



Original research



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

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ABSTRACT

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

Methods: Guidelines were developed according to AGREE II and GRADE principles. Guidelines were based on a systematic review (OMEC-1), clinical case discussions (OMEC-2), and a Delphi consensus study (OMEC-3) by 49 European expert centers for esophagogastric cancer. OMEC identified patients for whom the term OMD is

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considered or *could* be considered. Disease-free interval (DFI) was defined as the time between primary tumor treatment and detection of OMD.

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

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

1. Introduction

Overall survival in patients with esophagogastric (esophageal or gastric) cancer varies by disease stage [1,2]. Esophagogastric cancer patients with early-stage disease (stage I) have a 67-68% 5-year survival rate, compared to 19-47% for those with locally-advanced disease (stage II-III), and 2-3% for patients with distant metastatic disease (stage IV) [1,2]. Approximately 36-50% of esophagogastric cancer patients present with (synchronous) distant metastatic disease at the time of initial presentation [1,2].

A subset of patients with metastatic disease have a limited number of distant metastases, so-called “oligometastatic disease” [3]. The concept of oligometastatic disease was introduced in 1995 by Hellman and Weichselbaum to describe a biological state between localized and polymetastatic disease [3]. The concept of oligometastatic disease suggests that local treatment, for instance through metastasectomy or stereotactic body radiotherapy (SBRT), may prolong time to disease progression and, possibly, overall survival [3]. In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) provided a consensus recommendation on the characterisation and classification of oligometastatic disease [4]. In our study, only patients with de-novo oligometastatic disease are included (i.e. first-time diagnosis of oligometastatic disease without a previous history of polymetastatic disease) [4]. In this definition, patients with peritoneal or pleural metastases (i.e. polymetastatic disease) are excluded, as they are considered to have a distinct entity of metastatic disease, and may require specific treatment (e.g. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [HIPEC]) [5–7]. In addition, patients with brain metastases are outside the scope of this guideline since these patients often require immediate local treatment as well as patients with repeat oligometastatic disease (i.e. previous history of oligometastatic disease) or induced oligometastatic disease (i.e. previous history of polymetastatic disease) [4].

Oligometastatic disease in patients with esophagogastric cancer appears to be a significant healthcare burden worldwide. A multicenter retrospective cohort study suggested that the incidence of oligometastatic disease (defined in that study as ≤ 5 lesions) was 24% among patients with metastatic esophagogastric cancer [8]. A Chinese randomized controlled phase II trial in patients with oligometastatic squamous cell carcinoma has shown improved progression-free survival and overall survival after combined local treatment and systemic therapy as compared with systemic therapy alone [9]. In addition, four phase II non-randomized trials have shown favorable survival after local therapy for oligometastatic disease in patients with esophagogastric cancer [10–13]. Two Chinese studies in patients with esophageal squamous cell carcinoma investigated the value of SBRT for oligometastatic disease [12,13]. Median overall survival for patients with esophageal squamous cell carcinoma who underwent SBRT was 12.8 months [13] and 24.6 months [12], respectively. In addition, 1 German study [10] and 1 Chinese study [11] included patients with gastric

adenocarcinoma investigating the value of metastasectomy for oligometastatic disease. The median overall survival in this group was 31.3 months [10] or the median overall survival was not reached after a median follow-up time of 30.0 months [11]. Finally, some studies are still underway [14–22].

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

2. Methods

These clinical practice guidelines were developed in accordance with the AGREE II and GRADE principles for clinical practice guidelines (Supplementary file A) [23,24]. This guideline will be updated in 5 years using the same methodology.

To date, OMEC comprised of three completed subprojects, each detailed in the OMEC study protocol [25]. Firstly, a systematic review of the existing literature was performed on definitions of oligometastatic esophagogastric cancer, and a meta-analysis of survival outcomes following local treatment for oligometastatic esophagogastric cancer (OMEC-1) [26]. Secondly, multidisciplinary teams from European expert centers held discussions of real-life clinical cases, focusing on defining and treating oligometastatic esophagogastric cancer (OMEC-2) [27]. Thirdly, a Delphi consensus study was carried out among the same expert centers, with an initial meeting, 2 Delphi questionnaire rounds, and a final consensus meeting (OMEC-3) [28]. A visual representation of the OMEC subprojects is shown in Figure 1.

