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Impact of the 21-Gene Recurrence Score (Oncotype DX®) on adjuvant therapy decision-making: a collaborative multicenter cohort study from Argentina

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ABSTRACT

Introduction: At present, more than half of patients diagnosed with early-stage breast cancer (BC) and express hormonal receptors will receive some adjuvant chemotherapy scheme, but only a few of them would benefit in terms of survival. Genomic platforms allow a better understanding of the heterogeneity of different types of hormonal receptor-positive and HER2-negative BC. They have proven their validity as tools to identify those patients who will obtain a clear benefit with the indication of chemotherapy treatment. The aim of this study is to analyze the use of the genomic platform, namely, Oncotype Dx® and its impact on the indication of adjuvant treatment, evaluated mainly as the change in treatment indication. **Methods:** Multicenter observational cohort study was performed in different Mastology units in Argentina. Patients underwent the Oncotype Dx to clarify the adjuvant treatment. Treatment decisions were settled before and after performing Oncotype Dx. **Results:** From January 2013 to December 2018, 211 patients with luminal A or B and HER2-negative breast carcinomas, who underwent the Oncotype Dx, were included. Based on our records, 40% of the patients change the indication of adjuvant treatment after the performance of the Oncotype Dx. Of these, 24% of patients who underwent initial endocrine therapy only adjusted their treatment with the addition of chemotherapy. Among patients with an initial CTH recommendation, 49% were able to receive endocrine therapy only when, due to traditional prognostic factors, they would have received chemotherapy. **Conclusions:** In our population, the use of the Recurrence Score was clinically significant in relation to the change of the established treatments. Consequently, it is a very important tool and a decisive factor in the adjuvant indication in patients with positive hormonal receptors and HER2neu-negative early BC.

KEYWORDS: breast neoplasms; genomics; chemotherapy, adjuvant; medication therapy management.

INTRODUCTION

Over the past years, genomic and molecular analysis has played a major role of significant relevance in the treatment of patients with breast cancer (BC). Approximately 60% of patients diagnosed with early-stage hormone receptor-positive BC will be offered adjuvant treatment that includes chemotherapy, though only 2–10% of patients will receive the benefit in terms of survival[1,2]. The development and the use of gene expression assays have provided us with an in-depth understanding of the remarkable heterogeneity of the different types of BC[3]. These tests have proven their validity as tools that allow the identification of patients who are most likely to gain survival advantage from adjuvant chemotherapy[4]. Subsequently, this responds to two specific premises in the treatment of BC: tailoring of adjuvant systemic therapy and adjusting it according to each patient's specific risk for BC recurrence, which subsequently results in decreased exposure of patients to undesirable toxicity and potential side effects associated with chemotherapy[4-6].

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Based on the assessment of 21 tumor genes, Oncotype DX® is one of the most widespread and globally available gene expression assays. This diagnostic test results in a numerical prognostic index named Recurrence Score (RS) that ranges from 0 to 100, and it is the result of a mathematical algorithm, which correlates with the predicted risk of distant metastasis over the following 10 years. Traditionally, BC prognosis and, consequently, subsequent systemic adjuvant therapy were established through clinical and pathological parameters. The use of genomic assays, such as Oncotype DX, has been associated with a significant impact on clinical decision-making regarding the indication of adjuvant therapy, ranging between 27% and 74% according to different series[7,8].

The prospective randomized TAILORx study proved that most patients with early-stage hormonal receptor-positive and HER2neu-negative BC do not benefit from adjuvant chemotherapy and established Oncotype DX as a standard of care[9]. Regarding treatment decision-making in patients with node-positive BC, the results of the prospective trials are still awaiting publication. These trials will also probably validate the use of RS as a clinical tool for chemotherapy de-escalation in this subset of patients. Nonetheless, based on the available retrospective evidence, several workgroups have already begun to incorporate RS in the management of up to 51% of patients with axillary metastasis (1–3 positive nodes). In this subset of patients, the impact on treatment decisions is large, given that it frequently allows the avoidance of unnecessary and potentially toxic chemotherapy[10,11].

OBJECTIVES

The primary goal of this study was to explore the use of Oncotype DX RS and its impact on adjuvant treatment decision-making through the assessment of change in the indication of chemotherapy. The secondary goal was to describe the clinical and pathological characteristics of the study population and the adjuvant treatments offered to the included patients.

This study was carried out due to the collaborative efforts from some of the main breast units of Argentina. A novel cooperative initiative has not been previously performed throughout our country.

