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TITLE: Lymphedema Prophylaxis Uilizing Perioperative Education

PRINCIPAL INVESTIGATOR: Mary Ann Kosir, M.D.

CONTRACTING ORGANIZATION: Wayne State University
Detroit, Michigan 48202

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13. ABSTRACT (Maximum 200 Words)
The purpose is to evaluate perioperative training for lymphedema assessment and protection. The hypothesis is that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. The specific questions (scope)are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with are precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group? Major Findings: During the first 33 months of enrollment, the incidence of lymphedema was 49.6% overall. This includes acute and chronic lymphedema. The incidence in African American and Hispanic breast cancer survivors was higher than nonminority subjects. Significance: The lymphedema rate observed overall thus far, and including acute and chronic lymphedema, is greater than reported in the literature. This may shift established practice in lymphedema prevention and detection for breast cancer survivors. A manuscript has reported a comparison of different methods of measuring lymphedema to our "standard". A grant application has been submitted based upon the finding of increased lymphedema in minority subjects. Further analyses and statistics are delayed due to the power outage and computer problems with viruses and worms.

14. SUBJECT TERMS
Lymphedema, quality of life, education

15. NUMBER OF PAGES
39

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Table of Contents

INTRODUCTION

We were hit with the power blackout Aug 8-10,2003. Thereafter, the computer systems at WSU and Karmanos Cancer Institute were not functioning due to worms and viruses. The tabulation of data was planned for this time to cover enrollment through 7/31/03. I'm attaching an e-mail from the Information System at Karmanos (Appendix) regarding these events. At least 2 weeks were taken up with these problems. As instructed, I am sending in the report with the statistical analysis to follow in the next annual report (e-mail also in Appendix) Thank you for your consideration.

Response to Reviewer's comments (Technical Issues) from Year II report:

1. Why are initial quality of life questionnaires missing for some subjects?

Subjects have been given the questionnaires, but some did not want to fill them out at the time of enrollment and promised to fill them out and bring with them or mail back. However, by the day of surgery, they have not done so despite reminders. I believe this is a variable encountered with clinical studies.

Solution/plan: T here are three s pecific a ims t hat a ll d epend o n different d ata collection. Preoperative measurements are required for Specific Aim 1. Preoperative questionnaire completion is required for Specific Aim 2 and 3. Those who do not complete the initial questionnaires are not truly evaluable for QOL trends. However, their initial measurements which were done preoperatively, can be used and compared with subsequent measurements to support work in Specific Aim 1). Overall, we are listing those who are compliant with all facets of the initial study requirements as "truly evaluable".

Additionally, we attempt to obtain missing questionnaires for the few who have not completed them on the day of surgery. However, this is not always feasible w ith the preparations and routine in preop holding areas.

Narrative:

Subject: Increasing numbers of breast cancer survivors are at risk for long-term sequelae from treatment. Axillary surgery or radiation therapy to the breast may alter lymph channels, leaving the survivor with a lifetime risk for developing lymphedema. Lymphedema is a swelling of the upper extremity, which causes pain, debility, and reduced quality of life (QOL) that impacts choices about work, social and sexual interactions and self-esteem. Protective measures to reduce the risk of lymphedema become important life-long skills. However, there is inconsistent teaching of protective measures, and inattention to lymphedema detection in clinical practice. **Purpose:** The purpose of this study is to evaluate perioperative training for lymphedema assessment and protection. The **hypothesis** is that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. **Scope:** The **specific aims** are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group? **Methods:** Patients with resectable breast cancer also undergoing axillary lymph node surgery and/or radiation therapy to the breast will be prospectively randomized to two groups. In addition to receiving standard care (i.e., written breast rehabilitation materials and preoperative counseling by the breast surgeon), patients in Group 1, will receive structured education in Breast Surgery Rehabilitation including range of motion exercises, lymphedema arm precautions, and management of complications. Patients in Group 2 will receive standard care (written material and preoperative counseling by the surgeon). For both groups, preoperative and then quarterly volume measurements and exams of the upper extremities will be done for three years after surgery in order to determine lymphedema and infection incidence. The QOL will be measured longitudinally by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Medical Outcome Study Short Form Health Survey (MOS SF-36) and sexuality subscales of Cancer Rehabilitation Evaluation System (CARES). The knowledge of and practice of lymphedema protective skills will be measured by periodic testing longitudinally as well.

BODY

Research accomplishments associated with each task outlined in the approved Statement of Work. Therefore, the Year III report is cumulative.

Statement of Work

Task 1. Start-up, Months 1-2.

This was completely accomplished.

Task 2. Introduce study to physicians, nurses and clerks in clinics, Months 1-2.

This was completely accomplished.

Task 3. Subject recruitment and data collection, Months 3-60.

a. Enroll preoperative patients, obtain consent forms, randomize, conduct initial examinations and measurements, clinical data base including Omega Screening Questionnaire (OSQ), QOL instruments (FACT-B, MOS SF-36, CARES).

