mann Whitney U test. Categorical data were presented as frequencies with proportions and compared using Fisher's exact test. Factors previously identified in literature[27] as prognostic factors for OS in metastatic esophagogastric cancer were entered into univariable and multivariable Cox proportional hazard model, which included WHO performance score (WHO 0 versus >0 versus missing)[28], tumor differentiation grade (well/moderate versus poorly/undifferentiated versus missing)[29], histology (adenocarcinoma versus squamous cell carcinoma)[28], OMD state (synchronous versus metachronous)[30], primary tumor treatment status (controlled versus not controlled)[31], treatment of OMD (local treatment versus local treatment plus systemic therapy)[32], and location of OMD (extra-regional lymph node versus peritoneum versus organ)[14]. The disease-free interval for metachronous OMD was defined as the time interval between the diagnosis of the primary tumor and OMD. Complete-case analyses were performed. The median follow-up time was estimated using the reverse Kaplan-Meier estimator (i.e. reverse event indicator). Data were analyzed using R for Windows, version 3.6.3. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Between 2015 and 2016, 4265 patients with synchronous or metachronous metastatic esophagogastric cancer were identified from the NCR, of whom 594 patients who underwent local treatment or systemic therapy for OMD were included. First, the 105 patients undergoing local treatment for OMD with or without systemic therapy will be described. Subsequently, the 489 patients undergoing systemic therapy alone for OMD (Fig. 1).

The 105 included patients who underwent local treatment with or without systemic therapy were generally male (71%) with a mean age of 64 years (SD: ±8) and mostly had a WHO performance score of 0–1 at the time of treatment (62%). The primary tumor was predominantly an adenocarcinoma (80%) located in the distal third of the esophagus (57%). The predominant clinical tumor stage was cT3 (66%) and nodal stage cN1 (45%). For patients who underwent primary tumor resection (n=74), the predominant pathological tumor stage was pT3 (45%) and nodal stage pN0 (45%).

Most patients had metachronous OMD (62%, i.e. OMD detected after primary tumor treatment). OMD was located in 1 distant organ (79%), 1 extra-regional lymph node region (12%), or the peritoneum (9%). The median disease-free interval for metachronous OMD was 17 months (IQR: 14–24) after diagnosis of the primary tumor. OMD was confirmed with pathological assessment (71%) or repeated follow-up imaging (29 %, Table 1).

Primary tumor treatment consisted of surgery in 74 patients (71%), definitive chemoradiotherapy in 12 patients (12%), or no primary tumor treatment in 19 patients (17%). Treatment of OMD consisted of local treatment alone in 83 patients (79%), including stereotactic radiotherapy alone in 34 patients (33%), metastasectomy alone in 35 patients (32%), or both metastasectomy and stereotactic radiotherapy in 14 patients (14%). Local treatment of OMD was combined with systemic therapy in 22 patients (21%), including metastasectomy plus systemic therapy in 14 patients (14%), stereotactic radiotherapy plus systemic therapy in 7 patients (7%), or both metastasectomy and stereotactic radiotherapy plus systemic therapy in 1 patient (1%). Systemic therapy was predominantly administrated before local treatment of OMD (73%) and generally consisted of 2 chemotherapy agents (68%). The most common chemotherapy regimen consisted of capecitabine and oxaliplatin (36%, Table 2).

A total of 64 patients underwent metastasectomy. Metastasectomy was more commonly applied than stereotactic radiotherapy for OMD in the liver (80%), the extra-regional lymph nodes (67%), or the peritoneum (100%). A total of 56 patients underwent stereotactic

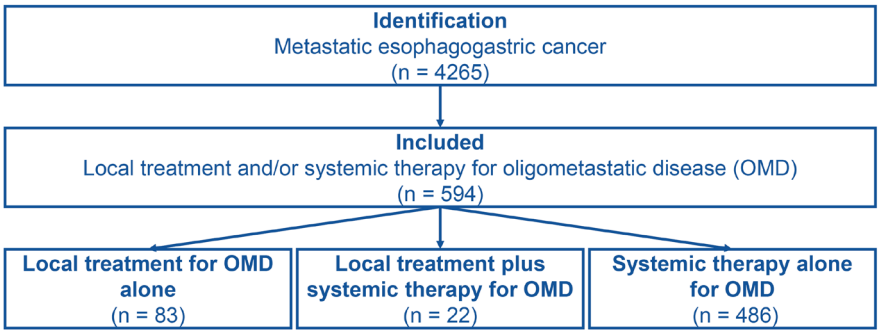

Figure. 1. Flowchart of patient inclusion.

radiotherapy. Applied stereotactic radiotherapy schedules are provided in Supplementary File B. SBRT was more often performed than metastasectomy for OMD in the lung (73%) or bone (75%). Local treatment of OMD plus systemic therapy was common in patients with OMD in the liver (50%) or peritoneum (78%, Supplementary File C).

Patients with synchronous as compared with metachronous OMD less often underwent primary tumor resection (47% versus 87%), more often underwent local treatment of OMD plus systemic therapy (37% versus 10%) and had extra-regional lymph node oligometastases (19% versus 2%). Patients with metachronous as compared with synchronous OMD more often underwent local treatment of OMD alone (90% versus 63%) and had brain oligometastases (45% versus 9%, Supplementary File D).

A total of 489 patients who underwent systemic therapy alone for OMD. Patients who underwent systemic therapy alone for OMD more often had gastric cancer (32% versus 15%, $p<0.001$), synchronous OMD (77% versus 41%, $p<0.001$), liver metastases (37% versus 10%, $p<0.001$), and an uncontrolled primary tumor (63% versus 18%, $p<0.001$) as compared with patients who underwent local treatment for OMD with or without systemic therapy (Table 1 and Table 2).

The median follow-up time for patients undergoing local treatment for OMD with or without systemic therapy was 49.8 months (IQR: 37.2-55.0) and for patients undergoing systemic therapy alone was 59.0 months (IQR: 50.0-62.0). The median OS after local treatment of OMD plus systemic therapy was 22.7 months (95% CI: 14.7-42.6), versus 16.0 months (95% CI: 12.7-21.8) after local treatment of OMD alone, and 8.5 months (95% CI: 7.9-9.6) after systemic therapy alone (Fig. 2).

Table 1. Patient and tumor characteristics of included patients.

Factor	Local +/- systemic therapy (n = 105)	Systemic therapy only (n = 489)	P-value
Mean age in years (±SD)	64 (± 8)	64 (± 10)	0.894
Sex			0.460
Male	75 (71%)	369 (75%)	
Female	30 (29%)	120 (25%)	
WHO performance score			<0.001
0	35 (33%)	119 (24%)	
1	27 (29%)	165 (34%)	
>1	6 (5%)	53 (11%)	
Missing	37 (33%)	152 (31%)	
Location of the primary tumor			<0.001
Upper or middle third esophagus	14 (13%)	51 (10%)	
Lower third esophagus	60 (57%)	187 (38%)	
Esophagus not specified	2 (2%)	14 (3%)	
Gastroesophageal junction / cardia	13 (12%)	80 (16%)	
Stomach	16 (15%)	157 (32%)	
Clinical tumor stage			<0.001
cT1b or cT2	25 (24%)	169 (35%)	
cT3 or cT4	74 (70%)	168 (35%)	
Missing	5 (5%)	102 (21%)	
Clinical nodal stage			0.124
cN0	30 (29%)	121 (25%)	
cN1	48 (46%)	165 (34%)	
cN2 or cN3	26 (25%)	168 (34%)	
Missing	1 (1%)	28 (6%)	
Pathological tumor stage*	Total (n = 74)	Total (n = 89)	0.349
pT0	12 (16%)	8 (9%)	
pT1 or pT2	25 (33%)	37 (42%)	
pT3 or pT4	36 (48%)	42 (47%)	
Missing	1 (1%)	2 (2%)	
Pathological nodal stage**	Total (n = 74)	Total (n = 89)	0.747
pN0	33 (44%)	34 (38%)	
pN1	19 (26%)	22 (25%)	
pN2 or pN3	21 (28%)	22 (25%)	
Missing	1 (1%)	11 (12%)	
Histology of the primary tumor			0.459
Adenocarcinoma	84 (80%)	407 (84%)	
Squamous cell carcinoma	21 (20%)	80 (16%)	
Signet ring cell carcinoma	7 (7%)	42 (9%)	0.695
Differentiation grade			<0.001
Good-moderate	40 (38%)	114 (23%)	
Poor/undifferentiated	46 (44%)	187 (38%)	
Missing	19 (18%)	188 (38%)	
Timing of detection			<0.001

Table 1. Continued

Factor	Local +/- systemic therapy (n = 105)	Systemic therapy only (n = 489)	P-value
Synchronous	43 (41%)	372 (77%)	
Metachronous	62 (59%)	114 (23%)	
Median disease-free interval [IQR]**	17 [14,24]	18 [15,27]	0.546
Location of OMD			<0.001
Distant organ	83 (79%)	298 (61%)	
Brain	32 (30%)	1 (0%)	
Lung	15 (14%)	39 (8%)	
Bone	12 (11%)	17 3%)	
Liver	10 (10%)	182 (37%)	
Soft tissue	8 (8%)	4 1%)	
Other distant organ	6 (6%)	55 (11%)	
Extra-regional lymph nodes	13 (12%)	111 (23%)	
Peritoneum	9 (9%)	80 (16%)	
Confirmation of OMD			<0.001
Histology	75 (71%)	226 (46%)	
Repeated follow-up imaging	30 (29%)	263 (54%)	

IQR = interquartile range; OMD = oligometastatic disease; SD = standard deviation; WHO = World Health Organization; *= For patients with a resected primary tumor; ** = For patients who received resection or definitive chemoradiotherapy of the primary tumor

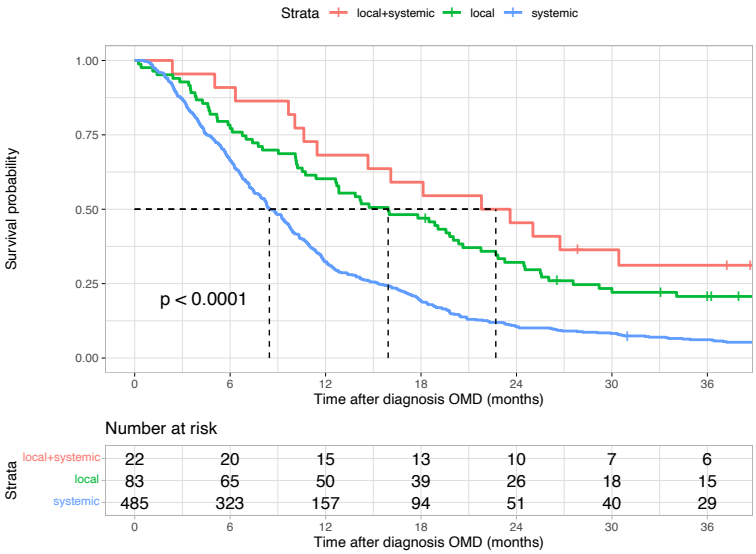

Figure 2. Overall survival curve stratified for treatment of oligometastatic disease.

Table 2. Treatment characteristics of included patients.

Factor	Local +/- systemic therapy (n = 105)		Systemic therapy only (n = 489)	
Treatment of primary tumor				
Surgery	75	71%	79	16%
Esophagectomy	59	55%	51	10%
Gastrectomy	16	15%	28	6%
Definitive chemoradiotherapy	11	12%	103	21%
No treatment	19	18%	307	63%
Treatment of OMD				
Local treatment alone	83	79%	0	0%
SBRT	34	33%	0	0%
Metastasectomy	35	32%	0	0%
Metastasectomy + SBRT	14	14%	0	0%
Systemic therapy plus:	22	21%	0	0%
SBRT	7	7%	0	0%
Metastasectomy	14	14%	0	0%
Metastasectomy + SBRT	1	1%	0	0%
Systemic therapy alone	0	0%	489	100%
Metastasectomy hospital type (n = 64)				
Academic hospital	38	60%	0	0%
Non-academic hospital	26	40%	0	0%
Radiotherapy hospital type (n = 56)				
Academic hospital	36	64%	0	0%
Non-academic hospital	20	36%	0	0%
Sequencing of systemic therapy (n = 22)				
Before local treatment for OMD	16	73%	0	0%
After local treatment for OMD	6	27%	0	0%
Systemic therapy hospital type (n = 489)				
Academic hospital			78	15%
Non-academic hospital			411	85%
First-line systemic therapy	Total (n = 22)		Total (n = 489)	
Monotherapy	0	0%	49	10%
Capecitabine	0	0%	49	10%
Doublet	15	68%	257	53%
CapOx	8	36%	118	24%
Carboplatine/paclitaxel (for metastases)	3	14%	100	20%
FOLFOX	2	9%	39	8%
Other	2	10%	27	6%
Triplet	6	27%	83	17%
EOX/EOC	6	27%	59	12%
ECC/ECX	0	0%	8	2%
DOC	0	0%	8	2%
ECF	0	0%	8	2%
Targeted therapy (trastuzumab)	1	1%	73	15%

CapOx = Capecitabine/oxaliplatin; DOC = Docetaxel/oxaliplatine/capecitabine; ECF = Epirubicine/cisplatine/5-fluorouracil; ECC/ECX = Epirubicine/cisplatine/capecitabine; EOX/EOC = Epirubicine/oxaliplatine/capecitabine; FOLFOX = 5-FU/oxaliplatin/leucovorin; OMD = oligometastatic disease; SBRT = stereotactic radiotherapy

Table 3. Results of univariable and multivariable Cox proportional hazard models for overall survival.

		Univariable		Multivariable	
	n=	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuous)		1.00 (0.99 - 1.02)	0.079	1.28 (1.00 - 1.02)	0.018
Performance score					
WHO 0	154	Reference	-	Reference	-
WHO >0	195	1.38 (1.11 - 1.72)	0.004	1.41 (1.32 - 1.75)	0.033
Missing	187	1.37 (1.10 - 1.72)	0.005	1.37 (1.09 - 1.73)	0.008
Tumor location					
Esophagus	328	Reference	-	Reference	-
Stomach	266	1.29 (1.10 - 1.53)	0.002	0.82 (0.57 - 1.01)	0.051
Clinical tumor stage					
cT1b or cT2	193	Reference	-	Reference	-
cT3	238	1.32 (0.62 - 0.92)	0.005	0.90 (0.73 - 1.12)	0.348
cT4	47	0.94 (0.77 - 1.47)	0.718	1.07 (0.77 - 1.51)	0.677
Missing	116	0.78 (1.00 - 1.61)	0.047	1.03 (0.80 - 1.33)	0.806
Clinical nodal stage					
cN0	151	Reference	-	Reference	-
cN1	213	0.78 (0.63 - 0.97)	0.029	0.80 (0.59 - 1.00)	0.050
cN2 or cN3	194	0.99 (0.80 - 1.24)	0.962	0.88 (0.69 - 1.12)	0.295
Missing	36	1.74 (1.20 - 2.50)	0.003	1.18 (0.81 - 1.72)	0.400
Histology					
Squamous cell carcinoma	491	Reference	-	Reference	-
Adenocarcinoma	101	1.32 (1.06 - 1.66)	0.015	1.18 (0.81 – 1.72)	0.227
Signet ring cell carcinoma					
No	545	Reference	-	Reference	-
Yes	49	0.68 (0.51 - 0.92)	0.011	1.03 (0.94 - 1.79)	0.170
Differentiation grade					
Good-moderate	114	Reference	-	Reference	-
Poor/undifferentiated	187	1.32 (1.04 – 1.67)	0.022	1.37 (1.06 - 1.76)	0.015
Missing	293	0.70 (0.56 - 0.87)	0.002	1.09 (0.85 - 1.40)	0.479
Timing of detection					
Synchronous	415	Reference	-	Reference	-
Metachronous	176	0.95 (0.62 - 1.46)	0.769	1.06 (0.85 – 1.32)	0.690
Location of OMD					
Extra-regional lymph node	124	Reference	-	Reference	-
Distant organ	320	1.03 (0.83 - 1.28)	0.791	1.08 (0.85 - 1.38)	0.529
Peritoneum	129	1.62 (1.26 – 2.09)	<0.001	1.39 (1.01 - 1.93)	0.047
Primary tumor controlled					
No	505	Reference	ref	Reference	ref
Yes	86	0.78 (0.44 - 1.36)	0.376	0.48 (0.27 - 0.86)	0.013
Treatment for OMD					
Systemic	486	Reference	-	Reference	-
Local	832	0.32 (0.24 - 0.41)	<0.001	0.52 (0.31 - 0.90)	0.018
Local + Systemic	22	0.32 (0.19 - 0.52)	<0.001	0.42 (0.22 - 0.82)	0.011

OMD = oligometastatic disese

Improved OS was independently associated with local treatment of OMD alone or combined with systemic therapy as compared with systemic therapy alone (HR 0.52, 95% CI: 0.31-0.90 and HR 0.42, 95% CI: 0.22-0.82, respectively), and a controlled primary tumor versus uncontrolled primary tumor (HR 0.48, 95% CI: 0.27-0.86; Supplementary File H).

DISCUSSION

This nationwide population-based cohort suggests that local treatment of OMD alone or combined with systemic therapy can be a preferred treatment approach for patients with oligometastatic esophagogastric cancer since this treatment approach was independently associated with improved OS as compared with systemic therapy of OMD alone (median OS of 16.0 months or 22.7 months versus 8.5 months). However, these results must be interpreted with care because selection may have resulted in a potential overestimation of OS after local treatment of OMD because patients with favorable patient- and tumor characteristics were more often selected for treatment (i.e. confounding by indication)[33]. In addition, the NCR did not record the number or size of OMD lesions which may have impacted on OS[27]. Therefore, randomized controlled trials are warranted to confirm our results.

The benefit of local treatment of OMD plus systemic therapy over systemic therapy alone has been previously suggested by a phase II non-randomized trial by Al-Batran et al.[14]. This study included patients with gastric or gastroesophageal junction adenocarcinoma with synchronous OMD. Patients who responded to fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy underwent resection of the primary tumor and metastases[14]. This study showed improved OS after resection of the primary tumor and metastases in patients who responded to FLOT chemotherapy as compared with patients who did not respond to systemic therapy (median OS of 31.3 months versus 15.9 months, respectively)[14]. These results have resulted in an ongoing phase III RENAISSANCE trial in which patients with gastric or gastroesophageal junction adenocarcinoma with synchronous OMD who respond to FLOT chemotherapy will be randomized to either continuation of FLOT chemotherapy or resection of the primary tumor and metastases[16]. In addition, the results of our study are comparable with the phase II trial by Liu et al.[16]. This study included patients with esophageal squamous cell carcinoma with metachronous OMD who underwent SBRT and 50 % received adjuvant systemic therapy[15]. This study showed an OS of 24.6 months[15].

