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Original Research

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

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Oligometastasis

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 oesophagogastric cancer is lacking. The aim of this study was to develop a multidisciplinary European consensus statement on the definition, diagnosis and treatment of oligometastatic oesophagogastric cancer.
Methods: In total, 65 specialists in the multidisciplinary treatment for oesophagogastric cancer from 49 expert centres 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 oesophagogastric 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. The agreement was scored to be either absent/poor ($<50\%$), fair (50%–75%) or consensus ($\geq 75\%$).
Results: A total of 48 experts participated in the starting meeting, both Delphi rounds, and the consensus meeting (overall response rate: 71%). OMD was considered in patients with metastatic oesophagogastric 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 considered as treatment (consensus). For metachronous OMD with a disease-free interval >2 years, either upfront local treatment or systemic treatment followed by restaging was considered as treatment (fair agreement).
Conclusion: The OMEC project has resulted in a multidisciplinary European consensus statement for the definition, diagnosis and treatment of oligometastatic oesophagogastric adenocarcinoma and squamous cell cancer. This can be used to standardise inclusion criteria for future clinical trials.

1. Introduction

Oligometastatic disease (OMD) is defined as an intermediate state between locoregional and widespread systemically metastasised disease [1]. The concept of OMD implies that local treatment for OMD could improve survival outcomes [1,2]. Recently, 2 phase II randomised controlled trials (RCTs) have shown improved overall survival (OS) or progression-free survival 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]. However, the results of the SABR-COMET study were confounded by unbalanced key prognostic factors [6]. In the intervention 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]. However, a post-hoc sensitivity analysis that excluded patients with prostate cancer was consistent with a treatment benefit, 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 study 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 favourable characteristics.

RCTs on local treatment for OMD in patients with oesophagogastric cancer are ongoing [8–15] and non-randomised 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 oesophagogastric junction adenocarcinoma with retroperitoneal lymph node involvement only whereas patients with liver metastases showed less favourable 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 oesophagogastric 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.

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

Characteristic	(n = 65)	(%)
Type of hospital		
Community medical centre	5	7.7%
Comprehensive cancer centre	8	12.3%
Academic medical centre	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%

For this purpose, the OligoMetastatic Oesophagogastric Cancer (OMEC) project was initiated [19], compromising of five OMEC subprojects. The current subproject (OMEC-3) builds on the results of a systematic review on the definitions of oligometastatic oesophagogastric cancer in the current literature (OMEC-1) and discussion of real-life clinical cases by multidisciplinary teams of European oesophagogastric cancer expert centres (OMEC-2) [20,21]. The aim of OMEC-3 was to achieve consensus among European oesophagogastric cancer experts on the definition, diagnosis and treatment for oligometastatic oesophagogastric cancer using the Delphi consensus methodology.

2. Methods

This Delphi consensus study was conducted between May 2021 and April 2022 to establish consensus on the definition, diagnosis and treatment of oligometastatic oesophagogastric 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, as well as for OMD in NSCLC [23,24]. 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.

2.1. 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].

2.2. Participants

An international European study was conducted as a collaborative project among various European specialists in the treatment of oesophagogastric cancer. The consortium consisted of 65 oesophagogastric cancer experts from 49 oesophagogastric cancer expert centres 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).

The oesophagogastric cancer experts were suggested by the board members of the European Organisation for Research and Treatment of Cancer, European SocieTy for Radiotherapy and Oncology, European Society of Medical Oncology, European Society of Surgical Oncology, European Society for Diseases of the Oesophagus, the European chapter of the International Gastric Cancer Association and the Dutch Upper GI Cancer Group. Additional experts were identified by a systematic review on first or last authors of published RCTs related to oesophagogastric cancer between 2015 and 2020.

2.3. Input for Delphi consensus rounds

Factors for the definition of OMD in oesophagogastric cancer were defined in a two-step process. First, a systematic review on the definitions of oligometastatic oesophagogastric 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 $\leq$3 metastases or 1 extra-regional lymph node station in patients with metastatic oesophagogastric cancer [20]. In addition, 'organ-specific' OMD burden could involve bilobar $\leq$3 liver metastases, unilateral $\leq$2 lung metastases, 1 extra-regional lymph node station with metastases, $\leq$2 brain metastases or bilateral adrenal gland metastases [20].

Second, 15 real-life anonymised clinical cases with metastatic oesophagogastric cancer were provided to multidisciplinary tumour boards of oesophagogastric cancer expert centres using an online survey tool (Castor EDC, Amsterdam, The Netherlands). The request was to discuss the cases in the local multidisciplinary team (with 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 tumour 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].

