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a consensus recommendation from the EORTC Imaging and Breast Cancer Groups

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Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups

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Breast cancer remains the most common cause of cancer death among women. Despite its considerable histological and molecular heterogeneity, those characteristics are not distinguished in most definitions of oligometastatic disease and clinical trials of oligometastatic breast cancer. After an exhaustive review of the literature covering all aspects of oligometastatic breast cancer, 35 experts from the European Organisation for Research and Treatment of Cancer Imaging and Breast Cancer Groups elaborated a Delphi questionnaire aimed at offering consensus recommendations, including oligometastatic breast cancer definition, optimal diagnostic pathways, and clinical trials required to evaluate the effect of diagnostic imaging strategies and metastasis-directed therapies. The main recommendations are the introduction of modern imaging methods in metastatic screening for an earlier diagnosis of oligometastatic breast cancer and the development of prospective trials also considering the histological and molecular complexity of breast cancer. Strategies for the randomisation of imaging methods and therapeutic approaches in different subsets of patients are also addressed.

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Introduction

The high incidence of breast cancer deaths among women (2·3 million women per annum are diagnosed with breast cancer, and 685 000 deaths occur, mainly due to metastases) and the loss of disability-adjusted life-years related to metastatic disease support the increasing interest for early recognition and treatment of metastases. An aggressive approach to oligometastatic breast cancer with a so-called curative intent has thus been suggested with the intention to treat an earlier stage of the disease and delay its evolution to polymetastatic disease and related complications.[1–3] The distinct metastatic patterns, specific treatment strategies, and prognoses of the histological and molecular subtypes of breast cancer all confound the evaluation of oligometastatic breast cancer and explain the paucity of dedicated studies.[4–7]

The concept of oligometastatic disease is not limited to breast cancer. In the absence of biomarkers defining the oligometastatic disease state,[8] a definition that refers to an imaging diagnosis of one to five extracranial metastases in a maximum of two different organs has been proposed.[9–11] However, heterogeneity remains regarding this definition in the literature. The European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) published a consensus document defining oligometastatic disease as a state with one to five metastatic lesions that are all amenable to safe locoregional treatment.[12] Another consensus publication by ESTRO and the European Organisation for Research and Treatment of Cancer (EORTC) provides an exhaustive categorisation of oligometastatic disease, distinguishing between synchronous and metachronous presentations and between various subgroups on the basis of the persistence, progression, or recurrence of lesions, with the perspective to optimise specific diagnostic and therapeutic pathways for each subgroup.[13]

The imaging methods used for the staging of early breast cancer crucially influence the recognition and incidence of oligometastatic disease.[14,15] An arbitrary classification into either standard imaging methods (SIMs) or modern (ie, emerging) imaging methods (MIMs) is based on what is formally considered as standard practice for a given application at a given point in time. We have thus used current breast cancer guidelines and standard practice at our various cancer centres to classify a specific imaging technique as either a SIM or a MIM.[16,17] Guidelines driven by oncologists from the European Society for Medical Oncology (ESMO) still recommend SIMs, such as bone scintigraphy, chest radiographs, and abdominal ultrasound, or bone scintigraphy and thoraco-abdomino-pelvic (TAP) CT, for assessing patients with breast cancer at high risk of metastases;[15] these methods might still be supplemented as needed with conventional brain, abdominal, or pelvic MRI, including the use of contrast agents as per clinical indication.

The use of MIMs, such as PET-CT or whole-body MRI, potentially provides a more accurate diagnosis of oligometastatic disease than SIMs. Axillary staging in breast cancer is enhanced with MIMs: PET-CT and dedicated MRI have a similar pooled specificity (93%), albeit with lower sensitivity for PET-CT (64% *vs* 82%).[18] In

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a meta-analysis, [18F]fluorodeoxyglucose ([18F]FDG)-PET has been shown to have a diagnostic accuracy of 93% for liver metastases.[19] Another meta-analysis[15] indicates that, overall, [18F]FDG-PET-CT outperforms other imaging methods for the detection of distant metastases and low-level evidence indicates that it can replace SIM for staging in patients at high risk.[15] Evidence for improved diagnostic accuracy of whole-body MRI for breast cancer staging is limited to single-centre studies.[20] However, whether the improved diagnostic accuracy actually translates to improved patient outcome (ie, survival and quality of life) remains to be established. Therefore, although [18F]FDG-PET-CT was shown to influence management in 24% of patients with metastases[19] and whole-body MRI has also been shown to alter decisions for systemic chemotherapy in patients with metastatic breast cancer,[21] multicentre prospective studies are still needed.

In the treatment of oligometastatic breast cancer, metastasis-directed therapy (MDT) might be effective management options, but prospective trials are scarce and mostly focus on the use of stereotactic body radiotherapy (SBRT).[22–26] Despite the promising results of a randomised phase 2 trial, the Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers trial,[27] there are still no published randomised trials in oligometastatic breast cancer. Of note, the randomised phase 2 trial NRG-BR002[28] reported no improvement in terms of median progression-free survival and overall survival when treating oligometastatic disease with SBRT added to standard-of-care (SOC) systemic therapy compared with SOC alone.[28]

MIMs and MDT are largely used on an empirical basis in oligometastatic breast cancer, both in research trials and in the clinic. Based on this observation, an international collaborative project was set up to elaborate oligometastatic breast cancer-focused consensus recommendations and devise required trials for evaluating (1) optimal diagnostic imaging pathways (including the use of MIMs, such as MRI and [18F]FDG-PET-CT) so that relevant MIMs eventually become formally established as SOC for oligometastatic breast cancer; and (2) potential benefits of the use of MIMs to enhance the delivery of MDT. Our multidisciplinary panel of international experts with active involvement in specialist societies ensured that the collective views were comprehensive and reflected a suitable range of relevant clinical interests and expertise.

