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# Axillary dissection in sentinel lymph node positive breast cancer: Is the staging information worthwhile for patients?

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**Abstract**

Aims:

The Z0011 randomised trial demonstrated no significant difference in axillary recurrence rate or survival with or without axillary dissection in patients with a positive sentinel node biopsy. However, there is continuing controversy regarding the generalizability of its results, and axillary dissection provides additional pathologic staging information that may guide adjuvant therapy. Thus, axillary dissection after positive sentinel node biopsy is being further investigated in an actively recruiting randomised trial. We elicited patients' preferences for axillary dissection versus no axillary dissection after positive sentinel node biopsy for early breast cancer.

Methods:

Patients who had undergone axillary dissection after positive sentinel node biopsy as part of breast conserving therapy were provided with a validated, self-rated questionnaire. The questionnaire comprised two trade-off questions to determine the maximum chance of developing arm side-effects from axillary dissection to justify the benefit of additional axillary staging information. Social, demographic and clinical details were collected.

Results:

Ninety-nine of the 126 eligible patients returned the questionnaire and 76 completed the trade-off assessment. The median age of participants was 62 years. The median numbers of sentinel and axillary nodes removed were 2 and 12, respectively. Forty-seven percent of participants had arm swelling or tenderness of any severity. Seventy-five percent of participants would have axillary dissection even if the chance of arm side-effects like they had experienced was 100%.

Conclusion:

Most patients with early breast cancer preferred axillary dissection after positive sentinel node biopsy for the additional staging information even though there was no survival benefit from axillary dissection.

Keywords: Axillary Lymph Node Dissection, Lymph Node Biopsy, Sentinel Lymph Node Biopsy, Patient Preference



**Introduction**

Sentinel lymph node biopsy (SLNB) is a safe and effective axillary staging procedure in the management of patients with clinically node-negative breast cancer. Randomised trials of SLNB alone versus axillary lymph node dissection (ALND) in pathologically node-negative patients showed that SLNB had lower rates of lymphedema, impaired shoulder movement and sensory disturbance (1, 2). Therefore, SLNB alone in node-negative patients enables reliable pathologic staging of the axilla with reduced risk of morbidity associated with ALND.

In patients with positive SLNB, the omission of ALND remains controversial. The American College of Surgeons Oncology Group (ACOSOG) Z0011 randomised controlled trial of ALND versus no ALND after positive SLNB involving 1–2 nodes in patients with invasive breast cancer showed no significant difference in 10-year overall survival, disease-free survival, local recurrence rates and regional recurrence rates (1-4). The rates of complications including wound infection, axillary seroma and paraesthesiae were significantly higher with ALND than no ALND. Lymphedema was significantly more common after ALND by subjective reporting but not by arm measurements (5). Although the study has rapidly led to a shift in surgical practice at some institutions, generalizability of its findings has been questioned. Its accrual did not reach the target sample size; a significant number of participants were lost to follow-up; and approximately 40% of the patients had

sentinel nodal micrometastases only with a risk profile that differed from those with nodal macrometastases (4). Importantly, a subset of patients received protocol-prohibited targeted nodal radiation which might have contributed to the apparent equivalence between the study arms (6).

ALND in SLNB-positive patients provides additional pathologic staging and prognostic information that could influence recommendations for adjuvant radiotherapy and systemic therapy (7, 8). This knowledge may outweigh the risk of morbidity associated with ALND for node-positive patients, and is often used to justify an ALND. Thus, the role of ALND following a positive SLNB remains highly controversial and is being examined in an actively recruiting randomised trial (9).

Incorporating patient preferences into treatment decision-making could improve treatment satisfaction, compliance and clinical outcomes (10). Several studies had provided valuable insight by evaluating patient preferences regarding breast cancer treatment. A study showed that patients with early breast cancer required a median 1% improvement in overall survival to justify adjuvant chemotherapy (11). Another study showed that women who had had ALND judged a median 3% improvement in overall survival and a 1% chance that ALND would change treatment recommendation sufficient to justify ALND (12).

To our knowledge, no study has examined patient preferences for ALND after a positive SLNB. The aim of this single-institution observational cohort study was to determine patient preferences for ALND versus no further surgical intervention after a positive SLNB.

