MOLECULAR CLASSIFICATION OF BREAST CANCER

Classificação molecular do câncer de mama

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Abstract: Breast cancer is an heterogeneous complex of diseases, with wide clinical, biological and molecular spectrum, that results in distinct patterns of response to the different types of treatments used. The advances in biotechnology allowed the evaluation of the genome and the genetic expression profiles of several of these tumors, and from that on the classification in the following molecular subtypes was possible: luminal A, luminal B, HER2 over-expression, basal-like, normal-like, claudin-low, molecular apocrine, interferon-rich and metaplastic breast cancer. The biological and molecular characteristics of the subtypes are presented and discussed, as well as their prognostic importance. It was also approached the further division of these molecular subtypes, proposed by the Molecular Taxonomy of Breast Cancer International Consortium, in ten integrative clusters that possess different clinical features and particular prognosis. The different genetic expression profiles of breast cancer that are presented in this article are evidence of the capability of the molecular approach to stratify the cancer in biologically and clinically significant subgroups, and, therefore, intervene directly in the conduct to be established.

Keywords: Breast cancer; Breast neoplasm; Molecular classification.

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Resumo: O câncer de mama é um complexo heterogêneo de doenças, com um amplo espectro clínico, biológico e molecular, que resultam em distintos padrões de respostas aos diferentes tipos de tratamento instituídos. Os avanços na biotecnologia permitiram a avaliação do genoma e do perfil de expressão gênica de vários desses tumores, e a partir disso foi possível a classificação nos seguintes subtipos moleculares: luminal A, luminal B, HER2 over-expression, basal-like, normal-like, claudin-low, molecular apocrine, interferon-rich e metaplastic breast cancer. As características biológicas e moleculares dos subtipos são apresentadas e discutidas, assim como sua importância prognóstica. Também foi abordada a posterior divisão desses subtipos moleculares, proposta pelo Molecular Taxonomy of Breast Cancer International Consortium, em dez agrupamentos integrativos que possuem características clínicas diferentes e prognóstico próprio. Os diferentes perfis de expressão gênica do câncer de mama apresentados neste artigo evidenciam o poder das abordagens moleculares para estratificar o câncer em subgrupos biologicamente e clinicamente significativos, e, portanto, interferir diretamente na conduta a ser estabelecida.

Palavras-chave: Câncer de mama; Neoplasias da mama; Classificação molecular.
INTRODUCTION

The breast neoplasias are the most common type more common among women in Brazil and in the world, after non-melanoma skin cancers, accounting for approximately 28% of new cases each year. This neoplasm has a high mortality rate, which describes a growing curve and represents the leading cause of death due to cancer in the female population. Thus becoming an important public health problem in Brazil.1,2

Breast cancer is a heterogeneous group of tumors, associated with different prognoses. The knowledge acquired by the end of the 20th century demonstrated, through immunohistochemical and morphological exams, that clinical and pathological factors were important variables of prognosis. Such factors, such as the tumor staging, the histologic types, the proliferative status and the lymphovascular involvement were widely used as indicative of pace of division and tumor aggressiveness3,4,5

Recently, the use of the technology of microarray of complementary DNA to evaluate profiles of gene expression revealed, with the parallel analysis of thousands of genes, a diversity and complexity related to different genetic content in each tumor and the own molecular characteristics underlying each neoplastic cell.6 The group of tumors genetically similar is essential in the clinical context for the best guidance of therapy and the determination of accurate prognostics. It has been demonstrated that the immunohistochemical panels present a correlation with the analyses of genetic profiles, which provided better applicability in daily clinical practice5

The factors known classically as most relevant for this purpose are the expression of estrogen receptors (ER), progesterone receptors (PR) and progesteron receptors type 2 of epidermal growth factor (HER2). From this, it was possible to initially identify five molecular subtypes: the lumen, the lumen B, HER2-enriched, basal-like and normal-like. Currently are also described the subtypes claudin-low, molecular apocrine, interferon-rich e metaplastic breast cancer.4,7

The aim of this review is to discuss the molecular subtypes of breast cancer and their main characteristics, highlighting the immunohistochemical markers used for its characterisation. The in-depth knowledge of molecular subtypes, besides estimating more concisely the prognosis of these patients, offer them a great impact on the therapeutic approach.