1. Enrollment should occur during Months 3-27 for a total of 176 subjects.

The human subjects approval occurred in mid-October, 2000. This report covers 33 months (Months3.5-35)

<u>Summary of human subject enrollment (Months 3.5-33)</u>
Enrolled: 173 subjects (98.3% of target)
Randomized: 154 subjects
Dropped after randomization: 5
Died after randomization: 1
Other drops: 14 (before randomization)
Total Dropped: 20 subjects (11.6%) (even if randomized)
Evaluable: 153 (173 minus 20 minus) (96.8% of target)

NEW for Year III report:
***Truly evaluable: 113 (113/158=71.5%)**

- **truly evaluable means those who have completed all preop questionnaires (100% compliance) as well as measurements (compliance), have been randomized, and have at least <u>two measurements</u> completed for comparison.**
  Some patients still require time for second measurement, some still need to be randomized as they have not have surgery yet.

As reported in the Year II report, it was anticipated that the Karmanos Cancer Institute would hire at least one surgeon in the past year to replace the two who left. However, the hiring was done by the Department of Surgery at WSU and the new surgeon

began in mid-August, 2003. Thus, enrollment in Year III has been under less than optimal conditions, but has nevertheless continued toward goal.

Table 1 summarizes characteristics of the randomized truly evaluable subjects. including mean age, gender, race, stage of breast cancer and broad category of type of surgery performed.

2. Since enrollment will be staggered, the follow-up period of three years will end at different time points for individual subjects.

October 15, 2003 will be 3 years since enrollment began.

3. Subjects randomized to Group 2 (control) will complete a knowledge questionnaire at first post-op visit.

This was accomplished.

Task 4. Perioperative teaching sessions, Months 3-27.

a. After randomization, subjects in Group 1 will be scheduled to a classroom session with Christine Rymal, MSN, BSN, during the first postoperative visit.

This was accomplished.

b. At the time of the class session, subjects will complete a knowledge questionnaire as a pretest and posttest.

This was accomplished.

Task 5. Quarterly measurements of subjects, Months 6-60.

a. Subjects in each group will have upper extremities measured and evaluated. While each subject will be followed for three months postoperatively, measurements for the entire enrollment occur up to 60 months of the study due to the staggered enrollment and follow-up design of the study.

This was accomplished, however, some subjects did not come each quarter for measurements. We will continue to encourage quarterly measurements, understanding that human subjects may be unable to come each time. For a given subject, during the course of 36 months of followup, there will be 12 opportunities for followup measurements. The Community Outreach Core at Karmanos Cancer Institute is now assisting us in contacting subjects to return for followup visits.

Table 1 Study Subject Characteristics (Truly evaluable and randomized)*

	Group 1 (Intervention) *n=51*	Group 2 (Control) *n=62*
race		
African American	20	18
Arab/Chaldean	1	1
Caucasian	22	30
Hispanic	1	2
Native. American	3	0
Asian	0	4
Other	1	1
Unknown	3	6
Stage		
O	3	9
I	14	15
IIA	12	8
IIB	8	15
IIIA	3	4
IIIB	2	0
IV	1	1
Surgery Type		
Mast. and ax. surgery+	22	30
Lumpectomy and RT	4	6
Lump.,RT, ax. surgery	21	22
Highest level of education		
Doctorate degree	2	1
Master's degree	1	6
Bachelor's degree	11	11
High school grad/GED	25	33
8-11 yrs	4	2
less than 8 years	2	0
Marital status		
Married/cohabitating	24	27
Divorced/separated	12	11
Widowed	5	9
Never married	6	7
Annual household income		
<$5,000/yr	3	5
$5,000-$15,000/yr	6	6
$15,001-$30,000/yr	5	6
$30,001-$50,000/yr	7	5
$50,001-$75,000/yr	6	8
>$75,000/yr	10	11

* Truly evaluable have completed all initial forms, randomized after surgery and at least two measurements for comparison.
all subjects are female except for one male participant
+ ax. surgery =axillary surgery that includes dissection, sampling, sentinel node biopsy (not separated for this report). Mast. = mastectomy; Lump. = lumpectomy; RT=radiation therapy

Table 1 (cont'd) Study Subject Characteristics (Truly evaluable and randomized)*

	Group 1 (Intervention) *n=51*	Group 2 (Control) *n=62*
Transportation		
Drive myself	**33**	**44**
Driven by someone else	**10**	**7**
Use public transportation	**4**	**1**
Other	**0**	**1**
Religious preference		
None	**1**	**2**
Protestant	**13**	**13**
Catholic	**13**	**14**
Buddhist	**0**	**0**
Jewish	**1**	**0**
Muslim	**1**	**0**
Hindu	**0**	**1**
Eastern Asian	**0**	**0**
Other	**3**	**1**

*** Truly evaluable have completed all initial forms, randomized after surgery and at least two measurements for comparison.**
all subjects are female except for one male participant
+ ax. surgery =axillary surgery that includes dissection, sampling, sentinel node biopsy (not separated for this report). Mast. = mastectomy; Lump. = lumpectomy; RT=radiation therapy

Task 6. QOL questionnaires at 6 months, 1-, 2-, and 3-years postop, Months 9-60.

a. FACT-B, MOS SF-36, and sexuality subscales of CARES will be administered for up to three years after surgery. Up to 60 months may be required to accomplish this in all enrolled subjects.

This is being accomplished. We will continue to offer the QOL questionnaires at 6, 12, 24 and 36 months of followup. For a given subject, during the course of 36 months of followup, there will be 4 opportunities for followup QOL questionnaires. The Community Outreach Core at Karmanos Cancer Institute is now assisting us in contacting patients to return for followup visits or else mailing out the questionnaires.

