Post-biopsy to Surgery Interval Tends to Increase Axillary Nodal Metastasis, Especially in Early Breast Cancer Patients

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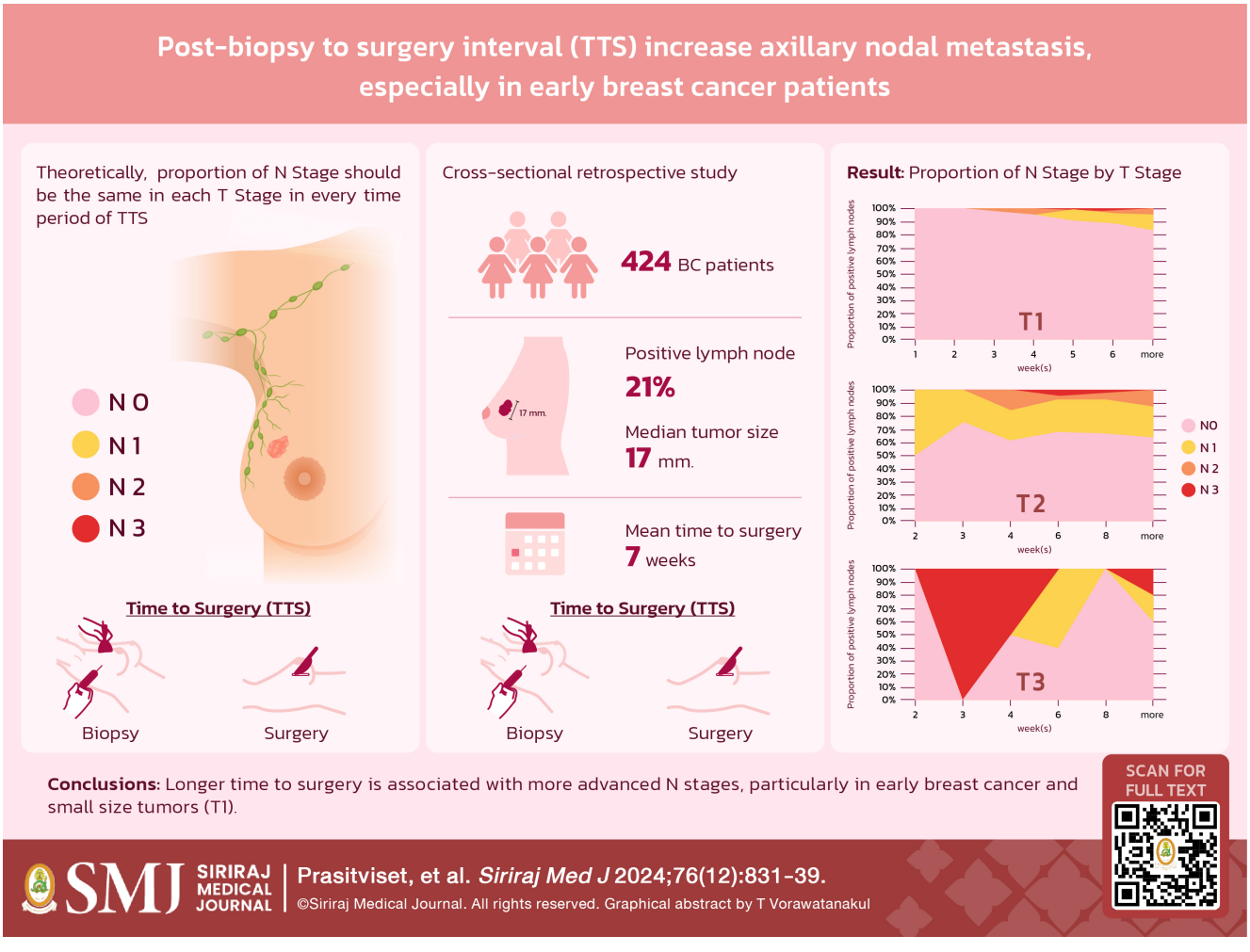

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ABSTRACT

Objective: Delays between diagnosis and breast cancer surgery may raise concerns about tumor progression. Tumors of the same size should exhibit same proportions of N staging. We aimed to evaluate the impact of time to surgery (TTS) on the proportion of metastatic axillary lymph nodes (N-Staging), controlled by tumor size.

Materials and Methods: A cross-sectional study of primary breast cancer patients treated between October 2021 - December 2022 at the Division of Head Neck and Breast Surgery, Siriraj Hospital, Thailand examined the association between lymph node staging and TTS, stratified by primary tumor size. Patients with neoadjuvant therapy, DCIS, or underwent excisional biopsy were excluded.

