World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Nuclear anaplasia of positive and negative hormonal receptor (estrogen and progesterone receptor) in breast cancer cytology

Nabila Aliya Rahmah Vansya [1], Willy Sandhika [2,*] and Desak Gede Agung Suprabawati [3]

[1] *Student at Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.*
[3] *Department of Surgery, Faculty of Medicine, Universitas Airlangga / Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.*

World Journal of Advanced Research and Reviews, 2024, 21(01), 1136–1139

Publication history: Received on 28 November 2023; revised on 06 January 2024; accepted on 08 January 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.1.0064

Abstract

Background: Breast epithelial duct cells show response to sex hormone such as estrogen and progesterone since they have receptor for estrogen and progesterone. Consequently, malignant cells from breast epithelial ductuli (Breast Ductal Carcinoma) show positivity for estrogen and progesterone receptor (ER and PR). However, when this neoplasm becomes poorly differentiated, they lost these characteristics and became ER and PR negative. On the other hand, poorly differentiated cancer cells show more nuclear enlargement that was accompanied by increase nuclear pleomorphism. This study wants to compare area of breast cancer cells nuclei and nuclear pleiomorphism in positive and negative ER and PR.

Material and method: Positive and negative ER and PR breast cancer cases were collected from archive of Anatomic Pathology Department each consisting of ten to fourteen cases. Image analysis was made from each case to measure the area, diameter, and nuclear pleiomorphism.

Result and discussion: There were no differences in nuclear size and pleomorphism of breast cancer cells with positive and negative ER and PR. This result show that poorly differentiated cancer cells did not accompany by increase of nuclear anaplasia.

Conclusion: There is no difference of cancer cells morphology in positive and negative ER and PR. Hormonal status and anaplasia of cell nuclei can be used as independent prognostic factor to breast cancer progression.

Keywords: Breast Cancer; Estrogen Receptor; Progesterone Receptor; Nuclear anaplasia

1. Introduction

According to the World Health Organization in 2020, the most common cancer case is breast cancer with 2.26 million new cases in the world [1]. Breast cancer in Indonesia has reached 68.858 new cases and the number of deaths has reached more than 22 thousand cases [2]. Breast cancer is clinically or pathologically heterogeneous. This makes it difficult to estimate the survival period and response to patient therapy because the degree of malignancy varies greatly [3]. Breast cancer has hormonal receptors in the form of Estrogen Receptor (ER), Progesterone Receptor (PR), and HER-2/Neu that play a role in the occurrence of cancer cells. ER/PR positive was defined as breast cancer that have estrogen/ progesterone receptors positive for more or equal than 10% of cells, while ER/PR negative was defined as breast cancer

* Corresponding author: Willy Sandhika

that have estrogen/ progesterone receptors positive for less than 10% of cells [4]. ER/PR status were assessed by immunohistochemistry method on breast cancer tissue [5]. The expression of ER/PR in each breast cancer cell generally varies, so the response in each patient will be different. The higher expression of ER/PR in cancer cells, the better prognosis the patient has [6].

Cancer cells cause morphological changes related to the degree of cancer cell differentiation of the patient. Morphological changes in cancer cell which indicates a possible malignant transformation can be known as nuclear anaplasia. Anaplastic cells show pleomorphism, high nuclear to cytoplasmic ratios, hyperchromatic nuclei, abnormal nuclear contours, prominent nucleoli, and loss of normal polarity [7]. Nuclear anaplasia is related with poorer prognosis and more aggressive clinical behavior. However, not all breast cancers have extensive anaplasia, and the level of anaplasia can greatly differ between different tumors [8]. Determination of the degree of differentiation of cancer cells can be done by measuring the nuclear grade of cancer cells which can be seen from the size and pleiomorphism of cancer cell nuclei. There is a significant relationship between the size of the cell nucleus and the expression of ER/PR so that it can affect the determination of prognosis and therapy. The expression of ER/PR negative indicates a larger cell nucleus size, while ER/PR positive has a smaller cell nucleus size compared to ER/PR negative [9]. Therefore, in this research the authors want to conduct research on the difference between the nuclear size and pleomorphism of breast cancer cells between ER/PR positive and negative cases. The results obtained are expected to prove that molecular changes in a cell can be seen morphologically.

2. Material and Method

Positive and negative ER/PR cases are collected from archive of Anatomic Pathology Department at Dr. Soetomo General Academic Hospital Surabaya each consisting of ten to fourteen cases. There were ten patients with ER positive, 10 patients with ER negative, 12 patients with PR positive, and 14 patients with PR negative that were enrolled in this study. Cell measurements are carried out using microscopic slides obtained from FNAB examination to measure the area and diameter of breast cancer cell nuclei. Each patient's data was subjected to Mann-Whitney statistical test to determine whether there was a significant difference between ER/PR status and nuclear size and pleomorphism. Data regarding ER/PR status was obtained from the results of IHC examinations in the patient's medical records at Dr. Soetomo General Academic Hospital Surabaya.