Task 7. Booster training session for Group 1 subjects, Months 9-33.

a. Christine Rymal will speak with each subject in Group 1 at the 6-month postoperative session, answering questions and passing out a summary sheet on "Precautions for Lymphedema Risk Reduction."
(see below)

b. A knowledge questionnaire will be administered as well as compliance questionnaire to subjects in Group 1 at this time.
Both of these have been accomplished during the reporting period. It will continue throughout the study until all accrued subjects have gone through 6 months in followup after being randomized postoperatively.

Task 8. Knowledge and compliance questionnaires, Months 9-60.

a. Subjects in Group 2 (control) will complete these questionnaires during their 6 month, 1 year, 2 year and 3 year postoperative follow-up sessions. Theses may occur up to 60 months of the study due to the staggered enrollment and follow-up design of the study.
(see below)

b. Subjects in Group 1 (intervention) will complete these questionnaires at 1 year, 2 year, and 3-year postoperative follow-up sessions. (They will have completed the 6-month questionnaires with Christine Rymal). These may occur up to 60 months of the study due to the staggered enrollment and follow-up design of the study.
Both of these are being accomplished during the reporting period. We will continue to offer the knowledge and compliance questionnaires at 6, 12, 24 and 36 months of followup. For a given subject, during the course of 36 months of followup, there will be 4 opportunities for followup knowledge and compliance questionnaires. The Community Outreach Core at Karmanos Cancer Institute is now assisting us in contacting patients to return for followup visits or else mailing out the questionnaires.

Task 9. Calculations of limb volumes and comparison of differences, Months 3-60.

a. Wenlien Wang will calculate limb volumes in a blinded fashion weekly based upon limb measurements obtained by the clinical research assistants.
This is being accomplished with the data manager now calculating the limb volumes and changes.

b. Serial volume measurements will be recorded on a master sheet for each subject and evidence of lymphedema determined weekly.
This is being accomplished.

c. The PI and Christine Rymal will review these calculations weekly.
This is being accomplished.

Task 10. Quarterly data entry and print out by the Psychosocial and Behavioral Core, Months 3-60.

a. Coded data sheets for limb measurements, QOL questionnaires, knowledge/compliance questionnaires, clinical data will be supplied to data entry personnel at the Core facility. After entry of data, a printout will be provided to the PI.

This is being accomplished with weekly data entry. Printout occurs quarterly. However, the Psychosocial and Behavioral Core has not been participating due to its own reorganization. Therefore, this is being performed by the data manager.

Task 11. Interim analysis of data after 1 year, 3 years, Months 14-16, 38-40.

a. Dr. Du (biostatistician) will analyze the data. Specifically, the lymphedema rate, infection rate, scores, and trends of serial QOL measures (FACT-B, MOS SF-36, sexuality subscales for CARES), scores on knowledge and compliance questionnaires will be tabulated. PI and Co-PIs will review trends and confirm study objectives.

These data will be analyzed as scheduled during months 38-40 although we had tried to provide for this report. Only LE confirmed cases are reported for the truly evaluable subjects in Table 2.

In Appendix, a manuscript in press is provided as an example of interim use of the statistician for the project.

Table 2. Specific interim data for study subjects

	Group 1 (Intervention) *n=51*	Group 2 (Control) *n=62*
lymphedema	27	29
lymphedema rate	52.9%	46.8%

TRENDS: Within the first 33 months of accrual, there have been 56 patients diagnosed with lymphedema (49.6%) in the truly evaluable group. This includes acute lymphedema (occurs within first year after surgery) and chronic lymphedema. For the truly evaluable subjects thus far (71.5% of target), the incidence of LE is not different between the intervention group and the control group lumping all cases together.

Plan: As the study continues, the sample size of 158 evaluable patients will permit determination of acute and chronic lymphedema. The pattern of LE will be a reportable result. Additionally, based upon the information reported in the manuscript in press, the methodology for detecting LE and therefore, its reporting may reflect the intervention. This will also be a reportable result.

Task 12. Analysis of data after 5th year, Months 61-65.

Not yet applicable.

Task 13. Annual report to USAMRMC, Months to be designated by USAMRMC.

a. Annual reports (Year 1,2,3,4) to summarize findings, scientific issues, and accomplishments.

Year I, Year II and Year III reports submitted.

b. Final report in the last year to report findings and accomplishments for the entire project.
Not yet applicable.

Task 14. Meeting in Baltimore, Maryland to disseminate results of DoD-sponsored Research during the second year, Month to be announced by USAMRMC.
Attended September, 2003, Orlando, FL. Poster presentation.

Task 15. Write journal articles. Submit abstract, Months 12-60+

a. Yearly opportunity to submit abstract to lymphedema and other professional meetings.
In Appendix, manuscript in press.
Oral presentation:
"Can a Surgical Practice Detect Early Lymphedema?" , presented at the 27th Annual Surgical Symposium of the Association of VA Surgeons Meeting, May 3-5, 2003, Nashville, TN.

b. Final report will be converted to journal format for submission.
Not yet applicable.

During this third annual year report, the Tasks in the Statement of Work are being accomplished and data are being collected as described in the study. The study objectives will be answered when at least three years of followup data (to occur during the five years of study) are collected.

KEY RESEARCH ACCOMPLISHMENTS

- **Lymphedema was detected in 49.6% of subjects over 33 months of the study, which includes acute and chronic lymphedema.**
- **A manuscript is in press comparing different standards of reporting LE.**

REPORTABLE OUTCOMES

Manuscript
Bland KL, Perczyk R, Du W, Rymal C, Koppolu P, McCrary R, Carolin KA, Kosir MA: Can a practicing surgeon detect early lymphedema reliably? Am J Surg, 2003, In Press.

