ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

A Review of Breast Cancer Cases Experiencing Ki-67 Expressions

Received: 25 October 2022, **Revised:** 27 November 2022, **Accepted:** 29 December 2022

Dr. J. M. Pawar [1]
Associate professor
Department of Pediatrics
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University",
Karad – 415110, Maharashtra
Email: - drjmpawar17@gmail.com

Dr. (Mrs) R. A. Langade [2]
Associate professor
Email:- rajkunvarlangade@gmail.com
Department of Pediatrics
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University",
Karad – 415110, Maharashtra

Dr. Prashant P. Shah [3]
Assistant professor
Email: - doc.pshah@gmail.com
Department of Pediatrics
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University",
Karad – 415110, Maharashtra

Dr. Beemarapu Venkata Sudheer [4]
P.G. Student
Department of Pediatrics
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University",
Karad – 415110, Maharashtra

Key Words
radiation, chemotherapy, breast carcinoma, tumor necrosis, hormone receptors, estrogen receptor

Abstract
The main purposes of Ki-67 examination today are prognosis estimation, choice of adjuvant therapy, and response prediction to neoadjuvant therapy.
Thus, it is vital that the pathologist accurately and reliably assesses the Ki-67 status of breast cancer. In order to determine the relationship between Ki-67 status and known prognostic factors like age, tumor size, histological type, and grade, axillary lymph node metastasis, lymph vascular invasion (tumor emboli), tumor necrosis, hormone receptors such as estrogen receptor (ER) and progesterone receptor (PR), Her-2 neu status, and molecular subtypes (Luminal A, Luminal B, Her 2

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

neu enriched, and triple-negative). Hence, diverse combinations of surgery, hormone therapy, postoperative radiation, and chemotherapy make up the current therapeutic approaches for treating breast cancer. A key duty of the clinician is to choose between hormone therapy, which has few side effects, and chemotherapy, which carries known morbidity and risk.

1. Introduction

Breast embryology: Due to the mammary gland's presence in the breast, Mammalia is so named. The apocrine glands give rise to the mammary gland, which is an epidermal appendage. The parenchyma and stroma, which are made up of ectodermal and mesodermal components, respectively, make up the human breast. The mammary ridges, which run down either side of the body from the future axilla to the future inguinal region and medial thigh, begin to form in the fourth week.

With the exception of where the breasts are, these ridges usually vanish in people. At the fifth week, the primary bud of the mammary gland is produced by the remaining mammary ridge. This bud descends into the dermis below. The primary bud starts to branch in the tenth week, and by the twelveth week, multiple secondary buds have formed. Throughout the remaining stages of gestation, these buds elongate and branch, and the ensuing ducts canalize as a result of the coalescence of tiny lumina. The mammary glands include 15 to 25 lactiferous ducts that flow into the breast pit, a little superficial depression. Within a few weeks of birth, the underlying mesoderm proliferates, turning this pit into an everted nipple, though occasionally the nipple remains depressed (inverted nipple). Moreover, the skin around the nipple extends outward from the areola.

Breast anatomy: "The pectoralis muscle supports the breast, which is a modified sweat gland covered in skin and subcutaneous tissue. The breast spans from the second to the sixth rib in the vertical axis and from the sternal border to the mid-axillary line in the horizontal axis. It rests on the pectoralis muscle. It is separated into upper outer and upper inner, lower outer and lower inner quadrants". The axillary tail of Spence, a brief extension of the upper quadrant, enters the axilla through a hole in the deep fascia. The foramen of Langer is the name of the entrance. The suspensory ligaments of Cooper, which run in bundles from the skin to the pectoral fascia and support the breast, are made up of dense fibrous connective tissue.

Breast blood flow is a concern : The internal and lateral thoracic arteries are responsible for the majority of the breast's vascular supply, while the thoracoacromial, intercostal, subcapsular, and thoracodorsal arteries have a modest impact.

Breast lymphatic drainage: The axilla and axillary lymph nodes, which receive >90% of the lymph drained, are the most important drainage basin for lymphatic flow from the breast. A minor amount of lymph drains into the internal mammary and posterior intercostals lymph nodes through the internal thoracic and posterior intercostals lymphatics, respectively.

