Research Article

Comparing Oncotype DX Recurrence Score Categories with Immunohistochemically Defined Luminal Subtypes

Yoshio Mizuno[1]*, Hiromi Fuchikami[1], Naoko Takeda[1,2], Junichi Yamada[3], Yuko Inoue[2], Hiroshi Seto[4] and Kazuhiko Sato[1]

[1]*Department of Breast Oncology, Tokyo-West Tokushukai Hospital, Japan*
[2]*Inoue Ladies Clinic, Japan*
[3]*Department of Clinical Pathology, Tokyo-West Tokushukai Hospital, Japan*
[4]*Seto Hospital, Japan*

Abstract

Background: At the 13th St Gallen International Breast Cancer Conference in 2013, a new definition of luminal A-like and luminal B-like breast cancer was proposed, involving the expression of Estrogen Receptor (ER), Progesterone Receptor (PgR), and Ki-67. We examined the rate of concordance between the risk groups using the Oncotype DX Recurrence Score (RS) and the previous and newly proposed luminal subtypes with the standardized Ki-67 assessment.

Method: The relationship between a previously and newly proposed, immunohistochemically defined luminal A and B subtype with the Oncotype DX RS of 41 cases of T1-2 N0-1 M0 (ER positive, HER2 negative) breast cancer was assessed. We first classified the patients into the previously defined luminal A and B subtypes, according to the level of Ki-67 as either "low" (<14%) or "high" (≥14%), as assessed by local pathologists. Next, to consider the necessity for standardizing Ki-67 measurement methods, we re-examined Ki-67 with a central review. By introducing PgR positivity (≥20%), we classified these patients to newly proposed luminal subtypes and compared them with the risk groups stratified by Oncotype DX RS.

Results: In the previously proposed luminal subtypes, the concordance rate between luminal A and the low RS category was 76.5% according to local pathologists and 90.1% by central review, whereas the rate between luminal B and the intermediate to high RS category was 46.7% and 45.8%, respectively. In newly proposed luminal subtypes, the concordance rate between luminal A and low RS category was 100% and between the luminal B and intermediate to high RS category was 53.6%.

Conclusion: Although this study was based on a retrospective chart review of a small sample size, the newly proposed luminal subtypes, including addition of PgR positivity, appeared to improve the precision of selecting patients with intermediate to high RS categories.

Introduction

Ki-67 is widely available as a prognostic factor and a predictive marker of chemotherapy benefit in breast cancer patients [1-6]. Ki-67 is frequently used as a key marker to guide systemic treatment decisions in both the neoadjuvant and adjuvant settings, although there is no standardized method with good reproducibility and reliable cutoff values [7]. In preanalytic validity, formalin fixation adversely affects the measurement results. Similarly, in terms of analytical validity, tumor heterogeneity and the lack of a standard measuring method by pathologists may also affect measurement of Ki-67 [8].

The Oncotype DX test (Genomic Health, Redwood City, CA, USA) is a multi-gene reverse transcriptase PCR (RT-PCR) assay that was developed for use with formalin-fixed paraffin-embedded tumors, and provides the Recurrence Score® (RS) that predicts chemotherapy benefit and the risk of distant breast cancer recurrence [9-14]. Based on RS, patients are divided into three risk groups: low risk (RS < 18), intermediate risk (18 ≤ RS < 31), or high risk (RS ≥ 31). The use of RS to guide clinical treatment decisions has been incorporated into clinical guidelines such as ASCO [15], NCCN [16], ESMO [17], and the St Gallen Consensus Guidelines [18,19].

Furthermore, research in recent years has shown that PgR should be included when considering chemotherapy, with a PgR cut-off of < 20% argued for inclusion in chemotherapy [20]. At the 13th St Gallen International Breast Cancer Conference in 2013, to distinguish between luminal A-like and luminal B-like breast cancer, a new definition was proposed, involving a combination of the expression of Estrogen Receptor (ER), Progesterone Receptor (PgR), and Ki-67.

