Timing of adjuvant radiation therapy and survival outcomes after surgical resection of intracranial non-small cell lung cancer metastases

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ABSTRACT

Objective: : To investigate if delay of adjuvant radiotherapy (ART) beyond 6 post-operative weeks affects survival outcomes in patients undergoing craniotomy or craniectomy for resection of non-small cell lung cancer (NSCLC) intracranial metastases.

Patients and methods: We performed a retrospective analysis of 28 patients undergoing resection of intracranial metastases and ART at our institution from 2001 to 2016. We assessed survival outcomes for patients who received delayed versus non-delayed ART, as well as associated risk factors.

Results: Among 28 patients, 8 (29%) had delayed ART beyond 6 post-operative weeks. Fifteen received stereotactic radiotherapy (SRT), 8 (29%) received whole brain radiotherapy (WBRT), and 5 (18%) received combination WBRT + SRT. There were no significant differences in ART modality or dosing, age, sex, number of intracranial metastases, primary metastasis volume, rates of chemotherapy, extracranial metastases, or post-operative functional scores between groups. Expected post-operative survival was shorter with delayed ART (7 months versus 28 months, $P = 0.01$). The most common reason for delayed ART was complicated post-operative course (n = 3.38%). Significant risk factors for delayed ART included non-routine discharge ($P = 0.01$) and additional invasive procedures between surgery and ART start date ($P = 0.02$).

Conclusions: Our results suggest delayed ART in patients undergoing surgical resection of intracranial NSCLC metastases is associated with shorter overall survival. However, risk factors for delayed ART, including non-routine discharge and the need for additional invasive procedures, may have in themselves reflected poorer clinical courses that may have also contributed to the observed survival differences.

1. Introduction

Cerebral metastases are the most common intracranial tumors with 30–60% of metastases coming from the lungs [1]. Lung cancer is a leading cause of cancer mortality in the United States, with an estimated survival of 4–7 weeks after diagnosis of cerebral metastases without receiving treatment [2]. Among cancers associated with intracranial metastases, lung cancer has by far the highest incidence, with

reported rates of 18–65% [1,2]. Only a subset of patients with lung cancer (10–20%) obtain a clinical diagnosis of cerebral metastases while living, although this varies by disease subtype [3,4]. However, cerebral metastases are observed in more than 40% of cases at autopsy for both small and non-small cell lung cancers [1,2].

Treatment of radiosensitive and chemosensitive cerebral metastases with a known primary cancer involves whole brain radiation therapy (WBRT) and chemotherapy [5]. Currently, the standard of care offered

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for patients with limited systemic disease, good pre-operative functional status, or life-threatening cerebral edema involves surgical resection of lesions followed by adjuvant WBRT or stereotactic radiation therapy (SRT), the latter encompassing either high-dose single-session radiosurgery (SRS) or fractionated radiotherapy (FSRT) [5].

WBRT is the most traditionally used modality for adjuvant radiotherapy (ART) in the setting of cerebral metastases from primary lung cancer, and is known to extend expected survival to 3–5 months compared to other modalities [2]. Several prospective studies, including that by Patchell et al., have reported decreased local recurrence and increased quality of life after surgical resection and adjuvant WBRT compared to biopsy alone [6]. More recently, stereotactic radiosurgery (SRS) has become a viable option for patients with a burden of up to 3–4 small metastases, providing a noninvasive targeted therapy as an alternative or adjunct to surgical resection. Recent studies have further delineated cognitive side effects associated with WBRT and determined that stereotactic radiosurgery (SRS) to the resection cavity may offer comparable survival and local control with less cognitive morbidity compared to WBRT [7].

At our institution, candidates for ART for intracranial metastases are scheduled to begin treatment as soon as reasonably achievable. Our radiation oncology department can typically have a patient planned for SRS or FSRT within five business days of referral, or sooner for WBRT. However, various medical and non-medical factors may delay prompt initiation of ART in practice. Benefits of early ART must be balanced against the need for adequate post-operative recovery time, particularly to allow for adequate surgical wound healing and avoid wound dehiscence. Other medical and non-medical factors may also delay initiation of ART in practice, including poor functional status of patients secondary to underlying illness, the need for other urgent procedures (e.g., first clinical presentation with advanced disease), patient decision-making regarding treatment, care coordination, or insurance-related issues. Our post-surgical patients requiring ART typically commence therapy within 4–6 post-operative weeks or sooner. This time frame generally gives ample time for post-operative recovery and wound healing. Nonetheless, a minority of our patients have been unable to initiate ART within 6 weeks of surgery.

Proposed benefits of early ART include improving local tumor control and lengthening progression-free survival time. However, although the standard of care in current practice is to initiate prompt ART as soon as reasonably achievable after surgical resection, clinical studies investigating the effect of radiation timing in lung cancer patients with intracranial metastases remain sparse, and a clear evidence-based consensus is lacking. For instance, a randomized trial of 176 patients with inoperable metastases undergoing primary WBRT with concurrent chemotherapy demonstrated no survival difference whether WBRT was initiated early or delayed by 8 or more weeks until imaging surveillance indicated neuroradiological non-response to chemotherapy. As such, optimal timing of radiation is a complex issue requiring further investigation.