For these clinical practice guidelines, two investigators performed an updated systematic search independently on November 28, 2023. The search encompassed clinicaltrials.gov and Medline (via PubMed) to identify ongoing trials (i.e. trial protocols) and published phase II-III trials involving patients with oligometastatic esophagogastric cancer. Keywords for this search were ‘esophageal or gastric cancer’, ‘oligometastatic disease’, and synonyms.

The objective of the OMEC definition of oligometastatic disease was twofold. Firstly, it aimed to identify patients for whom the term oligometastatic disease is considered and where a *substantial* benefit from local treatment of oligometastatic disease is expected (as categorized by *consensus* in Delphi rounds). Secondly, it sought to identify patients for whom oligometastatic disease *could* be considered and where *modest* benefit from local treatment of oligometastatic disease is expected (as categorized by *fair agreement* in Delphi rounds) [25].

OMEC is endorsed by the European Societies of Surgical Oncology (ESSO), Medical Oncology (ESMO), and Radiation Oncology (ESTRO), the European Organization for Research and Treatment of Cancer (EORTC), the International Gastric Cancer Association (IGCA), and the

Dutch Upper GI Cancer Group (DUCG) [25].

The OMEC consortium consisted of 69 esophagogastric cancer experts, located in 49 expert centers from 16 countries across Europe [25]. These experts were identified by the aforementioned medical societies as experts in the field of oligometastatic disease in esophagogastric cancer or were identified by reviewing first and last authors of randomized trials in the field of esophagogastric cancer [25]. The roles of the various members in the guideline development group are provided in the study protocol [25].

In both OMEC-2 and OMEC-3 studies, experts were requested to evaluate each statement using a 5-point Likert scale. The level of agreement was scored as either absent/poor (<50%), fair agreement (50%–75%) or consensus ($\geq 75\%$) [4,29,30]. This threshold for consensus was determined based on a recent systematic review, which indicated that a 75% agreement was the median threshold used to define consensus in 25 Delphi studies [31].

The disease-free interval (DFI) for metachronous oligometastatic disease was characterized as the time between the end of primary tumor treatment and the occurrence of metachronous oligometastatic disease. Overall survival was determined as the time between the diagnosis of (oligo)metastatic disease and either death or the last follow-up, whereas progression-free survival was defined as the time between the detection of oligometastatic disease and first progression or last follow-up. Response to systemic therapy was analyzed according to the RECIST v1.1 criteria [32].

3. Results

3.1. Quality of evidence

A total of 1 randomized and 4 non-randomized phase II clinical trials were identified (Table 1). The quality of evidence was scored as high for the randomized controlled trial and as moderate for the non-randomized controlled trials. Therefore moderate recommendations for the definition, diagnosis and treatment of oligometastatic esophagogastric cancer are provided (according to GRADE-criteria) [24].

3.2. Definition of oligometastatic disease

Oligometastatic disease is defined as patients with esophagogastric cancer with 1 organ affected by ≤ 3 metastases or 1 involved extra-regional lymph node station [23]. In addition, patients with oligometastatic disease at baseline without disease progression in number of metastases after systemic therapy (i.e. stable disease, partial response, complete response, or progression in size only) may continue to be regarded as having oligometastatic disease [28].

The disease is not classified as oligometastatic in patients with esophagogastric cancer with both organ and extra-regional lymph node metastases, or in patients with oligometastatic disease at baseline who develop progression in the number of metastases after systemic therapy [28]. An organ-specific definition of oligometastatic disease includes ≤ 3 unilobar liver metastases, ≤ 3 unilateral lung metastases, unilateral adrenal gland involvement, or 1 bone or soft tissue metastasis.

