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ORIGINAL ARTICLE

International consensus on the management of metastatic gastric cancer: step by step in the foggy landscape

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Paolo Morgagni[1] · Maria Bencivenga[2] · Fatima Carneiro[3] · Stefano Cascinu[4] · Sarah Derks[5] · Maria Di Bartolomeo[6] · Claire Donohoe[7] · Clarisse Eveno[8] · Suzanne Gisbertz[9] · Peter Grimminger[10] · Ines Gockel[11] · Heike Grabsch[12,13] · Paulo Kassab[14] · Rupert Langer[15] · Sara Lonardi[16] · Marco Maltoni[17] · Sheraz Markar[18] · Markus Moehler[19] · Daniele Marrelli[20] · Maria Antonietta Mazzei[21] · Davide Melisi[22] · Carlo Milandri[23] · Paul Stefan Moenig[24] · Bianca Mostert[25] · Gianni Mura[26] · Wojciech Polkowski[27] · John Reynolds[28] · Luca Saragoni[29] · Mark I. Van Berge Henegouwen[9] · Richard Van Hillegersberg[30] · Michael Vieth[31] · Giuseppe Verlato[32] · Lorena Torroni[32] · Bas Wijnhoven[33] · Guido Alberto Massimo Tiberio[34] · Han-Kwang Yang[35] · Franco Roviello[20] · Giovanni de Manzoni[2] · Bertinoro Workshop Working Group

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Abstract

Background Many gastric cancer patients in Western countries are diagnosed as metastatic with a median overall survival of less than twelve months using standard chemotherapy. Innovative treatments, like targeted therapy or immunotherapy, have recently proved to ameliorate prognosis, but a general agreement on managing oligometastatic disease has yet to be achieved. An international multi-disciplinary workshop was held in Bertinoro, Italy, in November 2022 to verify whether achieving a consensus on at least some topics was possible.

Methods A two-round Delphi process was carried out, where participants were asked to answer 32 multiple-choice questions about CT, laparoscopic staging and biomarkers, systemic treatment for different localization, role and indication of palliative care. Consensus was established with at least a 67% agreement.

Results The assembly agreed to define oligometastases as a "dynamic" disease which either regresses or remains stable in response to systemic treatment. In addition, the definition of oligometastases was restricted to the following sites: para-aortic nodal stations, liver, lung, and peritoneum, excluding bones. In detail, the following conditions should be considered as oligometastases: involvement of para-aortic stations, in particular 16a2 or 16b1; up to three technically resectable liver metastases; three unilateral or two bilateral lung metastases; peritoneal carcinomatosis with PCI ≤ 6. No consensus was achieved on how to classify positive cytology, which was considered as oligometastatic by 55% of participants only if converted to negative after chemotherapy.

Conclusion As assessed at the time of diagnosis, surgical treatment of oligometastases should aim at R0 curativity on the entire disease volume, including both the primary tumor and its metastases. Conversion surgery was defined as surgery on the residual volume of disease, which was initially not resectable for technical and/or oncological reasons but nevertheless responded to first-line treatment.

Keywords Stage IV · Oligometastatic gastric cancer · Consensus · Staging · Multimodal treatment

Extended author information available on the last page of the article

Introduction

Gastric cancer is still one of the leading causes of cancer-related deaths worldwide, with over one million of new cases in 2020 and an estimated 769,000 deaths, ranking fifth for incidence and fourth for mortality globally [1].

Due to the lack of screening programs in the West, 35–55% of patients present with metastatic disease at diagnosis [2] with a median overall survival of 9–11 months when treated with standard chemotherapy [3]. However, in recent years there has been a growing effectiveness of systemic therapy for metastatic patients both for the introduction of new chemotherapy schemes, target therapy, and immunotherapy, and for the optimization of the patient's general conditions.

At the same time, the evidence has grown that a subgroup of metastatic patients is in a transitional state between localized and widespread disease, this can be defined as oligometastatic gastric cancer (OGC) [4].

Oligometastatic GC is characterized by limited tumor burden. An aggressive multimodal integrated approach for such cases, including both systemic therapy and local ablative treatment after response to systemic therapy, demonstrates a non-negligible survival (about 31 months) that is significantly higher than that of poly metastatic GC undergoing systemic chemotherapy alone [3, 5].

The biological mechanisms of transition between oligo and poly metastatic disease are currently not well known. However, it is conceivable that in some cases resection of oligo metastases may prevent further dissemination of disease allowing survival benefit. The only way to select these patients, currently, is to observe their response to chemotherapy over time. Therefore, the definition of oligo metastatic disease should consider both the burden of disease at diagnosis and the response to chemotherapy [3, 6–8].

It is important to note that an improved prognosis was observed even in extremely selected patients with poly metastases treated with surgery after response to systemic therapy.

In this context, a major issue is to achieve a clear and shared definition of oligo and poly metastatic gastric cancer to be used in clinical practice as well as a definite treatment path. Recently, the attention to this specific issue has grown a lot and some projects have been designed to deal with it, but there is still no comprehensive and globally shared evidence on these topics [9–11]. It should be underlined that evidence available from the current literature is limited, as published randomized trials are still lacking.

The present project aimed at discussing the current status of diagnosis and treatment of synchronous metastatic gastric cancer (including Siewert 3, but excluding the other EGJ and esophageal tumors) by a multidisciplinary international team of specialists and trying to reach agreement on the definition and clinical pathway to be followed or identify areas for further research.

Methods

The methodology of this project was similar to that of other multicentric consensus reports [12, 13]. First, possible guidelines for metastatic gastric cancer were proposed by a central team of members, following a literature search. Second, a formal multi-disciplinary process was designed using a Delphi method, which involved two anonymous rounds.

A restricted working group (RWG) of the Italian Research Group for Gastric Cancer (GIRCG), composed of two oncologists, five surgeons, one radiologist, one pathologist and one biostatistician, established the project's aim and defined the topics for debate. The RWG generated statements based on the controversial results from the current medical literature identifying areas of uncertainty about defining and managing stage IV gastric cancers. Based on the controversial literature, a multiple-choice questionnaire was developed. It consisted of a total of 32 questions (see Table 1), divided into three macro-areas:

A. **How to stage (questions 1–8):** relating to the type of imaging used for diagnosis of gastric cancer (and metastatic disease), the role of laparoscopic staging, and biomarkers needed for treatment.
B. **How to treat (questions 9–29):** relating to definition and local and systemic treatment for different types of metastases (lung, bone, lymph nodes, peritoneal…).
C. **How to care (questions 30–32):** relating to role and indication for palliative care.

The RGW selected the expanded working group (EWG) of Worldwide experts in gastric cancer surgery and interpreted the results. Members of the EWG, who agreed to participate and got involved in the rating process, are listed in Supplementary Table 1.

In the first round, the questionnaire was sent out by e-mail to 96 experts. Answers were anonymously collected from June the 6th to the 1st of September 2022 through an online survey system. The first round was completed by 52 members. Thereafter, the EGW was invited to participate in a dedicated workshop held in Bertinoro, Italy, on the 10th of November 2022 for the second-round, which was attended by 78 experts.

Each expert was asked to comment and suggest modifications to the draft statements through a Delphi method implementation. During the workshop, the existing

Table 1 Summary questionnaire

Q1: Which imaging exams do you consider mandatory for staging gastric cancer?
A - Thoracic and abdominal Contrast-Enhanced CT (CECT)
B - Abdominal RMN
C - Total body FDG-PET
D - Other

Q2: How do you stage cancer regression to first-line treatment?
A - CT scan (using % of reduction not strictly limited to RECIST)
B - CT scan D Max
C - Texture Analysis
D - CT using RECIST

Q3: In the case of locally advanced GC (i.e. ≥T2) without radiological evidences of metastasis, when do you perform staging laparoscopy?
A - Never
B - In the case of cT3-T4 GC with diffuse histology
C - In the case of cT3-T4 GC with any histology
D - In all cases
E - Other

Q4: How do you perform staging laparoscopy?
A - Explore the four quadrants
B - Explore the four quadrants plus omental bursa
C - Explore the four quadrants plus omental bursa plus small bowel mesentery
D - Other

Q5: When do you perform staging laparoscopy in case of metastatic GC?
A - In all cases
B - Only in cases of clinical suspicion of peritoneal involvement without extraperitoneal disease
C - Only in cases of clinical suspicion of peritoneal involvement despite extraperitoneal disease
D – Never

Q6: Do you have a protocol to perform cytology lavage?
A - Yes
B - No

Q7: Which molecular bio-markers do you consider needful to evaluate at time of diagnosis?
A - HER2
B - HER2 AND MSI
C - HER2, MSI, PD-L1 (CPS), EBV, TMB
D - Others
E - HER2, MSI, PD-L1 (CPS), EBV[#]

Q8: Do you usually perform a biopsy of metastatic sites if possible?
A - Yes
B – No
C- Only in selected case [#]

Q9: Do you discuss in a Multidisciplinary Tumour Board the cases of metastatic GC?
A - Always at the time of first diagnosis
B - Only in case of oligometastases at first diagnosis
C - Only in case of response to first-line treatments

