

Elective nodal irradiation versus involved field radiotherapy for limited disease small cell lung cancer: a single-institution experience

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ABSTRACT

Elective nodal irradiation (ENI) and involved field radiotherapy (IFRT) are definitive radiotherapeutic approaches used to treat patients with limited-disease small cell lung cancer (LD-SCLC). However, no solid consensus exists on their optimal target volume. The current study aimed to assess the clinical outcomes of patients with LD-SCLC who received definitive ENI or IFRT. A retrospective single-institution study of patients who received definitive radiotherapy between 2008 and 2020 was performed. All patients underwent whole-body positron emission tomography/computed tomography before three-dimensional conformal radiotherapy. Among the 37 patients analyzed, 22 and 15 received ENI and IFRT, respectively. The thoracic radiotherapy dose was mostly either 60 Gy in 30 fractions delivered in 2-Gy fractions once daily or 45 Gy in 30 fractions delivered in 1.5-Gy fractions twice daily. The median follow-up period was 21.4 months. A total of 12 patients (32%) experienced locoregional relapse: 10 within and 2 outside the irradiation fields. One patient in the IFRT group experienced isolated nodal failure. Differences in locoregional relapse-free, progression-free, and overall survival rates between ENI and IFRT were not significant. Overall, IFRT did not promote a significant increase in locoregional recurrence compared to ENI. Our findings suggested the utility of IFRT in standard clinical practice and support its use for patients with LD-SCLC.

Keywords: small cell lung cancer, limited disease, chemoradiotherapy, involved field radiotherapy, elective nodal irradiation

Abbreviations:

BSC: best supportive care
CT: computed tomography
CTV: clinical target volume
ENI: elective nodal irradiation
FDG: 18F-fluorodeoxyglucose
GTV: gross tumor volume
IFRT: involved field radiotherapy

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IMRT: intensity modulated radiotherapy
INF: isolated nodular failure
LD-SCLC: limited-disease small cell lung cancer
LDH: lactate dehydrogenase
LRRF: locoregional relapse-free
MRI: magnetic resonance imaging
NSCLC: non-small cell lung cancer
OS: overall survival
PCI: prophylactic cranial irradiation
PET: positron emission tomography
PET/CT: positron emission tomography/computed tomography
PFS: progression-free survival
PS: Eastern Cooperative Oncology Group performance status
PTV: planning target volume
SCLC: small cell lung cancer
SCT: salvage chemotherapy
3D-CRT: three-dimensional conformal radiotherapy

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INTRODUCTION

Small cell lung cancer (SCLC) accounts for 15%–25% of all lung cancer cases, with 25%–40% exhibiting limited diseases.¹ Moreover, previous reports have shown that SCLC carries a poor prognosis, with a median overall survival (OS) of only 19–27 months and 2-year OS of 37%–55%, even for limited diseases.^{2–6} Thoracic surgery has evolved drastically in recent years,⁷ however, early concurrent chemoradiation remains the standard treatment for limited-disease SCLC (LD-SCLC) given its low degree of differentiation, shorter doubling time, and high sensitivity to chemotherapy and radiotherapy. Although etoposide- and cisplatin-based regimens chemotherapy continue to be the standard of care,^{8,9} no solid consensus on irradiation dose or radiotherapy target volume has been established. Historically, treatment volumes included all gross disease present at the time of initial diagnosis, as well as adjacent uninvolved nodal regions elective nodal irradiation (ENI). Recent reports, on the other hand, have suggested that omitting ENI might be appropriate.^{2,10–12} However, available literature on involved field radiotherapy (IFRT) strategies for LD-SCLC have been much more limited compared to that for locally advanced non-small cell lung cancer (NSCLC). Thus, the current study aimed to assess the clinical outcomes in patients with LD-SCLC who received definitive radiotherapy with either ENI or IFRT.

