European Journal of Cancer 204 (2024) 114062

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

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

Tiuri E. Kroese [a,b,c,1], Sebastiaan Bronzwaer [b,*,1], Peter S.N. van Rossum [d], Sebastian F. Schoppman [e], Pieter R.A.J. Deseyne [f,ak], Eric van Cutsem [g], Karin Haustermans [h], Philippe Nafteux [i], Melissa Thomas [j], Radka Obermannova [k], Hanna R. Mortensen [l], Marianne Nordsmark [m], Per Pfeiffer [n], Anneli Elme [o], Antoine Adenis [p], Guillaume Piessen [q], Christiane J. Bruns [r], Florian Lordick [s], Ines Gockel [t], Markus Moehler [u], Cihan Gani [v], Theodore Liakakos [w], John V. Reynolds [x], Alessio G. Morganti [y], Riccardo Rosati [z], Carlo Castoro [aa,bp], Francesco Cellini [ab,bq], Domenico D'Ugo [ac], Franco Roviello [ad], Maria Bencivenga [ae], Giovanni de Manzoni [ae], Mark I. van Berge Henegouwen [af], Maarten C.C.M Hulshoff [d], Jolanda van Dieren [ag], Marieke Vollebergh [ah], Johanna W. van Sandick [ai], Paul Jeene [aj], Christel Muijs [ak], Marije Slingerland [al], Francine E.M. Voncken [am], Henk Hartgrink [an], Geert-Jan Creemers [ao], Maurice J.C. van der Sangen [ap], Grard A.P. Nieuwenhuijzen [aq], Maaike Berbee [ar], Marcel Verheij [as], Bas Wijnhoven [at], Laurens V. Beerepoot [au], Nadia Haj Mohammad [av], Stella Mook [aw], Jelle P. Ruurda [b], Piotr Kolodziejczyk [ax], Wojciech P. Polkowski [ay], Lucjan Wyrwicz [az], Maria Alsina [ba], Josep Tabernero [bb], Manuel Pera [bc], Tania F. Kanonnikoff [bd], Andrés Cervantes [bd], Magnus Nilsson [be], Stefan Monig [bf], Anna D. Wagner [bg], Matthias Guckenberger [a], Ewen A. Griffiths [bh], Elizabeth Smyth [bi], George B. Hanna [bj], Sheraz Markar [bj], M. Asif Chaudry [bk], Maria A. Hawkins [bl], Edward Cheong [bm], Hanneke W.M. van Laarhoven [bn,bo], Richard van Hillegersberg [b,*], On behalf of the OMEC collaborators[2]

[a] Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[b] Department of Surgery, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[d] Department of Radiation Oncology, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
[e] Department of Surgery, Medical University of Vienna, Vienna University, Vienna, Austria
[f] Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium
[g] Department of Medical Oncology, KU Leuven, Leuven University, Leuven, Belgium
[h] Department of Radiation Oncology, KU Leuven, Leuven University, Leuven, Belgium
[i] Department of Surgery, KU Leuven, Leuven University, Leuven, Belgium
[j] Department of Radiation Oncology, AZ Sint-Maarten, Mechelen, Belgium
[k] Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk, University Brno, Brno, Czech Republic
[l] Danish Center of Particle Therapy, Aarhus University Medical Center, Aarhus University, Aarhus, Denmark
[m] Department of Oncology, Aarhus University Hospital, Aarhus University, Aarhus, Denmark
[n] Department of Medical Oncology, Odense University Medical Center, University of Odense, Odense, Denmark
[o] Department of Medical Oncology, Tallinn University Hospital, Tallinn University, Tallinn, Estonia
[p] Department of Medical Oncology, IRCM, Inserm, Université Montpellier, ICM, Montpellier, France
[q] Department of Surgery, Univ. Lille, CNRS, Inserm, CHU Lille, UMR9020-U1277 - CANTHER – Cancer Heterogeneity Plasticity and Resistance to Therapies, F-59000 Lille, France
[r] Department of Surgery, University Hospital Cologne, University of Cologne, Cologne, Germany
[s] Department of Medical Oncology, University Hospital Leipzig, University of Leipzig, Leipzig Germany

* Correspondence to: Department of Surgery UMC Utrecht, Heidelberglaan 100, 3584CX Utrecht, Netherlands.
E-mail addresses: r.vanhillegersberg@umcutrecht.nl (S. Bronzwaer), r.vanhillegersberg@umcutrecht.nl (R. van Hillegersberg).

