Original Article

# Radiation Therapy at the End of Life in Patients With Incurable Nonsmall Cell Lung Cancer

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**BACKGROUND:** Receipt of chemotherapy at the end of life (EOL) is considered an indicator of poor quality of care for medical oncology. The objective of this study was to characterize the use of radiotherapy (RT) in patients with nonsmall cell lung cancer (NSCLC) during the same period. **METHODS:** Treatment characteristics of patients with incurable NSCLC who received RT at the EOL, defined as within 14 days of death, were analyzed from the National Comprehensive Cancer Network NSCLC Outcomes Database. **RESULTS:** Among 1098 patients who died, 10% had received EOL RT. Patients who did and did not receive EOL RT were similar in terms of sex, race, comorbid disease, and Eastern Cooperative Oncology Group performance status. On multivariable logistic regression analysis, independent predictors of receiving EOL RT included stage IV disease (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.09-3.83) or multiorgan involvement (OR, 1.75; 95% CI, 1.08-2.84) at diagnosis, age <65 years at diagnosis (OR, 1.85; 95% CI, 1.21-2.83), and treating institution (OR, 1.24-5.94; $P = .02$). Nearly 50% of EOL RT recipients did not complete it, most commonly because of death or patient preference. **CONCLUSIONS:** In general, EOL RT was received infrequently, was delivered more commonly to younger patients with more advanced disease, and often was not completed as planned. There also was considerable variation in its use among National Comprehensive Cancer Network institutions. Next steps include expanding this research to other cancers and settings and investigating the clinical benefit of such treatment. ***Cancer*** **2012;118:4339-45.** © *2012 American Cancer Society.*

**KEYWORDS:** lung cancer, radiotherapy, palliative care, quality indicators, end-of-life care.

## INTRODUCTION

Nonsmall cell lung cancer (NSCLC) remains the most commonly diagnosed malignancy in the United States, and an estimated 200,000 Americans received this diagnosis in 2010.[1] Although advances in diagnosis and treatment have improved cancer-related mortality, most patients will die of progressive disease. Generally speaking, approximately half of all patients with NSCLC eventually will receive radiotherapy (RT) for either local disease or metastatic disease.[2] A previous Surveillance, Epidemiology, and End Results (SEER)-Medicare database analysis noted that 58% of patients who were diagnosed with metastatic NSCLC received some form of palliative RT.[3] However, there are no data on the frequency with which RT is given at the end of life (EOL).

The receipt of EOL chemotherapy has been examined previously by several investigators. Earle and his colleagues identified a cohort of patients in a SEER-Medicare data set and characterized the frequency of chemotherapy administered during the last 14 days of life. Receipt of chemotherapy in this time frame by >10% of patients was correlated significantly with higher rates of aggressive EOL care (eg, more frequent emergency room visits, intensive care unit/hospital admissions, and hospital deaths and less use of hospice and advanced care directives).[4] This "10% rule" has been validated at other institutions, confirming the finding that late chemotherapy administration is a barometer of health care over-use.[5]

In contrast, little is known regarding the frequency with which RT is delivered at the EOL. The primary objectives of this report were to determine the rate of use of RT near the EOL among patients with NSCLC and to identify the factors associated with such use. A secondary aim was to characterize the technical aspects of the RT received.

## MATERIALS AND METHODS

### *Patients*

The study cohort consisted of patients who were evaluated at 1 of 8 National Comprehensive Cancer Network (NCCN) member institutions participating in the NCCN NSCLC Outcomes Database Project between January 2007 and March 2010. Institutions included City of Hope Comprehensive Cancer Center, Dana-Farber Cancer Institute, Duke Cancer

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Institute, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Ohio State University Comprehensive Cancer Center, Roswell Park Cancer Institute, University of Michigan Comprehensive Cancer Center and The University of Texas MD Anderson Cancer Center. Patients were excluded from the analysis if they were previously diagnosed with NSCLC within 2 years or with any invasive malignancy within 5 years. Patients who presented for a second opinion were not eligible for inclusion in the database. An institutional review board at each center approved of the data collection, storage, and analysis for this project. For institutions that required patient informed consent, data collection was limited to patients who had provided consent.

