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COMPLICATION RATES IN PATIENTS WITH NEGATIVE AXILLARY NODES 10-YEARS AFTER LOCAL BREAST RADIOTHERAPY FOLLOWING EITHER SENTINEL LYMPH NODE DISSECTION OR AXILLARY CLEARANCE

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Abstract

Background—We assess complication rates in node negative breast cancer patients treated with breast radiotherapy (RT) only after sentinel lymph node dissection (SLND) or axillary lymph node dissection (ALND).

Materials and Methods—Between 1995 and 2001, 226 women with AJCC stage I-II breast cancer were treated with lumpectomy, either SLND or SLND+ALND, and had available toxicities in follow-up: 111/136 (82%) and 115/129 (89%) in SLND and ALND groups, respectively. RT targeted the breast to median dose of 48.2Gy (range, 46.0-50.4Gy) without axillary RT. Chi-square tests compared complication rates of two groups for axillary web syndrome (AWS), seroma, wound infection, decreased range of motion (ROM) of the ipsilateral shoulder, paresthesia, and lymphedema.

Results—Median follow-up was 9.9 years (range, 8.3 -15.3 years). Median number of nodes assessed was 2 (range, 1-5) in SLND and 18 (range, 7-36) in ALND ($p<0.0001$). Acute complications occurred during the first 2 years and were AWS, seroma, and wound infection.

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Conflict of interest: none

Incidences of seroma 5/111 (4.5%) in SLND and 16/115 (13.9%) in ALND ($p<0.02$, respectively) and wound infection 3/111 (2.7%) in SLND and 10/115 (8.7%) in ALND ($p<0.05$, respectively) differed significantly. AWS was not statistically different between the groups. At 10-years, the only chronic complications were decreased ROM of the shoulder 46/111 (41.4%) in SLND and 92/115 (80.0%) in ALND ($p<0.0001$), paresthesia 12/111 (10.8%) in SLND and 39/115 (33.9%) in ALND ($p<0.0001$), and lymphedema assessed by patients 10/111 (10.0%) in SLND and 39/115 (33.9%) in ALND ($p<0.0001$). Chronic lymphedema, assessed by clinicians, occurred in 6/111 (5.4%) in SLND and 21/115 (18.3%) in ALND cohorts, respectively ($p<0.0001$).

Conclusion—Our mature findings support that in patients with negative axillary nodal status SLND and breast RT provide excellent long-term cure rates while avoiding morbidities associated with ALND or addition of axillary RT field.

Keywords

sentinel lymph node; axillary lymph node dissection; breast cancer; radiotherapy; complication rates; lymphedema; paresthesia; decreased range of motion; seroma; axillary web syndrome

Introduction

Advances in breast cancer screening and treatment have markedly increased survival rate of patients [1, 2, and 3]. Improvement in survival of patients with early stage breast cancer raises concern about minimizing side effects associated with breast cancer therapy. Breast conserving therapy (BCT) has redefined the approach to breast cancer, with lumpectomy and adjuvant tangential breast radiotherapy (RT) achieving excellent local control rates [4, 5]. Only 4-7% of patients with negative sentinel nodes (SLN) may harbor occult malignant cells in the remaining axillary lymph nodes (ALN) [6]. While the benefit of axillary lymph node dissection (ALND) as a treatment of choice to reduce the risk of axillary recurrence remained undisputable for years, the risk of considerable morbidity and complications from this therapeutic modality has compelled exploration of other surgical treatment options [7,8]. A number of investigators have demonstrated that sentinel lymph node dissection (SLND) alone, without further ALND in light of negative axillary sentinel lymph node status, has proven a good alternative to axillary clearance with ALND [3, 8, 9-13].

Complications of the axillary surgery are generally known as acute and chronic. Amongst the acute, the recognized side effects are axillary web syndrome (AWS), seroma, wound infection, decreased range of motion (ROM) of the ipsilateral shoulder, and change in sensation (paresthesia). Long-term side effects may overlap with the acute morbidities and are comprised of such toxicities as lymphedema, decreased ROM of the ipsilateral shoulder, and paresthesia. Multiple institutions (3,6, 8-11) have published at best a modest follow-up of the rates of these morbidities, as associated with SLND alone and ALND.

