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Treatment of oligometastatic lung cancer with brain metastases using stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT)

John Nikitas
Washington University School of Medicine in St. Louis

Michael Roach
Cancer Center of Hawaii

Cliff Robinson
Washington University School of Medicine in St. Louis

Jeffrey Bradley
Emory University

Jiayi Huang
Washington University School of Medicine in St. Louis

See next page for additional authors

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Case Report

Treatment of oligometastatic lung cancer with brain metastases using stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT)

John Nikitas [a], Michael Roach [b], Cliff Robinson [a], Jeffrey Bradley [c], Jiayi Huang [a], Stephanie Perkins [a], Christina Tsien [a], Christopher Abraham [a,*]

[a] Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO 63110, United States
[b] Department of Radiation Oncology, Cancer Center of Hawaii, Honolulu, HI 96817, United States
[c] Department of Radiation Oncology, Emory School of Medicine, Atlanta, GA 30322, United States

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ABSTRACT

Background: There is increasing interest in treating oligometastatic non-small cell lung cancer (NSCLC) patients with stereotactic radiation. We aimed to address whether patients definitively treated with synchronous thoracic stereotactic body radiation therapy (SBRT) and brain stereotactic radiosurgery (SRS) had favorable outcomes with local therapy.

Materials and methods: We reviewed a database of patients receiving lung SBRT as well as a database for brain metastasis patients treated with SRS between June 2004 and January 2016. We selected for cT1-2aN0M1 NSCLC patients with brain metastases and calculated their overall survival (OS), freedom from progression (FFP), and local control (LC) rates.

Results: Six patients had oligometastatic NSCLC with 1–3 synchronous brain metastases treated with lung SBRT and brain SRS. No patients received immunotherapy and two-thirds did not receive systemic therapy. Median follow-up was 9 months for the entire cohort (range, 2–95 months) and 95 months for the surviving patient. Median OS was 12.4 months (95% confidence interval [CI], 7–18 months). At 1 year, patients had 67% OS (95% CI, 29–100%), 17% FFP (95% CI, 0–46%), and 100% LC. Their brain disease had 80% 1-year LC (95% CI, 45–100%) and 53% 1-year FFP (95% CI, 5–100%). Two patients had no distant progression, two had brain progression, one had adrenal gland progression, and one had bone and liver progression.

Conclusion: In patients presenting with oligometastatic lung cancer limited to the brain, treatment with both lung SBRT and brain SRS achieves good LC of all sites with encouraging OS.

1. Introduction

Lung cancer continues to be the number one cause of cancer-related death in the United States [1]. Among non-small cell lung cancer (NSCLC) patients, half initially present with metastatic disease, with the central nervous system (CNS) being the first site of failure in up to one-third of patients [2]. Stereotactic radiosurgery (SRS) has emerged as a preferred treatment option for controlling brain metastases [3].

With improvements to chemotherapeutic and supportive care agents, overall survival in patients with metastatic disease continues to improve. As such, there has been renewed interest in radiotherapy for primary thoracic disease. This trend is reflected in national guidelines, such as the National Comprehensive Cancer Network, which advocates primary treatment in patients with locally advanced thoracic disease and limited non-thoracic metastatic burden [4]. While brain metastases in patients with otherwise early-stage disease is rare, treating thoracic disease with stereotactic body radiation therapy (SBRT) and brain disease with SRS remains unexplored. We aimed to clarify the combined effect of lung SBRT and brain SRS in this patient cohort.

* Corresponding author at: 660 S Euclid Ave, Campus Box 8224, St. Louis, MO 63110, United States.
E-mail address: cabraham@wustl.edu (C. Abraham).

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2. Patients and methods

2.1. Eligibility criteria

Patients treated at the Siteman Cancer Center in St. Louis were identified from two institutional review board-approved databases. One was for patients receiving thoracic SBRT and the other was for patients receiving SRS for brain metastases. Patients were enrolled in the databases between June 2004 and January 2016. Patient, disease, and treatment information were extracted from the medical record in a retrospective fashion. The databases were queried to find a cohort of patients present in both databases who had T1a-T2aN0M1 NSCLC secondary to synchronous brain metastases at the time of diagnosis. Synchronous brain metastases were defined as tumors treated with brain-directed SRS within 3 months of thoracic SBRT. Patients with stage I NSCLC who later developed brain metastases and received salvage SRS were excluded from analysis as were patients who had other non-CNS metastatic sites. All eligible patients had received PET or CT chest and a brain MRI.

