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ORIGINAL RESEARCH

High-Dose Twice-Daily Thoracic Radiotherapy for Limited-Stage Small-Cell Lung Cancer: A Real-World Retrospective Experience from Two Tertiary Centers

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Background: Hyperfractionated thoracic radiotherapy (RT) is a standard component of curative treatment for limited-stage small-cell lung cancer (LS-SCLC). While 45 Gy in 30 twice-daily fractions remains the most validated regimen, recent Phase II data suggest that dose-escalated RT using 60 Gy in 40 fractions may improve outcomes. However, real-world data on this intensified regimen remain scarce.

Methods: We conducted a retrospective cohort study of LS-SCLC patients treated with 60 Gy in 40 twice-daily fractions and concurrent platinum-etoposide chemotherapy at two tertiary centers. Modern radiation techniques were employed. Key outcomes included overall survival (OS), progression-free survival (PFS), patterns of failure, and treatment-related toxicity.

Results: Thirteen patients were included in the analysis. The median age at diagnosis was 59 years; 61.5% were female. At a median follow-up of 15 months, the 2-year OS rate was 71.4%, and the median OS was 30.9 months. The overall response rate was 60%. Most failures were distant; only one local failure was observed. Acute grade ≥3 esophagitis occurred in 7.6%, and no patients experienced grade ≥2 pneumonitis. Hematologic toxicity, particularly neutropenia, was frequent but manageable. No treatment-related deaths occurred.

Conclusion: In this cohort, delivery of dose-escalated twice-daily thoracic radiotherapy using contemporary techniques was feasible and associated with acceptable toxicity in routine clinical practice. Survival outcomes were comparable to those reported in phase II studies of this approach. These findings warrant confirmation in larger, multi-institutional, or registry-based studies.

Plain Language Summary: Small-cell lung cancer is a fast-growing type of lung cancer that often spreads quickly. When it is found early and is still confined to one area of the chest, it is called "limited-stage" disease. In these cases, doctors treat patients with a combination of chemotherapy and radiation. A common approach is to give radiation twice a day for 3 weeks, which has been shown to help patients live longer. However, some recent studies suggest that giving a higher total dose of radiation over 4 weeks might work even better, without adding more side effects.

In this study, we looked at 13 patients with small-cell lung cancer who were treated at two major hospitals. All patients received the higher radiation dose (60 Gy) twice a day, along with standard chemotherapy. We aimed to see how well this treatment worked in real-world settings and whether it was safe.

We found that this treatment approach was generally well tolerated and showed promising results: most patients responded to the treatment, and serious side effects were uncommon. After 2 years, more than 70% of the patients were still alive, which is similar to results seen in clinical trials. Most cancer recurrences happened in other parts of the body, not in the thorax.

These findings suggest that giving a higher dose of radiation twice a day is a practical and effective option for treating limited-stage small-cell lung cancer outside of clinical trials. This approach could help improve survival in some patients without causing more harm.

Keywords: small-cell lung cancer, dose-escalation, radiation therapy

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Introduction

Small cell lung cancer (SCLC) represents approximately 15% of all lung cancer cases and is characterized by rapid growth, early dissemination, and high initial sensitivity to chemoradiotherapy.[1,2] Despite the recent advances in SCLC, prognosis remains poor, particularly in extensive-stage disease. For patients with limited-stage SCLC (LS-SCLC), combined modality therapy remains the cornerstone of treatment, with thoracic radiotherapy (RT) playing a pivotal role in achieving durable local control and improving survival.[3]

The historical foundation of thoracic RT in LS-SCLC was laid by the landmark Intergroup 0096 trial, which demonstrated a significant survival advantage with hyperfractionated twice-daily (BID) RT (45 Gy in 1.5 Gy BID fractions over 3 weeks) compared to conventional once-daily (OD) regimens, albeit at the cost of increased esophagitis.[4] This trial established BID RT as the standard of care and was incorporated into clinical guidelines, including those of the National Comprehensive Cancer Network (NCCN), which continue to recommend 45 Gy in 1.5 Gy BID fractions delivered with concurrent platinum-etoposide chemotherapy as a preferred regimen.[5]

