Targeted Screening of Latent Tuberculosis in Cancer Patients

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Abstract

With approximately 80% of active tuberculosis (TB) cases arising from reactivation of latent TB infection (LTBI), a key national strategy for TB elimination is targeted screening in high-risk groups. Although cancer is considered a high-risk condition for reactivation TB, baseline screening for LTBI is not considered standard care in this population. Targeted screening and treatment in cancer patients can lead to early diagnosis and treatment preventing reactivation and spread of disease. This study evaluated LTBI prevalence in Veteran's with cancer diagnoses, and compared patient and cancer-specific characteristics that may predict a positive result. Additionally, the use, reliability, and cost effectiveness of screening tests (T-SPOT.*TB*® and tuberculin skin testing) was examined. LTBI treatment acceptance, adverse events and completion rates were evaluated. Finally, the cost efficacy of targeting and treating LTBI in cancer patients was assessed. A retrospective chart review of cancer patients screened using the T-SPOT.*TB*® test was conducted between 1/1/2017 through 10/31/2017 from a Veterans Affairs oncology clinic. Descriptive statistics were used. Eight (4.6%) Veterans were screen-positive for LTBI (n=175). The median age was 70.5 years, with 62.5% from the Vietnam service era. No high-risk comorbidities or high-risk behaviors were identified as predictors of positive results. The number needed to screen (NNS) to detect a single LTBI case was 22 ($1,100 per detected case). Indeterminant test results burden was 11/175 (6.3%). Treatment acceptance was 62.5% (n=5) with 20% (n=1) associated adverse events. Cost efficacy comparing NNS to detect a single case with costs associated with TB contact investigations was 20-fold less than the 2012 TB contact investigation. This study adds to the understanding of LTBI prevalence in Veterans with cancer and can guide policy development for evidence-based screening and treatment.

Keywords: Tuberculosis; latent tuberculosis infection; reactivation tuberculosis; cancer

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Introduction

Tuberculosis (TB) remains a global public health threat, ranking as one of the top ten causes of death worldwide in 2015 (World Health Organization [WHO], 2016). It is estimated that one third of the world's population is infected with TB (Centers for Disease Control and Prevention [CDC], 2017). TB is a highly contagious infectious disease caused by the bacillus *Mycobacterium tuberculosis,* which is spread from person to person via airborne aerosolized droplets when a person with active TB coughs or sneezes. Following exposure, three outcomes are possible: clearance of the organism, onset of active TB, or development of latent infection (CDC, 2005). While TB disease is characterized by signs and symptoms caused by active replication of the tubercle bacilli and is contagious, those with latent TB infection (LTBI) have been infected but have no active symptoms of the disease and are not contagious. However, individuals with LTBI remain at risk of developing reactivation TB during their lifetime.

Changing Epidemiology

The epidemiology of TB in the United States (U.S.) has been highly dynamic since the early 1990s. This means that groups currently considered high priority for TB disease or infection may decrease over time, and groups currently not identified as being at risk may subsequently be considered high-priority. High-priority groups can be divided into two categories: persons at higher risk for TB exposure or infection and persons at higher risk for TB disease once infected. Approximately 30% of persons exposed to *Mycobacterium tuberculosis* are estimated to develop LTBI (Marks et al., 2000). Of those infected with latent disease, approximately 5-10% of healthy (immunocompetent) persons will progress to active TB disease (referred to as reactivation) in their lifetime (Kahwati et al., 2016). This estimation is based on data from placebo arms of treatment trials conducted before treatment of LTBI was routinely

recommended (American Thoracic Society, 2000; Ferebee, 1960). However, this range underestimates the risk of progression to active TB for some and over estimates the risk for others. Using a model to estimate the lifetime risk of reactivation, Horsburgh (2004), found the risk to be 20% or more among most persons with induration of ≥ 10mm on tuberculin skin test (TST) and either HIV infection or old, healed TB on radiograph; 10-20% among recent conversion of TST and among persons younger than 35 years of age receiving anti-tumor necrosis factor alpha inhibitors (TNF-α) (i.e. infliximab) and induration of ≥15mm on TST; and 10-20% for children ≤5 years of age. While advanced HIV infection was associated with the greatest relative risk of reactivation, the lifetime risk of TB among people with other immunosuppressive conditions including cancer, long term treatment with corticosteroids, cyclosporine or other immunosuppressive agents was suggested by Horsburgh to be equivalent to that of infliximab therapy (relative risk 2.0) until more data becomes available.

TB attributable to recent transmission cannot be distinguished clinically from TB resulting from reactivation of remotely acquired infection. The gold standard for determining which cases are likely to be due to recent transmission is field-based epidemiologic investigations to identify the source-case, however source-case investigations are extremely resource intensive and rarely conducted. TB genotyping is another method frequently used to estimate the proportion of TB cases attributable to recent transmission. Genotype-based methods rely on the assumption that cases related to recent transmission will have identical genotypes, while cases resulting from reactivation will have unique genotypes in the population. Shea, Kammerer, Winston, Navin and Horsburgh (2013) reported reactivation TB rates of 80% using data on genotyping reported to the CDC during 2006-2008. A more recent modelling analysis of

genotyping data within the U.S. by France, Grant, Kammerer, and Navin (2015), reported estimates of more than 85% of TB cases originating from reactivation of LTBI.

Since the 1989 strategic plan for TB elimination in the U.S. by the Advisory Council for Elimination of Tuberculosis was issued, major changes have occurred in the epidemiology of TB and the organization and delivery of public health care services challenging strategies to meet the goal (CDC, 1989 & CDC, 1995)). In May 2000, the Institute of Medicine (IOM) report, *Ending Neglect*: *The Elimination of Tuberculosis in the United States*, called for aggressive and decisive action to strengthen tuberculosis elimination efforts (Geiter, 2000). One of the main pillars identified was the need for increased focus on LTBI screening in high-risk groups including immigrants and refugees from intermediate to high-incidence TB burden countries, HIV infected, homeless persons and intravenous drug abusers (Geiter, 2000). The WHO, CDC and professional societies such as the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) have recommended targeted screening and treatment of high-risk individuals with LTBI as part of control strategies and efforts for TB elimination in the U.S. (American Thoracic Society, 2000; Getahun et al., 2015, Lewinsohn et al., 2017). Intensified efforts directed at identifying and treating LTBI in high-risk groups are vital to meet the goal of TB elimination.

There has been a steadily declining incidence of TB rates in the U.S. since 1993, however the goal of TB elimination defined as less than one case per 1,000,000 population will not be met this century with current rates of decline (Hill, Becerra & Castro, 2012). In 2015, there were 9,563 cases of TB reported in the U.S., corresponding to an incidence rate of 3.0 cases per 100,000 persons, a 1.6% increase from the previous year (CDC, 2016). Among reported TB cases, 33.5% occurred in U.S.-born persons and 66.2% among foreign-born persons (Salinas et

al., 2016). Foreign-born immigrants from TB-endemic areas represents the primary source of new TB cases. The incidence of TB varies substantially by geographic location with half of all cases combined in 2015 occurring in four states: California, Texas, New York, and Florida (Salinas et al., 2016). Asians represent the largest percentage of total cases (33%), followed by Hispanics (28%), African Americans (21%) and whites (13%); American Indian or Alaska Natives and Native Hawaiian or Pacific Islanders each represented approximately 1% of cases (Salinas et al., 2016). The highest burden of disease continues to be among older adults with an incidence rate of 4.8 cases per 100,000 in adults ≥65 years old (Salinas et al., 2016).

In 2015, Virginia ranked 19th in the nation for TB with 212 reported cases, with an incidence rate of 2.5 per 100,000 persons (CDC, 2016). The state incidence patterns mirror national trends with leveling rates from 2014-2015 (Virginia Department of Health, Office of Epidemiology, Tuberculosis Control [VDH], 2016). Foreign-born persons comprise 79% of Virginia TB cases with the top five countries of origin including the Philippines, India, Vietnam, Ethiopia, and Korea (VDH, 2016). The geographic distribution of TB cases by health planning region (Figure 1) was highest in the Northern health region which is overwhelming comprised of foreign-born people, comprising 129 cases (61%) of the Virginia state total. The Eastern health region reported 38 cases (18%), Central health region reported 16 cases (8%), Northwest region reported 20 cases (9%) and Southwest Region reported 9 cases (4%) (VDH, 2016).

Overview of the Problem

As previously stated, the CDC set an aggressive national goal to eliminate TB as a public health problem (CDC, 1989). Intensification of efforts to identify and treat persons at high-risk for LTBI has been a cornerstone strategy for TB prevention and control (CDC, 2015). Of concern in achieving this goal are findings by Miramontes et al. (2015) using nationally

representative data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES), reporting a relatively constant prevalence of LTBI between 2000 and 2011. A reservoir of 12.4 million persons still exists, with foreign-born persons representing an increasingly proportion of the reservoir (73%) (Mancuso, Diffenderfer, Ghassemieh, Home, & Kao, 2016). Similarly concerning are findings using the 1999-2000 and 2011-2012 NHANES data reporting less frequent testing for LTBI among multiple vulnerable groups over time (Vozoris & Batt, 2016). These finding raise concern for the possibility of an increase in active TB in the future and further support the need for scaled up efforts by public and private health systems to achieve the national TB elimination goal.

Treatment Options for LTBI

Persons who screen positive for LTBI are generally offered preventative treatment with antituberculosis medications. Four preventative treatment regimens are recommended by the CDC for adults with LTBI (Table 1). Isoniazid (INH) has been the mainstay of treatment in the U.S. for more than 50 years. Although a 9-month regimen of daily INH is the preferred regimen for the treatment of LTBI, a 6-month regimen also provides substantial protection. However, the application of INH for LTBI has been limited because of poor adherence, due to the relatively long duration of treatment required, and because of concerns about hepatotoxicity. Because of these problems, alternative regimens including 4-months of daily rifampin and 3-months of weekly INH and Rifapentine as direct observed therapy have been recommended. (CDC, 2013). Current available treatments have an efficacy ranging from 60% to 90% (Getahun et al., 2015). The potential benefit of treatment needs to be carefully balanced against the risk of drug-related adverse events however, the benefits are greater than the harms for infected individuals in highest-risk groups at danger of progression to active disease (Getahun et al., 2015). The

management of LTBI requires a comprehensive set of interventions that includes: identifying and testing those individuals who should be tested, delivering effective and safe treatment in a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and ensuring monitoring and evaluation of the process.

Cancer is a known risk factor for development of TB possibly secondary to impaired cellular immunity due to the cancer itself and/or its treatment (American Thoracic Society, 2000; Cheng et al., 2017; US Preventive Services Task Force, 2016). Guidelines from WHO, CDC, ATS, IDSA, and USPSTF recommend targeted screening and treatment of LTBI. In low-incidence TB countries such as the U.S., screening should be done only in persons at the highest risk of progression to active disease and when treatment is feasible. This approach is critical to the eventual elimination of TB because it is the only means of preventing TB in the substantial reservoir of persons with LTBI at high-risk for progression to active TB disease. Yet, despite the known higher clinical risk, baseline screening for LTBI in the cancer population is not considered standard care as part of disease management. This study proposed to measure the incidence of LTBI in Veterans with cancer undergoing active treatment for cancer by implementation of a program for routine screening for LTBI using the T-SPOT.*TB*® assay in the outpatient oncology clinic at the McGuire Veterans Affairs (VA) Medical Center. Additionally, the study examined the use, reliability, and cost effectiveness of screening tests (T-SPOT.*TB*® blood assay and tuberculin skin testing). LTBI treatment acceptance, adverse events and completion rates were evaluated. Finally, the cost efficacy of targeting and treating LTBI in cancer patients was assessed.

Review of the Literature

A comprehensive review of the literature was conducted using keywords. Search terms combined MESH terms, text words, and exploded terms including “mycobacterium tuberculosis,” “tuberculosis,” “cancer,” “neoplasms,” “prevalence, and “incidence”. Databases including Ovid Medline, PubMed, the Cochrane Database of Systematic Reviews, Web of Science, and Google Scholar were searched from data base inception to 1 May 2017. Searches were limited to human studies published in English. Additional studies were identified by ancestry references from relevant articles. A flowchart diagram of the search strategy can be found in Appendix A. A detailed review of the evidence can be found in Appendix B.

Guidelines for management of LTBI in cancer patients have changed since initial guidelines presented in 1970 which included leukemia and Hodgkin’s disease. Early studies of cancer and active TB by Kaplan, Armstrong, and Rosen (1974), conducted at Memorial Sloan-Kettering Hospital between 1950 and 1971, reported Hodgkin’s disease, lymphosarcoma (LSA), reticulum cell sarcoma (RCS) and lung cancer with high prevalence of 96, 88, 78 and 92 per 10,000 patients respectively. Head and neck cancer, stomach cancer, acute lymphocytic leukemia and acute myelogenous leukemia had a prevalence of 51, 55, 37 and 28 per 10,000 patients at risk respectively. A temporal relationship of TB to cancer was observed with lung and head and neck cancer developing early in the course while Hodgkin’s, LSA and RCS developed TB disease after the cancer had advanced and required intensive antineoplastic therapy suggesting increasing susceptibility as immunity becomes more impaired. Mortality due to TB was 17% with diagnosis made after death suggesting that TB had not been considered for treatment which could have possibly reduced the mortality from TB (Kaplan et al., 1974).

