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Influence of the Genetic Profile on the Therapeutic Conduct of Invasive Breast Ductal Carcinoma: A Systematic Review of Literature

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Abstract: *Breast cancer is the most frequently diagnosed type in the world and the leading cause of cancer-related death among women. Its central component of treatment is full knowledge of the extent of disease and biological characteristics, where the use of genetic profile has contributed to tumor characterization and therapeutic targeting. Then, the objective this study was evaluated the use of the genetic profile of invasive ductal carcinoma of the female breast and it's obtained scores. To verify its use or not for directing the treatment of breast cancer in surgery, radiotherapy and chemotherapy. A search was performed on the PUBMED and SCOPUS databases, with the following descriptors and their synonyms: breast neoplasm, gene expression profile, genetic test, radiotherapy, surgery, chemotherapy, recurrence, survival and prognostic marker, as well as their correspondents in English.We selected nine articles published in international journals. Results: The use of genetic profile is related to recurrence scores for chemotherapy treatment and evidence of its use for applicability in chemotherapy and surgical treatment. The definition of therapy in the treatment of breast cancer in the early stages has been widely discussed in the scientific community regarding clinical, pathological and immunohistochemical criteria. Genetic susceptibility studies may provide useful information to the clinical staff in deciding the most appropriate therapeutic approach in specific cases. There is a need for further studies in the application of molecular profiles for personalized treatment, especially for patients with specific genetic mutations.*

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I. Introduction

Breast cancer is one of the biggest causes of mortality in the world, it arises as a consequence of genomic alterations of healthy cells that by mutations become malignant.These mutations can occur by several mechanisms, including chromosomal breaks and losses, amplifications, instabilities, where proto-oncogenes, tumor suppressor genes and DNA repair are the main genomic groups involved[1].

It is the most frequently diagnosed in the world and the leading cause of cancer-related death in women. Under epidemiological aspects, expected in 2016 about 56.20 new cases of breast cancer per 100,000 inhabitants, representing 28.1% of the incidence of cancer in women.It is also the most frequent type of cancer in the South Region of Brazil with 74.30 cases per 100,000 inhabitants. In Rio Grande do Sul, around 5210 cases were expected in 2016, with a gross rate of 90.20 cases per 100,000 inhabitants[2,3].

It belongs to a heterogeneous group of diseases presenting more than 20 subtypes. Most tumors originate in the ductal epithelium, which is known as invasive ductal carcinoma, with about 80% of the cases, in addition to lobular, tubular, papillary, mucinous, medullary, micropapillary subtypes[2]. The proliferative anomalies of the breast are usually in the lobular and ductal epithelium, where about 85 to 90% of the invasive breast carcinomas are of ductal origin[1].

Breast cancer therapy varies according to disease staging and other biological characteristics and conditions of the patient. Treatment can be local (surgery and radiotherapy) and systemic (chemotherapy, hormone therapy and biological therapy)[2].A central component of breast cancer treatment is full knowledge of the extent of disease and biological characteristics, as they contribute to the determination of the stage of the disease and estimate the risk of recurrence, thus providing information that anticipates the response to therapy. There are several prognostic factors to predict future recurrence or death from breast cancer, such as patient's age, comorbidities, grade and HER-2 status of the tumor[1].

Currently genetic aspects of cancer have contributed to characterize the tumor and better target therapeutic management. Thus, gene expression may contribute to the measurement of the risk of recurrence and to guide the use of chemotherapy. Immunohistological biomarkers (ER-estrogen receptor, PR-progesterone receptor, HER-2 - Human Epidermal growth factor Receptor-type 2 and Ki-67 - cell proliferation marker) are used, as well as other expression as the profile of 21 genes and profile of 78 genes[4]. Studies have proven the clinical utility of multigene panels in clinical prediction and are increasingly being used in the clinical practice of cancer treatment. They have been shown to be promising tumor markers in predicting disease progress and personalized decision making[4].

Thus, the use of genetic profile research has facilitated the choice of targeted therapy, contributing to a lower risk of recurrence and increasing the survival of patients with breast cancer.

Genetic mapping is able to identify mutations or gene expressions that may have a decisive role in the use or not of systemic treatment. Specific therapy may also be able to decrease or prevent the incidence of adverse effects from radiotherapy and cytotoxic therapy, providing a gain in quality of life for the patient.

