*Original Article*

# The Refusal of Palliative Radiation in Metastatic Non-Small Cell Lung Cancer and Its Prognostic Implications

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## Abstract

**Context.** Patients with metastatic non-small cell lung cancer (NSCLC) have limited survival. Population studies have evaluated the impact of radiation refusal in the curative setting; however, no data exist concerning the prognostic impact of radiation refusal in the palliative care setting.

**Objectives.** To investigate the patterns of radiation refusal in newly diagnosed patients with metastatic NSCLC.

**Methods.** Patients with Stage IV NSCLC diagnosed between 1988 and 2010 were identified in the Surveillance, Epidemiology, and End Results database. Univariate and multivariate analyses were used to identify predictors for refusal of radiation and the impact of radiation and refusal on survival in the palliative setting.

**Results.** A total of 285,641 patients were initially included in the analysis. Palliative radiation was recommended in 42% and refused by 3.1% of patients. Refusal rates remained consistent across included years of study. On multivariate analysis, older, nonblack/nonwhite, unmarried females were more likely to refuse radiation ($P < 0.001$ in all cases). Median survival for patients refusing radiation was three months vs. five months for those receiving radiation and two months for those whom radiation was not recommended.

**Conclusion.** Patients with metastatic NSCLC who refuse recommended palliative radiation have a poor survival. Radiation refusal or the recommendation against treatment can serve as a trigger for integrating palliative care services sooner and contributes greatly to prognostic awareness. Further investigation into this survival difference and the factors behind refusal are warranted. J Pain Symptom Manage 2015;49:1081–1087. 

***Key Words***

*Palliative radiation, Stage IV, non-small cell lung cancer, refusal*

## Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) involving most cases.[1] Approximately 55% of patients with NSCLC have metastatic disease at the time of diagnosis.[2] Common sites of metastasis include brain, bones, liver, and nonregional lymph nodes.[3] Because of these varied presentations, metastatic NSCLC represents a very heterogeneous disease, and treatment recommendations are influenced by histology, tumor burden, performance status, comorbidities, and patient-specific goals of care.

Systemic chemotherapy remains the mainstay of treatment for metastatic disease. Multiple randomized trials have demonstrated an overall survival (OS) benefit with the addition of chemotherapy in eligible treatment-naïve patients.[4] Local treatment modalities

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such as radiation therapy (RT) are used to palliate active or impending symptoms in critical organs including the central nervous system and lungs.[5–10] The known benefits of palliative RT include improvements in quality of life (QOL)[11,12] as a result of alleviation of pain and respiratory and neurologic symptoms. Whether palliative RT impacts OS by improving QOL and preventing life-threatening sequelae remains unclear.

There are times when up-front palliative RT is recommended but patients refuse treatment. Given the known benefits of palliative RT, potential barriers to care and how refusal impacts survival in the metastatic setting are important issues worth investigating. This can assist in future decision making and contributes greatly to prognostic awareness. Here, we use the Surveillance, Epidemiology, and End Results (SEER) database to investigate the patterns of radiation refusal in newly diagnosed patients with metastatic NSCLC.

## Methods

Patients with Stage IV distantly metastatic NSCLC diagnosed between 1988 and 2010 were identified in the publicly available SEER database resulting in 285,641 records available for analyses. As all the information in the SEER database is deidentified, informed consent by the study participants was unnecessary before analysis.

Palliative RT was defined using the variable for radiation in SEER in combination with American Joint Committee on Cancer Stage IV (M1) NSCLC coding. Patients were considered recipients of palliative RT if coded during their disease course. Patients with radiation marked none or unknown were excluded from analysis. This analysis included only patients who were 18 years and older and who either received radiation defined as beam or combination beam, or refused radiation. Patients receiving implants or isotopes, radioisotopes, and radioactive implants were excluded. Patients diagnosed at autopsy were excluded from this analysis.

### *Statistical Analysis*

Statistical analysis was performed using R, version 3.0.2 (R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, http://www.R-project.org) (last change on September 25, 2013). Univariate statistics were run to quantify the characteristics of the patient population. Continuous variables were compared using the Wilcoxon rank sum test, and categorical variables were compared using the Chi-squared test. All univariate statistical tests were two-tailed, with a *P*-value of 0.05 or less considered significant.

Logistic regression was performed to model the probability of a patient who refused radiation. An immortal time bias was conducted by restricting the sample size to individuals who did not reach a two or more month survival point in the radiation recommended and refused groups.[13] Adjusted Kaplan-Meier (KM) estimates were performed to calculate the survival time for those patients who received radiation and for those who refused radiation. The median survival time is the time when approximately 50% of the patient population has died. The KM curve is based on an univariate survival fit. A Cox proportional hazards model was performed between the two groups, but all variables failed to meet significance. The median survival times are for overall mortality.

To evaluate constancy of these findings over time, the entire analysis was re-examined using patients diagnosed between January 1, 2000 and December 31, 2010. Results from the repeat analysis were compared with those of the original to assess for differences in a more modern cohort.

## Results

A total of 285,641 patients who were diagnosed with American Joint Committee on Cancer Stage IV (M1) NSCLC between Years 1988 and 2010 met our inclusion criteria. Patient demographics including age, gender, marital status, and race are summarized in Table 1. Palliative RT was delivered to 119,751 patients (42%) and recommended but refused by 3795 patients (3.1%). A total of 162,096 (56.7%) patients with Stage IV NSCLC were not recommended to undergo external RT. Univariate analysis of patient demographics showed significant differences in refusal based on age, sex, race, and marital status (Table 1). Patients who were older ($P < 0.001$), female ($P < 0.001$), nonblack/nonwhite ($P < 0.001$), and unmarried ($P < 0.001$) were more likely to refuse palliative RT. On multivariate logistic regression analysis, each of these demographics remained significant predictors for refusal. With this model, older patients are more likely to refuse radiation; a 75-year-old patient is 2.5 times as likely to refuse radiation compared with a 55-year-old patient (odds ratio [OR] 2.521). Females are more likely than men to refuse radiation (OR 1.111). Blacks and whites refuse radiation approximately the same, whereas other races are more likely to refuse radiation (OR 1.240). Nonmarried individuals are more likely to refuse radiation than married individuals (OR 1.763) (Table 2).

KM curves were generated to compare OS of patients who received radiation with those who refused (Fig. 1). The individuals who refused palliative radiation had worse median OS (three vs. five months, $P < 0.001$) compared with those who received