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Optimizing the use of adjuvant chemotherapy in non-small cell lung cancer patients with comorbidities

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ABSTRACT

Veterans with locoregional non-small cell lung cancer (NSCLC) may benefit from adjuvant chemotherapy. However, comorbidities and other factors may impact the harms and benefits of this treatment. Here, we identified the optimal indications for adjuvant chemotherapy in Veterans with NSCLC, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and/or coronary artery disease (CAD). We used data from randomized controlled trials (RCTs) and Veterans Administration (VA) databases to enhance a simulation model. Then, we conducted in-silico RCTs comparing adjuvant chemotherapy vs observation among Veterans with stage II-IIIA NSCLC. Among Veterans without COPD or CKD, adjuvant chemotherapy was the optimal strategy regardless of the presence or absence of CAD except for patients >70 years with squamous cell carcinoma. Conversely, most veterans without COPD but with CKD were optimally managed with observation. Veterans with COPD but without CKD, benefited from adjuvant chemotherapy if they were ≤70 years with stage II-IIIA adenocarcinoma or <60 years with stage II-IIIA squamous cell carcinoma.

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Adjuvant chemotherapy was only beneficial for Veterans with both COPD and CKD among stage II-IIIA adenocarcinoma <60 years of age. Veterans with stages II-IIIA squamous cell carcinoma, COPD, and CKD were optimally managed with observation. Many Veterans with comorbidities are optimally managed with observation post-surgical resection. However, we also identified several groups of Veterans whom the benefits of adjuvant chemotherapy outweighed the risks of early toxicity. Our findings could inform patient-provider discussions and potentially reduce physicians' uncertainty about the role of adjuvant chemotherapy in this population.

ARTICLE INFO

Keywords: Non-small cell lung cancer; Adjuvant chemotherapy; Comorbidities; Veterans

Introduction

Lung cancer burden among Veterans in the United States (US) is a major healthcare priority due to the high rates of smoking and exposures to environmental carcinogens associated with military service.[1] Veterans diagnosed with lung cancer are generally ≥70 years, have comorbidities, and are underrepresented in randomized controlled trials (RCTs).[2] As a result, evidence guiding management in this population is limited and less than half of Veterans with locoregional disease receive guideline-recommended therapy.[3] Surgery is the standard treatment for stage I-IIIA non-small cell lung cancer (NSCLC).[4] However, these patients are at substantial risk of recurrence following resection.[5] To mitigate the risk of recurrence, a number of large RCTs have evaluated whether adjuvant chemotherapy would improve survival in stage I-III disease. Outcomes of these individual trials were conflicting with several concluding there was no benefit to adjuvant therapy. However, a meta-analysis of 4,584 patients enrolled in 5 RCTs including cisplatin demonstrated that adjuvant platinum-based chemotherapy reduces recurrence and increases survival, with a 5.4% absolute improvement at 5 years.[6] Based on these findings many national guidelines recommend adjuvant chemotherapy for resected stage II-IIIA NSCLC.[7]

While highly internally valid, generalization of results from RCTs of cancer therapies can be challenging. RCTs are conducted among populations who meet eligibility criteria including good performance status and lack of concurrent illness, and thus often exclude older patients as well as those with multiple comorbidities.[2] Veterans with NSCLC often have major concurrent illnesses, limiting their ability to enroll in clinical trials. Chronic obstructive pulmonary disease (COPD, 25%-50%) and coronary artery disease (CAD, 25%-35%)[8] are the most common conditions; chronic kidney disease (CKD) is also frequent.[9] Prior studies have reported that Veterans with NSCLC are at a higher risk of developing major complications following surgery.[10] Thus, prolonged post-operative recovery may delay initiation and potentially lower the benefit of adjuvant chemotherapy. In addition, aging and comorbidities could substantially affect the harm/benefit ratio of adjuvant chemotherapy because of decreased tolerability, lower life expectancy, and poorer quality of life. Thus, it is crucial to examine the benefit and harms that are associated with adjuvant chemotherapy in Veterans with stage II-IIIA NSCLC and major smoking-related comorbidities. As benefits of adjuvant chemotherapy are limited, it is quite possible that use is not appropriate for every patient.