Nevertheless, the optimal RT dose and fractionation schedule in LS-SCLC remains a matter of controversy. Efforts to improve outcomes through dose escalation have primarily explored higher total doses using OD regimens. The CONVERT trial compared 45 Gy BID with 66 Gy in 33 OD fractions and found no significant difference in overall survival, though toxicity profiles were comparable.[6] Similarly, the CALGB 30610 (RTOG 0538) trial randomized patients to 45 Gy BID versus 70 Gy OD, again showing no survival benefit for the escalated dose and reaffirming 45 Gy BID as a valid standard.[7]

A notable divergence from the OD dose-escalation paradigm was the Norwegian phase II trial by Gronberg et al, which investigated a novel intensification approach using 60 Gy in 40 BID fractions over 4 weeks. This regimen preserved the BID schedule while increasing the total dose, aiming to improve tumor control without prolonging overall treatment time.[8] The study reported promising 2-year survival rates and acceptable toxicity, suggesting that BID dose escalation may overcome the limitations seen with OD intensification.

Although results were encouraging, adoption of the 60 Gy BID regimen has been limited outside of clinical trials, and there is a paucity of real-world data evaluating its effectiveness and safety. Most existing evidence derives from rigorously controlled studies with rigid eligibility criteria, which potentially limits generalizability to broader, unselected patient populations. Moreover, implementing modern radiation techniques, such as intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), may improve toxicity and outcomes, yet their use in BID dose escalation has not been well characterized.

In this study, we present a retrospective, multi-institutional analysis of LS-SCLC patients treated with 60 Gy in 40 BID fractions using contemporary radiation techniques at two tertiary centers. Our objectives were to assess the real-world feasibility and safety of this intensified regimen and to describe observed outcomes in the context of previously reported trial data. This study aims to contribute feasibility data relevant to the evolving use of twice-daily thoracic radiotherapy in limited-stage small-cell lung cancer.

Methods

Study Design and Patient Sample

This retrospective cohort study was conducted at two tertiary cancer centers. Consecutive patients diagnosed with LS-SCLC between 2020 and 2023 who received concurrent CRT with a dose-escalated, twice-daily RT regimen of 60 Gy in 40 fractions over 4 weeks were included. All patients underwent baseline staging with a PET-CT and brain MRI and were reviewed in a multi-disciplinary tumor board. Eligibility was based on a biopsy-confirmed SCLC, with disease classified as limited-stage and confined to a single hemithorax, making the patient suitable for definitive CRT. Patients were excluded if they had a history of prior thoracic RT.

Treatment Protocol

Chemotherapy consisted of platinum-etoposide regimens. Cisplatin (75–80 mg/m^2) or carboplatin (AUC 5–6) was administered on day 1, with etoposide (100 mg/m^2) given on days 1 through 3, repeated every 3 weeks for 4–6 cycles. Dose reductions were implemented based on hematologic and non-hematologic toxicities at the discretion of the treating physician.

Radiotherapy was delivered using intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) based on institutional protocols. Gross tumor volume (GTV) included the primary tumor and involved lymph nodes, delineated using pretreatment PET-CT. The total prescribed RT dose was 60 Gy, delivered in 40 fractions of 1.5 Gy twice daily, 5 days per week over 4 weeks. Clinical Target Volume (CTV) and Planning Target Volume (PTV) were at the treating physicians' discretion but usually consisted of a 3–5 mm GTV to CTV expansion and a 3–5 mm CTV to PTV expansion. This was based on daily IGRT imaging.

In case of disease volume reduction between the imaging done on staging and the planning CT (due to start of systemic therapy) - the primary tumor as seen on the planning CT was considered the GTV and the involved lymph-node stations were considered the CTV.

