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Deep Learning-Based LS-SCLC Patient Selection for the New First-Line Treatment Using High-Dose Hyperfractionated SIB Radiotherapy

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ABSTRACT

Purpose: By developing risk-stratification and prognosis-prediction models for limited-stage small cell lung cancer (LS-SCLC) patients, this work aims to suggest potential candidates that may benefit from the newly proposed first-line treatment protocol using high-dose hyperfractionated simultaneous integrated boost (SIB) radiotherapy to improve overall survival (OS) and avoid over-treatment.

Methods: A total of 182 SCLC patients from an open-label, randomized phase III trial were analysed between 45 Gy and 54 Gy SIB groups. CT deep learning radiomics signature (DLRS) and important clinical factors were incorporated into Logistic regression models to predict prognostic outcomes. Risk stratifications based on DLRS and prophylactic cranial irradiation (PCI) were used to evaluate the impact of 54 Gy SIB across groups.

Results: Models based on DLRS and clinical factors achieved mean time-dependent area under curve (AUCs) of 0.797 for predicting OS. Patients classified as having a high DLRS exhibited significantly worse OS. Notably, patients in the high-DLRS group derived significant benefits from 54 Gy SIB in terms of OS. This group also experienced a significant benefit from PCI, and regardless of whether PCI was administered, 54 Gy hyperfractionated SIB radiotherapy consistently provided a significant OS advantage.

Conclusions: High-DLRS patients are more recommended to receive 54 Gy SIB as an alternative first-line LS-SCLC treatment. By stratifying patient-specific risk, this work proposed predictive models to select LS-SCLC patients that may potentially benefit from the new 54 Gy hyperfractionated SIB radiotherapy and PCI, which reduced unnecessary over-treatment and radiation toxicity, as well as resource waste of follow-up examinations.

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INTRODUCTION

According to a recent phase 3 trial of high-dose, accelerated, hyperfractionated twice-daily thoracic radiotherapy published on Lancet Respir Med , prescription of 54 Gy to the GTV in 30 fractions using SIB significantly improved the median OS from 39.5 months to 60.7 months (P=0.003), compared with the results of using the conventional 45 Gy in 30 fractions. However, this new treatment regimen also increased the dose to OARs, particularly affecting the oesophagus. Consequently, increased late adverse events were observed, although the differences were not statistically significant: the incidences of grade 1-2 esophagitis, pneumonitis, and pulmonary fibrosis in the 54 Gy group were consistently higher than that of the 45 Gy group. Therefore, it is clinically desirable to establish a personalized strategy to distinguish the patients with higher risk hence may potentially benefit more from the 54 Gy SIB as a trade-off. Alternatively, the patients of lower risk may receive the conservative treatment of 45 Gy without sacrificing the tumour control probability, in order to avoid unnecessary radiation exposure and comply with the ALARA principle.

This work aims to identify the patients who may potentially benefit from the new treatment scheme using 54 Gy SIB, by developing predictive models based on the deep learning radiomics signature (DLRS) of the planning CT images and clinical factors.

METHODS AND MATERIALS

182 patients were included in the analysis hereafter, which were evenly distributed in the groups of 54 Gy and 45 Gy. The training cohort included 122 patients and the test cohort included 60 patients. To extracted features, a cross-attention-based deep learning model was developed. PTV was selected as the ROI and used together with the CT images as model inputs. The model consisted of three components: (1) 3D CNN encoders, designed to extract high-level feature embeddings from the input images; (2) an intermediate feature fusion module, which employed both self-attention and cross-attention mechanisms to capture dependencies within and between the CT and ROI embeddings; and (3) a feedforward module, in which the refined and fused representations were used to generate the final deep learning features. Cross-entropy loss was selected as the objective function. A deep learning radiomics signature (DLRS) was developed based on a fully connected neural network. The network was trained on the training cohort using Cox partial log-likelihood as the loss function to construct the signature associated with OS.

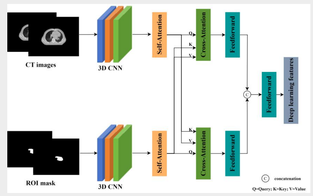

Figure 1. Model for feature extraction.

RESULTS

ECOG and DLRS were significant and independent prognostic factors. Considering the significant contribution of treatment prescription (45Gy vs. 54Gy) to the OS of LS-SCLC patients , it was also included in the analysis.

The time-dependent ROC of the DLRS and DLRS combined clinical models significantly outperformed the clinical model ($P < 0.05$) in the test set. Particularly, the mean AUC reached 0.797 in the combination model.

Patients were stratified into a low DLRS group (DLRS ≤ -0.55) and a high DLRS group (DLRS > -0.55).