The goal of this study was to determine the role for adjuvant chemotherapy in Veterans with stage II-IIIA NSCLC and COPD, CAD, and CKD by developing a microsimulation model using individual-level patient data from Veterans. Then, we simulated multiple RCTs and estimated the benefits and harms of adjuvant chemotherapy among Veterans according to their age, comorbidities, and cancer characteristics.

Table 1
Key input parameters for developing a microsimulation model of veterans with non-small cell lung cancer*.

Model parameter	Definition	Value		Sources
Lung Cancer Treatment Response	Treatment-specific lung cancer specific survival hazard ratios	Adjuvant chemotherapy vs observation	HR: 0.83, 95% CI: 0.76-0.90	[49,50]
Lung Cancer Treatment Complications	Probability of lung cancer treatment complications including perioperative mortality	Multiple complications	See Table A.1	Primary data; Table A.1
Non-Lung Cancer Mortality	Non-lung cancer death rates according to age and comorbidity	Comorbidity vs no comorbidity	See Table A.2	Primary data; Table A.2
		Comorbidity	**Utility**	
Quality of Life for Veterans with Comorbidities	Predicted quality of life for Veterans according to comorbidity	CAD	-0.018	Primary data; Table A.4
		COPD	-0.021	
		CKD	0*	
Quality of Life Associated with Lung Cancer Treatment Complications	Disutility associated with major complications of lung cancer treatment	Major complications of treatment	-0.35†	[20,21]

CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.
No significant difference in utility associated with CKD.
* indicates No significant difference in utility associated with CKD.
† Quality of life returns to baseline within 6 months, modeled as a linear recovery.

Methods

Overview of the Simulation Model

We developed a treatment-focused Lung Cancer Policy Model (LCPM-Treatment) that captures issues relevant to the use of adjuvant chemotherapy in Veterans with NSCLC and major comorbidities. LCPM-Treatment is an extension of LCPM, a well-validated microsimulation model of patient's (non-veterans) NSCLC cancer development, progression, detection, treatment, and survival.[11-15] Following extensive review of the literature and primary analyses of national Veteran data, we identified unique factors that affected treatment outcomes. Thus, the enhanced LCPM-Treatment reflects patient comorbidities, cancer characteristics, treatment complications, and survival from several national Veteran Administration (VA) sources.

LCPM-Treatment populates with Veterans with stage II and IIIA NSCLC and progresses through different health states with monthly transition probabilities determined from relevant VA databases, the results of RCTs, and/or the literature (Table 1). NSCLC can be adenocarcinomas or squamous cell carcinomas (the two most common cell types) with specific growth patterns based on validated parameters.[12-15] Simulated Veterans "underwent" lobectomy but remained at risk for recurrent disease, which varied by stage.[11] Following lobectomy, Veterans were 'randomized' to an observation arm or to undergo platinum-based adjuvant chemotherapy. The adjuvant chemotherapy arm did not differentiate between cisplatin- or carboplatin-based regimens, as these drugs are used interchangeably and associated with similar long-term outcomes and safety profiles.[16] However, we assumed that Veterans with CKD were treated with carboplatin.[17,18] Veterans who received adjuvant chemotherapy were at risk of developing complications (as described below) conditioned on age, sex, and comorbidities. Veterans in both arms were then followed until death, which could be related to NSCLC progression or competing risks (COPD, CAD, CKD, or other causes). After each monthly transition, Veterans accumulated 1 month of survival, which was weighted based on utilities related to their treatment, complications, and comorbidities.

Input Model Parameters and Data Sources

The input parameters for LCPM-Treatment are described in Table 1 and include treatment-related complications, NSCLC and competing risk mortality, and quality of life utilities.

