The prognostic effect of chemosensitivity on brain metastases in small-cell lung cancer: A retrospective analysis

Jintao Ma
Tianjin Medical University
Chunliu Meng
Tianjin Medical University
Jia Tian
Tianjin Medical University
Kai Ren
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Meng Yan
Tianjin Medical University
Liming Xu
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Lujun Zhao (zhaolujun@tjmuch.com)
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Ping Wang
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer

Article

Keywords: small-cell lung cancer, progression, brain metastases, chemosensitivity

Posted Date: August 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1850317/v1

Abstract

Purpose: To investigate the prognostic differences between small-cell lung cancer (SCLC) patients with different chemosensitivity to first line chemotherapy who developed brain metastasis as first site of progression.

Methods: Patients with brain metastases (BMs) after first-line treatment of SCLC in our hospital admitted from January 2012 to October 2020 were retrospectively analyzed. According to the time interval between the completion of first-line chemotherapy and the onset of BMs (TFI), the patients were divided into chemo-sensitive group (TFI ≥ 90 days, n = 145) and chemo-resistant group (TFI 90 days, n = 97). Survival time after the onset of brain metastasis (BM-OS), which was calculated from the diagnosis of brain metastases and overall survival (OS), which was calculated from the diagnosis of small-cell lung cancer, were analyzed in this study. Survival curves were plotted using Kaplan-Meier method and differences between groups were compared using the log-rank test. The Chi-square test or Fisher's exact test was used to compare categorical variables.

Results: In total, the median BM-OS and OS were 8.4 months and 18.2 months respectively. The median BM-OS in chemo-sensitive group was 8.8 months and it was 8.0 months in the chemo-resistant group (P = 0.538); and the median OS was 22.0 months and 15.6 months, respectively (P = 0.001). In patients without extracranial progression (n = 193), the median BM-OS in chemo-sensitive and chemo-resistant group were 9.4 months and 9.7 months (P = 0.947), and the median OS were 22.7 months and 16.3 months, respectively (P = 0.017). In patients with extracranial progression (n = 49), the median BM-OS were 5.4 months and 4.2 months (P = 0.161), and the median OS were 17.6 months and 12.3 months, respectively (P = 0.002).

Conclusions: After the development of brain metastasis as the first site of progression following chemotherapy in small cell lung cancer, the prognosis of chemo-sensitive patients not necessarily superior to chemo-resistant patients, especially in patients without extracranial progression.

Introduction

Small-cell lung cancer (SCLC) is highly aggressive and about two thirds are extensive disease (ED) at the time of diagnosis[1]. Brain is a common site of distant metastasis, accounting for about 18% at initial diagnosis, and can reach 50-65% within two years[2, 3]. It was previously believed that systemic chemotherapy played a limited role in the treatment of intracranial lesions because of the difficulty to across the intact blood-brain barrier (BBB). However, several researches have suggested that the BBB may not be the factor impeding the successful treatment of brain metastases (BMs) with chemotherapy agents, and the objective response rate (ORR) ranged 27-82%[4-6]. However, most of these were outdated studies with limited number of samples, and the effect of chemotherapy agents on BMs of SCLC is still unclear.

Although SCLC responds well to chemoradiotherapy, about 50% patients relapse within one year. Recurrent SCLC patients who progress after first-line chemotherapy are traditionally classified into chemo-sensitive cases (TFI≥90 days) and chemo-resistant cases (TFI 90 days). Previous studies have found that it was different in survival outcome and efficacy of second line treatment between sensitive relapse and resistant relapse, and the former patients had a better prognosis[7-9].

Radiation therapy is the standard of care in small-cell lung cancer patients who develop brain metastasis[1, 10]. However, it is unknown whether the prognosis is related to chemosensitivity in patients with brain metastasis. In this retrospective study, we analyzed the differences in prognosis between SCLC patients with different chemosensitivity to first line chemotherapy who developed brain metastasis as first site of progression in modern era.