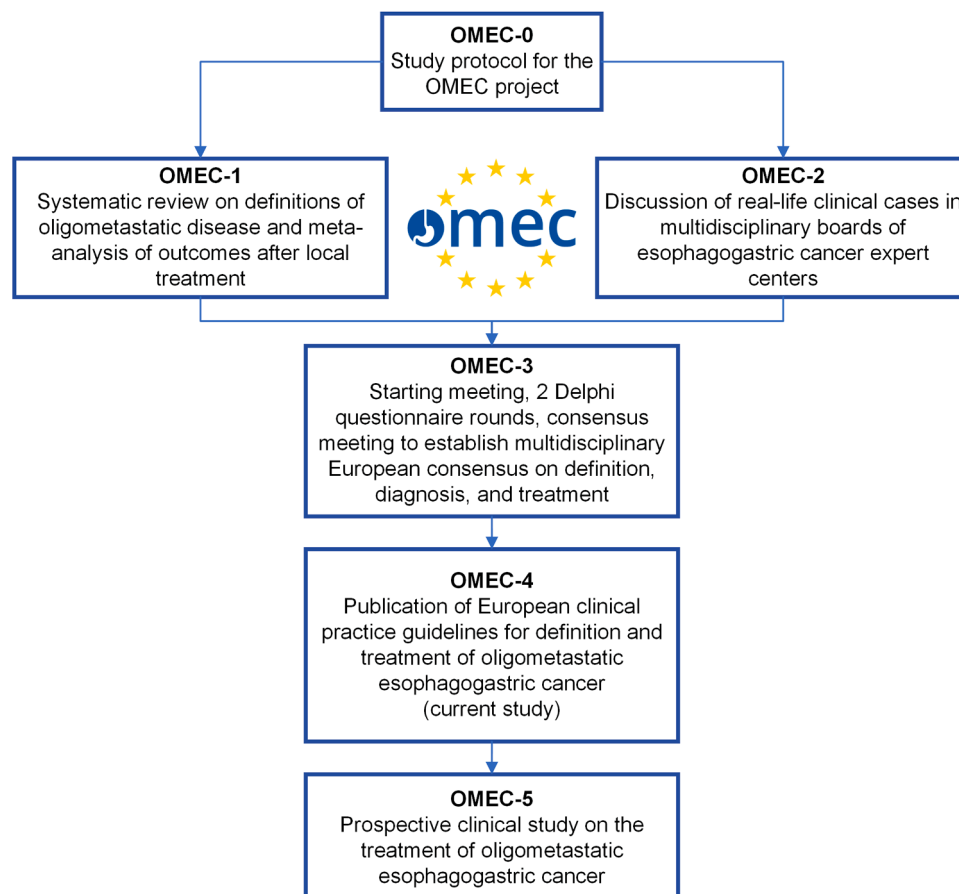








Fig. 1. Schematic overview of the OMEC project.

