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Basic Original Report

# Prospective Evaluation of Limited-Stage Small Cell Lung Cancer Radiotherapy Fractionation Regimen Usage and Acute Toxicity in a Large Statewide Quality Collaborative

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**Purpose:** National guidelines on limited-stage small cell lung cancer (LS-SCLC) treatment give preference to a hyperfractionated regimen of 45 Gy in 30 fractions delivered twice daily; however, use of this regimen is uncommon compared with once-daily regimens. The purpose of this study was to characterize the LS-SCLC fractionation regimens used throughout a statewide collaborative, analyze patient and treatment factors associated with these regimens, and describe real-world acute toxicity profiles of once- and twice-daily radiation therapy (RT) regimens.

**Methods and Materials:** Demographic, clinical, and treatment data along with physician-assessed toxicity and patient-reported outcomes were prospectively collected by 29 institutions within the Michigan Radiation Oncology Quality Consortium between 2012 and 2021 for patients with LS-SCLC. We modeled the influence of RT fractionation and other patient-level variables clustered by treatment site on the odds of a treatment break specifically due to toxicity with multilevel logistic regression. National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, incident grade 2 or worse toxicity was longitudinally compared between regimens.

**Results:** There were 78 patients (15.6% overall) treated with twice-daily RT and 421 patients treated with once-daily RT. Patients receiving twice-daily RT were more likely to be married or living with someone (65% vs 51%; $P = .019$) and to have no major comorbidities (24% vs 10%; $P = .017$). Once-daily RT fractionation toxicity peaked during RT, and twice-daily toxicity peaked within 1 month after RT. After stratifying by treatment site and adjusting for patient-level variables, once-daily treated patients had 4.11 (95% confidence interval, 1.31-12.87) higher odds of treatment break specifically due to toxicity than twice-daily treated patients.

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We are not authorized to share Michigan Radiation Oncology Quality Consortium data. The data are individually owned by the member institutions of the Michigan Radiation Oncology Quality Consortium.

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**Conclusions:** Hyperfractionation for LS-SCLC remains infrequently prescribed despite the lack of evidence demonstrating superior efficacy or lower toxicity of once-daily RT. With peak acute toxicity after RT and lower likelihood of a treatment break with twice-daily fractionation in real-word practice, providers may start using hyperfractionated RT more frequently.


## Introduction

The Intergroup 0096 trial first demonstrated superiority of twice-daily radiation therapy (RT) fractionation (45 Gy in 30 fractions over 3 weeks) to once-daily RT fractionation (45 Gy in 25 fractions over 5 weeks) with concurrent cisplatin-etoposide in the treatment of limited-stage small cell lung cancer (LS-SCLC), effectively establishing the former regimen as standard of care.[1] More recently, the CONVERT trial did not demonstrate superiority of a high-dose, once-daily RT fractionation (66 Gy in 33 fractions over 6.5 weeks) compared with the established standard of 45 Gy in 30 fractions given twice daily.[2] Therefore, the twice-daily regimen remains the preferred RT fractionation as recommended by national and international guidelines.[3,4] However, debate continues over the optimal dose fractionation with proponents of once-daily regimens, noting the initial Intergroup 0096 trial[1] compared the 45 Gy in 30 fractions twice-daily regimen to a once-daily regimen with lower biologically equivalent dose and, thus, possibly inferior tumor control, while those supporting the twice-daily regimen suggest that the lack of a difference seen in CONVERT, which was designed as a superiority trial, does not prove equivalence.[5] Given the lack of consensus, current guidelines allow for use of once-daily RT regimens as an alternative when a twice-daily regimen is not logistically feasible for patients or the clinic.[3,4] Despite this guideline preference for a twice-daily regimen, its use remains uncommon in the United States (US) at around 11% to 21% of patients with LS-SCLC as noted in prior reports.[6-9] These earlier studies are limited in part by their indirect measure of actual radiation treatment due to the nature of the survey study designs or reliance on data sets lacking robust RT information. Other prior studies reflect RT fractionation schedules predating publication of the CONVERT trial results and using older RT techniques.

Given the guideline preference but reported infrequent utilization of twice-daily RT, understanding actual rather than inferred modern RT practice patterns may help explain the apparent disconnect. Further, to our knowledge, no prospectively collected toxicity data comparing conventionally fractionated once-daily RT with twice-daily RT has been published outside the randomized CONVERT trial—which did not include patient-reported outcomes (PROs)—and the ongoing CALGB 30610/RTOG 0538 trial.[2,10,11] Some retrospective comparisons between once-daily and twice-daily RT regimens have been published but lack rigorous toxicity reporting.[12,13] Therefore, the objective of this study is to report on the use of once- and twice-daily RT fractionation regimens throughout a large statewide collaborative, analyze patient and treatment factors associated with each regimen, and describe real-world acute toxicity profiles using both physician-reported outcomes and PROs for once- and twice-daily RT regimens.

