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ORIGINAL ARTICLE

The value of Nottingham grade in breast cancer re-visited in the Sri Lankan setting

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Abstract

Objective: We aimed to assess the impact of Nottingham grade (NG) on breast cancer specific survival (BCSS) and recurrence free survival (RFS) of operable breast cancer (BC) patients presenting at different TNM stages in view of assessing the value of NG in prognostication of breast cancer in the Sri Lankan setting. *Method:* This retro-prospective study included a consecutive series of TNM stage I to III BC patients presented to our unit from 2006 to 2012. Data were collected through follow up visits, clinic and laboratory records. Grading and scoring of oestrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (Her2) expressions were done by a single investigator. Kaplan-Meier and Cox-regression models were used in the survival analysis. *Results:* A total of 742 (NG1-12%; NG2-45%; NG3-43%) patients with a median follow up of 39.5 (range: 12 - 138) months were included. Five-year BCSS was 94%-NG1, 80%-NG2 and 72%-NG3 ($p < 0.001$). Five-year RFS was 86%-NG1, 75%-NG2 and 67%-NG3 ($p = 0.001$). Only the lymph-node status (LNS) ($p = 0.001$) had an independent effect on the BCSS and RFS of NG3 patients. LNS ($p = 0.001$), PR ($p = 0.004$) and Her2 ($p < 0.001$) independently affected the BCSS of NG2 patients. None of the factors considered had an effect on the BCSS/RFS of NG1 patients. A significant decrease in BCSS and RFS was seen with an increase in NG in the sub-group of TNM stage III ($p = 0.01$ and 0.011). *Conclusion:* NG categorizes BC patients into prognostic groups with distinctly different survival outcomes. Sub-categorization of TNM stage III by NG is suggested.

Keywords: breast cancer, Nottingham grade, prognostic factors, survival

INTRODUCTION

The most well-known prognostic factors of breast cancer are tumour size, lymph node stage, histological grade, lympho-vascular invasion and pathological stage of the tumour.[1]Out of these features, clinically used strongest prognostic determinants in operable breast cancer are lymph node stage, tumour size and histological grade. The most widely used grading system of breast cancer is the Nottingham combined histological grade (Elston Ellis modification of Scarff-Bloom-Richardson grading system).[2,3] Nottingham grade is derived by adding scores 1 to 3 given for three histological features of breast cancer. Nottingham grade is assigned according to the final score (grade 1 = score 3 - 5, grade 2 = score 6 - 7 and grade 3 = score 8 - 9) where Nottingham grade 1 has the best and grade 3 has the worst prognosis.[4]

Lymph node status, tumour size and Nottingham grade make up the prognostic index; Nottingham prognostic index (NPI). It is widely used in the management of patients with breast cancer in UK.[5] However, Nottingham grade is not yet incorporated in the long used tumour-node-metastasis (TNM) staging system which is meant to stratify breast cancer patients into groups that are prognostically and therapeutically similar.[6] Many previous studies have emphasised the importance of grade on prognostication of breast cancer patients.[4,5]

In Sri Lanka too, the Nottingham grade and TNM stage are considered in planning and

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treatment, though the impact of grade on the prognosis has not been scientifically proven for Sri Lankan breast cancer patients. There are no published data on the impact of histological grade on the breast cancer specific survival (BCSS) of breast cancer patients in Sri Lanka. Therefore this study was designed to assess whether the three Nottingham grades affect only patients with a similar prognosis and to assess the impact of Nottingham grade on the survival of operable breast cancer patients in different TNM stages at presentation, based on the BCSS and recurrence free survival (RFS) of a cohort of operable breast cancer patients in southern Sri Lanka.

MATERIALS AND METHODS

This was a retro-prospective cohort study. A consecutive series of TNM stage[6] I to III breast cancer patients who had sought the immunohistochemistry (IHC) laboratory services of our unit from May 2006 to December 2012 was studied. This study was approved by the Ethical Review Committee of our institution. The histopathological findings of the breast cancers were retrieved from the records available in the laboratory. Clinical data were retrieved from the clinic records at the Oncology clinic of the teaching hospital which is the only oncology unit for the Southern Province of Sri Lanka.

