The Role of Axillary Lymph Node Dissection in Tubular Carcinoma of the Breast: A Population Database Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to investigate the role of axillary lymph node dissection on the outcome of patients with tubular carcinoma of the breast.

Material/Methods: Patients diagnosed with tubular carcinoma of the breast between 2000–2013 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Statistical analysis of the data was undertaken, including analysis of breast cancer-specific survival (BCSS).

Results: Of the 5,645 patients identified on the SEER database with tubular carcinoma of the breast, 5,032 (89.4%) patients had undergone axillary lymph node dissection, with significantly increased rates after 2002 compared with rates between 2000–2001 (p <0.001), which stabilized between 2002–2013 (p=0.330). Axillary lymph node metastases were present in 6.1% of all patients and in 5.3% of patients with a tumor size ≤2 cm. Lymph node-positive disease was associated with patient age ≤65 years, intermediate-grade or high-grade tumors, and tumor size >2.0 cm. Axillary lymph node dissection was an independent prognostic indicator. The 10-year BCSS was 97.3% and 96.6% in patients with and without axillary lymph node dissection, respectively (p=0.002). The number of removed lymph nodes was not related to breast cancer-specific survival.

Conclusions: In patients with tubular carcinoma of the breast, lymph node status was not associated with significant breast cancer-specific survival. However, axillary lymph node dissection may still be considered for patients with for tubular carcinoma of the breast even in patients with a small tumor size.

MeSH Keywords: Breast Neoplasms • Lymph Node Excision • Risk Factors • Survival Analysis

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Background

Tubular carcinoma is a rare subtype of breast cancer that is associated with an excellent prognosis, and most patients are diagnosed with small tumor size with a low incidence of lymph node involvement and recurrence [1–3]. Tubular carcinoma of the breast is characterized histologically by well-differentiated carcinoma cells that form small glandular structures or well-formed tubules that resemble ductules in non-neoplastic breast tissue [4]. The incidence of detection and diagnosis of tubular carcinoma of the breast has increased in the era of breast screening programs, accounting for approximately 1–5% of all breast cancers [1,2,5,6].

Sentinel lymph node biopsy has been confirmed to be an effective method of axillary lymph node staging and is part of the optimal management of patients with low-risk breast cancers, including tubular carcinoma [7]. However, controversy remains regarding the frequency of axillary metastases and the role of examination of the axillary tissues in patients with tubular carcinoma of the breast. Several studies have indicated that axillary lymph node dissection may be unnecessary in patients with tubular carcinoma with a small tumor size [8–10]. However, there remains no consensus on the role of axillary lymph node dissection in patients with tubular carcinoma. Also, although studies on invasive ductal carcinomas have confirmed a significant association between the size of the primary tumor and the probability of lymph node metastasis [11,12], the association between primary tumor size and the risk of lymph node metastasis in tubular carcinoma of the breast remains controversial [1,8,13–15].

Therefore, the aim of this study was to investigate the role of axillary lymph node dissection on the outcome of patients with tubular carcinoma of the breast using a patient population from the from the Surveillance, Epidemiology, and End Results (SEER) database.

Material and Methods

Patient characteristics from the patient database

Patients with tubular carcinoma of the breast who were diagnosed between 2000–2013 from the current Surveillance, Epidemiology, and End Results database (SEER) program were included in the study. The SEER database is maintained by the National Cancer Institute (NCI), which includes de-identified information regarding patient demographics, tumor characteristics, and survival outcomes for approximately 28% of the US population [16]. This study included women with non-metastatic, early-stage tubular carcinoma of the breast treated with either lumpectomy or mastectomy. The SEER records including patient demographics, tumor characteristics, treatment data, and survival status. Because the SEER program included only de-identified patient information, this study was exempt from evaluation by the institutional review board or the requirement for patient consents.

Statistical analysis

Binary logistic regression was performed to assess the predictive indicators for axillary lymph node dissection. The Kaplan-Meier method estimated breast cancer-specific survival (BCSS) curves and overall survival (OS) rates and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model with the backward version of the Wald parametric statistical method. All statistical tests were performed using SPSS, version 22 (IBM Corporation, Armonk, NY, USA). Tests were two-sided, and a p-value <0.05 was considered to be statistically significant.