## Methods and Materials

### Data collection and samples

The Michigan Radiation Oncology Quality Consortium (MROQC) is a multicenter, statewide collaborative quality initiative among 29 academic and community practice treatment sites in partnership with Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network (BCN). MROQC represents approximately 60% of the radiation oncology volume in the state and is financially supported by BCBSM and BCN as part of the BCBSM Value Partnership Program. Through the combined efforts of radiation oncologists, physicists, data abstractors, and administrators throughout the state, MROQC maintains a prospectively collected database containing a rich array of de-identified patient-level demographic, clinical, treatment, and dosimetric data in addition to physician toxicity and PROs. Eligible patients included those treated with RT at MROQC-participating institutions from February 1, 2012, through February 28, 2021, for LS-SCLC with curative intent and with sufficient dosimetric data to identify RT dose, fraction size, and fractionation regimen (once vs twice daily). Treating physicians reported patients as LS-SCLC upon entry into the database, and although we did not stipulate a requirement for certain imaging modalities, over 60% of patients had positron emission tomography (PET)/computed tomography (CT) used in treatment volume delineation, setting a lower bound for those who were staged by PET/CT.

### Outcome measures

Patient demographic information was self-reported. Social status was divided into married/living with someone or other, which included divorced, never married, separated, widowed, and single. Clinical information including age, performance status, comorbidities, height,

weight, and pulmonary function testing (if performed) was obtained at the patient's initial visit and reported by providers. Treatment information including concurrent chemotherapy use, RT dose and fractionation, imaging modalities used, and dosimetric data were also reported by providers. Distance to treatment site was calculated using the distance in miles between the centroid of the patient's home ZIP Code and ZIP Code for their MROQC treatment site. Weight loss percentage at the end of RT, 1 month, and 3 months following RT was calculated as the difference between weight at each time point and baseline weight divided by baseline weight. Physician assessments of toxicity were collected at baseline before RT, weekly during RT, 1 month after RT, and 3 months after RT. Toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, on standardized forms with incident grade 2 or worse (G2+) toxicity as the main outcome. "During RT" toxicity reflects the maximum incident toxicity on any assessment through the end of RT. Treatment breaks specifically due to toxicity were physician-reported on assessment forms collected at the end of RT. PROs included the validated Functional Assessment of Cancer Therapy −Lung Trial Outcome Index (FACT-L TOI), version 4.0, for lung cancer and a single-question swallowing assessment collected at baseline, end of RT, 1 month after RT, and 3 months after RT. The swallow assessment was also collected weekly during RT. For the swallowing assessment ("Select the one response that best describes your swallowing ability over the past week"), "No problems swallowing" and "Mild soreness only" were combined in analysis, as were "Can swallow solids with some difficulty," "Cannot swallow solids," and "Cannot swallow liquids," which were classified as G2+. Table E1 shows the assessment response rates.

## Statistical analysis

We assessed differences in patient demographic and clinical factors, treatment characteristics, physician-assessed toxicity, and patient swallowing assessment between the once-daily and twice-daily fractionation groups using Wilcoxon rank sum tests or Fisher exact tests as indicated. The proportion of patients treated twice daily over time was analyzed with a Cochran-Mantel-Haenszel statistic stratified by treatment site with comparison of years 2014 to 2016 versus 2018 to 2020. These were chosen to encompass periods of time before and after the publication of the CONVERT trial results in 2017. Between treatment site variability in proportion of twice-daily RT was tested with a $\chi^2$ statistic. We used multilevel logistic regression to model the influence of RT fractionation and other patient-level variables on the odds of a treatment break specifically due to toxicity as reported by the treating physician. A second level was used to cluster patients by treatment site to account for practice-pattern similarities in potential for treatment break among different practice groups. Differences in weight loss were assessed with $t$ tests (or paired $t$ tests if within the same group between timepoints). We modeled longitudinal FACT-L TOI and Functional Assessment of Cancer Therapy−Lung Cancer Subscale (FACT-LCS) scores using mixed-effects linear regression with a random intercept for each patient to account for correlated scores over time within each patient. Longitudinal FACT-L TOI and FACT-LCS scores at each timepoint were formulated as absolute change from baseline with clinically meaningful differences of 2 points for FACT-LCS and 5 points for FACT-L TOI as has been previously reported.[14] We assessed the influence of RT fractionation group on longitudinal FACT-L TOI and FACT-LCS changes at each timepoint by including an interaction term between fractionation group and time. SAS Studio, version 3.8, and RStudio, version 1.4.1106, were used for all analyses. A significance level of 0.05 was used with 2-sided testing and no formal multiplicity adjustments were made.