Although several non-randomized studies have suggested excellent OS in patients undergoing local treatment of OMD plus systemic therapy[14,15], this study shows that only 21% of patients undergoing local treatment received combined systemic therapy as compared with 100%[14]

and 50%[15] in these phase II trials. The limited use of combined local treatment plus systemic therapy in our population-based study was mainly seen in patients with brain oligometastasis, which formed a relatively large proportion of our study population (30%). Chemotherapy has limited activity in the brain, which has been mainly attributed to the blood–brain barrier [34]. Patients with brain oligometastasis were excluded from these phase II trials[14,15]. Besides the high portion of patients with brain oligometastasis, the limited use of systemic therapy combined with local treatment of OMD might also be explained by the lack of evidence-based guidelines to guide treatment decision-making and the lack of completed RCTs in the setting of esophagogastric OMD.

In addition to the German RENAISSANCE trial, several phase 3 trials are currently investigating the benefit of local treatment for OMD plus systemic therapy over systemic therapy alone[16-18]. In the American ECOG study (NCT04248452), patients with synchronous or metachronous OMD limited to 3 metastases will be included[17]. Patients with response to chemotherapy will be randomized to either SBRT plus continuation of chemotherapy or continuation of chemotherapy alone[17]. Finally, in the French SURGIGAST trial (NCT03042169), patients with synchronous gastric cancer with synchronous OMD limited to the retroperitoneal lymph nodes and/or 1 organ with metastases will be included[18]. Patients with response to "standard chemotherapy" will be randomized to either resection of the primary tumor and oligometastases or continuation of chemotherapy[18].

However, none of these studies have incorporated immunotherapy in the treatment algorithm for OMD, although several studies have shown improved survival outcomes for patients with esophagogastric cancer treated with immunotherapy in the first-line palliative setting[35] or in the adjuvant setting after a pathological incomplete response after neoadjuvant chemoradiotherapy and surgery[36]. Currently, it is unknown if immunotherapy also improves survival outcomes in the OMD setting before and/or after local treatment for OMD in patients with esophagogastric cancer. Therefore, a potential future study could assess the benefit of immunotherapy plus local treatment for OMD in patients with esophagogastric cancer.

Certain limitations apply to this study that warrants caution for the interpretation of results. First, no additional prognostic factors could be analyzed in the multivariable Cox proportional hazard model because of the risk of overfitting given the relatively limited sample size[37]. Second, missing data on performance status and differentiation grade may have reduced the power of the current study. Third, no propensity score-matching could be performed due to the limited number of patients in treatment subgroups. However, this is the first population-based cohort study, to the best of our knowledge, on the management and outcomes of local treatment and systemic therapy of esophagogastric OMD. Therefore, this is the first study that

provides real-world generalizability and applicability. Other strengths include the register-based follow-up resulting in complete follow-up information for all patients.

The OligoMetastatic Esophagogastric Cancer (OMEC) project aims to achieve consensus on the definition and treatment of oligometastatic esophagogastric cancer. OMEC is a consortium of 50 esophagogastric cancer expert centers across 16 countries in Europe. Studies of the OMEC-project include a systematic review of definitions of esophagogastric OMD (OMEC-1)[24], distribution of clinical cases to experts asking for multidisciplinary team responses on diagnosis and treatment (OMEC-2)[38], Delphi consensus through 2 Delphi rounds and a consensus meeting (OMEC-3). The OMEC project will result in a multidisciplinary European consensus statement for oligometastatic esophagogastric cancer (OMEC-4), laying the basis for a prospective clinical study incorporating immunotherapy and local treatment for OMD for these patients (OMEC-5).

CONCLUSION

In conclusion, our results suggest that the preferred approach to oligometastatic esophagogastric cancer includes local treatment of OMD alone (e.g. metastasectomy or SBRT) or a combined approach consisting of local treatment of OMD plus systemic therapy (e.g. chemotherapy). However, our results are most likely biased. Therefore, randomized controlled trials are warranted to confirm these results.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021. doi:10.3322/caac.21660
2. Koemans WJ, Luijten JCHBM, van der Kaaij RT, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma – A Dutch national cohort study. *Cancer Epidemiol*. 2020;69(October):101846. doi:10.1016/j.canep.2020.101846
3. Wu S-GG, Zhang W-WW, Sun J-YY, Li F-YY, Lin Q, He Z-YY. Patterns of Distant Metastasis Between Histological Types in Esophageal Cancer. *Front Oncol*. 2018. doi:10.3389/fonc.2018.00302
4. Bernards N, Creemers GJ, Nieuwenhuijzen GAPP, Bosscha K, Pruijt JFMM, Lemmens VEPPPP. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. *Ann Oncol*. 2013;24:3056-3060. doi:10.1093/annonc/mdt401
5. Parry K, Visser E, van Rossum PSNN, Mohammad NH, Ruurda JP, van Hillegersberg R. Prognosis and Treatment After Diagnosis of Recurrent Esophageal Carcinoma Following Esophagectomy with Curative Intent. *Ann Surg Oncol*. 2015;22 Suppl 3(S3):1292-1300. doi:10.1245/s10434-015-4840-5
6. Bernards N, Haj Mohammad N, Creemers GJ, et al. Improvement in survival for patients with synchronous metastatic esophageal cancer in the south of the Netherlands from 1994 to 2013. *Acta Oncol (Madr)*. 2016. doi:10.1080/0284186X.2016.1176249
7. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v50-v57. doi:10.1093/annonc/mdw329
8. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016. doi:10.1093/annonc/mdw350
9. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2019. doi:10.6004/jnccn.2019.0033
10. NCCN. NCCN Guidelines: Gastric cancer. *Natl Compr Cancer Netw*. 2019.
11. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
12. Gomez DR, Blumenschein GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol*. 2016;17(12):1672-1682. doi:10.1016/S1470-2045(16)30532-0
13. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet Oncol*. 2019;393(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5
14. Al-Batran S-EE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. *JAMA Oncol*. 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
15. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. 2020;108(3):707-715. doi:10.1016/j.ijrobp.2020.05.003
16. Al-Batran S-EE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: Effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III tri. *BMC Cancer*. 2017;17(1):893. doi:10.1186/s12885-017-3918-9
17. ECOG-ACRIN Cancer Research. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. *clinicaltrials.gov/NCT04248452*. 2020. doi:10.31525/ct1-nct04248452
18. Mariette C. Palliative Gastric Resection Plus Chemotherapy Versus Chemotherapy Alone in Stage IV Gastric Cancer. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03042169. Accessed July 11, 2019.

19. Averitt AJ, Weng C, Ryan P, Perotte A. Translating evidence into practice: eligibility criteria fail to eliminate clinically significant differences between real-world and study populations. *npj Digit Med*. 2020;3(1). doi:10.1038/s41746-020-0277-8
20. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: Partners in the evolution of medical evidence. *Br J Cancer*. 2014;110(3):551-555. doi:10.1038/bjc.2013.725
21. Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: a multicenter cohort study. *Radiother Oncol*. 2022;173:269-276. doi:10.1016/j.radonc.2022.06.012
22. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73. doi:10.7326/M14-0698
23. Allen PW. ICDO — International Classification of Diseases for Oncology. *Pathology*. 1991;23(3):280. doi:10.1016/s0031-3025(16)36112-8
24. Kroese TE, Laarhoven HWM Van, Nilsson M, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment : A systematic review and meta-analysis. *Eur J Cancer*. 2022;166:254-269. doi:10.1016/j.ejca.2022.02.018
25. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17(7):1721-1724. doi:10.1245/s10434-010-1024-1
26. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21(1):e18-e28. doi:10.1016/S1470-2045(19)30718-1
27. ter Veer E, van Kleef JJ, Schokker S, et al. Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis. *Eur J Cancer*. 2018. doi:10.1016/j.ejca.2018.07.132
28. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16(9):1090-1098. doi:10.1016/S1470-2045(15)00040-6
29. Rice TW, Ishwaran H, Blackstone EH, et al. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. *Dis Esophagus*. 2016. doi:10.1111/dote.12540
30. Kim JH, Rha SY, Kim C, et al. Clinicopathologic Features of Metachronous or Synchronous Gastric Cancer Patients with Three or More Primary Sites. *Cancer Res Treat*. 2010;42(4):217. doi:10.4143/crt.2010.42.4.217
31. Goense L, van Rossum PSN, Xi M, et al. Preoperative Nomogram to Risk Stratify Patients for the Benefit of Trimodality Therapy in Esophageal Adenocarcinoma. *Ann Surg Oncol*. 2018. doi:10.1245/s10434-018-6435-4
32. Depypere L, Lerut T, Moons J, et al. Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. *Dis Esophagus*. 2017;30(1):1-8. doi:10.1111/dote.12508
33. Kyriacou DN, Lewis RJ. Confounding by indication in clinical research. *JAMA - J Am Med Assoc*. 2016. doi:10.1001/jama.2016.16435
34. Brastianos HC, Cahill DP, Brastianos PK. Systemic Therapy of Brain Metastases. *Curr Neurol Neurosci Rep*. 2015. doi:10.1007/s11910-014-0518-9
35. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2
36. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384(13):1191-1203. doi:10.1056/nejmoa2032125
37. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984. doi:10.1002/sim.4780030207

38. Kroese TE, van Hillegersberg R, Schoppmann S, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *Eur J Cancer*. 2022;164:18-29. doi:10.1016/j.ejca.2021.11.032

CHAPTER 9

Liver oligometastatic disease in synchronous metastatic gastric cancer patients: a nationwide population-based cohort study

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Tiuri E. Kroese, Yuko Takahashi, Florian Lordick, Peter S.N. van Rossum, Jelle P. Ruurda, Sjoerd M. Lagarde, Richard van Hillegersberg, Rob H.A. Verhoeven, Hanneke W.M. van Laarhoven

ABSTRACT

Introduction

This population-based cohort study analyzed treatment, overall survival (OS), and independent prognostic factors for OS in gastric cancer patients with liver metastases.

Methods

Between 2015 and 2017, patients with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma limited to the liver were included from the prospectively maintained population-based Netherlands Cancer Registry. Liver oligometastatic disease (OMD) was defined as ≤3 liver metastases. The primary outcome was OS. Independent prognostic factors for OS were analyzed using multivariable Cox regression analysis.

Results

A total 295 patients with metastases limited to the liver were included. The primary tumor was resected in four patients (1.4%). Treatment for liver metastases consisted of chemotherapy alone (28.1%), trastuzumab plus chemotherapy (4.7%), surgery (1.0%), or best supportive care (67.5%). Median OS across all included patients was 4.0 months (95% confidence interval [CI]: 3.1-4.5). Liver OMD was detected in 77 patients (26%). Treatment for liver OMD consisted of chemotherapy alone (24.6%), trastuzumab plus chemotherapy (5.2%), surgery (3.9%), or best supportive care (67.5%). Median OS among patients with liver OMD was 5.7 months (95% CI: 4.8-7.5). Across all patients, better OS was independently associated with liver OMD (hazard ratio [HR] 0.66, 95% CI: 0.50-0.87), trastuzumab (HR 0.41, 95% CI: 0.23-0.72) but not with triplet compared with doublet chemotherapy (HR 0.94, 95% CI: 0.57-2.87). Worse OS was independently associated with unknown nodal stage versus cN0 (HR 1.74, 95% CI: 1.17-2.60), diffuse-type versus intestinal-type adenocarcinoma (HR 2.06, 95% CI: 1.32-3.20), and monotherapy or best supportive care versus doublet chemotherapy (HR 1.72, 95% CI: 1.03-2.87, and HR 3.61, 95% CI: 2.55-5.10, respectively).

Conclusion

In this population-based cohort study, liver OMD was detected in 26% of patients. Liver OMD and trastuzumab treatment were independently associated with better OS while triplet as compared with doublet chemotherapy was not. OS among patients with liver OMD nevertheless remained poor. The concept of OMD and the benefit of resection of liver OMD may still have been relatively unknown in this disease type during the study inclusion years.

INTRODUCTION

Gastric cancer is the 5th most common cancer worldwide[1]. Overall survival (OS) in patients with gastric cancer is poor since approximately 35–50% of patients present with synchronous metastatic disease[2]. The most common locations for metastatic disease in patients with gastric cancer are the extra-regional lymph nodes, followed by the liver[3]. More than 95% of gastric cancers are adenocarcinomas, which are commonly classified according to the Lauren classification in diffuse-type or intestinal-type[4]. Liver metastases are more common in intestinal than diffuse-type adenocarcinoma[5].

The recommended first-line systemic therapy regimen for patients with metastatic gastric cancer consists of doublet chemotherapy (platinum and fluoropyrimidine) and trastuzumab in case of HER2 overexpression[6,7]. Triplet chemotherapy (platinum, fluoropyrimidine, and taxane or anthracycline) may be used in patients with metastatic gastric cancer with good performance status although triplet chemotherapy has a higher toxicity rate and unclear OS benefit over doublet chemotherapy[8-10].

In patients with oligometastatic disease (OMD) limited to 1 organ and/or the retroperitoneal lymph nodes, surgery of the primary tumor and metastases may provide an OS benefit[11]. The FLOT-3 trial has shown that the OS of gastric cancer patients with synchronous OMD who underwent resection of the primary tumor and metastases was higher than the OS of patients who underwent chemotherapy alone (31.3 months versus 17.8 months)[11]. However, this comparison is biased because resection of the primary tumor and metastases in the FLOT-3 trial was only applied in those patients who responded well to chemotherapy[11].

In patients with OMD limited to the liver (i.e. ≤3 liver metastases and no extra-hepatic metastasis[12]), resection of liver metastases may provide an OS benefit[13-20]. Current Dutch and European gastric cancer guidelines do not incorporate specific recommendations for treatment of liver OMD[7,21] although resection of liver oligometastases is increasingly being performed in high expertise centers[22]. In addition, because studies have used various definitions of liver OMD[12], the incidence of liver OMD in esophagogastric cancer is currently unknown.

This population-based cohort study aimed to analyze the incidence and treatment of liver OMD (defined as ≤3 liver metastases and no extra-hepatic metastases), OS, and independent prognostic factors for OS in patients with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma with metastatic disease limited to the liver.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Research Commission of the Dutch Upper GI Cancer Group (DUCG), the Privacy Review Board of the Netherlands Cancer Registry (NCR), the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Trials Group and did not need approval by a medical ethical committee according to the Central Committee on Research involving Human Subjects in the Netherlands. The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File 1).

Patient inclusion

All patients ≥18 years of age with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma diagnosed in the Netherlands between 2015 and 2017 were identified from the prospectively maintained population-based NCR. Patients with metastatic disease limited to the liver were eligible for inclusion. Patients with an unknown number of liver metastases were excluded. Synchronous metastatic disease was defined as metastatic disease detected before the start of primary tumor treatment. Metastatic gastric or gastroesophageal junction cancer was classified according to ICD-0-3 as 16.0–16.9[23] and according to UICC as stage cTx-4b, cNx-3, cM1[24]. The NCR covers the entire Dutch population of 17 million inhabitants. The NCR is directly linked to the municipal personal records database to obtain vital status. The vital status was last updated on February 1, 2021. Data on the number of liver metastases could not be retrieved from two hospitals (i.e. 3% of all Dutch hospitals) due to logistical constraints.

Definition of OMD

The number of liver metastases was obtained by reviewing the imaging reports. Liver OMD was defined as ≤3 liver metastases and no extra-hepatic metastases in accordance with a recent systematic review on definitions of oligometastatic esophagogastric cancer[12]. Liver polymetastatic disease (PMD) was defined as >3 liver metastases[12]. The systematic review (OMEC-1) was the first subproject of the Oligometastatic Esophagogastric Cancer (OMEC) project to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer[25]. Subsequent subprojects of the OMEC project include discussion of real-life clinical cases by multidisciplinary teams of esophagogastric cancer expert centers in Europe (OMEC-2)[22], and Delphi consensus rounds with esophagogastric cancer experts (OMEC-3). The resulting European multidisciplinary

consensus statement (OMEC-4) will lay the foundation for a prospective European clinical trial on the treatment of oligometastatic esophagogastric cancer (OMEC-5). The OMEC project is endorsed by the EORTC, European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society for Diseases of the Esophagus (ESDE), the European chapter of the International Gastric Cancer Association (IGCA) and DUCG.

Staging

Dutch national gastric cancer guidelines recommend baseline staging with computed tomography (CT) for gastric cancer[21]. Since 2016, for patients with ≥cT3 and/or cN+ disease national guidelines recommend baseline ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT (^{18}F-FDG PET/CT) and diagnostic laparoscopy[21].

Treatment

Primary tumor resection was defined as total or distal gastrectomy, transhiatal or transthoracic esophagectomy, or non-specified primary tumor resection. Treatment for liver metastases was categorized into (1) chemotherapy alone, (2) trastuzumab plus chemotherapy, (3) surgery (with or without systemic therapy), or (4) best supportive care. Chemotherapy was categorized into monotherapy (one agent), doublet therapy (two agents), or triplet therapy (three agents). Surgery for liver metastases included radiofrequency ablation and/or metastasectomy. Best supportive care included no anti-tumor treatment for liver metastases.

Outcomes

The primary outcome of this study was OS. OS was defined as the time interval between the diagnosis of the primary tumor and death or last follow-up. Secondary outcomes were the incidence and management of liver OMD and independent prognostic factors for OS.

Variables

The primary tumor location was categorized into proximal stomach or gastroesophageal junction (gastroesophageal junction, cardia, or fundus), middle stomach (corpus, small and big curvature), distal stomach (antrum or pylorus), overlapping locations in the stomach, or non-specified location in the stomach. Diffuse-type adenocarcinoma included diffuse-type adenocarcinoma, linitis plastica, and signet ring cell carcinoma. Intestinal-type adenocarcinoma included intestinal-type adenocarcinoma, tubular adenocarcinoma, and mucinous adenocarcinoma. Other adenocarcinoma subtypes were grouped together into 'other'. Clinical staging was according to the TNM 7th edition[24]. The Charlson comorbidity index was grouped into 1–2, 3–4, and >4[26]. Body mass index (BMI) was defined as weight in kilograms/height in metres^2.