Results: Of 424 patients, mean age 60.95 years, had an average tumor size 17±13.38 mm, and 20.8% LNs metastasis. The mean TTS was 7 ± 3.11 weeks. The proportion of + LNs patients stratified by tumor size was 10.6% for T1, 34.56% for T2, and 43.75% for T3 lesions. There was no significant difference between TTS and the proportion of N-staging for all T2 and T3 tumors. In contrast, a significant finding was observed among T1 tumors. Axillary nodal metastasis became more advanced as TTS increased (p-value = 0.022); and increased N2 and N3 nodal staging was noted in patients with delayed surgery. No significant additional differences were found concerning breast cancer subtype, pathological grading, or lympho-vascular/perineural invasion.

Conclusion: Increasing TTS was significantly associated with more advanced N staging. This finding highlights the need for timely intervention in early breast cancer, particularly in T1 tumors.

Keywords: Breast cancer; time to surgery; lymph node staging (Siriraj Med J 2024; 76: 831-839)

INTRODUCTION

Breast cancer is the most common cancer and is the second leading cause of cancer-related deaths in women.[1] The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) stages based on tumor size (T), lymph node metastasis (N), and distant metastasis (M). Tumor size and lymph node metastasis are the most powerful factors to evaluate breast cancer prognosis.[2,3] Axillary lymph node status is also an important predictor of prognosis in primary breast cancer.[4,5] There are several other factors that can predict the occurrence of lymph node metastasis, including, tumor size, histological grading, lateral and retro-areolar tumor location, presence of lympho-vascular invasion, HER-2 expression, grade 3 tumor, elevated Ki-67 and triple-negative.[6,7]

Tumor size and nodal metastasis has been evaluated with evidence that increasing tumor size is associated with a greater number of metastatic lymph nodes.[8] Most studies demonstrated a correlation between primary tumor size and the likelihood of either metastasis to lymph nodes or distant sites with a consistent linear relationship between tumor size (range of 1.0 and 5.0 cm) and metastasis. This relationship is thought to extend in both directions, allowing for the prediction of the likelihood proportions of nodal or distant metastases in cases of very small or very large tumors.[9-11]

The delay between diagnosis and surgery (time to surgery: TTS) can cause concerns in breast cancer patients due to potential tumor progression. Several studies reported association between delays in surgical treatment are significantly associated with lower survival rates in breast cancer, particularly when delay time was extended beyond 1 - 3 months.[12,13] The overall mortality hazard ratio (HR) was 1.10 (p<0.001) for each 60-day increase in delay TTS, with significant effects observed in stages I (HR 1.16, p<0.001) and II (1.09, p<0.001), after adjusting for demographic, tumor and treatment factors. Time to surgery was statistically significant concerning OS in stage I (HR 1.13, p<0.001, 95% CI 1.08–1.18) and stage II (HR 1.06, p=0.010, 95% CI 1.01–1.11), but not in stage III (HR 1.06, p=0.17, 95% CI 0.97–1.16). A longer time to surgery is associated with lower OS and DFS especially in early breast cancer. Reduce time required for preoperative evaluation and considerations can offer benefits to improve survival.[13] Previous studies demonstrate the impact of TTS on breast cancer-specific survival but do not fully explain why more advanced disease may develop due to prolonged treatment delays either from tumor growth or significantly progress in nodal metastasis staging.

Our objective was to assess the impact of the time interval between biopsy for diagnosis and subsequent surgery on the incidence of metastatic lymph nodes, while controlling for tumor size. We hypothesized that, within tumors of identical dimensions, a shorter interval between diagnosis and surgical intervention would be associated with a lower incidence of nodal metastasis.

Furthermore, we sought to examine how tumor subtype influences the likelihood of nodal metastasis.

MATERIALS AND METHODS

This cross-sectional retrospective study was conducted with primary breast cancer patients without metastasis, treated between October 2021 and December 2022, at the Division of Head Neck and Breast Surgery, Siriraj Hospital, Thailand. Patients with neoadjuvant systemic therapy, excisional biopsy-proven cancers, male breast cancer, and carcinoma in situ with or without micro-invasion were excluded from the study

Age, tumor size, lymph node status, pathologic subtypes, histologic grading, lympho-vascular/perineural invasion, and tumor biology of patients were collected. Details of the biopsy and surgery dates (time to surgery) were also recorded.

