Radiotherapy and Oncology 219 (2026) 111516

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Guidelines

ESTRO-EORTC expert guideline on target delineation and radiotherapy details for stage I–III small cell lung cancer

ARTICLE INFO

Keywords:
Small cell lung cancer
Limited-stage
Chemoradiotherapy
Thoracic radiotherapy
Immunotherapy
Prophylactic cranial irradiation
Stereotactic body radiotherapy

ABSTRACT

Introduction: Stage I–III limited-stage small cell lung cancer (SCLC) is a highly aggressive yet potentially curable disease with concurrent chemoradiotherapy. Thoracic radiation therapy (RT) plays a central role in the management of stage I–III SCLC; however significant variation exists in staging, target volume delineation, dose prescription, and integration with systemic therapy. This document provides an updated European recommendations on the use of RT in stage I–III SCLC, reflecting recent evidence and advancements in clinical practice.

Material and Methods: A panel of European experts was convened under the auspices of the ESTRO Guidelines Committee, in collaboration with EORTC Lung Cancer Group, and to review the available evidence and develop recommendations. Key topics addressed included disease staging, radiotherapy planning and delivery, and the integration with chemotherapy and immunotherapy.

Results: Accurate staging should include PET-CT and brain MRI. Thoracic RT should be initiated early during chemotherapy. Standard dose schedules include 45 Gy in 30 fractions (BID) or 66 Gy in 33 fractions once daily, using conformal techniques such as IMRT/VMAT, involved field nodal irradiation, respiratory motion management (e.g., 4D-CT, breath-hold) and image guidance (e.g., cone-beam CT [CBCT]). Concurrent chemotherapy with 4–6 cycles platinum-etoposide followed by consolidation durvalumab for up to two years is the standard of care in fit patients. Prophylactic cerebral irradiation (PCI) continues to represent the standard approach following treatment response; while hippocampal-sparing PCI and MRI surveillance strategies are being actively evaluated in ongoing studies. In selected cases, stereotactic body radiotherapy (SBRT) may be appropriate for medically inoperable early-stage disease without nodal involvement, and adjuvant RT can be considered for R1 resections or pN2 involvement. Emerging strategies, including adaptive RT, dose escalation and the integration of precision medicine have the potential to improve the therapeutic ratio. Integration with immunotherapy and/or novel agents, such as delta-like ligand 3 (DLL3)-targeted therapies, is under active investigation. Biomarker-guided treatment personalisation remains investigational.

Conclusions: These updated European guidelines provide a comprehensive framework for standardized, high-quality care in stage I–III SCLC and establish a reference standard to harmonize radiotherapy approaches and inform the design of upcoming clinical trials.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 10–15% of all lung cancer cases and is closely associated with tobacco exposure, particularly in Western countries. In Europe, while incidence rates have slightly declined due to decreased smoking prevalence, SCLC continues to represent a major clinical challenge. Approximately 30% of patients are diagnosed with limited-stage disease (LS-SCLC), historically defined by the Veterans Administration Lung Study Group (VALSG) classification as disease confined to one hemithorax and amenable to safe inclusion within a thoracic radiotherapy (TRT) field. More recently, the 9th edition of the TNM staging system [1] has been recommended for routine use, offering more precise anatomical classification and prognostic stratification. Patients with stage I–III SCLC may be considered for curative-intent treatment, provided their general fitness is adequate and dose limits to thoracic organ are not exceeded.

SCLC is biologically aggressive, characterised by rapid tumour growth and early dissemination. Therefore, prognosis is poor without any treatment. However, stage I–III SCLC are a potentially curable condition, and concurrent chemoradiotherapy (cCTRT) has long represented the standard of care (SoC) [2–5]. In appropriately selected patients, 5-year overall survival (OS) reached 25–35% in the pre-immunotherapy era [6–9]. Prognosis depends on multiple factors, including stage at diagnosis (whether by TNM or VALSG), performance status, age, comorbidities, and response to initial therapy. In light of recent progress in the management of stage I–III SCLC, including

https://doi.org/10.1016/j.radonc.2026.111516
Received 17 March 2026; Accepted 23 March 2026
Available online 1 April 2026

advances in radiotherapy techniques and the integration of consolidation immunotherapy, these updated European guidelines, developed by a panel of experts convened under the auspices of the ESTRO (European Society for Radiotherapy and Oncology) guidelines committee in collaboration with the EORTC (*European Organisation for Research and Treatment of Cancer*) Lung Cancer Group, build upon prior ESTRO recommendations to reflect current best practice [3,10].

Search strategy and selection criteria

References for this expert guideline were identified through systematic searches of PubMed and ClinicalTrials.gov for published articles and ongoing clinical trials from Jan 1, 1999, to Jan 15, 2026. Only articles published in English were considered. Search terms included combinations of *"small cell lung cancer"*, *"radiation therapy"*, *"chemotherapy"*, and *"stereotactic body radiotherapy"*. Priority was given to high-quality narrative and systematic reviews, practice-changing studies, and prospective clinical trial data. Particular emphasis was placed on evidence published within the last 10 years and on studies specifically addressing the management of stage I–III small cell lung cancer.