Equivalently low failure rates with either SLND or ALND [8, 9, 11] still warrant further evaluation of acute and chronic morbidities associated with each one of these surgical modalities. The purpose of this study was to examine and compare the incidences of acute and long-term complications, with the latter available at very mature decade-long follow-up in patients with early stage breast cancer with negative SLN treated BCT and adjuvant

breast RT following SLND alone or ALND. As the vast majority of prospective trials have reported an exceedingly modest follow-up morbidity data, we present one of the longest follow-up studies of complications in the literature to date.

Materials and Methods

After obtaining IRB approval, through a retrospective chart review we identified 1,396 women with AJCC stages I-II breast cancer treated between 1995 and 2001. Of these, 265/1,396 (19%) consecutive node negative patients underwent lumpectomy and either a SLND or SLND followed by an immediate ALND. The standard ALND involved at least dissection of levels I-II axillary lymph nodes. The group of patients, who underwent a combination approach of SLND+ALND, sustained axillary clearance during the same surgery. Information on acute and long-term toxicities was collected in 226/265 (85%) of women, with 111/136 (82%) and 115/129 (89%) patients in the SLND and ALND groups, respectively. Assessment of the SLN is described previously [11].

Adjuvant Breast Radiotherapy and Systemic Therapy

Adjuvant RT with high energy photons targeted ipsilateral breast tissue alone in supine position. Whole-breast RT was delivered by means of tangential portals to a median dose of 48.2Gy (range, 46.0-50.4Gy) administered at 1.8-2.0Gy fractions, five times a week. An electron boost was subsequently administered to the lumpectomy bed at 2 Gy fractions as prescribed to 90% isodose line, bringing the total median dose to the tumor bed to 63.2Gy (range, 60.4 - 66.0Gy). The superior border of the tangential fields was clinically placed at the inferior edge of the clavicular head (Figure 1). The lateral border typically was set in the mid-axillary line, thus having standard tangential RT fields encompass the majority of the level I of lower echelon, at least partially level II, and occasionally level III of the ALN. No axillary RT was employed to treat ALN.

Adjuvant systemic therapy was determined and administered by the medical oncologist, based on the patients' risk factors, tumor characteristics, receptor status, and patient preference.

Complications and Morbidity Assessments

Chronic long-term complications are defined as the ones which persist to date at the last follow-up in the evaluable patients. The forms in the patients charts were filled out by medical professionals at each encounter with the patients. Lymphedema was assessed in two ways. One of which the patient was asked to evaluate the symptom of lymphedema as either present or absent. The second assessment was conducted via a clinical examination of the lymphedema. Measurements were performed by medical professionals (nursing staff in radiation, medical oncology or surgical oncology clinics) and consisted of objective measurements at baseline and at each follow-up visit in both arms at the antecubital fossa, 10cm superior, 10cm inferior, and at the wrists. Arm lymphedema was defined as the difference in the operated arm and the opposite arm by >1cm. Paresthesia was defined as numbness that was subjectively reported by patients. Decreased range of motion of the ipsilateral shoulder as compared to the contraletaral shoulder was defined as reduced

abduction and measured by the medical professionals. Axillary web syndrome (AWS), also known as lymphatic development of tight cords of tissue that extend from the middle of the axilla on the upper surface of the affected arm distally to the antecubital fossa and at times lower, was assessed. In addition, wound infection and seroma were recorded by the medical professionals and obtained from the clinic records.

Statistical considerations

Chi-Square test or Fischer's exact test were used to analyze the particular clinical symptoms that each cohort presented, thus each symptom along with each cohort was categorized. Calculation of Cohen's Kappa statistic was used to measure the agreement, if any, between the raters of patient measured lymphedema and patient assessed lymphedema. Chi-Square tests were employed in comparing outcomes of the two groups (axillary and supraclavicular failures, in-breast recurrences, and distant metastases). Log-rank test was used to compare progression-free survival (PFS) of each cohort. Ninety-five percent confidence intervals (95% CI) for median PFS-time and 10-year PFS probability estimates were calculated to assess the precision of the obtained estimates. All analyses were performed in SAS Version 9.2 (SAS Institute, Inc., Cary, NC), SPSS Version 18.0 (SPSS Inc., Chicago, IL), and STATA Version 11.0 (StataCorp, College Station, TX).