MATERIALS AND METHODS

Patients

Records of consecutive patients with histopathologically confirmed LD-SCLC who received definitive radiotherapy at our institution between January 2008 and April 2020 were retrospectively reviewed. Clinical stages were assessed using contrast-enhanced computed tomography (CT) from the neck to the abdomen, whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT), and magnetic resonance imaging (MRI) of the brain. Complete blood count, biochemical tests, and electrocardiography were also performed to assess fitness for chemotherapy. Disease stage was based on the latest TNM classification upon diagnosis (UICC 8th edition). Limited disease was defined as a tumor confined to one hemi thorax, including regional lymph

nodes, ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular nodes, without pleural effusion. Patients with a history of lung resection or thoracic radiation were excluded. All patients with early-stage disease were medically ineligible to undergo surgical resection or refused to undergo it. Treatment was decided by a tumor board that included surgeons, endoscopists, medical oncologists, and radiation oncologists. The study was approved by the institutional review board of Kyoto Prefectural University of Medicine (approval number: ERB-C-1934). Written informed consent was obtained from each patient to treatment and data collection.

Radiation treatment planning

Patients received either ENI or IFRT based on physician treatment philosophy. Physicians were consistent with treatment planning and treated all their patients with either ENI or IFRT. Although patients were not randomly assigned to either group, there was no predetermined selection process for assigning patients to the various physicians. Radiotherapy was delivered using a three-dimensional conformal radiotherapy (3D-CRT) technique typically employing 6–10 MV photons. All patients were CT-simulated, after which planning was done using the Monaco treatment planning system with dose correction for tissue heterogeneity. All plans were normalized to the isocenter or calculation point. For IFRT treatment planning, gross tumor volume (GTV) included the primary tumor and any suspected lymph nodes with a diameter at least 1 cm in the short axis in CT or positive by FDG-PET. The clinical target volume (CTV) was obtained by expanding the GTV using a margin of 5–8 mm. The ipsilateral lung hilum was electively included in the CTV. After adjusting for anatomical boundaries, the planning target volume (PTV) was determined from the CTV by a radiation oncologist who used an automatic margining tool that typically added a standard margin of 5–10 mm. For ENI treatment planning, all mediastinal lymph node stations were included in the initial treatment field as the CTV. Supraclavicular fields were treated when gross involvement of the supraclavicular nodes was observed. A subsequent cone-down included the primary tumor and, if feasible, any grossly involved lymph nodes. Thus, clinically uninvolved mediastinal lymph nodes received prophylactic radiation treatment with ENI but not with IFRT. The median PTV for the IFRT and ENI group were 179.6 mL (range, 20.4–755.3 mL) and 367.7 mL (range, 88.45–997.7 mL), respectively ($p = 0.06$). The dose constraints for critical structures were maximum spinal cord dose ≤ 45 Gy, lung mean dose ≤ 20 Gy, lung volume that receives at least 20 Gy $\leq 35\%$, and heart volume that receives at least 40 Gy $<50\%$. Although no special constraints were used for esophagus, special attention was paid to minimize the maximum doses applied to this structure.

Treatment schedules

The thoracic radiotherapy dose was mostly either 60 Gy in 30 fractions delivered in 2-Gy fractions once daily or 45 Gy in 30 fractions delivered in 1.5-Gy fractions twice daily. After 2016, patients with stage I disease were treated with stereotactic radiation therapy, and two received this treatment (48 Gy in 4 fractions once daily, $n = 1$; 60 Gy in 10 fractions once daily, $n = 1$). The median total dose delivered was 45 Gy in 30 fractions (range, 44–66 Gy). Twice-daily treatments were delivered with a minimum inter-fraction interval of at least a 6-hour. Our institutional policy indicates that early radiotherapy be delivered concurrently with platinum-based chemotherapy; however, due to patterns of referral or patient factors, not all patients were treated in this fashion. One patient received sequential rather than concurrent chemoradiotherapy, while another received radiotherapy alone. Although chemotherapy generally consisted of etoposide and cisplatin, usually given for 4 cycles every 3 weeks, an etoposide and carboplatin regimen was optionally used depending on the patient's general condition and age. Patients with a complete or near-complete response after the completion of chemoradiotherapy and had a favorable clinical

condition were offered prophylactic cranial irradiation (PCI; 25 Gy in 10 fractions).

