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Prognostic value of axillary lymph node status after neoadjuvant chemotherapy. Results from a multicentre study

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ABSTRACT

Background: The prognostic value of lymph node involvement after neoadjuvant chemotherapy for breast cancer is not straightforward. We evaluated whether lymph node involvement is associated with overall survival in patients treated with neoadjuvant chemotherapy and whether Lymph Node Ratio (LNR – ratio of the positive to excised axillary lymph nodes) is a superior prognosticator when compared to ypN status (according to the pTNM classification).

Methods: Three hundred and fourteen patients receiving neoadjuvant chemotherapy in Geneva, Singapore or Kuala Lumpur were pooled for analysis. We evaluate the prognostic value of the LNR [zero, low (>0 and <0.2), intermediate (0.2–0.65) and high risk (>0.65)] and ypN staging [ypN0, ypN1, ypN2 and ypN3] with multivariate Cox regression analysis.

Results: When using the LNR classification, 88 patients were categorised as zero, 91 as low, 82 as intermediate and 53 as high risk. For classic ypN staging, 88 were ypN0, 126 ypN1, 58 ypN2 and 42 ypN3. Compared to the low risk category, LNR zero corresponded to an adjusted hazard ratio [HRadj] of 0.4 (95%CI, 0.2–0.9), intermediate risk LNR to a HRadj of 1.2 (0.7–2.2) and high risk LNR to a HRadj of 2.7 (1.5–5.0). Similarly, the ypN0 category corresponded to a HRadj of 0.3 (0.2–0.7), ypN2 to a HRadj 1.1 (0.6–2.0) and ypN3 to a HRadj 2.2 (1.3–3.8) compared to ypN1 patients.

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Conclusion: Lymph node status after neoadjuvant chemotherapy predicts overall survival. In patients treated with neoadjuvant chemotherapy, LNR does not seem to be superior to classic ypN staging.

1. Introduction

Administration of neoadjuvant chemotherapy to women with locally advanced breast cancer serves not only to convert inoperable to operable disease but also to increase the likelihood of breast conservation.[1–5] Neoadjuvant chemotherapy may however modify the yield of involved axillary lymph nodes and may lead to an underestimation in prognostic value provided by nodal status.[6,7]

The number of positive lymph nodes is one of the most important prognostic factors for breast cancer[8–10] and to date, the American Joint Committee on Cancer (AJCC) staging system is based on the number of positive axillary lymph nodes[11] (ypN0: zero positive nodes, ypN1: 1–3 positive nodes, ypN2: 4–9 positive nodes, ypN3: $\geqslant$10 positive nodes). The number of positive lymph nodes (ypN stage) is however restricted by the number of nodes excised[12] which in turn depends upon the surgical approach to axillary dissection, physiological variations between patients as well as the effect of neoadjuvant chemotherapy. Variation in these factors leads to large differences in the number of lymph nodes retrieved across surgeons as well as institutions thereby influencing staging. Thus if a surgeon systematically excised only 8 axillary lymph nodes for each patient, these patients could never be classified as ypN3, potentially resulting in understaging and undertreatment of the patient. Several studies have suggested that the ratio of the number of positive nodes to the total number of nodes excised, known as the lymph node ratio (LNR), is a superior prognostic indicator than the absolute number of nodes.[13–16] Being a ratio, the LNR accounts for the discrepancies that might arise due to differences in the technique of axillary dissection across institutions.

In this study, we evaluated the prognostic value of lymph node status in patients treated with neoadjuvant chemotherapy and assessed whether LNR was superior to the absolute number of lymph nodes involved in predicting overall survival.

2. Patients and methods

For this study we combined data from three sources, i.e. the National University Hospital (NUH) Breast Cancer Registry in Singapore, University of Malaya Medical Centre (UMMC) Hospital Based Registry in Kuala Lumpur, Malaysia and the population-based Geneva Cancer Registry, Switzerland.

The NUH Breast Cancer Registry was described previously.[17] In summary, this registry was established in 1995, through prospective data collection on demographics, tumour characteristics, treatment and follow up of all patients presenting with invasive or *in situ* breast cancer. Data from 1990 to 1995 were collected retrospectively from medical records. Vital status information for a majority of the patients was determined through long term NUH follow up clinics. For those patients that did not regularly follow up at NUH, contact was made via telephone or letter annually. Causes of death were determined from the physician and hospital records, Hospice Associations and the Singapore Cancer Registry. Patients were followed to death or end of follow up (31st December 2008), whichever came first. The Breast Cancer Registry has been approved by the NUH Institutional Ethics Review Board. The UMMC Hospital Based Registry has been prospectively compiling patient and tumour characteristics for all patients diagnosed with breast cancer starting from 1993. Mortality data were updated by direct linkage with the Malaysian National Registry Department. This registry has been approved by the UMMC Institutional Ethics Review Board. Patients were followed to death or end of follow up (31st April 2010), whichever came first.