Results

Patient characteristics

There were 5,645 patients with tubular breast carcinoma identified from the Surveillance, Epidemiology, and End Results database (SEER) database who met the study inclusion criteria. Figure 1 shows the patient selection flowchart for the study. The median patient age was 65 years, and 85.5% (n=4,829) of the patients were non-Hispanic and Caucasian. Patients with tubular carcinoma of the breast had favorable clinico-pathologic characteristic including well-differentiated histology (low grade) (n=5,168, 91.6%), small tumor size ≤2 cm (n=5,411, 95.9%), lymph node negative disease (n=5300, 93.9%), estrogen receptor (ER)-positive tumor status (n=5,534, 98.0%), progesterone receptor (PR)-positive tumor status (n=4,767, 84.4%), and human epidermal growth factor receptor 2 (HER2)-negative tumor status (n=1050, 98.2%). Also, a total of 4,342 (76.9%) and 3,364 (59.6%) patients received breast-conserving surgery (BCS) and postoperative radiotherapy, respectively. The patient characteristics are shown in Table 1.

The temporal trends of axillary lymph node dissection

A total of 5,032 (89.4%) patients underwent axillary lymph node dissection. The median number of excised lymph nodes was 3 (range, 1–45), and 83.0% (n=4175) of patients had less than 10 excised lymph nodes. Figure 2 illustrates the temporal trends for axillary lymph node dissection between 2000–2013. Notably, the use of axillary lymph node dissection significantly increased after 2002 (p<0.001) compared with the years between 2000–2001, which was then stable from 2002–2013, with no significant change over time (p=0.330). In patients with
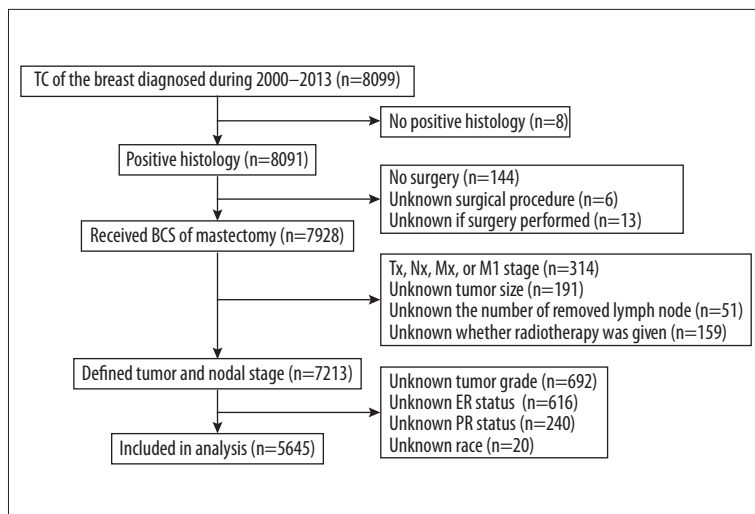
Figure 1. Flowchart of the patient selection used in the study.

Table 1. The baseline characteristics of 5645 patients with tubular carcinomas of the breast.

Variables	n (%)		Variables	n (%)	
Age (years)			ER		
<65	3529	(62.5)	Negative	111	(2.0)
≥65	2116	(37.5)	Positive	5534	(98.0)
Race			PR		
Non-Hispanic White	4829	(85.5)	Negative	878	(15.6)
Non-Hispanic Black	243	(4.3)	Positive	4767	(84.4)
Hispanic	315	(5.6)	HER2 (n=1069)		
Other	258	(4.6)	Negative	1050	(98.2)
Grade			Positive	19	(1.8)
Well differentiated	5168	(91.6)	Surgical procedures		
Moderately differentiated	424	(7.5)	Breast-conserving surgery	4342	(76.9)
Poorly/undifferentiated	53	(0.9)	Mastectomy	1303	(23.1)
Tumor size (cm)			Radiotherapy		
≤2	5411	(95.9)	No	2281	(40.4)
>2–≤5	204	(3.6)	Yes	3364	(59.6)
>5	30	(0.5)	Axillary intervention		
Tumor stage (n=5367)			No	613	(10.9)
T1a	1413	(26.3)	Yes	5032	(89.1)
T1b	2510	(46.8)	Number of removed lymph nodes (n=5032) (n)		
T1c	1444	(26.9)			
Nodal status			<10	4175	(83.0)
Negative	5300	(93.9)	≥10	857	(17.0)
Positive	345	(6.1)			