Nottingham grading for all breast cancers were done by a single investigator to eliminate inter-observer variation, using hematoxylin and eosin stained slides. All objective criteria given for Nottingham modification of Bloom-Richardson grading were strictly adhered to in assigning grades to each breast cancer[3].

Laboratory methods

All immunohistochemically stained slides of all study subjects were retrieved from the department files. When the slides were faded and not suitable for assessment, a new section was taken from the paraffin block and stained according to the same immunohistochemistry staining protocol used originally. Primary monoclonal mouse antihuman estrogen receptor α clone 1D5 (Dako-M7047), monoclonal mouse antihuman progesterone receptor (Dako-M3569) and polyclonal rabbit antihuman c-erbB-2 oncoprotein (Dako-A0485) have been used with the secondary antibody (Dako Real EnVision™) for IHC staining of all breast cancers to assess the ER, PR and Her2 expression respectively. Scoring of ER and PR expression were done using the Allred Score. Her2 expression was assessed using UK recommendations for all breast cancers[7]. Assessment of IHC stained slides too was done by a single investigator eliminating inter-observer variation. The complete absence of the staining for ER, PR and a score of 0 or +1 for Her2 were considered the criterion for categorizing as triple negative breast cancer (TNBC) for this analysis. Allred score of $\geqslant 3$ was considered the cut off for ER and PR expression (considered receptor negative, if <1% of tumour cells show staining of any intensity)[8]. Her2 immunohistochemical score of +3 was considered positive. Breast cancers which had +2 for Her2 had been referred for FISH and the Her2 status were determined accordingly. Breast cancers with +2 with no available FISH results were excluded from the study.

Follow up and outcomes

Study subjects were followed up for recurrence or death at six months intervals. The study ended on 31st December 2013. Median follow-up time was 39.5 months (range: 12-138 months). One third of the total population was followed up beyond four years from the date of diagnosis (81% for 24 months, 55.6% for 36 months, 40.4% for 48 months and 31% for five or more years).

The BCSS time was defined as the time elapsed from the date of diagnosis of breast cancer to the last follow up date or the date of death. Patients who died of breast cancer or who died with breast cancer (progression/ metastasis), were included.[9] Deaths from other causes or from unknown causes were censored to the date of death. The cause of death of the patient was obtained from the death certificate issued by the Department of Registrar General. Those who were lost to follow up or alive at the last follow up date were censored.

The RFS was calculated from the date of surgery/date of commencement of neoadjuvant chemotherapy to the date of diagnosis of the recurrence (local/distant metastasis).[9] Radiological and histopathological data were used to confirm the recurrence. Clinical details of the subjects were retrieved from their clinic records at the Oncology unit. The date on which the said investigation done was considered the date of recurrence. Patients who did not experience the relevant end point were censored at the last follow-up. Death was not considered as an event for RFS.[9]

Statistical analysis

The Pearson chi-square test and the chi-square test for trend were used to determine the

association between clinico-pathological features and scores of Nottingham grade. Kaplan-Meier model was used to estimate the BCSS and RFS and the log-rank test was used to compare the different groups. Univariate analysis was performed with the Kaplan-Meier model and multivariate analysis was performed with Cox-regression model using the backward factor retention method to estimate the predictors of survival. All the factors which had a $p < 0.100$ in the univariate analysis were considered for the multivariate analysis. A p value of less than 0.05 was considered significant in all analyses.

RESULTS

A total of 742 breast cancer patients were included; 86 (12%) were grade 1, 338 (45%) were grade 2 and 318 (43%) were grade 3 breast cancers. Clinico-pathological features of the cohort are given in Table 1. The majority of the patients in the cohort were between 36 to 60 years of age with mostly moderate to high grade (grade 2/3) tumours with the maximum diameter ranging from 2 cm to 5 cm. Most of them had lymph node metastasis at presentation. Either ER and PR or Her2 expression was negative in most breast cancers.

