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PROGNOSTIC VALUE OF LYMPH NODE RATIO IN BREAST CANCER PATIENTS WITH PATHOLOGICALLY POSITIVE AXILLARY LYMPH NODES; SINGLE INSTITUTE EXPERIENCE

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ABSTRACT

Purpose: To detect the prognostic impact of lymph node ratio (LNR) on type of relapse, disease free survival (DFS) and overall survival (OS) in breast cancer patients with pathologically involved lymph nodes in comparison to pathological nodal (pN) stage. **Methods:** This retrospective study included 306 breast cancer patients with positive axillary LN treated with upfront surgery in the period between January 2008 and December 2013 at Al Azhar University Hospital, Egypt. The LNR defined as positive lymph nodes number divided by excised lymph nodes number multiplied by 100. **Results:** After a median follow up period of 49 months, LNR classification into three groups (20%, >20-65% and >65%) found to be the most predictive factor for DFS and OS. Systemic relapse was affected significantly by pN stage and LNR (P= 0.008 and 0.001 respectively) while locoregional relapse rate did not affect significantly by either one (P= 0.078 and 0.077 respectively). In univariate analysis tumor stage, pN Stage, LNR, Capsular invasion, ER, PR, and HER2 neu had statistically significant effect on total relapse rate (P= 0.013, P= 0.013, P= 0.000, P= 0.002, P= 0.007, P= 0.044 respectively). However in multivariate analysis LNR and ER were the only factors affecting the relapse rate significantly (P= 0.01 and 0.03 respectively). Both pN stage and LNR (20/65) affected the DFS (P= 0.000 and 0.000 respectively) and OS significantly (P= 0.008 and 0.003 respectively). **Conclusion:** LNR classification (20/65) found to be the most sensitive one in this study. LNR was at least equal to pN stage as a prognostic factor for DFS and OS, while it was superior to pN stage in prediction of relapse rate; which makes LNR better alternative to pN stage.

KEYWORDS: Breast cancer; Lymph node ratio; Positive axillary lymph nodes and pN stage.

Abbreviation

ALN; axillary lymph node, BCS; breast conservative surgery, DFS; disease free survival, IDC; infiltrating duct carcinoma, ILC; infiltrating lobular carcinoma, LNR; lymph node ratio, MRM; modified radical mastectomy, OS; overall survival, pN; pathologic node.

INTRODUCTION

Breast cancer is the commonest cancer and leading cause of cancer death in women worldwide.[1] Its incidence has increased over several decades, while the death rate has fallen.[2] Based on the data from the National Cancer Registry Program of Egypt, breast cancer is the commonest malignancy in women (48.8%), and second common cancer (24.3%) after Hepatocellular carcinoma in both sexes[3]

Axillary lymph nodes (ALNs) receive 85 percent of the lymphatic drainage from all quadrants of the breast; the remainder drains to the internal mammary, infraclavicular, and/or supraclavicular lymph nodes. The likelihood of ALN involvement is related to tumor size and location, histologic grade, and the presence of lymphatic invasion.[4,5]

For patients who are subjected to axillary dissection as part of surgical management, the impact of resected axillary lymph nodes number on survival is unclear, however the suggested adequate number to be excised that my affect survival is often ≥10, based on some retrospective reports.[6-8] while others suggest no prognostic impact of number excised with incidental survival effect of involved and uninvolved ratio.[9,10]

Number of ipsilateral axillary nodes involved with metastatic tumor is a strong and independent negative prognostic factor. In women with no evidence of distant metastasis (M0), the five-year survival rate for those who present with localized breast only disease versus regional pathologic node involvement is 99 and 85 percent, respectively. Even with small tumors (<2 cm) prognosis is worse in the presence of pathologic node involvement,

according to the published data that included almost 25,000 cases, the five-year relative survival was 96, 86, and 66 % if patients were pathologically node-negative, had one to three nodes involved, or had greater than three nodes involved, respectively.[11]

Adjuvant chemotherapy and radiotherapy is strongly guided by lymph node staging that depends on the absolute number of positive axillary nodes regardless the total excised number, lymph node ratio (positive ALNs number divided by total excised number) may have impact on prognosis and hence decision making at the time of adjuvant treatment as suggested by many trials.[12] In this study we retrospectively assessed the impact of lymph node ratio on the outcome of breast cancer patients treated at our institution in a 6 years period.