Statistical analysis

Parametric data were presented as mean with standard deviation (SD) and were compared with the Student's T-test. Non-parametric data were presented as median with interquartile range (IQR) and were compared using the Mann-Whitney-U test. Categorical data were presented as frequencies with proportions (%) and were compared using Fisher's exact or chi-squared test. Multivariable Cox proportional hazard regression analyses were used to identify prognostic factors for OS. Pre-specified prognostic factors included in the Cox proportional hazard regression analyses were based on a recent systemic review on prognostic and predictive factors for OS in patients with metastatic esophagogastric cancer[27]. These prognostic factors included age, sex, BMI, performance status, Charlson comorbidity index (1–2, 3–4, >4, or missing), primary tumor location (proximal stomach or gastroesophageal junction, middle stomach, distal stomach, overlapping locations in the stomach, or non-specified location in the stomach), adenocarcinoma subtype (intestinal, diffuse, or other), clinical tumor and nodal stage, liver OMD (yes or no), primary tumor resected (yes or no), and liver metastases treatment (chemotherapy, trastuzumab plus chemotherapy, surgery, or best supportive care)[27].

Prognostic factors for OS were expressed using hazard ratios (HRs) with 95% confidence intervals (CIs). Results of subgroup analyses were reported in case ≥10 patients were included. Kaplan–Meier curves were constructed of independent prognostic factors for OS and categories were compared using the log-rank test. Missing data were not considered missing at random. Therefore, imputation was not performed but instead missing values were assigned as a separate category. The median follow-up time was estimated using the reverse Kaplan–Meier estimator (i.e. reverse event indicator). Sensitivity analyses were performed for 1 and 2 liver metastases. Subgroup analyses were performed for patients with and without OMD who underwent treatment. Data were analyzed using R for Windows, version 3.6.3[28]. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 2092 patients with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma were identified from the NCR, of whom 318 patients presenting with metastatic disease limited to the liver were eligible for inclusion. Subsequently, 23 patients with an unknown number of liver metastases were excluded. Consequently, 295 patients were included in this nationwide population-based cohort study. There was no loss to follow-up. Figure 1 demonstrates the flowchart of patient selection.

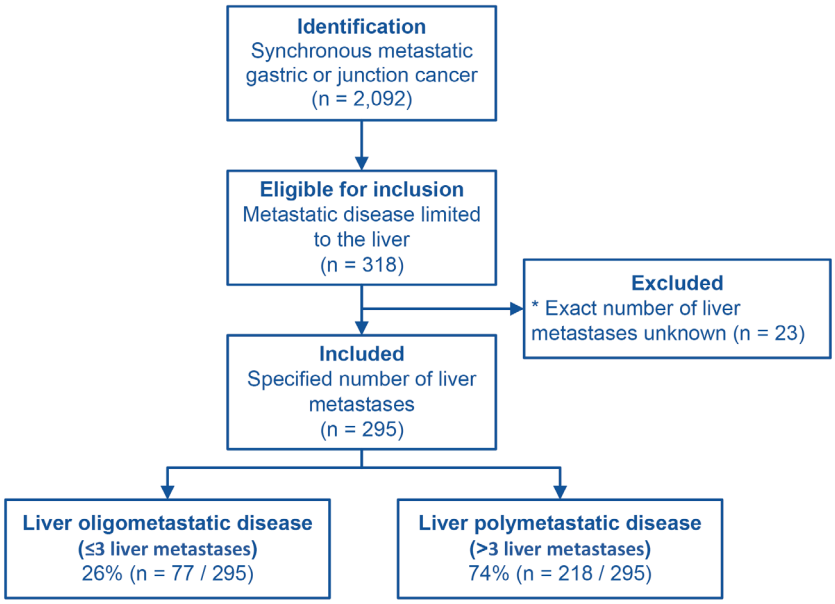

Figure 1. Patient selection flowchart

The median age of included patients was 75 years (IQR: 68–80), median BMI was 25 kg/m^2 (IQR: 23–27), and 74.2% of patients were male. The World Health Organization (WHO) performance status was 0–1 in 36.9%, and 53.6% had a Charlson comorbidity score of >4. The primary tumor was predominantly located in the proximal stomach or gastroesophageal junction (40.3%), and the disease stage was cT1-2 (35.3%) and cN1 (32.5%). The adenocarcinoma subtype was intestinal (40.0%), diffuse (10.8%), or other (49.2%).

Treatment for liver metastases among the 295 patients consisted of chemotherapy alone (28.1%), trastuzumab plus chemotherapy (4.7%), surgery (1.0%), or best supportive care (67.5%). The most common first-line chemotherapy regimen was doublet therapy (11.9% of total), followed by triplet therapy (9.8%), or monotherapy (6.4%). The most common first-line doublet regimens were capecitabine plus oxaliplatin (CapOx, 9.5%), and oxaliplatin, 5-fluorouracil, plus leucovorin (FOLFOX, 2.0%). The most common first-line triplet regimens were epirubicin, oxaliplatin, plus capecitabine (EOC, 7.8%) and docetaxel, oxaliplatin, plus capecitabine (DOC, 1.4%). The most common first-line monotherapy agents were capecitabine (5.8%) and 5-fluorouracil (0.7%). Trastuzumab was combined with doublet chemotherapy (3.7%) or monotherapy (1.0%).

Table 1. Patient and tumor characteristics of included patients.

	Liver OMD (n=77)		Liver PMD (n=218)		P-value
Median age in years [IQR]	75	[68-80]	74	[67-80]	0.745
Sex					0.553
Male	59	76.6%	160	73.4%	
Female	18	23.4%	58	26.6%	
Year of diagnosis					0.043
2015	32	41.6%	80	36.7%	
2016	23	29.9%	72	33.0%	
2017	22	28.5%	66	30.3%	
Body mass index (kg/m^2) [IQR]	25	[24-29]	25	[23-27]	0.529
WHO performance status					0.023
0	16	20.8%	26	11.9%	
1	23	29.9%	44	20.2%	
>1	10	13.0%	40	18.3%	
Missing	28	36.3%	108	49.6%	
Charlson comorbidity index					0.226
1-2	6	7.7%	16	7.3%	
3-4	26	33.7%	80	36.8%	
>4	44	57.1%	114	52.2%	
Missing	2	2.5%	8	3.7%	
Primary tumor location					0.472
Proximal stomach or GE junction	32	41.6%	87	39.9%	
Middle stomach	11	14.3%	40	18.3%	
Distal stomach	20	26.0%	48	22.0%	
Overlapping regions in the stomach	6	7.8%	27	12.4%	
Non-specified location in the stomach	8	10.3%	16	7.4%	
Clinical tumor stage					0.057
cT1-2	27	35.0%	77	35.3%	
cT3	21	27.3%	38	17.4%	
cT4	11	14.3%	18	8.3%	
cTx	18	23.4%	85	39.0%	
Clinical nodal stage					0.133
cN0	23	29.9%	56	25.7%	
cN1	30	39.0%	66	30.3%	
cN2	13	16.9%	57	26.1%	
cN3	4	5.2%	5	2.3%	
cNx	7	9.0%	34	15.6%	
AC subtype					0.726
Intestinal	28	37.3%	90	41.3%	
AC, intestinal type	26	33.8%	82	37.6%	
Tubular AC	0	0%	6	2.8%	
Mucinous AC	2	2.6%	2	0.9%	
Diffuse	11	14.3%	21	9.6%	

Table 1. Continued

	Liver OMD (n=77)		Liver PMD (n=218)		P-value
Linitis plastica	3	3.9%	6	2.8%	
AC, diffuse-type	7	9.1%	11	5.1%	
Signet-ring cell carcinoma	1	1.3%	4	1.8%	
Other	38	50.7%	107	49.0%	
AC NOS	37	48.1%	103	47.2%	
AC with mixed subtypes	1	1.3%	1	0.5%	
AC with neuroendocrine differentiation	0	0%	3	1.4%	
Median number of liver metastases	1	[1-3]	5	[4-5]	<0.001

AC: adenocarcinoma; GE: gastroesophageal; IQR: interquartile range; NOS: not otherwise specified; OMD: oligometastatic disease (i.e. ≤3 liver metastases); PMD: polymetastatic disease (i.e. >3 liver metastases)

The number of liver metastases was 1 (13%), 2 (7%), 3 (6%), 4 (4%), ≥5 (10%), or not liver OMD but with the exact number of liver metastases unknown (60%). Thus, liver OMD was detected in 77 of 295 patients (26%). There were no differences in baseline characteristics between patients with versus without liver OMD, besides a better performance status in patients with liver OMD (0–1 in 51% versus 32%, p=0.023). Table 1 demonstrates the patient characteristics stratified by liver OMD.

In patients with liver OMD (n=77), 4 patients underwent resection of the primary tumor (5.2%). These primary tumor resections included 2 distal gastrectomies, 1 transhiatal esophagectomy, and 1 non-specified primary tumor resection. Primary tumor resection was only performed in patients with liver OMD. Among patients with liver OMD, resection of liver oligometastases was performed in 3 patients (3.9%, 3/77). A patient underwent metastasectomy of liver OMD followed by CapOx chemotherapy (n=1), a patient underwent liver wedge resection of liver OMD and distal gastrectomy (n=1), and a patient underwent EOC chemotherapy, transhiatal esophagectomy, and radiofrequency ablation of liver OMD (n=1). Thus, resection of the primary tumor and liver OMD was performed in two patients with liver OMD (2.6%, 2/77).

In addition, in patients with liver OMD chemotherapy alone was performed in 24.6%, trastuzumab plus chemotherapy in 5.2%, and best supportive care in 67.5%. There was no difference in the rate of best supportive care between patients with and without liver OMD (68% versus 67%). Reasons for receiving best supportive care among patients with liver OMD were poor performance status (n=15), patient request (n=10), tumour burden (n=8), or not specified (n=20). Among patients for whom the reason for best supportive care was not specified (n=20), the median age was 81 years (IQR: 71–82), and the performance status was 0–1 in 4 patients, 2 in 3 patients, 3 in 2 patients, and not-specified in 7 patients. Table 2 shows

Table 2. Treatment characteristics of included patients.

	Liver OMD (n=77)		Liver PMD (n=218)		Total (n=295)	
Primary tumor resected						
Yes	4	5.2%	0	0.0%	4	1.4%
Distal gastrectomy	2	2.6%	0	0.0%	2	0.7%
Transhiatal esophagectomy	1	1.3%	0	0.0%	1	0.3%
Not-specified primary tumor resection	1	1.3%	0	0.0%	1	0.3%
No	73	94.8%	218	100.0%	291	98.6%
Liver metastases treatment						
Chemotherapy alone	19	24.6%	64	29.4%	83	28.1%
Monotherapy	2	2.6%	17	7.8%	19	6.4%
Capecitabin	1	1.3%	16	7.3%	17	5.8%
5-fluorouracil	1	1.3%	1	0.0%	2	0.7%
Doublet	5	6.5%	30	13.8%	35	11.9%
CapOx	3	3.9%	25	11.5%	28	9.5%
FOLFOX	2	2.6%	4	1.8%	6	2.0%
CX	0	0.0%	1	0.5%	1	0.3%
Triplet	12	15.6%	17	7.8%	29	9.8%
EOC	8	10.4%	15	6.8%	23	7.8%
DOC	2	2.6%	2	<1%	4	1.4%
ECC	1	1.3%	0	0.0%	1	0.3%
ECF	1	1.3%	0	0.0%	1	0.3%
Unspecified chemotherapy	1	1.3%	0	0.0%	1	0.3%
Targeted therapy (trastuzumab) plus chemotherapy	4	5.2%	10	4.6%	14	4.7%
Trastuzumab plus monotherapy	0	0.0%	3	1.4%	3	1.0%
Trastuzumab plus doublet chemotherapy	4	5.2%	7	3.2%	11	3.7%
Surgery for liver metastases	3	3.9%	0	0.0%	3	1.0%
Metastasectomy followed by CapOx	1	1.3%	0	0.0%	1	0.3%
Wedge resection	1	1.3%	0	0.0%	1	0.3%
EOC followed by radiofrequency ablation	1	1.3%	0	0.0%	1	0.3%
Best supportive care	52	67.5%	147	67.4%	199	67.5%
Resection of primary tumor and liver metastases	2	2.6%	0	0.0%	2	0.7%

CapOx = Capecitabin and oxaliplatin; CX = Capecitabin and cisplatinum; DOC = Docetaxel, oxaliplatin, and capecitabine; ECC = Epirubicin, cisplatinum, and capecitabine; ECF = Epirubicin, cisplatin, and 5-fluorouracil; EOC = Epirubicin, oxaliplatin, and capecitabine; FOLFOX = leucovorin, 5-fluorouracil and oxaliplatin; OMD: oligometastatic disease (i.e. ≤3 liver metastases); PMD: polymetastatic disease (i.e. >3 liver metastases)

the treatment characteristics stratified by liver OMD.

Patients who received best supportive care had higher age, more often male sex, higher Charlson comorbidity index, worse performance status, and more often an unknown clinical T-stage as compared with patients who did not receive best supportive care. Patient characteristics stratified by best supportive care are provided in Supplementary File 2.

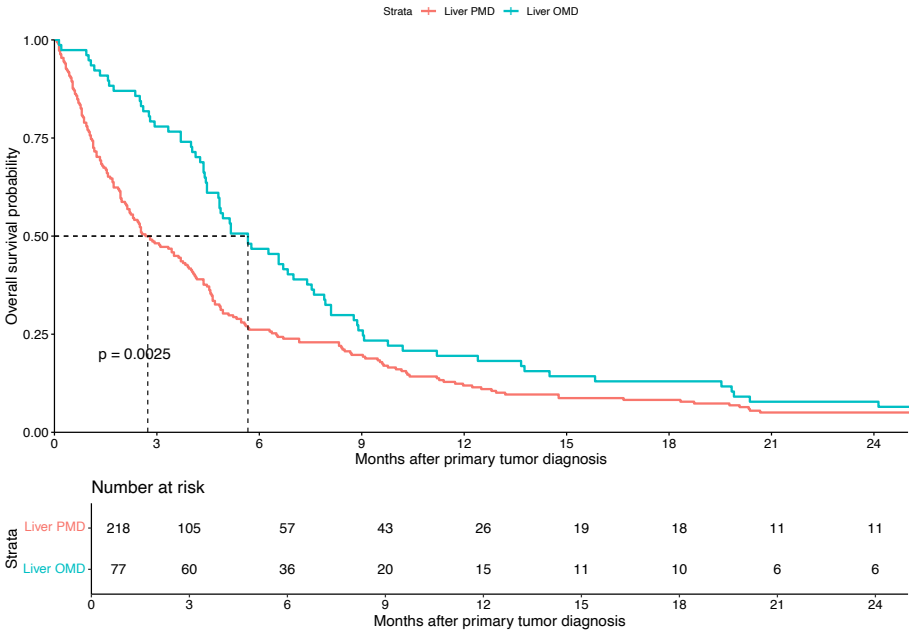

Figure 2. Overall survival curve stratified for treatment of oligometastatic disease.

The median follow-up time was 61 months (IQR: 56–62). A total of five patients were alive at the end of follow-up (February 1, 2021). Median OS across all patients was 4.0 months (95% CI: 3.1–4.5). Median OS among patients with liver OMD was 5.7 months (95% CI: 4.8–7.5). Superior OS was independently associated with liver OMD (HR 0.66, 95% CI: 0.50–0.87; Fig. 2) and with trastuzumab treatment (HR 0.41, 95% CI: 0.23–0.72; Supplementary File 3). Triplet compared with doublet chemotherapy was not independently associated with improved OS (HR 0.94, 95% CI: 0.57–2.87; Supplementary File 5).

Worse OS was independently associated with unknown nodal stage versus cN0 (HR 1.74, 95% CI: 1.17–2.60, Supplementary File 6), diffuse-type as compared with intestinal-type adenocarcinoma (HR 2.06, 95% CI: 1.32–3.20; Supplementary File 4), and best supportive care or monotherapy as compared with doublet chemotherapy (HR 3.61, 95% CI: 2.55–5.10 and HR 1.72, 95% CI: 1.03–2.87, respectively Supplementary File 5). Table 3 shows the results of the univariable and multivariable Cox regression analyses for prognostic factors for OS as well as median OS with 95% CIs for subgroups with ≥10 patients.

Table 3. Results of univariable and multivariable Cox proportional hazard models for overall survival.