Tumor size and degree of lymph node status were classified according to AJCC criteria (T1a = tumor size > 0.1 cm. but <= 0.5 cm, T1b = > 0.5 but <= 1.0 cm., T1c = > 1.0 but <= 2 cm., T2 = >2.0 but <= 5.0 cm, T3 = >5 cm. in greatest dimension, N0 = negative LNs, N1 = 1-3 positive LNs, N2 or 4-9 positive LNs, N3 or >= 10 positive LNs). The time from biopsy to surgery (TTS) was categorized into 7 interval period: weekly intervals during the first month, bi-weekly in the second month, and as beyond eight weeks.

The proportion of N staging: (N0, N1, N2, N3) in each TTS interval, controlled by T staging, was calculated as a prognostic indicator.

We also analyzed the influence of nodal metastasis, controlled by different tumor subtypes.

Statistical analysis

Statistical analyses were conducted using PASW statistics version 18 (Mahidol Licensed Software). Baseline characteristics and clinical data were divided by T staging, N staging, pathologic type and subtype, grading, lympho-vascular/perineural invasion. These were presented as numbers and percentages. Continuous variables, such as age, tumor size, and time to surgery after a core needle biopsy, were presented as mean ± SD or median (minimum, maximum) accordingly. Time to surgery was classified into intervals: weekly in the first month, bi-weekly in the second month, and beyond eight weeks to assess the effects of delayed treatment. The association between time to surgery and proportion of nodal status (N staging), stratified by T stage, was assessed using the Chi-square test and the Cochran–Mantel–Haenszel test was used for each tumor size sub-group. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among the 839 breast cancer patients treated during the study period, data were collected from 424 patients who met the eligibility criteria. Patient and tumor characteristics are presented in Table 1. The average age of the patients was 60.95 years (interquartile range, 25 to 97). The median tumor size was 17 ± 13.38 mm. Axillary lymph node metastasis was present in 21% of the patients (88 patients). The proportion of node-positive patients, stratified by tumor size, was 10.6% in T1 lesions, 34.56% for T2 lesions, and 43.75% in T3 lesions. The mean time to surgery after diagnosis was 7 ± 3.11 weeks, with only 12 patients (2.83%) undergoing surgery more than 12 weeks after diagnosis. Most patients had invasive ductal carcinoma (83%), with histologic grades 1, 2, and 3 accounting for 14.8%, 62%, and 23.2% respectively. Breast cancer subtypes included Luminal A (ER-positive and/or PR-positive with Ki 67 <=20%) at 28.6%, Luminal B (ER-positive and/or PR-positive with Ki 67 >20%) at 53.9%, HER-2 over-expression at 6.3%, and Triple negative at 11.3%. Lympho-vascular or perineural invasion was positive in only 18.7% of cases.

Almost half of the T3 tumors had lymph node involvement at the time of surgery, with N+ (nodal metastasis) present at the earliest time to surgery. Although more aggressive or advanced stages of N status (N2 and N3) were observed in the T3 group with increasing time to surgery, no significant difference was found between the time to surgery and the proportion of axillary nodal metastasis (p-value = 0.563) (Table 2 and Fig 1).

In patients with T2 tumors, lymph node involvement of at least N1 was observed in every patient group regardless of the time to surgery following diagnostic biopsy. However, a trend toward more aggressive nodal involvement was noted with increasing time to surgery: N2 involvement was seen after 3 weeks, and N3 after 4 weeks post-diagnosis. Despite these observations, there was no significant difference between the time to surgery and the proportion of axillary nodal metastasis (p-value = 0.562) as shown in Table 2. There was a trend toward conversion from N1 to N2 disease if delayed surgery was delayed beyond 4 weeks, with the proportion of N2 lymph node involvement increasing from 5% to 13.5% if the delay extended from 4 weeks to more than 8 weeks (Fig 1).

A significant finding was observed among patients with T1 tumors, where lymph node involvement was first detected in the 4th week after diagnosis, indicating more than 3 weeks of waiting time for surgery. Additionally, a higher proportion of node-positive patients was correlated with increased time to surgery. This difference was statistically

TABLE 1. Baseline characteristics of 424 breast cancer patients and tumor histologic reports.

