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Radiation Therapy for Intracranial Germ Cell Tumors

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Abstract

Although radiation therapy (RT) is essential to the management of intracranial germ cell tumors, the ideal radiation dose and field remain controversial. For the treatment of germinoma, whole central nervous system radiation, which was once the standard RT field, is being replaced by whole ventricle (WV) field radiation for localized disease. The use of induction chemotherapy has been expected to further reduce the RT field and dose; however, use of a localized field smaller than the WV field has resulted in a higher recurrence rate. Therefore, the WV field should be considered appropriate even after induction chemotherapy. With regard to the radiation dose to the primary tumor site, it can be reduced to 40–45 Gy in RT alone. The further reduction of the radiation dose when using a combination of chemotherapy and RT is yet to be determined. Unlike germinomas, nongerminomatous germ cell tumors, with the exception of mature teratomas, are refractory to conventional RT. The whole central nervous system field should thus be used for all but immature teratomas. Given that local progression is the primary pattern of recurrence even after effective induction chemotherapy, RT dose increase through the use of modern techniques, including stereotactic irradiation and intensity-modulated RT, should be investigated.

Primary central nervous system (CNS) germ cell tumors (GCTs) are rare, accounting for 1–2% of all brain tumors and for 3–10% of brain tumors in children. Approximately half occur in the pineal region. The second most predominant site is the neurohypophyseal region. Multifocal presentation in these regions is occasionally seen. Among intracranial GCTs, approximately 60% are germinomas [1–4]. Radiation therapy (RT) plays a primary role in the treatment of germinomas and a 90–100% curative rate can be expected after RT alone [1–4]. On the other hand, nongerminomatous GCTs (NGGCTs) are generally aggressive and most patients with nongerminomatous tumors treated conventionally with surgery and RT fail to survive longer than 3 years [1].

Table 1. Germinoma–WCNS RT

First author	Patients		Radiation dose, Gy					Follow-up years	Outcomes, %		Relapses	
	All	with Spinal dissemination	WONS	WB	WV	Primary	Dose per fraction		OS	RFS	All	Spinal W/Wo others
■■■	11	0	36	–	–	50	1.8	9.8	100(5)	100(5)	0 (0%)	0 (0%)
Bamberg [5]	49	0	30	–	–	50	1.5	7.4	92 (5)	87 (5)	5 (10.2%)	1 (2%)
Maity [6]	39	13	30.6	36	–	50.4	1.8	7.1	100 (10)	100 (10)	0 (0%)	0 (0%)
Merchant [7]	12	1	25.6	–	–	50.4	1.5–1.8	5.8	100	100	0 (0%)	0 (0%)
Schoenfeld [8]	31	0	21	–	30	49.5	1.5	7.0	88 (10)	94 (10)	2 (9.5%)	0 (0%)

Figures in parentheses in the outcomes columns indicate years.

Treatment of Intracranial Germinoma

Reduction of Whole Central Nervous System Dose

Historically, whole CNS (WCNS) radiation followed by a local boost has been the standard treatment for intracranial germinomas. Radiation doses of 30–36 Gy to the WCNS and 50 Gy to the primary tumor site have frequently been used. Although this treatment schedule has achieved a satisfactory outcome, several investigators have tried to reduce the dose of RT to the WCNS. A German multi-institutional prospective trial (MAKEI 83/86/89) assessed whether the dose to the WCNS could be reduced in an RT alone approach [5]. They initially used 36 Gy to the WCNS and then reduced this dose to 30 Gy. They observed only 1 recurrence within the CNS. Several others investigators assessed the possibility of reducing the WCNS dose to 30.6 Gy, 25.6 Gy, or 21 Gy [6–8]. The results of these attempts are summarized in table 1. The long-term relapse-free survival (RFS) and overall survival (OS) rates were 87–100% and 88–100%, respectively. It is notable that spinal failure was observed in only 1 case, which was treated with 30 Gy to the WCNS. Thus, it could be said that the prophylactic WCNS radiation dose could be reduced to around 21–25 Gy without increasing the risk of spinal relapses.

