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Research Article

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Correlation of OncotypeDx Recurrence Score, Nottingham Prognostic Index, and Ki67

Rufina Soomro[1*], Azmina valimohd[2], Naila zahid[3], Najeeb Naimatullah[4] and Noureen Durrani[5]

[1]*Prof. of Surgery & Consultant Breast Surgeon, Liaquat National Hospital & Medical College, Karachi, Pakistaan*

[2]*Consultant Medical Oncologist, Aga khan University hospital*

[3]*Consultant Medical Oncologist, Liaquat National Hospital & Medical College*

[4]*Consultant Medical Oncologist, Shaukat khanum hospital*

[5]*Biostatician- Publication Department, Liaquat National Hospital & Medical College*

[*]Corresponding author
Rufina Soomro, Prof. of Surgery & Consultant Breast Surgeon, Liaquat National Hospital & Medical College, Karachi, Pakistaan

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Abstract

Objective: *To identify the correlation between the OncotypeDx Recurrence score, Nottingham Prognostic Index (NPI), and Ki67.*

Material & Methods: *A retrospective study was conducted at Liaquat National Hospital where medical records of early-stage breast cancer patients, who had OncotypeDx RS done were reviewed from 2008-2019. The patient's age, Histopathology type, tumor grade, size, No. of nodes involved, ER, PR, Her neu and Ki67 were collected. OncotypeDx RS, NPI, and Ki67 were categorized into 3 groups and statistical analysis was done to find a correlation between OncotypeDx RS, NPI and Ki67.*

Result: *Total 76 patient's records were reviewed. The average age of study participants was 56.40 ± 10.32 years. Oncotype-Dx method categorized 34 (44.74%), 26 (34.21%) and 16 (21.05%) patients as low, moderate and high risk respectively. 18(23.68%), 56(73.68) and 2(2.63%) were classified as low, moderate and high-risk patients by the NPI method correspondingly. According to Ki67, 26(40.63%), 21(32.81%) and 17(26.56%) patients were low, moderate and high risk respectively. Statistically significant fair agreement was only observed between Oncotype-Dx& Ki67 ($k=0.33$, $p<0.001$) with weak positive correlation ($r=0.44$, $p<0.001$). Further on age-stratification, it was observed that significant fair agreement ($k=0.36$, $p<0.001$) and weak positive correlation ($r=0.45$, $p<0.001$) between Oncotype-Dx& Ki67 risk assessment categories was for age group >50 years. On age stratification, moderate agreement ($k=0.45$, 0.002) and moderate correlation ($r=0.57$, $p=0.005$) were also observed between OncotypeDx& NPI risk categories for age group ≤50 years.*

Conclusion: *No statistically significant strong agreement and correlation were observed among three risk assessment methods. Further investigations should be conducted with a larger sample size to assess agreement among these risk classification methods.*

Keywords: Ki67, Nottingham Prognostic Index, OncotypeDx® Recurrence Score, Prognosis

Introduction

Breast cancer is the commonest cancer in women, which is a heterogeneous disease with variable outcomes [1]. So in this day and age, every patient needs to know their prognosis so that individualized treatment can be offered. There are patients where the prognosis is bad and we lose the battle in no time, but there is a subset of patients whose outcome is so good that they may not get a meaningful benefit from chemotherapy. We may be able to avoid chemotherapy in this subset of patients if we can predict with certainty that their prognosis is good.

There are various ways to predict prognosis. Traditionally histopathology and immune histochemical variables have been used. The three strongest determinants in clinical practice for breast cancer patients are primary tumor size, lymph node stage, and histological grade. Hence, it is important to incorporate all three prognostic parameters. Nottingham grading is the most widely used grading system [2, 3]. Nottingham Prognostic Index calculated from the pathology report based on the above parameters and have been shown to have reasonable prognostic information and is widely used [4, 5]. There has been some correlation with ER/PR status that needs elaboration [6, 7]. Ki67 is a proliferating marker and it has been shown that high level of Ki67 is associated with advanced clinic pathological feature and poor outcome [8]. The most reliable

has been genetic testing like OncotypeDx, which has 21 genes and the Ki67 marker is one of them. OncotypeDx is a commercially available multi-gene assay that is used to quantify the risk of distant recurrence and predict the benefit of chemotherapy in early-stage breast cancer stage1 and 2 ER+ and PR+ and Her2 negative patients. The results are calculated in numerical score from 0 to 100 [9]. It has shown that patients with low recurrence scores on OncotypeDx have a very favorable outcome and one can safely avoid chemotherapy.

