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Multidisciplinary discussion on phenotypical characterization of metastatic breast cancer and patient pathway optimization from an expert panel across South Italian regions

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Breast cancer (BC) might change its receptor status during malignant progression, resulting in challenging clinical care. The project, developed during two residential meetings by expert Italian oncologists and pathologists, was aimed at optimizing metastatic BC management. A 17-point survey was administered to healthcare workers in centers of three regions, essentially to assess the perception of metastasis biopsy on treatment choice in different BC molecular subtypes, the appropriate timing for performing tissue and liquid biopsy in metastatic BC, the selection of target genes and the use of multidisciplinary approaches in tumour management. Nineteen centers participated in the survey. The first important finding was that most centers manage more than 150 patients yearly, and 95% have a pathology department. Some questions received a substantial agreement: tissue biopsy of metastatic BC was largely considered as mandatory, generally performed at onset of metastatic disease. Liquid biopsy is not used by all centers, confirming its strict dependency on the available technologies. The answers on the therapeutic line change in case of HER2 + disease becoming triple negative confirmed an attitude consistent with clinical practice. The survey also revealed that half of the interviewed oncologists discuss with multidisciplinary team only for selected cases. The survey revealed that while a shared consensus exists on the importance of metastasis biopsy, some areas still deserve attention to achieve standardized approaches: interdisciplinary collaboration and more effective communication between specialists and patients are necessary to optimize the diagnostic and therapeutic journey of women with metastatic BC.

Keywords Breast cancer molecular subtype, Intratumoral heterogeneity, Liquid biopsy, Metastasis biopsy, Metastatic breast cancer, Tumour phenotypical characterization

Breast cancer (BC) remains a major public-health issue, with 2,308,897 new cases and 665,684 deaths among women worldwide during 2022, as reported by the Globocan registry[1].

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BC is characterized by high intratumoral and intertumoral heterogeneity, resulting in large differences of clinical manifestations[2]. BC classification into molecular subtypes is based on combined approaches of histopathology evaluation of primary tumour, expression profiling of hormone receptors (estrogen and/or progesterone receptors-ER/PR) and epidermal growth factor receptor 2 (HER2), together with genomic-transcriptomic-epigenomic analysis[3–11]. However, receptor status might change over time[2,10–14], and this instability should endorse the role of re-biopsy, since revealing potential discrepancies between primary tumour and metastasis samples could guide therapeutic choices[15]. Recently, it has been reported that patients may experience receptor conversion between primary breast cancer and bone metastases, possibly influenced by prior treatments. The loss of hormone receptor expression in bone metastases was significantly associated with worse progression-free survival (PFS) and overall survival (OS), highlighting the critical role of re-biopsy of bone metastases to provide information for treatment planning[16].

Although the initial indication for re-biopsy is to exclude the presence of non-malignant lesions or second tumours[17], the procedure is performed in case of relapse or disease progression to check possible switches in hormone receptors expression of ER/PR/HER2 between primary BC and metastases[17–19]. Evidence confirmed that the shift is bidirectional, as both changes of ER expression from positive to negative and vice versa can occur[11,20–22]. Hence, re-biopsy should be adopted in metastatic BC (mBC), to define lesion nature and to re-evaluate receptor pattern, especially in triple negative (TNBC) and HR+/HER2− BC, as recommended by the latest national and international guidelines[17,23–25]. Nevertheless, since biopsy is an invasive procedure, liquid biopsies for the search of circulating tumour DNA (ctDNA) should be considered as a valuable surrogate strategy for BC molecular analysis to obtain a real-time picture of disease evolution[24–28]. Currently, the choice of treatment can be supported by the analysis of driver genes, including PIK3CA mutations, ERBB2 amplification, BRCA1/2 mutations, ESR1 mutations, MSI-H, NTRK 1/2/3 fusions)[26–29]. Liquid biopsy cannot anyhow completely replace the informativeness of tissue biopsy, as it only allows detection of genomic alterations and not receptor structure description.

