Original Article

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Prognostic factors of primary brain metastasis from SCLC treated by whole-brain radiotherapy

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Abstract

Background: Small-cell lung cancer (SCLC) has poor prognosis owing to the high risk of distant metastasis.
Purpose: To identify the prognosticators of brain metastasis from SCLC treated by whole-brain radiotherapy.
Material and methods: We evaluated patients diagnosed with primary brain metastasis from SCLC between 1 January 2010 and 30 September 2019. Age, sex, disease stage at the first examination, time to the diagnosis of brain metastasis, state of other lesions at the diagnosis of brain metastasis, haematological parameters, neurologic symptoms, whole-brain radiotherapy dose, imaging findings of the brain metastasis (single or multiple), and chemotherapy and radiotherapy status were investigated for correlations with survival from the diagnosis of brain metastasis.
Results: A total of 24 participants were evaluated. After radiotherapy, the median survival period was 118·5 (22–998) days, and 21 patients died during the follow-up period. Multivariate stepwise analysis of the four parameters of lactate dehydrogenase (LDH) level (within vs. above the reference value), platelet level (continuous variable), neurologic symptoms (with versus. without), and NSE (neuron-specific enolase) level (continuous variable) identified the following significant differences: neurologic symptoms were 3·81 (95% CI 1·07–13·5, $p = 0.04$), and NSE was 1·01 (95% CI 1·00–1·01, $p = 0.04$).
Conclusion: NSE and neurologic symptoms are prognosticators of brain metastasis from SCLC treated by whole-brain radiotherapy.

Introduction

Small-cell lung cancer (SCLC) accounts for 14–20% of lung cancers[1–3] and is characterised by rapid growth and poor prognosis.[4] In addition to the tumour, node, metastasis classification, SCLC is also classified as limited disease (LD) or extensive disease (ED) as a basis for treatment.[5] In LD, the entire lesion can be contained within the irradiation field and it is therefore treated with a combination of chemotherapy and radiotherapy. Distant metastasis at present when the entire ED lesion cannot be contained within the irradiation field, and therefore, chemotherapy alone is administered.[5] ED has a worse prognosis than LD; the 5 and 10-year survival rates of LD are around 4·8%, and 2·3%, respectively, whereas those for ED are only 2·5%, and 1·2%, respectively.[6]

SCLC has a high risk of distant metastasis; up to 10% of patients have brain metastasis at the initial examination and above 50% develop it during follow-up.[7,8] Whole-brain radiotherapy is the standard radiation treatment for brain metastasis from SCLC.[8] Among patients undergoing whole-brain radiotherapy for SCLC, those with neurologic symptoms, lactate dehydrogenase (LDH) levels above the reference value of 230 IU/L (international Unit/litre), brain metastasis at the initial SCLC diagnosis, brain metastasis showing poor response to initial chemotherapy and poor overall condition have poor prognosis.[9] Moreover, performance status, the timing of brain metastases, chemotherapy sensitivity and Radiation Therapy Oncology Group recursive partitioning analysis are prognostic factors for patients with brain metastases from SCLC.[10] The levels of carcinoembryonic antigen (CEA) may increase in SCLC, and high CEA levels have been reported to be an indicator of poor prognosis.[11] However, no study has evaluated the relationship of the tumour markers CEA, neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (ProGRP) with the prognosis of patients with brain metastasis from SCLC. Therefore, this study aimed to investigate the prognosticators of SCLC with brain metastasis.

Material and methods

Study design and patients

This was a single-centre retrospective case-control study. We evaluated patients pathologically diagnosed with SCLC between 1 January 2010 and 30 September 2019 at our institution who had

brain metastasis at the first examination or during follow-up. The inclusion criteria were (1) whole-brain radiotherapy within 4 months of the first brain metastasis, (2) a cumulative dose of at least 30 Gy and (3) available follow-up data. The exclusion criteria were (1) double cancer, (2) unknown treatment information, (3) interrupt the whole-brain radiotherapy, by aggravation of the state or complication, (4) received other therapy for brain metastasis before irradiation by complication and (5) delayed initiation of whole-brain radiotherapy. This study was approved by our institutional review board. Patients were recruited using opt-out methodology as provided on the hospital Website.

Radiation therapy protocol

Whole-brain radiotherapy was performed using PRIMUS (Canon Medical Systems, Ohtawara, Japan) or Synergy (Elekta, Stockholm, Sweden). Mevatron (Canon Medical System; Ohtawara, Japan) was used for external beam irradiation therapy until 2012. The gross tumour volume was defined as the area of brain metastasis seen on imaging, and the clinical target volume (CTV) included the whole brain plus a margin of 1·5–2 cm from the CTV. A multileaf collimator was used to shape the field.