2.2. Lung SBRT

SBRT planning and delivery were performed as previously described [5]. For peripheral lesions, patients received 5400 cGy in 3 every-other-day fractions. For lesions within 2 cm of the proximal bronchial tree, the mediastinum, or the pericardium, patients received 5000–5500 cGy in 5 fractions. Normal tissue dose limits were set in accordance to RTOG 0813[6] and RTOG 0236 [7].

2.3. Brain SRS

Single-fraction SRS planning and delivery was performed as previously described [8]. The radiation doses were generally 20–24 Gy for tumors $\leq$ 2 cm, 18 Gy for tumors 2.1–3 cm, and 15 Gy for tumors > 3 cm according to RTOG 90–05 [9].

2.4. Follow-up

Patients were followed every 3–4 months with CT or PET/CT imaging for thoracic disease and every 2–3 months with a brain MRI for CNS disease. If there was low suspicion for disease progression after 2 years, patients were followed in 6-month intervals.

2.5. Evaluation

Overall survival (OS), freedom from progression (FFP), and local control (LC) were calculated from the date of the first fraction of radiation. Progression was defined as any local, regional, or distant progression that occurred after the completion of radiation therapy. Local failure for lung tumors was defined as in-field progression that occurred after the completion of radiation therapy. Local failure for brain metastases was defined as an increase in size of the treated lesion at any time after SRS unless advanced imaging or pathology indicated radiation necrosis. Patients that died of causes other than disease progression or treatment complications were censored and not counted as progression or local failure.

2.6. Statistical analysis

Cumulative rates of OS, FFP, and LC were calculated using Kaplan-Meier survival analysis. All statistical analyses were performed by IBM SPSS Statistics, version 25 (IBM Corp., Armonk, N. Y., USA).

3. Results

3.1. Patient characteristics

Patient characteristics are listed in Table 1. 6 patients had oligometastatic disease treated with SBRT for primary lung cancer and SRS for 1–3 synchronous brain metastases. Among these patients, 2 received whole brain radiation therapy (WBRT) prior to an SRS boost and 2 received adjuvant chemotherapy (Table 2). Median follow-up was 9 months for oligometastatic group (range, 2–95 months). Median age at diagnosis was 76.6 years (range, 63.2–86.7) and median age-adjusted Charlson Comorbidity Score was 11 (range, 9–12). Four patients were former smokers, five had no previous cancer history, and all six had an ECOG performance status of 1 or better. Their lung tumors had a median tumor diameter of 3.2 cm and their brain metastases had a median tumor volume of 1.3 cm^3.

Table 1
Patient characteristics at diagnosis.

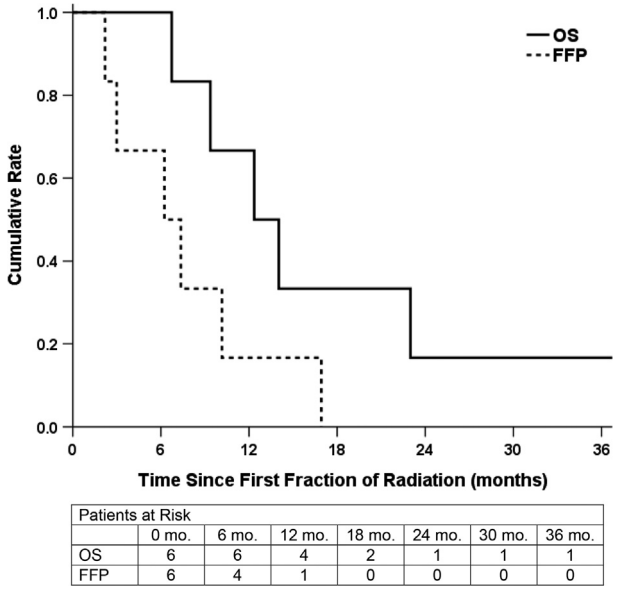
Patient Characteristics	
Sample size	*6 patients*
Age at diagnosis (years), mean	77.2
Gender	
Male	4 (67%)
Female	2 (33%)
Previous cancers?	
Yes	1 (17%)
No	5 (83%)
ECOG performance status	
0	1 (17%)
1	5 (83%)
≥2	0 (0%)
Age-adjusted Charlson Comorbidity Score, mean	10.5
Have ever smoked?	
Yes	4 (67%)
No	2 (33%)
Smoking history (pack years), mean	33.8
Thoracic Tumor Characteristics	
Sample size	*6 tumors*
Location	
Central	1 (17%)
Peripheral	5 (83%)
Diameter	
1–1.9 cm	1 (17%)
2–2.9 cm	2 (33%)
3–3. cm	1 (17%)
4–4.9 cm	2 (33%)
Biopsy-proven?	
Yes	5 (83%)
No	1 (17%)
Brain Tumor Characteristics	
Sample size	*9 tumors*
Location	
Frontal	4 (44%)
Parietal	2 (22%)
Temporal	2 (22%)
Cerebellum	1 (11%)
Volume	
0–0.9 cm^3	4 (44%)
1–2.9 cm^3	3 (33%)
3–4.9 cm^3	0 (0%)
5–8 cm^3	2 (22%)

