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LEADING ARTICLE

Patient-Reported Outcomes in Geriatric Oncology—Balancing Quality of Life and Therapeutic Effectiveness Using Primary Breast Cancer as a Model

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Abstract

Breast cancer remains the most prevalent cancer worldwide, necessitating advancements in its management. Surgery remains the recommended primary treatment although neoadjuvant or adjuvant treatments, such as chemotherapy, may also be indicated. However, such medications confer a risk of toxicity, often resulting in dose reductions and hospitalisations. This morbidity is particularly pertinent within older patients, for whom their experience of breast cancer is already faced through the lens of unique challenges often including comorbidity, socioeconomic decline and limited support networks. Quality of life (QoL) assessments acknowledge the impact of diagnosis and treatment on patients' psychological, emotional and physical well-being. Multiple tools exist (each with their own strengths and weaknesses) ranging from the more comprehensive [such as the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)] to the more broadly focused [including the General Functional Assessment of Cancer Therapy (FACT-G)]. However, while such tools have existed for some time, there remains a gap in clinical guidance as to their integration, particularly within older patient cohorts. This article seeks to address these complexities in breast cancer decision-making by exploring how QoL assessment can best be utilised inform efficacy-tolerability trade-offs, and subsequently facilitate optimal patient-centred care.

1 Introduction

1.1 Current Landscape of Primary Breast Cancer Management in Older Women

Breast cancer remains a significant challenge to global health as the leading cancer subtype in women both in terms of incidence (over 2.3 million cases annually) and mortality (over 650,000 deaths) globally [1]. This increased incidence has occurred alongside a shift towards older patients being predominantly affected, such that the median age of diagnosis is now 61 years old [2]. Surgery still remains the mainstay of clinical management in primary breast cancer [3], with decision between mastectomy and breast conserving surgery (BCS) dependent upon tumour and patient characteristics and wishes.

The range of neoadjuvant and adjuvant treatment options available for breast cancer has broadened significantly and depends on individual patient, surgical and tumour factors [4]. The aim in the neoadjuvant setting is to down-stage or down-size the tumour prior to surgery, potentially reducing the surgical burden, as well as treating micrometastatic disease to reduce the subsequent recurrence rate [3]. Adjuvant therapy can be composed of either pharmacological treatment (such as chemotherapy, hormone therapy or targeted therapies) or radiotherapy.

Chemotherapy is the backbone of neoadjuvant therapy, and is usually used in higher-risk patient groups with favourable biology, i.e. triple negative breast cancer (TNBC) or human epidermal growth factor receptor (HER)2 positive disease. The principle reason for preventing overprescription of chemotherapy comes with the associated risks of toxicity and adverse reactions—including fatigue, loss of appetite and diarrhoea [5]—which

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Key Points

Multiple tools exist to quantify quality of life in patients with breast cancer, the most common being the EORTC QLQ-C30 (with BR23) and the FACT-G (with FACT-B).

These tools provide valuable data which can inform treatment selection but need to be used repeatedly and interpreted in wider clinical context to maximise validity.

Older patients have a unique experience of breast cancer, and their quality of life is affected differently to that of younger patients.

accounts for up to 48% of those treated needing to reduce their chemotherapy dose and 33% attending hospital for treatment of their side effects [6]. It is for this reason that toxicity calculators, such as those by the Cancer and Aging Research Group (CARG) and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), have been developed, to estimate personalised risk of toxicity prior to commencing treatment. This is particularly pertinent in older patients who are even more susceptible to chemotherapy-induced adverse drug reactions [7], while generally being less likely to achieve pathological complete response compared with their younger counterparts [8].

Molecular profiling of HER2 expression has prompted the development of associated targeted therapies for the 23% of older patients with breast cancer who possess this traditionally challenging subtype [9]. Chiefly amongst these is trastuzumab, a monoclonal antibody as polytherapy alongside chemotherapy in the gold-standard management of HER2-positive tumours [10]. However,these therapies are also beset by troublesome side effect profiles; notably the increased risk of cardiotoxicity, congestive heart failure and opportunistic infections [11].