https://doi.org/10.1016/j.ejca.2024.114062
Received 15 December 2023; Received in revised form 28 March 2024; Accepted 6 April 2024
Available online 16 April 2024

[t] Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital Leipzig, University of Leipzig, Leipzig, Germany
[u] Department of Medicine, Johannes Gutenberg-University Clinic, University of Mainz, Mainz, Germany
[v] Department of Radiation Oncology, University Hospital Tubingen, University of Tubingen, Tubingen, Germany
[w] Department of Surgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[x] Trinity St James's Cancer Institute, St. James Hospital, Trinity College Dublin, Dublin, Ireland
[y] Department of Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; Department of Radiation Oncology, DIMES, Alma Mater Studiorum - Bologna University, Bologna, Italy
[z] Department of GI Surgery, IRCCS San Raffaele Scientific Institute, San Raffaele Vita-salute University, Milan, Italy
[aa] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, Pieve Emanuele, Milan 20072, Italy
[ab] Università Cattolica del Sacro Cuore, Dipartimento Universitario Diagnostica per immagini, Radioterapia Oncologica ed Ematologia, Roma, Italy
[ac] Department of Surgery, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy
[ad] Department of Surgery, Siena University Hospital, University of Siena, Siena, Italy
[ae] General and Upper GI Division, Department of Surgery, Dentistry, Paediatrics and Gynaecology, University of Verona, Verona, Italy
[af] Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[ag] Department of Gastrointestinal Oncology, Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, the Netherlands
[ah] Department of Medical Oncology, Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, the Netherlands
[ai] Department of Surgery, Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, the Netherlands
[aj] Department of Radiation Oncology, Radiotherapiegroep, Deventer, the Netherlands
[ak] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[al] Department of Medical Oncology, University Medical Center Leiden, University of Leiden, Leiden, the Netherlands
[am] Department of Radiation Oncology, University Medical Center Leiden, University of Leiden, Leiden, the Netherlands
[an] Department of Surgery, University Medical Center Leiden, University of Leiden, Leiden, the Netherlands
[ao] Department of Medical Oncology, Catharina Cancer Institute, Eindhoven, the Netherlands
[ap] Department of Radiation Oncology, Catharina Cancer Institute, Eindhoven, the Netherlands
[aq] Department of Surgery, Catharina Cancer Institute, Eindhoven, the Netherlands
[ar] Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht, the Netherlands
[as] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[at] Department of Surgery, Erasmus University Medical Center, University of Rotterdam, Rotterdam, the Netherlands
[au] Department of Medical Oncology, Elisabeth Tweesteden Ziekenhuis Tilburg, the Netherlands
[av] Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[aw] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[ax] Department of Surgery Jagiellonian University Medical College, Krakow, Poland
[ay] Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland
[az] Department of Oncology and Radiotherapy, Maria Skłodowska-Curie Institute, Warsaw, Poland
[ba] Department of Medical Oncology, Hospital Universitario de Navarra (HUN) and Navarrabiomed - Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain
[bb] Department of Medical Oncology, Vall D'Hebron Hospital Campus and Vall D'Hebron Institute of Oncology (VHIO), CIBERONC, Barcelona, Spain
[bc] Department of Surgery, Hospital del Mar, Universitat Autònoma de Barcelona, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain
[bd] Department of Medical Oncology, Hospital Clinico Universitario de Valencia, University of Valencia, Incliva Biomedical Research Institute, Valencia, Spain
[be] Division of Surgery and Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden
[bf] Department of Surgery, University Hospital Geneva, University of Geneva, Geneva, Switzerland
[bg] Department of Oncology, Division of Medical Oncology, University Hospital of Lausanne, University of Lausanne, Lausanne, Switzerland
[bh] Department of Upper Gastrointestinal Surgery, Queen Elizabeth Hospital Birmingham, University Hospital Birmingham, Birmingham, United Kingdom
[bi] Department of Oncology, Cambridge University Hospitals, Cambridge University, Cambridge, United Kingdom
[bj] Nuffield Department of Surgical Sciences, University of Oxford, United Kingdom, Department of Surgery, Imperial College London, London University, London, United Kingdom
[bk] Department of GI Cancer & Surgery, The Royal Marsden Hospital & Institute of Cancer Research University of London, London, United Kingdom
[bl] Department of Medical Physics and Biomedical Engineering, University College London, London, United Kingdom
[bm] Department of Upper GI and General Surgery, PanAsia Surgery, Singapore
[bn] Amsterdam UMC location University of Amsterdam, Department of Medical Oncology, Amsterdam, the Netherlands
[bo] Cancer Center Amsterdam, Cancer Treatment and Quality of Life, Amsterdam, the Netherlands
[bp] Upper GI and General Surgery Division, Department of Surgery IRCCS Humanitas Research Hospital, via Manzoni 56, Rozzano, Milan 20089, Italy
[bq] Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma, Italy