ECOG = Eastern Cooperative Oncology Group.

Table 2
Clinical outcomes.

Patient	# of Brain Mets	WBRT?	Chemo?	Location of progression	Time to progression	Local CNS failure?	CNS Progression?
1	1	No	No	–	–	Yes, 26.4 mo.	No
2	3	Yes	No	–	–	No	No
3	1	Yes	Yes	Brain	10.1 mo.	No	Yes, 10.1 mo.
4	2	No	No	Adrenal gland	6.8 mo.	No	No
5	1	No	Yes	Brain	2.3 mo.	Yes, 2.3 mo.	Yes, 2.3 mo.
6	1	No	No	Bone, Liver	5.7 mo.	No	No

CNS = central nervous system. WBRT = whole brain radiation therapy.



Patients at Risk	0 mo.	6 mo.	12 mo.	18 mo.	24 mo.	30 mo.	36 mo.
OS	6	6	4	2	1	1	1
FFP	6	4	1	0	0	0	0

Fig. 1. Overall survival (OS) and freedom from progression (FFP). Kaplan-Meier survival analysis was performed.

3.2. Clinical outcomes

Median OS was 12.4 months (95% CI, 6.8–18.0 months) in this patient cohort, with one patient remaining alive after 95 months of follow-up. The 1-year rates were 67% for OS (95% confidence interval [CI], 29–100%), 17% for FFP (95% CI, 0–46%), and 100% for thoracic LC (Fig. 1). They had 80% 1-year CNS LC (95% CI, 45–100%) and 53% CNS FFP (95% CI, 5–100%). Two of the patients had no distant progression: one remains alive at 95 months and the other died at 1.8 months. Of the remaining patients, two had progression in their brain at 2.3 and 10.1 months, one had progression to their adrenal gland at 6.8 months and one had progression to their bones and liver at 5.7 months (Table 2). The only documented toxicities were two grade 2 cases of chest wall toxicity (33%).

4. Discussion

We report the results of series of six patients with oligometastatic NSCLC with brain metastasis treated with lung SBRT and brain SRS. In general, these patients had a limited burden of thoracic and CNS disease with a good performance status, but they had high baseline comorbidities. Four of the six patients survived for longer than one year, with one patients still surviving at almost 8 years of follow-up. There were no cases of local thoracic failure and only two cases of local CNS failure. These results reflect favorably on national guideline recommendations to offer definitive management to both primary and metastatic sites. Unfortunately, we noted a significant rate of disease progression in this cohort, with all patients progressing by 18 months. This is not surprising given the presence of metastatic disease at baseline.

Five published studies have examined definitive management of CNS and thoracic disease in oligometastatic lung cancer. Table 3 summarizes the results of these studies.

Yang et al. [10] examined a group of 31 patients who received SRS for their brain metastases. 16 of the patients received thoracic surgery with or without adjuvant chemotherapy or lung radiation. They had a median OS of 64.9 months and a 5-year OS rate of 87.5%. The other 15 patients received either chemotherapy, lung radiation, or both. These patients had a median OS of 18.1 months and a 5-year OS of 22.5%. In the second group with less favorable outcomes, only 3 of the patients received lung radiation. The remaining patients in this group received chemotherapy alone.

Hu et al. [11] had a subgroup of 31 patients treated with brain SRS (n = 24) or brain SRS plus WBRT (n = 7) and radiation, chemotherapy, or both for their primary lung cancer. This cohort had a median OS of 7.4 months compared to 12.4 months among the patients in our study. Their results demonstrated inferior outcomes than our study because they included patients who were a thoracic stage I-III, unlike our study that included only thoracic stage I patients. They did not create a separate subgroup that received only stereotactic body radiation for both their brain metastases and their lung cancer.