Characteristic	Number (%)	Median ± SD
Age (years)		60.95 ± 12.31 (25-97)
Tumor size (mm.)		17 ± 13.38 (1-85)
T Staging		
T1 (<=2 cm.)	246 (58.02%)	
T2 (2.1-5 cm.)	162 (38.21%)	
T3 (>5 cm.)	16 (3.77%)	
Number of positive lymph nodes		0.68 (0-19)
N Staging		
N0 (negative node)	336 (79.2%)	
N1 (positive 1-3 nodes)	64 (15.1%)	
N2 (positive 4-9 nodes)	18 (4.2%)	
N3 (positive >=10 nodes)	6 (1.4%)	
Pathologic type		
Invasive ductal carcinoma	352 (83%)	
Invasive lobular carcinoma	32 (7.6%)	
Invasive mammary carcinoma	12 (2.8%)	
Favorable subtype *	28 (6.6%)	
Histologic grading		
1	62 (14.8%)	
2	259 (62%)	
3	97 (23.2%)	
Subtype		
Luminal A	119 (28.6%)	
Luminal B, HER2 negative	192 (46.2%)	
Luminal B, HER2 positive	32 (7.7%)	
HER2 over-expression	26 (6.3%)	
Triple negative	47 (11.3%)	
Lympho-vascular invasion/ Perineural invasion		
Negative	335 (81.3%)	
Positive	77 (18.7%)	
Time to surgery after core needle biopsy (weeks)		7 ± 3.11 (1-34)
Time to surgery after core needle biopsy by weeks		
1	1 (0.2%)	
2	17 (4%)	
3	24 (5.7%)	
4	39 (9.2%)	
6	103 (25.5%)	
8	109 (25.7%)	
More than 8 weeks	131 (54.1%)	

*favorable subtype: tubular, mucinous, cribriform, encapsulated or solid papillary carcinoma, adenoid cystic and other salivary carcinomas, secretory carcinoma, rare low-grade forms of metaplastic carcinoma

TABLE 2. Associations between time to surgery and nodal status by tumor size.

Tumor size N=424	Time to surgery within … week(s)	N0	N1	N2	N3	p-Value
T1	W1 (N=1)	1 (100%)	0	0	0	0.022 *
N=246	W2 (N=12)	12 (100%)	0	0	0	
(58.02%)	W3 (N=11)	11 (100%)	0	0	0	
	W4 (N=24)	23 (95.83%)	0	1 (4.17%)	0	
	W6 (N=59)	54 (91.53%)	5 (8.47%)	0	0	
	W8 (N=65)	58 (89.23%)	5 (7.69%)	1 (1.54%)	1 (1.54%)	
	More than 8 (N=74)	62 (83.78%)	9 (12.16%)	3 (4.05%)	0	
	Total	221(89.84%)	19 (7.72%)	5 (2.03%)	1 (0.41%)	
T2	W1 (N=0)	-	-	-	-	0.562
N=162	W2 (N=4)	2 (50%)	2 (50%)	0	0	
(38.21%)	W3 (N=12)	9 (75%)	3 (25%)	0	0	
	W4 (N=13)	8 (61.54%)	3 (23.08%)	2 (15.38%)	0	
	W6 (N=37)	26 (66.67%)	10 (25.64%)	2 (5.13%)	1 (2.56%)	
	W8 (N=42)	28 (66.67%)	11 (26.19%)	2 (4.76%)	1 (2.38%)	
	More than 8 (N=52)	33 (63.46%)	12 (23.08%)	7 (13.46%)	0	
	Total	106 (65.43%)	41 (25.31%)	12 (7.41%)	3 (1.85%)	
T3	W1 (N=0)	-	-	-	-	0.563
N=16	W2 (N=2)	1 (50%)	0	0	1 (50%)	
(3.77%)	W3 (N=1)	0	0	0	1 (100%)	
	W4 (N=1)	1 (100%)	0	0	0	
	W6 (N=5)	2 (40%)	3 (60%)	0	0	
	W8 (N=2)	2 (100%)	0	0	0	
	More than 8 (N=5)	3 (60%)	1 (20%)	0	1 (20%)	
	Total	9 (56.25%)	4 (25%)	0	3 (18.75%)	

