RESEARCH ARTICLE

Impact of Using Intra-Operative Ultrasound Guided Breast-Conserving Surgery on Positive Margin and Re-Excision Rates in Breast Cancer Cases with Current SSO/ASTRO Guidelines

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Abstract

Purpose: To review the impact of using intra-operative ultrasound guided breast conserving surgery with frozen sections on final pathological margin outcome with the current guidelines set forth by the Society of Surgical Oncology (SSO) and the American Society of Surgical Oncology (ASTRO). Materials and Methods: A retrospective review including all cases of intra-operative ultrasound guided breast conserving surgery was performed at the National Cancer Institute Thailand between 2013 and 2016. Patient demographics, tumor variables, intraoperative frozen section and final pathological margin outcomes were collected. Factors for positive or close margins were analyzed. Results: A total of 86 patients aged between 27 and 75 years with intra-operative ultrasound guided breast conserving surgery were included. Three cases (3.5%) of positive margin were detected by intra-operative frozen section and 4 cases (4.7%) by final pathology reports. There were 18 cases (20.9%) with a close margin (<1 mm). Factors affecting this result comprised multi-foci, presence of invasive ductal carcinoma (IDC) combined with ductal carcinoma in situ (DCIS) and invasive lobular carcinoma (ILC). Conclusions: With the current SSO/ASTRO for adequate margin guidelines, using intra-operative ultrasound to locate the boundary for resection with breast conserving surgery provided a high success rate in obtaining final pathology free margin outcomes and minimizing re-operation risks especially when combined with intra-operative frozen section assessment. The chance of finding positive or close margins appears higher in cases of IDC combined with DCIS, ILC and with multi-foci cancers.

Keywords: Breast cancer - breast conserving surgery - margin - US guided surgery - SSO/ASTRO guidelines

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Introduction

Breast conserving surgery (BCS) has been established as a standard of care in early stage breast cancer (NIH consensus conference, 1991) and become the preferable surgical treatment over mastectomy (Nattinger et al., 1992; Habermann et al., 2010). Not only a more positive body image and the patient's quality of life (Kiebert et al., 1991; Irwig et al., 1997), but also an equivalent, or even superior outcome in term of survival rate for the patients undergoing BCS with radio-therapy supported by randomized controlled trials data (Fisher et al., 1989; Veronesi et al., 1990; Lichter et al., 1992; Arriagada et al., 1996). Unfortunately, the major draw back of BCS is the possibility of having the second or the third operation to obtain for adequate margins. As margin status is one of the most important predicting factors for local failure, even in tumor bed radiation-boosted patients (Schnitt et al., 1994; Malik et al., 1999; Park et al., 2000). Therefore if final pathological result of resected tissue shows that margins are involved, an additional surgery is required to avoid ipsi-lateral breast tumor recurrence (IBTR) (Mullenix et al., 2004; Aziz et al., 2006; Houssami et al., 2014). According to the variety of definition for the "clean" margin, the rate of re-excision has been reported from lower than 10 to more than 40% (Neslihan et al., 2005; Olson et al., 2007; Bosma et al., 2016; Isaacs et al., 2016). To address this controversial issue, American Society of Clinical Oncology (ASCO) endorsed the consensus guidelines for adequate margin which defined as "no ink on tumor" proposed by Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) in 2014 (Thomas et al., 2014). The other challenge is how to obtain an adequate margin with minimizing loss of the breast volume especially in a single operation. Different approaches have been considered for

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intra-operative evaluation of surgical margins, depending on the tumor characteristic and availability of techniques such as gross pathological evaluation (Flemimg et al., 2004) with or without intraoperative frozen section (Neslihan et al., 2005; Olson et al., 2007), cavity shaving (Malik et al., 1999) or intraoperative ultrasound guided (US-guided) (Olsha et al., 2011) surgery.

To analyze the impact of using intraoperative evaluation with SSO/ASTRO guidelines for adequate margin to the re-excision rate, we conducted the retrospective study to compare the intraoperative frozen section and the final pathological margin positive rate by intraoperative US-guided breast conserving surgery for early stage breast cancer between 2013 and 2016 at the National Cancer Institute, Thailand.

