Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe

Tiuri E. Kroese, Richard van Hillegersberg, Sebastian Schoppmann, Pieter R.A.J. Deseyne, Philippe Nafteux, Radka Obermannova, Marianne Nordmark, 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, 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 b, Hanneke W.M. van Laarhoven az,* On behalf of the OMEC working group1

1 Department of Surgery, Utrecht University Medical Center, Utrecht University, Utrecht, the Netherlands
2 Department of Radiation Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
3 Department of Surgery, Medical University of Vienna, Vienna University, Vienna, Austria
4 Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium
5 Department of Surgery, KU Leuven, Leuven University, Leuven, Belgium
6 Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University Brno, Brno, Czech Republic
7 Department of Radiation Oncology, Aarhus University Medical Center, Aarhus University, Aarhus, Denmark
8 Department of Medical Oncology, Odense University Medical Center, University of Odense, Odense, Denmark
9 Medical Physics and Biomedical Engineering, University College London, London, United Kingdom
10 Department of Oncology, Cambridge University Hospitals, Cambridge University, Cambridge, United Kingdom
11 Department of Surgery, Imperial College London, London University, London, United Kingdom
12 Department of Upper GI Surgery, Norfolk & Norwich University Hospital NHS Foundation Trust, Norwich, United Kingdom
13 Department of Surgery, Royal Marsden Hospital, London University, London, United Kingdom
14 Department of Medical Oncology, Tallinn University Hospital, Tallinn University, Tallinn, Estonia
15 Department of Medical Oncology, Institute Du Cancer de Montpellier Val D’Aurelle, Lille University, Lille, France
16 Department of Surgery, University Hospital C. Huriez, Lille University, Lille, France
17 Department of Radiation Oncology, University Hospital Tubingen, University of Tubingen, Tubingen, Germany
18 Department of Surgery, University Hospital Cologne, University of Cologne, Cologne, Germany
19 Department of Medicine, Johannes Gutenberg-University Clinic, University of Mainz, Mainz, Germany
20 Department of Surgery, University of Athens Medical School, University of Athens, Athens, Greece
21 Department of Surgery, St. James Hospital, Trinity College Dublin, Dublin, Ireland
22 Department of Radiation Oncology, University Hospital Bologna, Bologna, Italy
23 Department of Surgery, San Raffaele Hospital, San Raffaele Vita-Salute University, Milan, Italy
24 Department of Surgery, Humanitas University Medical Center, Humanitas University, Milan, Italy
25 Department of Surgery, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy
26 Department of Surgery, Siena University Hospital, University of Siena, Siena, Italy
27 Department of Surgery, University Hospital Verona, University of Verona, Verona, Italy
28 Department of Radiation Oncology, Radiotherapy, Amsterdam University Medical Centers, Amsterdam, the Netherlands
29 Department of Surgery, Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, the Netherlands
30 Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
31 Department of Medical Oncology, University Medical Center Leiden, University of Leiden, Leiden, the Netherlands
32 Department of Surgery, Catharina Medical Center, Eindhoven, the Netherlands
33 Department of Surgery, Erasmus University Medical Center, University of Rotterdam, Rotterdam, the Netherlands
34 Department of Medical Oncology, Elisabeth Tweesteden Ziekenhuis Tilburg, the Netherlands
35 Department of Surgery, Jagiellonian University Medical College, Krakow, Poland
36 Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland
37 Department of Medical Oncology, Hospital Universitari Vall D’Hebron and Vall D’Hebron Institute of Oncology (VHIO), Barcelona, Spain
38 Department of Surgery, Hospital Universitari Del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain
39 Department of Medical Oncology, Hospital Clinico Universitario de Valencia, University of Valencia, Valencia, Spain
40 Division of Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institutet and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden
41 Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
42 Department of Surgery, Geneva University Hospitals, University of Geneva, Geneva, Switzerland
43 Department of Medical Oncology, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland
44 Department of Oncology and Radiotherapy, Maria Skłodowska-Curie Institute — Oncology Center, Warsaw, Poland
45 Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre+, Maastricht, the Netherlands
46 Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital Leipzig, University of Leipzig, Leipzig, Germany
47 Department of Medical Oncology, University Hospital Leipzig, University of Leipzig, Leipzig, Germany
48 Department of Upper Gastrointestinal Surgery, Queen Elizabeth Hospital Birmingham, University Hospital Birmingham NHS Trust, Birmingham, United Kingdom
49 Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
50 Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
51 Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands
52 Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

