Serum lactate dehydrogenase predicts brain metastasis and survival in limited-stage small cell lung cancer patients treated with thoracic radiotherapy and prophylactic cranial irradiation

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Abstract

Background Small cell lung cancer (SCLC) is characterized by a high risk of brain metastasis and poor survival. This study aims to assess the prognostic role of lactate dehydrogenase (LDH) in limited-stage small cell lung cancer (LS-SCLC) treated with thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI).

Methods This study retrospectively evaluated 197 consecutive patients who underwent TRT and PCI for LS-SCLC between November 2005 and October 2017. Both pretreatment and maximal serum LDH levels (mLDH) during treatment were checked, and an increased LDH level was defined as more than 240 IU/ml. Clinical factors were tested for associations with intracranial progression-free survival (IPFS) and overall survival (OS) after PCI. The Kaplan–Meier method was used to calculate survival rates, and multivariate Cox regression analyses were carried out to identify variables associated with survival.

The authors Jianjiang Liu and Dongping Wu contributed equally to the manuscript.

Availability of supporting data The data of this study have been recorded in the Science and Education Department of Zhejiang Cancer Hospital in Excel format.

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**Results**

Of the total patients, 28 had higher pretreatment LDH levels and mLDH levels were increased in 95 patients during treatment. In patients in the normal and elevated mLDH groups, the 1-, 2-, and 5-year IPFS rates were 96.7% vs. 90.1%, 91.7% vs. 73.8%, and 87.8% vs. 61.0% (\(P<0.01\)), respectively. Compared to those with normal LDH levels, patients with increased mLDH levels had a higher cumulative risk of intracranial metastasis (hazard ratio [HR] 3.87; 95% confidence interval [CI] 1.73–8.63; \(P<0.01\)) and worse overall survival (HR 2.59; 95% CI 1.67–4.04; \(P<0.01\)). The factors LDH level at baseline or changes between pretreatment level and maximum level during treatment failed to predict brain metastases or OS with statistical significance. In the multivariate analyses, both mLDH during treatment (HR 3.53; 95% CI 1.57–7.92; \(P=0.002\)) and patient age \(\geq 60\) (HR 2.46; 95% CI 1.22–4.94; \(P=0.012\)) were independently associated with worse IPFS. Factors significantly associated with worse OS included mLDH during treatment (HR 2.45; 95% CI 1.56–3.86; \(P<0.001\)), IIIB stage (HR 1.75; 95% CI 1.06–2.88; \(P=0.029\)), and conventional radiotherapy applied in TRT (HR 1.66; 95% CI 1.04–2.65; \(P=0.034\)).

**Conclusion**

The mLDH level during treatment predicts brain metastasis and survival in LS-SCLC patients treated with TRT and PCI, which may provide valuable information for identifying patients with poor survival outcomes and possible candidates for treatment intensification.

**Keywords**

Predictor · Limited stage · Thoracic radiotherapy · Prognostic · Intracranial progression-free survival

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**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| ATP          | Adenosine-triphosphate |
| BED          | Biologically effective dose |
| BM           | Brain metastasis |
| CCRT         | Concurrent chemoradiotherapy |
| CI           | Confidence interval |
| CR           | Complete response |
| CT           | Computed tomography |
| ECOG-PS      | Eastern Cooperative Oncology Group performance status |
| ECPFS        | Extracranial progression-free survival |
| ECT          | Emission computed tomography |
| ED           | Extensive disease |
| EP           | Etoposide and platinum |
| HR           | Hazard ratio |
| IMRT         | Intensity-modulated radiotherapy |
| IPFS         | Intracranial progression-free survival |
| LD           | Limited disease |
| LDH          | Lactate dehydrogenase |
| LS-SCLC      | Limited-stage small cell lung cancer |
| mLDH         | Maximal serum LDH levels |
| MRI          | Magnetic resonance imaging |
| NCCN         | National Comprehensive Cancer Network |
| NSCLC        | Non-small cell lung cancer |
| NSE          | Neuron-specific enolase |
| OS           | Overall survival |
| PCI          | Prophylactic cranial irradiation |
| PET          | Positron-emission tomography |
| PR           | Partial response |
| Pro-GRP      | Prosoma gastric secretin release peptide |
| PS           | Performance status |
| ROS          | Reactive oxygen species |
| SCLC         | Small cell lung cancer |
| SCRT         | Sequential chemotherapy and radiotherapy |
| SD           | Standard dose |

**Introduction**

Small cell lung cancer (SCLC) is a highly metastatic and challenging type of carcinoma. While worldwide data for SCLC are not available, it is estimated that SCLC accounts for \(\sim 15\%\) of lung cancers and causes more than 210,000 deaths per year [1]. The survival outcome for this malignancy is poor, with a 2-year survival rate ranging from 20 to 40% and \(<10\%\) for patients with limited-stage disease (LD) and extensive-stage disease (ED), respectively [2, 3]. The most important prognostic factors in SCLC are disease stage, performance status (PS) scores, prosoma gastric secretin release peptide (Pro-GRP), neuron-specific enolase (NSE), and lactate dehydrogenase (LDH) levels [4–6].