MATERIALS AND METHODS

This study is a multicentric observational cohort study. It was carried out in the breast units of the following hospitals and clinics of Argentina: Hospital Italiano (Buenos Aires), Hospital Universitario Austral, Hospital Italiano (La Plata), Hospital Británico, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno," Instituto Alexander Fleming, and Centro de Mastología de Rosario.

The study period was from January 2013 to December 2018. The inclusion criteria were patients diagnosed with luminal A or B and HER2-negative invasive BC who were diagnosed, treated, and followed at different participating breast units and who received Oncotype DX testing. Clinical and pathological data were obtained from a review of medical records at each center. All patients and adjuvant treatment decisions were discussed and documented during the weekly Tumor Boards at each corresponding center.

With regard to pathology analysis, hormone receptor status was assessed by automatized immunohistochemistry and quantification using Allred Score (intensity + proportion). HER2neu status was also examined using automatized immunohistochemistry and, in the case of equivocal results (2+), was confirmed using molecular biology techniques, according to availability at each center: fluorescent *in situ* hybridization, chromogenic *in situ* hybridization, or silver *in situ* hybridization. Luminal A and B tumors were stratified according to Ki67, which was assessed by calculating the average of three fields.

In all cases, adjuvant treatment was discussed and documented before performing Oncotype DX, based on the clinical and pathological characteristics of each patient and tumor. The pretest decision was registered on the treatment registry at each site. After posttest RS was available, the committee re-evaluated each scenario and redefined the proposed treatment plan. This adjuvant schema was also documented in the registry log, allowing the assessment of modifications in treatment decision-making. All patients were offered and agreed to undergo the posttest treatment plan. In patients with intermediate RS scores, adjuvant treatment was recommended based on traditional predictive and prognostic markers, while considering patient preference as well.

Statistical analysis

Continuous variables are presented using average (mean) and standard deviation. Quantitative variables are expressed as medians and interquartile ranges. Categorical variables are described by observed and relative frequency (percentage). Estimated probabilities below 5% were considered statistically significant. Statistical analysis was performed using PSPP 0.8 software.

Ethical considerations

Given the implications of this study, all the investigators involved in its development were familiar with the ethical, legal, and judicial requirements for clinical research, as established by National and International standards such as the Declaration of Helsinki. Since the information was obtained through detailed analysis of the medical records of the patients treated at different sites and that the result of this study under no circumstance has direct effects on the included patients, the need for informed consent was disregarded. To assure the maximum confidentiality and anonymity of patient data, each site entered data into a coded

database which was accessed only by the authorized investigators (Dr. Allemand and Dr. Valerio), according to the National Law of Protection of Personal Data 25.326 (*habeas data*).

RESULTS

Between January 2012 and December 2018, 211 patients with luminal A or B and HER2-negative invasive BC who underwent assessment with Oncotype DX were included. All the patients were diagnosed, treated, and followed up at one of the participating breast units. The clinical and pathological characteristics of these patients are given in Table 1. Most patients were at stage 1 (72%) ductal carcinomas (76%). Only 24 patients (11%) had positive lymph nodes.

The distribution of Oncotype DX RS in the study population (n=211) resulted as follows: 42 patients (20%) had a low-risk RS, 107 patients had an intermediate-risk RS (51%), and 62 patients had a high-risk RS (29%). If we consider the RS of those assays that were ordered before the modification of the cutoff points published in the TAILORx study (n=176), the distribution differed moderately: 92 patients (52%) had low-risk scores, 53 patients (30%) had intermediate scores, and only 31 patients (17%) had high-risk scores (Table 2).

Adjuvant endocrine therapy, alone or in combination with chemotherapy, was prescribed according to standardized international guidelines and consensus as well as site-specific clinical practice guidelines. To analyze the results, we considered the date at which Oncotype DX was performed, given that a significant number of patients were treated before TAILORx was published. Among 176 patients who were treated before the publication of this study, adjuvant treatment was distributed as follows: all patients with low-risk RS received endocrine therapy alone, and all patients with high-risk RS received chemotherapy and subsequent endocrine therapy, according to international standards. For patients with intermediate RS and for patients with RS greater than 24, chemotherapy was offered based on traditional prognostic factors (i.e., axillary status, size, grade, and lymphovascular invasion)[4].

Table 2. Recurrence score.

Pre Tailor Recruited Patients		Patients N=211	%
Low Risk	0-17	92	52
Intermediate risk	18-30	53	30
High risk	31-100	31	18
Pos Tailor Recruited Patients			
Low Risk	0-10	8	20
Intermediate risk	11-25	16	51
High risk	26-100	11	29

Table 1. Clinicopathological characteristics and recurrence score.