Because too many variations in analytical practice restrict the value for the clinical utility of

Table 1: Baseline clinicopathological characteristics.

Characteristics	All patients N=41 No. (%)	RS<18 n=26 No. (%)	18≤RS n=15 No. (%)
Median age, year (range)	54.6 (28-80)	51.8 (28-77)	59.7 (43-80)
menopause Yes No	21 (51.2) 20 (48.8)	10 (38.5) 19 (61.5)	11 (73.3) 4 (26.7)
Surgery mastectomy breast conserving surgery	8 (19.5) 33 (80.5)	4 (15.4) 22 (84.6)	4 (26.7) 11 (73.3)
Tumor size T < 2cm 2cm ≤ T < 5cm 5cm ≤ T	30 (73.2) 9 (22.0) 2 (4.8)	19 (73.1) 6 (23.1) 1 (3.8)	11 (73.3) 3 (20.0) 1 (6.7)
Node status 0 1-3	38 (92.7) 3 (7.3)	25 (96.2) 1 (3.8)	13 (86.7) 2 (13.3)
PgR status PgR < 20% 20% ≤ PgR	9 (22.0) 32 (78.0)	1 (3.8) 25 (96.2)	8 (53.3) 7 (46.7)
Ki-67 (local) Ki-67 < 14% 14% ≤ Ki-67	11 (26.8) 30 (73.2)	8 (30.8) 18 (69.2)	3 (20.0) 12 (80.0)
Ki-67 (central) Ki-67 < 14% 14% ≤ Ki-67	17 (41.5) 24 (58.5)	13 (50.0) 13 (50.0)	4 (26.7) 11 (73.3)

Ki-67 [8,21,22], the Oncotype DX test has often been introduced as a reliable biomarker test, although it is very expensive and the National Health Insurance Program in Japan does not cover its cost. Accordingly, we need to more efficiently select intermediate to high RS patients who should be considered for treatment with chemotherapy. To consider the possibility of selecting patients with an intermediate to high RS more accurately, we hypothesize that the newly proposed definition of luminal subtypes at the 13th St Gallen International Breast Cancer Conference and the standardized Ki-67 assessment are able to help determine the benefit from adjuvant chemotherapy. Here we examined the rate of concordance between risk groups from the Oncotype DX Recurrence Score (RS) and the previous and newly proposed luminal A and B subtypes with the standardized Ki-67 assessment. As a secondary end point, we compared the correlation of the Oncotype Dx RS with histopathological characteristics of the tumor including Ki67 and PgR status in these patients.

Methods

Patients and materials

The cohort included consecutive patients with early breast cancer who underwent surgery from December 2011 to January 2015 at the Tokyo-West Tokushukai Hospital (Tokyo, Japan) and who requested RS. Of these patients, the Oncotype DX assay was performed in 41

patients with early breast cancer (T1-2, N0-1, M0, ER-positive, and HER2-negative). The Oncotype DX test is intended to be used by patients with newly diagnosed, early-stage (stage I or II), lymph node-negative, ER-positive, and HER2-negative invasive breast cancer who will be treated with adjuvant therapy. The Oncotype DX test may also be used to select postmenopausal patients with stage II or III a, lymph node-positive, ER-positive, and HER2-negative (and those who will be treated with hormone therapy) invasive breast cancer.

Assessing Ki-67 scores and other biomarkers

An IHC score consisting of at least 10% positive cells was used to define ER/PgR positivity. A positive score for HER2 was either HER2 3+ by IHC analysis (defined as uniform intense membrane staining of >30% of invasive tumor cells) or fluorescence in situ hybridization (ratio of HER2 to chromosome 17 centromere of >2.0). Immunohistochemical staining was quantitatively evaluated by light microscopy, in which the entire tissue section was scanned at low-power magnification (10×) to determine areas with the highest number of positive nuclei (hot-spots) within the invasive component. Ki-67 was expressed as the percentage of cells positive for mind bomb E3 ubiquitin protein ligase 1 (MIB-1) among a total of at least 1000 malignant cells at high-power magnification (40×). Nuclear staining of the tumor cells was considered as negative if 14% or fewer of the cells were stained for Ki-67 and as positive if more than 14% were stained for KI-67. An MIB-1 clone (Dako, Carpinteria, CA, USA) was used for immunohistochemical analysis of Ki-67. All cases were evaluated by registered local pathologists. Although many different systems for grading pathological responses have been proposed, no standard method has yet been adopted.