* Statistically significant P <0.05

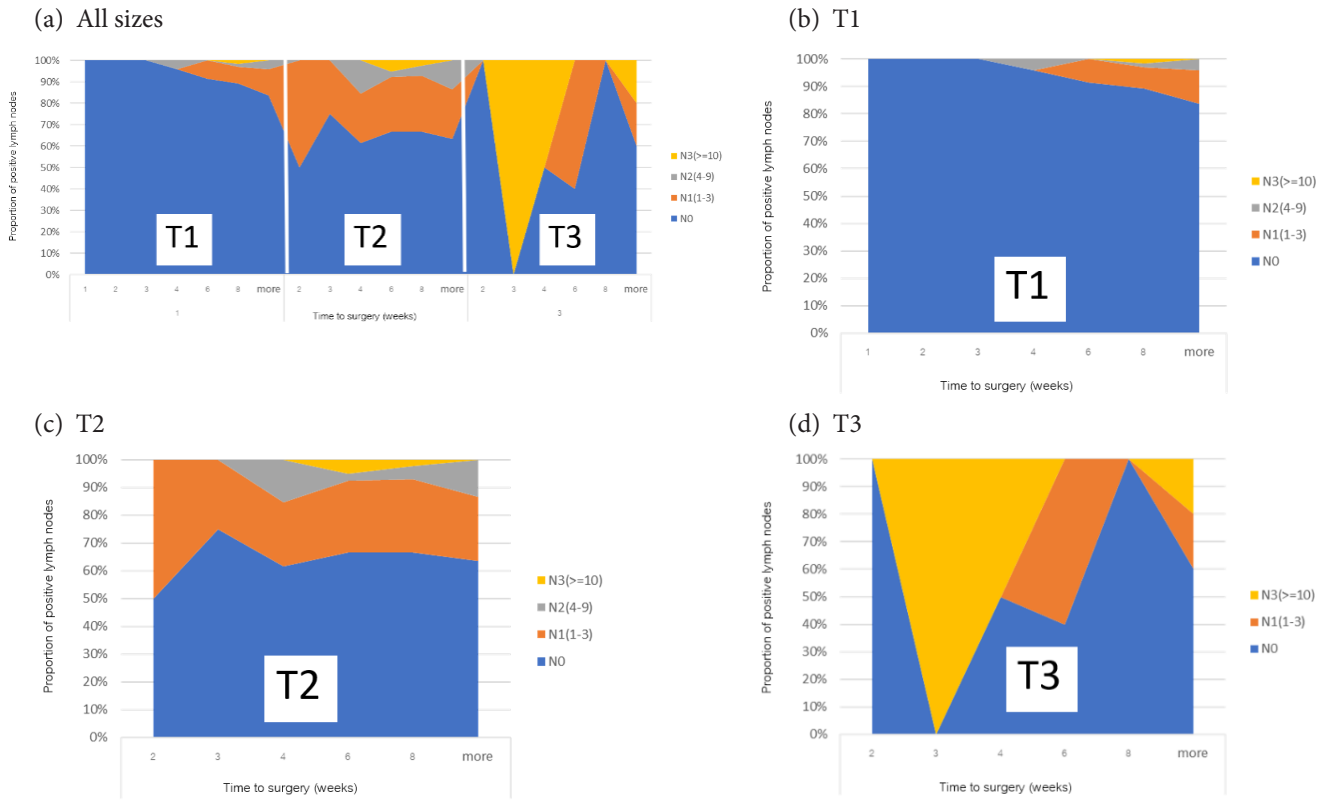
significant, with a p-value of 0.022, highlighting the relationship between the time to surgery and axillary nodal metastasis (N staging) in this group (Table 2).

Subgroup analysis of T1 tumors revealed distinct patterns regarding tumor size and the onset of lymph node involvement. Specifically, in patients with tumor sizes ranging from 1-2 cm (T1c), lymph node involvement was observed after the 3rd week post-diagnosis. In contrast, patients with tumors equal to or less than 1 cm exhibited no lymph node involvement until the 6th week (Table 3 and Fig 2 a, b, and c).

The findings regarding T1 tumors are particularly notable. Within less than three weeks after diagnosis, 89.84% of these cases (221 out of 246 patients) showed no lymph node metastasis, indicating that most patients with T1 tumors do not exhibit lymph node involvement early on.

There were no significant differences in lymph node metastasis based on breast cancer subtype, pathological grading, or lympho-vascular/perineural invasion (p-value = 0.147).

Among different breast cancer subtypes, Luminal A, Luminal B HER2 negative, Luminal B HER2 positive, HER-2 over-expression, and Triple negative, there was no significant difference correlation between the time to surgery and the proportion of axillary nodal metastasis. The p-values for these subtypes were 0.862, 0.253, 0.550, 0.357 and 0.941, respectively (Table 4).