**Patients and Methods**

Women who underwent SLNB and ALND as part of definitive breast-conserving therapy for invasive breast cancer 1-60 months prior to accrual were recruited to the study during routine follow-up visit at the Peter MacCallum Cancer Centre in Melbourne,

Australia. Patients with recurrent or metastatic breast cancer were excluded. The study was approved by the Human Research Ethics Committee of the Peter MacCallum Cancer Centre.

Patients were screened for study eligibility by the Principal Investigator. Upon arrival at the Cancer Centre for routine follow-up visit, eligible patients were provided with an introductory letter, questionnaire and a reply-paid envelope by the administrative staff. As stated on the introduction letter, consent was implied by the completion of the questionnaire.

Participants recorded their highest level of education, employment status, marital status, how much time their relatives and/or friends would have available to care for them if required, whether they had any dependents and whether they had any close friends or relatives who had died from cancer. The FACT-B+4 questionnaire was incorporated into the questionnaire to determine the impact of arm morbidity on patient preferences (13). As subjective measures of lymphedema were shown to have a greater impact on patients' quality of life than objective measures of lymphedema, only subjective measures of symptoms were collected in this study (14, 15).

Information on adjuvant therapies were not collected but based on the standards of care at the institutions involved, the vast majority of participants would have received adjuvant radiotherapy to the breast. Details on the adjuvant systemic treatments were not recorded as there is a lack of a clear relationship with lymphedema (16).

The questionnaire comprised of two trade-off questions based on standardised, hypothetical scenarios. The questionnaire was adapted from an interview used in earlier preference studies and the written version was validated in a study of preferences for adjuvant chemotherapy in patients with early colon cancer (17-19). The introduction to the scenario outlined the purpose of axillary dissection to obtain accurate staging information, and the implication that this information had on recommendations for adjuvant treatment and prognostic information. In light of the Z0011 study findings, the questionnaire specifically

stated that ALND might not result in a survival benefit. The scenario then asked patients to consider the side-effects that they had experienced from ALND, and choose the maximum chance of developing those side-effects that they judged acceptable for the benefit of obtaining staging information. The chance of developing those side-effects was presented to increase from 5% to 100% for the first trade-off question, and 15% to 100% for the second trade-off question. Completed questionnaires were collected at the clinic or returned via a reply-paid envelop.

The Principal Investigator reviewed the medical records and documented the patients' date of birth, date of SLNB, ALND, number of sentinel lymph nodes removed, number of sentinel nodes involved, number of axillary nodes removed and number of axillary nodes involved.

Statistical Analysis

A pragmatic sample size of 130 patients was determined that would allow simple proportions summarising patient preferences to be estimated with a 95% confidence intervals no wider than ± 9%. At an estimated accrual rate of 4 patients per week, it was expected that the target of 130 patients would be achieved in approximately 8 months. All statistical analyses were performed in R (version 3.3.2; R Development Core Team 2009) using standard and validated statistical procedures. Patient demographics, baseline characteristics and treatment details were described using descriptive statistics such as minimum, maximum, median, mean and standard deviation for quantitative variables. Qualitative variables were described in tabular form as counts and percentages. Fisher's exact tests, unpaired t-tests and Wilcoxon rank sum tests were used to assess whether patient demographic and quality of life factors were associated with patient preference to undergo an ALND. As the majority of the patients answered that they would agree to an ALND even if the chance of toxicity were

100%, the acceptable probability of toxicity was dichotomised to 100% versus less than 100%. All of the statistical tests and p-values were two-tailed, and p-values of <0.05 were considered significant.

## Results

### Patient characteristics

From 22 May 2014 to 11 February 2016, 126 eligible women were identified and there were 76 participants in the study. Recruitment was slower than expected and was ceased prior to the target of 130 patients being reached.

Patient characteristics are shown in Tables 1 and 2. The median age of the patients was 62 years. The majority of the patients were married with children. Most patients (92.1%) had 1–2 positive sentinel lymph nodes. ALND yielded no positive axillary nodes in 68.4% of patients (n=52) and 1–2 positive axillary nodes in 19.7% of patients (n=15).

The results of the individual FACT-B+4 items are listed in Table 3. The mean FACT-B+4 score (ARM subscale) was 17 with the majority having little or no symptoms. Severe arm symptoms were rare.

