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Short Communication

Feasibility and long-term outcomes of post-chemotherapy-based consolidation radiotherapy in extensive stage small-cell lung cancer

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ABSTRACT

Background: The target definition of consolidation radiotherapy (RT) for extensive stage small-cell lung cancer (ES-SCLC) has not been standardized. This study aimed to demonstrate the feasibility of post-chemotherapy based consolidation RT in ES-SCLC.

Methods: All ES-SCLC patients without initial brain metastases who completed ≥ 4 cycles of systemic therapy at Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University from 2012 to 2021 were included in this retrospective study. We correlated the site of first recurrence to the post-chemotherapy-based radiation volume (small-field). Relapse pattern, progression-free survival (PFS) and overall survival (OS) were compared between those received and did not receive consolidation RT.

Results: A total of 152 patients were followed up for a median of 31.7 months (interquartile range [IQR], 23.9–39.6 months). The median PFS and OS of the cohort were 8.3 months (IQR, 6.1–11.2 months) and 16.2 months (IQR, 9.9–24.9 months), respectively. Thoracic consolidation RT served not only as an independent prognostic factor for improved PFS in the entire cohort, but also significantly prolonged OS in the subgroup without synchronous liver metastases. Small-field consolidation RT markedly reduced in-field recurrences (hazard ratio [HR], 0.28 [95% CI, 0.12–0.38]; $P < 0.001$) without increasing out-of-field recurrences (HR, 0.40 [95% CI, 0.13–1.16]; $P = 0.080$). No relapse was observed at the margin of the targets. Treatment-related toxicities were moderate, with grade 3 acute radiation pneumonia, radiation esophagitis, and bone marrow suppression rates of 8.3%, 3.1%, and 12.5%, respectively. No grade 5 toxicity occurred.

Conclusion: Small-field consolidation RT based on post-chemotherapy volume is safe and can significantly improve local control in ES-SCLC.

1. Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15%-20% of all lung cancers.[1] In 2021, approximately 30,000 new cases of SCLC were diagnosed in the US, and it was the fifth leading cause of cancer death. About two-thirds of SCLC have extensive stage (ES) at diagnosis.[2,3] Conventional standard treatment for ES-SCLC is 4–6 cycles of platinum-based chemotherapy.[4-7] Recently, chemotherapy combined with programmed cell death-ligand 1 (PD-L1) antibodies has been recommended as the preferred first-line treatment for ES-SCLC.[8-10]

The role of radiotherapy (RT), including prophylactic cranial irradiation (PCI) and thoracic consolidation RT, in ES-SCLC is still under investigated. A randomized study from Europe showed that PCI improved overall survival (OS) in ES-SCLC showing any response to chemotherapy.[11] A subsequent multicenter study from Japan found that in cases where occult brain metastases had been ruled out by magnetic resonance imaging (MRI) scan PCI failed to prolong OS, although it could reduce the risk of brain metastases.[12]

Consolidation RT is recommended for ES-SCLC who have responded to systemic therapies, with benefit being most likely for those with low-bulk extrathoracic metastases.[13] The CREST study showed improved 2-

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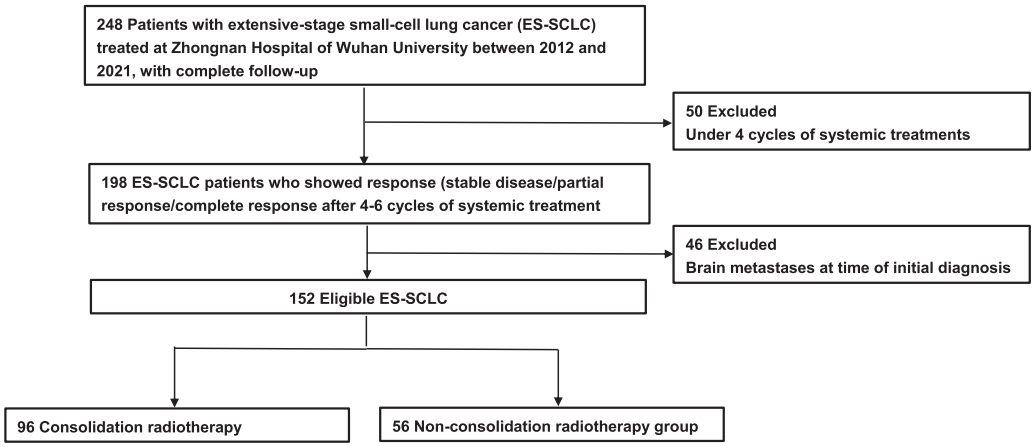