In this study, we investigated the impact of delayed ART on survival outcomes in patients with lung cancer after surgical resection of intracranial metastases. We reviewed 28 patients who underwent craniotomy or craniectomy for resection of lung cancer metastases at our institution followed by ART. Demographics, metastatic burden, post-operative functional status, and expected overall and progression-free survival times were compared between patients receiving non-delayed versus delayed ART. Potential risk factors for delayed ART were assessed, including post-operative complications, additional invasive procedures, non-routine discharge, and insurance-related issues. We hypothesized that non-delayed ART initiated before 6 post-operative weeks would be associated with improved survival outcomes relative to delayed ART.

2. Materials and methods

2.1. Study design

This study was approved by the UCLA institutional review board and ethics committee (Study Number 17-000578). First, neuropathology reports were requested from the UCLA Department of Pathology & Laboratory Medicine. A total of 529 neuropathology reports were obtained, corresponding to surgical pathology specimens received between 2001 and 2016. These reports were manually screened to identify the subset of cases involving surgical resections of pathologically confirmed primary non-small cell lung cancer (NSCLC). From this group, 101 patients with histologically confirmed primary lung cancer were identified and confirmed via chart review. Patients who did not undergo surgical resection followed by ART of these intracranial metastases or who had previously been diagnosed with other metastatic cancers were excluded from analysis. Furthermore, patients with a prior craniotomy or craniectomy for resection of intracranial metastases were excluded, including patients who underwent one or more prior craniotomies at outside hospitals. Finally, patients with primary lung cancer diagnoses other than NSCLC were excluded. This resulted in a retrospective series of 28 patients meeting inclusion criteria, all of whom had primary NSCLC with intracranial metastases, untreated at the time of presentation to our institution.

2.2. Data collection

Electronic medical records were reviewed, and baseline clinical characteristics collected for all patients. Peri-operative imaging and radiologist reports were reviewed to determine the number of intracranial metastases, presence of active pulmonary disease, presence of an unresected or recurrent primary lung tumor, and presence of other (i.e., extrapulmonary, extracranial) metastatic disease on PET or CT imaging. Metastatic disease progression was reviewed on surveillance neuroimaging throughout patients' post-operative course. Post-operative imaging reports, operative notes and radiation oncology notes were used to determine the surgery-to-radiation interval (SRI) as the number of days between tumor resection and initiation of ART.

The ART modality, number of fractions, and corresponding mean and cumulative doses were also recorded. Stereotactic radiotherapy (SRT) to unresected metastases was recorded for all patients but tabulated separately. For the purpose of classifying patients' primary ART modality, we only considered SRT targeted at sites of resected (not unresected) metastatic lesions.

Pre-operative tumor volumes were determined via direct voxel-wise segmentation of post-contrast T1-weighted MR images. Neuroimaging files were imported into the open-source image segmentation software ITK-SNAP 3.6.0 (ITK-SNAP, Philadelphia, PA).[1] Tumors were identified on T1-weighted MR images with gadolinium contrast, confirmed on T2-weighted images, and segmented in a semi-automated fashion using the active contour (i.e., "snake") tool. When necessary to ensure acute delineation of metastasis margins, fully manual segmentation was performed using the paintbrush tool. Metastatic progression data were collected and reported as local progression of metastasis in the resection cavity, remote progression from new intracranial metastases, and overall intracranial metastatic progression, including both local and remote metastatic progression.

Post-operative functional status was determined and quantified using Karnofsky Performance Status (KPS) [8] and Eastern Cooperative Oncology Group (ECOG) scores [9] as determined via chart documentation from the first post-operative day. Post-radiation cognitive status was quantified using the Radiation Therapy Oncology Group (RTOG) scoring scale for late morbidity from brain radiation [10]. Dates of last documented clinical and neuroradiological follow-up were recorded. For patients with delayed ART, charts were thoroughly reviewed to infer the primary documented reason for the delay. Any

mention of surgical complications, such as post-operative bleeds or hematomas, delayed wound healing or dehiscence, or return to operating room for incisional breakdown were noted, as well as non-routine discharge disposition, additional invasive procedures performed between surgery and start of ART, and health insurance-related issues.

2.3. Statistical analysis

2.3.1. Cohort analysis

Patients were separated into two groups based on SRI: non-delayed ART (SRI < 6 weeks) and delayed ART (SRI ≥ 6 weeks). Demographics, metastatic disease burden, and details of ART were tabulated. Summary statistics were determined for all measures across the entire cohort and separately for the two SRI groups (non-delayed vs. delayed ART). Statistical significance of group differences was evaluated using Welch t-tests for continuous variables and Fisher's exact tests for binary variables. For all reported statistical tests, significance was determined using a two-tailed α criterion of $P < 0.05$. All described statistical analyses described in this study were performed using the R (v3.4.3) statistical programming environment [11].

