Utilization of Hyperfractionated Radiation in Small-Cell Lung Cancer and Its Impact on Survival

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Introduction: Twice-daily radiation with concurrent chemotherapy is recognized as the standard of care for the treatment of limited stage small-cell lung carcinoma (SCLC), but its utilization in this setting is unclear. The objective of this study was to analyze modern patterns of treatment for limited stage SCLC and the impact on survival utilizing the National Cancer Database.

Methods: Between 1999 and 2012, there were 25,045 patients diagnosed with nonmetastatic SCLC who met the selection criteria, of whom 22,626 had survival data. Those receiving 45 Gy in 1.5 Gy fractions twice-daily (BID) were compared with those receiving 45 to 72 Gy in 1.8 or 2.0 Gy fractions. Overall survival was analyzed via Kaplan–Meier analysis and compared using the log-rank test. Multivariate Cox regression analysis was used to identify covariates associated with survival.

Results: The utilization of BID radiation overall was 11.3%. Treatment at an academic center was associated with a higher likelihood of receiving BID treatment (odds ratio: 2.29, 95% confidence interval [CI]: 1.95–2.69; $p < 0.001$). Median survival was 22.1, 17.2, 18.3, 19.2, and 19.5 months for patients receiving 45 Gy BID, 45 Gy once-daily, 46 to 59.4 Gy once-daily, 60 to 61.2 Gy once-daily, and 62 to 72 Gy once-daily, respectively ($p < 0.001$ for all pairwise comparisons to BID). On multivariate analysis, treatment at an academic center (hazard ratio: 0.88, 95% CI: 0.83–0.93; $p < 0.001$) and receipt of BID radiation (hazard ratio: 0.92, 95% CI: 0.86–0.98; $p = 0.008$) were associated with improved survival.

Conclusions: The adoption of BID radiation remains very limited, but is more commonly utilized in the academic setting. In this hospital-based study, BID fractionation was associated with improved survival over once-daily fractionation, even at doses ≥60 Gy.

Key Words: Small-cell lung cancer, Hyperfractionated radiation, Patterns of care, Chemotherapy.

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Small-cell lung cancer (SCLC) is an aggressive variant of lung cancer that presents with nonmetastatic (limited stage) disease in 30% of patients at the time of diagnosis.[1] Current guidelines support the use of concurrent chemoradiation for limited stage SCLC in excess of T1-2N0 and with a good performance status.[2] Radiation therapy has been shown to improve survival for limited stage SCLC,[3] although the timing, dose, and fractionation have been the subject of investigation. The Intergroup (INT) 0096 trial reported a 5-year survival of 26% with 45 Gy in 1.5 Gy per fraction twice-daily (BID), establishing this regimen as an accepted standard of care.[4] However, a patterns of care study analyzing patients from 1998 to 1999 reported that as of that point, twice-daily fractionation had not gained widespread acceptance.[5]

The most promising alternative regimen to the BID fractionation has been a dose of 70 Gy at 2 Gy/fx once-daily, based on three Cancer and Leukemia Group (CALGB) studies that reported a pooled 5-year overall survival (OS) of 20%.[6] As a result, the CALGB 30610/Radiation Therapy Oncology Group (RTOG) 0538 study is currently randomizing patients with limited stage SCLC to either 45 Gy in 1.5 Gy BID or 70 Gy in 2 Gy once-daily.

In this study, we sought to analyze the National Cancer Database (NCDB) to determine the modern patterns of care regarding which fractionation schedules are being used. We also sought to determine whether any survival differences would be noted between the BID and once-daily fractionation.

PATIENTS AND METHODS

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is estimated that 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study.

Adult patients with nonmetastatic small-cell lung cancer who were treated with definitive radiation between 1999 and 2012 were included. Patients had to have complete information regarding the total radiation dose as well as the number of radiation fractions. The NCDB does not specifically report whether radiation treatments were delivered once or twice daily. However, those who received 45 Gy in 30 fractions were classified as having undergone accelerated hyperfractionation rather than 1.5 Gy per day. Patients who received 45 to 72 Gy in 1.8 or 2.0

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Gy fractions were classified as receiving standard once-daily treatments. We excluded patients who were identified as AJCC M1 disease, or patients who were identified as having received their radiation treatments to a site other than the lung.