Libshitz, Pannu, Elting, and Cooksley (1997), studied the frequency of TB in cancer at M.D. Anderson Cancer Center between 1989 and 1994. The frequency of TB in cancer patients was found to be greater than the general population at 90 per 100,000 or nine times greater frequency. TB was found to more likely to occur in patients with hematologic malignancies. A temporal relationship was similarly observed with 48% of TB developing during therapy, 30% at diagnosis and 21% occurring greater than 18 months after therapy. TB was more frequent in foreign-born (34%) and racial ethnic minorities (55%) (Libshitz et al., 1997).

De La Rosa et al. (2004) studied the characteristics of TB in adults with cancer between 1990 and 2000 at M.D. Anderson Cancer Center with findings similar to previous studies that found higher frequency of TB and cancer in foreign-born persons (60%). Hematologic malignancy was the most frequent underlying cancer (63%), followed by solid-organ (37%), and hematopoietic stem cell transplantation (13%). Mortality rate attributed to TB was 21% with 100% mortality observed in patients receiving high dose systemic corticosteroids (De La Rosa et al., 2004).

Kamboj and Sepkowitz (2006) studied cancer-specific rates during a 25-year interval between 1980 and 2004 at Memorial Sloan-Kettering Cancer Center. The mean age was 57 years (range 9 months-82 years). The overall TB incidence rate was 55 cases per 100,000. TB was found to be highest among hematologic malignancies with a rate of 240 cases per 100,000 or 40 times greater than the current rate among the U.S. population. Head and neck cancer was found to have an increased TB rate of 135 per 100,000 unrelated to country of birth. TB rates among lung cancer varied between 52-320 cases per 100,000. Mortality rate was 25% within three months of TB diagnosis (Kamboj & Sepkowitz, 2006). Study findings suggested that U.S.-

born patients with solid tumors (excluding head and neck cancer) were not at increased risk for development of TB.

Cheng et al. (2017), conducted a systematic review and meta-analysis of 23 studies reporting 593 TB cases occurring in 324,041 patients between 1950 and 2011 to assess the risk of cancer patients developing active TB. A meta-analysis of the six U.S. studies conducted in 317,242 patients over six decades provided sufficient detail to stratify the results by cancer type. Cumulative incidence rate/100,000 population (CIR) of new cases of TB occurring in cancer patients and comparative incidence rates ratios (IRR) to the general population from the same country of origin were estimated. A random effect metaanalysis was conducted on the CIR and IRR. The results showed that there was a decrease by three-fold and 6.5- fold in hematologic cancers and solid cancers respectively, before and after 1980. After 1980 the CIR of TB was highest in hematologic (219/100,000 population and IRR = 26, head and neck (143; 16), lung cancers (83; 9) and was lowest in breast cancer and other solid tumors (28; 4). Individuals living in the U.S. with hematologic, head and neck, and lung cancer were found to have a nine-fold higher rate of developing active TB compared to those without cancer supporting benefit from targeted LTBI screening and treatment in this population (Cheng et al., 2017).

Evidence from the literature supports a significant decline in the incidence of TB among all types of cancers since 1980, however there remain cancer-specific risks for the development of active TB in this population. The incidence of active TB was highest among hematologic, head and neck, and lung cancer. Foreign-born persons and racial and ethnic minorities were found to be consistently at higher risk for development of active TB. Findings from the literature support a risk-stratified approach to LTBI screening in cancer patients to include hematological, head and neck, and lung cancer as well as all foreign-born persons from TB endemic countries

prior to start of cancer therapy. Despite a robust body of evidence highlighting the increased risk of active TB in patients with cancer, screening for LTBI in this population is not the standard practice for disease management in many oncology settings.

Gaps in the Literature

The changing epidemiology of TB infection in the U.S. necessitates targeted screening and treatment of high-risk populations to eliminate the substantial reservoir of infection to achieve the national goal of TB elimination. One population that may be at a higher risk for reactivation of LTBI, is U.S. Veteran population given their propensity for deployment during their military careers to TB endemic countries. No studies have specifically examined the prevalence of LTBI in the Veteran population with coexistent cancer diagnoses.

Theoretical Framework

The framework utilized for evaluation of this study is the Iowa Model of Evidence-Based Practice to Promote Quality Care (see Figure 2) by Titler et al. (2001). The definition of Evidence-Based Practice (EBP) used in this model is defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996, p. 71). The original model was developed in 1994 at the University of Iowa hospitals and clinics to serve as a guide for nursing and other health care providers to use research findings for improvement in patient care. The model was revised in 2015 to incorporate new terminology and feedback loops, address changes in the health care market and encourage use of other types of evidence when research findings are not available.

The first step in the process is to detect "triggers" which are defined as clinical question or problems that require further investigation. The trigger for the current study was cases of active TB infection originating from the outpatient oncology clinic necessitating extensive and costly contact investigations of health care workers and other patients coming in contact with the index case. In 2012, a TB contact investigation was triggered at our medical center involving 53 patients from the oncology clinic, 23 patients from the emergency department and 142 staff from various services in the healthcare facility. Another TB contact investigation was triggered in 2016 when an acid-fast bacilli (AFB) smear returned positive from a case-patient who was being treated in the outpatient oncology clinic for cancer. A post exposure contact investigation was launched while awaiting the AFB culture results (incubation can take up to 6-weeks) prompting screening of 89 patients for LTBI before the AFB was identified as *Mycobacterium avium complex* rather than *Mycobacterium tuberculosis*. Following the 2016 scare, the issue of reactivation TB in oncology patients and the risk of transmission to other immunocompromised patients was recognized as a priority for infection control, serving as the impetus to question current practice and to seek best evidence for use in decision to screen cancer patients for LTBI. The question raised was; "What is the of current state of evidence for screening LTBI in immunocompromised patients with malignancy?" A team of multidisciplinary stakeholders including the service chiefs of oncology, infectious disease, laboratory and nursing services were assembled to discuss and devise a plan for LTBI screening in the oncology population. The decision was made to implement a practice guideline change to screen all cancer patients undergoing active treatment in the outpatient oncology clinic using the T-SPOT.*TB*® blood test, to assess the prevalence of LTBI in the Veteran oncology population. The targeted screening pilot program commenced on January 1, 2017. The role of this DNP student was evaluation of

this process driven practice change to determine outcomes and value added. An extensive literature review was undertaken to evaluate the current state of evidence for targeted screening and treatment of LTBI in the oncology population which included evidence based guidelines, systematic research reviews, meta-analyses, and clinical studies. A feedback loop is included in the Iowa Model for reevaluation of structure, process and outcome data examining the environment, staff, costs and the patient and family.

Purpose of the Study

An evidence-based approach to screening and treatment of LTBI in high-risk groups at risk for TB reactivation can prevent active TB disease, reduce morbidity and mortality, and decrease transmission yielding a potential cost savings from contact investigations. Due to a discrepancy in guideline adherence for LTBI screening in at-risk patients with cancer diagnoses, opportunities may be missed to identify LTBI. Therefore, the purpose of this descriptive study was to investigate the prevalence of LTBI in Veterans with cancer undergoing active treatment, and to compare patient and cancer specific characteristics in relationship to screening results. Additionally, this study examined the use, reliability, and cost effectiveness of diagnostic testing with the T-SPOT.*TB*® assay and TST. LTBI treatment acceptance, adverse events and completion rates were also evaluated. Finally, the cost efficacy of targeting and treating LTBI in cancer patients was assessed.

Research Questions

This study sought to answer the following questions:

1. What is the prevalence of LTBI in Veterans with cancer undergoing treatment?
2. What are there host and cancer-specific characteristics that can identify patients at high-risk for LTBI?

3. What is the burden of indeterminant qualitative results of T-SPOT.*TB* ® whole blood assay sensitivity in cancer patients comparing test-retest reliability with TST by induration threshold for defining LTBI?
4. What is the epidemiology of latent TB treatment acceptance, frequency of adverse events, and rate of completion?
5. What is the cost efficacy of targeting and treating cancer patients for LTBI?

The study hypotheses are as follows:

RQ1: What is the prevalence of LTBI in Veterans with cancer undergoing active treatment compared to the general population?

H_0: The prevalence of LTBI in Veterans with cancer undergoing active treatment is the same as the general population.

H_1: The prevalence of LTBI in Veterans with cancer undergoing active treatment is higher than the general population.

Methods

Project Design

This study was conducted as per standard methodology of a retrospective chart review (Matt & Matthew, 2013). This method was compatible with what the study sought to discover. A systematic chart review of cancer patients being treated in the outpatient oncology clinic who were screened for LTBI using the T-SPOT.*TB* ® whole blood assay was conducted. A convenience sample of all screened cases over the specified time frame was included. The sample size was determined by the number screened during the study period meeting inclusion and exclusion criteria. The setting was a single site outpatient oncology clinic at the McGuire VA Medical Center located in Richmond, Virginia. Data were collected during the study period of 1 January 2017 through 31 October 2017. An electronic data abstraction-instrument was utilized for organization of data collection. A code book was developed by this investigator. Missing data were coded as "not reported". All data were entered into an excel spread sheet, coded, and uploaded into the statistical package for social sciences (SPSS, version 24). Data cleaning was completed to check for errors before analyzing. The study was descriptive by nature. Continuous variables are presented as means and standard deviation for symmetrical data, and by medians and ranges for skewed data. Categorical variables are presented as frequencies and percentages. The independent samples t-test was used to explore the relationship among continuous variables. Analysis was stratified by screen-positive, screen-negative, and indeterminate results groups.

Statement of Purpose of the Study

The purpose of this study was to evaluate the prevalence of LTBI in Veterans with a cancer diagnosis undergoing treatment comparing patient and cancer-specific characteristics in

relationship to screening results. Additionally, the study examined the use, reliability, and cost effectiveness of screening tests including the T-SPOT.*TB*® assay and TST in this population. Finally, treatment acceptance, adverse effects and completion rates are described.

Definition of Terms

- Latent tuberculosis infection: A state characterized by the presence of immune response to previously acquired *Mycobacterium tuberculosis* infection in individuals who are asymptomatic, noninfectious, normal chest x-ray and at variable risk for progression to active TB disease (Getahun et al., 2015).
- Active tuberculosis disease: A highly contagious disease caused by bacillus *Mycobacterium tuberculosis* spread from person to person by airborne aerosolized droplets (CDC, 2005).
- Reactivation tuberculosis: A state characterized by previously latent *Mycobacterium tuberculosis* seeded at the time of exposure which proliferates and progresses to cause active TB disease (Kahwati et al., 2016).
- Targeted screening: A strategic component of tuberculosis control that identifies persons at high-risk for developing TB who would benefit from systematic testing and treatment.
- Interferon gamma release assay (IGRA): A whole blood test used to detect and quantify the in vitro release of interferon from T cells stimulated by TB-specific antigens for LTBI diagnosis. Two IGRAs are available, the QuantiFERON-TB Gold In Tube test (Cellestis) (QFT-GIT) and the T-SPOT.*TB*® test (Oxford Immunotec). Results are classified as positive, negative, or indeterminant.
- Indeterminant T-SPOT.*TB*® results: Results are not clinically interpretable and may occur if the positive and/or nil (negative) control does not perform as expected.

- High-risk for TB: Individuals who have either been recently infected with *Mycobacterium tuberculosis* or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB.
- Number Needed to Screen (NNS): NNS to detect one case = total number screened / number of cases identified.
- Hepatotoxicity: Transaminase levels exceeding three times the upper limits of normal with symptoms or five times the upper limits of normal without symptoms.
- Demographic Variable: Characteristics or attributes of subjects collected to describe the sample including age, sex, race/ethnic group, and military service era.

Study Setting

This study was conducted at the Veterans Health Administration (VHA) Hunter Holmes McGuire Medical Center in Richmond, Virginia. The outpatient oncology clinic treats approximately 200 new cases of cancer with chemotherapeutic agents annually. The current clinical practice in the outpatient oncology clinic is baseline screening of LTBI in all Veterans with a cancer diagnosis who are undergoing treatment using the diagnostic screening test of T-SPOT.*TB*® whole blood assay rather than tuberculin skin testing (TST), which is consistent with recommendations from clinical practice guidelines from ATS, IDSA, and the CDC (Lewinsohn et al., 2016; US Preventive Services Task Force, 2016). This practice guideline was initiated January 1, 2017, in response to contact investigations of health care-associated TB transmission involving two discrete TB contact exposures over a four-year interval with the index case patient in each investigation originating from the outpatient oncology clinic. TB contact exposures result in resource-consuming investigations which are expensive and can create significant psychological distress in patients and clinical staff. The most recent 2016 contact investigation

involved 89 immunocompromised oncology patients in addition to clinical staff in the oncology clinic. Of these exposures, there were four positive T-SPOT.*TB*® assays and five indeterminant or insufficient sample results requiring repeat T-SPOT.*TB*® testing or TST. All contacts exposures with baseline negative TB results require a repeat test in two months as false-negative results may occur if the TB infection occurs within the eight-week window of testing following exposure. The clinical practice change for baseline screening for LTBI in all cancer patients undergoing cancer treatment in the oncology clinic was initiated by the Chief of Epidemiology in collaboration with oncology and laboratory services in response to recurrent healthcare-associated TB contact investigations.