The majority of patients with breast cancer (82%) demonstrate oestrogen receptor (ER) expression, making them candidates for endocrine therapies [10] which are increasingly used as an alternative to adjuvant chemotherapy. Current guidelines in the UK [12] recommend the use of aromatase inhibitors (which have been shown to be superior to tamoxifen [13]) in post-menopausal ER-positive disease .

Other targeted therapies include cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors and other tyrosine kinase inhibitors (TKIs) [14]; however, there remains a dearth of data pertaining to overall survival.

1.2 Quality of Life Assessment

Clinical research has long since recognised the value of quantitative data when assessing the efficacy and viability of treatments. However, there has been a growing recognition on the value of assessing patient experience particularly amongst those with increase vulnerability [15]. Patient-reported outcome measures (PROMs) have emerged as a means of capturing this experience, as first recognized by the Food and Drug Administration [16].

PROMs offer valuable insight into patient's own perceptions (being unmodulated by clinicians) of both their care and condition [17] and are known to improve levels of satisfaction [18]. Furthermore, it's since been suggested that their integration may improve overall survival in cancer care [19]. PROM analysis also spans between generic domains (such as QoL) and disease-specific domains (such as patient-reported pain levels following breast conserving therapy, for example) [20], offering multidimensional insight into nuanced aspects of patient care.

The profound impact of breast cancer diagnosis and treatment upon a patient's physical, psychological and emotional wellbeing is widely recognised [21]. The need for robust, sensitive tools which quantify and elucidate these ramifications is paramount, and multiple frameworks now exist. However, there is a need to evaluate the clinical utility of these tools and to determine how they can be deployed most pragmatically to maximise their clinical utility.

Likewise, isolated quantitative studies have used these tools to determine trends in patient decision making: we know for example that older patients are more likely to prioritise QoL over curative treatment [22] than their younger counterparts. However, there is a need to synthesise and summarise trends in the PROM data arising from QoL tools to help clinicians better predict the holistic effects of varying adjuvant and neoadjuvant treatments.

The objectives of this review are, primarily, to summarise the most prominent QoL tools currently implemented in clinical practice for breast cancer. Secondarily, to collate data arising from these tools to formulate key trends in older patients' experience of breast cancer therapy. Finally, we aim to formulate a clinical framework to contextualise the use of these tools and interpretation of results.

2 Methods

A broad-scoping review of literature was first performed to explore current approaches to assessing QoL and PROMs in breast cancer. Articles published in peer-reviewed journals were sourced from databases including PubMed and MEDLINE. Keywords, such as 'breast cancer', 'quality of life', 'patient-reported' and 'older' were used to refine the scope to pertinent studies. Publications were then screened for their relevance on the basis of their inclusion of QOL and/or PROM tools in a cancer setting, with greatest emphasis being placed upon those studies which exclusively examined their use in breast cancer.

A list of relevant tools designed for clinical practice was then formulated, with subsequent hand-searching of references allowing for analysis of their respective strengths and vulnerabilities. The primary data from studies reporting the implementation of these tools was then extracted and summarised to provide trends in QoL throughout breast cancer treatment, with a particular focus on older patients.

3 Quality of Life Tools in Breast Cancer

While our literature review found a multitude of different tools used in the context of breast cancer, the most frequently utilised was the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): a 30-item questionnaire used for cancer patients to assess health status, functional status and symptomatology [23]. The breadth of the question set allows for relatively comprehensive analysis of the multiple dimensions of QoL, and it is stratified such that it can be used iteratively throughout a patient's journey to monitor changes over time as they receive treatment. Given its widespread use, it has also been made readily accessible in multiple languages and has an associated electronic version of the questionnaire, which has shown good concordance with the paper-based version [24]. However, the exhaustive nature of the questions set may pose challenges to responders, especially if they are particularly symptomatic at the time of assessment, leading to responder fatigue or attrition. However, this duration is significantly reduced if using the app version [25]. Furthermore, whilst it is designed specifically for cancer patients the broad focus on cancer generally may limit the sensitivity of the tool for detecting changes in patient-reported outcomes specifically associated with breast cancer.

It is for this reason that the EORTC produced an addendum to the QLQ-C30: the EORTC QLQ-BR23 [26]. This 23-item questionnaire was designed exclusively for use with patients with breast cancer and complements the QLQ-C30 by exploring more nuanced areas of the patient experience specifically in breast cancer. However, proper procedure requires that it be performed alongside the broader QLQ-C30, potentially consolidating the issues posed by the overall length of the questionnaire.