Materials and Methods

The study comprised 86 patients under went conservative breast surgery with ultrasound guided for early stage breast cancer between January 2013 and February 2016 at the National Cancer Institute, Thailand and was approved for retrospective medical chart review by an Institutional Review Board. All patients had breast US examination preoperatively and intra-operatively [using the flex Focus 1202] to assess and locate the boundary of resection by a breast surgeon. Patients who were not scheduled for breast conserving surgery with this technique were excluded.

The patients' demographic, tumor characteristics, operative notes and pathological reports were reviewed and recorded.

After excision, surgical specimens were oriented by a surgeon with sutures according to convention "long lateral", "short superior" and "double deep" or small piece of skin for "anterior". The tumor edge was checked by ultrasound ex vivo and sent to pathological macro and microscopic assessment for margin by frozen section. If the margin involved with invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS), additional resection of the breast would be performed immediately and the new margins of additional resections were orientated by sutures. All specimens were fixed in 4% formaldehyde, and inked by the pathologist according to standard protocol for orientation. The new resection margins of additional intraoperative resection were also inked. The margins for each orientation were measured and recorded by pathologist for closet component of the tumor, regardless of whether this IDC or DCIS. Postoperative re-operation would be performed if any inked margin involved with tumor cells. All of the patients would be scheduled for adjuvant systemic treatment and whole breast irradiation with boosted dose at tumor bed.

For the clear margin definition, SSO/ASTRO guidelines for adequate margin was implemented. All cases with involved margins were recorded whether detected by intra-operative frozen section or final pathological reports to compare the positive margin rate. For the further analysis of effectiveness by ultrasound guided surgery and impact of guidelines to re-excision risks, the close margin status (<1 mm.) was included.

Statistical analysis was done using SPSS (version 18, SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for continuous and categorical variables. Data are presented as mean value ± standard deviation; a p-value <0.05 was considered to be statistically significant. Binary logistic regression analysis was used to reveal unadjusted and adjusted Odds ratio and determined associations between prognostic variables and the likelihood of "positive margin". For statistical analysis, positive and close margin group were merged into a "positive" group to identify possible risk factors predictive for additional surgery.

Results

From January 1,2013, to February 28, 2016, Eighty-six patients aged between 24 and 75 years underwent UG-guided BCS were included in the study. The mean (SD) age was 50.6 (11.5) years, with 48 (56.8%) women aged 50 years or older and 38 (43.2%) women aged 27 to 49 years. Mean (SD) tumor size was 2.11 (0.96) cm. Forty-two patients (47.7%) were pure IDC and 35 patients (40.7%) were IDC combined with DCIS. The majority of tumors (90.3%) were single lesion and ER/ PgR positive (79%).Their clinical and pathological details are outlined in Table1.

For final pathology margin status, 82 patients (95.3%) were deemed to have a clear margins status based on SSO/

Table 1. Patient Characteristics

Characteristic	Data (N=86)
Age mean (SD)	50.6 (11.5)
>50years	38 (44.2)
≥50 years	48 (55.8)
Tumor size, cm (SD)	2.11 (0.96)
Tumor type n (%)	
Invasive ductal carcinoma (IDC)	42 (48.8)
IDC + DCIS	35 (40.7)
Invasive lobular carcinoma (ILC+LCIS)	6 (7.0)
Others (metaplastic, mucinous, encapsulated papillary CA)	3 (3.5)
Histology n (%)	
Gr I	16 (18.6)
Gr II	32 (37.2)
Gr III	32 (37.2)
Un-classified or unknown	6 (7.0)
Single n (%)	78 (90.7)
Multi-foci n (%)	8 (9.3)
ER or PgR positive n (%)	68 (79.1)
ER and PgR negative n (%)	18 (20.9)

Table 2. Final margin result with or without SSO/ASTRO guidelines implementation

Pathology report	Clear margin	Positive margin	Close margin (<1 mm)
Final pathology n (%) (≥ 1mm. free margin guideline)	64 (74.4)	4 (4.7)	18 (20.9)
Final pathology n (%) (with SSO/ASCO guidelines)	82 (95.3)	4 (4.7)	0

Table 3. Factors among Clear Margins and Positive and Close Margins by US-guided BCS based on SSO/ASTRO Guidelines and ≥1 mm Free Margin Guidelines