Breast venodrainage: It mostly goes to the posterior intercostal veins, axillary vein, and internal thoracic vein.

Breast nerve supply: Via the 4th and 6th intercostal nerves' anterior and lateral cutaneous branches.

Breast histology: "The pectoralis muscle, from which the mammary gland is divided by a fascia, supports the mammary gland, which is covered by skin and subcutaneous tissue. The terminal duct-lobular unit (TDLU) and the big duct system are the two main parts of the solitary gland, which is the organ's morphological functional unit." Its complex branching structure is structured topographically into lobes.

The terminal ductule and lobule together make up the TDLU, which is the gland's secretory component. "It joins the subsegmental duct, which then links to the segmental duct and, from there, to the collecting (lactiferous or galactophorous) duct, which empties into the nipple. The lactiferous sinus is a fusiform dilatation beneath the nipple, situated between the collecting and segmental ducts." A stratified squamous epithelium covers the nipple. The breast of a prepubescent person lacks colour. Melanin pigmentation begins to form during menarche, increases during pregnancy, and then persists to varying degrees after. The nipple's skin contains sebaceous glands.

There is a ring of skin called the areola that surrounds the nipple, and it also experiences pigmentary changes. Montgomery glands are located in this specific area of the breast skin. The channels on the surface of the areola allow these modified sebaceous glands to enter through the Morgagni tubercles. During pregnancy, these tubercles are particularly noticeable near the nipple base. This is the moment

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

when the areola seems to be "studded over and rendered uneven by the prominence of glandular follicles, which range in number from 12 to 20." A sixteenth to an eighth of an inch is how far they extend from the surface. A milk-like substance that moistens the nipple is produced in part by the Montgomery glands, which increase during pregnancy.

A continuous layer of well-developed elastic tissue envelops the big ducts, which have less specialized stroma. According to age and physiologic and hormonal parameters, the relative amount of collagenous stroma and fat varies substantially between people.

Grades for Histology: Almost all invasive breast carcinomas should have their histological grade evaluated because it is a significant independent prognostic factor. Tumor grading has even been demonstrated to be useful in predicting prognosis in patients with breast cancer that is 1 cm or less in size. The microscopic development pattern of invasive ductal carcinomas and the cytologic characteristics of differentiation are described by histologic grading.

The following is the histology grading system:

1) Tubule formation: The tumor's capacity to develop glandular or papillary structure serves as a measure of how differentiated it is. In cases when the bulk of the tumor exhibits well-formed glandular features, the tumor is rated as 1, 3, or 2, depending on the presence or absence of these structures.
2) Pleomorphism: Tumor cells receive a score of 1 if they are regular, uniform, and resemble ductal epithelial cells, a score of 3 if they exhibit marked pleomorphism, and a score of 2 if they exhibit moderate pleomorphism.
3) Mitotic Index: Quick staining is performed at low power (10x) to locate locations with a high concentration of mitotic figures. The greatest number of all mitoses are counted in one high power field when the power is high (40x). Missing or 1 mitosis/HPF receives a point, 2 mitoses/HPF receives a point, and > then 2 mitoses/HPF receives a point.

Breast Cancer and The Function of Hormone Receptors

Human breast cell proliferation, multiplication, and the ability to distinguish between normal and malignant cells are all regulated by steroid hormone and peptide growth factor receptors. Hormone receptors are proteins that are located on and in breast cells and which, upon detecting hormonal signals, alert cells to growth.

One of the hormone-dependent tumors includes breast cancer. The proliferation and differentiation of normal, premalignant, and malignant cell types, particularly breast epithelial cells, are significantly regulated by female sex hormones.

Albert Schinzinger's initial proposal of the use of oophorectomy in the treatment of breast cancer occurred in 1889. He made the observation that older women tended to have a better prognosis for breast cancer than younger women and theorized that oophorectomy would cause the breast to atrophy and any cancer within it to grow. A woman with metastatic breast cancer underwent a bilateral oophorectomy for the first time in 1895 according to George Thomas Beatson, who also documented the procedure in 1896. Beatson proposed that the therapeutic effects of oophorectomy on breast cancer were due to the fatty degeneration of the cancerous cells brought on by the procedure. Knight and colleagues were among the first to link a lack of estrogen receptors in breast tumors to an early recurrence of cancer in 1977.

