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Abstarct- Breast Cancer (BC) is the most commonly diagnosed cancer amongst women worldwide and is a leading cause of death and disability among women in low- and middle-income countries (MICs) among which is Argentina. Nowadays in BC, beyond the standard determination of cancer stage according to the classic anatomical criteria of the TNM the study of genic profile (GP) of cancer has also been encouraged. Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with, early stage, *estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative* BC ensuring that patients at highest risk of recurrence are prescribed systemic treatment, while at the same time sparing low-risk patients potential adverse events from therapy unlikely to influence their survival. Multigene panels can provide better risk discrimination relative to clinic-pathological factors. Unfortunately, all these tests are expensive.

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Surrogate Parameters, Instead of the Genetic Profile, for Recurrence Risk Evaluation in "Early-Stage Breast Cancer Cases" in a Middle – Income Country Like Argentina

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Abstract- Breast Cancer (BC) is the most commonly diagnosed cancer amongst women worldwide and is a leading cause of death and disability among women in low- and middle-income countries (MICs) among which is Argentina. Nowadays in BC, beyond the standard determination of cancer stage according to the classic anatomical criteria of the TNM the study of genic profile (GP) of cancer has also been encouraged. Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with, early stage, *estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative* BC ensuring that patients at highest risk of recurrence are prescribed systemic treatment, while at the same time sparing low-risk patients potential adverse events from therapy unlikely to influence their survival.Multigene panels can provide better risk discrimination relative to clinic-pathological factors. Unfortunately, all these tests are expensive.Given the potential savings in cost and resource utilization, several algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP).

Purpose: We evaluate the possibility, in a MIC country such as Argentina, of having the data from the normally required clinical-pathological report of the BC, in order to apply 10 selected published algorithms that are offered as alternatives to ODX to predict the ODX RS specifically in patients with "*early-stage breast cancer*" cases.

Methods: From the total of 1832 (stage I to IV) BC cases reported, between 2012 and 2014, to PROYCAM2012 (www.cancerdemama2012.org.ar) a consortium (still in force) created for the study of BC in Argentina a subset of 706 (38,5%) "*early-stage breast cancer*", was identified and analyzed. An online search and selection of published scientific research on SP, (2010 onwards), was carried out. Ten publications were selected and analyzed and the SP used in them identified. The presence of the SP shared by the different studies selected on - line was analyzed in our series, namely: age, tumor size, histology, grade, Estrogen/ Progesterone receptor, Her2 / neu status and Ki-67.

Results: The subset of 706 (38,5%) showed the following characteristics: predominant in menopausal women (72%), average age of 61 years, 3.2% bilaterally and a personal (30,3%) and/or family history (9,3%) of BC. Pathologically, the average size of the tumors is between 1.8 -2.0, with predominance of infiltrating ductal lesions (67, 7%) grade2 (46,7%). From the total of 10 nomograms selected only in 1 our series can complete the required two SPs: HR (96, 6%) andHer2 / neu (100%). In a second nomogram our cases complete the three of the proposed SPs being: Grade (94 %), ER (100%) and PR (99.6%). In a third nomogram cases complete the required six SPs being these: tumor size (88.5%), patient age (100%), laterality (100%), ER receptor (100%), PR receptor (99.6%) and HER2 / neu (100%). In a fourth our cases nomogram completes the required six SPs, being these: size (88,5%), ER (100%), PR status (99,6%), HER2neu (100%), Nottingham (94%) and histomorphology (77,5%). In a fifth nomogram the cases complete the required five SPs: age (100%), tumor size (88.5%), grade (94), PR status (99,6) and histologic type (77,5). In the five remaining nomograms evaluated the percentage of cases that could complete the required SPs only reached 61.5% of the cases.

Conclusion: We demonstrate that, although there are gaps in the updated care process (for example: genetic profile) of BC, it is possible to use nomograms in our country through a comprehensive and complete collection and a careful subsequent analysis of the conventional parameters normally present in the diagnosis of BC. Special emphasis should be noted on the histopathological and immunohistochemical

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results, available almost routinely in our series, a fact that allows us to evaluate the RS and thus apply the corresponding therapy trying to achieve results similar to those that would be obtained with the use of GP.