Presentation (Oral)
"Can a Surgical Practice Detect Early Lymphedema?" , presented at the 27th Annual Surgical Symposium of the Association of VA Surgeons Meeting, May 3-5, 2003, Nashville, TN.

Presentation (Poster)
"Lymphedema Prophylaxis Utilizing Perioperative Education", presented at the Era of Hope Department of Defense Breast Cancer Research Program Meeting, September 25-28, 2002, Orlando, FL.

Funding Applied

Komen Foundation Postdoctoral Fellowship Research Award, "Increased Incidence of Lymphedema in African American and Hispanic Breast Cancer Patients", submitted 8/03.

CONCLUSIONS

By starting to measure limb volumes within the first year after surgery, the lymphedema rate overall is greater than predicted in the literature. and requires further analyses based upon variables of education, type of surgery, infection rate, race/ethnicity, and occupation.

"So What Section"

The awareness of lymphedema occurrence, protection, and treatment by many clinicians that are in contact with breast cancer survivors is not uniform. Furthermore, textbooks do not include enough detail regarding incidence, symptoms, measurement, and treatment, which lead to less attention to the survivor's observations. This study must be completed to rebut current opinion in the medical literature. It will "rock the boat" and challenge current practice. Already, lymphedema in the first year postoperatively is underreported and this study will be able to add to the literature. We have already presented and now are publishing a comparison of methods in detecting LE using our own rigorous detection as the "standard". The longitudinal collection of measurements in several dimensions (physical, quality of life, knowledge, behavior (compliance)) will provide strong data and conclusions that are absolutely necessary to shift established practices that have not really been the result of careful study. There are also several additional studies that will emanate from this study, with the potential to include additional disciplines in breast cancer research.

REFERENCES

n.a.

APPENDICES

1. E-mail from R. Rauscher regarding Virus problems, IT infrastructure at Karmanos Cancer Institute (8/26/03).
2. E-mail regarding format of report given difficulty with analysis of data without computer access and response from Judy Pawlus (8/25/03).
3. Manuscript in press:

Bland KL, Perczyk R, Du W, Rymal C, Koppolu P, McCrary R, Carolin KA, Kosir MA: Can a practicing surgeon detect early lymphedema reliably? Am J Surg, 2003, In Press.

Kosir, Mary A

From: Rauscher, Richard [rauscher@karmanos.org]
Sent: Tuesday, August 26, 2003 8:07 PM
To: to_staff@karmanos.org
Subject: Virus problems, IT infrastructure

Dear Faculty or Staff member:

During the last week, the Karmanos Cancer Institute, Wayne State University and The Detroit Medical Center have been severely impacted by a series of worms and viruses. Due to our lack of sufficient firewall protection, lack of centralized management of personal computers and a poorly designed internal network, the Institute's PCs were infected with viruses and worms en masse.

The infections didn't just affect the infected PCs - they generated network traffic that caused severe performance problems at several key points in the network. This caused the Hudson Webber Cancer Research Center (HWCRC) tower to essentially lose connectivity with the rest of WSU, which includes the Prentis building. Furthermore, Internet connectivity has been significantly negatively impacted for the entire university.

There are also a host of problems that led to the elongated affect that these viruses/worms had on us. They include a lack of network control in HWCRC, staff absences (both within the Institute and at WSU - both planned and unplanned) and a lack of network diagnostic equipment both within the Institute and at WSU.

Additionally, we were fortunate (lucky) to not have suffered any significant outage as a result of the massive power outage last week. All the Institute's systems were up and running within hours of the power being restored. Given our fragile infrastructure this was truly a pleasant surprise. Also, due to limitations of our current backup hardware, we have been forced to make tape backups of some servers every other day instead of daily.

So, in light of all of these problems, what are we doing to improve the infrastructure at the Institute?

1. For the last several days, I've been feverishly working with the DMC to ensure that we have a dedicated route from HWCRC back to the Prentis building. HWCRC will have its own separate Institute infrastructure and we'll be able to access the Institute's servers without touching DMC or WSU infrastructure. Control and responsibility from client to server will be the responsibility of my staff and me.

2. As you probably already know, we've been actively moving people from our Netscape email system to a new Microsoft exchange server.

3. I will be presenting to our board-level finance committee a capital budget for the purchase of a tape library system, a highly redundant disk storage system, a system for managing software development and a secondary wireless path to connect the HWCRC to Prentis.

I'd be happy to personally meet and talk in detail about these problems, how they will be fixed and how we'll avoid them in the future.

Richard Rauscher, M.S.
Vice President, Information Technology &
Bio/Medical Informatics/Chief Information Officer
Barbara Ann Karmanos Cancer Institute

Kosir, Mary A

From: Pawlus, Judy K Ms USAMRMC [judy.pawlus@us.army.mil]
Sent: Monday, August 25, 2003 9:29 AM
To: 'Mary.Kosir@med.va.gov'
Subject: RE: Annual Report DAMD17-00-1-0495

I would recommend that you file your report with a note to the reviewer that the statistical analysis will be filed in the next report due to blackout and computer problems.