# Results

## Patient characteristics associated with RT fractionation

Prospective patient-level demographic, clinical, and treatment data in addition to physician-assessed and patient-reported acute toxicity was collected from 29 participating academic and community practice treatment sites of 3884 patients treated with RT for lung cancer from 2012 to 2021, of whom 680 (17.5%) had SCLC. Of these 680 patients, 499 had LS-SCLC and known RT fractionation and represent the analyzed population. Throughout the consortium, 78 of 499 patients (15.6%) were treated with twice-daily RT fractionation, and this proportion was relatively constant over time comparing periods before (2014-2016, 13.9%) and after (2018-2020, 17.5%) publication of the CONVERT trial results (Fig. 1A; $P = .17$).

Table 1 depicts the patient clinical and demographic factors associated with once-daily or twice-daily RT. The groups were similar across a range of factors including age, pulmonary function, and Eastern Cooperative Oncology Group (ECOG) performance status with most patients (52% of each group) having a performance status of 0. More twice-daily patients had no major medical comorbidities than the once-daily patients (24% vs 10%, respectively; $P = .017$). Twice-daily patients were also more likely to report being married or living with someone than once-daily patients (65% vs 51%, respectively; $P = .019$). There was significant variability in the proportion of patients treated twice daily among all treatment

**Table 1 Patient characteristics**

| Characteristic | All patients, N = 499* | Radiation therapy fractionation | | *P* value† |
|---|---|---|---|---|
| | | Once daily, n = 421* | Twice daily, n = 78* | |
| Age | 66 (59-72) | 66 (59-72) | 65 (58-71) | .3 |
| Sex | | | | >.9 |
| Female | 303 (61%) | 256 (61%) | 47 (60%) | |
| Male | 196 (39%) | 165 (39%) | 31 (40%) | |
| ECOG performance status | | | | .4 |
| 0 | 227 (52%) | 191 (52%) | 36 (52%) | |
| 1 | 155 (36%) | 130 (36%) | 25 (36%) | |
| 2 | 40 (9.2%) | 32 (8.7%) | 8 (12%) | |
| 3+ | 13 (3.0%) | 13 (3.6%) | 0 (0%) | |
| Comorbidity count | | | | .017 |
| 0 | 63 (13%) | 44 (10%) | 19 (24%) | |
| 1 | 130 (26%) | 108 (26%) | 22 (28%) | |
| 2 | 144 (29%) | 128 (30%) | 16 (21%) | |
| 3 | 83 (17%) | 72 (17%) | 11 (14%) | |
| 4+ | 79 (16%) | 69 (16%) | 10 (13%) | |
| Body mass index | | | | .5 |
| Underweight | 83 (17%) | 71 (17%) | 12 (15%) | |
| Normal | 136 (27%) | 109 (26%) | 27 (35%) | |
| Overweight | 135 (27%) | 116 (28%) | 19 (24%) | |
| Obese | 145 (29%) | 125 (30%) | 20 (26%) | |
| Weight loss at diagnosis (%) | 0.0 (0.0-1.0) | 0.0 (0.0-0.0) | 0.0 (0.0-3.5) | .5 |
| Smoking status | | | | .14 |
| Current | 228 (46%) | 186 (44%) | 42 (55%) | |
| Former | 259 (52%) | 226 (54%) | 33 (43%) | |
| Never | 9 (1.8%) | 7 (1.7%) | 2 (2.6%) | |
| Smoking duration (pack-years) | 45 (30-60) | 45 (30-60) | 40 (30-52) | .3 |
| Oxygen at start of treatment | | | | .3 |
| No | 435 (88%) | 364 (87%) | 71 (92%) | |
| Yes | 59 (12%) | 53 (13%) | 6 (7.8%) | |
| Spirometry performed | 193 (39%) | 161 (39%) | 32 (41%) | .7 |
| $FEV_1$ (L) | 1.88 (1.38-2.42) | 1.83 (1.36-2.39) | 1.96 (1.69-2.48) | .3 |
| $FEV_1$ (% predicted) | 69 (52-85) | 69 (52-86) | 69 (48-80) | .5 |
| Diffusing capacity measured | 157 (33%) | 134 (33%) | 23 (31%) | .8 |
| DLCO (% predicted) | 58 (47-74) | 58 (46-73) | 59 (49-76) | .4 |
| Practice setting | | | | .5 |
| Academic | 99 (20%) | 86 (20%) | 13 (17%) | |
| Community | 400 (80%) | 335 (80%) | 65 (83%) | |
| Distance to treatment site (miles) | 11 (5-21) | 11 (5-22) | 11 (5-20) | .8 |
| Social status | | | | .019 |
| Married or living with someone | 265 (53%) | 214 (51%) | 51 (65%) | |
| Other | 234 (47%) | 207 (49%) | 27 (35%) | |

*Abbreviations:* DLCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; $FEV_1$ = forced expiratory volume in 1 second.
*Median (interquartile range); no. (%).
† Wilcoxon rank sum test; Fisher exact test.

