Challenges in the journey of breast cancer patients in Brazil.

Desafios na jornada de pacientes com câncer de mama no Brasil.

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ABSTRACT

The mortality rate of breast cancer (BC) in Brazil is increasing. Procedures that can improve the diagnosis and treatment of BC should be discussed by specialists to improve patient survival. Experts from five different specialties involved in the diagnosis and treatment of BC discussed possible problems and solutions in this context. The discussion focused on diagnosis and treatment of early and metastatic BC. The experts approached different phases of a patient’s journey and defined (1) which specialty should be involved, (2) when this specialty should act, (3) what the benefits of a multidisciplinary team might be, (4) what consequences might arise when there is no multidisciplinary team available, and (5) what possible strategies should be implemented to put the recommendations into practice in a setting of scarce resources. This text brings important insights regarding solutions that a multidisciplinary team can provide in the context of BC.

Keywords: Breast Neoplasms, Diagnosis, Interdisciplinary Communication, Treatment Outcome.

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Breast cancer overall scenario

Screening and appropriate treatment decrease overall breast cancer mortality\(^4\). Offering screening tests to the asymptomatic at-risk population allows the detection of precursor lesions and tumours at earlier stages. Early diagnosis also involves education and awareness of health professionals and the general population regarding signs and symptoms that could raise the suspicion of cancer\(^7\).

The Brazilian Ministry of Health recommends that women between 50 and 69 years old undergo mammography once every two years\(^7\). Although this information is widely disseminated in Brazil, only 30% of the 16 million Brazilian women in this age group underwent mammography between 2017 and 2018 in the public health system\(^8\). Moreover, according to the AMAZONA epidemiological study, the median age at diagnosis in the country is 53 years and 40% of patients are diagnosed before age 50; therefore, a significant proportion of the affected population develops a breast cancer before the age range for recommended screening\(^8\). Delays in scheduling appointments, performing exams, including mammography, and releasing results significantly compromise early diagnosis strategies\(^8\). Most mammograms performed in the country and reported in the public system occur in the South and Southeast regions of the country, where most mammography machines are located. Additionally, the operational capacity of the equipment is also reduced due to the lack of trained professionals and lack of equipment maintenance resulting in scheduling difficulties and delays in service\(^8\).

Furthermore, while the interval from suspicion to BC diagnosis is on average 31.7 days for patients paying out-of-pocket, it increases to 68.9 days for health insurance patients and 93.4 days for women assisted by the Brazilian National Health System (SUS). This results in a delay in treatment and it may lead to a more advance, less treatable disease at the time of diagnosis, which can worsen the prognosis and increase the demand for more aggressive and expensive treatments. These and other disparities between the public and private sectors are heterogeneously distributed in different parts of the country, with larger differences and worse outcomes in the poorest and underserved regions\(^8\). Technological advances and specialized professionals are mostly concentrated in the Southeast and South regions of Brazil \(^8\). An additional challenge is a significant delay in reporting biopsy results. This is mainly due to lack of pathologists, who are scarce in the North and Northeast regions of Brazil\(^10\).
A more even distribution and availability of health-related professionals is extremely important for an early diagnosis strategy to be successful. The result of the diagnosis can be early or metastatic BC. In the first case, after clinical evaluation, the patient may undergo surgery when the tumour is considered operable. However, most patients need to associate systemic treatment with surgery. This treatment can be administered before surgery (neoadjuvant), in patients who need to reduce the tumour size, or if the information of pathological complete response to presurgical treatment has prognostic value. Alternatively, this systemic treatment can be performed after surgery in patients with a higher risk of tumour recurrence (adjuvant). The type of systemic treatment (which may comprise endocrine therapy, chemotherapy, targeted therapy, and bone-modifying agents) or radiation used, will depend on the initial tumour burden and molecular expression pattern of the tumour.

On the other hand, metastatic BC (mBC) is a treatable but incurable disease. Metastases are the cause of death in most patients. The average survival is 2 to 3 years after diagnosis and the treatment of mBC is focused on symptom relief, increased life expectancy and quality of life.

