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TITLE: Optimizing Treatment of Lung Cancer Patients with Comorbidities

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14. ABSTRACT
The overall goal of this project is to improve the management of military personnel and Veterans with localized lung cancer and comorbidities. The Specific Aims are to: 1) Enhance and validate the Lung Cancer Policy Model to simulate the management and subsequent outcomes of military personnel and Veterans with early stage lung cancer and specific comorbidities; 2) Determine the optimal management and indications for lobectomy, elective limited resection, stereotactic body radiotherapy, and other treatments for military personnel and Veterans with stage I NSCLC and chronic lung or heart disease as well as by overall burden of comorbidities; and 3) Determine the optimal indications for adjuvant chemotherapy in military personnel and Veterans with stage II and IIIA NSCLC and chronic lung, heart, or renal disease and by overall burden of comorbidities.

We have completed the majority of analyses to inform the parameter estimates for our simulation models that will ultimately provide guidance regarding optimal treatment of lung cancer patients with major comorbid illnesses. Most contributing analyses involved national VA health data; we identified a cohort of >20,000 NSCLC patients and collected data on comorbidities, cancer treatments and outcomes to generate estimates of treatment complications, overall survival and quality of life. These results are currently being incorporated into the well-validated Lung Cancer Policy Model to generate specific treatment recommendations.

15. SUBJECT TERMS
Military personnel, Veterans, lung cancer, comorbidities

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INTRODUCTION:

The overall goal of this project is to improve the management of military personnel and Veterans with localized lung cancer and comorbidities. The Specific Aims are to: 1) Enhance and validate the Lung Cancer Policy Model (LCPM) to simulate the management and subsequent outcomes of military personnel and Veterans with early stage lung cancer and specific comorbidities; 2) Determine the optimal management and indications for lobectomy, elective limited resection, stereotactic body radiotherapy (SBRT), and other treatments for military personnel and Veterans with stage I NSCLC and chronic lung or heart disease as well as by overall burden of comorbidities; and 3) Determine the optimal indications for adjuvant chemotherapy in military personnel and Veterans with stage II and IIIA NSCLC and chronic lung, heart, or renal disease and by overall burden of comorbidities.

KEYWORDS:

Military personnel, Veterans, lung cancer, comorbidities

ACCOMPLISHMENTS:

What were the major goals of the project?

Major Goals	Target Dates
Enhance and validate the LCPM to simulate the management and subsequent outcomes of military personnel and Veterans with early stage lung cancer and specific comorbidities	1-12 months
Determine the optimal management and indications for lobectomy, elective limited resection, stereotactic body radiotherapy, and other treatments for military personnel and veterans with stage I NSCLC and chronic lung or heart disease as well as by overall burden of comorbidities	13-20 months
Determine the optimal indications for adjuvant chemotherapy in military personnel and Veterans with stage II and IIIA NSCLC and chronic lung, heart, or renal disease and by overall burden of comorbidities	18-24 months

What was accomplished under these goals?

1) Major activities:

   During the second grant year we accomplished the following activities:

   a. Continued to analyze VA databases to obtain data regarding cancer outcomes
   b. Enhanced and calibrate the LCPM

c. Simulated treatment outcomes using the modified LCPM for stage I lung cancer for Veterans with major comorbid illnesses
d. Writing of manuscript describing those results
e. Simulation of treatment outcomes using the modified LCPM for adjuvant chemotherapy for Veterans with stage II and IIIA NSCLC with major comorbidities

2) Specific objectives:

Since project inception:

a. Submit to local IRBs
b. Link different VA registries, code data regarding relevant variables
c. Analyze the MGH-RPDR, SEER-Medicaid, VACS, NHATS, VA-SQIP, and NHS-MDR databases to obtain data regarding comorbidities, quality of life, functional status, frailty, and surgical-related complications
d. Request HRPO/ACURO approval
e. Estimate the prevalence of comorbidities, estimate the prevalence of functional status impairment and frailty according to the presence or absence of comorbidities, estimate rates of surgical complications and chemotherapy and RT related toxicity in patients with specific comorbidities
f. Incorporate comorbidities and functional status into the LCPM and develop new treatment modules for limited resection and adjuvant chemotherapy
g. Calibration and validation of the enhanced LCPM
h. Performance of simulated randomized controlled trials of stage I lung cancer therapies for Veterans with major comorbid illnesses
i. Manuscript describing results of stage I lung cancer simulations
j. Performance of simulated randomized controlled trials of adjuvant chemotherapy for stage II and IIIA lung cancer in Veterans with major comorbidities