2.4. 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.

2.4.1. 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 oesophagogastric cancer. The discussion was recorded and used to construct the first online Delphi questionnaire.

2.4.2. 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.

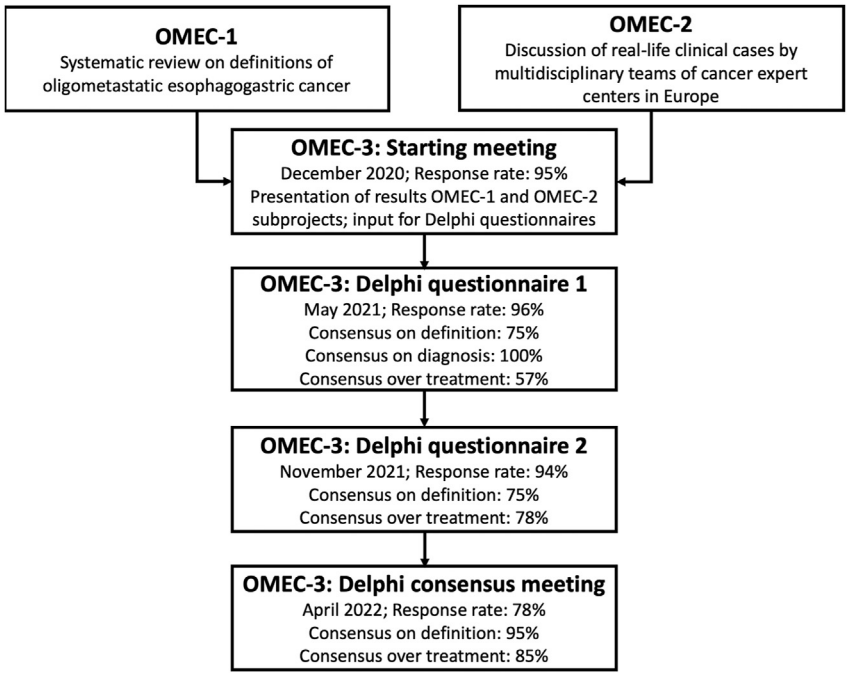

Fig. 1. Schematic overview of the Delphi consensus formation.

2.4.3. 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 analysed 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.

2.4.4. 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.

2.5. Statistical analysis

The disease-free interval was defined as the time interval between the completion of primary tumour treatment (surgery or radiotherapy) and the diagnosis of metachronous OMD and was categorised 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 tumours [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 analysed according to the RECIST v1.1 criteria [30].