Clinicopathological characteristics	N (%)	RS<11	11 . 25	>25	
Stage					
I	148 (72)	27 (12.7)	83 (39.3)	38 (18)	p=0.16
II	62 (29.3)	5 (2.3)	34 (16.1)	23 (10)	
III	1 (0.5)	0	0	1 (0.5)	
Histological Type					
Ductal invasive carcinoma	162 (76.7)	18 (11.1)	88 (54.3)	56 (34.6)	p=0.009
Lobular	30 (14.2)	6 (20)	20 (66.7)	4 (13.3)	
mucinous	3 (1.4)	2 (66.7)	1 (33.3)	0	
others	16 (7.5)	6 (2.8)	8 (3.7)	2 (0.9)	
Estrogen receptor					
Negative	1 (0.5)	0	0	1	p=0.299
Positive	210 (99.5)	32 (15.2)	117 (55.8)	61 (29)	
Progesterone receptor					
Negative	21 (9.9)	0 (0)	6 (28.5)	15 (7.5)	p=0.0001
Positive	190 (90.09)	32 (16.9)	111 (58.4)	47 (24.7)	
Nodal involvement					
Negative	178 (84.3)	20 (15.5)	100 (53.5)	58 (31)	p=0.45
Isolated tumor cells -micrometastases	9 (4.2)	2 (22.2)	6 (66.7)	1 (11.1)	
Macrometástasis	12 (5.6)	0	9 (75)	3 (25)	
Capsular perforation	4 (1.8)	1 (33.3)	3 (66.7)	0	

Thirty-five patients were included after TAILORx was published. Treatment offered in the high- and low-risk RS groups was similar to that of the previously described subset of patients. However, for patients with intermediate scores, age was factored into the treatment plan: patients who aged >50 years received endocrine therapy alone, and patients who aged <50 years were offered chemotherapy if the RS was greater than 21 and based on traditional prognostic factors.

Considering the information collected from the tumor board registry logs, we found that in 84 patients (40%), Oncotype DX was decisive in changing the initial treatment plan. Nineteen patients who had initially not been considered for chemotherapy were finally offered cytotoxic therapy (23%). The remaining 77% of patients who changed the initial treatment were considered eligible for chemotherapy based on traditional prognostic factors but ended up receiving endocrine therapy after RS was performed. Before RS, 63% of patients were considered for chemotherapy, and 37% of patients were considered for endocrine therapy (Figure 1). After RS was performed, most of them could receive only endocrine therapy (59%). When describing the relative impact of the change in treatment indication (percentage) and the distribution according to definitive treatment, 60% of patients were considered at initial indication, and 40% were not.

When analyzing adjuvant treatment as a whole, 85 of 211 patients (40%) received adjuvant treatment with both chemotherapy and endocrine therapy. Among these, 24 patients underwent chemotherapy with six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Thirty-three patients received combined anthracycline and taxane-based chemotherapy (4 cycles of adriamycin and cyclophosphamide + 12 cycles of weekly paclitaxel). Seven patients underwent 4 cycles of AC, and the remaining 23 patients received other chemotherapy regimens. As for endocrine therapy, 50 patients received tamoxifen, 23 patients received anastrozole, and 8 patients received a combination of tamoxifen or anastrozole plus ovarian suppression with luteinizing hormone-releasing hormone (LHRH) agonists (Goserelin). Notably, 130 patients received endocrine therapy exclusively. Among these, 78 patients received tamoxifen, 43 patients received aromatase inhibitors, and 9 patients received some form of endocrine therapy in addition to LHRH agonists (Goserelin).

We also included 24 patients with positive lymph nodes. Of note, 9 patients had sentinel lymph node micrometastases, and 15 had macrometastases. Two patients underwent axillary lymphadenectomy without the presence of other positive nodes. Of these 15 patients, 4 patients underwent anthracycline-based chemotherapy, and 11 patients received endocrine therapy based on their RS.