Q10: Which of the following conditions could be defined as oligometastatic GC with liver metastases?
A - Multiple bilobar liver metastases in response to chemotherapy
B - Up to 3 unilobar liver lesions, at least one of them unresectable/borderline for resection in response to chemotherapy
C - Up to 3 unilobar liver lesions, all technically resectable in response to chemotherapy
D - Up to 3 unilobar liver lesions, all technically resectable regardless the response to chemotherapy
E - Other
F - Up to 3 even bi-lobar all technically resectable in response or stable to chemotherapy[#]

Q11: Which para-aortic lymph nodes stations do you include in the definition of oligometastatic GC? [Multiple choice is possible]
A - 16 a1 (aortic hiatus)
B - 16 a2 (from the origin of the celiac trunk to the lower margin of the left renal vein)
C - 16 b1 (from the inferior margin of the left renal vein to the superior margin of the inferior mesenteric artery)
D - 16 b2 (from the origin of the inferior mesenteric artery to the aortic bifurcation)
E - none of the above

Q12: Which of the following conditions could be defined as oligometastatic GC with lymph node metastases? [Multiple choice is possible]
A - Clinically evident metastasis to para-aortic lymph-nodes in stations 16a2 and/or b1
B - Clinically evident metastasis to para-aortic lymph-nodes in stations 16a1 and/or b2
C - Clinically evident metastasis to other "posterior" stations (stations 12p, 13)
D - A combination of the previous, provided the response to chemotherapy
E - Clinically evident metastasis to para-aortic lymph-nodes in stations 16a2 and/or b1 provided the response to chemotherapy

Q15: Does oligometastatic peritoneal gastric cancer exist?
A - Yes
B - No

Q16: Do you think lung metastases could be considered as oligometastatic?
A - According to OMEC project, only 3 unilateral or 2 bilateral lesions
B - Yes, regardless the number and dimensions of lesions
C - No, in any case

Q17: Do you think bone metastases could be included in oligometastatic disease?
A- No, in any cases
B - Yes, in all cases
C - Yes, only if 1 or 2 lesions provided the stability during chemo and amenable of local treatment

Q18: Do you believe that oligometastatic GC:
A - Should involve one site only (liver, limph nodes, peritoneum)?
B - Can involve also more than one site
C - Can involve also more than one site provided that one of them is not peritoneum/Cyt+

Q19: Do you believe that in order to define a metastatic GC as oligometastatic:
A - There should be a response to chemotherapy both in terms of size and number of metastatic lesions
B - There should be a response to chemotherapy only in terms of number of metastatic lesions
C - The metastatic lesions can be in response or even stable to chemotherapy
D - The metastatic lesion can also progress to chemotherapy provided their technical resectability
E - Other (specify)

Q20: In case of oligometastatic HER2 negative GC, what kind of chemo do you suggest?
A - Standard first-line chemotherapy (FOLFOX)
B - FLOT
C - Immunotherapy OR chemo-immunotherapy in presence of biomarkers predictive of response
D - Other

Q21: In case of oligometastatic HER 2 positive GC, what kind of chemo do you suggest?
A - Platinum- based chemotherapy + trastuzumab
B - Chemotherapy + trastuzumab + immunoterapy
C - Other

Q22: Which is the surgical indication in Oligometastatic GC (excluding peritoneum) after first-line treatment?
A - Radical intent surgery based on the initial volume of disease if stable or in response to chemotherapy
B - Radical intent surgery based on the initial volume of disease regardless of the degree of response to chemotherapy provided technical resectability
C - Other

Q23: In case of positive cytology when do you consider surgery with radical intent?
A - Never
B - After first line chemotherapy, regardless it is converted into negative without HIPEC
C - After first line chemotherapy, regardless it is converted into negative with HIPEC
D - After first line chemotherapy, only in case of its conversion into negative, with HIPEC
E - After first line chemotherapy, only in case of its conversion into negative, without HIPEC

Q24: In case of surgery for Oligometastatic Peritoneal GC do you consider: [Multiple choice is possible]
A - Complete cytoreductive surgery including all the sites of positive biopsies at baseline considering HIPEC not necessary
B - Complete cytoreductive surgery in all the sites of positive biopsies at baseline considering HIPEC necessary
C - Complete cytoreductive surgery according to residual disease without HIPEC
D - Complete cytoreductive surgery according to residual disease with HIPEC
E - Other

Q25: Select the most suitable (first rank) of Oligometastatic GC:
A - Nodal metastases
B - Liver metastases
C - Peritoneal metastases
D - Positive cytology
E - Other

Q26: Which is your definition of conversion surgery?
A - Surgery on the residual disease after chemotherapy in case metastatic GC which was initially not resectable for technical and/or oncological reasons but nevertheless responded to first-line treatment
B - Surgery on the residual disease after chemotherapy in case metastatic GC which was initially not resectable for technical and/or oncological reasons regardless the response to first-line treatment
C - Surgery on the residual disease after chemotherapy in case metastatic GC which was technically and/or oncologically resectable at the time of diagnosis, regardless the response to first-line treatment

Q27: How do you manage the site that was responsible for initially unresectability in case of its clinical complete response?
A - Try to resect it
B - Never resect it
C - No resection, but place markers for subsequent possible radiotherapy

Q28: How do you consider the case of the previous question?
A - R0
B - R1
C - R2

Q29: Do you think that the conversion surgery could have the same benefits if first-line treatments did include the use of immunotherapy?
A - Yes
B - No
C - No data Available

Q 30: Do you have the possibility of palliative team in your centre?
A - Yes
B - No

Q 31: When do you stop oncologic palliative treatments?
A - On patient's request
B - In relation to performance status
C - In case of multiple metastatic sites
D - After progression despite of oncological treatments
E- Shared decision [#]

Q 32: What is the indication for nutritional support in end-stage patients?
A - Always
B - Never
C - In relation to patient's general condition and life expectancy
D - On patient's request

[#]New answer after second round discussion

evidence in the literature on each previously identified topic was presented by two experts and the specific topics and the answers given to the first-round questionnaire were discussed in the plenary. Finally, the questionnaire was administered for the second round and a draft Statement in response to each issue was recorded.

The answers of the experts were anonymously collected and reported below as percentages for each multiple-choice question. The RGW decided a priori the minimum cut-off level for Consensus that was two-thirds (≥ 67%) of agreement of effective answers [14–16]. The agreement was further categorized as satisfactory (67–69%), good (70–79%), excellent (80–89%) and exceptional (≥ 90%) [17].

The classic GRADE approach could not be used, as evidence from the literature was sparse and published randomized clinical trials were lacking [18–20]. Most studies on this topic are observational retrospective, but one non-randomized prospective phase 2 study (AIO-FLOT3) [5]. Indeed, a randomized phase III trial (AIO-FLOT5) is ongoing, aimed at comparing chemotherapy alone vs. chemotherapy followed by surgical resection in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction [21], but the results have not been published yet.

Results

(A) How to stage

1. Which imaging exams do you consider mandatory for staging gastric cancer?

   a. Thoracic and abdominal Contrast-Enhanced CT (CECT) **(100%)**
   b. b. Abdominal MRI **(0%)**
   c. Total body FDG-PET **(0%)**
   d. Other **(0%)**

Statement 1: CT scan as the most useful exam for staging of metastatic GC with exceptional agreement (100%)

Discussion Statement 1:

Evaluation by a "skilled" dedicated radiologist and *CT* with multiplanar reformation (MPR) have high accuracy, sensibility, and specificity: in early GC (T1-T2) Acc: 93.7-95%, Sens: 66.7-88%, Spec: 96-97% and in Advanced GC (T3-T4): Acc: 85.7-93%, Sens: 90-93%, Spec: 88.6-93% [22, 23]. Regarding the N staging, the short axis diameter (SAD) is different in regional versus distant nodes: cN-positive when SAD >/= 5/6 mm for perigastric nodes (N1-stations), SAD >/= 8mm for extra regional-nodes [24, 25].

Using FDG-PET/CT in staging advanced gastric cancer is not recommended [26]. Indeed, the evidence of the use of FDG-PET in staging advanced gastric cancer is not so strong as for esophageal cancer. The reasons are different: the low accuracy rate due to the low FDG uptake in diffuse and mucinous tumor types, the difficult distinction between T and peri gastric LN, the low sensitivity for peritoneal carcinomatosis (due to lesion dimension, burden of PCI and intestinal uptake). A possible role could be taken into consideration in centres in which is possible to perform a concurrent FDG-PET and CT examination with oral and IV contrast (excluding the search for peritoneal carcinomatosis and the diffuse and mucinous type staging) or where the FAPI-PET is available.

2. How do you stage cancer regression to first-line treatment?

   a. CT scan (using % of reduction not strictly limited to RECIST) **(41%)**
   b. b. CT scan D Max **(0%)**
   c. Texture Analysis **(0%)**
   d. CT using RECIST **(59%)**

Statement 2: CT scan should be used to stage tumor regression (exceptional agreement). Debate exists whether to strictly follow RECIST criteria (59%) or to introduce additional criteria (41%).

