

Stereotactic radiosurgery in the management of brain metastases: could it thoroughly replace whole brain radiotherapy?

Radiocirurgia estereotáctica no manuseio de metástases cerebrais: pode ela substituir completamente a radioterapia de todo o cérebro?

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ABSTRACT

A treatment relying solely on stereotactic radiosurgery (SRS), with the omission of whole brain radiotherapy (WBRT), is now increasingly applied to the patients with brain metastases that are limited in number, however, it has not been reached a general agreement if patients really receive benefit from this strategy. In response to this situation, we, Japanese Radiation Oncology Study Group (JROSG), carried out a prospective randomized control trial in which SRS-alone approach was compared with WBRT+SRS for patients with 1-4 brain metastases. This study proved that there was no significant difference in survival, mode of death (neurologic versus systemic), and functional preservation rate between two treatment arms. However, the omission of WBRT significantly increased the frequency of brain tumor recurrence, and as a result, salvage brain treatments were more frequently required among patients allocated to SRS-alone arm. In the analyses of neurocognitive function, it was shown that the brain tumor recurrence as well as late radiation toxicities could be a cause of the deterioration of neurocognitive function. Those results indicate that SRS-alone treatment can be a treatment option for 1-4 brain metastases, however frequent monitoring of the brain tumor status should be warranted in order to detect recurrence of brain metastases before they became symptomatic.

Key-words: Brain metastasis, Radiosurgery, Whole brain radiotherapy.

SUMÁRIO

A abordagem terapêutica baseada somente na radiocirurgia estereotática (SRS), com omissão da radioterapia de cérebro total (WBRT), está sendo cada vez mais utilizada em pacientes com metástases cerebrais, entretanto, não há um consenso geral se os pacientes realmente se beneficiam desta estratégia. Em resposta a esta questão, o Grupo Japonês de Estudos em Radioterapia (JROSG) conduziu um estudo prospectivo randomizado no qual a abordagem com SRS isolada foi comparada com WBRT + SRS em pacientes com 1-4 metástases cerebrais. Este estudo evidenciou que não houve diferença significativa na sobrevida, forma de mortalidade (neurológica versus sistêmica), e taxa de preservação funcional entre os dois grupos de tratamento. Entretanto, a omissão de WBRT aumentou significativamente a frequência de recorrência de metástases cerebrais, e como resultado, tratamentos “de resgate” foram mais frequentemente necessários entre pacientes submetidos a SRS isolada. Na análise da função neurocognitiva, foi demonstrado que a recorrência de metástases cerebrais bem como a toxicidade tardia da radiação podem ser a causa da deterioração da função neurocognitiva. Estes resultados indicam que o tratamento com SRS isolada pode ser uma opção em pacientes com 1-4 metástases cerebrais, entretanto a monitorização frequente da doença metastática cerebral deve ser mandatária no sentido de detectar metástases cerebrais recorrentes antes que elas se tornem sintomáticas.

Palavras-chave: Metástases Cerebrais, Radiocirurgia Estereotática, Radioterapia de cérebro total.

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INTRODUCTION

Brain metastases are commonly observed in cancer patients and usually related to poor prognosis. It is considered that the median survival is around 1-2 months with best supportive care only and is around 4 months after whole brain radiotherapy (WBRT). Stereotactic radiosurgery (SRS) has a potential to prolong survival when combined with WBRT for patients with solitary brain metastasis. Because the route of dissemination to the brain is hematogenous, it is logical to think that entire brain is "seeded" with micrometastases. As a result, whole brain radiation therapy (WBRT) has been a mainstay in the treatment strategy for brain metastases for a long while. However, deterioration of neurocognitive function as a result of late radiation toxicity after WBRT among long term survivors has been a matter of concern.

In early 1990's, a number of gamma knife units were installed in Japan, especially around Tokyo area. Since then, SRS-alone approach became widespread and dealt as new standard treatment for patients with brain metastases. Because of the lack of level 1 evidence to support this treatment, we, radiation oncologists in Japan, recognized the need for the prospective randomized comparison study between WBRT+SRS and SRS-alone and the study entitled Japanese Radiation Oncology Study Group Protocol 99-1 (JROSG99-1) was launched in 1999. In this study, we examined not only patient's survival, as a primary endpoint, but also neurocognitive function was monitored by means of Mini-Mental Score Examination (MMSE). To date, it is the only phase III study comparing these strategies. In this article, the results of JROSG99-1 are summarized and then the current status of SRS-alone policy will be discussed.