2.3.2. Survival analysis

Overall mortality-free survival (OS), or expected survival, was defined as months survived from date of surgery, with final mortality status noted at either date of death or last documented clinical follow-up. One post-operative month was defined as $365.25/12 = 30.4375$ days. Progression-free survival (PFS) was defined in post-operative months based on neuroimaging. Final progression status was noted as either the date of the first imaging study showing evidence of metastatic progression or tumor recurrence, or the date of last documented neuroimaging. Local PFS was defined as no evidence of metastatic recurrence at any resection site. Remote PFS was defined as no appearance of new metastatic lesions distant from the resection site(s). Overall PFS was defined as no local or remote progression noted on imaging. Metastatic burden was measured in number of metastatic lesions and volume of the primary (i..e, largest) lesion.

Survival analysis was implemented using the *survival* package for R [12,13]. Survival curves were compared between the non-delayed RT and delayed RT subgroups. Statistical comparisons of OS and PFS between subgroups was performed using log-rank tests. Right-censoring was applied for patients still living or without metastatic progression noted on neuroimaging at last available follow-up.

3. Results

3.1. Pre-operative patient characteristics

Patient demographics and measures of metastatic disease burden, such as number and volume of lesions at the time of surgery are presented in Table 1 for all 28 patients meeting study inclusion criteria. Across patients, median SRI was 31 days with a range of 4–213 days and a right-skewed distribution with skewness of + 2.35. Eight patients met our criteria for delayed ART (SRI ≥ 6 weeks), with median SRI of 60 days. The remaining 20 patients received non-delayed ART (SRI < 6 weeks), with median SRI of 26 days. The full distribution of SRI across patients is depicted in Fig. 1.

Median patient age at time of surgery was 62 years. Eight of 28 patients were male (29%). Histopathological diagnosis of adenocarcinoma was made in 25 cases (89%), and poorly differentiated NSCLC in 3 cases (11%). There were no significant differences in age, sex, or surgical pathology delayed and non-delayed ART groups (Table 1). On neuroimaging, patients presented with a median of 3 intracranial metastases, with 9 patients (32%) having a single metastasis at presentation and 6 patients (21%) having more than ten metastases. Median pre-operative volume of the primary intracranial metastasis was $18.9 \, \text{cm}^3$ across all patients (Table 1). Delayed and non-delayed ART

groups did not differ in average pre-operative volume of the primary metastasis (12.8 vs. $21.3 \, \text{cm}^3$, $P = 0.22$).

Twenty-three patients (82%) had active pulmonary disease noted on chest CT imaging at the time of surgery, and in 16 patients (57%) the underlying lung cancer was undiagnosed or newly diagnosed at the time of neurosurgical presentation or referral. Twenty patients (71%) had either an unresected or recurrent primary lung tumor observed on imaging at the time of surgery, and fifteen patients (54%) had evidence of pulmonary metastases. Nineteen patients (68%) had evidence of other systemic (i.e., extrapulmonary, extracranial) metastases on perioperative PET or CT imaging. These characteristics of metastatic disease burden were comparable between patients in the delayed and non-delayed ART groups, with no significant differences (Table 1).

Twenty-two patients (79%) had documentation of chemotherapy administered at some point in their clinical course, and three patients (11%) had documented adjuvant chemotherapy received between the time of neurosurgical resection and the first ART session. Rates of chemotherapy did not differ between delayed and non-delayed ART groups (Table 1).

3.2. Post-operative patient measures

Measures of post-operative functional status are summarized in Table 1 for patients in the non-delayed and delayed ART groups. Post-operatively, patients had a median KPS index of 80 (Mean ± SD: 77.5 ± 21.9). Median post-operative ECOG status was Grade 1 (Mean ± SD: 1.46 ± 1.14). Most patients were ambulatory in the post-operative period and able to carry out light activities. KPS and ECOG scores did not differ between patients who subsequently received non-delayed versus delayed ART (all $P \geq 0.8$; Table 1).

3.3. Adjuvant radiation therapy administered

The modalities of ART administered to patients are summarized in Table 2. Across all patients, 8 (29%) received WBRT monotherapy, 15 (54%) received SRT monotherapy, and 5 (18%) received combination therapy consisting of WBRT + SRT. For patients receiving SRT monotherapy, 7 (25%) received SRS and 8 (29%) received stereotactic body radiation (SBRT). For patients receiving combination therapy, 1 patient (4%) received WBRT + SRS, 2 patients (7%) received WBRT + SBRT, and 2 patients (7%) received WBRT + intensity modulated radiotherapy (IMRT). Fourteen patients (50%) additionally received SRT to other (unresected) metastases. Non-delayed and delayed ART groups exhibited no differences in the proportions of patients receiving specific ART modalities (Table 2). The number of radiation fractions and estimated absorbed radiation doses are tabulated in Table 3 for each ART modality, including mean dose per fraction and cumulative dose across all fractions. Table 4 summarizes patients' post-radiation neurological morbidity, quantified using the RTOG grade, for each combination of ART modalities. Overall, post-ART neurological morbidity was low at the latest follow up and for most patients ranged from no documented side effects to mild headaches and lethargy.