LITERATURE REVIEW

TECHNIQUES FOR THE CLASSIFICATION IN MOLLECULAR SUBTYPES

The profile of gene expression is the gold standard for the classification of breast cancer in molecular subtypes. Its analysis in breast cancer, even in tumors with morphological similar characteristics, showed a marked molecular heterogeneity, explaining the need for the development of new tools for stratification of these tumors.6 A study by Perou et al8 (2000), from the molecular analysis of various breast neoplasms, demonstrated that, although each tumor presenting a global profile of expression of unique genes (PGEG), the tumors can be separated into groups based on transcriptomic profiles.

The technique of microarray allows the simultaneous study of several genes. Probes have specific known positions, which form an
arrangement, and are able to identify partially or completely a gene. The messenger RNA of the tissue studied is converted into simple strips of complementary DNA, marked by fluorescent red and green dyes, which is then hybridized with the probes. The process is analyzed by a software, and the hybridization indicates the sequence of DNA that is searched for.\(^{5,9}\) Thus, the identification of which genes are up or down regulation allows the definition of characteristic profiles for each sample analyzed. Examples of this tests which are available in the market are: MapQuantDX\textsuperscript{TM}, ProSigna\textsuperscript{®}, Mammaprint\textsuperscript{®}, OncotypeDX\textsuperscript{®} and EndoPredict\textsuperscript{®}. The benefits of their application and subsequent molecular classification are guide therapy and define the prognosis and risk of recurrence of the tumor.\(^{4,10}\)

In the Brazilian context, the limitation of resources does not allow such techniques, more sophisticated, to be widely used. Therefore, the immunohistochemistry becomes more financially viable.\(^{6}\) The protein biomarkers identified by this review are the hormonal receptors, HER2 and Ki67, which is an indicator of cell proliferation, thus used to assess the rate of tumor growth.\(^{4,5}\)

Subsequent analysis of the global profile of expression of genes contributed to the classification as described below:

**Luminal A**

The so called luminal subtypes due to the similarity of neoplastic cells with epithelial cells differentiated located in the lumen of the lobular ducts Among them, the molecular subtype luminal A represents 40 to 60% of the cases of breast cancer.\(^{11,12}\)

The luminal subtype A, typically, has estrogen receptors and/or progesterone receptors, however, are negative for amplification of HER2. This subtypes therefore, are sensitive to hormone therapy and respond to antiestrogenic action and inhibitors of aromatase. Usually, the luminal group presents a better prognosis compared to other subtypes.\(^{11-13}\)

This group of tumors is what most presents genetic mutations, being that the mutation is the most common of the gene PIK3CA in 45% of cases.\(^{10}\)

**Luminal B**

Tumors of the luminal subtype B, also originate in cells of the lumen of the lobular, correspond to approximately 20 to 30% of breast cancers. They have in their majority, positive hormones as RE and RP. The progesterone receptors, however, can be expressed at high or low levels in tumor cells. This group shows, more frequently mutations in the genes TP53 and PIK3CA.\(^{10,11}\)

The subtype Luminal B expresses a more aggressive group of tumors, with an increased index of proliferation. The concomitant expression of HER2 gene, a contributing factor to this behavior, is due to the greater expression of genes GATA3, breast cancer L2 and ESR1, besides mutations in the gene GATA3. Other proliferation genes are expressed in a larger number in this subtype, which include the genes MKI67, CCNB1 and MYBL2. The highest rate of proliferation conferred by these genes results in a worse prognosis compared to the luminal subtype A.\(^{5,11,14}\)

A new subclassification for this group was proposed through the use of the index Ki 67, in which it is divided this subgroup in the lumen B and the lumen HER2. Therefore, it is described the luminal subtype B by the expression of at least one of the hormone receptors; by the positivity of the HER2 gene, by imposing the nomenclature of the lumen HER2; and, when it is negative for the expression of HER2, by an index Ki 67 equal to or greater than 14%.4%. These characteristics help in
the differentiation of luminal subtypes A and B.\textsuperscript{12-14}

**HER2 over-expression**

The overexpression of the oncogene HER2 occurs by gene amplification and is present in approximately 15% of the cases of invasive breast cancer.\textsuperscript{15} It shows no hormonal receptors, has a clinical aggressive behavior, highly proliferative, and its prognosis is considered the second worse, among others. They often show mutations in TP53 and PIK3CA\textsuperscript{5,10,16}.