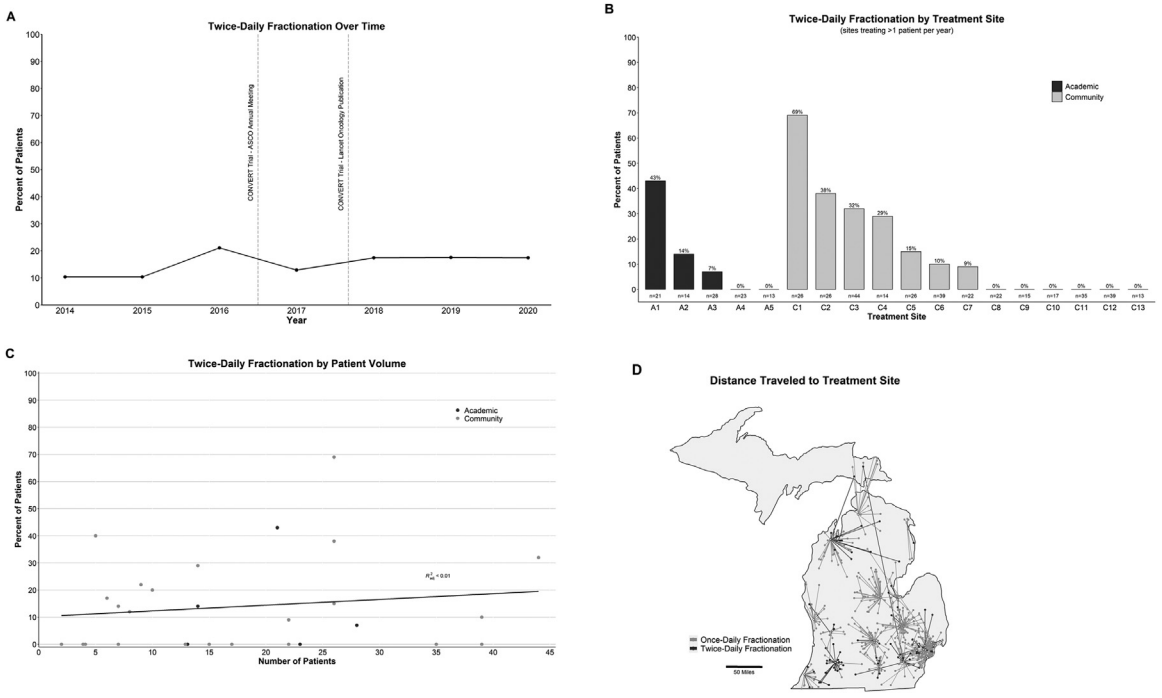


**Figure 1** Characterization of twice-daily fractionation use. The proportion of patients with limited-stage small cell lung cancer treated with (A) twice-daily radiation therapy fractionation did not change over time, (B) significantly varied based upon treatment site, (C) was not correlated with treatment site patient volume, and (D) was not associated with the distance a patient lived from their treatment site.

sites, as depicted in Figs. 1B and E1, ranging from 0% to 69% ($P < .001$). However, this was not explained by practice setting with rates of twice-daily RT use similar between academic (13 of 99 patients, 13%) and community (65 of 400, 16%) treatment sites when aggregated (Fig. 1B, Table 1; $P = .5$), nor was it correlated with patient volume (Fig. 1C; adjusted $R^2 < .01$). Furthermore, there was no difference between once- and twice-daily treated patients in average distance traveled to a treatment site for RT (Fig. 1D, Table 1; median, 11 miles both groups; $P = .8$).

## Treatment characteristics

Table 2 depicts the treatment specifics of the once-daily and twice-daily RT cohorts. In the once-daily RT group, the median dose was 60 Gy with a median number of 30 fractions with 351 patients (83.3%) receiving 59.4 Gy to 70.2 Gy in once-daily fractions at 1.8 to 2.0 Gy/fraction. Nearly all patients (75, 96%) in the twice-daily RT group were treated with 45 Gy in 30 fractions. The rates of concurrent chemotherapy were similar between groups with 91% receiving guideline-directed cisplatin or carboplatin plus etoposide. The rates of lymph nodes targeted in treatment and usage of intensity modulated RT were also similar between once-daily and twice-daily treated groups. There were no differences in proximity of the planning treatment volume (PTV) to the esophagus nor in mean size of the PTVs between the 2 groups (398 cc once daily vs 418 cc twice daily; $P = .4$). PET-guided target delineation was used in 62% of patients with rates similar between groups.