Organ-at-risk constraints included a mean lung dose ≤20 Gy, V20 lung ≤35%, mean heart dose ≤35 Gy, and esophageal maximum dose ≤60 Gy. Prophylactic cranial irradiation (PCI) was offered for patients achieving a complete or partial response following CRT.

Outcomes and Assessments

The study evaluated overall survival (OS) and progression-free survival (PFS) as key oncologic outcomes. OS was calculated as the time from systemic treatment initiation to death from any cause, while PFS was measured as the time from treatment initiation to documented disease progression or death, based on available follow-up data. Secondary outcomes included treatment response, patterns of failure, and treatment-related toxicity. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Response assessment was done per physician discretion, generally 4–8 weeks after completion of chemoradiation. Failure patterns were classified as local, regional, or distant based on imaging findings at disease progression. Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, treatment characteristics, and toxicity profiles. OS and PFS were estimated using the Kaplan–Meier method, with censoring applied for patients alive or progression-free at the last follow-up. Median survival estimates and 95% confidence intervals (CI) were reported. Statistical analyses were conducted using SAS version 9.4.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Rabin Medical Center institutional review board (IRB #0343-22) of both participating centers (a single IRB). Given the retrospective nature of the study, informed consent was waived. All patient data were handled in a de-identified manner, and strict confidentiality of medical records was maintained throughout data collection and analysis.

Results

Patient Characteristics

A total of 13 patients with small-cell lung cancer were included in the study. The median age at diagnosis was 59 years (range: 46–70), and 61.5% of patients were female. The majority of patients (69.2%) were current smokers at the time of diagnosis. ECOG performance status was 0 in 61.5% of patients and 1 in 38.4%. At diagnosis, 23% of patients had stage IIIA disease, 46% had stage IIIB and 7% had stage IIIC. Three patients (23%) were initially considered to have limited-stage disease based on clinical assessment and imaging but were subsequently upstaged to stage IV due to ambiguous or equivocal findings. These cases were retained to reflect real-world staging uncertainty and treatment decision-making in SCLC, recognizing this as a source of clinical heterogeneity. In all three cases, these findings were not definitively confirmed as metastatic disease at baseline and did not preclude treatment with curative-intent chemoradiation. Given the absence of widespread metastases and the multidisciplinary consensus that aggressive local therapy remained appropriate, these patients were managed using the same protocol as the limited-stage cohort (See Table 1 for patient characteristics).

Table 1 Patient Characteristics

Variable (at diagnosis)		All, n (%)
All patients, n (% of all)		13 (100)
Age, median (range)		59 (46–70)
Sex	Male	5 (38.4)
	Female	8 (61.5)
ECOG performance status	0	8 (61.5)
	1	5 (38.4)
Disease stage	IIIA	3 (23)
	IIIB	6 (46)
	IIIC	1 (7)
	IV	3 (23)
Smoking status	Former	4 (30.7)
	Current	9 (69.2)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Treatment Outcomes

All patients received concurrent platinum-based chemotherapy. The median number of chemotherapy cycles completed prior to the start of radiotherapy was 2 (range: 1–4). One patient (7.7%) had missing data regarding the start date of his chemotherapy. Chemotherapy dose reductions were required in 15.3% of cases. The planned thoracic radiotherapy was completed by 92.3% of patients. Prophylactic cranial irradiation (PCI) was administered to 15.4% of patients. The best response to chemoradiotherapy was a complete response (CR) in 46.2% of patients and a partial response (PR) in 15.4%, for total response rate of 60%. Three patients (23.1%) experienced progressive disease (PD), while two patients (15.4%) had non-evaluable response status. Among the patients who progressed, local failure was observed in only one patient (7.7%), while the remaining patients developed distant metastases as their first site of recurrence (see Table 2 for treatment outcomes). At a median follow-up of 15 months, the median OS was 30.9 months (95% CI: 14.3-NR). The 12-month OS rate was 100% and the 24-month OS rate was 71.4%. PFS was observed with a median of 9.1 months (95% CI: 6.1-NR). The 6-month PFS rate was 91.7% and the 12-month PFS rate was 34.9% (see Figure 1).