The present cohort of patients was given hormone therapy and chemotherapy according to the standard protocols. However, only 5.4% (8/147) received the complete number of cycles of trastuzumab, while 15% (22/147) received ⩾9 cycles which is claimed to be the minimum number of trastuzumab cycles.[10] Five-year BCSS of the cohort was; grade 1 = 94%, grade 2 = 80%, and grade 3 = 72% ($p < 0.001$) (Fig. 1a). Five-year RFS was; grade 1 = 86%, grade 2 = 75% and grade 3 = 67% ($p = 0.001$) (Fig. 1b).

In the univariate analysis of the whole study cohort, almost all clinico-pathological features had a significant effect on the BCSS and RFS except the age at presentation ($p = 0.189$) on the BCSS and lympho-vascular invasion ($p = 0.089$) on the RFS. Univariate analysis of the Nottingham grade subgroups revealed that lymph node status affected the BCSS of all

TABLE 1: Clinico-pathological features of operable breast cancer patients

Clinico-pathological features	*N*	%	Clinico-pathological features	*N*	%
Age at presentation			TNM stage		
<=35 years	56	7.5	I	140	18.9
36-60 years	523	70.5	II	354	47.7
>60 years	163	22.0	III	248	33.4
Tumour size			Expression of ER		
<20 mm	245	33.0	Positive	290	40.0
>20-50 mm	440	59.3	Negative	443	60.0
>50 mm	57	7.7	Unknown	9	
Nottingham grade			Expression of PR		
Grade 1	86	11.6	Positive	305	42.0
Grade 2	338	45.6	Negative	423	58.0
Grade 3	318	42.9	Unknown	14	
Lympho-vascular invasion			Expression of Her2		
Presence	218	31	Positive	147	21.0
Absence	494	69	Negative	541	79.0
			Unknown	54	
Lymph node stage			Triple negative breast cancer		
Stage 0	324	43.7	Presence	243	34.0
Stage 1	192	25.9	Absence	469	66.0
Stage 2	139	18.7	Unknown	30	
Stage 3	87	11.7			

n, number;%, percentage; TNM, tumour-node-metastasis; ER, oestrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor2

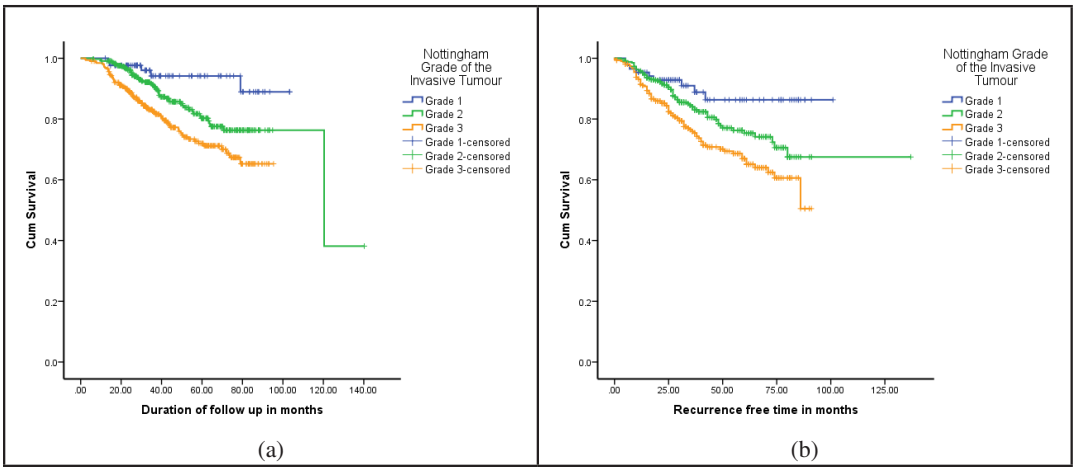

FIG. 1: Survival of the cohort by Nottingham grade (grade 1 = 86; grade 2 = 338; grade 3 = 318) (a) Breast cancer specific survival ($p < 0.001$); (b) Recurrence free survival ($p = 0.001$)