Discussion Statement 2:

RECIST criteria have several limitations: primary lesions and peritoneal lesions are both difficult to measure and the SAD cut-off for lymph nodes seems to be inadequate. Indeed, about 40% of metastatic LN in CG has a SAD < 10 mm, and at restaging also LN that shrinks below 10 mm may still be metastatic.
Radiomics, and in particular delta-radiomics, providing quantitative data on tumor microenvironment by analyzing the distribution and relationship of pixel or voxel gray levels in the CT scan between baseline and restaging examinations, seems to be able to predict survival and chemotherapy response to treatment, recognizing subset of responder patients according to Becker grade [27, 28].

Dmax represents the maximum tumour diameter; it is measured using a curved line through 2D multiplanar reconstruction to obtain the maximum tumour extension. Radiological and pathological D-max measurement methods are theoretically interchangeable, and there is a dependence of Dmax on depth of Invasion (T parameter), thus Dmax could be used to improve the CT performance in T-staging evaluation, since it is an easier parameter to assess by CT rather than the T-staging.

In previous experience [29] D-max reduction rate seems to be reliable for identifying responder patients and in particular Becker 1 patients after neoadjuvant therapy, but this deserve more evidence.

3. In the case of locally advanced GC (i.e., ≥ T2) without radiological evidence of metastasis, when do you perform staging laparoscopy?
   a. Never **(3%)**
   b. In the case of cT3-T4 GC with diffuse histology **(3%)**
   c. In the case of cT3-T4 GC with any histology **(35%)**
   d. In all cases **(56%)**
   e. Other **(3%)**

4. How do you perform staging laparoscopy?
   a. Explore the four quadrants **(14%).**
   b. Explore the four quadrants plus omental bursa **(8%).**
   c. Explore the four quadrants plus omental bursa plus small bowel mesentery **(59%).**
   d. Other—please specify **(19%).**

5. When do you perform staging laparoscopy in case of metastatic GC?
   a. In all cases **(6%).**
   b. b. Only in cases of clinical suspicion of peritoneal involvement without the extraperitoneal disease **(83%).**
   c. Only in cases of clinical suspicion of peritoneal involvement despite extraperitoneal disease **(3%).**
   d. Never **(8%).**

6. Do you have a protocol to perform cytology lavage?
   a. Yes (please specify) **(43%)**
   b. No (57%)

Statement 3: Staging laparoscopy and cytology

- There was a strong agreement on performing staging laparoscopy in c-stage T3/4 cancers, irrespective of histology (92%). 56% of experts would extend the procedure to all cases.

- A Consensus was not achieved as regards the extension of staging laparoscopy: indeed a satisfactory agreement (67%) was achieved as regards exploring the 4 quadrants and omental bursa, but the agreement decreased to 59% as regards inclusion of small bowel mesentery.

- An excellent agreement (83%) was reached on the indications of staging laparoscopy in radiologically detected metastatic GC, that is only in cases of clinical suspicion of peritoneal involvement without extraperitoneal disease, Only 57% of the experts have a standard protocol to perform peritoneal cytology lavage in their centers.

Discussion Statement 3:

According to the ESMO guidelines [30] diagnostic laparoscopy is recommended in all patients with resectable gastric cancer (IB-III), while for Italian guidelines (GIRCG and GAIN) [24, 31] it should be considered in all patients at risk for undiagnosed peritoneal disease (cT3/4 and/or cN+). The Japanese Gastric Cancer Association advises to perform a staging laparoscopy only in patients with advanced gastric cancer with an indication for neoadjuvant chemotherapy treatment [32].

7. Which molecular biomarkers do you consider necessary to test at time of diagnosis of metastatic gastric cancer ?

   a. HER2 **(2%)**
   b. HER2 and MSI **(7%)**
   c. HER2, MSI, PD-L1 (CPS), EBV, TMB **(16%)**
   d. Others, please specify **(2%)**
   e. HER2, MSI, PD-L1 (CPS), EBV (**new option added**) **(73%)**

Statement 4: HER2, MSI, PD-L1 (CPS), EBV are the biomarkers needed at time of diagnosis of stage IV GC, as agreed by 89% of experts.
As regards the TMB, this currently does not add anything for gastric cancers outside of research protocol, so that only a minority of experts (16%) would also consider TMB among biomarkers.

Discussion Statement 4:

According to literature and guidelines, testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients. HER2 and PD-L1 testing are recommended at the time of diagnosis if metastatic disease is documented or suspected [30,33].
For an accurate HER2 evaluation, it is recommended to use IHC and, if needed, ISH techniques [33].
Finally, PD-L1 testing should be evaluated according to the value of combined positive score (CPS) [33].

8. Do you usually perform a biopsy of metastatic sites if possible?

   a. Yes (31%).
   b. b. No **(21%).**
   c. Only in selected cases (**new option added**) **(48%).**

Statement 5: There was no agreement on performing whenever possible a biopsy of metastatic lesions. Of note, most of the experts (79%) perform the procedure at least in selected cases, if there is a potential impact on treatment strategy (i.e., HER2 + cases).

Discussion statement 5:

EBV and MMR protein status in the primary tumor and corresponding metastases were recently analysed in a large western cohort [34], showing concordance between the primary tumor and distant metastases. Thus, the evaluation of EBV or MMR protein status for immunotherapy eligibility testing seems to be sufficient either on primary or synchronous metastatic tumor tissue. Moreover, the primary tumor and its metastases probably have a similar response to immune check-point inhibition, as the molecular key events that predict response are preserved during the metastatic process in these specific subgroups. On the other hand, the CIN subgroup of GC, which is the most common subtype, is associated to the amplification of HER2 receptor, occurring in 15–20% of GC [35]. The addition of the anti-HER2 monoclonal antibody Trastuzumab to chemotherapy in HER2 positive patients is associated with a survival benefit. However, patients usually progress on first line trastuzumab-based therapy, probably due to intralesional heterogeneity of HER2 expression and amplification, in which individual oncogenes may be uniquely amplified in distinct subclones of the same tumor, or different oncogenes may be co-amplified within the same cancer cell. Additionally, also the rise of non-HER2-amplified clones that likely reflects pre-existing heterogeneity and selection of HER2-negative subclones during trastuzumab therapy could be a reason for resistance [36]. In such cases, a biopsy of metastatic disease should be considered. Of course, biopsy of metastatic disease should be performed only if deemed safe for the patient, always considering the risk-benefit balance.

(B) How to treat

9. Do you discuss in a Multidisciplinary Tumour Board the cases of metastatic GC?

   a. Always at the time of first diagnosis **(85%)**
   b. Only in case of oligometastases at first diagnosis **(4%)**
   c. Only in case of response to first-line treatments **(11%)**

Statement 6: All participants in the workshop reported that they participated in a multidisciplinary tumor board (MTB) including at least surgeons, oncologists, pathologists, radiologists, and radiation oncologists. At MTB treatment options for each newly diagnosed metastatic GC should be discussed (agreement 85%), according to the international guidelines [24, 30, 33].

10. Which of the following conditions could be defined as oligometastatic GC with liver metastases?

    a. Multiple bilobar liver metastases in response to chemotherapy **(2%)**
    b. Up to 3 unilobar liver lesions, at least one of them unresectable/borderline for resection in response to chemotherapy **(5%)**
    c. Up to 3 unilobar liver lesions, all technically resectable in response to chemotherapy **(50%)**
    d. Up to 3 unilobar liver lesions, all technically resectable regardless of the response to chemotherapy **(7%)**
    e. Other **(5%)**
    f. Up to 3 even bi-lobar, all technically resectable in response or stable to chemotherapy (**new option added**) **(32%).**

Statement 7: An excellent agreement (89%) was reached on considering as oligometastases a maximum of 3 technically resectable liver metastases.

However, no further agreement was achieved on unilobar/bilobar location and response to chemotherapy. Indeed, half of the experts had a stricter approach, requiring that the three lesions should be in same lobe and responsive to chemotherapy to be defined as oligometastasis. Another 32% proposed a wider definition, including also bilobar lesions stable during chemotherapy in the definition of oligometastasis.

Discussion statement 7:

According to inclusion criteria of the AIO FLOT 3 trial, definition of hepatic "limited metastases" included a maximum of 5 liver metastases, technically resectable or amenable of locally ablative procedure [6, 10]. A meta-analysis [11] performed in the frame of the first OMEC project, found that the maximum number of liver lobes was specified by 26 out of 43 studies or study protocols. Liver oligometastasis could be present in both liver lobes (i.e., bilobar) according to 23 out of 26 (88%, consensus). The maximum number of liver metastases was specified by 32 out of 43 studies or study protocols. A total of 3 metastases were considered OMD by 25 out of 32. Instead, according to second OMEC project, the definition by multidisciplinary expert of oligometastatic GC considered the presence of 1–2 metastases in the liver, but without agreement on response or partial response after treatment [10].