Protection of Human Subjects

This study received ethics approval by the McGuire Institutional Review Board (IRB) at the Hunter Holmes McGuire Veterans Affairs Medical Center, IRB tracking ID: 02361 (Appendix C). All policies and regulations of the institution were strictly adhered to prior to accessing data. The main ethical considerations within this study was data storage, confidentiality and anonymity of patient health information (PHI). All PHI collected was maintained in a password protected onsite VA facility hard drive and was accessible only to those on the study personnel list. A waiver of the requirement for informed consent was obtained.

Sample

All patients screened for LTBI using the T-SPOT.*TB*® whole blood assay at the McGuire Oncology Outpatient Clinic between 1 January 2017 and 31 October 2017 were identified from medical records. Screened patients lacking a cancer diagnosis or who were identified as having active TB were excluded from the study. A sample size of 175 (n=175) was determined from

188 screened following application of inclusion and exclusion criteria and elimination of duplicate screenings.

Procedures

For all case patients, demographic information, cancer-specific information, comorbidities, T-SPOT.*TB*® qualitative results, TST results and treatment results were extracted from a retrospective medical records review utilizing the VHA Computerized Patient Record System (CPRS). Administrative and ethics approval was obtained prior to undertaking data abstraction. Case subjects with screen-positive testing using either the T-SPOT.*TB*® assay or TST were ruled out for active TB by chest radiograph or computerized axial tomography (CAT) scan of the thorax and a clinical examination.

Data Analysis

Microsoft Excel was used for data entry. Data analysis were conducted using Statistical Package for Social Sciences, Version 24.0. Armonk, NY: IBM Corp. Descriptive statistics including frequencies, percentages and means, and standard deviation were used to access the incidence of LTBI in oncology patients, comparative characteristics of screen-positive and screen-negative cohorts to identify host characteristics and risk factors identifying cancer patients at high-risk of TB reactivation the burden of indeterminant qualitative results of the T-SPOT.*TB*® testing compared to test-retest reliability with TST by induration threshold for defining LTBI and LTBI treatment acceptance, adverse events and rate completion, and cost efficacy of universal screening for LTBI. The nonparametric test of Independent-Samples Mann-Whitney U was used to examine the relationship between age and screen-positive and screen-negative cohort groups and the relationship of age and indeterminant T-SPOT.*TB*® test results. Statistical significance with p value of < 0.05 was used. The costs of each T-SPOT.TB assay was applied to the number of TB cases diagnosed to give indicative costs per case of TB

detected: this was done by dividing the relative total cost of the tests by the number of new cases of TB identified.

Results

This section presents the results of the data analysis, including the prevalence of LTBI in the sample, and comparative characteristics of screen-positive and screen-negative cohorts to identify host characteristics and risk factors identifying cancer patients at high-risk of TB reactivation. Additionally, the burden of indeterminant qualitative results of the T-SPOT.*TB*® test compared to test-retest reliability with TST by induration threshold for defining LTBI is presented. Finally, treatment acceptance, adverse events and rate completion, and cost efficacy of targeted screening for LTBI will be described and key findings highlighted.

Sample Demographics

Sociodemographic characteristics of the sample are summarized in Table 2. The sample ranged in age between 33-94 years (mean 67.74, SD 10.02) and was predominately male at 95.4% (n=167). Racial/ethnic groups represented included 45.7% (n=80) Caucasians, 53.7% (n=94) African Americans, and 0.6% (n=1) American Indian. The service eras represented in the sample included 64% (112) Vietnam, 13.1% (n=23) Post-Vietnam, 6.9% (n=12) Persian Gulf, 6.3% (n=11) Korean, 5.1% (n=9) Post-Korean, 2.3% (n=4) World War II, and 1.7% (n=3) from other non-service era categories. The screen-positive cohort included eight males equally divided between the Caucasian and African American racial/ethnic groups. The mean age was 69.75 for screen-positive and 67.64 for the screen-negative cohorts. No statistically significant difference was seen in age between the cohort groups using the Independent-Samples Mann-Whitney U Test (p=.499). The majority of screen-positives were from the Vietnam service era (62.5%, n=5) consistent with findings from the screen-negative group (64.1%, n=107).

A total of 188 unique cases were identified with baseline testing for LTBI using the T-SPOT.*TB*® assay. Thirteen of the screened were excluded from the analysis because they did not have an established cancer diagnosis, leaving a final sample size of 175 screened cancer patients

for LTBI during the study period. There were eight screen-positives for LTBI representing 4.5% of the total sample with an incidence density of 0.0457 cases/10-month study period.

Cancer Specific Characteristics

Cancer specific characteristics of the sample are summarized in Table 3. Of total patients screened, the most frequent cancer diagnoses included hematologic, lung, rectal/anal/colon, prostate, and head and neck. Of the eight screen-positive cohort, there were three (37.5%) prostate cancers, two (25%) rectal/anal/colon cancers, one (12.5%) hematologic cancer, one (12.5%) lung cancer and one (12.5%) head and neck cancer. In comparison, the screen-negative cohort had 69 (41.3%) hematologic cancers, 36 (21.6%) lung cancers, 10 (6.0%) rectal/anal/colon cancers, nine (5.4%) prostate cancers, nine (5.4%) head and neck cancers, and 34 (20.3%) in other cancer categories. The screen-positive cohort had advanced cancer stages 3-stage 4 in 75% (n=6) in comparison to the screen-negative cohort findings of 49.7% (n=83).

Risk Factors

High-risk categories for exposure and reactivation of LTBI are summarized in Table 4. The screen-positive cohort included 25% (n=2) patients with the comorbid condition of diabetes, 75% (n=6) with no coexisting comorbid medical conditions, and 12.5% (n=1) with low body weight < 10% ideal. High-risk behaviors of intravenous drug use (IVDU) and incarceration were 12.5% (n=1) and alcohol use was 25% (n=2) respectively, in the screen-positive cohort. Imaging findings on chest radiograph and/or computerized axial tomography (CAT) were abnormal in half (n=4) of the screen-positive cohort however there were no fibrotic changes consistent with prior past TB. No active TB disease was identified. In comparison, the screen-negative cohort revealed a 31.7% (n=53) incidence of diabetes and more wide-ranging comorbid and multimorbid conditions. Alcohol use was slightly higher in the screen-negative cohort at 30.5%

(n=51) in comparison to the screen-positive group. High risk behaviors of IVDU was lower at 4.2% (n=7) as well as history of incarceration at 3.6% (n=6).

Indeterminant Results

Valid T-SPOT.*TB*® test results (i.e. positive or negative) were available for 164 of the 175 total sample. Of the total tested, 6.3% (n=11) were reported indeterminant or insufficient peripheral blood mononuclear cells (PBMC). A summary of indeterminant test results, re-test results, confirmatory TST results, and clinical information are provided in Figure 3. A total of four of the 11 indeterminant test results were retested later by clinicians. Valid results were obtained in two (50%) of these cases. Confirmatory testing with TST was performed in one case with a positive TST by induration threshold for LTBI. Of the 11 indeterminant results, 63% (n=6) were not retested. Using Independent-Samples Mann-Whitney U testing (Figure 4), age was found to not statistically affect the incidence of indeterminant test results with $p = .11$. Among the 11 indeterminant test results with clinical information on cancer staging, 81.8% (n=9) cases had advanced cancer stage 4 diagnoses which included prostate (n=3), breast (n=1), lung (n=1), rectal (n=1), multiple myeloma (n=1) and lymphoma (n=1) and head and neck (n=1).

LTBI Treatment

A summary of LTBI treatment groups are summarized in Table 5. There were eight screen-positives for LTBI. Of the total screen-positives, two (25%) were not considered for treatment based on poor clinical prognosis with hospice services or death noted in the chart. One (12.5%) was considered a poor treatment candidate based on a preexisting psychiatric history, in addition to consideration that his cancer diagnosis was not specific for high-risk TB reactivation. Five (62.5%) were treated in the Infectious Disease Clinic. Treatment regimens for LTBI included INH 6-months or INH 9-months regimens. Two subjects (40%) were prescribed INH 6-

months treatment courses and three subjects (60%) were prescribed INH 9-months treatment courses. Of the INH 6-months treatment course cohort, two (100%) completed the course with no adverse reactions. Of the INH 9-months treatment course cohort, two (68%) remain in active treatment and one (22%) ended treatment early due to adverse events of isolated bilirubin.

Cost Efficacy

The cost efficacy of LTBI screening in the cancer subpopulation sample were evaluated by the number needed to screen (NNS) to detect a single case of LTBI. In addition, cost estimates were calculated based on material cost per T-SPOT.*TB*® assay per individual and aggregate as well as costs per LTBI case detected. The costs of screening using the T-SPOT.*TB*® assay and NNS to detect a single case are presented in Table 6. The material cost for the T-SPOT.*TB*® assay is approximately $50 per test with an aggregate cost for the 175 screened plus the four additional T-SPOT.*TB*® assays for indeterminant test results yield an aggregate cost of $8950. The cost per detected case of LTBI is $1,118.75. The NNS to detect a single case of LTBI in this sample is 22 patients.

Discussion

This study sought to examine the relationship of LTBI in Veterans with a cancer diagnosis who were undergoing treatment at the McGuire VA Medical Center.

The questions answered were:

1. What is the prevalance of LTBI in Veterans with cancer undergoing treatment?
2. What are there host and cancer-specific characteristics that can identify patients at high risk for LTBI?
3. What is the burden of indeterminant qualitative results of T-SPOT.*TB* ® whole blood assay sensitivity in cancer patients comparing test-retest reliability with TST by induration threshold for defining LTBI?
4. What is the epidemiology of latent TB treatment, acceptance, adverse events and rate of completion?
5. What is the cost efficacy of targeting screening and treatment of cancer patients for LTBI?

The hypothesis that Veterans would have a higher prevalence of LTBI given their propensity for military deployment to TB endemic countries during their military careers was not supported by the study findings. The finding of a 4.6% prevalence of LTBI in the sample is equivalent to findings from the 2011-2012 NHANES survey data, with an estimated prevalence is 4.4%- 4.8% (Mancuso et al., 2016). However, this finding must be interpreted in the context of the small screen-positive sample size. Host characteristics of the screen-positive cohort reflected older age in the sixth through eight decades, all males with a majority from the Vietnam service era. Female veterans were less represented in the sample comprising only 4.6% of the total cancer subpopulation screened. Given the small screen-positive sample, we were unable to

stratify for important high-risk behaviors including alcohol, substance abuse, incarceration and underlying medical co-morbidities.

Cancer specific characteristics of the screen-positive cohort included hematologic, lung, head and neck, prostate and rectal/anal/colon cancers. Prostate cancer comprised 37.5% of screen positive cohort, raising the question if this group should be included in the screening. The literature supports that individuals with hematologic malignancies, head and neck cancer and lung cancers are at the highest risk (nine-fold higher rate) of developing active TB compared with the general population with other solid tumor cancers presenting a moderate risk in foreign-born (Cheng et al., 2017). Finally, findings from this study further support the need for risk-stratified LTBI screening in this population to avoid screening of individuals that would not be treatment candidates based on advanced disease states or inability to tolerate treatment if screen-positive.

The vast majority of T-SPOT.*TB*® tests performed during our study yielded valid results that were either positive or negative. Only a small portion of T-SPOT.*TB*® test results were indeterminant (n=11). Among the factors considered influencing indeterminant test results, including older age and advanced stage cancer contributing to cellular immunosuppression; no relationship can be demonstrated with these data. Re-testing of indeterminant test results was performed in four of the eleven results with 50% valid results on re-test. A tuberculin skin test (TST) was performed in only one case with positive results by induration threshold for defining TB infection and no meaningful conclusions can be formulated from these data. Seven of the 11 indeterminant test results were not repeated, perhaps due to clinical decisions based on advanced metastatic disease in these cases. Re-testing of indeterminant test results are necessary to draw any meaningful conclusions from the results. In studies with immunosuppressed cancer patients

undergoing cytotoxic and targeted antineoplastic drugs, T-SPOT.*TB*® assays have demonstrated interpretable results and maintenance of test sensitivity and performance (Piana et al., 2006; Rodriquez & Safdar, 2014).

Based on additional clinical parameters, only five of the eight T-SPOT.*TB*® positive subjects were considered for treatment of LTBI. Of these, all were offered treatment with isoniazid at either six or nine-month duration. Overall treatment was well tolerated with one early discontinuation due to isolated elevated bilirubin. There were no incidences of hepatitis.

The NNS to detect a single case of LTBI was 22 in this sample at an overall cost of $1,118.75 per case detected. The NNS can be utilized to provide guidance in setting priorities in the local context. Cost efficacy must be considered in the context of costs associated with TB exposure contact investigations. The 2012 TB exposure contact investigation identified a total of 218 exposed patients and staff (142 staff and 76 patients) with the source patient originating from the oncology clinic. At a cost of $50 per T-SPOT.*TB*® assay at baseline and repeat testing at 8-10 weeks with a second T-SPOT.*TB*® test, the screening costs of this contact investigation is estimated to be $21,800 which is a 20-fold increase from the current practice of targeted screening of all cancer patients. Of the 2012 TB contact exposure, no conversions occurred among staff, however four patients tested positive and one tested indeterminant. All were referred to the Infectious Disease Service for evaluation and treatment which incurs additional costs not considered in this discussion.