### Patient preferences

Patient preferences for ALND after SLNB are summarised in Figures 1 and 2. With a baseline chance of side-effects without ALND set at 5% or 15%, 74.6% (n=50) and 75.4% (n=52) of participants, respectively preferred ALND even if the chance of side-effects that they had experienced from ALND was 100%. Being married was associated with a higher rate of choosing ALND even if the chance of side-effects was 100% (p=0.04) (Table 4). The other demographic and clinical findings were not significantly associated with the patient

preferences. There was no significant association between the actual side-effects experienced by patients and their preferences.



**Discussion**

To our knowledge, this is the first report of patient preferences for the controversial subject of ALND after a positive SLNB involving 1–2 sentinel nodes in women with early stage breast cancer. In the preferences questionnaire, participants were told about a hypothetical scenario of a woman who had a positive sentinel lymph node biopsy and was facing the option of ALND. They were told that ALND may not improve the life expectancy but could aid staging and impact adjuvant therapy decisions. Despite the lack of impact on survival, most participants opted for ALND even if there was a 100% chance that the woman in the hypothetical scenario would experience the same toxicity that the participants had experienced thus far from ALND. We found that the majority of patients would choose to have ALND for additional staging information which could guide recommendations for adjuvant radiotherapy and/or systemic therapy even if ALND might not improve survival. This is despite the fact that 68% of participants had no positive axillary nodes from ALND and thus, unlikely to have benefited directly from ALND. These findings are consistent with published patient preferences studies on ALND which showed patients were generally willing to accept significant risks for small gains (12, 20, 21). In the study by Galper *et al*, patients who had ALND for early breast cancer required only a median of 1% chance of a change in treatment recommendation to justify ALND (12).

We found no significant association between the FACT+B+4 score and patient preference for ALND. This finding may be attributed to the small number of patients with moderate to severe symptoms of lymphedema and hence, inadequate power to find a

significant association. In addition, although the Z0011 study demonstrated increased morbidity in patients who had ALND after positive SLNB compared to patients who had SLNB only, our results suggested that the patients prioritised the gain of extra staging information from ALND over the risk of increased surgical morbidity (5).

Studies have shown that there are few predictors of patient preferences for cancer treatment other than treatment-related benefit and toxicity, experience of the treatment, and having dependents at home (22). Our finding of marital status as the only factor associated with patient preferences for ALND may be due to the small sample size. However, the consistent finding of few predictors for patient preferences across a number of studies suggests that preferences are not reliably predicted by patient characteristics but rather, are inherently individual and dependent on the values, attitudes and circumstances of the patients.

The strengths of our study include the novel data on patient preferences for ALND after a positive SLND based on their individual assessments of a trade-off between the morbidity of ALND versus the benefit of more accurate staging and prognostic information. We did not include survival as a consideration in the trade-off, which was consistent with contemporary literature (1-3). The main limitation of the study is the slower than expected patient accrual. After publication of the Z0011 study, the American Society of Clinical Oncology guidelines recommended that in general, women with 1–2 positive sentinel lymph nodes who had breast conserving surgery and were planned to have adjuvant whole breast irradiation should not undergo ALND (23). As a result, there had been a decline, albeit not a complete cessation, in the number of patients undergoing ALND after positive SLNB at our institution and elsewhere, reflecting the ongoing controversy (24, 25). In addition, the study patients had undergone both SLNB and ALND. Thus, their responses to the questionnaires might have been affected by cognitive dissonance reduction and bias in favour of ALND to view their previous decision to have an ALND in a favourable light (26). The option of

recruiting patients to the study prior to them making a decision on ALND was considered but we were concerned that this approach might increase the level of anxiety of the patients. Another option considered was inclusion of patients who had not had an ALND after positive SLNB. However, the option of ALND might not have been fully discussed with these patients given the change in surgical practice at our institution prior to commencement of the study and their inclusion could also potentially led to unnecessary anxiety, which would be unethical.

