Breast cancer phenotype, nodal status and palpability may be useful in the detection of overdiagnosed screening-detected breast cancers

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Background: Breast cancer remains the leading cause of female cancer death despite improvements in treatment and screening. Screening is often criticized for leading to overdiagnosis and overtreatment. However, few have attempted to identify overdiagnosed cases.

Patients and methods: A large, consecutive series of patients treated for primary operable, screening-detected, breast cancer (n = 1610). Details from pathology and clinical reports, treatment and follow-up were available from our prospectively managed database. Univariate and multivariate Cox proportional models were used to study the prognostic variables in screening-detected breast cancers for distant metastatic and breast cancer-specific survival.

Results: We included 1610 patients. The mean/median follow-up was 6.0/6.0 years. Univariate analysis: tumor size, palpability, breast cancer phenotype and nodal status were predictors of distant metastasis and breast cancer-specific death. Multivariate analysis: palpability, breast cancer phenotype and nodal status remained independent prognostic variables. Palpability differed by breast cancer phenotype.

Conclusion: Screening-detected breast cancer is associated with excellent outcome. Palpability, nodal status and breast cancer phenotype are independent prognostic variables that may select patients at increased risk for distant metastatic relapse and breast cancer-specific death. Overdiagnosed cases reside most likely in the nonpalpable node negative subgroup with a Luminal A phenotype.

Key words: breast cancer, palpability, prognosis, screening, subtypes

introduction

In the Western world, breast cancer remains the leading cause of female cancer death despite improvements in adjuvant treatment and screening [1–3]. Randomized research concluded that screening is independently associated with a 20% reduction in breast cancer mortality [4]. On the contrary, the effect of screening may be overestimated (due to lead-time and length bias and improved adjuvant treatment) and screening has been associated with overdiagnosis and overtreatment [4–7]. Indeed, the majority of screening-detected invasive breast cancers exhibit favorable tumor characteristics (small size, node negative and estrogen and progesterone positive tumors are overrepresented) [8, 9]. Furthermore, recent estimates suggest that ~25% of screening-
detected breast cancers may never progress and for every breast cancer-specific death prevented by screening, three patients will be overdiagnosed and unnecessary treated [4]. For these reasons, there is currently a hot debate between believers and nonbelievers of breast cancer screening. This is one of the first manuscripts that does not intend to participate in the discussion whether screening benefits outweigh harm(s), but rather poses the question on how to distinguish between indolent (overdiagnosed) and nonindolent (potentially life-threatening) screening-detected breast cancers. One of the recommendations in the recently published Lancet overview on the benefits and harms of breast cancer screening stated that efforts should be made to identify patients that may be actually overdiagnosed (and thus overtreated), exactly the purpose of this manuscript (4).

Few studies so far have examined the value of commonly used prognostic factors if breast cancers are detected through screening [10]. It might well be that size and phenotype have a different prognostic role if tumors are detected in an asymptomatic stage [11–13]. In this study, we investigate the prognostic role of the primary breast cancer phenotype, but also tumor size, grade and nodal status within a large group of consecutive screening-detected breast cancers treated in a single hospital. We additionally assess the prognostic role of palpability, a variable more likely to affect prognosis in screening-detected than symptomatic breast cancers. The primary objective of this manuscript is to identify which patients with a screening-detected breast cancer are at increased risk for distant metastasis and breast cancer specific death and which are at increased risk to represent overdiagnosed cases.

patients and methods

All patients with primary operable invasive breast cancer treated at UZ Leuven during the period January 2000 and December 2009 were included in this analysis. The following were exclusion criteria: preoperative systemic therapy (n = 407), metastases at diagnosis (n = 228), male patients (n = 28) and surgery carried out in another hospital (n = 530). Details on local and systemic treatment and pathology can be found elsewhere [14]. We defined Luminal A = ER and/or PR positive, HER2 negative and grade 1 or 2; luminal B = ER and/or PR positive, HER2 negative and grade 3; Luminal HER2 = ER and/or PR positive, HER2 positive; HER2 like = ER and PR negative, HER2 positive; Basal-like = triple negative (for the purpose of this manuscript) (ER and PR and HER2 negative) [15]. ER, PR, HER2, and grade were missing in 10, 23, 89 and 9 cases, respectively.

