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Survival prognostic factors for patients with synchronous brain oligometastatic non-small-cell lung carcinoma receiving local therapy

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Introduction: Clinical evidence for patients with synchronous brain oligometastatic non-small-cell lung carcinoma is limited. We aimed to summarize the clinical data of these patients to explore the survival prognostic factors for this population.

Methods: From September 1995 to July 2011, patients with 1–3 synchronous brain oligometastases, who were treated with stereotactic radiosurgery (SRS) or surgical resection as the primary treatment, were identified at Shanghai Chest Hospital.

Results: A total of 76 patients (22 patients underwent brain surgery as primary treatment and 54 patients received SRS) were available for survival analysis. The overall survival (OS) for patients treated with SRS and brain surgery as the primary treatment were 12.6 months (95% confidence interval [CI] 10.3–14.9) and 16.4 months (95% CI 8.8–24.1), respectively (adjusted hazard ratio =0.59, 95% CI 0.33–1.07, *P*=0.08). Among 76 patients treated with SRS or brain surgery, 21 patients who underwent primary tumor resection did not experience a significantly improved OS (16.4 months, 95% CI 9.6–23.2), compared with those who did not undergo resection (11.9 months, 95% CI 9.7–14.0; adjusted hazard ratio =0.81, 95% CI 0.46–1.44, *P*=0.46). Factors associated with survival benefits included stage I–II of primary lung tumor and solitary brain metastasis.

Conclusion: There was no significant difference in OS for patients with synchronous brain oligometastasis receiving SRS or surgical resection. Among this population, the number of brain metastases and stage of primary lung disease were the factors associated with a survival benefit.

Keywords: non-small-cell lung carcinoma, oligometastases, brain, stereotactic radiosurgery, surgery

Introduction

Worldwide, lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths.[1] Among newly diagnosed patients, almost half are diagnosed with distant metastases. Brain metastasis represents one of the most common forms of distant metastases[2,3] and are discovered in up to 10% of patients at initial diagnosis of non-small-cell lung carcinoma (NSCLC).[4] The prognosis of patients with brain metastasis is poor, with a median survival of 1–2 months without any treatment.[5] According to a previous research, selected patients who present with synchronous brain-only oligometastases might have a better survival rate than expected.[6] For this population, treatment of metastatic locations with surgery or stereotactic radiosurgery (SRS) has been proven to be an effective local therapy. However, clinical evidence in this distinct subset of the population is controversial. Some experts hold the view

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that neurosurgery provides longer survival time than SRS,[7] while other studies demonstrated that SRS alone can result in similar benefits compared with neurosurgery plus whole-brain radiation therapy (WBRT).[8–10] Furthermore, some studies showed that resection of the primary lung tumor might provide better survival benefits for synchronous brain oligometastases in patients receiving effective local therapy such as neurosurgery or SRS.[10] In this study, we summarized the clinical data of this population of patients with brain metastases in our institution to analyze survival results and prognostic factors.

Methods

Study design and patients

The study was approved by the Institutional Review Board of Shanghai Chest Hospital which waived the need to obtain patient consent. All patients were diagnosed at Shanghai Chest Hospital between September 1995 and July 2011. Inclusion criteria were as follows: 1) patients with identifiable primaries, 1–3 synchronous brain metastases by computed tomography, magnetic resonance imaging, or positron emission tomography, and no other evidence of distant metastatic disease confirmed by computed tomography, bone scan, or positron emission tomography and 2) patients underwent SRS or surgical resection as initial treatment for local control. Baseline clinical characteristics included age at diagnosis, tumor histology, smoking history, stage of primary tumor, and number of brain metastases. Patients without survival and therapy details were excluded from the analysis. Clinical follow-up exams included a physical examination, an imaging examination, and routine laboratory tests, which were performed every 4–8 weeks. Overall survival (OS) was defined as beginning from the date of diagnosis until the date of death or last follow-up visit.