The Z0011 trial demonstrated the non-inferiority of observation compared to ALND in patients with 1–2 positive sentinel nodes from breast cancer. However, it was criticised for not meeting the accrual target closing prematurely after recruitment of less than 50% of the target, which might be partly attributed to the lack of equipoise. There was significant missing data, including 11% of data on the number of lymph node metastases and 32% of data on tumor grade (1, 2). Importantly, generalizability of the study findings has been questioned. In distinction from the broad study eligibility criteria, the majority of patients randomised had a small (T1), estrogen receptor-positive cancer and approximately 40% of them had sentinel nodal micrometastasis only. In addition, comprehensive radiation treatment data was not reported. A subsequent review of a sample of patients with available radiation treatment data showed that half of them received adjuvant high tangential breast radiation and a further fifth of them received regional nodal irradiation using a third field (4, 6). On the basis of a recently reported randomised trial which demonstrated non-inferiority of axillary radiotherapy compared to ALND, the impact of radiation treatment protocol non-compliance on the Z0011 findings could not be excluded (27). Thus, although Z0011 study has changed surgical practice at many institutions, omission of ALND after a positive SLNB has not been routinely adopted worldwide (28, 29). While the American Society of Clinical Oncology guidelines recommend omission of ALND in patients with one or two sentinel nodal

metastases who are treated with whole breast irradiation after breast-conserving surgery, the European Society for Medical Oncology guidelines have not made this specific recommendation for patients with 1–2 sentinel nodal macrometastases (9, 23, 30).

The actively recruiting POSNOC trial aims to address some of the limitations of Z0011 study (9). It recruits patients with 1 or 2 sentinel nodal macrometastases, and randomises patients to axillary treatment (ALND or radiotherapy or no further axillary treatment). Until more definitive data are available, it is particularly important to consider patient preference on the trade-off between the value of staging and prognostic information derived from ALND against the risk of its morbidity.

**Conclusion**

Although the study did not achieve full recruitment, the findings suggest that after a positive SLNB, most patients with early stage breast cancer expressed a preference to accept the morbidity of ALND as a trade-off for the additional staging information even in the absence of a survival benefit. As the role of ALND in this context remains controversial, it is vital that patient preferences on ALND after a positive SLNB are routinely incorporated in treatment decision making.

**Compliance with ethical standards**

**Conflicts of interest** The authors declare that there is no conflict of interest regarding the publication of this paper

**Research involving human participants** The study was approved by the Human Research Ethics Committee of the Peter MacCallum Cancer Centre and conforms to the principles of the 1964 Declaration of Helsinki and all subsequent revisions. All persons gave their informed consent prior to their inclusion in the study.

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**Table 1.** Clinical characteristics of patients (n=76)

| **Variable** | **Statistic** | **Results** |
|---|---|---|
| Age (years) | Mean (SD) | 61 (10) |
| | Median [range] | 62 [30-84] |
| Highest level of education | Less than university or college degree | 44 (58%) |
| | University or college degree | 32 (42%) |
| How would you describe your employment in the year before your surgery? | Employed | 50 (66%) |
| | Unemployed | 26 (34%) |
| What is your marital status? | Married | 52 (68%) |
| | Not married | 24 (32%) |
| How much of the time would relatives/friends be available to care for you if you needed it during the time you were having radiotherapy? | Most/All of the time | 48 (63%) |
| | None/Some of the time | 28 (37%) |
| Children (missing n=1) | No | 7 (9%) |
| | Yes | 68 (91%) |
| Dependent children (missing n=2) | No | 58 (78%) |
| | Yes | 16 (22%) |
| Dependent people (missing n=2) | No | 56 (76%) |
| | Yes | 18 (24%) |
| Close friend or relative who died from cancer (missing n=3) | No | 12 (16%) |
| | Yes | 61 (84%) |

**Table 2.** Pathologic characteristics of patients (n=76)

| **Variable** | **Statistic** | **Results** |
|---|---|---|
| Number of sentinel lymph node removed | Mean (SD) | 2.8 (1.5) |
| | Median [range] | 2 [1-7] |
| | Interquartile range | 2-4 |
| Number of sentinel lymph nodes involved | Mean (SD) | 1.4 (0.7) |
| | Median [range] | 1 [0-4] |
| | Interquartile range | 1-2 |
| Number of axillary lymph nodes removed | Mean (SD) | 12.3 (4.8) |
| | Median [range] | 12 [3-25] |
| | Interquartile range | 9-15 |
| Number of axillary lymph nodes involved | Mean (SD) | 0.9 (2.0) |
| | Median [range] | 0 [0-10] |
| | Interquartile range | 0-1 |

