Research, Clinical Trials and Evidence-Based Medicine for Older Patients with Breast Cancer

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M. E. Hamaker and N. A. de Glas

Abstract

Evidence-based treatment is the golden standard of current oncology care. Treatment guidelines are developed by gathering, weighing and summarizing all available scientific research, and subsequent treatment recommendations are used to formulate criteria to assess, compare and improve quality of care. Older patients often require tailoring of care, which can conflict with the intrinsic rigidity of guidelines and quality criteria that focus primarily on optimal disease treatment, without taking the heterogeneity of an ageing cancer population into account. Although it is worthwhile to strive for evidence-based treatment in older patients, several important issues in current scientific research and treatment guidelines can limit their applicability to the older patient population. These issues include external validity of clinical trials, trial participation, confounding by indication in observational research and relevant patient-related outcome measures for older patients.

Keywords

Research · Evidence based medicine · Internal and external validity · Clinical trials · Observational studies · Patient-related outcome measures

M. E. Hamaker (✉)
Department of Geriatric Medicine, Diakonessenhuis, Utrecht, The Netherlands
e-mail: mhamaker@diakhuis.nl

N. A. de Glas
Department of Oncology, Leiden University Medical Centre, Leiden, The Netherlands

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Evidence-based treatment is the golden standard of current oncology care. Treatment guidelines are developed by gathering, weighing and summarizing all available scientific research, and subsequent treatment recommendations are used to formulate criteria to assess, compare and improve quality of care. Older patients often require tailoring of care, which can conflict with the intrinsic rigidity of guidelines and quality criteria that focus primarily on optimal disease treatment, without taking the heterogeneity of an ageing cancer population into account. Although it is worthwhile to strive for evidence-based treatment in older patients, several important issues in current scientific research and treatment guidelines can limit their applicability to the older patient population. These issues, which include external validity of clinical trials, trial participation, confounding by indication in observational research and relevant patient-related outcome measures for older patients, are discussed in this chapter.

16.1 Internal Versus External Validity

Internal and external validity are key terms when assessing the quality of a clinical trial. Internal validity is the extent to which the observed effects are true for the study participants [1]. It can be negatively affected by a non-randomized method of treatment allocation, lack of blinding, loss to follow-up and other issues that will not be further discussed in this chapter. One of the best ways to improve the internal validity is by performing a double blind randomized controlled trial (RCT) [1]. An RCT demonstrates what can be achieved with careful observation and under certain restrictions [2]. This is not the same as demonstrating what can be achieved in daily practice, since this is also affected by external validity [3].

External validity is the extent to which the results of a study are a true reflection of what can be expected in the target population, irrespective of the study population [1]. Often, internal and external validity are at conflict: measures taken to improve internal validity, such as patient selection through in- and exclusion criteria, can limit the generalizability of a trial [3].

16.2 Trial Participation of Older Patients

The study population of a clinical trial strongly affects the applicability of trial results for the general population of older patients. To allow for generalisation of trial results, the study population should resemble patients seen in daily clinical practice [4]. Thus, to obtain evidence on cancer treatment for older patients, it is important that these patients participate in clinical trials.

However, in- and exclusion criteria can be overly exclusive of older patients. These patients are often excluded based on age itself or on the basis of comorbidity, which is highly prevalent among older patients [3, 5–8]. In a review of 41 studies of the National Institutes of Health in the United States, 73% of patients with a specific disease did not meet the inclusion criteria and were excluded from trial participation

[9]. In another study that assessed 109 clinical trials from five major medical journals, 20% of all studies excluded patients above a specific age. In addition, nearly half of these studies used criteria that disproportionally excluded older patients [5]. Hence, improving evidence for older patients with breast cancer is only possible if researchers make their trials as inclusive as possible [10].

Even when researchers aim to include older subjects and use adapted in- and exclusion criteria to achieve this goal, patient populations may end up being highly selected [3, 5, 11], and there are often difficulties recruiting and maintaining older patients in research projects. Doctors appear reticent in suggesting a clinical trial to older patients, even if a suitable study is available [12–14]. For example, in a questionnaire, 50% of oncologists reported considering patients above a certain age not suited for clinical trial participation [13]. As a result, in clinical trials focusing on diseases that are not age-specific, only 9% of participants is older than 65 years, and 1% older than 75 years [15]. Interestingly, elderly patients are even underrepresented in studies investigating methodology of research and opportunities for improving trial participation [16].