During the meeting, data from OMEC 3 phase (Delphi consensus by European experts) were showed and oligometastatic organ-specific disease burden could be limited to 2 liver metastases if bi-lobar or to 3 unilobar liver metastases [20].

In addition, results from retrospective studies on large series of patients [37–39] showed that surgical resection of hepatic metastases in selected groups of patients is associated with a survival benefit.

11. Which para-aortic lymph nodes stations do you include in the definition of oligometastatic GC? [Multiple choice is possible].

    a. 16 a1 (aortic hiatus) **(6%)**
    b. 16 a2 (from the origin of the celiac trunk to the lower margin of the left renal vein) **(16%)**
    c. 16 b1 (from the inferior margin of the left renal vein to the superior margin of the inferior mesenteric artery) **(4%)**
    d. 16 b2 (from the origin of the inferior mesenteric artery to the aortic bifurcation) **(2%)**
    e. None of the above **(4%)**

    A + B = **6%**
    B + C = **22%**
    A + B + C = **2%**
    B + C + D = **2%**
    A + B + C + D = **35%**

12. Which of the following conditions could be defined as oligometastatic GC with lymph node metastases? [Multiple choice is possible].

    a. Clinically evident metastasis to para-aortic lymph-nodes in stations 16a2 and/or b1 **(4%)**
    b. Clinically evident metastasis to para-aortic lymph-nodes in stations 16a1 and/or b2 **(2%)**
    c. Clinically evident metastasis to other "posterior" stations (stations 12p, 13) **(4%)**
    d. A combination of the previous, provided the response to chemotherapy **(72%)**
    e. Clinically evident metastasis to para-aortic lymph-nodes in stations 16a2 and/or b1 provided the response to chemotherapy **(17%)**

13. Do you consider distant lymph nodes (e.g., supra-clavear, mediastinic, other abdominal excluding para-aortic in 16a2 and 16b1 stations) as oligometastatic disease?

    a. Yes, in any case **(2%)**
    b. Yes, if responsive to chemotherapy and technically resectable/amenable of local treatment **(11%)**
    c. Yes, if technically resectable regardless response to chemotherapy **(0%)**
    d. No, they should be considered as systemic metastatic disease in any cases, regardless response to chemotherapy and technical resectability **(87%)**

Statement 8: An agreement was reached (72%) that lymph nodes at posterior stations (12p, 13, 16 a1, 16 a2, 16 b1, 16 b2) should be considered as oligometastases provided their response to systemic therapies.

Discussion statement 8:

In the OMEC project, consensus was observed that 1 extra-regional lymph node station was considered oligometastatic disease. Extra-regional lymph node metastases were defined according to the AJCC/UICC 8th edition staging system.

Data from Japanese authors suggest that para-aortic lymph node dissection is associated with a significant survival advantage when positive para-aortic lymph nodes have responded to neoadjuvant systemic chemotherapy [40] Although not all the posterior lymph node stations were considered in the above-mentioned Japanese study, this evidence supports the definition of oligometastatic gastric cancer with lymph node disease given in Statement 8 in our Consensus. On the other hand, the experts did not consider as possible site of oligometastases any of the other extra-regional abdominal or distant extra-abdominal lymph node stations, such as the supraclavicular or mediastinal stations with the exceptions of stations 19, 20 and 111, included in D2 for gastric tumors involving the esophagus by the Japanese guidelines. This is at variance with the OMEC project, where extra-regional lymph node metastases were defined according to the AJCC/UICC 8th edition staging system. However, it should be considered that, while the OMEC project did not distinguish between esophageal and gastric cancer, the present Consensus only focuses on gastric tumors so that many of the stations, which were categorized as oligometastases by the OMEC project in relation to esophageal cancer, cannot be considered as such for gastric adenocarcinoma.

14. Does only positive cytology should be considered as oligometastatic disease?

    a. Yes (31%)
    b. No (**14%**)
    c. Only if a conversion from positive to negative cytology after chemotherapy is documented **(55%)**

15. Does oligometastatic peritoneal gastric cancer exist?

    a. Yes (specify the PCI cut off ….) **(91%).**
    b. No (9%).

Statement 9: Nearly all experts (88%) define positive cytology as oligometastases. However, the majority (55%) require response to chemotherapy as a prerequisite to define positive cytology as oligometastasis, while about one third (31%) define it as oligometastasis, irrespective of response to chemotherapy.

The vast majority (91%) agreed that oligometastatic peritoneal carcinomatosis does exist with a maximum PCI value of 6.

Discussion statement 9:
Cytological examination of peritoneal lavage is recommended by the ESMO [30] and the Japanese Gastric Cancer Treatment Guidelines, and positive cytology (CY1) is defined as a metastatic (M1) site by the TNM staging. Peritoneal metastasis localized at a limited area close to the primary tumor is defined as P1a [41]. Prognosis of patients with positive peritoneal cytology is rather favourable [42] when the Cyt + is converted into Cyt – by systemic therapy and the patient is subsequently treated with radical surgery [43, 44]. In agreement with this recent evidence, more than half of the experts in our Consensus would define Cyt+ as oligometastatis only if converted into Cyt. Survival after P1a after surgical resection of all visible lesions was reported to be not negligible [45, 46]. Of course, long-term survival after curative resection is much better when systemic chemotherapy manage to eliminate the limited metastatic peritoneal disease (P0 after surgical resection) [45–47].
The ideal cut off (considered as PCI score) for defining oligometastatic peritoneal disease is not clear yet. The stronger data have been published by Glehen et al. showing a hypothetical cut-off at a PCI value of 12, with the best results in terms of survival with a value ≤ 6 [48]. Of note, a low PCI allows to obtain a complete cytoreduction that is the main factor affecting survival.

Similarly, results from other studies [49, 50], showed that patients with a PCI < 7 had a significant survival advantage.

In the OMEC project, patients with peritoneal metastases were not included because these patients were considered to have polymetastatic disease requiring specific treatment (e.g., cytoreductive surgery and hyperthermic intraperitoneal chemotherapy).

16. Do you think lung metastases could be considered as oligometastatic?

a. According to OMEC project, only 3 unilateral or 2 bilateral lesions **(82%).**
b. b. Yes, regardless the number and dimensions of lesions **(7%).**
c. No, in any case **(11%).**

Statement 10: There was an agreement **(82%)** on considering lung metastases as oligomet till a maximum of 3 unilateral or 2 bilateral lesionsnot increasing during CHT [10].

17. Do you think bone metastases could be included in oligometastatic disease?

a. No, in any cases **(56%)**
b. Yes, in all cases **(4%)**
c. Yes, only if 1 or 2 lesions provided the stability during chemo and amenable of local treatment **(40%)**

Statement 11: Consensus was not reached on bone metastases as oligomet. Most experts (56%) exclude bone metastases from the definition of oligomet disease, while 40% consider as oligomet only 1 or 2 lesions provided that they are stable during chemotherapy and amenable of local treatment.

Discussion statement 11:
Recently, in a nationwide population-based study, Kroese et al. analyzed the outcomes of local treatment (i.e., stereotactic body radiotherapy [SBRT] or metastasectomy) or systemic therapy for oligometastatic disease in patients with esophagogastric cancer [51]. Of note, bone metastases were treated in 75% of cases with SBRT instead of metastasectomy. Results from this study showed that local treatment alone or combined with systemic therapy was independently associated with improved OS as compared with systemic therapy alone.

18. Do you believe that oligometastatic GC:

a. Should involve one site only (liver, lymph nodes, peritoneum)? **(53%)**
b. Can involve also more than one site **(32%)**
c. Can involve also more than one site provided that one of them is not peritoneum/Cyt + **(15%)**

19. **Do you believe that to define a metastatic GC as oligometastatic:**

a. There should be a response to chemotherapy both in terms of size and number of metastatic lesions **(34%)**
b. There should be a response to chemotherapy only in terms of number of metastatic lesions **(14%)**
c. The metastatic lesions can be in response or even stable to chemotherapy **(45%)**
d. The metastatic lesion can also progress to chemotherapy provided their technical resectability **(7%)**
e. Other (specify) **(0%.**

Statement 12: A consensus was not achieved as regards the number of sites involved by oligomet disease, as about half of the experts (53%) restricted the definition of oligomet to one site involvement, while the other half also included multiple site metastases. The latter group was further split in those excluding or not Cyt+/peritoneal carcinomatosis from multiple site oligometastases. Concerning the response to chemotherapy required to define a metastatic GC as oligomet, nearly all experts (93%) excluded lesions progressing during chemotherapy from the definition of oligomet and about half of the experts (48%) also excluded lesions remaining stable.

