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# Prediction of Neoadjuvant Chemotherapy Response in Breast Cancer

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## ABSTRACT

***Purpose:*** *The response to neoadjuvant therapy correlates with prognosis. Being able to predict the response before performing the neoadjuvant treatment with Ki 67, HER2 and Hormone Receptors (RH) of the tumour [estrogens' receptor (ER) and progesterone receptor (PR)] and the patient's body mass index (BMI) may help to define it.*

***Material and Methods:*** *We studied the response to neoadjuvant treatment in 170 patients with breast cancer using the Miller and Payne Grading System (MPG). Pathological response was considered with a MPG 4,5. Before the neoadjuvant treatment, Ki67, HER2, RH and BMI were studied and related to the response to neoadjuvant treatment by logistic regression.*

***Results:*** *The study of factors was: Ki67 <14 in 56 (32.9%) patients and Ki 67> 14 in 114 (67.1%) patients; RE negative in 40 (23.5%) patients and positive ER in 130 (76.5%) patients; Negative RP in 75 (44.1%) patients and positive RP in 95 (55'8%) patients; HER2 negative in 118 (69.4%) patients and HER2 positive in 52 (30.6%) patients.*

*MPG 4-5 was obtained in 86 patients (50'6%) with a mean age of 48'4 + 8'8 years. MPG 1-2-3 was obtained in 84 patients (49.4%) with a mean age of 48.82 + 9.7 years. The mean BMI in patients with MPG 1-2-3 was 23.35 + 4.64, and in patients with MPG 4-5 it was 25.24 + 4.25 (p = ns). MPG 4-5 was obtained in 22 (26%) tumours with Ki67 <14 and 64 (74%) tumours with Ki67> 14 (p <0.05); in 24 (28%) ER negative tumours and 62 (72%) ER positive tumours (p = ns); in 46 (53%) RP negative tumours and 40 (47%) RP positive. (P <0.05)*

*We grouped the 170 patients into eight subgroups of patients according to the status of Ki67, RP and HER2 assessing MPG 4-5. The MPG 4-5 in Ki67 <14 RP (-) HER2 (-) was obtained in 3 (27.3%) cases and was not obtained in 8 (72.7%), Ki67> 14 RP (-) HER2 (+) was obtained in 5 (83.3%) cases and was not obtained in 1 (10.7%) cases. (P <0.05). In the other subgroups there were no significant differences*

***Conclusion:*** *Ki67, HER2 and RP predict the response to neoadjuvant chemotherapy. BMI does not affect the response to neoadjuvant chemotherapy.*

## Keywords

Breast cancer, Neoadjuvant therapy, Tumours, Keratins.

## Introduction

Neoadjuvant treatment is the treatment of choice for high risk breast cancers and tumours larger than 2 cm. Its indication decreases the stage of the tumour and increases the possibility of a conservative treatment [1,2], allowing in addition to evaluate the tumour response to the adjuvant treatment in vivo, obtaining information about the biology of the tumour and its prognosis.

The response to neoadjuvant treatment is measured with the complete pathological response (PRC) of both the primary tumour and the lymph node metastases, which correlates with disease-free survival and overall survival [3-8], when hematoxylin eosin (HE) is not observed tumour cells it is necessary to use

immunohistochemical techniques for the detection of keratins [4].

The prediction of the response to neoadjuvant treatment would allow choosing the appropriate neoadjuvant treatment, improving the prognosis of the patient. The prediction of the response to neoadjuvant treatment would make it possible to choose the appropriate neoadjuvant treatment, improving the patient's prognosis.

Ki67 is a core protein, the gene encoding it is on the long arm of chromosome 10 [9], is a marker of cell proliferation that is present in the active phases of the cell cycle (G1, S, G2, and Mitosis) and is absent at rest GO [10].

Their values have been used to differentiate the molecular subtype of breast cancer between the Luminal A subtype and Luminal B when the Ki67 value is less than 14% expression in the nuclei of tumour cells [10-12]. On the other hand, high Ki67, regardless of axillary involvement, is associated with a higher probability of relapse, less disease-free survival and lower overall survival [13]. Patients treated with neo-adjuvant chemotherapy with pathologic complete response (pCR) have also been shown to have higher rates of Ki67 [14].

The prediction of the response to neoadjuvant treatment would allow choosing the appropriate neoadjuvant treatment, improving the prognosis of the patient. The body mass index (BMI) that is equal to the weight in kilograms divided by the square of the height. Breast cancers in patients with a high BMI, have a higher nuclear grade, size and Ki67, compared to women with a normal or low-weight BMI [15]. Valued independently has been postulated as a predictive factor of pCR [16-18].