An important reason for excluding older patients is that comorbidity - as a competing cause of death - and limitations in the ability to tolerate treatment may result in less significant treatment effects compared to a younger, healthier population [17]. Although this could appear to be a valid argument on one hand, it also underlines the importance of trial participation for older patients since this limits the applicability of trial results for the general older population.

16.3 External Validity in (Breast) Cancer Trials

There are few studies assessing the external validity of breast cancer trials. One study compared the participants of the randomized, double-blind TEAM-trial that assessed adjuvant hormonal therapy in postmenopausal breast cancer patients, with unselected breast cancer patients of corresponding age. The study showed that even when the in- and exclusion criteria of the trial were applied to the general population, trial participants had fewer comorbid diseases, a higher socioeconomic status and smaller tumours (all $p < 0.01$). A hazard ratio for mortality of 1.39 was found (95% confidence interval 1.05–1.82, $p = 0.02$) in favour of the trial patients. Thus, the patients in this trial did not adequately reflect the average older breast cancer patients, negatively affecting the external validity of this trial [11].

More data is available from other cancer types. For example, the Dutch CAIRO study assessed the effect of various types of chemotherapy in patients with metastatic colon cancer [4]. The results of this trial were subsequently compared to patients receiving the same treatment, who had not participated in the trial. In this comparison, patients who fulfilled the inclusion criteria but did not participate, achieved similar benefits as trial patients. However, non-eligible non-participants had significantly poorer results, with a hazard ratio for mortality of 1.70 (95% confidence interval 1.33–2.17, $p < 0.01$) [4]. A similar result was seen in a Norwegian

study in patients with metastatic colorectal cancer: trial patients had a 40% longer survival than non-trial patients receiving the same treatment [18].

While much research is done regarding the interval validity of RCTs and systematic reviews, external validity is addressed much less frequently [3]. For example, when assessing new drugs, agencies such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) do not require evidence that a new drug achieves a clinically meaningful effect or that the study population of registration studies is a good reflection of daily clinical practice [3].

Critically evaluating the extent to which the study population is similar to the target population treated in daily practice is only possible if key baseline characteristics of the participants in studies are recorded and reported. For older patients, these should include cognitive and physical function (such as capacity for performing (instrumental) activities of daily living), comorbidities and their treatment, and frailty [16]. The International Society for Geriatric Oncology, The Alliance and the European Organization for Research and Treatment of Cancer therefore recommend that all studies in oncology report baseline characteristics including a detailed age distribution and geriatric parameters [19]. Unfortunately, these data are often not reported. For example, in a systematic review assessing a random sample of 300 RCTs published in 2012, only a minority of studies specifically addressing older patients reported on physical (22% of studies) and mental functioning (14%) of study participants [20]. As a result, it remains unclear to which patients the study results are applicable.

In addition, for practical reasons, secondary publication such as meta-analyses and treatment guidelines require summarizing of study protocols. Along the way, vital information on patient selection is often lost, making a comparison of the trial population with the real-life patient in the consulting room even more difficult [3].

16.4 Validity of Observational Studies

An alternative to clinical trials for improving the evidence in treating older patients with breast cancer is using observational data. However, there is an important limitation of observational research in which two treatments are compared that influences the validity. In observational studies, treatment of patients is allocated by physician's judgement instead of randomization. There are always specific reasons that determine why a patient receives a specific treatment, resulting in the phenomenon of "confounding by indication" in observational studies [21]. For example, older patients with breast cancer who receive chemotherapy are relatively more "fit" and have less geriatric deficits than patients in whom chemotherapy is omitted, as is highly understandable. Thus, poorer outcome could be due to the a priori fitness of patients, rather than the chemotherapy or omission thereof. On the other hand, patients with more aggressive disease often receive more aggressive treatment (for example chemotherapy). Poorer outcome could therefore be the result of tumour characteristics rather than treatment choice. These two examples both result in bias

in observational studies, since differences in outcome could be incorrectly attributed to treatment choice rather than the patient or tumour characteristics that affected treatment choice. Although it is possible to adjust for some of these so-called confounders, there are always many factors that are unmeasured and cannot be adjusted for. Even using the concept of a propensity score, which could be seen as an average of all measured confounders, does not solve the problem of unmeasured (so-called residual) confounders.