Discussion statement 12:
According to OMEC projects 1 and 2 [9, 10], OMD is considered as the presence of 3 metastases in only one organ (e.g., liver, lung) or 1 extra-regional lymph node station [19] . The peritoneum is not considered as an oligometastatic location in the OMEC project because this reflects polymetastatic disease which is treated with hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery which is not comparable to oligometastatic disease.
Moreover, analyzing data from CONVO- GC1 study, it emerged that in Yoshida categories 1 and 2, that are metastatic cases without peritoneal involvement [52], also patients with more than one metastatic site are included [53], moreover Yoshida category 4 included all the multiple sites of metastases if one of them is peritoneum. Interestingly, the overall survival in patients who received surgery with R0 resection in all the Yoshida categories was better compared to not resected cases. It can, therefore, be assumed that if R0 resection can be achieved, surgery could be indicated even in patients with more than one metastatic site even if one of these is peritoneum/Cyt+ (categories 3 and 4).
Regarding question on response to chemotherapy to define oligometastatic disease, there is no agreement in the literature. The OMEC project identified a fair agreement (i.e., 50–75% agreement) that the minimum duration of systemic therapy was 3 months. In addition, oligometastatic disease was considered after systemic therapy in patients without progression (consensus) or progression in size of the oligometastatic lesion only (fair agreement) [19].
Conversely, oligometastatic GC according to the GIRCG is a dynamic concept of low burden disease in response to intensive first-line chemotherapy.

20 In case of oligometastatic HER2 negative GC, what kind of chemo do you suggest?

a. Standard first-line chemotherapy (FOLFOX) **(9%)**
b. b. FLOT **(23%)**
c. Immunotherapy OR chemo-immunotherapy in presence of biomarkers predictive of response **(63%)**
d. Other, please specify **(5%)**

21. In case of oligometastatic HER 2 positive GC, what kind of chemo do you suggest?

a. Platinum-based chemotherapy + trastuzumab **(86%)**
b. Chemotherapy + trastuzumab + immunotherapy **(14%)**
c. Other, please specify **(0%)**

Statement 13: Excellent Consensus was achieved (86%) on 'Platinum-based chemotherapy + trastuzumab' as standard first-line schedule in HER2 positive oligomet patients (Figure 2c). The agreement was lower as regards HER2 negative oligomet patients, nevertheless **(63%) of experts chose** Immunotherapy or chemo-immunotherapy in presence of biomarkers predictive of response as standard first-line schedule.

Discussion statement 13:

In the AIO-FLOT3 trial [5], the feasibility and efficacy of induction chemotherapy were prospectively evaluated. Four cycles of FLOT were administered, followed by surgery also for patients with limited metastatic GC who had additional favorable prognostic factors. Indeed, these patients exhibited a considerable median OS of 22.9 months, which was markedly better than the expected survival for metastatic disease (9–11 months).

Furthermore, different types of therapy are emerging. Recently, the use of nivolumab (PDL-1 inhibitor) plus standard chemotherapy in first line treatment was approved after the results of the CheckMate 649 showed a significant improvement in OS and PFS ($p<0{\cdot}0001$) compared to chemotherapy alone in patients with a PD-L1, CPS≥5 [54]. Even after 24 months of follow-up, nivolumab plus chemotherapy continued to demonstrate improvement in overall survival, both in patients with PD-L1 CPS ≥5 and in all randomized patients [54, 55].

In HER 2 positive patients, the role of Trastuzumab is already well known [56]. Moreover, more evidence has been published on this topic and combination of Trastuzumab with immunotherapy or antibody-drug conjugate showed a better survival and high response rates [57, 58].

22. Which is the surgical indication in Oligometastatic GC (excluding peritoneum) after first-line treatment?

    a. Radical intent surgery based on the initial volume of disease if stable or in response to chemotherapy **(75%)**
    b. Radical intent surgery based on the initial volume of disease regardless of the degree of response to chemotherapy provided technical resectability **(20%)**
    c. Other, please specify **(5%)**

Statement 14: There was a consensus (75%) on surgical indication in oligometastatic GC, which should be radically removed if the tumor responded to chemotherapy or remained stable. In this respect, the initial volume of the tumour should be considered.

Discussion statement 14:

Surgery for oligometastatic disease after chemotherapy should involve both primary and metastatic sites based on the initial volume of disease to show a benefit for the patient [5, 59].

23. In case of positive cytology when do you consider surgery with radical intent?

    a. Never **(0%)**
    b. After first line chemotherapy, regardless it is converted into negative without HIPEC **(27%)**
    c. After first line chemotherapy, regardless it is converted into negative with HIPEC **(38%)**
    d. After first line chemotherapy, only in case of its conversion into negative, with HIPEC **(22%)**
    e. After first line chemotherapy, only in case of its conversion into negative, without HIPEC **(14%)**

24. In case of surgery for Oligometastatic Peritoneal GC do you consider: [Multiple choice is possible].

    a. Complete cytoreductive surgery including all the sites of positive biopsies at baseline and considering HIPEC not necessary **(21%)**
    b. Complete cytoreductive surgery all the sites of positive biopsies at baseline and considering HIPEC necessary **(47%)**
    c. Complete cytoreductive surgery according to residual disease without HIPEC **(8%)**
    d. Complete cytoreductive surgery according to residual disease with HIPEC **(16%)**
    e. Other, please specify **(8%)**

Statement 15: No agreement was reached as regards the treatment of oligometastases GC with Cyt+. However, most experts (64%) were prone to perform surgery irrespective of conversion from positive to negative Cyt. Of note, this is at variance with Statement 9, where most experts (55%) considered isolated Cyt+ as oligometastases only if converted to Cyt- after chemotherapy. One could argue that several surgeons have a more strict approach when defining oligometastases from a theoretical point of view than when offering their patients the best chances of recovery. Consensus was achieved neither on HIPEC use which was supported by about 60% of experts, irrespective of persistence of Cyt+. As regards surgery for oligometastatic peritoneal GC, there was a borderline consensus (68%) on removing also metastatic sites undergoing regression after chemotherapy. About two thirds of surgeons favoured the use of HIPEC, and this percentage was about the same in people prone to remove only residual disease or also sites that were positive at baseline. Indeed, a clear widespread definition of peritoneal invasion and related treatments is lacking, so that studies on this topic are warranted.

Discussion statement 15:

According to what reported by systematic review and meta-analysis on 7900 patients, patients with initially positive cytology that became negative after neoadjuvant therapy had a significantly improved overall survival compared with positive cytology that remained positive despite therapy [60].

The role of intraperitoneal treatment added to systemic therapy should also be discussed. Indeed, in the systematic review and meta-analysis by Coccolini et al. it emerged that surgery combined with intraperitoneal chemotherapy could improve the 5-year survival rate and reduce the risk of recurrence in patients with free cancer cells without macroscopic carcinosis [61].

Recently, a new multicenter international retrospective study was proposed, called POPEC study, to evaluate the Prognosis of POsitive PEritoneal Cytology in gastric cancer evaluating the overall survival and recurrence-free survival.

With regard to the treatment of oligometastatic peritoneal GC, the CYTO-CHIP study, a retrospective French study, compared Cytoreductive surgery (CRS) +HIPEC or Cytoreductive alone (CRSa) for the treatment of 277 patients with peritoneal metastases [62]. CRS-HIPEC treatment yielded a 5-year OS of almost 20% and a 5-year RFS of 15%, whereas CRSa yielded corresponding rates of 7% and 3%. This suggests that addition of HIPEC may offer prolonged survival over CRSa for strictly selected patients, without increasing postoperative morbidity. Furthermore, completeness of cytoreduction seems pivotal for survival improvement. This suggests that CC-0 surgery should be an absolute requirement before performing HIPEC for peritoneal oligometastases from GC.

On this topic, many trials and projects are still ongoing, as "PREVENT" (FLOT9), GASTRICHIP, VerONE and PERISCOPE [63–65].

25. Rank the following sites from the most to the least consistent with the definition of Oligometastatic GC: Select the most suitable.

a. Nodal metastases **(69%)**
b. Liver metastases **(14%)**
c. Peritoneal metastases **(0%)**
d. Positive cytology **(14%)**
e. Other, please specify **(3%)**

Statement 16: Most experts (69%) considered lymph nodes as the site most consistent with the definition of oligometastatic disease.

Discussion statement 16:
As previously described, oligometastatic GC is represented by a heterogeneous type of metastases that could differently benefit from an aggressive multimodal approach. Indeed, in the AIO FLOT 3 trial, different sites of metastases were all included in the group where a benefit of radical-intent surgery after chemo was demonstrated. But by analysing the different organs involved, survival was shown to be different between patients with lymph node metastases (mOS 27 months), liver metastases (mOS 13,6 months) and other sites (mOS 20.4 months). In this last group are considered lung, peritoneal disease and other not specified organs [5].

26. Which is your definition of conversion surgery?

a. Surgery on the residual disease after chemotherapy in case metastatic GC which was initially not resectable for technical and/or oncological reasons but nevertheless responded to first-line treatment **(98%)**
b. Surgery on the residual disease after chemotherapy in case metastatic GC which was initially not resectable for technical and/or oncological reasons regardless the response to first-line treatment **(2%)**
c. Surgery on the residual disease after chemotherapy in case metastatic GC which was technically and/or oncologically resectable at the time of diagnosis, regardless the response to first-line treatment **(0%)**

Statement 17: Nearly perfect agreement (98%) was achieved on the definition of conversion surgery, described as surgery on the residual disease after chemotherapy in case of metastatic GC which was initially not resectable for technical and/or oncological reasons but nevertheless responded to first-line treatment.