Toxicity and Safety

Treatment-related toxicities were observed in the majority of patients (see Table 3). The most common adverse event was esophagitis, affecting 69.2% of patients. Grade 1–2 esophagitis was reported in 61.5%, while grade 3 esophagitis was seen in only 7.6%. Neutropenia occurred in 61.5% of patients, with grade 1–2 in 23% and grade 3–4 in 38.4%. Pneumonitis was observed in 38.4% of patients, all of whom experienced grade 1 pneumonitis. No grade 2> pneumonitis was seen. No grade 5 events or treatment-related deaths were reported.

Dosimetric Parameters

The median gross tumor volume (GTV) was 156 cc (range: 36–444 cc). The mean lung dose was 15.03 Gy (range: 7.9–24.0 Gy), while the V20 lung dose was 22.72% (range: 14.5–33%). The mean heart dose was 12.25 Gy (range: 1.2–26.0 Gy), and the V30 heart dose was 9.49% (range: 0–22.02%).

Table 2 Treatment Outcomes

Outcome		**n (%)**
Any Chemotherapy dose reduction		2 (15.3)
Concurrent platinum agent	Cisplatin	7 (53.8)
	Carboplatin	5 (38.5)
	Unknown	1 (7.7)
Number of chemotherapy cycles prior to start of RT, Median (range)		2 (1–4)
Number of patients that had dose reductions		2 (15.3)
Completed radiation therapy		12 (92.3)
Completed prophylactic cranial irradiation		2 (15.3)
Response to chemoradiotherapy	Overall Response	8 (61.5)
	Complete response	6 (46.2)
	Partial response	2 (15.3)
	Stable disease	0
	Progressive disease	3 (23.1)
	Unknown	2 (15.4)

Discussion

Our real-world analysis of 13 LS-SCLC patients treated with high-dose twice-daily RT (60 Gy in 40 fractions) provides context to recent dose-escalation trials. Notably, Gronberg et al reported that 60 Gy BID significantly improved survival compared to the standard 45 Gy BID, without increasing toxicity.[8] In that phase II trial, the dose-escalated arm achieved a 2-year OS of 74% versus 48% in the conventional arm. Our observed 2-year OS of 71.4% is similar to Gronberg's findings, supporting the potential feasibility and effectiveness of 60 Gy BID even outside of clinical trial settings. This is particularly encouraging given that our cohort included patients with more advanced stages – including 23% with stage IV disease – and a real-world level of heterogeneity not present in trial populations. While selection bias cannot be excluded (ie, these patients may have been offered dose-escalated RT because of favorable clinical features), the comparable survival outcomes suggest that intensive BID fractionation may be successfully implemented in practice. Our findings offer real-world support for the notion that dose intensification through BID fractionation, rather than through once-daily escalation, is feasible and safe. The survival outcomes in our study were higher than those seen in large contemporary trials. For instance, the CONVERT trial found a 2-year OS rate of 56% with 45 Gy BID,[6] while the CALGB 30610 (RTOG 0538) trial showed median OS values of 30.1 months (70 Gy OD) and 28.5 months (45 Gy BID), with 5-year OS rates of 32% and 29%, respectively.[7] These findings reinforce that higher total dose alone, especially when delivered once daily, may not yield additional benefit. In contrast, our results align with the hypothesis that intensified twice-daily delivery over a shortened overall treatment time may be more impactful.

