Journal of Gynecological Oncology

Research Article
Published: 17 Feb, 2020

Lymph Node Biopsy in Ductal Carcinoma of Breast *In Situ* with Micro-Invasion: A Propensity Score Matching Analysis

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Abstract

Objective: The retrospective study aimed to describe the prognostic value of lymph node biopsy and Positive Lymph Node Ratio (PLNR) in ductal carcinoma of the breast *in situ* with Micro-invasion (DCISM) patients.

Methods: The 4,311 patients diagnosed as DCISM were selected from the surveillance, epidemiology, and end results database from 2004 to 2016. The Propensity Score Matching (PSM) method and Kaplan-Meier analysis (log-rank test) was performed to analyze the Overall Survival (OS) and Cancer-Specific Survival (CSS). Risk factors were identified by the univariable and multivariable Cox proportional hazards regression model.

Results: Patients in the non-lymph node biopsy group had worse OS than lymph node biopsy group (P=0.001) but had no statistically significant impact on CSS (P=0.369). There was a better prognosis in PLNR <0.2 group than ≥ 0.2 group, showing statistically significant both on OS and CSS (P=0.004, and P=0.027). In multivariable Cox regression analysis, mastectomy was a positive factor on OS but a negative factor on CSS. Receiving radiation therapy and younger age (<50 year old) would benefit patients on OS, but receiving chemotherapy may increase risk in CSS.

Conclusion: Our propensity model confirmed that lymph node biopsy had a positive impact on the OS. PLNR ≥ 0.2 might increase the mortality risk in DCISM patients.

Keywords: Lymph node biopsy; Micro-invasion; Prognosis; Breast cancer; Propensity score matching

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Received Date: *23 Jan 2020*
Accepted Date: *12 Feb 2020*
Published Date: *17 Feb 2020*

Citation:
Sun Y, Zhu Z, Liu Z, Chen Y. Lymph Node Biopsy in Ductal Carcinoma of Breast In Situ with Micro-Invasion: A Propensity Score Matching Analysis. J Gynecol Oncol. 2020; 3(1): 1024.

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Introduction

Ductal Carcinoma *In Situ* with Micro-Invasion (DCISM) is a particular type between *in situ* and invasive breast cancer, accounting for about 10% of breast invasive ductal cancer and 1% of all invasive breast cancer [1-3]. The 8th American Joint Committee on cancer staging manual defined micro-invasive pathologic T1 tumors (pT1mi) as those measuring ≤ 1.0 mm in the greatest dimension [4]. Sentinel Lymph Node Biopsy (SLNB) and Axillary Lymph Node Dissection (ALND) were standard options of surgery for patients with invasive breast cancer. The results of sentinel axillary lymph node metastasis rate of DCISM among different retrospective clinical studies were inconsistent, ranging from 0% to 46.2% [5,6]. Magnoni et al. [7] suggested that DCISM patients who underwent SLNB may not be beneficial, and less aggressive surgery can contribute to the same level of OS and better life quality. However, the 5-year survival rate of patients with lymph node-positive DCISM was significantly lower than that of the lymph node-negative subgroup, which suggested the need for SLNB and ALND [8]. However, positive lymph node found after ALND in DCISM may not increase the risk of OS in another retrospective study [9]. There is still no consensus on whether SLNB or ALND should be performed in DCISM. On the other hand, Positive Lymph Node Ratio (PLNR) has been proposed to be a potential predictor in breast cancer. Numbers of studies have determined cut-off values between low and high-risk disease unequivocally at around 20% to 25% of positive lymph node ratio, and aggressive treatment such as post-mastectomy radiotherapy should be considered at high PLNR level patients [10-14]. Nevertheless, no prospective clinical studies explored the association of prognosis and PLNR in DCISM. This study divided DCISM patients

into three groups (Non-lymph node biopsy, PLNR <0.2, and PLNR ≥ 0.2), aiming to declare the above problems.

Methods and Materials

Database and patient's selection

The data was collected from the surveillance, epidemiology, and end results database. 4,311 patients met inclusion criteria as follow: 1) Diagnosis time was from 2004 to 2015 (2) Female (3) diagnosed with micro-invasive breast cancer pathologically (4) Detailed information about the patients' age (<50 and ≥ 50-year-old), histological tumor grade (grade I, II, III, and IV), surgical options (Mastectomy and breast-conserving), radiation (yes or not), chemotherapy (yes or not), ER (positive or negative) and PR (positive or negative) situation. Patients who have any incomplete clinicopathological information were excluded.

