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Breast Cancer in Argentina: Feasibility for the Implementation of the New TNM Staging System 2018 in A Middle-Income Country

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Abstract

Background: Breast Cancer (BC) is the most commonly diagnosed cancer amongst women worldwide and also in Argentine a "medium human development" and "middle-income" country with an estimated incidence rate of 71, 2 per 100,000 in 2012. The implementation of the new TNM system for the staging of BC proposed by the AJCC and published in the VIII edition (2017) implies a substantial change with respect to the number of parameters and the criteria used until the present.

Purpose: Given the importance of BC as a health problem present and future in our country and the need to study, as required, a larger number of parameters for the correct diagnosis and treatment of this pathology, we decided to study the feasibility of applying the new TNM system (2017) to the cases of BC already diagnosed in order to evaluate, with the current health system and medical benefits, what parameters are the most difficult to obtain and why in order to comply with the requirements of this new staging system.

Methods: The data of the necessary parameters were extracted from the database of the Collaborative Group for the Study of Female Breast Cancer in Argentine (www.cancerdemama2012.org.ar) a consortium of 64 physicians from 75, public (26) and private (49), health services, reported 1732 case patients studied during the years 2012-2013. The following parameters were recorded: a) anatomical (T, N, and M); b) biological factors (hormone receptors, Her-2-neu overexpression, tumor grade) and c) multigene panel testing performed in 1732 cases (2012-13); for this data a survey was also carried out on its current realization in 1063 cases (2016-17).

Results: Taking together the data of all the parameters required in the new system in 75.2% of the cases they are all present; in the remaining 24.8% cases, one or more of the parameters are missing. Breaking down this result among the 7 parameters that compose it, the anatomical results are: T (84.7%); N (88.8%) and M (94.5%); the study of hormone receptors is of 96.6%, the Her2-neu study of 92.5% and the tumor grade datum is 86.1%. The fulfillment of the gene-expression profile study (in both series) shows low frequencies of performance (0.23% v. 3, 19%). 41, 5% of cases fulfilled the established guidelines for recommendation of adjuvant chemotherapy on the basis of the gene-expression profile study.

Conclusion: With the current health system and the medical benefits available it was possible to apply the new staging system in 75% of the total cases already diagnosed. Paradoxically of the BF those that were less studied were the anatomical ones while the HR and the HER2 were studied in values close to 90%. The recommended study of the gene profile shows very low percentages of realization, both in the past series and in the current survey, far from being useful to define the "risk" of patients with early stages breast cancer. In that cases where they could not perform some of the studies it is due to ignorance of the value of the study of certain required parameters and most often to cost problems or lack of recognition or reimbursement by a health system. Until the present time we are able to meet, in a significant percentage of cases, the requirements of the new version and provide good and updated diagnostic procedures and adequate treatment to our breast cancer patients. But with our current infrastructure doubts arise about the possibility of fulfilling future demands, in a mandatory way, of certain

parameters (mainly genetic studies) for the staging of BC

Keywords: Breast cancer, Argentina, Epidemiology, 2017 TNM staging system.

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 [2] This makes the BC a public health problem in most developing countries as is the case of Argentina [3]. The BC is in Argentina the most frequent of all cancers in both sexes with an estimated 19386 new female cases and 6163 deaths due to this cancer in 2012 [1]. Argentina (with a Gross Domestic Product (GDP) of 11,970 US$ by 2016) belongs to the "medium human development" countries with a BC's estimated incidence rate of 31, 3 x100, 000 and also to "middle-income" countries with an estimated incidence rate of 26, 5x100, 000 [1,4].

Argentina also is located, according to the IARC, in a geographic region, South America, where the estimated incidence and the mortality of BC are about 52.2 and 15, 3 per 100,000 respectively [1]. But beyond all these previous mentioned conditions the incidence and mortality rates are much higher than expected: 71.2 and 19.7 per 100,000 respectively what constitutes one of the two striking exceptions (the other is Uruguay) in the region [1].

The implementation of the new TNM system for the staging of BC proposed by the AJCC and published in the VIII edition [5] implies a substantial change with respect to the criteria used until the present since the TNM system was created in 1962. TNM classification for breast carcinoma had not been changed for 15 years, since the publication of the IV edition in 1987 [6]. In this last version, biological factors (BF) evaluated, used to define AJCC prognostic stage groups [5], included: T, N, and M categories and tumor grade, as well as estrogen, progesterone receptors, and HER2 status.

Although the data (with respect BF) requested for the new staging have been studied prior [7-17] to the seventh edition in 2009 [18]. It is only in the current edition that it becomes mandatory to have this data in order to establish the extension of the BC and will be in full force from January 1, 2018 onwards [5].

