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Original article

Breast cancer in young women: Pathologic features and molecular phenotype

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ABSTRACT

Purpose: Controversy exists about the prognosis of breast cancer in young women. Our objective was to describe clinicopathological and prognostic features to improve adjuvant treatment indications.
Methods: We conducted a retrospective multi centre study including fifteen French hospitals. Disease-free survival's data, clinical and pathological criteria were collected.
Results: 5815 patients were included, 15.6% of them where between 35 and 40 years old and 8.7% below 35. In 94% of the cases, a palpable masse was found in patients ≤35 years old. Triple negative and HER2 tumors were predominantly found in patients ≤35 (22.2% and 22.1%, $p < 0.01$). A young age ≤40 years ($p < 0.001$; hazard ratio [HR]: 2.05; 95% confidence limit [CL]: 1.60–2.63) or ≤35 years ($p < 0.001$; [HR]: 3.86; 95% [CL]: 2.69–5.53) impacted on the indication of chemotherapy. Age ≤35 ($p < 0.001$; [HR]: 2.01; 95% [CL]: 1.36–2.95) was a significantly negative factor on disease-free survival. Chemotherapy ($p < 0.006$; [HR]: 0.6; 95% [CL]: 0.40–0.86) and positive hormone receptor status ($p < 0.001$; [HR]: 0.6; 95% [CL]: 0.54–0.79) appeared to be protector factors. Patients under 36, had a significantly higher rate of local recurrence and distant metastasis compared to patients >35–40 (21.5 vs. 15.4% and 21.8 vs. 12.6%, $p < 0.01$).
Conclusion: Young women present a different distribution of molecular phenotypes with more luminal B and triple negative tumors with a higher grade and more lymph node involvement. A young age, must be taken as a pejorative prognostic factor and must play a part in indication of adjuvant therapy.

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Introduction

About 2–7% of women will be diagnosed with breast cancer (BC) before the age of 40 [1–4]. While outcomes of treatment for breast cancer are improving and the five-year disease-free survival for all patients has risen from 75% to 85% thanks to detection through mammographic, breast cancer in young women appears before screening. Indeed, more than 90% of young patients with BC are symptomatic [5–7] with large tumors and nodal involvement.

Tumors in younger women were described to have a higher grade and proliferation fraction, more vascular invasion, and to express fewer estrogen and progesterone receptors compared to tumors in older women [2,8–10]. These differences in breast cancer risk factors, tumor characteristics, clinical outcomes and gene expression suggest that, breast cancer arising in young women represents a distinct entity [11–13]. Young age appears to be an independent negative predictor of cancer-specific survival [14–19] with a higher rate of local recurrence and an inferior 5-year survival [13,20]. Therefore, most young patients are candidates for chemotherapy [1,21,22]. However, in several studies, after adjustment for other prognostic variables, age was not related to overall or disease free survival. The negative prognostic effect of young age is almost exclusively seen in women diagnosed with low risk disease who did not receive adjuvant cytotoxic treatment [23].

Clinical features and prognosis factors of BC remains a widespread issue. Recently, an online prognostic tool based on data from 3000 women age $\leq$40 was developed. It offered reliable long-term (10-year) survival estimates for younger patients. However, for more accurate short-term estimates, the model requires more data from young onset cases [24,25]. Staging procedures, attention given to small metastases in axillary lymph nodes, assessment of overexpression of HER2/neu, immunohistochemical determination of estrogen and progesterone receptors, are features that have undergone changes in recent years. The indications and the choice of systemic treatment for invasive BC should not be based on age alone but driven by the biological characteristics of the individual tumor, especially as the definition of a 'young woman' in the field of breast oncology has not been clearly differentiated. Because of changing treatment modalities and remarkable improvement in the outcomes of breast cancer in the last decade, an update of the prognostic factors could potentially help us clarify if aggressive treatment for young women with breast cancer is justified [26]. Study of distributions of molecular subtypes could be useful, but there has been little study in this field so far [27].

