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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Research Article

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Abstract

Background: Small cell lung cancer (SCLC) is characterized with high risk of brain metastasis and poor survival. This study aimed to assess the prognostic role of 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, 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.

Results: Of the total patients, 95 had higher pretreatment LDH levels, and serum LDH levels were increased in 95 patients during treatment. In patients with the normal and elevated mLDH groups, the 1-, 2- and 5-year IPFS rate 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 level, patients with increased mLDH level had 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 of LDH level at baseline or changes between pretreatment level and maximum level during treatment failed to predict BMs 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 age ≥ 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: mLDH level during treatment, but not pretreatment level 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.

Introduction

Small cell lung cancer (SCLC) is a highly metastatic and recalcitrant carcinoma. While worldwide data for SCLC are not available, it is estimated that SCLC accounts for ~ 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 of ~ 20–40% and < 10% for patients with limited disease (LD) and extensive disease (ED), respectively [2, 3]. The most important prognostic factors in SCLC are disease stage, performance status (PS) scores, prostatic acid phosphatase (Pro-GRP), neuron specific enolase (NSE) and lactate dehydrogenase (LDH) levels [4–6]. Brain metastases (BMs) are common in SCLC, with ~ 10% of patients presenting with brain metastases at the time of diagnosis and an additional 40–50%

subsequently developing BMs [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]. Though PCI can obviously reduce the risk of brain metastases, there are still 4% patients in one year, 30% in two years, 11.2–38% in two years and 44% in four years developing BMs after PCI in LS-SCLC patients [11–14]. Therefore, it is meaningful to find a prognostic factor to predict BMs in these patients.

Lactate dehydrogenase (LDH), which regulates the processing of glucose to lactic acid, were found to be commonly increased in cancer patients and correlated with poor clinical outcome and resistance to therapy [15]. 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, it is supposed that there is some clinical connections between the level of serum LDH and BMs in SCLC.

The purpose of the present study was to identify LDH as a potential factor predicting BMs and overall survival (OS) of LS-SCLC after thoracic radiotherapy (TRT) and PCI.

Materials And Methods

Between November 2005 and October 2017, we identified 211 consecutive SCLC patients who underwent TRT and PCI in Zhejiang Cancer Hospital. All patients had signed informed consent for TRT and PCI. We excluded 6 patients who did not have serum LDH test before treatment or during treatment. In addition, 4 patients who had not completed PCI or TRT for various reasons and 3 patients who had underwent surgery resection were excluded from this study. Furthermore, 1 patient who had stable disease after chemotherapy and TRT were excluded. Therefore, a total of 197 patients were eligible for this analysis. The characteristics of the study patients are shown in Table 1.

Table 1
Summary of patient clinic pathological characteristics.

Clinicopathological characteristic	Maximal LDH level during treatment < ULN (n = 102)	Maximal LDH level during treatment ≥ ULN (n = 95)	P-value*
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-IIIB	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

* P-value: Pearson's χ^2 test was used to calculated the p-value;*ECOG-PS = Eastern Cooperative Oncology Group performance status, Chemo-RT = chemotherapy and radiotherapy, SCRT = sequential chemotherapy and radiotherapy, CCRT = concurrent chemo-radiotherapy, PCI = prophylactic cranial irradiation, SD = standard dose.

Clinicopathological characteristic	Maximal LDH level during treatment < ULN (n = 102)	Maximal LDH level during treatment ≥ ULN (n = 95)	P-value*
EP*	90(45.7%)	87(44.2%)	
Non-EP	12(6.1%)	8(4.1%)	
Combined model 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%)	
* P-value: Pearson's χ^2 test was used to calculated the p-value;*ECOG-PS = Eastern Cooperative Oncology Group performance status, Chemo-RT = chemotherapy and radiotherapy, SCRT = sequential chemotherapy and radiotherapy, CCRT = concurrent chemo-radiotherapy, PCI = prophylactic cranial irradiation, SD = standard dose.			

All patients had pathologically confirmed LS-SCLC without BMs, which was based on findings from computed tomography (CT) and/or magnetic resonance imaging (MRI). Serum LDH test data before treatment and during treatment were available. 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 PCI. 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 symptoms of BMs is earlier than the imaging diagnosis, the day of symptoms of BMs is the cutoff point. The upper limit of normal value (ULN) is 240 IU/L.

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); 78 (39.6%) patients in the normal group and 73 (37.1%) in the elevated group were male, while 24 (12.2%) in the normal group and 22 (11.2%) in the elevated group were female. At the initial TMN staging in the normal group, 30 (15.2%), 57 (28.9%) and 15 (7.6%) patients had IA-IIIB, IIIA and IIIB stage, respectively. In the elevated group, 26 (13.2%), 50 (25.4%) and 19 (9.6%) patients had IA-IIIB, IIIA and IIIB stage, respectively.