OncotypeDx is very expensive, despite that it is recommended by ASCO and NCCN guidelines in select patient subgroups to avoid the morbidity and costs related to unnecessary chemotherapy. Although very reliable, in under resource countries it is difficult to get the benefit of genetic testing, so the search to look for alternate markers continues, which could be equally reliable and financially viable.

The purpose of this study is to identify the correlation between the OncotypeDX Recurrence Score (RS), Nottingham Prognostic Index (NPI), and Ki67.

Material and Methods

This study was conducted at Liaquat National Hospital and Medical College, Karachi, Pakistan. Retrospectively data of early-stage breast cancer patients who got OncotypeDx test done from 2008 to 2019 was retrieved after approval from the hospital research committee. OncotypeDx was done on patients after surgery who were ER, PR positive and Her 2 neu negative. All surgery types mastectomy or Breast conservation surgery with or without axillary clearance were included. All those patients who did not have OncotypeDx done were excluded.

OncotypeDx test was only done in those patients who could afford it after detailed counseling of the patients about the utility of the test. For OncotypeDx the specimen was sent to the US as per their guidelines and results were sent to the requesting doctor and a copy was given to the patient as well.

OncotypeDx Scoring

The results are reported as the Recurrence Score

- Recurrence Score of 0-15: Low Score
- Recurrence Score of 16-25: Intermediate
- Recurrence Score of 26-100: High score

Nottingham Prognostic Index (NPI)

The index is calculated using the formula [10]:

NPI = [0.2 x S] + N + G

- S is the size of the index lesion in centimeters
- N is the node status: 0 nodes = 1, 1-3 nodes = 2, >3 nodes = 3
- G is the grade of tumor: Grade I =1, Grade II =2, Grade III =3

Group1- good prognosis (Score 2.08- 3.4)
Group2 -moderate prognosis (Score 3.42- 5.4)
Group3 - Poor prognosis (Score 5.42- 6.8)

KI67

Ki67 was quantified using a visual scoring system, with external control for validation. Only nuclear staining was incorporated into the Ki67 score, in which stained cells were counted and defined as the percentage of positively stained cells among the total number of malignant cells scored. If staining was homogeneous, at least 500 cells within ten randomly selected high-power fields were selected. The documentation of the percentage of Ki67 positivity was recorded. Ki 67 was considered low if the score was 14% or less, 15-30% was borderline and it was grouped as high when it was more than 30% according to the recommendations of the St Gallen International Consensus of Experts (Goldhirsch et al. [11, 12]).

Group 1(Low) = Ki67 14% or <
Group2 (Intermediate) = Ki67 15 to 30%
Group 3 (High) = >30% was high

Data Analysis

Categorical variables were expressed as frequencies and percentages. The quantitative variable age was summarized in terms of mean ± standard deviation. Clinic pathological parameters were compared among three risk categories using the chi-square or Fisher exact test as appropriate. The agreement was determined using weighted Kappa statistics. Spearman correlation was also applied to assess the correlation between three classification methods. Age-stratified (≤50 and >50 years) correlation and agreement were also determined. Statistical significance was considered for a two-sided p-value <0.05. Statistical analysis was performed on Stata version 14.

Results

Total 76 records were reviewed. The average age of patients was 56.40 ± 10.32 years. Majority of the study participants had tumor size >2cm (n=54, 71.05%). Most of the patients presented with grade 2 tumor (n=46, 60.52%) whereas 9(11.84%) and 21(27.63%) patients had tumor grades 1 and 3 respectively. There were only 1(1.31%) patients with lymph vascular invasion while progesterone was negative in 6(7.89%) patients only. The most frequent histologic type was ductal (n=61, 80.26%) followed by lobular (n=9, 11.84%) and others (n=6, 7.89%). Other histology included 2(2.63%) papillary and frequency for mucinous, ductal in situ and mixed lobular and ductal was 1(1.31%). OncotypeDx risk assessment method categorized 34 (44.74%), 26 (34.21%) and 16 (21.05%) patients as low, moderate and high risk respectively. 18(23.68%), 56(73.68) and 2(2.63%) were identified as low, moderate and high risk by NPI method respectively. Ki67 classified 26(40.63%), 21(32.81%) and 17(26.56%) patients as low, moderate and high risk respectively.