Statistical methods

For descriptive purposes, demographic and clinical data were summarized as medians with ranges for continuous variables and categorical variables by means of absolute and percentage numbers. Survival results were summarized as median values and two-sided 95% confidence interval (CI), and were analyzed using Kaplan–Meier technique. The log-rank test was used for comparisons among subgroups. Multivariable adjusted hazard ratios (HRs) for all-cause mortality by patient and treatment pattern were estimated using Cox regression analysis. HRs were calculated along with their corresponding 95% CIs as measurements of association. Statistical significance was defined as a *P*-value of less than 0.05. SPSS statistical software, version 22 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 76 patients (22 underwent brain surgery as the primary treatment and 54 received SRS) were available for survival analysis. Among the 76 patients who received SRS or brain surgery as an initial treatment for local control, 21 underwent resection of the primary tumor, while 54 did not. Patient identification flowcharts are illustrated in Figure S1. Demographic data of all patients are shown in Table 1.

OS for patients treated with SRS and brain surgery as the primary treatment were 12.6 months (95% CI 10.3–14.9) and 16.4 months (95% CI 8.8–24.1), respectively (adjusted

Table 1 Demographic data of all patients

Characteristic	n (%)
Median age, years (range)	58 (30–82)
Sex	
Male	52 (68.4%)
Female	24 (31.6%)
Smoking status	
Smoker	47 (61.8%)
Never-smoker	29 (38.2%)
Histology	
Adeno	57 (75.0%)
SCC	9 (11.8%)
Others	10 (13.2%)
Stage	
IA	0 (0.0%)
IB	1 (1.3%)
IIA	15 (19.7%)
IIB	11 (14.5%)
IIIA	49 (64.5%)
Number of brain metastasis	
1	48 (63.2%)
2	19 (25.0%)
3	9 (11.8%)
Size of largest lesion, mm (range)	17 (7–60)
PET–CT	
Yes	44 (57.9%)
No	32 (42.1%)
Brain therapy	
Surgery + WBRT	21 (27.6%)
Surgery only	1 (1.3%)
SRS + WBRT	5 (6.6%)
SRS only	49 (64.5%)
Thoracic therapy	
Surgery	21 (27.6%)
No therapy	55 (72.4%)

Abbreviations: SCC, squamous cell carcinoma; PET, positron emission tomography; CT, computed tomography; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery.

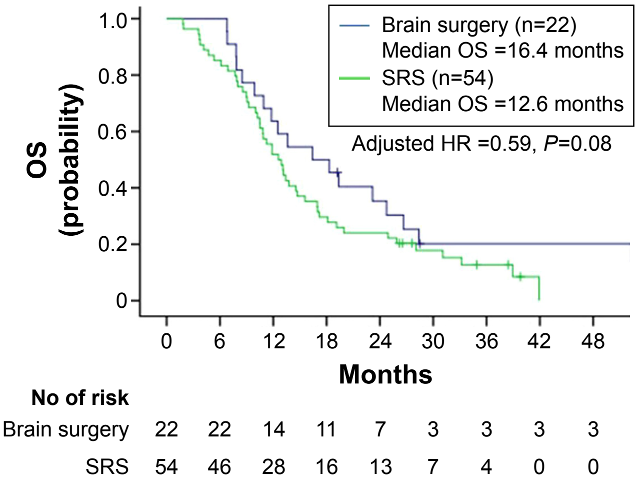

Figure 1 Kaplan–Meier plots of OS comparison for the brain surgery and SRS cohorts.
Abbreviations: OS, overall survival; SRS, stereotactic radiosurgery; HR, hazard ratio.

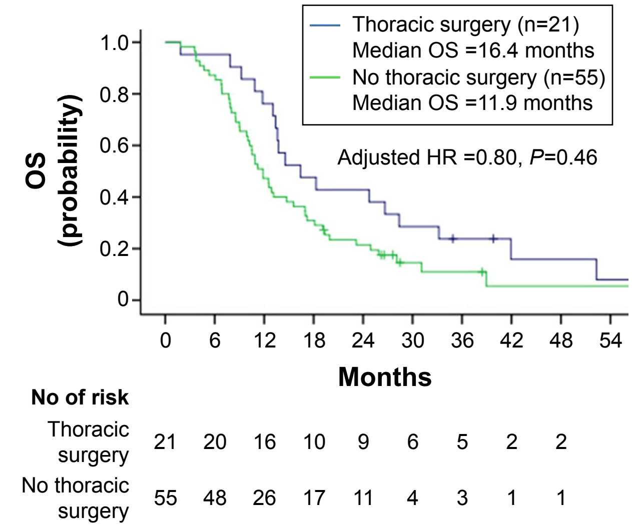

Figure 2 Kaplan–Meier plots of OS comparison for thoracic surgery and no thoracic surgery cohorts.
Abbreviations: OS, overall survival; HR, hazard ratio.