-----Original Message-----
From: Mary.Kosir@med.va.gov [mailto:Mary.Kosir@med.va.gov]
Sent: Monday, August 25, 2003 8:51 AM
To: judy.pawlus@us.army.mil
Cc: wdu@crcm.med.wayne.edu
Subject: RE: Annual Report DAMD17-00-1-0495
Importance: High

Ms. Paulus,

I have been informed by the statistician that the computer system at Karmanos is still not working well. We have just been through the power outage in the northeast area (as you are aware) and then were dealing with viruses and worms.

The VA computer system available to me has been expeditiously cleaned of these latest viruses and worms. However, the Karmanos and Wayne State University computers that the statistician depends on are not as functional. The database is on a Wayne State Computer as well. We have backup discs however.

Therefore, I am asking for an extension in order to complete the report.
Alternatively, I can submit a report that lists that we have worked on the Tasks required, but will have to submit the statistical analyses later.

I have planned for this and had the data to the statistician in early August. Nevertheless, there have been too many interruptions.
I am personally not able to handle the massive amount of data at this time without their assistance.

Please offer me your opinion.

Thank you in advance for your consideration.

Mary Kosir
immediate contact via 313-745-0203, pager 4294.

-----Original Message-----
From: Pawlus, Judy K Ms USAMRMC [mailto:judy.pawlus@us.army.mil]
Sent: Wednesday, July 02, 2003 10:37 AM
To: 'mary.kosir@med.va.gov'
Subject: Annual Report DAMD17-00-1-0495
Importance: High

See the attached letter. Your report is very important to this Command as the results of your

research are published in our report to the disease advocacy communities to solicit continued funding for our programs. Your report is due to this Command **no later than September 2, 2003**. Questions or concerns regarding this suspense may be directed to me at 301-619-7322.

Thank you.

Judy Pawlus
Technical Editor
Office of the Deputy Chief of Staff
for Information Management, USAMRMC
301-619-7322
FAX 301-619-2745

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July 15, 2003

Mary Ann Kosir, M.D.
VAMC (11S)
4646 John R
Detroit, MI 48201

RE: Can a practicing surgeon detect early lymphedema reliably?

Dear Doctor Kosir:

Thank you for your manuscript. We are pleased to inform you that it has been accepted for publication along with the other papers from the Association of VA Surgeons in the November 2003 issue.

We have reviewed your manuscript and found that we need the specific information indicated on the enclosed Checklist form. Please return the Checklist form together with the requested material by **Tuesday, July 22, 2003** to our office in **Louisville, Kentucky**.

Thank you for your interest in and support of the Journal. We look forward to publishing your article.

Yours truly,

Hiram C. Polk, Jr., M.D.

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Hiram C. Polk, Jr., MD, Editor

CHECKLIST

This manuscript has been accepted for publication. However, we need the material indicated by the checkmarks below. Please return the checklist along with the requested material within 1 WEEK to the Editor.

✓ TITLE PAGE Change titles as indicated

_____ Full first name of all authors.
_____ Degrees of all authors.
_____ Complete name and address, with zip code, for reprints.
_____ Short running title of 3 to 5 words (no abbreviations).
_____ City and state of all foundations, funds and institutions mentioned on the title page.
_____ Telephone and FAX numbers of corresponding author (include area code; European authors to include country code and city code).

ABSTRACTS AND KEY WORDS

_____ A structured abstract of about 150 words labeled as Background, Methods, Results, Conclusions.
_____ An unstructured abstract of about 150 words (120 words for short papers).
_____ A list of 3 to 6 key words or topics for indexing the article.
_____ Mini-abstract for Table of Contents (2-3 sentences).

FIGURES AND TABLES

_____ Mention of all figures and tables in the text in proper numerical sequence.
_____ A brief legend explaining each figure (and any abbreviations used in the figure).
_____ Three glossy or camera-ready photographs of each figure.

REFERENCES

_____ Inclusive page numbers for journal articles and chapters in books.
_____ List all authors for journal articles with 4 or fewer authors; for 5 or more authors, list the first 3 and add et al.
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Can A ~~Surgical Practice~~ Detect Early Lymphedema? reliably ?

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Abstract

Background: Lymphedema (LE) may be identified by simpler circumference changes as compared to changes in limb volume.

Methods: Ninety breast cancer patients were prospectively enrolled in an academic trial, and seven upper extremity circumferences were measured quarterly for three years. A 10% volume increase or >1 cm increase in arm circumference identified LE with verification by a LE specialist. Sensitivity and specificity of several different criteria for detecting LE were compared using the academic trial as the standard.

Results: Thirty-nine cases of LE were identified by the academic trial. Using a 10% increase in circumference at two sites as the criterion, we detected half the LE cases (sensitivity 37%). When using a 10% increase in circumference at any site, 74.4% of cases were detected (sensitivity 49%). Detection by a 5% increase in circumference at any site was 91% sensitive.

Conclusions: An increase of 5% in circumference measurements identified the most potential LE cases compared to an academic trial.

Key Words

Lymphedema

Measurements

Circumference

Summary for Table of Contents

Simpler identification of potential lymphedema may be achieved by circumferential measurements using a 5%, and not 10%, increase above baseline. This approach provides greater sensitivity in detecting potential cases that should be referred to a lymphedema specialist who may use more complex volumetric measurements and clinical evaluation. Even though some may not have lymphedema after evaluation by an expert, the risk of lifelong disability in treatable cases that would be missed justifies the referral.