Toxicity and Safety

Given these encouraging outcomes, it is worth considering why this intensified regimen has not been more widely adopted – one likely concern is the potential for increased toxicity. Reassuringly, the high-dose BID approach was tolerable in our cohort, aligning with the safety profiles seen in modern trials. Acute esophagitis is a key dose-limiting toxicity in concurrent chemoradiation for SCLC. In the historic Intergroup 0096 study,[4] 45 Gy BID yielded 27% grade 3 esophagitis, roughly double that seen with once-daily RT – even as it improved 5-year survival from 16% to 26%. By

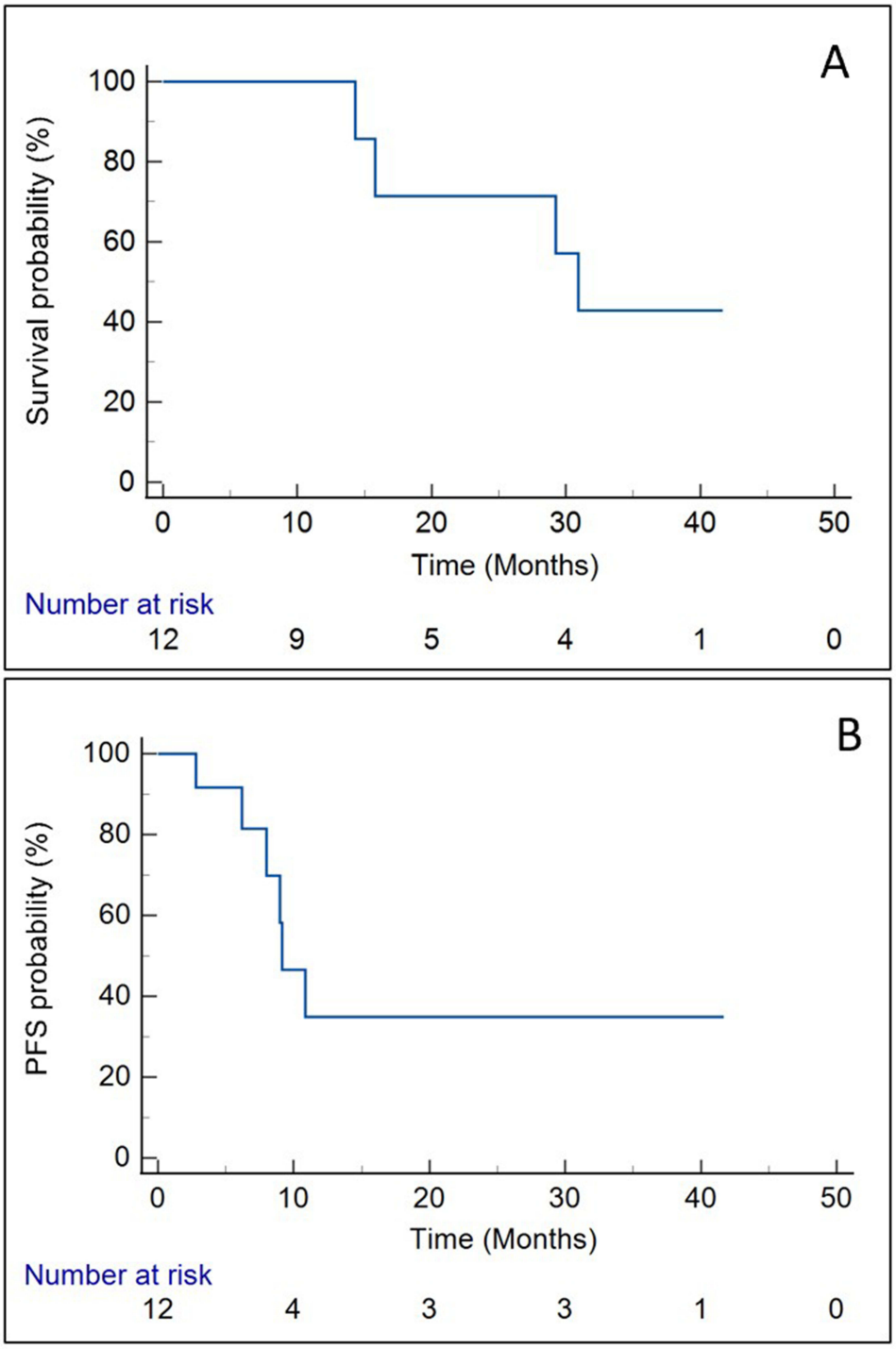

Figure 1 Survival outcomes for patients treated with dose-escalated radiation therapy. Kaplan–Meier curves for patients with limited-stage small-cell lung cancer treated with dose-escalated radiation therapy (60 Gy/40 fractions, bi-daily): Overall-survival (OS) (**A**) and progression-free survival (PFS) (**B**).