Methods

An overview of the Delphi process is provided in the appendix (p 1). To initiate a Delphi consensus process covering all relevant aspects of oligometastatic breast cancer, a panel of international experts in diagnosis and treatment of oligometastatic breast cancer—including surgeons, medical oncologists, radiation oncologists, radiologists, nuclear medicine physicians, and methodologists from EORTC (appendix pp 5–6)—was convened under the auspices of the EORTC Imaging and Breast Cancer Groups steering committees. From this panel, a representative subgroup of 25 physicians conducted an exhaustive literature review to summarise current knowledge and remaining uncertainties in the diagnosis and treatment of oligometastatic breast cancer, eventually providing the panel with a detailed written report. A steering committee consisting of physicians and scientists from each relevant discipline (nine people; appendix pp 5–6) coordinated the literature review, which was written by 25 people (including the steering committee), and synthesis.

Definition of imaging methods

Based on the literature review report and previous definitions,[16,17] and what is formally considered as breast cancer SOC in our various cancer centres, a distinction was made between different generations of imaging methods. Accordingly, SIMs are defined as any combination of ultrasound, bone scintigraphy, single-photon emission CT (SPECT; eg, as hybrid SPECT-CT), brain MRI, and TAP CT. MIMs are defined as any combination of [18F]FDG, [18F]sodium fluoride ([18F]NaF) or [18F]NaF-[18F]FDG cocktail PET (eg, as hybrid PET-CT or PET-MRI), [18F]fluoroestradiol, liver MRI, and whole-body MRI including anatomical (T1, T2, and short tau inversion recovery) and functional (ie, diffusion-weighted imaging) sequences.[16]

Delphi consensus process

The Delphi consensus process was structured on the basis of the literature review and addressed several main categories. After redaction and validation of the Delphi questionnaire by the steering committee, its 104 questions (grouped according to the following categories: indications for screening and choice of imaging method, definition and identification of oligometastatic disease in breast cancer, recommendations for imaging methods for oligometastatic disease screening and before MDT, necessary clinical trials for evaluating imaging methods, future clinical trials dedicated to MDT and imaging methods, and choice of MDT and treatment of the primary tumour; with a few additional questions on demographic data and further details) were then circulated to all members of the EORTC Imaging and Breast Cancer Groups. In total there were 35 respondents to the survey. Two rounds of a consensus-building Delphi survey were conducted with an anonymous online survey. Participants were asked to rate their agreement or disagreement with statements using a modified 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree) and an additional option for "not qualified or do not know". A question regarding the preferred main endpoints to consider in trials evaluating MIM and MDT in oligometastatic disease breast cancer was given as a single question and answer rather than as a 5-point Likert scale survey because of the nature of the question.

Screening for oligometastatic disease in breast cancer...	Consensus and round
Should apply the same indications as general metastatic screening in patients with breast cancer	Consensus agreement=78% in round 1; absolute number=28; total number of responses=37; non-qualified=1
Should be performed in newly diagnosed patients depending on clinical risk	Consensus agreement=81% in round 1; absolute number=30; total number of responses=37
Should be performed with SIMs in newly diagnosed patients at high risk	Neither consensus nor (dis)agreement
Should be performed with MIMs in newly diagnosed patients at high risk	Agreement=71% in round 1 (70% in round 2); absolute number=25; total number of responses=37; non-qualified=2
Should be performed with MIMs in newly diagnosed patients who are at high risk or symptomatic with oligometastatic disease diagnosed by SIMs (to confirm the true oligometastatic disease status)	Consensus agreement=89% in round 1; absolute number=33; total number of responses=37
Should be performed with MIMs in previously treated patients with early breast cancer becoming symptomatic	Consensus agreement=81% in round 1; absolute number=30; total number of responses=37
Should be performed with MIMs in previously treated patients with early breast cancer with oligometastatic disease diagnosed by SIMs (to confirm true oligometastatic disease status)	Consensus agreement=89% in round 1; absolute number=37; total number of responses=37
What criteria should be considered as indications for metastatic screening in newly diagnosed breast cancer or at diagnosis of locoregional recurrent breast cancer?	
Histological subtype	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Agreement=67% in round 2 (55% in round 1); absolute number=22; total number of responses=33
Stage	
Newly diagnosed breast cancer	Consensus agreement=89% in round 1; absolute number=33; total number of responses=37
Locoregionally recurrent breast cancer	Consensus agreement=82% in round 2 (69% in round 1); absolute number=27; total number of responses=33
Clinical symptoms	
Newly diagnosed breast cancer	Consensus agreement=92% in round 1; absolute number=34; total number of responses=37
Locoregionally recurrent breast cancer	Consensus agreement=89% in round 1; absolute number=33; total number of responses=37
Molecular subtypes	
Newly diagnosed breast cancer	Agreement=74% in round 1 (70% in round 2); absolute number=25; total number of responses=37; non-qualified=3
Locoregionally recurrent breast cancer	Consensus agreement=77% in round 2 (65% in round 1); absolute number=24; total number of responses=33; non-qualified=2
Genomic signatures	
Newly diagnosed breast cancer	Agreement=69% in round 2 (54% in round 1); absolute number=21; total number of responses=33; non-qualified=4
Locoregionally recurrent breast cancer	Agreement=66% in round 2 (50% in round 1); absolute number=19; total number of responses=33; non-qualified=4
Age	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement
Genetic mutations	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement

(Figure 1 continues on next page)

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See Online for appendix

Screening for oligometastatic disease in breast cancer...	Consensus and round
Availability of imaging methods	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement
Reimbursement policies and costs	
Newly diagnosed breast cancer	Disagreement=67% in round 2 (42% in round 1); absolute number=22; total number of responses=33
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement
Patients' preference	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement
Risk of psychological burden because of extra imaging, patient anxiety, possible false positive findings, and overrun	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement
Availability of clinical trials in which patients with metastatic disease or oligometastatic disease could be included	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement

Figure 1: **Indications for oligometastatic disease screening in breast cancer and choice of imaging method**
Absolute number refers to the number of responses towards the result from the total number of responses minus the number of non-qualified responses. Green cells (agreement) indicate consensus was reached (ie, ≥75%). Light green cells (agreement) and light red cells (disagreement) indicate a substantial result, but with the consensus threshold not met (ie, 66–74%). MIMs=modern imaging methods. SIMs=standard imaging methods.