Introduction

Halsted described Lymphedema of the upper extremity following treatment of breast cancer by mastectomy in the early 1920's[1]. It continues to be of significant lifelong concern even with modern treatment of breast cancer. The incidence of lymphedema (LE) has been reported from 6% to 30%[2]. Early and reliable diagnosis continues to be challenging because multiple methods of detection are reported that are difficult to compare. The delay in identification of LE contributes to the negative psychosocial impact already imposed by the potential physical limitations, discomfort, and disfigurement that result from the condition.

There are various methods reported for the detection of LE including water displacement measurement of arm volume, tissue tonometry, and radiographic means such as MRI and CT. However, more commonly, circumferential measurements are used to detect LE. As of yet, however, there are no well-established guidelines for diagnosis of LE using circumferential measurements and no consensus on what measurement change constitutes LE[3]. In a review of the literature by Petrek and Heelan, the definition of LE ranged from > 2 cm change to > 10 cm change[2]. There are reports citing that a greater than 2 cm difference from baseline (preoperative) measurements identifies LE[4,5]. Generally, two or more circumferential measurements are taken along the arm, including at bony landmarks, to evaluate for LE[5,6].

In a prospective trial from the American College of Surgeons Oncology Group (ACOSOG)[7], LE is described as greater than or equal to 2 cm increase over the baseline measurement or greater than 10% increase in circumference of the ipsilateral arm. In addition, for the purpose of the ACOSOG protocol, participating members are instructed to take the measurements 10 cm proximal and distal to the lateral epicondyle.

In order to verify and compare various circumference change criteria for LE detection, a group of LE cases were identified by volumetric determinations prospectively collected on breast cancer patients in an academic trial that included examination by a LE specialist. A 10% increase in limb volume was accepted as LE[8,9]. In addition, any change in circumference greater than one cm led to examination and measurement by a LE specialist, identifying additional LE cases. Then measurements in the LE cases identified in the academic trial were compared with other definitions of LE that used fewer sites for detection, and various changes in circumference in order to determine specificity and sensitivity of LE detection.

Methods

After approval by the Human Investigation Committee at Wayne State University and human subjects subcommittee of the DoD (DAMD 17-00-1-0495), patients from the Alexander J. Walt Comprehensive Breast Center at The Karmanos Cancer Institute were enrolled prior to surgery, and after signing the approved study consent form. Participants were 18 years old or over, male or female, with newly diagnosed, resectable breast cancer. Eligible subjects were scheduled to undergo mastectomy or lumpectomy with lymph node sampling, dissection, or sentinel node biopsy, or breast conservation therapy followed by radiation therapy. Exclusion criteria included previous axillary surgery or radiation, planned mastectomy without axillary surgery or radiation therapy, inability to provide consent, or no plans to follow up at any of the Karmanos facilities following surgery. Demographic information was collected by questionnaire, which included ethnicity, education level, and income. The type of surgery, breast cancer stage, occurrence of chemotherapy and radiation therapy was recorded during the study.

From June 1999 through December 2002, 107 subjects were enrolled and evaluated for LE after surgical treatment of breast cancer. Of 107 subjects, 90 subjects were evaluable. The reasons for nonevaluable subjects: did not want to continue in the study (10), did not meet study entry criteria upon review (5), did not undergo axillary surgery and/or radiation therapy as planned (2). Measurements were taken preoperatively of bilateral arms. The circumferential measurements were taken across the palm of the hand, at the wrist, and at 10 cm intervals proximal to the wrist, and at the elbow. The volume was then calculated based on the total volume of a series of frusta. A frustum, a cone with the top cut off so the upper surface is parallel to the base, is felt to be a more accurate representation of the upper extremity[10,11] [7,8]. Measurements and volume calculations were taken quarterly for up to 3 years. Quarterly limb volumes were compared to preoperative values on the ipsilateral side. In the event that a patient had a change in weight of 10 pounds or greater (gain or loss), then measurements were repeated and volumes calculated creating a new baseline. Percent change from preoperative volumes were calculated quarterly using the following equation: volume % change = (current volume – preop volume / preop volume) x 100[9]. A 10% increase in volume as compared to preoperative measures was considered to be LE after verification by a LE specialist. In addition, anyone with a circumference measurement increase of greater than 1 cm was also referred to the LE specialist for additional measurements and examination. Not all of these were judged to have LE, but this route identified some additional cases (38.5%).

For comparison, the criterion of a 10% change and 5% change in circumferential measurement was applied to the sites proximal and distal to the elbow. This was done to evaluate the effectiveness of the 2-site method to diagnose LE as compared the sites measured for the academic trial. Then 10% change and a 5% change in circumference at any of the

measured sites along the limb were calculated. Additionally, measures >2cm were also identified. The LE specialist evaluated all potential cases of LE identified by these comparison methods in order to determine true positive and true negative cases. The time of diagnosis of LE was determined as months after the date of surgery. The sensitivity and specificity of each of the methods using circumference changes were determined in comparison to the LE cases confirmed in the academic trial. The timing of the diagnosis of LE was one of the factors used in determining sensitivity and specificity. If the differences in the timing of diagnosis were within 3 months, they were coded as an agreement. SAS version 8.2 was used for all statistical analyses.