METHODS

This retrospective study included female non-metastatic breast cancer patients registered at the archive of the clinical oncology department, Al Hussein University Hospital in the period between January 2008 and December 2013. All included patients should have at least 6 month of regular follow up after finishing treatment. Patients who have no axillary lymph node metastasis, double malignancy other than breast cancer, those received neoadjuvant treatment, or did not experience axillary dissection were excluded from the study.

Files of patients included in this study have been retrieved from the archive and the following data were collected: Patient characteristics, disease and treatment related data, and details of outcome.

Staging was based on the 2009 7th edition of the American Joint Committee on Cancer (AJCC) staging system, Lymph node ratio (LNR) was defined as the percentage of pathologically positive ALNs, calculated through the following equation

$$LNR = \left[\frac{Number\ of\ Pathologically + ve\ ALNs}{Total\ Number\ of\ Dissected\ ALNs}\right] \times 100\%$$

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20. Numerical data were summarized using medians and ranges. Categorical data were summarized as percentages. Comparisons between the 2 groups with respect to normally distributed numeric variables were done using the t-test. For categorical variables, differences were analyzed with chi square test and Fisher's exact test when appropriate. Kaplan- Meier was used to estimate the overall and disease free survival, while comparisons between different prognostic factors were done using the Log rank test, P-values < 0.05 were considered significant.

RESULTS

Eligible patients included in this study were 306 out of 948 breast cancer patients registered at the archive of our center, during the period of the study. Median age (range) among included patients was 49 years (22–74), 150 patients (49%) were postmenopausal, 124 patients (40.5%) were premenopausal, and 32 patients (10.5%) were perimenopausal. Positive family history for breast cancer was reported by 50 patients (16.3%) while the rest 256 patients (83.7 %) reported negative family history. (Table 1).

Left sided tumor was identified in 155 patients (50.6%), right sided in 148 patients (48.4%), and only 3 patients had bilateral (1%) disease. Outer quadrant disease was recorded for 248 patients (81%), 49 patients (16.1 %) had inner quadrant disease and the remaining 9 patients (2.9 %) had central tumor or in between quadrants. (Table 1).

Modified radical mastectomy (MRM) was the primary surgical treatment in 247 patients (80.7 %), while the remaining 59 patients (19.3%) were managed by breast conservative surgery (BCS), axilla was managed surgically by axillary dissection in all patients. (Table 1).

Invasive ductal carcinoma (IDC) was the most common histopathological subtype that was reported in 288 patients (94.1%), while only 18 patients (5.9%) were having Invasive lobular carcinoma. Grade II tumors were observed in 285 patients (93.1%), while grade III was observed in 21 patients (6.9%). Pathological tumor stage T1, T2, T3 and T4 were reported for 21 (6.9%), 197 (64.4%), 60 (19.6%), and 28 patients (9.1%) respectively. (Table 1).

Median number (range) of dissected LNs was 20 (8-49), while the median number (range) of positive LNs was 5 (1-47), incidences of pathological nodal (pN) stages for pN1, pN2 and pN3 were 37.6%, 31% and 31.4% respectively. Capsular nodal invasion was reported in 37.3% of patients, while 62.7% of them had no capsular nodal invasion. (Table 1).

To study the distribution of different LNR among patients included in this study, we divided the LNR into 10 groups with 10% ascending intervals, starting from >0 - 10% and ending by >90 – 100% Most of patients (64.4%) have LNR ≤ 40% (Figure 1).

Adjuvant chemotherapy, radiotherapy and hormonal therapy were received by 298 (97.4%), 284 (92.8%) and 245 (80.1%) respectively. (Table 1).

After a median follow up period of 49 months (range 7-91), relapse was recorded in 98 patients (32%), of them 11.2% (11/98) developed isolated locoregional recurrence, 74.5% (73/98) developed distant relapse and 14.3% (14/98) had both types of relapse. Chest wall recurrence recorded for 17.3% (17/98), regional nodal

recurrence in 11.2% (11/98) including internal mammary lymph nodes that occurred in 4 patients, while local breast recurrence developed only in 2.0% (2/98). Bone metastasis was the most frequent site of distant relapse 51.0% (50/98), followed by liver metastasis 31.6% (30/98), lung metastasis 30.6% (30/98) and brain metastasis 18.3% (18/98). (Table 2).

The rate of locoregional relapse was not affected significantly by either the N stage or LNR (P= 0.078 and 0.077 respectively), while systemic relapse was significantly affected by N stage and LNR (P= 0.008 and 0.001 respectively).