Platinum-Based Adjuvant Therapy Efficacy

We estimated the benefits of adjuvant chemotherapy on NSCLC-specific mortality based on the results of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis conducted in non-Veterans under the assumption that the oncologic impact of chemotherapy will be independent of comorbidities and Veteran status.[6] The benefit of adjuvant chemotherapy was modeled by reducing the monthly probability of NSCLC death based on the summary hazard ratio (HR) reported in the meta-analysis (0.83, 95% confidence interval [CI]: 0.76-0.90). Since there was no observed interaction between the effects of adjuvant chemotherapy and age, histological type, or other patient's factors in the meta-analysis, the same HR was applied to all Veterans.

Complications of NSCLC Therapy

In LCPM-Treatment model, chemotherapy-related toxicity impacted survival and quality of life. The elevated risk of non-NSCLC death in the first 6 months following adjuvant chemotherapy was captured by modifying the non-LC death rate using a HR of 2.41 (95% CI: 1.64-3.55).[6] Thereafter, the non-NSCLC mortality returned to background levels. To further assess the impact of treatment-related toxicity specific to Veterans with comorbidities, we used data from the VA Corporate Data Warehouse (VA-CDW) to assess the expected rates of adjuvant chemotherapy- and surgery-related complications conditional on age, sex, and comorbidities. The VA-CDW is a national dataset with electronic medical record information including sociodemographic, outpatient and inpatient encounter data, pharmacy, laboratory, radiological tests, diagnostic procedures and progress notes. Linkage to VA-CDW Oncology files provides data on cancer characteristics and outcomes. From the VA-CDW, we identified Veterans >18 years of age with stage II-IIIA NSCLC diagnosed between 2000 and 2015. Presence of COPD, CAD, and CKD were ascertained using EMR information complemented by claims data. We selected 1,317 stage II-IIIA patients who underwent lobectomy, which was ascertained using linked VA cancer registry data. We then used inpatient diagnostic codes to identify Veterans who experienced complications including anemia, cellulitis, dehydration, fever, major infection, nausea, neuropathy, neutropenia, pneumonia, renal failure, sepsis, thrombocytopenia and/or urinary tract infection. The adjusted probability of these complications conditional on age, NSCLC stage and COPD, CAD, and CKD was estimated using logistic regression.

NSCLC-Specific and Non-NSCLC Mortality

We used VA-CDW data to estimate long-term survival in stage II-IIIA Veterans who underwent lobectomy but did not receive adjuvant chemotherapy ($n = 811$). Survival was calculated from the date of lobectomy to the date of death from either NSCLC or other causes; surviving Veterans were censored at their last known date of contact. Cause of death was determined from VA cancer registry data. Subhazards of death from NSCLC vs other causes were derived using the Fine-Gray competing risk model (Tables A.2-A.3). Cumulative incidence functions were generated for each mortality cause. We then used these cumulative incidence functions to calculate cause-specific survival curves and then to estimate monthly death rates from NSCLC and other causes. These estimates were incorporated into the model as monthly transition probabilities; using these data, we estimated 5-year overall survival rates, a common outcome in cancer RCTs, for Veterans treated with adjuvant chemotherapy or observation.

Health Utilities and Clinical Significance

Our modeling outcomes also included quality adjusted life expectancy (QALE), a measure that considers both quantity and quality of life.[19] Disutility reflecting the impact of NSCLC and chemotherapy-related complications were derived from the literature.[20,21] To generate quality of life parameters for Veterans with comorbidities we used data from 3,511 participants (without human immunodeficiency virus infection) in the Veterans Aging Cohort Study, which prospectively collected short-form 36 (SF-36) data.[22] Using a published equation to generate utility scores from SF-36 data, we then fitted a linear regression model with utility values as our dependent variable, conditioned on comorbidities (Table 1).[22,23]

We used QALE gains as our primary outcome measure for comparing therapeutic strategies. Using American Society of Clinical Oncology guidance for clinical significance,[24] we chose adjuvant chemotherapy as the optimal strategy in scenarios where it was associated with ≥3 month (0.25 years) increase in QALE.

Sensitivity Analyses

We performed probabilistic sensitivity analyses to evaluate the robustness of our results to assumptions about model parameters by varying all parameters within the ranges of their CIs.