Brain metastases (BMs) are common in SCLC, with \(\sim 10\%\) of patients presenting with this aggravation at the time of diagnosis and an additional 40–50% subsequently developing it [7, 8]. Prophylactic cranial irradiation (PCI) is also part of the standard management in most patients with non-metastatic SCLC who respond to initial treatment, as it significantly reduces the risk of BMs and improves survival [9, 10]. Although PCI is considered an effective method, some related studies have pointed out that the incidence of BMs even after PCI was still 4% at 1 year, 30% at 2 years, 11.2–38% at 3 years, and 44% at 4 years [11–14]. Therefore, it is meaningful to find a prognostic factor to predict BMs in these patients.

A study conducted by Forkasiewicz et al. found that lactate dehydrogenase (LDH), which regulates the processing of glucose to lactic acid, is commonly increased in cancer...
patients and correlated with poor clinical outcomes and resistance to therapy [15]. A recent study has indicated that LDH was a powerful predictor for overall survival (OS) after whole-brain radiation therapy (WBRT) in SCLC patients with BMs [16]. Therefore, we hypothesize that there is a clinical connection between the level of serum LDH and BM in patients diagnosed with SCLC.

Based on the aforementioned background data regarding this disease, the purpose of the present study was to identify LDH as a potential factor predicting BM and overall survival (OS) of LS-SCLC after thoracic radiotherapy (TRT) and PCI.

### Materials and methods

Between November 2005 and October 2017, we identified 207 consecutive SCLC patients who underwent TRT and PCI in Zhejiang Cancer Hospital. All patients had signed informed consent for TRT and PCI. Fig. 1 is the CONSORT diagram for patient selection. We excluded 6 patients who did not have serum LDH tests before or during treatment and 4 patients who had not completed PCI or TRT for various reasons. Therefore, a total of 197 patients were eligible for this analysis. This study has been approved by the Ethics Committee of Zhejiang Cancer Hospital and designed according to the principles of the Declaration of Helsinki. The individuals involved also signed informed consent for radiotherapy and chemotherapy.

All patients were pathologically diagnosed with LS-SCLC without BMs based on computed tomography (CT) and/or magnetic resonance imaging (MRI) findings. For pretreatment TMN staging, brain MRI (preferred) or brain CT with contrast, thoracic CT with contrast, whole-abdomen CT with contrast (preferred) or whole abdominal ultrasound, cervical lymph node ultrasound, positron-emission tomography (PET; preferred), or emission computed tomography (ECT) were all required. Serum LDH test data before treatment and during treatment were available. The upper limit of normal value (ULN) for LDH is 240 IU/L and the maximal serum LDH level (mLDH) was defined as the maximal LDH level tested from the beginning of radiotherapy or chemotherapy to the end of treatment.

IPFS was defined as the interval from pathological diagnosis to the onset of brain metastases or death or the last follow-up date. Diagnosis of intracranial progression mainly depends on imaging, but when the BM symptoms were identified before the imaging diagnosis, the first day of symptoms was considered the cutoff point. Within 1 year of the end of treatment, the patient underwent brain MRI (preferred) or brain CT every 3–4 months, and from the second year onwards, brain MRI (preferred) or brain CT was performed every 6 months. The diagnosis of extracranial metastases was mostly based on follow-up imaging examinations and serum tumor markers, and a small part was based on symptoms of extracranial metastases and subsequent examinations.

Furthermore, PET was not commonly used during follow-up unless metastases were detected by other tests and the patient’s financial conditions allowed. Other items (e.g., enhanced CT of chest and abdomen) were performed every 3–4 months within 2 years of the end of treatment and every 6 months after 2 years. Most of our patients had good follow-up compliance, and very few patients did not participate in the outpatient clinic for follow-up. Serum LDH levels at baseline and before each treatment (each cycle of chemotherapy and radiotherapy) were routinely measured as a part of biochemical tests using a Hitachi Modular 7600 Chemistry Analyzer. Therefore, the frequency of test-

