Original Article

Should Sentinel Lymph Node Biopsy be Performed in Ductal Carcinoma in situ Diagnosed on Core Needle Biopsy?

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Background: The implementation of sentinel lymph node biopsy (SLNB) when ductal carcinoma in situ (DCIS) diagnosed from core needle biopsy (CNBx) is controversial.

Objective: To investigate the value of SLNB in patients with a preoperative diagnosis of DCIS focusing on the requirement of re-operation and determine the factors associated with upstaging to invasive carcinoma.

Materials and Methods: Data of all patients with a preoperative CNBx-diagnosed of DCIS who underwent SLNB at the time of definitive surgery at the Division of Head-Neck and Breast Surgery, Department of Surgery, Siriraj Hospital, Mahidol University, Thailand from January 2001 to December 2011 were collected. The outcomes were then analyzed regarding clinical, radiographic and pathologic data in relation to histological upstaging and SLNB results.

Results: One hundred and seventy-five patients with a CNBx-diagnosed of DCIS underwent 178 SLNB at the time of definitive surgery while one hundred and ten patients (61.8%) were detected by screening mammogram without abnormal clinical findings. In addition, SLNB was successful in 168 patients (94.4%) and 10 patients (5.6%) had SLN metastases and sixty-eight patients (38.2%) had histological upstaging based on an invasive component identified on the final specimen and SLN was positive in 9 cases (13.2 %). Among 110 patients, there is 1 SLN metastasis (0.9%) found on a patient who had "pure DCIS" on final pathology. The independent predictors for existence of invasive components were presence of a palpable tumor (OR 4.105, 95% CI 1.745 to 9.656, $p = 0.001$), initial high nuclear grade DCIS (OR 2.370, 95% CI 1.156 to 4.860, $p = 0.019$) and focal microinvasion (OR 2.370, 95% CI 1.163 to 12.620, $p = 0.027$).

Conclusion: More than one-third of patients with diagnosis of DCIS by CNBx had invasive components in final pathology. Hence, SLNB should be performed during definitive surgery to avoid second operation especially in those who have high risk for harboring invasive cancer.

Keywords: Breast cancer, Ductal carcinoma in situ, Sentinel lymph node biopsy

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When ductal carcinoma in situ (DCIS) is found on core needle biopsy (CNBx), histological underestimation is possible as the consequence of sampling error. The progression to invasive carcinoma can be occurred in 8.8% to 51.5% of DCIS diagnosed by CNBx[1-11]. Axillary nodal staging is required when an invasive cancer is subsequently found. Moreover, sentinel lymph node biopsy (SLNB) enables nodal staging in clinical node negative patients. Theoretically, DCIS is confined in basement membrane that should not be metastases to the lymph nodes, but previous studies reported the rate of metastasis to the axillary lymph node up to 13% in DCIS[12,13]. For breast conserving surgery, retrospective studies from the NSABP B-17 and B-24 trials reported the low yield and risk of ipsilateral nodal recurrence. Therefore, the result does not support routine SLNB in conservative treatment of localized DCIS[14].

There was no consensus of predictive factor for invasive carcinoma upstaged from DCIS that diagnosed by CNBx[15-21]. We examined the value of SLNB in patients with a preoperative diagnosis of DCIS and determine factors correlated with upstaging to invasive carcinoma.

Materials and Methods

This is a retrospective study that included all 18 years or older patients with a preoperative CNBx of DCIS who underwent SLNB at the time of definitive surgery at the Division of Head Neck and Breast Surgery, Department of surgery, Siriraj Hospital, Mahidol University, Thailand from January 2001 to December 2011. The patients who received primary chemotherapy before definite surgery were excluded. The ipsilateral or metachronus lesion are also excluded.

Pathological records were retrieved using keywords

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of "Ductal carcinoma in situ" "DCIS" "Intraductal carcinoma" and "Biopsy" from January 2007 to December 2011 then intersect the data with keywords of "sentinel lymph node biopsy" that resulted in recruitment of 685 patients. The patients with invasive carcinoma or did not underwent CNBx were excluded. Finally, 175 records had initial diagnosis of pure DCIS or DCIS with microinvasion (DCISm) with needle biopsy then proceed to sentinel lymph node from 175 patients. 3 Patients have bilateral DCIS lesion. One patient had bilateral lesion at the same time and other two patients had metachronous contralateral lesion. The present study was approved by the Siriraj Institutional Review Board (761/2554(EC4)).

