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Original Research

Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial

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Abstract ***Aim:*** Due to increasing life expectancy, patients with breast cancer remain at risk of dying due to breast cancer over a long time. This study aims to assess the impact of age on breast cancer mortality and other cause mortality 10 years after diagnosis.
Methods: Postmenopausal patients with hormone-receptor positive breast cancer were included in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial between 2001 and 2006. Age at diagnosis was categorised as <65 years (n = 3369), 65–74 years (n = 1896) and ≥75 years (n = 854). Breast cancer mortality was assessed considering other cause mortality as competing event using competing risk analysis.
Results: After a median follow-up of 9.8 years (interquartile range 8.0–10.3), cumulative incidence of breast cancer mortality increased with increasing age (age <65 years, 11.7% [95% confidence interval {CI}: 10.2–13.2]; 65–74 years, 12.7% (11.2–14.2) and ≥75 years, 15.6% (13.1–18.0)). Univariate subdistribution hazard ratio (sHR) increased with increasing age (age: 65–74 years, sHR: 1.08, 95% CI: 0.92–1.27 and ≥75 years sHR: 1.30, 95% CI: 1.06–1.58, $P = 0.013$). Multivariable sHR adjusted for tumour and treatment characteristics

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increased with age but did not reach significance (age 65–74 years, sHR: 1.11, 95% CI: 0.94–1.31; ≥75 years, sHR: 1.18, 95% CI: 0.94–1.48, $P = 0.055$).
Conclusion: Ten years after diagnosis, older age at diagnosis is associated with increasing breast cancer mortality in univariate analysis, but it did not reach significance in multivariable analysis. This is not outweighed by a substantially higher other cause mortality with older age. This underlines the need to improve the balance between undertreatment and overtreatment in older patients with breast cancer. The trial was registered in International Trial Databases (ClinicalTrials.gov NCT00279448, NCT00032136, and NCT00036270; the Netherlands Trial Registry NTR267).

1. Introduction

Age is the strongest predictor for the development of breast cancer [1]. Due to ageing of the population, the number of older patients diagnosed with breast cancer is rapidly growing. With increasing life expectancy, older patients remain at the risk of dying because of breast cancer over a longer time period. At the same time, the risk of dying from other causes than breast cancer increases substantially with advancing age [2]. Survival estimates that take these competing causes of death into account are essential for individual decision-making to balance between benefits and toxicities of cancer therapy [3].

As older patients are poorly represented in clinical trials [4], the relation between age at diagnosis and breast cancer mortality was mostly investigated in observational studies, reporting a higher breast cancer mortality with increasing age [5–9]. Due to lack of information on cause of death, most studies use relative survival as a measurement of breast cancer–related survival. The Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial included a large number of older postmenopausal patients and contains reliable information on the cause of death. A previous analysis after 5 years of follow-up observed higher breast cancer mortality with increasing age, despite that increasing age was also associated with a higher proportion of other cause mortality [9].

However, as patients aged greater than 75 years currently have an anticipated life expectancy of 12 years and breast cancer can recur until 20 years after initial diagnosis [10], it is relevant to investigate how breast cancer mortality and other cause mortality compete over a longer time period after breast cancer. Therefore, the aim of this study was to assess the relation between age at diagnosis and breast cancer mortality and other cause mortality 10 years after diagnosis among postmenopausal patients with hormone receptor-positive early breast cancer included in the TEAM trial.

2. Patients and methods

The TEAM study is a randomised controlled trial including postmenopausal patients with nonmetastatic oestrogen and/or progesterone-positive breast cancer. Details of the trial have been extensively described in previous publications [11,12]. In short, patients were included between 2001 and 2006 and randomised to receive exemestane for 5 years or tamoxifen followed by exemestane for a total duration of 5 years. If patients had an Eastern Cooperative Oncology Group (ECOG) performance status higher than two, a previous malignancy with a disease-free interval of fewer than 5 years or significant cardiac or other diseases interfering with study participation they were ineligible. Cause of death was indicated on a case report form and categorised into 10 pre-specified groups (Table 2). Classification of cause of death was verified centrally by the TEAM data center. The database was locked on February 19, 2016 for the study end-points after 10 years of follow-up.

For the current analysis, only patients from countries that completed 10 years of follow-up were included (The Netherlands, Belgium, Luxembourg, United Kingdom, Ireland, Greece and Germany). After 10 years of follow-up, there was no difference in the primary end-point between the two treatment arms [11].

The trial was registered in International Trial Databases (ClinicalTrials.gov NCT00279448, NCT00032136 and NCT00036270; the Netherlands Trial Registry NTR267; Ethics Commission Trial 27/2001 and the University hospital Medical Information Network C000000057). Approvals from ethical committees and written informed consent from all patients were obtained [12].

2.1. Outcomes

For age at diagnosis, patients were categorised into three categories (<65 years [reference group], 65–74 years and ≥75 years) according to the guidelines of the International Society of Geriatric Oncology (SIOG) [13]. Breast cancer mortality was defined as time from randomisation to death due to breast cancer. Deaths that occurred after distant recurrence were defined as death due to breast cancer with other cause mortality as a competing event. Other cause mortality was defined as all other causes of death than breast cancer, and in the analyses, breast