### Data Collection/Data Sources

Patient data were collected longitudinally through a medical record chart review by trained abstractors at each institution. Baseline information is abstracted 6 months after presentation with a pathologically confirmed diagnosis of NSCLC and is then reviewed and updated every 6 months for the first 2 years of follow-up and annually thereafter. Baseline characteristics include the patient's date of birth, sex, race, ethnicity, type of insurance, number of comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, tumor-lymph node-metastasis (TNM) stage, and histology. Dates and locations of metastatic disease collected at diagnosis and during follow-up also are reported along with RT and systemic therapy data from both NCCN institutions and outside institutions. Detailed RT data include treatment sites, treatment indication, treatment type, and number of fractions. EOL data consists of death date, cause of death, and EOL discussion events. For the current analysis, RT data were limited to therapy received after a patient's earliest distant metastasis diagnosis.

The Outcomes Database Project uses rigorous quality-assurance procedures to maintain a high level of accuracy of the data. These include real-time, web-based edit checking; programmed logic check queries of the pooled data repository; quality-assurance reports that are reviewed by the data managers on a quarterly basis; monthly data-management training calls; biannual, in-person data-management training sessions; and on-site audits of a random sample of source documents against the submitted data performed within the first few months of data entry and annually thereafter.

### Definitions

Patients were defined as having received (EOL) RT if they received RT at an NCCN institution or a non-NCCN institution within 14 days of death. This included patients who started or ended any form of RT within 14 days of death. Receipt of systemic therapy within 14 days of death was similarly defined.

### Statistical Methods

Categorical variables were used to analyze age at diagnosis (age $\leq$54 years, 55-64 years, or $\geq$65 years), insurance type (Medicare with or without a second insurance type, managed care alone, other), ECOG performance status (0, fully active; 1, restricted activities; 2-4, cannot work/fully dependent; or unknown performance status), and NCCN institution. Binary variables were used to examine sex (men/women), race (Caucasian/other), Charlson comorbidity index score (0/1+), stage at diagnosis (IV/I-III), presence of multiple metastatic sites (yes/no), documented EOL discussion (yes/no), receipt of EOL RT (yes/no), and receipt of EOL systemic therapy (yes/no).

Baseline characteristics were stratified by the receipt of EOL RT. The association between the receipt of EOL RT and various demographic and clinical factors was assessed with logistic regression modeling. Individual factors were modeled first to check for univariate association with the receipt of EOL RT. Variables with a significance level of $\leq .2$ from the univariate analyses were considered for the final multivariable model. Multivariable logistic regression was performed to identify the factors associated with the receipt of EOL RT. The final significance level was set to an $\alpha$ level of .05. Point estimates from the multivariable model are reported as odds ratios (ORs) with the corresponding 95% confidence interval (CI) for each OR. All statistical analyses were conducted using the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC).

## RESULTS

### Patient Characteristics

Between January 1, 2007 and March 1, 2010, 3074 patients diagnosed with NSCLC were identified through the Outcomes Database Project. More than half of these (1749 patients) had stage IV or IIIB disease with a malignant effusion at time of database entry or had a metastatic recurrence. Of these, 1218 patients had a recorded death as of March 30, 2010. Thirty patients were excluded from further analysis because of incomplete baseline information, and 90 patients were excluded because of a past invasive cancer other than NSCLC. Therefore, the final cohort consisted of 1098 patients. Of these, 730 patients (66%) subsequently received RT at some point after being diagnosed with incurable disease, and 115 of those

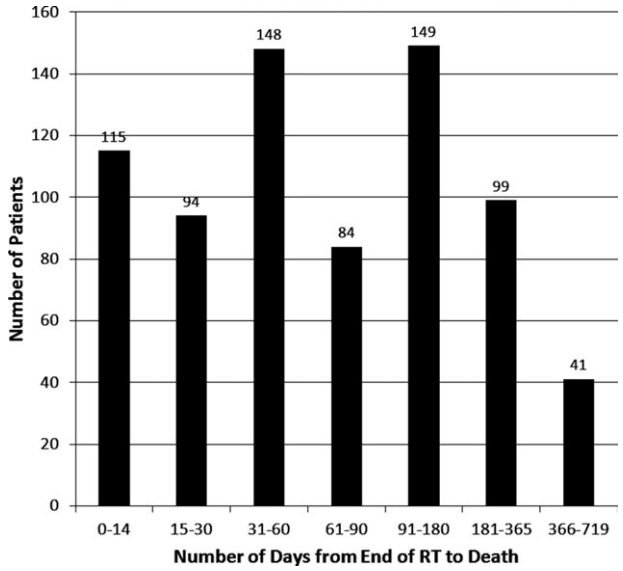


**Figure 1.** The time from the end of radiotherapy (RT) to death is illustrated among patients who received RT after diagnosis. In total, 115 patients with either stage IIIB or stage IV non-small cell lung cancer died within 14 days of receiving RT, representing approximately 10% of the 730 patients who received RT at any point after the diagnosis of incurable disease.

patients (10%) received this treatment at the EOL (Fig. 1).