The Geneva Cancer Registry records information on all newly diagnosed cancer cases arising in the Swiss canton of Geneva (population approximately 430,000). The registration is based on several sources of information and is extremely accurate, as attested by its low percentage (<2%) of cases recorded from death certificates only.[18] Patients were followed to death or end of follow up (31st December 2008), whichever came first. All hospitals, pathology laboratories and private practitioners in the canton are requested to report all cancer cases. Trained tumour registrars systematically abstract data from medical and laboratory records. Physicians regularly receive inquiry forms to complete missing clinical and therapeutic data. The Geneva Cancer Registry regularly assesses survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalisation (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office (office in charge of the registration of the resident population).

For the current study, we selected women diagnosed with primary invasive breast cancer, receiving neoadjuvant chemotherapy followed by surgery and with information on the number of excised and the number of positive axillary lymph nodes. Patients with distant metastases and patients not undergoing surgery were excluded from the study. All cause mortality of the selected patients was assessed. From the 2545 patients in the NUH breast cancer registry database, 156 patients received neoadjuvant chemotherapy (6.1%) and of these, 136 with complete information on excised and positive lymph nodes were included in the analysis. Similarly, from the 1001 patients diagnosed in Kuala Lumpur, 71 (7.0%) underwent neoadjuvant chemotherapy for locally advanced disease and of these 51 patients with complete information on excised and positive lymph node were included in the analysis. Of the 5236 patients in the Geneva Cancer Registry,

133 (2.5%) received neoadjuvant chemotherapy and for 127 patients we had complete information on. In total, 314 patients were included for analysis.

Information recorded for each patient included age at diagnosis, ethnicity (Asian versus Caucasian/other), nationality, year of diagnosis, place of diagnosis (Singapore, Geneva or Kuala Lumpur) and date of death or date of last contact. Tumour characteristics included tumour size based on prechemotherapy and was categorised into less than 2 cm, 2 to 5 cm, greater than 5 cm and unknown, stage (based on prechemotherapy – 1, 2, 3, unknown), oestrogen (ER) and progesterone receptor (PR) status (positive i.e. $\geqslant$10% of immunoreactive neoplastic cells expressing receptors, negative and unknown), differentiation (good, moderate, poor, unknown – based on the Scarff–Bloom–Richardson grading scheme[19]), were recorded for all patients. Treatment information included adjuvant radiotherapy (no, yes), adjuvant hormonal therapy (no, yes) and adjuvant chemotherapy (no, yes). Axillary dissection information included number of regional nodes examined and number of positive regional nodes. All excised axillary nodes were embedded for analysis. Information on chemotherapy regimens was not available from the Geneva center. Patients at the Kuala Lumpur center received FEC (ie 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2) given IV every 3 weeks for three cycles as neoadjuvant chemotherapy. A majority of the patients from Singapore received anthracyclines-containing combination chemotherapy with or without taxanes as neoadjuvant treatment. None of the patients in our study underwent sentinal lymph node biopsy.

For the purpose of comparability with the current ypN classification system, LNR was categorised into four categories including zero (0), low (>0 and <0.2), intermediate (0.2–0.65) and high risk (>0.65–1) groups based on previous findings.[13] These cut-off points were earlier identified as most optimal cut-off levels and internally validated in a population based study.[13] Additionally, using three cut-off points gave us four categories for LNR which facilitated comparison to the four ypN groups.

2.1. Statistics

After testing for proportionality, we performed a univariate Cox proportional hazard analysis to identify variables that were significantly associated with all cause mortality. Subsequently we performed multivariate Cox proportional hazard analysis, to look at the association between overall mortality and LNR and ypN respectively using two different models with similar adjustments. The first model had LNR as one of the independent variables and the second model had ypN staging as one of the independent variables.