So, it is a moment in the patient's journey where multidisciplinary medical care is essential.

There are several scientific articles and guidelines on BC patient care. However, disparities in diagnosis, treatment and results have been published for decades and remain a problem despite advances in medicine. Solving these disparities and defining a unique protocol to be followed by all professionals is a current challenge for the multidisciplinary team. The tumour biology, the patient's social status, the availability of an effective health system, the access to appropriate medications, and the participation of a multidisciplinary team are important points to be evaluated in each situation. So, understanding the overall scenario can help interested professionals to develop different and innovative strategies for BC patients.

The objective of this study was to promote a discussion and disseminate the insights addressed by a group of Brazilian experts from five different specialties (breast cancer surgery, clinical genetics, clinical oncology, pathology, and radiation oncology) on the patient journey from diagnosis to therapeutic planning and from early stage to metastatic BC. Table 1 gives a summary of that session.

<table>
<thead>
<tr>
<th>Table 1. Breast Cancer Overview</th>
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<tr>
<td>❖ BC is the most diagnosed malignancy in women worldwide [1]</td>
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<td>❖ It is estimated that 12% of women worldwide will be diagnosed with BC [1]</td>
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<td>❖ In developed countries, mortality has been falling over the past three decades as a result of improved detection tests and more effective and individualized treatments [1]</td>
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<td>❖ In Brazil, despite all the technology and the number of trained professionals, the BC incidence and mortality rate remain high [2]</td>
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**METHODOLOGY**

A multidisciplinary team of Brazilian experts has discussed three topics: (1) diagnosis; (2) early BC (eBC) and (3) metastatic BC (mBC). For each of these subjects, the experts used their experiences and knowledge to offer opinions about the following items: (1) which specialty should be involved at each stage of the process, (2) when this specialty should act, (3) what the benefits of a multidisciplinary team might be, (4) what consequences might arise when there is no multidisciplinary team available, and (5) what possible strategies should be implemented to put the recommendations into practice in a setting of scarce resources. The insights of this discussion were provided by experts from five different specialties (breast cancer surgery, clinical genetics, clinical oncology, pathology, and radiation oncology) and were compiled in this short review.

**RESULTS**

Breast cancer diagnosis

*Diagnostic procedures*

A good outcome in BC treatment is dependent on an early and accurate diagnosis. The main methods for an early diagnosis are self-examination, mammogram, and clinical examination by experienced physicians. Following clinical suspicion, the diagnosis needs to be confirmed by histopathological and immunohistochemical analysis of a tissue biopsy. Once the tumour characteristics are defined, a multidisciplinary team should discuss the ideal treatment which needs to be initiated quickly. All interventions must be offered in timely and appropriate intervals throughout the whole process. Unfortunately, 60% of BCs in Brazil are diagnosed at later stages, which significantly reduces the chances of a good outcome.
The path from clinical suspicion to BC diagnosis can be long. Experts indicated that (1) gynecologists, (2) breast cancer surgeons, (3) clinical oncologists, (4) radiologists, (5) pathologists, (6) clinical geneticists, (7) psychologists and (8) nurses are essential at this initial stage of the patient’s journey.

In Brazil, the gynecologist is the professional who usually raises the initial suspicion of BC during a routine clinic appointment. While all specialties should share this responsibility, expanding BC screening programs and educating patients about the importance of early diagnosis should be a focus for gynecologists. After the initial clinical suspicion, the breast cancer surgeon and the interventional radiologist are the professionals who coordinate the initial procedures, perform breast and axillary biopsies, and double-check the diagnosis in partnership with the pathologist. Together, they perform and interpret imaging tests, histopathology and immunohistochemical slides. Additionally, the clinical geneticist will provide genetic pre-counselling and define if the patient should undergo genetic testing. Genetic counseling may also be provided by an oncologist or a surgeon with adequate training for cancer genetics.16