In this study we evaluated the BMI and Ki67 value with the degree of pathological response in patients with breast cancer undergoing neoadjuvant chemotherapy.

## Material and Methods

The response to neoadjuvant treatment is studied in 170 patients with infiltrating breast cancer who were treated with neoadjuvant chemotherapy consecutively in our center from March 2000 to June 2106.

To measure the pathological response, the Miller and Payne gradation system (MPG) has been used, which consists of a scale of 5 categories. Grade 1 is the absence of response and grade 5 is the complete pathological response. When tumour cells are not observed by routine histological techniques it is necessary to use immunohistochemical techniques for the detection of keratins [4].

We considered pathologic response to MPG Grade 4 (reduction> 90%) and MPG Grade 5 (absence of infiltrating tumour). Ki 67 has been studied immunohistochemically using the antibody, anti-Ki-67 [5] (Ventana, Tucson AZ) and the positivity in tumour cell nuclei expressed as a percentage of the total tumour cells evaluated in the areas of greater immunohistochemical expression. To decrease the variability of the immunohistochemical evaluation has been correlated with the histological grade and the state of the hormonal receptors [21,34-36].

The BMI was assessed by the ratio of the weight expressed in kilograms and the square of the height in meters. It was considered low if it was below 18.5, normal between 18.5 and 24.9 and high if it was 30 or higher. The study of BMI and tumour Ki67 was done before to neoadjuvant chemotherapy. Treatment with neoadjuvant chemotherapy was done with Anthracyclines and Taxanes. In all cases after neoadjuvant treatment, a histological study was done to assess the response

A logistic regression of the pathological response according to MPG 4 and 5 was performed with continuous BMI values, levels of Ki67 (<14% and> 14%), estrogens' receptor (RE) positive and negative, progesterone receptor (RP) positive and negative, and human epidermal growth factor receptor 2 (HER2), a predictive graphic of the response to neoadjuvant chemotherapy was obtained.

## Results

The mean age of the patients was 48.6 years (+ 9.2). The degree of pathological response of MyP was Grade 1, 2 or 3 in 84 patients (49.4%) and 4.5 in 86 cases (50.6%).

The study of factors was: Ki67 <14 in 56 (32.9%) tumours and Ki 67> 14 in 114 (67.1%) tumours; RE negative in 40 (23.5%) tumours and positive ER in 130 (76.5%) tumours; Negative RP in 75 (44.1%) tumours and positive RP in 130 (76.5%) tumours; HER2 negative in 118 (69.4%) tumours and HER2 positive in 52 (30.6%) tumours.

MPG 4-5 was obtained in 86 patients (50'6%) with a mean age of 48'4 + 8'8 years. MPG 1-2-3 was obtained in 84 patients (49.4%) with a mean age of 48.82 + 9.7 years. The mean BMI in patients with MPG 1-2-3 was 23.35 + 4.64, and in patients with MPG 4-5 it was 25.24 + 4.25 (p = ns).

MPG 4-5 was obtained in 22 (26%) tumours with Ki67 <14 and 64 (74%) tumours with Ki67> 14 (p <0.05); in 24 (28%) ER-negative tumours and 62 (72%) ER-positive tumours (p = ns); in 46 (53%) RP negative tumours and 40 (47%) RP positive. (P <0.05); In 51 (43.2%) HER2 negative and 35 (67.3%) HER2 positive tumours (p <0.05) (Table 1).

| MyP 4-5 | | N | % |
|---|---|---|---|
| Ki67 < 14 | 22 | 26 | p<0’05 |
| Ki67 > 14 | 64 | 74 | |
| RE- | 24 | 28 | p=ns |
| RE+ | 62 | 72 | |
| RP- | 46 | 53 | p<0’05 |
| RP+ | 40 | 47 | |
| HER2- | 51 | 43’2 | p<0’05 |
| HER2+ | 35 | 67’3 | |

**Table 1:** Prognostic factors and MyP 4-5.

We grouped the 170 patients into eight subgroups of patients according to the status of Ki67, RP and HER2 assessing MPG 4-5. (Table 2).

| MyP 4-5 | | | NO | | SI | | |
|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | |
| Ki67>14 | RP- | HER2- | 8 | 72'7 | 3 | 27'3 | p<0'05 |
| Ki67>14 | RP- | HER2+ | 1 | 10'7 | 5 | 83'3 | |
| Ki67>14 | RP+ | HER2- | 22 | 68'8 | 10 | 31'3 | p=ns |
| Ki67>14 | RP+ | HER2+ | 3 | 42'9 | 4 | 57'1 | |
| Ki67<14 | RP- | HER2- | 15 | 40'9 | 22 | 59'5 | p=ns |
| Ki67<14 | RP- | HER2+ | 5 | 23'8 | 16 | 76'2 | |
| Ki67 <14 | RP+ | HER2- | 22 | 57'9 | 16 | 42'1 | p=ns |
| Ki67 <14 | RP+ | HER2+ | 8 | 44'4 | 10 | 55'6 | |