contrast, advances in RT planning have reduced esophageal toxicity in recent trials. Both CONVERT and CALGB 30610 reported roughly 15–20% incidence of grade 3–4 esophagitis in each arm,[6,7] with no significant difference between standard and high-dose regimens. Our real-world rate of severe esophagitis – grade 3 in one patient (7.6%) – is lower than to these figures, suggesting that 60 Gy BID did not lead to excessive esophageal toxicity outside of trial settings. We attribute this to modern IMRT techniques and strict dose constraints. Radiation pneumonitis was also low in our series –

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Table 3 Treatment-Related Toxicities

Adverse Evens		
Esophagitis	Grade 1–2	8 (61.5)
	Grade 3–4	1 (7.6)
Neutropenia	Grade 1–2	3 (23)
	Grade 3–4	5 (38.4)
Pneumonitis	Grade 1–2	5 (38.4)
	Grade 3–4	0

we recorded no grade 3+ pneumonitis – mirroring the low rates seen in other trials.[6,7] These data indicate that with contemporary practices, high-dose thoracic RT can be delivered without a surge in symptomatic pneumonitis. Hematologic toxicity, particularly neutropenia, remains a concern due to concurrent chemotherapy and mostly all patients in our cohort experienced significant myelosuppression, consistent with the trial experience. In CONVERT, 74% of patients had high-grade neutropenia. Interestingly, CONVERT noted slightly more grade 4 neutropenia with BID RT than OD (49% vs. 38%, $p = 0.05$), possibly reflecting the intensified schedule starting from cycle 1. In our study, concurrent cisplatin-etoposide led to several cases of grade 3–4 neutropenia, but these were medically managed without compromising the RT schedule. Importantly, we observed no treatment-related mortality. Overall, the safety profile of 60 Gy BID in practice appears comparable to historical 45 Gy BID regimens and to the high-dose arms of recent trials, with no new or unexpected toxicities. This suggests that the regimen's intensified dose did not translate into higher acute toxicity when delivered with modern supportive care.

Real-World vs. Trial Populations

Despite similar outcomes, our real-world cohort differed from trial populations in several ways. Trials typically enrolled healthier, younger patients with fewer comorbidities and more rigid treatment timelines. In contrast, our patients had more heterogeneity – 38% had ECOG 1, some had equivocal staging findings later deemed stage IV. Lower utilization of PCI in our series (15% vs. 80% in CONVERT and in Gronberg et al) could influence outcomes, as omitting PCI may increase brain relapse risk, which might translate into lower survival rates, as demonstrated in a meta-analysis by Auperin et al[9] In our cohort, the low PCI uptake likely reflects real-world factors, including patient preference, comorbidities, concerns regarding neurocognitive toxicity, and evolving practice patterns in which MRI surveillance is increasingly favored over routine PCI.[10] Given the very small sample size, we did not perform a subgroup analysis comparing outcomes with versus without PCI, as such analyses would be statistically unstable and potentially misleading.

Timing also varied, with RT starting after 1–4 chemotherapy cycles, potentially affecting disease control.[11] Nonetheless, outcomes were comparable, suggesting that 60 Gy BID can be safely and effectively delivered outside of trials. Selection bias likely played a role – these patients were probably deemed fit and motivated – but their inclusion still supports the regimen's generalizability. Real-world limitations, such as incomplete data and variability in follow-up, remain, yet our findings affirm that trial-era advances like modern RT planning have translated into practice. With thoughtful case selection and supportive care, this regimen appears feasible in non-trial settings.