This study provides baseline estimates of the prevalence of LTBI in Veterans with cancer at our medical center. Screening and treatment data provides an opportunity to evaluate the screening program effectiveness and identify gaps. These data add to the knowledge of the local epidemiology and can be used to further risk stratify screening to cancer-specific diagnoses. The

study results suggest that the T-SPOT.*TB*® test maintains its sensitivity and performance in immunocompromised patients.

Strengths and Limitations

This study is the first to provide an estimate of the burden of LTBI among Veterans with cancer advancing understanding of the local prevalence. It provides data to assess quality of adherence to current practice guidelines for targeted LTBI screening and treatment. Several study design limitations are identified. First, use of a convenience sampling method within the specified time frame generated a small screen-positive sample size. Females were under represented in the sample limiting generalizability. In addition, the single-center setting with the select cohort of the Veteran population who are mostly males further limits generalizability to non-VA healthcare systems.

Implications for Practice

This study evaluated the recently implemented clinical practice guidelines for targeted screening of LTBI in the cancer population adding to the understanding of local prevalence, T-SPOT.*TB*® reliability and LTBI treatment acceptance and tolerability in the cancer population. Findings suggest that the T-SPOT.*TB*® test maintains its sensitivity and performance in immunocompromised patients. The findings identified gaps and presented opportunities to address process issues of screening duplications, indiscriminate screening of patients with non-cancer diagnoses, and screening in situations such as advanced stages of cancer with short life expectancy in which patients would not be treatment candidates. These data can be used to provide feedback to oncology clinic providers to alter practice toward a risk-stratified LTBI screening approach. These changes may result in overall reduced costs associated with targeted

TB screening. In addition, findings can be used to guide policy development for evidence-based risk-stratified screening for an individualized approach to screening.

Conclusions

The current study adds to our understanding of the epidemiology of LTBI in Veterans with concomitant cancer diagnoses. Data from this pilot program study supports that targeted screening of LTBI in the high-risk cancer population yields early diagnosis and opportunity for treatment. Targeted screening and treatment in this high-risk population may result in prevention of reactivation disease with associated reduction in healthcare-associated transmission of TB among patients and staff in the clinic as well as the community. Identified gaps including testing of low-risk and indiscriminate testing of patients without cancer provide an opportunity for process improvements to refine risk-stratified screening in the target population. Targeted screening and treatment of LTBI in cancer-specific diagnoses is well supported in the literature and is a crucial intervention to strengthen TB control and elimination.

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Table 1

Drug regimens for treatment of latent tuberculosis infection (LTBI) in adults.

Drug	Interval	Duration	Adverse effects	Comments
Isoniazid (INH)	9 months	Daily	Hepatitis, rash, peripheral neuropathy	In HIV-infected persons, INH may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).
		Twice weekly		Directly observed therapy (DOT) must be used with twice-weekly dosing. Preferred treatment for pregnant women.
Isoniazid (INH)	6 months	Daily		Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs or children.
		Twice weekly		DOT must be used with twice weekly dosing.
Rifampin (RIF)	4 months	Daily	Hepatitis, rash; pruritis; thrombocytopenia; fever; orange colored body fluids including urine and tears, and can stain contact lenses.	Used for persons who are contacts with isoniazid resistant, rifampin-susceptible TB.
Isoniazid and Rifapentine	2 months	Once weekly	Hepatitis; rash; pruritis; thrombocytopenia, fever; orange colored body fluids including urine and tears, and can stain contact lenses; arthralgia.	DOT must be used. Not recommended for HIV infected taking antiretroviral treatment, presumed infected with INH or RIF-resistant M. tuberculosis, and women who are pregnant or expect to become pregnant within the 12–week regimen.

Note: Adapted from CDC. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. (2013).

Table 2

Sociodemographic Characteristics of T-SPOT.TB® Screened Patients

Demographics	Total Screened n = 175	Screen-Negative n = 159	Screen-Positive n = 8	Indeterminant Results n = 8	*p* value
Median age (range)	67.7 (33-99)	69 (33-99)	70.5 (48-84)	73.5 (57-81)	.28
Gender					
Male	167 (95.4)	151 (86.29)	8 (4.57)	8 (4.57)	
Female	8 (4.57)	8 (4.57)			
Race/ethnicity					
African American	94 (53.7)	72 (45.3)	4 (50.0)	4 (50.0)	
Caucasian	80 (45.7)	86 (54.1)	4 (50.0)	5 (50.0)	
American Indian	1 (0.6)	1 (0.6)			
Service Era					
WWII	4 (2.4)	4 (2.4)			
Vietnam	112 (64)	107 (64.1)	5 (62.5)	5 (62.5)	
Post-Vietnam	23 (13.1)	23 (13.8)		1 (12.5)	
Korean	11 (6.3)	9 (5.4)	2 (25.0)	1 (12.5)	
Post-Korean	9 (5.1)	9 (5.4)		1 (12.5)	
Persian Gulf	12 (6.9)	11 (6.6)	1 (12.5)		
Gulf War	1 (0.6)	1 (0.6)			
Other[a]	3 (1.7)	3 (1.7)			

Note. Other = ChampVA and unknown.

Table 3

Cancer Specific Characteristics of T-SPOT.TB® Assay Screened Patients

	T-SPOT.TB® Screen	
	Positive	Negative
Characteristic	n (%)	n (%)
Cancer Type		
Hematologic	1 (12.5)	69 (41.3)
Lung	1 (12.5)	36 (21.6)
Rectal/Anal/Colon	2 (25.0)	10 (6.0)
Prostate	3 (37.5)	9 (5.4)
Head & Neck	1 (12.5)	9 (5.4)
Hepatocellular		2 (1.2)
Breast		6 (3.6)
Melanoma		4 (2.4)
Pancreatic		4 (2.4)
Renal		3 (1.8)
Unknown primary		3 (1.8)
Gastric		2 (1.2)
Sarcoma		2 (1.2)
Testicular		1 (0.6)
Biliary		1 (0.6)
Glioblastoma		1 (0.6)
Penile		1 (0.6)
Bladder		1 (0.6)
Cancer Stage		
Stage 1		19 (11.4)
Stage 2	1 (12.5)	19 (11.4)
Stage 3	2 (25.0)	27 (16.2)
Stage 4	4 (50.0)	56 (33.5)
Unrecorded	1 (12.5)	47 (27.5)

Note. n = frequency; % = percentage.

Table 4

High Risk Categories for LTBI Exposure and Reactivation

High risk because of underlying medical conditions	Screen-Positive n (%)	Screen-Negative n (%)
No Coexisting High Risk Comorbidities	6 (75)	
Diabetes	2 (25)	53 (31.7)
Hemodialysis		2 (1.2)
HIV		5 (5.0)
Gastrectomy		3 (1.8)
IMID		3 (1.8)
Diabetes + Hemodialysis		2 (1.2)
Diabetes + HIV		1 (0.6)
HIV + Hemodialysis		1 (0.6)
Low Body Weight (<10% ideal)	1(12.5)	23 (13.8)
High risk because of increased likelihood of TB exposure		
History IVDU		
Yes	1 (12.5)	7 (4.2)
No	7 (87.5)	160 (95.8)
Alcohol Use	2 (25.0)	51 (30.5)
Yes	2 (25)	51 (30.5)
No	6 (75)	116 (69.5)
History of Incarceration		
Yes	1 (12.5)	6 (3.6)
No	4 (50.0)	13 (7.8)
Unrecorded	3 (37.5)	148 (88.6)
CXR/CT		
Abnormal – no fibrotic changes	4 (50)	
Normal	4 (50)	

Note: n = frequency. % = percent. HIV = human immunodeficiency virus. IMID = immune mediated inflammatory disease. IVDA = intravenous drug use. High risk comorbid conditions screened for include: diabetes, chronic renal failure, gastrectomy, solid organ transplant, alcohol use, injection drug use, low body weight < 10% ideal.

Table 5

LTBI Screen-Positive Cancer Cohort Treatment Groups

	LTBI Treatment			
	Accept		Decline	Not Recommended
	n (%)		n (%)	n (%)
	5 (62.5)		1 (12.5)	2 (25.0)
	6-INH	9-INH		
	n (%)	n (%)		
Adverse Effects[a]		1 (20)		
Treatment Completion	2 (40)			
Treatment Active		2 (40)		
Treatment Early Discontinuation		1 (20)		

Note. LTBI = latent tuberculosis infection. 6-INH = Isoniazid 6 months. 9-INH = Isoniazid 9 months.

[a] Adverse effects of isolated bilirubin.

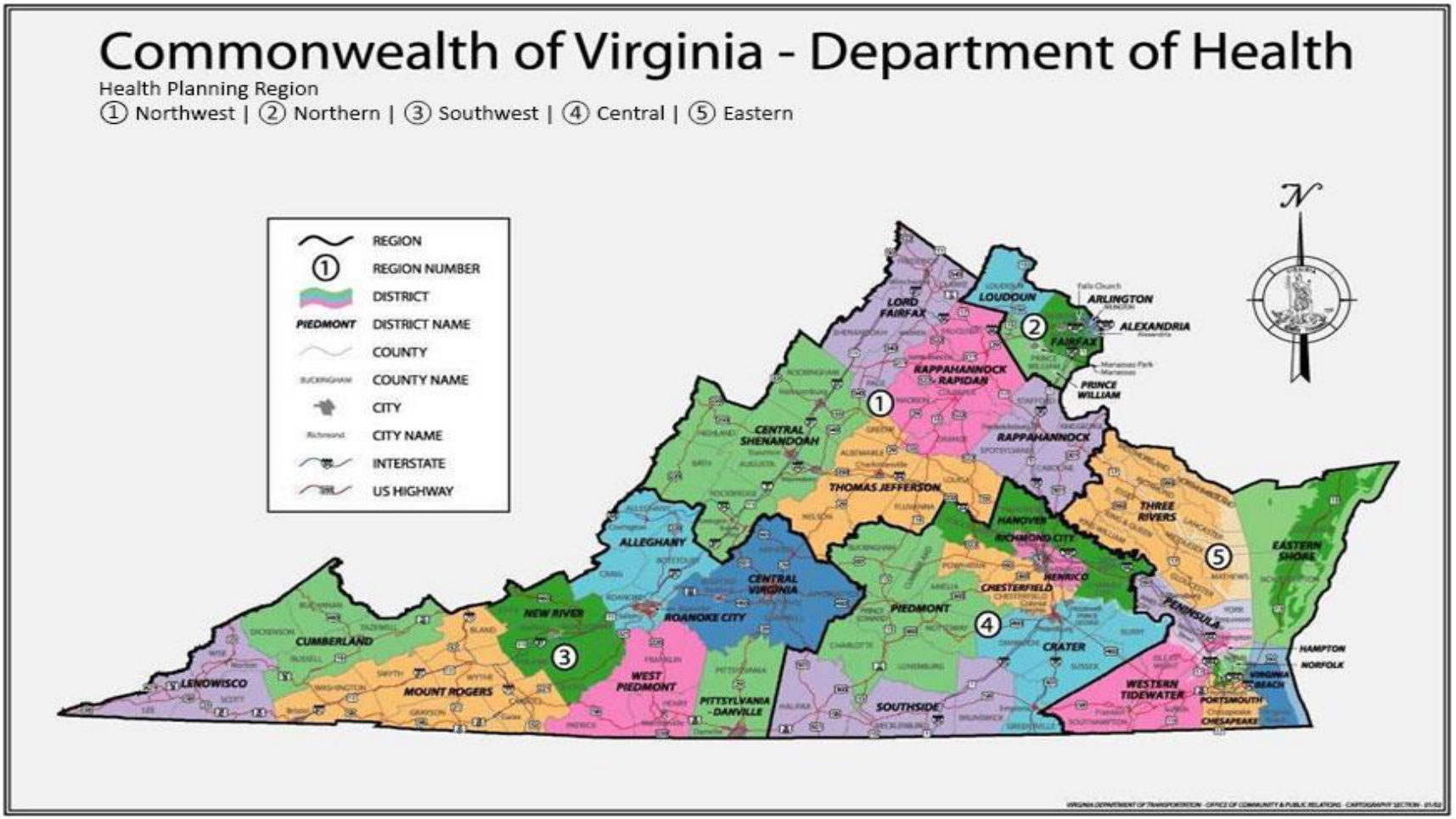
Table 6

T-SPOT.TB® screening costs and NNS to detect one LTBI case in cancer subpopulation

Number screened	Repeat Indeterminant Tests	Number LTBI diagnosed	NNS to detect one case	Aggregate costs (USD)	Cost per case detected (USD)
175	4	8	22	$8950	$1,118.75

Note. NNS = Number needed to screen to detect one case (total number screened / number of cases identified); USD = United States dollars.

