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Review Article

# Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project: A multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer

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*Abbreviations:* OMD, Oligometastatic disease; SBRT, Stereotactic body radiotherapy; OS, Overall survival; PFS, Progression-free survival; RCT, Randomized controlled trial; NSCLC, Non-small-cell lung cancer; FLOT, Fluorouracil, leucovorin, oxaliplatin and docetaxel; CapOx, Oxaliplatin and capecitabine; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, Hazard ratio; PET, Positron emission tomography; CT, Computed tomography; MRi, Magnetic resonance imaging.

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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.


## 1. 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 intraoperatively 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.

## 2. 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.

### *2.1. 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

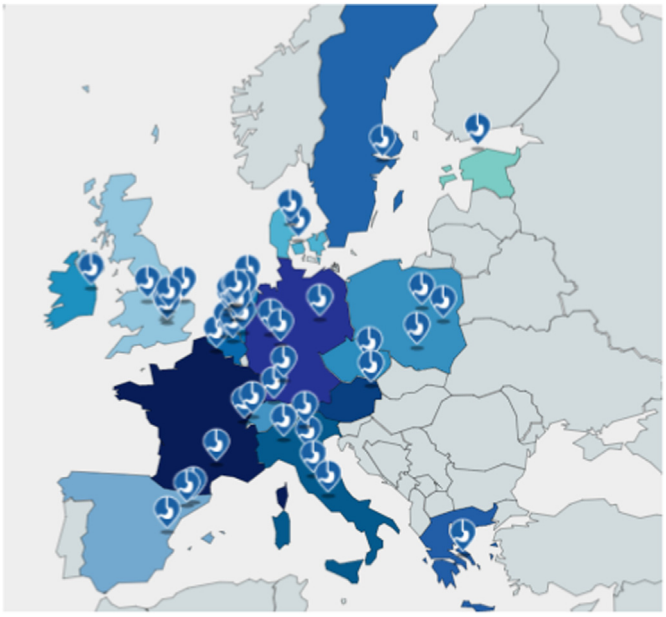

**Fig. 1.** Overview of the participating countries and centers in the OMEC project Colors representing the different countries.

**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% |

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.

*2.1.1. 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 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 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; 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-