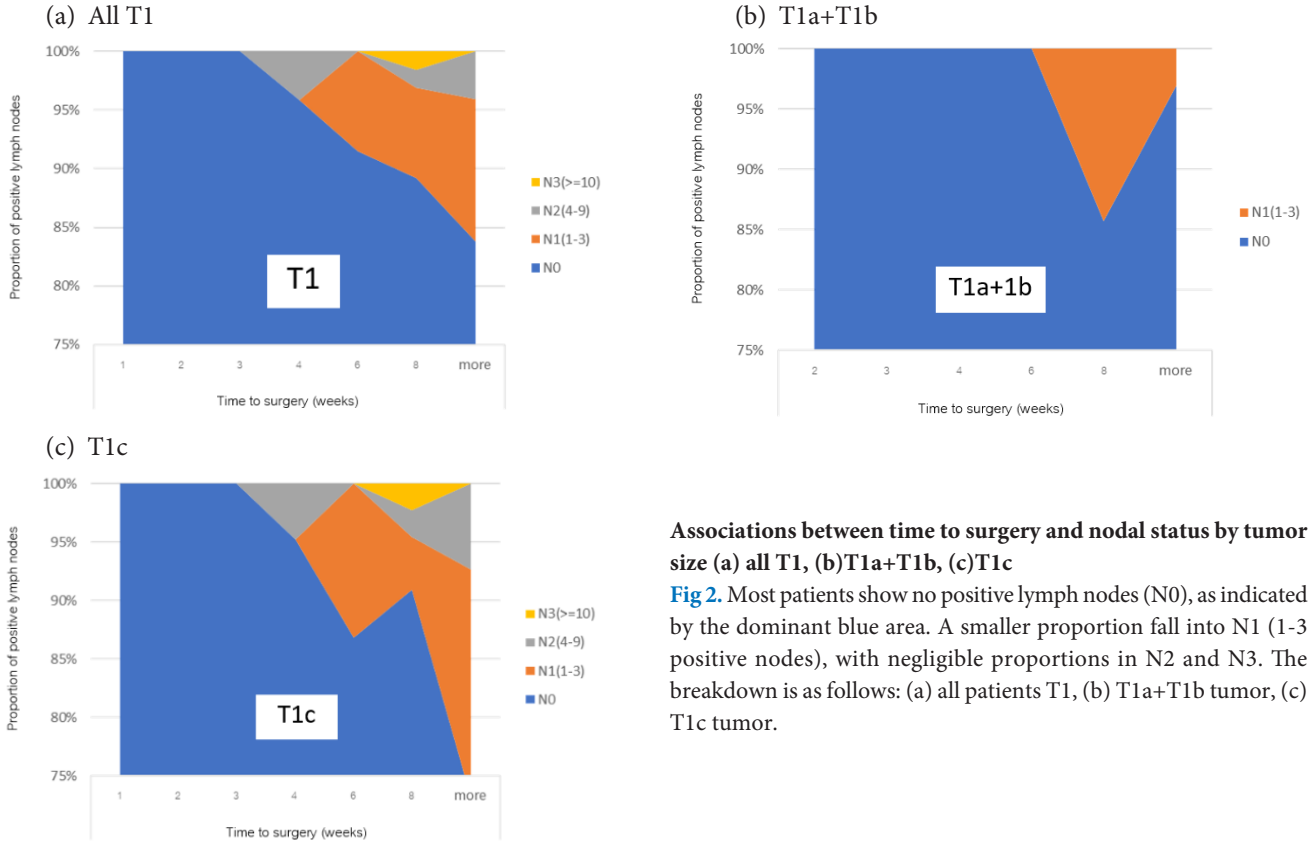


Associations between time to surgery and nodal status by tumor size (a) all sizes, (b) T1, (c) T2, (d) T3

Fig 1. Proportion of positive lymph nodes over time until surgery, categorized by the number of positive lymph nodes (N0, N1, N2, N3). The graph shows that as the time to surgery increases, the likelihood of having a greater number of positive lymph nodes also rises. Initially, most patients have no positive lymph nodes (N0), but with delays in surgery, es, there's a shift towards higher categories (N1, N2, N3). This trend suggests that earlier surgical intervention might help reduce the extent of lymph node involvement in (a) all patients, (b) those with T1 tumor, (c) those with T2 tumor, (d) and those with T3 tumor.

TABLE 3. Associations between time to surgery and nodal status by tumor size T1 only, T1a+T1b, T1c.