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

	Author/sponsor name or clinicaltrials.gov ID,	Primary tumor	Country	Study type	Maximum # organs	Maximum # metastases	Type of OMD	Staging	Treatment	Median overall survival	GRADE
Completed	Liu. et al., 2023	Esophageal SCC	China	II R	3	4	Synchronous /metachronous	CT	ChT +/- IO+ RT/ Surgeryvs ChT +/- IO	Not reached after 31 months follow-up vs 18.6 months	High
	Zhao et al., 2023	Esophageal SCC	China	II NR	ns	5	Synchronous/ metachronous	ns	IO+ChT+SBRT	12.8 months	Moderate
	Cui et al., 2023	Gastric AC	China	II NR	1	Organ-specific	Synchronous	CT or laparoscopy	ChT+Surgery+ChT	Not reached after 30 months follow-up	Moderate
	Liu et al., 2020	Esophageal SCC	Chins	II NR	ns	3	Metachronous	CT or ¹⁸ F-FDG PET	SBRT +/- ChT	24.6 months	Moderate
Ongoing	Al-Batran et al., 2017	Gastric AC or EGJ AC	Germany	II NR	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ¹⁸ F-FDG PET	ChT+Surgery	31.3 months	Moderate
	NCT04510064 (Fudan University)	Gastric AC or EGJ AC	China	II NR	1	Organ-specific	Synchronous	CT or MRI	IO+ChT+Surgery	NA	Not applicable
	NCT04248452 (ECOG-ACRIN Cancer Research Group)	Esophageal AC and Gastric	USA	III R	ns	3	Synchronous	CT or MRI	ChT + SBRT vs ChT	NA	Not applicable
	NCT03904927 (Fudan University)	Esophageal SCC	China	II R	2	4	Synchronous/ metachronous	CT	ChT + SBRT/ Surgery vs ChT	NA	Not applicable
	NCT03161522 (M.D. Anderson Cancer Cancer)	Esophageal AC	USA	II NR	1	3	Synchronous	¹⁸ F-FDG PET/ CT	ChT+SBRT/Surgery	NA	Not applicable
	NCT03399253 (Sun Yat-sen University)	Gastric AC	China	II-III R	2	Organ-specific	Synchronous	CT	ChT+Surgery vs ChT	NA	Not applicable
	NCT02578368 "FLOT5" (Krankenhaus Nordwest)	Gastric AC or EGJ AC	Germany	III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ¹⁸ F-FDG PET	ChT+Surgery vs ChT	NA	Not applicable
	NCT04512417 (Zhejiang Cancer Hospital)	Esophageal SCC or AC	China	II R	ns	4	Synchronous/ metachronous	ns	IO+ChT+SBRT vs IO+ChT	NA	Not applicable
	NCT03042169 "Surgigast" (University Hospital Lille)	Gastric AC or EGJ AC	France	III R	1 + RPLN	Organ-specific	Synchronous	CT/MRI or ¹⁸ F-FDG PET	ChT+Surgery vs ChT	NA	Not applicable

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

Recommendations for the definition of oligometastatic disease

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

3.3. *Diagnosis of oligometastatic disease*

Currently, the primary method for identifying oligometastatic disease and selecting patients for local treatment both at baseline and after systemic therapy involves imaging [33]. Modern imaging modalities, such as ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) with integrated computed tomography (CT), can detect small metastases, and can therefore assist in distinguishing oligometastatic disease from polymetastatic disease [33].

¹⁸F-FDG PET/CT imaging is recommended at baseline for patients with (suspected) oligometastatic disease and ¹⁸F-FDG PET-positive tumors to exclude polymetastatic disease [28]. In addition, ¹⁸F-FDG PET/CT imaging is recommended at restaging after systemic therapy in patients with ¹⁸F-FDG PET-positive tumors to consider local treatment for oligometastatic disease [28].

An important limitation of ¹⁸F-FDG PET-staging is that a substantial portion of patients with gastric cancer (especially those with poorly cohesive disease) have ¹⁸F-FDG PET-negative disease [34].

Recommendations for the diagnosis of oligometastatic disease

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

3.4. *Treatment of oligometastatic disease*

In patients with synchronous oligometastatic disease or patients with metachronous oligometastatic disease and DFI ≤ 2 years, recommended treatment starts with systemic therapy [28]. In the absence of progression in the number of metastases after systemic therapy (i.e. stable disease, partial response, complete response, or progression in size of existing lesions only), local treatment is considered for oligometastatic disease (and the primary tumor in case of synchronous oligometastatic disease) [28]. The local multidisciplinary team decides the type of local treatment for oligometastatic disease (e.g. metastasectomy, radiofrequency, radiofrequency ablation, or SBRT) or has the option to refer

the patient to an expertise center for local treatment.

Patients with metachronous oligometastatic disease and DFI > 2 years may either undergo upfront local treatment for oligometastatic disease, or systemic therapy followed by restaging to consider local treatment for oligometastatic disease [28].

At least 3 months of systemic therapy is considered for patients with oligometastatic disease before considering local treatment for oligometastatic disease. In addition, after systemic therapy and local treatment for oligometastatic disease, consolidating checkpoint inhibition could be considered [28].