Agreement (ie, answers of 4 or 5) and disagreement (ie, answers of 1 or 2) were concatenated together to provide compounded agreement and disagreement scores, and the sixth-option answers (ie, not qualified or do not know) were disregarded for calculating percentages. Based on standard metrics for such surveys,[29] an a-priori threshold of at least 75% of answers was required to reach consensus agreement or consensus disagreement; responses between 66% and 74% were considered as substantially expressed agreement or disagreement, but without reaching consensus. Questions that reached consensus in the first round were not repeated in the second round.

Results

Respondents' demographics and response rates

Although 37 and then 36 expert respondents answered only 35 of 104 questions and 28 of 104 questions, respectively, 35 respondents answered all 104 questions at round 1 and are thus considered the core cohort for both this round and the whole survey. Among the 35 full participants of the Delphi process, 19 (54%) were working in comprehensive cancer centres, 11 (31%) in general hospitals, three (9%) in university hospitals, and two (6%) in other settings. The specialties of participants were medical and clinical oncology (ten [28%] participants), radiology (seven [20%] participants), radiation oncology (seven [20%] participants), nuclear medicine (seven [20%] participants), surgical oncology (three [9%] participants), and others (one [3%] participant). The diversity and balance among the specialties involved in this topic and the management of these patients allow for a multidisciplinary expertise. Seven (20%) respondents reported having expertise in breast cancer for less than 10 years, 16 (46%) for 10–20 years, and 12 (354) for more than 20 years. Together, the respondents represented 13 European countries and Israel. The response rates were 35 (100%) of 35 participants during the first round and 33 (97%) of 35 participants during the second round of the Delphi process.

After the first round of the Delphi survey, 35 questions that reached consensus agreement and one question that reached consensus disagreement were not included in the second round. All questions that had reached agreement or disagreement without consensus (ie, 66–74%) after the first round were included in the second round alongside the questions that were below 66%. At the end of the second round, 45 questions had reached consensus agreement and two had reached consensus disagreement, with an additional 13 in agreement and three in disagreement without consensus. Due to the stability of the answers, the questions that remained indecisive after the two rounds of survey were considered unlikely to reach consensus in a third round, and thus the Delphi survey was limited to two rounds.

Indications for screening and choice of imaging method

The expert respondents agreed that indications for metastatic screening in oligometastatic breast cancer should be the same as indications found in current guidelines for metastatic screening in patients with breast cancer at high risk of metastases (figure 1). Of note, the statement that screening in patients with breast cancer at high risk of metastases should be performed with SIM reached neither agreement nor consensus. Conversely, consensus was reached in favour of the use of MIM in newly diagnosed patients with breast cancer at high risk of metastases as the first line or in suspected oligometastatic disease diagnosed via SIM because MIM provided a whole-body approach that was highly sensitive. There was a consensus that stage and clinical symptoms should be considered as indications for metastatic screening in newly diagnosed or locoregionally recurrent breast cancer. There was a consensus of agreement for considering molecular subtype for screening in locoregional recurrence, but not in newly diagnosed breast cancer. The main histological subtypes that should favour screening are triple-negative and HER2-overexpressing breast cancers.

Definition and identification of oligometastatic disease in breast cancer

A consensus was obtained to define oligometastatic disease as an intermediate disease stage between localised cancer and polymetastatic disease, characterised by a limited number of metastases that can be treated with MDT (figure 2). An agreement was obtained that the maximum number of lesions or sites to which MDT can be delivered with a curative intent should

Definition of oligometastatic disease	Consensus and round
Oligometastatic disease is an intermediate disease stage between localised cancer and polymetastatic disease, characterised by a limited number of metastases that can be treated with MDT	Consensus agreement=97% in round 1; absolute number=35; total number of responses=36
Oligometastatic disease is a disease stage that can be fully cured as long as MDT can be directed to all metastases	Neither consensus nor (dis)agreement
The concept of oligometastatic disease is not dependent on the histological and molecular subtype and histology of the primary breast cancer tumour	Neither consensus nor (dis)agreement
The concept of oligometastatic disease is not dependent on the site of the metastasis	Neither consensus nor (dis)agreement
The possibility to safely deliver curative-intent MDT determines the maximum number of lesions or sites	Agreement=70% in round 2 (69% in round 1); absolute number=23; total number of responses=33
A maximal size of lesions should be considered when diagnosing oligometastatic disease and planning MDT	Neither consensus nor (dis)agreement
For the oligometastatic disease definition to be valid, all lesions should be amenable to ablative local treatment	Consensus agreement=75% in round 1; absolute number=27; total number of responses=36
There are currently no validated biomarkers that differentiate between the oligometastatic and the polymetastatic state	Consensus agreement=94% in round 1; absolute number=33; total number of responses=36; non-qualified=1
Oligometastatic disease status and the initiation of MDT should only be considered when the primary tumour is either controlled or amenable to definitive local treatment	Consensus agreement=85% in round 1; absolute number=29; total number of responses=36; non-qualified=2
Oligometastatic disease should be solid (ie, meningeal involvement, pleural effusion or ascites exclude the diagnosis of oligometastatic disease)	Consensus agreement=92% in round 1; absolute number=33; total number of responses=36
The presence of intracranial metastases does not exclude the diagnosis of oligometastatic disease	Consensus agreement=82% in round 2 (67% in round 1); absolute number=27; total number of responses=33
Metastatic involvement of several lymph nodes in the same anatomical region (eg, contralateral axilla) should be counted as a single metastatic site	Consensus agreement=81% in round 1; absolute number=29; total number of responses=36
Lymph node-only oligometastatic disease should be differentiated from oligometastatic disease involving other organs, particularly bone or visceral metastasis	Agreement=70% in round 2 (57% in round 1); absolute number=23; total number of responses=33
Histological confirmation is mandatory before oligometastatic disease treatment with MDT	Neither consensus nor (dis)agreement
MDT might be considered in patients with uncontrolled primary tumour to avoid or limit secondary seeding	Neither consensus nor (dis)agreement
MDT might be considered to treat oligo-progressive lesions with no concurrent treatment of stable metastases to avoid or limit secondary seeding to eradicate resistant clones or lesions	Agreement=67% in round 2 (71% in round 1); absolute number=22; total number of responses=33

Figure 2: **Definition and rationale for identification of the oligometastatic status**
Absolute number refers to the number of responses towards the result from the total number of responses minus the number of non-qualified responses. Green cells (agreement) indicate consensus was reached (ie, ≥75%). Light green cells (agreement) indicate a substantial result, but with the consensus threshold not met (ie, 66–74%). MDT=metastasis-directed therapy.