Statistical analysis

The OS was defined as the time from breast cancer diagnosis to the date of death for any reason. The CSS was defined as the time from breast cancer diagnosis to death because of breast cancer. Categorical data were expressed as frequency and were analyzed using the χ^2 test. Propensity Score Matching (PSM) analysis was performed in order to reduce the imbalance of different groups. All the possible clinicopathological variables (age, histological tumor grade, surgical options, radiation, and chemotherapy, ER, and PR situation) were included in the propensity score matching analysis. A one-to-two nearest neighbor matching algorithm was utilized with a caliper of 0.1 and without replacement, standardized differences were used to assess the balance of variables in both groups, as the standardized differences < ± 20% were acceptable. All statistical analyses were performed using the SPSS (version 22.0) and R software version 2.15.1. The PS matching 3.04 was used for the propensity score matching in SPSS.

Univariate and multivariable Cox proportional hazards regression model of OS and CSS were conducted. The log-rank test was utilized to explore univariate analyses. Multivariate Cox proportional hazard regression models were used to calculate Hazard Ratio (HR) and 95% Confidence Interval (CI) and identified factors with a correlation between OS and CSS.

Results

Patient characteristics

A total of 4311 patients were included in the study and classified into three groups: Non-lymph node biopsy group (n=443, 10.3%), PLNR <0.2 group (n=3738, 86.7%) and PLNR ≥ 0.2 group (n=130, 3.0%). The median follow-up time was 70.7 months. Other detailed information about age, tumor histology grade, surgical options, radiation, chemotherapy, ER, and PR status were included. In PLNR ≥ 0.2 group, the patients were younger, worse differentiated, accounting for higher rates of negative ER or PR, more likely to receive chemotherapy and mastectomy. In non-lymph node biopsy, in contrast, patients tended to be older age, better grade, accounting for higher rates of positive ER or PR, more likely to receive chemotherapy and mastectomy, less likely to receive chemotherapy and mastectomy. The original patient's characteristics were shown in the Supplement Table 1.

Propensity score matching

Because of the disequilibrium between the groups, PSM analysis was performed to balance the differences, outputting 433 patients with a non-lymph node biopsy group and 433 patients with lymph node biopsy group. Relative multivariate imbalance before and after matching was 0.347 and 0.117, showing reduced imbalance standard differences of subsamples covariates, and the standardized difference was all within ± 20%. Meanwhile, PSM analysis was performed in PLNR <0.2 and ≥ 0.2 groups, resulting 124 patients with PLNR <0.2 and 127 patients with PLNR ≥ 0.2. Relative multivariate imbalance before and after matching was 0.664 and 0.327. PSM analysis had no covariate exhibiting a large imbalance (|δ| >0.25). Clinicopathologic characteristics after propensity score matching; we were showed in Table 1 and 2.

Table 1: Clinicopathologic characteristics between patients with or without lymph node biopsy in the propensity score matching cohort.

Variable	Non-lymph node biopsy	Lymph mode biopsy	P value
Number	443	443	
Age			
<50	54 (12.2%)	67 (15.1%)	0.203
≥ 50	389(87.8%)	376 (84.9%)	
Tumor histological grade			
Grade I	134 (30.2%)	124 (28.0%)	0.754
Grade II	175 (39.5%)	183(41.3%)	
Grade III	124 (28.0%)	129 (29.1%)	
Grade IV	10(2.3%)	7 (1.6%)	
ER			
Positive	349 (78.8%)	345 (77.9%)	0.744
Negative	94 (21.2%)	98 (22.1%)	
PR			
Positive	284 (64.1%)	274 (61.9%)	0.487
Negative	159 (35.9%)	169 (38.1%)	
Surgical options			
Breast-conserving	367 (82.8%)	370 (83.5%)	0.788
Mastectomy	76 (17.2%)	73 (16.5%)	
Radiation			
Yes	248 (56.0%)	242 (54.6%)	0.685
No	195 (44.0%)	201 (45.4%)	
Chemotherapy			
Yes	13 (2.9%)	14 (3.2%)	0.845
No	430 (97.1%)	429 (96.8%)	

OS and CSS in patients with or without lymph node biopsy

The mean OS of patients with and without lymph node biopsy was 143.4 months and 131.8 months, showing statistically significant (P=0.001). The mean CSS of patients with and without lymph node biopsy was 153.3 months and 152.3 months, showing no statistically significant (P=0.369). The survival curves were shown in Figure 1A, 1B.

OS and CSS in patients with PLNR <0.2 or ≥ 0.2

We performed a Kaplan-Meier method in patients with PLNR <0.2 and PLNR ≥ 0.2 groups. The OS of patients with PLNR <0.2 or ≥ 0.2 were 146.9 months and 133.8 months, and the CSS were 149.5 months and 143.0 months. The overall difference was statistically significant (P=0.004, and P=0.027). The survival curves were shown in Figure 1C, 1D.