Discussion statement 17:
Yoshida et al. for the first time described the conversion surgery strategy [53] as "adjuvant" surgery on the residual disease after chemotherapy in case of initial technically and/or oncologically not resectable metastatic GC in response to first-line treatment.
Based on such classification, Kinoshita et al. retrospectively investigated the efficacy of multimodal therapy with combined triple chemotherapy (docetaxel, cisplatin, and S-1 (DCS)) and after that conversion gastrectomy in 57 patients with stage IV GC. In their data, the rate of conversion gastrectomy following DCS therapy was 59.6% and patients undergoing conversion surgery had longer survival compared with patients receiving chemotherapy alone. Interestingly, the 3-year OS rate of potentially resectable cases was 92.9%, compared with a 3-year OS rate in initially unresectable cases of only 35.1%. Multivariate analysis identified potentially resectable disease is the only significant and independent factor associated with OS in patients undergoing conversion gastrectomy [66].

27. How do you manage the site that was responsible for initial unresectability in case of its clinical complete response?

a. Try to resect it **(74%)**
b. b. Never resect it **(21%)**
c. No resection, but place markers for subsequent possible radiotherapy **(5%)**

28. How do you consider the case of the previous question?

    a. R0 (97%)
    b. R1 **(3%)**
    c. R2 (0%)

Statement 18: In the scenario of conversion surgery, most experts (74%) would try to resect the site responsible for initial unresectability even in case of its clinical complete response. This is somewhat conflicting with the definition of conversion surgery as removal of residual disease according to the nearly perfect agreement achieved on Statement 17. Quite all experts (98 %) consider this result as R0 resection.

29. Do you think that conversion surgery could have the same benefits if first-line treatments did include the use of immunotherapy?

    a. Yes **(18%)**
    b. b. No **(5%)**
    c. No Data Available **(77%)**

Statement 19: According to most experts (77%), no data are available to give a sensible Statement on the role of conversion surgery after first-line treatment including immunotherapy.

Discussion statement19:

Nowadays, we still could not have an answer to this question, considering the few data available.

Future experimental studies are necessary to evaluate whether surgery could be beneficial in patients responding to immunotherapy. Indeed, it's doubtful whether surgery could elicit transient immunosuppression interfering with immune-checkpoint inhibitors. If surgery will prove beneficial, also the timing of surgery with respect to first line chemo-immunotherapy will need to be evaluated. In this regard, particular attention must be paid to those subgroups of patients, such as those with MSI tumors, who could remain under disease control for a long time with immunotherapy alone and who therefore should not undergo surgery.

(C) How to care

30. Do you have the possibility of palliative team in your centre?

    a. Yes **(97%)**
    b. No **(3%)**

31. When do you stop oncologic palliative treatments?

    a. On patient's request **(6%)**
    c. bIn relation to performance status **(6%)**
    d. In case of multiple metastatic sites **(0%)**
    e. After progression despite of oncological treatments **(26%)**
    f. Shared decision (**new option added**) **(63%)**

32. What is the indication for nutritional support in end-stage patients?

    a. Always **(12%)**
    b. Never **(6%)**
    c. In relation to patient's general condition and life-expectancy **(74%)**
    d. On patient's request **(9%)**

Statement 20: Nearly all experts cooperated with a team providing palliative care in the management of patients with advanced GC.
A consensus was not achieved regarding stopping rules for oncologic palliative treatments. Nevertheless, most experts (63%) agreed that treatment withdrawal should be based on "shared decision".

An agreement was achieved (74%) concerning the indication for nutritional support in end-stage patients, which should be provided "in relation to patient's general condition and life-expectancy".

Discussion

This is the first multidisciplinary consensus on metastatic gastric cancer covering all aspects that guide clinical management of the patients.

In recent years, novel and more effective oncological treatments for stage IV GC improved the prognosis or, in some individuals, led to cure. According to the AIO-FLOT3 trial [5], patients with "oligometastatic" GC which is defined as a low disease burden stage IV GCs may benefit from combined approaches including surgery. Although there are shared ideas about this concept, it remains difficult in clinical practice to identify patients with oligometastatic GC and who may benefit from more aggressive treatment. There are some papers aimed at creating consensus regarding the definition of oligometastases including the initiative by the European OMEC group. However, there is still no universal agreement on some issues. Furthermore, unlike other studies, this one focus only on stomach tumors (including Siewert 3), excluding tumors of the esophagus and EGJ which have different biological characteristics.

Furthermore, metastatic GC is often not oligometastatic. Many patients have an extensive burden of the disease at diagnosis and there are technical and/or oncological reasons that do not allow radical treatment including surgery. However, effective systemic treatment may move the patients towards conversion surgery aimed at removing residual tumor. But there are no universally agreed strategies for this.

The Workshop led to a better agreement among experts on several issues as shown in the Fig. 1. The agreement was reached on items related to diagnosis and staging, definition and anatomical details of oligometastatic GC, the concept behind possible surgical indications for stage IV GC.

Currently, CT scan is considered the best tool for staging GC, but this requires skilled radiologist. A more accurate dimensional cut-off for lymph node staging is also required. CT scan is the preferred method even for restaging GC, RECIST criteria are used to evaluate the regression after systemic treatments, but other information should be added to RECIST such as radiomics findings.

Of note, there was an agreement on performing staging laparoscopy in locally advanced GC irrespective of tumor histology. However, there are no standard protocols for staging laparoscopy neither for the evaluation of peritoneal cytology. Accordingly, during the Workshop, a specific project was proposed to fill this gap.

We had Consensus that to date, the following biomarkers should be evaluated on primary tumor biopsies at time of diagnosis in all the newly detected metastatic GC: HER2, PDL1 (CPS), MSI, EBV. However, guidelines on gastric cancer biomarkers should be tailored to different geographic areas, to take into account differences between Eastern Asia and Europe/North America.

Moreover, it should be noted that, since the questionnaire for this survey was designed, the results of two recent studies have been published documenting the effectiveness of the association of an anti-Claudin 18 antibody with chemotherapy in metastatic gastric cancer [67, 68]. Therefore, even if not yet approved in clinical practice, it is likely that this association will soon be the first-line option of choice in patients with Claudin 18 positive stage IV GC and that, therefore, the IHC evaluation for Claudin 18 must be included in the panel of standard biomarkers to be evaluated in all cases of newly diagnosed metastatic gastric cancer. Experts have not reached a consensus regarding the need to biopsy the metastatic site. Unfortunately, this need was discussed only to characterize the possible heterogeneity of predictive biomarkers between primary tumor and metastases, while the usefulness of biopsy in confirming the metastatic nature of distant lesions, especially for peritoneal lesions, was overlooked.

Regarding the definition of oligometastatic for the various sites, we agreed that (Fig. 2).

for the liver there is agreement on the maximum number of metastases which is 3, but then the experts are divided as to the distribution (uni- versus bilobular). Distant lymph nodes are considered as oligometastatic if the stations 16a2, 16b1 are involved. Other "posterior stations" (12p, 13, 16a1, 16b1) could be included in the oligometastatic definition provided their response to systemic treatments.

An important finding of our Consensus is the agreement on oligometastatic peritoneal disease and peritoneal cytology. Indeed, in other Consensus [10] peritoneal cytology and/or metastases have been excluded from oligometastatic setting as it is considered as an incurable condition. More

in detail, in our Consensus, a low burden peritoneal disease (PCI up to 6) is considered as oligometastatic GC.

For Cyt + there was not a clear agreement among all the experts, as some consider Cyt as oligomet only if it is converted from Cyt + to Cyt− after systemic treatment, while others always considered it ad oligometasis. However, by taking together all the expert's answers, there is a consensus in considering Cyt+ as oligomet when it has been converted by chemotherapy.

Another important result of the present consensus is that a disease can be defined as oligometastatic only after evaluating its response to systemic therapies. Indeed, it would be important to have biomarkers/predictors to select those cases of metastatic gastric cancer, who could benefit from aggressive multimodal treatment. However, such biomarkers/predictors are still lacking, to a large extent. Hence, response to chemotherapy is a good indicator to guide treatment choice. This "dynamic" definition of the concept of oligometastases is a relevant achievement of the present Experts Consesus.

Then the experts discussed the optimal first-line schedule in oligometastatic patients. Excellent agreement was achieved (86%) on 'Platinum- based chemotherapy + trastuzumab' as standard first-line schedule in HER2 positive cases. Of note, the KEYNOTE-811 study, a randomized phase III trial, showed a superior objective response with Pembrolizumab compared with placebo when added to Trastuzumab plus fluoropyrimidine and platinum-based chemotherapy as first-line treatment in patients with locally advanced or metastatic HER2-positive gastro-oesophageal junction carcinoma [57]. These results were recently confirmed also by a third interim analysis (with median FU of 38.4 months) of the study on 698 patients, in which both disease free survival (10.0 months versus 8.1 months (7.1–8.6; HR 0·73 [0.61–0.87]) and overall survival (20.0 months versus 16.8 months; HR 0.84 [0.70–1.01]) were significantly higher in patients treated with Pembrolizumab compared to placebo. This advantage is higher specifically in patients with tumour with PD-L1 combined positive score of 1 or more [69]. Accordingly, the EMA released the following Statement on August 2023: "KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1". However, this practice still needs to be implemented in several countries.