Pre-analytical pathology issues

BC diagnosis does not depend exclusively on the commitment of the professionals reported above. Proper biopsy processing for histopathological analysis is essential in tumour investigation. Most errors occur in the pre-analytical phase of biopsy processing.17 The adequate handling of surgically removed breast cancer specimens involves transport, fixation, and storage. In Brazil, many hospitals do not have their own pathology laboratories and need to outsource samples to larger laboratories. Proper postoperative handling of surgical specimens might reduce and avoid errors in the diagnosis (tumour typing and grading), and immunohistochemical or molecular breast cancer biomarker testing. Factors that influence pathological analysis include size of the specimen, time to fixation from tumour removal, type of fixative and duration of fixation. Additionally, the experts highlighted that samples obtained on the eves of days off (such as weekends) are more susceptible to diagnostic error. The breast specimens are likely to be stored without adequate grossing, cutting and fixation in formalin. The tumour sample will stay without adequate cutting and fixation for a longer time than recommended. Ideally, the breast biopsy should be immediately sliced and fixed in buffered formalin for at most 48 hours. Delays in fixation or over-fixation may interfere with morphology and the integrity of proteins and nucleic acids, and negatively affect testing for BC biomarkers.18-20 If the pre-analytical phase is not adequate, all subsequent processes will be compromised, resulting in improper treatment.

While more than 30-day delays in the exam result can compromise patient survival even shorter delays of more that 10-20 days should be considered unnecessary and unacceptable for the adequate management of a newly diagnosed BC.21,22 The quality of treatment depends on a correct diagnosis and the speed at which it is provided and passed on to the team responsible for the treatment.

To improve the pre-analytical phase of diagnosis, institutions need to develop workflows that must be strictly followed by the entire team involved in biopsy tissue removal and properly delegate the responsibility of the sample, from the operating room to its final destination, to one member of the team. The inclusion of automated steps was cited by the experts as an interesting solution that would reduce errors. In the state of São Paulo, a resolution obliges all hospitals that work with cancer to have a frozen section room with cryostat, microscope, and a pathologist available for analysis of suspicious breast samples close to operating suites. This resolution was made in partnership with the Regional Council of Medicine of the State of São Paulo (CREMESP), which inspects and penalizes centers that do not comply with the law. The experts agreed that this measure should be extended to all Brazilian states. Additionally, it was noted that there should be an official program that reviews the histology and immunohistochemistry slides and that centers specialized in performing these exams should be adequately certified with regard to the quality control of the services provided.

Analytical pathology issues

When a breast biopsy sample is appropriately handled, errors in the analysis or interpretation of the results by the pathologist should be minimal. Nevertheless, the group of experts recognized frequent communication problems among the professionals in the multidisciplinary team responsible for the BC patient care. Furthermore, in Brazil, most centers do not have all the specialties required for adequate screening, diagnosis, and BC treatment available in-house, and most professionals are not specifically dedicated or specialized in BC. This situation raises problems in the interaction among professionals. Details that would be critical for the diagnosis and management of a specific case may sometimes go unnoticed. Lack of integration among the multidisciplinary team involved in the BC diagnosis can result in misinterpretation of results and loss of important information.

Genetic counseling

Genetic counseling should be provided promptly to all early-onset BC patients, those that are triple negative before age 60 and those with a significant family history of cancer.23 The presence of pathogenic variants in high- and moderate penetrance genes may provide important insights and help surgical management decisions and overall management approaches.

21,22
However, there is a reduced number of trained professionals in Brazil to address current genetic counseling needs. Adequate training of health professionals in genetic counseling and oncogenetics is essential to provide a better care.

**Recommendations for the current scenario**

The ideal scenario for a rapid and accurate BC diagnosis in Brazil requires significant improvement in the education of the general population and the development of an effective screening program distributed throughout all regions of the country. Education includes the awareness that BC is a serious problem that must be diagnosed early and treated by specialized professionals in properly qualified centers. Although one of the experts raised the issue that the majority of mammography equipment in the country can be considered outdated or non-functional and suggested replacement with more modern and digital equipment, most experts agreed that before creating centers with the latest technology, it is necessary to improve access to currently available equipment and improving the number of women undergoing exams in a timely manner.