Attempts to Reduce the Radiation Field and Dose to the Primary Site

Despite the excellent outcome of tumor control with a WCNS RT approach, radiation-induced late sequelae have been a matter of concern. Reductions of

Table 2. Germinoma–Neoadjuvant chemotherapy followed by Focal Radiation

First author	Year	Patients	RT dose, Gy	Follow-up years	Outcomes, %		Relapses	
					OS	RFS	All	Spinal w/ wo others
Aoyama [14]	2002	28	24 (Focal)	4.8	93.8 (5)	66 (5)	6 (21%)	2 (7%)
Lafay-Cousin [12]	2006	6	24-40 WV	4	100	100	0 (0%)	0 (0%)
Bouffet [20]	1999	57	40 (Focal)	3.5	98 (3)	96.4 (3)	4 (7%)	2 (4%)
Matsutani [24]	2001	75	24 (Focal)	2.9	ND	ND	9 (12%)	ND
Nguyen [16]	2006	9	30.6 (Focal)	7.8	89 (10)	62/42 (5/10)	4 (44%)	2 (2%)

ND = Not documented
Figures in parentheses in the outcomes colums indicate years.

the radiation field and dose have been investigated in the context of RT alone or a combination treatment using chemotherapy and RT (table 2). Ogawa et al. [9] assessed the relationship between radiation field and treatment outcome in a review of 126 patients with intracranial germinoma who were treated by RT alone. More than half of the patients were treated with a whole brain (WB) radiation field, while a WCNS field was used only for 56 patients (44%). It is noteworthy that the incidence of spinal relapses was 4% (2 of 56) for patients treated with spinal irradiation and 3% (2 of 70) for those without spinal irradiation. Shirato et al. [10] reviewed 51 patients with germinoma treated by RT alone. The radiation field was the WCNS in 16, WB in 9, whole ventricle (WV) in 21, and local field without ventricle coverage in 5 patients. The 10-year cause-specific survival rates for pathologically verified and unverified germinomas were 100 and 96%, respectively. No relapse was noted in patients in whom the WV field radiation was used. They concluded that 40 Gy WV irradiation is appropriate for most intracranial germinomas. Haas-Kogan et al. [11] analyzed 41 cases of localized germinoma patients and reached a similar conclusion. Of 41 localized germinoma patients, 18 patients were treated with WV field radiation with a median dose of 32.4 Gy. None of them experienced tumor recurrence. Lafay-Cousin et al. [12] examined whether bifocal germinomas could be treated with chemotherapy followed by WV field radiation. The radiation field was WV with or without a boost to the primary tumor locations. All patients remain in complete remission at a median follow-up of 48.1 months. The authors suggested that bifocal germinoma can be considered a loco-regional rather than a metastatic disease and could be treated with WV RT. The use of an RT field smaller than the WV has been mainly investigated for the

