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Management of Early Node-Positive Breast Cancer in Australia: A Multi-Centre Study

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Abstract

Aims To examine practice patterns for breast cancer patients with limited sentinel node (SN) disease in light of the ACOSOG Z0011 results.

Methodology Retrospective analysis of patients with T1-2 breast cancer and positive sentinel lymph node biopsy (SLNB) admitted between January 2009 and December 2012. Patient demographics, tumour characteristics and treatments were recorded.

Results Eight hundred positive SLNBs were identified. 452 (56.5%) proceeded to completion lymph node dissection (cALND). cALND rate decreased from 65.1% to 49.7% from 2009-10 to 2011-12. cALND was performed for micrometastasis or isolated tumour cells in 39.3% in 2009-10 and 22.2% in 2011-12, while for macrometastases the rates were 83.1% and 68.6%, respectively. cALND rates diminished for both Z0011-eligible and ineligible patients.

Conclusion The ACOSOG Z0011 trial presentation and publication coincided with a reduction in cALND for breast cancer with limited nodal disease. There appears equipoise regarding management of macrometastatic SN disease.

Introduction

The axillary lymph node status for breast cancer patients is an important prognostic factor and may guide adjuvant therapy decisions. SLNB is the surgical standard of care for clinically node negative patients and has been traditionally followed by cALND if the SN is involved (1-3).

Whilst the use of SLNB has eliminated the need for cALND in SN negative patients (4-7), the situation for SN positive patients with early stage breast cancer is less certain (8). Institutional and national series of selective treatment of the axilla have yielded differing results (9-11). The American College of Surgeons Oncology Group Z0011 trial included clinically node negative patients with one or two positive SNs treated with breast conserving surgery (BCS) randomised to cALND or no further axilla-specific treatment. The lack of significant difference in survival or locoregional recurrence between the arms defined a select cohort of patients with a positive SN in whom cALND may be safely omitted (12).

The Z0011 trial is regarded by many as a practice-changing trial, with cALND changing from standard for SN positive patients to having a more limited role (13-15). The extent to which practice has been changed is uncertain – some argued that the limitations of the Z0011 trial restrict its clinical significance (16, 17). Regional and national differences are evident, with opinions from North American being more likely to embrace the findings of the Z0011 trial

as definitive (13-15), while those from Europe and Australia tending to be more guarded (16, 17).

We sought to examine current practice patterns in the management of patients with early breast cancer and SN involvement in Melbourne, Australia. A secondary objective was to assess the impact of the Z0011 trial in this setting.

Methods

This multi-center retrospective study included all patients at least 18 years of age with breast cancer ≤5cm in diameter, undergoing SLNB between January 1st 2009 and December 31st 2012 with at least one positive SN. Local protocols were followed for SN localisation and pathology processing and reporting, without central review. SN disease detected via immunohistochemistry (IHC), standard haematoxylin and eosin (H&E) stains of serial sections or routine histopathology was included. Data were collected from medical records and pathology reports of seven hospital-based breast units and one private pathology provider in Melbourne, Australia. Data were de-identified and entered into a central database. The breast units involved in this study were those of The Royal Melbourne & The Royal Women's Hospital, The Peter MacCallum Cancer Centre, Monash Medical Centre, The Austin Hospital, The Alfred Hospital, St Vincent's Hospital Melbourne and The Northern Hospital. The private pathology provider was Focus Pathology.

Demographics, pathology and treatment details were recorded for each eligible case. Patient age at diagnosis and tumour features including pathological type, maximal size, highest nuclear grade, hormone receptor status, lymphovascular invasion (LVI) and multifocality were recorded. The total number of lymph nodes removed, the number of positive lymph nodes, and the maximal size of metastatic deposits at SLNB and cALND were recorded. The type of breast surgery (total mastectomy (TM), or BCS) and the use of chemotherapy, radiotherapy and/or endocrine therapy were also recorded. For cases of multifocal breast cancer, the largest focus and the highest grade were recorded for primary tumour size and grade, respectively. Cases of bilateral breast cancer with bilateral axillary surgery were recorded with the details for each side as separate entries. Where more than one metastatic nodal deposit was present, the size of the largest deposit was recorded. Most treatment recommendations arose from hospital-based multi-disciplinary meetings.