Another tool which we found to be commonly used is the Functional Assessment of Cancer Therapy General (FACT-G) questionnaire. This is a 27-item questionnaire assessing the physical, social, emotional and functional well-being of a patient [27]. While initially designed for use in patients with cancer, it is applicable to all chronic illnesses. It is also shorter, requiring less time to complete than the EORTC QLQ-C30. Furthermore, the questions themselves are designed to be intuitive, allowing for greater ease of reply and scoring. However, similarly, to the QLQ-C30, the lack of specific focus upon breast cancer risks compromising the sensitivity of the tool, to combat this another breast cancer-specific addendum has been produced: FACT-B. This addendum explores areas, such as body image, sexual function and arm pain [28]. However, it also requires completion of the general FACT-G prior, and its comparative lesser use globally may result in reduced clinician familiarity when compared with the EORTC tools.

Other tools used in literature for the assessment of QoL in breast cancer include general questionnaires, such as the 36-item Short Form Survey (SF-36) [29] and EuroQol Five Dimension (EQ-5D) [30]: neither of these are cancer-specific, but rather assess physical and emotional domains for any patient with greater and lesser levels of comprehensiveness respectively. These are particularly effective for directly comparing the effect of various treatments upon QoL. For example, the application of chemotherapy is known to induce significant reductions in SF-36 across multiple cancer types [31] while radiotherapy used in breast cancer has a far less deleterious effect upon SF-26 scores [32].

Alongside these questionnaire tools, it is also important to consider both the subjective and objective assessments often performed by clinicians to determine functional status and general wellbeing. Frailty tools, such as the Eastern Cooperative Oncology Group Performance Status (ECOG PS), and the Rockwood Clinical Frailty Score (CFS), have been shown to indicate overall prognosis [33, 34], and can be used to ascertain the ability of a patient to tolerate increasingly toxic treatment formulations (Table 1).

4 Older Patient's Experience of Breast Cancer: Trends in Quality of Life

One of the most extensive papers on the topic of patient experience in breast cancer is the review by Montazeri et al. [22]; reviewing all pertinent literature dating back to 1974, when the first study investigating QoL in breast cancer was published [35]. While the 477 publications derived from literature search were not exclusive to older women specifically, common themes across patient age groups were noted when comparing the initial reaction to their new diagnosis, including distress and anxiety and depression. These feelings were often noted to persist for years after the initial diagnosis [22]. This assortment of shock and fear was termed

Table 1 Summary of the various QoL tools used in the clinical setting of primary breast cancer

Tool	References	Breast cancer-specific?	Number of items	Domains
EORTC-QLQ30	[23]	Yes, BR23 subset	53 (when combining EORTC QLQ C-30 and BR23)	Physical, emotional, social, role and cognitive
FACT-G	[27]	Yest, FACT-B subset	36 (when combining FACT-G and FACT-B)	Physical, emotional, social, functional
SF-36	[29]	No	36	Physical functioning, physical limitations, pain, energy, perceptions, social, emotional and mental.
EQ5D	[30]	No	6	Mobility, self-care, usual activities, pain, anxiety/depression

'high threat' emotions by Kendida et al., and encompassed trepidation about the future [22]. Perhaps unsurprisingly, the locus of fear varied depending on the nature of the diagnosis: Patients diagnosed with metastatic disease feared more about their own survival and the impact on their (and their family's) future, meanwhile those suffering from non-metastatic disease were primarily concerned about the process of adjusting to their new cancer diagnosis, and the knock-on effect on social interaction [36].