Prognostic factors of overall survival

Brain metastasis was diagnosed via computed tomography or magnetic resonance imaging. The date on which brain metastasis was first diagnosed was defined as Day 1 for the purpose of calculation. The relationships of overall survival (OS) with age, sex, disease stage at initial examination (LD or ED), time to the diagnosis of brain metastasis, state of other lesions at the time of brain metastasis diagnosis, baseline haematological findings before the initiation of whole-brain radiotherapy (leucocytes, red blood cells, and platelet counts and haemoglobin, total protein, albumin, LDH, alkaline phosphatase, CEA, NSE, and ProGRP levels), symptoms at the diagnosis of brain metastasis, whole-brain radiotherapy dose, imaging findings of brain metastasis (single or multiple, the maximise size and surrounding oedema of brain metastases), and type of treatment (combined chemotherapy or whole-brain radiotherapy) were investigated.

Statistical analysis

The last follow-up date was 30 September 2019. EZR (easy R) developed by Jichi Medical University Saitama Medical Center (Omiya Hospital) was used for all statistical analyses. OS curves were plotted using the Kaplan–Meier method and compared using the log-rank test and Cox proportional hazards model. A $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Overall, 24 consecutive patients (20 men and 4 women; mean age, 72·1 ± 6 years) were included in the study. Twenty patients were excluded for they corresponded to exclusion criteria (1 patient stopped whole-brain radiotherapy and died by complication and 1 patient received brain surgery by complication). The patient characteristics are shown in Table 1. Five patients had neurologic symptoms (1 patient each with dizziness, staggering, delirium, difficulty in walking, and visual disturbance). Among the 24 patients, 6 and 18 had LD and ED, respectively. Five patients had brain

Table 1. Patient characteristics ($n = 24$)

Characteristics	Number of patients
Sex	
Male	20
Female	4
Age, years (median)	72·1 ± 6·6
Disease stage	
LD	6
ED	18
Timing of diagnosis of brain metastasis	
At initial examination	5
During follow-up	19
Neurologic symptoms	
Yes	5
No	19
Number of brain metastases	
Single	4
Multiple	20
Maximus of brain metastases	
>2 cm	7
<2 cm	17
Surrounding oedema	
Yes	13
No	11
Other metastases at brain metastases	
Yes	18
No	6
Combination treatment with chemoradiotherapy	
Yes	14
No	10
Whole-brain radiotherapy dose	
30 Gy/10 fractions	12
37·5 Gy/15 fractions	11
30 Gy/12 fractions	1
Haematologic parameters, mean	
Leucocytes	6170 (±2233·2)/μL
Red blood cells	3·7 (±0·5) × 10^6/μL
Haemoglobin	11·6 (±1·4) g/dL
Platelets	21·6 (±4·2) × 10^3/μL
Total protein	6·7 (±0·7) g/dL
Albumin	3·9 (±0·4) g/dL
CRP	1·5 (±2·0) g/dL
LDH	291·2 (±190·2) IU/L
CEA	78·9 (±112·7) ng/mL
NSE	70·8 (±112·7) ng/mL
ProGRP	11,606·5 (±43,036·9) pg/mL

Abbreviations: LD, limited disease; ED, extensive disease; CRP, C-reactive protein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide.

metastasis at SCLC diagnosis, and 19 developed brain metastases during the follow-up. In total, 4 patients had a single brain metastasis, whereas 20 patients had multiple brain metastases. Seven patients had the maximise size of brain metastases above 2 cm and 13 patients had the surrounding oedema of brain metastases.

No patient had meningeal seeding. There were 19 patients with other metastases at the onset of brain metastasis. With respect to treatment, 14 patients received radiotherapy combined with chemotherapy (carboplatin + irinotecan, 4 patients; carboplatin + etoposide, 4 patients; cisplatin + etoposide, 1 patient; nogitecan, 2 patients; amrubicin, 2 patients; and paclitaxel, 1 patient), whereas 10 patients underwent radiation monotherapy. In total, 12 patients underwent radiotherapy of 30 Gy in 10 fractions, and 11 underwent radiotherapy of 37·5 Gy in 15 fractions. One patient discontinued a regimen of 30 Gy in 12 fractions.

Haematological findings

Data for leucocytes, red blood cells, and platelet counts and haemoglobin, total protein, albumin, C-reactive protein (CRP), NSE, and ProGRP levels were available in all 24 patients. Their mean levels were as follows: leucocytes, 6170 ($\pm$2233·2)/μL; red blood cells, 3·7 ($\pm$0·5) $\times$ 10^6/μL; haemoglobin, 11·6 ($\pm$1·4) g/dL; platelets, 21·6 ($\pm$4·2) $\times$ 10^3/μL; total protein, 6·7 ($\pm$0·7) g/dL; albumin, 3·9 ($\pm$0·4) g/dL; CRP, 1·5 ($\pm$2·0) g/dL; NSE, 70·8 ($\pm$112·7) ng/mL; and ProGRP, 11,606·5 ($\pm$43,036·9) pg/mL. Data on LDH and CEA levels were available in 23 and 12 patients, respectively. Their mean levels were 291·2 ($\pm$190·2) IU/L and 78·9 ($\pm$112·7) ng/mL, respectively. Overall, 11 patients had LDH levels within the reference value (<230 IU/L), and 4 patients had CEA levels within the reference value (<5 ng/mL). There were 8 patients whose NSE levels were within the reference value (<16·3 ng/mL), and 3 patients whose ProGRP levels were within the reference value (81 pg/mL).

