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Clinical Study

Stereotactic radiosurgery for brain metastases: Comparison of lung carcinoma vs. non-lung tumors

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Summary

In the medical literature, stereotactic radiosurgery (SRS) for brain metastases results in rates of local control of 65 to 85%. To define patient selection criteria, we measured the survival in a population with a high proportion of non-small cell lung carcinoma (NCS lung) metastases that occurred soon after primary diagnosis. Between 9/89 and 10/93 30 adults (21 M, 9 F) had SRS for metastatic NSC lung carcinoma (14 patients) vs. non-lung carcinomas (16 patients having breast (3), renal (3), melanoma (3), GI (2, thyroid (1) or carcinoma of unknown origin (4)). The metastases were solitary for 22 patients and multiple for 8 patients. Average ages (y) (± SD) were 58.6 ± 10.4 for NSC lung patients and 53.4 ± 12.5 ($p = 0.32$) for non-lung patients. The average interval (months) from diagnosis of the primary to metastasis was 23.8 ± 41.4 for all patients. This interval was shorter for NSC lung patients: 3.1 ± 6.0 vs. 48.0 ± 51.7 ($p < 0.001$) for non-lung patients. Twenty seven patients had conventional radiotherapy (XRT) before (24 patients) or after (3 patients) SRS. Doses (cGy) were 3303 ± 841 for 13 NSC lung patients and 4256 ± 992 for 14 non-lung patients ($p = 0.034$). The median time from primary diagnosis to SRS was shorter for the NSC lung patients (11 mo) compared to the non-lung patients (35 mo). SRS was given for recurrence of metastases after XRT for 11/14 NSC lung patients and 13/16 non-lung patients. The doses (cGy) of SRS were 1579 ± 484 vs. 1682 ± 476 ($p = 0.45$) for the NSC lung and non-lung groups, respectively. After SRS a decrease in metastasis diameter was observed in 10 of 14 NSC lung patients vs. 12 of 16 non-lung patients ($p = 0.85$ Chi-square). Twenty-seven of the 30 patients have died. For all patients, the median survival after diagnosis of the primary and after radiosurgery was 31.3 and 8.4 months, respectively. The median survival (95% CI) from primary diagnosis was 24.3 months (13.2–27.3) for NSC lung patients and 46.5 months (39.2–65.5) for non-lung patients ($p = 0.005$ logrank test). The median survival (95% CI) after SRS was 7.9 months (3.0–14.3) for the NSC lung patients and 8.4 (2.9–11.9) months for the non-lung patients ($p = 0.98$ logrank test). Within the two groups, no difference in survival was observed for patients who had SRS sooner (< 1 yr for NSC lung; < 3 yr for non-lung) after primary diagnosis: 9.3 vs. 6.5 mo for NSC lung ($p = 0.21$) and 10.5 vs. 7.2 mo for non-lung ($p = 0.87$). In this series, the shortened intervals from primary diagnosis to SRS for NSC lung metastases was associated with post-SRS survivorship that was equivalent to the more favorable non-lung group.

Introduction

Metastasis of systemic cancer is the leading cause of intracranial neoplasia [1, 2]. Clinically, 20 to 30 percent of the patients having invasive cancer will develop brain metastases [3] resulting in approximately 15% of the annual U.S. cancer deaths [4]. The standard treatment for brain metastases is fractioned, external beam radiotherapy. Survival increases from 1 month without treatment to 3–5 months after conventional radiotherapy [5].

Many factors determine the outcome of conventional treatment for these patients. Diener-West et al. [6] described the prognostic features of both the patient (age ≤ 60; KPS ≥ 70) and the tumor (absent or controlled primary tumor; brain the only site of metastases) that predict improved survivorship after radiotherapy for brain metastases. Higher total doses of radiation may cause improved survival of patients having these favorable prognostic features [7].