The eighth edition prognostic stage groups also take now into consideration, but in a non-mandatory way, multigene panel testing. There has been great interest in the development of prognostic and predictive gene expression profiles risk of breast cancer recurrence in patients with estrogen receptor (ER)-positive, HER2-negative, node-negative BC and is likely predictive of adjuvant systemic therapy benefit [19]. Unfortunately, these tests are expensive and are not affordable or available for the majority of the breast cancer patients globally [20].

Argentina has high health expenditure equal to 6.28% of GDP [21] and reaches about 8% of GDP if it includes resident's pocket expenditure. About 34% of Argentines with no health insurance rely solely on the public health sector of each province or district for free and irrespective of their origin or nationality. But provinces and municipalities have very different health budget endowments, thus geographical inequalities in health care arise. The social security sector (54%) aims at providing care to workers formally employed through about 300 different funds (OS) and the retirees and the disabled (10%) through an entity (PAMI). The OS vary in sizes and scope and mostly managed by trade unions. The private sector is composed of private providers, private insurances and out-of-pocket expenses, which account for 6% of health expenditures

In Argentina, the National Constitution guarantees access to health by placing the responsibility on the State (Provinces / Nation). This is shared with 23 provinces and the government of the Autonomous City of Buenos Aires, as well as with numerous municipalities. A minimum package of health services is guaranteed by law to the whole population. The so-called Compulsory Medical Plan (Plan Médico Obligatorio - PMO) establishes that the reimbursement of drugs will reach 100% in hospital drugs as well as special treatments such as oncology. All cancer patients in Argentina should have access to treatments, validated internationally [22]and authorized by the authorities local health (Ministry of Health and the National Administration of Medicines, Food and Medical Technology - ANMAT)

Given the importance of BC as a health problem present and future in our country and the need to study, as required, a larger number of parameters for the correct diagnosis and treatment of this pathology, we decided to study the feasibility of applying the new TNM system (2017) to the cases of BC already diagnosed in order to evaluate, with the current health system and medical benefits, what parameters are the most difficult to obtain and why in order to comply with the requirements ofthis new staging system.

Material and Methods

Data were obtained from a data-set of 1732 histologically confirmed primary invasive BC reported , during the years 2012 and 2013, by a consortium of 64 physicians from 75, public (26) and private (49), health services to an on-line database of a multicenter prospective cohort study (www.cancerdemama2012.org.ar), still in force. All BC from a dataset continue monitored for the study of quality of life and survival at 5 and 10 years in the follow-up.

BF and anatomical data source

The BF data of the tumor such as hormonal receptors, expression of growth factor receptors and tumor grade added to the classical anatomical criteria (tumor, nodes and metastasis) used to define AJCC new prognostic stage groups were obtained from a BC database [23]. The relative values (%) of the data for each variable analyzed were calculated from the available data; this means that for the total of each variable those cases reported as "unknown" were not included.

Survey on the realization of the genetic profile

In order to obtain updated data, a survey (annex 1) was conducted among 12 treating physicians. They were asked to indicate the number of cases of BC diagnosed in 12 months (June, 2016- May, 2017) and of these in how many cases the genomic study was performed. The results were distributed according to the health coverage system of the patients.

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." For retrospective studies (applies to our study): "for this type of study formal consent is not required".

Results

Demographic and clinical characteristics of the dataset population

The main demographic and clinical characteristics of the patients of the series studied are shown in Table 1. For the purposes of this study it is important to note that more than 60% of patients were covered by the social security system and less than 20% by the public. As previously reported [23] the profile shows a majority of menopausal women with a median age of almost 60 years. They were BC with predominance of unilateral forms, ductal infiltrative (NOS) histology and a median tumor size of 2 cm. Regarding the stages of presentation, according to the 2009 TNM version [18] close to 94% of BC corresponded to early-stages (0- IIIa).

TNM anatomical parameters required

In the new TNM system, the anatomical parameters correspond to the same structures studied (tumor, node and metastasis) and the same evaluation criteria as in the previous edition [18]. In about 85% of the cases of which the tumor size data are available, a predominance of BC between 1 and 1.9 cm was observed. Approximately 89% of the BC cases reported the node commitment data. In 35% it was positive with a predominance (52.6%) of the group of <4 nodes; in only 3% of cases, the number of affected lymph nodes was unknown. Distant metastasis: this data is available in almost 95% of the total cases, of which only 3% report metastasis. All the previously mentioned data are summarized in Table 2.

