ISSN: 2776-0960 Volume 4, Issue 11 November, 2023

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

MATHEMATICAL MODEL FOR PREDICTING SURVIVAL IN PATIENTS WITH TRIPLE NEGATIVE BREAST CANCER

Atakhanova N. E. [1]
Almuradov A.[2]
Almuradova D. M. [1]
Ziyaev Sh. V[3]
Tashkent Medical Academy. Uzbekistan [1] .
Tashkent State Economic University. Uzbekistan [2]
Tashkent City Branch of Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology. Uzbekistan [3].

Introductions

Triple negative breast cancer (TNBC) has a more aggressive clinical course compared to other breast cancer subtypes. The presence of a triple negative receptor status causes the ineffectiveness of such types of targeted treatment as hormonal therapy and targeted therapy with Herceptin , in contrast to luminal and Her-2/ neu -positive tumors. In this regard, chemotherapy today remains the only accepted method of systemic treatment in this category of patients. Over the past few years, great advances have been made in the comprehensive treatment of TNBC. But, despite this, TN breast cancer remains one of the aggressive forms of malignant breast tumors with a high level of metastasis and low survival compared to other subtypes of breast cancer. The study conducted an IHC study of AR status in patients with TN breast cancer and, based on the results obtained, a mathematical model was created to determine its significance in predicting the outcome of the disease. Using regression -correlation analysis, it is possible to assess the prognostic value of AR expression in patients with breast cancer, followed by the calculation of an equation that makes it possible to make a forecast and determine the significance of the main parameters. The use of developed mathematical models, which include the most important predictive criteria, makes it possible with sufficiently high sensitivity and specificity to predict the outcome of the disease depending on the AR status in patients with TN BC

Keywords: triple negative breast cancer , immunohistochemistry, androgen receptor , mathematical models.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Relevance

"Triple negative" breast cancer is a tumor whose cells do not contain estrogen receptors, progesterone receptors and do not have Her2/ neu amplification . According to various authors [4,7], tumors of this type make up 15% of all invasive breast cancer, and are characterized by large size and poor prognosis [1,2]. An interesting pattern of TN breast cancer and its association with the BRCA1 gene mutation has been revealed [1,6]. There is evidence that patients with TN breast cancer are insensitive to chemotherapy, with the exception of platinum drugs [2,3]. Studies published over the past 10 years have reported that detection of a triple negative immunophenotype can serve as a reliable prognostic marker in the early stages of the process, when there are no signs of lymph node involvement [2,8] .

No less important for correctly establishing the prognosis in patients with TN breast cancer is taking into account the state of the receptors not only of estrogen and progesterone, but also of androgens [6]. The introduction of the concept of TN BC into daily clinical practice is complicated by the fact that this group of BC included cancers of different traditionally accepted morphology and immunophenotype . A significant proportion of these neoplasms are occupied by so-called basaloid cancers.

According to various authors, TN breast cancer accounts for from 11% to 22% [4,7] of all histological variants of cancer of this organ. There is still no consensus on what to consider estrogen-positive tumors - neoplasms in which 10% [8], 5% [1,7] or even 1% [10] of nuclei are positively stained during IHC study. This is due to the lack of rational justification for threshold values for the frequency of cells that give a positive IHC reaction to estrogen receptors (ER). TN BC occurs predominantly in young and premenopausal patients .

There are data on occurrence in individual ethnic groups. Thus, in the United States, this type of breast cancer affects African Americans and women of Spanish origin more often [3,5]. According to Morris G. et al [4,8], the frequency of TN breast cancer in African-Americans and white patients was 20.8% and 10.4%, respectively. However, according to a number of clinical parameters in other ethnic groups (outside the USA), TN BC had its own characteristics. For example, according to Chinese authors, patients with TN breast cancer living in the south of China account for about 25% of all breast cancer in this country, are characterized by a pronounced family of lesions [7,9] and a poor prognosis, while Yin W. et al. [11] Having studied the population of patients with TN breast cancer

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

in another part of China (Shanghai), we came to the conclusion that the prognosis of the disease was more favorable than that of patients from Western countries.

