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Obstetrics & Gynecology International Journal

Research Article

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Association between ki67 antigen and other clinicopathological factors with the Oncotype DX Score in luminal breast cancer

Summary

Introduction: Luminal tumors show molecular differences and different behavior. The antigen Ki67 is one of the factors that differentiate between luminal A and B. Genomic platforms can identify which patients will benefit from chemotherapy.

Objectives: To establish if there is an association between ki67 and Oncotype Dx Score (RS). To assess the influence of ki67 and RS on the therapeutic decision, to evaluate the association between clinical risk and RS, between lymphovascular invasion (LVI) and RS, and between positive axillar nodes (up to 1 node) and RS.

Materials and methods: Retrospective, observational, descriptive study. We included 68 patients with negative Her2Neu luminal tumors, T1-T2, negative or positive axillary up to 1 node, who performed Oncotype DX between 2009 and 2020 at Hospital Alemán. They were classified into RS less than or equal to 25 and greater than 25 based on the TAILORx study, where it was shown that overall there is no benefit from chemotherapy between 0-25.

Results: An association was observed between ki67 and RS in 44 (64.7%) patients and it was greater between low ki67 and RS less than or equal to 25 (77.3%). The treatment was based on RS. An association between clinical risk and RS was observed in 43 (63.2%) patients, and it was greater between low clinical risk and RS less than or equal to 25 (87.5%). In 88.8% there was no association between LVI and RS, as well as between positive axillary up to 1 node and RS in 85.7%.

Conclusion: It is necessary to offer every patient with a luminal tumor a genomic platform since both ki67 and other pathological clinical factors alone did not prove to be superior or sufficient.

Keywords: Recurrence score, Oncotype, ki67, association

Volume 13 Issue 6 - 2022

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Received: November 20, 2022 | **Published:** December 01, 2022

Introduction

Worldwide, the three most common cancers in women are breast, lung, and colon. They constitute 50% of all new diagnoses. Breast cancer represents 30% of these cases, being the most frequent malignant tumor in women worldwide.[1] It is estimated that 1 in 8 women who reach the age of 85 will have had breast cancer in their lifetime. Mortality due to breast cancer in Argentina represents 9.3%, constituting the first cause of death due to cancer in women.[2]

Breast cancer today constitutes a therapeutic challenge since patients with the same stage present differences in the clinical evolution of the disease and in the response to treatment. It is important to be clear about the prognostic and predictive factors, understanding that prognostic is a variable that determines the evolution of the disease and predictive is a variable that determines the benefit of one treatment or another.[3]

The advent of molecular classification has made it possible to establish various prognostic groups with different presentation, development and evolution of the disease. Most breast cancer correspond to the luminal subtype, mainly luminal A (40%) followed in frequency by luminal B (20%), triple negative (15-20%), and Her2Neu positive (10-15%).[4] Luminal tumors have an immunophenotypic pattern similar to the luminal epithelial component of the mammary gland, they express luminal cytokeratins, estrogen receptors and less than 20% have p53 mutation.[5]

In this paper, only luminal tumors will be analyzed, which have molecular differences and different behavior. This is where the importance of ki67 lies, to differentiate, among other markers, between luminal A and B.

The ki67 antigen is a cell proliferation marker, which was detected in 1983 by a German work group (Gerdes et al) using a murine monoclonal antibody against a nuclear antigen found in Hodgkin lymphoma cell lines.[6] It has an important role in the regulation of the cell cycle since it is absent in quiescent cells in G0, present in low intensity in phases G1, S and G2 and reaches maximum levels during mitosis.[7–10]

The treatment of early stages of breast cancer depends on multiple clinical and pathological factors, among others, and must be individualized in each particular case.

Because luminal tumors behave differently, as stated above, it is important to resort to genomic platforms, as it is often difficult to identify which patients really benefit from chemotherapy. The importance lies in avoiding the known adverse effects of treatment in patients who, in many cases, are overtreated and, on the other hand, in avoiding patients being undertreated.

There are genomic platforms with different levels of evidence, which study different types of genes. In this work, the Oncotype DX genomic platform will be discussed, which is the one with the highest level of evidence and is the most recommended by international

guidelines, not only for its prognostic but also predictive value. This platform evaluates 21 genes, 16 associated with the tumor and 5 reference genes. According to the expression of these genes, a recurrence score is established that ranges from 0 to 100 and represents the risk of distant relapse at 10 years only with hormonal treatment.[11,12]

It should be noted that the patients who will undoubtedly benefit from the development of genomic platforms are those with node-negative luminal tumors, since this has been the most overtreated group, since 85% will be disease-free at 10 years with only hormone therapy.[13]

Although the genomic platforms must be offered to all patients who meet the necessary conditions for the application, not all patients have access to these tool due to its high economic cost, so in those cases ki67 has been considered a factor of weight for therapeutic decision.