ER – estrogen receptor; HER2 – human epidermal growth receptor 2; PR – progesterone receptor; T – tumor.
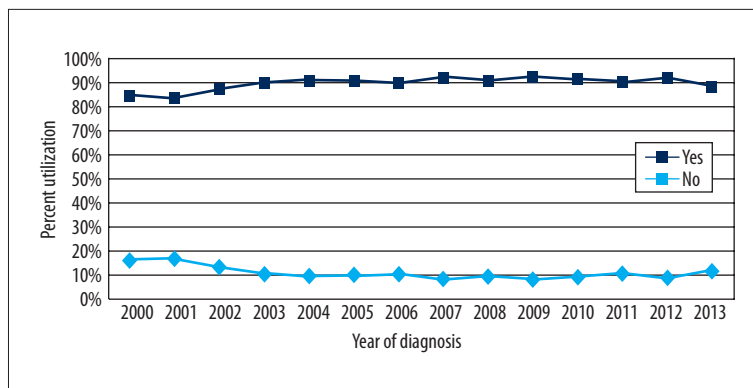
Figure 2. Comparison between patients with axillary lymph node clearance and without axillary lymph node clearance during the study period.
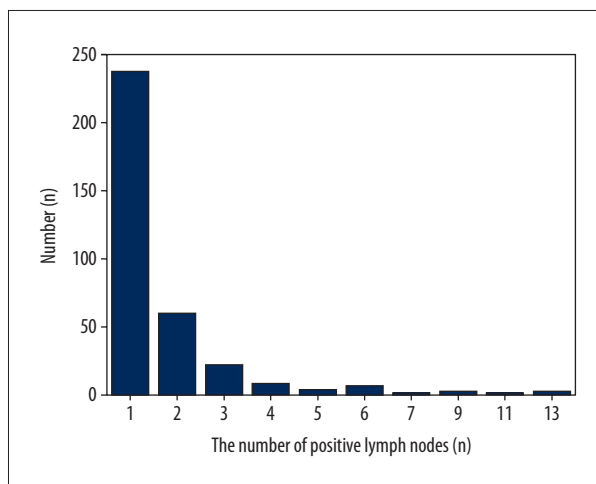

Figure 3. Distribution of the number of positive axillary lymph nodes.

node-positive disease, the median number of positive lymph nodes was 1 (range, 1–13). The distribution of the number of positive lymph nodes is shown in Figure 3.

Predictive factors for lymph node metastasis in tubular carcinoma of the breast

Multivariate logistic regression analysis was used to determine the predictive factors independently associated with lymph node-positive disease (Table 2). The results indicated that there was an increasing probability of lymph node metastasis in patients aged ≤65 years, patients with intermediate-grade and high-grade tumors, and tumor size >2 cm. In the entire cohort, 6.1% (n=345) of patients were lymph node-positive, and the distribution of lymph node-positive disease was 82.0% (n=283), 17.4% (n=60), and 0.6% (n=2) of the 345 patients with tumor size ≤2 cm, >2 cm, ≤5 cm, and >5 cm, respectively (p<0.001).

