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Intensity modulated radiotherapy for stage III non-small cell lung cancer in the United States: Predictors of use and association with toxicities☆

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ABSTRACT

Background: Intensity modulated radiotherapy for stage III lung cancer has become commonplace in the United States in the absence of randomized controlled trials. We used a large, population-based database to determine which factors led to increased utilization of IMRT and to evaluate associations of IMRT with toxicities.
Methods: The Surveillance, Epidemiology, and End Results (SEER)-Medicare records identified 3986 individuals aged 66 years or older diagnosed with stage III lung cancer between 2001 and 2007 and treated with IMRT or 3D conformal radiotherapy. Predictors of IMRT use were determined using logistic regression. Associations of IMRT use with diagnosis codes for radiation-related toxicities were evaluated with multivariate proportional hazards regression and propensity-score matching.
Results: Among the 3986 patients studied, the median age was 75 years, 54.1% were male, and 62% had IIIA disease. Two hundred and fifty seven (6.5%) patients received IMRT, with use increasing from 0.5% in 2001 to 14.7% in 2007 ($P < 0.001$). Key predictors of IMRT delivery included increasing year of diagnosis and treatment in a freestanding center (odds ratio, 2.10; 95% confidence interval [CI], 1.59–2.77, $P < 0.001$); tumor size, stage, and number of radiotherapy fractions delivered were not associated with IMRT use. IMRT use was not associated with a higher burden of lung or esophagus toxicities when compared to 3DCRT.
Conclusion: These findings suggest that practice environment strongly influenced adoption of IMRT for lung cancer. Patient and tumor factors were not significant predictors of IMRT use. Esophagus and lung toxicity rates were similar between IMRT and 3DCRT.

1. Introduction

The incidence of stage III non-small cell lung cancer (NSCLC) is likely to rise considerably in the coming decade due to demographic trends [1]. The majority of these patients will require radiation for definitive therapy or as an adjuvant to surgical management [2–4]. In contemporary practice, radiotherapy is mostly delivered with one of two technologies: 3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). In 3DCRT, axial imaging is used to target a tumor with several radiation fields, whose sizes, shapes, and angles of entry are selected by a radiation oncologist. With IMRT, the radiation oncologist instead delineates a volume containing the tumor. This volume is then targeted by many small beamlets whose contributions are determined by computer algorithm. Given the disparity in how each technique is implemented, it cannot be taken for granted that the two technologies will yield equivalent outcomes.

There are no prospective trials comparing the two techniques for any thoracic malignancy. In the absence of phase III data, one hopes that sound clinical rationale accounts for the choice of radiotherapy, but other factors may play a role. These factors include perceived dosimetric advantages [5,6], accessibility of technology [7], financial considerations [8,9], a desire to escalate dose [10], or a need to meet normal organ dose constraints [11–14]. Determining which of these issues influences everyday practice is important as the

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selection of radiation technique can have far-reaching consequences for patients and the health care system.

Population-based data can generate hypotheses regarding the factors that promote or slow the adoption of advanced technologies. Furthermore, this data can be used to evaluate the clinical impact of those technologies after their introduction. To that end, we performed a population-based analysis using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to identify predictors of IMRT use and associations of IMRT use with radiation-related toxicities among patients with stage III NSCLC diagnosed from 2001 to 2007. Specifically, we sought to determine the extent to which clinical versus non-clinical factors influenced adoption of IMRT and to compare acute pulmonary and esophageal toxicities associated with IMRT versus 3DCRT.

2. Methods

2.1. Data source and study sample

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database captures claims data for cancers diagnosed in Medicare beneficiaries who reside within 16 geographic catchment areas representing 26% of the US population. The case ascertainment rate for the SEER data is approximately 98%[15]. In this study, demographic and tumor characteristics for incident malignancies diagnosed from January 1, 2001 to December 31, 2007 were linked to Medicare claims from January 1, 2000 to December 31, 2009.

From 2001 to 2007, 113,681 patients aged ≥66 years without prior malignancy were diagnosed with NSCLC and reported in the SEER-Medicare cohort. From this population, patients with pathologically confirmed, stage III disease were selected for analysis (Supplementary Table 1). Patients were excluded from this study if they did not have complete Medicare Part A and B records from 12 months prior to diagnosis to 6 months after diagnosis (or until death); or if they had health maintenance organization (HMO) coverage within the same timeframe (Supplementary Table 1). Patients with any second cancer diagnosed within 6 months of the index lung cancer were also excluded as billing records could not discriminate between procedures performed for the index cancer versus the second cancer.