3.4. Risk factors for delayed ART

The primary reasons underlying delay in ART as inferred from chart review are tabulated in Table 5 for the 8 patients in the delayed ART group. The most common identified reasons for delayed ART were complicated post-operative course (3 cases, 38%) and poor post-operative functional status (2 cases, 7%). To test whether these and other plausible risk factors were significantly associated with delayed ART, we computed odds ratios and comparison tests to compare the prevalence of these potential risk factors between non-delayed and delayed ART groups (Table 6). Regarding length of hospital stay, the delayed ART group stayed in the hospital an average of 4.2 days longer than the non-delayed ART group. In terms of post-operative hospital days, this

Table 1

Patient demographics, metastatic disease burden at time of surgery, and post-operative functional status.

Demographics	All patients (n = 28)	Non-delayed ART (n = 20)	Delayed ART (n = 8)	P-value
SRI, days (median & range)	31 (4-213)	26 (4-38)	60 (42-213)	0.018
Age (median & range)	62 (43-75)	62 (43-73)	62 (55-75)	0.33
Sex				
Male	8 (29%)	6 (30%)	2 (25%)	1
Female	20 (71%)	14 (70%)	6 (75%)	
Surgical Pathology				
Adenocarcinoma	25 (89%)	18 (90%)	7 (88%)	1
Poorly differentiated NSCLC	3 (11%)	2 (10%)	1 (12%)	
Metastatic disease burden at time of surgery				
Number of intracranial metastases				
Median & Range	3 (1-30)	4 (1-30)	2.5 (1-11)	0.12
1 met	9 (32%)	6 (30%)	3 (38%)	1
2 mets	4 (14%)	3 (15%)	1 (13%)	1
3-5 mets	8 (29%)	5 (25%)	3 (38%)	0.29
6-10 mets	1 (4%)	1 (5%)	0 (0%)	1
11 + mets	6 (21%)	5 (25%)	1 (13%)	1
Primary met volume, cm^3 (median & range)	18.9 (1.5-83.9)	21.3 (5.1-83.9)	12.8 (1.5-50.8)	0.22
Active pulmonary disease	23 (82%)	17 (85%)	6 (75%)	0.61
Undiagnosed or newly diagnosed lung cancer at neurosurgical presentation	16 (57%)	12 (60%)	4 (50%)	0.69
Primary lung tumor (unresected or recurrent)	20 (71%)	14 (70%)	6 (75%)	1
Pulmonary metastases	15 (54%)	11 (55%)	4 (50%)	1
Other systemic metastases	19 (68%)	12 (60%)	7 (88%)	0.22
Treatment variables				
Chemotherapy (any documented)	22 (79%)	16 (80%)	6 (75%)	1
Chemotherapy (surgery to first ART)	3 (11%)	1 (5%)	2 (25%)	0.19
Post-op functional status				
KPS index	77.5 ± 21.9	77.5 ± 23.1	77.5 ± 19.8	1
ECOG status	1.46 ± 1.14	1.50 ± 1.1	1.38 ± 1.2	0.80

NSCLC, non-small/small cell lung cancer. SRI, surgery-to-radiation interval. *P-values* indicate significance of differences between patients in delayed and non-delayed ART groups.
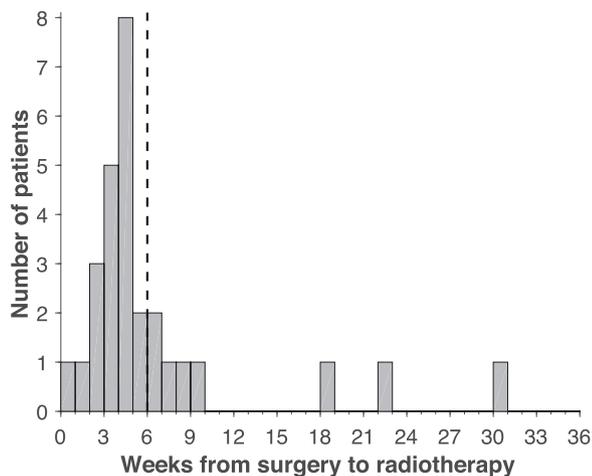

Fig. 1. Distribution of surgery-to-radiation interval across patients.

discrepancy increased to 5.2 additional days for the delayed ART group. Neither of these differences was statistically significant (both *P* > 0.3). However, delayed ART was associated with significantly higher odds of non-routine discharge (OR = 16.4 [1.2, 975], *P* = 0.015) and additional invasive procedures performed between surgical resection and the start of ART (8.5 [1.04, 92.3], *P* = 0.022).

3.5. Survival outcomes

3.5.1. Overall mortality-free survival

Follow-up intervals and survival outcome measures are tabulated in Table 7. Across all patients, median clinical follow-up was 8.3 months. Fifteen of 28 patients (54%) were living at the last clinical follow-up. Fig. 2a presents mortality-free survival curves for patients in the non-delayed and delayed ART groups. Thirteen of 20 patients (65%) in the non-delayed ART group were alive at last follow-up, compared to 2 of 8 patients (25%) in the delayed ART group. Expected OS was 21.4 post-operative months across all patients. Patients receiving delayed ART had shorter expected OS than patients receiving non-delayed ART (7.0 months vs. 28.3 months, *P* = 0.011).

3.5.2. Neuroradiological progression-free survival

Across all patients, median neuroradiological follow-up was 6.0 months. Thirteen of 28 patients (46%) had no evidence of overall intracranial metastatic disease progression at the time of the last neuroimaging follow-up. Twenty patients (71%) had no evidence of local metastatic recurrence at the resection site, and 14 patients (50%) had no evidence of new growth or progression of remote metastases at the last neuroimaging follow-up.