ARTICLE INFO

Keywords:
Esophageal cancer
Gastric cancer
Metastasis
Metastasectomy

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*

[1] Shared first author

[2] Tom Rozema, Joos Heisterkamp, Markus Schaefer, Esat-Mahmut Ozsahin, Jacco de Haan, Jan Willem van den Berg, Frederic Duprez, Eduard Callebout, Elke van Daele, Ulrich Hacker, Albrecht Hoffmeister, Thomas Kuhnt, Timm Denecke, Regine Kluge, Gerald Prager, A. Ilhan-Mutlu, Dajana Cuicchi, Andrea Ardizzoni, Camiel Rosman, Elske C. Gootjes, Francesco Puccetti, Stefano Cascinu, Najla Slim, Maria Eugenia Barrios, Maria Carmen Fernandez, Roberto Martí-Oriol, Marisol Huerta Alvaro, Almudena Vera, Esther Jordá, Fernando Lopez Mozos, Anna Reig, Laura Visa, Bogumiła Ciseł, Joanna Czechowska, Magdalena Kwietniewska, Agnieszka Pikuła, Magdalena Skórzewska, Aleksandra Kozłowska, Karol Rawicz-Pruszyński, Alexander Veenhof, Alexandros Charalabopoulos, Maren Knüdler

Stereotactic body radiotherapy
Oligometastasis

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 $\leq$ 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 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 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 $\leq$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 (≥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.

