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Clinical Article

Clinical Analysis of Novalis Stereotactic Radiosurgery for Brain Metastases

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Objective : The authors analyzed the effectiveness and therapeutic response of Novalis shaped beam radiosurgery for metastatic brain tumors, and the prognostic factors which influenced the outcome.

Methods : We performed a retrospective analysis of 106 patients who underwent 159 treatments for 640 metastatic brain lesions between January 2000 and April 2008. The pathologies of the primary tumor were mainly lung (45.3%), breast (18.2%) and GI tract (13.2%). We classified the patients using Radiation Therapy Oncology Group Recursive Partitioning Analysis (RPA) and then analyzed the survival and prognostic factors according to the Kaplan Meier method and univariate analysis.

Results : The overall median actuarial survival rate was 7.3 months from the time of first radiosurgery treatment while 1 and 2 year actuarial survival estimates were 31% and 14.4%, respectively. Median actuarial survival rates for RPA classes I, II, and III were 31.3 months, 7.5 months and 1.7 months, respectively. Patients' life spans, higher Karnofsky performance scores and age correlated closely with RPA classes. However, sex and the number of lesions were not found to be significantly associated with length of survival.

Conclusion : This result suggests that Novalis radiosurgery can be a good treatment option for treatment of the patients with brain metastases.

KEY WORDS : Brain metastasis · Stereotactic radiosurgery · Novalis system · Prognostic factors · RPA classification · Outcome evaluation.

INTRODUCTION

Brain metastases are diagnosed in approximately 30-40% of all patients with cancer and thus represent the most common type of intracranial tumor. The incidence of brain metastasis is increasing with improving systemic care of cancer patients, longer overall survival rates and extended life spans. Radiosurgical treatment for the brain metastases has now been well established in terms of effective high dose irradiation and reducing complication related with whole brain irradiation.

Many dedicated radiosurgical systems also have been introduced to enhance the advantages of this non-invasive treatment for improving quality of life in the advanced cancer patients with brain metastasis. Recent advances in linear accelerator-based radiosurgery have been able to expand the indication of the treatment and may overcome some of debatable issues in the typical SRS using fixed isocentric radiosurgical unit with a radioisotope such as Cobalt 60. There are many debates about shortcuts from the dose heterogeneity and limited fractionation and collimation even though cone collimators provide high conformal dose falloff.

Most LINAC-based radiosurgery have been obtaining many beneficial merits in these aspects which are applying versatile dose-fractions regimens, getting more homogeneous dose distribution and so forth. Using micro-multileaf collimators and rigid or non-invasive frame based or frameless stereotactic radiosurgery enable us to overcome the major limitations such as beam shaping, conformity, dose homogeneity and volume constraint in single session radiosurgery.

This report provides a retrospective analysis of our experiences using a Novalis shaped beam radiosurgery system for the treatment of metastatic brain tumors. We describe and

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detail the analysis of patient survival rates and key prognostic factors.

MATERIALS AND METHODS

A total of 159 cases of stereotactic radiosurgery were conducted for 640 metastatic brain lesions in 106 patients using a Novalis shaped beam radiosurgery system (BrainLAB, Heimstetten, Germany) between November 2000 and April 2008. A retrospective analysis was conducted to evaluate the clinical outcomes of patients based on their medical records and radiological findings. We first classified patients into three different groups using recursive partitioning analysis (RPA) classification based on age, sex, karnofski performance scale (KPS), site of primary tumor, histology and number of lesions. Male to female ratio was 58 versus 48 with a median age of 56.5 years (mean 58.7 years, ranging from 26 to 87 years). Fifty-eight cases had single brain metastases, 21 had two lesions, 17 had three lesions, and 63 had more than four lesions. Overall tumor volumes ranged from 1.28 to 158,110 mm^3 with a mean volume of 3,253 ± 8,994 mm^3. Single session radiosurgery was performed for 620 tumors while the remaining 20 tumors were treated using fractionated radiosurgery. The average total radiation dose was 19.7 Gy (ranging from 2 to 37.5 Gy) in a single session and 35.5 Gy (20 to 51 Gy) in 7.5 fractions (average). Dose fractionation regimes varied depending upon tumor volume, histology, location of the tumor and previous history of irradiation. The overall median KPS score of patients was 80 (ranging from 40 to 100). The most frequent primary pathology was lung cancer (45.3%) followed by breast cancer (18.2%), GI malignancy (13.2%), hepatobiliary cancer (5.7%) and others. The demographic characteristics of the patients are summarized in Table 1.