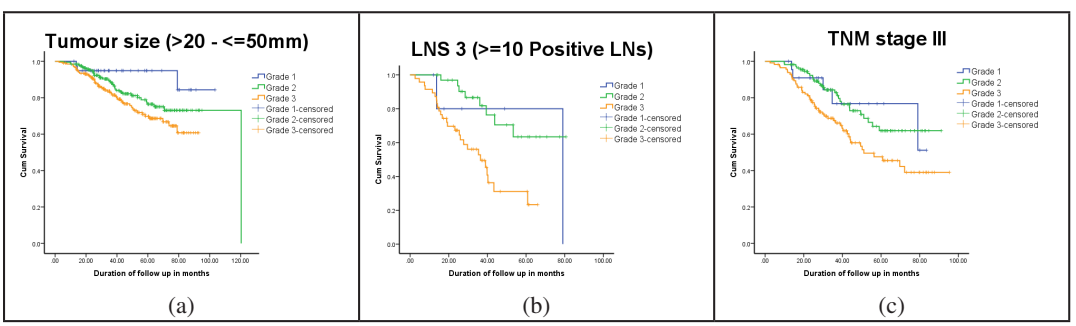

FIG. 2: Breast cancer specific survival curves of (a) T2 (>20 - ⩽50 mm) tumours, (b) N3 (positive lymph nodes >9) and (c) TNM stage 3, according to the Nottingham grade 1 - 3

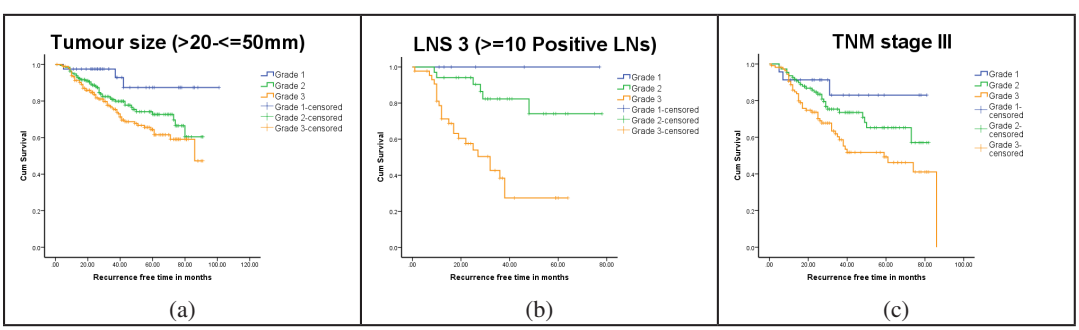

FIG. 3: Recurrence free survival curves of (a) T2 (>20 - ⩽50 mm) tumours, (b) N3 (positive lymph nodes >9) and (c) TNM stage 3, according to the Nottingham grade 1 - 3

patients irrespective of the grade. Tumour size and lympho-vascular invasion affected only the BCSS of grade 1 and 3 breast cancers. All three IHC markers; expression of ER, PR and Her2 affected the BCSS of grade 2 patients only, while none of the IHC markers affected the BCSS of grade 3 patients. Triple negative status had an effect on only the survival of grade 1 patients. None of the considered factors other than ER affected the RFS of grade 1 patients. The lymph node stage influenced the RFS of grade 2 and 3 breast cancers. Expression of PR and Her2 affected the RFS of grade 2 patients only.