Thoracic radiation therapy for stage I-III SCLC

Staging and indications

Accurate staging is essential for appropriate treatment selection. Standard workup includes contrast-enhanced CT of the chest and abdomen, brain MRI, and 18F-FDG PET-CT [2]. PET-CT improves target definition and patient selection by detecting occult nodal or metastatic disease, ideally with pathologic confirmation [11]. Baseline endoscopic staging can further increase accuracy [12], though access may be limited. For equivocal nodal involvement, mediastinal staging using endobronchial ultrasound (EBUS) is recommended; oesophageal ultrasound (EUS) or ultrasound-guided biopsy of supraclavicular nodes may also be used. Brain MRI is mandatory to exclude metastases prior to curative treatment.

TRT is indicated for all patients with stage I–III eligible for curative-intent treatment, preferably given with platinum-based cCTRT. Before TRT, patients should undergo full respiratory assessment, including pulmonary function tests (PFTs) with Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and evaluation for interstitial lung disease (ILD), which may be detected on diagnostic CT. Identifying impaired lung function or ILD is essential, as these conditions increase the risk of radiation-induced pneumonitis and may necessitate treatment modification or dose adjustment [13].

Radiotherapy planning

CT simulation should be performed in the supine position, with intravenous contrast (IV +) and appropriate immobilisation (e.g. lung board, expansive foam or customised alpha-cradle vacuum mattress) to ensure reproducible positioning. Reproducible setup may also be achieved using a stable arm support in combination with knee support to improve patient comfort. Several studies have shown that thoracic radiotherapy can be safely delivered without the use of rigid immobilisation casts [14]. Image acquisition should include all relevant thoracic anatomy (lungs, heart, and oesophagus), typically from the cricoid cartilage to the L2–L3 vertebral level, with $\leq$3 mm slice thickness. 4D-CT should be used for motion management to accurately assess respiratory tumour motion [15]. A motion management strategy, such as deep inspiration breath-hold (DIBH), abdominal compression, respiratory gating, or a mid-ventilation approach, may be used, provided that an appropriate verification protocol for tumour position is in place, especially for mid- and lower-chest tumours [16].

Target delineation strategy

Target delineation should ideally be performed on a contrast-enhanced simulation CT (non-contrast is acceptable if a recent diagnostic scan with IV contrast is available). Co-registration with a diagnostic PET-CT (or PET/CT simulation, if available) and the baseline pre-chemotherapy IV-enhanced thoracic CT is recommended to optimize target definition and accuracy [3,10].

Target volumes include:

- **Gross Tumour Volume (GTV):** Includes the primary tumour (GTV_T) and involved lymph nodes (GTV_N), typically defined as nodes $\geq$1 cm in short axis on IV-enhanced CT or exhibiting FDG uptake above blood pool on PET imaging. In the setting of SCLC, in case of close proximity of tumour and nodal disease, it can be appropriate to delineate a single combined GTV. Use of different CT window settings improves accuracy: lung window (W = 1600, L = -600) for peripheral lesions and mediastinal window (W = 400, L = 20) for central tumours or lymph nodes. The GTV encompasses all current visible tumour, regardless of response to chemotherapy [17] (Fig. 1). When using 4D-CT, an internal GTV (iGTV) or motion-adapted GTV should be defined by combining tumour position across all respiratory phases. This can be achieved by using the MIP (maximum intensity projection), which represents the tumour extent across all breathing phases and should be reviewed and edited on individual respiratory phases if required, or by using the mid-ventilation or mid-position datasets, which reflect the time-averaged tumour location. Motion from other internal structures like cardiac motion is generally much smaller and is typically encompassed within these imaging datasets.
- **Clinical Target Volume (CTV):** a margin of about 5 mm should be added around the GTV to cover microscopic disease.

  When 4D-CT is used, an Internal Target Volume (ITV) can be generated, which is defined as CTV plus an additional margin to encompass motion [18]. The ITV can be derived from the internal GTV (iGTV)/motion-adapted GTV (described above), to which a 5 mm margin is added to account for microscopic disease.

  For nodal disease (CTVn), some centres extend the CTV to include the entire nodal station using standard atlases (expert opinion) [10,19]. The tumour CTV (CTV_T) is generally derived from the post-chemotherapy volume GTV_T, whereas the nodal CTV (CTV_N) should also encompass the cranio-caudal extent of lymph nodes involvement identified before chemotherapy [6–8,17,20] (Fig. 1 and Table 1). By definition, the CTV should not extend into areas where disease is unlikely to spread, such as thoracic organs or across natural anatomical barriers such as vertebral bodies, and may be manually adjusted accordingly. Elective nodal irradiation (treating uninvolved lymph nodes) is not recommended, as it increases side effects without improving outcomes. Instead, involved-field radiotherapy (IFRT) should be used [11,21].
- **Planning Target Volume (PTV):** a margin of 4–8 mm should be added around the CTV or ITV to account for daily set-up uncertainties and residual organ motion. The exact margin depends on the accuracy of patient positioning and the type of image-guidance used during radiotherapy (IGRT), with surface-guided radiotherapy increasingly adopted to improve setup reproducibility [22,23].

