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Radiosurgery and Stereotactic Radiotherapy for Brain Metastases According the New Prognostic Indexes: our Preliminary Experience

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Abstract

Purpose: This work is a retrospective analysis of our experience in the treatment of patients with BMs using SRS or SRT with Cyberknife ® (CK) system (Accuray Inc., Sunnyvale, California, USA). The aim is to evaluate the local control of disease and overall survival according to modern prognostic indices.

Material and methods: From November 2012 to March 2014, we treated 116 patients, (178 brain metastases), with CK system, an image-guided frameless robotic SRS/SRT. We stratified the patients according to the Diagnosis-Specific GPA (DS-GPA) and we treated patients with a single fraction (10-24 Gy) in 72%, with two fractions (18-21 Gy) in 3%, with three fractions (18-24 Gy) in 23%, with five fractions (20-25Gy) in 2%. The dose was prescribed to 80% isodose line. All patients were evaluated with clinical and radiological follow-up using MRI every 2 months. We calculated the local tumor control rate according with RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

Results: Percentage of complete remission, partial remission, stable disease, was: 38% in NSCLC (Non-small-cell lung carcinoma) (16% in classes with best score), 28% in Melanoma (all in classes with best score), 52% in breast (43% in classes with best score). We noted a similar result for partial remission and stable disease, particularly in Melanoma and Breast cancer, who have a higher percentage of PR (partial response) and SD (stable disease) of 33-23%, and in Melanoma of 40-50% in classes with higher scores.

Conclusions: we confirm the precious contribution of the DS-GPA in correct selection of patients with brain metastases, and encourage the use of special technologies in properly selected patients.

Keywords: Brain metastases; Radiosurgery; Stereotactic radiotherapy; Whole brain radiotherapy; Prognostic index; Cyberknife

Introduction

Brain metastases (BMs) occur in approximately 20-40% of cancer patients. Patients with BMs typically have a poor prognosis with a median survival of 3-6 months [1-4]. Treatment options consist in whole-brain radiotherapy (WBRT), surgery, radiosurgery (SRS) and stereotactic radiotherapy (SRT) [5-9]. WBRT remains the standard of care for multiple BMs. In presence of 1-3 metastases in patients with a favorable prognosis SRS and SRT are preferred in order to preserve neurocognitive function [10-13].

The choice of treatment is based on patient factors (age, performance status), tumor factors (number and size of lesion, tumor histology, extracranial disease activity), and available treatment options (such as access to neurosurgery or stereotactic radiosurgery). For this purpose may be helpful to use a prognostic system. The most commonly used is the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA), proposed by Gaspar et al. based on the review of three RTOG studies [14,15]. The RPA stratifies patients in three prognostic categories according to age at diagnosis, absence or presence of extracranial metastases, Karnofsky Performance Status (KPS) scale, and status of the primary cancer. The median overall survival of patients with BMs ranges from 2.3 to 7.1 months according with RPA score.

A more recent analysis of the RTOG database of BMs led to the development of a revised prognostic scale called the Graded Prognostic Assessment (GPA) that is based on age, KPS, number of BMs, and presence or absence of extracranial metastases [14-16].

Than Sperduto et al reviewed the GPA in relation to primary tumor type creating a new index Diagnosis-Specific GPA (DS-GPA) [14-21].

This work is a retrospective analysis of our experience in the treatment of patients with BMs using SRS or SRT with Cyberknife ® (CK) system (Accuray Inc., Sunnyvale, California, USA). The aim is to evaluate the local control of disease according to modern prognostic indices.

Material and Methods

From November 2012 to March 2014, 116 patients (64 M and 52 F) with BMs (for a total of 178 lesions) were treated with SRS or SRT using CK. For every patient it was valuated age, KPS, primary tumor, number of brain metastases, presence of extracranial metastases and they were classified according with prognostic indexes using GPA or better DS-GPA score (Table 1).

A correct identification of volumes was performed on thin-slice contrast enhanced planning-CT scans fused with thin-section contrast enhanced MRI (Magnetic Resonance Imaging) scan. The gross tumor volume (GTV) was considered the same of clinical target volume (CTV). The planning target volume (PTV) was the CTV plus a 2-mm margin in all directions.

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GPA Significant prognostic factors	GPA scoring criteria				
NSCLC/SCLC	**0**	**0.5**		**1**	
Age	>60	50-60		<50	
KPS	<70	70-80		90-100	
ECM	Present	-		Absent	
BMs	>3	2-3		1	
Melanoma/RCC	**0**	**1**		**2**	
KPS	<70	70-80		90-100	
BMs	>3	2-3		1	
Breast cancer	**0**	**0.5**	**1.0**	**1.5**	**2.0**
KPS	<60	60	70-80	90-100	
ER/PR/Her2	Triple negative	-	ER/PR+HER2-	ER/PR-Her2+	Triple positive
Age	≥70	<70			
GI	**0**	**1**	**2**	**3**	**4**
KPS	<70	70	80	90	100

Table 1: Diagnosis-specific GPA score.

All treatments were delivered with the CyberKnife system, a frameless image-guided robotic radiosurgery system [22]. CK system consists of a small linear accelerator (LINAC, 6 MeV Photon) mounted on the robotic arm, which moves around the patient to provide a large number of beams from 1200 different positions. The X-rays are taken during treatment and are compared with the DRR (digital reconstructed radiography) of planning-CT scans to change the position of the robot according to the movement of the patient. Dose planning was performed with the Multiplan Software (Accuray Inc., Sunnyvale, CA, USA).

The treatments were delivered in 72% of cases in a single fraction (range10-24 Gy), in 3% in two fractions (range 18-21 Gy), in 23% in three fractions (range 18-24Gy), in 2% in five fractions (range 20-25Gy). The total dose and fractionation were decided according to radio-sensitivity of the primary tumor, lesion size (ranging from 1 mm to 36 mm), site of the lesion, distance from critical structures. Where the total dose was administered in several fractions, the dose of fraction was the same. The dose was prescribed to 80% isodose line. All patients were evaluated with clinical and radiological follow-up using MRI every 2 months for the first year. The clinical symptoms of the patients and a radiological measurement of lesions by MRI with contrast medium was relived.

Stratified the patients according to the Diagnosis-Specific GPA (DS-GPA), it was calculated the overall survival rate and local tumor control rate in terms of complete remission (CR), partial remission (PR), progressive disease (PD), stable disease (SD) according to Response Evaluation Criteria In Solid Tumors (RECIST criteria).

Results

The characteristics of patients are shown in Table 2. Patients, 64 M and 52 F, had median age of 62 years (range 29-86), Karnofsky performance status >70 in 97%. The most frequent primary tumor types were lung cancer (43%), breast cancer (20%) and melanoma (16%). The 55% of patients had single BM, 34% had 2-3 BMs, 11% more than 3 BMs. The majority of patient were classified with the score 1.5-2.0 (33%) and 2.5-3.0 (34%) DS-GPA. 36% of patients had no extracranial metastases. 22% have received a prior WBRT. Table 3 shows the number of patients stratified for diagnosis and DS-GPA.

The patients with at least two months of follow up (94 patients, 81% of patients treated) were evaluated for the analysis of overall survival and local tumor control rate. Ten patients were lost to follow-up (no FU), 12 patients treated too recently are non-evaluable (n-e). Table 4 shows the median of overall survival and local tumor control rate

	N°	%
Number of patients	**116**	**100%**
Gender		
M	64	55%
F	52	45%
Age		
median (y)	62	
range	29-86	
S.D.	11.69	
KPS scale		
<70	4	3%
70-80	12	10%
90-100	100	86%
DS-GPA		
3.5-4.0	29	25%
2.5-3.0	39	34%
1.5-2.0	38	33%
0-1.0	10	8%
N° of treated lesions		
1	64	55%
2	25	22%
3	14	12%
>3	13	11%
Extracranial metastatic organs		
0	42	36%
1	44	38%
≥2	30	26%
Prior WBRT	21	18%
Prior WBRT+boost	4	3%
Primary Site		
NSCLC	50	43%
SCLC	1	1%
Melanoma	18	16%
RCC	4	3%
Breast cancer	23	20%
GI cancer	7	6%
Other	13	11%

Table 2: Characteristics of patients.

	DS-GPA				
Primary tumor	**0-1.0**	**1.5-2.0**	**2.5-3.0**	**3.5-4.0**	**N° tot**
NSCLC	3(6%)	24 (48%)	18 (36%)	5 (10%)	**50**
SCLC	-	-	-	1 (100%)	**1**
Melanoma	1(5%)	1 (5%)	3(18%)	13(72%)	**18**
RCC	-	2 (50%)	2(50%)	-	**4**
Breast cancer	1 (5%)	6 (26%)	10 (43%)	6 (26%)	**23**
GI cancer	3(43%)	1 (14%)	1 (14%)	2 (29%)	**7**
Other	2 (15%)	4 (31%)	5 (39%)	2 (15%)	**13**

Table 3: Classification of patients according to Diagnosis-Specific GPA (DS-GPA).

Diagnosis	OS median (mo)	Local Tumor Control Rate							N°
		CR	PR	SD	PD	(n-e)	no FU	death	tot
NSCLC									
0-1.0	2	0	0	1(33%)	0	2(66%)	0	0	3
1.5-2.0	4(2-17)	2(8%)	5(21%)	3(13%)	3(12%)	4(16%)	3(12%)	4(16%)	24
2.5-3.0	5(2-17)	3(17%)	2(11%)	1(5%)	4(22%)	0	3(17%)	5(28%)	18
3.5-4.0	5(2-10)	1(20%)	1(20%)	0	3(60%)	0	0	0	5
SCLC									
0-1.0		0	0	0	0	0	0	0	0
1.5-2.0		0	0	0	0	0	0	0	0
2.5-3.0		0	0	0	0	0	0	0	0
3.5-4.0	4	0	0	0	0	0	0	1(100%)	1
Melanoma									
0-1.0	3	0	0	0	0	0	0	1(100%)	1
1.5-2.0	5	0	0	0	1(100%)	0	0	0	1
2.5-3.0	11(6-14)	0	1(33%)	0	1(33%)	0	0	1(33%)	3
3.5-4.0	3.5(2-5)	1(8%)	3(23%)	0	3(23%)	5(38%)	0	1(8%)	13
RCC									
0-1.0		0	0	0	0	0	0	0	0
1.5-2.0	4(3-5)	0	0	0	1 (50%)	0	0	1 (50%)	2
2.5-3.0	4.5(1-4)	0	0	1 (50%)	0	0	0	1 (50%)	2
3.5-4.0		0	0	0	0	0	0	0	0
Breast									
0-1.0		0	0	0	0	0	1(100%)	0	1
1.5-2.0	2.5(1-4)	0	1(17%)	1(17%)	0	0	0	4(66%)	6
2.5-3.0	8(4-12)	1(10%)	2(20%)	2(20%)	2(20%)	1(10%)	2(20%)	0	10
3.5-4.0	7(3-12)	2(30%)	0	3(50%)	1(20%)	0	0	0	6
GI									
0-1.0	3.0 (2-4)	0	0	0	0	0	0	3 (100%)	3
1.5-2.0	1	0	0	0	1 (100%)	0	0	0	1
2.5-3.0	6	0	0	1 (100%)	0	0	0	0	1
3.5-4.0	7(2-12)	1 (50%)	0	1 (50%)	0	0	0	0	2
Other									
0-1.0	3	0	0	1(50%)	0	0	1(50%)	0	2
1.5-2.0	2(2-10)	0	0	3(75%)	1(25%)	0	0	0	4
2.5-3.0	4(5-7)	1(20%)	1(20%)	0	2(40%)	0	0	1(20%)	5
3.5-4.0	9(6-12)	0	1(50%)	0	0	0	0	1(50%)	2

Table 4: Overall median survival and local tumor control rate stratified by diagnosis and diagnosis-specific GPA score.

stratified by diagnosis and diagnosis-specific GPA score. The analysis of response to treatment, in terms of local control (Figure 1), have shown that higher rates of complete response (CR) is recorded in classes with more favorable prognostic indexes, as in the case of NSCLC in which the complete response varies from 8% (in class with score of 1.5-2.0) to 20% (in class with score of 3.5-4.0). In Melanoma we noted a complete response rate of 8% only in the class 3.5-4.0. In Breast cancer a CR of 10-30% in the classes with best score. We registered a similar result for the partial response and stable disease to treatment, particularly in Melanoma and Breast cancer that reported 33-23% and 40-50% respectively in melanoma and breast cancer in classes with higher scores (Figure 2).

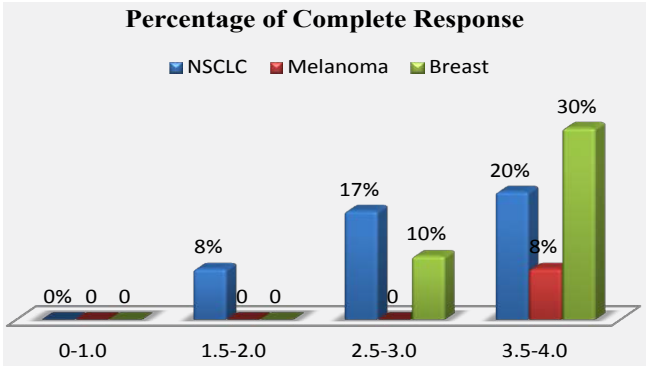

Figure 1: Percentage of complete response (CR) in NSCLC, Melanoma and Breast stratified by DS-GPA.

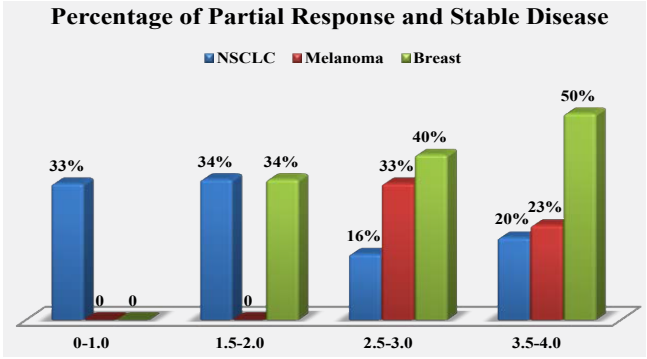

Figure 2: Sum of percentage of partial response (PR) and stable disease (SD) in NSCLC, Melanoma and Breast stratified by DS-GPA.

Discussion

Many randomized trials examining patients with 1 to 3 BMs treated with WBRT+SRS versus SRS alone, reported no difference in overall survival and an advantage on local tumor control in arm of WBRT+SRS but with a neurocognitive damage (decline in learning and memory) compared with SRS alone [10-13]. These trials concluded that in well-performing patients with stable systemic disease and 1 to 3 brain metastases, treated with initial SRS or surgery, WBRT can be omitted if serial imaging for follow up is performed [5-8].

According to these data, even in our institution after primary SRS or SRT for 1 to 4 BMs ≤ 3-4 cm, WBRT is omitted and contrast

enhancement MRI is performed every 2 months. The choice of the best treatment of patients with single or multiple BMs depends on estimated prognosis and the aims of treatment (survival, local tumor control, distant brain control, neurocognitive preservation) [20].

Because it is really difficult for physicians to accurately predict patient survival, prognostic systems may be useful.

In our experience we have not considered the RPA because based on prospective clinical trials dated considering only WBRT alone [14,15].

We prefer to stratify our patients with GPA score, primarily because it has been defined on a multi-institutional analysis of a large number of patients (4259 other) with brain metastases, and then because it also considered patients treated with surgery, WBRT, RSR, SRT or treatment combinations.

The original GPA was based on 4 criteria (age, KPS, number of brain metastases, presence or absence of extracranial metastases) and each of them is given a score of 0, 0.5, or 4 1.0. Patients with a GPA score of 4.0 had the best prognosis [17,18].

In 2010, new diagnosis-specific prognostic indices were defined using statistically significant prognostic factors [19-21]. Karnofsky performance status, age, presence of extracranial metastases, and number of BMs were the significant prognostic factors for non-small-cell lung cancer and small-cell lung cancer, as stated by original GPA. Karnofsky performance status and the number of BMs were the significant prognostic factors for melanoma and renal cell cancer. For breast and gastrointestinal cancer, the Karnofsky performance status was the only significant prognostic factor [19,20]. This new Diagnosis-Specific prognostic indices was also acquired by ASTRO guidelines [21]. Patients with BMs are a heterogeneous population; therefore, no single prognostic factor or index is appropriate for all patients with BMs.

We consider that multiple treatment options showed improved survival compared with WBRT alone in NSCLC and breast cancer, while in SCLC, WBRT remains the mainstay of therapy. Generally, surgery or SRS might be useful for patients with persistent BMs after WBRT in melanoma, while SRS alone was not significantly better than WBRT alone. Thus far in BMs from renal cell carcinoma, no treatment was significantly better than WBRT alone. In gastrointestinal cancer, the relatively small subset treated with surgery plus WBRT was the only group to do significantly better than WBRT alone [19-22]. Our experience partially confirms these trends in treatment but presents a more attention to SRS and SRT, which can be a major opportunity for these patients to delay the onset of cognitive impairment resulting from the WBRT and, at the same time, in patients without extracranial metastatic disease, SRS and SRT may allow, an improvement in survival with a good local control of the disease and an acceptable quality of life.

In our analyze we have evaluated OS that is not significant for too short follow up data due to our recent experience with CK system. On the other hand, the early data on OS relived are similar to those calculated in other studies.

The data we believe more interesting are the percentage of response in term of complete remission, partial remission, stable disease, which reaches the 38% (16% in classes with best score) in NSCLC, the 28% (all classes with best score) in melanoma, 52% (43% in the classes with best score) in breast cancer.

Conclusions

Our results confirm that the prognostic indexes, in particular of Sperduto DS-GPA, are useful for accurate patient's selection and the use of special techniques such as SRS or SRT with CK system in properly selected patients with BMs. Despite the not inconsiderable number of patients treated in only 16 months of experience with the Cyberknife system, the number of treatments is still too small to make optimal feedback. Early data encourage us to enrollment of patients for SRS or SRT with CK when appropriate.

References

1. Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neurooncol 75: 5-14.
2. Posner JB, Chernik NL (1978) Intracranial metastases from systemic cancer. Adv Neurol 19: 579-592.
3. Delattre JY, Krol G, Thaler HT, Posner JB (1988) Distribution of brain metastases. Arch Neurol 45: 741-744.
4. Nussbaum ES, Djalilian HR, Cho KH, Hall WA (1996) Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 78: 1781-1788.
5. Wong WW, Schild SE, Sawyer TE, Shaw EG (1996) Analysis of outcome in patients reirradiated for brain metastases. Int J Radiat Oncol Biol Phys 34: 585-590.
6. Kurup P, Reddy S, Hendrickson FR (1980) Results of re-irradiation for cerebral metastases. Cancer 46: 2587-2589.
7. Davey P, O'Brien PF, Schwartz ML, Cooper PW (1994) A phase I/II study of salvage radiosurgery in the treatment of recurrent brain metastases. Br J Neurosurg 8: 717-723.
8. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, et al. (2000) Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys 47:291-298.
9. van den Bent MJ1 (2003) The role of chemotherapy in brain metastases. Eur J Cancer 39: 2114-2120.
10. Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, et al. (2007) Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 68: 1388-1395.
11. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, et al. (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295: 2483-2491.
12. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, et al. (2011) Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 29: 134-141.
13. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, et al. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 10: 1037-1044.
14. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, et al. (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37: 745-751.
15. Gaspar LE, Scott C, Murray K, Curran W (2000) Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47: 1001-1006.
16. Videtic GM, Adelstein DJ, Mekhail TM, Rice TW, Stevens GH, et al. (2007) Validation of the RTOG recursive partitioning analysis (RPA) classification for small-cell lung cancer-only brain metastases. Int J Radiat Oncol Biol Phys 67: 240-243.
17. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W (2008) A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 70: 510-514.
18. Golden DW, Lamborn KR, McDermott MW, Kunwar S, Wara WM, et al. (2008) Prognostic factors and grading systems for overall survival in patients treated with radiosurgery for brain metastases: variation by primary site. J Neurosurg 109 Suppl: 77-86.

19. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, et al. (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4259 patients. Int J Radiat Oncol Biol Phys 77: 655-661.

20. Sperduto PW, Xu Z, Sneed P (2010) The graded prognostic assessment for women with brain metastases from breast cancer (GPA-Breast): a Diagnosis-Specific Prognostic Index. Int J Radiat Oncol Biol Phys 78: S6-S7.

21. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, et al. (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int. J. Radiation Oncology Biol. Phys 77: 655–661.

22. Adler JR, Chang SD, Murphy MJ, Doty J, Geis P, et al. (1997) The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 69: 124-128.