Fig. 2b displays survival curves depicting overall PFS data for the ART groups. Ten of 20 non-delayed ART patients (50%) were free of overall intracranial metastatic progression at last imaging follow-up, compared to 3 of 8 patients (38%) receiving delayed ART. Expected overall PFS, including both local and new lesion, was 15.0 months for non-delayed ART patients compared to only 3.2 months for delayed ART patients, but the difference was not significant (*P* = 0.39).

Survival curves depicting local PFS are depicted in Fig. 2c. Fifteen of 20 patients (75%) receiving non-delayed ART were free of local metastatic progression at last imaging follow-up, compared to 5 of 8 patients (63%) receiving delayed ART. There was no significant difference in expected local PFS between ART groups (*P* = 0.47).

Finally, survival curves are depicted for remote PFS in Fig. 2d. Eleven of 20 patients (55%) receiving non-delayed ART were free of evident remote metastatic progression at last imaging, compared to 3 of 8 patients (38%) patients receiving delayed ART. Expected remote PFS was 15.0 months for patients receiving non-delayed ART compared to only 4.6 months for patients receiving delayed ART. However, the difference was not significant (*P* = 0.42).

Table 2
Modalities and dosage of adjuvant radiation therapy administered.

Radiation therapy administered	# fractions	Fractional dose (Gy)	Cumulative dose (Gy)	All patients (n = 28)	Non-delayed ART (n = 20)	Delayed ART (n = 8)	P-value
WBRT	10-15 Avg: 13.4 ± 2.4	2.6 ± 0.3	33.9 ± 3.6	8 (29%)	7 (35%)	1 (13%)	0.37
SRT				15 (54%)	10 (50%)	5 (63%)	0.69
SRS	1	14 ± 1.8	14 ± 1.8	7 (25%)	5 (25%)	2 (25%)	1
SBRT	5	5.5 ± 0.5	27.5 ± 2.6	8 (29%)	5 (25%)	3 (38%)	0.65
IMRT	10	2.6 ± 0.5	26.3 ± 5.3	0 (0%)	0 (0%)	0 (0%)	1
SRT + WBRT				5 (18%)	3 (15%)	2 (25%)	0.61
SRS + WBRT				1 (4%)	1 (5%)	0 (0%)	1
SBRT + WBRT				2 (7%)	1 (5%)	1 (13%)	0.50
IMRT + WBRT				2 (7%)	1 (5%)	1 (13%)	0.50
SRT to other mets				14 (50%)	10 (50%)	4 (50%)	1

WBRT, whole-brain RT. SRT, stereotactic RT. SRS, stereotactic radiosurgery. SBRT, small body RT. IMRT, intensity modulated RT. *P-values.*
indicate significance of differences between delayed and non-delayed ART patients.

Table 3
Post-radiation RTOG grades by adjuvant radiation therapy modality.

RT modality	RTOG grade	
	Mean ± SD	Range
Overall	1.00 ± 1.02	0-4
WBRT	1.29 ± 0.76	0-2
No other RT	1.20 ± 0.84	0-2
+ SRT to other mets	1.00 ± 1.00	0-2
SRT	1.07 ± 1.16	0-4
SRS	0.67 ± 0.52	0-1
SBRT	0.88 ± 1.13	0-3
IMRT	–	–
SRT + WBRT	0.20 ± 0.45	0-1
SRS + WBRT	0	0
SBRT + WBRT	0.50 ± 0.71	0-1
IMRT + WBRT	0	0

RTOG grade based on RTOG Late Radiation Morbidity Scoring Schema for brain irradiation.
Increasing RTOG grade indicates increasing morbidity.

4. Discussion

The treatment of intracranial metastatic disease has progressed over the last century, and due to increasing survival of patients with this pathology, treatment options and elucidation of best practices have become more complex. Surgical resection is often considered for large symptomatic lesions, in combination with radiation therapy and chemotherapy. It is well known that radiation treatment has acute and chronic adverse effects, particularly due to ionizing damage to DNA and free radical production. While early efforts in radiation therapy were historically associated with dermatitis, the incidence of which has decreased greatly, modern post-surgical ART can still result in a decrease

in wound strength, angiogenesis, and collagen deposition [14,15]. Timing of radiation treatment after surgery must take into account multiple variables, including disease histopathology (which in turns influences recurrence rates and radiosensitivity), adjuvant chemotherapy, radiation effects on wound healing, corticosteroid use, and patient-specific factors.

There is scarce literature regarding the optimal time interval between surgical resection and initiation of ART for intracranial metastases. Published literature on this topic primarily consists of case series of soft tissue sarcomas and other extracranial pathologies, with some evidence suggesting that non-delayed ART may offer a slight benefit for enhanced local tumor control [16–19]. Prior studies with large patient series that mention the time interval of WBRT after surgical resection of intracranial metastases generally describe initiation of ART within 2–4 post-operative weeks [20–23]. A recent review addressing the optimal timing of WBRT after craniotomy for cerebral malignancies yielded limited concrete data, but advised at least a one-week interval between surgery and start of ART to eliminate tumor tissue that may remain [24]. However, this review emphasized the lack of sufficient evidence regarding whether delay of ART up to the first post-operative month had a significant impact on clinical outcomes [24].