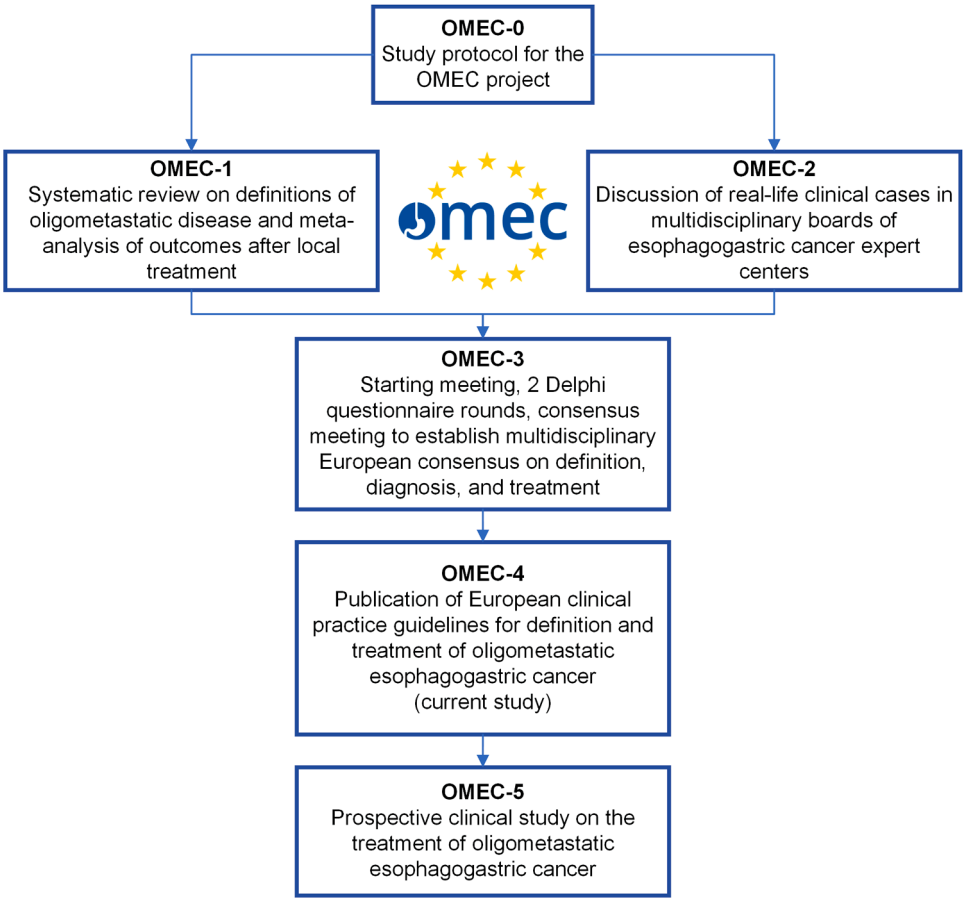

Fig. 1. Schematic overview of the OMEC project.

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
	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
Ongoing	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, ^{18}F FDG PET: fluorodeoxyglucose position emission tomography, II: phase II, III: phase III.

Recommendations for the definition of oligometastatic disease

	Oligometastatic disease (consensus)	Not oligometastatic disease (consensus)
	1 organ with ≤ 3 metastases *or*1 involved extra-regional lymph node station	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 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) with integrated computed tomography (CT), can detect small metastases, and can therefore assist in distinguishing oligometastatic disease from polymetastatic disease [33].

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

An important limitation of ^{18}F-FDG PET-staging is that a substantial portion of patients with gastric cancer (especially those with poorly cohesive disease) have ^{18}F-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)	Treatment for metachronous oligometastatic disease and DFI > 2 years (fair agreement)
Systemic therapy followed by restaging to consider local treatment for oligometastatic disease	Systemic therapy followed by restaging to consider local treatment for oligometastatic disease *or*Upfront local treatment for oligometastatic disease

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 ^{18}F-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 oligometastic 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 oligometastic 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).

Funding

Not applicable.

Declaration of Competing Interest

Dr. van Laarhoven reports a consultant or advisory role: Amphera, Anocca, Astellas, AstraZeneca, Beigene, Boehringer, Daiichy-Sankyo, Dragonfly, MSD, Myeloid, Servier; Research funding, medication supply, and/or other research support: Auristone, Incyte, Merck, ORCA, Servier; Speaker role: Astellas, Beigene, Benecke, BMS, Daiichy-Sankyo, JAAP, Medtalks, Novartis, Springer, Travel Congress Management B.V. Dr. Muijs reports institutional grants from: Elekta, IBA, RaySearch, Siemens, Mirada, Bergoz Instrumentation and Medical Data Works, KWF, all outside the submitted work. Dr. van Hillegersberg has a consulting and advisory role at Intuitive Surgical, Medtronic, Olympus and J&J Ethicon. Dr. de Manzoni reports personal fees from Lilly, outside the submitted work. Dr. Gani reports travel grants from Elekta and departmental research cooperation, outside the submitted work. Dr. Smyth is supported by the NIHR Biomedical Research Centre at Oxford (the views expressed in this Article are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health) and resports personal fees/grants from: Astra Zeneca, Beigene, BMS, Amal Therapeutics, Amgen, Daiichi Sankyo, Merck, Servier, Novartis, Pfizer, Roche, and Zymeworks, all outside the submitted work. Dr. Haj Mohammad reports consulation fees from: Merck, BMS, Eli Lilly, Astra Zeneca, and research funding from Servier, all outside the submitted work. Dr. Adenis reports grants and personal fees from Bayer, personal fees and non-financial support from MSD, personal fees from: BMS, Novartis, Pierre-Fabre, non-financial support from Servier, grants from Sanofi, all outside the submitted work. Dr. Lordick reports grants from: BMS and Gilead, personal fees from: Amgen, Astellas, Bayer, BMS, Daiichi Sankyo, Eli Lilly, Elsevier, Incyte, Merck, MSD, Roche, Servier, all outside the submitted work. Dr. Slingerland reports an advisory role at BMS and Lilly. Dr. van Berge Henegouwen received researcher-initiated grant from Stryker and is consultant for Alesi Surgical, Johnson and Johnson, Medtronic, BBraun and Viatris. Dr Nilsson reports advisory roles for BMS and Medtronic. Dr. Tabernero reports personal financial interest in form of scientific