Table 2: Clinicopathologic characteristics between patients with PLNR <0.2 and ≥ 0.2 in the propensity score matching cohort.

Variable	PLNR <0.2	PLNR ≥ 0.2	P value
Number	124	127	
Age			
<50	42(33.9%)	48 (37.8%)	0.571
≥ 50	82(66.1%)	79 (62.2%)	
Tumor histological grade			
Grade I	14 (11.3%)	16 (12.6%)	0.979
Grade II	40 (32.3%)	40(31.5%)	
Grade III	61 (49.2%)	63 (49.6%)	
Grade IV	9(7.3%)	8 (6.3%)	
ER			
Positive	73 (58.9%)	80 (63.0%)	0.503
Negative	51 (41.1%)	47 (37.0%)	
PR			
Positive	55 (44.4%)	59 (46.5%)	0.738
Negative	69 (55.6%)	68 (53.5%)	
Surgical options			
Breast-conserving	50 (40.3%)	45 (35.4%)	0.425
Mastectomy	74 (59.7%)	82 (64.6%)	
Radiation			
Yes	63 (50.8%)	57 (44.9%)	0.347
No	61 (49.2%)	70 (55.1%)	
Chemotherapy			
Yes	83 (66.9%)	86 (67.7%)	0.895
No	41 (33.1%)	41 (32.3%)	

PLNR: Positive Lymph Node Ratio

Risk factors in patients with PLNR <0.2

The independent factors of OS based on univariate analysis were age (P<0.001) and radiation (P<0.001). The univariate analysis showed that independent factors of CSS were age (P=0.024), surgery options (P=0.003), radiation (P=0.023), and chemotherapy (P=0.007) (Figure 2A-2F). We set age, surgical options, radiation, and chemotherapy into multivariate Cox proportional hazards model, and the results identified that age ≥ 50-year-old (P<0.001, Hazard Ration (HR) =3.189, 95% Confidence Interval (CI) =2.015 to 5.048), and no-radiation (P<0.001, HR=2.704, 95% CI=1.816 to 4.025), and breast-conserving surgery (P-0.034, HR=1.514, 95% CI=1.031 to 2.224) were risk factors of OS. Mastectomy surgery (P=0.010, HR=2.512, 95% CI=1.249 to 5.053) and chemotherapy (P=0.031, HR=2.504, 95% CI=1.089 to 5.758) increased the risk of CSS. Table 3 showed the Univariate analysis of OS and CSS in patients with PLNR <0.2 cohorts. Moreover, the multi-factor regression analysis was shown in Figure 3.

Discussion

DCISM represents a less frequent subtype of breast cancer. Some retrospective studies have suggested that DCISM has more aggressive manifestations and worse prognosis than ductal carcinoma of the breast *in situ* [15,16], but its local recurrence was low [15,17,18]. There is still no consensus on the standard treatment for DCISM, especially the execution of lymph node biopsy in the surgical

Table 3: Univariate analysis of OS and CSS in patients with PLNR <0.2 cohort.

Variable	Univariate analysis					
	OS			CSS		
	P value	HR	95% CI	P value	HR	95% CI
Age						
<50	<0.001*	1	1	0.024*	1	1
≥ 50	-	3.048	2.211-4.203	-	0.478	0.230-0.993
Grade						
Grade I	0.784	1	1	0.255	1	1
Grade II	-	0.995	0.677-1.464	-	1.116	0.396-3.147
Grade III	-	0.883	0.586-1.329	-	2.157	0.927-5.017
Grade IV	-	0.758	0.377-1.523	-	1.537	0.247-9.585
ER						
Positive	0.92	1	1	0.539	1	1
Negative	-	1.016	0.742-1.392	-	0.79	0.386-1.615
PR						
Positive	0.437	1	1	0.858	1	1
Negative	-	1.122	0.838-1.502	-	0.941	0.487-1.820
Surgical options						
Breast-conserving	0.355	1	1	0.003*	1	1
Mastectomy	-	1.147	0.856-1.536	-	2.702	1.396-5.232
Radiation						
Yes	<0.001*	1	1	0.023*	1	1
No	-	1.815	1.359-2.423	-	2.227	1.159-4.280
Chemotherapy						
Yes	0.409	1	1	0.007*	1	1
No	-	1.292	0.749-2.229	-	0.339	0.097-1.17