Fig. 1. Patient enrollment and treatment assignment.

year OS and 6-month Progressive-free Survival (PFS) with addition of consolidation RT.[14] However, the target volumes for consolidation RT has not been well defined. In the CREST study, consolidation RT targets included post-chemotherapy residual lesions as well as the hilar and mediastinal regions that involved prior to treatments. *Yee et al* conducted a phase II study exploring consolidation RT in ES-SCLC, in which the RT targets included only residual lesions after chemotherapy irrespective of the pre-chemotherapy tumor involvements, and showed that a reduced target indicated good tolerability as well as a low rate of local recurrence (only 5 relapse out of 32 patients).[15] In our institution, since 2012, we have been actively recommending consolidation RT for ES-SCLC who achieved radiological response and underwent systemic therapies. We adopt a small-field RT method. In brief only the residual lesions after chemotherapy are treated, without encompassing the involved locations at baseline. Herein, the aim of this study is to report the feasibility of the approach and its long-term outcomes.

2. Materials and methods

2.1. Study cohort

Patients with ES-SCLC who were treated at the Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University between June 2012 and October 2021 were considered for inclusion in this retrospective study. Patients were eligible if they 1) had newly diagnosed, pathologically confirmed ES-SCLC; 2) were treated with four or more cycles of systemic therapy (chemotherapy alone or chemotherapy plus immunotherapy); and 3) showed responses to systemic therapy, achieving stable disease (SD), partial response (PR) or complete response (CR). Patients with confirmed synchronous brain metastases at diagnosis were excluded. 152 patients met these criteria and were grouped into consolidation thoracic RT (n = 96) and non-consolidation RT (n = 56) groups. A flow diagram of patients' inclusion is shown in Fig. 1.

2.2. Treatment

Patients were first treated with systemic therapies, including platinum-based doublet chemotherapy or chemotherapy combined with immunotherapy. After completion of 4–6 cycles of treatments, patients were considered for consolidation RT or close surveillance if they achieved any response, i.e., CR, PR, or SD. The choice of PCI was at the discretion of the physician as well as the patients' wishes.

Both consolidation RT and PCI were delivered under the intensity-modulated radiotherapy technique. The dose of consolidation RT was based on the following factors: high-dose RT (≥ 50 Gy) was used for patients with good tumor regression after first-line chemotherapy (residual volume ≤ 30 cm^3 after systemic treatments), while lower dose (< 50 Gy) was considered for those with large target volumes due to poor tumor regression after chemotherapy (the residual volume above 30 cm^3). The median consolidation RT dose was 56 Gy in 28 fractions (interquartile range [IQR], 50 Gy in 25 fractions to 60 Gy in 30 fractions). The prescribed dose for PCI was 25 Gy in 10 fractions.

A small-field approach was used for consolidation RT. The gross tumor volume (GTV) included only post-chemotherapy residual lesions. After systemtic treatment, five patients achieved CR, for whom the pre-treatment computed tomography (CT) were registered with the CT simulated images for target determination. For them, GTV_{tb} (tumor bed) was contoured according to the involved scope of the primary tumor at baseline, tailored by sparing the normal structures such as bones, chest wall, mediastinal vessels, heart and trachea. Since all patients experienced tumor regression after first-line chemotherapy, we assumed a very low risk of subclinical tumor invasion; therefore, the planning target volume (PTV) was generated by adding a margin of 0.6 cm to the GTV or GTV_{tb} in the axial plane and 1.0 cm in the craniocaudal plane (Fig. 2).

In the non-consolidation RT group, GTV, GTV_{tb} and PTV were deliberately delineated as "virtual" target volumes using the same approach to help map the recurrences.