The agreement on the optimal first line treatment in HER2 negative oligometastatic patients, was lower, nevertheless (63%) of experts chose "immunotherapy or chemo-immunotherapy in presence of biomarkers predictive of response" as standard first-line schedule. Results of the KEYNOTE-859 study, a randomized phase III trial, designed for patients with Her 2 negative advanced unresectable or metastatic gastric/gastroesophageal junction carcinoma confirm this approach: patients treated with Pembrolizumab plus chemotherapy had a significant and clinically meaningful improvement in overall survival with manageable toxicity compared to participants treated with placebo plus chemotherapy (median overall survival of 12·9 months in Pembrolizumab [95% CI 11.9–14.0] vs 11·5 months in placebo group [10.6–12.1]; hazard ratio [HR] 0.78 [95% CI 0.70–0.87]; $p < 0.0001$).

The advantage on overall survival is higher in patients with tumours with PD-L1 CPS of 10 or higher [70].

Unfortunately, whether the best chemotherapy regimen in these HER2 negative oligometastatic patients, in ideal contitions, is FLOT or FOLFOX has not been discussed in the present Consensus, but it remains an important point of debate in clinical practice. Furthermore, in the meantime, the results of a new trial were presented at ESMO2023 [71] showing that a modified FLOT scheme (mFLOT/TFOX) is more effective than oxaliplatin and 5-fluorouracil (FOLFOX) for patients with metastatic/unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Furthermore, we aimed to clarify the possible surgical indication in stage IV gastric cancer. Of note, we had a good agreement on the planned extent of surgery within the oligometastatic concept that should be a radical-intent surgery on the initial volume of disease, as assessed at the time of diagnosis.

On the contrary, there are other cases with extensive, non-oligometastatic disease, in such cases, "conversion" surgery and/or ablative treatments should be a radical-intent procedure on the residual volume of disease after an exceptional response to systemic treatments.

Of note, even though there was a nearly perfect agreement on the definition of conversion surgery ("surgery on the residual disease after chemotherapy in case of metastatic GC which was initially not resectable for technical and/or oncological reasons but nevertheless responded to first-line treatment" nevertheless, in the subsequent questions there was consensus on the attempt to surgically resect the site responsible for initial unresectability even in case of its clinical complete response. This indicates that there is no clarity on some concepts in clinical practice.

It should be noted that the role of local ablation treatments other than surgery has been taken into consideration much more in the context of advanced metastatic than oligometastatic disease. Indeed, although in some oligometastatic cases with localizations difficult to surgically excise, other local ablative treatments can also be chosen with curative intent, the first-choice treatment remains surgery. As underlined several times during the plenary meeting, one of the objectives of the present Consensus was to identify the anatomical definitions of oligometastatic disease that were amenable to local and in particular to surgical treatment for gastric cancer only, including Siewert 3 but not the other

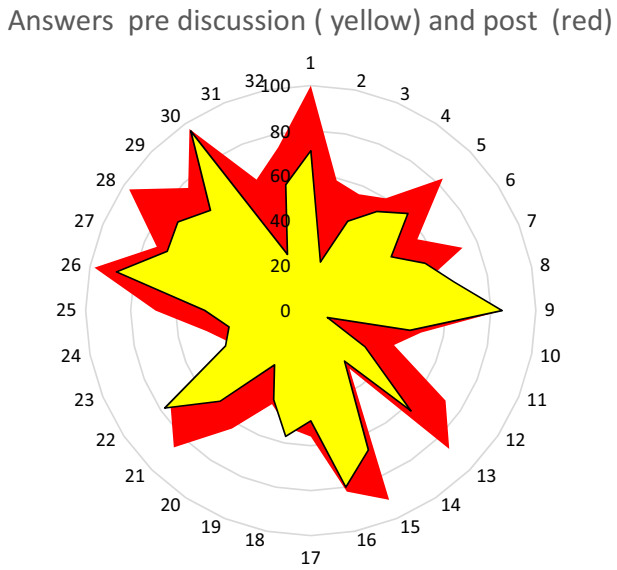

Fig. 1 Overview of issues before and after consensus

cardia adenocarcinomas or esophageal tumors. This marks a difference by the OMEC project, which considered also the latter locations. For instance, an isolated extraregional metastasis involving supraclavicular lymph nodes could be considered as oligometastatic disease for all cancers considered by the OMEC project (including gastric cancer) but not according to the present Consensus. Thus, the present consensus allows us to offer a vision that is not antithetical to OMEC, but complementary to it and of practical interest for the gastric surgeon.

The results of the eastern multicenter trial CONVO-GC-1[53] are among the most relevant pieces of evidence on the topic of metastatic GC. In the latter study metastatic GC was classified according to Yoshida [52]: category 1 (technically resectable, as solitary liver metastases < 5 cm, para- aortic lymphnode 16 a2/b1 or only positive peritoneal cytology) could be considered as oligometastatic disease, while in all the other categories (2–4) surgery was regarded as conversion surgery. Looking at radicality after surgery, R0 resections rates were higher in category 1 and 2 (about 75%) and progressively lower in categories 3 and 4 (59% and 56.4%, respectively). Of note, the median survival time (MST) was significantly longer in patients who underwent R0 resections. Interestingly, the MST in category 1 was not superior to that of other categories (47.8 months vs 116.7 months vs 44.8 months vs median not reached, respectively for category 1, 2, 3 and 4).

These results are interesting and bring new hope to patients with metastatic gastric cancer. A still open question is whether to remove the initial cancer volume or only residual volume after chemotherapy. The best surgical approach should be established thorough comparison of Eastern and Western series, followed by a randomized clinical trial on this specific problem.

Finally, experts agreed that patients' nutritional and psychologic support may improve the opportunities to propose new treatment in compromised situations, but ethics aspects,

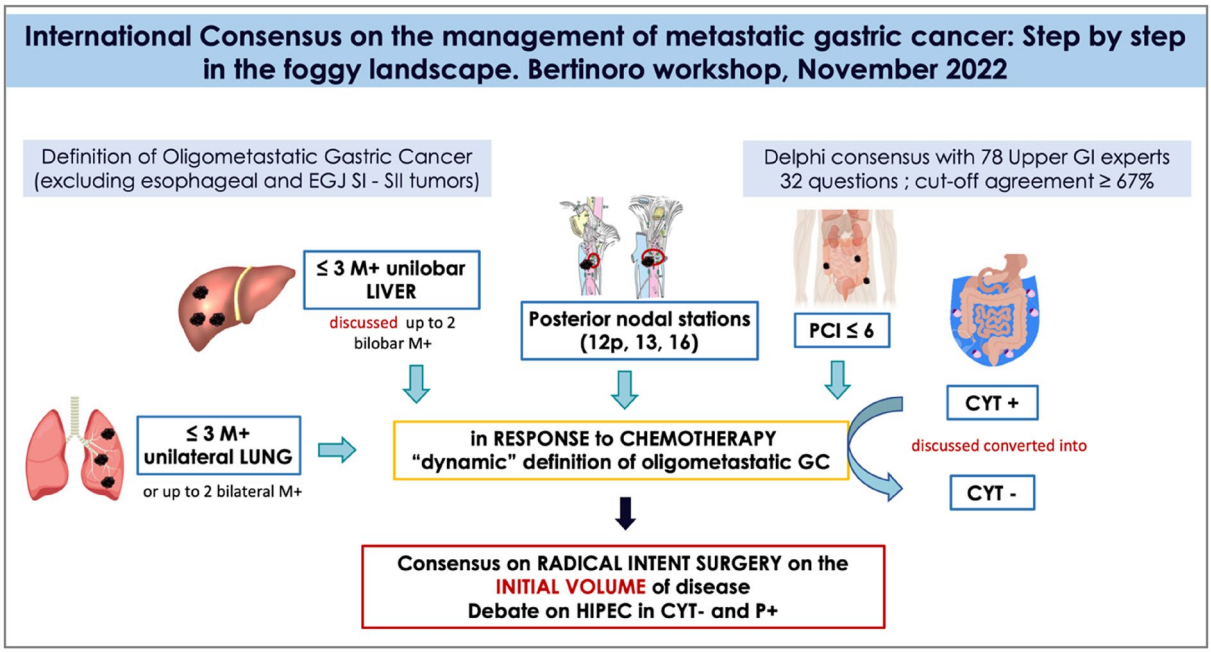

Fig. 2 Visual abstract of consensus main finding on oligometastatic GC

patient's respect, and human approach to the end of the life on metastatic non responders, must never be forgotten. The limitations of this manuscript are mainly related to the lack of a degree of evidence and the strength of the recommendations as the methodology used and the relevance of the studies currently present in the literature did not allow us to reach these. However, the representativeness of the participants and the extent of the topics covered allowed us to provide a first practical guidelines in this emerging scenario.