Further subgroup analysis in patients with stage T1a tubular carcinoma (tumor size >0.1 cm and ≤0.5 cm), stage T1b tubular carcinoma (tumor size >0.5 cm and ≤1.0 cm), and stage T1c

tubular carcinoma (tumor size >1.0 cm and v2.0 cm) (n=5367) was performed (Table 2). The results showed that patients aged ≤65 years, with intermediate-grade to high-grade tumors, and tumor size >0.5 cm, were associated with an increased risk of lymph node metastasis. In this subgroup, 5.3% (n=283) of patients had lymph node-positive disease, and the distribution of lymph node-positive disease was 11.7% (n=33), 38.5% (n=109), and 49.8% (n=141) in the 283 patients with stage T1a, T1b, and T1c tubular carcinoma, respectively (p<0.001).

The effect of axillary lymph node dissection on breast cancer-specific survival (BCSS)

The demographic, clinicopathologic, and treatment variables underwent multivariate analysis to evaluate the effect of axillary lymph node dissection on breast cancer-specific survival (BCSS) (Table 3). The results showed that the absence of axillary lymph node dissection was independently associated with poor BCSS. The 10-year BCSS was 97.3% and 96.6% in patients with and without axillary lymph node dissection, respectively (p=0.002) (Figure 4). Also, older age (≥65 years), non-Caucasian race, a previous mastectomy, and no history of postoperative radiotherapy were also the prognostic factors independently associated with a poor BCSS. Multivariate analysis of patients undergoing axillary lymph node dissection showed that the number of removed lymph nodes was not associated with BCSS (Table 3).

Discussion

Approximately 30% of patients with invasive ductal carcinoma (IDC) have lymph node metastases [12], while only between 6.0–16.0% of patients with tubular carcinoma present with lymph node-positive disease [1,2,5,15], which was similar to the findings in this our population database study. However, it was not possible to obtain data on lymph node morphology from the Surveillance, Epidemiology, and End Results database (SEER) database. However, previous studies have indicated that the rate of lymph node macrometastasis, micrometastasis,

Table 2. Multivariable logistic regression analysis for factors predictive of nodal-positive disease.

Variables	Entire cohort			T1 stage		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (years)						
<65	1			1		
≥65	0.737	0.580–0.936	0.012	0.677	0.520–0.881	0.004
Race						
Non-Hispanic White	1			1		
Non-Hispanic Black	1.382	0.858–2.226	0.183	1.157	0.669–2.001	0.602
Hispanic	1.422	0.936–2.160	0.099	1.348	0.842–2.159	0.213
Other	0.928	0.544–1.581	0.782	1.014	0.555–1.853	0.964
Grade						
Well differentiated	1			1		
Moderately, poorly/undifferentiated	1.534	1.098–2.144	0.012	1.525	1.057–2.200	0.024
Tumor size (cm)						
≤2	1			–		
>2	6.274	4.571–8.613	<0.001	–	–	–
ER						
Negative	1			1		
Positive	1.023	0.453–2.312	0.957	0.803	0.335–1.925	0.623
PR						
Negative	1			1		
Positive	1.256	0.892–1.768	0.192	1.223	0.846–1.767	0.285
Tumor stage						
T1a	–			1		
T1b	–	–	–	1.909	1.285–2.834	0.001
T1c	–	–	–	4.437	3.012–6.536	<0.001

CI – confidence interval; ER – estrogen receptor; OR – odds ratio; PR – progesterone receptor; T – tumor.

and single-cell metastasis was 26.1–28.6%, 42.9–65.2%%, and 8.7–28.6%, respectively, in patients with lymph node-positive disease [17,18]. Although lymph node status was not a prognostic factor for patient survival in tubular carcinoma in this study, patients with lymph node macrometastasis might be more prone to distant tumor dissemination [15]. The current National Comprehensive Cancer Network (NCCN) guidelines for the treatment of tubular carcinoma of the breast includes the evaluation of the patient's axillary lymph node status, with the requirement that it is necessary to assess the patient's axillary lymph node status to guide the choice of adjuvant therapy [19].

Previously published studies have shown that In patients with tubular carcinoma of the breast, approximately 11.7–17.4% of patients had no axillary lymph node dissection [14,20].