A central review by a professionally trained physician was performed by scanning magnification to count at least 1000 cells in the most densely labeled areas. For all nonmatching cases, the percentage of tumor cells with any nuclear staining was recorded. The central review used calculations based on the hot-spot counting method, because counting the area with the highest number of positive cells was more reproducible than random counting.

The relationship of the previous and newly proposed immunohistochemically defined luminal subtypes compared with the Oncotype DX RS

To assess the validity of the previous and newly proposed surrogate definitions of the "luminal A" and "luminal B (HER2-negative)" intrinsic molecular subtypes of breast cancer outlined at the 2011 and 2013 St Gallen International Breast Cancer Conference, we hypothesized that the newly proposed definition of luminal subtypes improves the precision of selecting patients with intermediate to high RS. We also considered the necessity of standardizing Ki-67 measurement methods by central review. For that reason, we examined the rate of concordance between the risk groups using the Oncotype DX RS and the previously defined and newly proposed luminal subtypes with the standardized Ki-67 assessment. We first classified these 41 patients into the previously proposed luminal A and B subtypes according to the level of Ki-67 with either a "low" (<14%) or "high" (≥14%) core as assessed by local pathologists. Next, to consider the necessity of standardizing Ki-67 measurement methods, we re-examined Ki-67 status by central review. Finally, by including PgR positivity (≥20%), we also classified patients who had

Table 2: Comparison between the risk groups as per Oncotype DX RS and previously proposed luminal subtypes according to the level of Ki-67 assessed by local pathologists.

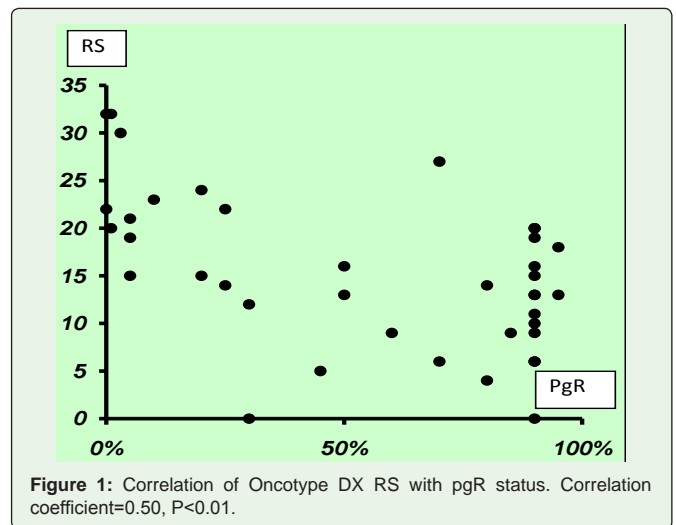|	RS low risk	RS int. – high risk	total
Luminal A	8	3	11
Luminal B	18	12	30
Total	26	15	41

Table 4: Comparison between the risk groups as per Oncotype DX RS and newly proposed luminal A and B subtypes with the level of Ki-67 assessed by central review.
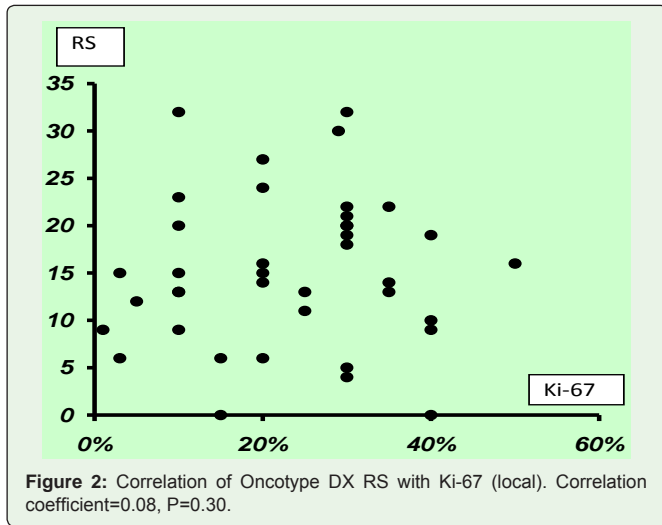
	RS low risk	RS int. – high risk	total
Luminal A	13	0	13
Luminal B	13	15	28
Total	26	15	41