As indicated by an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, 94 (47.7%) patients in the normal group and 93 (47.2%) in the elevated group had good general condition,

while 8 (4.1%) in the normal group and 2 (1.0%) in the elevated group had a poor general condition (ECOG-PS of 2). In addition, 55 (27.9%) patients in the normal group and 42 (21.3%) in the elevated group completed 1 ~ 5 cycles of chemotherapy, while 47 (23.9%) in the normal group and 53 (26.9%) in the elevated group completed 6 cycles of chemotherapy. 90 (45.7%) patients in the normal group and 87 (44.2%) in the elevated group were administered chemotherapy of etoposide and platinum (EP) regime while 12 (6.1%) in the normal group and 8 (4.1%) in the elevated group received non-EP regime. 41 (20.8%) patients in the normal group and 38 (19.3%) in the elevated group applied combined model of sequential chemotherapy and radiotherapy (SCRT) while 61 (31.0%) patients in the normal group and 57 (28.9%) in the elevated group applied model of concurrent chemo-radiotherapy (CCRT).

All patients were typically treated with PCI at a photon energy of 6 MV and lateral-opposed treatment fields that encompassed the entire brain. The prescribed dose was calculated at the isocenter of the radiation fields based on daily treatments. 7 (3.6%), 80 (40.6%) and 15 (7.6%) patients in the normal group underwent PCI with lower standard dose (SD) (20Gy/10F or 24Gy/12F), medium SD (25Gy/10F or 30Gy/10-15F) and higher SD (36Gy/18F or 40Gy/20F), respectively. 3 (1.5%), 79 (40.1%) and 13 (6.6%) patients in the elevated group underwent PCI with 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 conventional radiotherapy technique and 17 patients applied three-dimensional conformal radiotherapy or Intensity-modulated radiotherapy (IMRT) technique. 43 (21.8%) patients underwent TRT with conventional radiotherapy technique and 154 (78.2%) patients applied three-dimensional conformal radiotherapy or Intensity-modulated radiotherapy (IMRT) technique. Furthermore, 180 (91.4%) patients received PCI after chemotherapy and TRT completed and 17 patients did it before chemotherapy and TRT completed.

Statistical analysis

Data are reported as the 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 the estimation of the differences in clinical characteristics (smoking index, ECOG-PS, TMN stage, number of cycles of chemotherapy, chemotherapy regimen, combined model of Chemo-RT and 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. 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 (CIs). Significant factors that were identified in the univariate analyses were included in the multivariate model. GraphPad prism 7 software was used to draw the forest figure of survival analysis. The differences were considered statistically significant at P-values of < 0.05.

Results

Patient Characteristics and Outcomes

Of the total patients, 95 had higher pretreatment LDH level (≥ 1 ULN), and serum LDH levels were promoted in 95 of patients during treatment. As shown in Table 1, the patient distribution between the normal group 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 model of Chemo-RT ($p = 1.00$) and PCI dose ($p = 0.46$).

Of the eligible 197 patients, 99 died during the follow-up period, and 25 were lost to follow-up within 5 years after all treatments completed. 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). 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). 105 (53.3%) patients developed extracranial metastasis, and their median extracranial failure term was 9.5 months (range: 3.3–70.4 months). Figure 1 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% and 75.2%, the 1-, 2- and 5-year OS were 84.7%, 62.6% and 46.5%, respectively.

mLDH during treatment is associated with 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 the evaluation of various cut-off values. As shown in Table 2, univariate analyses revealed that longer IPFS was associated with mLDH during treatment < 1 ULN ($P < 0.01$) and age < 60 years ($P < 0.01$). In patients with the normal and elevated LDH groups, the 1-, 2- and 5-year IPFS rate 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. 2). Compared to those patients with normal LDH level, patients with increased mLDH level 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 during treatment level (as shown in Table 2).

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	2-year OS rate	HR (95% CI)	P
Age (years)				< 0.01			0.08
< 60	137(69.5%)	87.7%	1		65.5%	1	
≥ 60	60(30.5%)	72.5%	2.5(1.2-5.0)		55.9%	1.5(0.9-2.3)	
Sex				0.21			0.84
Female	47(23.9%)	89.4%	1		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				0.75			0.52
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				0.97			0.66
< 400	84(42.6%)	85.2%	1		63.2%	1	
≥ 400	113(57.4%)	82.0%	1.0(0.5-2.0)		62.1%	1.1(0.7-1.7)	
TMN stage at the initial diagnosis				0.50			0.02
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				0.50			0.79
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)	

* BMs = brain metastases, EP = etoposide and platinum, TRT = thoracic radiotherapy, IMRT = intensity modulated radiotherapy, BED = biological effective dose, LDH = lactate dehydrogenase, ULN = upper limit of normal value.