Primary lung cancer is the leading cause of death from cancer in the United States. In 1994 there were 170,000 new cases of lung cancer in the U.S., resulting in 153,000 deaths [8]. Approximately 80% of these cases were NSC lung carcinoma [9]. The rate of metastasis to the brain for NCS lung carcinoma is 25% [10], thus yielding approximately 30,000 patients who will develop brain metastases annually. The results of conventional treatment for these patients are poor. For patients with brain metastases, the median and one year survivorships for lung vs. non-lung primaries after conventional radiotherapy were 4.6 vs. 5.8 months and 24% vs. 30%, respectively [4]. Further, in the first two Radiotherapy Oncology Group (RTOG) studies of the treatment of brain metastases using external beam irradiation, the median times to progression and survival after treatment were shorter for patients having metastases from lung vs. non-lung primary tumors [5]. Stereotactic radiosurgery (SRS) allows the precise, focal delivery of high doses of radiation to brain metastases and causes high rates of local control [11–20]. In these series, BSC lung carcinoma primaries comprise a high percentage of the treated patients. When compared to patients with other primaries, patients with brain metastases from NSC lung primaries have a diminished average interval between the diagnosis of the primary malignancy to development of brain metastases [21]. The prognostic importance of this shortened interval in patients having radiosurgery for NSC lung metastases to the brain remains poorly defined, however.

We examined the outcome of stereotactic radiosurgery in a population with a high proportion of NSC lung carcinoma and concomitant short intervals from the diagnosis of the primary until radiosurgery for brain metastasis.

Methods and materials

Between September 1989 and October 1993, 30 adults were treated with stereotactic radiosurgery for brain metastases. All patients had histologic verification of the diagnosis of cancer. Eligibility for radiosurgery included a minimum KPS of 70%, controlled or absent primary tumor, and radiographically distinct metastases measuring ≤ 3.5 cm in diameter. All patients signed informed consent. After placement of the BRW (Brown-Roberts-Wells) frame, a contrast-enhanced CT scan of the brain was obtained. The CT images containing the BRW fiducials were analyzed using a computer program that was developed in-house. The borders of the contrast-enhanced metastases were defined. The position of the isocenter(s) and diameter of the collimator(s) were selected to enclose the periphery of the metastasis with the 60%–90% isodose line. Most plans enclosed the tumor with the 80% isodose line. The collimator diameters ranged from 13 to 34 mm, and for larger targets multiple isocenters were utilized. The prescribed doses varied inversely with the size of the collimator. Analysis of the dose-volume histogram allowed critical evaluation of the treatment plan. Stereotactic radiosurgery was delivered using a modified 10 MeV linear accelerator. We used 5 arcs, including 2 transverse (each 120 degrees), 2 oblique (each 100 degrees) and 1 sagittal (100 degrees).

Follow-up included both physician evaluation and imaging studies. Imaging was done approximately 1 month after radiosurgery and approximately every 3–6 months thereafter. We defined local control as the measured decrease or absence of change in the maximal diameter of the brain metastases as seen on the follow-up contrast-enhanced CT or MRI studies.

We collated the characteristics of the patients (sex, age, primary histology), metastases (number, size and site), external beam radiotherapy (dose) and stereotactic radiosurgery (collimator diameter, isodose percentile, and dose)) and interval (from diagnosis of the primary tumor until brain metastasis, external beam radiotherapy, stereotactic radiosurgery and death). Because of the high proportion of patients with NSC lung primaries and the comparatively small numbers of patients with each of the other non-lung primary histologies, the latter groups were combined and compared with the NSC lung group.

Unless otherwise stated, data are the mean ± SD. Differences were analyzed using the t-statistic for normally distributed observations or the Wilcoxon Rank Sum test [22]. Survival curves were calculated using the Kaplan-Meier product-limit method [23]. Differences in survival between subgroups were tested using the logrank test [24].

Table 1. Distributions of demographic, tumor and conventional radiotherapeutic characteristics for all patients, NSC lung and non-lung populations, respectively.