“Breast cancer's prognosis and treatment are impacted by the standard factors like histologic type and grade, tumor size, lymph node status, and the status of the estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu receptors.” First-line hormonal therapy have a positive response rate of between 30% and 40% in patients with ER positive metastatic illness, while another 20% of patients have their disease stabilize. The recurrence rate in patients with ER positive breast cancer is roughly cut in half by adjuvant hormone therapy. In both early and advanced disease, hormonal therapy is a first-line treatment for almost all patients with ER positive disease since it is also very harmless. Patients with ER negative tumors clearly do not benefit from endocrine treatment, particularly in the adjuvant situation. For endocrine treatment, ER serves both a target and a biomarker.

The ER pathway can be affected by methods that mimic the function of the receptor, such as selective ER modulators like tamoxifen, or powerful pure antagonists that can degrade the receptor, like fulvestrant, as well as methods that deprive the receptor of estrogen (such as aromatase inhibition and ovarian ablation).

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Ki-67: Genetic makeup, operation, detection, and function in breast cancer

In the 1980s, Gerdes et al. published the first description of the Ki-67 antigen. "He utilized it in a mouse monoclonal antibody to a nuclear antigen from the L428 cell line, which is derived from Hodgkin's lymphoma. It was finally identified by the same group in 1991, and this non-histone protein was given the names of the researchers' institutions: Ki stands for Kiel University in Germany, and the 67-label designates the clone number on the 96-well plate."

There are two known isoforms of the Ki-67 protein, weighing 345 and 395 kDa. The cell cycle has a significant impact on where the Ki-67 protein is found. The protein is mostly found in the nucleolar cortex and the dense fibrillar nucleolus components during the interphase. It connects to the condensed chromosomes' periphery during mitosis. Because the Ki-67 protein has a half-life of roughly 60–90 minutes, it can be used as a marker of proliferating cells regardless of where in the cell cycle they are.

Discussion on Ki-67 detection: Ki-67 expression in breast cancer can be measured using one of two methods:

(i) A quantitative examination of the Ki-67 (MKI-67) mRNA content in samples that have been frozen or Formalin Fixed Paraffin Embedded (FFPE).

(ii) Quantifying the percentage of cancer cells found by IHC that are Ki-67 positive.

When opposed to an RNA-based technique, the IHC staining method for Ki-67 detection has significant advantages. 1) Only cancer cells are taken into account and inflammatory or stromal cells that are positive can be excluded when a pathologist evaluates the IHC Ki-67 score. 2) The IHC technique is generally accessible. As a result, the IHC approach is most frequently used in everyday practice to measure Ki-67 on Formalin-fixed paraffin-embedded (FFPE) sections.

Ki-67 in breast tissues: Ki-67 is expressed at a modest level (3% in normal breast tissue). According to a large number of studies, the normal human breast epithelium exhibits ER expression and Ki-67 antigen in different cell types. It is crucial to note that Ki-67 is only expressed by ER-negative breast epithelial cells because ER-positive luminal cells cannot proliferate in healthy human breast tissue. Malignant breast tissue does not exhibit this distinction between ER expression and proliferation. It has been established that precancerous lesions and breast density are both correlated with Ki-67 expression. Also, it has been observed that the expression of Ki-67 increases continuously from benign breast disease to ductal carcinoma in situ to invasive breast cancer.

Ki-67 and its link to other breast cancer markers: Several studies have shown a significant association between Ki-67 and histological grade. Given that one of the three elements of histological grade is the mitotic index, these relationships are not entirely unexpected. In order to quantify proliferation, both Ki-67 and the mitotic index are frequently used. However, some experts suggest using Ki-67 as a prognostic marker rather than the mitotic index because it is more subjective to individual judgment and it can often be difficult to discern between apoptotic and mitotic figures.