Histopathological parameters

In about 93% of the cases the histology data is known with a clear predominance of the infiltrative forms (88.3%). The total of non-infiltrating correspond now to the ductal variant (DCIS) constituting 11.7% of the total BC diagnosed in this series; this is because according to the new TNM edition lobular carcinoma in situ (LCIS) has been eliminated as a neoplastic lesion *per se* remaining only as a "risk factor" (5). Of the other required histological parameter (tumor grade) the data is available in 87% of cases and in them grade II (50%) predominates. A synthesis of these data is shown in Table 3.

Immunohistochemical study of hormonal and Her2-neu receptors

For the three types of receptors the available data reaches near the 90% (Table 4). In our series the study of hormone receptors was performed in more than 96% of cases with a positivity of 83, 1% for estrogen and 77, 7% for progesterone. In 92.5 % of cases the Her2-neu study was performed with a positivity of 14, 9 %.

In 1415 (81,7%) cases the availability of the data from the 3 receptors allowed us to obtain the following molecular profiles: Luminal: HR (+),Her2 neu (-) 69,5% ; Luminal: HR (+),Her2 neu (+) 7,5 % ;Non – luminal: HR (-), Her2 neu (+) 5,9%; Triple negative: HR (-), Her2 neu (-) 10,0%; Others 17,1%.

Available data of all required BF parameters

In 75.2% of the cases, data are available for the seven variables (T, N, M, ER, PR, Her2-neu and tumor grade) required for the application of the new staging system. In the remaining 24.8% there is a lack of data for one or more of these variables.

Gene-expression profile

Table 5 shows the results of the fulfillment of the gene-expression profile study both in the total of cases of the original series (2012-13) of 1732 cases and in the current survey (6/2016 to 5/2017) of 1063 cases. In both series only in patients with private health coverage few gene-expression profile studies were performed. If frequencies of performance of the study are compared an increase of near 14 fold (0.23% v3, 19%) is observed.

There are 718 (41, 5%) cases with positive HR, negative HER2 and negative axillary nodes who fulfilled the established guidelines for the recommendation of adjuvant chemotherapy on the basis of the gene-expression profile study characteristics, and that could benefit from the performance of the study of the gene expression profile [24].

Discussion

Breast cancer (currently considered a heterogeneous disease) mortality decreased significantly over the past three decades worldwide [25-28] due to early detection [29-32] and adjuvant systemic therapy (AST) [32,33]. However the risk of recurrence is still high and dependent upon numerous factors including tumor size, involvement of regional lymph nodes, histologic grade, expression of hormone receptors (estrogen and progesterone), and human epidermal growth factor receptor 2 (HER2) amplification. These factors are used to determine which early breast cancer patients should be treated with AST including endocrine therapy (ET), chemotherapy, and HER2-directed treatments [34,35]. These factors aid in that sense but still the challenge is to identify those patients that would not benefit from

Table 1: Demographic and Clinical characteristics of 1732 breast cancer patients

Variables	All patients (n = 1732)
Coverage system	
Public health Pre-paid medicine Mutual health societies Social security Unknown	305 (18,2) 288 (17,2) 40 (2,4) 1042 (62,2) 57 (3,3)
Age at diagnosis,median (range)	59 (23-92)
Menopausal status	
Premenopausal, n (%) Postmenopausal, n (%) Unknown	396 (22,9) 1252 (72,3) 84 (4,8)
Reproductive history	
Ever full-term pregnancy (yes), n (%) Age at first full-term pregnancy (median, range) Age ≥30 years at first full-term pregnancy, n (%) Breastfeeding (yes), n (%)	1387 (80.9) 24 (14-46) 161 (11,6) 1387 (80,0)
History of personal breast pathology, n (%)	535 (30.9)
Mammary dysplasiaAtypical hyperplasia and carcinoma “in situ” Breast cancer (yes)	227 (13. 1)36(2.1) 170 (9.8)
Family history of breast cancer (yes),n (%)	483 (27,9)
History of personal non-breast cancer (yes), n (%)	57 (3, 2)
Localization, n(%)	
Unilateral,Bilateral,	1679 (96,9)53(3,1)
Size (cm), median (range)	2,00 (0,01-15,00)
Nodal involvement (yes),n (%)	466 (26,9)
Distal metastasis (yes), n (%)	43 (2,3)
TNM* clinical stages, n (%)	
Known	1632 (94,2)
0	162 (9,9)
I	598 (36,7)
IIA	452 (27,8)
IIB	179 (10,9)
IIIA	131 (8.0)
IIIB	58 (3,5)
IIIC	11 (0.7)
IV	41 (2,5)
Unknown	100 (5,8)
*[18]	

