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TITLE: Assessment of Lymphedema Risk Following Lymph Node
Dissection and Radiation Therapy for Primary Breast
Cancer

PRINCIPAL INVESTIGATOR: Andrea L. Cheville, M.D.

CONTRACTING ORGANIZATION: University of Pennsylvania
Philadelphia, Pennsylvania 19104-6205

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Pennsylvania Philadelphia, Pennsylvania 19104-6205 E-Mail: Andrea.Cheville@uphs.upenn.edu			8. PERFORMING ORGANIZATION REPORT NUMBER
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13. ABSTRACT (Maximum 200 Words) The purpose of this study are two fold: 1)To determine the feasibility of using concurrent lymphoscintigraphy and CT imaging to identify lymph nodes critical for upper extremity drainage and to establish their relation to radiation therapy ports, and 2)To determine whether the irradiation of level I and II axillary lymph nodes critical for upper extremity drainage predicts the development of lymphedema. In addition to funding this research project, the Career Development award supports Dr. Cheville's completion of a Masters Degree in Clinical Epidemiology. This degree program will provide Dr. Cheville with the knowledge and skills required to succeed as an independent investigator. Dr. Cheville's masters' thesis, required for the degree, will involve data collection, analysis, and presentation of the lymphoscintigraphy study. To date, Dr. Cheville has completed half of the course work required for the Masters Degree, including extensive training in biostatistical analysis. Through consultation with Dr. Cheville's faculty mentor and course work in protocol development, the study design has been refined to address potential bias and confounding. With the support of faculty mentors in epidemiology and biostatistics, study subject enrollment and data collection have begun.			
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Introduction

This award funds a study to determine whether lymphoscintigraphy can reliably identify lymph nodes critical for upper extremity drainage and whether irradiation of the identified nodes in the context of primary breast cancer treatment predicts the development of lymphedema. The award also provides salary support enabling the principal investigator, Dr. Andrea Cheville, to complete a Masters Degree in Clinical Epidemiology. Dr. Cheville's epidemiology course work will inform and facilitate completion of the lymphoscintigraphy study. For example, study of database creation and management, bias and confounding in study design, and biostatistical analysis all have immediate applicability to the lymphoscintigraphy project. The lymphoscintigraphy study will be the focus of Dr. Cheville's Masters' Thesis.

The lymphoscintigraphy study is a prospective cohort study of women receiving radiation therapy in the context of primary breast cancer treatment. A total of fifty breast cancer patients will be enrolled. Prior to their first radiation treatment, subjects will undergo combined lymphoscintigraphic and computed tomographic evaluation. By combining these imaging modalities, the precise anatomic location of critical lymph nodes can be determined and their total radiation exposure calculated. Subjects will be followed prospectively and repeat lymphoscintigraphic/computed tomographic evaluation completed one year after radiation therapy. Limb volume and rate of lymph clearance will be measured prior to and one year following radiation therapy to assess lymphedema.

This study is intended to establish a foundation for a larger interventional trial to determine if deliberate elimination of the critical nodes from the radiation field will attenuate patients' risk of lymphedema

Progress Report

Task 1. Conduct a prospective cohort study to estimate the increased lymphedema risk associated with radiation therapy delivered to chest wall and lymph node beds.

1. *Review Board Approval:* Approval has been granted for the study from the USAMRMC HSRB, University of Pennsylvania Institutional Review Board, and the University of Pennsylvania Cancer Center Clinical Trials Scientific Review. Due to slight revisions in the protocol (outlined in item 2)
2. *Refinement of Imaging and Informatic Logistics:* The technique of concurrently acquiring and merging lymphoscintigraphic and computed tomography images has been successfully developed. The capacity to transfer computer graphic files containing the study images from the nuclear medical department, where all scans are performed, to the radiation oncology data base has been established. This permits precise quantification of the radiation dose administered to each lymph node encompassed by the radiation field.
3. *Lymph Node Imaging:* By performing serial lymphoscintigraphic mapping of 10 patients we have established the optimal strategy for injecting radiolabeled tracer, interval between tracer injection and image acquisition, and positioning of study subjects

4. *Subject Enrollment:* Two subjects have been enrolled to date. Having resolved several unanticipated problems with data transfer, we now anticipate recruiting two patients per week.

Task 2. Complete course work and thesis preparation for a Master of Science degree in clinical epidemiology at the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

1. *Course work:* Dr. Cheville has now completed one half of the credits required for the Master of Science Degree, and all but one of the required courses. The courses that have been completed by the candidate and the course descriptions are listed below.

EPID 520 - Introductory Biostatistics

This course is a series of lectures and laboratory sessions designed to provide a working knowledge of the fundamental concepts of biostatistics. Topics covered include probability, estimation, confidence intervals, hypothesis testing including nonparametric techniques, correlation, regression, analysis of variance, and analysis of covariance. Emphasis in both lectures and labs is placed on understanding the proper application and underlying assumptions of the methods presented. Laboratory sessions focus on the use of statistical software as well as provide time for review of course material. This course provides the necessary foundation for higher level biostatistics and epidemiology courses. (The lectures for this course are the same lectures as for EP 502.)