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Abstract
Background: Consensus about the definition and treatment of oligometastatic oesophagogastric cancer is lacking.
Objective: To assess the definition and treatment of oligometastatic oesophagogastric cancer across multidisciplinary tumour 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, surgical, 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 tumour 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 categorised 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 oesophagogastric cancer was found among MDTs of oesophagogastric cancer expert centres in Europe. However, high practice variability in treatment strategies exists.

1. Introduction
Oligometastatic disease is defined as an intermediate state between loco-regional and systemic disease and reflects a potentially distinct and favourable tumour 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 randomised 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 and 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 oesophagogastric cancer, RCTs for oligometastatic disease are ongoing [4], [5] [10] while non-randomised 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 oesophagogastric cancer expert centers in Europe and is endorsed by 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). The OMEC project aims to develop a European consensus definition for oligometastatic oesophagogastric 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 oesophagogastric cancer (OMEC-1), the distribution of real-life clinical cases (OMEC-2), Delphi consensus rounds (OMEC-3), the publication of a multidisciplinary European consensus statement on oligometastatic oesophagogastric cancer (OMEC-4) and, finally, a prospective study for oligometastatic oesophagogastric 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 tumour 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 tumour [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 oesophagogastric cancer and to identify the currently used treatment options [22]. Therefore, oesophagogastric cancer expert centres were requested to discuss 15 real-life clinical cases in their MDT to assess the agreement in definition and treatment strategies for oligometastatic oesophagogastric cancer across MDTs in Europe.

2. 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].

2.1. Identification of cases

A search was performed of real-life patients with distant metastases from oesophagogastric 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 tumour treatment status (surgery with or without neoadjuvant chemoradiotherapy, definitive chemoradiotherapy or no primary tumour 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 tumour]) and microsatellite stability; and 6. Response to systemic therapy at restaging. The response to systemic therapy at restaging was categorised 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 tumours (RECIST 1.1) [25]. Table 1 shows the characteristics of the presented cases.

2.2. MDT case discussion

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

2.3. 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 August 2020. The case information consisted of 1. The patient history (including primary tumour stage and treatment), 2. The current problem (including location and size of distant metastasis), 3. Pathology of the primary tumour and metastasis (including histology, HER2 Neu status, and microsatellite stability), and 4. Imaging of the primary tumour 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 tumour and metastasis to systemic therapy) and 2. Restaging imaging of the primary tumour and metastasis (18F 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).

### 2.4. Outcome measure

The primary outcome of this study was the agreement across MDTs in Europe on the definition of oligometastatic oesophagogastric 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 oesophagogastric cancer. Treatment strategies for oligometastatic disease were categorised into upfront local treatment (e.g. metastasectomy, SBRT, or other local oligometastasis-directed treatment), systemic therapy followed by restaging to consider local treatment for oligometastatic disease, or systemic therapy alone (without considering local treatment for oligometastasis later).

2.5. 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 tumours [26–28]. According to a recent systemic review, the most common definition for consensus was percent agreement, with 75% being the median threshold to define consensus among 25 studies [29].

