ORIGINAL ARTICLE

Lower Incidence of Esophagitis in the Elderly Undergoing Definitive Radiation Therapy for Lung Cancer

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Received 31 October 2016; revised 14 November 2016; accepted 15 November 2016

ABSTRACT

Introduction: Most patients with lung cancer are elderly and poorly represented in randomized clinical trials. They are often undertreated because of concerns about their ability to tolerate aggressive treatment. We tested the hypothesis that elderly patients undergoing definitive lung radiation might tolerate treatment differently than younger patients.

Methods: A total of 125 patients who underwent definitive lung radiotherapy were identified from a prospective institutional database (University of Michigan cohort). Logistic regression modeling was performed to assess the impact of age on esophagitis grade 2 or higher or grade 2 or higher and pneumonitis grade 3 or higher or grade 2 or higher, with adjustment for esophageal and lung dose, respectively, as well as for chemotherapy utilization, smoking status, and performance status. The analysis was validated in a large cohort of 691 patients from the Michigan Radiation Oncology Quality Consortium registry, an independent statewide prospective database.

Results: In the University of Michigan cohort, multivariable regression models revealed a significant inverse correlation between age and rate of esophagitis for both toxicity levels, (adjusted OR = 0.93 for both models and 95% confidence intervals of 0.88–0.98 and 0.87–0.99), with areas under the curve of 0.747 and 0.721, respectively, demonstrating good fit. This same association was noted in the Michigan Radiation Oncology Quality Consortium cohort. There was no significant association between age and pneumonitis.

Conclusions: There is a lower incidence of esophagitis with increasing age even after adjustment for use of chemotherapy. This is a novel finding in thoracic oncology. No age dependence was noted for pulmonary toxicity. The elderly are able to tolerate definitive thoracic radiation well and should be offered this option when clinically warranted.

Keywords: Elderly; Esophagitis; Lung Cancer; Radiation; Toxicity

Introduction

Cancer is a disease of the elderly, with more than 60% of malignancies diagnosed in men and women older than 65 years.[1,2] As the elderly population in the

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Drs. Soni and Boonstra equally contributed to this work.

Disclosure: Dr. Boonstra has funding from CTI BioPharma. Dr. Schipper has a consulting role for Armune Bioscience and Hygieia Sciences. Dr. Matuszak has funding from Varian and the National Institutes of Health. Dr. Kong has funding and honoraria from Varian. Dr. Ten Haken received travel support from Varian. Dr. Kalemkerian has funding from OncoMed, Pfizer, Astex Pharmaceuticals, GlaxoSmithKline, and Millennium. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2016.11.2227

United States continues to increase, the cancer burden will escalate as well. It is estimated that from 2010 to 2030, there will be a 45% increase in the overall cancer incidence that will be disproportionately accounted for by the elderly population.[3] However, elderly patients are poorly represented in the clinical trials that have defined the standard of care for cancer treatment. There is a significant gap in our understanding of the risks and benefits of managing elderly patients with cancer with standard treatment regimens.

Lung cancer is the leading cause of cancer death for both men and women in the United States.[4] More than 65% of patients in whom lung cancer is diagnosed are older than 65 years.[5] Paradoxically, the average median age of patients on phase III randomized controlled trials for locally advanced NSCLC is 61 years,[6] even though approximately half of the patients in the United States in whom lung cancer is diagnosed are older than 70.[7,8] This raises concern about how applicable these trials are to older patients and poses a challenge for the oncologists who are managing the care of these patients. A large Surveillance, Epidemiology, and End Results–Medicare analysis of patients older than age 66 with locally advanced NSCLC demonstrated that approximately one-third receive no treatment.[9] Even elderly patients with good performance status and lack of comorbidities are less likely than younger patients to be offered aggressive treatments on the basis of age.[10] Given the concern for decreasing functional reserve in older patients, providers question the elderly's ability to tolerate standard cancer treatments.[11] Although the elderly are no different than younger patients in their willingness to accept aggressive treatment, they are less likely to sacrifice quality of life for incremental improvements in survival.[12] However, there is a paucity of data to inform toxicity in the elderly population, perpetuating the phenomenon of ageism in cancer management.

Radiotherapy is a key component of the definitive treatment regimen for locally advanced NSCLC. Esophagitis and radiation pneumonitis are potentially life-altering toxicities of thoracic radiation. There are limited data on the impact of age on incidence of these toxicities. We therefor, analyzed the association between age and radiation-induced toxicities in patients enrolled on our institutional prospective lung cancer protocols. We then sought to validate our results in an independent cohort of patients treated on a large observational study as part of a statewide radiation oncology consortium. We hypothesized that increasing age may predict higher rates of radiation-induced esophageal and pulmonary toxicity.

Methods

Primary Study Population

As part of an institutional review board–approved study, patients undergoing definitive radiation for lung cancer with or without chemotherapy from 2004–2013 were identified from a prospective institutional database in which patients of all ages were eligible for inclusion (the University of Michigan [UM] cohort). Patients were excluded if they were treated with stereotactic body radiation therapy (SBRT) or if complete dose-volume histograms (DVHs) were not available for review. Clinical records were reviewed to identify patient- and tumor-specific characteristics, including age, sex, smoking status, Karnofsky performance status (KPS), tumor histological subtype, tumor stage, and utilization of chemotherapy. Treatment plans were individually reviewed to collect actual dose received by the esophagus and lungs. All cases in the database utilized modern photon dose calculations (Analytical Anisotropic Algorithm [Varian Medical Systems, Palo Alto, CA]) and voxel-based biological corrections to equivalent dose in 2-Gy fractions (EQD2), using the linear quadratic model ($\alpha/\beta = 10$ Gy for esophagus and $\alpha/\beta = 3$ Gy for lung), to account for variable dose per fraction prescriptions. All organs at risk were defined by using the Radiation Therapy Oncology Group Lung Atlas.[13] Esophageal dose was primarily defined as the minimum dose to the most exposed 2 cm^3 of the esophagus (D2cc), and lung dose was defined as the volume of both lungs not involved with gross disease that received at least 20 Gy, both of which have been previously correlated with toxicity. Secondary dosimetric parameters were generalized equivalent uniform dose (gEUD) with $a = 5$ for the esophagus (a single dose value that is a biologically equivalent representation of the dose distribution across the organ) and mean dose for the lungs. As already noted, all dose values are in EQD2.

All patients had a toxicity evaluation by a radiation oncologist weekly during their radiation treatment. Follow-up schedules after completion of treatment varied; however, all patients were evaluated at least once in the first month after treatment, and every 3 months for the first 6 months. Physician-reported toxicity was collected at each of these visits and graded according to Common Terminology Criteria for Adverse Events, version 3.0, for esophagitis and pneumonitis. Maximum toxicity grade was used for this analysis.

Secondary Study Population

A second, independent cohort of patients with lung cancer was identified from the Michigan Radiation Oncology Quality Consortium registry (MROQC cohort).