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Breast cancer–related deaths according to grade in ductal carcinoma in situ: A Dutch population–based study on patients diagnosed between 1999 and 2012

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Abstract ***Background:*** The incidence of ductal carcinoma in situ (DCIS) has drastically increased over the past decades. Because DCIS is resected after diagnosis similar to invasive breast cancer, the natural cause and behaviour of DCIS is not well known. We aimed to determine breast cancer–specific survival (BCSS) and overall survival (OS) according to grade in DCIS patients after surgical treatment in the Netherlands.

Patients and methods: All DCIS patients diagnosed between 1999 and 2012 were selected from the Netherlands Cancer Registry. The cause of death was obtained from 'Statistics Netherlands'. BCSS and OS were estimated using multivariable Cox regression in the entire cohort and stratified for grades.

Results: In total, 12,256 patients were included, of whom 1509 (12.3%) presented with grade I, 3675 (30.0%) with grade II, 6064 (49.5%) with grade III and 1008 (8.2%) with an unknown grade. During a median follow-up of 7.8 years, 1138 (9.3%) deaths were observed, and 179 (1.5%) were breast cancer–related. Of these, 10 patients had grade I; 46 grade II; 95 grade

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III and 28 an unknown grade. After adjustment for confounding, grade II and III were related to worse BCSS than grade I with hazard ratios of 1.92 (95% confidence interval [CI]: 0.97–3.81) and 2.14 (95% CI: 1.11–4.12), respectively. No association between grades and OS was observed.

Conclusion: BCSS and OS in DCIS patients were excellent. Because superior rates were observed for low-grade DCIS, it seems justified to investigate whether active surveillance may be a balanced alternative for conventional surgical treatment.

1. Introduction

In the Netherlands, the incidence of ductal carcinoma in situ (DCIS) increased from 338 patients in 1990 to 2422 patients in 2016, initially accounting for 3.9% and nowadays 14.4% of the total number of breast cancer (including DCIS) diagnoses annually [1]. This increase is shown to be primarily a result of the national breast cancer screening program [2–4]. The Netherlands is one of the few countries where women aged 70–75 are also screened, which may lead to a greater number of DCIS diagnoses as compared to other countries. Although DCIS is a precursor for invasive breast cancer, a review that evaluated studies reporting on DCIS patients who were first misclassified as having benign disease and therefore treated with biopsy only suggested that between 14 and 53% of these DCIS diagnoses may progress to invasive cancer [5]. Moreover, a meta-analysis reported that surgery for low-grade DCIS did not significantly alter breast cancer–specific survival (BCSS) when compared to a biopsy alone without surgery [6]. Still, the Dutch guidelines, alongside guidelines from other countries, recommend surgical treatment for DCIS patients and in case of breast-conserving surgery, irradiated similarly to invasive breast cancer irrespective of the tumour grade [7]. This apparent contradiction emphasises the importance of obtaining increased insight into outcomes of DCIS patients as it confirms our little knowledge on the behaviour of DCIS. The first step in understanding this behaviour would be to investigate (breast cancer–related deaths) after a DCIS diagnosis. In this population-based study, we aimed to determine BCSS and overall survival (OS) in DCIS specified for tumour grade. Furthermore, we evaluated the effect of several clinicopathological characteristics on survival outcomes. Results are expected to guide shared treatment decision-making in future DCIS patients.

2. Methods

2.1. Study population

All patients diagnosed with DCIS in 1999–2012 were selected from the population-based Netherlands Cancer Registry (NCR) [8] and were linked to Statistics Netherlands (CBS). The Dutch guidelines advise an excision with a margin of 2 mm. In case of a non-radical resection (and remaining breast tissue), a re-excision is indicated. Radiation therapy is advised in addition to breast-conserving surgery but is not advised as a replacement of surgery in case of margins larger than 2 mm [9]. Patients with insufficient data for linkage or insufficient clinical or pathological data on tumour and/or nodal stage were excluded, as reported previously [10]. DCIS patients with a positive nodal stage, receptor and/or human epidermal growth factor receptor 2 (HER2) status evaluation (which is not recommended based on the Dutch national guidelines for DCIS), treatment with systemic therapy or with contralateral breast cancer were excluded to obtain a pure DCIS population. With respect to contralateral breast cancer, this included contralateral invasive breast cancer and DCIS both at the time of diagnosis and during follow-up. In this way, we could more reliably investigate the association between a primary DCIS diagnosis and the risk of breast cancer–related mortality. This study was approved by the privacy committee of the NCR.

2.2. Statistics Netherlands

The CBS registry is mandatory for clinicians to document the cause of death for all inhabitants of the Netherlands (Supplementary Fig. 1). Medically trained, specialised personnel coded the cause of death based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [11]. The primary cause of death is considered the disease or injury that led to a sequence of events that led to death or the circumstances of an accident or violence in which the fatal injury was caused [11]. An additional first, second and third contributing cause of death can be reported. The causes of death are registered based on selection rules as displayed in Supplementary Fig. 1 and expertise of the medically trained personnel. From 2013 onwards, only the underlying cause of death was reported, which was automatically composed using a coding program.

2.3. Procedures

Patient-, tumour- and treatment-related characteristics were obtained from the NCR. Through linkage with the