Methods

1. Patient characteristics

Consecutive cases admitted to Tianjin Cancer Hospital from January 2012 to October 2020 were

retrospectively analyzed (bc2022166). The use of samples and data involved in the study was approved by the Institutional Review Board of Tianjin Medical University Cancer Institute & Hospital. Informed consent for scientific usage of clinical data was obtained from all patients. Inclusion criteria: 1. The diagnosis of SCLC was confirmed by histopathology or cytology; 2. BMs documented by pathology or imaging (magnetic resonance imaging (MRI) with contrast or computed tomographic (CT) with contrast), with or without neurological symptoms; 3. The first site of initial treatment failure was brain; 4. The number of first-line platinum-doublet chemotherapy before BMs was more than two cycles. Patients with a second primary carcinoma were excluded.

According to the criteria, we enrolled 242 eligible patients with a median follow-up of 49.3 months. Among them, 145 patients were chemo-sensitive and 97 patients were chemo-resistant. According to Veterans Administration Lung Study Group (VALG) definition of limited disease (LD) and extensive disease (ED), 155 cases had limited disease and 87 cases had extensive disease at initial diagnosis. One hundred and ninety-three patients had intracranial progression alone and 49 cases had extracranial progression at the same time.

This study received a notification of fast evaluation of The Institutional Review Board from Tianjin Medical University Hospital. This research was performed in accordance with the Declaration of Helsinki.

Treatment

All patients received at least two cycles of etoposide-platinum regimens before BMs. For limited disease small-cell lung cancer (LD-SCLC) patients at initial diagnosis, 6 patients (3.9%) received surgery and adjuvant chemotherapy was underwent with or without thoracic radiation therapy (TRT), 63 patients (40.6%) received concurrent chemoradiotherapy, 76 patients (49.0%) received sequential

chemoradiotherapy and 10 patients (6.5%) received chemotherapy alone. For extensive disease small-cell lung cancer (ED-SCLC) patients at initial diagnosis, 27 patients (31.0%) underwent chemotherapy alone, 60 patients (69.0%) underwent TRT, and 10 patients (11.5%) combined with immunotherapy. The response to the first-line treatment was assessed every two cycles of chemotherapy, whereas patients underwent surgery, an evaluation was performed after the completion of postoperative adjuvant therapy. Surveillance after completion of primary therapy was performed every 3 months during 1-2 year, then every 6 months during the third year, then annually.

After the diagnosis of BMs, 109 patients (45.0%) received local therapy, 27 patients (11.2%) received systemic therapy, 86 patients (35.5%) received the combination of local and systemic therapy and 20 patients (8.3%) only received supportive care. Among the patients received local treatment, 142 (72.8%) treated with whole brain radiation (WBRT), 44 (22.6%) treated with WBRT plus a radiation boost, 4 (2.1%) treated with stereotactic radiation therapy (SRT) and 5 (2.5%) treated with surgical resection.

2. Outcome measures and statistical analysis

The endpoints were survival time after the onset of brain metastasis (BM-OS) and overall survival (OS). BM-OS was calculated from the date of diagnosis of BMs to the date of death from any cause, and OS was calculated from the date of diagnosis of SCLC to the date of death due to any cause. The last follow-up was on May 13, 2022. Median BM-OS and OS were evaluated by Kaplan-Meier survival analysis, and survival differences between groups were compared using the log-rank test. Comparison between the categorical variables was analyzed using the Chi-square test or Fisher's exact test. All statistical tests were bilateral, and $P<0.05$ was considered significant. Statistically analyses were undertaken using SPSS 26.0 software (IBM, Chicago, IL, USA).

Results

1. Characteristics

Figure 1 illustrated the inclusion and exclusion criteria for the study. A total of 662 small-cell lung cancer patients with BMs were screened. Of the 582 patients excluding second primary carcinoma, chemotherapy cycles less than two and no brain enhanced MRI or CT images, 165 patients (28.4%) have brain metastases at initial diagnosis, and others developed BMs due to disease progression. And in patients who developed BMs, 242 (58.0%) were diagnosed after the first-line chemotherapy and were eligible for the analysis.

The characteristics of patients between chemo-sensitive group and chemo-resistant group were provided in Table 1. In total, 242 patients had a median age of 61 years (range 29-78 years), 78.1% were male. More chemo-sensitive patients received TRT (87.6%) and prophylactic brain radiotherapy (PCI) (10.3%) during first-line treatment, and the other baseline characteristics were similar between two groups. The majority of patients (83.5%) received brain radiation after brain metastasis. As shown in Table 1.