Study Limitations

The most important limitation of this study is the very small sample size (n = 13), which substantially limits statistical power and makes survival estimates highly sensitive to individual events. With such a cohort, our calculated 2-year OS carries a wide confidence interval, and a single event can shift percentages substantially. Accordingly, results should not be interpreted as definitive estimates of treatment efficacy and comparisons to large trials should be interpreted with caution. The retrospective design is another inherent limitation – we relied on chart review, which is subject to

missing data and inconsistent reporting. Because toxicity data were collected retrospectively from medical records, lower-grade adverse events may be underreported or incompletely captured. Selection bias is likely present; patients treated with high-dose BID RT were probably those with better baseline health or disease factors favoring aggressive therapy. The absence of a concurrent comparator cohort, such as patients treated with standard-dose 45 Gy twice-daily chemoradiotherapy during the same period, limits the ability to attribute observed outcomes specifically to dose escalation. Additionally, the follow-up duration (median 15 months) limits our ability to assess long-term survival and late toxicities (eg, esophageal stricture and pulmonary fibrosis), so reported survival and toxicity outcomes should be considered preliminary. Our analysis also cannot account for unmeasured confounders like differences in chemotherapy delivery (dose reductions in 15%) or variations in supportive care (nutritional support, smoking cessation, G-CSF administration), which could impact outcomes. Furthermore, tumor response assessment was performed at the discretion of the treating physician without central radiologic review, which may introduce assessment variability and represents an additional source of potential bias. Finally, generalizability is limited by the single-country setting; practice patterns and patient demographics may differ elsewhere. These limitations underscore the need to interpret our results as hypothesis-generating and confirmatory of trial trends rather than definitive evidence. Larger multi-institutional studies or registry analyses would help validate the real-world efficacy of 60 Gy BID and clarify which patients benefit most.

Future Directions

The management of LS-SCLC is evolving, with ongoing trials and emerging therapies reshaping the standard of care. A major development is the incorporation of immunotherapy: the Phase III ADRIATIC trial showed significant improvements in PFS and OS with consolidation durvalumab after chemoradiation, leading to its recent FDA approval.[12,13] This mirrors the paradigm shift seen in stage III NSCLC after the PACIFIC trial,[14] and raises key questions about optimal radiation dosing. As systemic control improves, durable local control becomes increasingly important, potentially supporting dose escalation. However, if immunotherapy drives outcomes, minimizing toxicity with regimens like 45 Gy BID may be preferable. Ongoing studies will help define this balance. For instance, the NRG LU005 trial, although negative for concurrent atezolizumab, showed continued investigator preference for BID regimens, reflecting confidence in accelerated therapy.[15] Personalized strategies, such as mid-treatment PET or ctDNA-guided dose adaptation, and technologies like proton therapy or FLASH RT, could further optimize outcomes. Additionally, with more long-term survivors, attention to late effects (eg, cardiopulmonary toxicity and neurocognitive sequelae) will be critical. Furthermore, future studies with larger cohorts should explore correlations between dosimetric parameters and treatment-related adverse events, and large real-world registry studies and collaborations will be essential to validate and better define the role of dose-escalated radiation. In summary, our real-world study affirms the feasibility and effectiveness of high-dose BID RT, supporting further exploration of dose intensification, particularly as we integrate new systemic therapies into LS-SCLC management.

Conclusion

The results of this retrospective, real-world study suggest that high-dose, twice-daily chemoradiotherapy (60 Gy in 40 fractions) appears feasible and merits further investigation. Survival outcomes were encouraging and aligned with those reported in clinical trials evaluating this intensified regimen. However, given the small sample size and retrospective design, these findings should be interpreted with caution. Validation in larger, multi-institutional cohorts or prospective registry studies is essential to confirm the safety and efficacy of this approach and to better define which patients may benefit most.

Disclosure

Dr Mor Moskovitz reports honorarium and fees for attending advisory boards from Astra Zeneca, Roche, Pfizer, Amgen, Boehringer INgelheim, J&J. All authors declare no conflict of interest.

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