Clinicopathological parameter	Patients (n = 197)	Univariate analysis					
		2-year IPFS rate	HR (95% CI)	P	2-year OS rate	HR (95% CI)	P
Chemotherapy regimen at the initial treatment				0.27			0.09
EP*	177(89.8%)	81.8%	1		61.3%	1	
Non-EP	20(10.1%)	95.0%	0.5(0.1–1.9)		72.9%	0.5(0.2–1.1)	
TRT* technique				0.43			0.02
Three-dimensional conformal radiotherapy or IMRT*	154(78.2%)	84.8%	1		65.9%	1	
Conventional radiotherapy	43(21.8%)	78.1%	1.4(0.6–3.3)		50.8%	1.7(1.1–2.5)	
Combined model of Chemo-RT				1			0.14
SCRT	79(40.1%)	82.9%	1		61.0%	1	
CCRT	118(59.9%)	84.0%	1.0(0.5–2.0)		64.1	0.7(0.5–1.1)	
Time of PCI				0.86			0.44
After chemotherapy and TRT completed	180(91.4%)	84.4%	1		61.6%	1	
Before chemotherapy and TRT completed	17(8.6%)	76.9%	1.1(0.3–3.7)		73.3%	1.3(0.7–2.5)	
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)	

* BMs = brain metastases, EP = etoposide and platinum, TRT = thoracic radiotherapy, IMRT = intensity modulated radiotherapy, BED = biological effective dose, LDH = lactate dehydrogenase, ULN = upper limit of normal value.

Clinicopathological parameter	Patients (n = 197)	Univariate analysis					
		2-year IPFS rate	HR (95% CI)	P	2-year OS rate	HR (95% CI)	P
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)	
* BMs = brain metastases, EP = etoposide and platinum, TRT = thoracic radiotherapy, IMRT = intensity modulated radiotherapy, BED = biological effective dose, LDH = lactate dehydrogenase, ULN = upper limit of normal value.							

The results of multivariate analyses are shown in Fig. 4. mLDH level during treatment $\geq$ ULN ($P = 0.002$) and age ≥ 60 ($P = 0.012$) were identified as significant independent predictors of poor IPFS.

Univariate and multivariate models for overall survival

As shown in Fig. 3, mLDH level during treatment was associated with worse survival significantly, in patients with the normal and elevated mLDH groups, the 1-, 2- and 5-year OS rate were 89.6% vs. 79.8%, 74.2% vs. 51.1% and 58.2% vs. 29.4% ($P < 0.01$), respectively. However, no significant impact on OS after TRT and PCI was observed for pretreatment LDH levels or changes between pretreatment LDH and maximum during treatment levels (Table 2). Compared to patients with normal LDH level, patients with increased mLDH level had higher cumulative risk of worse overall survival [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 the 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).

Figure 4 was the OS results of multivariate analysis, in addition to the statistically significant indicators in the univariate analysis, other factors that might affect the results, such as age, sex, chemotherapy

regimen and pre-treatment LDH, were also included in this analysis. As shown in Fig. 4, mLDH level during treatment $\geq$ ULN ($P = 0.002$), conventional technique applied in TRT ($P = 0.034$) and IIIB stage at the initial diagnosis after treatment ($P = 0.029$) were identified as significant independent predictors of poor OS.

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]. Serum LDH has been proved to be a powerful predictor in various cancers. Some studies 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 level represents a high activity of glycolysis, which might promote cancer invasion and metastasis. Some studies have indicated that energy metabolism plays an important role in cerebral metastasis [24, 25]. Glycolysis inhibition might be a useful strategy to reduce the risk of cerebral metastasis in the LS-SCLC. Our previous study [26] has revealed that oxamate, an inhibitor of LDH-A, significantly suppressed the proliferation of NSCLC cells, while it exerted a much lower toxicity in normal cells. LDH-A inhibition resulted in ATP reduction and ROS (reactive oxygen species) burst in cancer cells, which lead to apoptosis and G2/M arrest and increase radiosensitivity in NSCLC cells [27].