Age (years)	Entire group (n = 30) n%	NSC lung (n = 14) n%	Non-lung (n = 16) n%	p[1]
30–49	10 (33.3%)	4 (28.6%)	6 (37.5%)	p = 0.83
50–64	12 (40.0%)	6 (42.9%)	6 (37.5%)	
65–80	8 (26.7%)	4 (28.6%)	4 (25.0%)	
mean ± sd	56.3 ± 12.0	58.6 ± 10.4	54.3 ± 12.5	p = 0.32
Sex				
Male	21 (70.0%)	11 (78.6%)	10 (62.5%)	p = 0.44
Female	9 (30.0%)	3 (21.4%)	6 (37.5%)	
Number of Mets				
1	22 (73.3%)	11 (78.6%)	11 (68.8%)	p = 0.69
> 1	8 (26.7%)	3 (21.4%)	5 (31.2%)	
External beam radiation dose (cGy)				
Median	3960	3000	4530	p = 0.034
Mean = sd	3797 ± 1026	3303 ± 841	4256 ± 992	

[1] Wilcoxon Rank Sum Test: NSC Lung vs. Non-Lung.

Results

Patients

For the entire population the distributions of age, gender and number of metastases are shown in Table 1. The combined group included 21 males and 9 females (Table 1) whose primary histologic categories included NSC lung (14 patients) vs. non-lung (16 patients). For the non-lung group, the histologies included breast (3), renal (3), melanoma (3), GI (2), thyroid (1), and unknown (4). The average ages (y) at the time of diagnosis of the primary were similar: 58.6 ± 10.4 for NSC lung patients and 54.3 ± 12.5 (p = 0.32) for the non-lung patients. Twenty two patients had radiosurgery for single brain metastases, four patients had 2, three patients had 3 and one patient had 6 metastases. Sites of metastases were cerebellar (12), parietal (12), frontal (11), occipital (4), and deep (thalamus, midbrain, or pons) (6).

Table 2. Distributions of intervals between diagnoses of the primary or metastatic tumors and conventional external beam radiotherapy or stereotactic radiosurgery for all patients, NSC lung and non-lung groups, respectively.

	Entire group			NSC lung			Non-lung			p-value[1]
	Median	Mean	Std dev	Median	Mean	Std dev	Median	Mean	Std dev	
Primary←MET[2]	12.0	23.8	41.4	0	3.1	6.0	30.2	48.0	51.7	0.0001
Primary←EBRT[3]	12.4	19.6	41.3	0.6	1.1	11.2	25.2	43.6	53.6	0.0002
Primary←SRS	24.4	33.5	41.0	10.9	13.8	15.7	35.1	56.4	49.6	0.0002
MET←SRS	7.8	9.4	10.5	8.5	10.8	13.9	7.0	8.3	6.5	0.82

[1] Wilcoxon Rank Sum Test: NSC Lung vs. Non-Lung.
[2] MET: Metastasis having subsequent SRS.
[3] EBRT: Fractionated external beam radiotherapy for initial diagnosis of brain metastasis.

Interval from primary to metastases having SRS

For the 14 patients having NSC lung primaries, 6 had metastases treated with SRS that were diagnosed a median of one month prior to the primary, 2 presented synchronously, and the remaining 6 were diagnosed a median of 11 months after the primary (Table 2). For the 12 patients with known non-lung primaries, metastases having SRS were diagnosed a median of 30 months after the primary. The diagnosis of the metastasis was earlier relative to the diagnosis of the primary for the patients having NSC lung primaries ($p = 0.0001$ Wilcoxon Rank Sum test).

External beam irradiation

The interval from diagnosis of the primary (for patients with known primaries) until the start of cranial external beam irradiation for the initial diagnosis of brain metastasis (for patients having external beam irradiation) was shorter for the patients having NSC lung primaries. Thirteen of 14 patients having NSC lung primaries and 10 of the 12 patients having known non-lung primaries had cranial external beam irradiation. The median intervals (months) were 0.6 and 25.2 ($p = 0.0002$ Wilcoxon Rank Sum test) for patients having NSC lung and non-lung primaries, respectively. This includes three patients having cranial external beam irradiation for adenocarcinomatous metastases 0.5, 15, and 25.7 months prior to histologic confirmation of the NSC lung carcinoma at the pulmonary site. No patient having non-lung primaries had cranial external beam radiotherapy before diagnosis of the primary. Cranial external beam radiotherapy began a median of 15 days vs. 21 days ($p = 0.22$ Wilcoxon Rank Sum test) days after the initial diagnosis of brain metastasis for NSC lung vs. non-lung primaries, respectively.