## RT fractionation toxicity

Although the majority of patients in each group completed treatment without a break, approximately 4-fold more patients were reported by physicians to require a treatment break specifically due to toxicity in the once-daily RT group than in the twice-daily RT group (Fig. 2A; 25% vs 6%, respectively; $P < .001$). The once-daily RT fractionation regimen remained significantly associated with increased odds of a treatment break even after clustering by treatment site and adjusting for other baseline patient and treatment factors, including the presence of the most common G2+ toxicities at baseline (esophagitis, fatigue, dyspnea) and comorbidity count. The adjusted odds ratio (aOR) for increased likelihood of a treatment break with once-daily RT fractionation was 4.11 (95% CI, 1.31-12.87). Other factors significantly associated with increased likelihood of treatment break include being underweight (aOR, 4.22; 95% CI, 1.54-11.56), being overweight (aOR, 3.82; 95% CI, 1.48-9.90), receiving concurrent chemotherapy (aOR, 5.39; 95% CI, 1.10-26.35), and a

**Table 2 Treatment characteristics**

| Characteristic | All patients, N = 499* | Radiation therapy fractionation | | *P* value† |
|---|---|---|---|---|
| | | Once daily, n = 421* | Twice daily, n = 78* | |
| Received any chemotherapy | 482 (98%) | 405 (98%) | 77 (99%) | >.9 |
| Received concurrent platinum-etoposide | 398 (91%) | 333 (92%) | 65 (89%) | .5 |
| Total dose (Gy) | - | 60.0 (60.0-64.8) | 45.0 (45.0-45.0) | - |
| Fractions | - | 30 (30-33) | 30 (30-30) | - |
| 4DCT acquired | 405 (81%) | 335 (80%) | 70 (91%) | .024 |
| PET used in planning | 302 (62%) | 249 (61%) | 53 (69%) | .2 |
| Lymph nodes targeted | 141 (56%) | 121 (57%) | 20 (56%) | >.9 |
| IMRT delivered | 349 (70%) | 294 (70%) | 55 (71%) | >.9 |
| Daily CBCT acquired | 295 (59%) | 236 (56%) | 59 (76%) | .001 |
| Esophagus within 2 cm of PTV | 470 (94%) | 398 (95%) | 72 (92%) | .4 |
| PTV volume (cc) | 402 ± 276 | 398 ± 278 | 418 ± 267 | .4 |

*Abbreviations*: 4DCT = 4-dimensional computed tomography; CBCT = cone beam computed tomography; IMRT = intensity modulated radiation therapy; PET = positron emission tomography; PTV = planning target volume.
*No. (%); median (interquartile range); mean ± standard deviation.
† Wilcoxon rank sum test; Fisher exact test.

larger PTV (aOR, 1.15/100 cc; 95% CI, 1.01-1.31). These and other factors' aOR are shown in Fig. 2B and detailed in Table E2. There was no trend between the percentage of patients requiring a treatment break and the percentage of patients treated with twice-daily fractionation (Fig. E2).

During RT, the once-daily treated patients had significantly greater rates of incident G2+ physician-assessed toxicity and numerically worse patient-reported swallow ability than the twice-daily treated patients as shown in Fig. 3A and Tables E3 and E4. Rates of G2+ toxicity in once-daily and twice-daily patients at any time during RT were esophagitis 55% versus 39% ($P$ = .013), esophageal pain 36% versus 23% ($P$ = .036), cough 14% versus 3.9% ($P$ = .009), fatigue 40% versus 21% ($P$ = .001), and swallow ability 61% versus 48% ($P$ = .082). Further, at the end of treatment, once-daily treated patients had lost significantly more weight as a percent of baseline than twice-daily treated patients (Fig. 3B; mean, −2.3% vs 0.8%; $P$ = .039).

Whereas the once-daily cohort had greater rates of toxicity during RT, the twice-daily cohort had more pronounced toxicity at 1 month following RT (Fig. 3A, Tables E3 and E4). At 1 month, 22% of twice-daily treated patients versus 8.6% of once-daily treated patients had G2+ esophagitis ($P$ = .02), and 40% of twice-daily treated patients versus 18% of once-daily treated patients