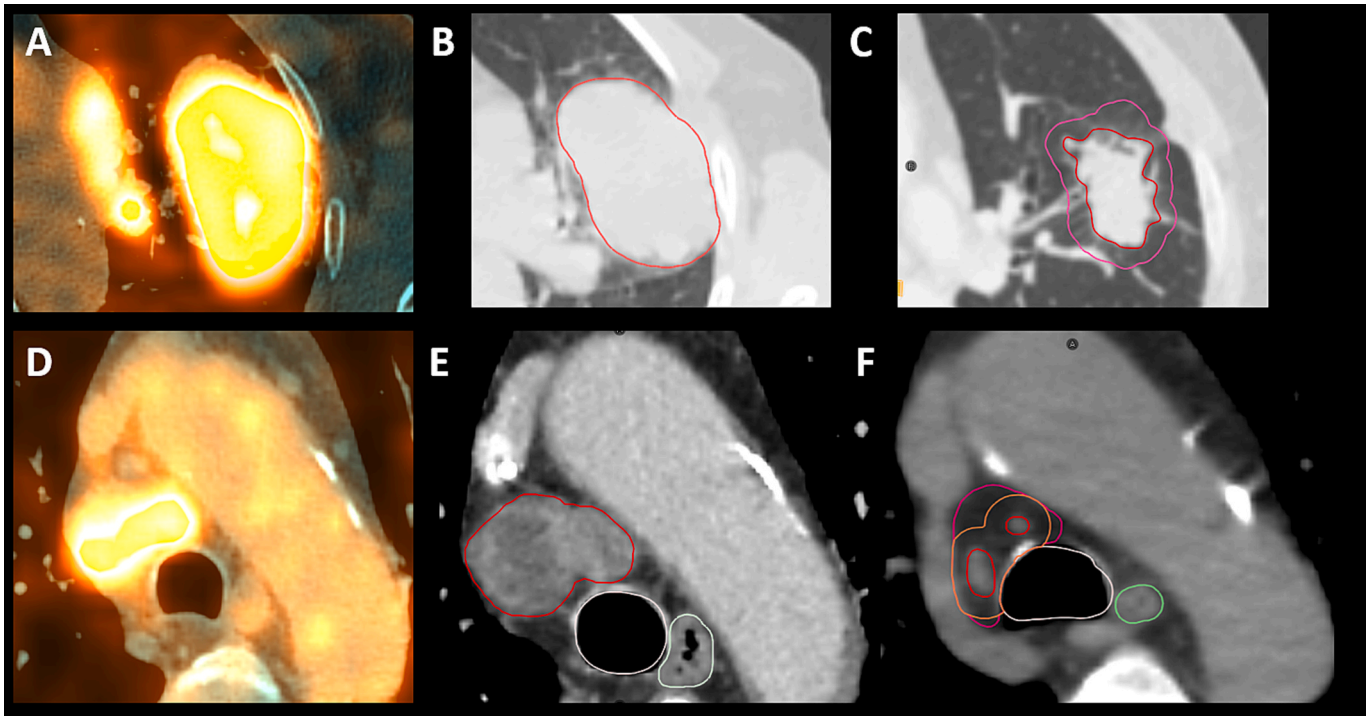

Fig. 1. Post-chemotherapy target volume delineation. A–E: A 69-year-old patient with left upper lobe cT4N3M0 small cell lung cancer began thoracic radiotherapy at cycle 3 of platinum–etoposide. Baseline pre-chemotherapy ^{18}F-FDG PET/CT (A, D) and contrast-enhanced CT (B, E) were co-registered for planning. The post-chemotherapy primary tumour (GTV_T, red, C) was expanded by 0.5 cm to form the clinical target volume (CTV_T, pink). No internal target volume (ITV) was generated, as treatment was delivered in deep inspiration breath-hold (DIBH). The post-chemotherapy nodal GTV (GTV_N, red, F) was similarly expanded (CTV_N, orange), respecting anatomical barriers (proximal bronchial tree, white), then manually enlarged (pink) to include pre-chemotherapy (E) microscopic extent. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Organs of interest

Key critical organs include the lungs, oesophagus, spinal cord, heart, and brachial plexus, contoured according to standard atlases (e.g., RTOG [24]). The dose limits extracted from contemporary randomised clinical trials are summarised in Table 2. Given the heterogeneity in the definition of organs of interest (for example, lung minus GTV versus lung minus PTV), the variation in dose limits, and differences in radiotherapy techniques (3DCRT, IMRT, VMAT) and image guidance (weekly versus daily) across contemporary randomised controlled trials (including spinal cord dose limits ranging from 41 Gy to 54 Gy), the guideline committee decided not to issue specific recommendations for dose limits to organs of interest. Notably, across all these trials, rates of acute and late adverse events (AEs) remained lower than those previously reported, suggesting that adherence to any of these evidence-based dose limits is unlikely to compromise patient safety.

Planning details and treatment delivery

Dose calculation for lung cancer treatment should be performed using a type B (convolution/superposition or collapsed cone) or type C (Monte Carlo) algorithm, which offer higher accuracy in low density tissue. Photon energies of 6–10 MV are preferred.

While three-dimensional conformal radiotherapy (3D-CRT) was historically the standard for many years, intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are now widely used due to their superior high-dose conformity and improved sparing of organs of interest [25,26]. VMAT offers similar or better conformity than fixed-field IMRT, with faster planning and delivery.

Dose prescription and planning should follow ICRU 50, 62, and 83 guidelines: at least 95% of the PTV should be covered by the 95% isodose, the median dose should match the prescription, and D2% should be <107%. Achieving near-prescription dose in very low-density lung regions using a type C algorithm may be challenging and is not always necessary. When combined with IFRT, this approach helps reducing severe AEs.