In this work, it will be mainly observed whether there is an association between ki67 and the Oncotype DX Score in luminal breast tumors.

Objective

The primary objective of this study is to establish whether there is an association between ki67 and RS in luminal breast tumors. Second, to evaluate the influence of ki67 and RS on the therapeutic decision, to assess whether an association is established between clinical risk (determined by tumor size and histological grade (GH)) and RS, between ILV and RS, and finally between the positive axilla (up to 1 node) and the RS.

Materials and methods

This is a retrospective, observational, descriptive study. We included 68 female patients with a median age of 57 years with infiltrating carcinomas of the breast whose pathological anatomies by immunohistochemistry corresponded to negative Her2Neu luminal tumors with a tumor size between 0.5 and 5 cm (T1-T2) with negative axilla or positive up to 1 node that Oncotype DX performed between 2009 and 2020 at the Hospital Aleman in Buenos Aires. The platform was requested from more patients in this period of time, who also met the necessary conditions previously mentioned for the request, but due to lack of coverage or for economic reasons they did not apply. The patients were classified into two groups according to the result of the recurrence score, less than or equal to 25 and greater than 25, based on the evidence of the TAILORx study, where it was shown that there is no global benefit with chemotherapy when the score is between 0 -25.[14]

Male patients, non-luminal and luminal Her2Neu positive tumors, bilateral, larger than 5 cm and axillary with more than 1 positive lymph node were excluded.

The variables that were measured were age, tumor size, histological grade, clinical risk using the same criteria as the TAILORx study (low: GH1 less than or equal to 3 cm, GH2 less than or equal to 2 cm, GH3 less than or equal to 1 cm and high: GH1 greater than 3 cm, GH2 greater than 2 cm or GH3 greater than 1 cm),[14] lymphovascular invasion, lymph node status, tumor immunohistochemistry (estrogen and progesterone receptors, Her2Neu and ki67) , the recurrence score and the therapeutic decision.

All the surgical specimens were analyzed in the Pathology Laboratory of the Hospital Aleman. Once the lumpectomy and mastectomy pieces were received, they were oriented according to repairs, they were sectioned into parallel slices with a maximum thickness of 0.3 cm and the parenchyma was evaluated searching the lesion. Once located, macroscopic measurements were taken, and the distance to the margins was evaluated. The material was fixed in 10% formalin for a minimum of 6 hours and a maximum of 72 hours, being strict at this point since prolonged fixation or subfixation can give false negatives. After studying the tumor with hematoxylin-eosin staining, an immunohistochemical study was performed to evaluate estrogen and progesterone receptors, Her2Neu and ki67.

Luminal A tumors were defined as hormone receptor positive, Her2Neu negative, and Ki67 <20%, and luminal B tumors as estrogen receptor positive, Her2Neu negative, progesterone receptor <20%, or Ki67 >20%.[15] Her2Neu positive luminals were excluded.

The standard method and the one used to determine cell proliferation was the evaluation of the percentage of tumor cells that expressed the ki67 protein using the monoclonal antibody MIB-1 in 5 foci (invasion front, 2 hot-spot and 2 intermediate) counting not less than 500 cells in formalin-fixed, paraffin-embedded tissue sections.

To date, no strict cut-off point has been established for ki67, since it varied over time. In 2009, the international consensus of experts from St. Gallen proposed 3 categories: low (<15%), intermediate (16 to 30%) and high (>30%),[16,17] then in 2011 they recommended a value of 14% and later in 2013 and 2015 of 20% and 20 to 29% respectively.[18–20]

In this study, 20% was considered as the cut-off point.

The data was collected through the digital clinical history.

Results

The age range of the patients was between 33 and 77 years with a median age of 57 years.