2.3. Study endpoints

The primary endpoints were to investigate the feasibility of post-chemotherapy based consolidation RT for ES-SCLC and its prognostic value. PFS was defined as the period from the date of diagnosis to the date of disease progression, death from any cause, or the last follow-up. OS was defined as the period from the date of diagnosis to the date of death from any cause or the last follow-up.

The site of first recurrence was used to determine the pattern of recurrence. In-field recurrence was defined as at least one recurrence occurring within the actual target volume (consolidation RT group) or the "virtual" target volume (non-consolidation RT group). Out-of-field recurrence was defined as at least one relapse arising outside the actual target volume (consolidation RT group) or the "virtual" target volume (non-consolidation RT group) but remaining limited to the intrathoracic region; ipsilateral and contralateral intrapulmonary disseminated metastases were excluded.

2.4. Statistical analysis

Categorical variables were summarized using descriptive statistics and compared between groups using the chi-square test. The in-field and out-of-field recurrences were analyzed using cumulative incidence functions. The impact of consolidation RT on OS and PFS was assessed by

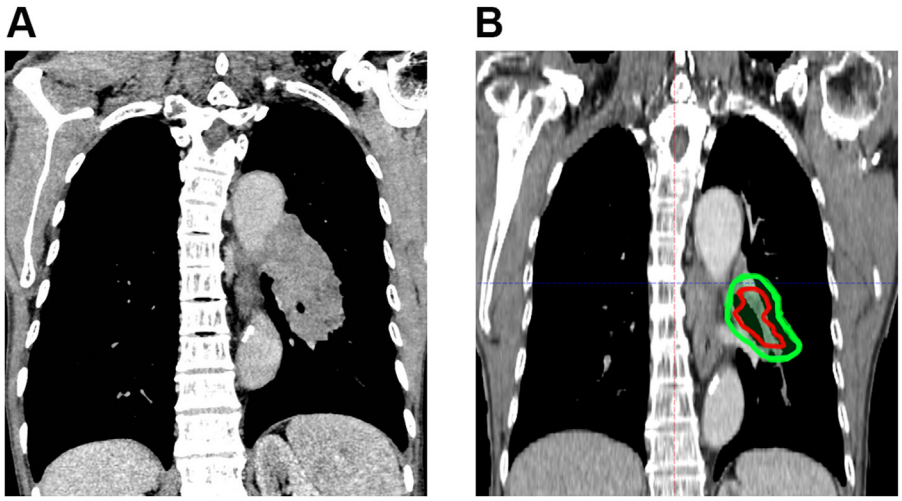

Fig. 2. An illustration of the small irradiation target volume. (A) The pretreatment image of an extensive stage small cell lung cancer patient who achieved partial response after four cycles of combination chemotherapy. (B) The target was based on the residual tumor. The red area represents the gross tumor volume and the green area the planning target volume.

the Kaplan-Meier method. Multivariate Cox proportional hazards analysis was performed to determine the association of different covariates with OS and PFS. All analyses were carried out using SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P \leq 0.05$; all *P*-values were derived from two-tailed tests.

3. Results

The median age of the included patients was 63 years (IQR, 56–69 years). Of them, 96/152 (63.2%) cases received consolidation RT and 56/152 (36.8%) did not. More patients in the non-consolidation RT group received PET-CT scans for staging than the consolidation RT group (35.7% vs. 22.9%, $P = 0.089$). A relatively higher proportion of patients in the consolidation RT group underwent PCI in comparison to the non-consolidation group (19.8% vs. 10.7%, $P = 0.145$). It was worth noting that the percentage of synchronous liver metastases was significantly higher in the non-consolidated RT group relative to the consolidated RT group (35.7% vs. 14.6%, $P = 0.003$). As of April 2022, 10/96 (10.4%) and 10/56 (17.9%) of cases in the consolidation and non-consolidation RT groups received chemo-immunotherapy modality [median cycles 6 (range 4–6) versus 8 (range 6–8)], while the median cycles of chemotherapy alone of the two groups was 5 (range 4–8) versus 6 (range 4–8), respectively. Baseline characteristics of the study cohort are presented in Table 1.