Results

Table 1 provides baseline characteristics of the patients in two cohorts and summarizes their breast cancer by histopathological type, location in the breast, and systemic therapies associated with the treatment of the tumors. At 10 years, complete follow up information was available on 111/136 (88%) patients in the SLND group and 115/129 (89%) of women in the ALND cohort. The median age of the patients in two cohorts SLND and ALND is 57.8 years (range, 36-86 years) and 56.0 years (range, 24-85 years), respectively. Both cohorts of women had predominantly small tumor size, were located in the upper outer quadrants of the breast, exhibited intermediate nuclear grade, expressed estrogen (ER) and/or progesterone (PR) receptors, and lacked lymphovascular invasion. The median number of axillary lymph nodes dissected varied in a statistically significant manner between the SLND (n=2) and ALND (N=18) cohorts, respectively ($p<0.0001$).

The patients' outcomes at 10 years are summarized in Table 2. At a 10-year follow-up, there are no axillary and supraclavicular failures in both SLND and ALND groups. The incidence of local in-breast recurrences did not differ in a significant manner between the two cohorts and was 4/111 (3.6%) in the SLND and 3/115 (2.6%) in the ALND cohorts, respectively. Similarly, the rate of distant metastases was not significantly different with 1.8% in the SLND cohort and 2.6% in the ALND group, respectively. All patients who recurred were treated with local therapy (surgery, radiotherapy, or combination of the two) and were given systemic therapy (hormonal therapy, chemotherapy). Patients who recurred and remain alive comprise a total of 3/111 (2.7%) in the SLND and 4/115 (3.5%) in the ALND groups, respectively.

The median follow-up for all patients was 9.9 years (range 8.3 -15.3 years). The median follow up was 9.4 years (range: 8.6-15.2 years) in the SLND cohort and 9.9 years (range:

8.3-15.3 years) in the ALND cohort. When assessed by a medical professional, lymphedema was detectable in 6/111 (5.4%) of patients in the SLND group in contrast with 21/115 (18.3%) of cases of lymphedema in the ALND group, respectively ($p<0.0001$). The patient self-assessment groups demonstrated the lymphedema in 10/111 (10.0%) of patients in the SLND cohort and 39/115 (33.9%) of women reporting this complication in the ALND group ($p<0.0001$). When the relationship between the two methods of assessment was examined, there was a correlation coefficient of $k=0.5$ ($p<0.0001$) (Table 3).

Acute complications related to axillary lymph node assessment were comprised of the following: AWS (Figure 2), seroma, and wound infection (Table 4). Acute complications occurred during the first 2 years were AWS, seroma, and wound infection. The rate of AWS was not statistically different between the groups 1/111 (0.9%) and 5/115 (5.2%) in the SLND and ALND cohorts, respectively ($p=0.12$). The incidences of seroma – 5/111 (4.5%) in SLND and 16/115 (13.9%) in ALND group ($p<0.02$, respectively) - and wound infection – 3/111 (2.7%) in the ALND and 10/115 in SLND cohorts ($p<0.05$, respectively) - differed in a significant manner. At a 10-year follow-up the only chronic complications in the SLND vs. ALND groups were decreased ROM of the shoulder 46/111 (41.4%) vs. 92/115 (80.0%), paresthesia 12/111 (10.8%) vs. 39/115 (33.9%), and lymphedema - all encountered at a significantly greater rate in the ALND vs. the SLND group ($p<0.0001$) (Tables 3, 4).

The median progression-free survival (PFS) for the SLND cohort was 14.6 years (95% CI 13.7-15.2 years) and for the ALND cohort 15.0 years (95% CI 14.2-15.3 years), and the were not statistically different. The 10-year PFS was similar between two groups and was 88.2% (95% CI 79.5%, 93.4%) and 85.7% (95% CI 77.3%, 91.2%) for the SLND and ALND cohorts, respectively (Figure 3).