Multivariate analysis of the whole cohort revealed that Nottingham grade ($p = 0.002$), lymph node status ($p < 0.001$), tumour size ($p = 0.036$), PR ($p < 0.001$) and Her2 ($p < 0.001$) expression had a significant independent effect on

the BCSS. Nottingham grade (p = 0.007), lymph node status (p < 0.001), age at presentation (p = 0.006), PR (p = 0.033) and Her2 (p = 0.006) expression independently affected the RFS but tumour size lost its effect on the RFS.

In the multivariate analysis of the Nottingham grade sub-groups, only the lymph node stage (p = 0.001) had an independent effect on both BCSS and RFS of grade 3 patients and BCSS of grade 2 patients. PR and Her2 had an independent effect on the BCSS of grade 2 patients in addition to the lymph node status. The same factors affected the RFS of grade 2 patients except the lymph node status. None of the factors considered for the multivariate analysis had an independent effect on the BCSS or RFS of grade 1 patients.

The survival patterns of patients in the three Nottingham grades were assessed against lymph node status (N0, N1, N2 and N3), TNM stages (stage I, II and III) and tumours in different sizes (T1: ⩽2 cm, T2: >2 cm – ⩽5 cm and T3: >5 cm). Nottingham grade 1 patients in TNM stage I and II had 100% five-year BCSS and stage III had 76.7% five-year BCSS. A significant decrease in BCSS and RFS was seen with an increase in Nottingham grade in the sub-groups of TNM stage III (p = 0.01 and 0.011), T2; tumours of 2 cm - 5 cm (p = 0.035 and p = 0.013) and N3 (p = 0.002 and p < 0.001) breast cancer patients (Figs. 2 and 3).

Although the survival difference among the three Nottingham grades (grade 1 to 3) were statistically significant, with reference to grade 1, Nottingham grade 2 had no significant impact on the BCSS or RFS of patients in this study population (BCSS; HR: 2.185, 95% CI: 0.865 - 5.518, p = 0.098, RFS; HR: 1.754, 95% CI: 0.868 - 3.545, p = 0.117). Therefore, this study was extended to analyze the grade 2 breast cancers separately.

Nottingham grade 2 consists of breast cancers with score 6 and 7 (score 6 = 185; score 7 = 153). Majority of the patients with score 6 had ER/PR positive and Her2 negative tumours while score 7 patients had ER/PR negative and Her2 positive tumours (ER p = 0.003, PR p = 0.014, Her2 p < 0.001) (Table 2). There was a significant survival difference between the patients who had score 6 and 7 (BCSS p = 0.009; RFS p = 0.020). There was no survival difference between the grade 1 and score 6 or grade 3 and score 7 patients (p = 0.428 and p = 0.451) respectively.

TABLE 2: Comparison of the clinico-pathological profile of the patients who had Nottingham grade score 6 and 7

Clinico-pathological features	Score 6 *N* (%)	Score 7 *N* (%)	*P*
Age at presentation			0.010
<=35 years	7(37)	12(63)	
36-60 years	124(52)	116(48)	
>60 years	54(68)	25(32)	
Tumour size			0.257
<20 mm	73(60)	48(40)	
>20-50 mm	101(51)	97(49)	
>50 mm	11(58)	8(42)	
Lympho-vascular invasion			0.145
Presence	46(48)	49(52)	
Absence	139(57)	104(43)	
Lymph node stage			0.970
Stage 0	83(56)	66(44)	
Stage 1	48(54)	40(46)	
Stage 2	35(52)	32(48)	
Stage 3	19(56)	15(44)	

Clinico-pathological features	Score 6 *N* (%)	Score 7 *N* (%)	*P*
TNM stage			0.768
I	28(52)	26(48)	
II	79(54)	68(46)	
III	77(57)	58(43)	
Expression of ER			0.003
Positive	105(63)	62(37)	
Negative	78(47)	89(53)	
Expression of PR			0.014
Positive	106(61)	68(39)	
Negative	75(47)	83(53)	
Expression of Her2			<0.001
Positive	12(28)	31(72)	
Negative	161(59)	112(41)	
TNBC			0.131
Presence	43(48)	47(52)	
Absence	137(57)	103(43)	

n, number; %, percentage; p, significance; TNM, tumour-node-metastasis; ER, oestrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor2; TNBC, triple negative breast cancer