Thirteen of 14 patients with NSC lung metastases and 14 of 16 patients with non-lung metastases (including 4 unknown primaries) had fractionated external beam radiotherapy (whole brain with or without boost to a smaller volume) either before (24 patients: 13 NSC lung and 11 non-lung patients) or after (3 patients: 1 NSC lung and 2 non-lung patients) stereotactic radiosurgery. All patients were treated using megavoltage linear accelerators or cobalt-60 over continuous courses. The fractional doses (cGy) ranged from 180 to 300. Doses were 3303 ± 841 vs. 4256 ± 992 cGy for non-lung patients vs. NSC lung patients ($p = 0.034$ Wilcoxon Rank Sum test), respectively.

For the metastases having radiosurgery, the interval (months) from the diagnosis of metastases to radiosurgery was 10.8 ± 13.9 vs. 8.3 ± 6.5 ($p = 0.82$ Wilcoxon Rank Sum test) for patients having NSC lung vs. non-lung primaries, respectively (Table 2).

Radiosurgery

At the time of radiosurgery, the NSC lung metastases tended toward larger volume. The diameters (cm) were 2.3 ± 0.8 for NSC lung and 1.9 ± 0.9 ($p \pm 0.135$) for non-lung metastases. Accordingly, for radiosurgery of NSC lung vs. non-lung mets the average collimator diameters (mm) were 24.9 ± 7.3 vs. 21.0 ± 7.4 ($p = 0.09$), respectively. The prescribed doses (cGy) and isodose percentiles were equivalent in the two groups. Doses were 1569 ± 484 vs. 1682 ± 476 ($p = 0.45$) and the prescribed isodose percentiles were 81.8 ± 8.3 vs. 80.5 ± 12 ($p = 0.69$) for the NSC lung vs. non-lung metastases, respectively.

Follow-up

With three exceptions all patients were followed until death. One patient with NSC lung metastasis remains alive 45.3 months after radiosurgery and 2 patients with non-lung metastases were lost to follow up 35.6 and 38.9 months after radiosurgery.

Local control

After radiosurgery a decrease in the diameter was measured in 12 of 18 metastases in 10 of 14 NSC lung patients and 12 of 27 metastases in 10 of 16 non-lung patients. No changes were noted in 6 NSC lung and

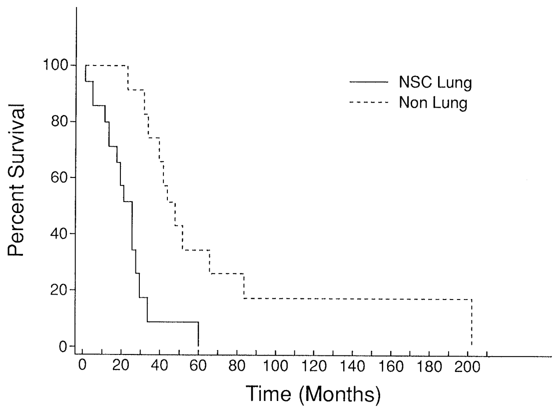

Figure 1. Cumulative survival from time of diagnosis of primary tumor in patients with NSC lung primary vs. non-lung primary.

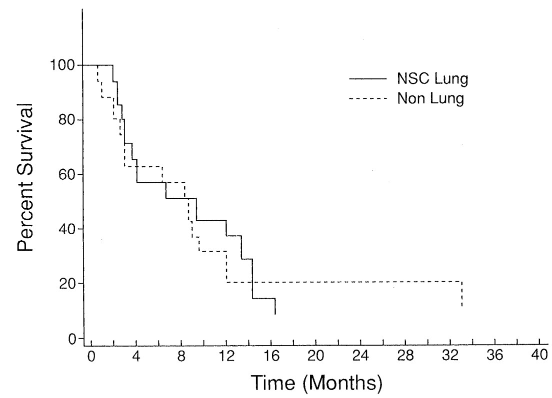

Figure 2. Cumulative survival after stereotactic radiosurgery in patients with NSC lung primary vs. non-lung primary.

2 of 27 non-lung patients. The local control rate (combined proportions of smaller and unchanged tumors) was 18 of 18 NSC lung vs. 14 of 27 non-lung tumors (p = 0.24 Chi-square).

