

Metastatic Breast Cancer Patients: QOL

Subjects: **Oncology**

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Metastatic breast cancer (MBC) remains incurable despite treatment improvements. The health-related quality of life is a multidimensional entity which covers physical, psychological and social dimensions. It is an important outcome particularly in patients with metastatic disease, as the primary goal of therapy is no longer curation, but to provide the best possible quality of life weighted against treatment risks and adverse symptoms. Patient-reported outcomes reflecting the quality of life are usually measured with validated questionnaires to evaluate treatment strategies based on symptom burden and to improve care delivery. This review shares insights into the role of patient-reported outcome measurements in MBC patients and describes the heterogeneity of current questionnaires. We conclude that an up-to-date and standardized outcome set is needed, containing relevant domains referring to individual needs to improve the quality of life assessment among MBC patients. This is a prerequisite to learn about how they could impact the clinical care pathway.

metastatic breast cancer

quality of life

patient reported outcomes

1. Overview

Metastatic breast cancer (MBC) patients are almost always treated to minimize the symptom burden, and to prolong life without a curative intent. Although the prognosis of MBC patients has improved in recent years, the median survival after diagnosis is still only 3 years. Therefore, the health-related quality of life (HRQoL) should play a leading role in making treatment decisions. Heterogeneity in questionnaires used to evaluate the HRQoL in MBC patients complicates the interpretability and comparability of patient-reported outcomes (PROs) globally. In this review, we aimed to provide an overview of PRO instruments used in real-world MBC patients and to discuss important issues in measuring HRQoL. Routinely collecting symptom information using PROs could enhance treatment evaluation and shared decision-making. Standardizing these measures might help to improve the implementation of PROs, and facilitates collecting and sharing data to establish valid comparisons in research. This is a prerequisite to learn about how they could impact the clinical care pathway. In addition, the prognostic value of intensified PRO collection throughout therapy on survival and disease progression is promising. Future perspectives in the field of PROs and MBC are described.

2. Background

Breast cancer is the most common cancer diagnosis among women, with a yearly incidence rate of 47.8 per 100,000 females worldwide that is still gradually increasing ^[1]. The past few years have seen rapid improvements in treatment strategies for breast cancer, both in the area of locoregional and systemic treatment. Although survival

rates of early-stage breast cancer have increased over the last few years [2][3], there remains a group of patients with incurable disease. Globally, metastatic breast cancer (MBC) comprises 5–10% of breast cancer patients at the time of diagnosis, and 20% to 50% of primary breast cancer patients will eventually develop metastatic disease [4][5]. Unsurprisingly, metastases are the worldwide major cause of death in breast cancer patients with a mortality rate of 13.6, resulting in more than half a million deaths in 2020 [6]. The estimated 5-year overall survival in MBC is 27%, which is still particularly poor [7]. However, therapeutic advances have also resulted in better outcomes for MBC patients, such as modest survival improvements, although without a curative intent [5][8][9]. Goals of therapy include diminishing symptoms, delay of disease progression, and prolongation of overall survival with the least negative impact on quality of life as possible [4]. Breast cancer patients face difficult challenges throughout their trajectory of disease, including numerous physical symptoms, emotional distress and impaired daily functioning [8][9]. These physical and psychosocial consequences of breast cancer diagnosis and treatment are reflecting the health-related quality of life (HRQoL), which has been increasingly recognized as an important endpoint in cancer treatment [10][11]. In MBC patients, the disease itself causes quality of life limiting symptoms and together with treatment-related symptoms, the impact on HRQoL may even be more substantial. The recently published Decade Rapport of Cardoso and colleagues showed a decline in overall quality of life in MBC patients over the last decade, based on a quantitative analysis of the EuroQol questionnaire [6]. The authors believe that this is as a result of unmet needs, less support and inconsistency of reported HRQoL data in MBC patients. The HRQoL is typically evaluated by patient-reported outcomes (PRO) and can be assessed by using validated instruments known as patient-reported outcome measurements (PROMs). The use of PROs has been associated with better patient satisfaction, quality of care and health outcomes [12]. While general cancer-related PRO measures have been used in MBC research, often to compare novel treatment strategies, previous studies recommend standardized and disease-specific HRQoL assessment methods [13][14][15]. In MBC patients with a future perspective of living longer with metastatic disease in particular, signaling changes in HRQoL during treatment is of great importance to maintain the quality of life weighed against the treatment benefits and toxicity. This demands a different approach compared to early stage breast cancer patients and emphasizes the need for an up-to-date HRQoL instrument dictated to patients with MBC.