DISCUSSION

Histopathological assessment is the gold standard for prognostication and therapeutic decision making in the management of breast cancer patients. Assessment of histological type, tumour size, grade, lymph node status, lympho-vascular invasion and margin clearance are done routinely and are essential for accurate decision making on adjuvant therapy.[11] Survival studies on breast cancer have revealed that these factors are the most important prognostic features.[4,12,13] Out of these features, the tumour grade plays a major role as a prognostic factor. It is a simple and an inexpensive tool in the prognostication of breast cancers. Even though Nottingham grade is used for making therapeutic decisions in Sri Lanka, there are no published scientific data on its validity in the Sri Lankan setting. Therefore, the objective of this study was to investigate the prognostic role of Nottingham grade of breast cancer patients in Southern Sri Lanka and to study its effect on the TNM staging.

In the present cohort, 88% of the patients had tumours with grade 2 and 3 and only 12% had grade 1 tumours. It is interesting to note that results of the current study tallies well with the previous studies done in Sri Lanka.[14,15] The prevalence of tumour grade may vary according to the geographic region. A study done in the UK stated that the prevalence of tumour grade 1 was 18.6%, grade 2 was 35.6% and grade 3 was 45.6%.[5] It is often claimed that high grade breast cancers are more often seen among the Asians.[16] The prevalence of grade 1 tumours in the present study was less compared to the UK while it was higher compared to the findings of an institutional study done in the neighbouring country, South India.[17]

The results of the present study demonstrate that histological grade had an inverse relationship with the BCSS and RFS; increase in the grade decreased the BCSS and RFS. Many previous publications agree with this relationship.[4,5,18,19] The present study too highlights that the Nottingham grade categorizes breast cancer patients into groups with distinctly different survival outcomes. This difference is significantly retained in the subgroups; TNM stage III, tumours of >2 cm - ⩽5 cm and N3 breast cancers in the current study population (Figs. 2 and 3). The survival of the patients in the other subgroups (TNM stage I and II, N1 and N2and T1 and T3) are unaffected by the Nottingham grade. Since both lymph node status and the tumour size make up the TNM stage in the absence of metastasis, the effect of grade on both these subgroups enhances the effect on TNM stage III. Although the TNM staging is used for therapeutic decision making, it measures anatomic extent of the tumour only. It can be improved by the addition of Nottingham grade which measures the intrinsic biological nature of the tumour and reflects the potential of a carcinoma to metastasize or cause death. Based on our study findings, sub-categorization of TNM stage III by Nottingham grade for making therapeutic decisions can be suggested.

This study was extended to find out whether there were other factors which predict the survival of patients in each grade. Nottingham grade 1 tumours were found to be a homogenous group as none of the important prognostic factors had an independent effect on the BCSS or the RFS of patient with grade 1 breast cancers. Lymph node status stood out as the most influential factor in changing the survival as it affected the survival (both BCSS and RFS) of grade 3 patients and the BCSS of grade 2 breast cancer patients. Lymph node stage lost its independent effect in grade 1 as described previously by Rakha *et al*.[20] There were two more factors independently influencing the survival of grade 2 breast cancers apart from the effect of lymph node status on the BCSS. Both PR and Her2 independently influenced both BCSS and RFS of grade 2 patients. Therefore, it is evident that Nottingham grade 2 breast cancer patients are a more heterogeneous group. Further, Nottingham grade 3 had a significant RFS difference with reference to grade 1 in this study population but this difference was not observed for grade 2 with reference to grade 1. Therefore, Nottingham grade 2 breast cancers were further analyzed to find out the characteristics of the breast cancers in this group. While keeping to the same criteria used for Nottingham grading we could identify two subsets of grade 2 patients; patients with a score of 6 and 7. Our findings highlights that the breast cancers with score 6 and 7 have distinctly different survival. Their prognosis is more in line with the preceding/ subsequent grade than the same grade, most probably due to the difference in ER/PR and Her2 expression. Our study therefore poses a question as to whether it is better to have two tier grading system than the present three tier system. One advantage of a two tier system is that the middle category which often becomes the dumping group in any uncertainties in assigning