There were some significant differences between patients who did and did not receive EOL RT (Table 1). Patients who received EOL treatment were younger (median age, 60 years vs 64 years), were less likely to have Medicare-related health insurance, and presented with more advanced disease (metastatic disease at the time of diagnosis and/or disease involving multiple organs). Otherwise, both groups were similar with regard to sex, race, comorbidity status, performance status, and documentation of EOL discussions. The rate of chemotherapy receipt at the EOL was 10% among those patients who received EOL RT and 11% among those who did not receive EOL RT ($P = .86$).

### *Multivariable Analysis of Radiotherapy at the End of Life:*

Patients who had stage IV (or IIIB) disease at the time of diagnosis were twice as likely to receive EOL RT as patients who had stage I, II, or III disease (OR, 2.04; 95% CI, 1.09-3.83) (Table 2). Furthermore, patients who were diagnosed initially with multiple sites of metastatic disease were 75% more likely to receive EOL RT than those who were diagnosed initially with a single site of metastasis (95% CI, 1.08-2.84). Younger patients (aged <65 years) were 1.85 times as likely as older patients to receive EOL RT (95% CI, 1.21-2.83). There also was significant inter-institutional variation in the EOL RT rate (OR range, 1.24-5.94; $P = .02$).

### *Treatment Characteristics*

Twenty-two percent of patients received more than 1 course of treatment at the EOL; thus, 115 patients received 131 courses of treatment (Table 3). Of the 131 courses, 25 courses (19%) involved ≤3 fractions (including 4 patients who received single-fraction stereotactic external beam or gamma-knife brain radiosurgery), 40 courses (30%) consisted of 10 fractions, and 23 courses (17%) involved >10 fractions (Fig. 2).

EOL RT was not completed as prescribed by 54 of the 115 patients (47%), including 19 patients who died during the course of treatment and 11 patients who elected not to finish their originally prescribed course. The remaining 24 patients discontinued treatment because of disease progression, treatment toxicity (either RT or chemotherapy), transfer of care, comorbid illness, or reasons that were not reported (Fig. 3).

Commonly treated sites at the EOL included the brain (28%), chest (27%), spine (25%), and bones other than spine (13%). Complexity of therapy was weighted toward 3-dimensional conformal therapy, as 42% of RT courses used this modality (Table 4). Simpler treatment techniques were used in 33% of RT courses, and 8% of courses used more technologically complex methods, such as intensity-modulated RT or stereotactic radiosurgery. Data regarding treatment modality were not available for 17% of courses.

## DISCUSSION

For this report, we examined the frequency with which RT was delivered to a group of patients with incurable NSCLC at 8 NCCN institutions during their last 2 weeks of life. Overall, 10% of these patients received radiation treatments within that period compared with 11% for chemotherapy. We observed that younger patients and those with more advanced disease were statistically more likely to receive RT at the EOL and that there was significant variation in its use between centers. Although most patients were prescribed a single course of therapy, nearly half did not complete it, most commonly because of intercurrent death, disease, or patient preference.

There is growing interest in optimizing the use of health care, especially at the EOL. EOL cancer treatment deserves closer examination, because cancer accounts for nearly 25% of all deaths in the United States.[1] It is estimated that 159,000 patients died of lung cancer alone in