Tumor size (T1 only) N=246	Time to surgery within … week(s)	N0	N1	N2	N3
T1a+T1b	W1 (N=0)	-	-	-	-
N=85	W2 (N=2)	2 (100%)	0	0	0
(34.55%)	W3 (N=5)	5 (100%)	0	0	0
	W4 (N=3)	3 (100%)	0	0	0
	W6 (N=21)	21 (100%)	0	0	0
	W8 (N=21)	18 (85.71%)	3 (14.29%)	0	0
	More (N=33)	32 (96.97%)	1 (3.03%)	0	0
	Total	81 (95.29%)	4 (4.71%)	0	0
T1c	W1 (N=1)	1 (100%)	0	0	0
N=161	W2 (N=10)	10 (100%)	0	0	0
(65.45%)	W3 (N=6)	6 (100%)	0	0	0
	W4 (N=21)	20 (95.24%)	0	1 (4.76%)	0
	W6 (N=38)	33 (86.84%)	5 (13.16%)	0	0
	W8 (N=44)	40 (90.91%)	2 (4.55%)	1 (2.27%)	1 (2.27%)
	More (N=41)	30 (73.17%)	8 (19.51%)	3 (7.32%)	0
	Total	140 (86.96%)	15 (9.32%)	5 (3.11%)	1 (0.62%)



Associations between time to surgery and nodal status by tumor size (a) all T1, (b)T1a+T1b, (c)T1c

Fig 2. Most patients show no positive lymph nodes (N0), as indicated by the dominant blue area. A smaller proportion fall into N1 (1-3 positive nodes), with negligible proportions in N2 and N3. The breakdown is as follows: (a) all patients T1, (b) T1a+T1b tumor, (c) T1c tumor.

DISCUSSION

In this study, 79% of the patient population had early-stage breast cancer, with 58% presenting with T1 lesions and no LN metastasis. The proportion of LN metastasis was 10.16% for T1 lesions, 34.56% for T2 lesions, and 43.75% for T3 lesions. The LN involvement rates for T1 lesions are consistent with other studies, which report 10-27% nodal metastasis. However, our findings for T2 and T3 lesions differ from other studies, which report 44-62% and 68-78% LN metastasis, respectively.[14]

We hypothesized that tumors of the same T stage would have a consistent proportion of LN metastasis regardless of other factors. Our study aimed to evaluate the impact of the interval between biopsy for diagnosis and subsequent surgery (time to surgery, TTS) on the number of metastatic lymph nodes (N staging), stratified by tumor size. We anticipated that shorter intervals between biopsy and surgery would be associated with less aggressive nodal metastasis. Our findings indicate that, for T2 and T3 tumors, there was no statistically significant difference in nodal metastasis related to the time to surgery. However, there was a trend toward increased axillary lymph node metastasis with delayed surgery. Specifically, T2 lesions showed more advanced N2 and N3 after 3 weeks, while T3 lesions showed more advanced N3 metastasis after 2 weeks, with p-values of 0.562 and 0.563, respectively.

Our study revealed that varying times to surgery significantly affect the proportion of axillary nodal metastasis in small tumor (T1), with a p-value of 0.022. Patients with T1 lesions are more likely to have positive lymph nodes after a waiting period of 3 weeks, with this trend being more pronounced in T1c lesions, as reported in Table 3. This finding is novel and has not been reported in other studies. The results underscore the impact of time to surgery on lymph node involvement, particularly for T1 tumors. Smaller tumors tend to show lymph node metastasis later compared to larger tumors, indicating that small tumors are less likely to have lymph node metastasis early on compared to bigger tumors. This observation helps explain why delays in surgery can adversely affect overall survival, as prolonged waiting times lead to more advanced disease due to increased N staging over time. We recommend the threshold or safety period for waiting list before surgery in T1 patients as not more than 3 weeks.

We acknowledge that histologic subtype, pathological grading, and lympho-vascular/perineural invasion did not show significant differences in the aggressiveness of nodal metastasis. This aligns with some research suggesting that the effect of these factors on metastatic potential and survival is independent of the intrinsic breast cancer subtype.[15]

TABLE 4. Associations between time to surgery and nodal status by breast cancer subtype.