In the present study, we evaluated the effect of timing of radiation therapy after neurosurgical resection of lung cancer metastases in 28 patients. We found that expected OS was significantly longer within the non-delayed ART group relative to the delayed ART group (28.3 vs. 7.0 months, $P = 0.01$). These differences persisted despite comparable demographics, peri-operative metastatic burden, modality of ART, and post-operative functional status. However, the difference in neuroradiological progression-free survival between non-delayed and delayed ART groups did not reach significance (15.0 months vs. 3.2 months, $P = 0.39$).

While pre-operative variables and post-operative functional scores

Table 4
Reasons for delayed start of adjuvant radiation therapy.

Reason	Patients affected	Case Comments
Complicated post-op course	3 (37.5%)	Post-obstructive pneumonia secondary to primary lung tumor requiring re-hospitalization
		Post-op epidural hematoma with d/c to acute rehabilitation unit
		Post-op intraparenchymal hemorrhage & hematoma requiring evac & EVD placement with d/c to acute rehabilitation unit
`Poor post-op functional status	2 (25%)	Post-op transfer to acute rehabilitation unit and diagnostic work-up for myopathy
		Post-op PT/OT, d/c to skilled nursing facility
Scheduling issues	1 (12.5%)	Uncomplicated post-op course with home d/c; first RT at 8 post-operative weeks
Multiple factors	1 (12.5%)	Insurance issues and multiple post-operative re-hospitalizations
Other	1 (12.5%)	Patient s/p GTR of solitary extra-axial met infiltrating left parietal bone with dural abutment.
		Followed post-operatively by neurosurgery and radiation oncology with monthly MRI surveillance
		Started ART upon radiological recurrence
		Expired 58 days after ART start from complications of post-obstructive pneumonia.
Total: 8		

Table 5
Assessment of risk factors for delayed ART.

Risk factor	Non-delayed ART	Delayed ART	Δ	Odds Ratio	t	adj df	*P-value*
Hospital LOS (days)	7.9 ± 8.3	12.1 ± 10.3	− 4.2 [-13.2, 4.8]	–	−1.03	8.01	.534
Pre-op LOS (days)	3.4 ± 6.7	2.3 ± 3.0	1.2 [-2.6, 4.9]	–	0.63	25.5	.149
Post-op LOS (days)	4.5 ± 3.9	9.9 ± 9.2	−5.4 [-13.1, 2.4]	–	−1.60	10.8	.324
Non-routine discharge	–	–	–	**16.4 [1.2, 975]**	–	–	**.015**
Complications	–	–	–	∞ [0.50, ∞]	–	–	.074
Invasive procedures	–	–	–	**8.5 [1.04, 92.3]**	–	–	**.022**
Insurance issues	–	–	–	∞ [0.06, ∞]	–	–	.286

LOS, length of stay. Δ = Non-delayed RT average – Delayed RT average. *t*, *t*-statistic. adj df, adjusted degrees of freedom for Welch's *t test*.

were largely comparable between ART groups, other important post-operative risk factors for delayed ART were identified that demand caution in interpreting our observed differences in survival measures. First, patients with delayed ART had significantly higher odds of non-routine (i.e., non-home) discharge to either a skilled nursing facility (SNF) or acute rehabilitation unit (ARU). Overall, 5 of 28 patients (18%) had a non-routine discharge following their initial hospitalization for neurosurgical resection of metastases. Four of these patients were among the minority of patients who received delayed ART, and only one patient with a non-routine discharge received ART within 6 post-operative weeks. Thus, non-routine discharge was a significant risk factor for delayed ART [OR = 16.4, P = 0.015]. In theory, discharge to a SNF or ARU does not exclude the possibility of prompt ART. Nevertheless, non-routine discharge may have posed a barrier to care for some patients. Patients who lacked nearby family or the means to arrange transport to outpatient appointments likely encountered more difficulty coordinating ART. Non-routine discharges were also associated with post-operative hospital stays over 11 days longer than routine discharges on average (15.4 days vs. 4.0 days). Longer inpatient recovery times could in turn delay time to outpatient radiation oncology follow-up. However, this difference did not reach significance (P = 0.053), nor did the difference in post-operative length of stay between delayed and non-delayed ART groups (9.9 days vs. 4.5 days, P = 0.32). Patients with delayed ART also had higher odds of additional invasive procedures performed between surgery and ART. Delayed ART may also have been associated with post-operative complications, though our sample size was insufficient to determine this conclusively. Rates of documented chemotherapy and extracranial metastatic disease at time of surgery were similar between groups.