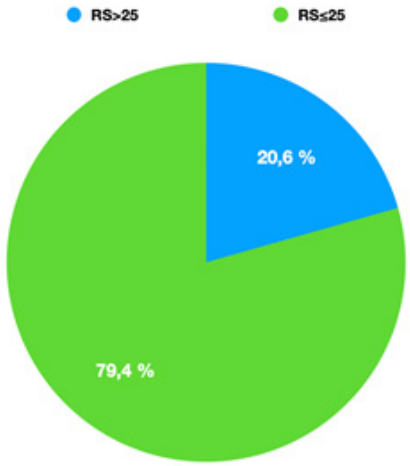
The average tumor size was 1.8 cm, 22 (32.4%) were T1 and 46 (67.6%) T2. Regarding the histological type, 45 (66.2%) tumors corresponded to the ductal or non-special type (NOS), while 10 (14.7%) to the lobular type, 10 (14.7%) to the mixed type, 2 (2.9%) to the micropapillary type and 1 (1.5%) to the mucinous type. Regarding histological grade, 9 (13.2%) tumors were GH1, 41 (60.3%) GH2, 17 (25%) GH3, and in 1 (1.5%) case there was no record of tumor grade.

The Oncotype DX platform was performed in 68 patients, in 54 (79.4%) cases the recurrence score was less than or equal to 25, and in 14 (20.6%) greater than 25 (Graph 1).

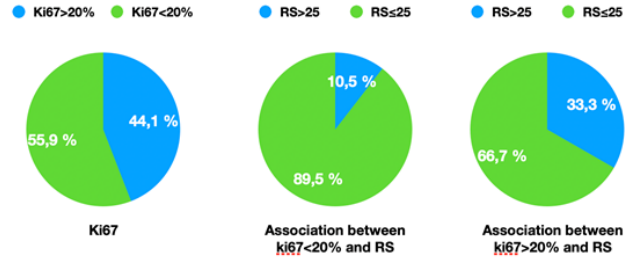
Of the total number of patients, 38 (55.9%) of them had ki67 less than 20%, of which 34 (89.5%) had a recurrence score less than or equal to 25 and 4 (10.5%) greater to 25. The remaining 30 (44.1%) patients had a ki67 greater than 20%, of which 20 (66.6%) had a recurrence score less than or equal to 25 and 10 (33.3%) greater to 25 (Graph 2).

Association between ki67 and recurrence score was observed in 44 (64.7%) patients, while in 24 (35.3%) there was no association.

Evaluating the 44 (64.7%) patients in whom there was an association, of the 34 (77.3%) who had ki67 less than 20% and recurrence score less than or equal to 25, 31 (91.2%) of they were treated with radiotherapy and hormonal therapy and 3 (8.8%) with hormonal therapy only because they had undergone mastectomy. The remaining 10 (22.7%) patients had high ki67 and recurrence score greater than 25, 9 (90%) were treated with chemotherapy, radiotherapy and hormone therapy and 1 (10%) with chemotherapy and hormone therapy only because they had undergone mastectomy.



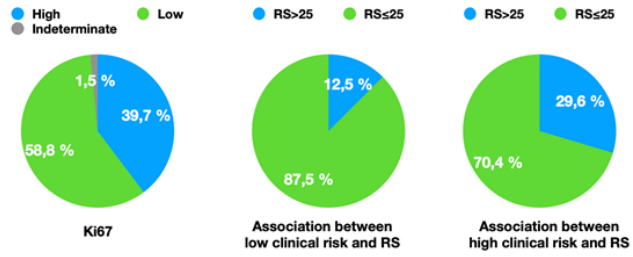
Graph 1 Result of the recurrence score.



Graph 2 Ki67 and association according to ki67 with the recurrence score.

Among the 24 (35.3%) patients in whom no association was observed, the 4 (16.6%) who had low ki67 and recurrence score greater than 25, 3 (75%) were treated with chemotherapy, radiotherapy and hormonal therapy and 1 (25%) with radiotherapy and hormonal therapy. Of the remaining 20 (83.3%) patients who had elevated ki67 and recurrence score less than or equal to 25, 14 (70%) were treated with radiotherapy and hormonal therapy and 6 (30%) with chemotherapy, radiotherapy and hormonal therapy.

Of the total number of patients, 40 (58.8%) of them had low clinical risk, of which 35 (87.5%) had a recurrence score less than or equal to 25 and 5 (12.5%) greater than 25. On the other hand, 27 (39.7%) patients had high clinical risk, of which 19 (70.4%) had a recurrence score less than or equal to 25 and 8 (29.6%) greater than 25 and in 1 (1.5%) case, the risk could not be established since the GH was not identified (Graph 3).



Graph 3 Clinical risk and association according to clinical risk with the recurrence score.

Association between clinical risk and RS was observed in 43 (63.2%) patients, while in 24 (35.3%) there was no association.