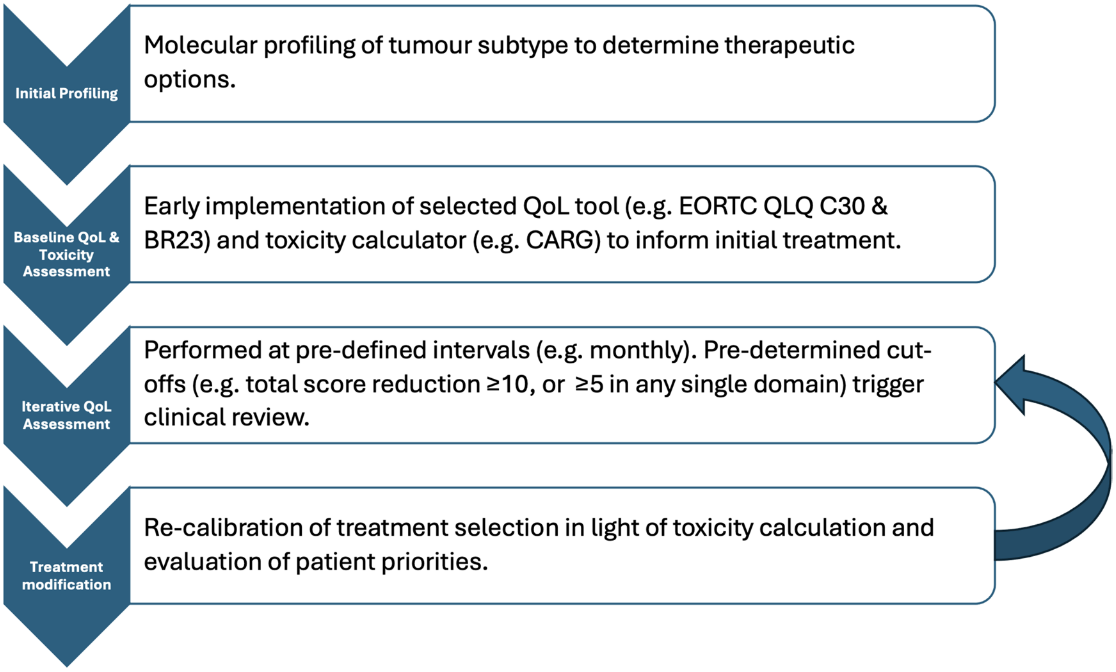
Studies have shown that breast cancer symptoms which presented the greatest imposition upon QoL were pain (either in the chest or arm), fatigue [22] and insomnia [37], although it should be expected that there is a wide discrepancy in terms of symptom severity from any one patient to another, particularly in older subsets whereby longstanding comorbidities could result in different pain reports [38].

At the point of choosing between management options, it emerges that there is some variability between age groups: It was found that older patients were more likely to opt for less invasive or disruptive interventions (or even decline treatment altogether) [39] compared with younger patients who were more likely to seek out more extensive treatment. Furthermore, this trend was not only seen when considering chronological age, but rather it also depended upon the subjective progression through the different 'stages of life', suggesting that one's treatment priorities change with age and perceived age [39]. This finding further identifies the necessity to measure PROMs iteratively throughout the patient journey, to ensure that their 'stage of life' is reflected in the information we are gathering as clinicians.

As mentioned above, the conventional wisdom within therapeutics is that chemotherapy induces significantly worse patient-related outcomes from the perspective of QoL compared with endocrine therapy [22]; however, direct comparisons between the two are unreliable given the different clinical settings within which the two are utilised. Notwithstanding, it was found that the negative effect upon patient-reported outcomes pertaining to sexual function were significantly greatest amongst those receiving chemotherapy, irrespective of the surgical approach that had been taken in each case [22]. This finding was more significant in the younger population; however, the trend did also occur in older patients (for whom sexual dysfunction may be under-reported). One study, however, has challenged this conventional wisdom: Ferreira et al. used EORTC QLQ-C30 and BR23 scores to determine that breast cancer treatment generally had a negative impact on QoL at 2 years after diagnosis. However, patients receiving chemotherapy tended to recover their QoL after this point, meanwhile those on endocrine therapy continued to have a negative impact upon C30 scores after this point [40]. The effect was also most evident in the older post-menopausal population. This highlights the necessity for adequate patient selection to ensure those exposed to a particular therapy are best suited to respond with minimal risk to their QoL.

One must also consider the numerous variables which have been shown to modulate the subjective perception of QoL. Support structures including strong family units are known to mitigate some of the harmful impact of the diagnostic and treatment journey; however, patients with young families tend to have greater trepidation about their ability to make future events and engagements depending on their prognosis [36]. From a sociological perspective, perceived economic burden has a strong statistically significant effect upon QoL scores. Those who feel they are most economically vulnerable are more likely to suffer from worse QoL outcomes during their breast cancer journey than those who are less financially challenged, even if their initial prognosis and management is similar [41]. Both of these should be considered in the context of age, whereby the oldest subset of patients may be more likely to consider themselves more socially isolated, economically vulnerable and reliant upon others when it comes to performing basic activities of daily living or requiring care assistance.