The therapeutic landscape of mBC has expanded greatly over the last decades, allowing an increasing prolongation of PFS and, to a lesser extent, of OS[30]. All the efforts to further enhancing the prognosis of women with mBC should rely to a careful evaluation of each therapeutic hub during tumour evolution, as confirmed in the last conference of the European Society of Breast Cancer Specialists (EUSOMA)[31]. Of note, the positive data obtained by new drugs to treat mBC have transversally concerned all subtypes, with the major achievement observed for HR + HER2− disease, which accounts for about two-thirds of all BCs[30]. Favourable outcomes were attained with combination regimens, particularly cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in association with endocrine therapy (ET), as demonstrated in multiple clinical trials and meta-analyses. Studies such as the PALOMA, MONALEESA, and MONARCH trials have consistently shown that CDK4/6 inhibitors, namely palbociclib, ribociclib, and abemaciclib, can significantly improve PFS and OS, when combined with ET in patients with HR+/HER2− advanced breast cancer[32–37]. Encouraging data have also arrived from trastuzumab deruxtecan in the setting of HER2 + mBC[38]. The CLEOPATRA study, a phase 3, double-blind, randomized trial compared pertuzumab plus trastuzumab and docetaxel vs. placebo plus trastuzumab and docetaxel in HER2-positive mBC. The final results showed significant benefits in terms of objective response rates, PFS and OS in the pertuzumab versus the control group[39].

Over the last few years, sacituzumab govitecan has also demonstrated promising results in treating TNBC. The phase 3 ASCENT trial showed that sacituzumab govitecan markedly improved PFS (5.6 vs. 1.7 months) and OS (12.1 vs. 6.7 months) compared to standard chemotherapy[38]. A successive analysis of the ASCENT data, comparing outcomes in patients with de novo vs. secondary TNBC provided further evidence to support the survival benefits across both groups of sacituzumab govitecan therapy[39].

Although the evolution of receptor profiles in mBC over time is well-documented, the extent to which this dynamic and largely unpredictable progression influences clinical decision-making, such as therapy modification or the necessity for re-biopsy, is less clear.

This project was developed by a multidisciplinary panel of oncologists and pathologists to describe the current state-of-art of mBC management in three regions of South of Italy (Basilicata, Campania and Puglia) from the clinicians' perspective. In an effort to identify areas of agreement or disagreement across healthcare providers of the regions, the purpose of the expert board was first to elaborate and then to evaluate (in two successive and distinct meetings) the results of a questionnaire on some central points, with a special focus on the following aspects: (i) actual impact of re-biopsy on treatment choice and on patients' outcome in different BC molecular subtypes; (ii) appropriate timing and identification of target genes for tissue and liquid biopsy in mBC; (iii) adherence to guidelines and the diagnostic-therapeutic care pathways (PDTA) in the management of mBC.

Methods

The "Metastatic Breast Cancer Project: multidisciplinary discussion for phenotypic characterization of the tumour and optimization of the diagnostic and therapeutic pathway" was developed by an expert board of oncologists and pathologists during two residential meetings held on 2nd February 2024 and 9th May 2024.

The first meeting was mainly focused on designing a survey which consisted of 17 multiple-choice questions administrated between 18th March and 10th April 2024 to healthcare entities of Basilicata, Campania and Puglia regions (local health authorities, regional hospitals, university hospitals, Scientific Institute for Research, Hospitalization and Healthcare-IRCCS, hospital facilities).

Questions 1 to 3 aimed at collecting basic data on centers, including institution's name, average yearly cases of mBC, and presence of a pathology department.

Questions 4 to 9 explored the attitude towards metastasis biopsy in relation to molecular subtype: how much necessary the procedure is deemed, proportion of biopsied cases among overall mBC, timing, BC subtype, metastatic sites guiding the decision of re-biopsy.

Question 10 investigated the changes therapeutic lines in the event of HER2 + disease becoming TNBC.

Questions 11–12 assessed whether the setting of mBC is managed though a multidisciplinary team (MDT) and interaction degree between oncologists and pathologists.

Questions 13–14 investigated liquid biopsy utilization in standard clinical practice and essential target genes studied in ctDNA.

Questions 15–16 dealt with the communication between oncologist and patient, focusing on the weight of woman's preference on metastasis biopsy and time spent by the doctor to explain risks and benefits.