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| SCLC patients records from November 2005 and October 2017 |
|---------------------------------------------------------|
| Extensive stage patients excluded by diagnostic directory (n=684) |
| Potentially limited stage patients (n=798) |
| Extensive patients excluded by medical records review (n=346) |
| Limited stage patients (n=452) |
| Patients without PCI excluded (n=146) |
| Patients without brain CT OR MRI (n=35) |
| Patients without TRT (n=23) |
| Patients lost to follow-up after the end date of PCI (n=22) |
| Patients not achieving CR or PR (n=19) |
| Patients preliminarily identified (n=207) |
| Patients without serum LDH test before or during treatment excluded (n=6) |
| Patients having not completed PCI or TRT excluded (n=4) |
| 197 eligible patients enrolled |
| Median follow-up time 27.8 (3.6-108.2 months) |
| Patients developing BMs (n=8) |
| Median time to intracranial failure 14.7 (6.0-47.0 months) |
| The 1-, 2- and 5-year IPFS rate were 96.7%, 91.7% and 87.8%, respectively. |

| Maximal LDH level during treatment< ULN (n = 102) |
| Median follow-up time 22.8 (2.3-107.8 months) |
| Patients developing BMs (n=24) |
| Median time to intracranial failure 14.6 (3.9-59.1 months) |
| The 1-, 2- and 5-year IPFS rate were 90.1%, 73.8% and 61.0%, respectively. |

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![Fig. 1 CONSORT diagram for patient selection](image-url)
Table 1  Summary of patient clinicopathological characteristics

| Clinicopathological characteristic | Maximal LDH level during treatment < ULN (n = 102) | Maximal LDH level during treatment ≥ ULN (n = 95) | P-value<sup>a</sup> |
|-----------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------|
| Age (years), median (range)       | 55 (27~73)                                    | 53 (35~76)                                    | 0.76                |
| < 60                              | 72 (36.5%)                                    | 65 (33.0%)                                    | –                   |
| ≥ 60                              | 30 (15.2%)                                    | 30 (15.2%)                                    | –                   |
| Sex, n (%)                        | –                                             | –                                             | 0.54                |
| Male                              | 78 (39.6%)                                    | 73 (37.1%)                                    | –                   |
| Female                            | 24 (12.2%)                                    | 22 (11.2%)                                    | –                   |
| Smoking index (number/d × years), n (%) | –                                             | –                                             | 0.89                |
| < 400                             | 44 (22.3%)                                    | 40 (20.3%)                                    | –                   |
| ≥ 400                             | 58 (29.4%)                                    | 55 (27.9%)                                    | –                   |
| ECOG-PS, n (%)                    | –                                             | –                                             | 0.15                |
| 0                                | 22 (11.2%)                                    | 24 (12.2%)                                    | –                   |
| 1                                | 72 (36.5%)                                    | 69 (35.0%)                                    | –                   |
| 2                                | 8 (4.1%)                                       | 2 (1.0%)                                       | –                   |
| TMN stage at initial diagnosis, n (%) | –                                             | –                                             | 0.62                |
| IA–IIB                            | 30 (15.2%)                                    | 26 (13.2%)                                    | –                   |
| IIIA                              | 57 (28.9%)                                    | 50 (25.4%)                                    | –                   |
| IIIB                              | 15 (7.6%)                                      | 19 (9.6%)                                      | –                   |
| Number of cycles of chemotherapy completed, n (%) | –                                             | –                                             | 0.20                |
| 1 ~ 5                             | 55 (27.9%)                                    | 42 (21.3%)                                    | –                   |
| 6                                | 47 (23.9%)                                    | 53 (26.9%)                                    | –                   |
| Chemotherapy regimen at the initial treatment, n (%) | –                                             | –                                             | 0.49                |
| EP                               | 90 (45.7%)                                     | 87 (44.2%)                                    | –                   |
| Non-EP                            | 12 (6.1%)                                      | 8 (4.1%)                                       | –                   |
| Combined modality of Chemo-RT, n (%) | –                                             | –                                             | 1.00                |
| SCRT                             | 41 (20.8%)                                     | 38 (19.3%)                                    | –                   |
| CCRT                             | 61 (31.0%)                                     | 57 (28.9%)                                    | –                   |
| PCI dose classification, n (%)    | –                                             | –                                             | 0.46                |
| Lower SD (20Gy/10F or 24Gy/12F)   | 7 (3.6%)                                       | 3 (1.5%)                                       | –                   |
| Medium SD (25Gy/10F or 30Gy/10~15F) | 80 (40.6%)                                     | 79 (40.1%)                                    | –                   |
| Higher SD (36Gy/18F or 40Gy/20F)  | 15 (7.6%)                                      | 13 (6.6%)                                      | –                   |

ECOG-PS Eastern Cooperative Oncology Group performance status, Chemo-RT chemotherapy and radiotherapy, SCRT sequential chemotherapy and radiotherapy, CCRT concurrent chemoradiotherapy, PCI prophylactic cranial irradiation, SD standard dose, EP etoposide and platinum