Results

One hundred and seventy-eight breast specimens from 175 patients with CNBx diagnosis of DCIS underwent simultaneous SLNB with definitive surgery. The median age was 49 year. One hundred and ten cases (61.8%) were analyzed by screening mammography while median palpable tumor size was 23 millimeters. Additionally, five patients had missing data for palpable size. The breast side is quite equal and the mass can be found via mammography or sonography in 90 patients. Furthermore, eighty-seven (48.9%) cases underwent sonographic-guided needle biopsy and other underwent stereotactic-guided CNBx. One hundred and sixty cases were diagnosed pure DCIS. Fifty percent of the patients had high nuclear grade whereas low nuclear grade was detected in 11% of them. Breast conserving surgery was performed in 41% of the patients and sixty-eight cases were upstaged to invasive cancer. Median number of sentinel lymph node was three nodes with overall metastasis of 5.6%.

Predominantly, 178 DCIS cases were 160 pure DCIS and 18 DCISm. Among DCIS by CNBx, 13 (8.1%) patients had no residual tumor left while pure DCIS was found in 92 (57.5%) patients. In addition, 9 (5.6%) patients and 46 (28.7%) patients had the upgraded DCISm and invasive ductal carcinoma respectively. Moreover, there are 5 (27.8%) patients with no residual invasive component left and 5 (27.8%) patients with DCISm although 8 (44.4%) patients had upstaging to invasive carcinoma among 18 DCISm by CNBx. Thus, overall 178 DCIS patients had upstaging 68 (38.2%) patients (Figure 1).

SLNB was successful in 168 (94.4%) operations and 10 (5.6 %) patients had SLN metastases. In DCISm, SLN was positive in 9 (13.2 %) and one hundred and ten pure DCIS with one (0.9 %) SLN metastases (Table 1).

Univariate analysis revealed significant correlation of the existence of invasive cancer in the tumor with 6 factors. The history of palpable mass and palpable mass on physical examination were related, so we selected only the presence of palpable mass to be analyzed. Multivariate analysis revealed that 3 factors shows independent predictive factors of the tumor harboring invasive component that is palpable mass, stromal invasion, nuclear grade. Palpable mass size and image size were significant in univariate analysis. However, because the population is lower than the other, it

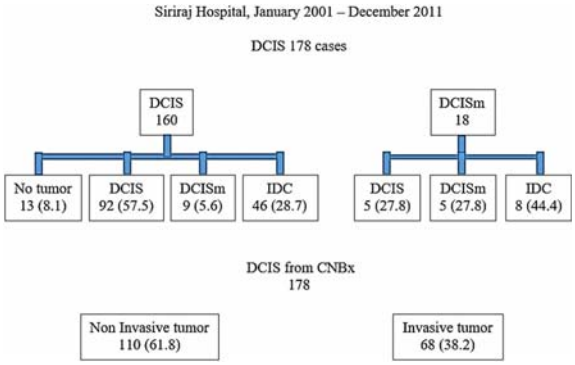

Figure 1. Final result of DCIS from CNBx.

Table 1. Demographic data of clinicopathological parameters of 178 patients diagnosed as DCIS by means of needle biopsy

Parameters	n (%)
Mean age, years (min-max)	49 (25 to 79)
Presenting symptom	
Screening mammography	110 (61.8)
Palpable mass	57 (32.0)
Nipple discharge	8 (4.5)
Palpable mass and nipple discharge	3 (1.7)
Median palpable tumor size, mm (min-max)	23 (10 to 70)
Mass detected by mammography or sonography	90 (50.6)
No mass detected	75 (42.1)
Unknown	13 (7.3)
Abnormal microcalcification	
Absence	31 (17.4)
Presence	134 (75.3)
Unknown	13 (7.3)
Needle biopsy procedure	
Sonography-guided	87 (48.9)
Stereotactic-guided	81 (45.5)
Unknown	10 (5.6)
Diagnosis on needle biopsy procedure	
Pure DCIS	160 (89.9)
DCISm	18 (10.1)
Nuclear grading	
Low	19 (10.7)
Intermediate	70 (39.3)
High	89 (50.0)
Breast surgery	
Breast conserving surgery	73 (41)
Total mastectomy	105 (59)
Final breast diagnosis	
DCIS	110 (61.8)
Invasive carcinoma	68 (38.2)
SLN status	
Negative	168 (94.4)
Positive	10 (5.6)

was probably not significant in multivariate analysis. Thus, more cases of mass detected lesion were required for further analysis (Table 2).