Lastly, question 17 analyzed if the current guidelines and PDTA for the management of mBC are sustainable in centers clinical practice. This latter question encompassed additional information under the main answers yes/sometimes/no. In case of positive response, the main points investigated were (among others) if the guidelines and/or Diagnostic and Therapeutic Care Pathways (PTDA) are considered regularly, if derived from scientific evidence, the importance given to medical-legal issues in complying with guidelines, the availability of the necessary resources and professionals within the MDT to facilitate adherence to guidelines/PDTA. The option "sometimes" was motivated by possible difficulties in providing timely pathology, radiology and molecular biology reports in certain realities, or unavailability of liquid biopsy. The answer "no" was related to the fact that investigations were considered too complex and time-consuming or not sustainable by the center.

Given the design of this analysis, conducted in the form if an anonymous survey administered to healthcare workers, no informed consent was needed because the results did not imply interventions on patients, or treatment of their sensitive data. Likewise, ethics committee approval was waived due to the fact that no patients were enrolled, and for the nature of collected data that were completely anonymous without any potential identifier of participant physicians.

The results deriving from the replies to the multiple-choice questions were elaborated in a purely descriptive, aggregated and anonymized form. The study in its current form has not any comparative and/or forecasting purpose and no statistical analysis was applied.

Results

The survey was proposed to 21 centers, 2 located in Basilicata, 10 in Campania and 9 in Puglia, and 19 accepted to participate. The results (Table 1) were discussed during the second multidisciplinary expert meeting in the perspective of understanding the current practices in mBC management and identifying areas that require further improvements.

The first observations emerged were that most centers followed above 150 patients yearly, and 18 out of 19 were equipped with a Pathology department.

To the question of how to consider tissue biopsy in case of mBC, 63% the participants answered "mandatory" and 37% "recommended".

The percentage of cases of mBC submitted to tissue biopsy was above 40% or from 10 to 40%, each in 47% of the centers, and lower than 10% in 5% of the centers.

Tissue biopsy resulted to be performed at onset of mBC by 68% of the participants, at exhaustion of therapeutic lines for that specific molecular subtype by 21%, at each progression by 11%.

The question on tumour subtype in which metastasis biopsy is performed gave rise to divided responses: in all luminal forms 47%; in TNBC 37%; in HER2 + 16%.

The answers on molecular subtypes for which biopsy is considered unnecessary were: HER2 + 72%; TNBC 17%; luminal 11%.

The most commonly biopsied metastatic sites were liver, lung, and soft tissues, each in 89% of the responders, distantly followed by bone and brain (both 6%).

Regarding the choice of changing therapeutic line in case of HER2 + disease becoming TNBC, 44% answered never, 22% in first-line, 17% in second-line, and 17% in third-line.

The answer on the habit to discuss cases of mBC in the MDT was divided into yes in 44% of the participants, for selected cases in 50% and no in 6%.

The largest majority of the oncologists (89%) referred to inform the pathologist on receptor status of mBC.

Liquid biopsy was regularly utilized in 22% of the centers, sometimes in 56% and never in 22%. The genes most frequently deemed as essential were PIK3CA for 100% of the participants, ESR1 for 89%, BRCA 1/2 for 44% and TP53 for 6%.

The answers on the communication with the patient revealed that women's preference had much weight on the recommendation of metastasis biopsy for 44% of the participants, little weight for 39%, and none for 17%. When asked on the time dedicated to communication with patients, 61% of the doctors spent on average 11–20 min, 33% spent 10 min and 6% more than 30 min.

Most centers (78%) referred to consider the management of mBC according to current guidelines and PDTA to be viable in their normal practice, while 17% answered sometimes and 5% answered no.

The details of the questionnaire with the plotted replies are provided in Supplementary materials.

Discussion

The project analyzed the current state-of-art of mBC management in three Southern Italian regions to identify strength points as well as possible grey areas that should be optimized.