<sup>a</sup>Pearson’s $\chi^2$ test was used to calculate the $P$-value

The median patient age was 55 years (range 27–73 years) for the mLDH during treatment < ULN group (the normal group) and 53 years (range 35–76 years) for the mLDH ≥ ULN group (the elevated group); at initial TMN staging in the normal group, 30 (15.2%), 57 (28.9%), and 15 (7.6%) patients had IA–IIB, IIIA, and IIIB stage cancer, respectively. In the elevated group, 26 (13.2%), 50 (25.4%), and 19 (9.6%) patients had IA–IIB, IIIA and IIIB stage cancer, respectively. Other characteristics of the patients involved in this study are shown in detail in Table 1.

All patients were typically treated with PCI at a photon energy of 6 MV and laterally opposed treatment fields that encompassed the entire brain. The prescribed dose was calculated at the isocenter of the radiation fields based on daily treatments. While 7 (3.6%), 80 (40.6%), and 15 (7.6%) pa-
tients in the normal group underwent PCI with a lower standard dose (SD; 20 Gy/10 fractions or 24 Gy/12 fractions), medium SD (25 Gy/10 fractions or 30 Gy/10–15 fractions) and higher SD (36 Gy/18 fractions or 40 Gy/20 fractions), respectively, 3 (1.5%), 79 (40.1%), and 13 (6.6%) patients in the elevated group underwent PCI with a lower SD, medium SD, and higher SD, respectively. The median biologically effective dose (BED) was 36 (range 24–48) Gy for both groups when prescription doses were corrected to the BED using the linear quadratic model with an assumed α/β ratio of 10 Gy for tumor tissue.

In addition, 180 (91.4%) patients underwent PCI with a conventional radiotherapy technique and 17 patients received three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (IMRT). In total, 43 (21.8%) patients underwent TRT with a conventional radiotherapy technique and 154 (78.2%) patients received three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (IMRT). Furthermore, 180 (91.4%) patients received PCI after chemotherapy and TRT were completed, and 17 patients before chemotherapy and TRT were completed. Various dose/fractionation schemes were employed in different treatment groups. Specifically, there were 64 patients with a thoracic radiotherapy dose of 60–66 Gy/30–33 fractions, 64 patients with 55.4–59.4 Gy/25–30 fractions, 51 patients with 50–54 Gy/25–27 fractions, and 9 patients with 46–48 Gy/23–24 fractions; 9 patients received hyperfractionated radiotherapy (45 Gy/30 fractions/twice a day).

**Statistical analysis**

The data used in this study are reported as median (range) or number (percentage). Time-to-event analyses were performed from the start of TRT to the emergence of the event. Descriptive statistical analyses were applied to characterize the patients in the normal and elevated groups. Chi-squared test, which was carried out with SPSS 22.0 software (IBM Corporation, Armonk, NY, USA), was adopted for estimation of the differences in clinical characteristics (smoking index, ECOG-PS, TMN stage, number of cycles of chemotherapy, chemotherapy regimen, combined modality of Chemo-RT, PCI dose, and demographic variables). The Kaplan–Meier method and the log-rank test were used to compare the curves for intracranial progression-free survival (IPFS) and OS. Thereafter, potential prognostic factors were evaluated using the Cox proportional hazards model, and the results were reported as hazard ratios (HRs) and the corresponding 95% confidence intervals (CI). Significant factors identified in univariate analyses were included in the multivariate model. GraphPad Software (San Diego, CA, USA), was used to draw the forest figure of survival analysis. We considered the differences statistically significant if P-values < 0.05.

**Results**

**Patient characteristics and outcomes**

The median number of LDH tests was 7 (range 4–12) for all patients during treatment, including those in the elevated and normal groups. The mLDH level during treatment (median 233 IU/L, range 74–2327) was significantly higher than the pretreatment LDH level (median 183 IU/L, range 73–1999), and the average level of LDH during treatment (median 172 IU/L, range 89–984) decreased slightly compared to the pretreatment level (median 183 IU/L, range 73–1999). The levels of LDH during treatment might be associated with therapeutic effect, glycolytic activity, liver function, body inflammation, tumor burden, and necrosis.