2. Clinical outcomes

To the end of last follow-up, 212 patients (87.6%) died and 30 (12.4%) survived. For all patients, the median OS was 18.2 months with 1- and 3-year OS rates of 81.7% and 13.4%, and the median BM-OS was 8.4 months with 1- and 3-year OS rates of 35.3% and 5.2%. The median OS in chemo-sensitive and chemo-resistant patients were 22.0 months and 15.6 months, respectively (P = 0.001). The median BM-OS were 8.8 months and 8.0 months between chemo-sensitive group and chemo-resistant group, respectively (P = 0.538), as shown in Figure 2.

In LD-SCLC patients (n = 155), the median OS was 21.8 months and the median BM-OS was 10.5 months. Between chemo-sensitive group and chemo-resistant group, the median OS were 24.8 months and 17.9 months (P = 0.01), and the median BM-OS were 10.4 months and 11.4 months (P = 0.867), respectively. In ED-SCLC patients (n = 87), the median OS was 15.2 months and the median BM-OS was 5.7 months. The median OS was 16.8 months in chemo-sensitive group versus 12.8 months in chemo-resistant group (P = 0.002). The median BM-OS were 5.8 months and 5.3 months between the two groups, respectively (P = 0.451).

In patients without extracranial progression, the median OS were 22.7 months and 16.3 months in chemo-sensitive group and chemo-resistant group (P=0.017), and the median BM-OS were 9.4 months and 9.7 months, respectively (P=0.947), as shown in Figure 3. In patients with extracranial progression (n = 49), the median OS were 17.6 months and 12.3 months in chemo-sensitive group and chemo-resistant group (P = 0.002), and the median BM-OS were 5.4 months and 4.2 months, respectively (P = 0.161), as shown in Figure 4.

Discussion

In this retrospective study, we observed that chemo-sensitive patients had longer overall survival (OS) than chemo-resistant patients regardless of the initial stage at diagnosis. However, after the development of brain metastasis, the differences in BM-OS between the two groups was no longer significant, especially in patients without extracranial progression. The study suggests that in patients who develop brain metastasis after the diagnosis of SCLC, local treatment should be actively given, no matter the disease is sensitive or resistant to first line chemotherapy.

The treatment of progressed SCLC is a challenge, especially in those who resistant to first line chemotherapy, because of lacking of effective second-line treatment[11-17]. Previous studies have suggested that chemosensitivity as an independent risk factor was associated with survival time and responding to second-line therapy in relapsed SCLC patients. Several researches have been carried out on whether chemotherapy sensitivity is related to prognosis in modern era, and they confirmed the prognostic value of chemotherapy sensitivity status for relapsed SCLC[15, 18-20].

However, brain as a special site of progression, the choice of local therapy or systemic therapy as the primary treatment has not been determined [21-26]. Whole brain radiation therapy (WBRT) is now the

standard treatment in many guidelines[1, 10]. For the patients with limited number of BMs, additional radiation boost to WBRT or stereotactic radiation therapy (SRT) can be recommended[21, 23, 25]. Several studies suggested that the occurrence of brain metastasis was a sign of systemic failure of tumor control, the treatment of brain metastasis should focus on chemoradiotherapy[27-29]. A respective study in 2021 observed that the combination of WBRT and etoposide-platinum agents could prolong overall survival of SCLC patients with BMs [28]. However, another prospective trial did not reach similar results[30]. In total, the efficacy of chemotherapy for BMs has not been fully clarified.

Whether the prognosis of patients who developed BMs after first-line treatment is related to chemosensitivity is worthy of further analyzing. In this study, we did not find that the prognosis after BMs was associated with chemosensitivity. The further stratified analysis demonstrated that the median BM-OS also failed to reach a statistical difference between chemo-sensitive group and chemo-resistant group in patients without extracranial progression. The reason why chemo-sensitive patients had a longer progression-free survival (PFS) but similar BM-OS with chemo-resistant patients is possibly related to the majority between two groups received brain radiation therapy. However, in patients with extracranial progression, the median BM-OS had a tendency to benefit from being sensitive to first-line treatment. This maybe owing to the better control for extracranial lesions with second line chemotherapy in chemo-sensitive patients than chemo-resistant patients.