Between groups differences were assessed using Chi-2 or Fisher's exact test for categorical variables and either two-sample t-tests or Wilcoxon rank-sum for all continuous variables.

Factors strongly associated with cALND based on univariable analysis and those of clinical relevance were included in a number of multivariate logistic regression models, with the adjustment for admitting hospital and number of nodes removed at SLNB. All models were compared using likelihood ratio test and the model with best fit was chosen to be the final one. All statistical tests were 2-sided and a $P < 0.05$ was considered statistically significant. Analyses were performed using Stata12 (StataCorp, Tx, USA).

Results

A total of 797 patients with T1 or T2 breast cancer underwent 800 SLNBs that yielded at least one positive SN between 1st January 2009 and 31st December 2012. There were 348/800 (43.5%) cases of SLNB only and 452/800 (56.5%) that proceeded to cALND. The clinicopathologic features for the SLNB only group versus the cALND group are shown in Table 1. Compared to those who had SLNB only, patients who received cALND were significantly younger (*P*<0.001) with larger tumours (*P*<0.001) of higher grade (*P*=0.004) with LVI (*P*<0.001) and multifocality (*P*=0.003). Due to different patient catchments, there were differences in the proportion of TMs and cALNDs performed between Hospitals (*P*<0.001) (data not shown).

The number of lymph nodes removed at SLNB and cALND is shown in Table 2. The likelihood of cALND was associated with the extent of SN involvement. Of those with ITCs or micrometastases, 97/325 (29.8%) proceeded to cALND, while 335/447 (74.9%) of those with macrometastases had cALND. There were a greater number of positive nodes identified in the SLNBs of those who had a cALND, compared to those who had SLNB alone (*P*<0.001). There was a strong association between the total number of SNs removed and the incidence of cALND with 44/452 (9.7%) patients in the cALND group having > 4 SNs removed, compared to 71/348 (20.4%) in the SLNB only group (*P*<0.001).

There were 153/452 (33.8%) positive cALNDs, 57/151 (37.7%) had a single non-SN involved, 35/151 (23.2%) had 2 and 59/151 (39.1%) had 3 or more positive non-SNs. For cases where the size of disease in cALND specimens was known, 25/106 (23.6%) had ITCs or micro-metastases and 81/106 (76.4%) had residual macrometastasis.

Consistent with the observation that cALND patients had higher risk disease, where treatment details were available, 294/370 (79.5%) patients in the cALND group received chemotherapy, compared with 101/229 (44.1%) in the SLNB only group (*P*=0.002). Endocrine therapy was given to 335/371 (90.3%) patients in the cALND group, compared to

203/229 (88.6%) patients in the SLNB only group (*P*=0.5). Of those who had TM 69/183 (37.7%) received radiotherapy, compared to 389/415 (93.7%) who had BCS. Whole breast radiotherapy after BCS was given to 162/175 (92.6%) of those having SLNB alone and 227/240 (94.6%) having cALND (*P*=0.4). Post mastectomy radiotherapy was given to 15/52 (28.8%) of those having SLNB only, compared to 54/131 (41.2%) of those having cALND (*P*=0.1)

There was a total of 242/800 (30.3%) TMs and 558/800 (69.8%) BCSs performed. Patients who had a TM were more likely to have larger primary tumours compared to those undergoing BCS (median size 2.5cm vs 2.0cm, *P*<0.001) as well as more LVI (49.8% vs. 40.8%, *P*<0.001), multifocality (40.3% vs. 12.9%, *P*<0.001) and a higher nuclear grade (grade 3: 45.0% vs 33.9%, *P*=0.002). Patients who had a TM more likely to receive chemotherapy (75.0% vs. 61.9%, *P*=0.002), compared to patients who received BCS (Table 1).