	Number	Univariable		Multivariable		OS in months
		HR (95% CI)	p-value	HR (95% CI)	p-value	Median (95% CI)
Age		1.03 (1.02-1.04)	<0.001	0.99 (0.97-1.01)	0.146	
Sex						
Male	219	reference	reference	reference	reference	4.8 (4.4-5.7)
Female	76	1.42 (1.11-1.82)	0.004	1.21 (0.91-1.60)	0.073	3.0 (2.5-4.6)
Performance status						
0	42	reference	reference	reference	reference	7.1 (3.9-13.8)
1	67	1.34 (0.94-1.92)	0.103	1.21 (0.76-1.64)	0.763	5.2 (4.5-8.1)
>1	50	2.71 (1.84-3.98)	<0.001	1.61 (1.06-2.45)	0.062	2.7 (1.4-4.4)
Missing	136	2.01 (1.46-2.77)	<0.001	1.23 (0.86-1.77)	0.068	2.4 (1.7-3.8)
Charlson comorbidity index						
>4	158	reference	reference	reference	reference	3.2 (2.5-4.1)
1-2	22	0.46 (0.29-0.75)	0.002	0.68 (0.33-1.37)	0.282	5.7 (4.1-18.7)
3-4	106	0.76 (0.60-0.98)	0.014	1.28 (0.75-2.19)	0.735	4.2 (2.9-5.2)
Missing	9	0.74 (0.38-1.45)	0.383	0.98 (0.52-1.87)	0.396	4.6 (4.4-NA)
Lauren						
Intestinal	118	reference	reference	reference	reference	4.2 (3.1-4.9)
Diffuse	32	1.11 (0.77-1.59)	0.341	2.06 (1.32-3.20)	0.001	2.7 (1.1-5.2)
Other	145	0.91 (0.72-1.70)	0.578	1.30 (0.99-1.69)	0.050	3.9 (2.8-4.6)
Clinical tumor stage						
cT1-2	104	reference	reference	reference	reference	4.4 (2.6-4.9)
cT3	59	0.80 (0.58-1.12)	0.193	1.21 (0.82-3.04)	0.976	6.6 (4.6-8.7)
cT4	29	1.05 (0.69-1.60)	0.803	2.03 (0.99-4.17)	0.500	3.6 (1.9-6.3)
cTx	103	1.34 (1.01-1.76)	0.039	1.79 (0.99-4.22)	0.748	2.4 (1.7-3.7)
Clinical nodal stage						
cN0	79	reference	reference	reference	reference	4.9 (4.4-6.6)
cN1	96	0.82 (0.60-1.05)	0.907	0.80 (0.60-1.07)	0.242	5.2 (4.3-8.3)
cN2-3	79	1.08 (0.66-1.27)	0.144	1.10 (0.78-1.56)	0.848	4.1 (2.9-5.2)
cNx	41	1.71 (1.17-2.49)	0.006	1.74 (1.17-2.60)	0.010	1.4 (1.1-3.0)
Liver OMD						
No	218	reference	reference	reference	reference	2.7 (2.2-3.8)
Yes	77	0.66 (0.52-0.84)	0.003	0.66 (0.50-0.87)	0.001	5.7 (4.8-7.5)
Primary tumor resected						
No	291	NA	NA	NA	NA	4.0 (3.1-4.5)
Yes	4	NA	NA	NA	NA	NA
Liver metastases treatment						
Doublet	46	reference	reference	reference	reference	9.6 (7.9-15.8)
No treatment	200	3.67 (2.67-4.77)	<0.001	3.61 (2.55-5.10)	<0.001	1.9 (3.9-2.8)
Mono	19	1.22 (0.87-2.17)	0.372	1.72 (1.03-2.87)	0.031	4.8 (3.9-12.2)
Triplet	29	1.37 (0.87-2.17)	0.168	0.94 (0.57-2.87)	0.848	6.7 (5.1-9.0)
Not specified	1	NA	NA	NA	NA	NA
Trastuzumab						
No	281	reference	reference	reference	reference	3.7 (2.8-4.3)
Yes	14	0.32 (0.20-0.52)	<0.001	0.41 (0.23-0.72)	0.008	13.3 (7.8-57.8)

HR: hazard ratio; CI: confidence interval; OS: overall survival; liver OMD: oligometastatic disease (i.e. ≤3 liver metastases); bold: statistically significant

OS of patients with OMD versus without OMD in case of no treatment was 4.8 months (95% CI: 4.1–6.3) versus 1.6 months (95% CI: 1.2–2.1), with monotherapy 6.1 months (95% CI: 4.8-NA) versus 4.8 months (95% CI: 3.8–12.2), with doublet chemotherapy 19.8 months (95% CI: 7.9-NA) versus 9.0 months (95% CI: 6.4–14.8), and with triplet chemotherapy 7.8 months (95% CI: 5.1-NA) versus 5.5 months (95% CI: 4.6–20.7).

Sensitivity analyses demonstrated that having 1–2 liver metastases as compared with >2 liver metastases was independently associated with improved OS (HR 0.60, 95% CI: 0.43–0.83) while 1 liver metastasis as compared with >1 liver metastases was not (HR 0.77, 95% CI: 0.53–1.14).

DISCUSSION

This nationwide population-based cohort study included all patients diagnosed with gastric or gastroesophageal junction adenocarcinoma in combination with metastatic disease limited to the liver and a specified number of liver metastases between 2015 and 2017 in the Netherlands. The incidence of liver OMD (defined as ≤3 liver metastases) was 26% among included patients. Patients with liver OMD were rarely treated as such in this cohort since best supportive care was applied in 68% of patients and only 3% underwent resection of the primary tumor and liver OMD. Patients with liver OMD (n=77) had a 44% lower chance of death over time as compared with patients without liver OMD (n=218). Nevertheless, OS in patients with liver OMD remained relatively poor (median OS 5.7 months).

The rate of best supportive care for patients with liver OMD was comparable to patients without liver OMD (68% versus 67%). At first sight, this is surprisingly high, considering that 51% of patients with liver OMD had a performance status of 0–1 which could suggest that these patients potentially could be able to undergo systemic therapy. However, the high rate of best supportive care among these patients could potentially be explained by high age and the patient request to refrain from treatment. Importantly, it should be noted that our perspective on what may be possible in terms of treatment options is biased by the fact that we often do not have a complete picture of the 'real world'. Furthermore, the publication showing that even if patients are considered to be frail, reduced-intensity chemotherapy can provide a better patient experience without significantly compromising cancer control than best supportive care had not been published at the time of our data collection[29].

The proportion of patients undergoing resection of the primary tumor and liver OMD was very low between 2015 and 2017 in the Netherlands (3%). This suggests that in the time period of

the study inclusion, the concept of OMD treatment was not generally applied in the Netherlands, which may be explained by two factors. First, the results of the FLOT-3 trial were published in 2017[11], which was at the end of the study inclusion period (2015–2017). Second, this population-based study included older and more fragile patients who would not have been eligible for inclusion in the FLOT-3 trial[11]. For example, 16% of patients included in our study had a WHO performance score of >1, while these patients were excluded from the FLOT-3 trial[11].

In addition, this study suggests that doublet chemotherapy was the preferred first-line systemic therapy regimen in this time period in the Netherlands. Importantly, doublet chemotherapy (mainly CapOx) was associated with comparable OS as triplet chemotherapy (EOC) and improved OS as compared with monotherapy or best supportive care. However, the equipoise in OS between doublet and triplet chemotherapy must be interpreted with care because FLOT chemotherapy was not used in this time period in the Netherlands. FLOT is associated with improved OS as compared with ECF/ECC chemotherapy in the perioperative setting[30]. Nevertheless, for the general metastatic patient population, docetaxel containing triplet chemotherapy provides marginal survival benefit, while toxicity is increased[10,31]. Thus, FLOT should not be considered the standard of care for all patients with metastatic gastroesophageal cancer.

In addition to best supportive care and monotherapy, other independent prognostic factors for OS identified in the current study, including Lauren classification, are in line with a recent systemic review for prognostic factors for OS in patients with metastatic esophagogastric cancer[28]. The lower proportion of patients with diffuse-type gastric cancer in this study as compared with population-based cohorts on gastric adenocarcinoma in the Netherlands (11% versus 38%[3] and 44%[32], respectively) confirms previous studies demonstrating that patients with diffuse-type gastric cancer are more likely to develop peritoneal metastases while patients with intestinal-type gastric cancer are more likely to develop liver metastases[3]. The worse OS in patients with an unknown nodal stage is not a known prognostic factor but perhaps could be explained by a higher disease stage, which may create increased complexity and less relevance in documenting and extracting all the data elements resulting in more missing data[33]. Recently, the randomized controlled CheckMate 649 trial has shown that the addition of programmed cell death (PD)-1 inhibition to chemotherapy (CapOx or FOLFOX) improves overall and progression-free survival as compared with chemotherapy alone in the first-line palliative setting for advanced or metastatic HER2 negative gastric or gastroesophageal junction adenocarcinoma[34]. Therefore, PD-1 inhibition in combination with chemotherapy can be considered a new standard of care in the first-line palliative treatment for these patients, depending on the PD-L1 expression status of their cancer[35]. Unfortunately, during our study period PD-1 inhibition was unavailable in the Netherlands. Therefore, we could not study the

effect of PD-1 inhibition on patients with liver OMD. A potential treatment approach for gastric cancer patients with liver OMD could be local treatment for liver metastases combined with palliative immunotherapy plus chemotherapy, which is currently being investigated in an ongoing phase II trial in China (NCT04510064).

Strengths of this study include the study design since it is the first population-based study to include data on the number of liver metastases. Therefore, this study uniquely provides information on a nationwide level on (1) the incidence of metastatic disease limited to the liver among patients with synchronous metastatic gastric cancer; (2) the incidence of liver OMD (defined as ≤3 liver metastases) among patients with metastatic disease limited to the liver. Moreover, this study offers real-world generalizability and applicability since frail and elderly patients were included. Other strengths include the register-based follow-up resulting in complete follow-up information for all patients. Potential weaknesses have been partly addressed in the discussion. Additional limitations include missing data on performance status, the size of liver metastases, and toxicity of systemic therapy resulting in a less optimal adjustment in multivariable analyses.

CONCLUSION

In conclusion, liver OMD was detected in 26% of patients with synchronous metastatic gastric limited to the liver. Patients with versus without liver OMD had independently superior OS. Nevertheless, OS in patients with liver OMD remained relatively poor, potentially because best supportive care was applied in 68% of patients, and only 3% underwent resection of the primary tumor and liver oligometastases. This suggests that the concept of OMD and the benefit of resection of the primary tumor and oligometastases may still have been relatively unknown in this disease type during the research years. Triplet chemotherapy (mainly EOC) compared with doublet chemotherapy (mainly CapOx) was not independently associated with improved OS. Future studies are warranted to identify which patients benefit from resection of liver oligometastases.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021. https://doi.org/10.3322/caac.21660.
2. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, Siersema PD, Lemmens VEPP, Rosman C, et al. Long-term survival improvement in oesophageal cancer in the Netherlands. Eur J Cancer 2018;94:138–47. https://doi.org/10.1016/j.ejca.2018.02.025.
3. Verstegen MHP, Harker M, Hugen N, Rosman C, van de Water C, Nagtegaal ID, et al. Metastatic pattern in esophageal and gastric cancer: Influenced by site and histology. World J Gastroenterol 2020;26:6037–46. https://doi.org/10.3748/wjg.v26.i39.6037.
4. LAUREN P. THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. Acta Pathol Microbiol Scand 1965;64:31–49. https://doi.org/10.1111/apm.1965.64.1.31.
5. Koemans WJ, Luijten JCHBM, van der Kaaij RT, Grootscholten C, Snaebjornsson P, Verhoeven RHA, et al. The metastatic pattern of intestinal and diffuse type gastric carcinoma – A Dutch national cohort study. Cancer Epidemiol 2020;69:101846. https://doi.org/10.1016/j.canep.2020.101846.
6. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, et al. Gastric Cancer, Version 3.2016; Clinical Practice Guidelines in Oncology. JNCCN J Natl Compr Cancer Netw 2016;14:1286–312. https://doi.org/10.6004/jnccn.2016.0137.
7. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016. https://doi.org/10.1093/annonc/mdw350.
8. Wagner AD, Syn NLX, Moehler M, Grothe W, Yong WP, Tai BC, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2017;2017. https://doi.org/10.1002/14651858.CD004064.pub4.
9. Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, Vos-Geelen J, Beerepoot L V., et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study. Int J Cancer 2019. https://doi.org/10.1002/ijc.32580.
10. Veer E Ter, Mohammad NH, Van Valkenhoef G, Ngai LL, Mali RMA, Anderegg MC, et al. The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. J Natl Cancer Inst 2016. https://doi.org/10.1093/jnci/djw166.
11. Al-Batran S-EE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: The AIO-FLOT3 trial. JAMA Oncol 2017;3:1237–44. https://doi.org/10.1001/jamaoncol.2017.0515.
12. Kroese TE, Laarhoven HWM Van, Nilsson M, Lordick F, Guckenberger M, Ruurda JP, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment : A systematic review and meta-analysis. Eur J Cancer 2022;166:254–69. https://doi.org/10.1016/j.ejca.2022.02.018.
13. Tang K, Zhang B, Dong L, Wang L, Tang Z. Radiofrequency ablation versus traditional liver resection and chemotherapy for liver metastases from gastric cancer. J Int Med Res 2020;48. https://doi.org/10.1177/0300060520940509.
14. Yazawa T, Hori T, Yamamoto H, Harada H, Yamamoto M, Yamada M, et al. Do liver metastases from gastric cancer contraindicate aggressive surgical resection? A 14-year single-center experience. World J Gastrointest Pharmacol Ther 2020;11:110–22. https://doi.org/10.4292/wjgpt.v11.i5.110.
15. Yu P, Zhang Y, Ye Z, Chen X, Huang L, Du Y, et al. Treatment of synchronous liver metastases from gastric cancer: A single-center study. Cancer Manag Res 2020;12:7905–11. https://doi.org/10.2147/CMAR.S261353.
16. Jagric T, Horvat M. Surgical resection of synchronous liver metastases in gastric cancer patients. A propensity score-matched study. Radiol Oncol 2020;55:57–65. https://doi.org/10.2478/raon-2020-0067.

17. Ito D, Kawaguchi Y, Yamashita H, Arita J, Akamatsu N, Kaneko J, et al. Intestinal-type histology is associated with better prognosis in patients undergoing liver resection for gastric/esophagogastric-junction liver metastasis. Glob Heal Med 2019;1:101–9. https://doi.org/10.35772/ghm.2019.01012.
18. Ryu T, Takami Y, Wada Y, Tateishi M, Matsushima H, Yoshitomi M, et al. Oncological outcomes after hepatic resection and/or surgical microwave ablation for liver metastasis from gastric cancer. Asian J Surg 2019;42:100–5. https://doi.org/10.1016/j.asjsur.2017.09.005.
19. Nonaka Y, Hiramatsu K, Kato T, Shibata Y, Yoshihara M, Aoba T, et al. Evaluation of Hepatic Resection in Liver Metastasis of Gastric Cancer. Indian J Surg Oncol 2019;10:204–9. https://doi.org/10.1007/s13193-018-0827-6.
20. Seesing MFJ, van der Veen A, Brenkman HJF, Stockmann HBAC, Nieuwenhuijzen GAP, Rosman C, et al. Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: a nationwide study. Dis Esophagus Off J Int Soc Dis Esophagus 2019;32:1–8. https://doi.org/10.1093/dote/doz034.
21. Netherlands Cancer Registry. Richtlijn Maagcarcinoom 2017.
22. Kroese TE, van Hillegersberg R, Schoppmann S, Deseyne PRAJ, Nafteux P, Obermannova R, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. Eur J Cancer 2022;164:18–29. https://doi.org/10.1016/j.ejca.2021.11.032.
23. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al. World Health Organization: International Classification of Diseases for Oncology 2000:240 pages.
24. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. Ann Surg Oncol 2010;17:3077–9. https://doi.org/10.1245/s10434-010-1362-z.
25. Kroese TE, Rossum PSN Van, Nilsson M, Lordick F, Smyth EC, Rosati R, et al. European Journal of Surgical Oncology Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project : A multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer. Eur J Surg Oncol 2022. https://doi.org/10.1016/j.ejso.2022.09.012.
26. Kroese TE, van Hillegersberg R, Schoppmann S, Deseyne PRAJ, Nafteux P, Obermannova R, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. Eur J Cancer 2022;164:18–29. https://doi.org/10.1016/j.ejca.2021.11.032.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–83. https://doi.org/10.1016/0021-9681(87)90171-8.
28. ter Veer E, van Kleef JJ, Schokker S, van der Woude SO, Laarman M, Haj Mohammad N, et al. Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis. Eur J Cancer 2018. https://doi.org/10.1016/j.ejca.2018.07.132.
29. The R Foundation. R: The R Project for Statistical Computing 2018. https://www.r-project.org/.
30. Hall PS, Swinson D, Cairns DA, Waters JS, Petty R, Allmark C, et al. Efficacy of Reduced-Intensity Chemotherapy with Oxaliplatin and Capecitabine on Quality of Life and Cancer Control among Older and Frail Patients with Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. JAMA Oncol 2021;7:869–77. https://doi.org/10.1001/jamaoncol.2021.0848.
31. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet 2019. https://doi.org/10.1016/S0140-6736(18)32557-1.
32. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. In: Wagner AD, editor. Cochrane Database Syst. Rev., Chichester, UK: John Wiley & Sons, Ltd; 2010, p. CD004064. https://doi.org/10.1002/14651858.CD004064.pub3.
33. van der Kaaij RT, Koemans WJ, van Putten M, Snaebjornsson P, Luijten JCHBM, van Dieren JM, et al. A population-based study on intestinal and diffuse type adenocarcinoma of the oesophagus and stomach in the Netherlands between 1989 and 2015. Eur J Cancer 2020;130:23–31. https://doi.org/10.1016/j.ejca.2020.02.017.
34. Yang DX, Khera R, Miccio JA, Jairam V, Chang E, Yu JB, et al. Prevalence of Missing Data in the National Cancer Database and Association with Overall Survival. JAMA Netw Open 2021;4. https://doi.org/10.1001/jamanetworkopen.2021.1793.

35. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27–40. https://doi.org/10.1016/S0140-6736(21)00797-2.
36. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 2022;20:167–92. https://doi.org/10.6004/jnccn.2022.0008.

9

PART III

Summary, general discussion, and future perspectives

CHAPTER 10

Summary

The aim of this thesis was to develop a multidisciplinary European consensus statement for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (PART I) and assess the incidence and treatment of oligometastatic disease in patients with esophagogastric cancer (PART II).

PART I The OMEC project

Chapter 2. Study protocol of the OMEC project

A study protocol for the OMEC project was developed. The protocol aimed to establish a multidisciplinary European consensus statement for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer. The protocol described 4 parts, including a systematic review and a meta-analysis (OMEC-1), discussion of real-life clinical cases (OMEC-2), a Delphi consensus study (OMEC-3), and a clinical practice guideline (OMEC-4). OMEC was endorsed by the medical societies of medical oncology (ESMO), radiation oncology (ESTRO), surgical oncology (ESSO), diseases of the esophagus (ESDE), European organization of research and treatment of cancer (EORTC), international gastric cancer association (IGCA), and Dutch upper gi cancer group (DUCG). Experts were identified by the aforementioned medical societies or by a systematic review of last authors of published trials in esophagogastric cancer. The agreement was categorized as either consensus (≥75% agreement), fair (50-75% agreement), or poor/absent (<50% agreement).

Chapter 3. Definitions of oligometastatic esophagogastric cancer and outcomes after local metastasis-directed therapy.

A systematic review of the literature was conducted on definitions of oligometastatic esophagogastric cancer. In addition, a meta-analysis was performed on hazard ratios for overall survival following local treatment for oligometastatic disease versus systemic therapy alone. A total of 97 studies, including 7 study protocols, and 2 prospective studies, were included. It was observed that current literature considers esophagogastric cancer spread limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station to be oligometastatic disease (consensus, i.e. ≥75% agreement). In addition, organ-specific oligometastatic disease burden could involve bilobar ≤3 liver metastases, unilateral ≤2 lung metastases, 1 extra-regional lymph node station with metastases, or bilateral adrenal gland metastases (consensus). Finally, local treatment with or without systemic therapy was associated with improved overall survival as compared with systemic therapy alone in patients with oligometastatic esophagogastric cancer and in patients with only liver oligometastases from esophagogastric cancer. However, the included studies were predominantly retrospective and non-randomized, and therefore, had high risk of bias.