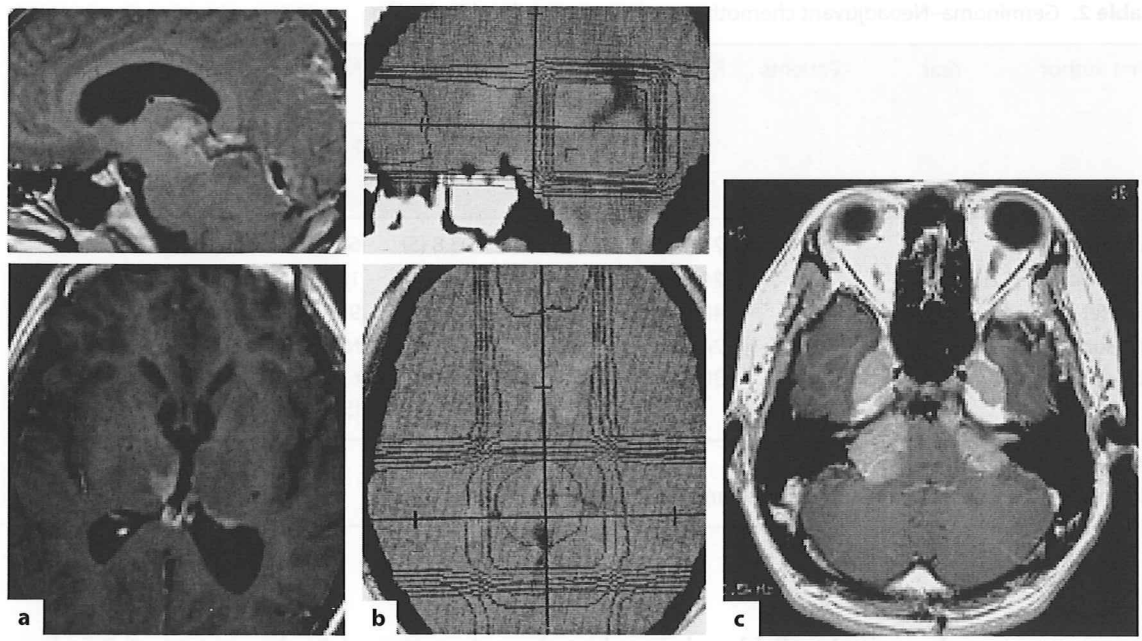

Fig. 1. Pineal germinoma treated with cisplatin-etoposide followed by focal radiation of 24 Gy. **a** Enhanced MRI after surgery. **b** Dose distribution of focal RT. **c** Tumor recurrence developed 34 months after treatment. The patient was successfully treated with WCNS radiation, and remains free of recurrence.

combination approach of induction chemotherapy and RT. A Group at Hokkaido University conducted a prospective study aimed at reducing the RT volume and dose after 3–4 cycles of cisplatin-based induction chemotherapy [13, 14]. Twenty-five patients with intracranial germinoma were enrolled in the protocol treatment. The actuarial survival rate and progression-free survival rate were 93.8 and 66%, respectively. Recurrence of disease was observed in 6 patients. The reason for these recurrences was examined in detail [15], and it was determined that all the relapses occurred in patients who received focal irradiation without WV coverage (fig. 1), while there were no relapses among those treated with a wider safety margin. Nguyen et al. [16] retrospectively compared 9 patients treated with neoadjuvant chemotherapy and focal radiation (median, 30.6 Gy) and 12 patients who received WCNS (median, 24 Gy) and a local boost up to 50 Gy. All 4 tumor recurrences occurred among those who received neoadjuvant chemotherapy and focal radiation. The 10-year progression-free survival was 41.5% in the focal radiation group versus 100% in the WCNS group. The rate of distant control in the spine at 5 years was 62% for patients who received focal irradiation and 100% for patients who received WCNS radiation ($p = 0.04$). The relation between the radiation field and pattern of recurrence in publications is summarized in table 3 [5–20]. The