Follow-up and outcome evaluation

Patients were followed up at regular intervals, usually every 3–4 months for the first 2 years after treatment, followed by every 6 months over 3–5 years. Follow-up examinations included basic laboratory tests, liver and renal function tests, chest CT, brain MRI, and PET/CT when needed. Locoregional relapse was defined as progression located inside the original primary tumor or in the hilar, mediastinal, and/or supraclavicular lymph nodes, irrespective of distant failure. Locoregional relapses located within the PTV were classified as in-field failures, whereas those occurring outside the PTV but inside the hilar, mediastinal, or/and supraclavicular area were classified as out-of-field failures. Toxicities were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Endpoints included locoregional relapse-free (LRRF), progression-free survival (PFS), and OS. PFS was defined as the date at which any recurrence was the first observation or death from any cause occurred. All endpoints were calculated from the first day of radiotherapy to the date of an event or censoring. Corresponding survival curves were estimated using the Kaplan–Meier method. Univariate analyses estimated differences between groups through the log-rank test. Comparisons between groups of patients were assessed using Chi-square test or Mann–Whitney U test. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Australia). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.¹³ The level of significance was conventionally set at $p < 0.05$ for all analyses.

RESULTS

Patient characteristics

Between January 2008 and April 2020, 37 patients with LD-SCLC were treated in our hospital, among whom 22 and 15 were irradiated with ENI and IFRT, respectively. Patients in both treatment groups had similar age, sex, baseline Eastern Cooperative Oncology Group performance status (PS), clinical stage, and TN stage, chemotherapy regimen, cycles of received chemotherapy, and pretreatment levels of serum lactate dehydrogenase. Patients' characteristics are summarized in Table 1. All but one patient completed the planned radiotherapy (97%). One patient's treatment was stopped after 44 Gy in 22 fractions because of prolonged recovery of grade 4 neutropenia and grade 3 esophagitis. Among the included patients, 28 (76%) and 4 (11%) started radiotherapy during their first and second cycles of chemotherapy, respectively. Given that some patients eligible for PCI after thoracic radiotherapy did not follow the doctor's advice or refused to receive it, four patients ultimately received PCI.

Table 1 Patient characteristics

Characteristics	ENI (n = 22)	IFRT (n = 15)	<i>p</i> value
Age			
Median (range), years	68 (25–83)	73 (59–81)	

ENI vs IFRT for small cell lung cancer

≤70	14	6	0.19
>70	8	9	
Sex, n			
Male	16	14	0.2
Female	6	1	
Performance status, n			
0	19	9	0.12
1–2	3	6	
Clinical stage			
I	3	3	0.72
II	5	4	
III	14	8	
T Stage, n			
1–2	14	9	0.99
3–4	8	6	
N Stage, n			
0	4	6	0.26
1–3	18	9	
Chemotherapy regimen, n			
Cisplatin-Etoposide	15	10	0.99
Others	7	5	
Cycles of chemotherapy, n			
0–3	4	7	0.08
4	18	8	
Fractionation scheme			
Once daily	7	6*	0.73
Twice daily	15	9	
Pre-treatment serum LDH, n			
<222 U/L	12	8	0.99
≥222 U/L	10	7	

ENI: elective nodal irradiation

IFRT: involved field irradiation

LDH: lactate dehydrogenase

* Including 2 cases treated with stereotactic radiotherapy.

Patterns of failure

Twenty-three patients (62%) experienced locoregional and/or distant failure, most of whom were treated with chemotherapy (18/23). The most common initial failure pattern was distant metastasis (15/23). In our patient cohort, 12 patients (32%) had a locoregional relapse; in 6 cases this was the first failure event and in 2 cases distant metastases have been diagnosed simultaneously. The remaining four patients relapsed distantly first. Out-of-field recurrence was observed in two patients in the IFRT group, one of whom experienced isolated nodular failure (INF) that represented a single out-of-field nodal failure in the absence of other recurrence sites.

Treatment outcomes

The median follow-up period was 21.4 months (range, 6.2–114.6). At the last follow-up, 23 patients (62%) had died. Among these patients, 21 died of SCLC and 2 died of other causes (acute aortic dissection, $n = 1$; oropharyngeal cancer, $n = 1$). The 2-year OS, PFS, LRRF rates were 54%, 35%, and 61%, respectively (Fig 1). Table 2 presents the results of univariate analysis for PFS, LRRF, and OS. Accordingly, the clinical stage was correlated with both OS and PFS, while the age factor was correlated only with PFS. No significant differences in LRRF, PFS, and OS were observed between the ENI and IFRT group (Fig 2). The use of salvage chemotherapy (SCT) after the identification of recurrence was determined by the physicians according to each patient's general condition, clinical course, and function of organs. Eighteen patients received amrubicin-based SCT and 5 patients received the best supportive care (BSC). SCT patients had a significantly better median OS (8.4 months versus 4.3 months, $p < 0.001$) compared with BSC patients.