A recent systematic review showed that of all observational breast cancer studies in older patients that were published between 2009 and 2013, 71% directly compared two treatments thereby resulting in confounding by indication [22]. Hence, there is a large proportion of studies that is currently performed and published using invalid statistical methods.

In the remaining 29%, some form of instrumental variable was used. This is a methodologically valid alternatives for circumventing confounding by indication. An instrumental variable is a factor that is associated with treatment allocation, but not with the outcome [23]. Examples of instrumental variables can be geographical region, country or time-period [22, 24]. Important conditions that must be met in order to use an instrumental variable, are that it must determine treatment allocation and cannot be associated with the outcome through any other way than through the difference in treatment. Hence, patient populations must be comparable, access to health care systems should be similar, etcetera. It has been shown that by using a (valid) instrumental variable, it is possible to approach the validity that is reached in a randomized clinical trial [25].

As an example, the EURECCA project compares outcome of treatment in European countries using population-based cancer registries [26]. Because of the limited evidence, there are large differences in current treatment strategies within, and between countries, which enables researchers to compare the effects of these differences on long-term outcomes [27, 28].

16.5 Validity of Prognostic Models in Older Patients with Breast Cancer

The issue of external validity is also highly relevant to prognostic models used in breast cancer care. There are many such models available, that can be used to calculate outcomes such as overall survival, breast-cancer survival and recurrence-risk [29]. Some models also incorporate expected benefits of treatment and can be used to counsel patients in clinical decision making. Here, we give an overview of the validity for older patients of the most commonly used prognostic models in breast cancer.

First, there are several clinical prognostic models available in breast cancer. Until it went offline in 2016, the most well-known and frequently used prognostic model in breast cancer is Adjuvant! Online [30]. This model was developed in a large dataset that was extracted from the SEER-database and included patients aged 36 to 69 years that who were diagnosed with breast cancer between 1988 and 1992 [31]. Hence, the model included no patients aged 70 years and older. Although the model

performed well in external validation studies of several populations [32, 33], it was recently shown in a large population-based study in the Netherlands that the model is not reliable in patients aged 65 years and older [34]. In particular, the risk of recurrence was strongly overestimated, most likely due to an underestimation of competing mortality. Also, the unstandardized comorbidity score that is used in Adjuvant! Online strongly influenced its predictions.

Alternatively, the PREDICT-tool predicts 5- and 10-year overall survival in patients with breast cancer. This tool was developed in a British cohort and included almost 1800 women aged 65 years and older [35]. It was recently shown that the tool predicts overall survival much better in older patients with breast cancer than Adjuvant! Online [36]. However, it must be noted that the tool does not incorporate comorbidity and only predicts overall survival outcome, which limits the applicability especially in older patients with a high risk of competing mortality.

Older clinical prediction tools include the Nottingham Prognostic Index, OPTIONS and the BC Nomogram. These models were all validated in external cohorts that included only few patients aged 70 years or older, which limits their external validity. This was shown in a recent systematic review that summarized all these validation studies: subgroups aged 76 years and older, and 66–75 years showed the largest differences in observed and predicted values, especially in the validations from the OPTIONS tool and BC Nomogram [29].

Second, there are several genomic profiles available in breast cancer, of which MammaPrint and Oncotype Dx are the most well-known. MammaPrint was developed in a Dutch cohort and includes patients with breast cancer with a maximum age of 70 years [37]. Validation studies only included very small numbers of patients aged 70 years and older [29, 38]. Oncotype Dx was developed in a cohort that included 300 patients aged 60 years and older, more detailed age distribution is not described. This profile was validated in several external cohorts, in which again only small numbers of older patients were described [29, 39, 40]. The largest validation study included 411 patients aged 70 years and older but did not report specific performance of the genomic profile in this subgroup [41].

