

MOLECULAR CLASSIFICATION OF BREAST CANCER IN ORAN (ALGERIA)

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Introduction: Breast cancer is a heterogeneous disease, by the variability of its clinical-pathological presentations, by its evolutionary potential as well as by its therapeutic sensitivity. This heterogeneity reflects a very large diversity in molecular alterations⁽¹⁾

The determination of molecular groups is currently essential for a better therapeutic strategy of patients according to the gene or protein profile of tumors. Other prognostic factors are also considered in estimating locoregional relapse after surgical treatment, such as tumor size, age, histological grade, lymph node status and molecular profile⁽²⁾. Molecular classifications are potentially interesting, but the manipulation of RNA from frozen tissue fragments and the interpretation of bioinformatics data are not always easily applicable in routine clinical practice. The transposition of these transcriptomic classifications into a morphological and immunohistochemical classification using tissue fragments attached to formalin and included in paraffin is easier. The main objective of our study is to classify the invasive mammary carcinomas in our series according to their molecular immunohistochemical profile and their correlation to clinico-pathological characteristics.

Materials and methods: This is a descriptive study with a retrospective collection from January 2016 to December 2018, concerning 313 patients with invasive breast carcinoma diagnosed within the Pathology CHU ORAN department. Our study involves a step of collection of clinico-pathological data on pre-established sheets containing the following information: age, sex, tumor size and other macroscopic parameters, histological type, histoprognostic grade, vascular embols, lymph node involvement, hormone receptors (estrogen, progesterone), HER2 expression, KI67 levels.

Results: Our study was done on samples composed of mastectomies with lymph node removal. The left breast is more reached with 51.4% against 47.0% at the right breast. Synchronous bilaterality is 1.6% of cases. The most common tumor sizes in our study population are between 2 and 5 cm (T2) with 72.8% of cases followed by 16.0% of cases less than 2 cm (T1) and 11.1% more than 5 cm (T3). The majority of our patients have a unifocal tumor is 96.5% while 2.6% of cases have a bifocal tumor and 1.0% of cases have a multifocal tumor. Invasive carcinoma of non-specific type is the most common histological type with a percentage of 90.7% followed in second position by invasive lobular carcinoma with 4.8% of cases, then mucinous carcinoma with 3.2% and metaplastic carcinoma with a percentage of 1.3%. We note that in our series of patients, the skin is not infiltrated at 92.3% of cases. Neoplastic embol are present in 35.1% of cases and the in situ component is found in 30.4% of cases. Fibro inflammatory stroma accounts for the majority with 74.1%, followed by fibrous stroma with 11.8% and 10.5% necrotic stroma while mucoid stroma represents only 3.5%. The histological grade II of Elston and Ellis is the most frequent with 80.2%, grades III and I respectively represent 14.9% and 4.9%. We note that most of our patients have received a lymph node removal of up to 20 nodes, a percentage of 94.8%. The rest of the patients received a lymph node cleansing of more than 20 nodes or a percentage of 5.2%. More than $\frac{3}{4}$ of the lymph nodes of our series of patients are

infiltrated or 75.3% of cases with 24.7% of patients without lymph node infiltration (N0), 39.1% of patients have between 1 and 3 infiltrated lymph nodes (N1), 29.6% of patients have between 4 and 9 infiltrated lymph nodes (N2) and 6.6% of cases have more than 10 infiltrated lymph nodes (N3). 33.8% of cases are stage IIB and 31.0% of cases are stage IIIA whereas 10.1% of patients are stage IIIB and 25.1% are stage IIA.

Estrogen receptor is positive at 63.3% of cases. The Progesterone Receptor is positive at 50.5% of cases [The threshold of positivity is 1% of marked cells (ASCO Recommendation)]⁽³⁾. 65.5% of tumors are positive hormone receptors, against 34.5% negative. The search for HER2 overexpression finds 226 negative cases or 72.2% of score [0 and 1+] and 68 cases of HER2 overexpression or 21.7% of score 3+ while 19 cases or 6.1% are of score 2+ doubtful. After in situ hybridization (FISH) technique on the 19 2+ score cases, only 2 cases show gene amplification. Overall, HER2 is positive in 22.4% of cases and negative in 77.6% of cases. For the proliferation index (Ki67) 26 tumors or 11.5% have a rate of Ki67 70% and 112 tumors or 49.7% a rate <10%. We considered in our study the cut-off at 14%⁽⁴⁾. Ki67 is above 14% in 39.9% and less than or equal to 14% in 60.1%. The distribution of patients according to the molecular classification shows a rate of 65.5% for luminal carcinomas, 22.0% for triple negative and 12.5% for the group overexpressing HER2. Luminal carcinomas are subdivided according to Ki67 (cut off 14%) in luminal A in 59.0% and luminal B in 41.0%.

Discussion: We analyzed clinical, histological parameters and their interaction to determine prognostic and predictive factors. The average age of patients is 49.78 ± 11.29 years very close to the national average⁽⁵⁾. Unlike in Western countries, breast cancer in Algeria is a young woman's disease with a low overall survival, hence the need for the implementation of a screening, early detection and treatment strategy. Breast self-management remains the most common mode of discovery of breast cancer in our population, and most patients present themselves with the diagnosis, unfortunately at a late stage of its evolution. On average, the tumor size of our patients is 2.4 ± 1.2 cm. In most series of developing countries, the tumor size is greater than 2 cm and the discovery of cancer is late, in contrast to countries where mammography breast tumor screening is part of their health policy⁽⁶⁻⁷⁻⁸⁾. Histological grade is an important and independent prognostic factor for metastatic risk and survival in both N+ and N- groups⁽⁹⁾. Our results show that lymph node status correlates with the presence of vascular emboli and the expression of hormone receptors. Our HER2 3+ rate is about 22% relatively increased compared to the data of the literature in relation to the young age of the patients and probably also with the validation of the technique of Immunohistochemistry which requires rigorous work rules dependent on the quality of the laboratory, hence the need for Standardisation of Pre-Analysis Factors, Analytical Factors and Post-Analysis Factors⁽³⁾

The molecular classification of mammary carcinomas in our series confirmed that morphological analysis remains very important, and that there is no more important prognostic information than the validated anatomoclinical and immunohistochemical factors.

Conclusion: Intrinsic molecular classification allowed a better understanding of the disease by demonstrating its molecular heterogeneity. Today in daily practice, the clinician always relies on clinical-pathological consensus parameters to define the prognosis of the tumor: age of the patient, tumor size, lymph node invasion, presence of vascular emboli, histological grade, hormone receptor status, HER2 and Ki67 proliferation index. Knowledge of the epidemiology of breast cancer in our population will help establish prevention actions and organize a screening program to improve the monitoring of this pathology in our population.

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