If indicated, the detection of oligometastatic disease breast cancer in patients with newly diagnosed breast cancer should rely on…	Consensus and round
A multimodality approach with bone scintigraphy (or SPECT-CT), liver ultrasound, and chest CT	Disagreement=73% in round 2 (61% in round 1); absolute number=24; total number of responses=33
A multimodality approach with bone SPECT-CT and TAP CT	Neither consensus nor (dis)agreement
A multimodality approach with [^{18}F]FDG-PET-CT and liver MRI	Agreement=73% in round 2 (56% in round 1); absolute number=24; total number of responses=33
[^{18}F]FDG-PET-CT or [^{18}F]FDG-PET-MRI alone	Neither consensus nor (dis)agreement
Whole-body MRI and diffusion-weighted imaging alone	Neither consensus nor (dis)agreement
A specific imaging approach considering the histological and molecular subtypes of the primary cancer	Neither consensus nor (dis)agreement
Brain MRI to be added to the diagnostic test before application of MDT to rule out intracranial lesions	Neither consensus nor (dis)agreement
When screening of oligometastatic disease is indicated and MDT is considered…	
Bone scintigraphy and TAP CT are not sufficient to confidently define the oligometastatic disease state	
Newly diagnosed breast cancer	Consensus agreement=78% in round 2 (74% in round 1); absolute number=25; total number of responses=33; non-qualified=1
Locoregionally recurrent breast cancer	Consensus agreement=82% in round 1; absolute number=28; total number of responses=35; non-qualified=1
[^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) should be performed (assuming liver MRI was completed by the time of screening)	
Newly diagnosed breast cancer	Agreement=67% in round 2 (60% in round 1); absolute number=22; total number of responses=33
Locoregionally recurrent breast cancer	Agreement=73% in round 2 (62% in round 1); absolute number=24; total number of responses=33
Whole-body MRI and diffusion-weighted imaging should be performed as a second-line imaging modality in patients who have negative first-line bone scintigraphy and TAP CT despite having high-risk disease	
Newly diagnosed breast cancer	Neither consensus nor (dis)agreement
Locoregionally recurrent breast cancer	Neither consensus nor (dis)agreement

Figure 3: **Recommendations regarding the choice of imaging methods for the screening of oligometastatic disease and before MDT**
Absolute number refers to the number of responses towards the result minus the number of non-qualified responses. Green cells (agreement) indicate consensus was reached (ie, ≥75%). Light green cells (agreement) and light red cells (disagreement) indicate a substantial result, but with the consensus threshold not met (ie, 66–74%). FDG=fluorodeoxyglucose. MDT=metastasis-directed therapy. SPECT=single photon emission CT. TAP=thoraco-abdomino-pelvic.

be considered in this definition, rather than a fixed number.

No consensus or agreement was found regarding the statement that oligometastatic disease is a disease stage that can be fully cured as long as MDT can be directed to all metastases, thus emphasising that metastatic breast cancer cannot be considered as curable. There was no consensus or agreement regarding the statement that the concept of oligometastatic disease is not dependent on the histological and molecular subtype of the primary breast cancer tumour, and on the sites of metastases. In line with ESTRO and ASTRO definitions,[12] meningeal, pleural, or peritoneal carcinomatosis exclude the diagnosis of oligometastatic disease (consensus). There was agreement that the presence of intracranial metastases does not exclude the diagnosis of oligometastatic disease. There was consensus that metastatic involvement of several lymph nodes in the same anatomical area (eg, contralateral axilla) should be counted as a single metastatic site. The experts also agreed that oligometastatic disease limited to nodal disease should be differentiated from oligometastatic disease involving other organs, particularly bone or visceral organs.

Recommendations for imaging methods for oligometastatic disease screening and before MDT

There was disagreement regarding the use of a multimodality diagnostic approach of oligometastatic disease with bone scintigraphy (ie, bone scintigraphy or SPECT-CT), liver ultrasound, and chest CT (figure 3). There was consensus on the statement that bone scintigraphy and TAP CT are not sufficient to confidently diagnose oligometastatic disease both in newly diagnosed and in recurrent breast cancer. On the basis of the diagnostic accuracy of these techniques, the experts agreed on a multimodality approach with [^{18}F]FDG-PET-CT and liver MRI for oligometastatic disease screening and before MDT, whereas [^{18}F]FDG-PET-CT

Imaging methods in clinical trials	Consensus and round
Use of imaging in trials	
[^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) staging should be mandatory in trials enrolling oligometastatic disease breast cancer patients to ensure the true oligometastatic disease status	Consensus agreement=79% in round 1; absolute number=27; total number of responses=35; non-qualified=1
Whole-body MRI and diffusion-weighted imaging staging should be mandatory in trials enrolling patients with oligometastatic disease breast cancer to ensure the true oligometastatic disease status	Neither consensus nor (dis)agreement
Necessary evaluation of imaging in trials	
Prospective trials are needed to compare SIMs and MIMs for staging and response assessment in advanced breast cancer, including oligometastatic disease	Consensus agreement=86% in round 1; absolute number=30; total number of responses=35
Clinical trials aiming to compare SIMs and MIMs for staging and response assessment in advanced breast cancer should be designed in specific histological and breast cancer subtypes (eg, lobular cancer and triple negative)	Consensus agreement=87% in round 2 (74% in round 1); absolute number=28; total number of responses=33; non-qualified=1
The diagnostic performance of different MIMs (eg, PET-CT or PET-MRI, whole-body MRI, liver MRI, and [^{18}F]NaF plus [^{18}F]FDG-PET cocktail) deserves further comparisons in trials	Consensus agreement=89% in round 1; absolute number=31; total number of responses=35
The diagnostic performance of MIMs (eg, PET-CT or PET-MRI, whole-body-MRI, liver MRI, or brain MRI) should be compared in the different subtypes of breast cancer (eg, ductal, lobular, HR, and HER)	Consensus agreement=94% in round 1; absolute number=33; total number of responses=35
Diagnostic trials should further validate quantification with MIMs (ie, second order statistics) for tumour characterisation and prognostic purposes (in whole-body diffusion-weighted MRI and PET-CT [or PET-MRI])	Consensus agreement=91% in round 2 (74% in round 1); absolute number=29; total number of responses=33; non-qualified=1
Diagnostic trials should compare technical and diagnostic performance and robustness of MRI and diffusion-weighted imaging sequences from hybrid PET-MRI modalities and from stand-alone MRI, with the purpose of optimising and standardising technical and diagnostic performance across various instruments	Consensus agreement=90% in round 1; absolute number=28; total number of responses=35; non-qualified=4
HER2 PET-CT imaging is still experimental and is not recommended outside of clinical trials	Consensus agreement=78% in round 1; absolute number=25; total number of responses=35; non-qualified=3