TN BC is characterized by an aggressive course, young age, more than 50% of patients are under 50 years of age. There was a marked difference in progression-free survival between patients with TN breast cancer and other subtypes. The peak of distant metastasis in TN breast cancer occurs 1–3 years after surgical treatment. For patients with other forms of breast cancer, the risk of progression is the same in all subsequent years after surgery [12,17].

Gene expression analysis shows that the basal-like “genetic” variant, TN BC is often associated with mutation of the BRCA genes : the occurrence of these mutations in TN BC ranges from 16 to 42% [13,16].

Unlike other subtypes of breast cancer, patients with TN breast cancer have a more aggressive course, characterized by early progression after treatment of localized disease, a high frequency of visceral metastases and metastases to the brain. In addition, in contrast to HER -2 positive and luminal subtypes, for the treatment of which targeted therapy can be used , the only treatment method for TN breast cancer to date remains only chemotherapy. These features of the tumor and clinical course, as well as the limited therapeutic arsenal, determine the unfavorable prognosis of the disease and, accordingly, low patient survival, even when treated in patients with early stages of the disease, especially with common processes. According to (Parise S. A. et al , 2014) 5-year survival rate of patients with localized TN breast cancer who received radical treatment is 75%, versus 85-98% for other subtypes. Based on the results of the analysis by Baser O. et al. (Baser O. et al ., 2012), the median survival of patients with metastatic TN breast cancer was 1.7 years compared to 3.2 years for other subtypes [10,11].

In connection with the development of oncomorphology and immunogenetics, we currently distinguish modern biomolecular markers that influence the assessment of the prognosis of the disease and its course, i.e. practically predict the outcome by determining the response of tumor tissue to chemotherapy. Given that the present study examined TN breast cancer, which is characterized by negative estrogen and progesterone status as well as Her /2- neu , it was interesting to examine androgen receptor status, which was both positive and negative. This was of particular interest, since changes in AR status determine the prognosis of the disease.

AR is a nuclear receptor that participates in a complex network of signaling pathways and regulates cell proliferation [8,9]. Recent studies in molecular

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

biology and genetics highlight the importance of AR in breast cancer, as it has a role in TN breast cancer. The absence of AR expression may correlate with early onset, high levels of nuclear and negative ER and ER, as well as Her /2 expression, i.e. with TN BC.

To date, the mechanisms responsible for the loss of AR expression in breast cancer carcinogenesis remain unknown. Based on this, the present study conducted an IHC study of AR status in patients with TN breast cancer, depending on the results obtained; subsequently, a mathematical model was created to determine the significance of AR status and its changes when making predictions among these patients.

The presence of AR expression in breast cancer cells in men has been known for a long time, which may have predetermined the study of this fact in breast cancer in women. The existing data on this is currently sparse and contradictory, which requires a search and a theoretical approach to this problem.

To be able to study the significance of AR status in breast cancer in patients with verified TN of breast cancer, a mathematical model was created. At the same time, the following parameters were studied as independent signs: age, menstrual function, duration of medical history, clinical stages, tumor size, localization of enlarged regional lymph nodes, Ki -67 status, histological forms, surgical and drug treatment, various modifications of NPCT regimens. AR expression is an informative biomarker for the survival of patients with breast cancer and creates conditions for a more complete study of the molecular basis of this phenomenon. Expressed in normal human breast tissue, where it is predominantly localized in the inner layer of epithelial cells lining the acini and intracavitary ducts, the role of AR in the normal biology of the breast epithelium remains unknown. AR has been implicated in the tumor syndrome, however, determining its precise function has proven difficult with AR-mediated androgenic effects shown to stimulate and inhibit the growth of breast cancer cells.