3. Result and discussion

3.1. Nuclear Size and Pleomorphism with Estrogen Receptor

The data of nuclear size, pleomorphism, and ER expression were analyzed for normality of the data using the Shapiro-Wilk test and showed that the data were not normally distributed ($p < 0.05$). The Mann-Whitney test result is 0.131 (p-value > 0.05), it can be concluded that there is no significant difference of area size between positive and negative ER cells. As for the Mann-Whitney test result of diameter size is 0.185 (p-value > 0.05), it can be concluded that there is no significant difference of diameter size between positive and negative ER cells. Based on the Mann-Whitney test result of 0.791 (p-value > 0.05), it can be concluded that there is no significant difference between the pleomorphism of the coefficient of variance of positive and negative ER cells. The Mann-Whitney test result is 0.406 (p-value > 0.05), it can be concluded that there is no significant difference between variance pleomorphism of positive and negative ER cells. Positive ER cells have an average nuclear size of 137.59 μm, while negative ER cells has an average size of 169.45 μm.

3.2. Nuclear Size and Pleomorphism with Progesterone Receptor

The data of nuclear size, pleomorphism, and PR expression were analyzed for normality of the data using the Shapiro-Wilk test and showed that the data were not normally distributed ($p < 0.05$). The Mann-Whitney test result is 0.382 (p-value > 0.05), it can be concluded that there is no significant difference of area size between positive and negative PR cells. As for the Mann-Whitney test result of diameter size is 0.898 μm (p-value > 0.05), it can be concluded that there is no significant difference of diameter size between positive and negative PR cells. Based on the Mann-Whitney test result of 0.642 (p-value > 0.05), it can be concluded that there is no significant difference in pleomorphism of the coefficient of variance between positive and negative PR cells. The Mann-Whitney test result is 0.959 (p-value > 0.05), it can be concluded that there is no significant difference of variance pleomorphism between positive and negative PR cells.

4. Discussion

Breast cancer cases at Dr. Soetomo General Academic Hospital Surabaya during 2022 reached 1,297 patients. In this study, the number of samples taken was 10 cases of positive ER, 10 cases of negative ER, 12 cases of positive PR, and 14 cases of negative PR. This study wants to compare the differences between nuclear size and pleomorphism in breast cancer between positive and negative ER/PR. Nuclear size were measured by area and diameter of cells, while pleomorphism were measured by variance and coefficient variance of nuclear size area. Most studies reported there was a significant difference in morphological status between positive and negative ER/PR. The negative ER/PR had larger nuclear differences and pleomorphism than positive ER/PR [10]. This study showed there is no statistically significant difference between between positive and negative ER/PR. It is consistent with a previous study that said there was no difference between the nuclear size with status of metastasis which related to the differentiation degree of breast cancer [11].

Breast cancer normally have receptors that bind to hormone Estrogen and Progesterone that related to cancer cell growth and morphological changes that related to differentiation cell [10]. Estrogen Receptors (ER) and Progesterone Receptors (PR) status can be considered as positive if ≥10% tumor cells show reaction to immunohistochemistry test. ER with <10% can categorized as ER negative [12]. Hormone receptor positive (ER positive and/or PR positive) tend to grow due to the presence of estrogen and progesterone. The presence of ER and PR in breast cancer cells is associated with a better prognosis and a reduced chance of the disease returning. Breast cancers with hormone receptors positive are typically less aggressive and may have a positive response to hormone therapy, which inhibits the impact of estrogen and progesterone on the cancer cells [13].

Differentiation cells related to morphological changes in cancer cell. Cancer cells that have lack of differentiation is called anaplasia. Anaplastic cells show pleomorphism, abnormal nuclear morphology, mitoses, and loss of normal polarity [14]. The higher degree of anaplasia tends to be more aggressive tumor invasion and progression [7]. Nuclear anaplasia is related with poorer prognosis and more aggressive clinical behavior, but not all breast cancers have extensive anaplasia, and the level of anaplasia can greatly differ between different tumors [8]. Anaplasia cells show pleomorphism nuclear size that related to expression of ER/PR. ER/PR negative cells tends to have a larger nucleus size than ER/PR positive cells while ER/PR positive cells tend to have smaller nucleus size [15].

5. Conclusion

The conclusion of this study is that there is no significant difference between the nuclear size and pleomorphism of breast cancer between positive and negative ER/PR. More extensive research with increased patient populations will be necessary to ascertain the significance of quantitative morphometry.

Compliance with ethical standards

Acknowledgements

The authors would like to thank Dr. Soetomo General Academic Hospital Surabaya for providing medical record during the thesis work.

Disclosure of Conflict of interest

The authors declare there is no conflict of interest in this study.

Ethical approval statement

This study has received permission and approval from the Health Research Ethics Committee of Dr Soetomo General Academic Hospital Surabaya with reference number 1317/LOE/301.4.2/V/2023.

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