We entered all the significant variables (as per Table 4) into a multivariate Cox model. Using backward stepwise selection, we eliminated variables that did not contribute significantly to the fit of the model and continued until the model consisted of variables that were significantly associated with all cause mortality. Using this procedure, only LNR or ypN, age, PR status, place of diagnosis and radiotherapy were significantly associated with all cause mortality.

The reference category for the models was low risk LNR group and ypN1 group respectively as these categories contained the highest number of patients. By using large groups as reference categories, we increased the stability of our models. The interpretation of our findings would not have changed had we used the 'zero' categories as the references for the two models.

Life tables were computed to gauge the survival probability for the group of patients stratified by the different LNR cutoffs and ypN classification.

Statistical analyses were performed with STATA (version 10) and SPSS (version 16).

3. Results

The median age of the 314 patients was 48 years (Table 1) and the majority (75.5%) had at least 10 axillary lymph nodes examined. All patients had undergone an axillary clearance. A large proportion of the patients (88.4%) received adjuvant radiotherapy and virtually all patients (98.8%) received adjuvant (completion) chemotherapy, which is standard procedure in the respective countries. The median number of involved nodes was two (range: 0–41 nodes) and the median LNR was 0.16 (range: 0–1.0) (Table 2). The number of patients at risk of death at 1, 3 and 5 years of follow up was 314, 205 and 107 patients, respectively.

When using the LNR classification, 88 patients were categorised as zero, 91 as low risk (>0 and <0.2), 82 as intermediate risk (0.2–0.65) and 53 as high risk (>0.65–1) LNR. For classic ypN staging, 88 were ypN0, 126 ypN1, 58 ypN2 and 42 ypN3. Five year survival probabilities for the patients stratified by LNR were 84%, 69%, 53% and 37% for zero, low (>0 and <0.2), intermediate (0.2–0.65) and high risk (>0.65–1) groups respectively (Table 3). In comparison to this, the 5 year survival probabilities for the patients stratified by ypN classification were 84%, 64%, 57% and 30% for ypN0, ypN1, ypN2 and ypN3, respectively.

In univariate analysis, place of diagnosis, year of diagnosis, ethnicity, receptor status (ER and PR), hormone therapy, differentiation, stage, tumour size, ypN staging and LNR were independently and significantly associated with all cause mortality (Table 4).

Compared to patient classified as low risk LNR (>0 and <0.2), those with LNR zero had an adjusted mortality (adjusted hazard ratio [HRadj]) of 0.4 (95%CI, 0.2–0.9), those with intermediate risk LNR had an HRadj of 1.2 (95%CI, 0.7–2.2) and those with high LNR an HRadj of 2.7 (95%CI, 1.5–5.0). Similarly, ypN classification adjusted mortality risks for ypN0 patients was HRadj 0.3 (95%CI, 0.2–0.7), for ypN2 patients was HRadj 1.1 (95%CI, 0.6–2.0) and for ypN3 patients was HRadj 2.2 (95%CI, 1.3–3.8) compared to ypN1 patients (Table 5).

Almost a quarter ($N = 77$) of the patients had less than 10 lymph nodes excised. Hence we performed a subgroup analysis to determine whether LNR had better prognostic value than ypN for this subset of patients. Compared to patient classified as low risk LNR (>0 and <0.2) ($N = 10$), the HRadj for LNR zero ($N = 28$) was 0.1 (95% CI, 0.02–0.9), intermediate risk LNR ($N = 24$) was 0.8 (95%CI, 0.2–3.7) and high risk LNR ($N = 15$) was 3.6 (95%CI 0.8–15.0). Similarly, when compared

Table 1 – Patient and tumour characteristics for patients treated with neoadjuvant chemotherapy.