Table 1. The main parameters taken as the basis for creating the model mathematical forecast

1. Age:
1) 20-39
2) 40-49 l
3) 50-59 l
4) >60
2. Duration of medical history before the first visit to the doctor:
1) up to 6 months
2) 7-10 months

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

3) 13-18 months
4) more than 18 months
3. Clinical stages upon admission:
1) first
2) second
3) third
4) fourth
4. Primary tumor size:
1) 2-4 sm
2) 5-7 sm
3) 7-9 sm
4) 10-12 sm
5. Localization of enlarged regional lymph nodes
1) in the axillary and/or subclavian region
2) supraclavicular and/or subscapular region
3) enlargement of two or more different groups of regional lymph nodes
4) lymph nodes are not visualized
6. Ki67 status, signs of tumor proliferation in immunohistochemical study:
1) up to 20%
2) 20-50%
3) 50-80%
4) 80-100%
7. Androgen receptor status by immunohistochemical study
1) 1 point
2) 2 points
3) 3 points
4) receptor negative
8. What histological forms were identified in TN BC:
1) medullary
2) apocrine
3) metaplastic
4) invasive nonspecific type
9. Surgical treatment of the primary lesion:
1) Madden radical mastectomy (RME)
Patey radical mastectomy (RPM)
3) radical resection
4) no treatment was carried out
10. Drug treatment was received in the form of:
1) only neoadjuvant polychemotherapy
2) only adjuvant polychemotherapy
3) neoadjuvant and adjuvant polychemotherapy
4) palliative chemotherapy
11. NPCT was carried out according to the scheme:
1) CAF, AC
2) taxane with anthracycline ;
3) taxane with platinum;
4) did not receive NPCT ;

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Using regression -correlation analysis, we assessed the prognostic value of AR expression in patients with TN BC and compiled an equation on the basis of which it is possible to make a forecast and determine the significance of the main parameters described above, according to the compiled questionnaire, which included 11 main signs (Table 1).

AR expression is an informative prognostic biomarker that determines the outcome of the disease in patients with TN breast cancer, which provides grounds for a more complete study of its molecular basis. The data obtained indicate the presence of a correlation, depending on the age of the patients, as well as the level of expression of Ki -67, which has a negative relationship with the response to the presence of AR(+) or AR(-) tumor status.

The presence of RA in tumor tissue has an important prognostic role, and also shows significance in the pathogenesis of breast cancer; this will make it possible in the future to identify a possible additional group of patients with TN breast cancer for the purpose of selecting individual therapy and including androgen antitumor therapy. The calculated sensitivity and specificity rates of the model were 63.7% and 72.6%.

Table 2. Correlation coefficients depending on AR status in patients with TN BC

N						
Tau-b Kendal -la	AR status on IHC (Y)	coefficient correlations	1,000	0.007	0.005	-0.055
		Meaning	-	0.928	0.954	0.493
	age X1	coefficient correlations	0.007	1,000	-0.232**	-0.036
		Meaning	0.928	-	0.005	0.644
	duration of medical history X3	coefficient correlations	0.005	-0.232**	1,000	0.080
		Meaning	0.954	0.005	-	0.335
	tumor size, X5	coefficient correlations	-0.055	-0.036	0.080	1,000
		Meaning	0.493	0.6440	0.335	-
	localization of enlarged regional l/u, X6	coefficient correlations	0.073	0.062	-0.032	0.171*
		Meaning	0.357	0.432	0.695	0.031
Ro Spearman	Ki-67 status, X7	coefficient correlations	-0.031	0.181 *	0.022	-0.014
		Meaning	0.706	0.026	0.798	0.862
	AR status on IHC (Y)	coefficient correlations	1,000	0.006	0.005	-0.060
		Meaning	-	0.945	0.956	0.508
	age, X1	coefficient correlations	0.006	1,000	-0.253 **	-0.041
		Meaning	0.945	-	0.004	0.645

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

	duration of medical history X3	coefficient correlations	0.005	-0.253 **	1,000	0.086
		Meaning	0.956	0.004	-	0.339
	tumor size, X5	coefficient correlations	-0.060	-0.041	0.086	1,000
		Meaning	0.508	0.645	0.339	-
	localization of enlarged regional l/u, X6	coefficient correlations	0.080	0.070	-0.035	0.192 *
		Meaning	0.375	0.433	0.695	0.031
	Ki 67 status , X7	coefficient correlations	-0.034	0.200 *	0.023	-0.015
		Meaning	0.708	0.025	0.798	0.864

Note: ** Correlation is significant at the 0.01 level

* Correlation is significant at the 0.05 level

This table shows the procedure for calculating the above variables with determining the significance of each of the selected features.