Figure 4: **Use and evaluation of imaging methods in clinical trials**
Absolute number refers to the number of responses towards the result from the total number of responses minus the number of non-qualified responses. Green cells (agreement) indicate consensus was reached (ie, ≥75%). FDG=fluorodeoxyglucose. MIMs=modern imaging methods. NaF=sodium fluoride. SIMs=standard imaging methods.

(or [^{18}F]FDG-PET-MRI) or whole-body MRI alone obtained neither agreement nor consensus. The perspective of tailoring the imaging choice according to the histological and molecular subtypes of the primary tumour did not obtain agreement or consensus. No agreement was reached regarding the addition of brain MRI to the diagnostic testing.

Necessary clinical trials for evaluating imaging methods

Among the most relevant results, the experts agreed on the need for more prospective trials to compare SIMs with MIMs for determining their actual clinical utility and to compare the different MIMs for staging and response assessment in advanced breast cancer, including oligometastatic breast cancer (figure 4). These trials should be designed in specific histological and molecular subtypes of breast cancer (lobular cancer, triple negative, etc). Additionally, a consensus was reached that [^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) staging should be mandatory in trials enrolling patients with oligometastatic breast cancer for ensuring the true oligometastatic disease status, and that trials should further validate disease quantification with MIM (second-order statistics) for tumour characterisation and prognostic purposes.

Future clinical trials dedicated to MDT and imaging methods

The experts reached consensus that further prospective trials are required before advocating the systematic use of MIM and MDT in routine practice (figure 5). Large trials in patients with breast cancer, with stratification on histological and molecular profiles, are still needed to assess the potential benefit of MDT for various profiles.

Concerning the main endpoints of randomised trials evaluating MIM and MDT in oligometastatic breast cancer, 19 (54%) experts favoured a combined endpoint of overall survival or progression-free survival and health-related quality of life, rather than single endpoints consisting of overall survival (favoured by eight experts; 23%), progression-free survival (six experts; 17%), time to subsequent treatment (one expert; 3%), or quality of life alone (one expert; 3%).

Regarding the use and validation of the clinical utility of specific imaging methods before MDT, a consensus was reached on the necessity of two main types of trials: (1) two-arm trials with MIM and SIM used in parallel to evaluate the added benefit of MIM on progression-free survival, overall survival, and quality of life (ie, to evaluate the benefit of bringing patients to MDT earlier; appendix p 2); and (2) trials with MIM after SIM to evaluate the

Clinical trials design	Consensus and round
The benefit of an earlier diagnosis of oligometastatic disease with MIMs requires more prospective trials before systematic indication of these MIMs is established	Consensus agreement=80% in round 1; absolute number=28; total number of responses=35
The benefit of MDT requires more prospective trials before systematic use of MDT is established	Consensus agreement=76% in round 2 (74% in round 1); absolute number=25; total number of responses=33
Breast cancer-specific clinical trials should be favoured to study MIMs and MDT because studies of multiple primary cancers might limit transposition of conclusions to each individual cancer	Consensus agreement=86% in round 1; absolute number=30; total number of responses=35
Large breast cancer trials with stratification or histology and molecular-specific clinical trials are needed to specifically characterise MDT and assess the potential benefit of MDT according to histology and subtypes	Consensus agreement=88% in round 1; absolute number=30; total number of responses=35; non-qualified=1
Multicentre observational (eg, basket and registry) trials should be considered for comparing outcomes of patients on the basis of different diagnostic approaches (eg, regional, national, or institutional), treatment modalities, and treatment indications of oligometastatic disease (following the OLIGOCARE model)	Consensus agreement=94% in round 1; absolute number=32; total number of responses=35; non-qualified=1
Trials that use MIMs and SIMs in parallel as two main arms are necessary to evaluate the benefit of the introduction of MIMs and measure the risk of bias	Consensus agreement=75% in round 2 (74% in round 1); absolute number=24; total number of responses=33; non-qualified=1
Trials that use MIMs after SIMs in series (consecutively) are needed to evaluate the importance of imaging for optimal diagnosis of oligometastatic disease and benefit from MDT	Consensus agreement=78% in round 2 (71% in round 1); absolute number=25; total number of responses=33; non-qualified=1
Verification of the true oligometastatic disease status with MIMs performed after SIMs, followed by randomised MDT *vs* MDT plus SOC, will allow the independent assessment of the value of MDT	Agreement=67% in round 2 (50% in round 1); absolute number=20; total number of responses=33; non-qualified=3
Verification of the true oligometastatic disease status with MIMs performed after SIMs, followed by randomised SOC *vs* MDT plus SOC, will allow the independent assessment of the value of MDT	Consensus agreement=85% in round 1; absolute number=29; total number of responses=35; non-qualified=1
Trials are needed to compare different MDTs (eg, SBRT, radio surgery, cryoablation or thermoablation, high-intensity focused ultrasound, and surgery)	Consensus agreement=75% in round 2 (67% in round 1); absolute number=24; total number of responses=33; non-qualified=1
Trials should evaluate the benefit of combinatorial therapeutic approaches (eg, immunotherapy plus MDT and change in systemic treatment plus MDT) compared with MDT alone	Consensus agreement=91% in round 1; absolute number=32; total number of responses=35
Trials should investigate the role of biomarkers (eg, circulating tumour DNA) to evaluate efficacy of MDT	Consensus agreement=97% in round 1; absolute number=33; total number of responses=35; non-qualified=1
Clinical trials should evaluate the SBRT plus immunotherapy combination (ie, modulation of antitumour immunity by SBRT)	Consensus agreement=94% in round 1; absolute number=30; total number of responses=35; non-qualified=4