As expected, the extent of lymph node disease with TM was greater than with BCS (Table 3) and these patients were more likely to undergo cALND (*P*<0.001). For those who had TM, 162/242 (66.9%) had cALND compared with 290/558 (52.0%) for those with BCS. There was no significant difference in the size (*P*=0.8) or number (*P*=0.2) of nodal deposits identified at cALND for those who had TM versus BCS.

Table 4 shows that there was a reduction in the rate of cALND performed in the two years after the release of the Z0011 trial in 2011-2012 (221/445, 49.7%), compared to the year of and year prior to the release in 2009-2010 (231/355, 65.1%) (*P*<0.001). The reduction in cALND rate was associated with an increase in the number SLNBs containing ITCs or micrometastases as the largest SN deposit that did not proceed to cALND (60.7% to 77.8%; *P*=0.001). Whilst cALND was performed in the majority of patients with macrometastases in the SN both before and after the release of the Z0011 trial, there was an increase in the number SLNBs containing macrometastases as the largest SN deposit that did not proceed to cALND (16.9% to 31.4%; *P*<0.001).

The Z0011 trial excluded patients who were male, had mastectomy, multifocal tumours, bilateral tumours, 3 or more positive nodes at SLNB, IHC detected SN deposits and matted nodes or gross extranodal disease at SLNB (12). The number of patients in this study with matted nodes or gross extranodal disease is unknown. Considering all other criteria, there were 400 (50%) patients in this study who would have met the Z0011 inclusion criteria.

Table 4 shows a reduction in the rate of cALND for this Z0011-eligible group of patients from 65.1% to 48.6% between 2009-10 and 2011-12 (P=0.001).

Of the 400 cases which would have been excluded from the Z0011 trial, 61 would have been excluded only due to containing IHC detected SN metastases as the largest nodal deposit. For these patients, there was a reduction in the rate of cALND from 3/24 (12.5%) to 0/37 (0%) between 2009-10 and 2011-12 (P=0.06). There were 120 cases that would have been eligible for the Z0011 but for the fact they had a TM. The rate of cALND for this group reduced from 42/57 (73.7%) in 2009-10 to 39/63 (61.9%) in 2011-12 (P=0.1). The remaining 219 patients were excluded on the basis of having one or more of male gender, multifocal tumour, bilateral tumour, or more than 2 positive nodes at SLNB. There were 158 patients in this study who had BCS but would have been excluded from the Z0011 trial. Seventy-five of these patients had multifocal disease, a further 21 had more than 2 positive SNs, 61 had IHC detected nodal deposits and one patient was of male gender.

Multivariate analysis of the total cohort for associations with cALND adjusted for admitting Hospital and number of nodes removed at SLNB, reveals that younger patients (P<0.001) with tumours of higher nuclear grade (P=0.003), larger SN deposits (P<0.001), a greater number of positive nodes at SLNB (P=0.005) and those who underwent mastectomy rather than BCS (P=0.020) were more likely to proceed to cALND. Each of these factors was an independent risk factor for cALND, as was the time period after Z0011 (P<0.001) (Table 5). The results indicate that patients with multifocal tumours were more likely to have TM (p<0.001) and be younger (p=0.031). Due to these confounding factors, it was decided to include TM and age in the multivariant analysis and to exclude multifocality. These results are similar to those reported in a study examining mulitfocality and multicentricity in breast cancer (19).

Discussion

Management of the axilla in early breast cancer has evolved from routine ALND for most patients to a selective and well-validated approach based on assessment of the SN, with no further axillary treatment for those with a negative SN. Completion ALND has remained standard for patients with a positive SN (1, 3). The low rate of locoregional recurrence and similar survival figures for patients in both arms of the Z0011 trial has challenged the need for routine further axillary treatment (12).