Using regression analysis, a regression equation was calculated, which has the following form:

$$Y = 3.23 + 0.007X_1 + 0.048X_2 + 0.071X3 - 0.153X_4 + 0.075X_5 - 0.026X_6$$

where Y is the regression level value;

3.23 - value of the regression coefficient of the free term;

X_1 - age (1 - 20-39 years; 2 - 40-49 years; 3 - 50-59 years; 4 - more than 60 years);

X_2 – duration of medical history before the first visit to the doctor (1 - up to 6 months; 2 - 7-10 months; 3 - 13-18 months; 4 - more than 18 months)

X_3 – clinical stages upon admission (1 – I ; 2 – II ; 3 – III ; 4 – IV)

X_4 – size of the primary tumor (1 - 2-4cm; 2 - 5-7cm; 3 - 7-9cm; 4 - 10-12cm;)

X_5 - localization of enlarged regional lymph nodes (1 - in the axillary and/or subclavian region; 2 - supraclavicular and/or subscapular region; 3 - enlargement of two or more different groups of regional lymph nodes; 4 - lymph nodes are not visualized ;)

X_6 – Ki-67 status, signs of tumor proliferation with IHC (1 - up to 20%; 2 - 20-50%; 3 - 50-80%; 4 - 80-100%;).

It should be noted that if the p value is < 0.5, the prognosis is unfavorable, and if p>0.5, the forecast is probable, with $X^2 = 639.3$.

The application of this prediction model can be seen in the following clinical examples:

Example 1. Patient S., 37 years old, with a verified diagnosis by IHC using the TN method for stage IIa breast cancer ($T_2 N_0 M_0$) AR (+), without lymph node involvement. In a retrospective analysis of IHC results, the tumor was characterized by a high level of Ki-67 expression.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Let's calculate the value of the regression equation:

$$Y = 3.23 + 0.007X_1 + 0.048X_2 + 0.071X3 - 0.153X_4 + 0.075X_5 - 0.026X_6 = 0.16.$$

Let us determine the probability value of the dependence AR :

$$p = e^Y / (1 + e^Y) = 2.72^{0.16} / (1 + 2.72^{0.16}) = 0.45.$$

The probability of significance of AR status was 45%.

This indicates the significance of the AR status, in this case because it is positive, the outcome of the disease is favorable

Example 2. Patient M., 53 years old. with TN BC stage IIb (T2N1M0) with lymph node involvement. In a retrospective analysis of the results of IHC studies, the tumor was characterized by high Ki-67 levels and the absence of AR (-) expression.

Calculation of the regression equation:

$$Y = 3.23 + 0.007X_1 + 0.048X_2 + 0.071X3 - 0.153X_4 + 0.075X_5 - 0.026X_6 = 0.22.$$

Let us determine the probability value of the dependence AR:

$$p = e^Y / (1 + e^Y) = 2.72^{0.22} / (1 + 2.72^{0.22}) = 0.75.$$

The probability of achieving a poor outcome is 75%. Thus, statistical calculation and determination of the correlation dependence showed that patients with TN breast cancer have a directly proportional correlation with the presence and expression level of AR status, which can serve as a prognostic determinant of the outcome of the disease factor.

Also, the creation and calculation of the correlation showed that with AR (-) negative status, breast cancer patients were younger than patients whose tumor contained AR (+), who were older.

Thus, the use of the developed mathematical models, which include the most important predictive criteria, makes it possible to predict the outcome of the disease in patients with TNBC with sufficiently high sensitivity and specificity (sensitivity 63.7%, specificity 72.6%).

In a statistical analysis of survival of patients with breast cancer, life expectancy was significantly longer ($P < 0.05$) in patients with high levels of AR expression, Figure 1.

