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Clinical Investigation

Radiation Treatment Time and Overall Survival in Locally Advanced Non-small Cell Lung Cancer

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Summary

Prolonged RTT has been associated with worse survival in several malignancies. Data from the National Cancer Database showed that for patients with NSCLC, prolonged RTT independently predicted poorer OS. Moreover, each cumulative interval of delay, including as low as a 1- to 2-day delay, was associated with worsened OS. The demographic and socioeconomic barriers influencing prolonged RTT were also detailed to address the health disparities in this regard.

Purpose: Prolonged radiation treatment (RT) time (RTT) has been associated with worse survival in several malignancies. The present study investigated whether delays during RT are associated with overall survival (OS) in non-small cell lung cancer (NSCLC).

Methods and Materials: The National Cancer Database was queried for patients with stage III NSCLC who had received definitive concurrent chemotherapy and fractionated RT to standard doses (59.4-70.0 Gy) and fractionation from 2004 to 2013. The RTT was classified as standard or prolonged for each treatment regimen according to the radiation dose and number of fractions. Cox proportional hazards models were used to evaluate the association between the following factors and OS: RTT, RT fractionation, demographic and pathologic factors, and chemotherapeutic agents.

Results: Of 14,154 patients, the RTT was prolonged in 6262 (44.2%). Factors associated with prolonged RTT included female sex (odds ratio [OR] 1.21, $P<.0001$), black race (OR 1.20, $P=.001$), nonprivate health insurance (OR 1.30, $P<.0001$), and lower income (<$63,000 annually, OR 1.20, $P<.0001$). The median OS was significantly worse for patients with prolonged RTT than that for those with standard RTT (18.6 vs 22.7 months, $P<.0001$). Furthermore, the OS worsened with each cumulative interval of delay (standard RTT vs prolonged 1-2 days, 20.5 months, $P=.009$; prolonged 3-5 days, 17.9 months, $P<.0001$; prolonged 6-9 days, 17.7 months, $P<.0001$; prolonged >9 days, 17.1 months, $P<.0001$). On multivariable analysis, prolonged RTT

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was independently associated with inferior OS (hazard ratio 1.21, $P<.0001$). Prolonged RTT as a continuous variable was also significantly associated with worse OS (hazard ratio 1.001, $P=.0007$).

Conclusions: Delays during RT appear to negatively affect survival for patients with locally advanced NSCLC. We have detailed the demographic and socioeconomic barriers influencing prolonged RTT as a method to address the health disparities in this regard. Cumulative interruptions of RT should be minimized.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide (1), and locally advanced NSCLC is most commonly treated with chemoradiation therapy. Concurrent chemoradiation therapy improves overall survival (OS) compared with sequential treatment (2, 3); however, this comes at the cost of increased toxicity, such as esophagitis. Such an increase in acute toxicity can lead to unplanned treatment breaks (4, 5).

A link between a prolonged radiation treatment (RT) time (RTT) and inferior OS has been documented for other malignancies, such as head and neck (6, 7) and cervical (8) cancer. Several previous studies have suggested that a prolonged RTT can also negatively affect OS for patients with NSCLC (4, 9, 10). However, these analyses were limited by older treatment paradigms, the techniques used, and modest sample sizes. We used the National Cancer Database (NCDB) to test the hypothesis that the RTT is associated with OS in a large, modern cohort of patients with stage III NSCLC who had undergone definitive concurrent chemoradiation therapy.

Methods and Materials

Data source

After institutional review board approval, data from 2004 to 2013 were obtained from the NSCLC participant use file of the NCDB. The NCDB is a collaborative project jointly sponsored by the American College of Surgeons Commission on Cancer and the American Cancer Society. It currently partners with >1500 institutions, gathering data on approximately 70% of new cancer diagnoses in the United States (11).

Patient selection

Patients with NSCLC (per the "International Classification of Diseases for Oncology, third edition" [12]) undergoing definitive concurrent chemoradiation therapy for nonoperative American Joint Committee on Cancer clinical stage III disease (13) were identified (Fig. 1). Patients receiving a diagnosis in 2013 were excluded to ensure ≥1 year of follow-up. Further requirements included receipt of fractionated external beam RT to a standard dose between 59.4 and 70.0 Gy, consistent with the National Comprehensive Cancer Network guidelines for NSCLC (14). We a priori specifically restricted the dose/fraction schedule to the following combinations: 59.4 Gy/33 fractions, 60 Gy/30 fractions, 61.2 Gy/34 fractions, 63 Gy/35 fractions, 64.8 Gy/36 fractions, 66 Gy/33 fractions, 66.6 Gy/37 fractions, 68.4 Gy/38 fractions, and 70.0 Gy/35 fractions. Patients who underwent surgery or palliative RT were excluded. Concurrent chemotherapy was defined as the start of chemotherapy within 14 days before or after the initiation of RT.

Variables

The definitions for the accrued demographic and pathologic NCDB variables (Table 1) have been extensively reported (11, 15-21). Insurance status was dichotomized as nonprivate (ie, Medicaid, Medicare, other government insurance, or no insurance) versus private insurance. The RT-specific variables of particular interest included RTT and number of RT fractions. RTT was classified as standard or prolonged for each dose level (standard: 59.4 Gy, 45-49 days; 60 Gy, 40-44 days; 61.2 Gy, 46-50 days; 63 Gy, 47-51 days; 64.8 Gy, 50-52 days; 66 Gy, 45-49 days; 66.6 Gy, 51-55 days; 68.4 Gy, 52-56 days; and 70.0 Gy, 47-51 days; prolonged: 59.4 Gy, >49 days; 60 Gy, >44 days; 61.2 Gy, >50 days; 63 Gy, >51 days; 64.8 Gy, >52 days; 66 Gy, >49 days; 66.6 Gy, >55 days; 68.4 Gy, >56 days; and 70 Gy, >51 days). These groups were created a priori to capture treatment delivery durations within the realities of clinical practice. The most efficient RTT would start on a Monday and entail daily 1.8-Gy or 2.0-Gy fractions delivered 5 days per week to the total prescribed dose without interruption. These RTT ranges were designed to additionally incorporate those patients who completed treatment without a break but started RT on a day other than Monday (increase of ≤2 calendar days in total RTT) and those whose treatment course encompassed 2 holidays (2 additional calendar days). Any further delay in the RTT was classified as prolonged. Patients who received RT within fewer days than the ranges listed for each dose/fractionation group were excluded, as were patients with an unknown RTT (Fig. 1). OS was defined as the interval between the date of diagnosis and the date of death or last contact.