Results

The patients eligible for inclusion in the study were of African-American (30%), Caucasian (51.1%), Hispanic (3.3%), Arab/Chaldean (2.2%), Asian (2.2%), Native American (3.3%), and other (6.7%) descent (Table 1). One subject did not indicate a race (1.1%). Overall, the average age of the patients enrolled was 53.7 years, and all were women, although men were eligible to enroll as well. The evaluable subjects had breast cancer stages from 0 through IV. Half (45) of the patients had mastectomy with axillary surgery, 38 (42.2%) had lumpectomy with axillary surgery, and the remaining 7 (7.8%) had lumpectomy with radiation therapy. In addition, half of the patients had radiation therapy.

The patients were followed in the trial for a mean of 13 ± 7.9 months (range 3 to 36 months), with enrollment occurring throughout. Thirty-eight (38) patients (with 39 limbs affected) of the 90 evaluable patients (42.2%) were found to have LE based on the academic trial standards of 10% increase in baseline volume and/or >1 cm change at one of the 7 measured sites with verification by the LE expert. One patient had bilateral disease. The mean age of

patients with LE was 54.8 years. Thirty-two of the 39 diagnoses (82.1%) of LE were made within the first year (acute LE). Most persisted past one year (86.7%). The average time until diagnosis of LE was 7.6 months and ranged from 3 months to 28 months (Table 2). There was no difference in incidence of LE based upon type of surgical procedure. There were not enough cases of sentinel lymph node biopsy (thirteen) to compare these LE criteria at this time. However, 5 of 13 were diagnosed with LE in the academic trial after SLNB.

Based on one of the ACOS-OG criteria for diagnosis of LE, 10% change in circumference for measurements 10 cm above and below the elbow, 20 patients (37% sensitivity, 92% specificity) were identified. The average interval until diagnosis was 11.7 months (Table III). When a 10% change in circumference was applied to any of the measurements along the limb, 29 patients (49% sensitivity, 81% specificity) were identified. The average interval until diagnosis was 10.7 months (Table IV).

Determining a >2 cm change in circumference above and below the elbow identified 28 cases (59% sensitivity, 85% specificity) which overlapped with the cases identified by 10% circumference increase in the same sites (Table V). Diagnosis of LE occurred at 9.3 months on average. When all measured sites were examined for a >2 cm change, then 32 cases were identified (70% sensitivity, 76% specificity) (Table V). The diagnosis occurred at 8.6 months on average.

In order to increase sensitivity, 5% changes in circumference were determined around the elbow (Table III), and at all measured sites (Table IV). With a 5% circumference change around the elbow, there were 36 cases identified at a mean of 8.3 months (80% sensitivity, 71% specificity) (Table III). However, when 5% circumference change was determined for any

measured site, the all 39 LE cases from the academic trial were identified at 7.5 months (91% sensitivity, 46% specificity) (Table V).

Discussion

Most patients do not have LE following surgery or radiation therapy. However, for the approximately 30% of post-surgical/post-radiation patients that do develop the condition, it can be life altering and affect their quality of life. Interestingly, it can start within the first year after surgery. Some resolve within that year, others persist. Still others occur at some interval after the first year. There are several treatment modalities available for therapy. However, a delay in diagnosis delays therapy. Earlier treatment can prevent acute LE from becoming more advanced and chronic, even if it doesn't resolve after one year. When it is left untreated, chronic LE can progress to chronic inflammation, fibrosis, swelling, and increased risk of cellulitis[12]. Therefore, early identification of potential LE remains a goal for surgical practices.

The diagnosis is more complex in those patients who experience a feeling of heaviness, swelling, and/or pain, in the absence of corroborating volume or circumferential changes. These individuals may be considered to have LE by subjective complaints and require evaluation a by LE specialist as well[13]. The subjective complaints often times precede the ability to clinically document LE[9]. The physical changes that accompany the condition create difficulty with tasks associated with jobs, households, and even personal care, especially in severe cases[14]. The psychological impact can be tremendous resulting in sexual dysfunction, depression, and feelings of isolation.

Modern day surgical practices in breast surgery are aimed at reducing post surgical and treatment morbidity. With the advent of sentinel lymph node biopsy (SNLB), it has been

reported that arm swelling and subjective complaints are decreased in comparison to traditional axillary lymph node dissection (ALND).[15-17] Sener et al reported 6.9% incidence of LE in patients undergoing SLNB followed by obligatory ALND.[17] The incidence of LE decreased to 3% with SNLB alone (LE was characterized by a minimum 20% volume change in that particular study). Although the data are promising, the number of LE cases was falsely low due to the determination of a > 20% circumference increase at sites 10cm above and below the elbow. This is predicted to increase the false negative rate for LE detection. Therefore, future studies examining the occurrence of LE in cases with SLNB require standardized criteria for identifying potential cases.

Although there are generally accepted criteria to diagnose LE, there are no universally applied methods to diagnose potential LE, thereby complicating interpretation of literature. This also has serious implications for surgical practice in making a presumptive diagnosis and referral to a LE specialist. While a LE specialist may apply multiple complex measurements and other clinical evaluations in arriving at the confirmation of LE, surgeons may need simpler screening criteria that would reliably detect LE in order to refer for consultation. For example, some authors have used or referred to a method of two measurements (one above and one below the elbow) with a 2 cm increase in circumference for diagnosis of LE.[2,4,15,18] When data from the subjects in this study was evaluated by this criterion, we found that 28 of the 39 (71.8%) cases diagnosed with LE would also have been diagnosed by this method [Table V]. When the 2 cm increase was applied to any site, the true positive diagnosis rate was 82.1%, missing 17.9% of the cases.