Grade: B+

EPID 510 - Introductory Epidemiology

This course is a series of lectures and workshops, designed to teach basic principles of epidemiologic research design. The course provides an overview of the types of research questions that can be addressed by epidemiologic methods. Topics covered include: definitions of epidemiology; measures of disease frequency; measures of effect and association; epidemiologic study designs, both experimental and non-experimental; and an overview of analysis of epidemiologic studies.

Grade: A

EPID 521 - Statistical Methods for Epidemiologic Research

This seminar focuses on statistical methods for analyzing case-control, cross-sectional, and cohort studies, and clinical trials. Topics include simple analysis of epidemiologic measures of effect; stratified analysis; ordinary linear, logistic, and Poisson regression methods; simple survival analyses including Cox regression; power and sample size calculations; confounding interaction; and the use of matching. All methods are practiced on existing data sets. Six laboratory sessions focus on the use of statistical software in epidemiologic research.

Grade: A

EPID 532 - Database Management for Clinical Epidemiology

This course provides students with an introduction to the techniques of database

management as they apply to clinical research. Students learn how to design and implement computerized databases, perform basic query and reporting operations, migrate data between various file formats, prepare databases for statistical analysis, and perform quality assurance procedures. This course focuses on the practical issues of database management and is intended to support each student's planned research enterprise.

Grade: A

EPID 560 - Issues in Research Protocol Development

This is a seminar that focuses on major issues in research protocol development, including methodological issues regarding different research designs, development of research questions, and plans for analysis. Each student will present his or her research proposal for open discussion during one of the seminar sessions.

Grade: A

EPID 570 - Critical Appraisal of the Medical Literature

This seminar focuses on techniques for critical appraisal of the medical literature. Each student will be responsible for at least one critical appraisal session covering different epidemiologic topics (including the evaluation of diagnostic tests, clinical course and prognosis of disease, disease etiology or causation, therapy, quality of clinical care, economic evaluation, and meta-analysis). For his/her session, each student will appraise critically a journal article and lead the discussion concerning that article.

Grade: A

EPID 610 - Tutorial in Epidemiologic Research

This is a tutorial given by each student's advisor. Advisor and student meet regularly, usually weekly, throughout the first year of study. Topics include: discussion and review of epidemiologic concepts and principles, guided readings in the epidemiology of a specific health area, and the development of the research protocol. Credit for this course is awarded upon completion of a research project proposal, the one to be used to fulfill the M.S.C.E. thesis requirement, which must be approved by the student's advisor. Evaluation is based on the grade received for the proposal.

Grade: Pending

EPID 900 and EPID 990 - Masters Thesis

These are a series of tutorial sessions conducted by the student's advisor, which are to support the student's efforts in developing a research protocol, designing a research project, and completing the study.

Grade: Pending

EPID 542 - Measurement of Health in Epidemiology

This course is a series of lectures and discussion sessions designed to introduce the student to the concepts of health measurement as applied to epidemiologic studies. Topics covered include: the basics of health measurement theory; critical evaluation of the current status of health measurement in a chosen field; and techniques for developing

and using measurement scales, including item analysis, validity and reliability testing, and qualitative methods.

Grade: Pending

EP 622 Applied Regression Models for Categorical Data

This course will provide in-depth treatment of several topics in categorical data analysis. After a brief review of methods for contingency tables, we will introduce the idea of generalized linear models, and focus on two special cases multiple logistic regression and loglinear models. Each topic will be presented in detail by stating the model and covering parameter estimation and interpretation, inference, model building, regression diagnostics and assessment of model fit. Finally, we will cover extensions to both models, including models for multinomial data, analysis of matched-pair data, and random effects models. Topics will be illustrated in class with examples, and we will discuss the use of Stata to conduct the analyses.

Grade: A

Key Research Accomplishments

1. Established methodology for identifying lymph nodes with in radiation fields utilized in primary breast cancer treatment.
2. Designed informatics to merge lymphoscintigraphic and computed tomographic images in order to precisely quantify radiation dose delivered to lymphatic critical for upper extremity drainage.
3. Developed clinical protocol for lymphoscintigraphic mapping of axillary and supraclavicular lymph nodes critical for upper extremity drainage.

Conclusions

The research conducted thus far demonstrates the feasibility of utilizing lymphoscintigraphic mapping techniques to identify lymph nodes critical for upper extremity drainage and their relationship to radiation therapy tangents. This approach is wholly novel and holds great promise as a means of deliberately customizing radiation therapy treatment in order to minimize normal tissue injury while preserving cure rates. Having established a successful protocol, we will now begin recruiting patients in earnest.