Results

We evaluated the benefits of adjuvant chemotherapy according to stage (II vs IIIA), histology (adenocarcinoma vs squamous cell carcinoma), age (<60, 60-70, 70-80 and >80 years) and comorbidities (COPD, CAD and CKD). Table 2 shows the optimal indications for adjuvant chemotherapy among Veterans without COPD and further stratified by the presence of CKD and CAD. Among Veterans without COPD, the optimal treatment for younger (<70 years) stage II and IIIA adenocarcinoma patients with CKD was adjuvant chemotherapy which resulted in a QALE gain ranging from 0.3 to 0.5 years (Table A.5A) and a 3%-4% improvement in 5-year survival (Table A.6A). Conversely, in Veterans >70 years with CKD, adjuvant chemotherapy only provided limited QALE benefit (ranging from 0.1 to 0.2 year gain). Among stage II and IIIA squamous cell patients without baseline CKD, adjuvant chemotherapy provided benefit for those <70 years with a 0.4-0.6 year QALE gain; while among those with baseline CKD, adjuvant chemotherapy only provided benefit for patients <60 years with stage IIIA squamous cell carcinoma but without CAD.

Veterans <70 years with stage II and IIIA adenocarcinoma and COPD but without CKD (Table 3), had a 0.4-0.6 life year gain in QALE (Table A.5B) and 3%-4% increase in 5-year survival (Table A.6B) when treated with adjuvant chemotherapy, irrespective of the presence of CAD. Among patients with stage II or IIIA squamous cell carcinoma and COPD, the benefit of adjuvant chemotherapy was only found in Veterans <60 years with CKD (QALE gain ranging from 0.3 to 0.4 years). Veterans >60 years with squamous cell NSCLC and COPD (with or without CKD) were optimally managed with observation.

We evaluated the robustness of the model output by conducting probabilistic sensitivity analysis varying the model input parameters (Figure A.1). For scenarios where adjuvant chemotherapy maximized QALE in the base-case, it was also the optimal treatment in the simulations for Veterans with stages II-IIIA NSCLC without COPD or CKD. The simulations also predicted that majority of patients with CKD are better managed with observation.

Discussion

The management of resectable NSCLC is critical, as patients diagnosed with locoregional disease have the highest probability of achieving meaningful long-term survival. Unfortunately, a

Table 2
Optimal indications for adjuvant chemotherapy for veterans without chronic obstructive pulmonary disease.

		No chronic kidney disease		Chronic kidney disease	
		No CAD	CAD	No CAD	CAD
Stage II Adenocarcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	70-80	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	>80	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
Stage II Squamous Cell Carcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation
Stage IIIA Adenocarcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	70-80	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	>80	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
Stage IIIA Squamous Cell Carcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation

Table 3
Optimal indications for adjuvant chemotherapy for veterans with chronic obstructive pulmonary disease.

Stage/Histology	Age, years	Optimal treatment			
		No chronic kidney disease		Chronic kidney disease	
		No CAD	CAD	No CAD	CAD
Stage II Adenocarcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation
Stage II Squamous Cell Carcinoma	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	60-70	Observation	Observation	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation
Adenocarcinoma Stage IIIA	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Adjuvant Chemotherapy
	60-70	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation
Squamous Cell Carcinoma Stage IIIA	<60	Adjuvant Chemotherapy	Adjuvant Chemotherapy	Observation	Observation
	60-70	Observation	Observation	Observation	Observation
	70-80	Observation	Observation	Observation	Observation
	>80	Observation	Observation	Observation	Observation

large proportion of patients experience recurrence following resection due to regional involvement beyond the surgical field or because of the presence of micrometastasis. In this study, we evaluated the role for adjuvant chemotherapy among Veterans with comorbidities, a group at increased risk of NSCLC recurrence[25,26] that has not been well represented in RCTs. We found that while some Veterans experience the benefits of adjuvant chemotherapy that outweigh early risks of toxicity, many were better managed with observation. These data can inform patient-provider discussions and can reduce physician uncertainty about the role of adjuvant chemotherapy among Veterans with multiple comorbidities.