There are several limitations in the analysis. Firstly, this is a respective study with limited by selection bias, and the conclusion should be validated in further prospective studies. Secondly, the proportion of patients with extracranial progression was relatively small, and the results demonstrate a trend, but failed to reach a statistical difference. Thirdly, a few cases in the study received immunotherapy in the first-line treatment, and the effect of chemoimmunotherapy on prognosis for SCLC patients with brain metastases require further study to confirm.

Conclusions

To the best of our knowledge, this is the first study to investigate the association between prognosis and chemosensitivity status in SCLC patients who developed BMs as first site of progression after chemotherapy. In the study, we observed that, after the development of brain metastasis, there was no significant difference between chemo-sensitive group and chemo-resistant group, especially in the subset of patients without extracranial progression. Our findings are worthy to be confirmed by prospective clinical studies.

Abbreviations

SCLC: Small-cell lung cancer; BMs: Brain metastases; LD: Limited disease; ED: Extensive disease; LD-SCLC: Limited disease small-cell lung cancer; ED-SCLC: Extensive disease small-cell lung cancer; BBB: Blood-brain barrier; ORR: Objective response rate; MRI: Magnetic resonance imaging; CT: Computed tomography; KPS: Karnofsky performance status; BM-OS: Overall survival after brain metastases; OS:

Overall survival; PFS: Progression free survival; VALG: Veterans Administration Lung Study Group (VALG); TRT: Thoracic radiation therapy; WBRT: Whole brain radiation therapy; SRT: Stereotactic radiation therapy; PCI: Prophylactic brain irradiation.

Declarations

Acknowledgements

Not applicable.

Disclosure

Jintao Ma comes from Tianjin Medical University; Chunliu Meng comes from Tianjin Medical University; Jia Tian comes from Tianjin Medical University; Ren Kai comes from Tianjin Medical University Cancer Institute and Hospital; Huijun Jia comes from Tianjin Medical University; Liming Xu comes from Tianjin Medical University Cancer Institute and Hospital; Lujun Zhao comes from Tianjin Medical University Cancer Institute and Hospital; Ping Wang comes from Tianjin Medical University Cancer Institute and Hospital.

Author contributions

Jintao Ma performed data acquisition, the statistical analysis and drafted the manuscript; Chunliu Meng performed data acquisition and the statistical analysis; Jia Tian, Kai Ren, Huijun Jia and Meng Yan performed data acquisition. Liming Xu, Lujun Zhao and Ping Wang critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

The data that support this study are not openly available due to ethical and privacy concerns and are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approval by Human Investigation Committee of Tianjin Medical University Cancer Hospital, Tianjin, China.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ganti A, Loo BW, Bassetti M, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19:1441–64.
2. Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. Radiother Oncol. 1998; 46:29–32.
3. Seute T, Leffers P, Ten VG, Twijnstra A. Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. Cancer-Am Cancer Soc. 2004; 100:801–06.
4. Kristjansen PE, Soelberg SP, Skov HM, Hansen HH. Prospective evaluation of the effect on initial brain metastases from small cell lung cancer of platinum-etoposide based induction chemotherapy followed by an alternating multidrug regimen. Ann Oncol. 1993; 4:579–83.
5. Seute T, Leffers P, Wilmink JT, Ten VG, Twijnstra A. Response of asymptomatic brain metastases from small-cell lung cancer to systemic first-line chemotherapy. J Clin Oncol. 2006; 24:2079–83.
6. Lee JS, Murphy WK, Glisson BS, Dhingra HM, Holoye PY, Hong WK. Primary chemotherapy of brain metastasis in small-cell lung cancer. J Clin Oncol. 1989; 7:916.
7. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006; 24:5441–47.
8. Kim YH, Goto K, Yoh K, et al. Performance status and sensitivity to first-line chemotherapy are significant prognostic factors in patients with recurrent small cell lung cancer receiving second-line chemotherapy. Cancer-Am Cancer Soc. 2008; 113:2518–23.
9. Owonikoko TK, Behera M, Chen Z, et al. A Systematic Analysis of Efficacy of Second-Line Chemotherapy in Sensitive and Refractory Small-Cell Lung Cancer. J Thorac Oncol. 2012; 7:866–72.
10. Dingemans AC, Fruh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(). Ann Oncol. 2021; 32:839–53.
11. Pujol JL, Greillier L, Audigier-Valette C, et al. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. J Thorac Oncol. 2019; 14:903–13.
12. Verma V, Sharma G, Singh A. Immunotherapy in extensive small cell lung cancer. Exp Hematol Oncol. 2019; 8:5.
13. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol. 2020; 15:426–35.
14. Baize N, Monnet I, Greillier L, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre,