In-depth research has also been done on the relationship between lymph node status and Ki-67, and multiple studies involving sizable patient populations have found a favorable correlation. Also proven is the link between tumor size and Ki-67. Although the hormone receptor (HR) status has been demonstrated to have an inverse relationship with Ki-67, ER and PR positivity is typically detected in tumors that are not actively proliferating. There is debate concerning the relationship between Ki-67 and Her2 expression. Breast tumors exhibiting higher levels of Ki-67 are more likely to have p53 oncogene mutations.

"In addition to ongoing debate on its prognostic utility, Ki-67 has also been investigated as a potential predictive marker in neoadjuvant and adjuvant settings. For neoadjuvant chemotherapy of breast cancer, Ki-67 was significantly associated with clinical or pathological response in several studies. However, in a recent research involving 506 breast cancer patients, Ki-67 did not represent an independent predictive potential for neoadjuvant therapy. In contrast to this, the systematic review by Luporsi et al. has determined a level of evidence of II-B for Ki-67 regarding neoadjuvant treatment response. The other setting for prediction of response to therapy is the evaluation of survival in adjuvant studies. In adjuvant setting, the predictive role of Ki-67 is even more uncertain. In the IBCSG 8/9 trial, no predictive potential of Ki-67 for response to chemotherapy vs. no chemotherapy was found. These elevated Ki-67 was associated with a higher efficacy of docetaxel in PACS01, but the evaluation of BCIRG001 did not confirm this. The controversial

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

predictive potential of Ki-67 between neoadjuvant and adjuvant settings was addressed in the review by Denkert et al. expounding that Ki-67 affects in opposite directions for assessment of prognosis and for assessment of response to neoadjuvant therapy."

2. Summary

The distinguishing three groups of tumours in relation with Ki-67 expression and responsiveness to therapy are:

i) Low Ki-67 tumours that do not respond to chemotherapy but also have a good prognosis i.e. Luminal A-like subtype (Low Ki- 67 associated with good outcome).

(i) High Ki-67 tumours with response to chemotherapy has better outcome (high Ki-67 associated to favourable outcome) compared to other markers and ER, PR.

(ii) High Ki-67 tumours that are chemotherapy-resistant (high Ki-67 associated to poor outcome).

3. Conclusions

Of the many potential biomarkers for breast cancer, Ki-67 stands out as one of the most disputed. Ki-67 has potential as a prognostic and/or predictive tool, however its approach for use in clinical practice is controversial. Hence, there is an immediate need for standardized ways of assessing Ki-67 LI that can be replicated. The challenge has been addressed by the introduction of a guideline for the use of Ki-67 IHC in routine practice by the International Ki-67 in Prostate Cancer Working Group. This suggests that pre-analytical, analytical, interpretation and scoring, and data processing phases are the most influential on Ki-67 IHC outcomes. Ki-67 measurement might be impacted adversely by the following pre-analytical issues: Several types of biopsies, different fixatives, different fixing times, and different long-term storage methods. According to the results of two separate investigations, the preanalytical variability of Ki-67 IHC is more forgiving than that of other IHC assays. Nonetheless, there were noticeable differences in the appearance of labeled nuclei: The nuclei of the well-fixed cores biopsies were well-circumscribed and evenly stained, whereas those of the poorly-fixed tissues displayed wildly varying degrees of staining. Ki-67 IHC may be performed using the same standard operating procedures as ER (8-72 hours after neutral buffered formalin fixation).

Reference

[1] BiganzoliL.Prognostic and predictive factors. In: Castiglione M,PiccartM editor. Adjuvant Therapy for Breast Cancer. Cancer TreatmentandResearch, vol 151. Boston: Springer; 2009: 13 – 30.

[2] Page DL, Ellis IO, Elston CW. Histologic grading of breast cancer: Let'sdo it. A JC P. 1995 Feb:123-124.

[3] Schnitt SJ, Collins LC. Invasive breast cancer. In: Biopsy Interpretation of the Breast. 2nd ed. Philadelphia: Lippincott Williams &Wilkins;2013:282-351.