the grade is eliminated by shifting to a two tier system of grading. At the same time, we need to consider whether this distribution of prognostic factors within grade 2 tumours is peculiar to our population. It has to be clarified by assessing the same effect in different populations. It is also identified that concordance of assigning grade 2 is low compared to grade 1 and 3 due to the expected phenomenon of scoring of a biological variable where scores in the overlap regions are usually most difficult to be categorized.[5]

The well-known reason for reluctance to use grading in patient management in the recent past was lack of reproducibility of the method. The validity of grading is claimed to be affected by inter-observer variation.[21] St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer also recommends that grade 1 and grade 3 be taken into consideration for the assessment of indication of adjuvant chemotherapy most probably due to the poor concordance in assigning grade 2.[22] In the present study, grading was done by a single investigator to eliminate inter-observer variation and the criteria stipulated by Elston and Ellis were strictly adhered to increase the objectivity.[3]

Bloom and Richardson in their original article on grading of breast cancer have stated that "the three classes of tumours are not disparate pathological entities; the lines of cleavage between the grades merely indicate arbitrary divisions of what is, in fact, a continuous scale of malignancy." Whilst neoplasms at either end of the scale are easily recognized, some on the borderlines may be more difficult to classify, and not infrequently it is a matter of opinion into which grade they should be placed.[2] In fact, the patient cohort they studied did not show a marked difference in survival between score 5 and 6 and between score 7 and 8.

The Ellis and Elston modification of the grading system described by Bloom and Richardson was based on long term follow up of a large cohort introducing more consistency to the grading.[3] Following the introduction of the modified version, grading became more popular and became a consistent parameter assessed. However the treatment offered to breast cancer patients has changed over the years and this improved treatment may have altered the survival outcome which may be different from the original cohorts on which Bloom *et al* and Ellis *et al* designed the breast cancer grading. Even in the present cohort of patients, most of those who have Her2 positive cancers have not received the full course of trastuzumab therapy as expected. Therefore, our data may be different to patients in high resource settings who receive full course of treatment with trastuzumab. Poor antiHer2 treatment could be one reason why the score7 grade 2 patients had a survival more in line with the grade 3 patients.

In this molecular era, molecular diagnostic methods are often used and they provide more refined prognostic and predictive information. Therefore traditional prognostic methods may become outdated. However, the assessment of Nottingham grade cannot be underestimated, because of its simplicity and cost effectiveness as a method of assessment of tumour biology. Tumour grade is much more useful for countries which have limited resources with less access to expensive new technologies. According to the World Bank report of 2015, Sri Lanka is a middle income country and most of the patients cannot afford expensive molecular diagnostic investigations unless the government bears the cost which again is too much to expect.[23] Therefore, routine histopathological evaluation including Nottingham grade is an important cost effective tool for prognostication in the Sri Lankan setting.

In conclusion, Nottingham grade is an independent factor influencing the BCSS and RFS. It categorizes breast cancer patients in our cohort into groups with distinctly different survival outcomes, validating its utility in our setting. However, the distinct survival difference observed between the breast cancers of grade 2 with score 6 and grade 2 with score 7, mostly due to the difference in ER, PR and Her2 expression, needs further investigations to see whether it is a characteristic of the Asian population or merely reflecting the pre-trastuzumab era. The effect of Nottingham grade on the survival of TNM stage III appears significant, reinforcing the current suggestions to include grading in the TNM staging, adding the biological variability of the tumour to the extent of spread in stratifying patients. Whether it should be a two tiered system, or the three tiered Nottingham grading, also needs further investigation.

Conflicts of interest

All authors declare no conflicts of interest.

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