Table 3. Germinoma–Radation field and Pattern of recurrences

First author	Year	RT field	Protocoled chemotherapy	Patients	Total relapses	Failure at spine w/wo other sites
Bamberg [5]	1999	WCNS	No	60	5 (8%)	1 (1.6%)
Maity [6]	2004	WCNS	No	39	0 (0%)	0 (0%)
Merchant [7]	2000	WCNS	No	12	0 (0%)	0 (0%)
Schoenfeld [8]	2006	WCNS	No	31	2 (6%)	0 (0%)
Ogawa [9]	2004	WCNS	No	56	3 (5%)	2 (3.5%)
Haddock [17]	1997	WCNS	No	10	0 (0%)	0 (0%)
Aoyama [18]	1998	WCNS	No	23	2 (9%)	0 (0%)
Shirato [10]	1997	WCNS	No	16	1 (6%)	0 (0%)
Shibamoto [19]	2001	WCNS	No	25	1 (4%)	0 (0%)
Shirato [15]	2004	WCNS	Yes	3	0 (0%)	0 (0%)
Nguyen [16]	2006	WCNS	No	12	0 (0%)	0 (0%)
				287	**14 (4.8%)**	**3 (1%)**
Ogawa [9]	2004	WB	No	62	3 (5%)	2 (3.2%)
Haddock [17]	1997	WB	No	10	1 (10%)	0 (0%)
Aoyama [18]	1998	WB	No	10	2 (20%)	1 (10%)
Shirato [10]	1997	WB	No	9	0 (0%)	0 (0%)
				91	**6 (6.5%)**	**3 (3.2%)**
Ogawa [9]	2004	WV	No	2	1 (50%)	0 (0%)
Shirato [10]	1997	WV	No	21	2 (10%)	1 (5%)
Haas-Kogan [11]	2003	WV	No	18	0 (0%)	0 (0%)
Shirato [15]	2004	WV	Yes	6	0 (0%)	0 (0%)
Lafay-Oousin [12]	2006	WV	Yes	6	0 (0%)	0 (0%)
				53	**3 (5.6%)**	**1 (1.8%)**
Ogawa [9]	2004	Focal	No	6	3 (50%)	0 (0%)
Haddock [17]	1997	Focal	No	11	5 (45.4%)	4 (36.3%)
Aoyama [18]	1998	Focal	No	8	5 (62.5%)	1 (12.5%)
Shirato [10]	1997	Focal	No	5	2 (40%)	1 (20%)
Haas-Kogan [11]	2003	Focal	No	3	1 (33.3%)	0 (0%)
Shibamoto [19]	2001	Focal	No	13	1 (7.6%)	0 (0%)
Shirato [15]	2004	Focal	Yes	18	6 (33.3%)	2 (11%)
Bouffet [20]	1999	Focal	Yes	57	4 (7.0%)	2 (3.5%)
Nguyen [16]	2006	Focal	Yes	9	4 (44.4%)	3 (33.3%)
				130	**31 (23.8%)**	**13 (10%)**

overall recurrence rates are around 5% when the WCNS, WB, or WV fields are used, whereas they range from 7 to 62% (mean, 23.8%, 31/130) and exceed 30% in most series when a focal field is used. The frequency of spinal failure with or without failure at other sites is about 1–3% when WCNS, WB, or WV fields are used, whereas it is significantly increased to 10% or more (range 0–36) when a focal field is used. Therefore, the radiation field could be reduced from WCNS to WV without deterioration of the frequency of tumor recurrence. However, an RT field smaller than the WV might result in a significant increase in tumor recurrence even after effective induction chemotherapy.

With regard to radiation dose, Shibamoto et al. [19] prospectively investigated the possibility of radiation dose reduction to 40–45 Gy for germinomas smaller than 4 cm. Although 2 patients developed meningeal dissemination, none had local failure. In the series of induction-chemotherapy followed by RT, The French Society for Pediatric Oncology (SFOP) used 40 Gy to the initial tumor volume and treated 59 germinoma patients [20]. After a median follow-up of 42 months, 4 recurrences of disease were observed. The 3-year actuarial progression-free survival was 96.4%. Lafay-Cousin et al. [12] used 24–40 Gy WV field RT and no recurrence was observed among 18 patients for 4 years. The Hokkaido University Group used 24 Gy to the primary tumor site. Although 6 recurrences were observed, these recurrences had more to do with the radiation field. That is, all the recurrences were seen among the 16 patients treated with a localized field, and no relapses were seen in the 9 patients treated with WV (24 Gy) or WCNS (24 Gy). Based on these findings, it is still unclear whether a radiation dose lower than 40 Gy can be safely used even after effective induction chemotherapy [13–15].