3) Significant results/developments:

a. Presented abstract at American Thoracic Society international meeting 2018 with results of analyses used to establish model parameters
b. Completion of simulations comparing stage I NSCLC treatments for Veterans with major comorbidities

We have conducted an extensive range of simulated trials comparing major therapies for stage I NSCLC in Veterans (Figure 1). These trials were conducted in several age groups, with different tumor sizes and histology. The model output provides clear estimates of benefit, in terms of life years gained, for each treatment. For instance, in Veterans aged 60-70 with coronary artery disease (CAD) with tumors <1cm, 7.58 life years are gained, on average, with lobectomy, while limited lung resection leads to an average of 7.62 life years gained, suggesting this may be the most beneficial treatment. In contrast, in a similar group of Veterans without CAD, lobectomy leads to 7.87 life years gained, as opposed to only 7.82 for limited resection. Lobectomy is likely, therefore, to be the most beneficial treatment for Veterans without CAD in this age and tumor group.

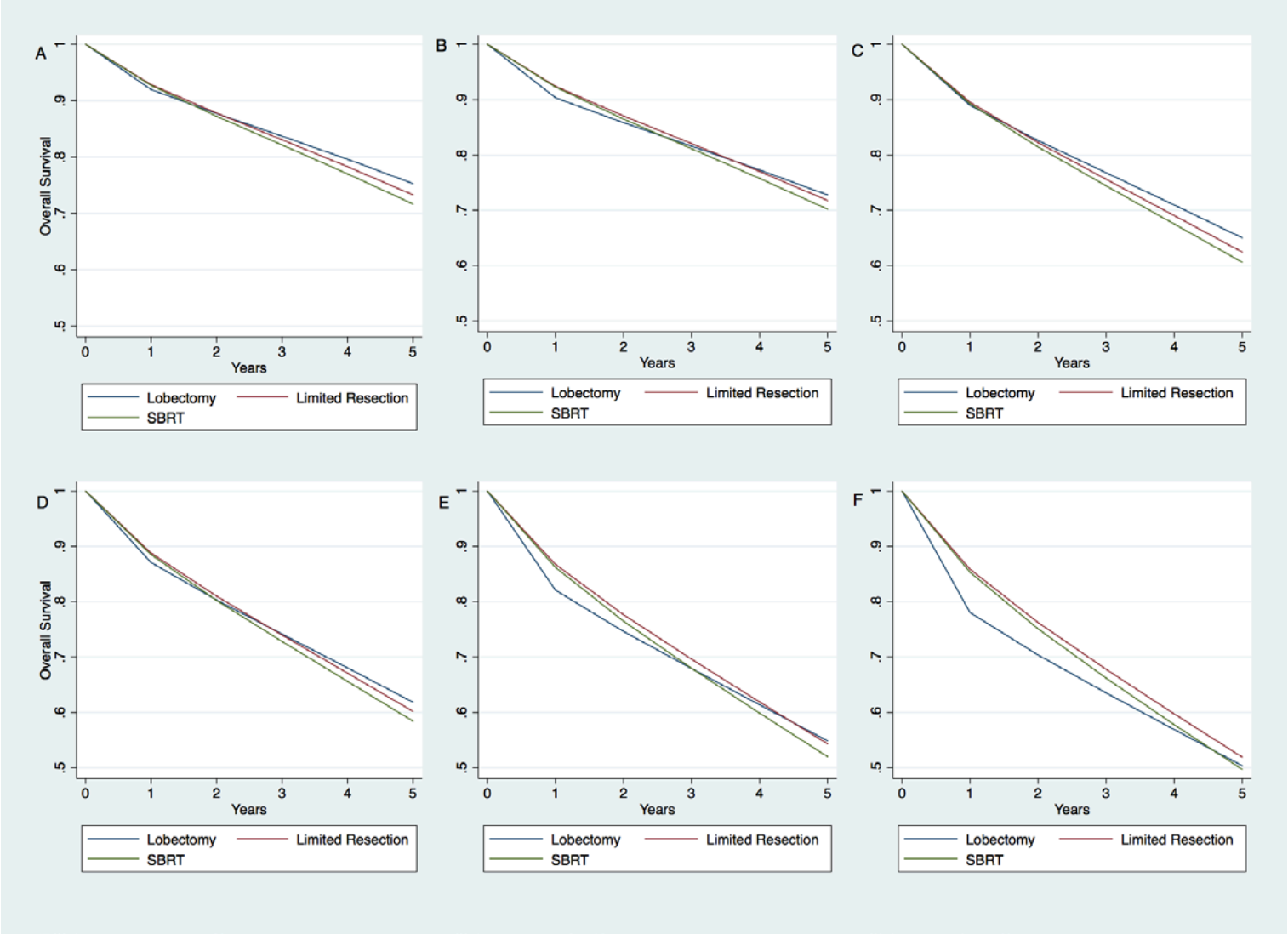

Figure 1. Results of simulated randomized trials of lobectomy versus limited lung resection versus stereotactic radiosurgery (SBRT) for stage I lung adenocarcinoma, sized 1-2cm. A) Veterans aged 60-70 without coronary artery disease (CAD). B) Veterans aged 60-70 with CAD. C) Veterans aged 70-80 without CAD. D) Veterans aged 70-80 with CAD. E) Veterans aged 80 and above, without CAD. F) Veterans aged 80 and above, with CAD.

4) Other achievements:
    a. Nothing to report

What opportunities for training and professional development has the project provided?

Patrick Yong, a medical student who is receiving training in comparative effectiveness research with our group, participated in the interpretation of our results and presented an abstract of the parameter analyses for this project at the American Thoracic Society international meeting in San Diego, May 2018. Benjamin Liu, a medical student, also receiving training in statistical methods with our research group, is completing an analysis evaluating the risk of long-term cardiotoxicity associated with radiotherapy for early stage lung cancer that will be incorporated into our simulations. This work is being prepared as a manuscript currently.

How were the results disseminated to communities of interest?

Results were presented as an abstract to American Thoracic Society at their 2018 conference.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue this project as a no cost extension and are completing a manuscript comparing stage I NSCLC treatments and beginning a manuscript comparing adjuvant chemotherapy for stage II and IIIA NSCLC.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This project is providing unique treatment guidance for early stage lung cancer in Veterans with major comorbidities. As this group is unlikely to be the focus of randomized clinical trials of lung cancer treatments, this project is providing high impact, actionable data for the management of this large group of patients.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the complexity of our underlying data sources analyses to generate model parameters took longer than expected. We expect that we will be able to complete the planned simulations under a no-cost extension.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