Comparing to the standard radiotherapy using 45 Gy, high DLRS patients achieved better OS using 54 Gy hyperfractionated SIB radiotherapy.

Among patients treated with 54 Gy hyperfractionated SIB, PCI did not provide additional prognostic improvement. To the contrary, a significant benefit from PCI remained evident in the 45 Gy group.

Table 1. Time-dependent performance of three models in the test cohort.

Models	Mean AUC 95%CI
Clinical	0.620 (0.551-0.688)
DLRS	0.789 (0.725-0.853)
DLRS+Clinical	0.797 (0.729-0.865)

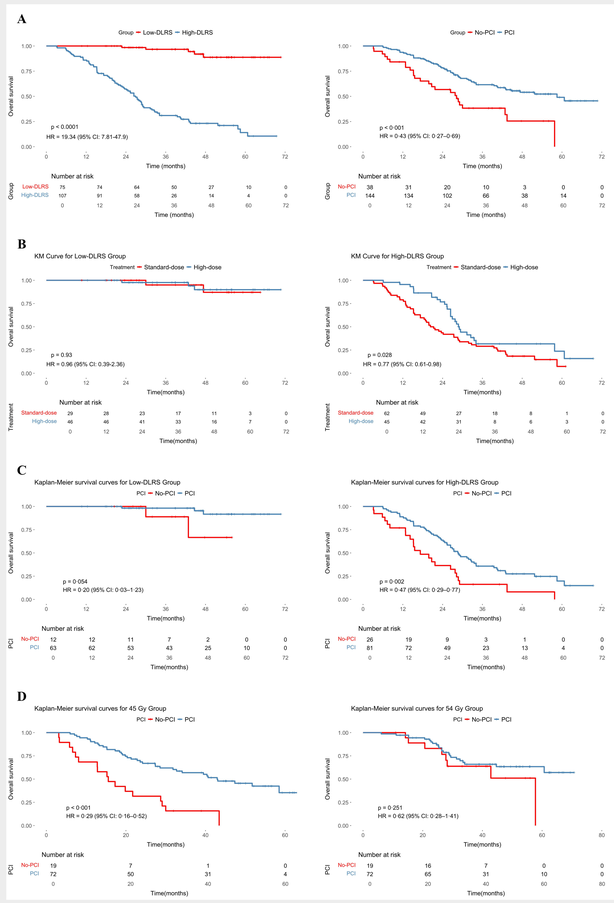

Figure 2. Benefit of overall survival from 54 Gy hyperfractionated SIB radiotherapy, stratified using DLRS and PCI respectively.

DISCUSSION

Based on the latest clinical evidence from a multicentre, open-label, randomised, phase 3 trial using new high-dose hyperfractionated SIB for LS-SCLC patients, the mean AUC values of the proposed DLRS models exceeded 0.75 in predicting OS , which were consistently higher than that of the conventional clinical model. By incorporating other significant factors such as treatment regime and ECOG performance status with the DLRS model, the AUC values were further improved.

Risk stratification revealed that low DLRS is significantly associated with better OS. To the contrary, for the patients with higher risk as suggested by larger DLRS in the planning CT images, the new 54 Gy hyperfractionated SIB radiotherapy significantly increased their survival benefit compared to standard treatment. However, such benefit from the new 54 Gy treatment was not observed in the low DLRS group, suggesting the conventional regime might be an alternative treatment to avoid unnecessary radiation. Considering that the high-dose hyperfractionated SIB is newly proposed for LS-SCLC patients as a first-line treatment, it is clinically desirable to identify candidates that may potentially benefit from this new treatment, as a trade-off for balancing the potentially increased toxicity and unnecessary radiation. Alternatively, over-treatment and resource waste can be avoided for patients with lower risk.

However, Figure2 (D) indicates that PCI did not further improve OS significantly for the 54 Gy group, whereas a significant benefit remained evident in the 45 Gy group. Therefore, 54 Gy hyperfractionated SIB radiotherapy might be used as an alternative to PCI for LS-SCLC patients to alleviate the financial burden and cognitive impairment. For the high-DLRS patients treated with conventional 45 Gy treatment, PCI remains a viable option to increase OS. In addition, patients with low DLRS can be used an indicator for more frequent follow-up using MRI to reduce the risk of brain metastases without wasting resources on all patients.

CONCLUSIONS

Based on a multicentre, open label, randomised, phase 3 trial, this study investigated the feasibility of patient-specific decision making for LS-SCLC patients, suggesting the candidates that may potentially benefit from the newly proposed high-dose hyperfractionated SIB radiotherapy and PCI. This work is potentially applicable to support precision radiotherapy by avoiding unnecessary over-treatment, resource waste and radiation toxicity such as esophagitis, pneumonitis, pulmonary fibrosis and cognitive impairment.

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