Figure 1. Virginia Health Planning Regions Map



Note: Map retrieved from the Virginia Department of Health http://www.vdh.virginia.gov

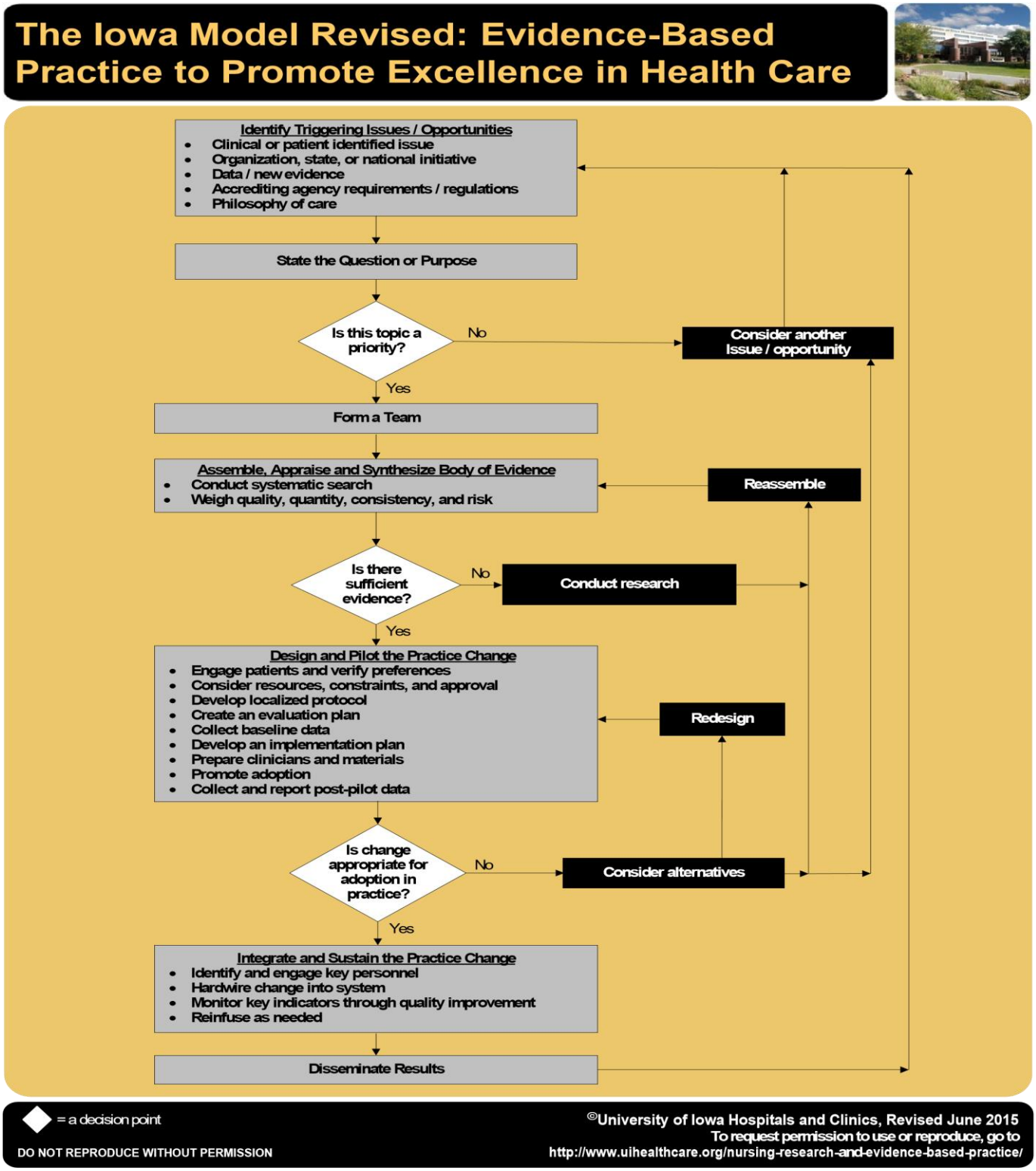


Figure 2. Iowa Model Collaborative. (in press). Iowa Model of Evidence-Based Practice: Revisions and validation. Worldviews on Evidence-Based Nursing.
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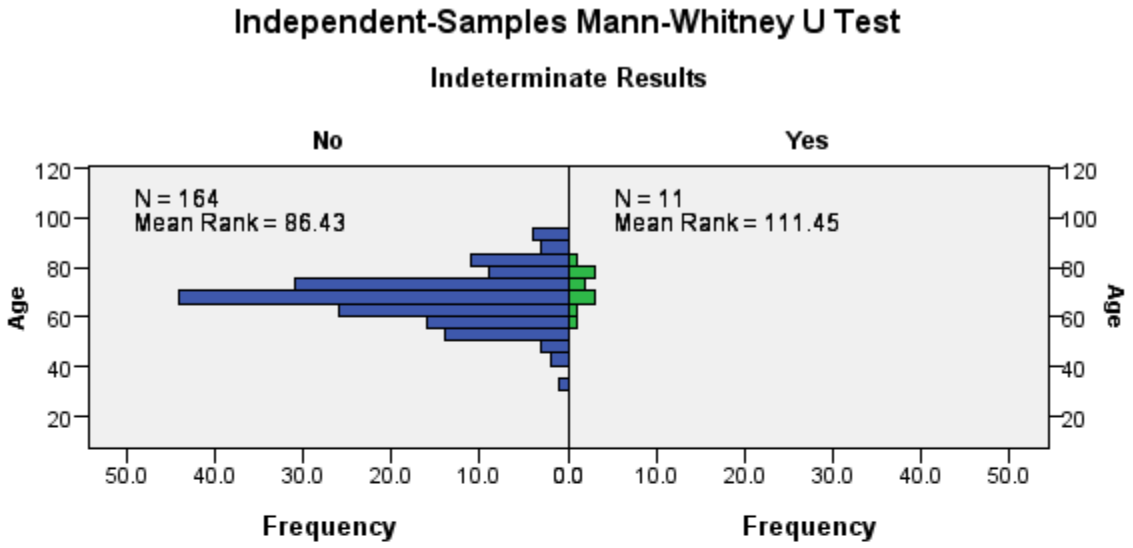
Figure 3. Indeterminant T-SPOT.*TB*® Test Results

Initial Testing Results	Re-test T-Spot.*TB*® Results				No Repeat Testing	Confirmatory Positive TST	Outcome
Indeterminant	Indeterminant	Insufficient PMNs	Positive	Negative			
x					x		Death Prostate Stage 4
x	x					x	Treatment declined Prostate Stage 4
x			x				Hospice Head & Neck Stage 4
x				x			BMT evaluation
Insufficient PMNs							
x					x		Hospice Breast Stage 4
x		x					Death Cytopenia Vasculitis
x					x		Death Stage 4 Multiple Myeloma
x					x		Lung Ca Stage 4
x					x		Rectal Stage 4
x					x		Stage 4 Prostate Ca
x					x		Death Lymphoma Stage 4

Note: PMN = Peripheral Mononuclear Cells

Figure 4. Indeterminant T-SPOT *TB*® Test Results Comparing Patient Age



Total N	175
Mann-Whitney U	1,160.000
Wilcoxon W	1,226.000
Test Statistic	1,160.000
Standard Error	162.510
Standardized Test Statistic	1.588
Asymptotic Sig. (2-sided test)	.112

Appendix A

PRISM Flow Diagram

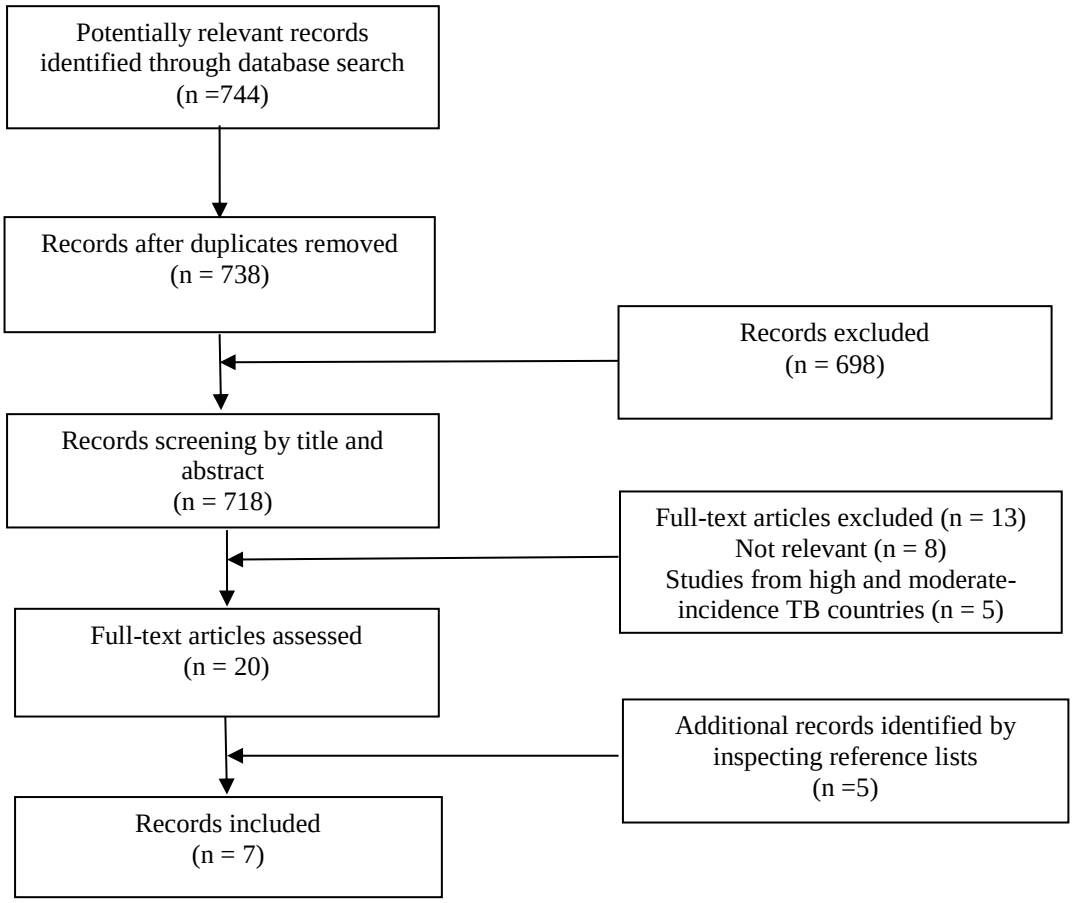


Figure 1. PRISMA flow diagram for the systematic review.
Note. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

Appendix B

Evidence Table: Studies of Patients with Tuberculosis and Concomitant Cancer

Study	Subjects and Setting	Design	Intervention and Comparison Intervention	Outcomes
Alhashimi et al., 1988	Subjects with lung cancer and TB Mean age 58.5 years (range, 40-69 years) VA Medical Center in Washington, D.C., U.S. from 1975 – 1982 Cancer patients N = 257 TB patients N = 89	Prospective analysis of incidence of tuberculosis in lung cancer patients	All patients received PPD prior to start of treatment. Treatment protocols incorporated combinations of chemo agents, usually at least 3 drugs; radiation therapy for palliation; corticosteroids as clinically indicated for CNS metastases or infrequently or other indications.	Positive TB reactivity was found in 89 (35%) of the 257 patients. TB developed in 1 patient before and 1 patient after chemotherapy. Median survival rate in lung cancer patients was 9.6 months. Lung cancer types: • 178 patients with small cell lung cancer • 58 patients with squamous cell lung cancer • 12 patients with adenocarcinoma • 9 patients with large cell carcinoma Incidence of TB in study population for all lung cancer patients undergoing chemo was 1,100 per 100,000 per year. This is 15 times higher than age-specific rate for Washington, D.C. over age 44 for same time period. Median duration of observation was 9.6 months (range 2.5 to 65.5 months); all but 8 patients had died by the end of the study.

				Due to limited survival and high risk of isoniazid (INH) hepatotoxicity, INH therapy for TB-positive was not recommended given risk of hepatotoxicity exceeds the risk of new TB infection. **Limitations:** Single center with selection bias of lung cancer patients only.

Kaplan et al., 1974	Subjects with active TB and concomitant cancer were included with average age 12 to 67 years of age
	
	Memorial Sloan-Kettering Cancer Center, New York, U.S. 1950 – 1971
	
	Cancer patients N = 58,245
	
	TB patients N = 201
		Retrospective analysis of culture confirmed M. tuberculosis in cancer patients	Patients were included who developed active TB during or after therapy for malignant neoplastic disease	Cancer types:
				
				• 44 lung cancer (prevalence of TB in case = 92/10,000)
				• 45 head & neck (prevalence of TB in case = 51/10,000)
				• 28 breast cancer (prevalence of TB in case = 19/10,000)
				• 29 lymphoproliferic disorders
				  ○ Hodgkins (prevalence of TB in case = 96/10,000)
				  ○ Lymphosarcoma (prevalence of TB in case = 88/10,000)
				  ○ Reticulum cell sarcoma (prevalence of TB in case = 78/10,000)
				• 20 gynecologic cancers
				• 7 leukemia
				• 9 stomach cancer
				• 19 other neoplasms
				TB most prevalent in Hodgkins disease, lung cancer, lymphosarcoma, reticulum cell sarcoma and least prevalent in colon cancer, bladder, uterus, breast, prostate and kidney.
				
				TB more often present when cancer first diagnosed in H&N cancer, lung cancer (defined as present at time of primary neoplasm).