Total Number = 86	Margin by SSO/ ASTRO guidelines			Margin by ≥ 1 mm. guideline		
	Clear	Positive	p-value	Clear	Positive	p-value
Age						
year (SD)	44.2 (11.9)	48.3 (6.8)	0.476	44.2 (11.9)	48.3 (6.8)	0.393
< 50						
n (%)	34 (39.5)	4 (4.6)		30 (34.9)	8 (9.3)	
≥ 50						
n (%)	45 (52.3)	3 (3.5)		34 (39.5)	14 (16.3)	
Size cm						
Mean (SD)	2.20 (1.1)	2.01 (0.8)	0.976	2.66 (1.0)	1.79 (0.9)	0.450
≤2.5 cm	56 (65.1)	5 (5.8)		44 (51.2)	17 (19.8)	
>2.5 cm	23 (26.7)	2 (2.3)		20 (23.3)	5 (5.8)	
Number of lesions		0.126		0.022*		
Single						
n (%)	73 (84.9)	5 (5.8)		61 (70.1)	17 (19.8)	
Multi-foci						
n (%)	6 (7.0)	2 (2.3)		3 (3.5)	5 (5.8)	
Histology type		0.185		0.025*		
Pure IDC+Others						
n (%)	44 (51.2)	1 (1.1)		39 (45.3)	5 (5.8)	
IDC + DCIS n (%)	30 (35.0)	5 (5.8)		23 (26.3)	13 (15.1)	
ILC						
n (%)	5 (5.8)	1 (1.1)		2(2.3)	4 (4.7)	
Histologic grade		0.401		0.621		
I n, (%)	15 (17.4)	1 (1.2)		11 (12.8)	5 (5.8)	
II n, (%)	31(36.0)	1 (1.2)		26 (30.2)	6 (7.0)	
III n, (%)	28 (32.6)	4 (4.6)		24 (27.9)	8 (9.3)	
Unknown/ unclassified						
n, (%)	5 (5.8)	1 (1.2)		3 (3.5)	3 (3.5)	
IHC status		0.337		0.116		
ER or PgR positive						
n, (%)						
	61 (70.9)	7 (8.2)		48 (55.8)	20 (23.3)	
ER and PgR negative						
n, (%)	18 (20.9)	0 (0)		16 (18.6)	2 (2.3)	

*statistic significant p < 0.05

Table 4. Crude ORs, Adjusted ORs and p-Values for Factors for Positive and Close Margins by US-guided BCS Based on ≥1mm Free Margin Guidelines

Total number n =86	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Number of lesions				
Single-foci tumors	baseline			
Multi-foci tumors	5.98 (1.30-27.59)	0.022*	13.03 (1.88-90.53)	0.009*
Histology type				
Pure IDC+others	baseline			
IDC+DCIS	4.41 (1.39-13.97)	0.012*	5.51 (1.51-20.11)	0.010*
ILC	15.60 (2.25-108.12)	0.005*	15.31 (1.99-117.72)	0.009*

*statistic significant p < 0.05; Number of lesions adjusted for Size, ER, Age and Histological type; Histological type adjusted for Size, ER, Age and Number of lesions

ASTRO guidelines, compared to 64 patients (74.4%) if not follow SSO/ASTRO guidelines. (Table 2)

In the negative margin group, there were 18 patients (20.9%) found to have close margin (<1 mm.). (Table 2). Additional 3 patients (3.5%) underwent intraoperative re-excision due to positive margins detected by frozen section.

The findings demonstrated that 73 (93.6%) of 78 patients with single lesion, and 6 (75%) of 8 patients with multi-foci lesions were successfully achieved free margin by using intra-operative US guided BCS and SSO/ASTRO guidelines compared to only 61 (78.2%) patients for single lesion and 3 (37.5%) for multi-foci lesions if follow ≥ 1mm. free margin guideline. (Table 3)

There are details of clear and positive margin associated factors based on SSO/ASTRO guidelines and ≥ 1 mm. free margin guideline outlined in Table 3 and Table 4 respectively. The un-adjusted Odds ratio of multi-foci lesions was 5.98 (95%CI 1.30-27.59; p = 0.022) compared to single lesion. This factor was also significant after adjusted of age, size, histologic type and immuno-histochemistry status (adjusted OR=13.03, 95%CI 1.88-90.53; p=0.009). Un-adjusted Odds ratio of IDC+DCIS was 4.41 (95%CI 1.39-13.97; p=0.012) and

un-adjusted Odds ratio of ILC was 15.60 (95%CI 2.25-108.12; p=0.005) compared to pure IDC+ others. These two factors were also significant after adjusted of age, size, number of lesions and immuno-histochemistry status which IDC + DCIS had adjusted OR = 5.51 (95%CI 1.51-20.11; p=0.010) and ILC had adjusted OR=15.31 (95%CI 1.99-117.72; p=0.009) (Table 4).