The prognostic value of AR expression in positive TNBC was characterized by a decrease in the frequency of lesions in the lymph nodes, smaller tumor sizes, and higher differentiation compared to AR(-) TN BC cells.

In this regard, lymph node status and tumor size can be used to select high- and low-risk patients at the time of primary surgery, which may also provide valuable information about treatment options for triple-negative tumors.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

In patients in the study groups, the distribution of patients was as follows: 61 (48.4%) had positive expression of AR (+), 65 (51.6%) had negative AR (-). The histological grade of malignancy in AR (-) tumors was higher than in patients with AR (+) tumors (Table 1 and Fig. 1).

Summarizing the data obtained from the research work, we can conclude that TN of breast cancer is certainly a problem that deserves special and close attention of clinical oncologists, as well as representatives of related theoretical disciplines. When planning the treatment of these patients, it is necessary to use non-standard schemes and regimens.

This study shows that the presence and detection of androgen receptor (AR) expression by IHC in TN breast cancer cells opens up prospects for the development of targeted therapy for this type, taking into account the presence or absence of androgen receptors.

To rationalize the treatment of TN breast cancer, it is certainly necessary to summarize a large number of materials with a thorough analysis of all clinical and morphological parameters, taking into account survival rates and the variants of chemotherapy regimens used.

Thus, TN breast cancer currently represents an unresolved scientific and practical problem in the field of oncology, requiring additional research both in relation to the search for optimal approaches to the use of already available treatment and diagnostic options, and for the search for new treatment options, as well as fundamental research in the field of studying the biological characteristics of the disease.

Determination of AR is an important factor that plays a role in prognosis of breast cancer in all molecular subtypes, especially in TN breast cancer, which can become a target for planning targeted therapy.

In conclusion, we can conclude that the lack of AR expression in breast cancer patients determines a worse prognosis, despite a more favorable molecular subtype of the tumor.

In the course of the study, informative and significant clinical, morphological and parameters were studied and determined based on the prognosis model, allowing with a sufficient degree of probability to predict the outcome of the disease in patients with TN BC, including when determining a positive AR status, which determines a more favorable prognosis .

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

Conclusions

In the present study, an IHC study of AR status in patients with TN breast cancer was carried out and, based on the results obtained, a mathematical model was created to determine its significance in predicting the outcome of the disease. The following parameters were studied as independent signs: age, menstrual function, duration of medical history, clinical stages, tumor size, localization of enlarged regional lymph nodes, Ki-67 status, histological forms, surgical and drug treatment, various modifications of NPCT regimens.

AR expression is an informative biomarker for the survival of patients with breast cancer and creates conditions for a more complete study of the molecular basis of this phenomenon. Loss of AR expression is associated with early onset, high levels of nuclear and negative ER, PR, including HER2 expression in breast tumors.

Using regression -correlation analysis, the prognostic value of AR expression in patients with breast cancer was assessed, followed by the calculation of an equation that allows for prediction and determination of the significance of the main parameters.

The presence of AR in tumor tissue has an important prognostic role, and also shows significance in the pathogenesis of breast cancer; this will allow identifying an additional group of patients with TN breast cancer in order to select individual therapy with the inclusion of androgen antitumor therapy in the treatment regimen.

The use of developed mathematical models, which include the most important predictive criteria, makes it possible to predict the outcome of the disease depending on the AR status in patients with TN BC with sufficiently high sensitivity and specificity (sensitivity 63.7%, specificity 72.6%).

The presence and detection of androgen receptor (AR) expression by IHC in TN breast cancer cells opens up prospects for the development of targeted therapy for this type, taking into account the presence or absence of androgen receptors.

References

1. Atakhanova N.E, Almuradova D.M, Gaziev L.T, Sadullaeva N.I, Erkinova Ch.O. Androgen receptor values for prediction of survival of patients with three times negative breast cancer. World Bulletin of Public Health, 22, 140-142, 2023.