consultancy role for Array Biopharma, AstraZeneca, Avvinity, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Seattle Genetics, Servier, Taiho, Tessa Therapeutics and TheraMyc; and also educational collaboration with Imedex, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resource (PER). Dr. Tabernero declares institutional financial interest in form of financial support for clinical trials or contracted research for Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm International SA, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Janssen-Cilag SA, MedImmune, Menarini, Merck Health KGAA, Merck Sharp & Dohme, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Pharma Mar, Sanofi Aventis Recherche & Développement, Servier, Taiho Pharma USA Inc, Spanish Association Against Cancer Scientific Foundation and Cancer Research UK. Dr. Nieuwenhuijzen reports advisory/speaker roles from Medtronic and Lilly. All remaining authors have declared no conflict of interest.

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.

References

[1] IKNL. Overlevingscijfers van slokdarmkanker. https://www.kanker.nl/kankersoorten/slokdarmkanker/algemeen/overlevingscijfers-van-slokdarmkanker.

[2] IKNL. Overlevingscijfers van maagkanker. https://www.kanker.nl/kankersoorten/maagkanker/algemeen/overlevingscijfers-van-maagkanker.

[3] Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13(1):8–10. https://doi.org/10.1200/JCO.1995.13.1.8.

[4] Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020;21(1):e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1.

[5] Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radio Oncol 2020;148:157–66. https://doi.org/10.1016/j.radonc.2020.04.003.

[6] Kerkar SP, Kemp CD, Duffy A, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. Trials 2009;10:121. https://doi.org/10.1186/1745-6215-10-121.

[7] Koemans WJ, van der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II. BMC Cancer 2019;19(1):420. https://doi.org/10.1186/s12885-019-5640-2.

[8] Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study. Radio Oncol 2022;173:269–76. https://doi.org/10.1016/j.radonc.2022.06.012.

[9] Liu Q, Chen J, Lin Y, et al. Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2023. https://doi.org/10.1016/S2468-1253(23)00316-3.

[10] Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. JAMA Oncol 2017;3(9):1237–44. https://doi.org/10.1001/jamaoncol.2017.0515.

[11] Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? a multicenter, prospective cohort study (Neo-REGATTA. BMC Cancer 2023;23(1):308. https://doi.org/10.1186/s12885-023-10773-x.

[12] Liu Q, Zhu Z, Chen Y, et al. Phase 2 study of stereotactic body radiation therapy for patients with oligometastatic esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2020;108(3):707–15. https://doi.org/10.1016/j.ijrobp.2020.05.003.

[13] Zhao W, Ke S, Cai X, et al. Radiotherapy plus camrelizumab and irinotecan for oligometastatic esophageal squamous cell carcinoma patients after first-line immunotherapy plus chemotherapy failure: An open-label, single-arm, phase II trial. Radio Oncol 2023;184:109679. https://doi.org/10.1016/j.radonc.2023.109679.

[14] Testing the Addition of Radiotherapy to the Usual Treatment (Chemotherapy) for Patients With Esophageal and Gastric Cancer That Has Spread to a Limited Number of Other Places in the Body. ⟨https://classic.clinicaltrials.gov/ct2/show/NCT04248452⟩.

[15] Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. BMC Cancer 2017;17(1):893. https://doi.org/10.1186/s12885-017-3918-9.

[16] PD-1 Antibody Combined With Modified FLOT Regimen in the Treatment of Unresectable Locally Advanced or Limited Metastatic Gastric Cancer. https://classicclinicaltrialsgov/ct2/show/NCT04510064. 2020;

[17] Local Therapy for Oligorecurrent and Oligometastatic Esophageal Squamous Cell Carcinoma. https://classicclinicaltrialsgov/ct2/show/NCT03904927. 2019;

[18] Conversion Therapy With Sintilimab Plus CAPOX in Patients With Unresectable Locally Advanced or Limited Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction (CTSCAPOXSEA). https://classicclinicaltrialsgov/ct2/show/NCT04263870. 2020;

[19] Chemotherapy With or Without Radiation or Surgery in Treating Participants With Oligometastatic Esophageal or Gastric Cancer.

