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Ki-67 proliferative index correlation to the immunohistochemistry profile in early female breast cancer: a review of 515 cases

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ABSTRACT

Introduction: Many biological markers are used as prognostic and predictive indicators in invasive breast cancers management. Among them, tumour size, grade, patho-morphological subtype, hormone receptors status and HER2 receptor expression in addition to Ki-67 proliferative index. Also, they play a key role in adjuvant treatment decision making. Our aim was to evaluate the association between Ki-67 proliferative index and breast cancer immunological subtype.

Material and methods: A total of 515 early invasive patients were enrolled, tumour biological characteristics as histopathological subtype, immune-histo-chemistry (ER,PR,HER2) status and Ki-67 proliferation index values have been collected. The Ki-67 index level of 20%, was used as the cut-off point to differentiate between low and high Ki-67 expression levels. Statistical analysis has been performed using the Chi square test online tool.

Results: In this cohort, about 42%, 33%, 7%, and 18% of the cases were grouped as luminal A-like, luminal B-like, HER2 enriched subtype, and triple-negative, respectively. All luminal A-like patients had Ki-67 level less than 20%. About 3% of the cohort, are luminal B-like tumours with Ki-67 level less than 20%, where 30.3% of the patients were luminal B-like tumours with Ki-67 level \geq 20%. In HER2 enriched subtype, Ki-67 of < 20% level seen in 1.9% of cases, and Ki-67 levels \geq 20% was observed in 5.2% of the cases. In the triple-negative group, Ki-67 was 20% or higher in 16% of cases, and only 1.7% of patients had Ki-67 level less than 20%.

Conclusion: Luminal A-like tumours were the most frequently encountered subtype, they have low Ki-67 levels and are known to be of a low histological grade tumour, and usually associated with a good prognosis. Also, data indicates that high Ki-67 levels are seen more often in Luminal B-Like breast cancers as well as in triple-negative breast cancers and HER2 enriched tumours.

Key words: breast neoplasms, Ki-67 proliferation index, oestrogen receptor, Progesterone receptor, HER2
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Introduction

According to 2018 WHO reports, breast malignancy is the most common cancer among the female gender with the lifetime risk of 12%. It is followed by colorectal, lung, cervical and thyroid cancer as the most common cancers in women [1, 2]. The previous reports showed that breast cancer immuno-histochemical subtypes have a real impact on the disease prognosis and to the response to hormonal blockade treatment and

chemotherapy. In 1983, Gerdes et al., described the Ki-67 protein, which is a nonhistone protein, works as a surfactant and helps the chromosomes to preserve discrete confirmations in a condensed state. If the Ki-67 coating layer is missing, during the metaphase of the cell cycle, the chromosomes remodelled into an unshaped or amorphous mass, where the cell division and replication will be compromised [3]. Ki-67 proliferation index significance has been widely studied, it is used as a diagnostic, prognostic and predictive marker in the

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management of cancers originated in breast, pancreas, colon and prostate in addition to endometriosis [4–8]. Tumours that express a higher levels of Ki-67 proliferation index have a worse prognosis than tumors that express lower levels [9].

Material and methods

A total of 515 patients were included in this study. All the patients had an early/loco-regional breast cancer diagnosis in the period between 2014–2020. Informed consent from the patients was not necessary, however, the study results were a secondary outcome of a regional audit which was approved by the Institutional Review Board under the number GSART336. After the diagnosis, they underwent the recommended management. Patients with metastatic disease at presentation or not fit for curative management has been excluded. The medical records have been retrieved, the data related to the patients' demographics, tumour biological characteristics as histopathological subtype, immune-histo-chemistry (ER, PR, HER2) status and Ki-67 proliferation index values have been collected and analysed. The Ki-67 index level of 20%, was used as the cut-off point to differentiate between low and high Ki-67 expression. The statistical analysis has been performed using Chi-square test on excel, the calculated p-values of less than 0.05 were considered statistically significant.