				Pulmonary TB most often seen when diagnosed at the time of malignancy. Severe disseminated or pneumonic TB was seen after treatment for cancer (within 18 months of therapy). Distant TB infection was seen in 31 patients (defined as after 18 months of therapy). More severe TB infection occurred with increasing immunosuppression. Overall mortality rate was 17% accounting for 38 deaths (14/29 or 48% from TB in Hodgkins disease, lymphosarcoma and reticular cell sarcoma). Those who died had disseminated or pulmonic TB. **Limitations:** Single center with only study duration was reported and not subject follow up.
Kamboj and Sepkowitz, 2006	Subjects with cancer and TB were included with mean age of 57 years (range 9 months - 82 years); (5 subjects were children) 57 patients (55%) were foreign born	Retrospective analysis of culture confirmed M. tuberculosis in cancer patients	Patients with cancer and culture confirmed M. tuberculosis infection were included	Overall TB rate 55 cases/100,000 persons. TB incidence was highest among patients with underlying hematologic neoplasms (240 cases per 100,000 persons) or ~ 40 times greater than current rate among U.S. population. TB rate among Head & Neck cancer was 135 cases per 100,000 persons unrelated to country of birth. TB rate among lung cancer varied 52-320 cases per 100,000. TB rate among solid tumor was 39 cases per 100,000 and varied according to country of birth: 24 U.S. born per 100,000 persons verses 100 foreign-born per 100,000 persons (P<.0001).

	Memorial Sloan-Kettering Cancer Center, U.S. 1980 – 2004 Cancer patients N = 186,843 TB patients N = 103			U.S.- born persons with solid tumors 24 per 100,000, P = .06 U.S.-born patients had significantly lower rates of TB than foreign-born patients (33 vs. 126 patients per 100,000 persons; P <.0001) 26 patients (25%) died within 3 months of TB diagnosis Findings suggest: U.S.-born patients with solid tumors (except head and neck) are not at increased risk for development of TB. Persons with hematologic neoplasms are at increased risk and should be included with high risk groups. **Limitations:** Single center with only study duration reported and not subject follow up. Study spanned 25 years with relatively few TB cases, patients receiving cancer care at Memorial Sloan-Kettering may have subsequently received a diagnosis of TB at another hospital, and did not include culture negative cases of TB.
Libshitz et al., 1997	Subjects were patients with cancer and TB with a mean group age of 55 years (range 21-88) University of Texas MD Anderson	Retrospective analysis of culture confirmed M. tuberculosis and malignancy		TB frequency in cancer patients was 90 per 100,000. The incidence of TB was 15 per 100,000. TB in cancer occurs at 9 times greater frequency than the general population. TB more frequent in foreign-born ($p<0.001$) and in racial and ethnic minorities of Hispanic, African American and Asian ($p<0.001$) than non-Hispanic whites. Minorities represented 55% of the patients with TB but only 20% of the entire cancer population. The racial and ethnic

	Cancer Center, Houston, TX, U.S. 1984-1994 Cancer patients N = 61,931 TB patients N = 56			distribution of cancer patients with TB is similar to that of TB in the general population. TB developed during therapy in 27 (48%) of subjects. TB was discovered synchronously (within 3 months) of cancer in 17 (30%). TB occurred ≥ 18 months after therapy in 12 (21%) of subjects. Pulmonary TB occurred in 50 (89%) cases and extra pulmonary TB occurred in 9 (16%) cases (supraclavicular lymph nodes. CNS involvement, renal, TB spondylitis and disseminated disease). TB incidence was higher in hematologic malignancy (acute leukemia most frequent). **Limitations:** Single center with only study duration included and not subject follow up.
De La Rosa et al., 2004	Subjects were cancer patients with active TB with a median age of 54 years (range 23-88 years) University of Texas MD Anderson, Houston, TX,	Retrospective analysis of M. tuberculosis positive patients with cancer	Patients with cancer and concomitant positive M. tuberculosis positive cultures	Types of underlying cancers: - 19 (63%) hematological malignancy - 4 (13%) hematopoietic stem cell transplant - 11 (37%) solid organ malignancy 19 (63%) pulmonary tuberculosis 18 (60%) were foreign-born

	U.S. 1990-2000 Cancer patients with TB N = 30			Death was attributed to TB for 6 (21%) of 29 patients who received anti-mycobacterial therapy The mortality rate was 100% for 4 patients (13%) who received high dose steroids within 4 weeks of diagnosis, whereas 2 (8%) deaths occurred in 25 individuals without steroid exposure ($p < 0.001$; OR 8.67) **Limitations:** Single center with only duration included.
Cheng et al., 2017	23 studies included in systematic review and 6 studies conducted in the U.S. included in the metaanalysis 1950 - 2011 Cancer patients N = 324,243 TB patients N = 593	Systematic review and metaanalysis	Studies of pathologically confirmed cancer cases with confirmed active TB concurrently or after diagnosis	TB incidence was higher in high tuberculosis incidence countries and higher in hematologic vs solid tumors. The metaanalysis of 6 studies conducted in the U.S. 317,243 cancer patients which accounted for 98% of all cancer patients at risk. • The rates of active TB decreased significantly among all types of cancers over the 6-decade study period in low tuberculosis-incidence settings. • Hematologic cancers had the highest rates of active TB followed by head & neck, lung cancer and breast cancer. • Active TB occurred concurrently or soon after the cancer diagnosis in more than half of patients with Head & Neck and lung cancer. • Relative risk remained high Cumulative index rate of TB decreased 3-fold and 6.5 fold in hematologic and solid cancers respectively, before and after 1980. After 1980 the cumulative index ratio of TB was highest in hematologic (219/100,000 population; incidence rate ratio = 26), head and neck cancer

				(143;6), lung cancer (83;9) and was lowest in breast and other solid cancers (38;4) In the U.S. individuals with hematologic, head & neck cancers and lung cancer had a 9-fold higher rate of developing active TB compared to those without cancer. Findings suggest: Individuals with hematologic, head and neck and lung cancer and would benefit from targeted LTBI screening and therapy. Limitation: Follow up time was not listed in most studies; potential for case detection bias with higher case detection in cancer patients as a result of closer monitoring and lower in the general population due to missed undiagnosed cases who died or self-healed.

Note: This chart presents condensed findings from the review of literature.

Appendix C

Research and Development Committee
McGuire VA Medical Center
1201 Broad Rock Blvd. (Room 3D-141) • Richmond, VA 23249 • 804-675-5151 • Fax: 804-675-5139

APPROVAL - Initial Review

Date: October 26, 2017
From: Michael F. Godschalk, M.D., Chairperson

Investigator: Edward Wong, M.D.

Protocol: Targeted Screening of Latent Tuberculosis in Cancer Patients

ID: 02361 Prom#: N/A Protocol#: N/A

The following items were reviewed at the 10/24/2017 meeting:

- Data Management Plan (09/05/2017)
- Facility Information Security Officer Review of Hu (09/14/2017)
- Privacy Officer Review of Human Subjects Research (10/17/2017; FINAL)
- IRB Approval Granted (10/06/2017)

Following approval by all relevant committees, subcommittees, or other entities, the Research and Development Committee gave full approval of the project. This is the required formal notification that this project may be initiated.

Approval by each of the following is required prior to study initiation (unless Exempt):
McGuire Institutional Review Board (IRB) [Approval Granted 09/26/2017] Research and Development Committee

Where applicable, approval by each of the following is also required prior to study initiation:
Biosafety Committee
Biohazard Committee
Radiation Safety Committee

Please make sure the VA receives proper credit for any publications resulting from this study.

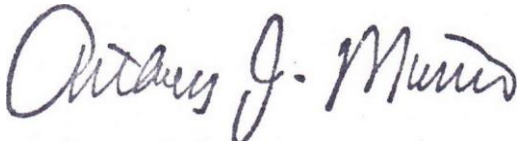
APPROVED
To
Initiate/Continue/Submit

ACOS, Research/Designee

McGuire Institutional Review Board
(IRB) McGuire VA Medical Center
1201 Broad Rock Blvd. (Room 3C-126) • Richmond, VA 23249 • 804-675-5676 • Fax: 804-675-5679

IRB APPROVAL - Initial Review

Date: October 6, 2017
From: Anthony J. Minisi, M.D., Chairperson
Investigator: Edward Wong, M.D.



Protocol: Targeted Screening of Latent Tuberculosis in Cancer Patients
ID: 02361 Prom#: N/A Protocol#: N/A

The following items were reviewed and approved at the 09/26/2017 meeting, contingent upon stipulations in each item marked with an asterisk (*):

- Research Protocol (08/15/2017)
- Conflict of Interest Disclosure Form - Fagan (09/05/2017)
- Conflict of Interest Disclosure Form - Wong (09/05/2017)
- Initial Review Submission - MINIMAL RISK (09/05/2017)
- Data Management Plan (09/05/2017)
- * Waiver of HIPAA Authorization (09/05/2017) • Project Data Sheet
- Facility Information Security Officer Review of Hu (09/14/2017) • Privacy Officer Review of Human Subjects Research (09/14/2017)
- Study Personnel List (09/03/2017)
- * Waiver or Alteration of Consent (09/05/2017) • Privacy and Data Security Plan (09/03/2017)

Waiver of HIPAA Authorization (09/05/2017) was returned to you with stipulations. The following revised items incorporate the stipulations and are now approved:

- Waiver of HIPAA Authorization (10/03/2017)

Waiver or Alteration of Consent (09/05/2017) was returned to you with stipulations. The following revised items incorporate the stipulations and are now approved:

- Waiver or Alteration of Consent (10/03/2017)

Conditions of Approval are attached. These conditions are further detailed in the HHS, FDA, and VA regulations, which are available in the Research Office.

The following McGuire Institutional Review Board (IRB) members recused themselves (or were otherwise excused) from deliberations and did not vote: Edward S. Wong, M.D.

Approval is granted for a period of 12 months and will expire on 09/25/2018. Your Continuing Review is scheduled for 08/28/2018, and the requirements are attached.

The protocol was determined to have the following level of risk:
Minimal (e.g. blood draw, non-sensitive survey)

The protocol was determined to have the following level of benefit to participants:
Little prospect for benefit to participants, but likely to yield generalizable knowledge

In the event that your employment at the Richmond VA Medical Center ends, you must:
1. Notify the IRB and take action to transition active and pending human research studies.
2. Notify Research Office staff and take action to archive paper and electronic research records.

Approval by each of the following is required prior to study initiation (unless Exempt):
McGuire Institutional Review Board (IRB)
Research and Development Committee

Approval for study initiation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Appendix D

Draft Manuscript Federal Practitioner

Targeted Screening of Latent Tuberculosis in Cancer Patients

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Abstract

With approximately 80% of active tuberculosis (TB) cases arising from reactivation of latent TB infection (LTBI), a key national strategy for TB elimination is targeted screening in high-risk groups. Although cancer is considered a high-risk condition for reactivation TB, baseline screening for LTBI is not considered standard care in this population. Targeted screening and treatment in cancer patients can lead to early diagnosis and treatment preventing reactivation and spread of disease. This study evaluated LTBI prevalence in Veteran's with cancer diagnoses, and compared patient and cancer-specific characteristics that may predict a positive result. Additionally, the use, reliability, and cost effectiveness of screening tests (T-SPOT.*TB*® and tuberculin skin testing) was examined. LTBI treatment acceptance, adverse events and completion rates were evaluated. Finally, the cost efficacy of targeting and treating LTBI in cancer patients was assessed. A retrospective chart review of cancer patients screened using the T-SPOT.*TB*® test was conducted between 1/1/2017 through 10/31/2017 from a Veterans Affairs oncology clinic. Descriptive statistics were used. Eight (4.6%) Veterans were screen-positive for LTBI (n=175). The median age was 70.5 years, with majority from the Vietnam service era. No high-risk comorbidities or high-risk behaviors were identified as predictors of positive results. The number needed to screen (NNS) to detect a single LTBI case was 22 ($1,100 per detected case). Indeterminant test results burden was 11/175 (6.3%). Treatment acceptance was 62.5% (n=5) with 20% (n=1) associated adverse events. Cost efficacy comparing NNS to detect a single case with costs associated with TB contact investigations was 20-fold less than the 2012 TB contact investigation. This study adds to the understanding of LTBI prevalence in Veterans with cancer and can guide policy development for evidence-based screening and treatment.

Keywords: Latent tuberculosis infection; reactivation tuberculosis; cancer; targeted screening

Targeted Screening of Latent Tuberculosis in Cancer Patients

Introduction

Tuberculosis (TB) remains a global public health threat, ranking as one of the top ten causes of death worldwide.[1] It is estimated that one third of the world's population is infected with TB.[2] Tuberculosis is a highly contagious disease caused by the bacillus *Mycobacterium tuberculosis,* which is spread from person to person via airborne aerosolized droplets when a person with active TB coughs or sneezes. Following exposure, three outcomes are possible: clearance of the organism; onset of active TB; or development of latent infection.[3] While active TB disease is characterized by signs and symptoms caused by active replication of the tubercle bacilli and is contagious, those with LTBI have been infected but have no active symptoms of the disease and are not contagious.