Discussion

The treatment of breast cancer has undergone evolution from a radical to a more conservative approach [14-16]. At a 20 year update of NSABP B-06 [4], , there was no significant difference in outcomes amongst the patients treated with modified radical mastectomy, lumpectomy alone, or lumpectomy with postoperative RT of the breast, with the latter providing strong evidence for using BCT. Maximizing local control, while minimizing damage to adjacent healthy tissues, has become the goal of therapy [17-19]. The extent ALND based on the magnitude of metastatic spread to the lymph nodes is one of the major deciding factors dictating the degree of conservatism with respect to examining axillary contents [20]. With the advent of radiolabelling axillary nodes, BCT has acquired yet another powerful tool to more accurately assess axilla [21]. Furthermore, the meta-analysis by Sanghani et al demonstrated that ALND does not provide any survival benefit [22]. Therefore, equipped with better identification of ALN and information about lack of impact of ALND on survival, SLN biopsy became a more recognized tool to examining axillary contents in patients undergoing BCT. The recently published American college of surgeons oncology group (ACOSOG) Z0011 trial in the Journal of the American Medical Association (JAMA) reports 5-year complication rates and disease outcomes among a total of 446 patients treated with SLND in a prospective randomized trial [23]. Our current study

endeavors to report on long-term (10-year) toxicity among a smaller similar population of patients.

A recent publication of outcomes at a 10-year follow up of patients with early stage breast cancer treated with BCT and tangential breast RT after either SLND or ALND demonstrated equivalently low rates of axillary failure, supraclavicular failure and local/distant recurrences, and excellent PFS in both cohorts [11]. These results largely corroborated Veronesi U et al in the Milan trial, i.e., the only other prospective trial with the longest follow-up available [9]. However, the literature by in large provides a rather short track record. With a limited follow-up of 24-60 months, the question about morbidity is not sufficiently answered, as many breast cancer survivors may experience long-term consequences years and even decades after their BCT. While advancement of surgical techniques and RT delivery revolutionized the approach to a patient with early stage breast cancer, the treatment still renders significant side effects and morbidity to survivors [24, 25]. Thus, elaborating on the issue of long-term morbidity is crucial and may aid both medical practitioners and the patients alike in improving management of patients with early stage breast cancer.

Our study presents acute and long-term morbidity data and 10 year follow-up rates of complications which patients may experience after SLND or ALND. Both cohorts had similar for age, tumor size, nuclear grade, presence or absence of lymphovascular invasion, receptor status, and systemic therapy. Chronic morbidity as determined at a 10-year follow-up is related to the following three complications: lymphedema, paresthesia, and decreased ROM of the ipsilateral shoulder (Table 3). When incidence of lymphedema was examined, it was evident that regardless of whether the assessment was performed by a medical professional or a patient, there was statistically significant difference in the rates of this complication between the two cohorts as experienced by patients. This difference appears to be sustainable even a decade after the surgery, and the percentage of patients that experienced chronic lymphedema is significantly greater in the ALND cohort as compared with the SLND one. Based on the findings of the medical professionals, the 10-year incidence of lymphedema is approximately 5.4% in the SLND and 18% in the ALND. These findings are not dissimilar to the prior reports in the literature [8, 10, 11, 13, 26-28]. However, when perception of lymphedema is reported by patients themselves, the rates stated are much higher - 10% and 34% for SLND and ALND cohorts, respectively.

Incidence of chronic paresthesia in the ALND cohort was nearly three times the rate of the SLND group. The majority of the published studies report the two-to-three times the incidence of paresthesia in the ALND patients than in the ones treated with SLND [26-29]. In the recent report of the 36-month follow-up in the NSABP B-32 [13], tingling and numbness experienced by the two groups was parallel to the difference in percent that was observed in our study. However, no explanation is provided in the recent update of the Milan study for why it demonstrated that 68 times as many patients experience similar symptoms when the ALND was compared with SLND [8].

One of the commonly reported long-term sequela has been a decrease in the ROM of the ipsilateral shoulder [13, 27, 28, 29]. In our observation, twice as many patients experienced

this side effect in the ALND group than in the SLND cohort (Tables 4, 5). While the NSABP B-32 study did show a slightly significant difference between the amount of patients with decreased ROM between the two cohorts [13, 29], the Milan study did not report a single patient who underwent SLND with a decrease of ROM [8].