Results

Our retrospective study was carried out on 515 patients with operable early invasive breast carcinomas. The age span of the cohort, ranges between 27–97 years, with a mean of 63 years. The different clinico-histo-pathological parameters of breast cancer varieties are shown in (Tab. 1). Among the 515 cases, 297 patients aged less than 70 years (57.6%) and 218 (42.3%) aged more than 70 years. In terms of the histopathological features, 436 cases (84.6%) were IDC, NST (invasive ductal carcinoma, of no special type), 48 tumours showed invasive lobular carcinoma (ILC) (9.3%), 12 (2.3%) cases were papillary carcinoma and 9 (1.7%) patients had mucinous carcinoma. About 49% (254) of the cases were grade II, 32% (166) grade III and about 18.4% (95) were grade I tumours (Tab. 1). With regard to the female sex hormone expression, the ER (Oestrogen receptor) positive expression tumours were 72.6% and PR (progesterone receptors) positive expression detected in 58% of the cases. Approximately 17% of tumours were HER2+ (score 3+ or amplified FISH test), where 18% of cases were triple-negative phenotype. We have used 20% as the cutting point for Ki-67 proliferation expression. Ki-67 nuclear positivity of $\geq 20\%$ was detected in 52% (262) of the cases (Tab. 1). We have classified the 515 cases according to the available immune-phenotyping results into four groups: 1) luminal-A like (ER-positive or PR-positive and HER2-negative), 2) luminal-B like (ER-positive and/or

Table 1. Tumour characteristics and its relation to different immuno-histochemical subtypes, % (n)

Criteria	All	Luminal A-Like	Luminal B-like	HER2 Enriched	Triple-negative	P value
Age (years)						
< 70	57.6% (297)	23% (117)	18% (93)	4.85% (25)	12% (62)	0*
≥ 70	42.3% (218)	19.2% (99)	15.1% (78)	2.3% (12)	5.6% (29)	
Tumour grade						< 0.00001
G I	18.4% (95)	15% (78)	02.9% (15)	0	0.38% (2)	
G II	49% (254)	25% (128)	18% (95)	02.3% (12)	03.7% (19)	
G III	32% (166)	2% (10)	12% (61)	4.85% (25)	13.4% (70)	
Ki-67						0.0003
< 20%	48% (249)	42% (216)	2.9% (15)	1.9% (10)	1.7% (9)	
$\geq 20\%$	52% (266)	–	30% (156)	5.2% (27)	16% (82)	
Histological subtype						< 0.0001
IDC, NST	84.6% (436)	33% (172)	29% (151)	06.6% (34)	15% (79)	
ILC	09.3% (48)	06.6% (34)	2% (10)	0	0.77% (4)	
Papillary	02.3% (12)	0.77% (4)	1.1% (6)	0.2% (1)	0.2% (1)	
Mucinous	1.7% (9)	1.1% (6)	0.6% (3)	0	0	
Others	2% (10)	0	0	0.2% (1)	1.7% (9)	

PR-negative and HER2-positive or HER2 negative with high Ki-67 levels), 3) HER2 enriched (ER-negative, PR-negative and HER2-positive), and (4) triple-negative (ER-negative, PR-negative, HER2-negative), the cases distribution in the cohort was 42%, 33%, 8%, and 17.6% of the cases, respectively (Tab. 2).

As showed in (Fig. 1), luminal B-Like breast cancers showed the highest proportion of high Ki6-7 index value, 30.3 % (156) of the cohort, followed by triple-negative breast cancer, 15.9% (82), and the least was Her2 enriched subtype, 05.2% (27). Nonetheless, luminal A-Like cancers showed the highest proportion of low Ki6-7 index value, 42% (216), followed by lu-

minal B-Like cancers with 02.9% (15), triple-negative breast cancers were 01.7% (n = 9) and HER2 enriched tumours were 1.9% (n = 10). Our data discloses a statistically significant correlation between tumour grade and Ki-67 proliferative index levels among the different histopathological tumour subtypes (P values of $0 < 0.00001$).