Of the 68 patients under study, 9 of them presented positive LVI, that is, 13.2%, of which 8 (88.8%) presented a recurrence score less than or equal to 25 and 1 (11.1%) greater to 25.

Of the total number of patients, 53 (77.9%) had negative sentinel node, 7 (10.3%) micrometastasis, 7 (10.3%) positive sentinel node (macrometastasis), while in 1 (1.5%) case no sentinel node biopsy was performed. Within the group of 7 (10.3%) patients with positive nodes, 6 of them (85.7%) had a recurrence score less than or equal to 25 and 1 (14.3%) greater than 25.

Discussion

In breast carcinoma, it is known that a high value of ki67 is associated with worse evolution and that it constitutes by itself a prognostic factor for the probability of being free of distant metastases and disease-free survival without being so conclusive for overall survival.[7,21]

On the other hand, Oncotype DX is a genomic platform validated as a prognostic and predictive factor and the most recognized nationally and internationally. Although it has a high cost, it is available in Argentina. The panel of 21 genes includes the ki67 gene, but its expression is only reported as part of the recurrence score and not individually.[13]

The Oncotype DX in our Hospital was performed in 68 female patients with a median age of 57 years with tumors with an average size of 1.8 cm. Most were ductal or non-special type carcinomas, GH2, sentinel node negative and all had positive hormone receptors and negative Her2Neu. Although they are usually good prognosis tumors, on certain occasions, they raise the possibility of chemotherapy treatment. Hence the importance of genomic platforms.

Of the 68 patients who underwent Oncotype DX, it was observed that in 44 (64.7%) cases there was an association between ki67 and the recurrence score and in 24 cases there was not (35.3%). The association was greater between low ki67 and recurrence score less than or equal to 25, which occurred in 34 (77.3%) patients, while the association between high ki67 and recurrence score greater than 25 was only observed in 10 (22.7%) patients. Based on this, it is interesting to observe the established therapeutic conduct.

Of the 34 (77.3%) patients who had low ki67 and recurrence score less than or equal to 25, radiotherapy was indicated to those who had undergone breast conservation treatment and all were treated with hormone therapy only, avoiding chemotherapy, coinciding with the studies published, in which it was shown that this group does not benefit from chemotherapy, regardless of the value of ki67. Of the 10 (22.7%) patients who had high ki67 and recurrence score greater than 25, radiotherapy was indicated for those with breast conservation treatment and all received chemotherapy and hormone therapy, since the benefit in patients with RS greater than 25.[12,22]

Of the 24 (35.3%) patients in whom no association was observed between ki67 and recurrence score, the 4 (16.6%) who had low ki67 and recurrence score greater than 25, all received chemotherapy, radiotherapy and hormone therapy but 1 (25%) of them did not accept chemotherapy. In these patients, if we had based ourselves on the value of ki67, they would have been undertreated. The remaining 20 (83.3%) patients who had elevated ki67 and recurrence score less than or equal to 25, 14 (70%) were treated with radiotherapy and hormonal therapy based on the recurrence score, otherwise they would have been overtreated and the remaining 6 (30%) patients were treated with chemotherapy, in addition to radiotherapy and hormone therapy. If we analyze these last 6 (30%) patients, we observe that

Citation: Ramilo T, Camargo A, Bianchi F, et al. Association between ki67 antigen and other clinicopathological factors with the Oncotype DX Score in luminal breast cancer. *Obstet Gynecol Int J.* 2022;13(6):368–372. DOI: 10.15406/ogij.2022.13.00678

they were under 50 years of age and had a score between 18-25, a range that corresponds to the intermediate risk of the Oncotype DX publications prior to the publication of TAILORx, which motivated at that time the indication for chemotherapy due to RS and age. It is important to mention that it is in this group of patients that, after the publication of TAILORx, a decrease in distant relapse was seen at 9 years of approximately 1.6% for RS between 16-20 and 6.5 % for RS between 21-25 with the addition of chemotherapy.[14,22] Of note, it is not clear whether this benefit is due to the effect of chemotherapy or to endocrine suppression caused by chemotherapy-induced menopause.

Regarding the association between clinical risk and recurrence score, an association was observed in 43 (63.2%) patients and was greater in the group with low clinical risk and recurrence score less than or equal to 25, represented by 35 (81 .4%) patients compared to the group that had a high clinical risk and a recurrence score greater than 25, represented by 8 (18.6%) patients.