I. Introduction

Breast Cancer (BC) is the most commonly diagnosed cancer amongst women worldwide [1] and is a leading cause of death and disability among women in low- and middle-income countries (MICs)among which is Argentina [2].

Nowadays in BC, beyond the standard determination of cancer stage according to the classic anatomical criteria of the TNM classification, expression of estrogen and progesterone receptors and HER2/neu receptor are required. The study of genic profile (GP) of cancer has also been encouraged although, for now, not in mandatory form [3]Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with,early stage, *estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative*[*ER (+) / HER2 (-) / lymph node-negative*], BC ensuring that patients at highest risk of recurrence are prescribed systemic treatment, while at the same time sparing low-risk patients potential adverse events from therapy unlikely to influence their survival [4,5].

Multigene panels can provide better risk discrimination relative to clinic-pathological factors, which are significantly superior to traditional prognostic factors in predicting clinical outcome and identifying patients who can be spared chemotherapy safely. There are several tests available at the moment. The Oncotype DX (ODX) BC recurrence test (ODXRS) is the one recommended based on the experience accumulated since its implementation in 2010 [6]

Unfortunately, all these tests are expensive. Oncotype DX (ODX) is expensive and is performed in only 1/3 of patients with BC positive for the estrogen receptor (ER) in developed countries [7,8]and are not affordable or available for the majority of the breast cancer patients globally [9]. The economic non-accessibility and / or technical availability are also the main reasons why in a middle-income country (MIC), such as Argentina, the study is only carried out in very few cases (0,23%) who fulfilled the established guidelines for gene-expression profile study and in a sporadic way [10].

Given the potential savings in cost and resource utilization, several algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP). These studies reached different conclusions regarding which model demonstrated the best statistical discrimination power, mainly due to differences in clinical and pathologic variables used [11-20].

In this study we evaluate the possibility, in a MIC country like Argentina, of having the necessary data from the normally required clinical-pathological report of the BC, in order to apply some selected published algorithms that are offered as alternatives to ODX to predict the ODX RSspecifically in patients with "early-stage breast cancer".

II. Material and Methods

a) Data source

We retrospectively reviewed the pathology reports from successive incident BC cases reported, between 2012 and 2014, to PROYCAM2012 (www.cancerdemama2012.org.ar) a consortium (still in force) created for the study of BC in Argentina [10]. The PROYCAM2012 recruited a total of 1832 (stage I to IV) BC until the end of the period under study. From the total of cases reported a subset of 706 (38,5%) *"ER (+) / HER2 (-) / lymph node-negative"* BC, was identified and analyzed.

b) Surrogate parameters

An online search and selection of published scientific research on the same thematic from 2010 onwards, was carried out[11-20]. The presence of the SP shared by the different studies selected was analyzed in our series, namely: age, tumor size, histology, grade, Estrogen/Progesterone receptor, Her2 / neu status and Ki-67.

c) Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, the National Law 25326 of Habeas Data Personal Data Protection and the National Patient Rights Act 26529. For retrospective studies (applies to our study): "for this type of study formal consent is not required''.

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III. Results

a) Substitute parameters in selected publications

The selected 10 publications were analyzed and the SP used in them identified as shown in table 1.

Table 1: Publications on surrogate parameters published and selected. Characteristics of the selected series.