Discussion

Breast cancer is regarded as a heterogeneous disorder, tumour detailed assessment and categorization into certain immuno-histochemical subtype based on molecular studies is recommended to predict disease prognosis and facilitate management decisions and planning. In addition to the Ki-67 proliferation index, many other biomarkers and online tools have been utilised to assess the prognosis and disease recurrence prediction. These biological criteria include ER (Oestrogen Receptor) expression, PR (Progesterone Receptor) expression, HER2 (*Human Epidermal Growth Factor Receptor — type 2*) expression, and Oncotype DX recurrence score, where the online tools include; NPI (Nottingham Prognostic Index) and PREDICT (Tab. 3). This is required to identify cases associated with a sufficiently high risk of disease relapse to warrant them adjuvant chemotherapy and prolonged hormonal manipulation treatment if appropriate. Assessment of the Ki-67 proliferation index is based on IHC (immuno-histochemical) staining of the tumour cells for the Ki67 protein, it is detected in the active course of the cell cycle (Late G1, S, G2, and M), and not detected during

Table 2. Ki-67 proliferation index and breast cancer phenotypes

Breast cancer IHC subtype	Low Ki-67 % (n)	High Ki-67 % (n)
Luminal A Like ER+VE, PR+VE, HER2-VE ER+VE, PR-VE, HER2-VE	42 (216)	-
Luminal B Like ER+VE, PR+VE, HER2+VE ER+VE, PR-VE, HER2+VE ER+VE,PR+VE,HER2-VE	02.9 (15)	30.3 (156)
Triple-negative ER-VE, PR -VE, HER2-VE	01.7 (9)	15.9 (82)
Her2 Enriched ER-VE, PR-VE, HER2+VE	01.9 (10)	05.2 (27)

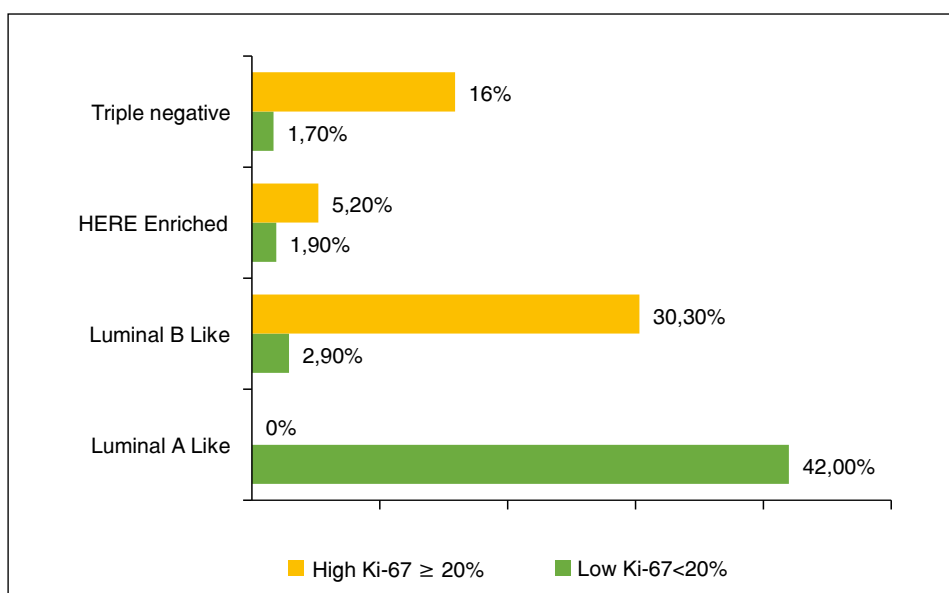


Figure 1. Ki-67 proliferation index value in different subtypes of breast cancers based on immuno-histo-chemistry classification

G0 and early G1 [1, 10, 11]. The Ki-67 proliferative index has value in cancer diagnosis as a cell proliferation indicator, the cancer tissues show a significantly higher expression of Ki-67 proliferative index than in