Age and histologic type didn't differ among three risk categories determined by OncotypeDx, NPI and Ki67. Three risk categories determined by OncotypeDx (p=0.493) and Ki67 (p=0.862) were not significantly different for tumor size. However, tumor size differed in three risk categories when determined by NPI (p<0.001). Among moderate-risk patients, most of the patients had tumor size >2cm (n=48, 85.71%) whereas most of the patients had tumor size ≤2 cm who were labeled as a low-risk patient (n=15, 83.3%) and all of the patients had tumor grade >2cm who were at high risk. All three methods, OncotypeDx (p=0.014), NPI (p<0.001) and Ki67 (p=0.008) differed based on tumor grade. Among all three methods, most of the patients had tumor grade 2 in low-risk groups whereas the majority had tumor grade 3 in high-risk categories.

The higher concordance was observed between OncotypeDx and Ki67 methods that showed concordance on 32 (50%) observations followed by the concordance of OncotypeDx& NPI with 33(43.42%) matched categories and NPI & ki67 with 22(34.38%) same observations. Assessment of agreement with weighted kappa revealed that there was a significant slight agreement between Oncotype and NPI risk categories (k=0.13, p=0.035). Agreement between NPI and Ki67 was poor (k= 0.01, p=0.457) whereas significantly fair agreement was observed between OncotypeDx and Ki67 risk

categories (k=0.33, p<0.001). The agreement was also determined between two age-strata (≤50 and >50 years). On age stratification, a moderate agreement was determined for only ≤50 years group between OncotypeDx and NPI risk categories (k=0.45, p=0.002). A statistically significant fair agreement was also seen in >50 years group between OncotypeDx and Ki67 (k=0.36, p<0.001).

Spearman correlation was applied to assess the correlation between risk categories that also showed there was no significant correlation between OncotypeDx and NPI risk categories (r=0.19, p=0.101) and NPI and Ki67 risk categories (r=0.027, p=0.827). A weak positive correlation was observed between OncotypeDx and Ki67 risk categories which were statistically significant (r=0.44, p<0.001). On age stratification, a statistically significant moderate positive correlation was found for <50 years age group between OncotypeDx& NPI categories (r=0.58, p=0.005). Weak positive correlation between OncotypeDx& ki67 categories (r=0.45, p<0.001) was seen for age group >50 years.

Discussion

The most widely practiced prognostic assay is OncotypeDX, 21-gene recurrence score (RS) and is used in Estrogen receptor (ER)/ Progesterone (PR) positive, Her2 neu negative and lymph node-negative breast cancer patients for risk assessment and to identify patients who can avoid adjuvant chemotherapy [13].

This 21 gene assay has been validated in the large Tailor X trial and has proven to be a good prognostic model so that we can safely decide about chemotherapy considering the age of the patient and nodal involvement [14]. In this trial it has been shown that when RS is low (< than 10) or high (> than 25) the decision is clear about the benefit of chemo. However, when the score is between11-25 and especially in women younger than 50 years correlation with clinical risk is useful and aided value to the prognostic information. The clinical risk is calculated by keeping morphological features like the size of the tumor and histological grade. In our study, we calculated clinical risk by NPI, which has size, grade and no. of nodes involved. In our study, tumor size differed in three risk categories when determined by NPI (p<0.001). All three methods, differed based on tumor grade whereas the majority had tumor grade 3 in high-risk categories, which was statistically significant. A strong correlation of NPI with RS especially in the low-risk group was noticed [15, 16]. NPI though has been extensively used, one wonders that it is not incorporating tumor biology and in this Genomic era how useful it would be. André Albergaria showed that Nottingham Prognostic Index is a good tool for prognosis in Triple-negative breast cancer (TNBC) [17].

Like in the Tailor X study(13), in our results on age stratification, a moderate agreement was determined for only ≤50 years group between OncotypeDx and NPI risk categories (k=0.45, p=0.002).