A summary of all prospective studies to date with a rather short follow-up morbidity data associated with SLND alone and SLND followed by ALND is provided in Table 5 [8, 13, 26-31]. There is great variability amongst the studies with respect to the methodology of assessment of some of the complications. In the Sentinella/GIVOM study [30], the recording of lymphedema was performed only by the treating physician, and the numbers were computed as odds ratio of SLN/ALN. The ALMANAC study [28] used a scale of mild, moderate, and severe symptoms, which for the purposes of comparison, we summated and used for comparison to our data. Unlike other studies, the ALMANAC study recorded symptoms of paresthesia as reported by the patient and by the physician. The method of deconstructing the category of paresthesia was seen in the NSABP B-32 morbidity study [13], where paresthesia was assessed as tingling and numbness. Of interest, the NSABP B-32 outcome study [29] used assessment of arm pain and arm numbness. We summated the subcategories into “paresthesia” and a “decreased ROM of the ipsilateral shoulder” for the purposes of comparison across the trials and our study. To date, while only the technical outcomes are available from NSABP B-32 [33-34] and no more than a 3-year follow-up of morbidity [35-36], our report provides clinically important information not only with regard to the outcomes but also the rates of complications at 10 years.

As per the so-called acute toxicities – AWS, seroma and wound infection – we found that none persisted beyond the 2-year surgery mark. Upon reviewing the incidences of seroma with either SLND or ALND in the literature, we found paucity of data. To the best of our knowledge, the best account of this toxicity was recorded by the study which examined positive SLN - ACOSOG trial Z0011 study [23, 26]. When we compared the results of our studies, it was evident, that the data were similar. While in our study there was a 13.9 % incidence of seroma in the ALND and 4.5% in the SLND groups, respectively, the Z0011 study reported similar results: 14% rate of seroma with ALND and 6% with SLND, respectively. One needs to keep in mind that the Z0011 trial was for lymph node positive patients in contrast to lymph node negative patients in our study. Though positive nodes may have adversely influenced the rates of morbidity, it appears that it did not and thus eliminated the influence of tumor contribution to the side effects.

Similar to the scarcity of reporting of the rates of seroma, recording of wound infections was not very prevalent in the published studies. Our data demonstrated that wound infections were present in both ALND and SLND patients. The rate of this toxicity in our study - 2.7% in the SLND group and 8.7% in the ALND group - was similar two other studies that provided data on wound infection [26, 27]. These are very close to the findings as published by McLaughlin et al [27]. Unlike our results and the McLaughlin study, the Z0011 trial showed slightly higher incidences of wound infections in both cohorts: 3% and 14% in the SLND and ALND groups, respectively [26].

AWS is the most short-lived of the three acute side effects and is typically resolved by 6 months after the surgery. While a rare complication, AWS is a significant cause of morbidity of axillary surgery and is not only found in the early postoperative period but also in the more advanced phases of the post-operative period. In our study, the so-called webbing or “the cords are lymphatic in origin” appeared at a significantly higher rate in the ALND cohort (5.2%) as compared to the SLND group (0.9%). A number of retrospective and small prospective studies examine AWS and report variable rates of its incidence in the post-operative setting in both SLND and ALND settings [32-37]. Of the large prospective studies available in the literature which compare morbidities associated with either SLND or ALND, not one listed the syndrome as a complication of either SLND or ALND treatment. Research is needed to test therapies that can shorten the natural course of the condition.

Could RT be a contributing factor to the complications of axillary surgery? If a low incidence of ALN failures lies in sterilization of the occult metastases in the ALN with the conventional breast tangential ports delivering RT to a patient in a supine position [11], we maintain that RT is at least in part responsible for the morbidity attributable to surgery. Goodman et al reported that with the standard radiation tangents, 90% of the Berg level I axilla and up to 70% of level II ALN received 95% of the prescribed dose to the breast [38]. The vast majority of literature, with only a few negative studies, supports the fact that modern 3-D tangential port RT of the breast administered in supine position will at least partially irradiate the undissected ALN stations [38-47], which may explain why even patients with SLND experience long-term toxicity. All our patients were treated with 3-D RT in the supine position (Figure 1) with the standard tangential RT fields targeting the breast tissue and inadvertently providing at least partial coverage for at least two of the Berg axillary levels.