We performed a subanalysis considering the result of the RS and its correlation with different clinical and pathological factors such as patient age, size, tumor grade, and Ki67 status (Figures 2-5). When analyzing age, 25% of women who were below 40 years had a high-risk RS (>25), 54% had an intermediate-risk RS (11–25), and 21% had a low-risk RS. In addition, 26% of women who were above 70 years had a high-risk RS. Considering tumor size, 24% of patients with tumors up to 2 cm presented a high-risk RS, while patients with larger tumors had more high-risk RS (50%; p=0.001). When analyzing histological grade, only two patients with low-grade tumors had a high-risk RS; and 50% of high-grade tumors had low (8%) and intermediate (43%) RS (p=0.0001). Considering Ki67, we can observe a certain correlation

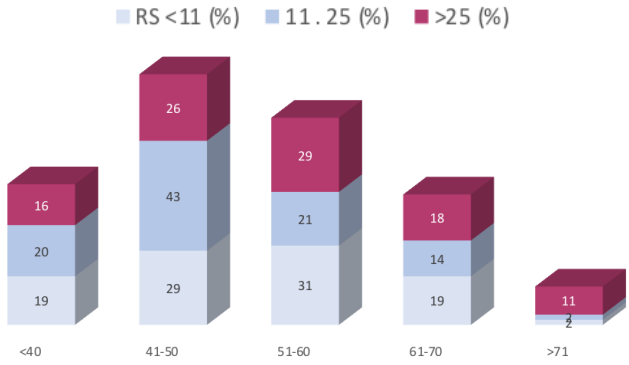

Figure 2. Age and recurrence score.

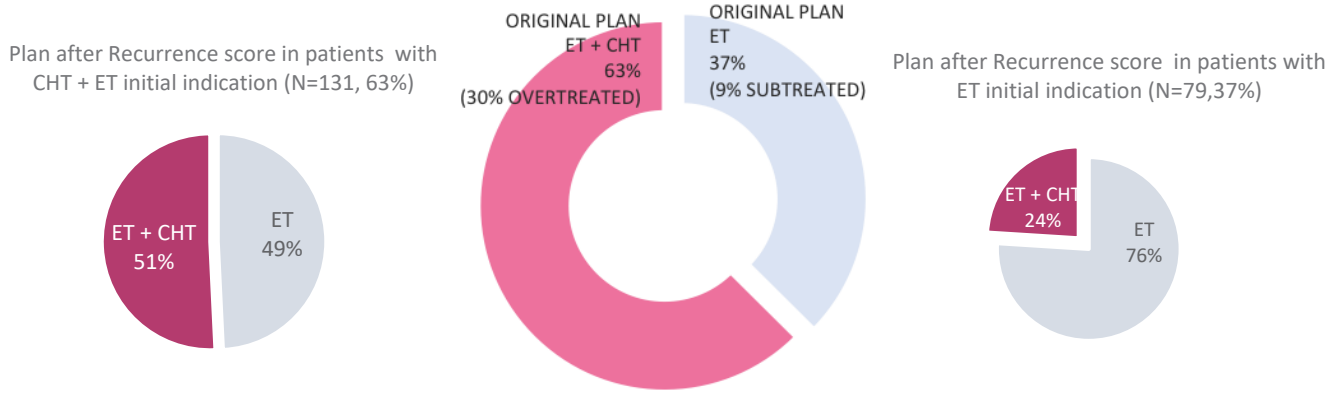

Figure 1. Treatment indication before and after recurrence score (N=211).

between this value and the RS. However, it is not absolute as 16% of patients with Ki-67 <14% had a high-risk RS (RS>25), and 12% of the patients with Ki-67 >30% had a low-risk RS. These results are similar to those published in the literature. Gluz in Plan B already showed this correlation and mentioned that approximately 15% of patients with Ki-67 <20 presented a high-risk RS (RS>25), and also a non-negligible percentage of patients with Ki-67 >30 had a low-risk RS[12].

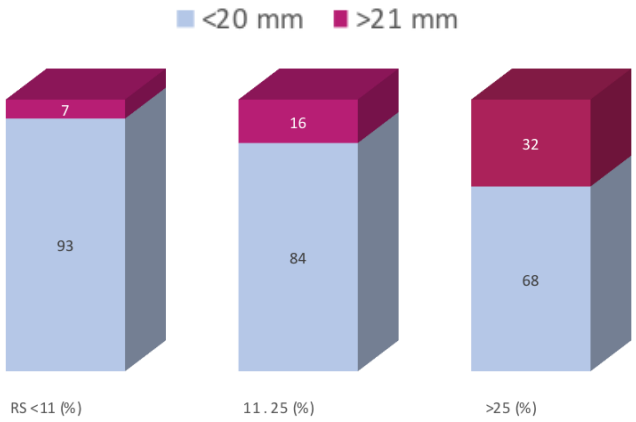

Figure 3. Size and recurrence score.