The high value of Ki-67 has been associated with adverse clinic pathologic factors. In low-grade invasive breast carcinomas increased stromal cellularity (Ki67) could contribute to an increased risk of recurrence according to OncotypeDx Recurrence Score [18]. Ki67 may be of value in prognosis and prediction of response to systemic therapy. CuzickJ suggested that the amount of prognostic information contained in four widely performed IHC assays is similar to that in the genetic RS and one of the 4 components is KI 67 [19]. International Ki67 Breast Cancer Working Group opinion is that it is one of the most robust biomarkers measured by IHC, but it has not reached its due importance because of the lack of standardization and inter-laboratory variability [20].

In our study between OncotypeDx and Ki67 risk categories a statistically significant weak positive correlation was observed and on age stratification, a fair correlation was seen for age group >50 years. There are studies with fairly good correlation between OncotypeDx and Ki67, while others do not show any correlation [21, 22]. In our study, we didn't find correlation between NPI and Ki67. However, Chetana R observed a good correlation between NPI and KI67 [23]. The reason could be that we could get Ki67 only in 64 patients, if we had it in all or may be with larger sample size we might find the correlation between ki67 and NPI. It looks logical to have proportional relationship between NPI and Ki67 as enough evidence is there that in St. Gallen International consensus meeting, the histologic grade which is one of the major components of NPI is considered an alternative to KI67 in Luminal classification by IHC [11].

Table 1: Summary of clinic pathological parameters

Variables	Frequency (%)
Age (in years)#	56.40 ± 10.32
Tumor size (in cm)	
<2	23 (30.26)
>2	52 (68.42)
Tumor Grade	
1	9 (12%)
2	46 (61.3%)
3	20 26.7%)
Histologic Type	
Ductal	61 (80.26)
Lobular	9 (11.84)
Others	6 (7.89)
Progesterone receptor	
Positive	70 (92.11)
Negative	6 (7.89)
Lymph vascular invasion	
Positive	1 (1.31)
Negative	75 (98.68)

#: age is expressed as mean ± standard deviation

Table 2: Comparison of Clinicopathological parameters among three risk categories

	Oncotype-Dx Categories				NPI Categories				aKi67 Categories			
	Low n=34	Moderate n=26	High n=16	P-value	Low n=18	Moderate n=56	High n=2	P-value	Low n=26	Moderate n=21	High n=17	P-value
	f(44.7%)	f(34.2%)	f(21.0%)		f(23.6%)	f(73.6%)	f(2.6%)		f(40.6%)	f(32.8%)	f(26.5%)	
Age (in years)												
≤50	8 (23.5)	11 (42.3)	3 (18.8)	0.169	7 (38.9)	15 (26.8)	0 (0)	ł0.425	6 (23.1)	4 (19)	7 (41.2)	0.268
>50	26 (76.5)	15 (57.7)	13 (81.2)		11 (61.1)	41 (73.2)	2 (100)		20 (76.9)	17 (81)	10 (58.8)	
Tumor size (in cm)												
≤2	12 (35.3)	8 (30.8)	3 (18.8)	0.493	15 (83.3)	8 (14.3)	0 (0)	**ł<0.001	8 (30.8)	5 (23.8)	5 (29.4)	0.862
>2	22 (64.7)	18 (69.2)	13 (81.2)	0.493	3 (16.7)	48 (85.7)	2 (100)		18 (69.2)	16 (76.2)	12 (70.6)	
Tumor grade												
1	5 (14.7)	4 (15.4)	0 (0)	**ł0.014	8 (44.4)	1 (1.8)	0 (0)	**ł<0.001	3 (11.5)	1 (4.8)	2 (11.8)	**ł0.008
2	25 (73.5)	14 (53.8)	7 (43.8)		10 (55.6)	36 (64.3)	0 (0)		20 (76.9)	14 (66.7)	5 (29.4)	
3	4 (11.8)	8 (30.8)	9 (56.2)		0 (0)	19 (33.9)	2(100)		3 (11.5)	6 (28.6)	10 (58.8)	
Progesterone receptor												
Positive	33 (97.1)	24 (92.3)	13 (81.2)	* ł0.143	17 (94.4)	51 (91.1)	2 (100)	ł1	26 (100)	19 (90.5)	14 (82.4)	ł 0.059
Negative	1 (2.9)	2 (7.7)	3 (18.8)		1 (5.6)	5 (8.9)	0 (0)		0 (0)	2 (9.5)	3 (17.6)	
Histologic type												
Ductal	25 (73.5)	25 (73.5)	15 (93.8)	ł 0.645	14 (77.8)	45 (80.4)	2 (100)	ł 0.924	21(80.8)	18 (85.7)	15 (88.2)	ł 0.977
Lobular	5 (14.7)	3 (11.5)	1 (6.2)		2 (11.1)	7 (12.5)	0 (0)		3 (11.5)	2 (9.5)	1 (5.9)	
Others	4 (11.8)	2 (7.7)	0 (0)		2 (11.1)	4 (7.1)	0 (0)		2 (7.7)	1 (4.8)	1 (5.9)	