Table 1. Characteristic findings of the patients

	No.	%
Male to female ratio	58 : 48	54.7 : 45.3
Tumor volume (mean ± SD)	3,253 ± 8,994 mm^3 (1.28-158,110)	
Primary pathologies	No. of lesions	%
Lung	72	45.3
Breast	29	18.2
G-I tract	21	13.2
Hepatobiliary	9	5.7
Productive	9	5.7
Nasopharyngeal	5	3.1
RCC	2	1.3
Undertermined	8	5.0
Others	4	2.5
Sum	159	100
Number of metastases	No. of lesions	%
Single	38	35.8
Multiple		
2-3	26	24.5
> 3	42	39.7
Sum	106	100

ca : cancer, No : number, G-I : gastro-intestinal, RCC : renal cell carcinoma, SD : standard deviation

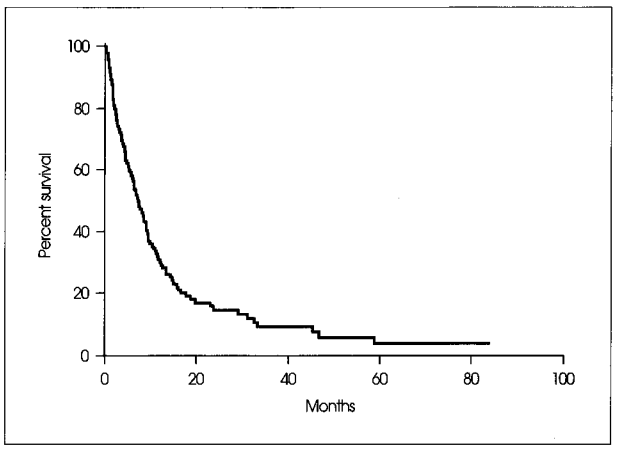

Fig. 1. Overall survival. Median survival = 7.3 months (n = 106) (1-84.2 mos), Mean survival = 11.6 ± 14.2 months, 1-year vs. 2-year actuarial survival (%) = 31 vs. 14.4.

Stereotactic procedures

High-resolution MRI scans were obtained from all patients prior to conducting stereotactic procedures. For single session radiosurgery and where tumor volumes were less than 15 cc, a stereotactic head frame was affixed to the skull prior to the irradiation of the tumors. For larger tumors or those adjacent to critical organs, a thermoplastic mask frame was used to localize the patient during the fractionated treatment regimes. High contrast CT scans were also employed following stereotaxis for further treatment planning. Fused MRI and CT images [BrainScan® software (version 5.2)] were used to delineate tumors and ensure precise targeting. Following the treatment planning stage data was transferred directly to a work station controlling a Novalis shaped beam radiosurgical system incorporating a multileaf collimator.

Clinical evaluation and statistical analysis

Patients were evaluated according to survival time and

duration of tumor control and this was correlated with radiological data. Accurate patient data from regular follow-ups with intervals of 1-3 months over a 6 months period after radiosurgery enabled us to make reliable calculations. Some data from extended follow ups was also available. Key findings included : 1) the overall survival period correlated with treatment; 2) survival times correlated with tumor type, status of primary tumors, disseminated status, time interval of brain metastases, number of lesions treated, age, gender, and KPS score. Univariate and multi-variate analysis were performed to identify the prognostic indicators using SAS 9.1.3. The survival data were analyzed and compared with Kaplan-Meier survival curves using GraphPad Prism (version 5.02).