Because our goal was to compare patients treated with 3DCRT and IMRT, patients treated with other radiation modalities (proton therapy, brachytherapy, and 2-D radiotherapy) were excluded from the analysis. Finally, to ensure that radiotherapy was not directed at metastatic targets, we excluded patients with diagnosis codes for brain metastasis, adrenal, bone or liver metastases submitted in the period 2 weeks before the date of diagnosis until the start of radiotherapy. These criteria yielded a final sample of 3986 patients (Supplementary Table 1).

2.2. Treatment strategies

Medicare claims using International Classification of Diseases, 9th Revision (ICD-9) and Clinical Modification and Current Procedural Terminology/Healthcare Common Procedure Coding System (CPT) codes were utilized to extract claims for diagnostic procedures, treatments, and toxicity outcomes. Therapies occurring within 6 months of diagnosis were considered to be part of the initial treatment strategy (Supplementary Table 2). We classified patients as having received IMRT if a claims code confirming actual delivery of intensity-modulated treatment (77418, 0073T, G0174) was present. Three-dimensional conformal radiation was defined by the presence of both a claim for "three dimensional reconstruction of the tumor volume" (77,295) and non-IMRT external beam radiation delivery (77,402–77,416) [16]. The number of radiotherapy fractions was calculated by counting the number of unique CPT codes for radiation delivery using a time window from the start of radiation delivery until 3 months thereafter. Based on treatment claims, the overall treatment strategy was stratified into four categories: trimodality therapy, chemotherapy and radiation, surgery and radiation, and radiation alone.

2.3. Other covariates

Patient demographic variables from the SEER data included age at diagnosis, race, and gender. Baseline patient characteristics were determined using Medicare claims from an interval of 12 months before to 1 month after diagnosis [17]. The Charlson comorbidity index with Klabunde modification was determined from ICD-9 codes using published methods [18–20]. Chronic obstructive pulmonary disease (COPD) (491.2x, 493.2, 496) was not included in the index and was reported separately. Patients were classified as oxygen users if durable medical equipment claims included oxygen equipment. Using the method of Davidoff et al., a performance status covariate was generated using claims for medical assistance services or devices (canes, walkers, home hospital beds, or home health care) [21].

Tumor characteristics extracted from the SEER data included AJCC version 6 stage (IIIA, IIIB), laterality, and lung subsite [22]. Tumor size classifications are based upon maximum length of the tumor in centimeters and stratifications were applied using AJCC version 7 T-stage thresholds; invasion of local structures is not reflected in the tumor size classifications. To adjust for stage migration, the use of mediastinal sampling and positron emission tomography (PET) within a time period extending from 2 weeks prior to diagnosis to the start of radiotherapy were assessed (Supplementary Table 2).

Practice environment characteristics reflective of the patient's county of residence were evaluated. Year of diagnosis, geographic region, and whether the setting was urban or rural were obtained from the SEER data. County-level density of radiation oncologists was determined using the Area Resource File for 2001–2005 in accordance with published methods [8]. The type of treatment center was determined from claims for radiation delivery, also in accordance with published methods [8,23,24].

2.4. Toxicity outcomes

Toxicities were determined from Medicare claims (Supplementary Table 3). We evaluated the incidence of lung toxicity using two definitions. A narrow definition only included the ICD-9 diagnosis code for "unspecified acute pulmonary toxicity due to radiation". The broad definition also included claims codes for nonspecific lung infiltrates (i.e., not attributed to volume overload and no infectious organism identified). Acute esophagus toxicity was defined using diagnosis codes for esophagitis, dehydration, feeding tube placement, and mucositis. These components were analyzed individually and in aggregate.

In accordance with the natural history of radiation toxicities, toxicities were scored if the relevant claims code was submitted within 8 months after the start of radiotherapy in order to capture 2 months of radiation therapy and 6 months of follow-up. Sensitivity analyses were performed wherein the 8-month cutoff was shortened to 4 months and extended to 14 months. Due to a low number of toxic events, chronic toxicities were not able to be robustly studied using this data set.

2.5. Statistical analysis

Predictors for IMRT use were determined using logistic regression. Bivariate associations at a significance level of 0.20 or less