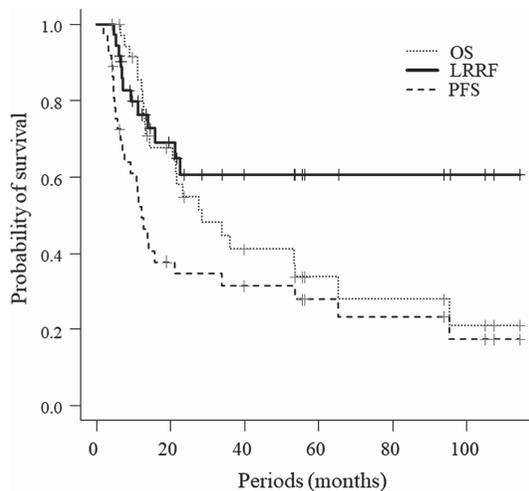


Fig. 1 Overall survival, progression-free survival, and locoregional relapse-free rate for patients with limited-disease small cell lung cancer treated with radiotherapy

OS: overall survival

LRRF: locoregional relapse free

PFS: progression-free survival

Table 2 Univariate analysis for PFS, LRRF, and OS rates

Factors	n	PFS rate (%)			LRRF rate (%)			OS rate (%)		
		1 year	2 years	<i>p</i> value	1 year	2 years	<i>p</i> value	1 year	2 years	<i>p</i> value
Age										
≤70	20	69	50	0.016	87	73	0.2	94	61	0.1
>70	17	37	20		67	48		78	50	
Stage										
I	6	80	80	0.01	100	100	0.09	80	80	0.02
II	9	52	26		64	32		88	44	
III	22	38	18		76	60		80	44	
PS										
0	28	45	26	0.1	76	55	0.59	81	52	0.32
1–2	9	63	63		75	75		87	63	
LDH (U/L)										
<222	20	58	43	0.42	79	65	0.55	81	54	0.34
≥222	17	44	25		74	56		89	55	
CT regimen										
PE	25	48	36	0.43	75	68	0.42	84	54	0.5
Others	12	61	31		68	46		90	57	
Cycles of CT										
0–3	11	51	34	0.71	74	81	0.78	92	61	0.31
4	26	55	36		59	65		73	41	
FR scheme										
Once daily	13	58	49	0.17	74	64	0.87	75	75	0.21
Twice daily	24	49	27		78	58		91	46	
RT field										
IFRT	15	53	40	0.72	72	62	0.82	87	47	0.77
ENI	12	51	36		80	60		85	62	

PFS: progression-free survival
 LRRF: locoregional relapse free
 OS: overall survival
 PS: performance status
 LDH: lactate dehydrogenase
 CT: chemotherapy
 PE: cisplatin-etoposide
 FR: fractionation
 RT: radiotherapy
 IFRT: involved field irradiation
 ENI: elective nodal irradiation

