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**Is there a place for optimizing thoracic radiotherapy in limited-stage small cell lung cancer after twenty years?**

Barros JM *et al*. Thoracic radiotherapy in LS-SCLC

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**Abstract**

Thoracic radiotherapy (TRT) is one of the main treatments in limited-stage small cell lung cancer (LS-SCLC). Hyperfractionated TRT (45 Gy, 1.5 Gy twice daily) has been the standard of care (SOC) since Turrisi and colleagues published the results of their clinical trial in 1999. Two meta-analyses have demonstrated the benefits of concurrent chemotherapy and TRT in terms of intrathoracic disease control at 2 years and 3-year overall survival (OS). The phase 2 trial by Grønberg *et al* (2016) comparing once-daily hypofractionated TRT to twice-daily hyperfractionated TRT in LS-SCLC found similar outcomes in both groups in terms of response rate, progression-free survival (PFS), grade 3-4 adverse effects, and OS. The CONVERT trial, published in 2017, failed to demonstrate the superiority of the conventional scheme (once-daily TRT) *vs* twice-daily radiotherapy, despite the application of modern radiotherapy techniques and a quality assurance programme, thus confirming the twice-daily hyperfractionated regimen as the SOC. At the 2020 American Society of Clinical Oncology (ASCO) annual meeting, Grønberg *et al* reported preliminary findings from a phase 2 trial comparing two different TRT dose regimens (45 Gy *vs* 60 Gy), both administered twice daily. Those data demonstrated a marked improvement in 2-year survival rates in the high dose arm (70.2% *vs* 46.1%, *P* = 0.002), despite similar objective response rates and PFS outcomes. Those findings provide a new treatment alternative to consider: Hyperfractionated, high-dose TRT. However, the results of that trial will need to be validated in a large, randomized phase 3 study.  The results of the phase 2 CALCG 30610 trial will help to clarify the optimal dose and regimen. The potential role of upfront immunotherapy, which early data suggest may improve OS, also needs to be determined.

**Key Words:** Thoracic radiotherapy; Limited-stage small cell lung cancer; Hyperfraction-ated; High dose; American Society of Clinical Oncology; Small cell lung cancer

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**Core Tip:** There is a lot of research regarding the role of thoracic radiotherapy in limited-stage small cell lung cancer looking for the best strategy to improve local control and overall survival. The CONVERT trial confirmed, in the contemporary era, the standard 45 Gy in 30 fractions during three weeks, concurrent with chemotherapy. High dose hyperfractionated thoracic radiotherapy in a phase II trial, presented during American Society of Clinical Oncology (ASCO) 2020, showed a better 2-year survival and a nonsignificant difference in median overall survival.

**INTRODUCTION**

Small-cell lung cancer (SCLC) accounts for 13% of all lung cancers. Less than 50% of cases of SCLC present with early stage disease that include tumor node metastases (TNM) stages I through III[1,2]. Thoracic radiotherapy (TRT) combined with chemotherapy is the one of the main treatment approaches in patients with limited-stage (LS)-SCLC. This combined treatment, which has been in use since the early 1990s, has been shown to improve both local disease-free survival and overall survival (OS)[3]. Moreover, two meta-analyses comparing TRT combined with chemotherapy to chemotherapy alone, found that the combined approach improved intrathoracic disease control at 2 years (47% *vs* 24%, respectively) as well as OS at 3 years by 5.4%, thus consolidating the role of TRT in LS-SCLC[3,4].

The optimal dose of TRT has not yet been definitively established. The intergroup 0096 trial, considered a landmark study in the treatment of SCLC[5], randomized patients to receive 45 Gy in 5 wk (25 daily sessions of 1.8 Gy once-daily) or 45 Gy in 3 wk (30 daily fractions of 1.5 Gy each, twice-daily). TRT was initiated simultaneously with the first of four cycles of chemotherapy, later followed by prophylactic cranial irradiation (PCI).  The median OS in the twice-daily arm was 23 mo *vs* only 18 mo in the once-daily arm. The 5-year OS in the hyperfractionated (twice-daily) group was 26% *vs* 16% in the conventional treatment group (*P* = 0.04). The local failure rate was also lower in the hyperfractionated group (36% *vs* 52%, *P* = 0.06). However, acute toxicity (grade 3 esophagitis) was higher in the hyperfractionated group (27% *vs* 11%; *P* < 0.001), perhaps due to the use of two-dimensional radiotherapy techniques with prophylactic irradiation of the mediastinum involving large volumes of normal tissue. Although twice-daily radiotherapy administered concurrently with chemotherapy was established as the standard of care, this approach was not widely used due to concerns about toxicity, logistical issues, and low doses in the control group[6].