The future in this field is undoubtedly the advancement of knowledge in the translational field on the complex interplay between tumor, tumor microenvironment and how this impacts the response to treatments. The design of innovative trials on this basis will open new horizons and new treatment possibilities for this lethal condition.

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Mansfield[62], Chiara Molinari[60], Manlio Monti[60], Yusef Moulla[64], Magnus Nilsson[65], Sara Patuzzo[65], Manuel Pera[46], Osvaldo Antonio Prado Castro[14], Alberto Quinzii[22], Ilario Giovanni Rapposelli[60], Stefano Rausei[66], Rossella Reddavid[47], Fausto Rosa[67], Riccardo Rosati[68], Romina Rossi[17], Giandomenico Roviello[69], Julia Rudno-Rudzinska[52] , Michele Sacco[2], Massimiliano Salati[70], Paul M Schneider[71], Leonardo Solaini[51], Masanori Terashima[72], Anna Tomezzoli[43], Martina Valgiusti[60], Antonio Carlos Weston[73], Kielan Wojciech[52], Goetze Thortsen[74]. [36] Department of Surgery, Royal Marsden Hospital, London, UK; [37] Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; [38] Chief of Surgery Department of National Cancer Institute ASSE, Uruguay; [39] Chief of Surgery Department Las Piedras Hospital ASSE, Uruguay; [40] Ex Associate Professor of General Surgery Medicine Faculty Udelar, Uruguay; [41] Department of Surgery, National University Hospital, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [42] Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy; [43] Section of Pathology, Department of Diagnostics and Public Health University of Verona, Verona, Italy; [44] Department of Oncology, Torino University, Candiolo Cancer Institute-FPO, IRCCS Italy; [45] Departamento de Cirurgia, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; [46] Section of Gastrointestinal Surgery, Hospital Universitario del Mar, Hospital del Mar Medical Research Institute (IMIM). Department of Surgery, Universitat Autònoma de Barcelona, Barcelona, Spain; [47] Department of Oncology, Surgical Oncology and Digestive Surgery Unit, San Luigi University Hospital, University of Turin, Orbassano, Turin, Italy; [48] Department of Digestive Surgery, European Institute of Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), 20141 Milan, Italy; [49] General and Emergency Surgery, University of Perugia, Perugia, Italy; [50] Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [51] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Morgagni-Pierantoni Hospital, Forlì, Italy; [52] 2nd Department of General and Oncological Surgery, Wroclaw Medical University Hospital, Wrocław, Poland; [53] Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands; [54] Head Contilia Center for Esophageal Diseases Elisabeth Hospital Essen, Cooperation Partner of West German Tumor Center, University Medicine Essen, Germany; [55] Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [56] Federal University of São Paulo, São Paulo, SP, Brazil; [57] Surgical Oncology Department, Portuguese Oncology Institute of Porto (IPO-Porto), 4200-072 Porto, Portugal; [58] Department of Pathology, GROW School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, the Netherlands; [59] Department of Medical Oncology, University Cancer Center Leipzig, Leipzig University Medical Center, Leipzig, Germany; [60] IRCCS Istituto Romagnolo per Lo Studio Dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [61] German Society of Surgery, Berlin, Germany; [62] Department of Surgical Oncology, UT MD Anderson Cancer Center, Houston, Texas, USA; [63] Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig AöR, Leipzig, Germany; [64] Division of Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden; Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden; [65] School of Medicine and Surgery, University of Verona, 37134, Verona, Italy; [66] Depertment of Surgery, Ospedale S. Antonio Abate, ASST Valle Olona, Gallarate, Italy; [67] Digestive Surgery Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [68] Department of Gastrointestinal Surgery, IRCCS - San Raffaele Research Hospital, Milan, Italy; [69] Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Viale Pieraccini, 6, 50139, Florence, Italy; [70] Division of Oncology, Department of Oncology and Hematology, University Hospital of Modena, 41121 Modena, Italy; [71] Digestive Oncology Tumor Center, Hirslanden Medical Center, Zurich, Switzerland; [72] Department of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan; [73] Chef do Serviço de Cirurgia Geral da Santa Casa, Diretor Médico da Ingastro, Department of Surgery, Porto Alegre, Brazil; [74] Institute of Clinical Cancer Research, Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany; IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest, Frankfurt, Germany. 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Authors and Affiliations

Paolo Morgagni[1] · Maria Bencivenga[2] · Fatima Carneiro[3] · Stefano Cascinu[4] · Sarah Derks[5] · Maria Di Bartolomeo[6] · Claire Donohoe[7] · Clarisse Eveno[8] · Suzanne Gisbertz[9] · Peter Grimminger[10] · Ines Gockel[11] · Heike Grabsch[12,13] · Paulo Kassab[14] · Rupert Langer[15] · Sara Lonardi[16] · Marco Maltoni[17] · Sheraz Markar[18] · Markus Moehler[19] · Daniele Marrelli[20] · Maria Antonietta Mazzei[21] · Davide Melisi[22] · Carlo Milandri[23] · Paul Stefan Moenig[24] · Bianca Mostert[25] · Gianni Mura[26] · Wojciech Polkowski[27] · John Reynolds[28] · Luca Saragoni[29] · Mark I. Van Berge Henegouwen[9] · Richard Van Hillegersberg[30] · Michael Vieth[31] · Giuseppe Verlato[32] · Lorena Torroni[32] · Bas Wijnhoven[33] · Guido Alberto Massimo Tiberio[34] · Han-Kwang Yang[35] · Franco Roviello[20] · Giovanni de Manzoni[2] · Bertinoro Workshop Working Group

✉ Maria Bencivenga
maria.bencivenga@univr.it

[1] Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì, Italy

[2] General and Upper GI Surgery, Department of Surgery, University Hospital Verona, University of Verona, Verona, Italy

[3] Department of Pathology, Centro Hospitalar de São João, Institute of Molecular Pathology and Immunology of the University of Porto (Ipatimup), Porto, Portugal

[4] Department of Medical Oncology, Comprehensive Cancer Center, Università Vita-Salute, IRCCS Ospedale San Raffaele, Milan, Italy

[5] Department of Medical Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[6] Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[7] Medicinal Chemistry, Trinity Translational Medicine Institute, Trinity Centre for Health Sciences, Trinity College Dublin, The University of Dublin, St. James's Hospital, Dublin 8, Ireland

[8] Department of Digestive and Oncologic Surgery, Claude Huriez University Hospital, Centre Hospitalier Universitaire (CHU) Lille, Université de Lille, Lille, France

[9] Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[10] Department of General, Visceral and Transplant Surgery, University Medical Center, University of Mainz, Mainz, Germany

[11] Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig, Leipzig, Germany

[12] Department of Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands

[13] Pathology and Data Analytics, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, United Kingdom

[14] Gastric Surgery Division, BP Gastric Surgery Department, Santa Casa Medical School, São Paulo, Brazil

[15] Institute of Pathology and Microbiology, Johannes Kepler University Linz, Altenberger Strasse 69, 4040 Linz, Austria

[16] Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy

[17] Unit of Palliative Care, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Forlì-Cesena, Italy

[18] Surgical Interventional Trials Unit, University of Oxford, Oxford, UK

[19] Department of Medicine, Johannes-Gutenberg University Clinic, Mainz, Germany

[20] Unit of General Surgery and Surgical Oncology, Department of Medicine Surgery and Neurosciences, University of Siena, 53100 Siena, Italy

[21] Unit of Diagnostic Imaging, Department of Medical, Surgical and Neuro Sciences and of Radiological Sciences, Azienda Ospedaliero-Universitaria Senese, University of Siena, 53100 Siena, Italy

[22] Medical Oncology at the Department of Medicine, University of Verona, Verona, Italy

[23] Department of Oncology, San Donato Hospital, 52100 Arezzo, Italy

[24] Surgery Department, Geneva University Hospitals, Geneva, Switzerland

[25] Department of Medical Oncology, Erasmus MC Cancer Institute, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

[26] Department of Surgery, San Donato Hospital, Arezzo, Italy

[27] Department of Surgical Oncology, Medical University of Lublin, Radziwiłłowska 13 St, 20-080 Lublin, Poland

[28] Trinity College, Dublin, Ireland

[29] Pathology Unit, Santa Maria delle Croci Ravenna Hospital, Ravenna, Italy

[30] University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

[31] Institute of Pathology, Klinikum Bayreuth, Bayreuth, Germany

[32] Department of Diagnostics and Public Health, Section of Epidemiology and Medical Statistics, University of Verona, Verona, Italy

[33] Department of Surgery, Erasmus MC-University Medical Centre Rotterdam, Rotterdam, Netherlands

[34] Surgical Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[35] Surgical Department, SNUH National Cancer Center, Seoul, Korea