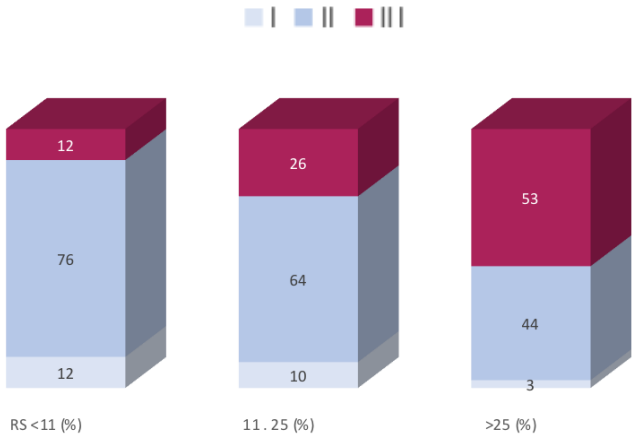

Figure 4. Tumor grade and recurrence score.

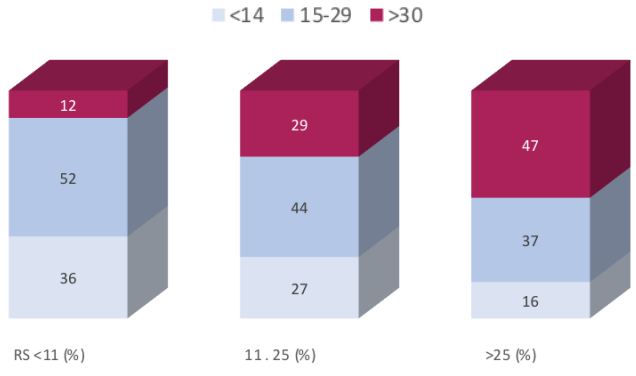

Figure 5. Ki 67 and recurrence score.

DISCUSSION

Adjuvant systemic treatment has significantly increased disease-specific survival for patients with BC. Nonetheless, even when optimum treatment is readily available, many patients do not receive the treatment that best fits their specific needs. This frequently leads to overtreatment (the indication of cytotoxic drugs from which benefit will not be derived) and undertreatment. This underscores the importance of developing biomarkers that may offer a chance to correctly stratify patients according to their risk of recurrence, thus allowing greater precision in therapeutic decision-making[6,13].

Until the past decade, adjuvant treatment recommendations were based primarily on traditional, clinical, anatomical, and pathological factors as well as immunohistochemistry. Aside from the role of the estrogen receptor as a predictive factor for endocrine therapy response or the expression of *her2neu* and its prediction of response to monoclonal antibody therapy, up to now, there has been scarce evidence of any specific biomarker that could predict benefit from chemotherapy.

The development of Oncotype DX and, consequently, the RS® has provided a valuable tool for the correct stratification of patients based on their specific risk for distant metastasis. The RS has been studied both prospectively and retrospectively. The retrospective validation studies were designed based on the long-term follow-up of the NSABP B-14 and NSABP B-20 trials, which evaluated and surveilled the patients treated with upfront tamoxifen versus tamoxifen plus chemotherapy with CMF[7,8,14].

In the published literature, a variable impact of using the RS has been described in the indication of adjuvant systemic treatment. This variability is evidenced in therapeutic changes from its use, which ranges between 27% and 74% depending on the series that are taken into consideration, the adjuvant treatment guidelines most commonly consulted in each population, and also the availability to perform the genomic study[10,11,15]. Publication of prospective validation studies in patients with positive axilla is still awaited in order to extend the utility spectrum of RS. However, based on retrospective validation studies, several groups have already published reports showing a therapeutic change in 51% of patients with positive nodes (1–3 lymph nodes); according to RS, up to 33% of patients with a positive lymph node have not shown the indication of potentially non-beneficial chemotherapy[16,17].

The TAILORx study, published in 2018[9], showed that most patients with early-stage hormone receptor-positive BC do not benefit from the combination of chemotherapy and endocrine therapy. This prospective validation study positioned the Oncotype DX RS as a standard of care in the management of early-stage luminal, *her2*-negative BC, which currently allows a more tailored approach to adjuvant therapy planning. TAILORx reported that up to 73% of patients who were considered at high risk based on traditional features

obtained an RS between 0 and 25 and were thus likely to have been overtreated if adjuvant therapy had been indicated based only on clinical variables. In contrast, 43% of patients with RS ranging between 26 and 100 had previously been considered at low clinical risk and would probably have received inadequate treatment. It has been proposed that RS could allow the identification of up to 85% of women who could be spared adjuvant chemotherapy, especially in the postmenopausal subgroup with RS who aged below 25 and in patients who aged below 50 years, with an RS of £15. In our series, 44% of the patients with RS >26 were considered at low clinical risk based on traditional features, similar to what Sparano reported, while 16% of patients with RS <10 were considered at high clinical risk (Figure 6).