In 2016, Grønberg *et al*[7] published the results of a randomized phase 2 trial that compared twice-daily TRT to once-daily hypofractionated TRT administered in 15 fractions. A total of 157 patients (mean age, 63 years) were evaluated. The study arms were well-balanced in terms of patient characteristics. All patients received 3D-TRT three to four weeks after the first course of chemotherapy. The therapeutic target included the pathological lesion plus elective nodal irradiation (ENI), including lymph node stations 4-7 bilaterally. The completion rates for TRT were similar, and more than 80% of patients received PCI. There were no between-group differences in response rates, or in one or two year OS rates. The median OS for the hypofractionated scheme was 18.8 mo *vs* 25.1 mo for the standard scheme [95% confidence interval (CI): 16.9-33.3; *P* = 0.61]. Grade 3-4 toxicity rates were comparable. Despite the higher complete response rate in the control arm and longer median OS, there were no between-group differences in progression-free survival (PFS), and the differences in OS were not statistically significant. Based on these results, no firm conclusions can be drawn from this trial.

The CONVERT trial (published in 2017) was another landmark study in the treatment of LS-SCLC. This superiority trial compared concurrent once-daily to twice-daily chemoradiotherapy in patients with LS-SCLC[8]. All patients were randomly assigned to receive conformal three-dimensional-radiotherapy administered either twice daily (45 Gy in 30 fractions of 1.5 Gy) or once daily (66 Gy in 33 fractions of 2 Gy) concurrently with platinum-etoposide chemotherapy. The compliance rate was close to 90%.  While most patients in both arms (approximately 80%) received an optimal number of fractions, a higher proportion of patients in the twice-daily regimen received the full radiotherapy dose. Unfortunately, the trial failed to demonstrate the superiority of the once-daily scheme; in fact, the 2-year OS was slightly higher (but not significantly) in the twice-daily arm. Acute and late radiation toxicity rates were lower than expected in both arms, perhaps due to the use of modern radiotherapy techniques and a quality assurance programme.

At the 2020 ASCO annual meeting, Grønberg *et al*[9] presented results from a phase 2 trial comparing conventional dose (45 Gy) to high dose (60 Gy) TRT administered twice daily in 30 and 40 fractions, respectively. This well-designed study was powered to show at least a 25% improvement (from 53% to 66%) in 2-year survival rates. Treatment was well-tolerated and completion rates were high (nearly 96% in both arms). There were no signiﬁcant between-group differences in most grade 3 toxicities, or in treatment-related mortality. Surprisingly, the lower dose arm had a higher rate of neutropenic infections. The objective response rate was comparable in both groups, but the high dose group had a markedly better 2-year OS (70.2% *vs* 46.1%, *P* = 0.002). Preliminary findings showed a trend towards better PFS in the high-dose arm [19.9 *vs* 14.4 mo, hazard ratio (HR) 0.8, *P* = 0.257], with a significantly higher median OS in that same arm (41.6 mo *vs* 22.9 mo, HR 0.63; *P* = 0.027).

The results of that trial are highly encouraging, especially the OS outcomes, which were the best reported to date in this patient profile. However, those findings should be interpreted cautiously given that this was a phase 2 trial not stratified by prognostic variables. Moreover, the analysis was not performed in the intention-to-treat population. The two groups had a similar toxicity profile, which may be attributable to the use of modern radiotherapy techniques, treatment of involved fields, or better supportive care. However, the similar toxicity profile could also be explained by between-group differences in tumour burden, patient selection, or other unreported biases. Indeed, there are many aspects of this trial that are and will remain unknown until the full results are published, including the use of positron-emission tomography (PET) and the specific radiotherapy techniques applied. Despite the comparable response rates in the two groups, the longer survival time in the high-dose arm is noteworthy. While the reasons for this difference are not entirely clear, it is likely that other factors may be involved, such as between-group differences in patterns of relapse and/or causes of death.

Despite the growing body of evidence, the once-daily scheme (2 Gy fractions to a total of 60-66 Gy) is considered an acceptable alternative to twice-daily TRT, especially considering that some patients are unwilling or unable to undergo twice-daily treatments. Moreover, the once-daily regimen is quite common in clinics where the twice-daily schedule is not feasible; in fact, the once-daily regimen is more common in the United States[6].

In patients with LS-SCLC who are prescribed combined chemotherapy and TRT, it is generally accepted that TRT should be initiated early (together with chemotherapy or soon thereafter) and that all involved nodal stations should be irradiated. Two meta-analyses have confirmed the benefits of TRT and concurrent chemotherapy in terms of intrathoracic disease control at 2 years and 3-year OS (Table 1)[10,11].

The American Society for Radiation Oncology (ASTRO) recently published the 2020 clinical practice guidelines[12]. These guidelines, which were based on a review of the scientific evidence, recommended TRT for patients with LS-SCLC who can tolerate definitive treatment.  The twice-daily scheme (≥ 45 Gy) is considered the standard of care. However, in patients who receive the once-daily regimen, the total dose should be increased to 60 Gy. The guidelines suggest that TRT should be initiated with the first or second cycle of chemotherapy; however, in certain cases, TRT can be started with the third cycle of chemotherapy. Involved field radiotherapy [fluorodeoxyglucose uptake on PET, enlarged areas on computed tomography (CT), and/or biopsy-positive areas] is recommended as the SOC. The use of highly conformal techniques is recommended to minimize radiation doses to normal tissues.