While 28 patients presented higher pretreatment LDH levels (≥1 ULN), serum mLDH levels were promoted in 95 patients during treatment. Both pretreatment LDH and mLDH during treatment were ≥1 ULN in 15 patients and <1 ULN in 88 patients. Pretreatment LDH ≥1 ULN but mLDH during treatment <1 ULN was identified in 13 patients. Also, pretreatment LDH <1 ULN but mLDH during treatment ≥1 ULN was identified in 80 patients. As shown in Table 1, the patient distribution between the group of individuals with normal mLDH during treatment and the elevated group was well balanced based on the prognostic factors, including age (p = 0.76), sex (p = 0.54), smoking index (p = 0.89), ECOG-PS (p = 0.15), TMN stage (p = 0.62), number of chemotherapy cycles (p = 0.20), chemotherapy regimen (p = 0.49), combined modality of Chemo-RT (p = 1.00), and PCI dose (p = 0.46).

Of the 197 eligible patients, 99 died during the follow-up period. The median follow-up time was 24.2 months (range 2.3–108.2 months). After chemotherapy and TRT, 33 (16.8%) patients developed partial response (PR) and 164 (83.2%) developed complete response (CR). Moreover, 32 (16.2%) patients developed intracranial failure after PCI, and their median intracranial failure term was 14.6 months (range 3.9–59.1 months). A total of 15 patients had elevated LDH both before and during treatment. Among them, 5 patients (5/15, 33.3%) developed BMs and 12 patients (12/15, 80.0%) were dead, a rate much higher compared with 32 (32/197, 16.2%) and 99 (99/197, 50.3%), respectively. We have also identified that 105 (53.3%) patients developed extracranial metastasis, and their median extracranial failure term was 9.5 months (range 3.3–70.4 months). Fig. 2 shows IPFS and OS after TRT and PCI treatment. The 1-, 2-, 3-, and 5-year IPFS rates were 94.0%, 83.5%, 79.5%, 73–1999).
Fig. 2  Intracranial progression-free survival (IPFS) and overall survival (OS) of 197 patients after prophylactic cranial irradiation

and 75.2%, respectively, and the 1-, 2-, and 5-year OS was 84.7%, 62.6%, and 46.5%, respectively.

**mLDH during treatment is associated with a higher risk of brain metastasis and predicts IPFS**

The upper limit of the normal range was chosen as the cutoff value for LDH based on the results of evaluation of various cutoff values. As shown in Table 2, univariate analyses revealed that longer IPFS was associated with mLDH during treatment < ULN (P < 0.01) and age < 60 years (P < 0.01). In patients in the normal and elevated LDH groups, the 1-, 2-, and 5-year IPFS rates were 96.7% vs. 90.1%, 91.7% vs. 73.8%, and 87.8% vs. 61.0% (P < 0.01), respectively (as shown in Fig. 3a). Compared to those patients with normal LDH levels, patients with increased mLDH levels had a higher cumulative risk of intracranial metastasis (hazard ratio [HR] 3.87; 95% confidence interval [CI] 1.73–8.63; P < 0.01). No significant impact on IPFS after TRT and PCI was observed for pretreatment LDH level or changes between pretreatment LDH and maximum LDH levels during treatment (Table 2).

**Univariate and multivariate models for overall survival**

As shown in Fig. 4a, b, mLDH levels during treatment were associated with worse survival. In patients in the normal and elevated mLDH groups, the 1-, 2-, and 3-year extracranial progression-free survival (ECPFS) rates were 71.6% vs. 50.9%, 63.6% vs. 36.3%, and 60.6% vs. 31.8% (P < 0.01), respectively. However, no significant impact on OS after TRT and PCI was observed for pretreatment LDH levels or changes between pretreatment LDH and maximum LDH levels during treatment (Table 2). Compared to patients with normal LDH levels, patients with increased mLDH levels had a higher cumulative risk of death (HR 2.59; 95% CI 1.67–4.04; P < 0.01). Factors associated with improved OS were mLDH during treatment < ULN (P < 0.01), IA-IIIA stage at initial diagnosis (P = 0.02), and three-dimensional conformal or IMRT applied in TRT (P = 0.02). Other factors, such as age and chemotherapy regimens, were suspected predictors, although the P-value was slightly greater than 0.05 (Table 2).

**mLDH during treatment is associated with a higher risk of extracranial metastasis and predicts extracranial progression-free survival**