The results of the Z0011 trial are impressive and informative; however, its limitations restrict the extent to which its findings can be applied. It included a select group of predominately older patients with small ER-positive tumours of ductal histology and low axillary tumour burden. It is unknown whether the results of the Z0011 trial are applicable to a more heterogeneous population. Furthermore, there was extensive use of systemic adjuvant therapy in the Z0011 trial patients. Over 95% of patients received adjuvant chemo- and/or endocrine therapy, which are known to reduce locoregional recurrence (18). Most patients in the Z0011 trial received whole breast irradiation without well-defined fields and so although no axillary-specific irradiation was performed, it is likely that a significant portion of the axilla was treated in patients on both study arms (20). Others received no radiotherapy at all and some received directed nodal irradiation via a 3rd field (21).

Findings similar to those of the Z0011 trial have been reported in the IBCSG trial 23-01, that randomised patients with SN micrometastases to SLNB only or cALND (22). At a median follow-up of 5 years, there was no difference in disease free survival or locoregional recurrence between the two study arms. Unlike the Z0011 trial, the IBCSG trial 23-01 included a small proportion of patients treated with mastectomy. In contrast to the Z0011 and IBCSG 23-01 trials, the Dutch MIRROR study assessed the 5-year outcome of patients with micrometastases or ITCs in the SN treated with minimal adjuvant systemic therapy and reported an increased risk of regional recurrence if cALND was omitted (9). A recent review of studies examining axillary recurrence after positive SLNB without cALND showed a local recurrence rate of 0% to 7.1% for over 7000 patients after a median follow-up of 45 months (23).

The European AMAROS trial, published in 2014, was a randomised, multicenter, phase 3 non-inferiority trial that enrolled 4832 patients and found that axillary radiotherapy provides comparable regional control to cALND with significantly less morbidity for patients with T1-2 primary breast cancer, no palpable lymphadenopathy and a positive SN (24). While this shows that surgery and radiotherapy provide equivalent control, it does not address the fundamental question of the need for any further axilla-specific local therapy in patients with limited disease in the SN.

There has been a mixed international response to the Z0011 trial. Some institutions have embraced the findings of the Z0011 trial and changed clinical practice accordingly (13-15). A recent survey of 849 respondents from the American Society of Breast Surgeons concluded that the Z0011 trial has changed surgical practice with respondents embracing the findings of

the Z0011 trial and hence changing their practice accordingly (25). The American Society of Clinical Oncology guidelines have recently been updated to incorporate this change (26). Others urge caution, suggesting that a single randomised trial in a select subgroup of patients treated in a distinct medical system is inadequate data on which to base large scale change in long-standing practice (16, 17). The application of Z0011 to a European population led to the omission of cALND in less than 10% of all SLNBs and it was therefore concluded that the perception that Z0011 was a "practice changing" trial was unjustified (16). An Australian study reported that the Z0011 trial is relevant to 9.3% of all breast cancer patients and 21.5% of node-positive breast cancer patients (27). We found that 50% of patients with T1 or 2 tumours and positive SNs met the Z0011inclusion criteria and that coinciding with the publication of this Trial, there has been a significant reduction in the rate of cALND for these patients ($P<0.001$).

This study also demonstrates that the Z0011 findings may have been extrapolated in some cases not meeting the trial's inclusion criteria, for example in patients undergoing mastectomy. There were 80/242 (33.1%) patients in the current study who underwent mastectomy and did not proceed to cALND. Given that the Z0011 trial excluded patients who underwent mastectomy and the IBCSG 23-01 trial was restricted to patients with micrometastases and only 9% of its participants underwent mastectomy, it is unknown whether the findings of these trials can be safely applied to this subset of patients (12, 22).

