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Original article

Triple negative breast cancer: Clinical characteristics in the different histological subtypes

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ABSTRACT

Purpose: To investigate the clinical behavior of triple negative breast cancer (TNC), including age distribution, occurrence of LN (lymph node) invasion and prognosis in different histological subtypes.
Methods: For this cohort study we used data on 476 patients with newly diagnosed TNC at the University Hospitals Leuven (Belgium) between 1999 and 2009. Of these, 395 received upfront surgery, 68 neo-adjuvant chemotherapy and 21 had metastases at diagnosis.
Results: Apocrine and invasive lobular TNC occur more often in older patients compared to IDC-NOS. Of the primarily operated patients with TNC, 35.1% has pathological LN involvement. There were no significant differences in nodal invasion between different histological subtypes, but most subtypes contained few patients. In contrast to previous reports, 6/14 of apocrine TNC had LN involvement. Disease free survival (DFS) was different in different histological subtypes, but group sizes were insufficient to be able to draw firm conclusions. Within the histologically 'homogeneous' IDC-NOS group with primary surgery and outcome data ($n = 300$), DFS with 3.5 year median follow-up decreased with increasing age, but chemotherapy and radiotherapy were much less frequently given with increasing age. In multivariable analysis, lower age, presence of LN involvement, lack of administration of chemotherapy and radiotherapy were significant predictors of relapse.
Conclusion: TNC is not a uniform disease. Different histological subtypes have different age distribution and behavior. The prognosis of the most common histological subgroup, IDC-NOS, is better in older patients, but this is counterbalanced by significantly decreased use of chemotherapy and radiotherapy.

Introduction

Invasive breast cancer is an important cause of cancer death.[1] But a heterogeneous disease in terms of outcome as well as histopathological classification. Most tumors are derived from mammary ductal epithelium, principally the terminal duct-lobular unit, and up to 50–80% of the diagnosed infiltrating ductal carcinomas are defined as invasive ductal carcinoma, not otherwise specified (IDC-NOS). The second most common epithelial type is (classical) invasive lobular carcinoma, which compromises 5–15% of all invasive breast tumors. The other 10–25% consists of more rare histological subtypes including mucinous, apocrine, metaplastic, medullary, invasive micropapillary, neuroendocrine, pleomorphic lobular and mixed lobular-ductular carcinoma.[2-6] Based on gene expression studies, breast tumors can also be divided into several subtypes. The most valid subdivision contains two subtypes of ER negative tumors, the basal like tumors and HER2-enriched, and two subtypes of ER positive tumors, luminal A and luminal B.[9,10] These

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subtypes differ in prognosis and in the therapeutic targets they express.[11–13] The term triple negative is often used synonymous for basal like tumors but there is a significant discordance up to 30%.[14] In this article we will focus on the triple negative carcinomas (TNC), defined as the absence of hormone receptors (estrogen and progesterone) and negativity for HER-2 either by immunohistochemistry (0–1+) or by fluorescent in situ hybridization (FISH negative).

TNC account for 11–24% of all breast cancers and have a worse relapse-free and overall survival.[15–18] Recent research identifies specific (genetic) aberrations in (subsets of) TNC, for instance TP53 mutations, alterations in BRCA1 and mismatch repair genes, PIK3CA mutations, EGFR expression, and also androgen receptor expression.[19] These molecular alterations have generated interest in developing 'targeted therapy' for this type of breast cancer. For instance, a study with addition of EGFR antagonists chemotherapy showed enhanced tumor response.[20] PARP inhibitors showed interesting activity in a randomized Phase II trial with clearly improved overall survival compared to standard therapy,[21] but the subsequent phase III trial unfortunately did not confirm this. Also angiogenesis inhibitors have shown positive results in studies with TNC,[22,23] and studies with androgen blocking agents are ongoing. A major problem with triple negative breast tumors is that they comprise a very heterogeneous group of histological diagnosis, with different tumor behavior and prognosis. For example, worse prognosis of metaplastic tumors compared to medullary carcinomas has been reported.[2,3,7] And even the group of metaplastic tumors is heterogeneous, where the presence of high-grade spindle cells may indicate aggressive behavior.[8] Triple negative tumors are often studied as one 'uniform' group, but this does not take into account the different biology of the different histological subtypes. A recent study from our group indicated that tumors might behave differently in older individuals, for instance by metastasizing more rapidly (at smaller tumor sizes) into lymph nodes compared to younger women.[24] In this study, we wanted to describe in detail different histological subtypes of TNC in a large clinical database of the UH Leuven, and focus on clinical behavior including age distribution, occurrence of lymph node invasion and prognosis.

