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Outcome in breast molecular subtypes according to nodal status and surgical procedures

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Breast cancer;
Luminal B;
Molecular subtype;
Triple negative

Abstract

BACKGROUND: The purpose of our study was to evaluate the surgical treatment and outcome of breast cancer according to molecular subtypes.

METHODS: We identified 1,194 patients consecutively treated for primary breast cancer from 2004 to 2010. The type of surgery, pathological findings, local recurrence, and distant metastasis were evaluated for 5 molecular subtypes: luminal A and B, luminal HER2 (Human Epidermal Growth Factor Receptor 2), HER2 , and triple negative.

RESULTS: Breast-conserving surgery (BCS) was performed more frequently in luminal A (70.6%), triple-negative (66.2%), and luminal HER2 tumors (60.9%) ($P < .001$). A sentinel node biopsy was performed more frequently in luminal A (60%), and luminal HER2 (29.3%) types ($P < .001$). Among the 791 BCS, positive nodes were observed more often in HER2 (50%) and luminal B (44.9%) types ($P = .0003$). The number of local recurrences was higher in the node-negative luminal B subtype (3.4%).

CONCLUSIONS: Molecular subtypes exert an impact on BCS and nodal surgery rates. The local relapse rates are influenced by the molecular subtypes according to the nodal status.

Breast molecular classification, as described by Perou et al[1] and Sorlie et al[2] in the early 2000s, has enhanced our understanding of breast cancer (BC) heterogeneity. Significant differences have been observed in response to treatment and in the long-term outcome of these BC subtypes.[3] Three levels of evidence I markers,[4,5] namely the estrogen receptor (ER), progesterone receptor (PR), and HER2 (Human Epidermal Growth Factor Receptor 2) associated with nuclear grading, represent the pivotal factors used to identify BC molecular subtypes.[6]

Adjuvant systemic therapy has improved in terms of efficacy on prognosis and has limited drugs' toxicity; different targeting strategies have been initiated during recent years as a result of molecular classification. For instance, triple-negative (TN) tumors identified as being associated with a higher risk of metastatic disease[7] have been the model chosen for developmental trials of poly (ADP-ribose) polymerase (PARP) inhibitors, antiangiogenics, or molecules targeting epidermal growth factor receptor (EGFR) in the metastatic setting,[8–10] whereas HER2-expressing tumors are the target of anti-HER2 agents such as trastuzumab or agents targeting the vascular endothelial growth factor, the mammalian target

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of rapamycin, and phosphatidylinositol 3-kinase (PI3) kinase pathways.[11–14]

Will this molecular classification have an impact on the surgical strategy and allow a personalized surgical approach? With regard to locoregional treatment, recent studies have suggested that the molecular subtype exerts an impact on locoregional recurrences even if this risk is strongly dependent on the patient's age.[15] In addition, other authors have suggested that the status of nonsentinel nodes is influenced by the molecular subtype.[16] The purpose of this study was to evaluate the surgical strategy and outcomes according to different BC molecular subtypes and to stratify this analysis according to nodal involvement.

Patients and Methods

Patient selection

The study cohort consisted of 1,194 consecutive women with clinical stage I or III invasive BC surgically treated through March 2004 to March 2010 at the Institut Gustave Roussy, Villejuif, France. This study was a retrospective chart review. Patients with incomplete data for the ER (n = 121), PR (n = 120), and HER2/*neu* status (n = 317) and the histologic grade of the primary tumor (n = 47) were not selected nor were patients with synchronous bilateral BC or synchronous metastasis (n = 104) or who had received preoperative systemic therapy (n = 596). BC staging was defined by TNM classification as proposed by the American Joint Committee on Cancer (AJCC) for grouping patients with respect to prognosis.

Pathology

Patients were grouped into 5 subgroups according to the BC subtype as previously described[6,15]: ER positive or PR positive, HER2 negative, and grade1 or 2 (luminal A); ER positive or PR positive, HER2 negative, and grade 3 (luminal B); ER positive or PR positive and HER2 positive (luminal HER2); ER negative, PR negative, and HER2 positive (HER2 subtype); and ER negative, PR negative, and HER2 negative (triple negative). ER, PR, and HER2 levels were assessed immunohistochemically. Tumors were deemed positive for these receptors if at least 10% of the invasive tumor cells in a section exhibited nuclear staining. Histologic grading was defined according to the Scarff-Bloom-Richardson system.[17] HER2 positivity was defined as a 3+ staining intensity score at immunohistochemical analysis for the HER2 protein or for HER2 gene amplification by fluorescence in situ hybridization.

Treatment

All patients submitted to breast-conserving surgery (BCS) received whole-breast irradiation. For patients who underwent a mastectomy, chest wall and regional nodal irradiation including the supraclavicular fossa was performed if the patient had $\geq$4 positive lymph nodes or invasive cancer measuring $\geq$4 cm. Indications for adjuvant chemotherapy were in accordance with the St. Gallen guidelines.[18] Women with ER-positive BC were to receive 5 years of endocrine therapy, which began after the completion of all chemotherapy. After treatment completion, patients were seen every 6 months for the first 5 years and yearly thereafter, with a yearly mammography and a clinical examination at each visit. A bone scan, liver ultrasound, and chest x-ray were not included among the routine follow-up examinations and were performed exclusively in symptomatic cases. The sites of metastases were prospectively recorded.

Statistical methods

The chi-square test was used to compare the distribution of baseline characteristics among BC subtypes for categoric factors, whereas the Kruskal-Wallis test was used for continuous variables. The endpoints studied were recurrence-free survival (RFS) and distant metastasis-free survival (MFS) rates. The RFS rate was defined as the time from surgery to the date of any ipsilateral in-breast recurrence (invasive or noninvasive) without evidence of distant metastasis or death from cancer if no earlier recurrence had occurred. The distant MFS time was defined as the time to distant metastasis or death if the latter event occurred before the diagnosis of a distant metastasis. Survival rates were calculated using the Kaplan-Meier method and compared between groups with the log-rank test. A 5% significance level was used, and all P values were 2 sided. All analyses were performed in R, an open source statistical package (http://www.r-project.org/) using the Design library.[19]

Results

Patient characteristics and BC subtypes

The percentage distribution of BC subtypes among the 1,194 patients in the study was as follows: luminal A in 63.2%, luminal B in 13.8%, luminal HER2 in 6.9%, HER2 in 5%, and TN in 11.1%. The analysis of patient characteristics and surgical procedures shows significant differences among BC subtypes in terms of age ($P < .001$), menopausal status ($P < .001$), the rate of BCS ($P < .001$), and sentinel node biopsy (SNB) (Table 1). Patients with the HER2 or TN subtypes were younger ($\leq$40 years) than in the other groups. There were also significant differences in the distribution of tumor characteristics including tumor size ($P < .001$), grade ($P < .001$), and node positivity ($P < .001$). BCS was possible in 791 patients (66.2%). Among these 791 cases, an SNB was performed in 53.1%. Nodal positivity was observed in 227 patients (28.7%) and was more frequent in HER2 and luminal B subtypes ($P < .001$). Additionally, patients were classified as stage I in 47.2% (n = 564), stage IIa in 33.8% (n = 403), stage IIb in 16.6% (n = 198), and stage IIIa in 2.4% (n = 29).