Finally, patients also require insurance authorization to cover costs of care. For the purposes of this study, we defined insurance-related issues as those involving chart documentation of problems obtaining insurance authorization for procedures, medication, or other care, and which care providers explicitly documented as resulting in a delay of planned ART (i.e., denial of coverage by the insurance provider for referrals or follow-up with radiation oncology, or denial of coverage for ART). In almost all cases, insurance authorization was obtained expediently and did not contribute to delayed ART. However, insurance problems were encountered by one patient who initially presented to our ED with undiagnosed Stage IV lung cancer with multi-system metastatic disease. This patient underwent prompt resection of a symptomatic cerebellar metastasis during the initial hospitalization, but despite extensive efforts from numerous physicians and administrative staff, over seven months transpired before insurance authorization for oncological care was finally obtained and the patient could begin ART and adjuvant chemotherapy. While insurance-related issues were not a significant risk factor for delayed ART across our cohort overall (P = 0.26), it was the sole factor resulting in delayed ART for this patient.

Previously, a well-controlled randomized clinical trial by Robinet, Mornex & colleagues compared survival differences in 176 patients with inoperable NSCLC brain metastases who received cisplatin/vinorelbine combination chemotherapy in conjunction with either early or delayed WBRT [25]. Early WBRT was initiated within the first twelve days of study enrollment (with first chemotherapy cycle starting on Day 1), while delayed WBRT was begun only after intracranial disease progression was noted upon imaging surveillance conducted at 8, 16, and 24 weeks (i.e., after 2nd, 4th, and 6th chemotherapy cycles, for a maximum of 6 chemotherapy cycles). This study reported a median survival of 21 weeks for early WBRT and 24 weeks for delayed WBRT (P = 0.83) [25], whereas we observed median estimated survival of 123 weeks for non-delayed ART patients and 30.4 weeks for delayed ART patients (P = 0.01). Several differences in study designs and patient characteristics may explain these discrepancies. The study by Mornex & colleagues was a randomized, controlled trial that prospectively controlled radiation timing [25]. Thus, potential confounding factors such as more aggressive disease or poorer clinical

Table 6
.Follow-up and clinical outcomes.

Clinical variable	All patients (n = 28)	Non-delayed ART (n = 20)	Delayed ART (n = 8)	*P-value*
Median follow-up, months				
Clinical f/u	8.3 (1.6-115)	9.9 (1.6-115)	6.3 (2.8-20.7)	0.13
Radiological f/u	6.0 (0-114)	7.0 (0-114)	4.4 (0.2-18.0)	0.24
OS at last clinical f/u				
Pts living	15 (54%)	13 (65%)	2 (25%)	0.10
PFS at last neuroradiological f/u				
Pts w/o any progression	13 (46%)	10 (50%)	3 (38%)	0.69
Pts w/o local progression	20 (71%)	15 (75%)	5 (63%)	0.65
Pts w/o remote progression	14 (50%)	11 (55%)	3 (38%)	0.68
Expected median post-op survival, months				
OS	21.4 [> 8.4]	28.3 [> 11.3]	7.0 [> 3.7]	**0.011**
Neuroradiological PFS	13.2 [> 1.8]	15.0 [> 1.8]	3.2 [> 1.4]	0.39
Local PFS	NE [> 4.6]	NE [> 10.8]	4.6 [> 3.2]	0.47
Remote PFS	13.2 [> 4.1]	15.0 [> 3.5]	4.6 [> 1.4]	0.42

Brackets demarcate lower 95% confidence limits of expected median survival times. Upper confidence limits were not estimable due to limited follow-up. Unless otherwise indicated, values denote median values of corresponding measures within each cohort. f/u, follow-up time. PFS, progression-free survival. NE, not estimable. *P-values* indicate significance of differences between delayed and non-delayed RT patients.
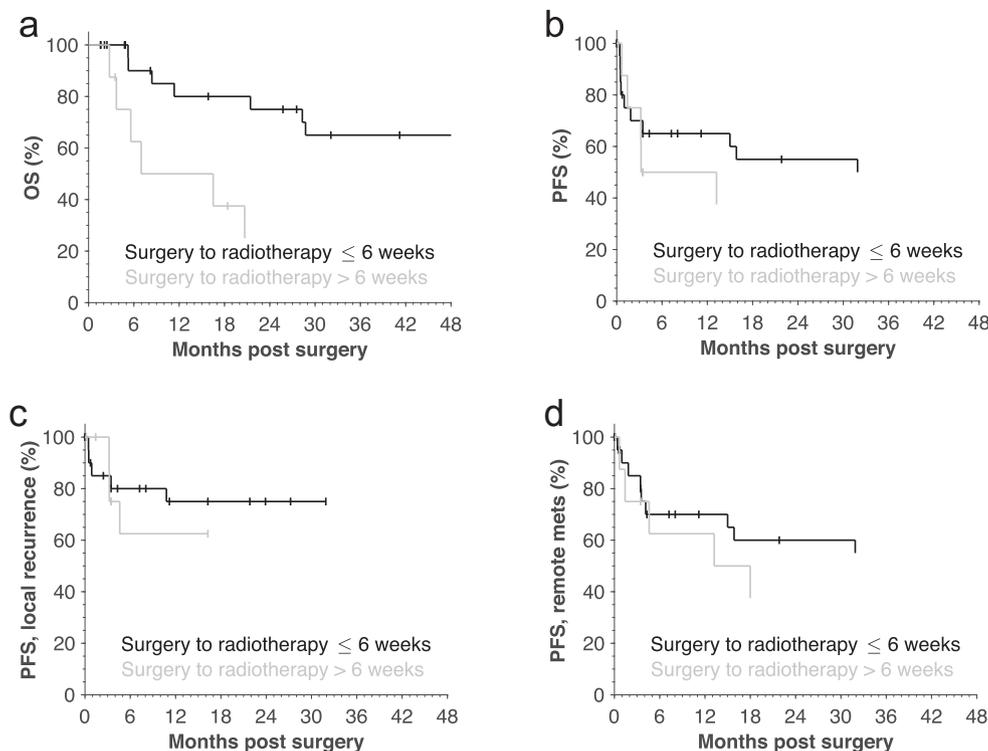
Fig. 2. Survival curves for patients undergoing craniotomy or craniectomy for resection of intracranial lung metastases and adjuvant radiation therapy with SRI less than or greater than 6 weeks. Results are plotted for **(a)** overall survival, **(b)** overall progression-free survival, **(c)** local progression-free survival (tumor recurrence at resection site), and **(d)** remote progression-free survival (metastatic growth distant from resection site). Tick marks indicate times of last follow-up for patients still living or without metastatic progression.