Variable	Place of diagnosis			
	Singapore N = 136	Geneva N = 127	Kuala Lumpur N = 51	Combined N = 314
Age				
Median	48 years	49 years	48 years	48 years
Lower–upper quartile	25-81 years	24-86 years	26-66 years	24-86 years
<50 years	77 (56.6%)	66 (52.0%)	33 (64.7%)	176 (56.1%)
⩾50 years	59 (43.4%)	61 (48.0.%)	18 (35.3%)	138 (43.9%)
Year of diagnosis				
1990–2000	14 (10.3%)	127 (100%)	43 (84.3%)	57 (18.1%)
2001–2007	122 (89.7%)		8 (15.7%)	257 (81.9%)
Ethnicity				
Asian	125	–	50 (98%)	175 (55.7%)
Caucasian and other	(91.9%) 11 (8.1%)	127 (100%)	1(2%)	139 (44.3%)
Oestrogen receptor status[a]				
Negative	61 (46.9%)	47 (37.0%)	18 (46.1%)	126 (42.5%)
Positive	69 (53.1%)	80 (63.0%)	21 (53.9%)	170 (57.5%)
Unknown	6	–	12	18
Progesterone receptor status[a]				
Negative	67 (51.5%)	68 (53.5%)	2 (33.3%)	137 (52.0%)
Positive	63 (48.5%)	49 (46.5%)	4 (66.7%)	126 (48.0%)
Unknown	6	–	45	51
Grade[a]				
Good	16 (12.8%)	14 (11.2%)	2 (5.0%)	32 (11.2%)
Moderate	46 (36.8%)	68 (56.8%)	18 (45.0%)	132 (46.4%)
Poor	63 (50.4%)	37 (32.0%)	20 (50.0%)	120 (42.4%)
Unknown/not reported	11	8	11	30
Clinical tumour size (prechemotherapy)[a]				
<2 cm	2 (2.3%)	10 (11.3%)	2 (4.0%)	14 (6.3%)
2–5 cm	17 (20%)	52 (59.0%)	9 (18.0%)	78 (35.0%)
⩾5 cm	66 (77.7%)	26 (29.7%)	39 (78.0%)	131 (58.7%)
Unknown/not reported	51	39	1	91
Clinical stage (prechemotherapy)				
I	3 (2.2%)	3 (2.4%)	–	6 (1.9%)
II	32 (23.5%)	57 (44.9%)	3 (5.9%)	92 (29.3%)
III	97 (71.3%)	55 (43.3%)	48 (94.1%)	200 (63.7%)
Unknown/not reported	4 (2.9%)	12 (9.4%)	–	16 (5.1%)
Adjuvant radiotherapy				
No	18 (13.2%)	14 (11.0%)	4 (7.8%)	36 (11.6%)
Yes	118 (86.8%)	113 (89.0%)	47 (92.2%)	278 (88.4%)
Adjuvant hormone therapy				
No	55 (40.4%)	44 (34.6%)	20 (36.7%)	117 (38.1%)
Yes	81 (59.6%)	83 (65.4%)	31 (63.3%)	197 (61.9%)
Adjuvant chemotherapy				
No	4 (3%)	–	–	4 (1.3%)
Yes	132 (97%)	–	51 (100%)	183 (58.2%)
Unknown	–	127 (100%)	–	127 (40.5)

[a] Valid proportion has been calculated (i.e. not considering 'unknown').

to ypN1 patients (*N* = 36), the HRadj for ypN0 patients (*N* = 28) was 0.1 (95%CI, 0.01–0.5) and for ypN2 patients (*N* = 13) was 2.1 (95%CI, 0.7–6.1). Even though it seems that LNR may have some added value over ypN in identifying patients at highly increased risk of death, the number of patients in our study was too limited to allow firm conclusions for this subset of patients.

4. Discussion

The results of this study show that axillary nodal status of patients treated with neoadjuvant chemotherapy is strongly associated with overall mortality. Both the absolute number of positive lymph nodes involved (current ypN staging) as well as the LNR are among the strongest prognostic factors in this

Table 2 – Axillary nodal status of the patients treated with neoadjuvant chemotherapy.

Variable	Place of diagnosis			
	Singapore N = 136	Geneva N = 127	Kuala Lumpur N = 51	Combined N = 314
Regional nodes examined				
Median	13	14	10	13
1–3	2 (1.5%)	2 (1.6%)	7 (13.7%)	11 (3.5%)
4–9	27 (19.9%)	24 (18.9%)	15 (29.4%)	66 (21.0%)
⩾10	107 (78.7%)	101 (79.5%)	29 (56.9%)	237 (75.5%)
Regional nodes positive (ypN stage)				
Median	2	2	2	2
0	44 (32.4%)	34 (26.8%)	10 (19.6%)	88 (28.0%)
1–3	48 (35.3%)	57 (44.9%)	21 (41.2%)	126 (40.1%)
4–9	25 (18.4%)	22 (17.3%)	11 (21.6%)	58 (18.5%)
⩾10	19 (14%)	14 (11%)	9 (17.6%)	42 (13.4%)
LNR				
Median	0.14	0.13	0.38	0.16
0	44 (32.4%)	34 (26.8%)	10 (19.6%)	88 (28.0%)
0.01–0.2	37 (27.2%)	44 (34.6%)	10 (19.6%)	91 (29.0%)
0.201–0.65	33 (24.3%)	33 (26.0%)	16 (31.4%)	82 (26.1%)
0.651–1	22 (16.2%)	16 (12.6%)	15 (29.4%)	53 (16.9%)

Table 3 – Survival probabilities by LNR and ypN classification.