Overall survival

Twenty-one patients died during the follow-up period. The median survival period was 118·5 (22–998) days. The Kaplan–Meier method and log-rank test revealed that patients with LDH levels within the reference value ($n = 12$) had significantly better OS than those with LDH levels higher than the reference value (>230 IU/L) ($n = 11$) (median survival: 349 days [95% confidence interval {CI}: 73–513] vs. 52 days [95% CI: 25–85], $p < 0.01$). The Kaplan–Meier method and log-rank test revealed that patients without neurologic symptoms ($n = 19$) had significantly better OS than those with neurologic symptoms ($n = 5$) (median survival: 198 days [95% confidence interval {CI}: 73–363] vs. 52 days [95% CI: 22–NA], $p = 0.04$).

The receiver operating characteristic curve (ROC) analysis showed the cut off value 13·0 ng/mL about the death or survival and AUC (area under the curve) value was 0·75 (95%CI 0·41–1·00).The Kaplan–Meier method and log-rank test revealed that patients with NSE levels within 13·0 ng/mL ($n = 4$) had significantly better OS than those with NSE levels higher than 13·0 ng/mL ($n = 20$) (median survival: 544 days [95% confidence interval {CI}: 349-NA] vs. 80·5 days [95% CI: 35–198], $p = 0.01$).

The Cox proportional hazards model showed significant differences in survival according to the LDH level (within vs. above the reference value: hazard ratio [HR]: 6·45, 95% CI: 1·90–21·5, $p < 0.01$), neurologic symptoms (with vs. without: HR: 2·90, 95% CI: 1·00–8·40, $p = 0.049$), platelet level (continuous variable: HR: 0·24, 95% CI: 0·08–0·72, $p = 0.01$), CEA level (continuous variable: HR: 1·01, 95% CI: 1·00–1·02, $p = 0.03$), and NSE level (continuous variable: HR: 1·01, 95% CI: 1·00–1·01, $p < 0.01$), NSE level ($\geq$ 13·0 ng/ml: HR: 9·11, 95% CI: 1·18–70·25, $p = 0.03$) by single variate analysis.

Multivariate stepwise analysis of the four parameters of LDH level (within vs. above the reference value), platelet level (continuous variable), neurologic symptoms (with vs. without), and NSE level (continuous variable) identified the following significant differences: neurologic symptoms were 3·81 (95% CI 1·07–13·5, $p = 0.04$), NSE was 1·01(95% CI 1·00–1·01, $p = 0.04$).

Multivariate stepwise analysis of the four parameters of LDH level (within vs. above the reference value), platelet level (continuous variable), neurologic symptoms (with vs., without), and NSE level ($\geq$ 13·0 ng/ml) identified the following significant differences: neurologic symptoms were 5·18 (95% CI 1·15–23·3, $p = 0.03$), NSE was 14·5 (95% CI 1·50–140·4, $p = 0.02$). The results of the Cox proportional hazards model are shown in Table 2.

Discussion

The present study investigates the prognosticators of brain metastasis from SCLC. We found significant differences in OS according to the neurologic symptoms, LDH, CEA, NSE, and platelet levels. The median survival of patients with brain metastasis from SCLC treated by whole-brain radiotherapy is 232 days, and the 1- and 2-year survival rates are 34·4 and 5·8%, respectively[9]. The median survival in the present investigation was 118·5 (22–998) days. This variation may be explained by the difference in the time of brain metastasis diagnosis. Patients with neurologic symptoms and those with LDH levels above the reference range have a poor prognosis[9]. The present study shows the same conclusion about the LDH levels and neurologic symptoms.

Several studies have reported that LDH is a prognosticator of SCLC[6,12,13,14] and NSE[14] is a prognosticator of SCLC. LDH has also been reported to be an effective predictor of prognosis[15]. LDH may have prognostic value because patients with high LDH are likely to have phenotypic transformation and microinfiltrations[9,13]. Indeed, in this study, patients with LDH levels within the reference range had better OS than those with LDH levels above the reference range by single variate analysis. But LDH level did not show the statistically significant vale by multivariate analysis. This reason is difficult, but we think that there is some confounding factor between LDH and OS.