Reference	Breast cancer cases (n, %) ER(+; HER2 (-);lymph node-negative/Total	Notification period (years). Country	Clinical and pathologic markers required as SP
Auerbach J et al., 2010 [11]	138 cases with available Oncotype DX recurrence scores	USA	Tumor size, patient age, laterality, ER receptor, PR receptor results and HER2/neu result
Dellapasqua S et al. 2012 [12]	378/1063 (35,5%)	1990-1999 Australia, Canada, Hungary, Italy, New Zealand, Slovenia, South Africa, Spain, Sweden, and Switzerland.	Age, Histotype, Tumor size, Grade, ER/PgR , Her2/neu status and Ki-67.
Rouanet R et al.,2013 [13]	714/1271 (56,1%)	1994-2004 France	HR and HER2 status.HER2-HR+; HER2-HR-; HER2+HR+; HER2+HR-
Turner B et al; 2015 [14]	299 cases with available Oncotype DX recurrence scores	2009-2013 USA	ER, PR, HER-2, and Ki-67, Nottingham score (NS) and tumor size.
Gage MM et al.2015 [15]	221ODX-tested ER(+)/HER2(-)/lymph node-negative	2006–2013 USA.	-Low grade and positive progesterone receptor tumors (LG+PR). -High grade or low estrogen receptor (ER) (ER < 20%) tumors (HG/ LER).
Özmen V et al., 2016 [16]	165 ODX-tested ER(+)/HER2(-) /lymph node-negative	Turkey	Age, LN Status, Grade, ER score ≤10%, PR score ≤20% and Ki67 score.
Harowicz MR et al., 2017 [17]	305ODX-tested ER (+) /HER2(-)/lymph node-negative	2000-2014 USA	Estrogen receptor status and progesterone receptor status along with different combinations of grade, proliferation indices (Ki-67, mitotic rate), HER2 status, and tumor size.
Farrugia DJ et al,2017 [17]	237/614 (38,5%)	2010-2014 USA	Magee Equation 3 test: ER, PR, HER2 status and Ki-67.
Hanna MG et al.2017 [19]	536 ODX-tested ER (+)/ lymph node-negative	2007-2013 USA	Size, ER, PR status, HER2neu, Nottingham and histomorphology.
Orucevic et al,2019.[20]	65,754 ODX-tested ER (+) /HER2 (-)/lymph node-negative	2010-2014USA	Age,tumour size, grade, PR status and histologic type.

b) Clinical-pathological characteristics

The subset of 706 (38,5%) "*ER (+) / HER2 (-) / lymph node-negative" cases* selected from a database of 1832 cases of BC (stages I-IV) showed the following clinic-pathological characteristics (Table 2). The main clinical characteristics that define this group are: predominant in menopausal women (72%), average age of 61 years, 3.2% bilaterally and a personal (30,3%) and/or family history (9,3%) of BC. Pathologically, the average size of the tumors is between 1.8 -2.0, cm according to the left and right side, with predominance of infiltrating ductal lesions (67, 7%) grade2 (46,7%).

c) Substitute parameters evaluated

The frequency of the presence, in the 706 cases of "ER (+) / HER2 (-) / negative lymph node" BC, of the selected SPs is shown in Table 3. Of the total of 8

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parameters, 4 (50%) (Age, ER / PR and Her2 / neu) are present between 96 and 100% of cases.The next most frequently found SP were grade (94%) and size (88.5%). Finally, the least frequent were histology 77.5%) and Ki67 expression (61.5%).

d) Coincidence between substitute parameters

The percentages in which, in our series, each of the SPs required in the different nomograms is fulfilled and also according to the possibility of a complete application of all SP of each proposed nomogram are shown in table 4. From the total of 10 nomograms selected only in 1 [13] our series can, in the 99.6% of the cases, complete the required two SPs being them: HR (96, 6%) and the Her2 / neu (100%). In a second nomogram [15] at least 94% of our cases complete the three of the proposed SPs being these: Grade (94 %), ER (100%) and PR (99.6%). In a third nomogram [11] at least 88.5% of the cases complete the required six SPs being these: tumor size (88.5%), patient age (100%), laterality (100%), ER receptor (100%), PR receptor (99.6%) and HER2 / neu (100%). In a fourth nomogram [19] 77,5% of cases complete the required six SPs, being these: size (88,5%), ER (100%), PR status (99,6%), HER2neu (100%), Nottingham (94%) and histomorphology (77,5%). In a fifth nomogram [20] also a 77,5% of the cases complete the required five SPs: age (100%), tumor size (88.5%), grade (94), PR status (99,6) and histologic type (77,5).Finally, in the five remaining nomograms evaluated [12,14,16-18] the percentage of cases that could complete the required SPs only reached 61.5% of the cases in each of them because this was the percentage of cases in which the Ki67 status study was conducted to evaluate the rate of tumor proliferation.