Image-guided radiotherapy (IGRT) is essential for accurate treatment delivery. Daily cone-beam CT (CBCT) is optimal, while surface-guided radiotherapy, with or without X-ray verification, is increasingly used, although its application has been mostly studied in lung stereotactic body radiotherapy (SBRT) [27,28]. For tumours with significant motion (e.g. lower lobe lesions), motion-management techniques such as DIBH, abdominal compression, respiratory gating, or a mid-ventilation approach can be considered. Four-dimensional CBCT (4D-CBCT) is now available on most modern C-arm linear accelerators.

Fractionation

The standard radiotherapy regimen for stage I–III SCLC remains 45 Gy in 1.5 Gy twice-daily (BID) fractions over 3 weeks, based on the pivotal Intergroup 0096, CONVERT and CALGB 30610/RTOG0538 trials. In the Intergroup 0096 trial, this BID schedule improved survival compared to the once-daily (OD) 45 Gy in 25 fractions (median OS 23 vs 19 months, p = 0.04, 5-year survival 26% vs. 16%), though it was associated with higher rates of acute oesophageal AEs (grade 3 esophagitis 27% vs. 11%) [29]. Recent randomised trials, including the CONVERT trial (comparing 45 Gy BID to 66 Gy OD) [6,30] and the CALGB 30610 (Alliance)/RTOG 0538 trial (comparing 45 Gy BID to 70 Gy OD) [7], support the BID fractionation as the SoC, as the OD regimen were not superior. Crucially, in both trials, the use of modern radiotherapy techniques, including 3D-CRT and IMRT, reduced the risk of severe AEs, particularly oesophageal, compared with the Intergroup 0096 BID regimen. OD regimens, such as 66 Gy in 33 fractions can also be considered, as they may be more convenient for some patients and

Table 1
Selected randomised trials informing target delineation, doses schedules and outcomes.

Trial	Phase	Year	N pt.	TEP	IMRT	TRT starts at chemo cycle (n cycle)	GTV	CTV (mm)	PTV (mm)	Design / dose	PCI	G3-4 Oesoph	2Y-PFS	2Y-OS
INT-0096 [29]	3	1999	417	None	None	C1 (4)	Tumour	ENI: bilateral mediastinal and ipsilateral hilar, inferior border extended 5 cm below the carina	CTV + 10–15	45 Gy BID (3w) vs. 45 Gy OD (5w)	NR	27%*	29%*	47%*
CONVERT [6]	3	2017	547	57%	17%	C2 (4 to 6)	Postchemo volume	GTV + 5	CTV + 10 (8 laterally)	45 Gy BID (3w) vs. 66 Gy OD (6.5w)	82%	19%*	40%*	56%*
CALGB 30,610 / RTOG 0538 [7]	3	2023	638	100%	60%	C1 or C2 (4 to 6)	Postchemo volume	GTV + ipsilateral hilum	CTV + 15 (10 laterally); if breath hold: same minus 0.5	45 Gy BID (3w) vs. 70 Gy OD (7w)	NR	16%*	36%*	58%*
THORA [8,69]	2	2021	170	100%	32%	C2 (4)	Postchemo volume	GTV + 5	Local practice	45 Gy BID (3w) vs. 60 Gy BID (4w)	82%	21%+	44%+	74%+
Yu [20]	3	2024	224	100%	100%	C1, C2 or C3 (4)	Postchemo volume	GTV + 5; include initial LN drainage area	Local practice	45 Gy BID (3w) +/- 54 Gy SIB BID (3w)	82%	13%+	52%+	76%+
ADRIATIC [44]	3	2024	500	NR	NR	C1 or C2 (4)	NR	NR	NR	Durva vs placebo consolidation; 28% BID, 72% OD	54%	NR	49%+	68%+
NRG-LU005 [45]	3	2026	544	100%	92%	C2 (4)	Postchemo volume	GTV + 5	CTV + 5	Concurrent and consolidation atezo vs placebo; 47% BID, 53% OD	45%	11%+	33%+	59%+

N pt., number of patients; SIB, simultaneous-integrated boost, ENI, elective node irradiation; PET, positron emission tomography–computed tomography; TRT, thoracic radiotherapy; Oesoph, oesophagitis; Chemo, chemotherapy; atezo, atezolizumab; durva, durvalumab; OD, once-daily; BID, twice-daily; PFS, progression-free survival; OS, overall survival; NR, not reported; PCI, prophylactic cerebral irradiation.
* BID arm.
+ Experimental arm.

radiotherapy departments [31–33]. BID dose escalation above 45 Gy and moderate hypofractionation [34] are under investigation but not yet standard practice (see perspectives section).

Timing with chemotherapy and immunotherapy

The recommended regimen consists of four cycles of intravenous (IV) platinum–etoposide chemotherapy (with at least three cycles delivered overall). Cisplatin 60–80 mg/m^2 should preferably be administered concurrently with radiotherapy. Carboplatin may be used if cisplatin is contraindicated [35]. IV etoposide 100–120 mg/m^2 should be administered on days 1–3 every 3 weeks. Additional cycles may be considered on an individual basis.