PRODUCTS:

Publications, conference papers, and presentations

Nothing to report.

Website or other internet site

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licences

Nothing to report.

Other products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Juan Wisnivesky	No change
Keith Sigel	No change
Kimberley Stone	Project role: Data analyst Nearest person month worked: 1.8 Contribution to project: Ms. Stone has participated in biweekly conference calls to assist in planning for what analyses will be incorporated into the LCPM as well as managing and preparing new data being collected and their analyses.
Joey Kong	No change
Andrew Eckel	No change
Renda Wiener	No change
Susan Bates	No change
Andrew Bean	No change

Has there been a change in the active other support of the PD/PI or senior/key personnel since the last reporting period?

Juan Wisnivesky	No change
Keith Sigel	No change
Joey Kong	No change

Andrew Eckel	No change
Renda Wiener	No change
Susan Bates	No change
Andrew Bean	No change

What other organizations were involved as partners?

Organization name: Massachusetts General Hospital (MGH)
Location of organization: Boston, MA
Partner's contribution to the support: Dr. Kong, our collaborator from MGH, is the primary simulation modeler in this project. He has been actively involved in review of data analysis to ensure that these results will be appropriate and accurate model parameters. He is supervising the modification of the Lung Cancer Policy Model to generate treatment recommendations for Veterans and Military Personnel with lung cancer and major comorbid illnesses.

Organization name: Bedford VA Research Corporation
Location of organization: Bedford, MA
Partner's contribution to the support: Dr. Wiener is the site PI for Bedford. She has significant expertise using national data resources and has helped oversee our use of these resources in parameter analyses. Her input has been very valuable for ensuring the integrity of our analyses. National VA oncologic data has only been available in recent years, and there is little published literature regarding the use of these data. The presence of an investigator with experience using these data has been critical for the efforts of the team.

Organization name: Bronx Veterans Medical Research Foundation
Location of organization: Bronx, NY
Partner's contribution to the support: Dr. Bates is the site PI for the Bronx VA. She coordinates, along with Dr. Sigel (who is a "without compensation" VA employee), the access to national VA lung cancer data. Dr. Bates is a clinical oncologist, and provides valuable oncologic input for the project as well. She has provided important oversight regarding the clinical importance of certain findings, as they are incorporated into our simulation modeling efforts.

SPECIAL REPORTING REQUIREMENTS

Not applicable

APPENDICES

Nothing to report