The median follow-up time for this cohort was 31.7 months (IQR, 23.9–39.6 months). Univariate analysis showed that consolidation RT significantly improved PFS and OS, with median PFS improving from 7.5 months to 9.2 months ($P = 0.001$, Supplementary Fig. 1A) and the median OS improving from 12.8 months to 17.1 months ($P = 0.011$, Supplementary Fig. 1B). Multivariate analysis showed that consolidation RT was an independent prognostic factor for PFS (hazard ratio [HR], 0.65 [95% CI, 0.45–0.94]; $P = 0.024$, Supplementary Table 1) but not for OS (HR, 0.70 [95% CI, 0.46–1.08]; $P = 0.107$, Supplementary Table 2).

Given that liver metastases being an important confounder for OS, we then stratified the entire cohort by the synchronous liver metastases, and found that consolidation RT could only improve PFS and OS in patients without synchronous liver metastases (Fig. 3A and B), but failed to bring any survival benefits in subgroup of synchronous liver metastases (Fig. 3C and D).

Relapse was observed in 78/96 (81.2%) and 51/56 (91.1%) patients in the consolidation and non-consolidation RT groups, respectively. In the consolidation RT group, 21/96 (22%) patients experienced in-field recurrence, with median time to recurrence of 20.4 months (95% CI, 16.3–24.5 months), while in the non-consolidation RT group 32/56 (57%) patients experienced in-field recurrence, with median time to recurrence of 8.9 months (95% CI, 6.9–10.8 months). Consolidation RT significantly reduced the risk of in-field recurrence at 1-year from 76.1% to 26.9% (HR, 0.28 [95% CI, 0.12–0.38]; $P < 0.01$).

Out-of-field recurrence occurred in 9/96 (9.4%) and 6/56 (10.7%) patients in the consolidation and non-consolidation RT groups, respectively; the out-of-field recurrence risk at 1-year was not significantly different (8.3% vs. 28.8%; HR, 0.40 [95% CI, 0.13–1.16]; $P = 0.080$). Despite the small irradiation volume, only one patient in each group experienced out-of-field relapse alone, with the interval from diagnosis to relapse being 24.5 months versus 4.6 months between the consolidation and non-consolidation RT groups, (HR, 0.33 [95% CI, 0.02–5.75]; $P = 0.430$). Fig. 4 and Supplementary Table 3 summarized the cumulative risk and the characteristics of recurrence in the two groups.

The first site of distant metastasis was presented in the Supplementary Table 4, where the highest risk site of the first metastasis was the brain (41.9%), followed by the liver (14.3%). Adding consolidation RT could not alter the pattern of the first metastasis in ES-SCLC.

Within the consolidation RT group, 74/96 (77.1%) patients received high doses (≥ 50 Gy). All patients completed RT as planned without treatment interruptions. After RT, 18/96 (18.8%) patients developed radiation pneumonitis. Eight out of 96 (8.3%) had grade 3 or greater toxicity. Acute radiation esophagitis was recorded in 23/96 (24.0%) patients, with 3/96 (3.1%) cases being above grade 3. Grade 3 or greater hematological toxicities were observed in 12/96 (12.5%) patients (Table 2). No grade 5 toxicities were observed.

4. Discussion

The benefit of consolidation RT in ES-SCLC is primarily seen in patients who responded to systemic therapy and achieved control of metastatic lesions. Pre-chemotherapy target volume is commonly considered for consolidation RT. In our center, we adopted a small-field approach, targeting only the post-chemotherapy residual lesions. In this study with long-term follow-up, we showed that our approach could confer a survival benefit for ES-SCLC patients, especially for those without liver metastases at diagnosis. Treatment-related toxicities are moderate, and there is no significant increase in marginal or out-of-field recurrence.

Jeremic et al first demonstrated that consolidation RT can significantly improve OS and relapse-free survival rates in ES-SCLC patients who achieved CR of metastatic lesions after induction chemotherapy.[16] Subsequently, the prospective CREST study showed that although consolidation RT did not improve 1-year OS (the study's primary end-point), it significantly improved 2-year OS from 3% to 13%. The authors reported that consolidation RT predominantly reduced intrathoracic recurrences.[15] Consistent with previous studies, our study confirmed that consolidation RT improved PFS in ES-SCLC. Although consolidation RT

Table 1
Clinical characteristics of ES-SCLC patients (n = 152) in the two groups.