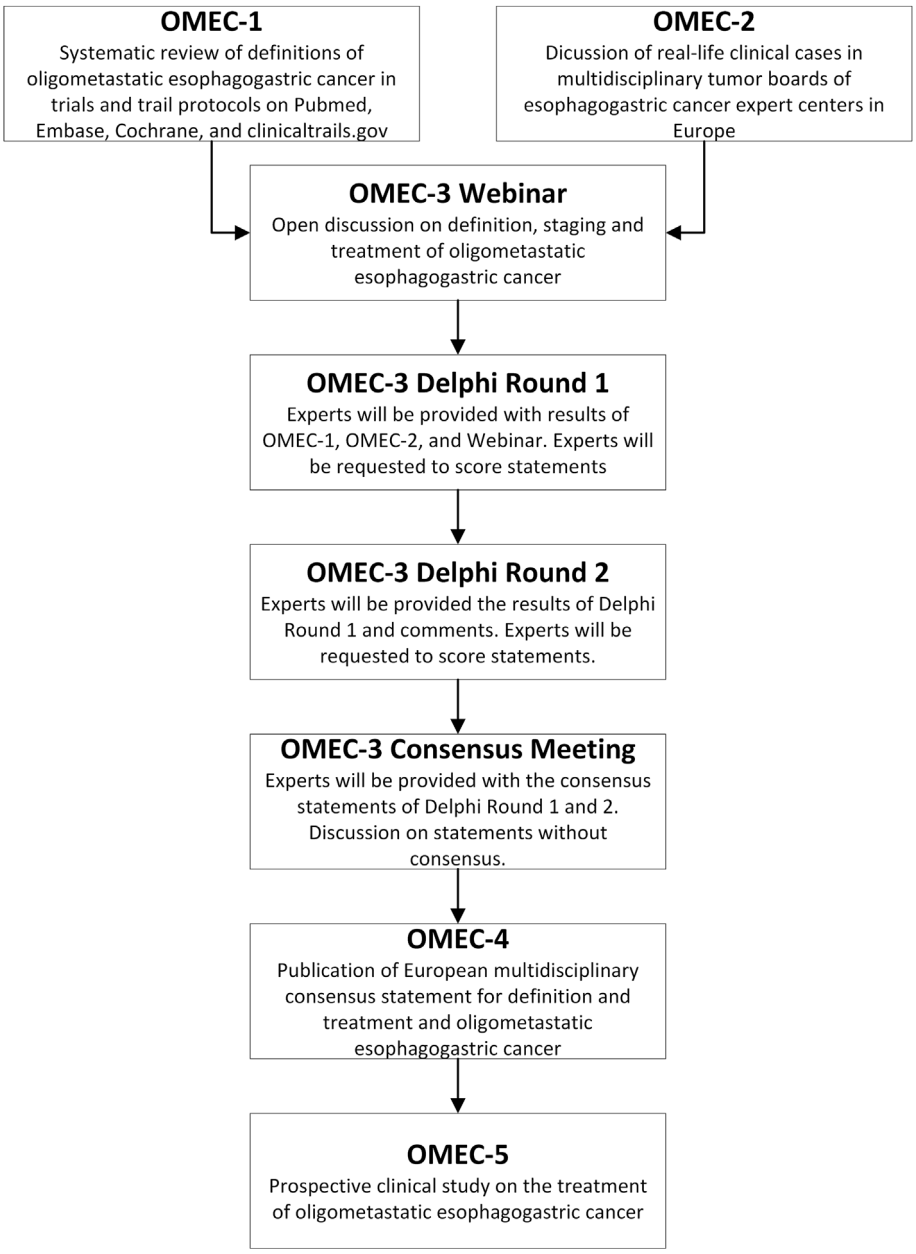


**Fig. 2.** Schematic overview of the OMEC project.

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.