their Ki-67 status re-examined by central review to newly proposed luminal subtypes, and compared them with the risk groups as per Oncotype DX RS.

The correlation of the Oncotype Dx RS with PgR status and Ki-67

The stat2008 software (statistical program file developed with Microsoft Excel, Igakutoshoshuppan, Tokyo, Japan) was used for Spearman's correlation analysis.

According to the policies of our institutional ethics committee, general consent was obtained from all patients receiving medical care.

Results

Baseline clinical characteristics

In this study, 41 patients with early breast cancer, who were eligible for the Oncotype DX test, were identified. These patients were divided into two groups according to Oncotype DX RS (i.e., RS < 18 *vs.* 18 ≤ RS). A total of 26 (63.4%) of 41 patients had a RS < 18, whereas 15 (36.6%) of the 41 patients had a RS of 18 or more. The distribution of clinicopathological features in both groups is shown in (Table 1). The median patient age was 54.6 years (range, 28-80 years) with 20 premenopausal and 21 postmenopausal. A total of 33 (80.5%) patients had breast conserving surgery. The median tumor size was 1.54 cm (range, 0.3-7.0 cm).

Comparing risk groups using oncotype DX RS and the previously proposed luminal subtypes

According to the level of Ki-67 assessed by local pathologists in the previously proposed luminal subtypes, 11 patients were categorized into the luminal a subtype, whereas 30 were categorized into the luminal B subtype. Among the luminal a subtype, 8 of 11 cases were identified as low risk. Among the luminal B subtype, 12 of 30 cases were identified as being at an intermediate to high risk. As assessed by local pathologists, the concordance rate between the luminal A and low risk group was 72.7% (8/11) and that between the luminal B and intermediate to high risk group was 40% (12/30) (Table 2).

According to the level of Ki-67 assessed by central review in the

previously proposed luminal subtypes, 17 patients were categorized into the luminal a subtype and 24 patients were categorized into the luminal B subtype. Among the luminal a subtype, 13 of 17 cases were identified in the low risk group. Among the luminal B subtype, 11 of 24 cases were included in the intermediate to high risk group. As assessed by local pathologists, the concordance rate between the luminal A and low risk group was 76.5% (13/17), whereas the concordance rate between the luminal B and intermediate to high risk group was 45.8% (11/24) (Table 3).

Comparing risk groups using Oncotype DX RS and newly proposed luminal A and B subtypes

Among patients who had their Ki-67 status re-examined by central review and according to the newly proposed luminal subtypes, 13 patients were categorized into the luminal A subtype, and the remaining 28 patients were categorized into the luminal B subtype. Among the luminal A subtype, all of the 13 cases were included in the low risk group. Among luminal B subtype, 15 of 28 cases were included in the intermediate to high risk group. The concordance rate between luminal A and low risk group were 100% (13/13) as determined by the central review, whereas the concordance rate between luminal B and the intermediate to high risk group was 53.6% (15/28) (Table 4). We found that 53.6% (15 patients) who were identified in the intermediate to high risk group were considered for adjuvant chemotherapy in our cohort. When introducing the newly proposed luminal subtypes and Ki-67 status as assessed by the central review to order the Oncotype Dx test, the concordance rate between the luminal A and low risk group, and the luminal B and intermediate to high risk group improved from 72.7% to 100% and 40.0% to 53.6%, respectively.