Discussion

Upstaging from DCIS on CNBx to invasive carcinoma at the time of definitive surgery can be occurred with vary frequency. In this study, we identified the factors that associated with the upstaging and we then proposed the decision tree for axillary management in the patients with DCIS diagnosed by CNBx.

Occult invasive carcinoma can be missed diagnosed by CNBx as a result of tissue sampling error[22]. One-fourth of the patients with DCIS had upstage to invasive carcinoma at definitive surgery[23-25]. The current study reported that the rate of upstaging can be around 40%, similar to the report from Park et al[26].

DCIS is theoretically does not metastasize to lymph node and positive SLN can be found 4% of the patients with DCIS who underwent SLNBx[22]. CNBx or excisional biopsy they could be the reason for iatrogenic tumor cell displacement theory. The rate of positive SLN was 4-times higher in the patients who underwent surgical excision before definitive surgery[27].

In the patients with DCIS diagnosed by CNBx, the rate of positive SLN in the final diagnosis of pure DCIS is very low. On the other hand, those patients with final diagnosis of invasive carcinoma, the rate of positive SLN can be up to 15%[26] whereas the percentage of positive SLN in the upstaging to invasive carcinoma group is approximately half of that in early breast cancer patients underwent SLNBx[28]. Smaller in size of invasive portion of the tumor in the patients with initial DCIS diagnosed by CNBx when compare to that of the patients with initial diagnosis of invasive carcinoma could be the leading factor. Based on the results of the present study, we designed a decision tree for the management of patients diagnosed with DCIS by core needle biopsy preoperatively (Figure 2). SLNBx should be performed in all DCIS patients with any high-risk factor for upstaging to invasive carcinoma and all of the patients who will be treated with total mastectomy from subsequent SLNBx cannot be performed in post-mastectomy patients. Patients without high-risk factor, SLNBx can be omitted in the patients who will receive breast conserving surgery as subsequent SLNBx can be performed in these patients. In both circumstances, the intra-operative assessment of SLN might not be necessary due to low rate of positive SLN in this group of patients.

Pure DCIS theoretically does not metastasize to lymph nodes. Sentinel lymph node metastases were found up to 12%, but in the series of "pure DCIS" the metastases were present up to 7%. Most study and our study indicate the rare lymph node metastasis in pure DCIS. Some paper has high (7%) node metastasis[12]. Based on the results of the present study, we designed a decision tree for the management of patients diagnosed with DCIS by needle biopsy preoperatively (Figure 2).

Table 2. Assessment of factors predictive of invasive cancer in tumors diagnosed as DCIS pre-operatively by means of needle biopsy

	Total	DCIS	Invasive carcinoma (%)	*p*-value
Presenting				
Screening mammography	110	79 (71.8)	31 (28.2)	<0.001
Any symptom	68	31 (46.6)	37 (54.4)	
Mass				
No mass	118	84 (71.2)	34 (28.8)	0.001
Palpable mass	60	26 (43.3)	34 (56.7)	
Size by physical examination [a]				
≤20 mm	16	11 (68.8)	5 (31.2)	0.038
>20 mm	39	14 (35.9)	25 (64.1)	
Size by imaging [b]				
≤15 mm	41	31 (75.6)	10 (24.4)	0.042
>15 mm	44	23 (52.3)	21 (47.7)	
CNBx result				
DCIS	160	105 (65.6)	55 (34.4)	0.002
DCISm	18	5 (27.8)	13 (72.2)	
Nuclear grade				
High	89	48 (53.9)	41 (46.1)	0.045
Low/ intermediate	89	62 (69.7)	27 (30.3)	

[a] = Included only the patients with palpable mass, [b] = Included only the patients with visualized mass by ultrasound

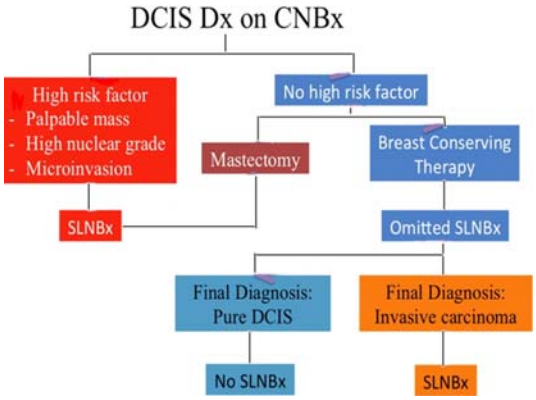

Figure 2. Decision tree for the management of patients diagnosed with DCIS by needle biopsy preoperatively.