In univariate analysis the rate of relapse was not statistically affected by menopausal status (P= 0.945), family history (P= 0.627), histological subtype (P= 0.082), grade (P= 0.485), LVI (P= 0.239), side (P= 0.777) or location (P= 0.907) of tumor; one the other hand T stage, N Stage, LNR, Capsular invasion, ER, PR, and HER2 neu had statistically significant effect on relapse rate (P= 0.013, P= 0.013, P= 0.000, P= 0.002, P= 0.007, P= 0.044 respectively). However in multivariate analysis only LNR and ER significantly affected the relapse rate (P= 0.011 and 0.034 respectively).

For the whole study group, disease free survivals (DFS) at 2, 3 and 5 years were 83.5%, 70.2% and 55.2% respectively, while the 2, 3 and 5 years overall survival (OS) were 87.9%, 80.4% and 67.6% respectively.

Different LNR groups had initiated to find the most representing classification that has the biggest statistical difference in term of DFS and OS, the first group included 5 risk levels of 20% interval, 2nd group included 4 risk levels of 25% interval, 3rd group included 3 risk levels of 33.3% interval, while the last group included LNR ≤ 20%, >20-65% and >65%. (Figures 2&3).

The DFS and OS were studied in this four different LNR groups and all showed statistically significant difference, however the separation between curves for LNR ≤20%, >20-65% and >65% group at DFS was the widest one without any intersection compared to the other groups, and had the lowest p value (P= 0.000) compared to the other groups (Figure 3A).

The 5 years DFS for patients with pN1, pN2 and pN3 disease was 78.7%, 61.1%, and 44% respectively, with statistically significant P value (P= 0.000), while 5 years OS was 87.5% , 72.6% and 59.2% respectively, with statistically significant p value (P= 0.008). On the other hand the 5 years DFS for patients with LNR of ≤20%, >20-65% and >65% was 75.9%, 58.4% and 44.7% respectively (P= 0.000), while the 5 years OS was 83.1%, 67.4% and 58.4 respectively (P= 0.003). (Figure 3).

Table 1: Patients Demographic and Disease Characteristics

Characteristics	Total Number (306 Pts)	%
Median Age (Range)	**49 (22-74)**	
Menopausal Status		
• Premenopausal	124	40.5%
• Perimenopausal	32	10.5%
• Postmenopausal	150	49%
Family History		
• **Negative**	256	83.7%
• Positive	50	16.3%
Tumor Side		
• Left	155	50.6%
• Right	148	48.4%
• Bilateral	3	1%
Tumor Site		
• Outer	248	81%
• Inner	49	16.1%
• Other	9	2.9%
Surgery Type		
• MRM	247	80.7%
• BCS	59	19.3%
Tumor Stage		
• T1	21	6.9%
• T2	197	64.4%
• T3	60	19.6%
• T4	28	9.1%
LN Stage		
• N1	115	37.6%
• N2	95	31.0%

• N3	96	31.4%
Multiplicity		
• No	261	85.40%
• Yes	45	14.60%
Capsular Invasion		
• No	114	37.3%
• Yes	192	62.7%
Histo-Pathological Subtype		
• **IDC**	288	94.1%
• ILC	18	5.9%
Tumor Grade		
• I	0	0.0%
• II	285	93. 1%
• III	21	6.9%
Lympho-vascular invasion		
• No	245	80.1%
• Yes	61	19.9%
ER Status		
• Negative	59	22.4%
• Positive	247	77.6%
PR Status		
• Negative	77	22.4%
• Positive	229	77.6%
HER 2 Neu Status		
• Negative	127	41.5%
• Positive	61	19.9%
• Equivocal	16	5.2%
• NA	102	33.3%
Adjuvant Treatment (Received)		
• Chemotherapy	289	97.4%
• Radiotherapy	284	92.8%
• Hormonal treatment	245	80.1%

Table 2: Pattern of Relapse

Site of relapse	Pt. Number	%
Disease relapse (total)	98	32%
• **Isolated Loco-regional relapse**	11	11.2%
• **Distant relapse**	73	74.5%
• **Both types of relapse**	14	14.3%
Site of Loco-regional relapse		
• **Chest wall**	17	17.3%
• **Regional nodes**	11	11.2%
• **Breast**	2	2%
Site of distant relapse		
• **Bone**	50	51%
• **liver**	31	31.6%
• **lung**	30	30.6%
• **brain**	18	18.3%