We included 1610 asymptomatic patients with screening-detected breast cancer. We allowed patients that attended organized screening (2-yearly, mammography only), opportunistic or high-risk program screening (interval at discretion of the physician, imaging modalities are one or more of the following: mammography, ultrasound and MRI). Palpability was assessed by the treating physician(s) at the time of the first visit (before or after diagnostic biopsy). Missing data for palpability were n = 2. A CONSORT diagram is presented (supplementary diagram S1, available at Annals of Oncology online). Multivariable Cox proportional hazard models were used adjusting for age, size, grade, nodal status, ER, PR and HER2 receptor status and adjuvant therapy. The proportional hazard assumption for the Cox model was evaluated by including time-dependent covariates in the models, which were included when significant. The distant metastasis-free interval is the time between surgery and metastasis. The breast cancer-specific survival is the time between surgery and death due to breast cancer.

First, we fitted a univariate model for each covariate (supplementary Table S1, available at Annals of Oncology online), and identified the predictors significant at P = 0.15. We then fitted a multivariate model with all significant univariate predictors, and used the backward selection procedure to eliminate nonsignificant variables at P = 0.10. We also considered each of the nonsignificant variables in a multivariate model using forward selection, with significance level of 0.10. A final model, by using all the significant variables in the two previous steps, at P-value of 0.10 based on stepwise selection was determined (Table 1). Grade, ER, PR and HER2 status were excluded and phenotype was used as a summary variable for these variables.

results

The total cohort included 1610 screening-detected breast cancers with a mean age at diagnosis of 58 years. Median and mean follow-up were both 6.0 years. Most women were postmenopausal (73.4%) and diagnosed with an invasive ductal breast cancer (86.1%) of <2 cm in size (68.6%). Most cancers were node negative (71.2%) and belonged to the so-called

| Table 1. Significant prognostic variables in screen-detected breast cancers in final multivariate model |
|---|---|---|---|---|
| Breast cancer phenotype | Hazard ratio | Lower confidence level | Upper confidence level | P-value |
| Luminal A | Reference | | | |
| Luminal B | 2.487 1.366 4.527 0.0029 | | | |
| Luminal HER2 | 1.872 0.651 5.385 0.2448 | | | |
| Basal-like | 3.649 0.997 13.349 0.0505 | | | |
| HER2 like | 3.536 1.090 11.472 0.0354 | | | |
| Luminal B | 4.996 2.357 10.588 <0.0001 | | | |
| Luminal HER2 | 3.752 1.200 11.726 0.0230 | | | |
| Distant metastasis-free interval | | | | |
| Palpability | | | | |
| No | Reference | | | |
| Yes | 2.834 1.486 5.406 0.0016 | | | |
| Nodal status | | | | |
| pN0 | Reference | | | |
| pN1 | 1.905 0.933 3.892 0.0768 | | | |
| pN2 | 2.589 0.922 7.270 0.0709 | | | |
| pN3 | 6.224 1.770 21.888 0.0044 | | | |
Luminal A phenotype (67.1%). The majority received endocrine systemic therapy (85.5%), adjuvant chemotherapy was given in 27.6% of cases (supplementary Table S1, available at Annals of Oncology online). Approximately half (52%) of the lesions were palpable at clinical examination; palpable tumors were significantly more likely seen in older women but also more frequently higher grade, lobular type, larger in size and lymph node positive (supplementary Table S1, available at Annals of Oncology online). The distribution of the different breast cancer phenotypes clearly differed between palpable and nonpalpable lesions (supplementary Table S1, available at Annals of Oncology online).