**CONCLUSION**

While the results of the large phase 2 trial by Gronberg and colleagues require validation studies, the findings suggest that it may be possible to optimize TRT through the use of high-dose hyperfractionated radiotherapy.  In this regard, we are also awaiting the results of the phase 3 CALCG 30610/RTOG 0538 trial comparing chemotherapy plus standard TRT (45 Gy twice-daily) to once-daily TRT (70  Gy). That trial initially had three study arms, but one of the experimental arms was discontinued due to the findings of an interim toxicity assessment. Both TRT regimens — 70 Gy daily and 61.2 Gy concomitant boost — administered concurrently with cisplatin and etoposide chemotherapy appear to be tolerable, with no unexpected toxicities. The final results of the trial (70 Gy *vs* 45 Gy of TRT) are expected soon[13].

Several other trials are also currently underway, including a trial to assess upfront immunotherapy administered concurrently with chemotherapy plus TRT (NRG LU005 and ETOP), or immunotherapy as consolidation therapy after chemotherapy plus TRT (ADRIATIC trial). Both of these treatment approaches may be useful in this clinical setting[14], but we will have to wait for the published results to determine the true value of these treatment modalities. In the meantime, the approach used in the CONVERT trial will remain the standard of care, as this approach yields similar outcomes to those achieved in the intergroup 0096 trial by applying new imaging techniques such as PET-CT and more advanced radiotherapy techniques.

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**Footnotes**

**Conflict-of-interest statement:** The authors declare no potential conflict of interest.

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**Table 1 Key studies of thoracic radiotherapy in limited-stage small cell lung cancer**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patient (*n*)** | **PET** | **ENI** | **PCI** | **RT technique** | **RT timing** | **Dose** | **Chemotherapy scheme** | **PFS** | **2-yr survival** | **Median OS (mo)** | **Higher grade 3-5 adverse event** |
| Intergroup 0096 (1999) | BID 211, OD 206 | 0%,0% | No | Allowed | 2D (100%) | W1 | 45 Gy/1.5 Gy/30 F/3 wk, 45 Gy/1.8 Gy/25F/5 wk | EP: W 1, 4, 7, 10 | 29% 2 yr, 24% 2 yr (*P* 0.10) | 47%,41% | 23, 19 (*P*  0.04a) | Esophagitis (55% *vs* 37%a)  |
| Grønberg *et al*[7] (2016) | BID 73, OD 84 | 0%,0% | No | 84%,82% | 3D (100%) | W4 | 45 Gy/1.5 Gy/30F/3 wk, 42 Gy/2.8 Gy/15F/3 wk | EP: W 1, 4, 7, 10 | 49% 1 yr, 45% 1 yr (*P* 0.93) | 52%,42% | 25.1,18.8 (*P* 0.61) | None |
| CONVERT trial (2017) | BID 274, OD 273 | 57%, 57% | No | 84%,81% | IMRT (16%), IMRT (17%) | W4 | 45 Gy/1.5 Gy/30F/3 wk, 66 Gy/2.0 Gy/33F/7 wk | EP: W 1, 4, 7, 10, 13, 16 | 15.4 mo, 14.3 mo (*P* 0.26) | 56%,51% | 30, 25 (*P* 0.14) | Neutropenia (49% *vs* 38%a) |
| Grønberg *et al*[9] (2020) | BID 76, BID 84 | ?, ? | ? | 82.9%, 84.5% | ?, ? | W1 | 45Gy/1.5Gy/30F/3W, 60Gy/1.5Gy/40F/4W | EP: W 1, 4, 7, 10 | 14.4 mo, 19.9 mo, (*P* 0.025a) | 46%,70% | 22.9, 41.6 (*P* 0.02a) | Neutropenia (21% *vs* 36%a) |
| CALGB 306101 | BID 365, OD 365 |  | Yes | Allowed | ? | W1 | 45 Gy/1.5 Gy/30F/3 wk, 70 Gy/2 Gy/35F/7 wk  | EP o ECb: W, 4, 7, 10 | Secondary endpoint |  | Primary endpoint | Secondary endpoint |

1Active, not recruiting. Estimated Primary Completion Data June/2023.

a*P* statistically significant. BID: Twice-daily; OD: Once-daily; Gy: Grays; EP: Etoposide/cisplatin; ECb: Etoposide/carboplatin; F: Fractions; PCI: Prophylactic cranial irradiation; ENI: Elective nodal irradiation; RT: Radiotherapy; PFS: Progression-free survival; OS: Overall survival.



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