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ABSTRACT

Background: Breast Cancer (BC) is the main cause of death and disability among women in low- and middle-income (MIC) countries like Argentina. In BC the study of genic profile of cancer has 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. Unfortunately, all these tests are expensive. Given the potential savings in cost, algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as surrogate parameters (SP).

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Breast Cancer in Argentina. Surrogate Parameters, Instead of the Genetic Profile, for Recurrence Risk Evaluation in Early Stages, Estrogen Receptor-Positive, Her2-Neu Negative, Lymph Node-Negative" Cases in a Middle – Income Country

Roberto P. Meiss Kress MD Path^α, Roberto Chuit MD PhD^σ & Ariel Gualtieri PhD^ρ

ABSTRACT

Background: Breast Cancer (BC) is the main cause of death and disability among women in low- and middle-income (MIC) countries like Argentina. In BC the study of genic profile of cancer has 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. Unfortunately, all these tests are expensive. Given the potential savings in cost, algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP).

Materials and Methods: We evaluate the possibility, in a MIC country, of having the necessary data from the normally required report of the BC, in order to apply some of the ten (10) selected published algorithms offered as alternatives to ODXRS. From 1832 (stage I to IV) BC cases reported, between 2012 and 2015, a subset of 706 (38,5%) early stages “ER (+) / HER2 (-) / lymph node-negative” BC, was identified and analyzed. An online search and selection of published scientific research on same thematic, from 2010 onwards, was carried out. The selected 10 publications were analyzed and the SP used in them identified. The presence of the SP shared by the different studies was analyzed in our series, namely: age, tumor size,

histology, grade, Estrogen/Progesterone receptor, Her2 / neu status and Ki-67.

Results: From the total of 10 nomograms selected only in five our series can complete the required two SPs (HR/HER2) with percentages over 90% 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 our country in the updated care process of BC, it is possible to use nomograms in through a comprehensive and complete collection and subsequent analysis of the conventional parameters normally present in the routine diagnosis of BC with special emphasis on the histopathological and immunohistochemical results, available almost routinely in our series.

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I. BACKGROUND

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 surrogate 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 such as 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 RS specifically in patients with "ER (+) / HER2 (-) / negative lymph node" cases.

II. MATERIALS AND METHODS

2.1 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.

2.2 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.

III. RESULTS

3.1 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⁾	305 ODX-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	2010-2014 USA	Age, tumour size, grade, PR status and histologic type.

3.2 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%).

Table 2: Clinical-Pathological Characteristics of 706 “ER (+) / HER2 (-) / Negative Lymph Nodes” BC Cases

Age at diagnosis, mean, median (range), n (%)	Mean = 61, Median = 62, (0-93)
Distribution by age groups, n (%)	
< 40 years	54 (7,6)
40-49	118 (16,7)
50-59	145 (20,5)
60-69	175 (24,8)
70 +	214 (30,3)
Unknown	---
Menopause (yes) n, (%)	538 (76,2)
Personal history of breast cancer, n (%)	66 (9,3)
Family history of breast cancer, n (%)	216 (30,6)
Bilaterality, n (%)	21 (3,0)
Size right breast, mean, median (range); cm, n (%)	Mean = 2.30, Median = 2.00 (10.00-01)
Size left breast, mean, median (range); cm, n (%)	Mean = 2.18, Median = 1.80 (14.00-0.01)
Histology, n (%)	
<u>Not infiltrating</u>	
Ductal	83 (11,8)
<u>Infiltrating</u>	
Lobular:	24 (3,4)
Ductal:	478 (67,7)
Unknown	117 (16,6)
Tumor grade (histological grade) n (%)	
1	181 (25,6)
2	330 (46,7)
3	153 (21,7)
unknown	42 (5,9)

3.3 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 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%).

Table 3: Selected Surrogate Parameters Available in 706 “ER (+) / HER2 (-) / Negative Lymph Nodes” BC Cases

Parameters available	n (%)
Age	706 (100)
Histotype	547 (77,5)
Size	625 (88,5)
Grade	664 (94)
Estrogen receptors	706 (100)
Progesterone receptors	703 (99,6)
Her2/neu status	706 (100)
Ki-6 expression	434 (61,5)

3.4 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.