Nongerminomatous Germ Cell Tumors: Prognosis after a Conventional Approach

Unlike germinomas, the treatment outcomes of NGGCTs are less than satisfactory (table 4). With the exception of mature teratomas, NGGCTs are generally refractory to treatment: most patients with NGGCTs treated conventionally with surgery and RT fail to survive longer than 3 years [1]. Spinal dissemination is more common than in germinomas and systemic metastases, especially to the lung and bone, and occurs in 3% of patients [1]. In a review by Sawamura et al. [2] of 111 cases treated at Hokkaido University, the probability of 10-year survival was 67% for immature teratomas, but only 25% for GCTs that included a highly malignant component. In a review of 153 histologically verified GCTs by Matsutani et al. [3], the 10-year survival rates of patients with mature teratomas and malignant teratomas were 92.9 and 70.7%, respectively, whereas those with pure malignant GCTs (embryonal carcinoma, yolk sac tumor, or choriocarcinoma) had a 3-year

Table 4. NGGCTs, Prognosis

First author	Patients	Pathology	Follow-up years	OS, %	Recurrences	
					Total	Local w/wo other site
Sawamura [2]	9	Immature teratoma		67 (10)	ND	ND
	7	IMT with Germinoma	7.2	69 (10)		ND
	15	Highly malignant GCTs		25 (10)	ND	ND
Matsutani [3]	11	Malignant teratomsa		70.7 (10)	6 (54.5%)	6 (54.5%)
	11	Pure malignant GCTs (embryonal carcinoma, yolk sac tumor, choriocarcinoma)	8.1	27.3 (5)	10 (90.9%)	8 (72.7%)
	10	Mixed (germinoma or teratoma)		35 (10)	4 (40%)	2 (20%)
	12	Mixed (embryonal carcinoma, yolk sac tumor, choriocarcinoma)		9.3 (5)	10 (83.3%)	8 (66.7%)
Schild [21]		Immature teratoma		67 (3)	ND	ND
	57	Mixed GCTs	3	44 (3)	ND	ND
		Others		13 (3)	ND	ND

Figures in parentheses in the OS column indicate years.

survival rate of as low as 27.3%. In the review of 57 cases reported by Schild et al. [21], the 3-year survival rate was 86% for patients with mature teratomas, 67% for patients with immature teratomas, 44% for patients with mixed GCTs, and 13% for patients with the other histologic types. A retrospective review by Aoyama et al. [22] considered the cases of 24 NGGCT patients: 5 patients with mature teratoma with/without germinoma (group 1), 6 patients with immature teratoma with/without germinoma (group 2), and 13 patients with other highly malignant tumors (group 3). The 5-year actuarial RFS rate was 100% for group 1, 63% for group 2, and 44% for group 3.

RT constitutes an essential part of treatment strategy. Schild et al. [21] reported that patients who received radiotherapy had a 3-year survival rate of 46% compared to 11% for those patients who did not receive radiotherapy ($p = 0.0015$). The radiation field should be selected according to the frequency of spinal dissemination. Immature teratomas have a generally lower rate of spinal relapse compared

with other highly malignant histologies. Aoyama et al. [22] examined 12 patients with immature teratomas with/without germinomas. There was no spinal failure in patients with immature teratoma, irrespective of the fact that 5 of the 6 did not receive WCNS radiation. There were 2 patients who experienced tumor recurrence at the primary tumor site. In the above-mentioned review of Matsutani et al. [3], all 6 recurrences among the 11 cases of malignant teratomas arose in the primary tumor site. On the other hand, teratomas with malignant transformation are thought to have a higher risk of spinal dissemination [21, 22]. For other highly malignant NGGCTs, the risk of spinal dissemination is also high. Aoyama et al. [22] reported that spinal failure was observed in 3 of 8 patients (37.5%) who did not receive WCNS radiation, but in none of the 5 who did receive it. Matsutani et al. [3] observed a 21.7% (5/23) rate of spinal failure in patients with highly malignant NGGCTs treated with WB RT. The radiation dose must be determined according to the probability of local tumor recurrence. When a conventional radiation dose (around 50 Gy) is used, the local tumor control rate is generally low. Matsutani et al. [3] reported that 34 (55.7%) of 61 NGGCTs recurred or metastasized. Twenty-five of those 34 patients (73.5%) suffered from tumor recurrence at the primary site with or without recurrence at a remote site. Hass-Kogan et al. [11] reported that in 5 of the 7 NGGCT patients with disease progression or relapse, the primary site was a component of failure. This high incidence of failure at the primary site after a conventional radiation dose highlights the need for more intensive chemotherapy or higher radiation doses to the primary site for patients with poor responses to chemotherapy or radiation.