It is estimated that approximately 30% of persons exposed to *Mycobacterium tuberculosis* will develop LTBI.[4,5] Of those infected with latent disease, approximately 5-10% of healthy (immunocompetent) persons will reactivate to active TB disease in their lifetime.[4,6,7] This range underestimates the risk of progression to active TB disease for some and over estimates the risk for others. Using a model to estimate the lifetime risk of reactivation, Horsburgh (2004) found the risk to be 20% or more among most persons with induration of ≥ 10mm on tuberculin skin testing (TST) and either HIV infection or old, healed TB on radiograph; 10-20% among recent conversion of TST and among persons younger than 35 years of age receiving anti-tumor necrosis factor alpha inhibitors (TNF-α) (i.e. infliximab) and induration of ≥15mm on TST; and 10-20% for children 5 years of age or less.[8] While advanced HIV infection was associated with the greatest relative risk of reactivation, Horsburgh suggests that the lifetime risk of TB among people with other immunosuppressive conditions including

cancer, long term treatment with corticosteroids, cyclosporine or other immunosuppressive agents should be assumed to be equivalent to that of that of infliximab therapy (relative risk of 2.0) until more data become available.[8]

There has been a steadily declining incidence of TB rates in the U.S. since 1993, however the goal of TB elimination defined as less than one case per 1,000,000 population will not be met this century with current rates of decline.[9] In 2015, there were 9,563 TB cases reported in the U.S., for a rate of 3 cases per 100,000 population, a 1.6% increase from the previous year.[2.10] It has been estimated that approximately 80% of active TB cases arise from reactivation of LTBI.[11,12] Based on data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES), the prevalence of LTBI has been reported as 4.4% as measured by the TST and 4.8% based on QuantiFERON-TB Gold In-Tube screening test, corresponding to 12.4 million and 13.6 million individuals respectively[13] with no statistically significant decline in overall prevalence over the past decade.[13,14] These findings suggest a substantial reservoir of infection which threatens TB control and elimination in the U.S.

Since the 1989 strategic plan for TB elimination in the U.S. by the Advisory Council for Elimination of Tuberculosis was issued, major changes have occurred in the epidemiology of TB and the organization and delivery of public health care services challenging strategies to meet the goal. Renewed commitment to TB elimination continues to emphasize the importance of improving diagnosis and treatment of LTBI in high-risk populations which is the cornerstone for the TB elimination strategy.[15,16,17] The World Health Organization (WHO), Centers for Disease Prevention (CDC) and professional societies such as the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) have recommended targeted screening and

treatment of high-risk individuals with LTBI as part of control strategies and efforts for TB elimination in low-incidence countries.[6,18]

Groups at high-risk for progression from latent to active TB are well-defined. These groups include coinfection with HIV; injection drug use; radiographic evidence of prior healed tuberculosis; low body weight (10% below ideal); recent conversion on TST; infants and children under five years of age; recent immigrants from TB endemic countries; and medical conditions including silicosis; poorly controlled diabetes; chronic renal failure; gastrectomy; solid organ transplant; individuals preparing to undergo hematologic transplant; head and neck cancer; lymphoma, leukemia; lung cancer; and conditions that require prolonged use of corticosteroids or other immunosuppressive agents, and TNF-α therapy.[4,6,8] Intensified efforts directed at identifying and treating LTBI in these high-risk groups are vital to meet the goal of TB elimination.

Concerning however, are findings by Vozoris and Batt, reporting less frequent LTBI testing in the U.S. among vulnerable groups.[19] These findings raise concern for the possibility of an increase in active TB in the future and further support the need for scaled up efforts for targeted screening and treatment by health care professionals. Although cancer has been identified as a high-risk condition for developing active TB, baseline screening for LTBI is not considered standard care in this population.

The U.S. Veteran population with coexistent diagnosis of cancer may be at an even higher risk for LTBI reactivation given their propensity for deployment during military careers to TB endemic countries. No studies have been conducted to specifically examine the incidence of LTBI in Veterans with concurrent cancer. The purpose of our study was to investigate the prevalence of LTBI in Veterans in a medical oncology clinic being treated for active cancer, and

to compare patient and cancer specific characteristics in relationship to screening results. Additionally, the use, reliability, and cost effectiveness of diagnostic screening tests including T-SPOT.*TB*® interferon-gamma release assay (IGRA) and TST were examined. LTBI treatment acceptance, adverse events and completion rates were evaluated. Finally, the cost efficacy of targeting and treating LTBI in cancer patients was assessed.

Review of the Literature

Cancer has been a well-recognized risk factor for the development of active TB since the 1970s. In a systematic review and metaanalysis of six U.S. studies by Chen et al, rates of active TB decreased significantly among all types of cancer over the six-decade study period. The highest rates of active TB was seen among hematologic cancer patients, followed by head and neck, lung cancer, and breast cancer patients.[20] Foreign-born persons and racial and ethnic minorities were found to be consistently at higher risk for development of active TB.[20] Findings from the literature support a risk-stratified approach to LTBI screening in cancer patients to include hematological, head and neck, and lung cancer as well as all foreign-born persons from TB endemic countries prior to start of cancer therapy. Despite robust evidence highlighting the increased risk of active TB in patients with cancer and published guidelines,[20,21] screening for LTBI in the cancer population is not the standard practice for disease management in many oncology settings.

Methods

Study Setting

Our study site is a Veterans Affairs (VA) tertiary care medical center in Richmond, Virginia. Services are provided to more than 200,000 Veterans coming from 52 cities and counties covering 22,515 miles of central and southern Virginia and parts of northern North

Carolina. The outpatient medical oncology clinic treats approximately 200 new cases of cancer with chemotherapeutic agents annually. The current clinical practice protocol in the oncology clinic is to test at baseline all Veterans with a cancer diagnosis undergoing chemotherapy using the IGRA diagnostic screening test, T-SPOT.*TB*® whole blood assay as first line testing rather than TST, consistent with recommendations from clinical practice guidelines from ATS, IDSA, and the CDC.[21,22] This clinical practice change was initiated January 1, 2017, in response to contact investigations of healthcare-associated transmission of TB involving two discrete TB contact exposures over a four-year interval with the index case patient in each contact investigation originating from the oncology clinic.

Study Design and Ethics

After approval by the McGuire Institutional Review Board (IRB tracking ID: 02361), a retrospective chart review was conducted using standard methodology.[23] The computerized medical record system (CPRS) was used to identify patients with baseline LTBI testing using the T-SPOT.*TB* ® whole blood assay or TST during the study period of January 1, 2017 through October 31, 2017. A convenience sample of consecutive cases were considered for inclusion in the study. Inclusion criteria included subjects with a diagnosis of cancer. Subjects with active tuberculosis were excluded.

All data was collected from the CPRS with an electronic case report form and entered into a Microsoft Excel spread sheet, coded, and uploaded into the statistical package for social sciences (SPSS, version 24). The study was descriptive by nature. Continuous variables are presented as means and standard deviation for symmetrical data, and by medians and ranges for skewed data. Categorical variables are presented as frequencies and percentages. The

independent samples t-test was used to explore the relationship among continuous variables. Analysis was stratified by screen-positive, screen-negative, and indeterminate results groups.

For all case patients, demographic information, cancer-specific information, comorbidities, T-SPOT.*TB*® qualitative results, TST results and treatment results were extracted. Case subjects with screen-positive results using either the T-SPOT.*TB*® assay or TST were ruled out for active TB by history, physical examination, and chest radiograph or computerized axial tomography (CAT) scan of the thorax.

Descriptive statistics including frequencies, percentages and means, and standard deviation were used to access the prevalence of LTBI in oncology patients, comparative characteristics of screen-positive and screen-negative cohorts to identify host characteristics and risk factors identifying cancer patients at high-risk of TB reactivation the burden of indeterminant qualitative results of the T-SPOT.*TB*® testing compared to test-retest reliability with TST by induration threshold for defining LTBI and LTBI treatment acceptance, adverse events and rate completion, and cost efficacy of universal screening for LTBI. The nonparametric test of Independent-Samples Mann-Whitney U was used to examine the relationship between age and screen-positive and screen-negative cohort groups and the relationship of age and indeterminant T-SPOT.*TB*® test results. Statistical significance with $p < 0.05$ was used. The costs of each T-SPOT.*TB*® assay was applied to the number of TB cases diagnosed to give indicative costs per case of TB detected: this was done by dividing the relative total cost of the tests by the number of new cases of TB identified.

Results

A total of 188 unique cases were identified originating from the medical oncology clinic with baseline testing for LTBI using the T-SPOT.*TB*® assay. Thirteen of the screened were excluded from analysis because they did not have an established cancer diagnoses, there were 19

duplicate tests thus leaving a final sample size of 175 screened subjects during the study period. There were eight screen-positives for LTBI representing 4.5% of the total sample with an incidence density of 0.0457 cases/10-month study period.

Sample Demographics

Sociodemographic characteristics of the sample are summarized in Table 1. The sample ranged in age between 33-94 years (mean 67.74, SD 10.02) and was predominately male at 95.4% (n=167). Racial/ethnic groups represented included 45.7% (n=80) Caucasians, 53.7% (n=94) African Americans, and 0.6% (n=1) American Indian. The service eras represented in the sample included 64% (112) Vietnam, 13.1% n=23%) Post-Vietnam, 6.9% (n=12%) Persian Gulf, 6.3% (n=11) Korean, 5.1% (n=9) Post-Korean, 2.3% (n=4) World War II, and 1.7% (n=3) from other non-service era categories. The screen-positive cohort included eight males equally divided between the Caucasian and African American racial/ethnic groups. The median age was 69.75 for screen-positive and 67.64 for the screen-negative cohorts with no statistically significant difference in age between the cohort groups using the Independent-Samples Mann-Whitney U Test (p=.499). The majority of screen-positives were from the Vietnam service era (62.5%, n=5) consistent with findings from the screen-negative group (64.1%, n=107).

Cancer Specific Characteristics

Cancer specific characteristics of the sample are summarized in Table 2. Of the total patients screened, the most frequent cancer diagnoses included hematologic, lung, rectal/anal/colon, prostate and head and neck. Of the eight screen-positive cohort, there were three (37.5%) prostate cancers, two (25%) rectal/anal/colon cancers, one (12.5%) hematologic cancer, one (12.5%) lung cancer and one (12.5%) head and neck cancer. In comparison, the 167 screen-negative cohort had 69 (41.3%) hematologic cancers, 36 (21.6%) lung cancers, 10 (6.0%)

rectal/anal/colon cancers, nine (5.4%) prostate cancers, nine (5.4%) head and neck cancers, and 34 (20.3%) in other cancer categories. The screen-positive cohort had six (75%) with advanced stage 3-4 cancer in comparison to the screen-negative cohort with 83 (49.7%) advanced stage 3-4 cancer.

Risk Factors

High-risk categories for exposure and reactivation of LTBI are summarized in Table 3. The screen-positive cohort included 25% (n=2) patients with the comorbid condition of diabetes, 75% (n=6) with no coexisting comorbid medical conditions, and 12.5% (n=1) with low body weight < 10% ideal. High-risk behaviors of intravenous drug use (IVDU) and incarceration were 12.5% (n=1) and alcohol use was 25% (n=2) in the screen-positive cohort. Imaging findings on chest radiograph and/or computerized axial tomography (CAT) were abnormal in half (n=4) of the screen-positive cohort however there were no fibrotic changes consistent with prior past TB. No cases of active TB disease were identified. In comparison, the screen-negative cohort revealed a 31.7% (n=53) incidence of diabetes and more wide-ranging comorbid conditions and multimorbidity. Alcohol use was higher in the screen-negative cohort at 30.5% (n=51) in comparison to the screen-positive group. High risk behaviors of IVDU was lower at 4.2% (n=7) as well as history of incarceration at 3.6% (n=6).

Indeterminant Results

Valid T-SPOT.*TB*® test results (i.e. positive or negative) were available for 164 of the 175 total sample. Of the total tested, 11 (6.3%) were reported indeterminant or insufficient peripheral blood mononuclear cells (PBMC). A summary of indeterminant test results, re-test results, confirmatory tuberculin skin test (TST) results, and other clinical information are provided in Figure 1. A total of four of the 11 indeterminant test results were retested later by

clinicians. Valid results were obtained in two (50%) of these cases. Confirmatory testing with TST was performed in one case with a positive TST by induration threshold for LTBI. Of the 11 indeterminant results, six (63%) were not retested. Age was not a statistically significant factor for indeterminant test results ($p = .11$). Among the 11 indeterminant test results with clinical information on cancer staging, 81.8% (n=9) cases had advanced cancer stage 4 diagnoses which included prostate (n=3), breast (n=1), lung (n=1), rectal (n=1), multiple myeloma (n=1) and lymphoma (n=1) and head and neck (n=1).

LTBI Treatment

A summary of LTBI treatment groups are summarized in Table 4. There were eight screen-positives for LTBI. Of the total screen-positives, two (25%) were not considered for treatment based on poor clinical prognosis with hospice services or death noted in the chart. One (12.5%) was considered a poor treatment candidate based on a preexisting psychiatric history, in addition to consideration that his cancer diagnosis was not specific for high-risk TB reactivation. Five (62.5%) were treated in the Infectious Disease Clinic. Treatment regimens for LTBI included INH 6-months or INH 9-months regimens. Two subjects (40%) were prescribed INH 6-months treatment courses and three subjects (60%) were prescribed INH 9-months treatment courses. Of the INH 6-months treatment course cohort, two (100%) completed the course with no adverse reactions. Of the INH 9-months treatment course cohort, two (68%) remain in active treatment and one (22%) ended treatment early due to adverse events of isolated bilirubin.