Large meta-analyses of RCTs and retrospective analyses of observational data have demonstrated the benefits of adjuvant chemotherapy for stage II-IIIA NSCLC (absolute increases in 5-year overall survival from 4.1% to 8.6%).[6,27-29] Few studies have also suggested that patients with tumors ≥4 cm may also benefit from adjuvant chemotherapy.[30,31] Observational data from the Surveillance, Epidemiology and End Results registry suggests that the benefits of adjuvant chemotherapy can be also observed among older patients treated in the community, except for those >80 years of age.[32] However, toxicity can be significant with >30% of patients experiencing severe side effects. The tradeoffs of using cisplatin vs carboplatin-based regimens were evaluated in a large meta-analysis.[33] This study showed that the overall survival of cisplatin- vs carboplatin-treated patients was not statistically different. However, patients treated with carboplatin were more likely to develop thrombocytopenia, whereas leucopenia, neutropenia, and anemia were similar in the two groups. Additionally, carboplatin-based therapy was associated with lower risk of gastrointestinal and renal toxicity. Patients with CKD are particularly at risk for renal toxicity from cisplatin. Thus, balancing the survival benefits and potential harms of adjuvant chemotherapy is important, particularly for populations such as Veterans, who may be at increased risk of toxicity due to high prevalence of smoking-related comorbidities.

While the use of adjuvant chemotherapy for stage II and IIIA NSCLC is well supported by RCT conducted in non-Veteran populations,[6,27] the generalizability of these findings to Veterans with comorbidities is unclear. COPD, CAD[8] and CKD,[34] the conditions evaluated in this study, are among the most common comorbidities in Veterans with NSCLC and are major criteria for excluding NSCLC patients from RCT. Comorbidities can increase the risk of serious adverse events and may also lead to a shortened life expectancy truncating the long-term survival benefits of adjuvant chemotherapy. Quality of life can also be negatively impacted by serious comorbidities, which can attenuate the benefits of adjuvant chemotherapy on QALE. These concerns have translated into lower rates of adjuvant chemotherapy use among patients with multiple comorbidities leaving these Veterans at increased risk of recurrence and NSCLC mortality.[3] Our goal was therefore to show which Veterans could benefit from adjuvant chemotherapy, despite their comorbidities.

An observational study evaluated the outcomes of 4,929 Veterans who underwent resection for stage IB-IIIA NSCLC and showed that adjuvant chemotherapy was associated with approximately 20% improved survival.[35] A second study by the same group assessed the potential benefits of adjuvant chemotherapy among Veterans >70 years of age and found that while older patients were less likely to receive adjuvant therapy, they derived a similar magnitude of benefit from treatment. However, these studies suffer from potential selection bias and did not explicitly evaluate the benefits of chemotherapy in Veterans with specific patterns of comorbidities. Conversely, simulation modeling allowed us to investigate specific comorbidities, helping personalize the management of Veterans with locoregional NSCLC.

Our analyses showed that most Veterans with comorbid CKD did not benefit from chemotherapy. The prevalence of CKD rises dramatically with aging with >30% of individuals >70 years in the general population having moderate to severe CKD.[36] CKD is particularly common among Veterans with a prevalence as high as 68%.[9] Potential reasons for the lack of benefit of adjuvant chemotherapy in Veterans with CKD include higher rates of toxicity and competing risks of death. Platinum-based chemotherapy is associated with substantial kidney toxicity. Though carboplatin is less nephrotoxic, a transient but clinically significant decline in kidney function can still occur,[37] especially among patients with underlying kidney disease. The impact of toxicity

on quality of life and ensuing non-LC mortality likely outweighs the small (5% absolute survival benefit at 5 years) oncologic benefit of adjuvant chemotherapy.