status delaying treatment were largely mitigated. However, other differences between our studies further limit direct comparison. Patients in our study all had operable intracranial disease and underwent resection of one or more metastases; they had more favorable prognoses associated with longer median survival as compared to the inoperable patients in Robinet et al. While all patients in the Robinet et al. study received WBRT, 71% of our patients were candidates for stereotactic RT (alone or as combination therapy) and only 46% received WBRT. Furthermore, patients in our cohort had highly variable chemotherapy regimens, with some patients having previously received chemotherapy, other patients initiating adjuvant chemotherapy after ART, and other patients refusing any chemotherapy whatsoever, as opposed to the standardized regimens in Robinet et al [25]. Still, the lack of a survival difference in the study by Mornex & colleagues is noteworthy. Their results highlight the need for additional rigorous prospective studies to investigate the impact of radiation timing on survival outcomes for other subgroups of patients with intracranial metastatic disease, including postsurgical patients undergoing ART and those with limited intracranial disease burden amenable to stereotactic ART.

4.1. Limitations

Our results must be interpreted in the context of the patient data, which included several limitations. First, our sample size of 28 patients had limited power to detect significant differences in clinical variables and survival outcomes, and included different histopathological subtypes of NSCLC. In equal measure, sample size constraints increased the risk of type II errors, and we may have failed to detect meaningful differences in patient characteristics or risk factors. Additionally, our study included patients who underwent different modalities of ART, including WBRT, SRT, or multimodal ART. Since these radiotherapy modalities have distinct clinical indications and radiobiological effects on wound healing and tumor control, it is possible that the optimal timing of ART may depend on the specific ART modality or other factors not considered in the present study, such as patient-specific metastatic burden. A clearer picture of optimal ART timing also depends upon patient-centered goals of care, such as quality of life and time

spent arranging and receiving treatment. These factors were not considered in the present study but are critical for any individualized treatment decision. Finally, our suboptimal range of clinical follow-up times (median: 8.3 months) limited our ability to accurately assess survival outcomes. Indeed, in agreement with the median survival estimates in our study, several recent studies report median survival to be greater than one year in patients with intracranial lung cancer metastases undergoing surgical resection and ART [20,23].

Another important limitation of our approach was the necessity of choosing a threshold to define "delayed" versus "non-delayed" ART. Our chosen threshold of six post-operative weeks was a compromise between achieving adequate sample size in both subgroups while also selecting for patients with a meaningful departure from the typical delays observed in most patients (Fig. 1). Of course, there is no single "correct" threshold, and the relationship of ART timing to survival outcomes likely requires more rigorous characterization than simple dichotomization. In a controlled trial, patients could be randomized uniformly into groups with well-defined timing of ART, yet this was not feasible in our retrospective analysis.

5. Conclusions

We evaluated the effect of post-operative timing of adjuvant radiation therapy after surgical resection of intracranial lung cancer metastases in a single institution cohort of 28 patients. Our study revealed significant survival benefits for patients beginning ART within 6 weeks of surgical resection compared to those receiving ART 6 weeks or more postoperatively, and adds to a literature that remains relatively sparse in this area. Overall, our findings raise the question of whether poorer survival outcomes in the delayed ART group were explained by delayed ART *per se*, post-operative risk factors that predisposed patients to delayed ART, or a combination of both. Results interpretation is limited by our sample size, suboptimal granularity after dichotomization of subgroups, and the various underlying factors that delayed adjuvant treatment in some patients. Despite this ambiguity, retrospective analysis is critical to investigate the factors delaying ART in routine practice, and to understand how delayed ART and its associated risk

factors may relate to clinical outcomes. Definitively addressing these limitations will require well-powered and controlled prospective studies. Nevertheless, our results suggest that developing strategies to expedite ART for patients with complicated post-operative courses would be prudent if extended survival is the goal. Our results provide motivation for future work, including prospective studies exploring strategies to coordinate more prompt ART in complicated patients. Such studies might investigate whether achieving earlier ART improves survival outcomes, as cannot be ascertained from this retrospective study.

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Declaration of competing interest

The authors report no conflicts of interest related to this study.

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