Importantly, these recommendations were not broken down for the histology of the primary tumor (e.g. adenocarcinoma or squamous cell carcinoma, human epidermal growth factor receptor 2 [HER2] positivity, microsatellite instability [MSI], or combined positive score [CPS]).

In general, patients should receive the most optimal treatment for metastatic disease as defined in ESMO guidelines [35,36]. Of note, triplet chemotherapy (e.g. fluorouracil, leucovorin, oxaliplatin, and docetaxel [FLOT]) may be considered as a chemotherapy backbone, but no consensus was reached among the experts regarding doublet versus triplet chemotherapy in this setting [28].

Recommendations for the treatment of oligometastatic disease

Treatment for synchronous or metachronous oligometastatic disease and DFI ≤ 2 years (consensus) Systemic therapy followed by restaging to consider local treatment for oligometastatic disease	Treatment for metachronous oligometastatic disease and DFI > 2 years (fair agreement) Systemic therapy followed by restaging to consider local treatment for oligometastatic disease or Upfront local treatment for oligometastatic disease
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4. Discussion

These clinical practice guidelines provide practical recommendations for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer based on moderate to high quality of evidence (phase II studies [10–13] and a randomized controlled trial [9]) as well as a systematic review [26], clinical case discussions [27], and Delphi consensus of European expert centers [28]. These guidelines can be used to identify patients with oligometastatic disease and to standardize inclusion criteria in future clinical trials. In addition, these guidelines could be an important step into the use of a uniform treatment approach in these patients, addressing the significant variation in treatment approaches that was observed across Europe [27]. However, the guidelines largely reflect the view of European experts and may therefore be more applicable to Western patients (with esophageal or gastric adenocarcinoma) than Asian patients (with esophageal squamous cell carcinoma) [25]. In addition, these guidelines are only applicable to patients with de-novo oligometastatic disease [4,5]. Accordingly, these guidelines are not applicable to patients with repeat oligometastatic disease or induced oligometastatic disease (i.e. patients who underwent systemic therapy for polymetastatic disease and were found to have oligometastatic disease after restaging).

The definition of oligometastatic esophagogastric cancer used in the current guideline was in agreement with the literature defining oligometastatic disease as 1 organ affected by ≤ 3 metastases or 1 involved extra-regional lymph node station [26]. Furthermore, in line with these guidelines, ongoing trials for patients with oligometastatic esophagogastric cancer are predominantly using ¹⁸F-FDG PET/CT imaging for baseline staging and for restaging after systemic therapy to consider local treatment for oligometastatic disease [15,19,22]. Regarding the treatment of patients with synchronous oligometastatic disease or those with metachronous oligometastatic disease and DFI ≤ 2 years, phase III trials are also using systemic therapy followed by restaging to consider

local treatment for oligometastatic disease [14,15,22].

In the context of oligometastatic disease, it is important to consider 1) primary tumor treatment, 2) local oligometastasis-directed treatment, 3) systemic therapy, and 4) harm or risks. The phase III REGATTA trial, including gastric cancer patients with synchronous oligometastatic disease, has shown that primary tumor resection plus systemic therapy does not improve overall survival compared with systemic therapy alone [37]. Importantly, in this trial a gastrectomy plus D1-lymphadenectomy was performed [37], which is not considered an adequate lymphadenectomy for gastric cancer patients in the curative setting, and metastases were not locally treated [36]. The negative result of this trial presumably suggests that in case of oligometastatic disease, the primary tumor and all (oligo)metastases may require adequate local treatment. Accordingly, the non-randomized FLOT-3 phase II trial including gastric cancer patients with synchronous oligometastatic disease has shown favorable overall survival in carefully selected patients who underwent gastrectomy with D2 lymphadenectomy and resection of all metastases (i.e. cytoreductive surgery) after responding to ≥ 4 cycles of FLOT chemotherapy [10]. A single-arm, phase 2 clinical trial found that the incidence of grade ≥ 3 toxicity after SBRT for oligometastatic prostate, colorectal, breast, or lung cancer was less than 5% [38], suggesting that local treatment for oligometastatic disease can be performed with limited morbidity. Finally, it is important that clinicians and patients discuss potential harms and benefits of treatment and that a shared decision is made.