**Table 2:** MyP 4-5 in patient subgroups.

The MPG 4-5 in Ki67 <14 RP (-) HER2 (-) was obtained in 3 (27.3%) cases and was not obtained in 8 (72.7%) cases, Ki67> 14 RP (-) HER2 (+) was obtained in 5 (83.3%) cases and was not obtained in 1 (10.7%) cases. (p<0.05).

There were no significant differences in the other subgroups; Ki67 <14 RP + HER2- was obtained in 10 (31.3%) cases and was not obtained in 22 (68.8%), in Ki67> 14 RP + HER2 + 4 (57.1%) was obtained and not obtained in 3 (42.9%) cases (p = ns); Ki67 <14 RP (-) HER2 (-) was obtained in 22 (59.5%) cases and was not obtained in 15 (40.9%) cases, Ki67 <14 RP (-) HER2 (+) was obtained in 16 (76.2%) cases and was not obtained in 5 (23.8%) cases (p = ns); Ki67 <14 RP (+) HER2 (-) was obtained in 16 (42'1%) cases and was not obtained in 22 (57'9%) cases, Ki67 <14 RP + HER2 + was obtained in 10 (55'6% ) cases, and was not obtained in 8 (44.4%) cases (p = ns).

## Discussion

Neoadjuvant chemotherapy allows in vivo evaluation of the treatment effect on the tumour, increasing the possibility of conservative surgery by decreasing tumour size. The response to neoadjuvant chemotherapy is a prognostic factor, with the complete pathological response being a marker of increased progression-free survival and increased overall survival [3-6,19-25].

The possibility of being able to predict the response to neoadjuvant chemotherapy based on the patient's tumour characteristics, with Ki67, HER2 and RP, may allow to design a better chemotherapy model and to have better information to establish the treatment.

A high BMI is associated with an increase in the incidence of breast cancer [16], with more aggressive tumours and worse prognosis [27], some authors [18,19] have found that obese women develop breast cancer with a significantly higher proliferation index, high nuclear grade, and a larger size compared to women with normal or low BMI.

Controversy exists whether obesity may affect the response to chemotherapy because conversion to active metabolite and / or clearance of cytotoxic drugs may be altered by increased body weight without a corresponding increase in toxicity [20].

There are authors who report that obese women are more likely to have hormone-receptor-positive tumors with a worse response to neoadjuvant chemotherapy [21], but others report that subgroups of obese patients have tumours with negative hormone receptors [22] and respond better to neoadjuvant chemotherapy [23].

In our study, BMI did not affect the response to neoadjuvant chemotherapy. Expression of the Ki 67 protein is a marker for cell proliferation [24] that is present during all active phases of the cell cycle (G1, S, G2 and mitosis), but is absent in resting cells (G0) [25].

The measurement of Ki67 by immunohistochemistry is the method of choice [26], but it has great variability, which can be reduced by correlating it with the histological grade and the state of the hormonal receptors [27].

There is an association between Ki 67 and prognosis [28]. The predictive value of Ki67 generates controversies, a high Ki67 value is seen in patients with pCR [29], being predictive of a higher rate of pCR [30] but there are also patients with progression during neoadjuvant chemotherapy who have a higher proliferation index than those responding to chemotherapy [31,32], suggesting a nonlinear effect of Ki67 on response to treatment [33].

In tumours expressing hormone receptors, the likelihood that neoadjuvant chemotherapy will reach a 4-5 MPG response is lower [34-41], but in many studies don't differentiate between estrogens' receptor and progesterone, in our results the status progesterone receptor, but not the estrogens' receptor status predict the response to neoadjuvant chemotherapy.

Neoadjuvant treatment with chemotherapy and anti-HER2 therapy is currently recommended in patients with HER2-positive tumours [42], with a good response.

The statistically significant predictive factors with a MyP 4-5 that we have seen are Ki67, RP and HER2. We have evaluated them together in the same patient, establishing 8 subgroups of patients with predictive factors: Ki 67, RP and HER2.

Only the subgroup of patients with Ki67> 14, RP (-), HER2 (+) obtained a higher MPG IV-V (p <0.05).

In conclusion, according to our data, the response to neoadjuvant treatment is better in the subgroup of patients with a Ki67> 14, RP (-) and HER2(+) tumour.

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