Early initiation of thoracic radiotherapy (TRT) in fit patients, with the first or second chemotherapy cycle, improves local control and survival, as supported by meta-analyses demonstrating the benefit of combined modality therapy [36,37]. Initiating TRT with the second chemotherapy cycle may be advantageous, as significant tumour regression often occurs, potentially enabling smaller target volumes and reduced radiation exposure to surrounding healthy tissues [38]. However, chemotherapy should not be delayed solely to initiate TRT with cycle 1 or 2, as a phase 3 trial suggested that starting TRT in cycle 3 may be non-inferior and better tolerated [39,40]. cCTRT remains superior to sequential treatment in LS-SCLC [41,42]. Rather than reducing the dose, particularly during the first 2 cycles, cisplatin can be split over 3 days (cisplatin 25 mg/m2 and etoposide 100 mg/m2 on days 1–3) to improve tolerance and reduce hydration needs [6]. Concomitant granulocyte colony-stimulating factor (G-CSF) during CRT can also be safely administered [43].

Consolidation immunotherapy with the anti-PD-L1 durvalumab has recently become SoC for patients without progression after cCTRT. Durvalumab should be initiated within 42 days after cCTRT (BID TRT of 45 Gy or OD TRT of 60–66 Gy) and continued for up to 2 years. In the phase 3 ADRIATIC trial, durvalumab reduced the risk of death by 27% (median OS, 55.9 months [95% CI, 37.3–not reached] vs. 33.4 months [95% CI, 25.5–39.9]; HR 0.73; 98.3% CI, 0.54–0.98; P = 0.01) [44]. Of note, exploratory analyses from the ADRIATIC study suggested a numerically greater benefit with durvalumab in patients receiving BID compared with OD radiotherapy. However, the study was not designed or powered to evaluate the impact of different radiation schedules, and these findings should therefore be interpreted with caution. In contrast, the NRG Oncology/Alliance phase 3 LU-005 trial reported that

Table 2
Organs of interest dose limits in stage I–III SCLC from contemporary randomised clinical trials [6–8,20,45].

	Once daily (OD)	Twice-daily (BID)
CONVERT *(Dmax: ND)*		
Spinal cord	Dmax ≤ 48 Gy	Dmax ≤ 42 Gy
Lungs minus PTV	V20Gy ≤ 35%	V20Gy ≤ 35%
Heart	V50Gy < 50%; V30Gy < 100%	V50Gy < 50%; V30Gy < 100%
CALGB/RTOG *(Dmax: ND)*		
Spinal cord	Dmax ≤ 50.5 Gy	Dmax ≤ 41 Gy
Lungs minus CTV	V20Gy ≤ 40%; mean < 20 Gy	V20Gy ≤ 40%; mean < 20 Gy
Oesophagus	Mean ≤ 34 Gy	Mean ≤ 34 Gy
Heart	V60Gy < 1/3; V45Gy < 2/3; V40Gy < 100%	V60Gy < 1/3; V45Gy < 2/3; V40Gy < 100%
THORA *(Dmax: 0.05 cc)*		
Spinal cord	NA	Dmax ≤ 54 Gy
Lungs minus GTVt	NA	V20Gy ≤ 35%; V5Gy ≤ 65%; Mean < 20 Gy
Oesophagus	NA	Mean ≤ 34 Gy; Dmax ≤ 60 Gy
Heart	NA	Mean ≤ 46 Gy; V; V40Gy ≤ 80%; V45Gy ≤ 60%; V60Gy ≤ 30%
Brachial plexus	NA	Dmax ≤ 60 Gy
Yu *(Dmax: 1 cc)*		
Spinal cord	NA	Dmax ≤ 40 Gy
Lungs	NA	V20 ≤ 30%; V5Gy ≤ 60%; Mean < 15 Gy
Oesophagus	NA	Dmax ≤ 49.5 Gy; V54Gy ≤ 5%; V45Gy ≤ 40%
Heart	NA	Dmax ≤ 45 Gy; V54Gy ≤ 30%; V50Gy ≤ 50%
ADRIATIC *(Dmax: ND)*		
Lungs	Mean < 20 Gy and/or V20Gy < 35%	Mean < 20 Gy and/or V20Gy < 35%
Heart	V50Gy < 25%	V50Gy < 25%
NRG-LU005 *(Dmax: 0.03 cc)*		
Spinal cord	Dmax ≤ 50 Gy	Dmax ≤ 41 Gy
Lungs minus iGTV	V5% ≤ 70 Gy; V20 ≤ 37%; mean ≤ 20 Gy	V5% ≤ 58 Gy; V20 ≤ 31%; Mean ≤ 17 Gy
Oesophagus	Dmax ≤ 75.9 Gy, Mean ≤ 40 Gy	Dmax ≤ 51.75 Gy, Mean ≤ 33 Gy
Heart	Dmax ≤ 75 Gy; Mean ≤ 22 Gy; V30Gy ≤ 66%	Dmax ≤ 51 Gy; Mean ≤ 20 Gy; V30Gy ≤ 46%
Brachial plexus	Dmax ≤ 70 Gy	Dmax ≤ 60 Gy

ND = not defined.
NA = not applicable.
Dmax values specify max or near-max doses to each organ (point or volume).
Lung limits refer to the evaluation of normal lung tissue with the tumour volume excluded.

concurrent and post-cCTRT atezolizumab for one year did not improve OS (median 33.1 vs. 36.1 months; HR, 1.03; 95% CI, 0.80–1.32) [45]. Similarly, consolidation immunotherapy following CRT, as evaluated in the randomized phase II STIMULI (nivolumab plus ipilimumab) [46] and ACHILES (atezolizumab) [47] trials, failed to demonstrate improved outcomes compared with observation.