It is interesting to analyze in depth the association between clinical risk and recurrence score. Of the total number of patients, 40 (58.8%) of them had low clinical risk, of which 35 (87.5%) had a recurrence score less than or equal to 25, therefore, in this group, as previously mentioned association existed. However, there remains a non-negligible percentage of patients (12.5%), with a recurrence score greater than 25, who, if we had based ourselves on clinical risk to decide on treatment, would have been undertreated. On the other hand, 27 (39.7%) patients had a high clinical risk, of which only 8 (29.6%) had a recurrence score greater than 25, therefore, although in this group, as previously mentioned, there was an association, it was low. The remaining 19 (70.4%) patients had a recurrence score less than or equal to 25 and if we had based the therapeutic decision on clinical risk, they would have been overtreated. These data confirm the importance of Oncotype DX in the therapeutic decision, since clinical risk does not always represent the need or not to perform chemotherapy. On the other hand, it is interesting to show the similarity of our results with those published in TAILORx$_{14}$. In TAILORx, an association was seen between low clinical risk and a recurrence score less than or equal to 25 in 91%, and the remaining 9% corresponded to low clinical risk and a recurrence score greater than 25, which represents the percentage of undertreated patients. while in high clinical risk, an association was seen with a recurrence score greater than 25 in only 27%, and 73% represented those patients with high clinical risk and a recurrence score less than or equal to 25, which is the percentage of patients overtreated.

Regarding the association between lymphovascular invasion and the recurrence score, it was observed that of the total number of patients under study, 9 (13.2%) of them presented positive LVI, of which 8 (88.8%) presented a recurrence less than or equal to 25 and only 1 (11.1%) presented a recurrence score greater than 25, therefore, although the number of patients with positive LVSI is low, in 88.8% of cases no association could be established.

Of the total number of patients, 7 (10.3%) had positive sentinel node, of which in 6 (85.7%) of them the result of the recurrence score was less than or equal to 25 and only in 1 (14.3 %) the score was greater than 25, for which, although the sample is not representative, in 85.7% of the cases no association could be established.

Although some studies maintain that the combination of immunohistochemical data with clinicopathological parameters provides prognostic information superior to Oncotype DX alone, this genomic platform has great weight by itself when establishing prognosis and response to treatment. Therefore, it is necessary to offer all patients with a luminal tumor the possibility of performing a genomic platform, since both ki67 and other clinicopathological factors by themselves did not prove to be superior or sufficient.[23,24]

One of the biases that we must mention in this study is that the request for the Oncotype DX platform is often influenced by the levels of ki67, either from the medical point of view or from the health insurance, being ki67 a data already known at the time of requesting the platform. On the other hand, it would be interesting for the future to recruit more cases to obtain more evidence and be able to draw more solid conclusions.

Conclusion

Today both ki67 and Oncotype DX are essential tools for therapeutic decision-making in luminal breast cancer. Although these are patients who generally have a good prognosis, it is really important to identify which patients really benefit from the use of chemotherapy.

As we saw in this study, there was a high association between low ki67 and recurrence score less than or equal to 25, but not between high ki67 and recurrence score greater than 25 where the association was low. In all cases, treatment was decided based on the Oncotype DX Score, even in those with disagreement due to the high level of evidence and predictive value. Therefore, we can say that ki67 is a useful prognostic factor to take into account for decision making when Oncotype DX is not available to identify patients with a higher risk of recurrence, but it is not enough as an individual factor for implementation or not of chemotherapy.

On the other hand, it is worth mentioning that a patient with low clinical risk provides us with reliable prognostic information in the event that Oncotype DX is not available, despite the fact that some patients will be undertreated, since in our study an association of 87.5 was observed % between low clinical risk and a recurrence score less than or equal to 25, while in a patient with a high clinical risk it is transcendental to have Oncotype DX to avoid overtreatment, since between a high clinical risk and a recurrence score greater than 25, a poor association of only 29.6%.

Although we would need a larger sample to draw conclusions, we saw that no association was observed in most cases between positive LVI and the recurrence score or between the axillary status with up to 1 positive lymph node and the recurrence score these would not be influencing factors in the result of the RS.

Finally, it is important to highlight the need of multidisciplinary work in these cases, agreeing on therapeutic strategies in each particular patient. At the Hospital Aleman, a group of doctors from different specialties participated, who discussed and established the treatment of each of the patients included in this study to maximize benefits and minimize harm.

Acknowledgments

None.

Funding

None.

Conflicts of interest

There are no conflicts of interest.

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