randomised, phase 3 trial. Lancet Oncol. 2020; 21:1224–33.

15. Chouaïd C, Baize N, Monnet I. Second-line therapy for disseminated small-cell lung cancer: optimal management remains to be defined. Translational Lung Cancer Research. 2020; 9:1732–35.
16. Horiuchi K, Sato T, Kuno T, et al. Platinum-doublet chemotherapy as second-line treatment for relapsed patients with small-cell lung cancer: A systematic review and meta-analysis. Lung Cancer. 2021; 156:59–67.
17. Kim YJ, Keam B, Ock CY, et al. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. Lung Cancer. 2019; 136:122–28.
18. Lara PN, Moon J, Redman MW, et al. Relevance of Platinum-Sensitivity Status in Relapsed/Refractory Extensive-Stage Small-Cell Lung Cancer in the Modern Era: A Patient-Level Analysis of Southwest Oncology Group Trials. J Thorac Oncol. 2015; 10:110–15.
19. Nagy-Mignotte H, Guillem P, Vignoud L, et al. Outcomes in recurrent small-cell lung cancer after one to four chemotherapy lines: A retrospective study of 300 patients. Lung Cancer. 2012; 78:112–20.
20. Naito Y, Yamada K, Imamura Y, et al. Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer. Med Oncol. 2018; 35.
21. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study. Jama Oncol. 2020; 6:1028–37.
22. Liu Q, Yin Q, Dong Y, Li F, Li W, Wang X. Microsurgery vs. radiosurgery for the treatment of multiple metastases in the brain: a retrospective cohort study. Cancer Biol Med. 2021.
23. Sun H, Xu L, Wang Y, et al. Additional radiation boost to whole brain radiation therapy may improve the survival of patients with brain metastases in small cell lung cancer. Radiat Oncol. 2018; 13:250.
24. TWELVES CJ, SOUHAMI RL, HARPER PG, et al. The response of cerebral metastases in small cell lung cancer to systemic chemotherapy. Brit J Cancer. 1990; 61:147–50.
25. Viani GA, Gouveia AG, Louie AV, Moraes FY. Stereotactic radiosurgery for brain metastases from small cell lung cancer without prior whole-brain radiotherapy: A meta-analysis. Radiother Oncol. 2021; 162:45–51.
26. Postmus PE, Haaxma-Reiche H, Smit EF, et al. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy–a phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol. 2000; 18:3400–08.
27. Liu WJ, Zeng XT, Qin HF, Gao HJ, Bi WJ, Liu XQ. Whole brain radiotherapy plus chemotherapy in the treatment of brain metastases from lung cancer: a meta-analysis of 19 randomized controlled trails. Asian Pac J Cancer Prev. 2012; 13:3253–58.
28. Li H, Xue R, Yang X, et al. Best Supportive Care Versus Whole-Brain Irradiation, Chemotherapy Alone, or WBRT Plus Chemotherapy in Patients With Brain Metastases From Small-Cell Lung Cancer: A Case-Controlled Analysis. Front Oncol. 2021; 11:568568.

29. Neuhaus T, Ko Y, Muller RP, et al. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. Br J Cancer. 2009; 100:291–97.
30. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014; 32:4012–19.

Table

Table 1. Patient characteristics by sensitivity to first-line treatment.