Chapter 4. Definitions and treatment of oligometastatic esophagogastric cancer according to multidisciplinary tumor boards in Europe

A total of 15 real-life clinical cases were distributed to 49 multidisciplinary tumor boards of esophagogastric cancer expert centers in Europe to assess the definition and treatment of oligometastatic esophagogastric cancer. Oligometastatic disease was considered in patients with esophagogastric cancer with 1-2 metastases in either the liver, lung, retroperitoneal lymph nodes, adrenal gland, soft tissue or bone (consensus, i.e. ≥75% agreement). At follow-up, oligometastatic disease was considered after a median of 18 weeks of systemic therapy when no progression or progression in size only of the oligometastatic lesion(s) was seen (consensus). However, no consensus was identified among multidisciplinary tumor boards on treatment strategies to be followed in the case of oligometastatic disease. In fact, high practice variability in treatment strategies for oligometastatic esophagogastric cancer exists in Europe. This practice variability could potentially affect the quality of care.

Chapter 5. Definition and treatment of oligometastatic esophagogastric cancer: a Delphi consensus study in Europe

A Delphi consensus methodology was used to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer. A total of 65 esophagogastric cancer experts from 49 expert centers across 16 European countries were requested to participate in a starting meeting, 2 Delphi questionnaire rounds, and a consensus meeting. Oligometastatic disease in patients with esophagogastric cancer was limited to 1 organ with ≤3 metastases or 1 extra-regional lymph node station (consensus, i.e. ≥75% agreement). In addition, oligometastatic disease was considered at restaging after systemic therapy in patients without progression (consensus) or progression in size only (fair agreement). For patients with synchronous or metachronous oligometastatic disease with a disease-free interval ≤2 years, systemic therapy followed by restaging to consider local treatment for oligometastatic disease was the recommended treatment approach (consensus). For patients with metachronous oligometastatic disease with a disease-free interval >2 years either upfront local therapy or systemic therapy followed by restaging to consider local treatment could be performed.

Chapter 6. A clinical practice guideline for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4)

Clinical practice guideline for definition, diagnosis, and treatment for oligometastatic esophagogastric cancer were developed. Guidelines were developed according to AGREE II and GRADE principles. Guidelines were based on an updated systematic review (including 1 randomized and 4 non-randomized phase II trials), clinical case discussions, and a Delphi consensus study by 49 European expert centers for esophagogastric cancer, resulting in

moderate recommendations. OMD is considered in esophagogastric cancer patients with 1 organ with ≤3 metastases or 1 involved extra-regional lymph node station. In addition, OMD continues to be considered in patients with OMD without progression in number of metastatic sites after systemic therapy. ^{18}F-FDG PET/CT imaging is recommended for baseline staging and for restaging after systemic therapy when local treatment is considered. For patients with synchronous OMD or metachronous OMD and a disease-free interval ≤2 years, recommended treatment consists of systemic therapy followed by restaging to assess suitability for local treatment. For patients with metachronous OMD and disease-free interval >2 years, upfront local treatment is additionally recommended.

PART II Oligometastatic esophagogastric cancer in clinical practice

Chapter 7. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study

The incidence, characteristics, and treatment of patients with oligometastatic esophagogastric cancer were analyzed in a multicenter retrospective cohort study. Oligometastatic disease (≤5 metastases in ≤2 organs) was present in 24% of patients with synchronous or metachronous metastatic esophagogastric cancer. The rate of oligometastatic disease was comparable between the two tertiary referral cancer centers in the Netherlands and Switzerland. Combined local treatment and systemic therapy was independently associated with improved overall survival as compared with either systemic therapy alone or local treatment alone for oligometastatic disease. The improved overall survival in the combined treatment group was mainly the result of improved progression-free survival, probably due to the synergistic effect of local and systemic control. Randomized controlled trials are warranted to confirm these results.

Chapter 8. Metastasectomy or stereotactic radiotherapy for oligometastatic esophagogastric cancer: a nationwide population-based cohort study

The treatment and outcomes of patients who underwent local treatment for oligometastatic esophagogastric cancer were analyzed in this population-based study in the Netherlands. Esophageal cancer was the most common type of cancer (85%), with adenocarcinoma being the most predominant histology (80%). Most patients underwent local treatment for oligometastatic disease located in 1 organ (79%), 1 extra-regional lymph node region (12%), or the peritoneum (9%). Combining local treatment with systemic therapy was independently associated with improved overall survival as compared with either local treatment or systemic therapy for oligometastatic disease. These results suggest that combining local treatment of metastases with systemic therapy is preferred treatment approach for patients with oligometastatic esophagogastric cancer. However, a randomized controlled trial is desired to confirm the results due to potential selection bias.

Chapter 9. Oligometastatic disease in gastric cancer patients with liver metastases

The incidence and treatment of oligometastatic disease in gastric cancer patients with synchronous metastatic disease limited to the liver was analyzed in this population-based cohort study. Oligometastatic disease (i.e. ≤3 metastases) was present in 26% of gastric cancer patients with metastatic disease limited to the liver. Patients with liver oligometastatic disease had improved overall survival as compared with patients without liver oligometastatic disease. Nevertheless, overall survival among patients with liver oligometastatic disease remained poor (median overall survival of 5.7 months). Among gastric cancer patients with liver oligometastatic disease, 2% had resection of the primary tumor and oligometastasis, 30% received chemotherapy alone, and 68% received best supportive care. The portion of patients receiving best supportive care (68%) may explain the poor overall survival as it was often related to poor performance status, patient request to refrain from further treatment, or comorbidities. In addition, these results suggests that the concept of oligometastatic disease and the benefit of resection of liver oligometastatic disease may still have been relatively unknown in this disease type during the study inclusion years.

CHAPTER 11

General discussion, future directions, and conclusion

Based on Oligometastatic disease in esophagogastric cancer: an update of recommendations on definition, diagnosis and treatment

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Tiuri E. Kroese, Sebastiaan F.C. Bronzwaer, Richard van Hillegersberg, Peter S.N. van Rossum, Hanneke W.M. van Laarhoven

This chapter provides a comprehensive overview of the implications and challenges that arise from the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer within the context of clinical practice. Additionally, this chapter addressed potential advancements and future directions.

Oligometastatic disease represents a unique category within the spectrum of metastatic diseases, challenging the conventional belief in its incurability[1]. A shift in approach towards combining local therapy with systemic therapies introduces a potential pathway to cure for carefully selected patients[2]. The OMEC initiative has led to a unified consensus among European experts on defining, diagnosing, and treating oligometastatic esophagogastric cancer, offering a potential pathway for improved overall survival rates (Chapter 5). The endorsement by medical societies (ESTRO, ESMO, IGCA, EORTC, DUCG, and ESSO) as well as the multidisciplinary collaborative design, involving radiation oncologists, medical oncologists, and surgical oncologists with expertise in oligometastatic disease, ensures a comprehensive perspective on clinical decision-making (Chapter 2). However, the project's European focus is predominantly applicable to esophagogastric adenocarcinoma, potentially overlooking the insights of experts beyond Europe, especially considering squamous cell carcinoma's prevalence in Asian countries[3]. Therefore, it is worth investigating whether the approach to clinical decision-making in Europe for oligometastatic esophagogastric squamous cell carcinoma differs from that in Asian countries.

DEFINITION OF OLIGOMETASTATIC DISEASE

Patient selection is a critical aspect of managing oligometastatic disease. Patient selection involves the differentiation between patients with oligometastatic disease who could benefit from local treatment (and systemic therapy) versus those with polymetastatic disease who benefit from systemic therapy alone[1]. However, accurate patient selection is hindered by the scarcity of clinical evidence to inform clinical decision-making (Chapter 3). Consequently, healthcare professionals must predominantly rely on single-center experience (Chapter 3).
The objective of the OMEC definition of oligometastatic disease is to provide a clinical practice guideline for clinical decision making in oligometastatic esophagogastric cancer. This clinical practice guideline is structured around three main principals (Chapter 6). Firstly, to identify patients who *should* be classified as having oligometastatic disease and would experience the *most* benefit from local treatment of metastases (categorized by *consensus* in Delphi rounds). Secondly, to identify patients who *could* be considered to have oligometastatic disease and who might experience *modest* benefit from local treatment of metastases (categorized by *fair agreement* in Delphi rounds). Thirdly, patients who *should not* be considered to have oligometastatic disease and are expected to experience limited/no benefit from local treatment of metastases (Figure 1).

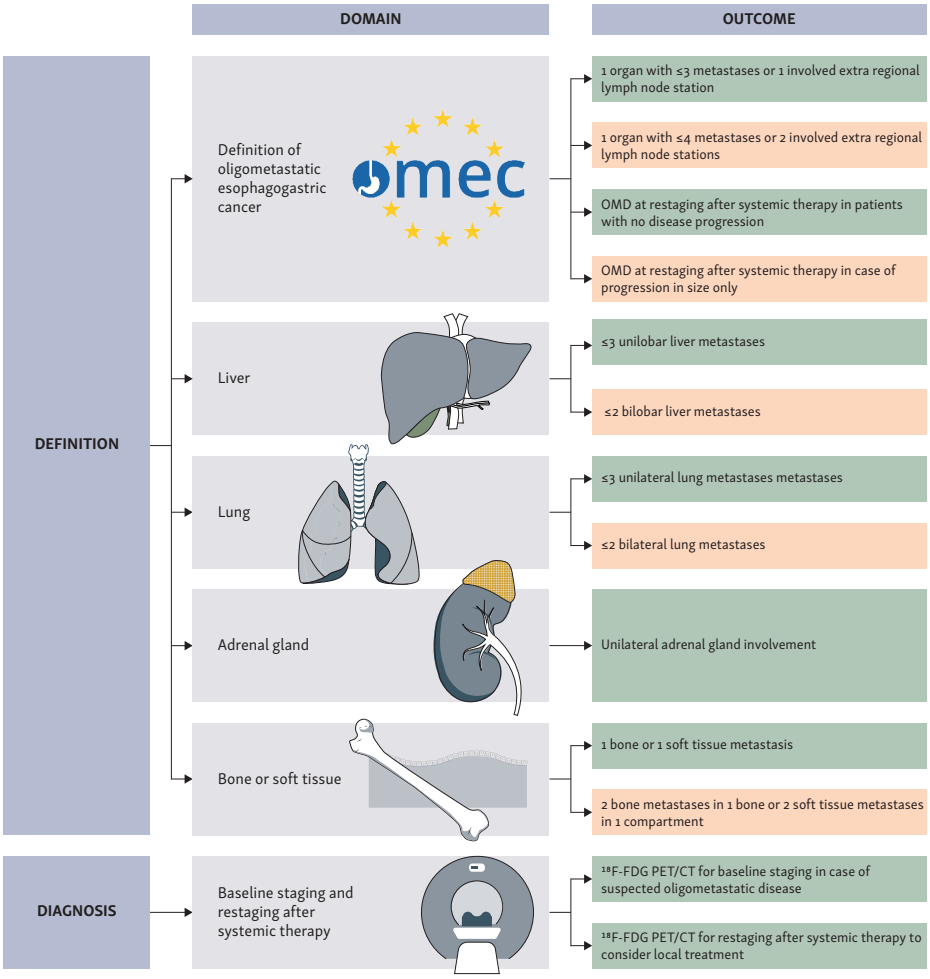

Figure 1. Definition and diagnosis of oligometastatic esophagogastric cancer.

The OMEC clinical practice guidelines for the definition, diagnosis and treatment of oligometastatic esophagogastric cancer is strengthened by the presence of substantial clinical evidence. This evidence, gathered from a randomized controlled trial[4] and various retrospective and prospective studies[5-9] as well as exert opinion (Chapter 3-9), provides substantial support for the proposed definition (Chapter 6). The inclusion of clinical evidence adds credibility and reliability to the consensus statement, reinforcing its validity and enhancing its acceptance within the medical community. However, we do acknowledge that the validity of this clinical practice guideline would be further strengthened by randomized controlled data, which is expected in the coming years[10-16].

Besides the OMEC multidisciplinary European consensus definition of oligometastatic esophagogastric cancer (Chapter 6), several other definitions of oligometastatic esophagogastric cancer exist (Table 1). For example, the German FLOT-5 phase III trial[10] and the French SURGIGAST phase III trial[17] use ≤5 metastases as cut-off for the definition of oligometastatic disease while the American phase III trial[14] by the National Cancer Institute use ≤3 metastases as cut-off for the definition of oligometastatic disease (comparable with OMEC). Furthermore, the German FLOT-5 trial[10] and the French SURGIGAST trial[17] enroll patients with up to 2 metastatic sites (including organ and extra-regional lymph node metastases) as well as patients with peritoneal metastases, which are classified as not oligometastatic disease based on OMEC (Chapter 5). Finally, the German FLOT-5 trial[10], French SURGIGAST trial[17], and American trial by the National Cancer Institute[14] consider oligometastatic disease only in patients without progression after systemic therapy. Consequently, these studies[10,14,17] exclude patients with progression in size only after systemic therapy, while these patients *could* be considered to still have oligometastatic disease based on OMEC (Chapter 6).

Therefore, it would be worth investigating to examine the prognostic difference among patients who have various definitions of oligometastatic disease. Such analysis could focus on differentiating the outcomes for varying burden of oligometastatic disease, as well as varying response to systemic therapy. While baseline tumor burden is an important prognostic factor for overall survival in (oligo)metastatic disease (Chapter 9), it is possible that the response to systemic therapy holds greater significance. Therefore, defining oligometastatic disease at baseline may not be the optimal approach for selecting patients for local treatment for oligometastatic disease.

DIAGNOSIS OF OLIGOMETASTATIC DISEASE

At present, the primary approach for identifying oligometastatic disease is with imaging. According to OMEC, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with intergraded computed tomography (CT) is recommended at baseline in patients with (suspected) oligometastatic esophagogastric cancer to exclude polymetastatic disease (Chapter 6). In addition, ^{18}F-FDG PET/CT imaging is recommended at restaging after systemic therapy to exclude polymetastatic disease and consider local treatment for oligometastatic disease (Chapter 6).

This recommendation of ^{18}F-FDG PET/CT imaging for baseline staging and for restaging after systemic therapy of oligometastatic disease, is in line with current EMSO clinical practice guidelines recommendation for baseline staging of esophageal cancer[18]. However, the EMSO

Table 1. Prospective trials in patients with oligometastatic esophagogastric cancer.

Author or sponsor name or clinicaltrials.gov ID,	Primary tumor	Country	Study type	Maximum # organs	Maximum # metastases	Type of OMD	Staging	Treatment
NCT04510064 (Fudan University)	Gastric AC or EGJ AC	China	II NR	1	Organ-specific	Synchronous	CT or MRI	IO+ChT+ Surgery
NCT04248452 (ECOG-ACRIN Cancer Research Group)	Esophageal AC and Gastric	USA	III R	ns	3	Synchronous	CT or MRI	ChT + SBRT vs ChT
NCT04263870 "CTSCAPOXSEA" (Sichuan University)	Gastric AC or EGJ AC	China	II NR	1 + RPLN	Organ-specific	Synchronous	CT or MRI	ChT+ IO + Surgery
NCT03904927 (Fudan University)	Esophageal SCC	China	II R	2	4	Synchronous/ metachronous	CT	ChT + SBRT/ Surgery vs ChT
NCT03161522 (National Cancer Institute)	Esophageal AC	USA	II NR	1	3	Synchronous	^{18}F-FDG PET/CT	ChT+ SBRT/Surgery
NCT03399253 (Sun Yat-sen University)	Gastric AC	China	II-III R	2	Organ-specific	Synchronous	CT	ChT+Surgery vs ChT
NCT02578368 "FLOT5" (Krankenhaus Nordwest)	Gastric AC or EGJ AC	Germany	III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ^{18}F-FDG PET	ChT+Surgery vs ChT
NCT04512417 (Zhejiang Cancer Hospital)	Esophageal SCC or AC	China	II R	ns	4	Synchronous/ metachronous	ns	IO+ChT+ SBRT vs IO + ChT
NCT03042169 "Surgigast" (University Hospital Lille)	Gastric AC or EGJ AC	France	III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ^{18}F-FDG PET	ChT+ Surgery vs ChT

AC: adenocarcinoma, CT: computed tomography, ChT: chemotherapy, IO: immune-oncology, MRI: magnetic resonance imaging, NR: non-randomized, OMD: oligometastatic disease, R: randomized, RPLN: retroperitoneal lymph nodes, SBRT: stereotactic body radiotherapy, SCC: squamous cell carcinoma, USA: United States of America, ns: not specified, ^{18}F FDG PET: fluorodeoxyglucose position emission tomography, II: phase II, III: phase III.

clinical practice guidelines for esophageal cancer does not routinely recommend ^{18}F-FDG PET/CT imaging during follow-up after curative treatment for esophageal cancer[18]. In fact, surveillance protocols after primary curative treatment for esophageal cancer are varied and inconsistent, reflecting a lack of evidence[19].

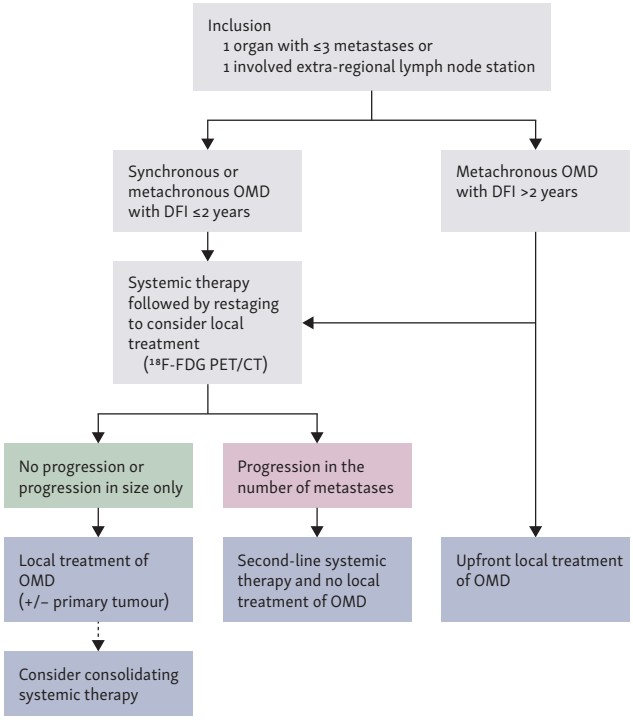

Figure 2. Treatment for oligometastatic esophagogastric cancer.