OS: Overall Survival; CSS: Cancer-Special Survival; PLNR: Positive-Lymph Node Ratio
*indicates statistically significant

procedure [8,9]. Many retrospective studies have demonstrated that in DCISM cohorts, the rate of positive axillary lymph node was low [19-23]. It has been verified that ALND remained indicated for those who had positive Sentinel Lymph Node (SLN) [24], but many researches showed the rate of positive lymph node after ALND was still low [1,18,25]. Otherwise, PLNR has become a potential predictor for breast cancer patients, and PLNR ≥ 0.2 might play an unfavorable role in disease-free survival, overall survival and cancer-specific survival [26-28]. This study has shown that lymph node biopsy cohorts had better prognosis than non-lymph node biopsy, and non-lymph node biopsy and PLNR ≥ 0.2 group had similar prognosis, which suggested that in clinical practice, for older patients, we might consider not performing ALND and chemotherapy, and this kind of mild treatment method could also reduce surgical complications and side effects of chemotherapy. Many studies showed that DCISM has a low incidence of a positive lymph node in SLNB [7,29]. Another research came up with the conclusion that examination of fewer than six lymph nodes is an adverse prognostic factor in node-negative breast cancer patients because it could lead to under staging [30]. However, few studies reported the necessity of ALND in DCISM. This study used PSM to reduce the imbalance of different groups. The result indicated that lymph node dissection could improve the OS of DCISM patients, but it had no significant impact on CSS. Maybe this PSM analysis could help clinical doctors to make a more accurate

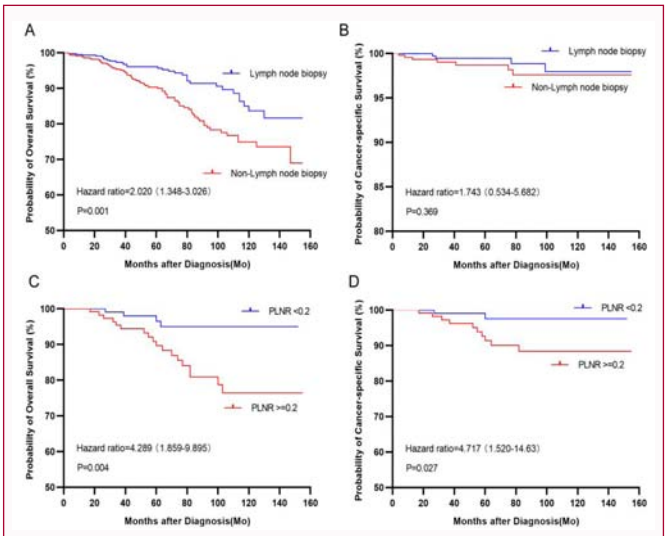

Figure 1: Overall Survival (A) and Cancer-specific Survival (B) in 433 patients with lymph node biopsy (Blue) and 433 patients with non-lymph node biopsy (Red) after propensity score matching. Overall Survival (C) and Cancer-specific Survival (D) in 124 patients with PLNR <0.2 (Blue) and 127 patients with PLNR ≥ 0.2 (Red) after propensity score matching. The hazard ratios and 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the log-rank test.

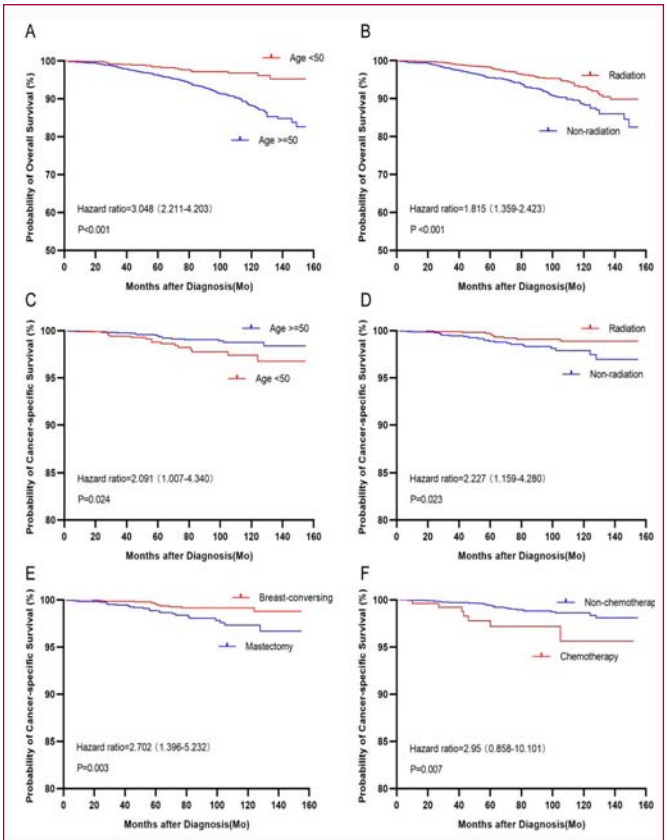

Figure 2: Univariable Cox regression analysis of OS (A-B) and CSS (C-F) in patients with PLNR <0.2 cohorts, which included in 3738 patients. The hazard ratios and 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the log-rank test.

surgery option according to case to case.