Conclusion

Performing a SLNB during the initial procedure may circumvent a second operation in some DCIS patients who are diagnosed with invasive disease at their definitive operation. SLNB is recommended in the management of selected high-risk DCIS patients such as palpable mass, high nuclear grade and microinvasion.

What is already known on this topic?

When ductal carcinoma in situ (DCIS) is found on core needle biopsy (CNBx), histological underestimate can occur due to sampling error. When an invasive cancer is subsequently found, axillary nodal staging is required. Sentinel lymph node biopsy (SLNB) enables nodal staging in clinical node negative patients.

What this study adds?

More than one-third of patients with diagnosis of DCIS by CNBx had invasive components in final pathology. SLNB is recommended in the management of selected high-risk DCIS patients, such as palpable mass, high nuclear grade and microinvasion.

Acknowledgement

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Potential conflicts of interest

The authors declare no conflict of interest.

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การผ่าตัดต่อมน้ำเหลืองเซนติเนลมีความจำเป็นในผู้ป่วยมะเร็งเต้านมชนิดไม่ลุกลามที่ได้รับการวินิจฉัยโดยการเจาะตรวจชิ้นเนื้อหรือไม่

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ภูมิหลัง: การตรวจต่อมน้ำเหลืองเซนติเนลในผู้ป่วยมะเร็งเต้านมชนิดไม่ลุกลามที่ได้รับการวินิจฉัยโดยการเจาะชิ้นเนื้อยังไม่มีข้อสรุปถึงความจำเป็น

วัตถุประสงค์: เพื่อประเมินความจำเป็นในการผ่าตัดต่อมน้ำเหลืองเซนติเนลและปัจจัยที่สัมพันธ์กับการเป็นมะเร็งชนิดลุกลามในผู้ป่วยที่เป็นมะเร็งชนิดไม่ลุกลามวินิจฉัยโดยการเจาะชิ้นเนื้อ

วัสดุและวิธีการ: ข้อมูลของผู้ป่วยผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งชนิดไม่ลุกลามโดยการเจาะชิ้นเนื้อถูกนำมาวิเคราะห์เพื่อหาอัตราและปัจจัยที่มีความสัมพันธ์กับการเป็นมะเร็งชนิดลุกลาม

ผลการศึกษา: ผู้ป่วยทั้งหมด 178 ราย ผู้ป่วย 168 ราย ได้รับการผ่าตัดต่อมน้ำเหลืองเซนติเนลสำเร็จ โดยผู้ป่วย 10 ราย (5.6%) มีมะเร็งกระจายไปยังต่อมน้ำเหลืองเซนติเนล ผู้ป่วย 68 ราย (38.2%) มีการตรวจพบมะเร็งชนิดลุกลามในชิ้นเนื้อที่ได้จากการผ่าตัดในผู้ป่วยกลุ่มนี้ 9 ราย (13.2%) มีมะเร็งกระจายไปยังต่อมน้ำเหลืองเซนติเนลในผู้ป่วย 110 ราย ที่เป็นมะเร็งชนิดไม่ลุกลามมีมะเร็งกระจายไปยังต่อมน้ำเหลืองเซนติเนลเพียง 1 ราย ปัจจัยที่สัมพันธ์กับการเป็นมะเร็งชนิดลุกลามประกอบด้วย การคลำได้ก้อน เป็นมะเร็งเกรดสูง และมีมะเร็งส่วนที่ลุกลามขนาดเล็กตรวจพบจากการเจาะชิ้นเนื้อ

สรุป: มากกว่าหนึ่งในสามของผู้ป่วยที่ได้รับการวินิจฉัยเป็นมะเร็งชนิดไม่ลุกลามโดยการเจาะชิ้นเนื้อมีมะเร็งชนิดลุกลามตรวจพบในชิ้นเนื้อที่ได้จากการผ่าตัด การผ่าตัดต่อมน้ำเหลืองเซนติเนลจึงขวรทำในผู้ป่วยกลุ่มนี้เพื่อหลีกเลี่ยงการผ่าตัดอีกในภายหลัง โดยเฉพาะผู้ที่มีปัจจัยที่สัมพันธ์กับการมีมะเร็งชนิดลุกลาม