Demographic details and chemotherapy use were compared between patients who received BID and once-daily treatments via χ^2, Fisher's exact test, and Mann–Whitney test where appropriate. Multivariate logistic regression was used to determine whether there were any differences in the selection of BID radiation by age group, race, sex, time interval from chemotherapy to radiation therapy initiation, T-stage, N-stage, and facility type. Multivariate Cox regression of OS was also performed based on age group, race, sex, time interval from chemotherapy to radiation therapy initiation, facility type, radiation fractionation, and N-staging. The interval between the start of chemotherapy and the start of radiation was calculated and divided into four quartiles for the purposes of this analysis. Survival data were only available from the NCDB on patients diagnosed through 2011, due to the short follow up available for patients diagnosed in 2012. To analyze facility type, only patients who were treated at one facility were included in the multivariate analyses. Kaplan–Meier analyses of OS were performed comparing patients who received 45 Gy BID with all patients receiving radiation once-daily together and separately in increasing dose levels (45 Gy once-daily, 45–59.4 Gy, 60–61.2 Gy, 62–72 Gy). Significant values were defined as those with a p value less than 0.05. Statistical analysis was performed using SPSS, Version 21 (IBM Inc, Armonk, NY).

RESULTS

Patient Characteristics

There were 25,045 patients who met the criteria outlined above, of which survival data was available for 22,626. At a median of 18 months follow up, 77.8% of the patients with survival data available were deceased. Most patients (89.2%) received multiagent chemotherapy. An additional 7.7% received either single agent chemotherapy or the number of agents was not documented. Chemotherapy was started a median of 21 days from the date of diagnosis. The most common fractionation scheme was a dose of 46 to 59.4 Gy in 1.8 to 2 Gy per fraction (44.4%). A dose of 1.5 Gy delivered BID was utilized in 2821 patients (11.3%). Radiation therapy was started a median of 46 days after the date of diagnosis. Further details regarding patient characteristics are available in Table 1.

TABLE 1. Patient Characteristics

	No (%)
Age (median)	65 years
Sex	
Male	11,295 (45.1%)
Female	13,750 (54.9%)
Race	
Caucasian	22,729 (90.8%)
African American	1747 (7.0%)
Other	569 (2.3%)
Facility type	
Community cancer program	3534 (14.1%)
Comprehensive community cancer program	15,554 (62.1%)
Academic/research program	5905 (23.6%)
Other	52 (0.2%)
Fractionation	
45 Gy/1.5 Gy BID	2821 (11.3%)
45 Gy/1.8 Gy QD	996 (4.0%)
46–59.4 Gy/1.8–2 Gy QD	11,116 (44.4%)
60–61.2 Gy/1.8–2 Gy QD	5095 (20.3%)
62–72 Gy/1.8–2 Gy QD	5017 (20.0%)
Receipt of chemotherapy	
Yes	24,294 (96.9%)
No	751 (3.1%)
T-stage	
Tx	4057 (16.2%)
T0–1	5065 (20.2%)
T2	7332 (29.3%)
T3	2847 (11.4%)
T4	5744 (22.9%)
N-stage	
Nx	3034 (12.1%)
N0–1	6634 (26.5%)
N2	11,931 (47.6%)
N3	3446 (13.8%)

BID, twice-daily; QD, once-daily; Gy, Gray.

Receipt of BID or Once-Daily Radiation Therapy

Patients who received BID radiation therapy were a median age of 63 years, compared with a median age of 66 years for those receiving once-daily treatments ($p < 0.001$). BID radiation was received in 17.9% of patients who were treated at an academic/research facility, compared with 8.1% to 9.7% at other facilities ($p < 0.001$). The median number of days until receipt of chemotherapy was 21 days for patients receiving BID radiation as well as for those receiving once-daily radiation ($p = 0.92$). Both the median number of days until the start of radiation treatments and the duration of radiation treatments were shorter in the BID group. The median number of days until the start of radiation treatments was 38 days in the BID group and 47 days in the once-daily group ($p < 0.001$). The median duration of radiation treatments was 22 days for the BID group and 50 days in the once-daily group ($p < 0.001$).

On multivariate analysis, treatment at an academic center was the strongest variable associated with the receipt of BID radiation treatment (odds ratio: 2.29, 95% confidence interval [CI]: 1.95–2.69; $p < 0.001$). In addition, treatment at a comprehensive community cancer program, earlier initiation of radiation, and N-stage ≤2 were more likely to be treated with BID radiation. In contrast, increasing age and female sex were associated with a lower likelihood of BID fractionation. Further details are available in Table 2.