In patients in the normal and elevated mLDH groups, the 1-, 2-, and 3-year extracranial progression-free survival (ECPFS) rates were 71.6% vs. 50.9%, 63.6% vs. 36.3%, and 60.6% vs. 31.8% (P < 0.01), respectively (as shown in Supplementary Figure A). Compared to those patients with normal LDH levels, patients with increased mLDH levels had a higher cumulative risk of extracranial metastasis (HR 2.34; 95% CI 1.57–3.49; P < 0.01). No significant impact
Table 2  Univariate analysis for intracranial progression-free survival time (IPFS) and overall survival (OS)

| Clinicopathological parameter | Patients (n = 197) | Univariate analysis | 2-year IPFS rate | HR (95% CI) | P-value | 2-year OS rate | HR (95% CI) | P-value |
|--------------------------------|-------------------|---------------------|------------------|-------------|---------|----------------|-------------|---------|
| Age (years)                    |                   |                     |                  |             |         |                |             |         |
| <60                            | 137 (69.5%)       | 87.7%               | 1                | <0.01       |         | 65.5%          | 1           |         |
| ≥60                            | 60 (30.5%)        | 72.5%               | 2.5              | (1.2–5.0)   | 0.08    | 55.9%          | 1.5         | (0.9–2.3) |
| Sex                            |                   |                     |                  |             |         |                |             |         |
| Female                         | 47 (23.9%)        | 89.4%               | 1                |             | 0.21    | 64.9%          | 1           |         |
| Male                           | 150 (76.1%)       | 81.5%               | 1.8              | (0.7–4.7)   |         | 61.8%          | 1.0         | (0.6–1.7) |
| ECOG-PS                        |                   |                     |                  |             |         |                |             |         |
| 0, 1                           | 187 (94.9%)       | 83.3%               | 1                |             |         | 63.2%          | 1           |         |
| 2                              | 10 (5.1%)         | 87.5%               | 0.7              | (0.1–5.3)   |         | 50.8%          | 1.3         | (0.5–3.3) |
| Smoking index                  |                   |                     |                  |             |         |                |             |         |
| <400                           | 84 (42.6%)        | 85.2%               | 1                |             |         | 63.2%          | 1           |         |
| ≥400                           | 113 (57.4%)       | 82.0%               | 1.0              | (0.5–2.0)   | 0.06    | 62.1%          | 1.3         | (0.7–1.7) |
| TNM stage at initial diagnosis |                   |                     |                  |             |         |                |             |         |
| IA-III A                       | 163 (82.7%)       | 84.8%               | 1                |             |         | 65.9%          | 1           |         |
| IIIB                           | 34 (17.3%)        | 77.1%               | 1.4              | (0.6–3.3)   |         | 47.1%          | 1.8         | (1.1–2.9) |
| Number of chemotherapy cycles at the initial treatment |                   |                     |                  |             |         |                |             |         |
| 1–5                            | 97 (49.2%)        | 82.9%               | 1                |             |         | 63.3%          | 1           |         |
| 6                              | 100 (50.8%)       | 84.4%               | 1.3              | (0.6–2.6)   |         | 62.1%          | 1.1         | (0.7–1.6) |
| Chemotherapy regimen at initial treatment |                   |                     |                  |             |         |                |             |         |
| EP                             | 177 (89.8%)       | 81.8%               | 1                |             |         | 61.3%          | 1           |         |
| Non-EP                         | 20 (10.1%)        | 95.0%               | 0.5              | (0.1–1.9)   | 0.02    | 72.9%          | 0.5         | (0.2–1.1) |
| TRT technique                  |                   |                     |                  |             |         |                |             |         |
| Three-dimensional conformal radiotherapy or IMRT | 154 (78.2%) | 84.8% | 1 | 0.43 | 0.6–2.6 | 65.9% | 1 | (0.2–1.1) |
| Conventional radiotherapy      | 43 (21.8%)        | 78.1%               | 1.4              | (0.6–3.3)   |         | 50.8%          | 1.7         | (1.1–2.5) |
| Combined modality of Chemo-RT  |                   |                     |                  |             |         |                |             |         |
| SCRT                           | 79 (40.1%)        | 82.9%               | 1                |             | 0.27    | 61.0%          | 1           |         |
| CCRT                           | 118 (59.9%)       | 84.0%               | 1.0              | (0.5–2.0)   | 0.14    | 64.1           | 0.7         | (0.5–1.1) |
| Time of PCI                    |                   |                     |                  |             |         |                |             |         |
| After chemotherapy and TRT completed | 180 (91.4%) | 84.4% | 1 | 0.86 | 0.3–3.7 | 61.6% | 1 | (0.7–2.5) |
| Before chemotherapy and TRT completed | 17 (8.6%) | 76.9% | 1.1 |             | 73.3% | 1.3 |         |

on ECPFS after TRT and PCI was observed for pretreatment LDH level (HR 1.47; 95% CI 0.89–2.42; P = 0.13; Supplementary Figure B) or changes between pretreatment LDH and maximum LDH level during treatment (HR 1.47; 95% CI 0.86–2.51; P = 0.15; Supplementary Figure C).