Prophylactic cranial irradiation (PCI) and hippocampal avoidance (HA-PCI)

Indications

PCI is SoC for stage I–III patients who achieve a response after cCTRT, significantly reducing the rate of brain metastases and improving OS [48]. However, improved staging with brain MRI, increased use of immunotherapy and concerns about AEs have led to more selective use of PCI, particularly in early stage I disease [49,50] and in patients with higher risk of cognitive decline [51,52]. Following on from the Japanese trial in patients with metastatic SCLC [53], MRI surveillance is being investigated as an alternative to PCI in selected cases. Ongoing trials include EORC1901-PRIMALung (NCT04790253) and the SWOG 1827-MAVERICK (NCT04155034) [54]. Hippocampal avoidance PCI (HA-PCI), implemented using techniques such as VMAT or IMRT, is an emerging approach aimed at reducing neurocognitive side effects by sparing the hippocampal regions. In three randomised trials, HA-PCI demonstrated non-inferior intracranial relapse rates and similar OS compared with standard PCI. Neurocognitive outcomes were mixed: the PREMER trial [55] showed improved delayed free recall, the NRG-CC003 trial [56] reported reduced overall neurocognitive decline without improvement in delayed recall, while the Belderbos et al. study found no significant neurocognitive differences between treatment arms [57].

Dose, fractionation and techniques

The conventional regimen is 25 Gy in 10 fractions [58]. PCI is simulated in a supine position, using a thermoplastic mask. However, open-mask or maskless techniques are increasingly being implemented [59]. For HA-PCI, MRI fusion is used to delineate the hippocampi, which are then excluded from the treatment volume, with a 5 mm planning organ-at-risk volume (PRV) margin around each hippocampus. HA-PCI reduces the dose to the hippocampi (D100% ≤ 7.5 Gy and D0.03 cc ≤ 13.5 Gy [57]), potentially minimising the risk of memory decline. Other critical organs include optic nerves/chiasm, lenses, and brainstem. IGRT such as daily CBCT is critical to ensure the accuracy of HA-PCI.

Timing with chemotherapy and immunotherapy

PCI is typically administered within 6 weeks after completing chemotherapy, ideally following a brain MRI to confirm the absence of metastases. The optimal sequencing with immunotherapy remains unclear. In case of patients considered for PCI, the ADRIATIC study mandated commencement of durvalumab only after planned PCI was completed (Fig. 2) [44]. Durvalumab showed a survival benefit over placebo irrespective of prior PCI. Patients who had received PCI (54%) had higher 3-year OS and progression-free survival rates compared to those who had not; however, the study was not designed to evaluate the effects of PCI on outcomes [60].

Special scenarios

Elderly and frail patients

Chronologic age alone should not preclude curative-intent treatment. Comprehensive geriatric assessment can be considered to guide decision-making, including evaluation of functional status, comorbidities, and frailty [61,62]. In the CALGB 30610–RTOG 0538 phase 3 trial comparing BID (45 Gy in 3 weeks) and OD (70 Gy in 7 weeks) TRT, older patients (≥70 years) had inferior OS with BID treatment, despite similar rates of grade ≥3 AEs compared to younger patients [63]. These findings highlight the need for a better understanding of the tolerability and adverse effects of BID TRT and chemotherapy in patients aged ≥70 years (excluded in Yu trial [20]) with stage I–III SCLC.

A separate phase 3 trial [34] compared once-daily hypofractionated cCTRT (45 Gy in 15 fractions over 3 weeks) with conventional OD TRT (60 Gy in 30 fractions over 6 weeks). The hypofractionated schedule showed comparable survival (median OS 40.2 vs 47.9 months; HR 1.04, 95% CI 0.81–1.33) and significantly fewer grade ≥3 AEs (48.7% vs 67.7%; $P < 0.001$), primarily due to reduced hematologic AE. However, patients ≥70 years were excluded from this trial [34]. These findings support hypofractionated OD cCTRT as a shorter, safer, and more convenient option for selected or frail patients, without compromising