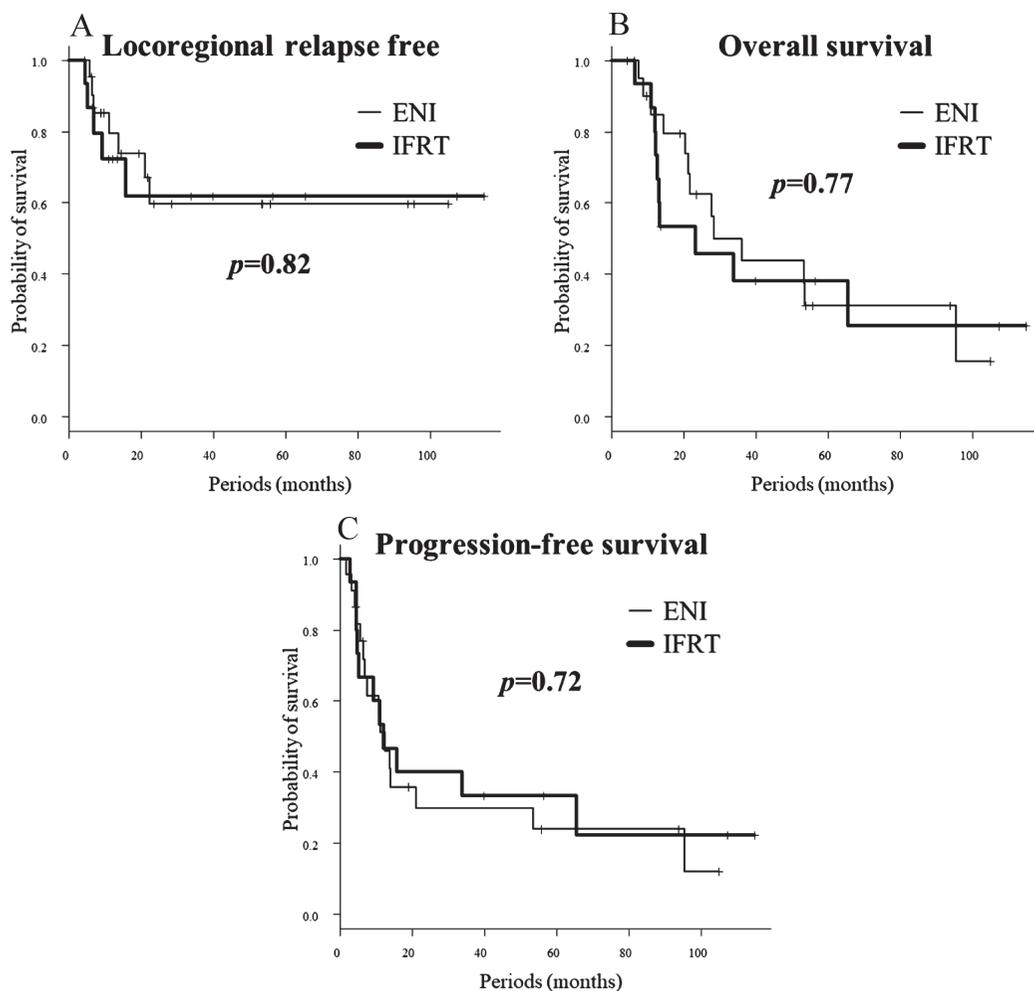


Fig. 2 Kaplan-Meier curves for patients treated with involved field radiotherapy (IFRT) versus elective nodal irradiation (ENI)

Fig. 2A: Locoregional relapse free

Fig. 2B: Overall survival

Fig. 2C: Progression-free survival

Toxicity

In the ENI group, all patients experienced grade ≥ 3 acute hematological adverse events (AEs); leukopenia of grades 3 and 4 was seen in 6 (27%) and 12 patients (55%), anemia in 4 (18%) and 1 (5%) patient, and thrombocytopenia in 2 (9%) and 2 patients (9%), respectively. On the other hand, for non-hematological acute AEs, radiation esophagitis of grades 2 and 3 was seen in 11 (50%) and 4 patients (18%), respectively. Pneumonitis of grade 2 was seen in 3 patients (14%). In the IFRT group, regarding the hematological AEs throughout the treatment period, leukopenia of grades 3 and 4 occurred in 2 (27%) and 9 patients (55%), anemia in 1 (7%) and 1 (7%) patient, and thrombocytopenia in 2 (13%) and 2 patients (13%), respectively. Acute radiation esophagitis of grades 2 and pneumonitis of grades 2 was seen in 5 (33%) and

2 patients (13%), respectively. Rates of acute radiation esophagitis (grade ≥ 2) were higher in the ENI group than in the IFRT group ($p = 0.014$). Grade ≥ 3 non-hematological AEs were not seen in the IFRT group. Regarding late AEs, in the ENI group, there were two AEs of grades 3, including pneumonitis in one patient (at 5 months after chemoradiation) and pericardial/pleural effusion in one patient (at 18 months after chemoradiation). In the IFRT group, no patients experienced grade ≥ 3 late AEs. Table 3 shows treatment-related toxicity of grade 2 or higher.