Radiotherapy after surgery is recommended for patients with advanced stage-tumor, those with positive or close surgical margins,

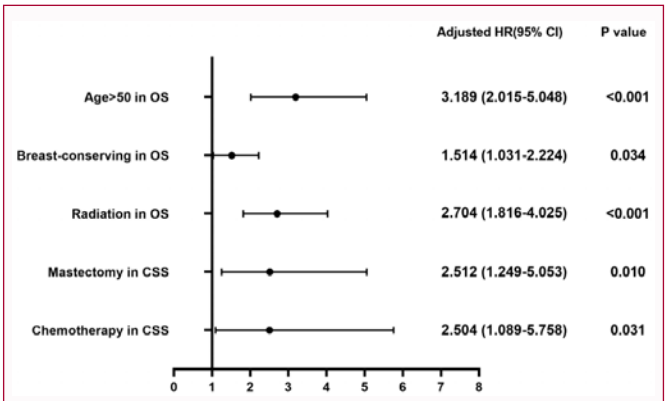

Figure 3: Forest plot after multivariable Cox regression analysis of OS and CSS in patients with PLNR <0.2 cohorts. The horizontal lines represent the 95 percent confidence intervals, and the spot corresponds to the hazard ratios. P values were calculated with the use of the log-rank test.

and those with four or more axillary lymph nodes metastases [11]. A study showed that radiation could reduce early local recurrence risk after Breast-Conserving Surgery (BCS) and radiotherapy, but it lacked longer follow-up time [31]. A PSM analysis showed that DCIS patients could not benefit from receiving radiotherapy after BCS [32]. However, another study determined that the presence of multiple foci of micro-invasion in DCIS is associated with higher 15-year risks of invasive LR after breast-conserving therapy compared to women with pure DCIS but treatment with the whole breast and boost RT can mitigate this risk [33]. In the analysis of subgroup PLNR <0.2, we found that radiation is an essential factor that could influence survival, which suggested that compared with DCIS, DCISM tended to benefit more from radiotherapy.

As for the choice of surgery options, the rate of BCS remained increased in the latest few decades, and till now, it seemed to be similar even more than mastectomy in some areas. Although no clinical studies have evaluated the efficacy of mastectomy, surgery was still considered as the standard treatment to reduce the local recurrence rate. The option of surgery, performing mastectomy, or BCS remains controversial. The management pattern of DCISM was more likely to invasive breast cancer than pure *in situ* [34]. Comparing with DCIS, patients with DCISM were more likely underwent a mastectomy. In a retrospective cohort study, mastectomy was performed in 25.1% of DCIS patients and 41.4% of DCISM patients [35]. Another research demonstrated the same result DCISM 43.5% *vs.* 31.2% for DCIS and 36.2% for DCISM [34]. In this study, we found that the rate of mastectomy increased with increasing PLNR. This could be explained that the lymph node was usually conducted after mastectomy. From the forest plot in this study, it was clear that mastectomy was an opposite effect on OS and CSS in PLNR <0.2 group. This result indicated that in clinical practice, the surgery option of DCISM needed to be keeping with invasive breast cancer for mastectomy could benefit the survival of DCISM patients.

However, this study has several limitations. It did not obtain data on specific chemotherapy regimens, which might affect prognosis. Because the patients with Her-2 expression information only started in 2010, we excluded this factor on account of most patients who lack this information. Moreover, it would be better to acquire data about Local Recurrence Rate (LRR), Recurrence-Free Interval (RFI), and Distant Relapse-Free Survival (DRFS) data to make a complete analysis.

Summarize above; this study indicated that lymph node biopsy on DCISM patients had a positive impact on the OS but had no influence on the CSS and PLNR <0.2 group had the best prognosis. Radiation therapy could improve the OS but had no significant influence on CSS in PLNR <0.2 group.

Acknowledgment

Thanks to the SEER database for patient information.

Funding

This work was supported by the National Natural Science Foundation of China (81300236, 81670433, and 81970398), the Project of Zhejiang Medical Young Talents (2017), and Zhejiang Medical and Health Science and Technology Project (2020RC014).

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