[20] Chemotherapy Alone Versus Surgery Plus Chemotherapy for Distal Gastric Cancer With One Non-curable Factor. https://classicclinicaltrialsgov/ct2/show/NCT03399253. 2018;

[21] A Clinical Study Of Camrelizumab With Or Without Radiotherapy In The Treatment Of Esophageal Cancer. https://classicclinicaltrialsgov/ct2/show/NCT04512417. 2020;

[22] Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer (SURGIGAST). https://classicclinicaltrialsgov/ct2/show/NCT03042169. 2017;

[23] Brouwers MC, Kerkvliet K, Spithoff K, Consortium ANS. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ 2016;352:i1152. https://doi.org/10.1136/bmj.i1152.

[24] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924–6. https://doi.org/10.1136/bmj.39489.470347.AD.

[25] Kroese TE, van Rossum PSN, Nilsson M, et al. Study protocol for the OligoMetastatic Esophagogastric Cancer (OMEC) project: a multidisciplinary European consensus project on the definition and treatment for oligometastatic esophagogastric cancer. Eur J Surg Oncol 2023;49(1):21–8. https://doi.org/10.1016/j.ejso.2022.09.012.

[26] Kroese TE, van Laarhoven HWM, Nilsson M, et al. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: a systematic review and meta-analysis. Eur J Cancer 2022;166:254–69. https://doi.org/10.1016/j.ejca.2022.02.018.

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

[28] Kroese TE, van Laarhoven HWM, Schoppman SF, et al. Definition, diagnosis and treatment of oligometastatic oesophagogastric cancer: a Delphi consensus study in Europe. Eur J Cancer 2023;185:28–39. https://doi.org/10.1016/j.ejca.2023.02.015.

[29] Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. J Thorac Oncol 2019;14(12):2109–19. https://doi.org/10.1016/j.jtho.2019.07.025.

[30] Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic prostate cancer: results of a dutch multidisciplinary consensus meeting. Eur Urol Oncol 2020;3(2):231–8. https://doi.org/10.1016/j.euo.2019.07.010.

[31] Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67(4):401–9. https://doi.org/10.1016/j.jclinepi.2013.12.002.

[32] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[33] Lecouvet FE, Oprea-Lager DE, Liu Y, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. Lancet Oncol 2018;19(10):e534–45. https://doi.org/10.1016/S1470-2045(18)30571-0.

[34] Gertsen EC, Brenkman HJF, van Hillegersberg R, et al. 18F-Fludeoxyglucose-positron emission tomography/computed tomography and laparoscopy for staging of locally advanced gastric cancer: A Multicenter Prospective Dutch Cohort Study (PLASTIC). JAMA Surg 2021;156(12):e215340. https://doi.org/10.1001/jamasurg.2021.5340.

[35] Obermannova R, Alsina M, Cervantes A, et al. Oesophageal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):992–1004. https://doi.org/10.1016/j.annonc.2022.07.003.

[36] Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):1005–20. https://doi.org/10.1016/j.annonc.2022.07.004.
[37] Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016;17(3):309–18. https://doi.org/10.1016/S1470-2045(15)00553-7.
[38] Olson R, Jiang W, Liu M, et al. Treatment with stereotactic ablative radiotherapy for up to 5 oligometastases in patients with cancer: primary toxic effect results of the nonrandomized phase 2 sabr-5 clinical trial. JAMA Oncol 2022;8(11):1644–50. https://doi.org/10.1001/jamaoncol.2022.4394.
[39] Mehrens D, Unterrainer M, Corradini S, et al. Cost-effectiveness analysis of local treatment in oligometastatic disease. Front Oncol 2021;11:667993. https://doi.org/10.3389/fonc.2021.667993.
[40] Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384(13):1191–203. https://doi.org/10.1056/NEJMoa2032125.
[41] Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398(10302):759–71. https://doi.org/10.1016/S0140-6736(21)01234-4.
42] Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398(10294):27–40. https://doi.org/10.1016/S0140-6736(21)00797-2.
[43[Cohen SA, Liu MC, Aleshin A. Practical recommendations for using ctDNA in clinical decision making. Nature 2023;619(7969):259–68. https://doi.org/10.1038/s41586-023-06225-y.
[44] Dhiman A, Vining CC, Witmer HDD, et al. Phase II prospective, open-label randomized controlled trial comparing standard of care chemotherapy with and without sequential cytoreductive interventions for patients with oligometastatic foregut adenocarcinoma and undetectable circulating tumor deoxyribose nucleic acid (ctDNA) levels. Ann Surg Oncol 2022;29(7):4583–92. https://doi.org/10.1245/s10434-021-11249-7.