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

2. Almuradova D.M, Odilova Sh.Sh, Ubaydullaev I.A, Sharobiddinov B.B. Islamov S.B. A Modern Approach to Diagnosis and Treatment of Breast Cancer Releases. Central Asian Journal of Medical and Natural Science, 2(5), 294-298, 2021.
3. Khakimova G.G, Khakimov G.A, Khakimova Sh.G, Khakimov A.T, Almuradova D.M. Changes In Tumor Infiltrating Lymphocytes Of Peripheral Blood And Tissue During Chemotherapy In Patients With Gastric Cancer. The American Journal of Medical Sciences and Pharmaceutical Research. T 3 (03), 20-31, 2020.
4. MD Juraev, NE Atakhanova, DM Almuradova, LT Gaziev. Androgen receptor values for prediction of survival of patients with three times negative breast cancer. EPRA International Journal of Research and Development (IJRD) 8 (6), 104-106, 2023
5. M.N Tilyashaikhov, L.T Gaziev, A. Almuradov, D.M Almuradova. A Modern Approach to Diagnostics, Prediction and Course of Renal Cell Cancer. Annals of the Romanian Society for Cell Biology, 4429–4451, 2021.
6. Атаханова Н.Э, Алмурадова Д.М. Влияние экспрессии андрогеновых рецепторов на прогноз трижды негативного рака молочной железы. Клиническая и экспериментальная онкология. Т 10 (2), 112-115, 2022.
7. Atakhanova N.E, Almuradova D.M, Gaziev L.T, Ziyayev Sh.V. Results of Drug Treatment of patients with metastasis of triple times negative breast cancer. EPRA International Journal of Research and Development (IJRD) 9 (6), 125-128, 2023.
8. Atakhanova N.E, Almuradova D.M, Ziyayev Sh.V, Хамидов Х, Юсупов А. Значения андрогенных рецепторов для прогнозирования выживаемости больных трижды негативным раком молочной железы. International Bulletin of Medical Sciences and Clinical Research. 3 (6), 5-8 , 2023.
9. D.M Almuradova, D.I Mukumova, X.Kh Turaeva, Karlibaev A.O. Modern endocrine therapy in locally advanced estrogen or progesterone receptor-positive breast cancer. Образования и наука в XXI веке. 24 (2), 773-780, 2022.
10. Н.Э Атаханова, Д.М Алмурадова, И.А. Дудина. Молекулярно-биологические характеристики трижды негативного рака молочной железы. Российский биотерапевтический журнал. 17 (1), 23-27, 2018
11. Бабешкин Р, Н., Оптимизация лекарственного лечения больных трижды

ResearchJet Journal of Analysis and Inventions
https://reserchjet.academiascience.org

негативным раком молочной железы: Дис... канд. Мед. наук: 14.01.12 / Бабешкин Р. Н.; 56-72. 2017.

12. Брагина О.Д. Оценка предсказательной значимости клинико-морфологичеких и молекулярных параметров у больных трижды негативным раком молочной железы. Москва. Дис... канд. Мед. наук: С. 109-11. 2014..
13. Жукова Л. Г. Клинические и фундаментальные аспекты прогноза и рационального лечения рака молочной железы с тройным негативным фенотипом: Дис. д-ра мед. наук. М., 2015. С. 196.
14. Зикиряходжаев А.Д., Фролова М.А., Рассказова Е.А., Глазкова Е.В. Лечение тройного негативного подтипа рака молочной железы. Опухоли женской репродуктивной системы 2017;13(2): С.20–6.
15. Игнатова Е.О. «BRCA1-дисфункция у больных тройным негативным вариантом рака молочной железы, получающих неоадъювантную платиносодержащую химиотерапию»: дис ... Канд. Мед. наук: 14.01.12 (www.ronc.ru).- Москва, 2015.С.172-78.
16. Карселадзе Д. А. ТН РМЖ (клинико-биологические особенности): Автореф. дис. … канд. мед. наук. М., 2010. С.25-31.
17. Крылов А.Ю., Крылов Ю.В. Андрогены и рак молочной железы (обзор литературы). Вестник Витебского государственного медицинского института. 2015; 14 (5): С. 5–15.