Discussion

The result of the involved margin on the final pathology of BCS under US- guided in this cohort was very low and similar to the report from COBALT trial (Krekel et al., 2013), indicating that the acceptable gross margin could be successfully obtained by using US to optimize the boundary of resection in carefully selected patients for BCS and the impact of closer margin threshold for the SSO/ASTRO guidelines recommendation (Thomas et al., 2014) which could possible reduce the close margin re-excision indication for 20.9% of total BCS (18/86) or possibly cut down 81.8% (18/22) of possible re-excision rate for previous inadequate-margin indication (positive + close margin).

Although prior-observational studies showed that the multi-foci of tumors present in T1-2 breast cancer (Holland et al., 1985) and the possibility of residual tumor remained in the close margin specimens (Merrill et al., 2016). However, the retrospective SSO/ASTRO meta-analysis concluded that these rates of residual tumor would likely to manage successfully with modern radiotherapy and systemic therapy (Thomas et al., 2014) which also supported by the long-term result of low IBTR in other studies (Bosma et al., 2016; Dixon et al., 2016).

In our study, we found that intra-operative assessment by frozen section would provide an additional benefit in decreasing almost half of positive margin cases (3/7) or 3.5% (3/86) of total US- guided BCS.

We observed significantly increased risks of positive or close margin in women presented with IDC + DCIS (OR = 5.51 95%CI 1.51-20.11; p=0.010), ILC (OR=15.31 95%CI 1.99-117.72; p=0.009) and multi-foci tumors (OR=13.03, 95%CI 1.88-90.53; p=0.009) compared to pure IDC+ others and single lesion tumors especially if follow ≥1 mm free margin guideline. These trends had also been found in positive margin cases while following the SSO/ASTRO guidelines although they had not reached statistically significant. Because it may be more difficult to evaluate the full extent of disease by intra-operative US. These factors were concordance to the prior report (Bani et al., 2009).

This study has several important limitations. First, it was the retrospective descriptive cohort, the patient characteristics and surgeon practice may not generalizable to all treatment settings. Additionally, there was no long term result of local recurrence to correlate the findings.

Despite these limitations, there were a numerous meta-analysis studies from SSO/ASTRO guidelines for adequate margin (Thomas et al., 2014), results from Danish Breast Cancer Cooperative Group Study (Bodilsen et al., 2015) and other (Dixon et al., 2016) disproved the benefit of wider margin to the long term local failure rate. And this study has identified the significant impact of following the current margin guidelines with intraoperative evaluation procedures including US and frozen section to optimize the breast tissue resection with low re-excision risks. However, the future prospective study with a larger number of patients and the long term results are warranted to explore this concept.

In conclusion, with the current SSO/ASTRO for adequate margin guidelines, using of intra-operative ultrasound to locate the boundary for resection in breast conserving surgery presents a high success rate in obtaining final pathology free margin outcome and minimize re-operation risks especially when combined with intra-operative frozen section assessment. The chance of positive margin or close margin would be higher in cases of IDC combined with DCIS, ILC and multi-foci cancers.

References

Arriagada R, Lê MG, Rochard F, Contesso G (1996). Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. institut gustave- roussy breast cancer group. *J Clin Oncol*, **14**, 1558-64.

Aziz D, Rawlinson E, Narod SA, et al (2006). The role of re-excision for positive margins in optimizing local disease control after breast-conserving surgery for cancer. *Breast J*, **12**, 331-7.

Bani MR, Lux MP, Wenkel HE, et al (2009). Factors correlating with reexcision after breast-conserving therapy. *EJSO*, **35**, 32-7.