Variables	Consolidation RT group (n = 96)	Non-Consolidation RT group (n = 56)	P
Sex, No. (%)			0.694
Male	86 (89.6)	49 (87.5)	
Female	10 (10.4)	7 (12.5)	
Age, years (%)			0.356
≤ 65	67 (69.8)	35 (62.5)	
> 65	29 (30.2)	21 (37.5)	
Smoking, No. (%)			0.530
No	23 (24.0)	16 (28.6)	
Yes	73 (76.0)	40 (71.4)	
ECOG PS, No. (%)			0.396
0–1	83 (86.5)	51 (91.1)	
> 1	13 (13.5)	5 (8.9)	
Staging PET-CT, No. (%)			0.089
Yes	22 (22.9)	20 (35.7)	
No	74 (77.1)	36 (64.3)	
Staging MRI liver performed, No. (%)			0.950[a]
Yes	5 (5.2)	2 (3.6)	
No	91 (94.8)	54 (96.4)	
Synchronous liver metastases, No. (%)			0.003
No	82 (85.4)	36 (64.3)	
Yes	14 (14.6)	20 (35.7)	
Tumor site, No. (%)			0.671
Left	48 (50.0)	26 (46.4)	
Right	48 (50.0)	30 (53.6)	
T-stage, No. (%)			0.433
T1/2	24 (25.0)	9 (16.1)	
T3/4	67 (69.8)	44 (78.6)	
Unknown	5 (5.2)	3 (5.3)	
N-stage, No. (%)			0.073[b]
N0/1	11 (11.5)	2 (3.6)	
N2	43 (44.8)	19 (33.9)	
N3	41 (42.7)	33 (58.9)	
Unknown	1 (1.0)	2 (3.6)	
Response to chemotherapy, No. (%)			0.997
SD	10 (10.4)	6 (10.7)	
PR	81 (84.4)	47 (83.9)	
CR	5 (5.2)	3 (5.4)	
Systemic therapy regimen, No. (%)			0.191
ChT	86 (89.6)	46 (82.1)	
ChT+ImT	10 (10.4)	10 (17.9)	
PCI, No. (%)			0.145
Yes	19 (19.8)	6 (10.7)	
No	77 (80.2)	50 (89.3)	

Abbreviations: ChT, chemotherapy; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; ImT, immunotherapy; PCI, prophylactic cranial irradiation; PR, partial response; RT, radiotherapy; SD, stable disease.
[a] By the chi-square test with continuous correction.
[b] Fisher's exact test.

Table 2
Administration and toxicities of consolidation RT group (n = 96).

Variables	Patients, No. (%)
Total dose, Gy	
≥ 50	74 (77.1)
< 50	22 (22.9)
CTCAE acute toxicities	
Radiation pneumonitis (any grade)	18 (18.8)
Grade (≥ 3)	8 (8.3)
Radiation esophagitis (any grade)	23 (24.0)
Grade (≥ 3)	3 (3.1)
Myelosuppression (any grade)	48 (50.0)
Grade (≥ 3)	12 (12.5)
Any toxicity	5 (5.2)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; Gy, gray; RT, radiotherapy.

was not associated with favorable OS in the whole cohort, in a subgroup analysis, we found that it produced additional survival benefit in patients without synchronous liver metastases. Liver metastasis is a detrimental factor for prognosis.[17-20] ES-SCLC with synchronous liver metastases are at a high risk of dissemination, which may counteract the improved local control from consolidation RT, leading to difficulties in OS and PFS prolongation.

The target volume of consolidation RT in ES-SCLC has not been well defined. In the study by *Jeremic et al*, consolidation RT included all post-chemotherapy residual lesions, and the ipsilateral hilum and all mediastinal regions.[17] However, the CREST study mandated irradiation of residual post-chemotherapy lesions, as well as the ipsilateral hilar and mediastinal lymph nodes involved at baseline, regardless of their responses to chemotherapy. Different from them, we only treated with the residual disease after chemotherapy. We found that small-field RT reduced recurrence within the irradiated field, and did not result in an increasing relapse at the margins of targets or out-of-field regions, indicating that our method is adequate.