Cost Efficacy

The cost efficacy of LTBI screening in the cancer subpopulation sample were evaluated by the number needed to screen (NNS) to detect a single case of LTBI. In addition, cost estimates were calculated based on material cost per T-SPOT.*TB*® assay per individual and

aggregate as well as costs per LTBI case detected. The costs of screening using the T-SPOT.*TB*® assay and NNS to detect a single case are presented in Table 5. The material cost for the T-SPOT.*TB*® assay is approximately $50 per test with an aggregate cost for the 175 screened plus the four additional T-SPOT.*TB*® assays for indeterminant test results yield an aggregate cost of $8950. The cost per detected case of LTBI is $1,118.75. The NNS to detect a single case of LTBI in this sample is 22 patients.

Discussion

This study sought to examine the relationship of LTBI in Veterans with a cancer diagnosis who were undergoing cancer treatment. The hypothesis was that Veterans would have a higher prevalence of LTBI given their propensity for military deployment to TB endemic countries during their military careers. The findings of a 4.6% prevalence of LTBI in the sample supports the null hypothesis. This prevalence is equivalent to findings from the 2011-2012 NHANES survey data, with an estimated prevalence is 4.4%- 4.8%.[13] However, this finding must be interpreted in the context of the small screen-positive sample size. Host characteristics of the screen-positive cohort reflected older age in the sixth through eight decades, all males with a majority from the Vietnam service era. Female veterans were less represented in the sample comprising only 4.6% of the total cancer subpopulation screened. Given the small screen-positive sample, we were unable to stratify for important high-risk behaviors including alcohol, substance abuse, incarceration and underlying medical co-morbidities.

Cancer specific characteristics of the screen-positive cohort included hematologic, lung, head and neck, prostate and rectal/anal/colon cancers. Prostate cancer comprised 37.5% of screen positive cohort, raising the question if this group should be included in the screening. The literature supports that individuals with hematologic malignancies, head and neck cancer and

lung cancers are at the highest risk (nine-fold higher rate) of developing active TB compared with the general population with other solid tumor cancers presenting a moderate risk in foreign-born.[20] Finally, findings from this study further support the need for risk-stratified LTBI screening in this population to avoid screening of individuals that would not be treatment candidates based on advanced disease states or inability to tolerate treatment if screen-positive.

The vast majority of T-SPOT.*TB*® tests performed during our study yielded valid results that were either positive or negative. Only a small portion of T-SPOT.*TB*® test results were indeterminant (n=11). Among the factors considered influencing indeterminant test results, including older age and advanced stage cancer contributing to cellular immunosuppression; no relationship can be demonstrated with these data. Re-testing of indeterminant test results was performed in four of the eleven results with 50% valid results on re-test. A tuberculin skin test (TST) was performed in only one case with positive results by induration threshold for defining TB infection and no meaningful conclusions can be formulated from these data. Seven of the 11 indeterminant test results were not repeated, perhaps due to clinical decisions based on advanced metastatic disease in these cases. Re-testing of indeterminant test results are necessary to draw any meaningful conclusions from the results. In studies with immunosuppressed cancer patients undergoing cytotoxic and targeted antineoplastic drugs, T-SPOT.*TB*® assays have demonstrated interpretable results and maintenance of test sensitivity and performance.[24,25]

Based on additional clinical parameters, only five of the eight T-SPOT.*TB*® positive subjects were considered for treatment of LTBI. Of these, all were offered treatment with isoniazid at either six or nine-month duration. Overall treatment was well tolerated with one early discontinuation due to isolated elevated bilirubin. There were no incidences of hepatitis.

The NNS to detect a single case of LTBI was 22 in this sample at an overall cost of $1,118.75 per case detected. The NNS can be utilized to provide guidance in setting priorities in the local context. Cost efficacy must be considered in the context of costs associated with TB exposure contact investigations. The 2012 TB exposure contact investigation identified a total of 218 exposed patients and staff (142 staff and 76 patients) with the source patient originating from the oncology clinic. At a cost of $50 per T-SPOT.*TB*® assay at baseline and repeat testing at 8-10 weeks with a second T-SPOT.*TB*® test, the screening costs of this contact investigation is estimated to be $21,800 which is a 20-fold increase from the current practice of targeted screening of all cancer patients. Of the 2012 TB contact exposure, no conversions occurred among staff, however four patients tested positive and one tested indeterminant. All were referred to the Infectious Disease Service for evaluation and treatment which incurs additional costs not considered in this discussion.

This study provides baseline estimates of the prevalence of LTBI in Veterans with cancer at our medical center. Screening and treatment data provides an opportunity to evaluate the screening program effectiveness and identify gaps. These data add to the knowledge of the local epidemiology and can be used to further risk stratify screening to cancer-specific diagnoses. The study results suggest that the T-SPOT.*TB*® test maintains its sensitivity and performance in immunocompromised patients.

Strengths and Limitations

This study is the first to provide an estimate of the burden of LTBI among Veterans with cancer advancing understanding of the local prevalence. It provides data to assess quality of adherence to current practice guidelines for targeted LTBI screening and treatment. Several study design limitations are identified. First, use of a convenience sampling method within the

specified time frame generated a small screen-positive sample size. Females were under represented in the sample limiting generalizability. In addition, the single-center setting with the select cohort of the Veteran population who are mostly males further limits generalizability to non-VA healthcare systems.

Implications for Practice

This study evaluated the recently implemented clinical practice guidelines for targeted screening of LTBI in the cancer population adding to the understanding of local prevalence, T-SPOT.*TB*® reliability and LTBI treatment acceptance and tolerability in the cancer population. Findings suggest that the T-SPOT.*TB*® test maintains its sensitivity and performance in immunocompromised patients. The findings identified gaps and presented opportunities to address process issues of screening duplications, indiscriminate screening of patients with non-cancer diagnoses, and screening in situations such as advanced stages of cancer with short life expectancy in which patients would not be treatment candidates. These data can be used to provide feedback to oncology clinic providers to alter practice toward a risk-stratified LTBI screening approach. These changes may result in overall reduced costs associated with targeted TB screening. In addition, findings can be used to guide policy development for evidence-based risk-stratified screening for an individualized approach to screening.

Conclusions

The current study adds to our understanding of the epidemiology of LTBI in Veterans with concomitant cancer diagnoses. Data from this pilot program study supports that targeted screening of LTBI in the high-risk cancer population yields early diagnosis and opportunity for treatment. Targeted screening and treatment in this high-risk population may result in prevention of reactivation disease with associated reduction in healthcare-associated transmission of TB

among patients and staff in the clinic as well as the community. Identified gaps including testing of low-risk and indiscriminate testing of patients without cancer provide an opportunity for process improvements to refine risk-stratified screening in the target population. Targeted screening and treatment of LTBI in cancer-specific diagnoses is well supported in the literature and is a crucial intervention to strengthen TB control and elimination.

Declaration of Conflict of Interest

All authors declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Table 1

Sociodemographic Characteristics of T-SPOT.TB® Screened Patients

Demographics	Total Screened n = 175	Screen-Negative n = 159	Screen-Positive n = 8	Indeterminant Results n = 8	*p* value
Median age (range)	67.7 (33-99)	69 (33-99)	70.5 (48-84)	73.5 (57-81)	.28
Gender					
Male	167 (95.4)	151 (86.29)	8 (4.57)	8 (4.57)	
Female	8 (4.57)	8 (4.57)			
Race/ethnicity					
African American	94 (53.7)	72 (45.3)	4 (50.0)	4 (50.0)	
Caucasian	80 (45.7)	86 (54.1)	4 (50.0)	5 (50.0)	
American Indian	1 (0.6)	1 (0.6)			
Service Era					
WWII	4 (2.4)	4 (2.4)			
Vietnam	112 (64)	107 (64.1)	5 (62.5)	5 (62.5)	
Post-Vietnam	23 (13.1)	23 (13.8)		1 (12.5)	
Korean	11 (6.3)	9 (5.4)	2 (25.0)	1 (12.5)	
Post-Korean	9 (5.1)	9 (5.4)		1 (12.5)	
Persian Gulf	12 (6.9)	11 (6.6)	1 (12.5)		
Gulf War	1 (0.6)	1 (0.6)			
Other[a]	3 (1.7)	3 (1.7)			

Note. Other = ChampVA and unknown.

Table 2

Cancer Specific Characteristics of T-SPOT.TB® Assay Screened Patients

	T-SPOT.TB® Screen	
	Positive	Negative
Characteristic	n (%)	n (%)
Cancer Type		
Hematologic	1 (12.5)	69 (41.3)
Lung	1 (12.5)	36 (21.6)
Rectal/Anal/Colon	2 (25.0)	10 (6.0)
Prostate	3 (37.5)	9 (5.4)
Head & Neck	1 (12.5)	9 (5.4)
Hepatocellular		2 (1.2)
Breast		6 (3.6)
Melanoma		4 (2.4)
Pancreatic		4 (2.4)
Renal		3 (1.8)
Unknown primary		3 (1.8)
Gastric		2 (1.2)
Sarcoma		2 (1.2)
Testicular		1 (0.6)
Biliary		1 (0.6)
Glioblastoma		1 (0.6)
Penile		1 (0.6)
Bladder		1 (0.6)
Cancer Stage		
Stage 1		19 (11.4)
Stage 2	1 (12.5)	19 (11.4)
Stage 3	2 (25.0)	27 (16.2)
Stage 4	4 (50.0)	56 (33.5)
Unrecorded	1 (12.5)	47 (27.5)

Note. n = frequency; % = percentage.

Table 3

High Risk Categories for LTBI Exposure and Reactivation

High risk because of underlying medical conditions	Screen-Positive n (%)	Screen-Negative n (%)
No Coexisting High Risk Comorbidities	6 (75)	
Diabetes	2 (25)	53 (31.7)
Hemodialysis		2 (1.2)
HIV		5 (5.0)
Gastrectomy		3 (1.8)
IMID		3 (1.8)
Diabetes + Hemodialysis		2 (1.2)
Diabetes + HIV		1 (0.6)
HIV + Hemodialysis		1 (0.6)
Low Body Weight (<10% ideal)	1(12.5)	23 (13.8)
High risk because of increased likelihood of TB exposure		
History IVDU		
Yes	1 (12.5)	7 (4.2)
No	7 (87.5)	160 (95.8)
Alcohol Use	2 (25.0)	51 (30.5)
Yes	2 (25)	51 (30.5)
No	6 (75)	116 (69.5)
History of Incarceration		
Yes	1 (12.5)	6 (3.6)
No	4 (50.0)	13 (7.8)
Unrecorded	3 (37.5)	148 (88.6)
CXR/CT		
Abnormal – no fibrotic changes	4 (50)	
Normal	4 (50)	

Note: n = frequency. % = percent. HIV = human immunodeficiency virus. IMID = immune mediated inflammatory disease. IVDA = intravenous drug use. High risk comorbid conditions screened for include: diabetes, chronic renal failure, gastrectomy, solid organ transplant, alcohol use, injection drug use, low body weight < 10% ideal.

Table 4

LTBI Screen-Positive Cancer Cohort Treatment Groups

	LTBI Treatment			
	Accept		Decline	Not Recommended
	n (%)		n (%)	n (%)
	5 (62.5)		1 (12.5)	2 (25.0)
	6-INH	9-INH		
	n (%)	n (%)		
Adverse Effects[a]		1 (20)		
Treatment Completion	2 (40)			
Treatment Active		2 (40)		
Treatment Early Discontinuation		1 (20)		

Note. LTBI = latent tuberculosis infection. 6-INH = Isoniazid 6 months. 9-INH = Isoniazid 9 months.

[a] Adverse effects of isolated bilirubin.

Table 5

T-SPOT.TB® screening costs and NNS to detect one LTBI case in cancer subpopulation

Number screened	Repeat Indeterminant Tests	Number LTBI diagnosed	NNS to detect one case	Aggregate costs (USD)	Cost per case detected (USD)
175	4	8	22	$8950	$1,118.75

Note. NNS = Number needed to screen to detect one case (total number screened / number of cases identified); USD = United States dollars.

Figure 1. Indeterminant T-SPOT.*TB*® Test Results

Initial Testing Results	Re-test T-Spot.*TB*® Results				No Repeat Testing	Confirmatory Positive TST	Outcome
Indeterminant	Indeterminant	Insufficient PMNs	Positive	Negative			
x					x		Death Prostate Stage 4
x	x					x	Treatment declined Prostate Stage 4
x			x				Hospice Head & Neck Stage 4
x				x			BMT evaluation
Insufficient PMNs							
x					x		Hospice Breast Stage 4
x		x					Death Cytopenia Vasculitis
x					x		Death Stage 4 Multiple Myeloma
x					x		Lung Ca Stage 4
x					x		Rectal Stage 4
x					x		Stage 4 Prostate Ca
x					x		Death Lymphoma Stage 4

Note: PMN = Peripheral Mononuclear Cells

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