Characteristics	resistant group (%)	sensitive group (%)	p value
Gender			0.693
male	77 79.4	112 77.2	
female	20 20.6	33 22.8	
Age/year			0.755
65	72 74.2	105 72.4	
≥65	25 25.8	40 27.6	
KPS score			0.477
80	8 8.2	16 11.0	
≥80	89 91.8	129 89.0	
Smoke			0.235
yes	81 83.5	112 77.2	
no	16 16.5	33 22.8	
Disease extent at initial diagnosis			0.561
LD	60 61.9	95 65.5	
ED	37 38.1	50 34.5	
Initial treatment modality			0.003
chemotherapy	22 22.7	18 12.4	
sequential chemoradiotherapy	36 37.1	86 59.3	
concurrent chemoradiotherapy	39 40.2	41 28.3	
If PCI after first line treatment			0.013
yes	2 2.1	15 10.3	
no	95 97.9	130 89.7	
Extracranial progression at diagnosis of BM			0.907
yes	20 20.6	29 20.0	
no	77 79.4	116 80.0	
Radiotherapy for brain metastasis			0.733
yes	80 82.5	122 84.1	
no	17 17.5	23 15.9	

Abbreviations: LD: Limited-stage; ED: Extensive-stage; PCI: Prophylactic cranial irradiation; BM: Brain metastases.

Figures

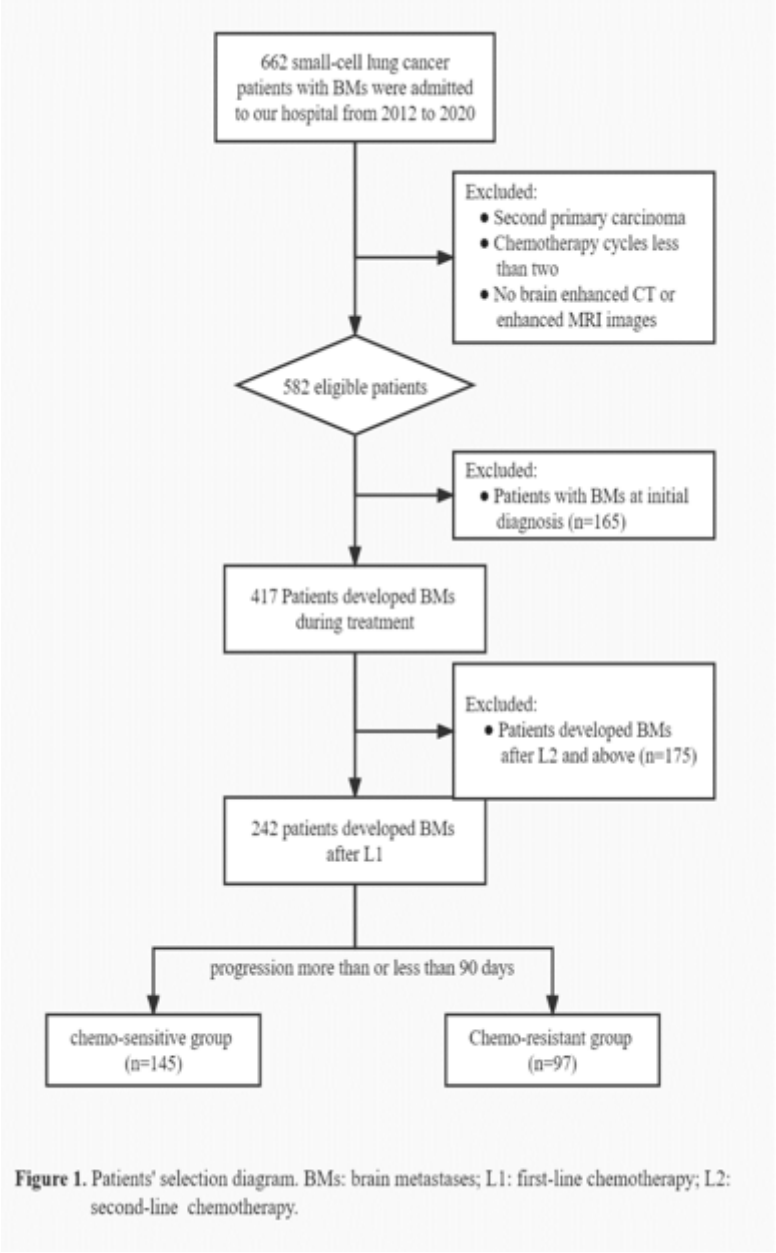

Figure 1. Patients' selection diagram. BMs: brain metastases; L1: first-line chemotherapy; L2: second-line chemotherapy.