When ACOS-OG criteria for LE were applied to the measurement data (10% increase in circumference around elbow), 48.7% of the documented LE cases would have been missed as compared to evaluating sites along the arm (Table III). Ten cases (25.6%) would have been missed based on the ACOSOG criteria of 10 % circumferential change if applied to any site. In addition, the academic trial identified patients with LE three months earlier on average in comparison to ACOS-OG criteria. It should be noted, however, that if the ACOS-OG criteria of 10% change over baseline measurement was lowered to 5%, all of the patients identified by the academic trial would have been positively diagnosed with LE by that standard (Table III, IV). On average, patients would have been diagnosed 3.7 months earlier if this criterion were utilized instead of 10% and 0.6 month earlier than using a 10% volume change.

In addition, we used a >1 cm change in circumference at any site as a trigger for referral to the LE specialist who would further evaluate for LE.[3,19,20] Thirty-seven of 39 LE cases had a > 1 cm change. We feel that this is a reliable indicator of LE. However, although the sensitivity was 76% for this approach, the specificity was only 39%. This may lead to a greater number of referrals to the LE specialist than would have the diagnosis. With confirmation of the diagnosis, LE therapy could begin.

In conclusion, methods of LE diagnosis that are readily available, inexpensive, quantifiable, and easily reproduced are ideal for evaluation of patient in a surgical practice.[6] The academic trial utilizing frequent measurements and volumetric determinations identified LE in 43.3% of the total patients evaluated, which is higher than the general incidence of LE reported in the literature.[2] The methodology is also more complex than would be practical in a surgical practice. However, simpler determination of circumference change at multiple sites along the affected limb may identify potential cases for referral, leading to earlier treatment and

lessen the psychosocial and physical impact. By using a 5%, rather than 10% change in circumference and/or using a >1 cm change in measurement at sites along the length of the arm, reliable detection of probable LE in a clinical setting can be accomplished without complicated volume determination. The later can be utilized by LE specialists along with other complex evaluations.

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Table I Patient Characteristics

	With lymphedema	Without lymphedema
N	38[#]	52
Mean age (yrs ± S.D.)	54.8 ± 13.4	54.4 ± 10.3
Race		
African American	14	13
Caucasian	16	30
Hispanic	3	0
Arab/Chaldean	1	1
Asian	0	2
Native American	0	3
Other	4	2
Unknown	0	1
Breast Cancer Stage		
0	3	6
I	7	17
IIA	11	11
IIB	5	14
IIIA	8	1
IIIB	3	2
IV	1	1
Chemotherapy	16	15

Radiation Therapy	**16**	**27**
Employment status		
Working	**15**	**28**
Not working	**10**	**7**
Retired	**10**	**8**
Not answered	**3**	**9**
Highest education level		
Less than high school	**4**	**1**
High School/GED	**21**	**28**
Associate degree	**0**	**0**
Bachelor degree	**8**	**9**
Masters degree	**1**	**4**
Doctorate/professional school	**1**	**1**
n.a.	**3**	**9**
Annual Income		
<$5,000/yr	**3**	**4**
$5,001-$15,000/yr	**6**	**4**
$15,001-$30,000/yr	**5**	**5**
$30,001-$50,000/yr	**3**	**2**
$50,001-$75,000/yr	**3**	**8**
>$75,000/yr	**10**	**13**
n.a.	**8**	**16**

[#] one patient had bilateral disease

Table II

Lymphedema detection in academic trial by type of surgery[+]

	Type of breast cancer surgery			
	Mastectomy with axillary surgery (n=45)	Lumpectomy with axillary surgery and RT* (n=38)	Lumpectomy and RT (n=7)	All (n=90)
With lymphedema	19	18	2	39*
Acute LE [#]	13	18	2	33
Mean time to LE diagnosis (months)	8±6	7±6	6.5±0.7	7.6±5.8

[+] Academic trial LE criteria: 10% or greater volume change or 1 cm or greater circumference change at any site-all verified by LE specialist)

[*]RT = radiation therapy

[@]LE= lymphedema

[#]acute LE=lymphedema diagnosed within the first year after surgery

Table III

Comparison of LE detection using 10% and 5% circumference change above and below the elbow to the academic trial

	10% change around elbow	5% change around elbow
Potential LE cases[@]	18	45
Mean time to LE diagnosis (months)	11.7 ± 6.3	8.3 ± 5.9
Sensitivity	37%	80%
Specificity	92%	71%

*one patient had bilateral disease

[@]LE=lymphedema

Table IV

Comparison of LE detection using 10% and 5% circumference change at any site to the academic trial

	10% change any site	5% change any site
Potential LE cases[@]	28	62*
Mean time to LE diagnosis (months)	10.7 ± 6.1	7 ± 5
Sensitivity	49%	91%
Specificity	81%	46%

[@]LE=lymphedema

* one patient had bilateral surgeries and was positive bilaterally

Table V

Comparison of LE detection using >2 cm circumference change at any sites, and specifically above and below the elbow to the academic trial

	> 2 cm around the elbow	> 2cm at any sites
Potential LE cases[@]	30	39
Mean time to LE diagnosis (months)	9.3 ± 6.2	8.6 ± 5.9
Sensitivity	59%	70%
Specificity	85%	76%

*one patient had bilateral disease

[@]LE=lymphedema