Table 2. Univariate statistical analysis of prognostic factors

Prognostic factors	No. of patients	Median survival (mos)	Hazard ratio (95% CI)	p-valus (log-rank)
Age (< 65 vs. > 65)	69 vs. 37	8.5 vs. 5.5	0.661 (0.42-1.05)	0.078
Sex (Male vs. Female)	58 vs. 48	6.3 vs. 8.5	0.93 (0.62-1.39)	0.696
KPS (< 70 vs. > 70)	30 vs. 76	1.7 vs. 10.22	5.09 (2.54-10.20)	< 0.0001*
No. of metastases				
< 3 vs. > 3	64 vs. 42	8.3 vs. 6.3	0.67 (0.44-1.03)	0.069
Single vs. multiple	38 vs. 68	8.8 vs. 6.5	0.72 (0.47-1.08)	0.111
Interval from primary				
diagnosis (< 24 mos vs. > 24 mos)	65 vs. 32	5.8 vs. 13.6	1.75 (1.14-2.70	0.0106*
Dissemination				
yes vs. no	32 vs. 65	7.3 vs. 7.2	1.10 (0.71-1.71)	0.6728
Pathology				
Lung vs. breast vs. others	49 vs. 17 vs. 40	8.5 vs. 5.3 vs. 5.9	Undetermined	0.815

KPS : Karnofski performance scale, No. : number

RESULTS

Analysis of survival curve and prognoses

To date the average follow-up period for all patients is 11.6 months (ranging from 0.3 to 84.2 months). In overall, 10 patients (9.4%) were alive median 23.4 months following treatment (range; 10-84.2 months) while 96 patients (90.7%) died during the follow-up period. The overall median actuarial survival time was 7.3 months from the time of first radiosurgical treatment. The 1 year and 2 year actuarial survival rates were 31% and 14.4%, respectively (Fig. 1).

Age was not a significant indicator of length of survival following treatment with patients younger than 65 years demonstrating extended survival times versus those over 65 with their median survival times being 8.5 months versus 5.5 months, respectively, that was not a statistically significant difference ($p < 0.078$, by log-rank test) (Table 2). Those with a better KPS score of over 70 showed extended survival times as compared to those with a KPS score of less than 70. Median survival time was again a statistically significant improvement; 10.2 months for patients with a KPS score of over 70 and 1.7 months respectively for those with scores of less than 70 respectively ($p < 0.0001$, by log-rank method) (Table 2, Fig. 2). In addition, there was strong correlation between lengthy survival time and controlled status of primary pathology or longer interval of brain metastases from primary cancer ($p < 0.0001$ or $p = 0.01$, respectively, by log-rank method) (Table 2).

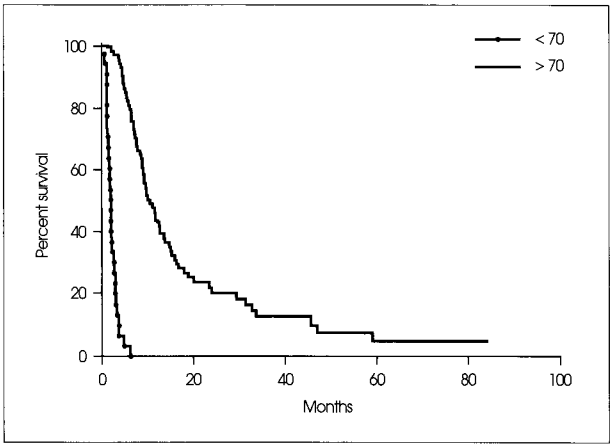

Fig. 2. Comparison of Kaplan Meier survival curve according to the initial performance status (KPS). Median survival = 1.7 vs. 10.2 mos (< 70 vs. > 70, respectively, n = 30 vs. 76, $p < 0.0001$)