Figure 1

See image above for figure legend.

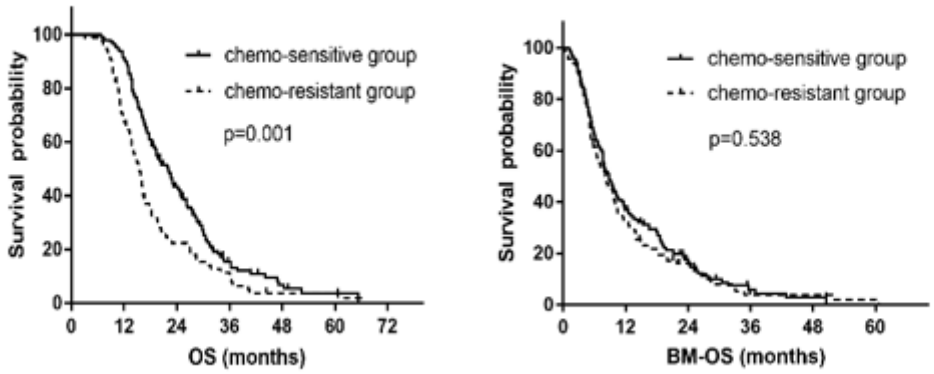

Figure 2

Kaplan-Meier curves for overall survival and survival time after BMs in all patients between two groups. **a** Overall survival. **b** Survival time after BMs.

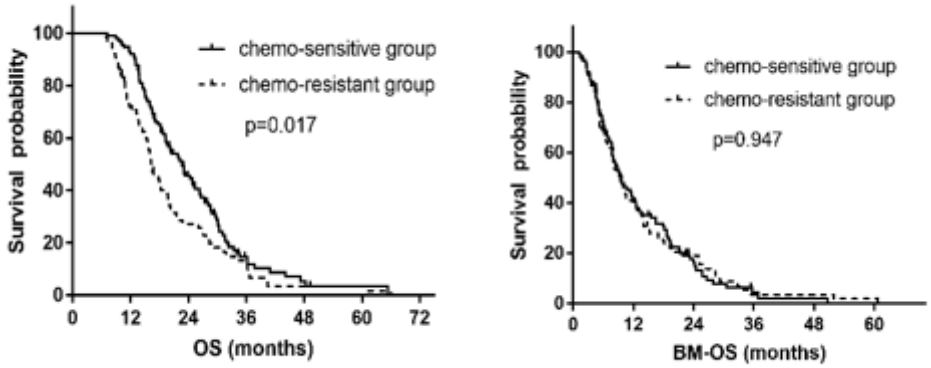

Figure 3

Kaplan-Meier curves for overall survival and survival time after BMs in patients without extracranial progression. **a** Overall survival. **b** Survival time after BMs.

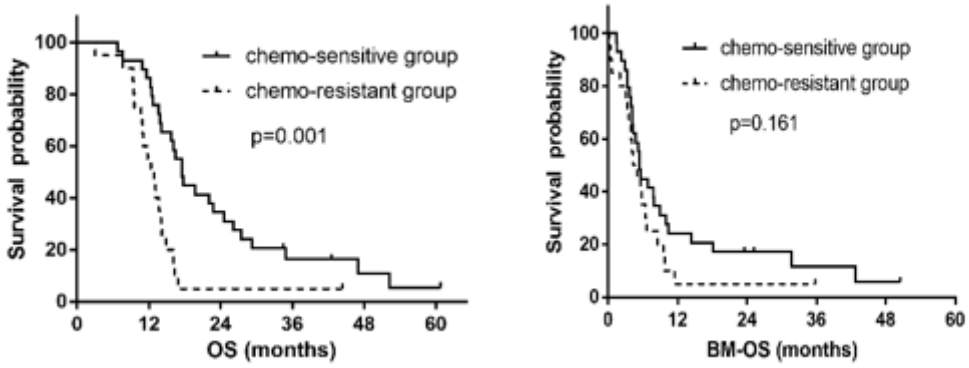

Figure 4

Kaplan-Meier curves for overall survival and survival time after BMs in patients with extracranial progression. **a** Overall survival. **b** Survival time after BMs.