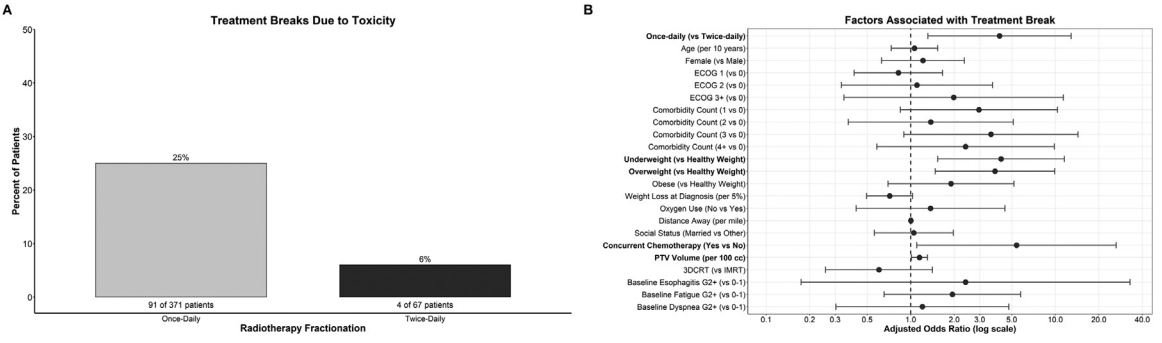


**Figure 2** Treatment breaks for toxicity by radiation therapy fractionation. (A) Patients treated with once-daily radiation therapy fractionation were significantly more likely to experience a treatment break for toxicity. (B) This significant association persisted in multivariable logistic regression analysis controlling for patient-level variables. *Abbreviations:* 3DCRT = 3-dimensional conformal radiation therapy; ECOG = Eastern Cooperative Oncology Group; IMRT = intensity modulated radiation therapy; PTV = planning target volume.

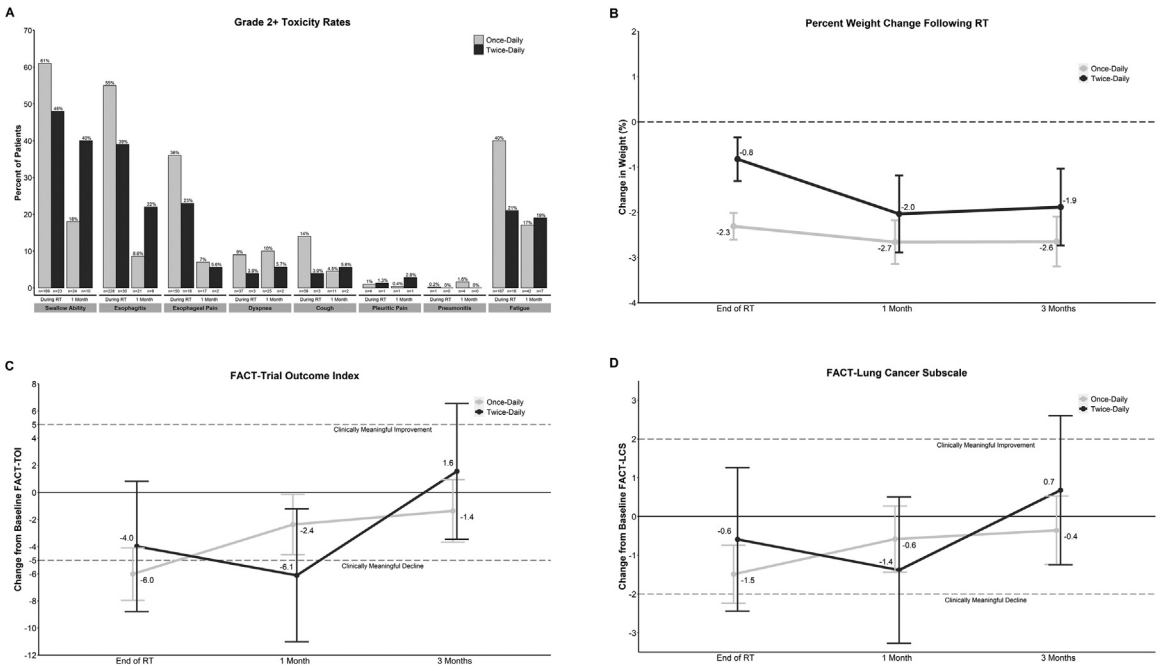


**Figure 3** Time-course of physician- and patient-reported toxicity by radiation therapy fractionation. The time-course of peak toxicity differed between patients treated with once-daily and twice-daily radiation therapy (RT) regimens. (A) The pattern of peak toxicity during or at the end of RT for once-daily treated patients and peak toxicity 1 month after RT for twice-daily treated patients was consistent across physician-assessed toxicity, (B) an objective measure of toxicity, and (C, D) patient-reported outcomes. (A) Rates of incident G2+ toxicity during and 1 month after RT. (B) Average percent weight loss ± standard error of the mean in each group over time. (C, D) Mixed-effects linear regression model estimate of change from baseline score in Functional Assessment of Cancer Therapy (FACT)-Trial Outcome Index and FACT-Lung Cancer Subscale ±95% confidence interval over time. Score changes of ±5 (FACT-Trial Outcome Index) and ±2 (FACT-Lung Cancer Subscale) were used as clinically meaningful differences with higher scores indicative of better quality of life.

reported G2+ swallow ability ($P$ = .017). The rate of G2+ fatigue followed a similar trend. The twice-daily RT group also continued to lose weight from the end of treatment through 1 month (mean, −0.8% vs −2.0%; $P$ = .023), while the once-daily RT group's weight loss largely plateaued (mean, −2.3% vs −2.7%; $P$ = .3).