Discussion

As a key enzyme in glycolysis, LDH has been reported to be enhanced in transformed cells and play a vital role in tumor initiation, proliferation, invasion, and metastasis [17]. Furthermore, serum LDH has been proven to be a powerful predictor of survival in various cancers.
Table 2 (Continued)

| Clinicopathological parameter | Patients (n = 197) | Univariate analysis | 2-year IPFS rate | HR (95% CI) | P-value | 2-year OS rate | HR (95% CI) | P-value |
|-------------------------------|-------------------|---------------------|------------------|------------|--------|----------------|------------|--------|
| PCI dose classification (BED10), Gy | – – – | 0.40 – – – | 0.55 – – – |
| ≤31.25 | 84 (42.6%) | 82.0% | 1 | – | 60.1% | 1 | – |
| >31.25 | 113 (57.4%) | 84.5% | 0.7 | (0.4–1.5) | – | 64.5% | 1.1 | (0.7–1.7) |
| Short-term efficacy | – – – | 0.76 – – – | 0.52 – – – |
| CR | 164 (83.2%) | 83.6% | 1 | – | 62.6% | 1 | – |
| PR | 33 (16.7%) | 82.7% | 0.8 | (0.3–2.7) | – | 57.2% | 1.2 | (0.7–2.2) |
| Maximal LDH during treatment | – – – | <0.01 – – – | – | <0.01 |
| <ULN | 102 (51.8%) | 91.7% | 1 | – | 74.2% | 1 | – |
| ≥ULN | 95 (48.2%) | 73.8% | 3.8 | (1.7–8.6) | – | 51.1% | 2.6 | (1.7–4.0) |
| LDH at baseline | – – – | 0.48 – – – | 0.10 – – – |
| <ULN | 169 (85.8%) | 84.6% | 1 | – | 65.0% | 1 | – |
| ≥ULN | 28 (14.2%) | 76.9% | 1.4 | (0.6–3.4) | – | 50.0% | 1.5 | (0.9–2.6) |
| Changes between pretreatment and maximum during treatment LDH level | – – – | 0.21 – – – | – | 0.21 |
| Decreased | 40 (20.3%) | 87.2% | 1 | – | 70.5% | 1 | – |
| Elevated | 157 (79.7%) | 81.4% | 1.9 | (0.7–5.5) | – | 60.8% | 1.4 | (0.8–2.6) |

BM = brain metastases, ET etoposide and platinum, TRT thoracic radiotherapy, IMRT intensity-modulated radiotherapy, BED biological effective dose, LDH lactate dehydrogenase, ULN upper limit of normal value

Fig. 3 Kaplan–Meier curve of groups of higher and normal maximal lactate dehydrogenase (LDH) groups (a), and multivariate analysis (b) for Intracranial progression-free survival. ULN upper limit of normal value
predictor in various cancers, and some studies have also confirmed that serum LDH could strongly predict survival in LS-SCLC [18–23]. However, none of these studies have identified LDH as a prognostic indicator to predict brain metastasis and survival in LS-SCLC after PCI or explored the relationship between LDH and brain metastasis.

Elevated LDH levels represent higher glycolysis activity, which might promote cancer invasion and metastasis. Different scholars have looked into this phenomenon and concluded that energy metabolism plays an important role in cerebral metastasis [24, 25]. In such cases, glycolysis inhibition might be a useful strategy to reduce the risk of cerebral metastasis in LS-SCLC. Our previous study [26] revealed that oxamate, an inhibitor of LDH-A, significantly suppressed the proliferation of NSCLC cells while it exerted much lower toxicity in normal cells. LDH-A inhibition resulted in ATP reduction and reactive oxygen species (ROS) burst in cancer cells, which led to apoptosis and G2/M arrest and increased radiosensitivity in NSCLC cells [27].

Up to now, scholars and clinicians have still not found the best method to select early-stage SCLC patients with good prognoses for possible avoidance of PCI. Previous meta-analysis identified five retrospective studies and included a total of 1691 patients, among which 315 of received PCI. For all the resected patients, PCI was associated with improved overall survival (HR 0.52, 95% CI 0.33–0.82) and reduced brain metastasis risk (RR 0.50, 95% CI 0.32–0.78). However, regarding p-stage I patients, no survival benefit was brought by PCI (HR 0.87, 95% CI 0.34–2.24) [28]. Due to this study, NCCN guidelines 2019 version 1 did not recommend PCI for p-stage I (T1-2N0M0) patients who had undergone radical surgical interventions (category IIA).