***Figure 5*: Design of future clinical trials**
Absolute number refers to the number of responses towards the result from the total number of responses minus the number of non-qualified responses. Green cells (agreement) indicate consensus was reached (ie, ≥75%). Light green cells (agreement) indicate a substantial result, but with the consensus threshold not met (ie, 66–74%). MDT=metastasis directed therapy. MIMs=modern imaging methods. SBRT=stereotactic body radiotherapy. SIMs=standard imaging methods. SOC=standard of care.

relative importance of optimal imaging methods for diagnosing oligometastatic disease before MDT (ie, to refine patient populations that can then be randomised to separately assess the benefit of adding MDT to SOC treatment; appendix p 3). Outcome measures would include the percentage of patients proceeding to MDT based on specific imaging techniques and response evaluation based on SIM versus MIM. The experts also agreed that more trials are necessary to compare the different MIMs (eg, PET and whole-body MRI), both globally and in patients with specific breast cancer subtypes.

Regarding treatment approaches, a consensus was reached on the need for randomised studies to independently assess the value of MDT by comparing SOC with MDT plus SOC treatments, performed either in oligometastatic breast cancer diagnosed through MIM or after verification of the true oligometastatic disease status with MIM performed after SIM (appendix p 3). More controversially, experts agreed (ie, agreement rather than full consensus) on the need for randomised studies comparing MDT with MDT plus SOC treatments in oligometastatic breast cancer diagnosed with the same imaging strategy.

Choice of MDT and treatment of the primary tumour

A consensus was reached that surgery, SBRT, thermoablation or cryoablation, and high-intensity focused ultrasound treatments could all be used to treat oligometastatic disease depending on location and size of the tumour, and available equipment. Nevertheless, the experts came to a consensus that only surgery and SBRT had sufficient supporting evidence to advocate their use. No consensus or agreement was reached for the other methods. The experts also reached a consensus on the need for locoregional treatment of the primary tumour in oligometastatic breast cancer, and on the use of the same treatment principles for this primary tumour, as in patients with non-metastatic breast cancer.

Discussion

The consensus recommendations, for the first time, focused on oligometastatic disease in breast cancer.[1,2] Our recommendations rely on a Delphi survey of a European expert panel that comprehensively represents the whole spectrum of medical specialties managing this complex disease. Additionally, these recommendations cover both the diagnostic and therapeutic aspects of oligometastatic breast cancer and provide proposals for relevant trial designs and endpoints.

Screening of metastases

Our recommendations are in favour of the use of the same indications for oligometastatic breast cancer screening as for metastatic screening in the general breast cancer population. The panel strongly recommends the use of MIMs for metastatic screening in patients with asymptomatic breast cancer at high risk of metastases as the first line. The use of MIMs is also recommended in the second line in patients with oligometastatic disease diagnosed via SIMs, hence questioning the validity of SIMs for an early and confident diagnosis of oligometastatic disease. The National Comprehensive Cancer Network recommendations for breast cancer staging do not indicate systemic staging in the absence of symptoms at diagnosis, but acknowledge that future studies incorporating the breast cancer subtype, as a determinant feature in the staging pathway, are needed.[30] In patients with suspected metastatic disease, National Comprehensive Cancer Network guidelines still recommend SIMs (eg, chest CT, bone scintigraphy, abdominal CT or MRI, brain MRI, and spine MRI in patients with suspicious symptoms), whereas the use of MIMs (eg, [^{18}F]FDG-PET-CT) is regarded as optional. The ESMO guidelines also discourage routine exhaustive staging in patients at low risk and recommend metastatic screening for patients with clinically positive axillary nodes, tumours greater than 5 cm, aggressive biology, and clinical signs, symptoms, or laboratory values suggesting the presence of metastases.[15] The experts further recommend considering molecular subtype and genomic signatures for metastatic screening at diagnosis and recurrence of breast cancer, with aggressive phenotypes, such as triple-negative breast cancer, being stronger indications for screening.

Definition of the oligometastatic disease status

Contrary to previous definitions of oligometastatic disease that use a maximum number of lesions and involved organs,[11,31] the panel agreed that the maximum number of lesions used to define oligometastatic disease should be determined by the feasibility to safely deliver MDT with a curative intent rather than with a fixed maximum number of three or five lesions. The same definition is provided in the latest ESTRO and ASTRO consensus.[12] Furthermore, we reached a consensus that the presence of intracranial metastases does not exclude the diagnosis of oligometastatic disease. Of note, brain metastases are an exclusion criterion in most randomised studies, whereas a maximum of three brain metastases is allowed in the OLIGOMA trial (appendix p 4).[32] The inclusion of these patients could be allowed in future trials, given the possibility of ablative local treatment for patients with a small number of brain metastases (eg, via surgery, radiosurgery, or fractionated stereotactic radiotherapy). Our panel did not limit the definition of oligometastatic disease to the involvement of two organs. Another original recommendation is that metastatic involvement of several lymph nodes in the same anatomical region (eg, contralateral axilla) should be counted as a single metastatic site. This question had not yet been addressed and this expanded definition could be implemented in future trials.

Although the prognosis of oligometastatic disease is better than that of polymetastatic disease,[33] no agreement was reached on the curability of oligometastatic disease even if MDT can be directed to all metastases. This statement reflects the persistent uncertainty about the prognosis of these patients and the current belief that metastatic breast cancer cannot be cured.