SUMMARY OF JROSG 99-1: PROSPECTIVE RANDOMIZED COMPARISON BETWEEN WBRT PLUS SRS AND SRS ALONE¹

Patients with 1–4 brain metastases, each 3 cm or less in diameter were randomized to WBRT plus SRS (n = 65) or SRS alone (n = 67). The dose of WBRT was 30 Gy given in 10 fractions over a 2–2.5 week period. For metastatic lesions up to 2 cm and greater than 2 cm in diameter, the SRS doses were 22–25 Gy and 18–20 Gy, respectively. In patients undergoing WBRT+SRS, the SRS dose was reduced by 30%. The primary endpoint was overall survival. The median survival time did not differ significantly (P = 0.42) between the two treatment groups (WBRT plus SRS, 7.5 months; SRS alone, 8.0 months). The brain tumor recurrence rate was, however, significantly higher in patients who received SRS alone (P < 0.001) and more patients in the SRS group had developed new brain metastases than those in the combined therapy group (P = 0.003). The

12-month actuarial rate of developing new brain metastases was 41.5% in the WBRT+SRS arm and 63.7% in the SRS-alone arm. Multivariate analyses revealed a significantly reduced risk of tumor recurrence (P < 0.001) in patients who underwent WBRT plus SRS. Among other factors, the number of brain metastases (1 vs. 2-4) was related to a significant reduction of brain tumor recurrence in univariate analyses (Figure 1). Salvage treatment for progression of brain tumor was required more frequently in the SRS-alone (29 patients) than in the WBRT+SRS arm (10 patients) (P < 0.001). However, there was no difference in the mode of death in two arms. Death was attributed to neurologic causes in 13 patients (22.8%) in the WBRT+SRS arm and in 12 patients (19.3%) in the SRS-alone arm (P = 0.64). Symptomatic acute neurologic toxicity was observed in 4 patients in the WBRT+SRS arm and in 8 patients in the SRS-alone arm (P = 0.39) including 1 and 2 Grade 3 toxicity, respectively, in each arm.

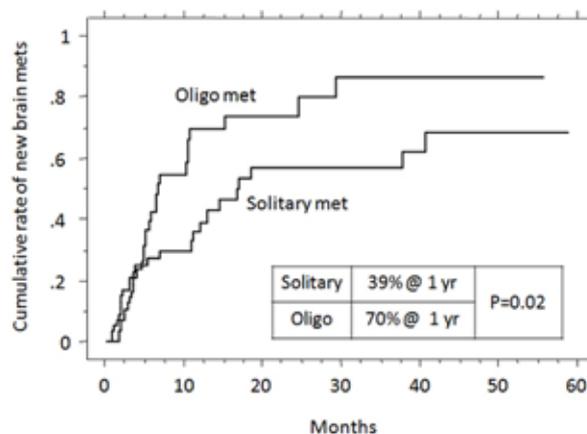


Figure 1. Cumulative incidence of the development of new brain metastases of patients presented with solitary metastasis and oligo metastases.

ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER WBRT+SRS VERSUS SRS ALONE IN JROSG 99-1²

Neurocognitive function was optionally assessed by means of Mini-Mental Score Examination (MMSE) in 110 patients out of 132. In the baseline MMSE analyses, a statistically significant difference was observed for total tumor volume, extent of tumor edema, age, and KPS. Among 92 patients who received follow-up MMSE, 39 patients had a baseline MMSE of 27 or lower (17 in the WBRT+SRS, 22 in SRS-alone). An improvement of ≥ 3 points in the MMSEs of 9 patients in the WBRT+SRS and 11 in the SRS-alone (P = 0.85) was observed. Among eighty-two patients who had baseline MMSEs ≥ 27 or

whose baseline MMSE was ≤ 26 but improved to ≥ 27 after the initial brain treatment, 12-, 24-, and 36-months' actuarial free rates of the 3-point drop of MMSE were 76.1%, 68.5%, and 14.7% in the WBRT+SRS. They were 59.3%, 51.9%, and 51.9% in SRS-alone. The average duration until the deterioration was 16.5 months in WBRT+SRS and 7.6 months in SRS-alone ($P=0.05$). Therefore, we thought that the control of the brain tumor, as well as the avoidance of late radiation toxicities, might be an important factor for stabilizing neurocognitive function for brain metastatic patients.