Third, geriatric assessment parameters such as physical functioning, cognition and nutritional status have been shown to be highly predictive for toxicity of chemotherapy in older patients with cancer [42]. Two tools have been developed specifically for predicting grade III toxicity or higher in older patients: the CRASH-score (Chemotherapy Risk Assessment Scale for High-Age Patients), which predicts haematological and non-haematological toxicity [43], and the Cancer and Ageing Research Group (CARG) Score, which predicts overall grade III or higher toxicity [44, 45]. These tools are not breast cancer-specific but can aid in the selection of patients who are fit enough to undergo chemotherapy.

Geriatric parameters are also predictive of prognosis (irrespective of cancer-related prognosis) in older patients. Many of the available instruments for estimating survival can be found on the Eprognosis-website, including a range of time scales (6 months to 10 years) and settings (community-dwelling, nursing home, hospital) [46, 47]. However, these have generally not been developed or validated specifically in (older) patients with cancer.

16.6 Patient-Related Outcome Measures

A final issue to address when assessing the value of current evidence for decision making in older breast cancer patients, are patient-related outcome measures. While simple clinical outcomes are often easiest to assess objectively, these may not necessarily be a good reflection of a patient's priorities [3]. Both the FDA and the EMA emphasize the importance of including the patients' perspective when evaluating the outcome of oncologic treatment [48].

Several studies have demonstrated that patients and doctors have different priorities when it comes to treatment outcomes. A study among 350 breast cancer patients demonstrated that they gave higher priority to patient-related outcome measures than to clinical outcomes such as survival [49]. Other studies showed that while doctors focussed more on the physical effects of treatment, patients gave the highest priority to their mental health, emotional well-being, general health and vitality [50, 51]. Older patients were shown to be as willing to receive life-prolonging chemotherapy as younger patients [52], but less accepting of toxicity [53], particularly when this could affect their independence, cognitive functioning or social situation [19, 54, 55].

When weighing various treatment options, information regarding the effect of the treatment on the patient is as important as tumour effect. However, the majority of oncology studies still focus primarily on clinical outcomes such as survival, progression-free survival and toxicity [56, 57]. In an overview of 463 current breast cancer trials listed in the National Institutes of Health clinical trial registry – by far the largest registry in the world – only 20% included any patient-related endpoint, primarily quality of life. Functional status or cognitive functioning were included in less than 5% of studies [58]. In addition, results with regards to quality of life often remain unpublished: in an analysis of 201 phase III trials in poor prognosis malignancies, less than half of studies that assessed quality of life, incorporated these results in trial publications [59]. Studies addressing both quality of life and prolongation of life generally base their overall conclusions on the survival results, even when quality of life results demonstrated an opposite pattern of benefit between treatment arms [60, 61]. Particularly when the primary trial results are negative, the results regarding quality of life appear to be considered irrelevant in terms of selecting from available options. Thus, despite their importance to decision making in older cancer patients, patient-related outcome measures are insufficiently considered in current research.

16.7 Conclusion

The need for tailored care in older cancer patients is increasingly acknowledged. However, making specific treatment recommendations for this patient population in clinical guidelines or based on prognostic models is difficult due to insufficient participation of older patients in clinical trials, affecting external validity. In addition, observational data are often affected by confounding by indication and

Table 16.1 Recommendations for clinical trial design and observational studies in older patients

Subject	Recommendation
Clinical trials	Geriatric assessment to describe population [62] Choose relevant endpoints [51] Consider composite endpoints [51] Use appropriate inclusion criteria (not too stringent) in order to increase enrolment [10] Consider abandoning an upper age limit for trials [10]
Observational studies	Avoid direct comparisons of treatment resulting in confounding by indication [22] Use alternative study designs such as the instrumental variable or studying time trends [22]

outcome measures most relevant to the older population are often not incorporated in research. Table 16.1 summarizes the recommendations from several key (position) papers regarding clinical trial design and observational studies in the older patients with cancer. Without a significant shift in the research agenda and methodology, tailoring of care will remain to be based on expert opinion rather than solid scientific evidence.

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