The present study aims to evaluate the use of the genetic expression profile of invasive ductal carcinoma of the female breast in addition to the scores used to evaluate prognosis. To verify the use or not of specific therapy according to the genetic signature expressed in women with invasive ductal carcinoma of the breast. To evaluate the use of sensitivity profiles in chemotherapy and radiotherapy for the determination of the treatment protocol.

II. Material And Methods

This is a systematic review of the literature using the methodology proposed by the Cochrane Collaboration[5]. In order to define the research question and the inclusion and exclusion criteria, the PICO strategy was used (acronym for Patient, Intervention, Comparison, Outcomes or outcomes)[6]. The defined population was of female patients with invasive ductal carcinoma of the breast in the initial stages, the intervention to be researched was of gene expression profile through the use of genetic panels. The control was compared with the surgical, radiotherapy and systemic treatment defined by immunohistological diagnosis and an expected outcome of obtaining recurrence scores and more favorable prognostic markers (with increased survival due to the use or not of oncologic treatment).

The eligibility criteria for the papers used were original articles found in the Pubmed and Scopus databases for a period of ten years (January 2008 to January 2017).Sources were recovered presenting results for search terms related to invasive ductal breast carcinoma, from descriptors and synonyms in the English language: "Breast Neoplasms". Terms related to gene expression profile, from English descriptors and synonyms: "gene express profiling" OR "genetic testing". Terms related to treatment, from the following English descriptors and synonyms: "radiotherapy" OR "chemotherapy" OR "surgery". Terms related to survival and recurrence, from the following English descriptors and synonyms: "recurrence" OR "survivor" OR "prognostic marker".

During the information retrieval procedure we considered the keywords found preferentially in Titles, Abstracts and Keywords of each database. In the initial survey, 110 articles were identified, which were evaluated by 2 researchers (authors) according to the inclusion criteria: publications in English, Portuguese or Spanish, with availability in the full and free version, whose study has been applied in humans which addressed the topic of invasive ductal carcinoma in women and genetic profile. Repeated articles in the different databases were excluded and those referring to other tumor sites, male breast cancer, in situ breast carcinoma, metastatic breast carcinoma or neoadjuvant therapy, publications not related to genetic profile, case reports, other review articles and qualitative studies. The process of selecting the works is shown in table 1.

Table 1. Articles selected from the databases consulted

DATABASES CONSULTED	PUBMED	SCOPUS
Articles initially identified (n =110)	48	62
Articles excluded by repetition (n =24)	00	24
Articles excluded by content incompatible with the object of the study (n = 44)	19	25
Eligible articles for the study (n =42)	29	13
Eligible articles after consensus (n =9)	06	03

III. Result

The final research material consisted of 42 selected articles, of which 9 were included in this review and classified in the units of analysis: recurrence scores and influence of genetic panels on the therapeutic management of breast cancer.

From the reading of the studies included in this systematic review, it can be verified that the majority of the articles dealt with the use of genetic profiles in the use of adjuvant chemotherapy[7-14]. Only one study used

the genetic profile evaluation in a surgical procedure15. The articles that compose this systematic review can be visualized in Table 2.