Patients with metachronous brain metastasis have also been reported to have poor prognosis[10]. However, we found no significant differences in survival based on these factors. In this study, LD/ED is not a prognostic factor. We think that at the time of brain metastases, the all LD-SCLC patients had other metastases and may cancer cell get the resistance for anticancer drug.

Our investigation showed that CEA, as a continuous variable, was a prognosticator associated with OS by single variate analysis. It has been reported that CEA levels can increase in SCLC. In a previous study, the incidences of liver metastasis and ED were higher among patients with high CEA levels[11]. Further, patients with high CEA levels have a poor prognosis[16,17]. The reason for this may be the limitations of pathological examinations. For example, in one study, 18 of the 28 SCLC patients who underwent surgery for residual lung cancer after chemoradiotherapy had pure SCLC, 4 patients had mixed SCLC and non-SCLC, and the remaining 6 had non-SCLC[18]. It is possible that high CEA levels may indicate pure SCLC as well as tumours with latent non-SCLC components.

Table 2. Results of the Cox proportional hazards model analysis

Factor	Single variate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age	1·02	0·96–1·10	0·50			
Sex	1·30	0·43–3·92	0·65			
Disease stage	1·07	0·38–2·98	0·90			
Time of onset	0·80	0·28–2·23	0·66			
Symptoms	2·97	1·02–8·59	0·045	3·86	1·10–13·7	0·04
Other metastases	1·06	0·38–3·00	0·92			
Dose (30 Gy vs. 37·5 Gy)	0·50	0·20–1·29	0·15			
Number of brain metastases (single vs. multiple)	2·00	0·57–6·95	0·28			
maximise size of brain metastases (<2 cm vs. >2 cm) and	1·31	0·75–0·27	0·33			
the surrounding oedema of brain metastases	1·46	0·61–3·45	0·40			
Chemotherapy (combination vs. monotherapy)	0·60	0·25–1·44	0·26			
Leucocytes	1·00	1·00–1·00	0·11			
Red blood cells	0·47	0·17–1·31	0·15			
Haemoglobin	0·90	0·62–1·31	0·59			
Platelets	0·84	0·75–0·94	< 0·01	0·91	0·80–1·03	0·12
Total protein	1·07	0·56–2·01	0·83			
Albumin	1·73	0·47–6·30	0·40			
LDH (continuous variable)	1·00	1·00–1·00	0·06			
LDH (within vs. above reference range)	5·60	1·75–8·50	< 0·01	2·23	0·48–10·5	0·31
CRP	1·08	0·86–1·37	0·50			
Neuron-specific enolase (continuous variable)	1·00	1·00–1·01	< 0·01	1·01	1·00–1·01	0·04
Neuron-specific enolase (within vs. above reference range)	2·51	0·94–6·72	0·07			
Neuron-specific enolase (under and above 13·0 ng/ml)	8·90	1·15–68·6	0·04			
Pro-gastrin-releasing peptide (continuous variable)	1·00	1·00–1·00	0·14			
Pro-gastrin-releasing peptide (within reference range vs. above reference range)	6·15	0·77–49·1	0·08			
Carcinoembryonic antigen (continuous variable)	1·01	1·00–1·02	0·03			
Carcinoembryonic antigen (within vs. above reference range)	4·92	0·58–41·6	0·14			

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; CRP, C-reactive protein; NA, not available.

Non-SCLC components may also confer resistance to therapy. But, in this study, the sample size is small, so we did not use CEA by multivariate analysis. Future study is necessary.

The present study found that NSE as a continuous variable was a prognosticator associated with OS, that is, patients with higher NSE also had poorer OS. The prognosis of SCLC patients with high NSE before any therapy were worse.[19] While both ProGRP and NSE have been reported to indicate poor prognosis, NSE is a stronger prognostic factor (cut off value 7·5 ng/ml).[20] In the present study, patients with higher NSE tended to have a poor prognosis. This may be because cells with high NSE levels have shifted to a glycolytic and hypoxic state and are more resistant to radiotherapy.

The present study found that platelet level as a continuous variable was a prognosticator associated with OS, patients with higher platelet also had poorer OS. The platelet level before chemoradiotherapy is a prognostic factor in LD small lung cancer patients and patients with higher platelet also had a poorer OS.[21] The reason is that platelet is an inflammatory condition indicator associated with cancer.[21] We think that the platelet level reflects the inflammatory level in SCLC patients with brain metastases in our study. But platelet level is affected by chemotherapy and the onset of brain metastases is not the same in this study. More detailed research is necessary.

There are several limitations to this study. First, it was a single-centre study with a small sample size. Given the retrospective study design, the timing for the assessment of brain metastasis onset was not standardised. Prospective studies with a larger sample size are warranted for further investigation.

In conclusion, neurologic symptoms, and NSE levels are prognosticators of brain metastasis from SCLC treated by whole-brain radiotherapy.

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