The therapeutic target-specific with the humanised monoclonal antibody trastuzumabe has important positive effect on the prognosis of patients with this type of tumor. It has the effect of reducing the progression of the disease and improve the life expectancy. It is effective when used alone or in combination with chemotherapy, if there is metastasis.\textsuperscript{14-17}

**Basal-like**

They represent 10 to 25% of cancers of breast cancers, are more common in young women, descendants of african americans or Hispanics and in multiparous women, unlike other molecular subtypes. In these tumors, 90% of cases result from mutations in the gene TP53.\textsuperscript{18,19}

The representatives of this class are so called by expressing genes present in the basal myoepithelial cells, although they do not originate from them, but from luminal stem cells. TSuch genes are responsible for the expression of cytokeratins (CK) of high molecular weight, also known as basal, which are the CK 5/6, 14 or 17. However, they can also express the CK 8/18, typical of the luminal epithelium, however to a lesser amount than the luminal subtypes.\textsuperscript{4,20,21} There is also an expression of receptors type 1 of epidermal growth factor (EGFR/HER1). Another striking feature in basaloid tumors is not expression of genes of hormone receptors and HER2, which defines as triple-negative patients in the immunohistochemical studies\textsuperscript{20-22}.

A growing number of basal immunohistochemical markers has been used to define the basal tumors, among which the CK 5-6, 14, 17, 8/18, EGFR are the most widely accepted. Various combinations of these baseline marker were used to identify the basal subtype, however, the more pragmatic and widely accepted definition in the basal subtype is negative RE, negative PR, HER2-negative tumors with positive expression of CK5 & 6 and EGFR.\textsuperscript{21-23}

The carcinomas of this subgroup compared to the superexpressores of HER2 in a matter of clinical aggressive behavior, are the most likely to result in metastasis and have the worst prognosis among all cancers of the breast, despite the good sensitivity to chemotherapy. To the histological examination, high mitotic index overexpression f genes that induce cell proliferation is expressed. Its edges are retracted, there is important lymphocytic infiltrate and a central necrosis.\textsuperscript{22-25}

Additionally, it has been demonstrated that basaloid carcinomas has suppression of BRCA1 gene, by inactivation of its transcription or methylation of its promoter genes, or even by both mechanisms. In addition, it is known that tumors that originate from mutations of BRCA1 have basaloid triple-negative phenotype. Therefore, it is concluded that mutations in BRCA1, hereditary or not, will be common with basal-like tumor. These data are consistent with the hypothesis that basaloid non-hereditary cancers may be regarded as phenotypic copies of neoplasia in individuals with mutation of the BRCA1 gene.\textsuperscript{5,18,20-24}

**Normal-like**

In theory, this group has high expression of genes present in normal luminal cells, fat cells
and other cells of the breast stroma, and there is no expression of tumor biomarkers, such as RE, RP and HER2. The markers present in the basal-like subtype, as the CK basal and HER1 are also not expressed.\textsuperscript{8,16,24}

It is believed, however, that the description of this subtype is due to the existence of bulky artifacts of breast epithelial tissue and normal stromal in the samples subjected to analysis of gene expression profile\textsuperscript{5,24}.

**Claudin-low**

First described in 2007 by Herschkowitz et al\textsuperscript{26}, this subgroup of triple-negative non-basaloid tumors predominates in approximately 7 to 14% of the cases of breast neoplasia. It was demonstrated relation of this subtype with underlying mutation of the BRCA1 or TP53 gene. It does not have protocol of specific biomarkers for its classification, and it has not been described in a distinct therapeutic approach.\textsuperscript{22,27}

In this subtype, there is notable downregulation by epigenetic silencing of genes of claudins 3, 4 and 7, the occludina and E-cadherin. As a result, there is low or no expression of these transmembrane proteins, which are necessary for cell adhesion. There is also an important expression of genes related to the epithelial-mesenchymal transition, as the genes Snail-1, Snail-2, TWIST1, TWIST2, ZEB1 and ZEB2.\textsuperscript{22,28,29}

It is believed that the subtype claudin-low originates from more primitive cells than the other subtypes. The expression of markers of stem cells (CD44, CD24, EpCAM, CD10, CD49, CD29, MUC1, THY1 and ALDH1A1) identifies this tumor as the most similar to stem cells. In addition, it also expresses markers of starting cells of tumor and endothelial and lymphocytic markers.\textsuperscript{24,27-30}