3. Results

3.1. 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

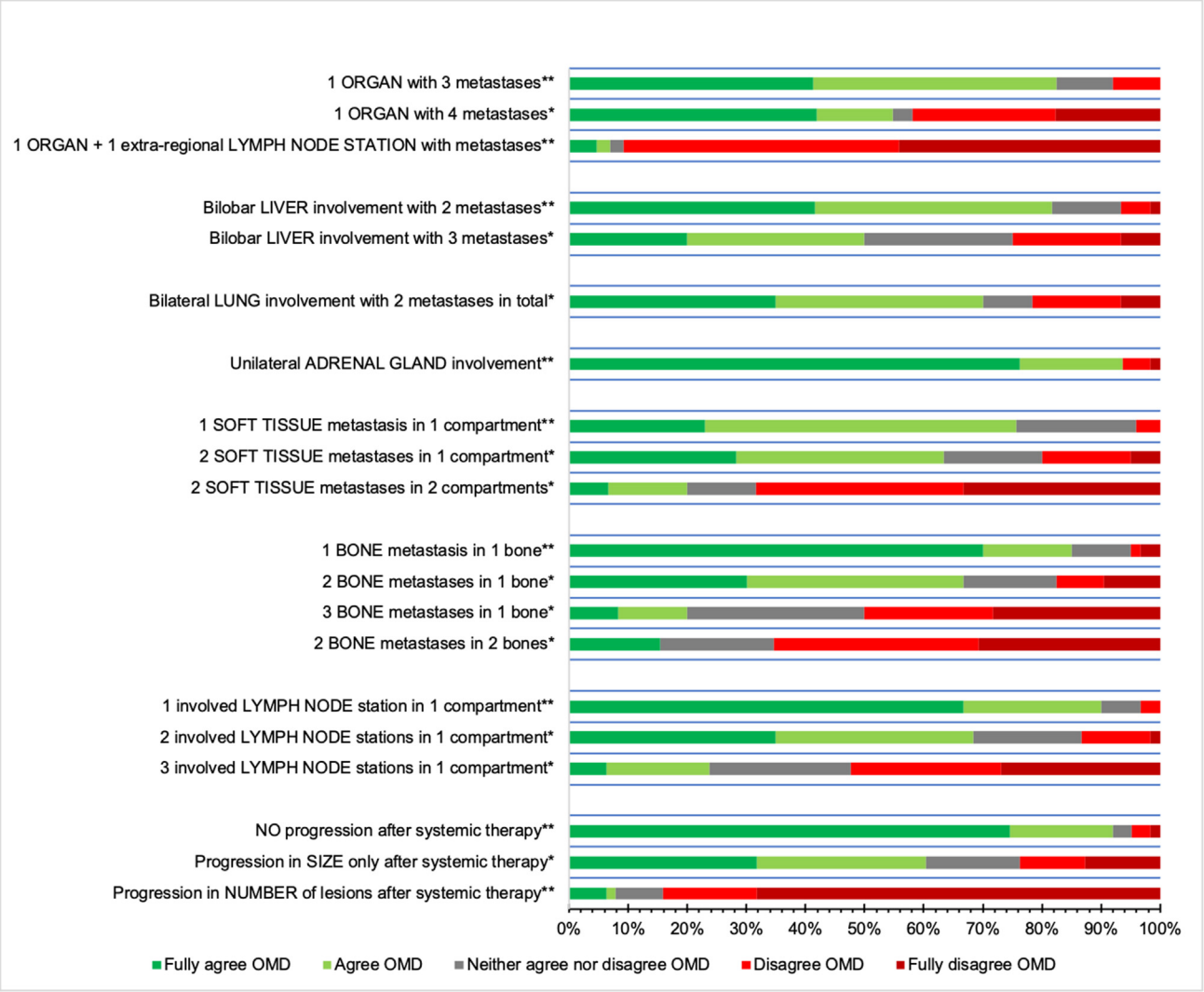

Fig. 2. Statements on the definition of oligometastatic oesophagogastric cancer with consensus or fair agreement. OMD: Oligometastatic disease.

(overall response rate: 71%). Fig. 1 demonstrates a schematic overview of the Delphi consensus finding process.

3.2. Definition of oligometastatic esophagogastric cancer

A consensus (i.e. ≥75% agreement) was reached that OMD in patients with metastatic oesophagogastric 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 oesophagogastric 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 oesophagogastric cancer with consensus or fair agreement.

3.3. Diagnosis and treatment of oligometastatic esophagogastric cancer

In patients with metastatic oesophagogastric cancer with (suspected) OMD, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography

