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Original article

Tumor biology in older breast cancer patients – What is the impact on survival stratified for guideline adherence? A retrospective multi-centre cohort study of 5378 patients

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ABSTRACT

Purpose: The tumor biology of older breast cancer patients (oBCP) is usually less aggressive, however applied adjuvant treatment is often less potent resulting in an impaired disease free survival and overall survival in this group. This study tries to answer the following questions for the biological subtypes of oBCP (70+ y):

(1) Is there a significant difference in the distribution of the biological subtypes of oBCP vs younger breast cancer patients (yBCP; 50–69 y)?
(2) Which biological subtype has the highest rate of non-guideline-adherent-treatment (GL–) among oBCP?
(3) Is a single GL– (i.e. radiotherapy/surgery/endocrine-therapy/chemotherapy) significantly associated with the survival outcome in each biological subgroup?

Methods: Between 1992 and 2008 the BRENDA ('BRENDA' = quality of BREast caNcer care unDer evidence-bAsed guidelines) study group recorded medical data of 17 participating certified breast cancer centers in Germany.
We performed a retrospective multi-center database analysis of 5632 patient records. Guideline-adherent-treatment (GL+) of oBCP(n = 1918) was compared to GL+ of yBCP(n = 3714).
Results: OBCP were more likely to have hormone receptor positive (HR+) and HER2*neu* negative (HER2–) breast cancer (77.5% vs 74.5%). The rate of GL– was significantly different ($p < 0.001$) between the age groups and the biological subgroups (yBCP vs oBCP: 21.8%vs38.8% (HR+/HER2–); 30.6%vs49.7% (HR+/HER2+); 23.6%vs69.5% (HR–/HER2+); 31.4%vs67.8% (TNBC)).
The survival parameters for HR+/HER2– and TNBC were significantly worse in case of GL– regarding chemotherapy, and if applicable endocrine therapy. A similar association only existed in HR–/HER2+ tumors for GL– for radiotherapy and in HR+/HER2+ tumors for chemotherapy.
Conclusions: Beside the significantly different distribution of biological subtypes in the age groups there is an association between biological subtype, and GL+ influencing survival parameters in oBCP.

Introduction

Previous analysis showed that a large proportion of older breast cancer patients (oBCP) receive non-guideline-adherent treatment (GL–) [1–5] with a major impact on overall survival (OS) and disease free survival (DFS). Most of these analysis focused on staging

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including tumor size, number of positive lymph nodes and hormone receptor status (HR). In recent years the understanding of breast cancer has shifted from these clinical/pathological systems towards genetic/intrinsic markers. Guidelines and treatment decisions for early breast cancer are more and more based on biological/molecular subtypes or scores [6]. Whilst this is very well documented for the average aged patients very little has been published for the subgroup of oBCP. Additionally, GL+ in regard to these subtypes has not been investigated for the oBCP. Gnant et al. [7] demonstrate an overlap of histopathological markers and intrinsic subtypes (Table 1) using HR, HER2*neu* (HER2) status and Ki67 antigen to simulate the intrinsic subtypes. The present study investigates correlations between the biological subgroups, age and GL+ and demonstrates how GL− concerning radiotherapy, surgery, endocrine-therapy and chemotherapy are associated with survival among the four biological subgroups of younger and older breast cancer patients.

Material and methods

Patient/database

In this retrospective multicenter cohort study, we analyzed data from patients with primary breast cancer diagnosed and treated in the Department of Gynecology and Obstetrics of the University of Ulm and the surrounding 16 hospitals between 1992 and 2008. For this purpose, a new documentation system BRENDA was designed and used. This included a retrospective chart review to abstract TNM-stage, histological subtype, grading, lymphatic and vascular invasion, estrogen/progesterone/erb-2-expression, date of diagnosis, and all adjuvant therapies. Data on adjuvant therapies including surgery, systemic chemotherapy, endocrine therapy and radiotherapy was collected. Inclusion criteria were histological invasive breast cancer, non-metastasized breast cancers and primary diagnosis of breast cancer in female patients. Exclusion criteria were phylloides tumor, sarcoma or carcinoma of unknown primary and non-invasive carcinoma in situ. To compare the oBCP to the yBCP, women aged <50 years or data with missing values (T-stage, nodal status, grading, uncertain or missing hormone receptor status and missing HER2 status) were excluded (Fig. 1). We considered estrogen/progesterone expression negative for IRS0, HER2 status negative for 0, 1+, 2+ and FISH negative.