Table 4: Frequency of Application of Each Nomogram Proposed According to the Available SP in 706 “ER (+) / HER2 (-) / Negative Lymph Nodes” BC Cases

Reference	Published series clinical and pathologic markers required as SP	Frequency (%) of clinical and pathologic markers required as SP available in the series under study	Cases of 706 BC according to possible complete application of the proposed nomogram; n (%)
Auerbach J et al., 2010 ⁽¹¹⁾	Tumor size, patient age, laterality, ER receptor, PR receptor results and HER2/neu result	Tumor size (88,5), patient age (100), laterality (100), ER receptor (100), PR receptor (99,6) results and HER2/neu (100) result	625 (88,5)
Dellapasqua S et al. 2012 ⁽¹²⁾	Age, Histotype, Tumor size, Grade, ER/PgR, Her2/neu status and Ki-67.	Age (100), Histotype (77,5), Tumor size (88,5), Grade (94), ER (100)/PgR (99,6), Her2/neu (100) status and Ki-67 (61,5)	434 (61,5)
Rouanet R et al., 2013 ⁽¹³⁾	HR and HER2 status. HER2-HR+; HER2-HR-; HER2+HR+; HER2+HR-	HR (100/99,6) and HER2 status (100)	703 (99,6)
Turner B et al; 2015 ⁽¹⁴⁾	ER, PR, HER-2, and Ki-67, Nottingham score (NS) and tumor size	ER (100), PR (99,6), HER-2 (100), and Ki-67 (61,5), Nottingham score (NS) (94) and tumor size (88,5)	434 (61,5)
Gage MM et al. 2015 ⁽¹⁵⁾	-Low grade and positive progesterone receptor tumors (LG+PR). -High grade or low estrogen receptor (ER) (ER < 20%) tumors (HG/ LER).	Grade (94), ER (100) and PR (99,6)	664 (94)
Özmen V et al., 2016 ⁽¹⁶⁾	Age, LN Status, Grade, ER score ≤10%, PR score ≤20% and Ki67 score	Age (100), LN Status (100), Grade (94), ER (100) score ≤10%, PR score (99,6) ≤20% and Ki67 (61,5) score	434 (61,5)
Harowicz MR et al., 2017 ⁽¹⁷⁾	Estrogen receptor status and progesterone receptor status along with different combinations of grade, proliferation indices (Ki-67, mitotic rate), HER2 status, and tumor size.	Estrogen receptor status (100) and progesterone receptor status (99,6) along with different combinations of grade (94), proliferation indices (Ki-67 (61,5), mitotic rate), HER2 status (100), and tumor size (88,5).	434 (61,5)

Farrugia DJ et al, 2017 ⁽¹⁸⁾	Magee Equation 3 test: ER, PR, HER2 status and Ki-67.	ER (100), PR (99,6), HER2 (100) status and Ki-67 (61,5).	434 (61,5)
Hanna MG et al., 2017 ⁽¹⁹⁾	Size, ER, PR status, HER2neu, Nottingham and histomorphology.	Size (88,5), ER (100), PR (99,6) status, HER2neu (100), Nottingham (94) and histomorphology (77,5)	547 (77,5)
Orucevic et al, 2019 ⁽²⁰⁾	Age, tumour size, grade, PR status and histologic type	Age (100),tumour size (88,5), Grade (94), PR status (99,6), and histologic type (77,5)	547 (77,5)

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 qualifiers in the BC over 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 in 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.

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 them and 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.

Addendum: while the present work was being carried out, a pandemic was hitting the world. COVID 19 has a major negative effect on stretched

health care systems in low- and middle-income countries and also places a financial burden on households. Our country with 4100 000 of cumulative number of confirmed cases and 85075 cumulative number of confirmed deaths (between March 20, 2020 and June 12, 2021) is now obliged to invest abundant health resources in the fight against covid. The new needs would make it very difficult to develop, in the immediate future, new and expensive methodologies such as, for example, genetic study,

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”.

Conflicts of Interest

The authors declare no conflict of interest.

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