Subtypes of breast cancer	Time to surgery within … week(s)	N0	N1	N2	N3	p-value
Luminal A	W1 (N=1)	1 (100%)	0	0	0	0.862
N=119	W2 (N=4)	4 (100%)	0	0	0	
(28.06%)	W3 (N=8)	8 (100%)	0	0	0	
	W4 (N=15)	12 (80%)	2 (13.30%)	1 (6.70%)	0	
	W6 (N=28)	25 (89.30%)	2 (7.10%)	0	1 (3.60%)	
	W8 (N=26)	24 (92.30%)	2 (7.70%)	0	0	
	More than 8 (N=37)	32 (86.50%)	4 (10.80%)	1 (2.70%)	0	
	Total	106 (89.10%)	10 (8.40%)	2 (1.70%)	1(0.80%)	
Luminal B,	W1 (N=0)	-	-	-	-	0.253
HER2 negative	W2 (N=10)	8 (80%)	2 (20%)	0	0	
N=192	W3 (N=12)	8 (66.70%)	3 (25%)	0	1 (8.30%)	
(45.28%)	W4 (N=10)	8 (80%)	0	2 (20%)	0	
	W6 (N=43)	31 (72.10%)	10 (23.30%)	2 (4.70%)	0	
	W8 (N=60)	44 (73.30%)	13 (21.70%)	3 (5%)	0	
	More than 8 (N=57)	33 (63.20%)	14 (24.60%)	6 (10.50%)	1 (1.80%)	
	Total	135 (70.30%)	42 (21.90%)	13 (6.80%)	2 (1%)	
Luminal B,	W1 (N=0)	-	-	-	-	0.550
HER2 positive	W2 (N=2)	-	-	-	-	
N=32	W3 (N=1)	-	-	-	-	
(7.55%)	W4 (N=4)	3 (75%)	1 (25%)	0	0	
	W6 (N=14)	11 (78.6%)	3 (21.4%)	0	0	
	W8 (N=4)	4 (100%)	0	0	0	
	More than 8 (N=10)	7 (70%)	2 (20%)	1 (10%)	0	
	Total	25 (78.10%)	6 (18.8%)	1 (3.10%)	0	
HER2	W1 (N=0)	-	-	-	-	0.357
Overexpression	W2 (N=2)	2 (100%)	0	0	0	
N=26	W3 (N=1)	1 (100%)	0	0	0	
(6.13%)	W4 (N=1)	1 (100%)	0	0	0	
	W6 (N=6)	4 (66.70%)	2 (33.30%)	0	0	
	W8 (N=4)	2 (50%)	0	0	2 (50%)	
	More than 8 (N=8)	5 (62.50%)	1 (12.50%)	2 (25%)	0	
	Total	18 (69.20%)	3 (11.50%)	2 (7.70%)	3 (11.50%)	
Triple negative	W1 (N=0)	-	-	-	-	0.941
N=47	W2 (N=1)	1 (100%)	0	0	0	
(11.08%)	W3 (N=3)	3 (100%)	0	0	0	
	W4 (N=4)	4 (100%)	0	0	0	
	W6 (N=10)	9 (90%)	1 (10%)	0	0	
	W8 (N=12)	11 (91.70%)	1 (8.30)	0	0	
	More than 8 (N=5)	16 (94.10%)	1 (5.90%)	0	0	
	Total	44 (93.60%)	3 (6.40%)	0	0	

Consistent with other studies, the SMDB cohort of 94,544 patients showed that each increase in delay interval was associated with lower overall survival (hazard ratio [HR] 1.09, $p<0.001$), particularly in stage I (HR 1.13, $p<0.001$) and stage II (HR 1.06, $p=0.010$) patients. Breast cancer-specific mortality also increased with each 60-day delay (sub-hazard ratio 1.26, $p= 0.03$). The NCDB study, which included 115,790 patients >=18 years old, diagnosed between 2003 and 2005, found a similar trend of overall mortality for each additional interval, significant in stages I (HR 1.16, $p<0.001$) and II (1.09, $p<0.001$), adjusting for demographic, tumor and treatment factors. The overall mortality increase regardless of stages and causes was 9% (HR 1.09, $p<0.001$) for each preoperative interval. Time to surgery (TTS) was statistically significant in relation to OS in stage I (HR 1.13, $p<0.001$) and stage II (HR 1.06, $p=0.010$, 95% CI 1.01–1.11). Longer TTS is associated with lower overall and disease-specific survival, and reducing the delay is linked to benefits comparable to some standard therapies.[13] Our study provides a more precise evaluation of TTS effects on increasing N-stage, which could inform guidelines for recommending expedited treatment for breast cancer especially in early breast cancer.

CONCLUSION

In summary, our results suggest that longer time to surgery is associated with nodal negative/positive status especially in early breast cancer and small size tumors (T1). Performing surgery sooner may improve prognosis, highlighting the importance of timely intervention.

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Conflict of Interest

At the time of submission for IRB approval, the title of research was “The association between post-biopsy interval and axillary nodal metastasis with the same tumor size in breast cancer” and the title has been changed to “Post-biopsy to surgery interval tends to increase axillary nodal metastasis, especially in early breast cancer patients” at the time of submission.

Author Contributions

Conceptualization and methodology, Ph.P., P.P. and A.R.; Investigation, Ph.P. and A.R.; Formal analysis, Ph.P. and A.R.; Visualization and writing – original darft, Ph.P.; Writing – review and editing, Ph.P., P.P. and A.R.; Supervision, A.R.. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

No artificial intelligence used

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