We found that Veterans with adenocarcinoma benefited more from adjuvant chemotherapy than those with squamous cell carcinoma. Adenocarcinoma is the most common NSCLC histology in the US[38] and more frequent among women and nonsmokers. Additionally, adenocarcinomas are frequently located in peripheral areas of the lung while squamous carcinomas are most likely to present at central locations.[39,40] Given the sex distribution and smoking patterns, squamous cell carcinoma is the most common cell type in Veterans.[38] The impact of histology on survival in non-Veteran patients with early-stage NSCLC remains controversial.[39] However, prior studies and our own analyses showed that adenocarcinoma has a higher propensity for distance recurrence and is associated with worse outcomes.[38] Thus, it is possible that adenocarcinomas in Veterans behave more aggressively and consequently, patients with this histology may experience a greater benefit from adjuvant chemotherapy.

This study has strengths and potential limitations. Our simulation approach was adapted from LCPM, a well-established simulation model that has been used to inform the current US Preventive Services Task Force LC screening recommendations.[15,41] We used several nationally representative VA databases to generate new parameters relevant to the treatment of NSCLC in Veterans. Thus, the validity of our simulations should be robust. However, simulation models are based on assumptions and may not capture all the possible parameters relevant to a clinical scenario. Thus, the level of evidence of our findings are not as strong as those provided from a RCT. Given that RCT focused on chemotherapy for Veterans with multiple comorbidities are unlikely to be conducted, our approach is preferred to extrapolating data from trials conducted among healthy, highly selected patients with NSCLC. Another advantage of using simulation modeling is the ability to test multiple specific scenarios, which allowed us to evaluate the role of adjuvant chemotherapy based on age, sex, histology specific comorbidity profile and stage of disease, stratifications that would be very difficult to obtain in any RCT. Thus, these results can be used by physicians to provide personalized information regarding the potential harms and benefits of adjuvant chemotherapy to Veterans with locoregional NSCLC. We assumed that all CKD patients were treated with carboplatin, which may not be equivalent to cisplatin in terms of oncological outcomes. However, an observational study of Veterans found no difference in survival between cisplatin and carboplatin-containing combination chemotherapy for NSCLC.[17]

Our simulations were limited to patients treated with lobectomy, the standard of care and most common surgical approach for stage II-IIIA NSCLC patients. Limited resection is generally reserved early stage NSCLC patients who are older or have decreased pulmonary function.[42] However, limited resection is associated with increased risk of local recurrence and lower survival.[43,44] Veterans who undergo limited resection may experience a greater benefit from adjuvant chemotherapy, a scenario that was not evaluated in this study. Although several groups of Veterans experienced survival benefits, we did not evaluate the cost-effectiveness of adjuvant chemotherapy. Prior research has demonstrated that adjuvant chemotherapy is cost-effective for NSCLC patients with stage II and III disease[45,46]; however, these results may not directly apply to Veterans with comorbidities. Recent RCT have evaluated the potential role of adjuvant targeted therapy for NSCLC patients with actionable mutations.[47,48] While we did not assess this scenario in our study, actionable mutations are more common among Asians, women, and non-smokers, while Veterans with NSCLC tend to be males with relatively extensive smoking exposure.

Conclusions

In summary, we used simulation modeling to estimate the relative benefits and harms associated with adjuvant chemotherapy in Veterans with stage II-IIIA NSCLC and major comorbidities. We found that many Veterans who underwent lobectomy for locoregional NSCLC benefitted from adjuvant chemotherapy despite having major comorbidities. These results could be used to guide patient-provider discussions regarding the optimal post-surgical management of these Veterans to make personalized decisions regarding therapy.

Author Contributions

Stacyann Bailey, PhD: Writing - original draft; review & editing. Qian Wang, MD, MPH: Writing - original draft; review & editing. Chung Yin Kong, PhD: Methodology, Formal analysis, Writing - review & editing. Kimberly Stone, MPH: Data curation; Formal analysis. Rajwanth Veluswamy, MD, MSCR: Writing - review & editing. Susan E. Bates, MD: Writing - review & editing. Cardinale B. Smith, MD, PhD: Writing - review & editing. Juan P. Wisnivesky, MD, DrPh: Conceptualization, Methodology, Supervision, Writing - original draft; review & editing. Keith Sigel, MD, PhD: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - review & editing.