a:64 observations were recorded for ki67
ł denotes Fisher-Exact test is reported
** denotes significant at p<0.01 level

Table 3: Correlation & Agreement between OncotypeDx& NPI risk categories

	Oncotype Dx categories			Spearman Correlation	p-value	Kappa	p-value
NPI categories	**low**	**moderate**	**high**				
low	11	5	2	0.19	0.101	0.13	*0.035
moderate	22	21	13				
high	1	0	1				
≤50 years							
low	5	1	0	0.58	**0.005	0.45	**0.002
moderate	3	10	3				
high	0	0	0				
>50 years							
low	6	4	2	0.06	0.653	0.04	0.329
moderate	19	11	10				
high	1	0	1				

* denotes significant at p<0.05 level
** denotes significant at p<0.01 level

Table 4: Correlation & Agreement between Oncotype Dx & Ki67 risk categories

	Oncotype Dx categories			Spearman Correlation	p-value	Kappa	p-value
NPI categories	**low**	**moderate**	**high**				
low	17	6	3	0.44	**<0.001	0.33	**<0.001
moderate	7	8	6				
high	2	8	7				
≤50 years							
low	3	3	0	0.41	0.105	0.27	0.060
moderate	1	2	1				
high	1	4	2				
>50 years							
low	14	3	3	0.45	**0.001	0.36	**<0.001
moderate	6	6	5				
high	1	4	5				

a:64 observations were recorded for ki67
** denotes significant at p<0.01 level

Table 5: Correlation & Agreement between NPI & Ki67 risk categories

	Oncotype Dx categories			Spearman Correlation	p-value	Kappa	p-value
NPI categories	**low**	**moderate**	**high**				
low	6	19	1	0.027	0.827	0.01	0.457
moderate	4	16	1				
high	3	14	0				
≤50 years							
low	1	5	0	-0.12	0.644	-0.06	0.689
moderate	1	3	0				
high	2	5	0				
>50 years							
low	5	14	1	0.10	0.497	0.046	0.307
moderate	3	13	1				
high	1	9	0				

a: 64 observations were recorded for ki67

Conclusion

No statistically significant strong agreement and correlation were observed among three risk assessment methods. Further investigations should be conducted with a larger sample size to assess agreement among these risk classification methods. For better estimation of prognosis relying only on one tool is not enough, but combining OncotypeDx RS and clinic pathologic information and proliferation markers will be more meaningful [6-23].

Limitations

The small sample size is a limiting factor here, larger sampling may be able to show some strong correlation

Disclosure and conflict of interest

The author(s) indicated no potential conflicts of interest.

References

1. Polyak K (2011) Heterogeneity in breast cancer. J Clin Invest 121: 3786-3788.
2. Bloom HJ (1957) Richardson WW: Histological grading and prognosis in breast cancer: A study of 1409 cases of which 359 have been followed for 15 ears.Br J Cancer 11: 359-377.
3. Elston CW (1991) Ellis IO: Pathological prognostic factors in breast cancer I: The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 19: 403-410.
4. Ahmad Z, Khurshid A, Qureshi A, Idress R, Asghar N, et al. (2009) Breast carcinoma grading, estimation of tumor size, axillary lymph node status, staging, and nottingham prognostic index scoring on mastectomy specimens. Indian J PatholMicrobiol 52: 477-481.

5. Galea MH, Blamey RW, Elston CE, Ellis IO (1992) The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Research & Treatment 22: 207-219.

6. A Goldhirsch, J N Ingle, R D Gelber, A S Coates, B Thürlimann, et al. (2009) Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 20: 1319-1329.