Table 2. Characterization of the articles

AUTHORS / YEAR	COUNTRY	OBJECTIVE	METHODOLOGY	GENETIC PROFILE (COURSE OF CONDUCT)
ALBAIN et al., 2010[7]	U.S	Verify that the 21 gene assay identifies benefit to anthracycline treatment.	Retrospective analysis evaluating the effect of recurrence rate on disease-free survival in 3 groups of patients: patients using tamoxifen only, cyclophosphamide + doxorubicin + fluorouracil protocol followed by tamoxifen (CAF-T) and cyclophosphamide + doxorubicin + fluorouracil + tamoxifen (CAFT)	Disease-free survival was higher in patients who used the caft and caf-t protocols compared to the tamoxifen group. The 21 gene assay can predict which patients benefit from the use of anthracyclines, even in patients with positive lymph nodes.
GEFFEN et al., 2011[8]	Israel	Experience with the SR of 21 genes in a single oncology practice in Israel with a unified treatment policy in 135 patients treated between 2006 and 2009 and assessed its impact on the selection of adjuvant systemic therapy.	Retrospective analysis of treatment recommendations before and after the 21 gene assay.	The 21-gene assay, when applied consistently in the early stage of breast cancer, changes treatment recommendations in a quarter of the patients tested.
GRANT et al., 2013[9]	South Africa	To evaluate the use of panel test of 70 genes as screening for diagnosis of breast cancer.	The study population included 104 patients with early stage breast cancer referred to the MammaPrint trial by the participating clinicians.	60% of the samples were classified as low risk and 40% as high risk of recurrence of breast cancer. Patients with early low-risk breast cancer can effectively be spared from chemotherapy. The 70-gene profile ranks as low-risk approximately 40% of patients with early-stage breast cancer compared to 15% using conventional criteria. In this way, a more aggressive chemotherapy treatment is prevented.
SANFT et al., 2015[10]	U.S	To verify therapeutic conduct after use of the BCI (Breast Cancer Index) and conflict of decision of medical conduct.	Application of the BCI genetic test in a group of patients with hormone receptor positive for subsequent disclosure of results and conduct verification.	Discordance of pre and post-test medical conduct in the recurrence of breast cancer and reduction of the recommendation of endocrine therapy.
SHEPPARD et al., 2015[11]	U.S	Evaluation of sociodemographic, clinical and attitudinal factors associated with the SR test and its effect on the use of chemotherapy in black and white women patients.	Recruitment of women with invasive and non-metastatic breast cancer and subsequent evaluation of SR tests and receipt of chemotherapy	Association between use of chemotherapy and increased risk of recurrence was found.
CARDOSO et al., 2016[12]	U.S	Search for candidates to prove the clinical usefulness of MamaPrint as a selection criterion for adjuvant chemotherapy.	Patients included in the study = patients from 112 institutions from 9 European countries from 2007 to 2011. Age 18 and 70 years. Patients with confirmed invasive carcinoma with up to 3 positive lymph nodes. 6693 women with early-stage breast cancer.	It is concluded that approximately 46% of women with high-risk clinical breast cancer can be treated without the need for chemotherapy.

SHAH et al., 2016[13]	U.S	Evaluates the SR assay in patients with BRCA mutations and patients with sporadic breast cancer.	Case-control study where it was found by review of medical records the result of the test 21 genes mutated BRCA patients and non-mutated.	Greater benefit of chemotherapy for mutated BRCA patients
HENRY et al., 2017[14]	U.S	To examine the patterns of use of the 21 gene assay for selection of chemotherapy regimens in a state registry from 2006 to 2013.	Extraction of demographic, pathological and medical records data from 16,666 women with breast cancer. Treatment patterns were examined based on the RS score (Recorrence Score). Cohort Study.	Anthracycline-containing chemotherapy in eligible patients appears to vary with use of the SR assay, despite the lack of evidence to support the use of the assay to guide regime selection. The results of ongoing prospective trials should help define the role of the SR assay in this configuration.
NILSSON et al., 2014[15]	Sweden	To compare the use of conservative breast therapy and mastectomy in patients with BRCA1/2.	Group cohort who performed conservative breast therapy and group with mastectomy and recurrence risk analysis	Women with a BRCA1/2 mutation had a high risk of relapse. Genetic testing could positively influence treatment.

IV. Discussion

The effect of SR[7] on disease-free survival was assessed through the 21 genes test in postmenopausal women with hormone receptor positive breast cancer and positive lymph nodes treated only with tamoxifen or cyclophosphamide + doxorubicin + fluorouracil followed by tamoxifen (CAF-T) and cyclophosphamide + doxorubicin + fluorouracil + tamoxifen (CAFT). In this study, the 21-gene assay proved to be a predictor of the benefit of using chemotherapy for patients with a higher recurrence score and non-benefit for low-index patients. The study challenges the current standard of adjuvant chemotherapy for all breast cancer patients with estrogen receptor positive and lymph node positive, but emphasizes a need for a larger study and limits its results to only one group of patients and antineoplastic treatment.