Variable	1 year survival probability (95% CI)	3 year survival probability (95% CI)	5 year survival probability (95% CI)
LNR			
0	1.00 (0.98–1.02)	0.89 (0.86–0.91)	0.84 (0.81–0.87)
Low ⩽0.20	0.99 (0.97–1.00)	0.82 (0.64–1.00)	0.69 (0.67–0.71)
Intermediate >0.20 and ⩽0.65	0.99 (0.97–1.00)	0.76 (0.74–0.77)	0.53 (0.51–0.54)
High >0.65	0.91 (0.90–0.92)	0.55 (0.54–0.56)	0.37 (0.35–0.38)
ypN			
0	1.00 (0.98–1.02)	0.89 (0.86–0.91)	0.84 (0.81–0.87)
ypN1	0.97 (0.96–0.98)	0.78 (0.77–0.79)	0.64 (0.62–0.65)
ypN2	0.97 (0.96–0.98)	0.74 (0.72–0.75)	0.57 (0.55–0.59)
ypN3	0.98 (0.95–1.00)	0.59 (0.57–0.61)	0.30 (0.29–0.31)

patient category. LNR and ypN classifications were comparable in predicting mortality in this group of patients.

The past few decades have seen a rapid rise in the role and complexity of neoadjuvant chemotherapy for breast cancer.[20] Neoadjuvant chemotherapy enables doctors to *in vivo* monitor the response to chemotherapy,[21] although it is not associated with improved survival as compared to adjuvant chemotherapy.[21,22] The broader use of neoadjuvant chemotherapy has led to challenging complexities in breast cancer staging. Clinical staging, i.e. preoperative staging based on clinical and radiographic examination and pathological staging, i.e. postoperative staging based on lymph node involvement and tumour size might vary significantly for patients who have responded well to neoadjuvant chemptherapy.[23] It is unclear whether the initial clinical staging or the final pathological staging is more meaningful in terms of prognosis and treatment options for patients receiving neoadjuvant chemotherapy[23] and the effect of neoadjuvant chemotherapy on lymph node involvement is still uncertain. The number of lymph nodes retrieved and examined is highly dependent on surgical expertise, the institution's protocol and the pathologists' experience.[24] Removal of at least 10 axillary lymph nodes is considered adequate for reliable lymph node staging.[25–27] In the neoadjuvant setting, certain studies have shown that patients undergoing neoadjuvant chemotherapy have a significantly lower number of lymph nodes excised compared to patients undergoing surgery without preoperative chemotherapy[28,29] while another study concluded otherwise.[12] Since the number of positive lymph nodes is one of the most important and well established prognostic factors in patients treated with primary surgery it is important for us to elucidate its role in the neoadjuvant setting.

To date only one comprehensive study has looked at the prognostic value of the lymph node ratio in the neoadjuvant setting.[6] This study concluded that the LNR was an independent prognostic factor for relapse free and overall survival. Another study (only presented in abstract form[30]) also looked into the prognostic value of the LNR in the neoadjuvant setting and also concluded that LNR was a significant prognostic factor for overall survival and superior to ypN.

Our research indicates that patients with higher LNR had a poorer survival probability which was in accordance with

Table 4 – Univariate Cox analysis for variables associated with all cause mortality.