IV. Discussion

BC in Argentina, as we reported earlier, has an epidemiological pattern and an incidence rate typical of a "western" and "developed" country [10] without major variations of both qualifiersin the BCover the last 40 years [21]We also report that, with the resources currently available, the BC can be staged properly, according to the latest version of the TNM, in 75% of cases [22]

That a subset of no more than 706 (38.5%) of "early" BC "*ER (+) / HER2 (-) / negative nodes*" come from a database of 1832 new cases of BC, (stages I-IV) recorded between 2012 and 2014, presents its logic. The highest incidence of the whole "early stages" BC in developed countries, due to a massive and continuous use of mammogram screening in these populations [23-25] entails a high frequency of "*ER (+) / HER2 (-) / negative nodes*" BC. On the contrary, in our population, although the mammography is known and applied, but not in a massive and systematic way the frequency of this kind of BC *("ER (+) / HER2 (-) / negative nodes")* is related to a lowest diagnosis of the whole types of "early stages BC" [10,22].

Genomic platform tests are now considered "standard of care" to maintain treatment decision-making for patients "*ER (+) / HER2 (-) / negative lymph node*" BC. Previous analyses of genomic platforms testing have assessed hypothetical cohorts under ideal conditions and concluded that testing had low costs relative to its benefits; the application of gene panels in clinical practice avoids overtreatment, with its possible adverse effects, in the short term and toxic in the longer term [26-28] as well as reducing treatment cost [29-31]

MIC countries, such as Argentina, where gross national income per capita is between US$9,950 and $12,055 per year [32] are mainly characterized by fragmented and poorly coordinated medical care, moderate or high levels of poverty and disparities to access a basic standard of care not only for cancer but also for other complex diseases beyond of being covered by law. Patients in the public environment cannot pay for targeted therapy, so there are currently no hospital laboratories offering genomic platforms.

OncotypeDx® is expensive [the current estimated cost is U$4000 [9]. The cost of the study is the main reason for the almost no realization in the past (2012-13) and nowadays in the MIC countries such as Argentina. None of the health sub-sectors recognizes this study (not included in the oncological diagnosis and treatment protocols accepted by law in our country) for which they do not reimburse their cost. The few cases performed were done privately, paid by the patients and performed abroad the country. For all the mentioned the current tendency, encouraged by research groups, is to use clinic pathologic variables for prediction of low-risk or high-risk OncotypeDx® Recurrence Score (ODXRS) using nomograms models.

Quality prediction models depends on the amount and quality of data derived. In some aspects of the diagnosis of BC our country performs better than expected due to its economic development level. For example, immunohistochemistry (IHC) for HR and Her2 / neu is performed routinely in a high percentage of cases, in almost most laboratories for at least more than a decade. As such, IHC is an accessible and relatively inexpensive test and one that can be performed quite quickly. This is in sharp contrast to genomic test that are routinely performed abroad the country resulting in a prolonged time of realization and increased costs. Having, in our series, the results of HR and Her2 / neu in almost all cases, this allows us to apply 5/10 of the selected nomograms in which these required SPs are available between 88.5% and 99.6% of the cases. On the contrary, when it is necessary to know the proliferation index studied by the Ki67 expression as SP to fulfill a nomogram, this data is only present in 61.5% of the cases in the remaining 5 nomograms.

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V. Conclusion

Despite the fact that MIC oncologists are theoretically well informed in the use of genomic platforms [8,33-36] they are far away from developed in the real-world a practice based in precision oncology; this kind of practice is a great challenge for themand frequently limited, when it is possible, to private practice. Our study, despite its limitations, provides some evidence for the design and orientation in our country of health policies and diagnostic interventions such as nomograms in the treatment of BC cancer, especially in early stages. These nomograms are useful tools to help to decide whether further OncotypeDx® testing is necessary and are excellent surrogates for patients for which OncotypeDx® testing is not affordable or even available. We demonstrate that, although there are gaps in the updated care process (for example: genetic profile) of BC, it is possible to use nomograms in our country through a comprehensive and complete collection and a careful subsequent analysis of the conventional parameters present in the diagnosis of BC. Special emphasis should be noted on the histopathological and immunohistochemical results, available almost routinely in our series, a fact that allows us to evaluate the RS and thus apply the corresponding therapy trying to achieve results similar to those that would be obtained with the use of GP.

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