Bodilsen A, Bjerre K, Offersen BV, et al (2016). Importance of margin width and reexcision in breast conserving treatment of early breast cancer. *J Surg Oncol*, **113**, 609-15.

Bosma SC, van der Leij F, van Werkhoven E, et al (2016). Very low local recurrence rates after breast-conserving therapy:analysis of 88485 patients treated over a 28-year period. *Breast Cancer Res Treat*, **156**, 391-400.

Dixon JM, Thomas J, Kerr GR, et al (2016). A study of margin width and local recurrence in breast conserving therapy for invasive breast cancer. *EJSO*, **42**, 657-64.

Fisher B, Redmond C, Poisson R, et al (1989). Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in treatment of breast cancer. *N Engl J Med*, **320**, 822-8.

Flemimg FJ, Hill ADK, McDermott EW, et al (2004). Intraoperative margin assessment and re-excision rate in breast conserving surgery. *EJSO*, **30**, 233-7.

Habermann EB, Abbott A, Parsons HM, Virnig BA, Al-Refaie WB, Tuttle TM (2010). Are mastectomy rates really increasing in the United States? *J Clin Oncol*, **28**, 3437-41.

Holland R, Veling SHJ, Mravunac M, et al (1985). Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer*, **56**, 979-90.

Houssami N, Macaskill P, Marinovich ML, et al (2014). The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*, **21**, 717-30.

Irwig L, Bennetts A (1997). Quality of life after breast conservation or mastectomy: a systematic review. *Aust N Z J Surg*, **67**, 750-4.

Isaacs AJ, Gemignani ML, Pusic A, et al (2016). Association of

breast conserving surgery for cancer with 90-day reoperation rates in New York State. *JAMA Surg*, **151**, 648-55.

Kiebert GM, de Haes JC, van deVelde CJ (1991). The impact of breast-conserving treatment and mastectomy on the quality of life of early-stage breast cancer patients: a review. *J Clin Oncol*, **9**, 1059-70.

Krekel NMA, Haloua MH, Cardozo AMFL, et al (2013). Intraoperative ultrasound guidance for palpablebreast cancer excision (COBALT trial): a multicentre, randomised controlled trial. *Lancet Oncol*, **14**, 48-54.

Lichter AS, Lippman ME, Danforth DN Jr, et al (1992). Mastectomy versus breast- conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. *J Clin Oncol*, **10**, 976-83.

Malik HZ, George WD, Mallon EA, et al (1999). Margin assessment by cavity shaving after breast-conserving surgery: analysis and follow-up of 543 patients. *Eur J Surg Oncol*, **25**, 461-9.

Merrill AL, Coopey SB, Tang R, et al (2016). Implications of new lumpectomy margin guidelines for breast-conserving surgery: changes in reexcision rates and predicted rates of residual tumor. *Ann Sug Oncol*, **23**, 729-34.

Mullenix PS, Cuadrado DG, Steele SR, et al (2004). Secondary operations are frequently required to complete the surgical phase of therapy in the era of breast conservation and sentinel lymph node biopsy. *Am J Surg*, **187**, 643-6.

Nattinger AB, Gottlieb MS, Veum J, Yahnke D, Goodwin JS (1992). Geographic variation in the use of breast-conserving treatment for breast cancer. *N Engl J Med*, **326**, 1102-7.

Neslihan C, Kelly KH, Aysegul AS, et al (2005). Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. *Ann of Surg Oncol*, **14**, 1458-71.

NIH consensus conference (1991). Treatment of early-stage breast cancer. *JAMA*, **2653**, 391-5.

Olsha O, Shemesh D, Carmon M, et al (2011). Resection margins in ultrasound-guided breast-conserving surgery. *Ann Surg Oncol*, **18**, 447-52.

Olson TP, Harter J , Munoz A, et al (2007). Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rate of re-excision and local recurrence. *Ann Surg Oncol*, **14**, 2953-60.

Park CC, Mitsumori M, Nixon A, et al (2000). Outcome at 8 years after breast conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol*, **18**, 1668-75.

Schnitt SJ, Abner A, Gelman R, et al (1994). The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer*, **74**, 1746-51.

Thomas AB, Mark RS, Jennifer JG, et al (2014). Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol*, **32**, 1502-6.

Veronesi U, Volterrani F, Luini A, et al (1990). Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J Cancer*, **26**, 671-3.