Choice of imaging for screening and before MDT

Echoing the results for general screening, the expert panel recommended the use of MIMs before MDT and considered the use of SIMs alone as insufficient. Specifically, they recommended [^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) and liver MRI when metastatic screening is indicated in newly diagnosed or recurrent breast cancer and when MDT is considered, with PET alone being deemed as insufficient to map the disease in the liver before intended therapy. In contrast with the ESTRO/ASTRO and Advisory Committee for Radiation Oncology Practice consensus recommendations that include both SIMs and MIMs,[12] our panel experts were in favour of readily adopting the most sensitive imaging methods (ie, MIMs) whenever possible. However, the effect of MIMs on treatment decisions and outcomes regardless of their diagnostic success also needs to be established.

Use and evaluation of imaging methods in clinical trials

A consensus was reached for a mandatory use of [^{18}F]FDG-PET-CT (or [^{18}F]FDG-PET-MRI) staging in trials enrolling patients with oligometastatic breast cancer to ensure a true oligometastatic disease status. This statement echoes the results of the randomised phase 2 trial (NRG-BR002) presented in 2022.[28] This trial compared SOC with or without MDT (ie, SBRT or surgical resection) in newly diagnosed oligometastatic breast cancer. Patients with oligometastatic breast cancer with a maximum of four extracranial metastases on SIM and with controlled primary disease were eligible. Overall, 125 of the 129 randomised patients were eligible, and the median follow-up was 30 months. The median progression-free survival was 23·0 months (70% CI 18·0–29·2) in the SOC group and 19·5 months (17·0–35·6) in the SOC plus MDT group (p=0·36). As

the trial was considered negative, a phase 3 trial will not be launched.[28] An important note is that in the NRG-BR002 trial, the expected progression-free survival in the standard group was considerably lower than the actual progression-free survival (hypothesis hazard ratio 0·55, corresponding to a median progression-free survival from 10·5 to 19·0 months) and that MIMs were optional for patient selection. MIMs are mandatory in only two of six ongoing or completed prospective randomised trials of SBRT for oligometastatic breast cancer (appendix p 4).

In addition to the experts' recommendation to use MIMs for oligometastatic disease screening in patients with breast cancer who are at high-risk when MDT was being considered, there was also consensus for elaborating new trials to compare SIMs and MIMs for diagnosing oligometastatic disease, noting that what is considered either a SIM or a MIM will evolve with time, the availability of a technique, and its formal translation to clinical application. Such apparent discrepancy reveals the frequent absence of in-depth trials when a new method, imaging or otherwise, is perceived to be so superior that it is readily integrated into the routine testing without thorough comparison with previous approaches.[34] Taken together, these survey results suggest that there is still a window of opportunity for an objective comparison of imaging methods for metastatic screening and their actual effect in breast cancer through suitably designed prospective trials. Additionally, the panel recommended the comparison of different MIMs in different breast cancer subpopulations because their added value might vary upon the histological and molecular breast cancer subtypes.[35]

A consensus was also reached on the shortage of biomarkers, outside imaging, to assess oligometastatic disease and to evaluate the indication of MDT. The potential of quantitative imaging has been poorly explored in oligometastatic breast cancer, which also warrants further investigation and related trials. In the future, approaches such as quantitative imaging and radiomics analysis might complement biological and clinical data for improving diagnosis and providing indications on which patients will most likely benefit from MDT.[36]

Rationale and design of future clinical trials to assess SIMs, MIMs, and MDT

Little information has been gathered regarding SBRT in oligometastatic breast cancer. In a 2021 meta-analysis of ten studies regrouping 467 patients and 653 treated metastases,[37] the 2-year local control rate was 90% (95% CI 84–94) and overall survival was 81% (72–88). In the subgroup analysis, the 2-year overall survival figures were significantly different when comparing HER2-positive (100%), HR-positive HER2-negative (86%), and triple-negative (32%) breast cancer (p=0·001). HR status was significantly associated (p=0·01) with improved local control on meta-regression analysis.[37] Similar outcomes were seen in the NRG-BR002 trial, in which patients with HR-negative disease had inferior outcomes in the experimental group.[28] These results further reinforce the conclusions of our Delphi survey in favour of stratifying breast cancer-dedicated trials according to histology and tumour subtypes, even though this approach does require more patients.

Accordingly, one of the main recommendations is that further prospective trials are needed before systematic deployment of MIMs and MDT in the clinic. Taken together with the experts' separate recommendation to use MIMs in patients with asymptomatic breast cancer at high risk of metastases, their plea for more prospective trials simply entails that stronger evidence is still necessary to objectively evaluate the benefits of MIMs.

Although SIMs and MIMs have been used in previous or ongoing trials, the choice of imaging methods was primarily because of site capabilities and without direct comparison between these two approaches.[24–26,32] Only trials designed to compare the respective sensitivity and specificity of SIMs and MIMs, and separate trials assessing the possibly different outcomes of patients with oligometastatic disease treated according to SIMs and MIMs, will assess the potential overall benefit of MIMs. The question of different outcomes of patients with oligometastatic disease diagnosed based on SIMs and MIMs will also be addressed through observational trials, such as the OLIGOCARE project (EORTC 1822, the first cohort of the joint EORTC–ESTRO E²-RADIatE study [EORTC 1811]; NCT03818503), which will provide an opportunity to compare outcomes of oligometastatic disease patients diagnosed through SIMs or MIMs and treated with MDT.

Concerning the design of necessary and new trials established in the survey, a consensus was reached for two types of randomised trials for objectively comparing imaging methods with them either in parallel or in series (ie, randomisation on MIMs *vs* SIMs with no further imaging, or addition of MIMs in patients diagnosed with oligometastatic disease after SIMs; appendix pp 2–3). Although the parallel design (appendix p 2) will allow for assessing the potential added clinical value of MIMs, it is at risk of poor accrual in centres and countries that have already largely adopted MIMs. By contrast, the serial design (appendix p 3) will allow the comparison of two treatment groups (ie, randomisation between SOC *vs* SOC plus MDT) in an optimised oligometastatic disease population due to the established higher accuracy of MIMs in these patients. However, sequential designs are subject to lead-time bias when treating asymptomatic metastases on the basis of MIMs, and this bias will have to be acknowledged and accounted for in the corresponding trials.