Our findings render a 10-year follow up on the incidences and rates of complications of acute and chronic complications which occur as a result of two methods of assessments of axillary contents – SLND or SLND followed by ALND – as part of BCT in patients with early stage breast cancer. The option of SLND alone in light of negative sentinel lymph nodes provides a significantly lower profile of both acute and late toxicities, while it maintains equivalent rates of local-regional control to the ALND approach. While awaiting a more mature and comprehensive long-term follow-up from the prospective studies, our data provide critical information for both clinicians and patients and may aid in counseling, prevention, and ultimately management of anticipated complications.

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Table of Abbreviations

SLN	Sentinel Lymph Node
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ALN	Axillary Lymph Node
SLND	Sentinel Lymph Node Dissection
ALND	Axillary Lymph Node Dissection
BCT	Breast Conserving Therapy
RT	Radiotherapy
ER	Estrogen Receptor
PR	Progesterone Receptor
L	Lumpectomy
MRM	Modified Radical Mastectomy
AWS	Axillary Web Syndrome

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Figure 1.

A. A relationship between local breast tangent radiation field and regional lymph nodes as depicted in the lateral beam's eye view with a tangential portal, where the superior border of the radiation portal is set below the heads of the clavicles (navy). **B.** The axial image through the dissected axilla demonstrates Level I (blue), Level II (purple), and Level III (dark green) axillary lymph nodal stations which are partially covered by the 90% isodose area covering the breast tissue (orange).

Figure 2.

A. A patient who 4 weeks after sentinel lymph node dissection (SLND) presented with axillary cords (arrow). **B.** Her symptoms were pain and a decreased of range of motion in the ipsilateral arm. **C.** A different patient who is 3 months after sentinel lymph node sampling followed by an axillary lymph node dissection (ALND) and adjuvant chemotherapy presented with the cords. **D.** The axillary cords extended from the axilla down to the wrist along the medial aspect of the arm (arrows).

Figure 3. Progression-free survival calculated for the sentinel lymph node dissection (SLND) group and the cohort which underwent SLND followed by the axillary lymph node dissection (ALND).

Table 1

Characteristics of the patients and tumors, and systemic therapy in the 2 cohorts.

Cohorts	SLND (N=111)	ALND (N=115)	p-value
Mean age (years)	57.8 range, (36-86)	56.0 range, (24-85)	ns
T stage			
T1	82%	81%	
T2	18%	19%	ns
Nuclear grade			
1	16%	18%	
2	63%	59%	
3	21%	23%	ns
Tumor location			
outer quadrants	71%	72%	
inner/central quadrants	29%	28%	ns
Histological tumor type			
ductal	82%	81%	
lobular	7%	6%	
other	11%	13%	ns
Receptor status			
ER/PR+	69%	73%	
ER/PR-	15%	12%	
ER+/PR-	13%	12%	
ER-/PR+	2%	1%	
unknown	1%	2%	ns
Lymphovascular invasion			
yes	19%	21%	
no	75%	74%	
unknown	6%	5%	ns
Median number of axillary lymph nodes assessed	2 (range, 1-5)	18 (range, 7-36)	< 0.0001
Chemotherapy			
yes	25%	15%	
no	75%	85%	ns
Hormonal therapy			
yes	54%	56%	
no	46%	44%	ns

Table 2

Long-term outcomes with regard to local, distant failures, and patients alive with breast cancer after such recurrences in the two cohorts.

Outcomes at 10 years	SLND	ALND	p-value
Local recurrences			
Axillary failures	0/111 (0%)	0/115 (0%)	N/A
Supraclavicular failures	0/111 (0%)	0/115 (0%)	N/A
In-breast tumor recurrences	4/111 (3.6%)	3/115 (2.6%)	>0.99
Distant recurrences			
Distant metastases	2/111 (1.8%)	3/115 (2.6%)	>0.99
Patients alive with breast cancer after local and/or distant recurrences			
	3/111 (2.7%)	4/115 (3.5 %)	>0.99

Table 3

Lymphedema as determined by medical personnel and reported by patients, and correlation of the two methods of detection

Lymphedema assessed by either medical professionals or patients	SLND	ALND	p-value
Lymphedema assessed by medical professionals	6/111 (5.40%)	21/115 (18.3%)	<0.0001
Lymphedema as reported by patients	10/111 (10.0%)	39/115 (33.9%)	<0.0001
Correlation is k=0.5			<0.0001

Table 4

Acute^{*} and late^{**} complications in patients treated with either sentinel lymph node dissection (SLND) or a completion axillary lymph node dissection (ALND).