Studies showed that PCI could reduce the occurrence of brain metastases and prolong PFS in ES-SCLC,[11,12] which is consistent with our observation. We believe that the beneficiary population of PCI should be those who respond well after systemic therapy.[21] Therefore, we did not perform PCI to all patients as in the CREST study. Meanwhile, for patients who received consolidation RT, intracranial metastasis was still

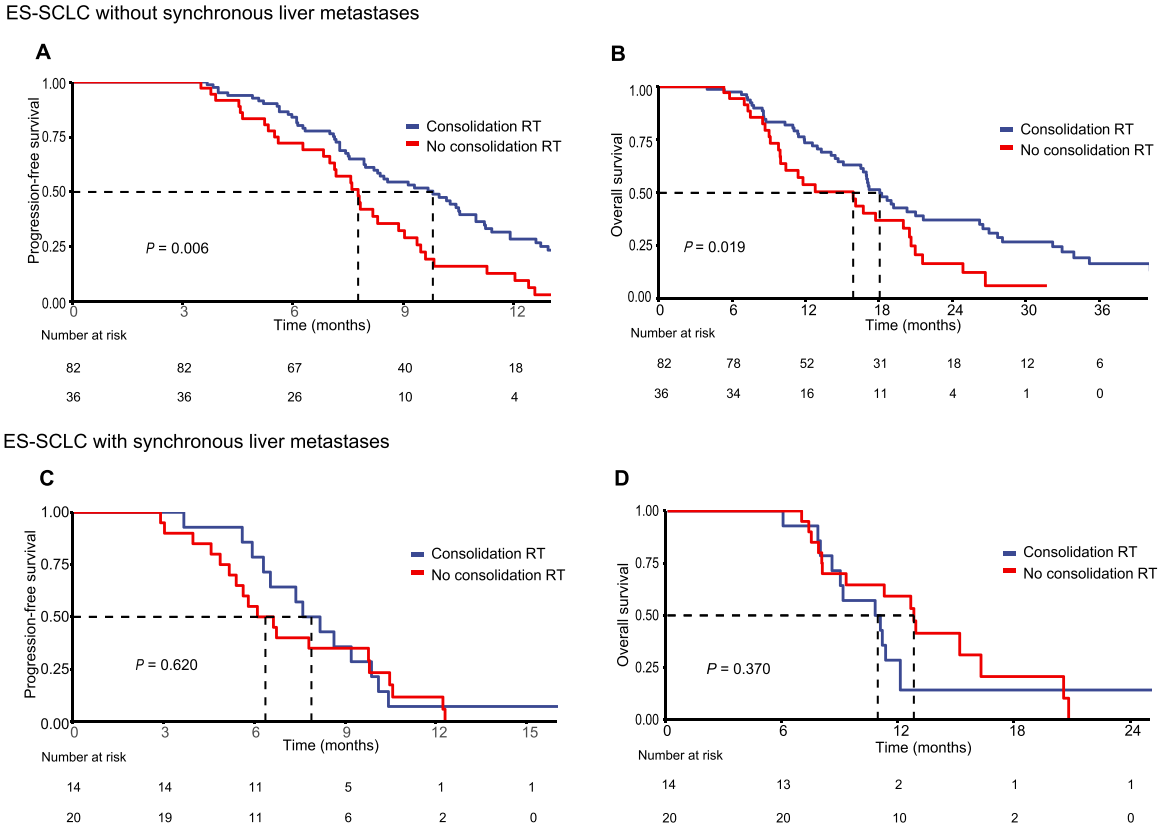

Fig. 3. PFS (A) and OS (B) in ES-SCLC patients without synchronous liver metastases treated with and without consolidation RT. PFS (C) and OS (D) in ES-SCLC patients with synchronous liver metastases treated with and without consolidation RT. ES-SCLC, extensive-stage small cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