The antigen Ki67 has not been tested by the pathologists and is not recorded in the database as this marker was not established at the time the database was designed. Follow-up data was acquired on recurrences, secondary malignancies, and date and cause of death by sending questionnaires to the physicians involved in follow up care and local death registrars. Further database details have been published elsewhere [8,9]. The definition of guideline adherence was based on international guideline for diagnosis and treatment of breast cancer [10] and has been published in detail previously [11]. The treatment modalities (radiotherapy/surgery/endocrine therapy/chemotherapy) were retrospectively evaluated concerning their adherence to the guideline. Non-guideline-adherent-treatment (GL−) was defined as not applied adjuvant treatment per modality or missing of any adjuvant treatment.

Table 1
Intrinsic subtype correlation to tumor biology according to Gnant et al. (7) and classification into study subgroups for further analysis; HR = hormone receptor status; HER2 = HER2neu status; TNBC = triple negative breast cancer; ER = estrogen receptor; PR = progesterone receptor.

Subtype	HR (ER/PR)	HER2	Ki67	Study subgroups
Luminal A	+	−	low	HR+/HER2−
Luminal B (HER2−)	+	−	high	
Luminal B (HER2+)	+	+	~	HR+/HER2+
HER2+	−	+	~	HR−/HER2+
Basal like/TNBC	−	−	~	HR−/HER2−

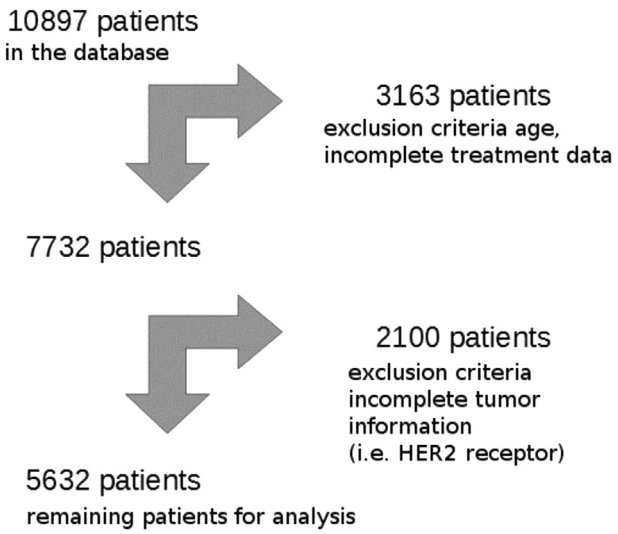

Fig. 1. Application of the inclusion and exclusion criterias leaving data on 5632 patients for analysis.

Statistical analysis

The data was divided into two age groups: 50–69 and 70+ years. Using the criteria of Gnant et al. [7] and in the absence of the Ki67 marker the study subgroups were defined as described in Table 1. The first step was an analysis of the subgroup distribution in both age groups. For statistical testing, χ^2-tests were used. Next, for each of the four subgroups, we compared whether GL− (any GL−/GL− on radiotherapy/surgery/endocrine therapy/chemotherapy) occurred more frequently among those aged 70+ than among those aged 50–69. For this a five logistic regressions (one for each type of guideline violation) of guideline conformity status on four indicators designating the four biological subgroups was run. Each of these indicators was interacted with a dummy variable indicating whether a patient was <70 years. P-values <0.05 (two-tailed test) were considered significant throughout the present study.

Next, the subgroup of oBCP was taken and DFS/OS among the four subgroups was compared using Cox regressions. Reference category in these analysis were the HR+/HER2−patients as they are the largest group. The Cox regressions were adjusted for tumor size (4 categories), nodal status (0, 1–3, or 4+ positive nodes), year of diagnosis, grading (3 categories), treatment center (university hospital or other clinic), HR (positive, negative or unknown), HER2 and comorbidities. To accommodate for missing values on HER2 and comorbidities, dummy variables indicating missing values were included as co-variates. Comorbidities were measured using the scale of the New York Heart Association (NYHA; NYHA class 3 or more), the American Society of Anesthesiologists (ASA; ASA 3 or more), history of apoplexy, transient ischemic attack (TIA) or myocardial infarction and history of any prior cancers. Hazard ratios are presented with 95% confidence intervals (CI) and two-sided *p* values.

Results

After applying the inclusion and exclusion criteria 5632 breast cancer patients were left for analysis. Of these, 1918 were aged 70