The experts also indicated that the multidisciplinary team involved in BC diagnosis should be properly trained to deal specifically with the disease. Guidelines need to be defined to standardize diagnostic procedures. Finally, the experts suggested that large centers specialized in BC should be created with specialized multidisciplinary teams to lead the treatment of BC patients in all Brazilian states. However, the multidisciplinary professionals should exchange information by phone or video call as alternatives, until these centers become a reality in Brazil. Multidisciplinary discussions should ensure that dubious exams are analyzed from different perspectives and specialties. Furthermore, part of this interaction should also include the creation of a simple and informative online platform that can disseminate information prospectively about the approaches to BC being undertaken across Brazil. Table 2 gives a brief summary of this session.

**Table 2. Main points raised by the experts regarding BC diagnosis**

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<tr>
<td>BC diagnosis should be early and accurate</td>
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<td>Sixty percent of BCs cases in Brazil are diagnosed at later stages [2]</td>
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<tr>
<td>BC diagnosis health team: gynecologist, breast cancer surgeon, clinical oncologist, radiologist, pathologist, clinical geneticist, psychologist, and nurse</td>
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<tr>
<td>The main source of pathology diagnostic errors occurs in the pre-analytical phase, when excision specimens are obtained remotely from the grossing laboratory, including transport, fixation, and storage before tissue processing</td>
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<tr>
<td>Difficulty in integrating the multidisciplinary team, involved in the BC diagnosis, can result in misinterpretations of results and loss of important information</td>
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**Therapeutic planning of patients with early breast cancer**

**Introduction and overall strategies**

Early stage BC is a highly curable disease. Broadly, tumours can be subdivided into four subtypes: (1) luminal A-like subtype; (2) luminal B-like subtype; (3) triple-negative subtype; and (4) HER2-positive subtype. Guideline recommendations clearly indicate that patients should be managed in specialized breast centers by a trained multidisciplinary team.

The breast cancer surgeon and the oncologist are the main decision-makers in the early stage of BC; nevertheless, other specialists also have important roles in the treatment discussion. The participation of (1) breast cancer surgeons, (2) plastic surgeons, (3) radiation oncologists, (4) clinical oncologists, (5) radiologists, (6) nuclear medicine physicians, (7) clinical geneticists, (8) psychologists and (9) nurses is essential to ensure quality care for women with eBC.

The therapy of BC should be individualized and depends on the precise extension of the tumour. According to the experts, in non-palpable lesions, the correct diagnostic and therapeutic definition initially relies on the interaction between the radiologist, the nuclear medicine physician and the breast cancer surgeon. Image-guided localization should be performed. At this point, sentinel lymph node biopsy (SNB) should be planned by the breast cancer surgeon and the nuclear medicine physician. The latter, however, is not available in most Brazilian medical centers. In fact, according to the Brazilian Society of Nuclear Medicine, there are fewer than 300 registered professionals in Brazil, and in some states, there are no specialists at all.

In this scenario, patent blue dye should be used for SNB. Meanwhile, triple-negative tumours or initial HER2-positive tumours are potential candidates for treatment with neoadjuvant chemotherapy (NACT). Importantly, a multidisciplinary meeting is essential to define the best treatment for each case. Tumours should be clipped before systemic therapy to facilitate localization at the time of surgery and after neoadjuvant treatment.
Radiation therapy situation in Brazil

Radiation therapy (RT) is an important component of eBC treatment because it reduces local/regional recurrence and improves BC mortality for patients after breast conservation and for node positive patients after mastectomy, respectively. Unfortunately, there are not enough radiation machines to address the demand in Brazil. According to the World Health Organization (WHO), there is a need for one linear accelerator for every 300,000 individuals. Even accounting for a young demographic distribution, there are parts of Brazil with one machine for every 1,000,000 people or more. Approximately only half of the machines needed are available, and sadly, half of those will be obsolete by 2021 (i.e., over 15 years old and no longer subject to maintenance programs by the manufacturer). Human resources are also scarce but still adequate for the underserved machine infrastructure. There are 738 registered radiation oncologists in the Federal Council of Medicine (CFM) and 426 certified by the National Nuclear Energy Commission (CNEN). Overall, there are approximately 550 to 600 physicians directly working in the 242 radiotherapy departments in the country. Approximately 30 to 35% of patients treated by radiation oncologists have BC, emphasizing the need for constant interaction between the breast cancer surgeon, the clinical oncologist and the radiation oncologist.