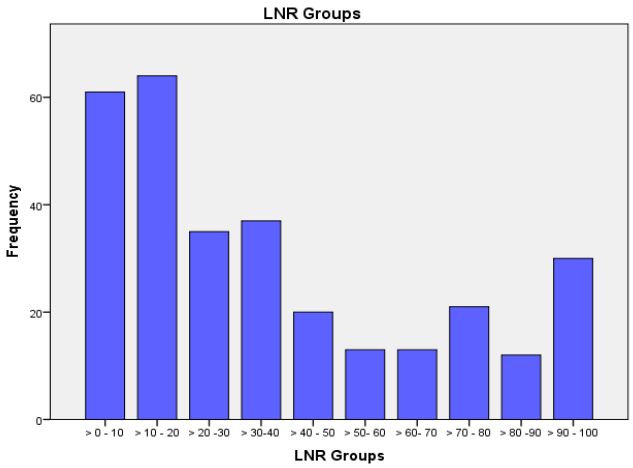
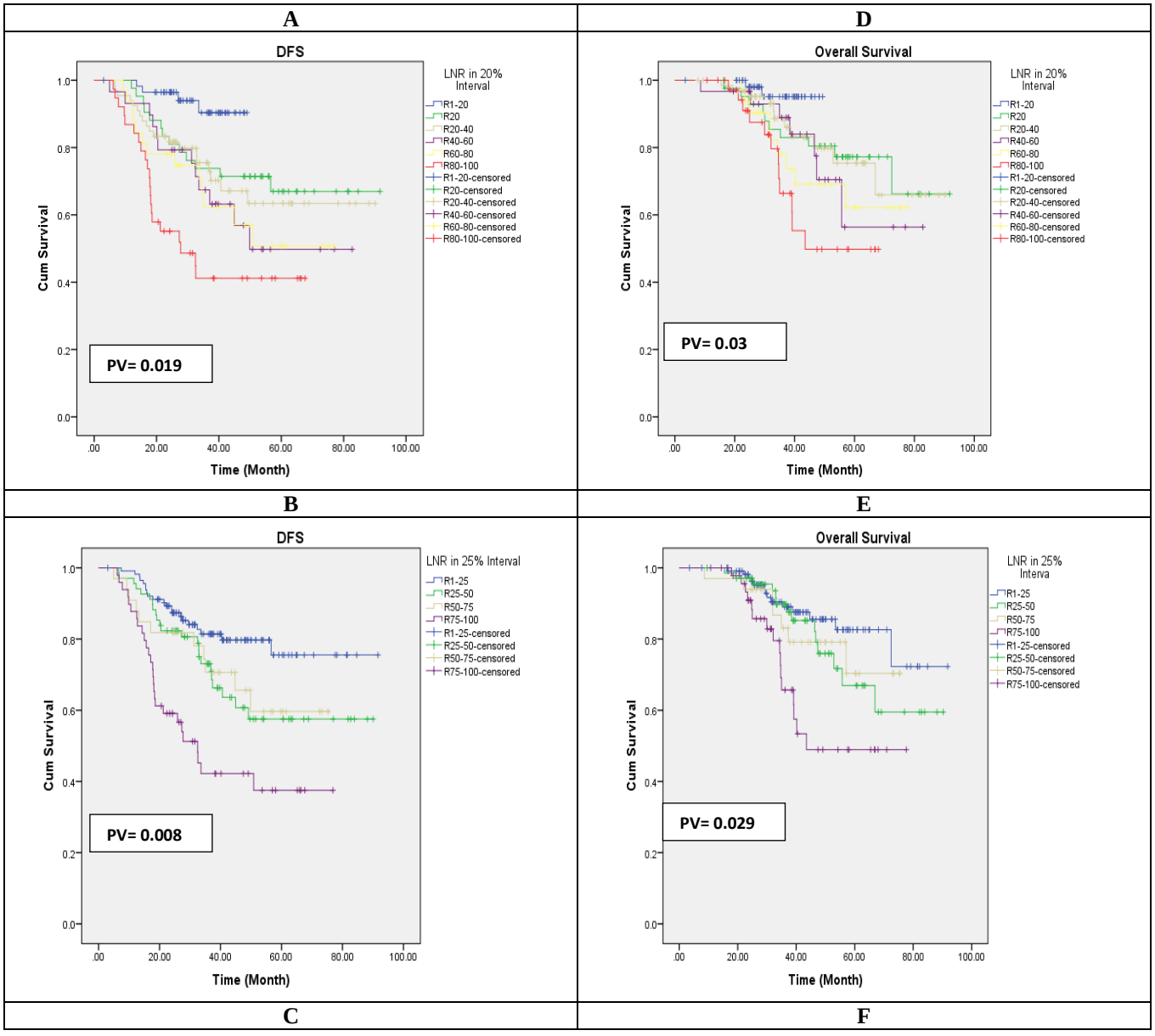