3. Results

3.1. Participant characteristics

A total of 47 MDTs across 16 countries in Europe fully discussed the cases (response rate: 96%). The hospital type

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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 oesophagectomies 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 (consensus). Moreover, the definition of oligometastatic disease was not limited to a specific primary tumour treatment status, as a resected or definitively irradiated primary tumour 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 tumour, or with squamous cell carcinoma histology were considered oligometastatic (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 (consensus). Table 3 shows the agreement across MDTs on the definition of oligometastatic oesophagogastric cancer.

3.3. Restaging of oligometastatic disease

18F-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 18F-FDG PET/CT imaging was used for restaging after systemic therapy (fair agreement). Table 4 shows the agreement in

| Table 3 | Agreement in definitions of oligometastatic oesophagogastric cancer |
|---------|---------------------------------------------------------------------|
| **Factor** | **Number of cases** | **Agreement** | **Conclusion** |
| 1. 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 |
| 2. Number of lesions | | | |
| One | 10 | 79 - 100% | Consensus |
| Two | 3 | 81 - 100% | Consensus |
| 3. Primary tumor treatment | | | |
| nCRT and surgery | 5 | 83 - 100% | Consensus |
| Surgery alone | 1 | 98% | Consensus |
| Definitive chemoradiotherapy | 1 | 100% | Consensus |
| 4. 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 |
| 5. Timing of detection | | | |
| Synchronous | 5 | 83-94% | Consensus |
| Interval** | 1 | 79% | Consensus |
| Metachronous | 7 | 83-100% | Consensus |
| 6. 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; green = consensus; orange = fair agreement
restaging modalities for oligometastatic oesophago-gastric cancer.

3.4. Treatment strategies for oligometastatic disease

No consensus on treatment strategies for oligometastatic oesophagogastric 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 tumour 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 HER2-Neu mixed tumours. 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 oesophagogastric cancer across MDTs.

4. Discussion

This is the first study investigating the agreement in the definition and treatment of oligometastatic oesophagogastric 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 oesophagogastric 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 oesophagogastric cancer across European oesophagogastric 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 oesophagogastric 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 tumour 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 für Internistische Onkologie (AIO) [5] and the Eastern Cooperative Oncology Group (ECOG) [6]. In both trials, including patients with synchronous oligometastatic gastric or oesophagogastric cancer, local treatment for the primary tumour and metastases will be performed at restaging after systemic therapy in patients with a partial or complete response. 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 oesophagogastric 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 tumour, metachronous or interval HER2neu negative oligometastasis. 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 tumour.

A consensus statement for the definition and treatment strategies of oligometastatic oesophagogastric cancer was recommended with a fair agreement across MDTs for presented cases with soft tissue oligometastasis, a resected or a definitively irradiated primary tumour, metachronous or interval HER2neu negative oligometastasis. 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 tumour.

A consensus statement for the definition and treatment strategies of oligometastatic oesophagogastric 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 oesophagogastric cancer (OMEC-1), will be used for a multidisciplinary consensus statement on the definition and treatment of oligometastatic oesophagogastric cancer (OMEC-4). This consensus statement will result in a prospective study for oligometastatic oesophagogastric 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 oesophagogastric 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 generalisability. 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.

In conclusion, 47 multidisciplinary tumour boards of European oesophagogastric cancer expert centers fully discussed 15 real-life clinical cases. A multidisciplinary consensus was identified on the definition of oligometastatic oesophagogastric 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 oesophagogastric cancer will be used for a
consensus statement on the diagnosis and treatment of oligometastatic oesophagogastric cancer in the OMEC project.

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**Data sharing**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

**Credit author statement**

Conceptualisation: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Data curation: all authors.

Formal analysis: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

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Methodology: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Project administration: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Resources: NA.

Software: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Supervision: Peter van Rossum, Richard van Hillegersberg, Jelle Ruurda, Hanneke van Laarhoven.

Validation: all authors.

Visualization: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Roles/Writing - original draft: Tiuri Kroese, Peter van Rossum, Richard van Hillegersberg, Hanneke van Laarhoven.

Writing - review and editing: all authors.

**Conflict of interest**

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