An international multicenter study of 27 high-volume European and North American esophagogastric cancer expert centers highlighted significant variation in surveillance policies after curative therapy for esophageal[19]. In this study, a total of 4682 patients with curative treatment for esophageal cancer were included of whom 46% underwent an intensive surveillance policy (i.e. annual CT or PET/CT for 3 years postoperatively)[19]. An intensive surveillance policy *was not* associated improved overall survival after correction for confounders among all patients[19]. In patients with lower pathological (y)pT stage (i.e. Tis-2), an intensive surveillance policy was associated with improved overall survival[19]. These results suggest that an intensive surveillance policy should not be performed for all patients with esophageal cancer after curative therapy, and perhaps only in patients with lower pathological (y)pT stage.

The question of structured follow-up with regular radiological and endoscopic investigations for patients who have had surgical treatment for esophageal and gastric cancer is currently being evaluated in nation-wide study in the UK (SARONG)[20].

Imaging alone might therefore not be a perfect method for selecting patients to undergo local treatment for oligometastatic disease. Recent studies have indicated a potential new way of selecting patients for local treatment for oligometastatic disease using biomarkers such as circulating tumor DNA[21]. Circulating tumor DNA are small fragments of DNA containing specific genetic alterations characteristics of the tumor that are released into the bloodstream by tumors cells[21]. Circulating tumor DNA can be analyzed from blood samples but also from non-blood samples such as urine or spinal fluid and are therefore less invasive to obtain as compared with traditional tumor biopsies[21].

Recently, studies in patients with gastric cancer as well as esophageal cancer have demonstrated the prognostic value of circulating tumor DNA[22,23]. Multivariable analysis showed that circulating tumor DNA status and clinical disease stage were independently associated with survival outcomes[23]. In addition, circulating tumor DNA enables earlier detection of recurrence after treatment compared to standard imaging[24].

Another applicability of circulating tumor DNA is monitoring of treatment response. A phase II randomized controlled trial is currently evaluating the clearance of circulating tumor DNA to select patients with oligometastatic esophageal, gastroesophageal junction, gastric, duodenal, or ampullary adenocarcinoma who would benefit from metastasectomy and/or cytoreductive surgery[25]. In this trial patients receive induction chemotherapy and those with undetectable circulating tumor DNA after systemic therapy (i.e. good response) will be 1:1 randomized to surgery or continuation of chemotherapy alone[25]. However, it should be noted that the applicability of this study is unclear because in this study also patients with peritoneal metastases are included who are considered *not* to be oligometastatic disease according to OMEC.

The role of circulating tumor DNA in patients with oligometastatic esophagogastric cancer has not yet been established but an important role could be to monitor treatment response. Patients without progression on restaging ^{18}F-FDG PET/CT and with undetectable circulating tumor DNA (i.e. circulating tumor DNA clearance) could be offered local treatment for oligometastatic disease, while patients with progression of imaging or no circulating tumor DNA clearance (i.e. circulating tumor DNA persistence) could be offered second-line systemic therapy.

TREATMENT OF OLIGOMETASTASIS DISEASE

Developing a consensus treatment algorithm for oligometastatic esophagogastric cancer was crucial to address the considerable variation in treatment approaches for oligometastatic disease across Europe (Chapter 3). In fact, our study on the treatment of patients with gastric cancer with liver oligometastatic disease suggested that the concept of oligometastatic disease treatment was generally not applied in the Netherlands during 2015 and 2017 (Chapter 8).

According to OMEC, patients with synchronous or metachronous oligometastatic disease with a disease-free interval of ≤2 years should first receive systemic therapy followed by restaging to consider subsequent local treatment for oligometastatic disease (Chapter 6). This treatment approach is necessary to assess the biological behavior of this heterogeneous patient group using a "test-of-time"[26]. If the patient at restaging after systemic therapy does not develop disease progression (stable disease, partial or complete response), local treatment is recommended (Chapter 5). Our retrospective data support the recommendation of combined local treatment and systemic therapy for oligometastatic disease in esophagogastric cancer since it was associated with improved overall survival compared to either systemic therapy or local treatment (Chapter 6 and 7). However, it is important to note that the results of these retrospective studies could be influenced by confounding-by-indication, as more often patients responded to systemic therapy underwent subsequent local treatment for oligometastatic disease.

For patients with metachronous oligometastatic disease and a disease-free interval of >2 years, both upfront local treatment and systemic therapy followed by restaging are considered suitable treatment options (Chapter 5). Thus, a "test-of-time" may not be necessary for patients with relatively favorable biological behavior[26]. This recommendation was in line with phase II non-randomized trial by Liu et al.[5], which included patients with oligometastatic esophageal squamous cell cancer. In this trial, 50% patients received combined chemotherapy (in addition to SBRT)[5]. The use of chemotherapy was not associated with improved overall survival[5]. However, the results of this trial should be interpreted with care because no patients with oligometastatic esophageal adenocarcinoma were included and immunotherapy was not applied[5].

The OMEC project did not reach a consensus regarding the type and duration of systemic therapy for oligometastatic disease (Chapter 5). Although ≥3 months of systemic therapy, including triplet chemotherapy, could be used, our retrospective study did not find a significant improvement in overall survival with triplet compared to doublet chemotherapy in patients with gastric cancer and liver metastases (Chapter 8). However, it is important to note that the

study period of this study predated the use of FLOT/CapOx chemotherapy in the Netherlands, which has been shown to improve overall survival compared to ECF/ECC chemotherapy in the perioperative setting[27]. Therefore, the equipoise in overall survival between doublet and triplet chemotherapy should be interpreted cautiously. Accordingly, a network meta-analysis of randomized controlled trials showed that fluoropyrimidine, oxaliplatin, and taxane (FOxT) was the only triplet that was more effective compared with fluoropyrimidine-doublets but was also associated with increased toxicity compared with fluoropyrimidine and oxaliplatin[28]. Therefore, FOxT should be reserved to the physically fit patients[28].

Currently, no available data indicates the optimal duration of systemic therapy for oligometastatic disease. Consequently, ongoing trials are exploring different durations and agents of systemic therapy (Table 1). For example, the German FLOT-5 trial[10] and French SURGIGAST trial[17] use 4 cycles of induction FLOT chemotherapy over a period of 2 months. Patients without progression are randomized to 4-8 cycles of consolidating FLOT chemotherapy alone or 4-8 cycles of consolidating FLOT chemotherapy plus surgery[10,17]. The American phase III trial[14] conducted by the National Cancer Institute utilizes 4 cycles of induction FLOT chemotherapy or 6 cycles of induction CapOx chemotherapy over a period of 4.5 months. Patients without progression are randomized to 2 years of consolidating FLOT or CapOx chemotherapy alone or 2 years of consolidating FLOT or CapOx chemotherapy plus surgery[14].

This variation in the duration on the type and duration of systemic therapy can be explained by 2 perspectives. One perspective is that patients with oligometastatic disease undergo a palliative treatment. Therefore, a longer course of systemic therapy may be more effective to eliminate patients with disease progression early during treatment. Another viewpoint is that patients with oligometastatic disease undergo a potentially curative treatment. Therefore, the aim is to treat the disease aggressively and promptly, before it can develop new metastases or drug resistance, which suggests a short but more intensive course of systemic therapy.

This question is again relevant if we look at the role of immunotherapy for oligometastatic disease. Immunotherapy is a new form of systemic therapy that targets immune checkpoints[29]. One of these immune checkpoints is programmed cell death protein 1 receptor (PD-1) and its ligand PD-L1[29]. Therapeutic antibodies for this immune checkpoint pathway are nivolumab (which targets the PD-L1) and pembrolizumab (which targets the PD-1)[29]. The PD-1/PD-L1 expression can be assessed using various methods including the combined positive score (CPS) or tumor proportion score (TPS)[29].

Recently, combined nivolumab plus chemotherapy or pembrolizumab plus chemotherapy (i.e. chemo-immunotherapy) have been shown to improve overall survival in the *first-line palliative*

setting for patients with metastatic esophagogastric cancer, specifically those with a adenocarcinoma and CPS ≥ 1% (CheckMate 649[30]) or squamous cell carcinoma and CPS ≥ 10% (KEYNOTE-590[31]). Additionally, nivolumab *monotherapy* has been shown to improve disease-free survival in the *adjuvant setting* for patients with esophageal cancer with a pathologic incomplete response after neoadjuvant chemoradiotherapy plus surgery (CheckMate 577[32]) while adjuvant nivolumab plus chemotherapy did not improve relapse-free survival in the *adjuvant setting* for gastric cancer patients with incomplete response after neoadjuvant chemotherapy plus surgery (ATTRACTION-5)[33].

Give the different immunotherapy regimens used depending on the disease stage (immunotherapy monotherapy in the curative *adjuvant* setting or chemo-immunotherapy in the first-line *palliative setting*), it currently unclear if patients with oligometastatic disease should receive chemo-immunotherapy as an induction regimen or immunotherapy monotherapy as consolidation after systemic therapy and local treatment.

OMEC-5

The final subproject of OMEC, is a phase III clinical trial (OMEC-5). We designed a phase III randomized clinical trial that was recently accepted for central support by EORTC to prospectively evaluate the suggested treatment approach.

The aim is to determine the best timing of local metastasis-directed therapy for antitumor immune-stimulation. In this EORTC-supported trial involving 15-20 European expert centers from the OMEC consortium, the primary aim is to assess the potential benefit in progression-free survival of prolonged versus short chemo-immunotherapy duration before local metastasis-directed treatment in patients with oligometastatic esophageal cancer.

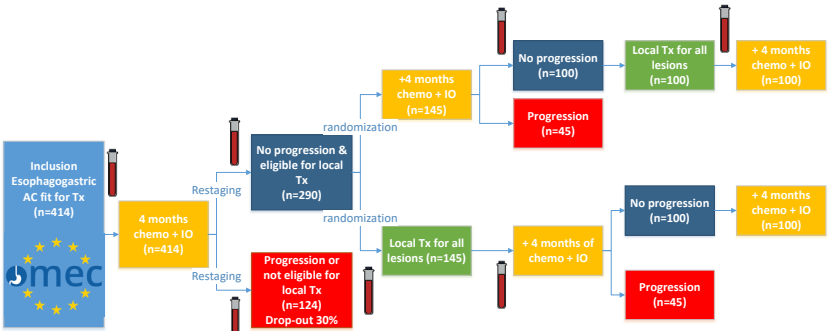

Figure 3. Study flowchart for the EORTC OMEC-5 randomized phase III trial.

Eligible patients will receive standard chemo-immunotherapy. Those without progression at 4 months and eligible for local treatment will be randomly assigned (1:1) to receive either an additional 4 months of immunotherapy with subsequent local treatment to all disease sites (Arm 1) or direct local treatment (Arm 2; Figure 3). The type of local treatment can involve SBRT, metastasectomy, radiofrequency/microwave ablation.

The primary outcome is progression-free survival. Secondary outcomes include translational outcomes, such as assessment of ctDNA as prognostic/predictive markers of survival, local treatment efficacy, and early detection of progression. The trial aims to include 290 patients to detect a hazard ratio for progression-free survival of 0.70, increasing median progression-free survival from 11 to 16 months. The total expected study duration is 53 months.

CONCLUSIONS

The conclusions reached in this thesis can be summarized as follows (Figure 4):

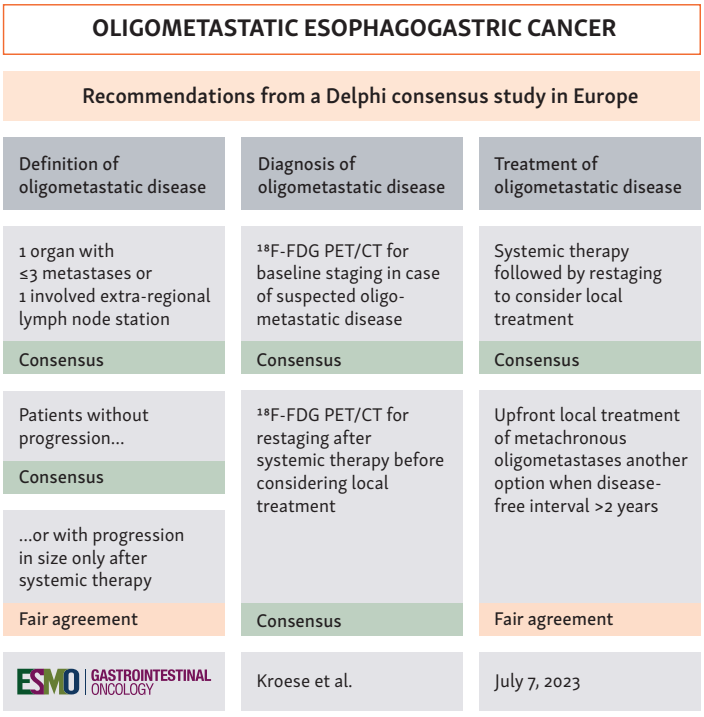

Figure 4. Summary of conclusions of this thesis.

PART I The OMEC project

- The first multidisciplinary European consensus statement for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer was developed.
- Oligometastatic disease should be considered in patients with esophagogastric cancer with ≤3 metastases in 1 organ or 1 involved extra-regional lymph node station.
- Patients with esophagogastric cancer with synchronous or metachronous oligometastatic disease with a disease-free interval of ≤2 years should undergo systemic therapy followed by restaging to consider local treatment.
- Patients with esophagogastric cancer with metachronous oligometastatic disease with a disease-free interval of >2 years, could also undergo upfront local treatment.
- At restaging after systemic therapy, local treatment for oligometastatic disease should be considered in patients without progression or could be considered in patients with progression in size only.
- After systemic therapy and local treatment for oligometastatic disease, consolidating immunotherapy could be considered.
- Baseline staging and restaging after systemic therapy (when local treatment is considered) in patients with oligometastatic esophagogastric cancer should be performed with 18F-FDG PET/CT.

PART II Oligometastatic esophagogastric cancer in clinical practice

- Oligometastatic disease was present in 24% of patients with synchronous or metachronous metastatic esophagogastric cancer.
- Liver oligometastatic disease (≤3 liver metastases) was present among 26% of patients with gastric cancer with metastatic disease limited to the liver.
- Liver oligometastatic disease in gastric cancer was associated with improved overall survival as compared with liver polymetastatic disease (>3 liver metastases).
- Retrospectively, combined local treatment and systemic therapy for oligometastatic esophagogastric cancer was associated with the best overall survival.
- Retrospectively, no improvement in overall survival was associated with triplet compared to doublet chemotherapy in patients with gastric cancer and liver metastases.
- The concept of oligometastatic disease treatment for patients with gastric cancer and liver metastases was generally not applied in the Netherlands during 2015 and 2017.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. Jan 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. Jun 2011;8(6):378-82. doi:10.1038/nrclinonc.2011.44
3. Jiang Y, Lin Y, Wen Y, et al. Global trends in the burden of esophageal cancer, 1990-2019: results from the Global Burden of Disease Study 2019. *J Thorac Dis*. Feb 28 2023;15(2):348-364. doi:10.21037/jtd-22-856
4. Liu Q, Chen J, Lin Y, et al. Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. Nov 16 2023;doi:10.1016/S2468-1253(23)00316-3
5. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. Nov 1 2020;108(3):707-715. doi:10.1016/j.ijrobp.2020.05.003
6. Zhao W, Ke S, Cai X, et al. Radiotherapy plus camrelizumab and irinotecan for oligometastatic esophageal squamous cell carcinoma patients after first-line immunotherapy plus chemotherapy failure: An open-label, single-arm, phase II trial. *Radiother Oncol*. Jul 2023;184:109679. doi:10.1016/j.radonc.2023.109679
7. Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? a multicenter, prospective cohort study (Neo-REGATTA). *BMC Cancer*. Apr 4 2023;23(1):308. doi:10.1186/s12885-023-10773-x
8. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol*. Sep 1 2017;3(9):1237-1244. doi:10.1001/jamaoncol.2017.0515
9. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol*. Mar 2016;17(3):309-318. doi:10.1016/S1470-2045(15)00553-7
10. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer*. Dec 28 2017;17(1):893. doi:10.1186/s12885-017-3918-9
11. Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction (CTSCAPOXSEA). *https://classicclinicaltrialsgov/ct2/show/NCT04263870*. 2020;
12. Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. https://classic.clinicaltrials.gov/ct2/show/NCT04248452
13. A Clinical Study Of Camrelizumab With Or Without Radiotherapy In The Treatment Of Esophageal Cancer. *https://classicclinicaltrialsgov/ct2/show/NCT04512417*. 2020;
14. Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer.
15. PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment of Unresectable Locally Advanced or Limited Metastatic Gastric Cancer. *https://classicclinicaltrialsgov/ct2/show/NCT04510064*. 2020;
16. Local Therapy for Oligorecurrent and Oligometastatic Esophageal Squamous Cell Carcinoma. *https://classicclinicaltrialsgov/ct2/show/NCT03904927*. 2019;
17. Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer (SURGIGAST). *https://classicclinicaltrialsgov/ct2/show/NCT03042169*. 2017;

18. Obermannova R, Alsina M, Cervantes A, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2022;33(10):992-1004. doi:10.1016/j.annonc.2022.07.003
19. Elliott JA, Markar SR, Klevebro F, et al. An International Multicenter Study Exploring Whether Surveillance After Esophageal Cancer Surgery Impacts Oncological and Quality of Life Outcomes (ENSURE). *Ann Surg*. Jan 27 2022;277(5):e1035-44. doi:10.1097/SLA.0000000000005378
20. markar S. Open label randomised controlled trial of intensive surveillance vs. standard postoperative follow-up in patients undergoing surgical resection for oesophageal and gastric cancer (SARONG). https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/surveillance-after-resection-of-oesophageal-and-gastric-cancer-trial/
21. Tivey A, Church M, Rothwell D, Dive C, Cook N. Circulating tumour DNA - looking beyond the blood. *Nat Rev Clin Oncol*. Sep 2022;19(9):600-612. doi:10.1038/s41571-022-00660-y
22. van Velzen MJM, Creemers A, van den Ende T, et al. Circulating tumor DNA predicts outcome in metastatic gastroesophageal cancer. *Gastric Cancer*. Sep 2022;25(5):906-915. doi:10.1007/s10120-022-01313-w
23. Huffman BM, Aushev VN, Budde GL, et al. Analysis of Circulating Tumor DNA to Predict Risk of Recurrence in Patients With Esophageal and Gastric Cancers. *JCO Precis Oncol*. Dec 2022;6:e2200420. doi:10.1200/PO.22.00420
24. Azad TD, Chaudhuri AA, Fang P, et al. Circulating Tumor DNA Analysis for Detection of Minimal Residual Disease After Chemoradiotherapy for Localized Esophageal Cancer. *Gastroenterology*. Feb 2020;158(3):494-505 e6. doi:10.1053/j.gastro.2019.10.039
25. Dhiman A, Vining CC, Witmer HDD, et al. Phase II Prospective, Open-Label Randomized Controlled Trial Comparing Standard of Care Chemotherapy With and Without Sequential Cytoreductive Interventions for Patients with Oligometastatic Foregut Adenocarcinoma and Undetectable Circulating Tumor Deoxyribose Nucleic Acid (ctDNA) Levels. *Ann Surg Oncol*. Jan 5 2022;29(7):4583-92. doi:10.1245/s10434-021-11249-7
26. Chiapponi C, Berlth F, Plum PS, et al. Oligometastatic Disease in Upper Gastrointestinal Cancer - How to Proceed? *Visc Med*. Mar 2017;33(1):31-34. doi:10.1159/000455683
27. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. May 11 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1
28. Ter Veer E, Haj Mohammad N, van Valkenhoef G, et al. The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. *J Natl Cancer Inst*. Oct 2016;108(10)doi:10.1093/jnci/djw166
29. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. Mar 22 2012;12(4):252-64. doi:10.1038/nrc3239
30. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. Jul 3 2021;398(10294):27-40. doi:10.1016/S0140-6736(21)00797-2
31. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy a lone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. Aug 28 2021;398(10302):759-771. doi:10.1016/S0140-6736(21)01234-4
32. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. Apr 1 2021;384(13):1191-1203. doi:10.1056/NEJMoa2032125
33. Terashima M, Kang Y-K, Kim Y-W, et al. ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer. *Journal of Clinical Oncology*. 2023-06-01 2023;41(16_suppl):4000-4000. doi:10.1200/jco.2023.41.16_suppl.4000

11

APPENDICES

Summary in Dutch (Nederlandse samenvatting)
Authors and affiliations
Review committee
Acknowledgement (Dankwoord)
List of publications
Curriculum Vitae

SUMMARY IN DUTCH – NEDERLANDSE SAMENVATTING

Jaarlijks krijgen ongeveer 4.000 patiënten in Nederland de diagnose slokdarm- of maagkanker. Het aantal nieuwe gevallen van slokdarmkanker neemt in Nederland toe en bedroeg in 2019 ongeveer 3.000 patiënten. Hiermee heeft Nederland relatief gezien het hoogste aantal nieuwe gevallen van slokdarmkanker in Europa. Daarentegen neemt het aantal nieuwe gevallen van maagkanker af; in 2019 bedroeg het aantal nieuwe gevallen ongeveer 1.000 patiënten.