Figure 1: Number of Patients in Different LNR Arranged in 10% Ascending Intervals.



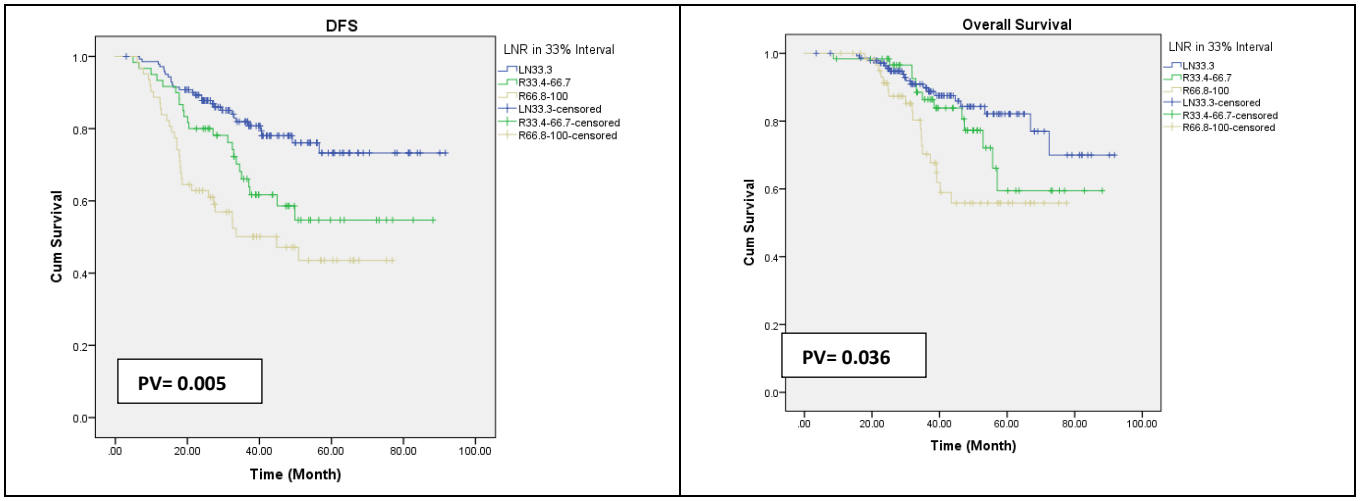


Figure 2: A, B and C Showing DFS Curves for LNR at 20%, 25% and 33% Intervals Respectively. D, E and F Showing Overall Survival Curves for LNR at 20%, 25% and 33% Intervals Respectively.