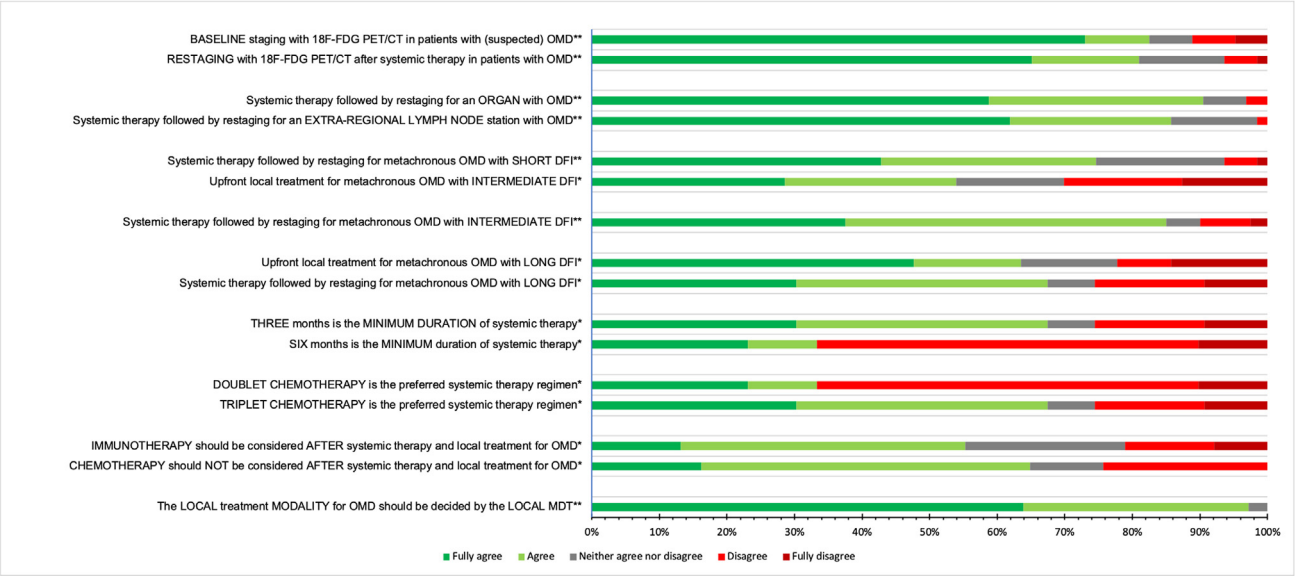

Fig. 3. Statements on the diagnosis and treatment of oligometastatic oesophagogastric cancer with consensus or fair agreement. OMD, Oligometastatic disease; DFI, disease-free interval; MDT, multidisciplinary team.

(PET/CT) imaging was considered for baseline staging and for restaging after systemic therapy (consensus). For patients with synchronous or metachronous OMD with a short or intermediate disease-free interval (i.e. $\leq$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 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 oesophagogastric 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 oesophagogastric cancer with consensus or fair agreement.

4. Discussion

In this OMEC project, a first multidisciplinary European consensus on the definition, diagnosis and treatment of oligometastatic oesophagogastric 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 centres, comprehensive cancer centres and community medical centres), 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 oesophagogastric cancer, we believe they 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 oesophagogastric 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 generalisability across Europe. This definition and treatment algorithm can be used to carefully design a RCT for patients with oligometastatic oesophagogastric cancer in which the control arm is 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, oesophagogastric oligometastatic esophagogastric cancer was defined case-by-case to argue for

individualised treatment. Herein the OMEC project clearly formulated and settled on a clinically relevant consensus (which was defined as ≥75% agreement between experts) thus avoiding controversial extremes. The aim of the OMEC project was to identify patients with metastatic oesophagogastric cancer for whom the term OMD should definitely be considered and who might benefit the most from radical (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 randomised 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 a short or intermediate disease-free interval (i.e. ≤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 tumour to show its true biological behaviour [38]. 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 could be a suitable treatment approach. These patients with a long disease-free interval form a less heterogeneous group. Therefore, the 'test-of-time' with systemic therapy is not considered essential for the tumour to show its true biologically behaviour. Also, upfront local treatment could be performed in these patients, in line with the SABR-COMET study [5]. If a patient with OMD who undergoes systemic therapy and then 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 tumour treatment vary and are inconsistent across Europe [39]. A minority of European centres performs intensive surveillance after surgery (defined as annual CT for 3 years postoperatively) while the majority of centres perform imaging on clinical indication only [39]. Trials are needed to link the various surveillance strategies to both (metachronous) OMD detection rates and survival outcomes.

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

Importantly, ongoing trials in oesophagogastric 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 oesophageal 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 tumours [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 oesophagogastric 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 on survival and adverse events in patients with adenocarcinoma of the stomach or oesophagogastric junction in the OMD setting [9]. Patients without disease progression after 4 FLOT cycles are randomised 1:1 to receive additional chemotherapy cycles or surgical resection of the primary tumour 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

oesophagogastric adenocarcinoma in the OMD setting [9]. Patients without disease progression after 4 months of FOLFOX or CapOx cycles are randomised 1:1 to receive additional chemotherapy cycles or radiotherapy to metastases (and the primary tumour) 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 oesophagogastric cancer experts only. Other limitations include the lack of stratification of results for adenocarcinoma versus squamous cell carcinoma histology and oesophageal versus gastric cancer, although the differences in management for the metastatic setting as opposed to the locoregional 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 oesophageal adenocarcinoma, rather than patients with gastric cancer or oesophageal 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 oesophagogastric 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 oesophagogastric cancer and the structured study protocol.

5. Conclusion

In this OMEC project, a first multidisciplinary European consensus on the definition, diagnosis and treatment of oligometastatic oesophagogastric 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 definitely be considered and who might benefit from (radical) 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 oesophagogastric cancer in which the control arm is to continue systemic therapy alone. We acknowledge that for patients with squamous cell carcinoma different choices regarding treatment decision-making may be made.

Author contribution

Conceptualization: HvL, PvR, RvH, TK.
Methodology: HvL, PvR, RvH, TK.
Formal analysis: PvR, TK.
Writing original draft: HvL, PvR, RvH, TK.
Writing review and editing: all authors.
Visualization: TK.
Supervision: HvL, PvR, RvH.

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Data sharing agreement

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

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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advisory roles for BMS and Medtronic. All remaining authors have declared no conflict of interest.

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