In univariate analysis, tumor size and grade, lymph node status, breast cancer phenotype and adjuvant chemo- and endocrine therapy were significant prognostic variables in screening-detected breast cancer (univariate hazard ratio’s (HR) and confidence intervals (CI) for breast cancer-specific survival and distant metastasis free survival are given in supplementary Table S1, available at Annals of Oncology online). Significant differences in overall survival, breast cancer-specific survival and distant metastasis-free survival between palpable and nonpalpable screening-detected breast cancers were found as well, favoring the latter (supplementary Table S1, available at Annals of Oncology online, Figures 1 and 2).

In multivariate analysis (Table 1), palpability remained an independent prognostic variable both for distant metastasis-free survival [HR 2.8 (95% CI 1.5–5.4) (P = 0.0016)] and breast cancer-specific survival (HR 2.8 (95% CI 1.2–6.1) (P = 0.00124)), together with the primary breast cancer phenotype and lymph node status. Tumor size however, did not have prognostic significance in multivariate analysis. As shown in Table S2 (supplementary Table S2, available at Annals of Oncology online) (only considering distant metastasis-free survival), the univariate HR of tumor size [HR 1.10 (CI 1.06–1.15) (P < 0.0001)] was only slightly attenuated [HR 1.07 (CI 1.03–1.13) (P = 0.003)] by the introduction of palpability in a bivariate model. After additional inclusion of nodal status (number of involved lymph nodes) to the bivariate model, tumor size remained significant [HR1.06 (CI 1.01–1.11) (P = 0.03)]. Only with the further introduction of the primary breast cancer phenotype, the prognostic value of tumor size became insignificant [HR 1.15 (CI 0.99–1.11) (P = 0.08)].

Luminal A, Luminal B, Luminal HER2, HER2-like and Basal-like breast cancers were palpable in 51.5%, 63.7%, 44.3%, 59.6% and 53.7%, respectively. In univariate analysis, breast cancer phenotype is related to palpability (χ² = 18.7, P < 0.001). In multivariable analysis, breast cancer phenotype is a significant and independent predictor of palpability, also taking into account age, tumor size, nodal status and histological type (likelihood ratio test, P < 0.001).

Discussion

Although breast cancer screening lowers breast cancer mortality screening is also associated with overdiagnosis and overtreatment [4–7]. Screening-detected breast cancers have an excellent outcome due to favorable tumor characteristics and this was also the case in our series. However, only few studies identified which patients with screening-detected breast cancers are truly at risk for distant relapse and breast cancer-specific death [10]. The recent Lancet review on the benefits and harms of breast cancer screening also recommended further research in order to try to identify which patients are confronted with an overdiagnosed breast cancer (4). In this study, we report that the breast cancer phenotype, palpability and nodal status are independent prognostic variables for distant relapse and breast cancer-specific death in screening-detected breast cancers. Screening-detected breast cancers that are not-palpable, lymph node negative and have a favorable (i.e. Luminal A) phenotype (n = 424) are most likely to harvest the majority of overdiagnosed breast cancer cases (total number of events over the entire follow-up period was: distant metastases n = 3, breast cancer related mortality n = 2). With such an excellent prognosis, one could question whether benefits still outweigh harms from adjuvant radiotherapy (i.e. ischemic heart disease) and endocrine therapy (i.e. endometrial cancer) [15–17]. In the recently published ATLAS study for example, the 15-year absolute risk for endometrial cancer is reported to be 2%–3% for 5 years of adjuvant tamoxifen and 4%–5% for 10 years of adjuvant tamoxifen.