Complications	SLND	ALND	p-value
Axillary web syndrome	1/111 (0.90%)	6/115 (5.20%)	0.12
Seroma	5/111 (4.50%)	16/115 (13.9%)	0.02
Wound infection	3/111 (2.70%)	10/115 (8.70%)	0.05
Decreased shoulder range of motion	46/111 (41.4%)	92/115 (80.0%)	<0.0001
Paresthesia	12/111 (10.8%)	39/115 (33.9%)	<0.0001
Lymphedema	6/111 (5.40%)	21/115 (18.3%)	<0.0001

* Acute complications are defined as the ones which resolved by 24 months

** Late complications are defined as the ones which remained at a 10-year mark

Table 5

A Summary of morbidities from the published prospective studies.

Prospective studies	Median follow up (years)	N	Inclusion Criteria	Lymphedema by medical professionals (%)	Lymphedema by patients (%)	Paresthesia (%)	Decreased ROM of ipsilateral shoulder (%)	AWS (%)	Wound Infection (%)	Seroma (%)
MILAN [8,9] (negative SLN in 341 patients (167SLN+174ALND) (1998-1999)	3	516	<2cm, L only (wide excision or quadrantectomy)	* 7/100 (7) #75/100 (75)	N/A	* 1/100 (1) #68/100 (68)	* 0/100(0) #21/100 (21)	N/A	N/A	N/A
Sentinella/GIVOM [29] (1999-2004)	4.6	749	<3cm, L, MRM	0.52 ²	N/A	0.90 ² - pain 0.54 ² - numbness	0.44 ²	N/A	N/A	N/A
ALMANAC-UK [27] (1999-2003)	1	1031	<2, 2-5,>5cm, L, MRM, axillary RT	N/A	* 20/412 (5) #53/403 (13)	* 46/407 (11) #124/401 (31) * 35/400 (9) #120/384 (31) ³	* 2.5 ⁴ #1.9 ⁴	N/A	N/A	N/A
ACOSZOG Z0011 Trial [25] (1999-2004)	3	891	<2cm, L, with 1-2 +SLN	* 14/226 (6) #26/242 (11)	* 14/253 (5) #52/272 (19)	* 24/268 (9) #113/287 (39)	N/A	N/A	* 11/371 (3) #31/373 (8)	* 21/371 (6) #53/373 (14)
NSABP B-32 Morbidity results [13] (1999-2004)	3	5611	2.0, 2.1-4.0, >4.0 cm, L or M	* 303/1459 (20.8) #431/1421 (30.3)	N/A	* 110/1463 (7.5) - tingling * 119/1463 (8.1) - numbness #193/1431 (1.4) - tingling #445/1430 (3.1) - numbness	* 276/1744 (1.6) #352/1667 (2.1)	N/A	N/A	N/A
NSABP B-32 Outcome study [28] (2001-2004)	3	749	2.0, 2.1-4.0, 4.1 cm, L or M	N/A	* 10/320 (3) #25/307 (8)	* 41/320 (1.3) #71/307 (2.3) ⁵	* 25/320 (7.8) #28/307 (9) ⁶	N/A	N/A	N/A
CURRENT STUDY	10	265	<5.0cm, L	* 6/111 (5.4) #21/115 (18.3)	* 10/111 (10.0) #39/115 (33.9)	* 12/111 (10.8) #39/115 (33.9)	* 46/111 (41.4) #92/115 (80.0)	* 1/111 (0.9) #6/115 (5.2)	* 3/111 (2.7) #10/115 (8.7)	* 5/111 (4.5) #16/115(13.9)

MRM=modified radical mastectomy

RT=radiotherapy

* SLND=Sentinel Lymph Node

SLN +ALN=Sentinel Lymph Node+Axillary Lymph Node

¹ Summation of patients with mild and severe symptoms.

² Odds ratio (SLN/ALN)

³ Clinician's assessment.

⁴ Prior to treatment a score of 20 was assigned at baseline. The arm scores are subtractions from the pretreatment range.

⁵ Arm pain and arm numbness were combined.

⁶ Arm weakness and reach above shoulder were combined.