hazard ratio (HR) =0.59, 95% CI 0.33–1.07, P=0.08) (Figure 1). Comparison of baseline characteristics of the brain surgery cohort and the SRS cohort is shown in Table S1. During the course of their disease, five patients (22.7%) in the brain surgery cohort developed new brain metastasis and 13 (24.1%) patients in the SRS group had distant brain failure (P=0.90). The 1-year local tumor control rates for the brain surgery group and the SRS group were 81.8% and 88.9%, respectively (P=0.408).

Among the 76 patients treated with SRS or surgical resection, factors associated with improved OS included stage I–II of the primary lung tumor (adjusted HR =0.53, 95% CI 0.29–0.98, P=0.042) and solitary brain metastases (adjusted HR =0.46, 95% CI 0.26–0.80, P=0.006) (Table 2). Patients who underwent resection of the primary tumor failed to experience a significantly improved OS (16.4 months, 95% CI 9.6–23.2) compared with those who did not undergo primary tumor resection (11.9 months, 95% CI 9.7–14.0) (Figure 2). Comparison of baseline characteristics of the thoracic surgery cohort and the no thoracic surgery cohort is shown in Table S2.

Table 2 Multivariate Cox regression analysis of factors associated with overall survival

All patients	HR	*P*-value
Female vs male	0.51	0.38
Stage I–II vs stage III	0.53	0.042
Solitary brain metastasis vs 2–3 brain metastases	0.46	0.006
Smoker vs non-smoker	0.23	0.05
Age <60 years vs ≥60 years	0.78	0.34

Abbreviation: HR, hazard ratio.

Discussion

Several prospective randomized trials have established surgical resection followed by WBRT or SRS as the standard local therapy for patients with synchronous brain oligometastatic NSCLC.[11–14] However, this topic remains controversial. In this study, we summarized clinical data of patients with synchronous brain oligometastatic NSCLC in our institution to explore the prognostic factors associated with better survival in this population. The results demonstrated that surgical resection of brain metastasis and SRS appeared to provide a similar survival benefit. Among patients receiving SRS or brain surgery as local therapy, the number of brain metastases and stage of lung disease were the factors associated with a survival benefit. OS for patients undergoing primary tumor resection appeared to be longer than those who did not. However, after adjusting for age, stage, initial brain therapy, and number of brain metastasis, this difference was not found to be statistically significant.

Previous clinical trials compared survival outcomes for patients treated with SRS versus SRS + WBRT, and the results suggested that the addition of WBRT did not provide a survival advantage.[14,15] Patchell et al[11] showed that surgical resection followed by consolidative WBRT is better than surgery alone for local control of brain metastases. However, clinical evidence regarding surgical resection + WBRT versus SRS is limited. In a Phase III study, distant tumor control was less frequently achieved in the radiosurgery group compared with the microsurgery + WBRT group;[8] and the treatment results did not differ in terms of survival (*P*=0.8). In another randomized trial, OS for radiosurgery + WBRT and surgery + WBRT were 6.2 and 2.8 months, respectively (*P*=0.20).[16] However, both of those clinical trials were stopped early due to slow patient accrual. A retrospective study collected clinical data of patients with solitary brain metastasis, and demonstrated that radiosurgery alone can result in distant tumor control rates and OS comparable to that of surgery plus WBRT in selected patients.[17] Similar results were also achieved in another retrospective study, which demonstrated no significant difference between surgical resection (SR) and SRS groups in terms of local control. The 6-, 12-, and 18-month local control rates were 84%, 73%, and 63% for patients in the SR group and 91%, 66%, and 66% for patients in the SRS group, respectively.[18] In the present study, the 1-year local tumor control rates after surgery and SRS were 81.8% and 88.9%, respectively. There was no significant difference between brain surgery and SRS with regard to recurrence of brain metastasis. The OS appeared to be longer in the brain surgery cohort versus the SRS cohort. However, in the brain surgery cohort, 45.5% patients were stage I–II, while 72.7% patients had a solitary metastasis. Meanwhile, in the SRS cohort, 31.5% of patients were stage I–II and 59.3% patients had a solitary metastasis. Furthermore, patients in the brain surgery group appeared to be younger. After adjusting for these factors, OS in the brain surgery and SRS cohorts failed to achieve a statistical significant difference. The limitation of small sample size in this distinct population subset might partly explain the discrepancy of results in different studies. Recently, a system review summarized the clinical evidence in patients with single brain metastasis from NSCLC who underwent surgical resection and SRS.[19] The results were consistent with those of the present study, which demonstrated comparable local control of brain metastases and OS benefits.