**Table 1.** Baseline Patient Characteristics Stratified by Receipt of End-of-Life Radiation Therapy (N = 1098)

| Characteristic | No. of Patients (%) | | *P* |
|---|---|---|---|
| | Radiation Within 14 Days of Death, N = 115 | No Radiation Within 14 Days of Death, N = 983[a] | |
| **Age at diagnosis: Median [range], (y)** | 60 [37-84] | 64 [25-96] | <.01 |
| ≤54 | 34 (30) | 249 (25) | |
| 55-64 | 46 (40) | 285 (29) | |
| ≥65 | 35 (30) | 449 (46) | |
| **Sex** | | | .45 |
| Men | 56 (49) | 515 (52) | |
| Women | 59 (51) | 468 (48) | |
| **Caucasian** | | | .30[b] |
| No | 18 (16) | 196 (20) | |
| Yes | 95 (83) | 784 (80) | |
| Unknown | 2 (2) | 3 (0) | |
| **Insurance[c]** | | | <.01[b] |
| Medicare-related | 37 (32) | 463 (47) | |
| Managed care alone | 69 (60) | 384 (39) | |
| Other | 9 (8) | 134 (14) | |
| Unknown | 0 (0) | 2 (0) | |
| **Stage** | | | <.01 |
| I-III | 12 (10) | 205 (21) | |
| IV | 103 (90) | 778 (79) | |
| **NCCN institution** | | | .09 |
| A | 4 (5) | 74 (95) | |
| B | 5 (6) | 75 (94) | |
| C | 16 (12) | 122 (88) | |
| D | 11 (13) | 74 (87) | |
| E | 6 (7) | 86 (93) | |
| F | 32 (10) | 302 (90) | |
| G | 12 (20) | 49 (80) | |
| H | 29 (13) | 201 (87) | |
| **ECOG performance status** | | | .90 |
| 0: Fully active | 23 (20) | 215 (22) | |
| 1: Restricted activities | 40 (35) | 359 (37) | |
| 2-4: No work/dependent | 20 (17) | 156 (16) | |
| Unknown | 32 (28) | 253 (26) | |
| **Charlson Comorbidity Index score** | | | .81 |
| 0 | 66 (57) | 553 (56) | |
| ≥1 | 49 (43) | 430 (44) | |
| **Multiple metastatic sites** | | | .01 |
| No | 26 (23) | 339 (34) | |
| Yes | 89 (77) | 644 (66) | |
| **Documented end-of-life discussion** | | | .34 |
| No | 56 (49) | 525 (53) | |
| Yes | 59 (51) | 458 (47) | |
| **Receipt of chemotherapy in last 14 d of life** | | | .86 |
| No | 103 (90) | 875 (89) | |
| Yes | 12 (10) | 108 (11) | |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network.

[a] Includes patients who never received RT treatment in the metastatic setting (N = 368) and those who received RT in the metastatic setting, but not during the last two weeks of life (N = 615).

[b] Analysis performed after excluding patients with unknown values.

[c] Medicare-related insurance refers to Medicare alone, Medicare plus supplemental insurance, and Medicare plus managed care. Other insurance also includes indemnity, Medicare/indigent, and/or self-pay.

**Table 2.** Factors Associated with Receipt of Radiation within 14 Days of Death in Multivariable Logistic Regression Analysis (N = 1098)[a]

| Variable | OR | 95% CI | *P* |
|---|---|---|---|
| **Stage at diagnosis** | | | .03 |
| I-III | 1.00 | | |
| IV | 2.04 | 1.09-3.83 | |
| **Age at diagnosis, y** | | | <.01 |
| ≥65 | 1.00 | | |
| <65 | 1.85 | 1.21-2.83 | |
| **NCCN institution** | | | .02 |
| A | 1.00 | | |
| B | 1.24 | 0.33-4.59 | |
| C | 1.25 | 0.32-4.88 | |
| D | 1.85 | 0.63-5.42 | |
| E | 2.26 | 0.72-7.07 | |
| F | 2.58 | 0.87-7.64 | |
| G | 2.82 | 0.85-9.34 | |
| H | 5.94 | 1.77-19.96 | |
| **Multiple organs involved at diagnosis** | | | .02 |
| No | 1.00 | | |
| Yes | 1.75 | 1.08-2.84 | |

Abbreviations: CI, confidence interval; NCCN, National Comprehensive Cancer Network; OR, odds ratio.
[a] The analysis was performed after excluding patients with unknown values.