Breast cancer treatment options, however, generally involve frequent hospital stays and clinic visits, and must fit with the other self-care tasks, medication regimens and recommendations for the management of chronic conditions that might co-occur with breast cancer, as multimorbidity increases following breast cancer diagnosis [42]. In this



Molecular profiling of tumour subtype to determine therapeutic options.

Early implementation of selected QoL tool (e.g. EORTC QLQ C30 & BR23) and toxicity calculator (e.g. CARG) to inform initial treatment.

Performed at pre-defined intervals (e.g. monthly). Pre-determined cut-offs (e.g. total score reduction ≥10, or ≥5 in any single domain) trigger clinical review.

Re-calibration of treatment selection in light of toxicity calculation and evaluation of patient priorities.

Fig. 1 Proposed clinical framework for the adoption of QOL tools into breast cancer clinical practice

patient population the degree of burden of treatment (different than illness burden), which consists of the interaction with the health system, negotiating conflicting information about symptoms and treatments, adapting recommendations into daily routines, managing medications, relying on supportive services and resolving trade-offs, is unknown. Adverse health outcomes during breast cancer care can result from these burdens and often time these impact the overall QoL [43]. Few studies address if management of multiple chronic conditions leads to higher treatment burden during breast cancer care.

Finally, when considering the impact of physical symptoms and/or side effects may have on a patient, it is prudent to consider the burden of comorbidities often associated with older patients. This may mean that phenomena, which may not have posed any great difficulty in isolation, have a more negative effect when considered in the wider context of the cumulative toll imposed by multiple pathologies. Furthermore, the effect of polypharmacy has the potential to exacerbate many perceived symptoms, serving only to obscure the real source of the morbidity experienced by the patient.

5 Clinical Interpretation of Patient-Reported Outcome Measures

While the vast array of tools available to assess QoL in breast cancer provide extensive data to elucidate the patient experience throughout treatment, there remains a comparative lack of guidance on translating these results into actionable clinical decisions, with much emphasis still placed upon individual clinician instinct. Furthermore, the substantial variability in the magnitude of score changes in the EORTC-QLQ30 which various clinicians would deem to be 'clinically significant' has been demonstrated by Cocks et al. [44], who also went on to propose objective guidelines to define cut-offs for the minimally clinically important difference (MCID); providing a framework for determining if dynamic changes to QoL are defined as small, medium or large [44].

Secondly, there remains little consensus as to how often, and at what points during treatment these tools should be utilised. Kotronoulas et al.'s review of QoL assessment in clinical practice supported the iterative use of such tools, and found that their implementation in a longitudinal manner allowed for greater analysis of symptom-related PROMS [45].

Finally, it is important to consider QoL tools in the context of predictive frameworks including toxicity calculators (such as CARG and CRASH) rather than in isolation [46]. By integrating them in this manner, it allows clinicians to make better baseline assessment of prospective treatment options, and form more informed management plans on the basis of predictive rather than just reactive data.

We propose the formulation of a clinical framework that encapsulates defined timepoints for QoL assessment from the outset, defined cut-offs which would trigger a clinical review and integration of toxicity calculators to pre-emptively inform any proposed modifications to the therapeutic plan as below (Fig. 1)

6 Summary and Future Directions

The landscape of breast cancer management is ever evolving. The increasing range of therapeutic options will be associated with a new range of side-effects which are likely to disproportionately impact the older population. The importance of making regular, accurate assessment of QoL in light of this is vital to inform clinical decision-making, and a variety of tools exist to facilitate this.

In the future, it is hoped that the current trend towards producing increasingly specific tools aimed at measuring QoL in breast cancer continues and allows us to fully represent and recognise the nuanced impacts within this patient group. Concurrently, the increased uptake of genomic tools into mainstream clinical practice, such as Oncotype Dx [47], has the potential to improve the specificity of patient populations recommended for more intensive treatments, such as chemotherapy, therefore reducing the number exposed to unnecessary treatment [48].

Declarations

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