In general, the answers appeared to reflect the clinical practice properly. The first relevant findings were that most centers manage above 150 patients annually, and 95% have a pathology department. Moreover, the

1. What is the name of your center?	Not disclosed (2 in Basilicata, 10 in Campania, 9 in Puglia)	
2. How many patients with metastatic BC are treated on average in one year at your center?	0–50	11%
	51–100	16%
	101–150	26%
	≥151	47%
3. Is there a Pathology Department in your center?	Yes	95%
	No	5%
4. In the case of metastatic BC, do you consider a tissue biopsy to be:	Mandatory	63%
	Recommended	37%
	Advisable	-
	Unnecessary	-
5. In what percentage of metastatic BC cases do you perform tissue biopsy in your clinical practice?	<10%	5%
	10–40%	47%
	>40%	47%
6. In the case of metastatic BC, when do you perform a tissue biopsy, if clinically feasible?	At the onset of the disease	68%
	At each progression	11%
	At exhaustion of therapeutic lines for that specific molecular subtype	21%
	Never	-
7. Would you biopsy the metastasis:	In all luminal forms	47%
	In triple negative	37%
	In HER2+	16%
8. In which molecular subtypes do you consider biopsy unnecessary?	HER2+	72%
	Triple negative	17%
	Luminal	11%
9. If feasible, at which site would you biopsy BC metastasis? (you can choose more than one option)	Liver	89%
	Lung	89%
	Soft tissues	89%
	Brain	6%
	Bone	6%
10. In the case of HER2 + disease becoming triple negative, the change of therapeutic lines takes place:	First line	22%
	Second line	17%
	Third line	17%
	Never	44%
11. Do you discuss metastatic cancer cases in the multidisciplinary team?	Yes	44%
	Only in the event of treatment of selected cases	50%
	No	6%
12. Do you report to the pathologist the necessary information on the receptor status of the primary metastatic tumour?	Yes	89%
	Only in the event of treatment of selected cases	11%
	No	-
13. Do you use the liquid biopsy procedure in your clinical practice?	Yes	22%
	Sometimes	50%
	No	22%
14. Which genes do you consider essential to study in the liquid biopsy (you can choose more than one option):	PIK3CA	100%
	ESR1	89%
	BRCA 1/2	44%
	TP53	6%
15. How much does patient preference weigh on the recommendation of metastasis biopsy?	Much	44%
	Little	39%
	None	17%
16. How much time do you spend explaining the risks and benefits of the diagnostic procedure to patients?	10 min	33%
	11–20 min	61%
	21–30 min	6%

Continued

17. Do you consider the management of metastatic BC according to current guidelines and diagnostic and therapeutic care pathways (PDTA) to be sustainable in your practice?	Yes We do it regularly Derived from scientific evidence In order to be protected from the medical-legal point of view (unfortunately) In order to share the treatment pathway within the multidisciplinary team Each case is discussed in the multidisciplinary team and each specialist takes charge of the patient I personally worked on the drafting of the PDTA and apply the guidelines Because all the figures are there to manage the diagnostic process Good supporting multidisciplinary team Availability of sufficient resources to implement the PDTA A multidisciplinary approach has long existed in our center Not to go outside the guidelines and be prosecuted criminally	78%
	Sometimes Timing is not always easy to meet, in some realities pathology and radiology are in great difficulty and often late in giving adequate answers Timing of diagnosis (especially biological-molecular); Unavailability of liquid biopsy	17%
	No Because of the timing of the pathway, the complexity of the investigations and sustainability	51%

Table 1. Results of the survey.

willingness of finding operational solutions resulted to be independent from the specific ability of the centers to guarantee biopsy testing. This point concerns the ability of the centers to provide interventional radiology services, especially when they do not have a department for biopsy investigations, despite already having a pathology department. Interestingly, even in the absence of direct access to such services, alternative routes are identified in the centers that still allow the investigation to be conducted. This highlights a general commitment from all the centers involved to seek operational solutions. All the answerers showed a satisfying awareness of biopsy diagnostic value in mBC setting, largely considered as mandatory, especially in case of de novo metastatic disease. These replies are consistent with the recommendations of the Italian Association of Medical Oncology (AIOM), which emphasize the role of biopsy of metastasis in case of recurrence of primary BC, to obtain both diagnostic confirmation and updated assessment of tumour biological profile. Besides, the search for additional predictive tissue biomarkers is essential to complete tumour classification and guide treatment pathway[24].