Genetic counseling

Genetic counseling followed by molecular testing for genes that predispose to breast cancer, regardless of tumour histopathology, were considered by the experts as important steps in eBC diagnosis and treatment. However, as clinical geneticists in Brazil are scarce and cannot fulfill the current needs, alternative models of providing minimum information to patients required before testing should be sought.

Physician-patient communication

Streamlined education provided by the medical oncologist and/or breast surgeon are important in informing and treating the patient. In this way, the process is somehow abbreviated allowing the patient and physician to make initial treatment decisions (i.e. extension of the initial surgery). Nevertheless, it is important that questions regarding cancer predisposition and its consequence on patient management be discussed at some point with a clinical geneticist, a breast cancer surgeon, and the clinical oncologist.

Multidisciplinary team involvement

In this stage of the patient journey as well, the experts also noted that lack of communication between the members of the professional health team involved in eBC management can result in inappropriate therapy. In an ideal scenario, multidisciplinary meetings should be held at least once a week. Complicated cases or those difficult to diagnose or treat should always be highlighted and discussed. This interaction enhances knowledge, educates, and allows an exchange of experiences between all professionals involved. The experts believe that a multidisciplinary approach can improve the diagnosis, the treatment, and consequently, the prognosis of BC patients. However, these discussions and decisions need to be made in a timely manner. As face-to-face meetings with the entire multidisciplinary team are not always feasible, the experts suggested that communications be as practical as possible using the virtual tools currently available as an alternative. Additionally, it would be interesting if the discussions of the multidisciplinary meetings could address potentially available research protocols and address guidelines published via online platforms and be made available to other physicians. This practice is common abroad and should be stimulated in Brazil. Table 3 gives a brief summary of this session

**Therapeutic planning for patients with metastatic breast cancer**

**Metastatic breast cancer characteristics**

On average about 10% of breast cancer patients have distant metastasis at the time of diagnosis. Furthermore, between 20 and 30% of women with eBC develop metastatic disease that is considered incurable. Currently, less than 5% of patients survive long term. In some cases, the idea of mBC as a chronic disease that remains under clinical control by a long time with sequential therapies is a realistic expectation.

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**Table 3. Main points raised by the experts regarding eBC**

- Early detected BC has excellent chances of cure
- The BC surgeon and clinical oncologist are the main decision-makers in the early stage of the disease
- eBC health team: breast cancer surgeon, plastic surgeon, radiation oncologist, clinical oncologist, radiologist, nuclear medicine physician, pathologist, clinical geneticist, psychologist, and nurse
- There are not enough radiotherapy machines to treat all the demand in Brazil
- Lack of communication between the professional health team members can result in inappropriate therapy
The therapeutic objectives for mBC are palliation of symptoms and maintenance of the patient’s quality of life. Based on that, the experts indicated that (1) palliative care physicians, (2) clinical oncologists, (3) radiation oncologists, (4) clinical geneticists, (5) pathologists, and (6) general surgeons should be mainly involved at this point of the patient’s journey. Therapy principles are generally more individualized in mBC than in eBC, as patients differ regarding preferences, pre-treatments and residual side effects from previous therapies.11,34

Management of metastatic disease

During metastatic disease, delivering the most effective and at the same time the less toxic treatment should be the rule. In the group of patients with expression of hormone receptors, different endocrine therapies should be recommended sequentially. After documentation of endocrine resistance, different chemotherapies initially as combinations in earlier lines and as single agents in later lines is the main treatment strategy. Radiotherapy can have a significant and very positive impact on the patient’s quality of life mainly addressing treatment of painful or symptomatic lesions.