The present study showed that elevated mLDH levels during treatment might indicate disease recurrence and brain metastasis. Therefore, for those patients, MRI is necessary. Recently, Anami et al. evaluated 48 consecutive patients who underwent WBRT for BMs from SCLC, and the results revealed that the presence of symptoms due to BMs and...
LDH values independently predicted prognosis [16]. Suzuki et al. also identified that high pretreatment platelet counts (1.649, 95% CI 1.130–2.408; \( P = 0.010 \)) and pretreatment LDH > 543 U/L (HR 1.870, 95% CI 1.290–2.710; \( P = 0.001 \)) were associated with increased rates of brain metastasis in patients with SCLC with no evidence of brain disease at diagnosis [29]. These studies suggested some clinical links between BM and elevated LDH. In our research, elevated mLDH levels during treatment were treated as a significant independent prognostic indicator for IPFS in LS-SCLC after TRT and PCI (HR for IPFS 3.53, 95% CI 1.57–7.92; \( P = 0.002 \)). These data further confirm the connections between BM and elevated LDH. Thus, for the patients with elevated LDH during treatment, more positive therapies should be administered to reduce the risk of BM. At least PCI, which has been proven to improve IPFS, should be applied urgently. Other options, such as LDH inhibitors or glycolysis inhibitors, can be used for BM prevention. At present, these drugs are still not widely available, and there is a lack of research focusing on these substances, randomized trials on the use of relevant drugs for BM prevention should be conducted in the future.

In this study, the pretreatment LDH level or changes between pretreatment and maximum LDH level during treatment predicted IPFS and OS without statistical significance. Our outcomes are not consistent with the results reported by Sagman et al. and He, et al. [21, 22]. In Sagman’s study, patients with LS-SCLC and elevated levels of pretreatment LDH manifested a higher relative death rate (1.63:1) when compared to patients with LS-SCLC and LDH in the normal range (\( P = 0.0083 \)), but the survival of patients with extensive-stage disease did not differ between patients with normal and elevated levels of LDH (\( P = 0.273 \)). Contrastingly, in He et al.’s study, multivariate analysis revealed that pretreatment LDH > 215.70 U/L was an independent prognostic factor for poor survival (HR 1.468, 95% CI 1.069–2.017; \( P = 0.018 \)). The subgroup analysis showed that pretreatment LDH level was significant for predicting survival in both limited and extensive disease. Further, Suzuki et al. [29] also identified pretreatment LDH as an influential prognostic factor for BM in patients with SCLC with no evidence of brain disease at diagnosis. Our results are different from others reported in the aforementioned studies, probably because in these papers, the sample of patients with SCLC included all TMN or limited stages without PCI, and diverse samples may make a difference in the prediction of BM and survival. Other factors, such as small patient samples and inconsistency of clinicopathological parameters, may also contribute to the different results.

In addition, our study showed that the 1-, 2-, 3-, and 5-year IPFS rates were 94.0%, 83.5%, 79.5%, and 75.2%, and the 1-, 2-, and 5-year OS were 84.7%, 62.6%, and 46.5%, respectively. The 2-year OS rate of our study was relatively high, which was much better than the one reported by Kamran et al. [30] (62.6% vs. 47%). We assume that there may be several possible reasons behind this discrepancy, including the fact that 40% of the patients included in their study did not undergo PCI, while all of the patients in our study completed PCI. This difference may have directly affected our results, as we know, PCI can improve OS of LS-SCLC by 5.4% [31]. Secondly, 18% of Kamran et al.’s patients have an ECOG-PS of 2–3, while only 5.1% of patients in our study have ECOG-PS of 2, and since ECOG-PS is also a prognostic factor, these different rates may have also impacted the final results. Lastly, the proportion of stage IA-IIIA patients in our study is much higher than that in Kamran et al.’s study (40% vs. 17.3%), and TMN stage is considered a very powerful predictor by many scholars, which is in agreements with the preconditions applied in our analyses. In conclusion, this retrospective dataset provides evidence that maximum elevated LDH levels during treatment of patients with LD SCLC may predict for the development of brain metastases and survival. However, given the limited number of patients and unseasonal follow-up of very few patients, our findings still need to be confirmed by more studies. In addition, future research should develop a comprehensive scoring tool to assist clinicians to decide whether to administrate PCI in LS-SCLC patients.

**Supplementary Information** The online version of this article (https://doi.org/10.1007/s00066-022-01977-4) contains supplementary material, which is available to authorized users.

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**Author Contribution** Jianjiang Liu and Dongping Wu are responsible for data collation and paper writing, Yang Yang is responsible for paper guidance and revision, and the remaining authors are responsible for paper revision.

**Declarations**

**Conflict of interest** J. Liu, D. Wu, B. Shen, M. Chen, X. Zhou, P. Zhang, G. Qiu, Y. Ji, X. Du, and Y. Yang declare that they have no competing interests.

**Ethical standards** This study has been approved by the Ethics Committee of the Zhejiang Cancer Hospital. For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. Consent for publication: All authors agree to publish.

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