Comparing RPA classification survival curves with the median length of survival was significantly different among the three groups, Class I, II, and III [31.3 months, 7.5 months and 1.7 months respectively, ($p < 0.0001$, by log-rank method)] (Table 3, Fig. 3). The 1 and 2 year actuarial survival estimates were also different for these groups, 85.2%, 17.3%, and 0% for 1 year survival versus 51.4%, 2.16% and 0% for 2 year survival. RPA class I or II was associated with significantly improved survival times (Table 3), however, there was no statistically significant correlation between extended survival times according to the sex, pathologies, disseminated status or the number of metastatic lesions (Table 2, Fig. 4). Following analysis of patients with single or multiple lesions we found that there was no statistically significant difference in overall survival periods for patients with singular, two or three metastases and those with more than three metastases, 8.8 months versus 7.1 months versus 6.3 months respectively ($p = 0.431$) indicating that SRS is a

Table 3. Patients' summary in RPA classifications

Classification	No. of patient	Median survival (mo)	1-year survival (%)	2-year survival (%)	*p*-value (log-rank)
Class I	27	31.3	85.2	51.4	
Class II	50	7.5	17.3	2.2	<0.0001*
Class III	29	1.7	0	0	

mo : month, RPA : recursive partitioning analysis, No. : number

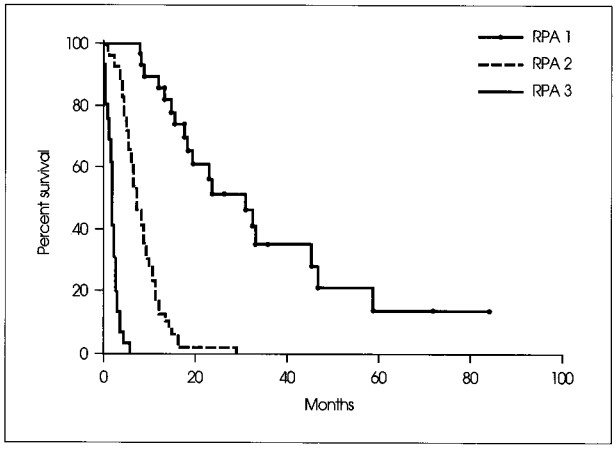

Fig. 3. Comparison of Kaplan Meier survival curve according to the recursive partitioning analysis classification. Median survival = 31.3 vs. 7.5 vs. 1.7 months, respectively (Class I, II, III), *p*-value < 0.0001 by log rank test (n = 27, 50, 29). RPA : recursive partitioning analysis.

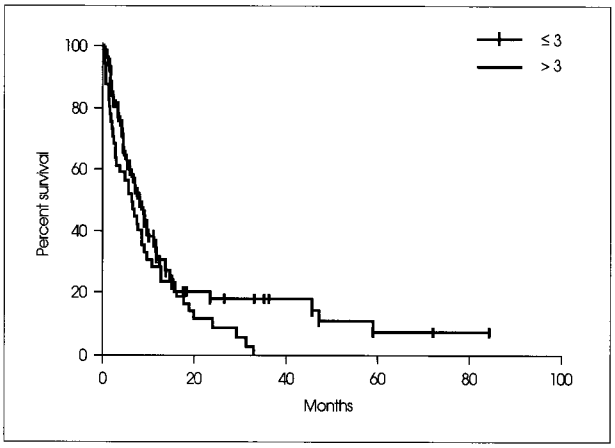

Fig. 4. Comparison of Kaplan Meier survival curve according to the multiplicity. Median survival 8.3 vs. 6.2 mos (< 3 vs. > 3, respectively, n = 64 vs. 42, *p*-value = 0.069).

viable treatment option for those groups of patient (Fig. 4). Although significant improvements in survival length were observed according to positive prognostic factors, there was no statistically significant improvement of survival time among the independent parameters in multivariate analysis (Table 4).

Local control

Among total of 159 cases, we were able to evaluate 109 cases but remaining fifty cases were unable to obtain follow-up. In most cases where we were able to complete follow-up, tumor volumes were significantly decreased and local tumor control was achieved. However, in 15 cases we saw increased tumor volume on follow-up MRI's. Among these 9 cases involved radiation necrosis with increased surrounding brain edema and required subsequent surgery. In the remaining 6 cases local tumor control was not achieved. Where local control was not achieved patients had previously received conventional radiotherapy thus limiting the doses that could be used for SRS. Overall, we were able to achieve 86.2% local tumor control.