Up until now, 1 randomized controlled trial in patients with oligometastatic esophagogastric squamous cell cancer has demonstrated a benefit of combined local treatment and systemic as compared with systemic therapy alone for oligometastatic disease [9]. The applicability of this trial for patients with esophagogastric adenocarcinoma is currently unclear because of the higher expected response rates to (chemo)radiotherapy of esophageal squamous cell cancer compared to adenocarcinoma and the limited use of checkpoint inhibition, which is current standard-of-care. Therefore, the results of the FLOT-5 (RENAISSANCE) trial including patients with oligometastatic gastric and gastroesophageal junction adenocarcinoma are eagerly awaited [15].

Implementation of these guidelines can pose significant challenges, particularly in low- or middle-income countries. These challenges are primarily attributed to elevated costs and the extended travel distances required for accessing specialized esophagogastric cancer treatment centers. The incremental costs stem from the intensified ^{18}F -FDG PET/CT imaging and additional local treatment (e.g. SBRT or metastasectomy). It is important to note that we have not conducted a formal cost assessment for this guideline, which would have enabled us to evaluate the incremental financial burdens associated with these recommendations when compared to conventional metastatic treatment approaches. However, a recent study from the United States suggested that local treatment with SBRT adds quality-adjusted life years for patients with oligometastatic prostate, colorectal, breast, or lung cancer and represents an intermediate- and long-term cost-effective treatment strategy as compared with standard of care alone [39].

In our guidelines, primary tumor treatment was not specified but it is recommended to follow the contemporary international treatment guidelines for locally advanced esophagogastric cancer. These guidelines recommend gastrectomy with D2 lymphadenectomy for patients with gastric cancer [35] and a transthoracic esophagectomy with adequate two-field lymphadenectomy for patients with esophageal cancer [36].

A growing body of evidence demonstrates an important role for immunotherapy in esophagogastric cancer patients with locally-advanced [40] or metastatic disease [41,42]. The relative benefit and best sequence of immunotherapy and local ablative treatments for different biomarker-defined subgroups of patients needs to be determined by future studies. In addition, future studies should evaluate new methods to select patients for local treatment for oligometastatic disease. Some studies have shown an additional prognostic value of the

clearance of circulating tumor DNA after treatment [43]. For example, an ongoing phase III trial including patients with oligometastatic disease and esophageal, gastroesophageal junction, gastric, duodenal, or ampullary adenocarcinoma with circulating DNA clearance after systemic therapy, is evaluating the benefit of adding local treatment to systemic therapy for oligometastatic disease compared with continuation of systemic therapy only [44].

In conclusion, a multidisciplinary European clinical practice guideline for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer is presented using the results of OMEC-1 [26], OMEC-2 [27], and OMEC-3 [28]. A consensus was reached that oligometastatic disease is considered in patients with 1 organ affected by ≤ 3 metastases or 1 involved extra-regional lymph node station and in those with oligometastatic disease at baseline who do not develop progression in the number of metastases at restaging after systemic therapy. Patients with synchronous oligometastatic disease or those with metachronous oligometastatic disease and DFI ≤ 2 years treatment consists of systemic therapy followed by restaging to consider local treatment of oligometastatic disease. Patients with metachronous oligometastatic disease and DFI > 2 years could also undergo upfront local treatment for oligometastatic disease. ^{18}F -FDG PET/CT imaging is recommended for baseline staging and for restaging after systemic therapy to consider local treatment. Results of randomized controlled trials are warranted to assess the exact value of local treatment for oligometastatic esophagogastric cancer. This clinical practice guideline requires validation in a clinical study (OMEC-5).

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Declaration of Competing Interest

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Data Availability

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2024.114062](https://doi.org/10.1016/j.ejca.2024.114062).

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