Table 3: Comparison between the risk groups as per Oncotype DX RS and previously proposed luminal subtypes according to the level of Ki-67 assessed by central review.

	RS low risk	RS int. – high risk	total
Luminal A	13	4	17
Luminal B	13	11	24
Total	26	15	41

Figure 1: Correlation of Oncotype DX RS with pgR status. Correlation coefficient=0.50, P<0.01.

Figure 2: Correlation of Oncotype DX RS with Ki-67 (local). Correlation coefficient=0.08, P=0.30.

The correlation between Oncotype Dx RS with Ki-67 and PgR status

We also analyzed the correlation between other histopathological characteristics of the tumor with Oncotype RS. In our study, there was a significant correlation between PgR status and Oncotype RS (correlation coefficient = 0.50, P < 0.01; Figure 1). However, there was no significant correlation between Ki-67 status as assessed by either a local pathologist or central review and the Oncotype RS (correlation coefficient = 0.08, P = 0.30; correlation coefficient = 0.09, P = 0.28, respectively; Figures 2 & 3).

Discussion

Identification of intrinsic subtypes is most precise using molecular technologies; however, where such assays are unavailable, surrogate definitions of subtype can be obtained by IHC measurements of ER, PgR, Ki-67, and HER2 with in situ hybridization confirmation. There is adequate evidence to support the critical role estrogen plays in the breast and its involvement in the pathogenesis of breast cancer [23]. In comparison, the role of progesterone in the human adult mammary gland and in breast cancer is less clear. A recent study has reported that progesterone/progestins are able to inhibit and stimulate proliferation of breast cancer cells, whereas human breast cancer cell lines expressing PR have also been used to elucidate mechanisms associated with the proliferative and tumorigenic roles of progesterone. In cancer cells, progesterone/progestin's can both promote and inhibit proliferation [24]. Furthermore, recent studies have demonstrated that patients with early breast cancer and those who are ER positive and/or PR positive (i.e., luminal) have lower risks of recurrence and mortality compared with women who are ER-negative and/or PR-negative disease [25,26]. Women with ER-positive/PR-negative, ER-negative/PR-positive, or ER-negative/ PR-negative tumors experienced higher risks of mortality compared with women with ER-positive/PR-positive tumors, independent of various demographics and clinical tumor characteristics [27].

The International Ki-67 in Breast Cancer Working Group published their recommendations for Ki-67 assessment in breast cancer in 2011. However, these recommendations included no established quality assurance schemes to ensure that the procedures for Ki-67 analysis in one laboratory lead to comparable scores in others, and this article did not recommend standardizing an

evaluation method of Ki-67 [8]. Thus, the direct application of specific cut-off rates for comparison must be considered unreliable unless the analyses are performed in a high-volume laboratory with its own reference data. Our previous study analyzed 287 primary breast cancer patients who underwent preoperative CNB to compare the concordance rates for assessing Ki-67 status evaluated either by automated or central/local pathology assessment and showed that central review and the use of an automated analyzer can improve the accuracy of Ki-67 assessment. We then confirmed the necessity of a standardized evaluation method for Ki-67 expression in breast cancer to overcome the disadvantages of variable counting methods and measurement sites [20,21].

Current immunohistochemical markers do not allow accurate prediction of the risk of recurrence, and improvements are required to clearly identify which women are at sufficiently low risk to be able to safely avoid the use of chemotherapy. A previous study reported that the Oncotype DX RS provided additional prognostic information regarding distant recurrence beyond classical clinicopathologic factors. However, its cost is a barrier for its use in many other countries. It is therefore important to select appropriate patients for the Oncotype DX test. In this study, the newly proposed definition of luminal subtypes with standardizing Ki-67 measurement methods by the central review improved the precision of selecting patients with intermediate to high RS from 40.0% to 53.6%. In addition, all non-selected patients showed a low RS. A major limitation of this study is that it is a retrospective chart review with a small sample size, non-randomized, and limited to a single oncology center. Despite these limitations, this approach may have wide applicability and improve clinical information when selecting appropriate patients for the Oncotype DX assay.