Flannery et al. [12] reported on 26 patients treated definitively for thoracic disease and brain metastases. All the patients received SRS with or without adjuvant WBRT. For their thoracic disease, 9 patients received chemoradiation, 12 patients received surgical resection with or without adjuvant chemotherapy, and 5 received surgery and chemoradiation. The inclusion of surgical candidates in their study caused their patients to have a higher median OS of 26.4 months compared to 12.4 months in our study and a 5-year OS rate of 34.6% compared to 17% in our study.

Gray et al. [13] had a less comparable group of 38 patients who received surgery, radiation, and/or chemotherapy for both their primary lung cancer and their brain metastases. They did not separate patients based on their treatment modality. Like Flannery et al., this study included surgical candidates, which likely caused their patient cohort to have a higher median OS of 26.4 months compared to our study.

Lo et al. [14] had subset of 3 patients who received surgery for primary lung cancers and SRS for brain metastases. They found a median OS of 17.3 months.

These studies demonstrate that delivering local therapy to both the primary tumor and the metastases improves patient outcomes in oligometastatic NSCLC cancer patients with brain metastases. A number of these studies reported a median OS of at least one year with a subset of patients surviving several years with aggressive management of both thoracic and CNS disease. This suggests that a subset of oligometastatic patients may achieve survival comparable to more early-stage patients.

The advantage of this study is that the patient cohort includes those who received both definitive lung SBRT and brain SRS. Unlike

Table 3
Treatment modalities and clinical outcomes of oligometastatic NSCLC patients with solitary brain metastases.

Authors	Brain Treatment	Lung Treatment	Sample Size	Median OS (months)	1-yr OS Rate	5-yr OS Rate
Hu et al.	SRS ± WBRT	Rad and/or Chemo	31	7.4	–	–
Flannery et al.	SRS ± WBRT	Surg or rad ± Chemo	26	26.4	–	35%
Yang et al.	SRS	Surgery ± Chemo ± Rad	16	64.9	100%	88%
		Chemo and/or Rad	15	18.1	66.7%	23%
Gray et al.	Surg, SRS, and/or WBRT	Surg, Chemo, and/or Rad	38	26.4	71%	29%
Lo et al.	SRS	Surgery	3	17.3	67%	33%
Current Study	*SRS ± WBRT*	*SBRT*	6	*12.4*	67%	17%

OS = overall survival. SBRT = stereotactic body radiation therapy. SRS = stereotactic radiosurgery. WBRT = whole brain radiation therapy.

other studies, patients who received either surgical resection, conventionally-fractionated thoracic radiation, or chemotherapy alone were excluded. As a result, this cohort accurately reflects outcomes in non-surgical candidates with limited metastatic disease in the modern era.

One limitation to this study is that even though it had one of the larger sample sizes of exclusively lung SBRT and brain SRS patients, the small sample size limited the generalizability of the results. Another limitation was that the oligometastatic patient group was heterogeneous with respect to whether patients received chemotherapy or WBRT. These varied according to the patient's specific disease burden, provider preference, and patient preference and could not be controlled retrospectively.

Advances in SBRT and brain SRS have revolutionized the treatment of oligometastatic lung cancer and may be offered to more patients moving forward. Several phase II randomized control trials studies have tested the upper limit for the number of oligometastatic sites that can be targeted using local stereotactic radiation therapy. Gomez et al. [15] included NSCLC patients with up to three sites of metastatic disease and Iyenger et al. [16] included NSCLC patients with up to five sites of metastases. Both of these papers found significantly higher PFS in patients treated with adjuvant stereotactic radiation compared to patients who only received first-line systemic therapy. These results have also been shown in patients with other primary cancers as well. In the SABR-COMET trial [17], which did not select for a specific primary cancer histology, oligometastatic cancer patients with up to 5 metastases had significantly improved PFS and OS. As the data for treatment of oligometastatic disease matures, SBRT and SRS are likely to play larger roles in patients who were previously excluded from local therapy.

5. Conclusions

In oligometastatic lung cancer patients secondary to brain metastases, local treatment of both the primary lesion and the metastases with lung SBRT and brain SRS, respectively, lead to favorable OS outcomes. Lung SBRT and brain SRS achieved excellent LC rates with well-tolerated toxicities. These results are consistent with what other studies have found and support the use of stereotactic radiation therapy for NSCLC patients with oligometastases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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