Overall, patients in our cohort who underwent a mastectomy had higher risk disease and were more likely to receive cALND and chemotherapy than those who underwent BCS. Other studies have shown that patients with low volume SN disease who undergo mastectomy experience low regional recurrence rates, despite the lack of axillary dissection and rare axillary irradiation (28, 29). Milgrom et al showed that the 4-year rate of regional nodal recurrence in these patients was 1.2%, similar to that of analogous patients undergoing BCS (28). Omission of axillary-specific treatment may be possible in this select group of patients, however, further studies comparing outcomes of mastectomy patients with a positive SLNB treated with and without axillary treatment are needed to identify patients who may benefit from additional therapy and those who may safely avoid over-treatment.

Conclusion

This study shows that in Melbourne, Australia, the management of the axilla for patients with early node-positive breast cancer has changed with the presentation and publication of the Z0011 trial, but that not all Z0011-eligible patients are being managed according to the trial,

and trial results have been extrapolated to some non-eligible patients. Given that the Z0011 trial has limitations and is applicable to only 50% of SN positive early breast cancer patients, additional trials are needed to better define the patient population in which cALND can be safely omitted.

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TABLE 1 Clinicopathologic Characteristics for SLNB only vs cALND

	SLNB only (N=348)	cALND (N=452)	*P*
Age, yr			
Median (SD)	61.7 (12.7)	56.1(11.8)	
			<0.001
Age, yr, no. (%)			
≤ 50 years	77 (22.1)	159 (35.2)	
			<0.001
>50 years	271 (77.9)	293 (64.8)	
Tumour type, no. (%)			
IDC	287 (82.5)	364 (80.5)	
			0.068
ILC	38 (10.9)	67 (14.8)	
Mixed IDC/ILC	9 (2.6)	14 (3.1)	
Other	14 (4.0)	7 (1.5)	
Tumour size, cm			
Median (min, max)	1.9 (0.1, 5.0)	2.2 (0.2, 5.0)	
			<0.001
Tumour size, no. (%)			

≤ 2cm	203 (58.3)	202 (44,7)
<0.001		
>2cm	145 (41.7)	250 (55.3)
Nuclear grade, no. (%)		
I	63 (18.2)	46 (10.2)
0.004		
II	167 (48.1)	224 (49.8)
III	117 (33.7)	180 (40.0)
Missing	1	2
Hormone receptor status, no. (%)		
Positive	318 (91.6)	409 (90.5)
0.572		
Negative	29 (8.4)	43 (9.5)
Missing	1	0
HER2 status, no. (%)		
HER2-	304 (87.6)	383 (84.7)
0.246		
HER2+	43 (12.4)	69 (15.3)
Missing	1	0
LVI, no. (%)		
Yes	122 (36.2)	219 (49.1)
<0.001		
No	215 (63.8)	227 (50.9)
Missing	11	6
Multifocality, no. (%)		
Yes	56 (16.7)	113 (25.3)
0.003		

No	292 (83.3)	338 (74.7)
Missing	0	1
Breast operation, no. (%)		
BCS	268 (77.0)	290 (64.2)
<0.001		
TM	80 (23.0)	162 (35.8)
Endocrine therapy, no. (%)		
Yes	203 (88.6)	335 (90.3)
0.519		
No	26 (11.4)	36 (9.7)
Missing	119	81
Chemotherapy, no. (%)		
Yes	101 (44.1)	294 (79.5)
0.002		
No	128 (55.9)	76 (20.5)
Missing	119	82
Radiotherapy, no. (%)		
Yes	177 (78.0)	281 (75.7)
<0.001		
No	50 (22.0)	90 (24.3)
Missing	121	81