Regarding the time driving the decision to biopsy mBC, approximately 7/10 centers reported to perform biopsy at disease onset, consistent with the standard medical practice and guidelines[23,24]. Nonetheless, a point that deserves attention is the low rate of metastasis biopsies for HER2 + subtype (16% of the answerers), considering that changes in HER2 status are common[11–13]. A large meta-analysis reported HER2 receptor positive to negative conversion and vice versa in 22.5% and 9.5% of the cases, respectively[22]. Likewise, in a successive study on Italian 190 patients with mBC treated consecutively between 2017 and 2021, about one-fourth underwent re-biopsy of the metastasis, and 19% of them had HER2 receptor conversion into positive status compared to the primary tumour[21]. Taken together, these data underline the importance of re-biopsy, when clinically feasible, in HER2 + disease, and in overall mBCs, given the potential rebounds on treatment choice in the event of receptor status change[22]. Such unfulfilled expectations regarding the frequency of biopsy of HER2 + disease open some points for reflection. First, this result suggests the need of exploring in-depth the answers provided by individual centers to gain a more comprehensive and contextualized overview. Secondly, understanding how the various centers responded could deliver useful information on circumstances and factors influencing the answers. This strategy might help to detect any discrepancies between expectations and actual data, and to identify any necessary corrections in the provision of services.

Among the most commonly biopsied metastatic sites, liver and lung accounted for 89%, while bone, brain and soft tissues for 6% only. Such rates might be partly affected by bias due to the fact that tumour molecular subtype was not specified in the question. Indeed, large evidence indicates that each BC subtype has a clear tropism in terms of organ-specific colonization[40–42]. Bone metastases preferentially occur in luminal forms, lung metastases are more frequent in TNBC, liver metastases are predominantly found HER2 + subtype, and brain metastasis in basal-like and HER2 + BC[43]. Although bone is the most common metastatic site in BC, the survey showed a low proportion of bone biopsies, feasibly explicated by some disadvantages, especially technically complexity (i.e. decalcification that may alter the assessment of the tumour phenotype)[44].

To the question on change of therapeutic line in the event HER2 + disease becoming TNBC, most of the interviewed centers (44%) answered never, confirming an attitude in line with oncological clinical practice[45,46].

The point regarding the degree of discussion of mBC cases in MDT raises some concerns, since half of the answers revealed that such synergistic approach takes place only when treating selected cases. Hence, although this response indicates an effective communication flow at diagnosis or at each progression, it is also necessary to point out that therapists, radiologists and pathologists are involved only when necessary and in certain cases, rather than being constantly part of a structured MDT. This suggests that in 50% of the centers, the participation of multiple professionals in all cases and throughout the whole disease course is still far from being a regular habit. Nevertheless, the replies also highlight the importance of identifying the 44% of the centers that responded positively about the presence of MDT to better understand how patients are managed in such settings. Spending further efforts to enhance MDT role on the entire disease course is crucial, considering the described significant survival benefits in BC patients involved in well-organized multidisciplinary discussions[47].

The survey also showed that 89% of the oncologists inform the pathologist with all the necessary data on receptor structure of primary tumour, eliciting some considerations. A surprising result was that no center selected

the option "in selected cases": given that in some realities there is the possibility of independently verifying the receptor structure of the primary tumour, this reply seems to suggest nearly 9 of 10 centers perform the biopsy or that 90% of physicians provide the pathologist with information about the biopsy, rather than performing the evaluation themselves. There may have been a misinterpretation of the question for suboptimal wording, as the answers do not seem to correlate exactly with the previous ones. An effective information exchange between oncologists and pathologists is a fundamental step to make a definite diagnosis, obtain accurate staging and choose the most appropriate therapy[48]. Hence, the survey also underlines the importance of identifying the reasons beyond the negative responses given by two centers that reported a lacking communication between these professionals.