healthy tissues [6]. Nagao et al., in 2011, presented a cohort of 119 patients treated for prostate cancer, the paper concluded that the Ki-67 proliferation index is an independent factor for survival rate, this included tumour grade and stage [12]. Nielsen et al., in 2013, published a result of a prospective 190 patient cohort with primary cutaneous melanoma. Also, this study concluded that Ki-67 proliferation index was a strong prognostic marker in primary cutaneous melanoma [7]. Some recent studies revealed that the administration of antibodies targeted against the Ki-67 protein was shown to result in a slower rate of cell division. This fact makes Ki-67 a promising factor for targeted molecular cancer therapy. ASOs (Antisense oligonucleotide) are small-sized single-stranded nucleic acids that are used as Ki-67 peptide nucleic acid antagonists affects the cancer cells proliferation and apoptosis [13]. Another field where the Ki-67 proliferation index could be useful is monitoring the tumour response to upfront chemotherapy prior to surgery, Mukai et al, in 2014, in research related to 237 HER2 positive breast cancer patients. The response to upfront chemotherapy was assessed using pre-chemotherapy, mid-chemotherapy (3 cycles of paclitaxel and trastuzumab) and postoperative Ki-67 proliferation index. The cohort divided into the control arm or the Ki-67 response-guided arm (Ki-67 arm).

The control arm continued the same treatment regardless of the achieved result of the Ki-67 proliferation index, where Ki-67 arm group further treatment was modified according to the interim Ki-67 index. They have found that there was a linear correlation between the Ki-67 proliferation index reduction rate at interim evaluation and the pathological complete response to upfront chemotherapy [14]. In addition to its diagnostic

Table 3. Conventional and genomic prognostic factors as well as online prognostic tools [1]

Patient factors	Age Gender Fitness for treatment Patient compliance
Tumour factor	Size Histological subtype Histological grade Axillary lymphadenopathy Lympho-vascular invasion Extra-capsular extension
IHC	ER PR HER2 Ki-67 Proliferation index
Genetic mutations	BRCA1 BRCA2 TP53
Genomic tests	Oncotype DX MammaPrint
Online tools	NPI(Nottingham Prognostic Index) PREDICT

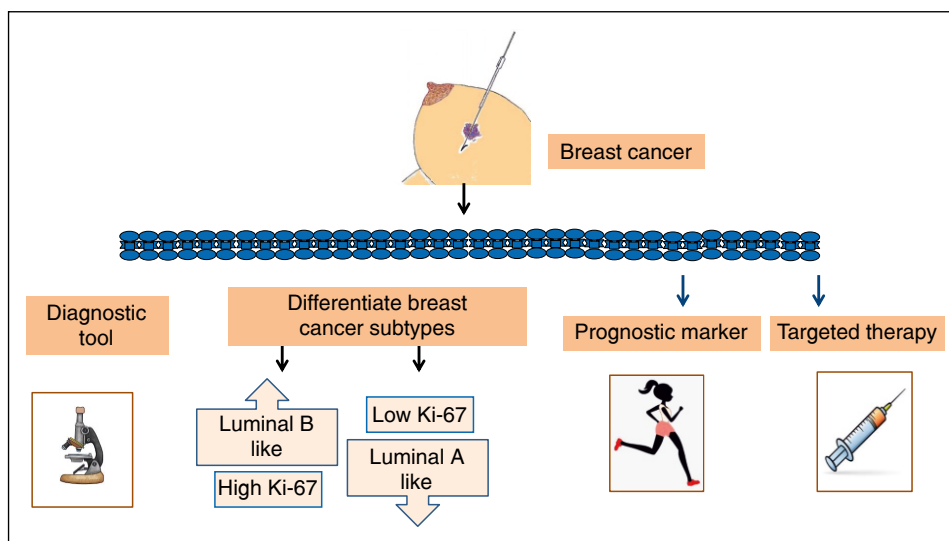


Figure 2. Current and potential future utilization of Ki-67 proliferation index in cancer management

Table 4. Breast cancer molecular subtypes and their criteria [15, 17–19, 25]

Breast cancer subtype	Sex hormone, HER2 and cytokeratins expression	Incidence	Ki-67	Grade	Prognosis
Luminal A	ER+VE and/or PR+VE, HER2-VE, CK5/6-VE, Keratin 8/18+VE	71%	Low	Low	Good
Luminal B	ER+VE and/or PR+VE, HER2+VE, CK5/6-VE, Keratin 8/18	8%			
Luminal B-like	ER+VE, any PR, HER2-VE with high K-i67		High		
Triple-negative “Basal-like”	ER-VE, PR -VE, HER2-VE, CK5/6+VE	15%		High	Poor
HER2-enriched	ER-VE, PR-VE, HER2+, CK5/6-VE	6%		High	Poor
Normal breast-like group	Not classified				