More recently, the identification of patients with oligometastatic disease has spurred treatment plans with a more aggressive combination of approaches that may be warranted as control of the disease and prognosis could be particularly improved in individual patients. An added difficulty in Brazil, is the access to specific drugs or treatments. As many of the new agents take some time to go through the regulatory approval process and are not included in the list of the National Supplementary Health Agency (ANS), many health insurances do not approve their routine use. Is essential that treatment for metastatic disease to be individualized based on the biology of the tumour, prior treatments and the patient's comorbidities. In this regard and in accordance with the previous discussion, mBC treatment should also be addressed with a multidisciplinary team to allow for the best possible prognosis. Additionally, the close relationship between the patient and the main treating physician needs to be considered. The decision-making process and any change in the patient's treatment should include the opinion and experience of the medical team and include patient expectations, family context and previous experiences during the journey. Table 4 gives a brief summary of this session.

Table 4. Main points raised by the experts regarding mBC

| ❖ Main objectives of mBC management are palliation of symptoms and whenever possible, prolongation of life |
| ❖ mBC health team: palliative care physician, clinical oncologist, radiation oncologist, clinical geneticist, pathologist, and surgeon |
| ❖ Palliative radiotherapy can have a positive impact on mBC patient's quality of life |
| ❖ Access to new treatments can be a problem for mBC patients in Brazil |
| ❖ mBC needs to be individualized based on the biology of the tumour, the behavior of the disease and previous treatments |
| ❖ Throughout the patient's journey while dealing with a diagnosis of BC, all decisions should consider current best practices, the experience of all members of the multidisciplinary team and above all, the expectations of an informed patient |

DISCUSSION

BC is the second most prevalent type of cancer in women in Brazil and the mortality rate is still rising. This problem reflects delays in diagnosis and, consequently, in starting treatment. If the patient waits more than three months after the onset of the first symptoms to begin treatment, the survival rate decreases significantly. In Brazil, geographic and socioeconomic factors strongly influence BC patient's journey because delays in patient care varies depending on the region where the patient resides. These discrepancies from one region to another, misdiagnosis, and inadequate treatments, result in less than optimal outcomes. Therefore, this study pursues to recognize the many barriers in the current management process.

Treatment of BC should be individualized, as the clinical course of the disease and survival vary from patient to patient. Factors such as the rate of tumour duplication, the potential for metastasis and immunological, hormonal, and nutritional conditions of the patient can dramatically modify the course of the disease. Therefore, treatment for breast cancer must be carried out by a multidisciplinary team aiming at the comprehensive care of patients. The UK Department of Health made an appropriate definition for these professionals: “a group of people of different healthcare disciplines which meets together at a given time (whether physically in one place or by video or teleconferencing) to discuss a given patient, and who are each able to contribute independently to the diagnostic and treatment decisions about the patient.”
Therefore, it was recommended that in Brazil these meetings occur more frequently so that professionals, from different regions and different specialties, exchange experiences in favor of the patient's better prognosis. This integration of the different professionals involved in BC care was one of the main points of the debate. Face-to-face and weekly discussions with all specialties would be ideal, but in the absence of this possibility, telemedicine should be used as an alternative option, since this practice has been regulated in Brazil since 2002³⁹.

The benefit of a multidisciplinary team is the provision of coordinated, consistent, expert-driven, and cost-effective care to the patient, but is not sufficient without social projects and patient education⁴⁰.

These are important aspects, once the participative and informed patient is essential to obtain the best possible adherence to procedures and treatment demands⁴⁰. More expert meetings, with greater representations of specialists from different regions of the country are recommended for proposing different approaches regarding the diagnosis and treatment of BC patients considering the resources available in each region. It is also recommended that the meeting insights be published to reach the largest possible medical audience. The experts conclude that there is still a lot to be done. The magnitude and importance of the problem and its societal and economic consequences should gather the interest and dedication of all involved to improve the outcomes of BC in Brazil.

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