As we mentioned earlier, the distribution of Oncotype DX results based on the current RS classification was as follows: 20% received a low RS, 51% received an intermediate RS, and 29% received a high RS similar to what was published in the TAILORx study: 27%, 43%, and 30%, respectively[9].

In our series, we have described a change in adjuvant therapy decision in approximately 40% of patients, with a significant reduction in the use of chemotherapy. When analyzing the original treatment plan, 79 patients (37%) received endocrine therapy exclusively according to clinicopathological features, while 131 patients (63%) received chemotherapy combined with endocrine therapy. After RS was performed, we could notice changes in treatment recommendations: 25% of patients who underwent initial endocrine therapy only finally added chemotherapy treatment, and in patients with an initial CTH recommendation, 49% were able to receive endocrine therapy only. In other words, one-fourth of patients in the initial endocrine therapy only treatment would have been undertreated, and almost half of patients in the initial CTH recommendation would have been overtreated according to the genomic platform (Figure 1).

This proportion correlates with the published literature, although it tends toward the higher end. We believe that this may be attributed to a selection bias. As shown in Table 1, most of the patients included were patients with luminal B-like tumors, stratified according to Ki67. This is related to the fact that in our country, Oncotype DX is not covered by most health insurance providers for patients clinically at low risk but is usually covered when Ki67 is above a specific cutoff point. This means that patients often need to finance the assay on their own, and many do not have the means to do so. This distribution probably explains why the proportion of decision change is at the higher end of the range.

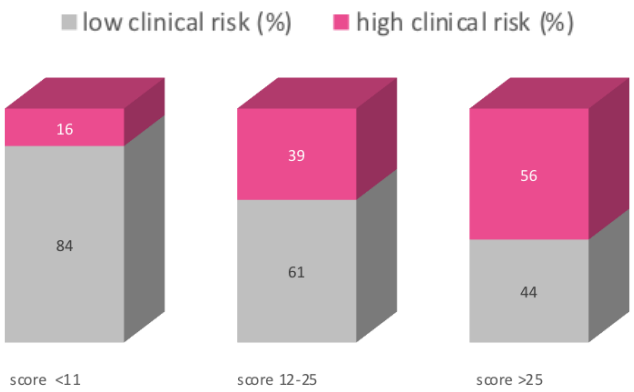

Figure 6. Clinical risk and recurrence score.

Currently, due to the advancement in adjuvant endocrine therapy, events during follow-up (local and distant recurrences) are significantly reduced. We acknowledge that a longer follow-up time is warranted in order to increase the power to long-term events and to assess survival.

CONCLUSIONS

In our study population, the use of the genomic platform Oncotype DX and the RS resulted clinically significant in terms of the change in prescription of adjuvant therapy, thus constituting a decisive factor for treatment decision in patients with early-stage hormonal receptor-positive and HER2neu negative BC. Although availability is still a limiting factor in developing countries such as Argentina, we find that RS is a desirable and valuable marker that will allow treatment tailoring and avoidance of exposure to undesirable side effects as well as not withholding adjuvant chemotherapy from those who are most likely to obtain a benefit in terms of survival.

Impact of Recurrence Score (RS) on adjuvant therapy decision-making is a multicenter observational cohort study performed in different Mastology units in Argentina. In our country, this is a novel cooperative initiative that joined us with the aim of analyzing the use of the RS and its impact on the treatments, evaluated mainly as a change in indication.

AUTHORS' CONTRIBUTIONS

C.A.: conceptualization, formal analysis, writing — original draft, writing — review and editing, project administration, resources, software, and supervision.
A.C.V.: conceptualization, formal analysis, writing — original draft, writing — review and editing, project administration, resources, and software.
M.F.C.: writing — original draft, and writing — review and editing.
G.I.: formal analysis, and methodology.
I.M.: conceptualization, data curation, and resources.
F.T.: conceptualization, data curation, and resources.
J.L.U.: conceptualization, data curation, and resources.
F.C.: conceptualization, data curation, and resources.
F.V.S.: conceptualization, data curation, and resources.
L.B.G.: conceptualization, data curation, and resources.

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