The goal of this review is to describe the current use of questionnaires in real-world MBC patients by providing an overview of the available literature. We will highlight the importance of routinely monitoring appropriate PROs throughout treatment, including the implications and benefits of using PROs in daily clinical practice. This review concludes with opportunities and recommendations for the harmonized approach of HRQoL measurement applicability in MBC patients in clinical breast cancer care.

3. Future Perspectives

In a constantly improving and changing health care system, where patient-centered care is being more prioritized, measuring HRQoL should be a routine clinical assessment. Although many researchers and clinicians agree, a wide variety of questionnaires resulting in different values make it difficult for healthcare professionals to become familiar with PRO data and could also hamper the exchange of information between treating physicians and

disciplines. Particularly in the field of breast cancer research, with major developments in PROs over the last years, the necessity for comparable outcome data is apparent. Yet traditional questionnaires each result in an instrument-specific score that is difficult to compare. One approach to address this challenge is the development of common metrics for the specific outcomes of interest such as fatigue and depression [16][17]. Common metrics are statistical models based on modern test theory (item response theory, IRT), that cover multiple questionnaires and, therefore, allow different questionnaires to be scored on a common scale. However, standardizing outcome sets has also been proven effective and efficient, enabling the comparison of quality of life scores between institutes [13][18].

Some clinicians are concerned about the patient burden due to frequent questionnaire assessments. However, it is likely that intensified surveillance and detection of short-term changes in metastatic disease will require shorter time intervals and more frequent surveys than in early-stage breast cancer patients. For example, in a landmark study evaluating an intensified digital PRO elicitation, Denis et al. defined a time interval of only one week between self-reports during lung cancer treatment [19]. Initiatives such as the EORTC or PROMIS developed IRT-based, construct-specific measurement models and established standardized item banks, offering the prospect of a less burdensome and more valid PRO assessment through tailored short forms and computerized adaptive testing (CAT) [20][21]. CAT describes an assessment of the respective construct (e.g., pain, fatigue, physical functioning) which specifically asks questions deemed most informative based on currently available information. This results in greater precision without extending the test length which might decrease the effort, respectively, the burden, for patients to answer the questionnaires [22]. Even if institutions struggle to implement CAT due to technical prerequisites, an IRT-based standard set for metastatic breast cancer would only need to include the domains of interest rather than specific questionnaires or items. Use of common metrics and construct-specific item-banks would enable comparable data despite different items or instruments.

Another interesting topic is the additional prognostic value of PRO-supported care on survival. Studies have shown an increase in overall survival through intensified HRQoL monitoring using, among others, the EQ-5D and FACT-L [19][23]. In a randomized controlled trial by Basch et al. including 766 metastatic cancer patients, digital PRO assessment for symptom monitoring in the intervention group led to an alert email to the treating center in case of symptom deterioration. The control group received the usual care with symptom monitoring during routine clinical visits only. Patients in the PRO group showed significantly higher HRQoL scores at 6 months after enrollment and overall survival increased by 5 months compared with usual care [23][24]. Moreover, in a study among 121 lung cancer patients taking a similar approach, Denis et al. presented an overall survival of 22.5 months in the PRO group compared to 14.9 months in the control group [19]. Against this backdrop, one can assume that PRO monitoring might facilitate an early detection of symptoms associated with adverse events or disease progression, thus enabling timely countermeasures, which ultimately result in improved overall survival. In addition, a recent meta-analysis of Efficace et al. identified several PRO domains (e.g., fatigue, appetite loss) to be independent predictors for overall survival in metastatic cancer patients [25]. The strongest association was found with physical functioning, showing a 12% increase in risk of death for every 10-point decrease on a scale of 1 to 100. The results underline the importance of baseline measurements and the systematic administration of PROs to also capture prognostic information. However, PROs comprise more than only symptom burden and, apart from possible aforementioned survival benefits, minimizing the physical and psychosocial impact of MBC is important in itself.

Studies performed in MBC patients to identify the optimal patient-centered approach for electronic PRO collection in routine clinical care concluded that physical symptoms or treatment toxicity are not always a priority, but financial concerns or emotional well-being even so, and that PRO collection should be multidimensional [26][27]. The EORTC QoL questionnaires are used frequently in cancer research and the need for an MBC specific questionnaire has not gone unnoticed by the EORTC workgroup. They are currently working on a comprehensive questionnaire for HRQoL assessment in MBC patients, with the aim to conduct phases 1 to 3 of the module development process in the next two years. The European Innovative Medicines Initiatives Funded Health Outcomes Observatory (H2O) project is a recently developed initiative to improve the quality of care by creating 'health outcomes observations', which also aims to collect standardized health data, among which (metastasized) breast cancer.

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