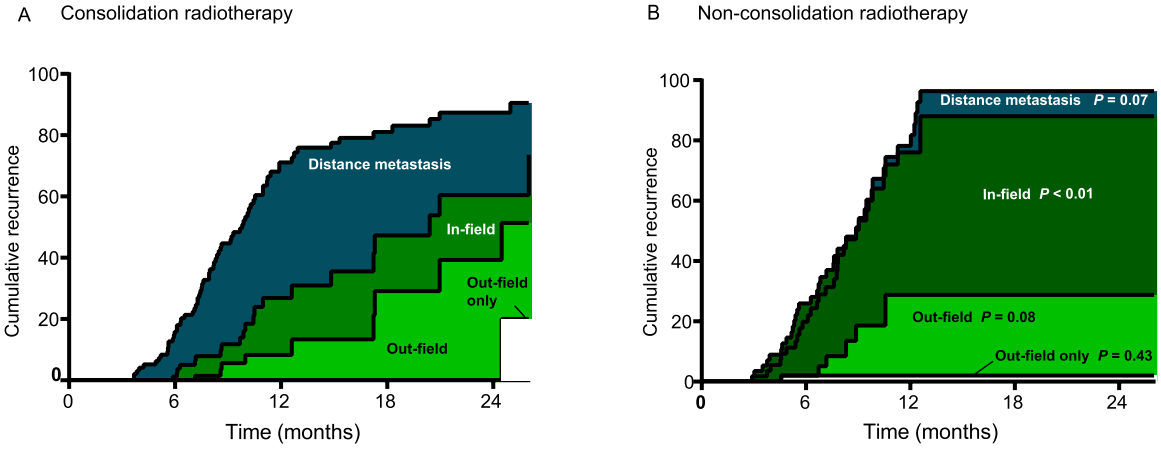

Fig. 4. Cumulative risk of recurrence in ES-SCLC patients treated with (A) and without (B) consolidation RT. ES-SCLC, extensive-stage small cell lung cancer; RT, radiotherapy.

the highest risk location of dissemination, with the cumulative failure rate exceeding 50%, highlighting PCI should be actively considered for ES-SCLC with well-controlled extracranial lesions.[21,22]

Currently, the optimal dose of consolidation RT for ES-SCLC is still uncertain. Although *Slotman et al* concluded that a dose of 30 Gy in 10 fractions or 40 Gy in 15 fractions would provide the best balance between survival and side effects, we assume that higher doses may ensure better control of lesions. Therefore, we adopted a more flexible approach, i.e., higher doses for patients with smaller treatment volumes.

In the present study, we performed detailed evaluation of all treatment-related toxicities. Although 50 Gy in 25 fractions was the most common dose in our cohort, the radiotherapy-related toxicities was modest, which might be attributed to a small irradiation volume.

Our study has several limitations. First, this was a retrospective study, and the dose of consolidation RT was not uniform. Second, about 13% of patients received chemotherapy and immunotherapy, and although we did not observe any grade 3–5 treatment toxicities in this cohort, the results have to be interpreted with caution as the number of patients was small; we cannot be certain of similar survival benefit in this

era of chemo-immunotherapy in larger cohorts. Previously published series have shown a possible synergy between immunotherapy and RT, with RT apparently promoting release of neoplastic antigens and activating immunogenicity and thereby improving treatment efficacy.[23-25] The ongoing prospective phase II study of low-dose RT combined with immunotherapy in ES-SCLC (ClinicalTrials.gov number NCT04462276) may clarify the value of RT in the context of immunotherapy.

5. Conclusions

Small-field consolidation RT in ES-SCLC patients with post-chemotherapy residual lesions is safe and results in good local control. It may improve survival in the absence of synchronous liver metastases.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Ethics statement

This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethical Committee of Zhongda Hospital (approval number: 2020ZDSYLL018-P01) with waiver of the need for informed consent.

Consent for publication

The patients whose medical images are presented in this manuscript provided consent for publication of their medical images for the manuscript. Only de-identified data and images are used in this research article.

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Author contributions

Y.Y., Y.C., C.Y. and J.Y. designed the study, wrote and revised this manuscript. C.J., B.Y. and R.L. collected the data, provided suggestions for revisions and reviewed the manuscript.

Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.07.003.

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