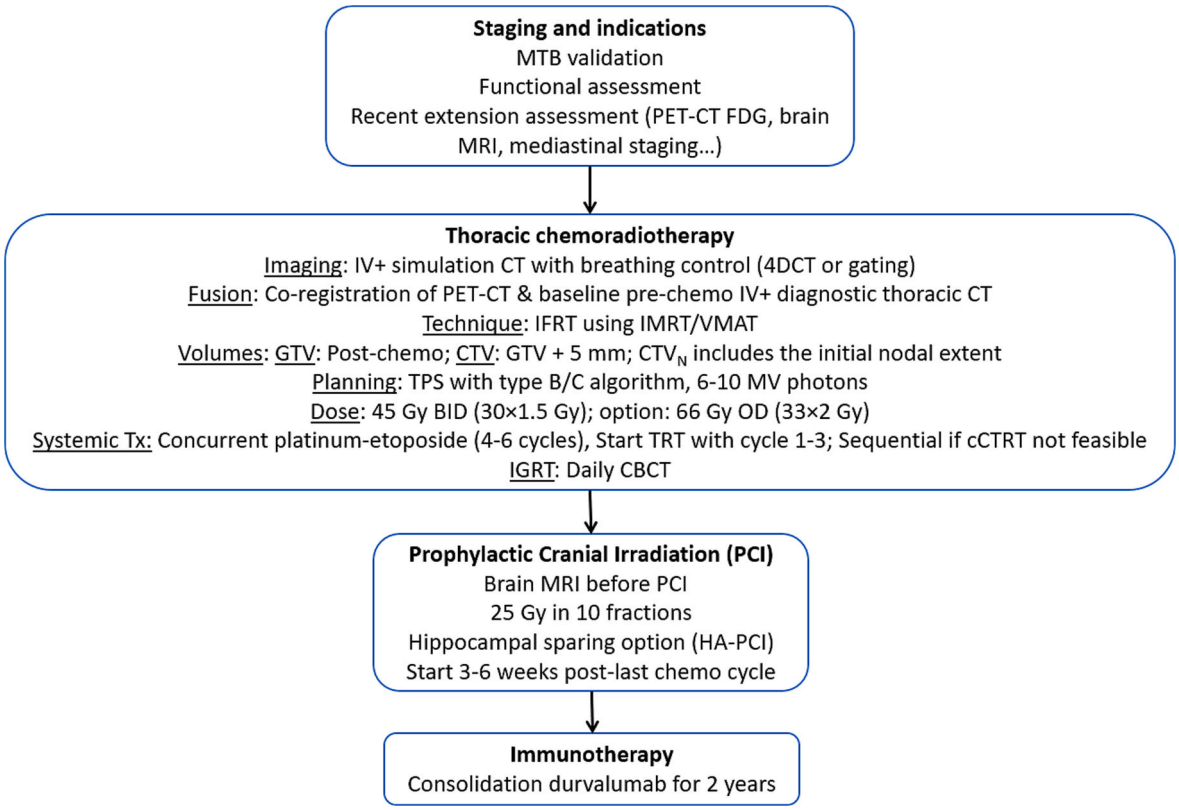

Fig. 2. Key recommendations for radiotherapy in stage I–III SCLC. MTB, Multidisciplinary Tumour Board; PET, positron emission tomography; TRT, thoracic radiotherapy; cCTRT, concomitant chemoradiotherapy.

efficacy. Based on NSCLC experience [64], further adaptations, such as reduced-dose cCTRT, sequential chemotherapy followed by moderately hypofractionated TRT, or TRT alone, may be appropriate for patients with poor performance status (PS > 2) or significant comorbidities.

SBRT in early-stage SCLC

For medically inoperable patients with peripheral stage T1–T2N0 SCLC, SBRT is an emerging and recommended option [4]. No randomised trials have directly compared SBRT with standard regimens such as 45 Gy in 30 fractions BID. Although evidence is more limited than in NSCLC, retrospective studies report excellent local control [65]. Accurate nodal staging and close follow-up are essential due to the high risk of regional failure, and chemotherapy should be administered to eligible patients. SBRT should ideally begin early, before chemotherapy, to avoid rapid tumour shrinkage that may complicate accurate target delineation. SBRT is less suitable for (ultra)central tumours, where nodal involvement is more likely; in such cases, conventional cCTRT remains the preferred approach.

Postoperative TRT (PORT)

Surgery may be considered only in highly selected patients with very limited disease, specifically clinical stage T1–2N0M0, after thorough mediastinal staging [2]. In these rare cases, surgery should be followed by adjuvant platinum-etoposide chemotherapy.

Given the limited evidence in the SCLC setting, decisions regarding postoperative radiotherapy (PORT) should be individualised based on surgical outcomes, recurrence risk, and patient tolerance [66]. The decision should be discussed within a multidisciplinary tumour board. Currently, there is no universally accepted standard for PORT indications or target volume delineation in the postoperative SCLC setting; recommendations are therefore often extrapolated from NSCLC practice.

Adjuvant radiotherapy is conditionally recommended for patients with positive surgical margins (R1), pN2 disease or inadequate mediastinal lymph node sampling [67]. When PORT is indicated, IFRT using conformal techniques tailored to the pre-surgical CT scan, PET-CT scan, and pathological findings is recommended. For R1 resections, adjuvant cCTRT can be considered. If pN2 involvement is unexpectedly detected intraoperatively without prior nodal staging, sequential chemoradiotherapy (sCTRT) may offer a disease-control benefit that outweighs potential risk of adverse events (AEs) [68].

Perspectives and conclusion

Dose escalation

Two recent randomised studies have investigated higher TRT doses delivered BID to improve outcomes as compared to the standard 45 Gy in 30 fractions in the pre-immunotherapy era [20,69]. The Scandinavian THORA phase 2 trial compared 45 Gy in 30 fractions BID to 60 Gy in 40 fractions BID, reporting a significantly longer median OS in the 60 Gy group (43.5 versus 22.5 months, HR: 0.68, 95% confidence interval 0.48–0.98, p = 0.037), and no significant increase in AEs. A Chinese phase 3 trial compared 45 Gy in 30 fractions BID using VMAT with 54 Gy in 30 fractions BID delivered via a simultaneous integrated boost (SIB) to the GTV. Median OS was significantly longer in the 54 Gy (60.7 months [95% CI 49.2–62.0]) compared with the 45 Gy group (39.5 months [27.5–51.4]; HR: 0.55 [95% CI 0.37–0.72]; p = 0.003). The tolerance was encouraging, though possibly underestimated due to limited radiotherapy quality assurance. Randomised phase 3 trials comparing the standard regimen of 45 Gy in 30 fractions BID with higher dose BID regimen and integrating immunotherapy are awaited.