Supplementary materials

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References

1. Tanner NT, Egede LE, Shamblin C, et al. Attitudes and beliefs toward lung cancer screening among US veterans. *Chest*. 2013;144(6):1783–1787.
2. Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. *J Clin Oncol*. 2017;35:3745–3752.
3. Wang S, Wong ML, Hamilton N, et al. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. *J Clin Oncol*. 2012;30:1447–1455.
4. Vansteenkiste J, Crinò L, Dooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25:1462–1474.
5. Varlotto JM, Recht A, Flickinger JC, et al. Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer. *Cancer*. 2009;115:1059–1069.
6. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. *J Clin Oncol*. 2008;26(21):3552–3559.
7. Pisters KMW, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of clinical oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non-small-cell lung cancer guideline. *J Clin Oncol*. 2007;25(34):5506–5518.
8. Farwell WR, Scranton RE, Lawler EV, et al. The association between statins and cancer incidence in a veterans population. *J Natl Cancer Inst*. 2008;100(2):134–139.
9. Patel N, Golzy M, Nainani N, et al. Prevalence of various comorbidities among veterans with chronic kidney disease and its comparison with other datasets. *Ren Fail*. 2016;38:204–208.
10. Geraci T, Baratta V, Young J, et al. Lobectomy for lung cancer at veterans administration medical center versus academic medical center. *Ann Thorac Surg*. 2017;103:1715–1722.
11. Kong CY, McMahon PM, Gazelle GS. Calibration of disease simulation model using an engineering approach. *Value in Health*. 2009;12(4):521–529.
12. Criss SD, Cao P, Bastani M, et al. Cost-effectiveness analysis of lung cancer screening in the United States. *Ann Intern Med*. 2019;171(11):796–804.
13. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;160:311–320.
14. Kong CY, Sigel K, Criss SD, et al. Benefits and harms of lung cancer screening in HIV-infected individuals with CD4 + cell count at least 500 cells/μl. *AIDS*. 2018;32(10):1333–1342.
15. Meza R, Ten Haaf K, Kong CY, et al. Comparative analysis of 5 lung cancer natural history and screening models that reproduce outcomes of the NLST and PLCO trials. *Cancer*. 2014;120(11):1713–1724.
16. Jiang J, Liang X, Zhou X, et al. A meta-analysis of randomized controlled trials comparing carboplatin-based to cisplatin-based chemotherapy in advanced non-small cell lung cancer. *Lung Cancer*. 2007;57:348–358.
17. Santana-Davila R, Szabo A, Arce-Lara C, et al. Cisplatin versus carboplatin-based regimens for the treatment of patients with metastatic lung cancer. an analysis of veterans health administration data. *J Thorac Oncol*. 2014;9:702–709.
18. Ezer N, Smith CB, Galsky MD, et al. Cisplatin vs. carboplatin-based chemoradiotherapy in patients >65years of age with stage III non-small cell lung cancer. *Radiother Oncol*. 2014;112:272–278.
19. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. New York, NY: Oxford University Press; 2006.
20. Grutters JPC, Joore MA, Wiegman EM, et al. Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax*. 2010;65(10):903–907.
21. Möller A, Sartipy U. Predictors of postoperative quality of life after surgery for lung cancer. *J Thorac Oncol*. 2012;7(2):406–411.