TABLE 2 Extent of Lymph Node Disease

	SLNB-only Group	cALND Group	
		SLNB	cALND*
P for SLNB comparison	(N=348)	(N=452)	(N=452)
Total no. nodes removed			
Median	2	2	13
0.010			
IQR	1, 4	1, 3	9, 17
Missing	0	0	15
Positive nodes, no. (%)			
0	0	0	299 (66.2)
<0.001			
1	302 (86.8)	324 (71.7)	57 (12.6)
2	38 (10.9)	90 (19.9)	35 (7.7)
≥3	8 (2.3)	38 (8.2)	59 (13.1)
Missing	0	0	2
Largest nodal metastasis, no. (%)			
ITC/Micro	228 (67.1)	97 (22.5)	25 (23.6)
<0.001			
Macro	112 (32.9)	335 (77.5)	81 (76.4)
Missing	8	20	47

NOTE: *cALND refers only to nodes removed at the cALND, nodes removed at SLNB are listed separately in the preceding column.

Table 3 Extent of Sentinel Node Disease for BCS vs TM

	BCS (N=558)	TM (N=242)	*P*
Total no. nodes removed at SLNB			
Median	2	2	0.004
IQR	1, 3	2, 4	
Positive nodes at SLNB, no. (%)			
1	458 (82.1)	168 (69.4)	<0.001
2	76 (13.6)	52 (21.5)	
≥3	24 (4.3)	22 (9.1)	
Size of metastasis at SLNB, no. (%)			
ITC/Micro	244 (45.3)	81 (34.8)	0.007
Macro	295 (54.7)	152 (65.2)	
Missing	19	9	
Positive nodes at ALND, no. (%)			
0	190 (65.7)	109 (67.7)	0.236
1	40 (13.8)	17 (10.6)	
2	26 (9.0)	9 (6.0)	
≥ 3	33 (11.4)	26 (16.1)	
Missing	1	1	

Size of metastasis at ALND, no. (%)		
ITC/Micro	19 (22.8)	6 (17.6)
0.463		
Macro	53 (77.8)	28 (82.4)
Missing	28	19

TABLE 4 Changes in Lymph Node Management

	2009-10 (N=355)	2011-12 (N=445)	*P*
Axillary surgery, no. (%)			
SLNB only	124 (34.9)	224 (50.3)	
<0.001			
cALND	231 (65.1)	221 (49.7)	
Largest SN metastasis, no. (%)			
ITC/Micro			
SLNB only	88 (60.7)	140 (77.8)	
0.001			
cALND	57 (39.3)	40 (22.2)	

Macro			
SLNB only		33 (16.9)	79 (31.4)
<0.001			
cALND		162 (83.1)	173 (68.6)
Missing		15	13
Z11 Eligible, no. (%)			
SLNB only		65 (34.9)	110 (51.4)
0.001			
cALND		121 (65.1)	104 (48.6)

TABLE 5 Multivariate Association with cALND

	Odds Ratio (CI)	Multivariate *P*
Age, yrs		
≤ 50 vs > 50	2.43 (1.64 - 3.61)	<0.001
Tumour size, cm		
> 2 vs ≤ 2	1.10 (0.76 - 1.58)	0.61
Nuclear grade		
Grade III vs I, II	1.51 (1.15 - 1.98)	0.003
Largest SN metastasis		
Macromet vs ITC/Micromet	7.81 (5.42 - 11.25)	<0.001
Breast surgery		
TM vs BCS	1.61 (1.08 - 2.40)	0.020
Number positive nodes at SLNB		
≤ 2 vs >2	3.87 (1.52 - 9.86)	0.005
Time period, yrs		
2009-10 vs 2011-12	0.46 (0.32 - 0.65)	<0.001

NOTE: Multivariate analysis for admitting Hospital and total number of nodes removed at SLNB

References

1. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-33
2. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25:3657-3663
3. Mansel RE, Fallowfield L, Kissin M, et al. Randomised multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst.* 2006;98:599-609
4. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med.* 2003;349(6):546-53

5. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. *Ann Surg*. 1997;226:271-6
6. Giuliano AE, Haigh PI, Brennan MB, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *J Clin Oncol*. 2000;18:2553-9
7. Bergkvist L, de Boniface J, Jonsson PE, et al. Axillary recurrence rate after negative sentinel node biopsy in breast cancer: three-year follow-up of the Swedish Multicenter Cohort Study. *Ann Surg*. 2008;247:150-156
8. Chu KU, Turner RR, Hansen NM, et al. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg*. 1999;229:536-541
9. Pepels MJ, de Boer M, Bult P, et al. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumour cells. *Ann Surg*. 2012; 255:116-21
10. Bilimoria K, Bentrem D, Hansen N, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. *J Clin Oncol*. 2009;27(18):2946-53
11. Jeruss JS, Winchester DJ, Sener SD, et al. Axillary recurrence after sentinel node biopsy. *Ann Surg Oncol*. 2005;12:34-40
12. Giuliano AE, Mcall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010;252:426-432
13. Yi M, Kuerer HM, Mittendorf EA, et al. Impact of the American College of Surgeons Oncology Group Z0011 criteria applied to a contemporary patient population. *J Ann Coll Surg*. 2013;216(1):105-13
14. Caudle AS, Hunt KK, Kuerer HM, et al. Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: a practice-changing trial. *Ann Surg Oncol*. 2011;18(9):2407-12
15. Caudle AS, Hunt KK, Tucker SL, et al. American College of Surgeons Oncology Group (ACOSOG) Z0011: impact on surgeon practice patterns. *Ann Surg Oncol*. 2012;19(10):3144-51
16. Guth U, Myrick ME, Viehl CT, et al. The post ACOSOG Z0011 era: does our new understanding of breast cancer really change clinical practice? *Eur J Surg Oncol*. 2012;38(8):645-50

17. Gatzemeier W, Mann GB. Which sentinel lymph-node (SLN) positive breast cancer patient needs an axillary lymph-node dissection (ALND) – ACOSOG Z0011 results and beyond. *Breast*. 2013;22(3):211-21
18. Buchholz TA, Tucker SL, Erwin J, et al. Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy. *J Clin Oncol*. 2001;19:2240-2246
19. Lynch SP, Lei M, Chavez-MacGregor, et al. Multifocality and multicentricity in breast cancer and survival outcomes. *Ann Oncol*. 2012;0: 1-6
20. Schlembach PJ, Buchholz TA, Ross MI, et al. Relationship of sentinel and axillary level I-II lymph node to tangential fields used in breast irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51:671-678
21. Jagsi R, Chadha M, Ballman K et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. *J Clin Oncol.* 2014;32 (32):3200-3206
22. Galimberti V, Cole BF, Zurrida S et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14:297-305
23. Francissen CMTP, Dings PPJM, van Dalen T, et al. Axillary recurrence after a tumour-positive sentinel lymph node biopsy without axillary treatment: a review of the literature. *Ann Surg Oncol*. 2012;19:4140-4149
24. Donker M, van Tienhoven G, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicenter, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014; 15(12):1303-1310
25. Gainer SM, Hunt KK, Beitsch P, et al. Changing behavior in clinical practice in response to the ACOSOG Z0011 trial: A survey of the American Society of Breast Surgeons. *Ann Surg Oncol*. 2012;19:3152-3158
26. Lyman GH, Temin S, Edge SB et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Update. *J Clin Oncol.* 2014; 32 (11):1-22
27. Ngui NK, Elder EE, Jayasinghe UW, et al. Relevance of the American College of Surgeons Oncology Group Z0011 Trial to breast caner in the Australian setting. *ANZ J Surg*. 2013;83:924-928
28. Milgrom S, Cody H, Tan L, et al. Characteristics and outcomes of sentinel node-positive breast cancer after total mastectomy without axillary-specific treatment. *Ann Surg Oncol*. 2012;19:3762-3770

29. Zumsteg ZS, Morrow M, Arnold B, et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer. *Ann Surg Oncol*. 2013;20:3469-3476