7. Y Fong, J Evans, D Brook, J Kenkre, P Jarvis, et al. (2015) The Nottingham Prognostic Index: five- a d ten-year data for all-cause Survival within a Screened Population.Ann R CollSurg Engl 97: 137-139.

8. B Z Clark, D J Dabbs, K L Cooper, R Bhargava (2013) "Impact of progesterone receptor semiquantitative immuno-histochemical result on OncotypeDx recurrence score: a quality assurance study of 1074 cases," Applied Immunohistochemistry and Molecular Morphology 21: 287-291.

9. J Auerbach, M Kim, S Fineberg (2010) "Can features evaluated in the routine pathologic assessment of lymph node-negative estrogen receptor-positive stage I or II invasive breast cancer be used to predict the OncotypeDx recurrence score?" Archives of Pathology and Laboratory Medicine 134: 1697-1701.

10. Aman N A, Doukoure B, Kouadio Donatien Koffi, Baumaney Sylvanus Koui, Zie Cheick Traore, et al. (2019) Immunohistochemical Evaluation of Ki-67 and Comparison with Clinicopathologic Factors in Breast Carcinomas. Asian Pac J Cancer Prev 20: 73-79.

11. T P McVeigh, LM Hughes, N Miller, M Sheehan, M Keane, et al. (2014) the impact of OncotypeDx testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre. European Journal of Cancer 50: 2763-2770.

12. A Goldhirsch, W C Wood, A S Coates, R D Gelber, B Thürlimann, et al. (2011) Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 23: 2997-3006.

13. Paik S (2007) Development and clinical utility of a 21- gene recurrence score prognostic assay in patients with early breast cancer treated with tamoxifen. The Oncologist 12: 631-635.

14. J A Sparano, R J Gray, P M Ravdin, D F Makower, K I Pritchard, et al. (2019) Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. N engl j med 380: 2395-2405.

15. Maura Bríd Cotter, Alex Dakin, Aoife Maguire, Janice M Walshe, M John Kennedy et al. (2017) Comparison of OncotypeDx® Recurrence Score® with other risk assessment tools including the Nottingham Prognostic Index in the identification of patients with low-risk invasive breast cancer. Virchows Arch 471: 321-328.

16. Hanna M G, Bleiweiss I J, Nayak A, Jaffer S (2017) Correlation of OncotypeDx Recurrence Score with Histomorphology and Immunohistochemistry in over 500 Patients. International Journal of Breast Cancer 2017: 6.

17. Albergaria A, Ricardo S, Milanezi F, Carneiro V, Amendoeira I, et al. (2011) Nottingham Prognostic Index in Triple-Negative Breast Cancer: a reliable prognostic tool?. BMC Cancer 11: 299.

18. Acs G, Esposito NN, Kiluk J, Loftus L, Laronga C (2012) A mitotically active, cellular tumor stroma and/ or inflammatory cells associated with tumor cells may contribute to intermediate or high OncotypeDx Recurrence Scores in low-grade invasive breast carcinomas. Modern Pathology 25: 556-566

19. Jack Cuzick, Mitch Dowsett, Silvia Pineda, Christopher Wale, Janine Salter, et al. (2009) Prognostic value of a combined ER, PgR, Ki67, HER2 immunohistochemical (IHC4) score and the comparison with the GHI recurrence score—results from TransATAC. Cancer Res 69: 503.

20. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, R Coombes C, et al. (2011) Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 103: 1656-1664.

21. Nasser Mulla, Anwar Alnouri, Muneera Majed Al Majed, Olga Aleynikova, Manuela Pelmus, et al. (2016) Determine the relationship between Ki 67 and OncotypeDx. Journal of Clinical Oncology 34: 12017.

22. Tan AC, Li BT, Nahar K, Danieletto S, Fong ES, et al. (2018) Correlating Ki67 and Other Prognostic Markers with OncotypeDx Recurrence Score in Early Estrogen Receptor-Positive Breast Cancer. Asia Pac J ClinOncol 14: 161-166.

23. Ruangpratheep CH, Piyaisrakul S (2019) The Correlation of Nottingham Prognostic Index with Immunoexpression of ER, PR, HER2, and Ki67 in Breast Cancer 30: 93.