Others have previously studied and confirmed the prognostic role of the primary breast cancer phenotype in small (T1a/b) node negative breast cancer, but detection mode was not taken into account [11–13]. This marks a fundamental difference in study population compared with our study, since breast screening may preferentially detect biological distinct (more indolent, slower growing) breast cancers (length bias). To our knowledge, we are the first to demonstrate that breast cancer phenotype remains prognostic within screening-detected breast cancers. This represents additional evidence preferentially supporting the fact that breast cancer screening constitutes more than length bias and overdiagnosis only [5–7]. If this were not the case, one would per definition expect that length bias would filter out the prognostic effect of the primary breast cancer phenotype within screen detected cases.

Although the prognostic role of palpability has been studied before, palpability has not previously been shown to have independent prognostic value in screening-detected breast cancer. Previously, Gill et al. [10], did not withhold palpability for prognostic purposes and although their cohort is larger (n = 2108 versus n = 1610), our multivariate model was more challenging, also including the primary breast cancer phenotype. In addition, others have also alluded to the potentially prognostic role of palpability in very low-risk breast cancer [18]. A mathematical hypothesis could presume that palpability (compared with tumor diameter) may represent a better estimation of a tumor’s volume and therefore may represent a better predictor of prognosis in screening-detected (small) breast cancers. However as recently described by Güth and colleagues, three-dimensional pathologic assessment of tumor size in primary breast cancers is not superior to the traditional pathologic assessment of the maximal-diameter in predicting axillary lymph node involvement [19]. Thus we speculate that palpability could reflect cell density within a tumor rather than only tumor volume. For instance, an increased number of malignant cells within the same volume could reflect a differential metastatic potential. Yet another,
more biological hypothesis could be that palpable breast cancer express (i.e. immunogenic) antigens that elicit favorable or nonfavorable (i.e. host) reactions, leading to increased cellularity and/or fibrosis and thus palpability. Also, different types of stroma might influence palpability and prognosis. The observation that breast cancer phenotype is a significant and independent predictor of palpability supports the hypothesis that biological variables predict palpability.

Body mass index (BMI) has been reported to influence both palpability and prognosis in breast cancer, but BMI and breast size were not taken into account in our study [20–22]. Since our population is not very obese, we do not anticipate this impacts on our study results.

Nodal status was confirmed as the most important prognostic variable in screening-detected breast cancer [10]. Lymph node involvement has repeatedly been shown to be the

**Figure 1.** Distant metastasis-free interval by breast cancer phenotype (upper figure) or by palpability and nodal status (lower figure) within screen-detected breast cancers.
strongest prognostic variable in breast cancer [23] and, more recently, it was appreciated that extensive lymph node involvement in very small tumors may be a surrogate of extremely aggressive breast cancers indeed [24].

In this study, we were not able to correct for the number of previous screening mammograms, a possible confounder. It is possible that the biology of screening-detected breast cancers differs in women with a previous normal mammogram compared with women diagnosed with a breast carcinoma attending the screening for the first time (latent pool of breast cancers). A first-screening-ever breast cancer may be slightly more advanced (and thus more likely palpable) with inferior prognosis, compared with a breast cancer that is detected in a women that already had several negative screening rounds. We are however not able to correct for the number of screening rounds since this information was not available.

In conclusion, screening-detected breast cancer has an excellent outcome. Palpability, nodal status and breast cancer

**Figure 2.** Breast cancer-specific survival by breast cancer phenotype (upper figure) or by palpability and nodal status (lower figure) within screen-detected breast cancers.
phenotype are independent prognostic variables that may select patients at increased risk for distant metastatic relapse and breast cancer-specific death. Breast cancer screening is associated with overdiagnosis and, based on our study, these cases most likely reside in the nonpalpable lymph node negative compartment, with a favorable (i.e. Luminal A) phenotype. These breast cancers might be overtreated in the adjuvant setting, although further research needs to confirm this. Palpability may represent a distinct biological subgroup of breast cancers warranting further research. Palpability should be considered as a prognostic variable in prognostic models for screening-detected breast cancers.

disclosure

The authors have declared no conflicts of interest.

references