Advanced radiotherapy techniques

Adaptive radiotherapy (ART) enables personalised treatment by adjusting plans in response to changes such as tumour shrinkage, which are common in SCLC. Online ART uses real-time imaging (e.g., CBCT, MRI) for same-day re-planning, whereas offline ART involves periodic plan updates based on interval imaging [70]. ART, including CBCT and MR-guided workflows requires thorough evaluation to determine its potential to improve precision and reduce side effects [71]. The integration of artificial intelligence (AI) tools may further streamline adaptive planning. Given the high sensitivity of SCLC to chemoradiotherapy, mid-treatment adaptation can reduce dose to thoracic organs and potentially allow for dose escalation, without treatment delays. 4D imaging and deformable registration are essential in this context. Advanced RT techniques also include proton therapy, which theoretically may lower AEs by better sparing normal tissue, though prospective data in SCLC are limited and its use remains investigational [72].

Personalisation and newer systemic treatment

Molecular profiling in SCLC is currently limited by tumour heterogeneity and a paucity of actionable mutations. However, emerging biomarkers (e.g., circulating tumour DNA, transcriptomic subtypes: ASCL1, NEUROD1, POU2F3, and Inflamed) may guide future personalisation [73,74]. Integration of such biomarkers in the management of stage I–III holds promise but remains investigational.

Promising systemic strategies under investigation in SCLC include bispecific T-cell engagers (e.g., tarlatamab targeting DLL3), antibody–drug conjugates (ADCs) directed at B7-H3, TROP2, DLL3, and SCZ6, and cellular therapies such as DLL3-targeted CAR-T cells [75,76]. Trials are ongoing to assess T-cell engagers and ADCs as consolidation approaches after cCTRT (NCT06117774, NCT06526624). Key challenges in stage I–III include ensuring safety with radiotherapy, managing overlapping AEs such as ILD/pneumonitis, optimising treatment timing and duration, and identifying high-risk subgroups for relapse.

Conclusion

Radiotherapy remains a cornerstone of treatment in the stage I–III SCLC setting. Standardised and more accurate target delineation guidelines are essential to promote consistency in clinical practice (Fig. 2). While conventional cCTRT approaches have delivered meaningful survival benefit, advances in thoracic radiotherapy – including PET-CT–guided tumour delineation, conformal techniques such as IMRT and VMAT, involved-field strategies, IGRT, and respiratory motion management – are reshaping the therapeutic landscape and led to significant reductions in severe AEs, particularly oesophageal. In the current SoC, consolidation immunotherapy with durvalumab following cCTRT has been established as a key component of treatment, improving survival outcomes. Alongside these developments, BID TRT dose-escalation, emerging systemic therapies and integration of precision medicine represent potential avenues to improve outcomes. Ongoing clinical trials and close multidisciplinary collaboration will be key to optimising efficacy while improving tolerance in this aggressive disease.

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Preparation of the guideline

The guideline was prepared following the ESTRO SOP for guidelines and is an expert guideline. The writing committee consisted of the following experts: AL, CFF, BS and CLP coordinated the guideline panel and drafted the manuscript. All authors were part of the expert panel, and participated in the preparation of the manuscript. All authors read and approved the final manuscript. The reviewing of the guideline was performed by Tine Schytte, Suresh Senan, Ursula Nestle and Myriam Ayadi- their advice is highly appreciated.

Guideline update

This guideline is planned to be updated within a 5 years-time frame unless there are fundamental scientific changes which require an earlier update. Amendments will be made if changes are minor but of clinical significance.

Funding statement

No funding was received or reported for this guideline.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PR reports honoraria from Amgen; consulting or advisory roles for Daiichi Sankyo and IGES Pharma; and travel or accommodation support from AstraZeneca, Bristol Myers Squibb, Kyowa Kirin, MSD, PharmaMar, and Roche. NR reports personal fees for advisory board participation and/or invited speaking from AbbVie, Amgen, ArriVent Biopharma, AstraZeneca, Bayer, BMS, Boehringer, Gilead, Harpoon, Janssen, Johnson & Johnson, Merck, MSD, Novartis, Pfizer, PharmaMar, Regeneron, Revolution Medicine, Roche, Sanofi, Summit Therapeutics, Takeda, and Tubulis. The author also received institutional support from Amgen for manuscript writing. The author serves as principal investigator of an investigator-initiated trial (PEERS) sponsored by MSD. AL reports academic research funding from AstraZeneca, Roche, PharmaMar, MSD, and BeiGene. JM reports personal fees for advisory board participation and/or invited speaking from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Johnson & Johnson, Lilly, MSD, Novartis, Roche, and Summit Therapeutics; expert testimony for AstraZeneca,

Boehringer Ingelheim, MSD, and Novartis; and institutional support from Ipsen (travel grant). The author serves as principal investigator for sponsored clinical trials with Amgen, Daiichi Sankyo, HiFiBio, and MSD, and as a guideline author for AIOM and ESMO, and committee member of the IASLC Rare Tumor Committee. CFF reports research funding from Astra Zeneca. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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