The aim of this study was to investigate the most recently available details of biological characteristics and stage at disease presentation in a large group of very young patients with operable breast cancer. We used a multivariate analysis to evaluate whether young age alone is a significant independent adverse prognostic factor for women with breast cancer.

Patients and methods

Population description

From 1980 to 2014, we conducted a retrospective multicentre study in fifteen French hospitals. All data was obtained from the medical records of patients. This work was approved by the local ethic committee. According to the French law, as it was a retrospective work without treatment modification, it was not considered mandatory to obtain an informed consent from patients, but the data was analyzed after all patient information had been fully anonymized.

All patients under 50 years with a pathological diagnosis of breast cancer, on a preoperative biopsy or surgical specimens, were included in the study from 1980 to 2014 in Paoli Calmettes Institute, and from 2000 to 2010 in other centers. All patients underwent breast surgery with axillary lymph node sampling (sentinel node biopsy or lymph node dissection). Radiation therapy, adjuvant endocrine therapy, and chemotherapy and were performed according to standard guidelines at the time of diagnosis. Postoperative breast irradiation was proposed to all the patients who received breast-conserving surgery and in some of case of radical surgery. Systemic adjuvant therapy was recommended according to St. Gallen's treatment guidelines. Depending on hormone receptor statute, adjuvant endocrine therapy alone was indicated. In patients at higher risk, chemotherapy was added. Chemotherapy containing Anthracyclines was considered as the first option for duration of six cycles. Stage III or IV patients or neo-adjuvant therapy were excluded. Follow-up was measured from the date of diagnosis to the date of last follow-up information for censored patients. Disease-free survival (DFS) was defined as the duration from diagnosis to any recurrence (local and loco regional lymph nodes recurrences, contralateral breast cancer, second cancer, distant metastasis or death of any cause). Overall survival (OS) was defined as the duration from diagnosis to death of any cause.

Groups in terms of age

The main objective of this study was to evaluate the clinical, pathological and therapeutic characteristics of breast cancer according to age. Analysis was conducted by dividing the population into four age groups: women under 36 years, those over 35–40 years of age, those over 40–45 years of age and those over 45–50 years of age.

Clinicopathological features

The following characteristics were collected for each patient: age, clinical size of the tumor (cT), type of surgery (conservative or radical), pathological features (pathological size of the invasive tumor, histological type, pathological lymph node involvement, SBR grade, vascular invasion, progesterone and estrogen receptor status, HER2 status, adjuvant therapies (chemotherapy, radiation therapy, hormone therapy)). Hormone receptors expression was assessed using immunohistochemistry (IHC) and was scored as positive when more than 10% of tumor cells expressed estrogen receptor and/or progesterone receptor. HER2 status was assessed in the invasive component at time of diagnosis according to the ASCO-CAP recommendations [28].

The diversity of breast cancers makes complex their classification. In the case of our study, besides the usual histological criteria, we studied two other tumors rankings: one based on the results of immune histochemical analysis on HR and HER2 called "HR HER2 expression" and the other on molecular types of breast cancers called "Molecular types". This classification depends on HR and HER2 status and the grade of the tumor. The molecular types can be divided into two major subtypes, depending on the expression of estrogen receptor (ER). These differ according to the expression of HER2: in case of negative HR status with no HER2 over expression, tumor was defined as "triple negative type", while it was defined as "HER2+ type" when HER2 was over expressed. In case of HR positive status, we distinguished three types: "Luminal A" for tumor with SBR grade from 1 to 2, Luminal B type 1" for tumor with SBR grade 3 and "Luminal B type 2" when HER2 was overexpressed.

Statistical analysis

Statistical analyses were performed using SPSS statistical program (Statistical Package for Social Sciences; SPSS, Inc, Chicago, IL). Follow-up was measured from the date of diagnosis to the date of