Up to now, we still have no idea whether some early stage (e.g. stage IA-IIIB) SCLC patients with good prognosis could avoid PCI. Our previous meta-analysis identified five retrospective studies and included a total of 1691 patients, 315 of them 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, with regard to 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 underwent radical surgery (category IIA). Our present study showed that elevated LDH during treatment might indicated disease recurrence and brain metastasis. For those patients, MRI is necessary. Recently, Anami S et al. evaluated 48 consecutive patients who underwent WBRT for BMs from SCLC, and the results revealed the presence of symptoms due to BMs and LDH values independently predicted prognosis [16]. Suzuki R et al. also identified 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 suggest that there are some clinical links between BMs and elevated LDH. In the present study, elevated mLDH during treatment represent significant independent prognostic indicators for IPFS in LS-SCLC after TRT and PCI (HR for IPFS, 3.53; 95% CI, 1.57–7.92; $P = 0.002$). This further confirmed the connections between BMs and elevated LDH. Thus, for the patients with elevated LDH during treatment, more positive treatments should be taken so as to reduce the risk of BMs. At least, PCI, which has been proved strongly to improve IPFS, should been

applied urgently. Others, such as drugs of LDH inhibitors or glycolysis inhibitors, can be used for BMs prevention. At present, these drugs were lack, and randomized trials on the use of relevant drugs for BMs prevention can be conducted.

In this study, pretreatment LDH level or changes between pretreatment and maximum during treatment LDH level failed to independently predict IPFS and OS in our study. This is not consistent with the results reported by Sagman U et al. and He M et al [21, 22]. In Sagman U's study, patients with LS-SCLC and elevated levels of pretreatment LDH manifested a higher relative death rate (1.63:1) when compared with patients with LS-SCLC and LDH in the normal range ($P = 0.0083$), but the survival of patients with extensive stage did not differ between those with normal and elevated levels of LDH ($P = 0.273$). In He M's study, the multivariate analysis revealed that pretreatment $LDH \geq 215.70$ U/L was an independent prognostic factor for poor survival (HR: 1.468, 95% CI: 1.069–2.017, $P = 0.018$); In the subgroup analysis, pretreatment LDH level was significant for predicting survival in both limited and extensive disease. Further, Suzuki R et al. [29] also identified pretreatment LDH as a powerful prognostic factor for BMs in patients with SCLC with no evidence of brain disease at diagnosis. Our results are different from others reported in above studies, probably because in those studies, the sample of patients with SCLC included all TMN stage or limited stage without PCI, and diverse samples may make difference in performance of predicting BMs and survival. Others such as small patient sample and inconsistency of clinicopathological parameters in various studies may also contribute to the different results.

In addition, the 1-, 2-, 3- and 5-year IPFS rates were 94.0%, 83.5%, 79.5% and 75.2%, 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 report of Kamran SC et al [30] (62.6% vs. 47%). Some possible reasons might be explained as follows: Firstly, 40% patient in their study have not underwent PCI while all of the patients in our study completed PCI, and as we know PCI can improve 5.4% OS of LS-SCLC [31]; Secondly, 18% patients in their study have ECOG-PS of 2–3 while only 5.1% patients in our study have ECOG-PS of 2, and ECOG-PS is also a potential prognosis. Thirdly, the proportion of stage IA-IIIa patients in our study is much higher than it in their study (40% vs. 17.3%), and TMN stage is a very powerful predictor in many studies as well as our study.

In conclusion, mLDH levels during treatment predicts brain metastasis and survival in LS-SCLC patients treated with TRT and PCI, which may provide valuable information for identifying patients underwent PCI for LS-SCLC who could have with poor survival outcomes. Future studies should develop a comprehensive scoring tool to better help clinicians make decision whether to administrate PCI in LS-SCLC patients.

Declarations

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Conflict of interest statement

The authors declare no conflicts of interest.

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Figures

Figure 1

Intracranial progression-free survival and overall survival of 197 patients after PCI.

Figure 2

Kaplan-Meier survival and cumulative risk curves between groups of higher and normal LDH groups for IPFS.

(C): K-M survival curve of IPFS between higher mLDH and normal groups during treatment;

(D): Cumulative risk of IPFS between higher mLDH and normal groups during treatment;

(E): K-M survival curve of IPFS between higher pretreatment LDH and normal groups;

(F): K-M survival curve of IPFS between elevated group and decrease group after comparison between pretreatment and maximum during treatment LDH level;

Figure 3

Kaplan-Meier survival and cumulative risk curves between groups of higher and normal LDH groups for OS.

(G): K-M survival curve of OS between higher mLDH and normal groups during treatment;

(H): Cumulative risk of OS between higher mLDH and normal groups during treatment;

(I): K-M survival curve of OS between higher pretreatment LDH and normal groups;

(J): K-M survival curve of OS between elevated group and decrease group after comparison between pretreatment and maximum during treatment LDH level;

Figure 4

Multivariate analysis for IPFS and OS.