In the present study, 10.6% of patients were omitted from axillary lymph node dissection, and there was a significant increase in axillary lymph node dissection from 2002 onwards. Three previous randomized clinical trials have been reported that enrolled patients between 1998–2004 to compare the regional tumor control, patient survival and treatment side-effects between the time of sentinel lymph node biopsy and axillary lymph node dissection [21–23]. Therefore, a possible explanation for this trend may be related to the increased use of sentinel lymph node biopsy in early-stage breast cancer. Although the SEER data did not record the details of the axillary lymph node dissection of patients, the data from the present study support the hypothesis that most patients who underwent sentinel lymph node biopsy had a median number of three removed axillary lymph nodes.

Table 3. Multivariate Cox regression analysis of prognostic factors of patients with tubular carcinomas of the breast.

Variables	Entire cohort			With axillary intervention		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (years)						
<65	1			1		
≥65	2.409	1.498–3.874	<0.001	2.597	1.539–4.385	<0.001
Race						
Non-Hispanic White	1			1		
Non-Hispanic Black	3.572	1.761–7.244	<0.001	3.291	1.397–7.749	0.006
Hispanic	0.951	0.298–3.042	0.933	0.844	0.204–3.484	0.814
Other	1.323	0.478–3.656	0.590	1.573	0.565–4.379	0.386
Grade						
Well differentiated	1			1		
Moderately, poorly/undifferentiated	0.745	0.318–1.743	0.497	0.930	0.392–2.206	0.869
Tumor size (cm)						
≤2	1			1		
>2	1.290	0.494–3.369	0.603	1.421	0.536–3.768	0.480
Nodal status						
Negative	1			1		
Positive	1.475	0.672–3.236	0.332	1.561	0.694–3.512	0.282
ER						
Negative	1			1		
Positive	0.501	0.172–1.458	0.205	0.806	0.186–3.503	0.774
PR						
Negative	1			1		
Positive	0.837	0.467–1.499	0.550	0.909	0.461–1.794	0.783
Surgical procedures						
BCS	1			1		
Mastectomy	1.866	1.031–3.378	0.039	1.572	0.780–3.170	0.206
Radiotherapy						
No	1			1		
Yes	0.528	0.288–0.968	0.030	0.417	0.246–0.706	0.001
Axillary intervention						
No	1			–		
Yes	0.535	0.297–0.964	0.037	–	–	–
Number of removed lymph nodes (n)						
<10	–			1		
≥10	–	–	–	0.803	0.425–1.517	0.500

BCS – breast-conserving surgery; CI – confidence interval; ER – estrogen receptor; HR – hazard ratio; PR – progesterone receptor.
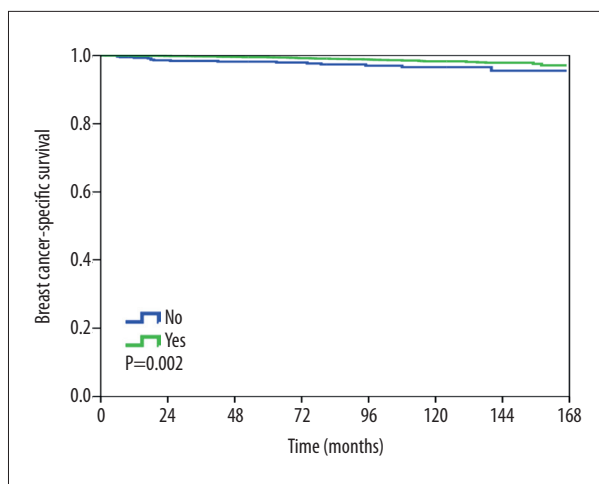
Figure 4. The impact of axillary lymph node clearance on breast cancer-specific patient survival.