Li et al[20] demonstrated that patients undergoing resection of brain metastasis and stage I and II NSCLC patients (34.9 months) had a significantly longer survival compared with stage III patients (8.9 months). Similarly, in the present study, favorable outcomes were associated with patients with stage I–II primary lung cancer. In the current study, multivariate analysis showed that the number of brain metastases was one of the most important factors to affect survival. Similarly, Wroński et al[21] retrospectively collected survival data of patients undergoing surgical treatment of brain metastases; patients with single metastatic lesion survived longer than those with multiple metastases (11.1 vs 8.5 months, $P<0.02$). Another meta-analysis that summarized the data of three clinical trials demonstrated that patients with a single metastasis had significantly better survival rates compared with patients with 2–4 metastases.[13]

Previously, several studies demonstrated that primary lung tumor resection might be an option for synchronous oligometastatic NSCLC patients undergoing effective local therapy for distant metastasis.[22,23] Hanagiri[24] showed that selected patients who undergo surgical resection for the primary tumor and effective local therapy for metastatic lesions still have a chance to achieve long-term survival. Another prospective study demonstrated that clinical T1-2 N0-1 lung cancer with a single-organ metastatic lesion was appropriate for surgical resection. A 5-year survival rate of ~40% can be expected, which is comparable to that of stage II NSCLC.[25] In the current study, OS for patients undergoing resection of the primary tumor also appeared to be longer than for patients who did not. After adjusting for age, stage, initial brain therapy, and number of brain metastasis, OS in the brain surgery and SRS cohorts failed to achieve a statistically significant difference. These results were different from previous reports, which demonstrated that aggressive therapy including resection of the primary lung tumor can help patients with synchronous brain oligometastases to significantly improve survival. The different characteristics of patients might partly explain the discrepancy of the results. In the current study, of the 21 patients who underwent brain surgery, only two patients did not have abnormal mediastinal lymph nodes. According to a previous study, the survival benefit of surgical treatment for lung cancer was significant if no abnormal mediastinal lymph nodes were found.[26]

This study has several limitations, including its retrospective nature. Also, the small sample size in each cohort might have affected the statistical analysis. A treatment selection bias may be present, affected mainly by initial clinical presentation and brain metastasis characteristics. What is more, the imbalance of additional WBRT therapy in different cohorts can cause a bias.

Conclusion

There was no significant difference in OS for patients with synchronous brain oligometastasis receiving SRS or surgical resection as local therapy. Among these, thoracic surgery appeared to result in a longer OS; however, after adjusting for baseline characteristics, this difference was not found to be statistically significant. The most important factors associated with a survival benefit are the number of brain metastases and stage of the primary lung disease.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