Patients and methods

Design and patients

This is an observational cohort study based on data from the breast cancer database of the University Hospitals (UH) Leuven, Belgium. The database contains 5667 patients treated for an invasive breast tumor from January 1999 till November 2009. We selected 542 triple negative tumors based upon the following criteria: ER and PgR negative (H-score or Allred score is zero), Her-2 negative (0 or 1 IHC, or 2+ with neg FISH). We excluded patients with previous invasive breast cancer events and unknown tumor histology subtype, resulting in a data set of 476 primary tumors. This group is divided into 395 patients with upfront surgery, 68 with neo-adjuvant treatment and 21 patients were metastatic at diagnosis.

Variables studied

The following variables were included for analysis: age at diagnosis, microscopic tumor size, axillary lymph node status, tumor grade, histopathological subtype, upfront surgery (received or not), radiotherapy and adjuvant or neo-adjuvant chemotherapy. In patients with upfront surgery, lymph node status was analyzed as a binary variable (pN0 vs pN1-2–3). Tumor grade was assessed according to the Ellis and Elston grading system.[25] Expression of ER, PgR and HER-2 was demonstrated by IHC according to the Envision method using the primary monoclonal antibodies NLC-ER-6F11 for ER, NCL-PgR-312 for PgR and CB11 for HER-2 (Novocastra Laboratories, Newcastleon-Tyne, UK). IHC staining was performed according to standard procedures for clinical purposes as previously described.[26] Breast tumor histological subtypes were scored in agreement with the WHO criteria.[27]

In the data set of 476 primary tumors, there were missing values for axillary lymph node status ($n = 55$, $n = 9$ in the upfront surgery group), tumor grade ($n = 2$, $n = 2$ in the upfront surgery group), microscopic tumor size ($n = 92$, $n = 12$ in the upfront surgery group), radiotherapy ($n = 5$, $n = 5$ in the upfront surgery group) and chemotherapy ($n = 5$, $n = 5$ in the upfront surgery group). For each statistical analysis, we excluded patients with missing values for variables used in the analysis. For the analysis involving lymph node status, we only used the upfront surgery group because LN status cannot be optimally assessed in metastatic patients or in patients receiving neoadjuvant systemic therapy. In the survival analyses, tumors were used from patients receiving upfront surgery ($n = 395$), excluding patients with neo-adjuvant chemotherapy or primary metastases. Histological groups with less than 5 tumors were excluded from the survival data set in order to attain reasonable group sizes ($n = 5$ tumors). In the case of a bilateral tumor, the tumor with the highest Nottingham Prognostic Index (NPI) was considered determinative for prognosis and the contralateral tumor was omitted from the analysis ($n = 1$). After omitting an additional 21 tumors with unknown follow-up, this resulted in a survival data set of 379 tumors, of which 300 IDC-NOS tumors. This subgroup was used in order to have a histologically uniform group for the multivariable survival analysis. Stratification according to histological type was impossible because of small sample sizes. In the 300 IDC-NOS tumors with survival outcome, 6 tumors had unknown lymph node status pNx, and were not included in the corresponding uni- and multivariate models.

Statistical analysis

Age at diagnosis and microscopic tumor size were considered as continuous variables in all analyses. Only for descriptive purpose, age was arbitrarily divided into three groups: younger than 50 years, 50–70 years and older than 70 years. All other variables were considered categorical.

Comparison of a continuous variable between groups was performed using the Kruskal–Wallis rank sum test. For the comparison of a categorical variable between groups, Fisher's exact test was used in order to avoid problems with small cell sizes.

Survival analyses were performed using univariable and multivariable Cox regression and Kaplan–Meier curves. Events were defined as locoregional relapse or distant metastasis (disease-free survival, DFS). The validity of the proportional hazards assumption was checked using a residuals test.[29] Significance testing for Cox model coefficients was performed using the Wald test and model variables were selected using a backward selection procedure. Linearity of the effect of age on DFS was investigated using smoothing splines.

All statistical tests were two-sided. All analyses were performed in R version 2.14.2 using the packages survival, gmodels, car, and coxphf.

Results

The 476 triple negative primary tumors showed the following histological subtypes: invasive ductal carcinoma, not otherwise specified (IDC-NOS) ($n = 380$), invasive lobular carcinoma (ILC) ($n = 10$), mixed ductal-lobular (IDC + ILC) ($n = 1$), metaplastic ($n = 28$), pleomorphic lobular ($n = 19$), medullary ($n = 18$), apocrine