Previous studies have demonstrated that lower expression of PgR has been associated with higher Oncotype RS [28-29]. Moreover, another paper reported that a strong correlation existed between the Ki-67 value and Oncotype DX RS, especially in tumors with a Ki-67 value ≥25%. They also found that the likelihood of a tumor with a Ki-67 value ≥25% having an intermediate or high Oncotype RS is >90% and these patients may benefit from adjuvant chemotherapy [30]. In this study, there was a statistically significant correlation between PgR and Oncotype DX RS, but there was no significant correlation between Ki-67 status as assessed by either a local pathologist or central review and Oncotype RS.

Figure 3: Correlation of Oncotype DX RS with Ki-67 (central). Correlation coefficient= 0.09, P=0.28.
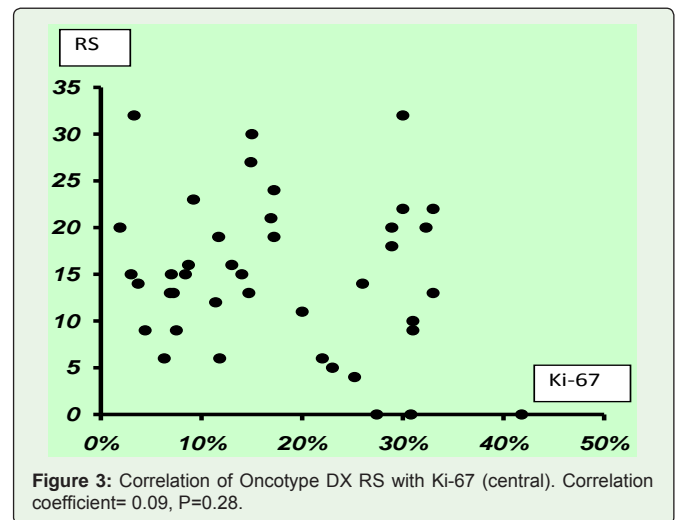
In conclusion, we found that the newly proposed luminal subtypes from the 13th St. Gallen International Breast Cancer Conference in 2013 and Ki-67 assessment by a central review in order to select patients who would benefit from Oncotype DX improved the precision of selecting patients with intermediate to high RS. Although this study was based on a retrospective chart review of a small number of patients, newly proposed luminal subtypes by inclusion of PgR positivity appears to improve the precision of selecting patients within low RS categories and for whom adjuvant chemotherapy could be avoided.

Acknowledgement

References

1. Lopez F, Belloc F, Lacombe F, Dumain P, Reiffers J, Bernard P, et al. Modalities of synthesis of Ki67 antigen during the stimulation of lymphocytes. Cytometry. 1991; 12: 42-49.

2. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol. 2005; 23: 7212-7220.

3. Trihia H, Murray S, Price K, Gelber DR, Golouh, R, Goldhirsch A, et al. Ki-67 expression in breast carcinoma: its association with grading systems, clinical parameters, and other prognostic factors-a surrogate marker? Cancer. 2003; 97: 1321-1331.

4. Spyratos F, Ferrero-Poüs M, Trassard M, Hacène K, Phillips E, Tubiana-Hulin M, et al. Correlation between MIB-1 and other proliferation markers: clinical implications of the MIB-1 cutoff value. Cancer. 2002; 94: 2151-2159.

5. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009; 101: 736-750.

6. Bouzubar N, Walker KJ, Griffiths K, Ellis IO, Elston CW, Robertson JF, et al. W. Ki67 immunostaining in primary breast cancer: pathological and clinical associations. Br J Cancer. 1989; 59: 943-947.

7. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst. 2011; 103: 1656-1664.

8. Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol. 2010; 28: 1829-1834.

9. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006; 24: 3726-3734.

10. Chen C, Dhanda R, Tseng WY, Forsyth M, Patt DA. Evaluating use characteristics for the oncotype dx 21-gene recurrence score and concordance with chemotherapy use in early-stage breast cancer. J Oncol Pract. 2013; 9: 182-187.