Complications

Complications resulting from RS included a range of adverse reactions such as cerebral edema which was closely related to radiation necrosis and seizures but these usually only occurred in patients who had previously undergone RT or for tumors located in specific locations such as the parietal white matter. Sixteen patients experienced worsening neurologic symptoms associated with increased tumor mass or radiation necrosis related brain edema. In 2 cases cerebral edema related with radiation necrosis was noted 1 to 12 months after radiosurgery. Two patients had seizure following radiosurgery which were strongly related with postradiosurgical edema and necrosis or immediate post radiosurgery.

DISCUSSION

Brain metastases commonly develop in patients with a wide range of cancers. In addition, detection rates for brain metastases have also been increasing as a result of recent advances in neuroimaging techniques and cancer treatments resulting in the patients with primary cancers surviving longer[23]. Multi-modal therapies have been developed for the treatment of brain metastases[28]. As a palliative and adjuvant treatment, whole brain radiotherapy (WBRT) is a well established therapy that improves median survival times by up to 4 months[5,21]. Dose constraints for normal brain tissue limit the effective high dose irradiation.[6,10,12]. Late delayed effects such as neurocognitive dysfunctions, radiation necrosis, atrophy, leukoencephalopathy, and dementia may also appear as long as 6 months or more after WBRT and are usually irreversible and often progressive[6,10-12]. WBRT is frequently combined with surgical intervention and in our review, clinical outcomes were much better for the patient group who underwent surgery and subsequent WBRT as compared to the group who was

Table 4. Multivariate analysis of overall survival from of radiosurgery

Variables	Test for favorable status	Hazard ratio	*p*-value(log-rank)
Age	< 65 vs. > 65	5.969	0.0793
Sex	Male vs. Female	0.919	0.9409
KPS	< 70 vs. > 70	Undetermined	Undetermined
No. lesion	< 3 vs. > 3	0.615	0.7264
Interval from primary diagnosis	< 24 mos vs. > 24 mos	Undetermined	Undetermined
Disseminated status	Yes vs. No	1.234	0.8081
Pathology	Lung vs. breast vs. others	2.251	0.5446

KPS : Karnofski performance scale

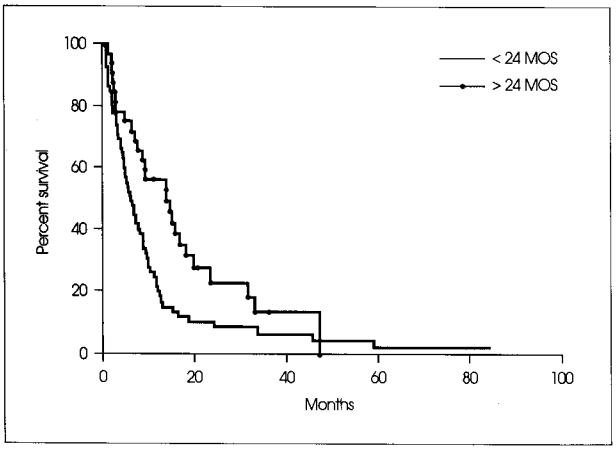

Fig. 5. Comparison of Kaplan Meier survival curve according to the time interval between diagnosis of primary cancer and brain metastases. Median survival = 5.8 vs. 13.6 mos (< 24 vs. > 24 mos, respectively, n = 65 vs. 32, *p*-value = 0.0106).

treated with WBRT only[19]. Clinical results from surgery were usually better for those patients with a single brain metastasis with an improvement in median survival times ranging from 8 to 16 months[1,13,25].

As radiosurgery has come to play an increasingly important role in treating brain metastasis, the effectiveness of WBRT has been debated[4]. Median survival times for patients treated with SRS were significantly improved to as long as between 11 to 13 months for patients with for a solitary metastasis, bringing the results for SRS in line with those achieved via surgery. Although one-year survival times were not statistically different for either the surgical resection group or the radiosurgery group, local tumor control was significantly better in patients who underwent stereotactic radiosurgery[17]. Sneed et al.[27] reported that a survival rates and the levels of effective local control in patients treated with radiosurgery alone versus those treated with radiosurgery and WBRT were the same. Their interpretation was that better local tumor control was achieved in the WBRT group, however, new metastatic lesions frequently occurred and subsequent treatment options were limited due to the radiation doses that had already been applied. Hasegawa et al.[9] reported the result of radiosurgical treatment of 172 patients with brain metastases, in which local control rates was 79% at 1 year and the median survival time was 8 months. In our experience, the selective use of high dose targeted radiosurgery without WBRT is a viable efficacious treatment for new brain metastases and results in high levels of local tumor control and provides extended survival times.

To evaluate the potential clinical outcomes and determine the optimal therapeutic option(s) for the patients with brain metastases, three major factors must be considered; 1) the extent of systemic disease dissemination, 2) the patient's functional status, 3) and the number of brain metastases[22]. Various outcome evaluation tools have been used and useful prognostic factors have been identified using retrospective analysis including the KPS score, the status of systemic disease, histology, number of metastases, volume of metastases and RPA class[4,8,24,30]. The KPS score is now established as one of the most significant prognostic factors in cancer patients[29]. Although the RPA classification is also often used to evaluate clinical results and predict the outcome for patients with brain metastases that have undergone radiation treatments[8]. The RPA system classifies patients into three groups according to the three key prognostic factors to estimate the likely impact of different treatment modalities based upon the patients' systemic conditions, age and KPS. Since the usefulness of this system is now well established it is interesting to note that there is a high degree of concurrence between our results and the results reported by others in that median survival times are significantly different among the groups of RPA class 1, 2, and 3 patients. Lutterbach et al.[16] reported the median survivals lengths of 13.4, 9.3, and 1.5 months, respectively and Andrews documented median survival times for RPA class 1, 2, and 3 patients of 16.1 months, 7.2 months, and 1.4 months, respectively[18]. In our study, we obtained very similar results indicating that reliable and predictable clinical outcomes are achievable with radiosurgery. Although multivariate analysis demonstrates that there seems to be no significant prognostic indicators, we conclude that the results of insignificance were caused by small sample size of our study.

Many reports in the literature also support the theory that repeated high dose, targeted radiosurgery is more effective in the treatment of multiple brain metastases than combined whole brain radiotherapy in terms of preventing late delayed

effects such as neurocognitive dysfunction which results in reduced overall performance (KPS) scores for the patients and reduced overall survival times. Notably in our study, there was a significant improvement in survival times in patients treated with radiosurgery for single metastases and no statistically significant difference for patients treated for two to three or three or more lesions. It has been suggested that radiosurgery may not be the treatment of choice for patients with more than three lesions and may result in poor clinical outcomes. However, Petrovich et al.[20], however, reported that the number of metastatic lesions (between one and five) had little or no influence on survival and tumor control rates. These results are also in keeping with our result and the data provided in other reports for patients with brain metastasis[2,3,7,14,15,26,31]. Many reports support that repeated radiosurgery is more effective in the treatment of multiple brain metastases than combined whole brain radiotherapy in terms of preventing late delayed effects such as neurocognitive dysfunction which causes to reduce overall performance (KPS) of the patients resulting in lessening overall survival length.

CONCLUSION

Stereotactic radiosurgery has become a treatment of choice in selected patients with newly diagnosed and/or recurrent metastatic tumors. We found that key factors for success in achieving extended life spans are age at time of diagnosis, a KPS score greater than 70, and RPA class of I or II. Following analysis of the data we conclude that for patients with multiple lesions the number of metastases have little influence on the viability of treatment and there is no statistical difference in the clinical outcomes for patients with less than three matastases or more than three lesions indicating that positive results can still be achieved for these patients.

Although further investigation is required, we believe that m-MLC mounted dedicated LINAC-based SRS is an appropriate treatment option for patients with multiple metastases and that it is not necessary to revert to WBRT with the attendant risks of short-term toxicity and long-term neurocognitive deficits. Its unique dosimetric features such as dose homogeneity and different dose fraction scheme are not included in our study. Further investigation may be necessary regarding these issues.

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