and prognostic value, Ki-67 proliferation index is used to differentiate between Luminal A-like and Luminal B-like subtypes in ER+VE/HER2-VE breast cancer (Fig.2). The main histological breast cancer subtypes have been identified according to ER (oestrogen receptor), PR (progesterone receptor), and HER2 (*Human Epidermal Growth Factor Receptor — type 2*) expression (Tab. 4). Additional molecular classification is based on gene expression profile studies also is increasingly used to categorize different molecular subtypes of breast cancer. The subtype luminal type A which is the most frequent identified breast cancer subtype is strong ER+VE and/or PR+VE/HER2-VE status. These tumours are known to be of a low histological grade tumour, and usually associated with a good prognosis, it forms about 71% of breast cancers, likely to benefit from hormonal blockade treatment and may benefit from chemotherapy [15, 16] in our cohort, luminal A-like tumours are encountered in 42% of cases. The luminal B subtype is weak/moderate ER+VE and/or PR+VE with HER2+VE (overexpression or amplification), this subtype has higher Ki-67 levels than luminal A tumours, and it is encountered in about 8% of breast cancers. These tumours are likely to benefit from neo/adjuvant chemotherapy and may benefit from hormonal manipulation therapy in addition to the HER2 targeted treatment [17]. Luminal B-like tumours are ER+VE and/or PR-VE with HER2-VE expression, however, has a high Ki-67 index value. The basal-like breast cancer (BLBC), given this name as they are characterized by high expression of genes characteristic of normal breast tissue basal epithelial cells as CK 5/6, CK14, CK15 and CK17. Most of them (but not all) are triple-negative breast cancer (i.e. has a receptor expression ER-VE, PR-VE, HER2-VE), encountered frequently in young premenopausal patients with high BMI. They are high-grade tumours, forms about 15% of all invasive ductal carcinoma of no special type, associated with an aggressive clinical course, often relapsing rapidly either loco-regional or as a distant metastatic disease and linked to a high mortality rate [18–20]. The HER2-E (HER2 enriched) subtype tumors have HER2+VE/ER-

VE/PR-VE expression, these tumours are less common however some of them are characterized by high-grade histology and poor prognosis [21]. A recent systematic review and meta-analysis published by Schettini et al. from Naples, Italy in 2020, the paper stating that HER2-E tumours are associated with a higher likelihood of achieving a complete pathological response following neoadjuvant anti-HER2-based therapy [22]. Some previous reports has stated that, the triple-negative breast cancer is associated with the highest Ki-67 index values, where the HER2 positive tumours were in second place. Looking at the histological subtypes, the observations revealed that the metaplastic and medullary breast cancers showed a significantly higher Ki-67 proliferative index as compared to invasive ductal carcinoma, NST [23, 24]. Our cohort showing that luminal B-like cancers has the highest Ki-67 index values (30%), followed by triple negative breast cancer (16%). Perez-Lopez et al., in 2016, presented a series of 680 patients, using the Saint Gallen criteria, the cohort was divided in IHC subtypes. The prognosis of the groups was analysed. It was found the luminal B NO had the most unfavorable prognosis, the other criteria which were associated with this group are those of the luminal B tumours as PR negative, HER2 positive as well as high Ki-67 proliferation index expression [24]. Our results show that in addition to the luminal B-like cancers, other subtypes of breast cancer also has high Ki-67 index values, these subtypes include triple-negative breast cancer (16%) and HER2 enriched tumours (5.2%). These tumours are less common than luminal A tumours, however, some of them are characterized by high-grade histology and poor prognosis. These findings are in accordance with the published researches data.

Conclusion

Generally, this data showed that the majority of the cases of low Ki-67 index expression belongs to the luminal A-like group, where the majority of cases with a high Ki-67 index expression are of non-luminal A-like

subtype as luminal B-Like and triple-negative tumours ($P < 0.00001$). The Ki-67 level is regarded as a helpful biomarker in breast cancer management, its expression is strongly associated with disease aggressiveness and prognosis, also it has an additional value, currently is considered as a promising therapeutic target in breast cancer.

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