**Table 3.** FACT-B+4 Score (n=76)

| Variable | Statistic | Result |
|---|---|---|
| One or both arms are swollen or tender (missing n=1) | Not at all | 40 (53%) |
| | A little | 21 (28%) |
| | Somewhat | 8 (11%) |
| | Quite a bit | 4 (5%) |
| | Very much | 2 (3%) |
| Movement of my arm on the operated side is painful (missing n=1) | Not at all | 52 (69%) |
| | A little | 18 (24%) |
| | Somewhat | 4 (5%) |
| | Quite a bit | 0 (0%) |
| | Very much | 1 (1%) |
| I have a poor range of arm movements on this side | Not at all | 56 (74%) |
| | A little | 15 (20%) |
| | Somewhat | 3 (4%) |
| | Quite a bit | 2 (3%) |
| | Very much | 0 (0%) |
| My arm on this side feels numb | Not at all | 27 (36%) |
| | A little | 27 (36%) |
| | Somewhat | 13 (17%) |
| | Quite a bit | 7 (9%) |
| | Very much | 2 (3%) |
| I have stiffness of my arm on this side | Not at all | 54 (71%) |
| | A little | 16 (21%) |
| | Somewhat | 4 (5%) |
| | Quite a bit | 2 (3%) |
| | Very much | 0 (0%) |

| | | |
|---|---|---|
| FACT-B+4 Score (ARM subscale) | Mean (SD) | 17.0 (2.8) |
| | Median [range] | 18 [8-20] |
| | Interquartile range | 15-19 |



**Table 4.** Association between patient preferences and clinical-pathologic characteristics

| | **Accept ALND for 100% chance of arm side effects** | | | |
|---|---|---|---|---|
| **Variable** | **Statistic** | **No** | **Yes** | **p-value** |
| Age (years) | Mean (SD) | 62 (12) | 61 (10) | **0.69*** |
| | Median [range] | | | |
| Number of sentinel lymph nodes removed | Mean (SD) | 62 [30-84] | 61 [40-84] | **0.52**** |
| | Median [range] | 3.1 (1.7) | 2.7 (1.4) | |
| | Interquartile range | 2-4 | 2-3.5 | |
| Number of sentinel lymph nodes involved | Mean (SD) | 1.4 (0.6) | 1.3 (0.5) | **0.46**** |
| | Median [range] | 1 [1-3] | 1 [0-3] | |
| | Interquartile range | 1-2 | 1-2 | |
| Number of axillary lymph nodes removed | Mean (SD) | 12.1 (4.4) | 12.6 (5.0) | **0.80**** |
| | Median [range] | 12.5 [4-20] | 12 [3-25] | |
| | Interquartile range | 9-15 | 9-15.5 | |
| Number of axillary lymph nodes involved | Mean (SD) | 0.7 (1.7) | 0.7 (1.7) | **0.79**** |
| | Median [range] | 0 [0-7] | 0 [0-10] | |
| | Interquartile range | 0-0.5 | 0-1 | |
| What is the highest level of education you have completed? | Less than University or college degree | 15 (37%) | 26 (63%) | **0.06***** |
| | University or college degree | 4 (14%) | 25 (86%) | |
| How would you describe your employment in the year before your surgery? (grouped) | Employed | 11 (24%) | 35 (76%) | **0.41***** |
| | Unemployed | 8 (33%) | 16 (67%) | |
| What is your marital status? | Married | 10 (20%) | 40 (80%) | **0.04***** |
| | Not married | 9 (45%) | 11 (55%) | |