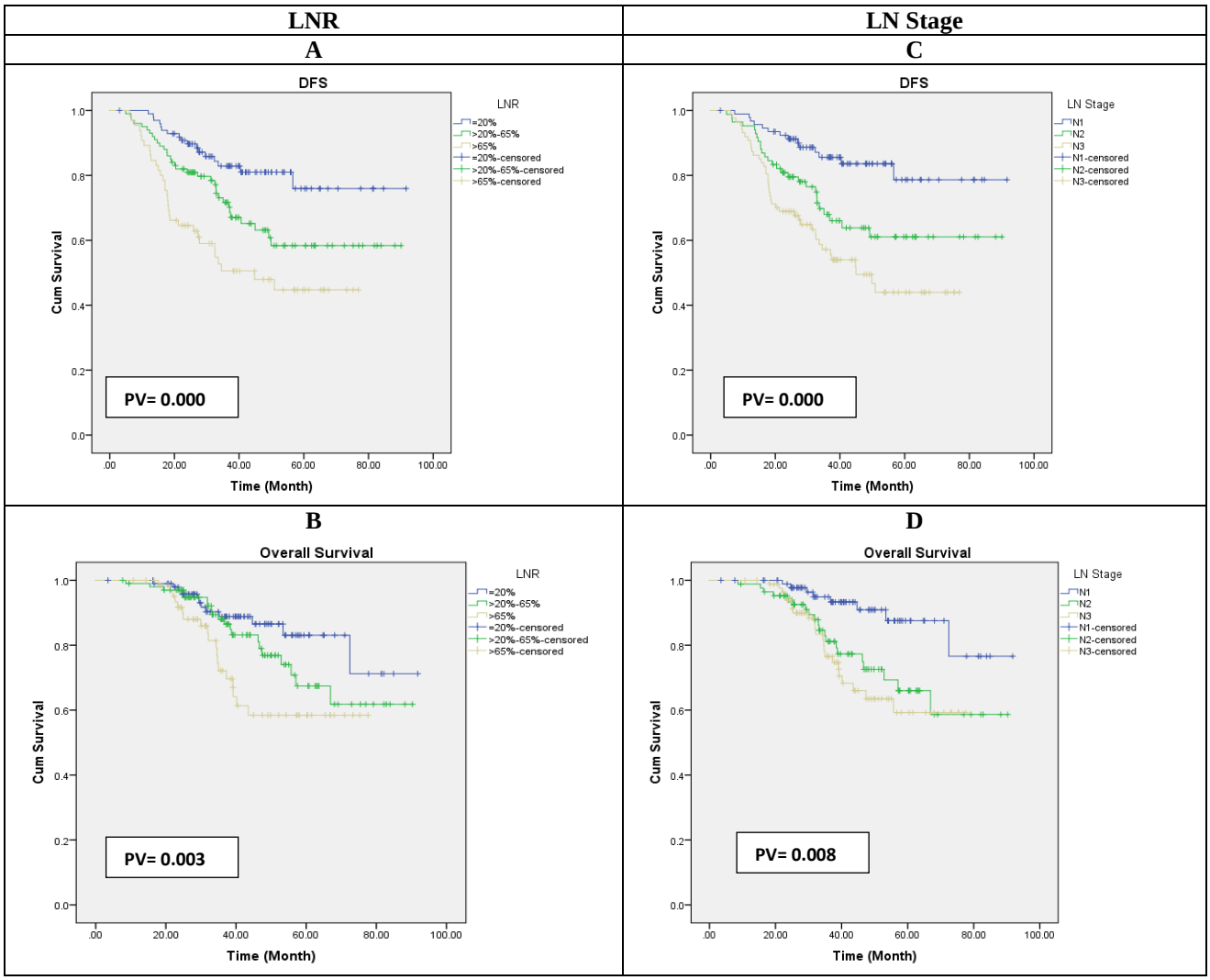


Figure 3: A and B Showing DFS and OS curves for LNR at 20%, >20-65% and >65%, C and D Showing DFS and O curves for different Nodal stages respectively.

DISCUSSION

In Egypt breast cancer crude rate among both sexes is 17.8% according to the National Population Cancer Registry Program based data that published recently.[3] According to the registry of our center 948 new breast cancer cases have been registered during the 6 years period of this study, this cases representing about 21% of all new cases presented to our center during the same

period, which is almost consistent with the previously published national data.

The median age of patients included in this study was 49 (22-74), which is about 10 years less than what is reported in LNR European study (58.9 years)[13], and the United States statistics (61 years)[14], while the median age in the LNR Chinese study was 47 years[15] which nearly consistent with our study, and this may reflect the change of breast cancer natural history between different areas of the world and may return in part to the higher life expectancy in west Europe and United States.

During the last few years molecular types of breast cancer became an important prognostic factor that helping in the choice of adjuvant treatment, however Lymph node stage is still having a great impact on the choice of adjuvant therapy. Current LN staging system is not taking in account the number of excised lymph nodes[16], which make patients with one positive lymph node equal regardless the number of excised LN for each one, this pushed many investigators to study the prognostic impact of LNR on outcome of breast cancer patients who having positive nodal metastasis.