Table 2: Anatomical parameters and tumor grade in 1732 breast cancer evaluated according to the VIII edition 2017 TNM system

Parameters	n (%)
Tumor (size, cm)	
Known data	1467 (84.7)
< 0,5	71 (4,8)
0,6 a 0,9	61 (4,1)
1,0 a 1,9	400 (27,2)
2,0 a 2,9	351 (23,9)
3,0 a 3,9	208 (14,1)
4,0 a 4,9	145 (9,8)
> 5,0	231 (16,1)
Unknown data	265(15,3)
Node	
Known data	1538 (88,8)
Yes	537 (34,9)
< 4 nodes	302 (56,2)
≥4 nodes	221(41,1)
Nodes unknown	14 (2,7)
No	1001 (65,1)
Unknown data	194 (11,2)
Metastasis	
Known data	1636 (94,5)
Yes	43 (2,6)
No	1593 (97,4)
Unknown data	96 (5,5)

Table 3: Histopathology of 1876 breast cancer in 1732 patients

Parameters	n (%)
Histology	
Known data	1722 (91,8)
Unknown data	154 (8, 2)
Infiltration	
Non-infiltrative *(DCIS only)*	201 (11,7)
Infiltrative	1521 (88,3)
Subtypes (Infiltrative only)	
Lobular	198 (13, 0)
Ductal	1323 (87, 0)
Tumor Grade, Bloom and Richardson grade	
Knowndata	1492 (86,1)
I	243 (16,3)
II	750 (50,3)
III	499 (33,4)
Unknown data	**240 (13,9**)

adjuvant chemotherapy, resulting in an over-treatment. To solve this dilemma, there has been great interest in prognostic and predictive gene expression profiles development [36-41].

The incorporation and recommendation of the use henceforth of biomarkers (in a mandatory form) and multi-genic panels (in a non-mandatory way yet) into the eighth edition AJCC staging

Table 4: Results of Estrogen, Progesterone and Her 2-neu receptors studies (ICH) in cases performed and subsequent molecular profile

Receptors	(n, %)
Estrogen	
Performed	1498 (96,8)
Positive	1245 (83,1)
Negative	253 (16,9)
Non- performed	49 (3,2)
Progesterone	
Performed	1495 (96,6)
Positive	1162 (77,7)
Negative	332 (22,2)
Unknown	1 (0,1)
Non- performed	52 (3,4)
HER2-neu	
Performed	1427 (92.5)
Positive	212 (14,9)
Negative	1214 (85,1)
Unknown	1 (0,1)
Non- performed	116 (7.5)
Molecular profiles	
Known data	1415 (81,7)
Luminal: ER (+) ;PR (+) ;Her2 neu (-)	983 (69,5)
Luminal: ER (+) ;PR (+) ;Her2 neu (+)	106 (7,5)
Non – luminal: ER(-);PR(-); Her2 neu (+)	84 (5,9)
Triple negative: ER(-);PR(-) ;Her2 neu (-)	141 (10,0)
Others	101 (17,1)
Unknown data	317 (18,3)

Table 5: Survey of cases of breast cancer with gene profiling study* performed by period 01/2012-12/2013 and 06/2016-05/2017

Period (years)	Coverage	Total BC	Studies, n (%)
2012-2013	Public	1082	0 (0)
	Social security	362	0 (0)
	Private	288	4 (0,23)
	Total	**1732**	**4 (0,23)**
2016-2017	Public	311	0 (0)
	Social security	-	-
	Private	752	34 (4,52)
	Total	1063	34 (3,19)
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system allows for more refined staging that reflects the prognostic and predictive significance of biologic factors [42].

In the new TNM system, the anatomical parameters correspond to the same structures studied (tumor, node and metastasis) and with the same evaluation criteria as in the previous edition [18]. Data of the three components are available between 80 and about 95% of the cases; it is in tumor size that the least data are available. The recommendation acknowledged that there are many countries where biomarker assays and multi-genic panels are not routinely used so, it is necessary to maintain the anatomical criteria in force since this will allow the comparison with past or current series in which it has not been possible to study these parameters [42]. The absence of data (between 5 to 15%) of the classic TNM system anatomical data (present since the creation of the system and maintained throughout all editions) may be due to the fact that these data come from the first studies performed in institutions that serve in primary form to the BC patients. These public or private institutions have different levels of complexity so that homogenous, quality information cannot be guaranteed in all cases. But nevertheless these highly results obtained are more than enough to make a correct staging in most cases based on the traditional anatomical criteria [18]. BC care is complex and a multidisciplinary team approach to diagnosis and treatment is necessary for ensuring best practice outcomes. There was a strong consensus that anatomic stage groups be maintained, as they could be applied to all patients with breast cancer worldwide, regardless of the availability of biomarker analysis or multigene assays [42, 43].