### 2.2. 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).

### 2.3. 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.

### 2.4. 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]. 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].

## 3. 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

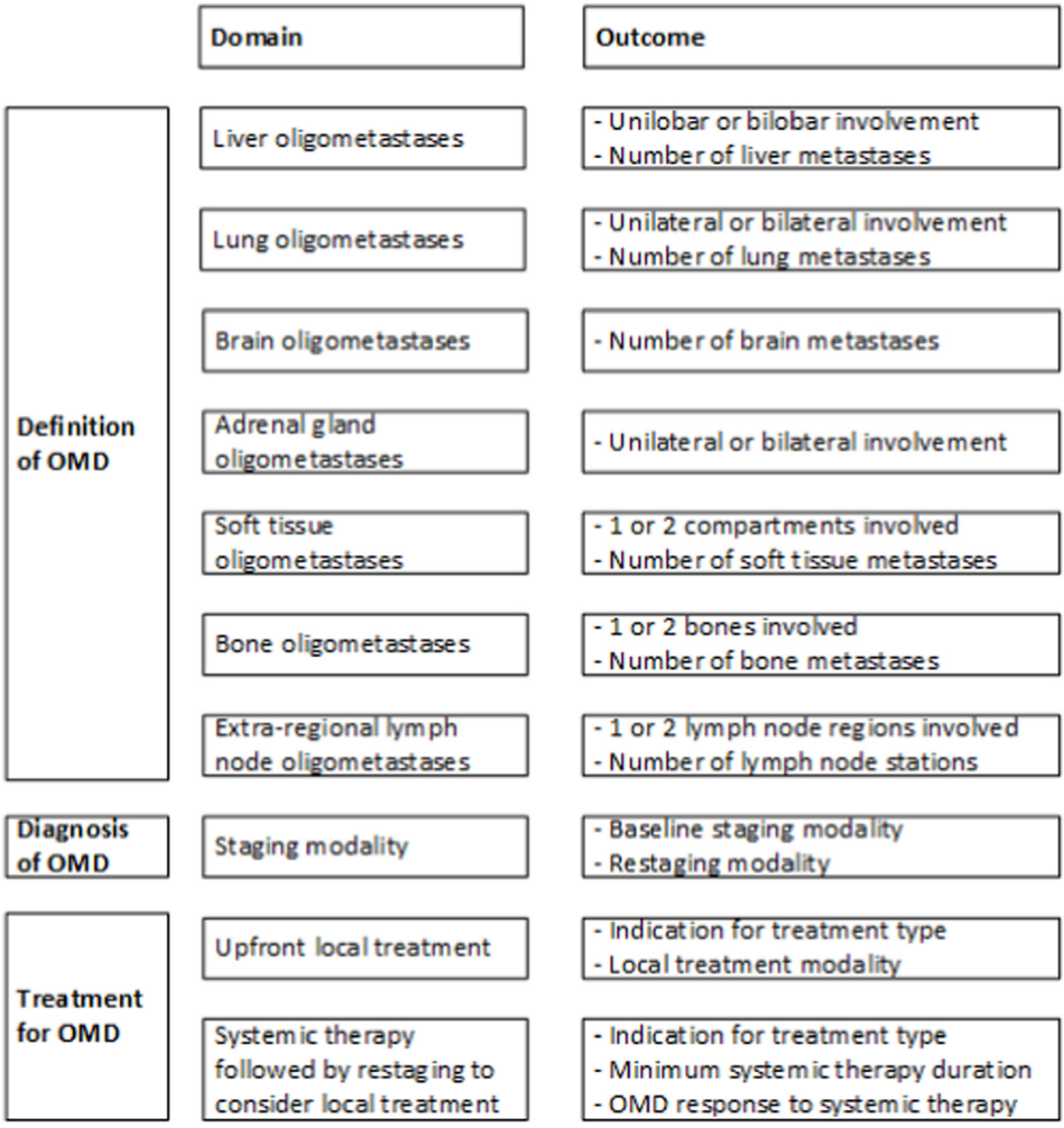


**Fig. 3.** Schematic overview of the outcomes of the OMEC project.

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.

## 4. 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.

## Data sharing agreement

The datasets of this study will be available from the corresponding author on reasonable request after completion.

## CRediT authorship contribution statement

**Tiuri E. Kroese:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Peter S.N. van Rossum:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Elizabeth C. Smyth:** Writing – review & editing. **Riccardo Rosati:** Writing – review & editing. **Philippe Nafteux:** Writing – review & editing. **Domenico D'Ugo:** Writing – review & editing. **M. Asif Chaudry:** Writing – review & editing. **Wojciech Polkowkski:** Writing – review & editing. **Franco Roviello:** Writing – review & editing. **Ines Gockel:** Writing – review & editing. **Piotr Kolodziejczyk:** Writing – review & editing. **Karin Haustermans:** Writing – review & editing. **Matthias Guckenberger:** Writing – review & editing. **Marianne Nordsmark:** Writing – review & editing. **Maria A. Hawkins:** Writing – review & editing. **Andres Cervantes:** Writing – review & editing. **Tania Fleitas:** Writing – review & editing. **Eric van Cutsem:** Writing – review & editing. **Markus Moehler:** Writing – review & editing. **Anna D. Wagner:** Writing – review & editing. **Hanneke W.M. van Laarhoven:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Richard van Hillegersberg:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Hawkins reports grants from NIHR Biomedical Research Centre at University College London Hospitals NHS Foundation Trust, outside the submitted work; Dr. Smyth reports personal fees from AMAL Therapeutics, Astellas Pharma, AstraZeneca, Beigene, Five Prime Therapeutics, Merck, Pfizer, Roche, Servier and Zymeworks and institutional funding for clinical trials research from Astra Zeneca, Astellas, Basilea, BMS, Daiichi Sankyo, Roche, Macrogenics and MSD. Dr. Moehler reports grants and non-financial support from EORTC, grants and non-financial support from AIO, grants and non-financial support from German Cancer Aid, grants and non-financial support from BMBF, during the conduct of the study; personal fees from Falk Foundation, personal fees from Lilly, grants and personal fees from MSD, personal fees from Roche, grants and personal fees from Pfizer, grants, personal fees and non-financial support from Amgen, grants, personal fees and non-financial support from Bristol-Myers Squibb, grants and personal fees from Merck Serono, personal fees from MCI Group, personal fees from Taiho, outside the submitted work; Dr. van Laarhoven reports consultant or advisory role: BMS, Dragonfly, Lilly, Merck, Nordic Pharma, Servier, outside the submitted work; research funding and/or medication supply: Bayer, BMS, Celgene, Janssen, Incyte, Lilly, Merck, Nordic Pharma, Philips, Roche, Servier, outside the submitted work; Dr. van Hillegersberg is proctor for Intuitive Surgical and consultant for Medtronic, the other authors have nothing to disclose.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.09.012.

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