The prognostic value of LNR has been shown for many cancer sites including the esophagus[17], colon[18], and corpus uteri.[19] In breast cancer there is growing evidence establishing the prognostic value of the LNR. Woodward and his colleagues had conducted a systematic review of 24 studies including 32,299 patients published between 1994 and 2005, that locked at a prognostic role for the LNR, using both prospective and retrospectively collected data sets, in this review LNR was confirmed to be superior to the number of involved nodes as a prognostic indicator.[12]

The relation between locoregional recurrences (LRR) and LNR has been studied by Truong and his colleagues, they found LNR more accurate than pN stage in predicting postmastectomy LRR in patients with 1–3 positive nodes treated without postmastectomy radiotherapy (PMRT), this was based on data of 82 patients treated in the British Columbia (BC) randomized trial, compared with data of 462 patients treated in prospective chemotherapy trials at the M. D. Anderson Cancer Center (MDACC). The median number of excised nodes was 10 in BC and 16 in MDACC ($p < 0.001$). Using the number of positive nodes, the LRR rate at 10-year was higher in BC compared with MDACC (21.5% vs. 12.6%; $p = 0.02$). However, when LNR is used, no differences were found between institutions, on the other hand patients with LNR >0.20 was found to have LRR >20%, that warranting PMRT consideration.[20]

We included in our trial any non-metastatic breast cancer patient with positive LNs treated at the defined period of time regardless the type of surgery, the number of positive LNs or whether they received postoperative radiotherapy or not. We found MRM the dominant surgery (77 %), this may reflect the attitude of surgeons at our institution and/or the relative late presentation of patients, as about 25 % was having either T3 or T4 tumor stage, and found median number of excised and positive axillary lymph nodes 20 and 5 respectively, with 80 % received postoperative radiotherapy. This difference in selection criteria between this study and Troung study may explain why we did not find significant relation between LNR and locoregional relapse like what was observed by Troung.[20]

In contrast to the previous study, Kim and his colleagues had studied the prognostic value of LNR in positive axillary nodes patients who received postoperative radiotherapy and they used 0.25 and 0.55 as cutoff values of LNR, where the most significant difference in DFS and DSS was observed. The LNR based classification yielded a statistically larger separation of the DFS curves than pN staging. However in multivariate analysis, the LNR was highly significant ($p<0.0001$), and pN staging was not statistically significant ($p>0.05$), on the other hand he found no statistical significant relation between either LN Stage or LNR and local relapse that is like what we have observed in our study.[21]

Many other attempts in different studies had done to define LNR risk groups that have the highest prognostic value, such as 0.33/0.67[22], 0.1/0.[23], 0.25/0.5[24], and 0.25/65%[13] however the bases upon which they decided to use such cutoff points were not always described in their articles.

The most widely studied LNR classification was low (≤ 0.20), intermediate- (>0.20 and ≤ 0.65), and high risk (>0.65), primarily used by Vinh Hung and his colleagues, based on bootstrap iterations statistical analysis that generated 1.67 million comparisons between the continuous LNR and the various categorized LNR models, and he found these 3 LNR risk group (0.20/0.65) more accurate than pN staging in survival prediction and considered it better than pN staging.[13] They also considered several limitations, like assuming all lymph nodes are similarly examined, accounting for the size of nodal metastases or factors like extracapsular or vascular invasion, and addressing supraclavicular or internal mammary chain involvement.

The same LNR classification (0.20/0.65) had been used in Chinese study, the univariate analysis in this study showed prognostic significant effect of both LNR and pN stage on LRFS and OS ($p<0.05$), however the multivariate analysis indicated that only LNR was an independent prognostic factor of LRFS and OS ($p<0.05$), while pN stage had no significant effect on LRFS or OS ($P>0.05$).[15] Patients characteristics in both current and Chinese studies are much similar and this may explain why distribution of patients between the different LNR groups and results of both trials are consistent for great extent where patients with LNR ≤20%, >20-65% and

>65% were 60 %, 24 % and 16 % respectively in our study, compared to 64 %, 25% and 11% respectively in Wu study.

The different LNR classification used in the previous studies were examined in the current study and all found having significant prognostic value in term of DFS and OS, however survival curves for LNR ≤20%, >20-65% and >65% were the most separated ones, and this is almost similar to what was seen in the previous studies. This confirm the significant prognostic value of the different LNR classification especially 25/65%, which make prognostic value of LNR at least equal to the of the current AJC nodal staging system in DFS and OS prediction and superior to LN staging in prediction of relapse.

CONCLUSION

In this study the 3 risk LNR groups (20/65%) found to be the best classification that can predict the relapse rate, DFS and OS in comparison to other LNR risk group classification used by some other trials. LNR was at least equal to pN stage as a prognostic factor for DFS and OS, while it was superior to pN stage in prediction of relapse rate; which makes LNR better alternative to pN stage at the time of adjuvant treatment choice.

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