As a related example from prostate cancer, the ORIOLE randomised phase 2 trial compared observation with

SBRT in patients with oligometastatic prostate cancer.[35] The primary outcome was progression at 6 months, and a secondary objective was the evaluation of the concordance between SIMs and MIMs (eg, prostate-specific membrane antigen–targeted PET) for the identification of metastatic disease. Both SIMs and MIMs were used for each patient in the SBRT group; the SBRT targets were defined according to the results of SIMs and the physicians were blinded to the results of MIMs. Treatment with SBRT improved median progression-free survival based on SIMs and showed fewer positive lesions (eg, lesions that had not been treated with SBRT) compared with subsequent imaging with MIMs; the patients with lesions on subsequent MIMs had an inferior outcome in terms of distant metastases-free survival.[38] Such trials, which were designed to compare SIMs and MIMs, show the feasibility and implementation of randomisation for assessing imaging methods.[39,40]

In oligometastatic breast cancer, consensus was reached for the design of randomised trials comparing SOC with SOC plus MDT, following an approach already most commonly used in oligometastatic disease trials. Among the expert panel, an agreement was also reached in patients with established oligometastatic disease as identified by MIMs about the potential interest of a trial design comparing MDT only with SOC, with the aim to assess whether postponement of SOC systemic therapy would be possible and its potential side-effects. Although MDT has been used alone in oligometastatic prostate cancer, such a design could be more controversial in the setting of breast cancer.[38,41] Additionally, these trials might need to be repeated whenever more sensitive imaging or other biomarkers of metastatic disease become available.

Regarding the treatment of oligometastatic disease once the diagnosis is established, a consensus was reached on the need for trials comparing different MDTs (eg, SBRT, cryoablation or thermo-ablation, and surgery). Although a randomised trial comparing these techniques seems difficult to carry out in practice, because availability varies between centres and expected adherence is low, a prospective evaluation of these treatments could allow their indirect comparison.[42]

Another original outcome of our survey is the hierarchisation of the main endpoints for the proposed trials, which differs from other Delphi consensus studies that simply list important criteria without ranking them.[12] Concerning the main endpoint of a randomised trial evaluating MIMs and MDT in oligometastatic breast cancer, the panel favoured a combined endpoint including overall survival or progression-free survival and quality of life. Although quality of life was only recently considered as a metric in trials, a relevant note is that the coprimary endpoint (ie, progression-free survival and quality of life) is the main endpoint of the OLIGOMA trial,[32] whereas the main endpoint of other ongoing trials is only progression-free survival (appendix p 4).

Search strategy and selection criteria

The literature search was non-systematic because of the number and diversity of aspects to be investigated. References were identified through searches of PubMed, Embase, Scopus, and the Cochrane Library. Search terms were "breast cancer", "oligometastatic", "metastatic disease", "screening", "molecular subtype", "guidelines", "recommendations", "computed tomography", "positron emission tomography", "magnetic resonance imaging", "whole body magnetic resonance imaging", "metastasis directed therapy", and "stereotactic body radiotherapy". Although the period initially covered was from Jan 1, 1984, to June 30, 2021, literature surveys were conducted by the steering committee after this date, throughout the project, and up to the completion of the analysis on June 30, 2022. Relevant papers were also identified through searches of the panel experts' own databases. Only papers published in English were reviewed. They were selected for review when addressing the following topics: incidence and location of metastatic disease according to molecular breast cancer subtypes; the definition of oligometastatic breast cancer; current guidelines for imaging metastatic breast cancer; the diagnostic value of standard imaging methods and modern imaging methods (ie, sensitivity and specificity according to location of metastases, histology, and molecular subtypes); management and outcomes of oligometastatic breast cancer, including systemic treatment and metastasis-directed therapy; and completed and ongoing trials of metastasis-directed therapy for oligometastatic breast cancer.

A final reference list of 168 articles was generated through this process on the basis of originality and relevance to the intended Delphi process. After careful synthesis and editing of the literature review to avoid redundant entries, the steering committee used the results of this review to iteratively elaborate and refine the Delphi consensus questionnaire ahead of distribution to the intended respondents.

Conclusion

Although the Delphi survey results logically supported continued enrolment in ongoing trials, the expert panel specifically recommended developing new oligometastatic breast cancer-specific trials to assess the actual effect of new imaging and therapeutic approaches and tackle perceived weaknesses of previous trials. As confirmed through the panel's answers to the survey and proposed designs, these new trials should adopt novel designs combining stratification based on histology and molecular subtypes, the use of imaging methods on two levels (ie, either in parallel or serially), and the comparison of MDT plus SOC with SOC in patients with true oligometastatic disease identified through optimised imaging tests.

Contributors

DP, FvD, DK, FC, KH, NMdS, LB, DEO-L, and FEL conceived the study concept and initiated the study design. DP, DK, ADC, FC, KH, NMdS, LB, FEL, DEO-L, YB, MGB, L-FDG-O, CD, OG, IK, MK, EL, ES, J-NT, FvD, BL, AS, J-NT, JJCV, HDZ, and WM-vdHvO wrote the literature review. DP, DK, ADC, FvD, KH, NMdS, LB, ES, and FEL (steering committee) coordinated the literature review and wrote the Delphi questions. LC organised the logistics of circulating the literature review and Delphi questions and centralising and analysing the answers with other listed in the Acknowledgments. DP, LB, DEO-L, NMdS, ADC, AS, WM-vdHvO, CC, CD, DK, ES, FvD, FC, FEL, HDZ, IM, KH, L-FDG-O, LU, LF, MGB, NR, NH, OG, OK-P, PT, PP, SK, and VV responded to Delphi rounds. LB, DP, and FEL contributed to the formal analysis of the data from the consensus process, in collaboration with all the members of the steering committee. DP and FEL supervised all aspects of the study. DP, NMdS, LB, DEO-L, KH, DK, ADC, FvD, and FEL wrote the original draft. All authors approved and edited the final manuscript.

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