Tumor grade consigned in the pathological reports since 1990 maintained its prognostic value over the years [6,18] and its value was reconfirmed in recent years with studies of its correlation with the molecular and genetic profiles [44, 45]. In our series it is reported in near the 90 % of cases.

Histology data is known in 93% of cases. One of the novelties in the new system is the elimination of LCIS as a carcinoma and its location in the category of potentially malignant lesion. Thus in the re-staging the total of carcinomatous lesions in situ (11.3% of the total) correspond to DCIS [5, 42].

The high percentages of studies of hormonal receptors performed (96, 8%) are due to the fact that these studies have been carried out in the country (with different methodologies) since the early nineties [46, 47]. These studies are now carried out both in the social security, the private sector and the public one all of them with their own resources and technologies.

Regarding the study of the overexpression of Her-2neu (92, 5%), it was disseminated in medicine practice mainly since 2005 [48], and is currently carried out in all health subsectors either with their own resources or outsourced practice in reference centers.

The study of both HR and the Her-2neu has a very high percentage of realization similar to that of the developed countries [49, 50].

If we check the data of the 7 parameters required in the new system we see that in 75.2% of the cases they are all present; in 24.8% of the remaining cases, one or more of the parameters are missing. The percentage difference (in less) between this whole value and the individual values of each parameter is because the greater number of variables studied decreases the number of coincidences.

The implementation of genomic sequencing approaches in routine laboratory practice has increased the potential for the identification of multiple breast cancer targets suitable for future therapeutic interventions in order to improve cancer outcomes [51-54]. This potentiality is the main reason for the indication of its realization in the VIII edition [5]. Aware of the difficulties in carrying it out, the indication does not, for now, have a mandatory character, as does the study of BF.

Until now the most extensively studied profile is the 21-gene expression assay (OncotypeDx®). This assay has established analytic validity, clinical validity, and clinical utility and that is why it is the only multi-genic panel included in the prognostic stage group of the eighth edition [5,51-54].

In the original series (2012-13), the number of cases that would have benefited from the genetic study corresponds to 41.5%; this percentage is higher than the 33% reported in the USA [55],and the 20% of a study that groups several European countries [56]. Despite this high percentage of cases, which would have benefited from its realization, the study was only carried out in less than 0, 3% of them. On the other hand the survey, updated 5 years later it shows an increase of almost 14 times (0.23 % vs. 3,19%) but always in patients with private health coverage. This value is far from reaching the expected theoretical percentage of cases that would have benefited from this study, avoiding thus the over-treatment of "low-risk" cases [57].

OncotypeDx® is expensive (the current estimated cost is U$4000 [58]. The cost of the study is the main reason for the almost no realization in the past (2012-13) and nowadays. None of the health sub-sectors recognizes this study (not included in the diagnosis and treatment protocols accepted by law) 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. It was observed that age, tumor size, tumor grade, PR status, LVI, and histologic tumor type were significantly associated with a low-risk or a high-risk ODXRS test result [59-62]. These nomograms will be 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 available [63,64].

Now we are able to meet, in a significant percentage of cases, the requirements of the new version of the TNM. In the future, the need to study all the parameters proposed in the new edition should be firmly inculcated. Research on the development of nomograms should be encouraged as surrogates for patients for which genomic sequencing testing is not yet affordable or available while the health system works to find ways to pay for genomic technology and medical care of all those patients who needed it.

In that cases where some of the studies, either of the BF or of the genetic studies, it is due to ignorance of the value of the study of certain required parameters and most often to cost problems or lack of recognition or reimbursement by a health system highly decentralized and characterized by the inarticulate coexistence of subsystems that not only duplicate (sometimes eventriplicate) the coverage but also bureaucratize it.

Conclusion

With the current health system and the medical benefits available it was possible to apply in Argentina the new staging system in 75% of the total cases already diagnosed. Paradoxically of the BF those that were less studied were the anatomical ones while the tumor grade, HR and the HER2 were studied in values close to 90%. The recommended study of the gene profile shows very low percentages of realization, both in the past series and in the current survey, far from being useful to define the recurrence "risk" of patients with early stages BC. Until the present time we are able to meet, in a significant percentage of cases, the requirements of the new version and provide good and updated diagnostic procedures and adequate treatment to our BC patients. But,with our current infrastructure, doubts arise about the possibility of fulfilling future demands, in a mandatory way, of certain parameters (mainly genetic studies) for the staging of BC.

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