To the histopathological examination is usually characterized as a invader carcinoma poorly characterized (associated with the lower response to therapies and worse prognosis), and with a high lymphocyte infiltration. Often it differs in the following morphological types: the spinal cord, a situation often related to good prognosis; and metaplastic.\textsuperscript{25,30}

**Molecular apocrine**

The molecular subtype apocrine, described by Farmer et al\textsuperscript{31} in 2005, was named by its apocrine histological features, such as the abundant cytoplasm and prominent nucleoli, although this morphology is not always present in this subtype. It is present in approximately 13% of the mammary neoplasms.\textsuperscript{27} In a study of Lehman et al\textsuperscript{32}, carried out in 2011, these tumors are named luminal receptors of androgen.

These tumors have a wide expression of androgenic receptors (RA), are RE-negative and may or may not express HER2. It is possible that the overexpression of RA is directly related to mutations of the gene PIK3CA.\textsuperscript{5,27,32}

The neoplastic cells of this subtype have a high autophagic activity and, although clinically these tumors show a good response to neoadjuvant chemotherapy are associated to an early recurrence.\textsuperscript{27,32}

**Interferon-rich**

Described by Hu et al\textsuperscript{33} in 2006., this subtype, referred to in approximately 10% of cases of mammary neoplasms, characteristically has high expression of genes regulated by interferons. It does not express either hormone receptors or HER2, so it is a triple-negative.\textsuperscript{15,27}

The genes of major importance to
distinguish the tumors interferon-rich from other triple-negative are the STAT1 and the SP110. The first acts as a transcription factor whose function is to mediate the regulation of gene expression exerted by interferons. The second has prognostic value reported.\textsuperscript{16,27}

**Metaplastic breast cancer (MBC)**

The MBC is a triple-negative non-basaloid tumor highly aggressive, corresponds to 1% of breast cancers and is characterized by the coexistence between carcinoma and non-epithelial cell elements. They are prone to local recurrence and to metastasize.\textsuperscript{27}

Additionally, they can be subdivided by their pathological characteristics in homogeneous, heterogeneous, or malignant tumor pure epithelial with metaplasia. In the first group are the carcinomas of fusiform cells and the sarcomatoid carcinomas. The second group comprises the carcinosarcomas and the carcinomas with sarcomatous differentiation, which may be bone, chondroid or rhabdoid. The Adenosquamous carcinoma and squamous carcinoma cells are pure representatives of the third group. However, this classification has no clinical relevance, and the MBC should be seen as a single entity.\textsuperscript{27,34}

These tumors are similar to subtype claudin-low for the characteristics of the tumor, the genomic aberrations, response to therapy and prognosis. Both have overexpression of markers of the epithelial-mesenchymal transition group, have markers of stem cells, and probably arise from a more primitive cell than the progenitor cell of other subtypes. The difference between them is the mutation of genes PIK3CA, AKT OR KRAS, present in SUBTYPE MBC and absent in the claudin-low. Still, it was evident that the existence of one does not exclude the existence of another, and, in a small proportion of cases, there is overlap among them.\textsuperscript{27,34}

A relationship between each subtype intrinsic molecular described and its profile of biomarkers is presented in table 1.

### Table 1 - Summary of molecular subtypes of breast cancer according to the biomarkers.

<table>
<thead>
<tr>
<th>Macro Group</th>
<th>Molecular Subtype</th>
<th>Biomarkers Profile</th>
<th>Other markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal</td>
<td>Luminal A</td>
<td>RE+, RP+, HER2-, Ki67 &lt;14%</td>
<td>Luminal cytokeratin+, FOXA1+, ADH1B high</td>
</tr>
<tr>
<td></td>
<td>Luminal B</td>
<td>RE+, RP+, HER2-, Ki67&gt;14%</td>
<td>HER2+, RE+, RP+, Ki67&gt;14%</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>HER2</td>
<td>RE-, RP-, HER2+</td>
<td>TP53--; GRB7 high</td>
</tr>
<tr>
<td>Basal-like</td>
<td>RE-, RP-, HER2-, CK5/6+ and/or EGFR+</td>
<td>BRCA1-, TP53--; CDKN2A high; RB1 low; FGFR2 amp</td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>Claudin-low</td>
<td>RE-, RP-, HER2-, marker EMT+, marker Stem-cell+, Claudin-</td>
<td>GATA3-regulated genes, cell-cell adhesion genes low; CDH1 low; Claudins low</td>
</tr>
</tbody>
</table>
|             | MBC               | RE-, RP-, HER2-, marker EMT+, marker Stem-cell+ | GATA3-regulated genes, cell-cell adhesion genes low; PIK3CA-, AKT- ou KRAS-
|             | Interferon-rich   | RE-, RP-, HER2-, genes regulated by interferon+ | STAT1, SP110 high |
|             | Molecular apocrine| RE-, RP-, RA+ | Ki67+ |
PROGNOSIS