Jaarlijks overlijden ongeveer 3.000 patiënten in Nederland aan slokdarm- of maagkanker. De overleving bij slokdarm- of maagkanker is relatief slecht, aangezien bij ongeveer 35-45% van de patiënten de ziekte al (synchroon) gemetastaseerd is op het moment van eerste presentatie. Bovendien ontwikkelt ongeveer 35% van de patiënten na curatieve behandeling van de primaire tumor (metachroon) gemetastaseerde ziekte. Een groot deel van de patiënten met gemetastaseerde ziekte kan niet meer worden genezen, en de prognose voor deze groep is somber, met een mediane overleving van 6 maanden.

Bij een deel van de patiënten met gemetastaseerde ziekte is het aantal metastasen beperkt; dit wordt aangeduid als 'oligometastasen'. Het concept van oligometastasen werd voor het eerst geïntroduceerd in 1995 door Hellman en Weichselbaum en beschrijft een ziektestadium tussen lokale ziekte en uitgebreide gemetastaseerde ziekte. Dit concept suggereert dat lokale behandeling van oligometastasen, bijvoorbeeld door metastasectomie of stereotactische bestraling (SBRT), kan leiden tot een verbeterde overleving of zelfs genezing. Toch blijft systeemtherapie tot op heden de standaardbehandeling en wordt dit nog steeds aanbevolen in de huidige Europese en landelijke behandelrichtlijnen.

Recent is aangetoond in verschillende gerandomiseerde studies dat lokale behandeling van oligometastasen daadwerkelijk leidt tot een verbetering van de overleving. Twee van deze studies hebben laten zien dat bij patiënten met oligometastasen van longkanker, SBRT in combinatie met systeemtherapie een betere overleving biedt dan alleen systeemtherapie. Een andere gerandomiseerde studie toonde aan dat SBRT in combinatie met standaard palliatieve behandeling (met chemotherapie of observatie) een verbeterde overleving oplevert vergeleken met alleen standaard palliatieve behandeling bij patiënten met prostaat-, long-, darm-, of borstkanker.

Momenteel is er één gerandomiseerde studie verricht naar de lokale behandeling van oligometastasen bij slokdarm- of maagkanker, naast zes niet-gerandomiseerde prospectieve studies. Sommige van deze studies suggereren dat lokale behandeling van oligometastasen kan leiden tot een verbeterde overleving. Hierdoor wordt lokale behandeling van oligometastasen in toenemende mate toegepast.

Echter, de resultaten van verschillende studies over de lokale behandeling van oligometastasen bij slokdarm- of maagkanker zijn moeilijk te vergelijken, omdat er tot op heden geen eenduidige definitie van oligometastasen bij slokdarm- of maagkanker bestaat. Daarnaast is het onduidelijk welke behandelaanpak het meest geschikt is bij oligometastasen: alleen lokale behandeling, of systeemtherapie gevolgd door lokale behandeling in het geval van een goede respons op de systeemtherapie.

Om de verschillen in diagnose en behandeling van oligometastasen bij slokdarm- of maagkanker te identificeren en te overbruggen, hebben wij het OligoMetastatic Esophagogastric Cancer Project (OMEC) opgezet. Het doel van het OMEC-project is het ontwikkelen van een multidisciplinaire consensus statement voor de diagnose en behandeling van oligometastasen bij slokdarm- of maagkanker.

DEEL I Het OMEC-project

Hoofdstuk 2. Het studieprotocol van het OMEC-project

Het OMEC-project bestaat kort samengevat uit vijf studies. Allereerst wordt een systematische review naar de definities van oligometastasen bij slokdarm- of maagkanker in de literatuur uitgevoerd, gevolgd door een meta-analyse van de uitkomsten na lokale behandeling van oligometastasen vergeleken met alleen systeemtherapie (OMEC-1). Ten tweede worden real-life casussen besproken binnen multidisciplinaire teams van expertisecentra voor slokdarm- of maagkanker in Europa, met als doel te bepalen of een casus oligometastasen betreft en wat de optimale behandeling zou moeten zijn. Ten derde omvat het project een Delphi-consensusstudie, bestaande uit een introductiebijenkomst, twee online Delphi-vragenlijstrondes, en een consensusbijeenkomst (OMEC-3), waarbij de resultaten van de twee voorgaande OMEC-studies als input dienden voor de Delphi-rondes. Het OMEC-project wordt ondersteund door de Europese verengingen voor medische oncologie (ESMO), radiotherapie (ESTRO), chirurgische oncologie (ESSO), maagkanker (IGCA), slokdarmkanker (ESDE), onderzoek naar de behandeling van kanker (EORTC), en de Nederlandse slokdarm- of maagkanker groep (DUCG). De mate van overeenstemming in de OMEC-studies wordt geclassificeerd als slecht/afwezig (<50% overeenstemming), matig (50-75% overeenstemming), of consensus (≥75% overeenstemming).

Hoofdstuk 3. Definitie van oligometastasen bij slokdarm- of maakanker en uitkomsten na lokale behandeling van oligometastasen

Er werd een literatuurstudie uitgevoerd naar studies of studieprotocollen die een definitie rapporteerden van oligometastasen bij patiënten met slokdarm- of maagkanker met een adenocarcinoom of plaveiselcelcarcinoom. De primaire uitkomstmaat was het maximale aantal organen en metastasen dat werd beschouwd als oligometastasen. Samenvattend beschouwt

de huidige literatuur (bestaande uit 97 studies of studieprotocollen) een patiënt met slokdarm- of maagkanker met 1 orgaan en ≤3 metastasen of 1 extra-regionaal lymfeklierstation met metastasen als oligometastasen (consensus). Ook wordt een patiënt met slokdarm- of maagkanker met ≤3 bilaterale levermetastasen, ≤2 hersenmetastasen, ≤2 unilaterale longmetastasen, of unilaterale bijniermetastasen beschouwd als oligometastasen. Ten slotte bleek uit niet-gerandomiseerde studies, met een hoog risico op bias, dat lokale behandeling van oligometastasen, met of zonder systeemtherapie, tot een verbetering van de overleving leidt in vergelijking met alleen systeemtherapie, zowel bij patiënten met oligometastasen als bij patiënten met alleen lever oligometastasen van slokdarm- of maagkanker.

Hoofdstuk 4. Definitie van oligometastasen bij slokdarm- of maakanker volgens multidisciplinaire tumor teams in Europa

Expertisecentra in Europa werden verzocht om 15 real-life casussen te bespreken in hun multidisciplinaire teams, met specifieke vragen over de diagnose en behandeling van oligometastasen. In totaal hebben 47 centra de casussen volledig besproken (96%). Casussen met 1-2 metastasen in de lever, longen, retroperitoneale lymfeklieren, bijnieren, weke delen, of botten werden als oligometastasen beschouwd (consensus). Bij herstadiëring na systeemtherapie werden patiënten zonder progressie of met progressie in alleen de grootte, maar niet in het aantal oligometastasen, eveneens als oligometastasen beschouwd (consensus). Er was echter geen consensus over de behandeling van oligometastasen. Deze studie toont aan dat er onder verschillende expertisecentra in Europa wel overeenstemming is over de definitie van oligometastasen, maar niet over de behandeling ervan. Deze variabiliteit in behandelingsbenaderingen zou mogelijk kunnen leiden tot een verminderde kwaliteit van zorg.

Hoofdstuk 5. Definitie en behandeling van oligometastasen bij slokdarm- of maakanker: een Delphi consensus studie in Europa

Om een multidisciplinaire Europese consensusstatement te formuleren over de definitie, diagnose, en behandeling van oligometastasen bij slokdarm- of maagkanker, werden 65 experts uit 49 expertisecentra in 16 verschillende Europese landen uitgenodigd om deel te nemen aan deze Delphi-consensusstudie. De input voor de Delphi-consensusvragenlijst was gebaseerd op twee onderdelen: 1) een literatuurstudie naar de definities van oligometastasen in de huidige literatuur en 2) de bespreking van real-life casussen in multidisciplinaire teams van slokdarm- of maagkankerexpertisecentra. Het Delphi-consensusproces bestond uit een introductiebijeenkomst, twee online Delphi-vragenlijstrondes, en een consensusbijeenkomst. Er werd consensus bereikt dat een patiënt met slokdarm- of maagkanker met 1 orgaan met ≤3 metastasen of 1 extra-regionaal lymfeklierstation met metastasen, als oligometastasen wordt beschouwd. Ook werd vastgesteld dat bij herstadiëring na systeemtherapie, als er geen

progressie in het aantal metastasen is opgetreden, dit eveneens als oligometastasen wordt beschouwd. De aanbevolen behandeling voor een patiënt met slokdarm- of maagkanker met synchrone of metachrone oligometastasen met een ziektevrij interval van ≤2 jaar bestaat uit systeemtherapie, gevolgd door herstadiëring om de mogelijkheid van lokale behandeling van oligometastasen te overwegen. Bij patiënten met een ziektevrij interval van >2 jaar is directe lokale behandeling een aanvullende behandel optie. Concluderend heeft het OMEC-project geleid tot het eerste Europese multidisciplinaire consensusstatement voor de definitie, diagnose, en behandeling van oligometastasen bij patiënten met slokdarm- of maagkanker. Deze consensusstatement moet nog gevalideerd worden in een prospectieve studie.

DEEL 2 Klinische studies over oligometastasen bij slokdarm- en maagkanker

Hoofdstuk 6. Metastasectomie of stereotactische bestraling voor oligometastasen van slokdarm- of maagkanker

De incidentie en behandeling van slokdarm- of maagkankerpatiënten met oligometastasen werden geanalyseerd in deze retrospectieve cohortstudie. Oligometastasen waren aanwezig bij 21% van de patiënten met synchroon of metachroon gemetastaseerde slokdarm- of maagkanker. Lokale behandeling van oligometastasen in combinatie met systemische therapie leidde tot een significante verbetering van de overleving, vergeleken met alleen systeemtherapie of alleen lokale behandeling. De verbetering in overleving bij de groep die een gecombineerde behandeling onderging, was met name te danken aan een verbeterde progressievrije overleving, waarschijnlijk als gevolg van een synergistisch effect tussen lokale en systemische controle. Gerandomiseerde studies zijn echter noodzakelijk om deze bevindingen te bevestigen.

Hoofdstuk 7. Metastasectomie of stereotactische bestraling voor oligometastasen van slokdarm- of maagkanker: een populatie studie

De behandeling en uitkomsten na lokale behandeling van oligometastasen bij slokdarm- of maagkanker in Nederland werden geanalyseerd in deze populatiestudie. Lokale behandeling van oligometastasen met metastasectomie of stereotactische bestraling was onafhankelijk geassocieerd met een verbeterde overleving in vergelijking met alleen lokale behandeling of een referentiegroep van patiënten met slokdarm- of maagkanker die in dezelfde periode alleen chemotherapie kreeg. Deze bevindingen bevestigen eerdere studies die suggereren dat de voorkeursbehandeling voor patiënten met oligometastasen bestaat uit een combinatie van lokale behandeling en systeemtherapie. Gerandomiseerde studies zijn echter noodzakelijk om deze resultaten te bevestigen.

Hoofdstuk 8. Oligometastasen in patiënten met maagkanker en lever metastasen

De incidentie en behandeling van oligometastasen bij patiënten met maagkanker en synchrone metastasen beperkt tot de lever werden geanalyseerd in deze populatiestudie. Lever

oligometastasen (≤3 lever metastasen) kwamen voor bij 26% van de patiënten met synchroon gemetastaseerde maagkanker beperkt tot de lever. Patiënten met oligometastasen in de lever hadden een betere overleving dan patiënten zonder oligometastasen in de lever (>3 lever metastasen) Desondanks was de overleving bij patiënten met lever oligometastasen relatief laag, met een mediane overleving van 5,7 maanden. De behandeling van lever oligometastasen bestond bij 2% van de patiënten uit resectie van de primaire tumor en metastasen, bij 30% uit chemotherapie, en bij 68% uit ondersteunende zorg (geen kankergerichte therapie). De relatief slechte overleving bij patiënten met oligometastasen kan mogelijk worden verklaard door het feit dat 68% van de patiënten ondersteunende zorg ontving, waarbij factoren zoals slechte conditie en comorbiditeiten een rol speelden.

AUTHORS AND AFFILIATIONS

Amsterdam University Medical Center, Amsterdam the Netherlands
Department of Medical Oncology
Hanneke W.M. van Laarhoven

Department of Radiation Oncology
Maarten C.C.M Hulshoff
Peter S.N. van Rossum

Department of Surgery
Mark I. van Berge Henegouwen

Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, the Netherlands
Department of Medical Oncology
Jolanda van Dieren
Marieke Vollebergh

Department of Radiation Oncology
Francine E.M. Voncken

Department of Surgery
Johanna W. van Sandick

Radiotherapiegroep, Deventer, the Netherlands
Department of Radiation Oncology
Paul Jeene

Catharina Cancer Institute, Eindhoven, the Netherlands
Department of Medical Oncology
Geert-Jan Creemers

Department of Radiation Oncology
Maurice J.C. van der Sangen

Department of Surgery
Grard A.P. Nieuwenhuijzen

A

University Medical Center Groningen, Groningen, the Netherlands
Department of Radiation Oncology
Christel Muijs

University Medical Center Leiden, Leiden, the Netherlands
Department of Medical Oncology
Marije Slingerland

Department of Surgery
Henk Hartgrink

GROW School for Oncology and Developmental Biology, Maastricht, the Netherlands
Department of Radiation Oncology (MAASTRO)
Maaike Berbee

Radboud University Medical Center, Nijmegen, the Netherlands
Department of Radiation Oncology
Marcel Verheij

Erasmus University Medical Center, Rotterdam, the Netherlands
Department of Surgery
Sjoerd M. Lagarde
Bas P.L. Wijnhoven

Elisabeth Tweesteden Ziekenhuis Tilburg, the Netherlands
Department of Medical Oncology
Laurens V. Beerepoot

University Medical Center Utrecht, Utrecht, the Netherlands
Department of Medical Oncology
Nadia Haj Mohammad

Department of Radiation Oncology
Stella Mook

Department of Surgery
George Buijs
Matthijs D.L. Burger
Richard van Hillegersberg

Sylvia van der Horst
Nikita K.N. Jorritsma
Jelle P. Ruurda

Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands
Department of Research & Development
Willemieke P.M. Dijksterhuis
Rob H.A. Verhoeven

Medical University of Vienna, Vienna University, Vienna, Austria
Department of Surgery
Sebastian Schoppman

Ghent University Hospital, Ghent, Belgium
Department of Radiation Oncology
Pieter R.A.J. Deseyne

KU Leuven, Leuven University, Leuven, Belgium
Department of Medical Oncology
Eric van Cutsem

Department of Radiation Oncology
Karin Haustermans

Department of Surgery
Philippe Nafteux

AZ Sint-Maarten, Mechelen, Belgium
Department of Radiation Oncology
Melissa Thomas

Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk, University Brno, Brno, Czech Republic
Department of Comprehensive Cancer Care
Radka Obermannova

Aarhus University Medical Center, Aarhus University, Aarhus, Denmark
Department of Clinical Medicine and Oncology
Hanna R. Mortensen

A

Department of Radiation Oncology
Marianne Nordsmark

Odense University Medical Center, University of Odense, Odense, Denmark
Department of Medical Oncology
Per Pfeiffer

Tallinn University Hospital, Tallinn University, Tallinn, Estonia
Department of Medical Oncology
Anneli Elme

Institute Du Cancer de Montpellier Val D'Aurelle, Lille University, Lille, France
Department of Medical Oncology
Antoine Adenis

University Hospital C. Huriez, Lille University, Lille, France
Department of Surgery
Guillaume Piessen

University Hospital Cologne, University of Cologne, Cologne, Germany
Department of Surgery
Christiane J. Bruns