PROs using change from baseline FACT-L TOI and FACT-LCS (higher values indicate better quality of life) depict a similar temporal trend in greatest toxicity as the other metrics. Once-daily treated patients had a clinically meaningful decline in their quality of life that was most pronounced at the end of RT (−6.0; 95% CI, −8.0 to −4.1; $P$ < .001) and then improved through 1 and 3 months of follow-up (Fig. 3C, light line). The twice-daily treated patients' quality of life was not statistically different from baseline at the end of RT (−4.0; 95% CI, −8.8 to 0.8; $P$ = .092) and only reached the greatest clinically meaningful decline at 1 month after treatment (−6.1; 95% CI, −11.0 to −1.2; $P$ = .025) before improving at 3 months (Fig. 3C, dark line). Figure 3D shows that the FACT-LCS change from baseline scores followed a similar trend as the FACT-L TOI scores with peak toxicity at the end of RT in the once-daily patients and at 1 month after RT in the twice-daily patients. Although the mean score changes never surpassed a clinically meaningful decline, some patients likely did experience meaningful worsening of their FACT-LCS score.

## Discussion

Despite evidence in its favor, the twice-daily fractionation regimen for LS-SCLC remains infrequently prescribed (15.6%) in this large contemporary multicenter prospectively collected cohort. There was no change in utilization rates within our statewide quality consortium following the publication of the CONVERT trial results. MROQC's twice-daily fractionation rate is slightly lower than contemporary physician survey data of the US (24%) and Canada (33%), but this may reflect a possible optimistic estimation bias when responding to surveys.[8,9] Reasons physicians have cited a preference for a once-daily fractionation regimen include logistical considerations (more convenient for the clinic and patient), the perception that it is better tolerated than twice-daily regimens, and the incorrect

interpretation of treatment equivalence of the superiority-designed CONVERT trial.[8,15,16]

Prior US national and international studies have found an increased rate of twice-daily RT use with high patient volume, more recent treatment, male sex, and closer living proximity to the treatment site in addition to greater twice-daily RT rates at academic versus community practices.[6-8,17] Younger age and better performance status have inconsistently been associated with increased use of twice-daily fractionation.[6,7,17] In our cohort, we found no difference in twice-daily fractionation use between academic and community practices, patient volume, sex, or distance from treatment site and no change over time in contrast to the aforementioned published reports. We also saw no difference based upon patient age or performance status as has been reported but did note that a greater percentage of twice-daily treated patients had no major medical comorbidities. A possible explanation for the disparity between our current findings and prior reports is that previous differences were primarily detected in large database studies that made indirect inferences on RT fractionation[6,17] or reflected physician opinion that may not correlate with treatment delivered.[8,9] Our findings are more aligned with those from the Quality Research in Radiation Oncology study that collected robust RT dosimetric data and saw no difference in twice-daily RT utilization by age or performance status.[7] No data has been reported in prior studies on number of comorbidities or marital status. The consistent variability seen across nearly all prior studies, and our present work is a high variation in twice-daily use by treatment site, with a reasonable explanation that practicing physicians have adopted a preferred RT regimen for LS-SCLC and continue with it.[6-9,16,17] The high treatment site variability in RT fractionation practice patterns has also been noted before in a breast cancer fractionation analysis.[18]

An interesting finding in our work not previously seen is a greater proportion of twice-daily treated patients reporting being married or living with someone. Perhaps this is a surrogate, albeit imperfect, for the presumed easier logistic burden of twice-daily treatment when one has a close personal connection that may share in or assume the commute or other inconveniences. These inconveniences of 2 treatments per day, a minimum of 6 hours apart, which may include 2 daily roundtrips to a treatment center, are often cited and easy to see in the upfront setting as a reason patients and providers may elect a longer course of once-daily treatment.[8,15,16] However, our data indicate there is a potential hidden inconvenience with once-daily treatment given the approximately 4-fold increased odds of a treatment break due to toxicity. For 25% of once-daily treated patients, their treatment length was extended from a median of 45 days to 52 days in contrast to the 94% of twice-daily treated patients with median treatment length of 20.5 days. This discrepancy was indicated on the CONVERT trial, where 63% of patients treated twice-daily versus 48% of those treated once-daily completed RT in the planned overall treatment time of 19 days and 45 days, respectively ($P = .0004$).[2] Therefore, with this knowledge, it is possible a patient may ultimately elect for the most likely shorter 3-week, twice-daily regimen if they knew they may have a 1 in 4 chance of a treatment break for toxicity and nearly 2 months of daily RT.