One of the main functions of the classification of breast cancer into subtypes molecular intrinsic is to enable the prediction of the clinical evolution of the patients affected. The group of luminal neoplasias have the best prognosis, high sensitivity to hormone therapy and low rate of mortality when compared to triple-negative. These are associated with a higher rate of recurrence and the overall survival rate, and do not respond to endocrine therapy.\(^{35,36}\)

The division of luminal group presents prognostic relevance, in that the luminal exhibits more favorable evolution. Approximately 90% of patients present life expectancy without signs of disease in five years. Whereas the B luminal behaves more aggressively, resulting in worse outcomes than the intraluminal A. Nevertheless, there is good therapeutic arsenal for the luminal B, since it is sensitive to hormone therapy and benefits from the use of Trastuzumabe when expresses HER2. The double therapy-targetsignificantly improves the prognosis. The response to chemotherapy is generally low in the luminal tumors, but is apparently higher in cancers of the lumen B type.\(^{35,36-38}\)

The overexpressor subgroup of HER2, due to aggressive behavior, has badly prognosis, and the prognostic value of the presence of HER2 is higher in patients with lymph node involvement. The introduction of therapy-target anti-HER2 with the trastuzumabe, that can be associated with chemotherapy, provided great improvement in the prognosis of these patients.\(^{36,39}\)

The basaloid tumors are breast neoplasia of worse prognosis, although they are the most responsive to neoadjuvant chemotherapy. Highly aggressive, even small tumors without nodal impairment are related to low survival rate. In fact, tumor size and metastases in lymph nodes do not have documented relationship with the prognosis, in this subtype. The subtype claudin-low is similar to basaloid in aggressiveness and low overall survival, despite the sensitivity to chemotherapy. Its prognosis is worse in relation to luminal, but slightly better than the basaloid and HER2.\(^{37,40,41}\)

The prognosis of apocrine molecular tumors, although does not have RE and RP, is comparable to that of the luminal subtypes, and has low capacity of metastasis formation. The anti-androgenic therapy-target can be used.\(^{36,38}\)

Cancers of the type interferon-rich are the best prognosis among the triple-negative. The survival without disease is comparable to that of the luminal subtype B. This suggests that immune activation against the tumor is related to better clinical evolution and the best response to appropriate therapy.\(^{27,42}\)

The neoplasias of the type MBC differ from other triple-negative by high recurrence rate, between 2 to 5 years after the initial diagnosis in patients without nodal involvement. This rate reaches 45 to 62%, against 17 to 20% chance of recurrence of the other triple-negative effects of the same size. Another difference is the scarce benefit of this subtype to chemotherapy, which may result from mutations in the signaling pathway phosphatidylinositol 3-kinase (PI3K/AKT. This pathway is, therefore, a possible therapeutic target in this subtype.\(^{38-40}\)

The most common metastatic occurs in bones, to luminal A and B (80% of cases) and overexpressors of HER2 (65%); and in the lung, for basaloid and claudin-low (50%). The Brain Metastases are more common in triple-negative,
and the hepatic, in overexpressors of HER2. The subgroup of greater propensity to metastasize is the basal-like.39-42

INTEGRATIVE CLASSIFICATION

After the study of the genome and the profile gene expression of 2000 cases of breast cancer, the international consortium METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) has identified forty-five changes in the number of copies (copy number Jul-CNA) applicants and discussions, which have great impact on gene expression in these regions. Among them are genes drivers with involvement known or alleged in the oncogenesis, as amplifications mapped in ERBB2, MYC, EGR1, CCNE1, MDM2 and MDM4; and deletions in PTEN, PPP2R2A and MAP2K4.5,16,43