Another study that examined the patterns of use of 21 genes for selection of chemotherapy regimens[14], where there was an increase in their use over time and a decline in use of chemotherapy for patients with low SR both for patients without lymph node involvement as without. "*It is important to note that we found that use of the SR trial was associated with a change in the use of anthracycline-based regimen chemotherapy regimens for non-anthracycline regimens".* However, it was not possible to determine how much of the decreased use of anthracycline-containing regimens is due to the use of the SR assay and how much is due to published findings from other clinical trials. In particular, the results of the SR assay seem to influence the selection of chemotherapy regimens by physicians, despite the lack of evidence to support the use of this assay.

The study's impact study of 21 genes[8] also concluded that the number of patients for the evaluation of therapeutic efficacy was 22%, proving its effectiveness in the treatment of MS patients for the diagnosis of estrogen-positive mammary carcinoma in stages initials. This study did not evaluate the patients in a randomized and still lymphonodal manner.

The study of test patterns of 21 genes[11] showed that women in the highest risk category who received SR had the highest use of chemotherapy (55%), suggesting that SR results may have influenced treatment decisions. These results further support studies that demonstrate that SR affects the use of treatment. It also points out that the recurrence score is underutilized in some populations. Despite the low number of the sample and study and it is also not known whether the non-performing test of 21 genes was attributed to medical orders.

One study compared recurrence scores in patients with BRCA mutations to patients with sporadic breast cancer, where there were distinct gene expression profiles[13]. In this analysis, BRCA mutation carriers were more likely to be at risk of intermediate to high recurrence compared to a control of patients without BRCA mutation. It is suggested that the presence of mutation may increase chemosensitivity as compared to sporadic breast cancers. No statistically significant differences were found in terms of risk of recurrence in tumors associated with BRCA1 versus tumors associated with BRCA2.

Despite limitations in the size, distribution, and size of the tumor tissue collected, this study agrees with the National Comprehensive Cancer Network (NCCN) guidelines in using the 21-gene test as a complementary test regardless of the BRCA ½ mutation.

The evaluation of the 70 genes profile had a favorable outcome to reduce the exposure of patients to adjuvant chemotherapy at an early stage[9,12]. It emphasizes, therefore, the importance of incorporating this type of analysis together with the traditional diagnostic standards. One of these studies[12] found 32% disagreement in clinical and genomic risk assignment methods, suggesting that the biological characteristics of the tumor are important for treatment decisions.

In the BCI genetic trial, a change in therapeutic management was observed in 26% for less use of prolonged endocrine therapy[10]. The evaluation of the risk of late recurrence by the physicians before the test was strongly discordant with the molecular results. The incorporation of the test led to a decreased perception of risk of late recurrence and reduced rate of recommendation for prolonged endocrine therapy.

The study chosen in this review where the genetic profile in the use of surgical treatment was verified, compared recurrence and disease-free survival among patients with BRCA mutations, who used breast conserving therapy and mastectomy[15]. It reported that the risk of recurrence was substantially higher in patients after conservative breast therapy than mastectomy for BRCA ½ mutation carriers. In addition to the type of surgery, the younger age was also associated with an increased risk of new primary breast cancers and / or recurrence, thus confirming the importance of the use of genetic tests in indicating treatment and in choosing the type of surgical approach.

V. Conclusion

The definition of therapeutics in the treatment of early stage breast cancer has been widely discussed in the scientific community with respect to clinical, pathological and immunohistochemical criteria, and may benefit from genetic susceptibility studies to avoid exposing patients to overtraining, improving quality and life expectancy.

Genetic susceptibility studies may provide useful information to the clinical staff in deciding the most appropriate therapeutic approach in specific cases. The diagnosis of genetic mutations can be used to aid in the management of oncologic treatment in order to benefit patients at high risk of recurrence, to reduce exposure to toxic damages of antineoplastic therapy in patients with low risk of recurrence. In patients with intermediate risk, the use of molecular markers is still a challenge, since the cost-benefit ratio of antineoplastic therapy to the radical approach (radical bilateral mastectomy) is not a consensus in the scientific community. The studies listed in this systematic review did not find reports of the application of molecular profiles in the decision-making power of radiotherapy, demonstrating the need for further studies in this area, since the radiotherapeutic toxic effect may be more evident in patients with specific genetic mutations, case of mutations in Mutant Ataxia-Telangiectasia (TMJ)[18], which would have exponentially increased the risk of recurrence at the irradiated site.

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