Table 3 Treatment-related toxicity

	ENI (n = 22)			IFRT (n = 15)			p value
	G2	G3	G4	G2	G3	G4	
Worst grade of hematological parameters during chemoradiotherapy							
Decreased leucocytes	1 (5%)	6 (27%)	12 (55%)	0	2 (13%)	9 (60%)	0.99
Decreased hemoglobin	8 (36%)	4 (18%)	1 (5%)	3 (20%)	1 (7%)	1 (7%)	0.11
Decreased platelets	7 (32%)	2 (9%)	2 (9%)	2 (13%)	2 (13%)	2 (13%)	0.84
Non-hematologic acute toxicity							
Esophagitis, dysphagia	11 (50%)	4 (18%)	0	5 (33%)	0	0	0.014
Pneumonitis	3 (14%)	0	0	2 (13%)	0	0	>0.99
Nausea	1 (5%)	0	0	0	0	0	0.44
Non-hematologic late toxicity							
Lung	3 (14%)	1 (5%)	0	2 (13%)	0	0	0.68
Pericardial/pleural effusion	0	1 (5%)	0	1 (7%)	0	0	0.84

G: grade

IFRT: involved field irradiation

ENI: elective nodal irradiation

DISCUSSION

The present study aimed to assess the clinical outcomes in patients with LD-SCLC who received definitive radiotherapy with either ENI or IFRT. There have been no studies directly comparing the treatment outcomes of ENI and IFRT incorporating the PET staging/target definition. Our findings showed 1- and 2-year LRRF rates of 72% and 62% in the IFRT group and 80% and 60% in the ENI group, respectively, with no significant differences having been observed between both treatment groups. Moreover, no significant differences in OS and PFS were observed between the treatment groups. Results regarding the OS and locoregional control in our patient cohort are in line with those presented in previously published studies.²⁻⁶

Modern thoracic radiotherapy has tended toward using more conformal and smaller fields.^{14,15} Although IFRT has been proven to be considerably adequate in NSCLC,¹⁶⁻²³ no final consensus exists on omitting ENI in LD-SCLC. A phase II study that omitted ENI in patients with LD-SCLC based solely on CT scans resulted in a high proportion (3/27, crude rate of 11%) of INF despite its small sample size.²⁴ Another phase II trial by Baas et al that evaluated recurrence patterns in 36 patients in whom ENI was omitted based on CT scan observed INF in 2 patients (5.5%).²⁵ Moreover, Xia et al showed an INF rate of 4.6% in a retrospective IFRT based on the CT scan study of 108 patients.⁵ PET/CT has been shown to improve the staging accuracy of patients with LD-SCLC and could potentially clearly identify involved nodal sites.²⁶⁻²⁸ Several

more modern series, both retrospective and prospective, have suggested that omitting ENI resulted in lower rates of INF, particularly when incorporating PET staging/target definition.^{2,10-12} van Loon et al evaluated the impact of PET scan usage on elective nodal irradiation in patients with LD-SCLC, with their results subsequently showing a low INF rate of 3%.^{2,10} Shirvani et al showed that only 2% of patients experienced INF when PET/CT-guided omission of ENI,¹¹ with Reymen et al reporting similar outcomes for PET-based omission of ENI.¹² In our patient cohort staged using PET/CT, only one case of INF occurred. Omitting ENI, while still unresolved, may be a reasonable choice, particularly when PET is incorporated into the staging and target definition.

Thoracic radiotherapy with a reduced irradiation field for LD-SCLC has been reported to decrease esophageal and lung toxicity and improve the patient's quality of life.²⁹ Our results show that acute esophageal toxicity can be reduced with IFRT compared to ENI. An online survey in 2016 to determine the patterns of practice in the United States regarding ENI in the treatment of LD-SCLC revealed that nearly two thirds of respondents did not recommend ENI.³⁰ This suggests a shift in practice over the past decade, with a 2007 survey reporting that only 18% did not recommend any form of ENI for LD-SCLC.³¹ Moreover, current prospective clinical trials (eg, CALGB 30610/RTOG 0538 and the EORTC 08072 trial) have omitted ENI, seemingly suggesting the emergence of a new era in which ENI is avoided in an effort to reduce toxicity.

Some limitations of the current study include its single-institution and retrospective nature. Moreover, only a small number of patients had been included, while the selection of radiotherapeutic options had not been randomized. Furthermore, the radiation oncologists made a clinical decision on the choice of the irradiation field, but there may be a bias among physicians to not select IFRT especially for patients with mediastinal lymph node metastases on PET/CT. As such, larger studies with standardized, uniform procedures should be performed to validate our results.

In conclusion, our findings suggested the utility of IFRT in standard clinical practice and support its use for patients with LD-SCLC.

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CONFLICT OF INTEREST STATEMENTS

The authors declare that they have no conflicts of interest regarding this study.

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