[4] Schwartz AM, Henson DE, Chen D, Rajamarthandans. Histologicgrade remains a prognostic factor for breast cancer regardless of thenumber of positive lymph nodes and tumor size: A study of 161708cases of breast cancer from the SEER program. Arch Patho Lab Med.2014; 138:1048-1052.

[5] Doussal VL, Hulin MT, Freidman S, Hacene K, Spyratos F, Brunet M.Prognostic value of histologlc grade nuclear components of scarfbloom-richardson (SBR): An improved score modification based on amultivariate analysis of 1262 invasive ductal breast carcinomas.Cancer. 1989; 64:1914-1921.

[6] Shaikh F, Jamal Q, Baig S, Hadi NI, Majeed N. Correlation of hormonereceptor and HER-2/neu expression with clinicopathologicalparameters in primary breast tumors. Asian Pac J Cancer Prev. 2016;17(7): 3363-3367.

[7] Lowery AJ, Sweeney KJ. The role of prophylactic oophorectomy in themanagement of hereditary breast & ovarian cancer syndrome. In: Al-Hendy A, Sabry M. Hysterectomy: lnTech, 2012: 345-364.

[8] Singh G. Oophorectomy in breast cancer - Controversies and currentstatus. Indian J Surg 2012; 74(3):210-212.

[9] Duffy MJ. Biochemical markers as prognostic indices in breast cancer.ClinChem.1990; 36(2)186-191.

[10] Corben AD, Brogi E. Ductal carcinoma In situ and other Intraductallesions: Pathology, Immunohistochemistry, and Molecular alterations.In: Harris JR, Lippman ME, Morrow M, Osborne CK. Disease of thebreast. 5th ed. Philadelphia: Wolters Kluwer ; 2014: 309 - 322.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[11] Goncalves R, Cakar B, Bose R, Ma CX, Ellis MJ. Genomic events inbreast cancer progression. In: Harris JR, Lippman ME, Morrow M,Osborne CK. Disease of the breast. 5th ed. Philadelphia: WoltersKluwer; 2014: 361-378.

[12] Siadati S, Sharbatdaran M, Nikbakhsh N, Ghaemian N. Correlation ofER, PR and HER-2/Neu with other prognostic factors in infiltratingductal carcinoma of breast. Iran J Pathol. 2015; 10(3):221-226.

[13] Dowsett M, Miller W. Estrogen and progesterone receptor testing forprognosis and prediction. In: Harris JR, Lippman ME, Morrow M,Osborne CK. Disease of the breast. 5th ed. Philadelphia: WoltersKluwer; 2014: 411- 421.

[14] Lal P, Tan LK, Chen B. Correlation of HER-2 status with estrogen andprogesterone receptors and histologic features in 3,655 invasive breastcarcinomas. Am J Clin Pathol. 2005 ; 123:541-546.

[15] Alfred DC. Should immunohistochemical examination replacebiochemical hormone receptor assays in breast cancer. Am J ClinPathol. 1993; 99(1): 1- 3.

[16] Gerdes J, Schwab U, Lemke H, Stein H. Production of a mousemonoclonal antibody reactive with a human nuclear antigen associatedwith cell proliferation. Int J Cancer, 1983;31 (1):13-20.

[17] Fonatsch C, Duchrow M, Rieder H, Schluter C, Gerdes J. Assignmentof the human Ki-67 gene (MK167) to 10q25-qter. Genomics, 1991;11(2):476-477.

[18] Schluter C, Duchrow M, Wohlenberg C, Becker MH, Key G, Flad HD,et al. The cell proliferation-associated antigen of antibody Ki-67: a verylarge, ubiquitous nuclear protein with numerous repeated elements,representing a new kind of cell cycle-maintaining proteins. J Cell Biol,1993;123 (3):513-522.

[19] Duchrow M, Schluter C, Wohlenberg C, Flad HD, Gerdes J. Molecularcharacterization of the gene locus of the human cell proliferationassociatednuclear protein defined by monoclonal antibody Ki-67. CellProlif, 1996;29 (1):1-12.