Variable	Unadjusted HR (95% CI)	P-value
Place of diagnosis[a]		<0.001
Singapore	1	
Geneva	0.2 (0.1–0.4)	
Kuala Lumpur	1.2 (0.7–2.0)	
Age (continuous)[a]	1.02 (1.00–1.04)	0.048
Year of diagnosis (continuous)[a]	0.9 (0.8–1.0)	0.024
Ethnicity[a]		<0.001
Chinese	1	
Malay	1.9 (1.1–3.3)	
Indian	1.3 (0.7–2.6)	
Caucasian and other	0.3 (0.1–0.5)	
ER status[a]		0.032
Negative	1	
Positive	0.6 (0.3–0.9)	
Unknown	1.1 (0.5–2.2)	
PR status[a]		0.002
Negative	1	
Positive	0.5 (0.3–1.0)	
Unknown	1.7 (1.0–2.7)	
Radiotherapy		0.102
No	1	
Yes	0.6 (0.3–1.1)	
Hormone Therapy[a]		0.002
No	1	
Yes	0.5 (0.3–0.7)	
Grade[a]		0.011
Good	1	
Moderate	2.5 (0.7–8.2)	
Poor	4.2 (1.3–13.8)	
Unknown	2.1 (0.5–7.9)	
Tumour size[a]		<0.001
<2 cm	1	
2–5 cm	2.2 (0.2–18.5)	
>5 cm	4.3 (0.6–31.9)	
Unknown	1.7 (0.2–12.6)	
Stage[a]		0.015
1	0.1 (0.05–0.5)	
2	1	
3	2.6 (1.4–4.7)	
Unknown	2.9 (1.1–7.8)	
Regional nodes examined		0.632
1–3	1.5 (0.6–3.9)	
4–9	1.0 (0.6–1.7)	
⩾10	1	
LNR[a]		<0.001
0	0.5 (0.2–1.0)	
Low, ⩽0.20	1	
Intermediate, >0.20 and ⩽0.65	1.3 (0.7–2.4)	
High, >0.65	2.9 (1.6–5.2)	
ypN stage[a]		<0.001
0	0.4 (0.2–0.7)	
1	1	
2	1.2 (0.7–2.2)	
3	2.2 (1.2–3.8)	

[a] Indicated variable is significant.

Table 5 – Hazard ratios for LNR and ypN classification for all cause mortality.

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P value for adjusted HR
LNR			<0.001
0	0.5 (0.2–1.0)	0.4 (0.2–0.9)	
Low, ⩽0.20	1	1	
Intermediate, >0.20 and ⩽0.65	1.4 (0.8–2.5)	1.2 (0.7–2.2)	
High, >0.65	3.0 (1.7–5.4)	2.7 (1.5–5.0)	
ypN			<0.001
0	0.4 (0.2–0.7)	0.3 (0.2–0.7)	
ypN1	1	1	
ypN2	1.3 (0.7–2.2)	1.1 (0.6–2.0)	
ypN3	2.4 (1.4–4.0)	2.2 (1.3–3.8)	

HR, hazard ratio.
HRs adjusted for age, PR status, place of diagnosis and radiotherapy.

other studies.[13,15,31,32] On comparing the current ypN classification and LNR, we did not notice substantial differences in hazard ratios for all cause mortality. Even though it seems that for patients with less than 10 lymph nodes removed, LNR may have some added value over ypN in identifying patients at highly increased risk of death, the number of patients in our study was too limited to allow firm conclusions for this subset of patients.

Patients from Singapore and Kuala Lumpur presented with larger tumours that were poorly differentiated as compared patients from Geneva. Although the median number of positive nodes for the three centres was the same, a greater proportion of patients from the Singapore and Kuala Lumpur centers were categorised into the ypN2 and ypN3 categories than patients from the Geneva center. This could suggest that larger tumour size led to greater number of lymph nodes being involved as seen from the Singapore and Kuala Lumpur centers which is in accordance with previous studies.[33]

This is one of the first studies indicating that lymph node status, be it ypN or LNR, is of prognostic value in patients treated with neoadjuvant chemotherapy. Even though several studies in the non-neoadjuvant setting have shown that the LNR is a superior prognostic indicator than the current ypN staging,[13–16] our findings do not support this.

We acknowledge that our study suffers from several shortcomings, including a limited number of patients and a relatively short follow up time. In addition, we assessed all cause mortality as our end point as no data on cause of death or local recurrence were available. Lastly, there were chances of residual confounding since we did not have information on variables such as HER2/NEU receptor status and socio-economic status. During our period of study, the South East Asian institutes (Kuala Lumpur and Singapore) followed a different pattern of chemotherapy administration as compared to the regimens adopted in Western countries. Although the chemotherapy regimens have now been redesigned in these institutes, we do agree that the difference in chemotherapy regimens could limit our findings.

The strength of this study lies in the fact that it is an international multicentre study. Data from the three registries

were merged, justified by the similar distribution of age and tumour characteristics. Secondly, detailed information on treatment and tumour characteristics was available.

5. Conclusion

This international multicentre study shows that lymph node status after neoadjuvant chemotherapy is informative. In the neoadjuvant setting, lymph node ratio does not seem to be superior to the ypN classification.

Conflict of interest statement

None declared.

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