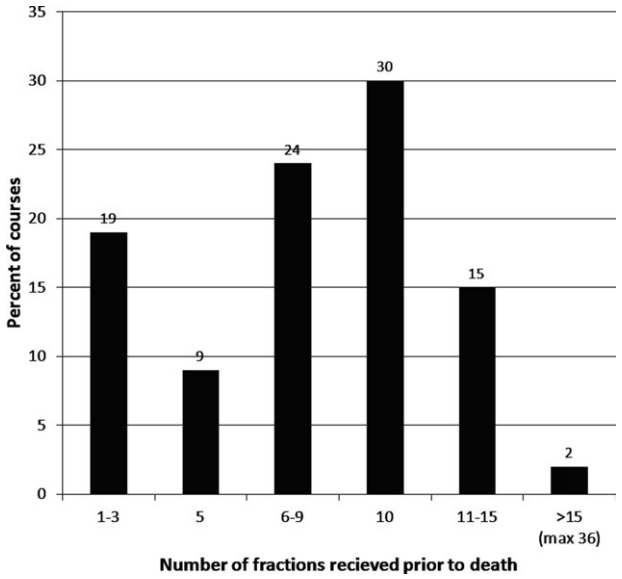


**Figure 2.** This chart illustrates the number of radiotherapy fractions received per course before death. The numbers below each bar indicate the number of fractions received as part of the 131 courses. Included in the single-fraction data are 4 patients (3% of courses) who underwent single-fraction stereotactic radiosurgery. Note that the number of courses is greater than the number of patients, because some patients received multiple courses of treatment in the 14 days before death. Max indicates maximum.

**Table 3.** The Number of End-of-Life Radiotherapy Courses per Patient[a]

| No. of Courses Prescribed per Patient, n = 115 | No. of Patients (%) |
|---|---|
| 1 | 90 (78) |
| 2 | 20 (17) |
| 3 | 4 (4) |
| 4 | 1 (1) |

[a] The data exclude patients whose treatment technique was not reported or who received single-fraction stereotactic body radiotherapy, and the number of courses is greater than the number of patients treated, because some patients received multiple courses of radiotherapy at the end of life.

2009[6] and that a considerable share of these patients' health care expenses were incurred during the last months of life.[6-9] However, it is not clear whether more aggressive EOL care improves either the duration or the quality of life. For example, Temel et al observed that, for patients with newly diagnosed metastatic NSCLC, there were statistically significant survival and quality-of-life benefits among patients who used fewer health care services.[10]

After accounting for confounding variables, we observed that younger patients were more likely to receive EOL RT, which concurs with previously reported American and Canadian data.[7,8,11,12] Although the reasons for this are not entirely clear, it is possible that younger patients and/or their providers pursue more aggressive treatment despite the finding that their survival rates are similar to the rates among older patients who receive more conservative treatment.[13] Previous studies that aimed to define the factors associated with palliative RT indicated that patients with metastatic disease who have lower socioeconomic status[3,7,11] and those who live in nursing homes or rural settings are less likely to be referred for RT and, thus, to receive less treatment.[7,8,11] Unfortunately, the NCCN database does not currently capture information on patients' socioeconomic status or living situation, so we were not able to assess these factors as part of our analysis.

We also were able to detect differences in the frequency with which EOL RT was prescribed between centers. Other investigators previously noted geographic variation in the receipt of palliative RT, citing the type of center (academic vs freestanding)[3] or variation in logistic challenges between centers as factors that affect the likelihood of being referred for or receiving palliative RT.[7] Although all centers that were included in the current report were affiliated with academic institutions, it is possible that the variation we observed may have been caused by variation in local practice patterns or even the relative

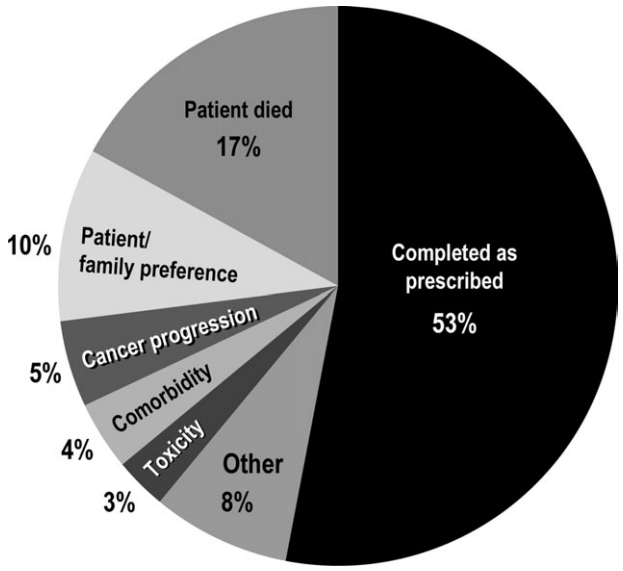


**Figure 3.** This chart indicates the percentage of patients who stopped radiotherapy for various reasons. Slightly more than half of the 115 patients who died within 14 days of receiving radiotherapy finished their course as prescribed (indicated in black). The remaining patients did not finish treatment for other reasons (indicated in shades of gray).