University Hospital Leipzig, University of Leipzig, Leipzig Germany
Department of Medical Oncology
Florian Lordick

Department of Visceral, Transplant, Thoracic and Vascular Surgery
Ines Gockel

Johannes Gutenberg-University Clinic, University of Mainz, Mainz, Germany
Department of Medicine
Markus Moehler

University Hospital Tubingen, University of Tubingen, Tubingen, Germany
Department of Radiation Oncology
Cihan Gani

University of Athens Medical School, University of Athens, Athens, Greece
Department of Surgery
Theodore Liakakos

St. James Hospital, Trinity College Dublin, Dublin, Ireland
Department of Surgery
John Reynolds

University Hospital Bologna, Bologna, Italy
Department of Radiation Oncology
Alessio Morganti

San Raffaele Hospital, San Raffaele Vita-salute University, Milan, Italy
Department of Surgery
Riccardo Rosati

Humanitas University Medical Center, Humanitas University, Milan, Italy
Department of Surgery
Carlo Castoro

Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy
Department of Surgery
Domenico D'Ugo

Siena University Hospital, University of Siena, Siena, Italy
Department of Surgery
Franco Roviello

University Hospital Verona, University of Vero, Verona, Italy
Department of Surgery
Maria Benciveng
Giovannide Manzoni

University Hospital, Okayama, Japan
Department of Breast and Endocrine Surgery
Yuko Takahashi

Jagiellonian University Medical College, Krakow, Poland
Department of Surgery
Piotr Kolodziejczyk

Medical University of Lublin, Lublin, Poland
Department of Surgical Oncology
Wojciech P.Polkowski

Maria Skłodowska-Curie Institute, Warsaw, Poland
Department of Oncology and Radiotherapy
Lucjan Wyrwicz

Hospital Universitari Vall D'Hebron and Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain
Department of Medical Oncology
Maria Alsina
Josep Tabernero

Hospital Universitario Del Mar, Universitat Auto, Barcelona, Spain
Department of Surgery
Manuel Pera

Hospital Clinico Universitario de Valencia, University of Valencia, Valencia, Spain
Department of Medical Oncology
Tania F.Kanonnikoff

Karolinska Institutet, Stockholm, Sweden
Department of Surgery and Department of Clinical Science, Intervention and Technology
Magnus Nilsson

Geneva University Hospitals, University of Geneva, Geneva, Switzerland
Department of Surgery
Stefan Monig

Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland
Department of Medical Oncology
Dorethea Wagner

University Hospital Zurich, University of Zurich, Zurich, Switzerland
Department of Radiation Oncology
Nicolaus Andratschke
Matthias Guckenberger

Department of Nuclear Medicine
Martin Hüllner
Urs Mühlematter

Department of Surgery
Christian A. Gutschow

Queen Elizabeth Hospital Birmingham, University Hospital Birmingham, Birmingham, United Kingdom
Department of Upper Gastrointestinal Surgery
Ewen A. Griffiths

Cambridge University Hospitals, Cambridge University, Cambridge, United Kingdom
Department of Oncology
Elizabeth Smyth

Imperial College London, London University, London, United Kingdom
Department of Surgery
George B. Hanna
Sheraz Markar

Royal Marsden Hospital, London University, London, United Kingdom
Department of Surgery
M. Asif Chaudry

University College London, London, United Kingdom
Department of Medical Physics and Biomedical Engineering
Maria A. Hawkins

PanAsia Surgery, Singapore, Singapore
Department of Upper GI and General Surgery,
Edward Cheong

REVIEW COMMITTEE

Prof. dr. Matthias Guckenberger
Professor of Radiation Oncology, University Hospital Zurich, Switzerland

Prof. dr. Martijn P.W. Intven
Professor of Radiation Oncology, University Medical Center Utrecht, the Netherlands

Prof. dr. Marnix G.E.H. Lam
Professor of Nuclear Medicine, University Medical Center Utrecht, the Netherlands

Prof. dr. Anne M. May
Professor of Clinical Epidemiology of Cancer Survivorship, University Medical Center Utrecht, the Netherlands

Prof. dr. Bas P.L. Wijnhoven
Professor of Oesophagogastric Surgery, Erasmus Medical Center Rotterdam, the Netherlands

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LIST OF PUBLICATIONS

2017

1. Wendrich AW**, Kroese TE**, Peters JPM, Cattani G, Grolman W. Systematic Review on the Trial Period for Bone Conduction Devices in Single-Sided Deafness: Rates and Reasons for Rejection. *Otol Neurotol.* 2017 Jun;38(5):632-641.

2018

2. **Kroese TE**, Goense L, van Hillegersberg R, de Keizer B, Mook S, Ruurda JP, van Rossum PSN. Detection of distant interval metastases after neoadjuvant therapy for esophageal cancer with ^{18}F-FDG PET(/CT): a systematic review and meta-analysis. *Dis Esophagus*. 2018 Dec 1;31(12).

2019

3. **Kroese TE**, Tapias L, Olive JK, Trager LE, Morse CR. Routine intraoperative jejunostomy placement and minimally invasive oesophagectomy: an unnecessary step? *Eur J Cardiothorac Surg*. 2019 Oct 1;56(4):746-753.

2021

4. Sachdeva UM, Axtell AL, **Kroese TE**, Chang DC, Morse CR. Impact of Obesity on Treatment Approach for Resectable Esophageal Cancer. *Ann Thorac Surg*. 2021 Oct;112(4):1059-1066.

5. Damen PJJ, **Kroese TE**, van Hillegersberg R, Schuit E, Peters M, Verhoeff JJC, Lin SH, van Rossum PSN. The Influence of Severe Radiation-Induced Lymphopenia on Overall Survival in Solid Tumors: A Systematic Review and Meta-Analysis. *Int J Radiat Oncol Biol Phys*. 2021 Nov 15;111(4):936-948.

6. **Kroese TE**, Jairam J, Ruurda JP, Lin SH, Mohan R, Mook S, Haitjema S, Hoefer I, Haj Mohammad N, Peters M, van Hillegersberg R, van Rossum PSN. Severe lymphopenia acquired during chemoradiotherapy for esophageal cancer: Incidence and external validation of a prediction model. *Radiother Oncol.* 2021 Oct;163:192-198.

2022

7. **Kroese TE**, Dijksterhuijs WPM, van Rossum PSN, Verhoeven RHA, Mook S, Haj Mohammad N, Hulshof MCCM, van Berge Henegouwen MI, van Oijen MGH, Ruurda JP, van Laarhoven HWM, van Hillegersberg R. Prognosis of Interval Distant Metastases After Neoadjuvant Chemoradiotherapy for Esophageal Cancer. *Ann Thorac Surg*. 2022 Feb;113(2):482-490.

8. Sachdeva UM, Axtell AL, **Kroese TE**, Chang DC, Mathisen DJ, Morse CR. Contributing factors to lymph node recovery with esophagectomy by thoracic surgeons: an analysis of the Society of Thoracic Surgeons General Thoracic Surgery Database. *Dis Esophagus*. 2022 Sep 14;35(9):doab101

9. **Kroese TE**, van Hillegersberg R, Schoppmann S, Deseyne PRAJ, Nafteux P, Obermannova R, Nordsmark M, Pfeiffer P, Hawkins MA, Smyth E, Markar S, Hanna GH, Cheong E, Chaudry A, Elme A, Adenis A, Piessen G, Gani C, Bruns, CJ, Moehler M, Liakakos T, Reynolds J, Morganti A, Rosati R, Castoro C, D'Ugo D, Roviello R, Bencivenga M, de Manzoni G, Jeene P, van Sandick JW, Muijs C, Slingerland M, Nieuwehuijzen G, Wijnhoven B, Beerepoot LV, Kolodziejczyk P, Polkowski WP, Guckenberger M, Monig S, Wagner D, Wyrwicz L, Berbee M, Gockel I, Lordick F, Griffiths EA, Verheij M, van Rossum PSN, van Laarhoven, OMEC working group. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. *Eur J Cancer*. 2022 Mar; 164:18-29.

10. **Kroese TE**, van Rossum PSN, van Hillegersberg R. ASO Author Reflections: Role of Local Treatment for Oligometastatic Esophagogastric Cancer. *Ann Surg Oncol.* 2022 Aug;29(8):4858-4860

11. **Kroese TE***, Dijksterhuijs WPM*, Verhoeven RHA, van Rossum PSN, Mook S, Haj Mohammad N, Hulshof MCCM, Gisbertz SS, Ruurda JP, van Oijen MGH, van Hillegersberg R, van Laarhoven HWM. A population-based study on treatment and outcomes in patients with gastric adenocarcinoma diagnosed with distant interval metastases. *Eur J Surg Oncol*. 2022 Mar 18;S0748-7983(22)00125-1 [*joint first authorship]

12. **Kroese TE**, van Laarhoven HWM, Nilsson M, Lordick F, Guckenberger M, Ruurda JP, D'Ugo D, Haustermans K, van Cutsem E, van Hillegersberg R, van Rossum PSN. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis. *Eur J Cancer*. 2022 Mar 24;166:254-269.

13. **Kroese TE**, Buijs GS, Burger MDL, Ruurda JP, Mook S, Brosens LAA, van Rossum PSN, van Hillegerserg. ASO Visual Abstract: Metastasectomy or Stereotactic Body Radiation Therapy With or Without Systemic Therapy for Oligometastatic Esophagogastric Cancer. *Ann Surg Oncol.* 2022 Aug;29(8):4848-4857.

14. **Kroese TE**, Buijs GS, Burger MDL, Ruurda JP, Mook S, Brosens LAA, van Rossum PSN, van Hillegersberg R. Metastasectomy or Stereotactic Body Radiation Therapy With or Without Systemic Therapy for Oligometastatic Esophagogastric Cancer. *Ann Surg Oncol.* 2022 Aug;29(8):4848-4857

15. **Kroese TE**, Ruurda JP, Bakker AN, Jairam J, Mook S, van der Horst S, Meijer GJ, Haj Mohammad N, van Rossum PSN, van Hillegersberg. Detecting Interval Distant Metastases With 18F-FDG PET/CT After Neoadjuvant Chemoradiotherapy for Locally Advanced Esophageal Cancer. *Clin Nucl Med.* 2022 Jun 1;47(6):496-502.

16. Damen PJJ, **Kroese TE**, Peters M, Lin SH, Verhoeff JJC. In Reply to Chow and Simone. Int J Radiat Oncol Biol Phys. *2022 May 1;113(1):236-237.*

17. **Kroese TE**, Christ SM, van Rossum PSN, *Burger* MDL, Buijs GS, Mühlematter U, Andratschke N, Ruurda JP, Hüllner M, Gutschow CA, van Hillegersberg R, Guckenberger M. Incidence and survival of patients with oligometastatic esophagogastric cancer: a multicenter cohort study. Radiother Oncol. 2022 Aug;173:269-276

18. **Kroese TE,** van Rossum PSN, van der Horst S, Mook S, Haj Mohammad N, Ruurda JP, van Hillegersberg R. Long-term survival after sequential local treatments for oligometastatic esophageal squamous cell carcinoma: A case report. Int J Surg Case Rep 2022 Aug;97:107423

19. **Kroese TE**, van Rossum PSN, Nilsson M, Lordick F, Smyth EC, Rosati R, Nafteux P, D'Ugo D, Chaudry MA, Polkowkski W, Roviello F, Gockel I, Kolodziejczyk P, Haustermans K, Guckenberger M, Nordsmark M, Hawkins MA, Cervantes A, Fleitas T, van Cutsem E, Moehler M, Wagner AD, van Laarhoven HWM, van Hillegersberg R; OMEC-working group. Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project: A multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer. *Eur J Surg Oncol*. 2023 Jan;49(1):21-28.

20. **Kroese TE**, Jorritsma NKN, van Laarhoven HWM, Verhoeven RHA, Mook S, Haj Mohammad N, Ruurda JP, van Rossum PSN, van Hillegersberg R. Stereotactic radiotherapy or metastasectomy for oligometastatic esophagogastric cancer: A nationwide population-based cohort study. *Clin Transl Radiat Oncol*. 2022 Aug 24;37:109-115

21. Christ SM, Heesen P, Muehlematter UJ, Pohl K, William Thiel G, Willmann J, Ahmadsei M, **Kroese TE**, Mayinger M, Balermpas P, Wicki A, Andratschke N, Huellner M, Guckenberger M. Recognition of and treatment recommendations foroligometastatic disease in multidisciplinary tumor boards. *Clin Transl Radiat Oncol.* 2022 Nov 15;38:123-129.

2023

22. **Kroese TE**, Takahashi Y, Lordick F, van Rossum PSN, Ruurda JP, Lagarde SM, van Hillegersberg R, Verhoeven RHA, van Laarhoven HWM. Liver oligometastatic disease in synchronous metastatic gastric cancer patients: a nationwide population-based cohort study. *Eur J Cancer.* 2023 Jan;179:65-75.

23. **Kroese TE**, van Laarhoven HWM, Schoppman SF, Deseyne PRAJ, van Cutsem E, Haustermans K, Nafteux P, Thomas M, Obermannova R, Mortensen HR, Nordsmark M, Pfeiffer P, Elme A, Adenis A, Piessen G, Bruns CJ, Lordick F, Gockel I, Moehler M, Gani C, Liakakos T, Reynolds J, Morganti AG, Rosati R, Castoro C, Cellini F, D'Ugo D, Roviello F, Bencivenga M, de Manzoni G, van Berge Henegouwen MI, Hulshof MCCM, van Dieren J, Vollebergh M, van Sandick JW, Jeene P, Muijs CT, Slingerland M, Voncken FEM, Hartgrink H, Creemers GJ, van der Sangen MJC, Nieuwenhuijzen G, Berbee M, Verheij M, Wijnhoven B, Beerepoot LV, Mohammad NH, Mook S, Ruurda JP, Kolodziejczyk P, Polkowski WP, Wyrwicz L, Alsina M, Pera M, Kanonnikoff TF, Cervantes A, Nilsson M, Monig S, Wagner AD, Guckenberger M, Griffiths EA, Smyth E, Hanna GB, Markar S, Chaudry MA, Hawkins MA, Cheong E, vanHillegersberg R, van Rossum PSN; OMEC collaborators. Definition, diagnosis and treatment of oligometastatic oesophagogastric cancer: A Delphi consensus study in Europe. *Eur J Cancer*. 2023 May;185:28-39.

24. Guckenberger M, Andratschke N, Ahmadsei M, Christ SM, Heusel AE, Kamal S, **Kroese TE**, Looman EL, Reichl S, Vlaskou Badra E, von der Grün J, Willmann J, Tanadini-Lang S, Mayinger M. Potential of ChatGPT in facilitating research in radiation oncology? *Radiother Oncol.* 2023 Nov;188:109894.

25. Ahmadsei M, Christ SM, **Kroese TE**, Kühnis A, Willmann J, Balermpas P, Andratschke N, Tanadini-Lang S, Guckenberger M. Efficacy and safety analysis in metastatic cancer patients treated with multiple courses of repeat radiation therapy. Clin Transl Radiat Oncol. 2023 Oct 2;43:100687.

26. Guninski RS, Cuccia F, Alongi F, Andratschke N, Belka C, Bellut D, Dahele M, Josipovic M, **Kroese TE**, Mancosu P, Minniti G, Niyazi M, Ricardi U, Munck Af Rosenschold P, Sahgal A, Tsang Y, Verbakel WFAR, Guckenberger M. Efficacy and safety of SBRT for spine metastases:

A systematic review and meta-analysis for preparation of an ESTRO practice guideline. *Radiother Oncol.* 2024 Jan;190:109969.

2024

27. **Kroese TE**, Bronzwaer S, van Rossum PSN, Schoppman SF, Deseyne PRAJ, van Cutsem E, Haustermans K, Nafteux P, Thomas M, Obermannova R, Mortensen HR, Nordsmark M, Pfeiffer P, Elme A, Adenis A, Piessen G, Bruns CJ, Lordick F, Gockel I, Moehler M, Gani C, Liakakos T, Reynolds JV, Morganti AG, Rosati R, Castoro C, Cellini F, D'Ugo D, Roviello F, Bencivenga M, de Manzoni G, van Berge Henegouwen MI, Hulshoff MCCM, van Dieren J, Vollebergh M, van Sandick JW, JeeneP, Muijs C, Slingerland M, Voncken FEM, Hartgrink H, Creemers GJ, van der SangenMJC, Nieuwenhuijzen GAP, Berbee M, Verheij M, Wijnhoven B, Beerepoot LV,Mohammad NH, Mook S, Ruurda JP, Kolodziejczyk P, Polkowski WP, Wyrwicz L, AlsinaM, Tabernero J, Pera M, Kanonnikoff TF, Cervantes A, Nilsson M, Monig S, WagnerAD, Guckenberger M, Griffiths EA, Smyth E, Hanna GB, Markar S, Chaudry MA, Hawkins MA, Cheong E, van Laarhoven HWM, van Hillegersberg R; OMEC collaborators. European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4). Eur *J Cancer. 2024* Jun;204:114062.

28. ESO-Shanghai 13: another milestone in the treatment of oligometastatic disease? Grabenbauer A, **Kroese TE**, Guckenberger M. Chin Clin Oncol. 2024 Aug;13(4):62

CURRICULUM VITAE

Tiuri E. Kroese was born on the 14th of February 1994 in Wageningen, the Netherlands. He started attending medical school at the University Utrecht in 2012, after graduating from bilingual secondary school at the Revius Lyceum in Doorn. During his studies, Tiuri was awarded the Nijbakker Morra Student Grant for best cancer research project by a medical student. Tiuri performed his research internship at Harvard Medical School / Massachusetts General Hospital with Dr. Morse and graduated from medical school and its accompanying Honours Class with distinction (*cum laude*).

Under the supervision of Prof. dr. Richard van Hillegersberg, Prof. dr. Jelle Ruurda, Prof. dr. Hanneke van Laarhoven and Dr. Peter van Rossum, Tiuri started with a PhD on oligometastatic esophagogastric cancer at the University Medical Center Utrecht, Utrecht, the Netherlands. In 2021, Tiuri was awarded stipendia from the Foundations “Prof. Michael van Vloten”, “Cultuurfonds”, and “Drie Lichten” which enabled him to perform a research fellowship at the University Hospital Zurich, Zurich, Switzerland, to collaborate with Prof. dr. Matthias Guckenberger and Prof. dr. Christian Gutschow. In 2022, Tiuri started with his residency in radiation oncology at the Department of Radiation Oncology at University Hospital Zurich.

Tiuri currently lives in Zurich.