DISCUSSION

In 1990's, the role of surgery was investigated in three randomized trials comparing Surgery + WBRT and WBRT alone (TABLE 1). In the first trial authored by Patchell et al., 48 patients with solitary brain metastasis were randomized to Surgery + WBRT ($n=25$) or WBRT alone ($n=23$)⁷. Surprisingly, the median survival of participants in Surgery + WBRT was 40 weeks as compared to only 15 weeks ($p<0.01$). The neurologic death was more frequent in WBRT alone group (50%) as compared to 29% in Surgery + WBRT. Noordijk et al.⁵ and Mintz et al.⁴ conducted similarly designed randomized trial with 63 patients and 84 patients respectively. In the Noordijk's study, median survival times of Surgery + WBRT and WBRT alone were 10 months and 6 months ($p=0.04$) respectively. However, in the Mintz's study with largest patients number in this comparison setting, there was no difference in median survival; 6.3 months in Surgery +WBRT versus 5.6 months in WBRT alone (NS). Therefore, it is considered that the role of surgery for single brain metastatic patients, specifically in terms of prolongation of survival time, still remained controversial.

Table 1. Summary of Randomized Trials of Brain Metastases

Author	Year	Journal	Treatment	n	Median Survival	P	Neuro-logic death
Patchell ⁹	1990	NEJM	WBRT + Surg.	25	40 weeks	<0.01	29%
			WBRT	23	15 weeks		50%
Noordijk ⁴	1993	Cancer	WBRT + Surg.	32	10 months	0.04	35%
			WBRT	31	6 months		33%
Mintz ⁵	1996	Ann Neurol	WBRT + Surg.	41	6.3 months	NS	46%
			WBRT	43	5.6 months		63%
Andrews ⁷	2004	Lancet	WBRT + SRS	164	6.5 months	0.13	--
			WBRT	167	5.7 months		--
Patchell ⁶	1998	JAMA	WBRT + Surg.	49	48 weeks	0.39	14%
			Surg.	46	43 weeks		44%

Aoyama ¹	2006	JAMA	WBRT + SRS	65	7.5 months	0.43	19%
			SRS	67	8.0 months		23%

In 1998, a group in United States reported the results of prospective randomized comparison between surgery only and surgery followed by WBRT for solitary brain metastatic patients⁶. They reported that 1) no survival advantage by the use of WBRT was observed, 2) brain tumor recurrence was more frequently observed in surgery only arm compared to patients in surgery + WBRT arm (70% versus 18%, $p<0.001$), 3) death attributed to neurological causes were more frequent among patients in surgery only arm than in surgery + WBRT arm (44% versus 18%, $p<0.001$). Another important publication from United States is multi-institutional prospective randomized study of WBRT alone versus WBRT+SRS conducted by Radiation Therapy Oncology Group (RTOG 9508)¹. Three-hundred thirty three patients with 1-3 brain metastases were randomized to WBRT alone (167 patients) or WBRT + SRS boost (164 patients). Although they did not find significant difference in survival in analyses of all participants, they did find a statistically significant difference in survival in analyses including patients with solitary metastasis only (median survival, 6.5 months versus 4.9 months). Based on the results of those RCTs, WBRT with or without focally aggressive treatments including SRS or surgical resection has been established as a standard treatment in the United States.

On the other hand, treatment strategy relying on SRS is now becoming new standard in Japan as mentioned before. Presumably it is because the availability of SRS is totally different from other parts in the world. It is reported that approximately 25% of gamma knife is installed in Japan, and the majority of them are around Tokyo area. However, it was found in JROSG 99-1 that the risk of brain tumor recurrence was high when WBRT was omitted and approximately half of the patients who received SRS-alone for the initial brain management required salvage brain treatment². More importantly, this frequent brain tumor recurrence was strongly associated with the deterioration of neurocognitive function³. Therefore, it will be crucial to recognize the importance of the follow-up MRI (at least once in every 3 months) in order to maximize the merit of SRS-alone approach, which is the avoidance of potential late radiation toxicities resulting from WBRT.

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