Better tolerance of the once-daily RT regimen is another frequently cited reason to prefer daily treatment over twice-daily RT.[5,8,16] However, the randomized evidence from the CONVERT trial and abstract report of the ongoing CALGB 30610/RTOG 0538 trial combined with our prospectively collected toxicity data from patients treated with modern RT techniques unequivocally shows this to be simply incorrect—there is not sufficient evidence to conclude toxicity superiority of either regimen. Rates of G3+ esophagitis on the CONVERT trial were equal at 19% in each arm and appear similar on CALGB 30610/RTOG 0538 with rates of G3+ dysphagia and esophageal pain ranging from 9.5% to 11.6%.[2,10,11] Our data show similar rates and magnitudes of acute toxicity as on the randomized trials. However, some temporal differences between once- and twice-daily RT toxicity profiles start to appear when analyzed for incident toxicity more granularly by time. We found that peak toxicity for once-daily treated patients occurs during RT in contrast to toxicity for twice-daily treated patients, who appear to peak after treatment is completed. This difference in peak toxicity timing between RT fractionation regimens would be predicted radiobiologically, and a recent study including PRO measures and an oral intake catalog is in agreement with our findings.[19] In this study, 10 of 12 patients were treated with twice-daily or moderate hypofractionation with concurrent chemotherapy for LS-SCLC, and we found that peak toxicity across a variety of measures was at 1 month after treatment.[19] This difference in peak toxicity timing between RT fractionation regimens likely partially explains the difference in treatment breaks seen in our data.

Our work has some limitations, most notably the nonrandomized nature of the design and lack of oncologic outcomes data, which has only recently been collected as part of the MROQC collaborative and with too small numbers in the LS-SCLC cohort for meaningful analysis. While 98% of patients received any chemotherapy and the overwhelming majority (91%) received guideline-recommended concurrent platinum-etoposide, the dose and number of chemotherapy cycles received and infusion dates were not captured, potentially confounding our results. More patients treated twice daily had no comorbidities, potentially decreasing their likelihood of treatment break due to toxicity; however, the once-daily fractionation regimen remained significantly associated with higher likelihood of break after adjusting for comorbidity count, and it should be noted that the 2 cohorts were otherwise similarly aged, had similar performance status, and had similar proportions of patients with a high number of comorbidities (33.5% once daily and 26.9% twice daily with 3+ comorbidities). The use of

prophylactic cranial irradiation was not collected as part of the prospective database; therefore, the rates could vary between the once-daily and twice-daily groups. Yet generally this is recommended to start after acute toxicity from thoracic RT has resolved and, therefore, is unlikely to affect the toxicity differences reported here in earlier periods during RT and 1 month after RT. Additional limitations with the nonrandomized design include the smaller number of patients treated twice daily, and the majority of them receiving care from a few treatment sites could make our results more susceptible to confounding by treatment site-related factors such as the willingness of individual physicians to give patients a treatment break. Patients' desire for a treatment break could also have been unbalanced without randomization. Nevertheless, we believe the prospective collection of a rich array of patient, treatment, and toxicity data in a cohort nearly as large as the randomized CONVERT trial allow for significant conclusions about real-world acute toxicity profiles of physician-reported outcomes and PROs for once- and twice-daily RT regimens.

## Conclusion

Overall, with modern RT techniques, the majority of patients complete concurrent chemotherapy RT delivered either once or twice daily as intended with reasonable rates of expected moderate acute toxicity that predominantly recover by 3 months. The toxicity differences between RT fractionations seen on the Intergroup 0096 trial[1] can be attributed to the different biologically equivalent doses delivered and now older RT techniques. In the modern era with the widespread availability of 4-dimensional computed tomography simulation, PET-guided treatment planning, intensity modulated RT, and daily cone beam CT alignment, which were used in many of the patients in our cohort, these toxicity differences are no longer seen and should not be a factor in RT fractionation decision making. Rather, our work highlights peak toxicity timing differences between once- and twice-daily RT fractionation regimens and higher rates of treatment breaks specifically for toxicity with once-daily regimens. Therefore, these factors should be used instead to frame the shared decision-making process about which RT fractionation regimen to select when discussing with a patient who has LS-SCLC. With a lack of superior efficacy of once-daily fractionation and the lower likelihood of a treatment break with twice-daily fractionation, more providers and patients may start using the twice-daily regimen.

## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2023.04.007.

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