The utilization rates of liquid biopsy revealed an occasional use in 56% of the responders, supporting the view that its adoption is highly dependent on the resources available in each center. Currently, many centers are not appropriately equipped or do not have a well-defined pathway for implementation of "omics" technologies. As an alternative, it is therefore more practical to rely on traditional tissue biopsy, anyhow with the limitations related to its invasive nature.

Among the genes most commonly searched in ctDNA of liquid biopsies, an unexpected low frequency of BRCA testing was noticed. It can be speculated that this might be due to the fact that this test is mistakenly not yet considered a biomarker in the current clinical practice, but only a mutational analysis to predict cancer risk as when originally introduced[50,51]. This misperception might have limited its regular inclusion in diagnostic and treatment protocols, although BRCA1/2 testing has been proven to provide valuable insights into tailoring of therapeutic interventions[52,53]. On the other hand, the elevated proportion of analyses of mutational status of PIK3CA and ESR1 emerged from the survey represents a positive finding, in view of the upcoming introduction of drugs to be used specifically in the presence of PIK3CA and ESR1 mutations[54].

The answers on the communication between oncologist and patient suggests that in many cases the patient's opinion has a limited influence on medical decisions. Moreover, most doctors spend between 15 and 20 min explaining the risks and benefits of biopsy procedure, and this can be problematic, given the typical duration of outpatient visits, which is only 15 min. In some centers, the time devoted to obtaining informed consent must also be considered. Hence, this appears to be a theoretical answer, suggesting that time management during medical visits should be reassessed to ensure effective and comprehensive communication with patients. A recent web-based survey sent to oncologists members of the AIOM from 19 Italian regions confirmed that communication between patients and healthcare providers is a complex process encompassing multiple areas, like diagnosis, prognosis and treatment[55]. While a patient-tailored approach together with their involvement in clinical decision should be encouraged, the survey revealed that the time dedicated to doctor-patient communication was considered "quite sufficient" in 16% of the answers, "little but sufficient" in 44%, "scarce" in 31% and "insufficient" in 10%[55]. Consistently, the results of the present project highlight an unmet need and a noticeable heterogeneity in the management of an adequate interaction with mBC patients across the involved centers.

The feasibility of being compliant with current guidelines and PDTA received positive replies in 78% of the centers, and this seems to mirror the daily clinical experience. From the answers pattern, the management of a metastatic patient appears to be somehow less demanding compared to de novo disease. However, in some contexts, pathology and radiology departments have great difficulty and are often late in providing adequate responses. This can affect the timing of diagnosis and the overall patient's management.

To summarize, the survey showed a growing utilization of re-biopsy and an improved awareness of its diagnostic value in the setting of mBC. This finding is of paramount importance given the large literature evidence on the close relationship between tumour receptor changes and its implications on therapeutic decisions[4,13,14,56]. Nonetheless, in case of discordance between primary tumour and recurrence, there is not a shared consensus yet about the biological features that should guide the treatment decision-making process[57]. The approach should be multidisciplinary and based on the molecular characteristics of the disease at baseline, the degree of heterogeneity of biomarkers, the type of treatment received that could potentially induce selection of clones resistant to a specific targeted therapy. Tumour heterogeneity must be considered for each successive line of treatment, and a new biopsy may be appropriate in discordant cases[57]. The survey also indicated that the multidisciplinary management of mBC is a well-acquired practice in some key steps of tumour course, in particular initial diagnosis and changes of therapeutic lines, but a structured and continuous collaboration between specialists in each center, although desirable, is not regularly accomplished.

It is important to stress that the ability of correctly interpreting the results of biopsies, both tissue and liquid, is a milestone for the optimization of mBC management. The survey unveiled a few areas having some room for improvement. The rate of metastasis biopsy in patients with HER2 + subtype resulted to be below the expectations (16%) considering the likelihood of HER status changes extensively described in the literature[11–13,21,22]. Moreover, despite its undisputed value, liquid biopsy is not a routine practice for many centers and, when executed, the testing rate for BRCA1/2 mutations is suboptimal, feasibly because it is not deemed as a biomarker yet, but rather as a susceptibility mutational analysis to predict the risk of BC during lifetime. This current drawback might markedly benefit from the development of NGS (Next Generation Sequencing) panels for liquid biopsy, including candidate genes (ESR1, PIK3CA, BRCA 1, AKT) with a predictive role on therapy responsiveness.