However, the effect of omitting axillary lymph node dissection on the survival of patients remains controversial. The results of the univariate analysis in the study by Hansen et al. indicated that patients undergoing axillary lymph node dissection had a significantly improved relapse-free survival (RFS) compared with patients who did not undergo axillary lymph node dissection (5-year RFS 95% *vs.* 99–100%; p=0.04). However, these results were not confirmed by multivariate analysis [14]. Nodal involvement in tubular carcinoma does not seem to provide prognostic information, and lymph nodes are infrequently involved in tubular carcinoma of the breast. However, in the present study, multivariate analysis indicated that patients undergoing axillary lymph node dissection had and improved breast cancer-specific survival (BCSS), which suggests that axillary lymph node dissection may reduce the risk of residual lymph node lesions and potentially lead to improved patient survival. However, the findings of the present study did not confirm that an increased number of excised axillary lymph nodes was related to improved patient prognosis, which was similar to the findings of Hansen et al. [14]. The results of this study might be due to the limited number of positive lymph nodes in patients with lymph node-positive disease. Therefore, it is possible that extensive axillary lymph node dissection in tubular carcinoma of the breast may not be necessary.

The relationship between tumor size and the probability of lymph node metastasis in tubular carcinoma of the breast is controversial. Several previous studies have not supported that tumor size was a determinant of axillary lymph node positivity [13,14]. However, some studies have shown that the risk of lymph node metastasis increased with tumor size [8,9,13,15,24,25]. In the present study, tumor size was shown to be an independent risk factor for lymph node-positive disease. The results by Diab et al. also found that the probability of lymph node metastasis was 8%, 14%, and 43%

in patients with tumor size ≤1 cm, >1 cm, ≤2 cm, and >2 cm to ≤5 cm, respectively [1]. To the best of our knowledge, at this time, the present study was the most extensive study to confirm that a larger tumor size in patients with tubular carcinoma of the breast was associated with an increased risk of lymph node metastasis. Also, the findings of this study also indicated that patients with younger age and intermediate-grade and high-grade disease had an increased risk of lymph node metastasis.

It remains controversial as to whether patients with a tumor size of less than 1 cm should undergo axillary lymph node dissection. Several previous studies have indicated that axillary lymph node dissection may be unnecessary in patients with a tumor diameter of less than 1 cm due to the rare incidence of lymph node metastasis [8–10,17,18]. However, a Korean population-based study found that the probability of lymph node metastasis in tubular carcinoma was 8.6% (6/70), while three patients with tumor size less than 1 cm had lymph node-positive disease including two patients with axillary lymph node macrometastasis and one patient with sentinel lymph node micrometastasis [15]. Also, in a study from the MD Anderson Cancer Center in the USA, investigators also found that in seven patients with lymph node-positive tubular carcinoma of the breast, four patients had a tumor size of less than 1 cm [26]. In this previous study, in 283 patients with T1 stage lymph node-positive disease, approximately half of the patients had a tumor size less than 1 cm [26]. Both chemotherapy and hormonal treatment are recommended for tubular carcinoma of the breast, mainly when associated with lymph node metastases [19,26]. As sentinel lymph node biopsy has been widely used in the clinical management of breast cancer, axillary lymph node dissection with sentinel lymph node biopsy for these tumors must be considered mandatory, even in patients with small tumor size.

This study had several limitations. First, this study was a retrospective analysis of data from a population database, with possible limitations including data recording, patient selection bias, and inherent bias. Second, the cases identified from the SEER database lacked central pathology review and confirmation of the tumor diagnosis, size, and grade, and there may have been a difference in the presentation of lymph node metastasis between pure and mixed tubular carcinoma. Also, axillary lymph node dissection, lymph node morphological characteristics, and the patterns of disease recurrence were also not documented in the SEER database. However, the primary strength of this study was that it involved a large population-based register to assess the probability of lymph node metastasis, risk factors affecting lymph node metastasis, and treatment outcomes in tubular carcinoma of the breast.

Conclusions

The results of this study showed that tubular carcinoma is a subtype of breast cancer with favorable biological behavior including a lower risk of lymph node metastasis. Although the status of lymph nodes was not associated with breast cancer-specific survival (BCSS), axillary lymph node dissection must be considered for tubular carcinoma of the breast even in patients with a tumor size of less than 1 cm. Also, well-designed and controlled randomized studies with long-term follow-up are required to adequately evaluate the role of axillary lymph node dissection in tubular carcinoma of the breast and patient prognosis.

Conflict of interest

None.

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