**Table 4.** End-of-Life Radiotherapy Sites Treated and Treatment Types (N = 146 Courses)[a]

| Variable | No. of Patients (%) |
|---|---|
| **Distribution of sites treated with RT** | |
| Brain | 41 (28) |
| Chest | 39 (27) |
| Spine | 36 (25) |
| Bone, other than spine | 19 (13) |
| Other | 11 (8) |
| **Treatment technique per course of RT** | |
| Conventional 2D therapy | 48 (33) |
| 3D conformal therapy | 62 (42) |
| Intensity modulated RT | 7 (5) |
| Stereotactic radiosurgery | 4 (3) |
| Unknown | 25 (17) |

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.
[a] The number of courses is greater than the number of patients treated, because some patients received multiple courses of RT at the end of life.

ease and urgency with which patients who are referred for palliative care are seen and treated.

With regard to the technical aspects of EOL RT, we observed that most patients received a palliative course of treatment that consisted of 10 fractions. Although recent data from the United States and France suggest that this is consistent with the standard of care,[3,14,15] surveys of practice patterns elsewhere in Europe, Canada, and Australia favor the use of single-fraction or 5-fraction regimens.[7,11,15] Certainly, shorter treatment courses decrease the number of clinic visits, thereby reducing the direct and indirect costs to the patient. From the referring physician's perspective, the prolonged nature of palliative RT has even been cited as a perceived barrier to care.[12]

It was beyond the scope of the current study to determine whether clinical factors, routine practice patterns, or other incentives explained the providers' preference for longer treatment regimens. Regardless, it is important to note that abbreviated courses are most appropriate for patients at the EOL, because several studies have demonstrated that consolidated therapy can result in earlier and more frequent retreatment if patients survive longer than expected.[16,17] Unfortunately, oncologists often are poor at predicting their own patients' survival; the accuracy of survival estimates among experienced physicians only ranges between 20% and 30%, and the majority of errors are over estimates.[18-21] In a recent study, for example, radiation oncologists only accurately identified 5 of 33 patients who would die within 1 month of starting palliative RT.[22] Moreover, they predicted that 7 of the 33 patients who died were going to live for at least 6 months. Reflecting this optimism, only 61% of their patients completed treatment as prescribed, which is only slightly better than the rate of 53% identified in the current study.

Although our data were audited for accuracy, this report does have several limitations. First, we have compared EOL RT rates with rates of chemotherapy use at the EOL, and this may not be fair. Because RT is prescribed for local (often acute) symptom management, whereas chemotherapy is offered to reduce systemic disease burden (and prolong life), it may be argued that EOL RT is a wholly different treatment and, thus, should not be prescribed in the same fashion or frequency as chemotherapy. Second, the practice patterns at the 8 NCCN institutions studied may not be representative of radiation oncologists in general. Although all the centers contributing to the database are academic research institutions, most RT in the United States is provided in the private setting.[23] Therefore, it may be inaccurate to generalize our findings to the field as a whole. Third, we have limited this report to patients with NSCLC. It has been demonstrated that the rates of palliative RT differ widely, depending on the primary disease site[7,8,11]; thus, if other cancers were investigated, there could be differing rates of EOL RT. Finally, our database did not collect detailed data on the palliative versus curative intent of therapy, making it difficult to determine whether treatment was clinically appropriate. Along these lines, it would have been helpful to know the number of planned treatments; unfortunately,

only the number of treatments received was reported as part of the database.

In conclusion, to the best of our knowledge, this study provides the first data on the use of EOL RT, the factors associated with its use, and how it is delivered, albeit at a limited number of academic centers for a single type of cancer. It is our hope that future investigations of this issue will be expanded to include other cancers in a wider variety of facilities. It is also important to note that our study does not help to define an appropriate rate of use of RT for patients at the end of their lives. This, too, is an important issue for future study and will be greatly aided by having more accurate tools for predicting the life-span of patients with metastatic disease who present for consideration of treatment with radiation. With such information in hand, we can be more confident that our patients not only will complete the treatments we intend to deliver but also will achieve some durable benefit from them. By doing so, we may come closer to answering the key question: How often should radiation therapy be offered at the end of life?

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## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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