| | | | | |
|---|---|---|---|---|
| How much of the time would relatives/friends be available to care for you if you needed it during the time you were having radiotherapy? | Most/All of the time | 12 (26%) | 35 (75%) | **0.78*** ** |
| | None/Some of the time | 7 (30%) | 16 (70%) | |
| Do you have any children? | No | 0 (0%) | 5 (100%) | 0.32*** |
| | Yes | 18 (28%) | 46 (72%) | |
| Do you have any children who are dependent on your support? | No | 14 (26%) | 39 (74%) | 1.00*** |
| | Yes | 4 (27%) | 11 (73%) | |
| Do you have any people who are dependent on your support? | No | 11 (21%) | 41 (79%) | 0.20*** |
| | Yes | 6 (38%) | 10 (63%) | |
| Has a close friend or relative of yours died from cancer? | No | 2 (18%) | 9 (82%) | 0.71*** |
| | Yes | 16 (28%) | 41 (72%) | |
| One or both arms are swollen or tender | No | 9 (24%) | 28 (76%) | 0.59*** |
| | Yes | 10 (31%) | 22 (69%) | |
| Movement of my arm on the operated side is painful | No | 12 (24%) | 38 (76%) | 0.55*** |
| | Yes | 6 (32%) | 13 (68%) | |
| I have a poor range of arm movements on this side | No | 13 (25%) | 39 (75%) | 0.55*** |
| | Yes | 6 (33%) | 12 (67%) | |
| My arm on this side feels numb | No | 7 (28%) | 18 (72%) | 1.00*** |
| | Yes | 12 (27%) | 33 (73%) | |
| I have stiffness of my arm on this side | No | 12 (24%) | 38 (76%) | 0.38*** |
| | Yes | 7 (35%) | 13 (65%) | |
| FACT-B+4 Score (ARM subscale) | Mean (SD) | 17.0 (2.8) | 17.3 (2.4) | 0.78** |
| | Median [range] | 17 [11.25-20] | 18 [11-20] | |
| | Interquartile range | 14.5-19.5 | 15.5-19 | |

* Unpaired t-test; ** Wilcoxon rank sum test; *** Fisher exact test

**Figure 1.** Maximum acceptable chance of arm side effects from ALND when chance without ALND is 5% (n=67)

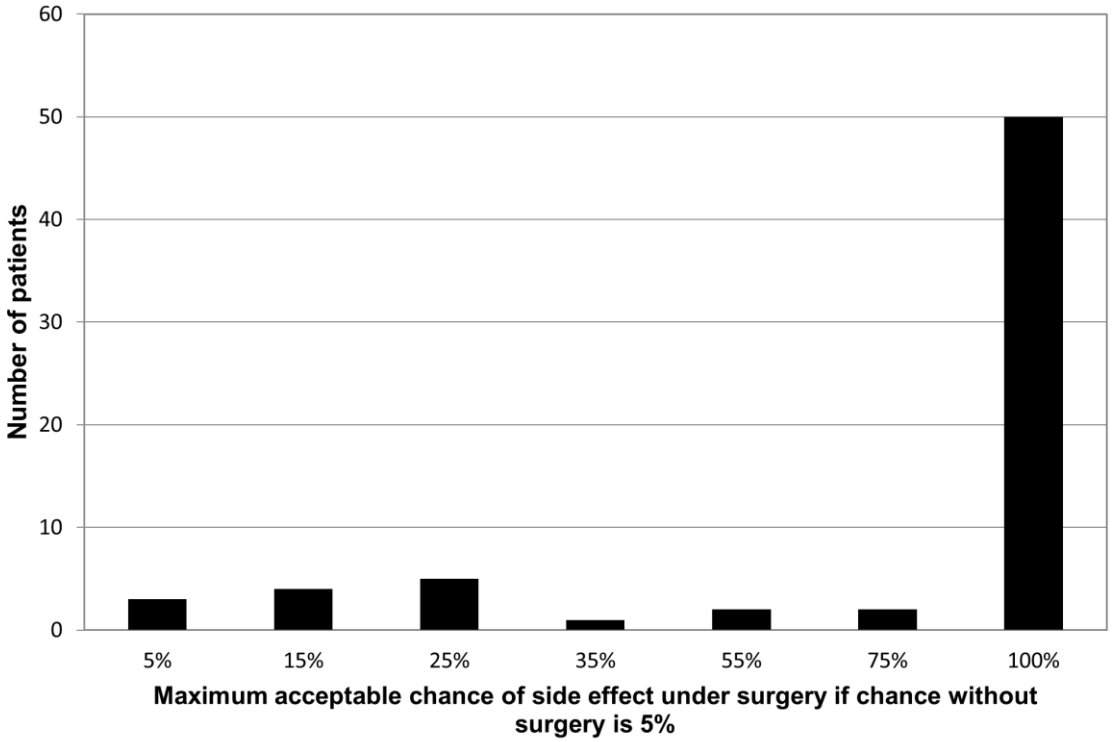

**Figure 2.** Maximum acceptable chance of arm side effects from ALND when chance without ALND is 15% (n=69)