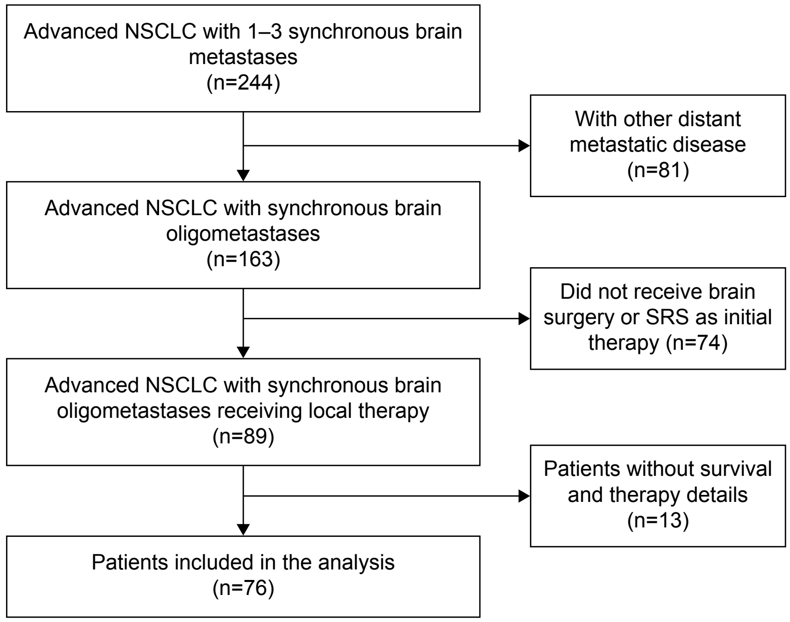

Figure S1 Flow diagram of patients studied.
Abbreviations: NSCLC, non-small-cell lung carcinoma; SRS, stereotactic radiosurgery.

Table S1 Comparison of baseline characteristics of the brain surgery cohort and SRS cohort

Characteristic	Brain surgery (n=22)	SRS (n=54)	*P*-value
Median age, years (range)	55 (34–71)	61 (30–82)	0.465
Sex, n (%)			
Male	18 (81.8%)	34 (63.0%)	0.102
Female	4 (18.2%)	20 (37.0%)	
Smoking status, n (%)			
Smoker	16 (72.7%)	31 (57.4%)	0.212
Never-smoker	6 (33.7%)	23 (42.6%)	
Histology, n (%)			
Adeno	21 (95.5%)	36 (66.7%)	0.082
SCC	0 (0.0%)	9 (16.7%)	
Others	1 (4.5%)	9 (16.7%)	
Stage, n (%)			
IA	0 (0.0%)	0 (0.0%)	0.123
IB	1 (4.5%)	0 (0.0%)	
IIA	5 (22.7%)	9 (16.7%)	
IIB	3 (13.6%)	8 (14.8%)	
IIIA	12 (54.5%)	37 (68.5%)	
Number of brain metastasis, n (%)			
1	16 (72.7%)	32 (59.3%)	0.098
2	5 (22.7%)	14 (25.9%)	
3	1 (4.5%)	8 (14.8%)	
Size of largest lesion, mm (range)	31 (8–60)	15 (7–30)	0.003
WBRT or not			
Yes	21 (95.5%)	4 (7.4%)	<0.001
No	1 (4.5%)	50 (92.6%)	
Thoracic therapy, n (%)			
Surgery	10 (45.5%)	11 (20.4%)	0.027
No surgery	12 (54.5%)	43 (79.6%)	

Abbreviations: SRS, stereotactic radiosurgery; SCC, squamous cell carcinoma; WBRT, whole-brain radiation therapy.

Table S2 Comparison of baseline characteristics of thoracic surgery cohort and no thoracic surgery cohort

Characteristic	Thoracic surgery (n=21)	No thoracic surgery (n=55)	*P*-value
Median age, years (range)	50 (41–74)	63 (30–82)	0.018
Sex, n (%)			
Male	15 (71.4%)	37 (67.3%)	0.449
Female	6 (28.6%)	18 (32.7%)	
Smoking status, n (%)			
Smoker	13 (61.9%)	34 (61.8%)	0.994
Never-smoker	8 (38.1%)	21 (38.2%)	
Histology, n (%)			
Adeno	17 (81.0%)	40 (72.7%)	0.058
SCC	1 (4.8%)	8 (14.5%)	
Others	3 (14.3%)	7 (12.7%)	
Stage, n (%)			
IA	0 (0.0%)	0 (0.0%)	0.120
IB	1 (4.8%)	0 (0.0%)	
IIA	6 (28.6%)	9 (16.4%)	
IIB	4 (19.0%)	7 (12.7%)	
IIIA	10 (47.6%)	39 (70.9%)	
Number of brain metastasis, n (%)			
1	16 (76.2%)	32 (58.2%)	0.081
2	5 (23.8%)	14 (25.5%)	
3	0 (0.0%)	9 (16.4%)	
Size of largest lesion, mm (range)	15 (7–42)	19 (7–60)	0.012
Brain therapy, n (%)			
Surgery + WBRT	10 (47.6%)	11 (20.0%)	0.121
Surgery only	0 (0.0%)	1 (1.8%)	
SRS + WBRT	0 (0.0%)	4 (7.3%)	
SRS only	11 (52.4%)	39 (70.9%)	

Abbreviations: SCC, squamous cell carcinoma; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery.