TUMOR

Validity of Prognostic Grading Indices for Brain Metastasis Patients Undergoing Repeat Radiosurgery

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Key words
- Brain metastases
- Prognostic index
- Radiosurgery
- Recurrence

Abbreviations and Acronyms
BM: Brain metastasis
BSBM: Basic Score for Brain Metastases
DS-GPA: Diagnosis-Specific Graded Prognostic Assessment
GPA: Graded Prognostic Assessment
KPS: Karnofsky Performance Status
MRI: Magnetic resonance imaging
MST: Median survival time
RPA: Recursive Partitioning Analysis
SIR: Score Index for Radiosurgery
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiotherapy

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■ OBJECTIVES: **We tested the validity of 5 prognostic indices, Recursive Partitioning Analysis (RPA), Score Index for Radiosurgery (SIR), Basic Score for Brain Metastases (BSBM), Graded Prognostic Assessment (GPA), and Modified-RPA, for patients who underwent repeat stereotactic radiosurgery (re-SRS).**

■ METHODS: **For this study, we used our database, which included 804 patients who underwent gamma knife re-SRS during the period 1998–2013.**

■ RESULTS: **There were statistically significant survival differences among patients stratified into 3 or 4 groups based on the 5 systems ($P < 0.001$). With RPA, SIR, BSBM, and the Modified-RPA, there were statistically significant median survival time (MST) differences between any 2 pairs within the 3/4 groups. With the GPA system, however, the MST difference between the GPA 3.5–4.0 and GPA 3.0 groups did not reach statistical significance ($P = 0.48$). There were large patient number discrepancies among the 3/4 groups in the RPA, SIR, BSBM, and GPA whereas patient numbers were very similar among the 3 Modified-RPA system groups. Our present results show the RPA and BSBM systems to reflect changes less well, with 86%–95% of patients remaining in the same categories between the first and second SRS procedures. However, with SIR, GPA, and the Modified-RPA, 25%–31% of patients were categorized into different subclasses, either better or worse. With the modified-RPA system, such categorical change correlated well with post-re-SRS MSTs.**

■ CONCLUSIONS: **Among the 5 systems, based on patient number proportions, MST separation among the 3/4 groups, and/or detailed reflection of status changes, the Modified-RPA system was shown to be most applicable to re-SRS patients.**

INTRODUCTION

Stereotactic radiosurgery (SRS), with or without whole-brain radiotherapy (WBRT), has emerged as an important modality for managing patients with newly diagnosed brain metastases (BMs). Aoyama et al's (1) randomized controlled trial comparing treatment results between SRS plus WBRT and SRS alone groups indicated the former to be superior to SRS alone for suppressing newly appearing tumors, although there was no significant median survival time (MST) difference between the 2 groups. Debate persists, however, as to whether WBRT is necessary for all patients with BMs. The primary argument against WBRT stems from the risk of deterioration of neurocognitive function, which cannot be ignored in long-surviving patients (2). Second, because WBRT generally is considered to be unrepeatable, the availability of an alternative treatment for BMs allows WBRT to be reserved for subsequent treatment attempts, i.e., in cases with meningeal dissemination or miliary metastases for which only WBRT is effective. Therefore, an increasing number of patients with BM have been treated with SRS alone.

In patients with BM who undergo SRS alone, new BMs inevitably appear with relatively high incidences during post-SRS follow-up. Hanssens et al (7) recently reported that, using high-performance magnetic resonance imaging (MRI), new tumors were diagnosed in 40% of 835 patients with BM who had undergone SRS alone. Recently published studies based on more than 1000 patients with BM treated with SRS alone disclosed that re-SRS for new tumors was required in 22%–34% of all cases (9, 17, 18, 34). Several retrospective studies, based on relatively small patient numbers, have documented re-SRS to be safe and effective (3, 13, 19, 28). However, although the 5 prognostic grading indices discussed herein for initially treated patients with BM are well established (5, 15, 20, 27, 31, 34, 36), none was developed for or has yet been validated in the re-SRS setting.

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The goal of this retrospective cohort study, based on our SRS-treated patients with BM, was to reappraise whether 5 previously proposed prognostic indices are generally applicable or can be recommended for historical comparison. These 5 indices are Recursive Partitioning Analysis (RPA) (5), Score Index for Radiosurgery (SIR) (27), Basic Score for Brain Metastases (BSBM) (15), Graded Prognostic Assessment (GPA) (20), and our Modified-RPA (31, 34, 36), as outlined in Table 1.

MATERIAL AND METHODS

Study Population

This was an institutional review board–approved, retrospective cohort study using our prospectively accumulated database including 2825 consecutive patients who underwent SRS alone using a Gamma Knife, without WBRT, for BMs at the Katsuta Hospital Mito GammaHouse during the 15-year-period between July 1998 and June 2013 (Tokyo Women's Medical University; institutional review board #1981). Among the 2825 patients, excluding 37 patients who underwent WBRT before SRS, we studied 804 (28.5%) undergoing re-SRS mostly for newly developed lesions only (682 patients, 84.8%) and, uncommonly, recurrence of treated lesions (122, 15.2%). Table 2 summarizes clinical characteristics before re-SRS.

All patients had been referred to us for SRS by their primary physicians. Therefore, patient selections had mostly been made outside of our facilities. Patient selection criteria may well have differed somewhat among the referring physicians. Therefore, the first author (M.Y.) ultimately decided whether a patient would be accepted for SRS in all cases. We did not perform SRS on patients with low Karnofsky Performance Status (KPS) scores (10) attributable to systemic diseases, patients who were noncooperative due to poor neurocognitive function, who had meningeal dissemination, and/or who had an expected survival period of 3 months or less. Therefore, only 4.2% of the 804 patients were categorized into RPA class 3 (5). Also, the treating physicians responsible for each patient decided the indications for both surgery and radiotherapy.

The treatment strategy was explained in detail to each patient and at least one of their adult relatives by the first author (M.Y.), and written informed consent was obtained from all patients before SRS. Because our previous report described our radiosurgical techniques in detail, they are not repeated herein (33, 34).

Table 1. Outline of Reported Grading Indices for Patients with Brain Metastases (BMs)

Recursive Partitioning Analysis (RPA) (5)

Class 1	Age <65 years
	KPS ≥70%
	Controlled primary tumor
	No extracranial metastases
Class 2	All patients not in Class I or III
Class 3	KPS <70%

Subclassification System of RPA Class II Patients (31, 36)

	Scoring Criteria 0	Scoring Criteria 1
KPS (%)	90–100	70–80
No. of BMs	1	≥2
Controlled primary tumor	Yes	No
Extracranial metastases	No	Yes

Grading Criteria

0 or 1	2	3 or 4
RPA Class 2a	RPA Class 2b	RPA Class 2c

Modified-RPA (15)	Grading Criteria
Modified RPA class 1+2a	Original RPA class 1 and Subclass 2a
Modified RPA class 2b	Subclass 2b
Modified RPA class 2c+3	Subclass 2c and original RPA class 3

Score Index for Radiosurgery (SIR) (27)

	SIR Scoring Criteria 0	1	2
Age	≥60	51–59	≤50
KPS (%)	≤50	60–70	80–100
Systemic disease	Progressive	Stable	CR or NED
No. of BMs	≥3	2	1
Volume (mL) of largest BM	>13	5–13	<5

Continues

Table 1. Continued

Basic Score for Brain Metastases (BSBM) (15)

	BSBM Scoring Criteria 0	1
KPS (%)	50–70	80–100
Control of primary tumor	No	Yes
Extracranial metastases	Yes	No

Graded Prognostic Assessment (GPA) (34)

	GPA Scoring Criteria 0	0.5	1
Age	>60	50–60	<50
KPS (%)	<70	70–80	90–100
Extracranial metastases	Present	–	Absent
No. of BMs	>3	2–3	1

KPS, Karnofsky Performance Status (10); CR, complete response; NED, no evidence of disease.

Patient Selection Criteria for re-SRS

For patients developing new BMs after the first SRS, our approach is similar to that in patients with initially diagnosed BMs. As to tumor size, if follow-up MRI demonstrates a tumor with a diameter of 2–3 mm in the brainstem or optic apparatus, we perform re-SRS without further observation. Otherwise, re-SRS usually is postponed with close MRI follow-up until the tumor diameter exceeds approximately 1 cm.

Generally, local recurrence criteria were increased size of an enhanced area on postgadolinium T1-weighted MRI and enlarged tumor core on T2-weighted MRI (more than 10% increase in the maximum diameter). However, in cases in which MRI alone was not sufficient to confirm recurrence, positron emission tomography with