The main emerging message from the presents project is that the largest majority of the centers are in general able to be satisfyingly adherent to guidelines and PTDA, although some obstacles have been reported in limited cases, maybe attributable to organizational rather than strictly clinical problems (e.g. lack of proper equipment or dedicated facilities).

The variability in the responses can be attributed to the diversity of hub and spoke centers. Even though several centers reported treating more than 150 patients per year, this does not imply that they have all the mandatory prerequisites of BC specialist center, as described by Biganzoli and colleagues[59]. A reference BC

center should have a sufficient size to manage at least 150 newly diagnosed cases of early BC and at least 50 cases of mBC per year, regardless of the line of treatment, together with a critical mass of professionals in MDT and exams to guarantee good quality data[59]. These characteristics in terms of expertise and caseload might represent the starting point for future research to investigate which of the participating centers fulfil such requirements and the possible areas for improvement.

To the best of our knowledge this is the first investigation in South Italy to gather opinions from clinicians and fieldworkers on some crucial aspects of mBC, which remains a challenging pathology for its molecular, pathological and clinical heterogeneity.

The survey provided several relevant data, although some limitations must be acknowledged. First, perhaps a few questions were formulated using a too synthetic wording, and the possible misperception might explain some inconsistencies. Moreover, the data provided are purely descriptive and no statistical analysis was applied in this phase, thus no comparative or forecasting outputs were considered. In addition, the project involved a restricted area of the Italian territory, and this prevents the generalizability of the results that should be validated on a larger sample size. Nevertheless, this study might represent a basis to possibly enlarge the investigation to other Italian areas and then deploy a successive model structured as a Delphi consensus with different outputs, including multiple-round questionnaires, statistical aggregation to assess the convergence of opinions to reach a well-defined agreement (or acknowledgment of disagreement) on the aforementioned topics, as a measure of consensus. Future research could also leverage machine learning-based models, such as neural networks and random forests, which are increasingly employed in the development of advanced algorithms for disease classification, potentially enhancing predictive accuracy and diagnostic reliability across various medical conditions[60–62]. A recent machine learning model was deployed for BC prediction, enhancing classification accuracy through advanced hyperparameter optimization and highlighting AI's potential to discriminate between malignant and benign BC cases[62].

Conclusion

The results emerged from the project provided valuable insights into mBC management across three Southern Italian regions, highlighting both strengths and areas for improvement. While most centers follow guidelines and deliver high-quality care, some challenges remain. A strong awareness of biopsy diagnostic value was observed, especially at disease onset, but gaps in metastasis biopsies for HER2 + patients were noted, despite the potential impact of receptor status changes on treatment decisions. The survey also revealed variability in liquid biopsy use, with many centers still relying on traditional tissue biopsies due to resource limitations. Additionally, BRCA1/2 testing in liquid biopsies was underused, potentially hindering targeted therapy options. This underscores the need for better integration of "omics" technologies in the clinical practice.

Another key finding was the inconsistency in MDT involvement in all the phases of patients' care. While some centers involve MDT in decision-making, others do so only for select cases. A more consistent MDT approach could improve patient outcomes. Despite these challenges, the survey indicates a commitment to personalized, guideline-based care. There is an opportunity to optimize practices through better resource allocation, communication, and molecular profiling. Future research, including the use of advanced technologies like machine learning, could help standardize and improve mBC management.

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Author contributions

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Declarations

Competing interests

The authors declare no competing interests.

Institutional review board statement

Ethics committee approval was not required because no patients were enrolled, and for the nature of collected data that were completely anonymous without any potential identifier of participant physicians.

Informed consent

Given the design of this analysis, conducted in the form if an anonymous survey to healthcare centers, no informed consent was needed because the results did not imply patients' sensitive data.

Consent for publication

All responders consented to have the information published anonymously.

Compliance with guidelines and regulations

All the methods were carried out in accordance with relevant guidelines and regulations.

Additional information

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