



Targeted therapy in older women with breast cancer – What's the target?

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Abstract

In this review, the results of the FOCUS (Female breast cancer in the elderly: Optimizing Clinical guidelines USING clinico-pathological and molecular data) program are summarized. This study was originally designed with the aim to define guidelines for the treatment of older women with breast cancer. With data from several studies within FOCUS, a prediction model can be constructed. Such a model helps to define individualized treatment for older patients with breast cancer, taking into account tumour characteristics and patient-related factors. At a clinical level, this model can provide the physician and the patient with accurate prediction to assist on the decision making of treatment strategies: this results into individualized treatment, not based on one individual marker, but on different pillars related to the patient, the tumour and the most suitable, appropriate treatment.

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Introduction

The management of breast cancer among older women is complicated for several reasons. First, there is no specific level one evidence for the treatment of older women with breast cancer.¹ Treatment guidelines are based on clinical trials recruiting in mostly young, otherwise healthy patients. Results from these trials cannot be extrapolated to older individuals.² Second, less is known about the tumour biology in older women. One of the hypotheses is that tumours in elderly behave different than breast tumours in younger women, which can affect treatment efficacy. Third, older women are more likely to suffer from different comorbidities at the time of diagnosis of breast cancer. Fourth, life expectancy is substantially shorter and patients' expectations also differ from the general population.

Finally, the heterogeneity of this population should be taken into account: that older women diagnosed with breast cancer are very heterogeneous. Some are very fit, whilst others are frail. Therefore, some patients can be treated more aggressively, whilst others benefit more from a cautioned treatment strategy.

'The FOCUS study'

With the aim to develop guidelines for the treatment of older women with breast cancer, the FOCUS study was initiated in 2007: "Female breast cancer in the elderly: Optimizing Clinical guidelines USING clinico-pathological and molecular data". The FOCUS database is the largest, most detailed population-based database of older women with breast cancer. Worldwide, no other database of this size included only older women, and gathered this detailed data about the patients, tumour characteristics, treatment and follow-up. In addition to clinical data, tumour tissues of a very large part of the included patients, was collected. The database consists of 3672 consecutive breast cancer

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patients, aged 65 years or older at the time of diagnosis, diagnosed between 1997 and 2004 in the South West region of The Netherlands. In addition to the standard data included in the cancer registry, detailed information was gathered on the tumours' treatment and the occurrence of a recurrence during follow-up. Also, patient-related information was registered, including comorbidity and social economic status.

Within the FOCUS project, also large datasets from (national) cancer registries were shared for research projects. In addition, data from the TEAM trial were used. The Tamoxifen Exemestane Adjuvant Multinational was a large multicentre phase III trial on endocrine therapy. This is one of the few trials without an upper age limit, which results in a relative large number of older participants.

Prognosis

An important early finding from the FOCUS studies is that cancer specific prognosis of women with breast cancer declines with age, independent of tumour and treatment characteristics. This was studied both in the national cancer registry, as well as in the FOCUS cohort and the TEAM trial.^{3–6} The first of these studies, published in 2010, was performed in a large dataset, made available by the Netherlands Cancer Registry. Overall, 127,805 unselected breast cancer patients of all ages were included. Within this database, tumour characteristics, treatment and outcome in terms of relative survival, were compared between different age groups. Interestingly, with increasing age, patients were more likely to be diagnosed with breast cancer in a more advanced tumour stage. The proportion of patients with metastatic (stage IV) disease at the time of diagnosis, increased from 3.7% for patients aged 15–64 years, to 8.5% for the group aged 80–84 years. Regarding treatment, a decline in the performance of surgery was observed with increasing age. The proportion of breast surgery in all tumours, except T4 and M1 tumours, declined from 99.2% among patients younger than 65 years to 41.2% among patients ≥ 90 years. In concordance, the proportion of axillary lymph node surgery declined from 66.2% to 19.9%. In addition, a decrease in the proportion of the provision of any adjuvant systemic treatment was observed with increasing age, but an increase in the proportion of hormonal treatment alone (from 0.8% among patients aged 18–64 years, 47.3% among patients aged ≥ 90 years). Finally, relative survival was calculated for all age groups, which is a measure for breast cancer specific survival. With increasing age, relative survival decreased, indicating an increase in breast cancer deaths.³

A similar study was published in the JAMA in 2012. This study was performed among the participants of the TEAM study ($N = 9766$), who were postmenopausal women with hormone receptor positive breast cancer. The objective was to assess breast cancer specific mortality

among different age groups. Causes of death were well registered in this clinical trial. Data were divided in three age groups: <65 years, 65–74 years and ≥ 75 years. Again, it was shown that older women presented with a more advanced stage (larger tumours, more often node-positive). In line with the previous study, it was shown that treatment strategies were more reluctant among elderly. This was especially observed in the provision of adjuvant chemotherapy: 51.3% among women aged <65 years, 22.9% in the age group 65–74 years and finally, 5.2% among women aged ≥ 75 years. Regarding survival, disease specific mortality was observed to increase with age, from 5% among the youngest group, to 8% among the oldest age group, corresponding with a multivariable hazard ratio (HR) of 1.63 (95% confidence interval 1.23–2.16; $P < 0.001$) (ref: van de Water, JAMA 2012). To investigate this finding further, this study was followed up by a study in the same population (TEAM participants). The objective was to study the incidence of breast cancer recurrences in the three age categories (<65 years, 65–74 years and ≥ 75 years). In this study, it was shown that the risk of locoregional recurrences was similar between the age groups. However, the risk of distant recurrences increased with increasing age: from 8% among the youngest group, to 10% among the oldest age group, corresponding with a multivariable hazard ratio (HR) of 1.39 (95% confidence interval 1.08–1.79; $P = 0.024$).⁴

The analyses of the previous studies were also performed in data from the FOCUS cohort, in which detailed data of follow-up, including the occurrence of recurrences was registered. Patients, all aged 65 years or older, were divided in two age groups: 65–74 years and ≥ 75 years. Five-year relative survival was 91.9% in the younger group, as compared to 84.3% in the oldest group. In this population-based study, there was no association between age and the occurrence of locoregional and distant recurrence, neither of contralateral breast cancer. In a supplementary analysis, in which patients were stratified on the number of comorbidities, it was shown that among the patients with no or only 1 comorbid disease, older patients had a higher risk on developing distant metastases, probably reflecting the longer general life expectancy of this group, and thus, more time to develop a breast cancer recurrence.⁶

In summary, from these studies it was concluded that not only relative survival and breast cancer specific survival declined with age, also, the risk of distant recurrences increased with age, especially among the otherwise healthy older women. There are several possible explanations for these findings. First, there may be intrinsic characteristics of older patients, which could influence prognosis or treatment efficacy. Second, the type and efficacy of treatment for older women can be different, due to under- or over-treatment. A third possible explanation could be tumour behaviour, which was never thoroughly studied among older women with breast cancer.

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