Post diagnosis survival

Twenty seven of the 30 patients have died, including 13 of 14 NSC lung patients and 14 of 16 non-lung patients. The median survival (95% confidence interval) from the date of diagnosis of the primary was 24.3 (13.2–27.3) months for the NSC lung and 46.5 (39.2–65.5) months for the non-lung patients (p = 0.0005 logrank) (Figure 1). However, this difference is confounded by the large difference in time from primary diagnosis to SRS between the two groups, which was a median of 10.9 vs. 35.1 months for the NSC lung and non-lung groups, respectively.

Post radiosurgery survival

Survival after radiosurgery was equivalent: 7.9 (3.0–14.3)) vs. 8.4 (3.0–12.1) (p = 0.98 logrank) months for patients having NSC lung vs. non-lung primaries, respectively (Figure 2). Within the two groups, patients who had radiosurgery sooner (< 1 yr for NSC lung; < 3 yr for non-lung) after diagnosis of the primary had longer average post-radiosurgery survival: 9.3 vs. 6.5 (p = 0.21) months for NSC lung and 10.5 vs. 7.2 (p = 0.87) months for non-lung, although these differences were not statistically significant.

Discussion

Stereotactic radiosurgery for brain metastases results in a high local control rate [11–20]. The histology of the primary tumor, however, has only rarely predicted differences in survival [13].

For patients with brain metastases, NSC lung carcinoma is the most frequent primary, comprising the majority of the treated cases in most published series [11–15, 28–21, 25]. These series, however, have not examined the prognostic importance of the interval between diagnosis of the primary and stereotactic radiosurgery in regards to survivorship.

In published series the numbers of patients having NSC lung primaries as a proportion of the total patients studied are 105/248 [11], 11/40 [15], 41/116 [13], 24/69 [25], 6/24 [17], 17/33 [14] and 7/18 [19]. Some studies describe the radiosurgery of metastases from adenocarcinomatous primaries that are not otherwise specified [16, 12, 20]. Survivorship is not measured in some studies [14, 15, 19]. When measured in others, survival is not stratified by histology of the primary neoplasm [11, 13, 17]. When stratified by the histology of the primary neoplasm, no difference in survival was noted by Engenhart et al. [25], but the intervals from diagnosis of the primary to metastasis or radiosurgery were not specified. Survival after diagnosis of the primary tumor has been compared with survival after radiosurgery [12] but this comparison was not stratified by the histology of the primary tumor.

Our results show that survivorship after diagnosis of the primary tumor is shorter for the NSC lung group and that this shortened interval is associated foremost with a comparatively shortened interval between diagnosis of the primary and metastasis to the brain and subsequent initiation of radiotherapy for brain metastasis.

These results further show that after radiosurgery, survival of the NSC-lung group was equivalent to the non-lung patients and that the shortened interval from the diagnosis of the primary to radiosurgery does not predict inferior post-radiosurgery survival. The equivalence of post-radiosurgery survival for patients having NSC lung and non-lung mestases has been described [25]. Patients having breast carcinoma showed prolonged post-radiosurgery survival in one study [13]. In that study, survival of patients having NSC lung primaries were equivalent to the remaining non-lung primaries.

More recently one report suggests that decreased intervals between diagnosis of the primary and metastasis to the brain predict inferior survival after radiosurgery [12]. For patients who developed new or recurrent intracranial disease within 1 year of diagnosis of the primary tumor, the median survival was approximately 4 months after radiosurgery in that study. Further, for patients who developed brain metastases more than 1 year after diagnosis of the primary, the median survival was not reached an average of 7.5 months after radiosurgery. However, the statistical diffference in survival (post primary diagnosis vs. post-radiosurgery) between the two groups (< 1 year vs. > 1 year from diagnosis of the primary to brain metastasis) narrowed considerably ($p = 0.0001$ vs. 0.047). These results appear to support the findings of the current study. Our results show that for radiosurgery of NSC lung mets, the comparatively short intervals between diagnosis of the primary and cranial irradiation for brain metastasis predict survivorship after radiosurgery that is equivalent to the more favorable group of patients having non-lung primaries. For these patients having brain metastases from NSC lung primaries, stereotactic radiosurgery should remain an important therapeutic option.

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