22. Justice AC, Dombrowski E, Conigliaro J, et al. Veterans Aging Cohort Study (VACS): Overview and description. *Med Care*. 2006;44(8 Suppl 2):S13–S24.
23. Hanmer J. Predicting an SF-6D preference-based score using MCS and PCS scores from the SF-12 or SF-36. *Value in Health*. 2009;12(6):958–966.
24. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014;32:1277–1280.
25. Institute of Medicine Committee on Smoking Cessation in M, Veteran P. In: Bondurant S, Wedge R, eds. *Combating Tobacco Use in Military and Veteran Populations*.Washington (DC): National Academies Press (US) Copyright 2009 by the National Academy of Sciences. All rights reserved.; 2009.
26. Walker MS, Vidrine DJ, Gritz ER, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2370–2377.
27. Pathak R, Goldberg SB, Canavan M, et al. Association of survival with adjuvant chemotherapy among patients with early-stage non-small cell lung cancer with vs without high-risk clinicopathologic features. *JAMA Oncol*. 2020;6:1–10.
28. Group IALCTCCisplatin-based adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer. *N Engl J Med*. 2004;350:351–360.
29. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. 2015(3):1–70.
30. Speicher PJ, Gu L, Wang X, et al. Adjuvant chemotherapy after lobectomy for T1–2N0 non–small cell lung cancer: Are the guidelines supported? *J Natl Compr Canc Netw*. 2015;13:755–761.
31. Strauss GM, Herndon JE, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non–small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26(31):5043–5051.
32. Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: Observational cohort study. *BMJ (Online)*. 2011:343–353.
33. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2007;99(11):847–857.
34. Yamamoto Y, Kanzaki R, Kanou T, et al. Long-term outcomes of pulmonary resection for lung cancer patients with chronic kidney disease. *World J Surg*. 2019;43:3249–3258.
35. Williams CD, Gajra A, Ganti AK, et al. Use and impact of adjuvant chemotherapy in patients with resected non-small cell lung cancer. *Cancer*. 2014;120(13):1939–1947.
36. Prakash S, O'Hare AM. Interaction of aging and chronic kidney disease. *Semin Nephrol*. 2009;29:497–503.
37. Hardy JR, Tan S, Fryatt I, et al. How nephrotoxic is carboplatin? *Br J Cancer*. 1990;61(4):644.
38. Assi H, Koutroumpakis E, Kang SJ, et al. Non–small cell lung cancer in veterans: Disparities in prevalence and survival among different histologic subtypes. *J Clin Oncol*. 2016;34(15_suppl):e20590.
39. Wang BY, Huang JY, Chen HC, et al. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. *J Cancer Res Clin Oncol*. 2020;146:43–52.
40. Wisnivesky JP, Henschke C, McGinn T, et al. Prognosis of Stage II non-small cell lung cancer according to tumor and nodal status at diagnosis. *Lung Cancer*. 2005;49:181–186.
41. McMahon PM, Meza R, Plevritis SK, et al. Comparing benefits from many possible computed tomography lung cancer screening programs: Extrapolating from the National Lung Screening Trial using comparative modeling. *PLoS One*. 2014;9(6):e99978.
42. Dong S, Roberts SA, Chen S, et al. Survival after lobectomy versus sub-lobar resection in elderly with stage I NSCLC: a meta-analysis. *BMC Surgery*. 2019;19(1):1–8.
43. Veluswamy RR, Ezer N, Mhango G, et al. Limited resection versus lobectomy for older patients with early-stage lung cancer: impact of histology. *J Clin Oncol*. 2015;33(30):3447.
44. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines. *Chest*. 2007;132(3):234S–242S.
45. Samson P, Patel A, Robinson CG, et al. The role of surgical resection in stage IIIA non-small cell lung cancer: A decision and cost-effectiveness analysis. *The Annals of thoracic surgery*. 2015;100(6):2026–2032.
46. Ng R, Hasan B, Mittmann N, et al. Economic analysis of NCIC CTG JBR.10: A randomized trial of adjuvant vinorelbine plus cisplatin compared with observation in early stage non-small-cell lung cancer - A report of the Working Group on Economic Analysis, and the Lung Disease Site Group, National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(16):2256–2261.
47. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole–induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol*. 2007;25:829–836.
48. Tang W, Li X, Xie X, et al. EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations. *Lung Cancer*. 2019;136:6–14.
49. Bryant AK, Mundt RC, Sandhu AP, et al. Stereotactic body radiation therapy versus surgery for early lung cancer among US Veterans. *Ann Thorac Surg*. 2018;105:425–431.
50. Ezer N, Veluswamy RR, Mhango G, et al. Outcomes after stereotactic body radiotherapy versus limited resection in older patients with early-stage lung cancer. *J Thorac Oncol*. 2015;10:1201–1206.