From there, there was an integrative grouping when using the 1000 genes whose expression is more affected by the CNA, with the definition of ten new molecular subgroups. These groups represent a subsequent stratification to intrinsic subtypes previously described, and have distinct clinical changes5,16

The integrative grouping (AI) 1 comprises neoplasias with expression of RE, especially the high-grade tumors of type B luminal, with high genetic instability and amplification of the locus 17q23. AI 2, which also includes positive tumors for RE, shows the amplification of 11q13-q14 and gain in the number of copies in firestorm pattern. Whereas the AI 3 presents low levels of genetic instability, and includes tumors of low grade and good prognosis. A large part of the neoplasias of AI 4 have important lymphocytic infiltrate, and 20% of them show a deletion of the loci of receptors of T cells in chromosomes 7 and 14. AI 5 comprises the cancers expressor of HER2, which have a high degree, and the patients in general are younger. Positive tumors for RE, high genetic instability and amplification of the locus 8q12 make up the AI 6. In the AI 7 are the tumors that express RE and RM, with loss of 16q, gain of 16p and amplification of 8p. AI8 is characterized by gain of 1q and loss of 16q. Changes in 8q and amplifications in 20q define the AI9. Deletion of PP2R2A, an important component of the process of signal transduction, is present in many of the cancers grouped in AI 1, 6, 8 and 9. Finally, the AI10 fits the majority of triple-negative tumors, of high degree and with the highest rates of mutation in TP53.16,43,44

Table 2 lists each integrative grouping with its frequency in the study of METABRIC, its clinical character and prognosis.

<table>
<thead>
<tr>
<th>AI</th>
<th>Frequency (%)</th>
<th>Clinical Character</th>
<th>Prognosis (Survival probability specific-disease in 5 and 10 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7%</td>
<td>High Degree</td>
<td>Intermediate 0.80; 0.69</td>
</tr>
<tr>
<td>2</td>
<td>4%</td>
<td>Without specific characteristics</td>
<td>Bad 0.78; 0.51</td>
</tr>
<tr>
<td>3</td>
<td>15%</td>
<td>Low degree</td>
<td>Good 0.93; 0.88</td>
</tr>
<tr>
<td>4</td>
<td>17%</td>
<td>Low degree</td>
<td>Good 0.89; 0.76</td>
</tr>
<tr>
<td>5</td>
<td>10%</td>
<td>Diagnosis in early age; High Degree; High degree of lymph node impairment</td>
<td>Bad 0.62; 0.45</td>
</tr>
</tbody>
</table>
Continuação da tabela 2.

<p>| | | | |</p>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>4%</td>
<td>Without specific characteristics</td>
<td>Intermediate 0.83; 0.59</td>
</tr>
<tr>
<td>7</td>
<td>10%</td>
<td>Diagnosis in late age Low degree</td>
<td>Good 0.94; 0.81</td>
</tr>
<tr>
<td>8</td>
<td>15%</td>
<td>Diagnosis in late age Low degree</td>
<td>Good 0.88; 0.78</td>
</tr>
<tr>
<td>9</td>
<td>7%</td>
<td>High Degree</td>
<td>Intermediate 0.78; 0.62</td>
</tr>
<tr>
<td>10</td>
<td>11%</td>
<td>Diagnosis in early age High Degree Big tumors</td>
<td>Bad 0.71; 0.68</td>
</tr>
</tbody>
</table>

CONCLUSIONS

The advances in molecular tests have broadened the understanding of the underlying biological processes to breast cancer, providing better actions for the prevention, diagnosis and therapy. These advances demonstrate the power of molecular approaches to stratify the cancer into subgroups biologically and clinically significant, and, therefore, directly interfering in the workup to be instituted. Although the molecular analysis has uncovered some highlights in the genomic profiles of breast cancer, the systems of molecular classification are still evolving and are currently of limited value in clinical scenario, in which the management of patients still depend on the pathologic evaluation of tumors.

The recent evolutions in the technologies of DNA sequencing have been useful to identify the genomic heterogeneity among the subclonal populations of tumor cells, but the extent of this heterogeneity remains largely unknown. It will be necessary further research on a large scale that comprise multiple stages of breast cancer in order to determine a more reliable clinical value of such variation in the genomic profile. In addition, advances in the molecular profile of the cancer in areas of epigenetics, microRNA and proteomics may play important roles in clinical trials in the near future.

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