11. Sparano JA, Paik S. Development of the 21-gene assay and its application in clinical practice and clinical trials. J Clin Oncol. 2008; 26: 721-728.

12. Tang G, Cuzick J, Costantino JP, Dowsett M, John F, et al. Risk of Recurrence and Chemotherapy Benefit for Patients With Node-Negative, Estrogen Receptor-Positive Breast Cancer: Recurrence Score Alone and Integrated With Pathologic and Clinical Factors. J Clin Oncol. 2011 Nov 20; 29: 4365-4372.

13. Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol. 2010; 28: 1677-1683.

14. Dowsett M, Ebbs SR, Dixon JM, Skene A, Griffith C, Boeddinghaus I, et al. Biomarker changes during neoadjuvant anastrozole, tamoxifen, or the combination: influence of hormonal status and HER-2 in breast cancer--a study from the IMPACT trialists. J Clin Oncol. 2005; 23: 2477-2492.

15. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007; 25: 5287-5312.

16. National Comprehensive Cancer Network Practice Guidelines in Oncology. Breast Cancer version v2. 2011.

17. Wang R, Wu P, Shi D, Zheng H, Huang L, Gu W, et al. Risk Factors of Synchronous Inguinal Lymph Nodes Metastasis for Lower Rectal Cancer Involving the Anal Canal. PLoS One. 2014; 9: 111770.

18. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn H-J, et al. 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. Ann Oncol. 2011; 22: 1736–1747.

19. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn H-J, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Annals of Oncology: official journal of the European Society for Oncology. 2009; 20: 1319-1329.

20. Prat A, Cheang MC, Martín M, Parker JS, Carrasco E, Caballero R, et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. J Clin Oncol. 2013; 31: 203-209.

21. Mizuno Y, Natori T, Takeda N, Yamada J, Abe H, Inoue Y, et al. The reliability of assessment of Ki-67 expression on core needle biopsy and the surgical specimens of invasive breast cancer: Comparison of local pathologists' assessment and central review. Journal of Cancer Therapy. 2012; 3: 841-845.

22. Mizuno Y, Fuchikami H, Natori T, Takeda N, Inoue Y, Yamada J, et al. Standardized Assessment of Ki-67 in Breast Cancer Patients Using Virtual Slides and an Automated Analyzer in Comparison to Central/Local Pathological Assessments. Journal of Cancer Therapy. 2014; 5: 141-146.

23. Le Romancer M, Poulard C, Cohen P, Sentis S, Renoir JM, Corbo L. Cracking the estrogen receptor's posttranslational code in breast tumors. Endocr Rev. 2011; 32: 597-622.

24. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013; 34: 130-162.

25. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000; 406: 747-752.

26. Bauer K, Parise C, Caggiano V. Use of ER/PR/HER2 subtypes in conjunction with the 2007 St Gallen Consensus Statement for early breast cancer. BMC Cancer. 2010; 10: 228.

27. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007; 9: 6.

28. Flanagan MB, Dabbs DJ, Brufsky AM, Beriwal S, Bhargava R. Histopathologic variables predict Oncotype DX recurrence score. Mod Pathol. 2008; 21: 1255-1261.

29. Tang P, Wang J, Hicks DG, Wang X, Schiffhauer L, McMahon L, et al. A lower Allred score for progesterone receptor is strongly associated with a higher recurrence score of 21-gene assay in breast cancer. Cancer Invest. 2010; 28: 978-982.

30. Sahebjam S, Aloyz R, Pilavdzic D, Brisson ML, Ferrario C, Bouganim N, et al. Ki 67 is a major, but not the sole determinant of Oncotype Dx recurrence score. Br J Cancer. 2011; 105: 1342-1345.

Citation: Mizuno Y, Fuchikami H, Takeda N, Yamada J, Inoue Y and Seto H et al., Comparing Oncotype DX Recurrence Score Categories with Immunohistochemically Defined Luminal Subtypes. SM J Surg. 2015;1(1):1005.

Page 5/5