Prospective Clinical Studies: Chemotherapy with Radiation

Calaminus et al. [23] reported the long-term outcome of 41 patients with intracranial malignant NGGCTs enrolled in the German prospective protocol MAKEI 89. The protocol recommended, after a clinically or histologically proven diagnosis and cisplatin-based chemotherapy, a resection of tumor and WCNS RT (30 Gy) with a tumor boost (20 Gy). The 5-year RFS rate was 74% in those treated according to the protocol. The use of WCNS RT had a significant influence on survival ($p = 0.035$), as did a cumulative cisplatin dose ≥ 400 mg/m^2 ($p = 0.002$). The Japanese Pediatric Brain Tumor Study Group is now conducting a phase II study of platinum-based induction chemotherapy followed by RT [24]. The 5-year OS and event-free survival for malignant teratoma with/without germinoma were 93.6 and 83%, respectively. The 3-year OS of 23 patients with highly malignant GCTs was 65.5%. The 3-year survival rates of 74% obtained from the German trial and 65.5% obtained from the Japanese trial seem to be significantly better than those obtained by a conventional approach.

Late Radiation Toxicities

Cranial RT has a potential risk of causing late radiation sequelae. This is especially true for medulloblastoma patients. Perhaps the most devastating sequela in cranial radiation in medulloblastoma patients, IQ decline, progresses more rapidly in association with several risk factors, including younger age, hydrocephalus, use of radiation, radiation dose and field. However, it is not fully understood if the findings obtained in patients with medulloblastoma could be extrapolated to patients with GCTs. Recently, two authors reported a favorable outcome in cognitive function after WCNS radiation for germinomas. In one study, Merchant et al. [7] observed no IQ decline in 25 patients with germinoma who were treated with WCNS RT. In another study, Sutton et al. [25] assessed the QOL of 22 patients treated for intracranial germinoma with WCNS irradiation. All 22 patients are in or have completed high school, 9 are in or have completed college, and 5 have higher degrees. Intracranial GCTs are usually diagnosed after puberty, and thus the influence of RT on the brain parenchyma or pituitary gland must be smaller than that in patients with medulloblastoma. Therefore, in reporting late radiation toxicities, great care must be taken not to include changes caused by the tumor itself or other confounding factors.

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Revisão

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

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

Hidefumi Aoyama[1]

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, salvages 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 estereotáxica (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 freqüencia 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 mandatória no sentido de detectar metástases cerebrais recorrentes antes que elas se tornem sintomáticas.

Palavras-chave: *Metástases Cerebrais, Radiocirurgia Estereotáxica, 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 WRBT+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 ALONE[1]

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.

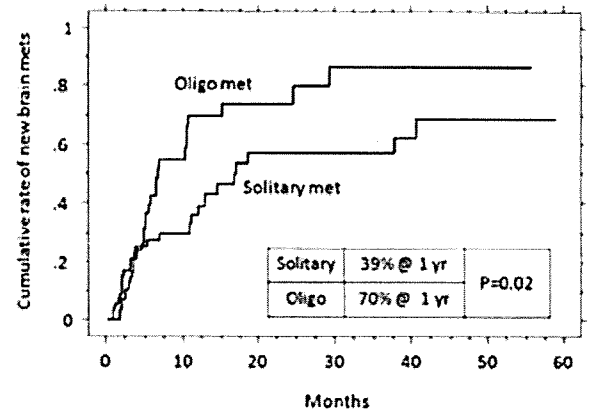

Figure 1. Cumulative incidence of the development of new brain metastases of patients presented with solitary metastasis and oligo metastases.

ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER WBRT+SRS VERSUS SRS ALONE IN JROSG 99-1[2]

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 Noordjik'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	Neurologic death
Patchell[7]	1990	NEJM	WBRT + Surg.	25	40 weeks	<0.01	29%
			WBRT	23	15 weeks		50%
Noordijk[5]	1993	Cancer	WBRT + Surg.	32	10 months	0.04	35%
			WBRT	31	6 months		33%
Mintz[4]	1996	Ann Neurol	WBRT + Surg.	41	6.3 months	NS	46%
			WBRT	43	5.6 months		63%
Andrews[1]	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 patients[6]. 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 treatment[2]. More importantly, this frequent brain tumor recurrence was strongly associated with the deterioration of neurocognitive function[3]. 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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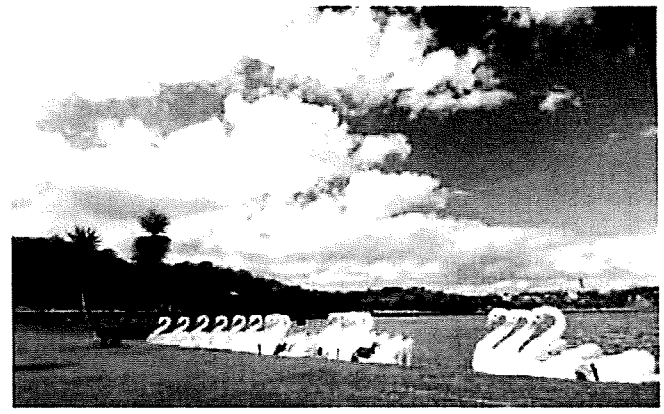

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CLINICAL INVESTIGATION **Lung**

CLINICAL OUTCOMES OF STEREOTACTIC BODY RADIOTHERAPY FOR SMALL LUNG LESIONS CLINICALLY DIAGNOSED AS PRIMARY LUNG CANCER ON RADIOLOGIC EXAMINATION

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Purpose: Image-guided biopsy occasionally fails to diagnose small lung lesions, which are highly suggestive of primary lung cancer. The aim of the present study was to evaluate the outcome of stereotactic body radiotherapy (SBRT) for small lung lesions that were clinically diagnosed as primary lung cancer without pathologic confirmation.
Methods and Materials: A total of 115 patients were treated with SBRT in 12 institutions. Tumor size ranged from 5 to 45 mm in diameter, with a median of 20 mm.
Results: The 3-year and 5-year overall survival rates for patients with a tumor size ≤20 mm in diameter (n = 58) were both 89.8%, compared with 60.7% and 53.1% for patients with tumors >20 mm (n = 57) (p <0.0005), respectively. Local progression occurred in 2 patients (3.4%) with a tumor size ≤20 mm and in 3 patients (5.3%) with tumors >20 mm. Among the patients with a tumor size ≤20 mm, Grade 2 pulmonary complications were observed in 2 (3.4%), but no Grade 3 to 5 toxicity was observed. In patients with a tumor size >20 mm, Grades 2, 3, and 5 toxicity were observed in 5 patients (8.8%), 3 patients (5.3%), and 1 patient (1.8%), respectively.
Conclusion: In patients with a tumor ≤20 mm in diameter, SBRT was reasonably safe in this retrospective study. The clinical implications of the high local control rate depend on the accuracy of clinical/radiologic diagnosis for small lung lesions and are to be carefully evaluated in a prospective study. © **2009 Elsevier Inc.**

Lung cancer, Stereotactic radiotherapy, Stereotactic body radiotherapy.

INTRODUCTION

Pathologic diagnosis is essential for the treatment of primary lung cancer. However, image-guided biopsy occasionally fails to diagnose small lung lesions, which are highly suggestive of primary lung cancer. When patients refuse re-biopsy or surgical resection, watchful waiting is usually indicated. There are other groups of patients in whom a pathologic diagnosis is very difficult to make, such as those with medical reasons for not being able to undergo biopsy and those with a history of surgical resection of non–small-cell lung cancer (NSCLC) and a small peripheral lung lesion on follow-up computed tomography (CT). The patients in the latter group often have difficulty undergoing a second surgical resection because of lowered respiratory function resulting from the previous surgery. Patients with cancer who are under watchful waiting are at risk for invasive growth of the primary tumor, lymphatic spread, and distant metastasis. Patients who choose to receive elective surgical resection of the small lung lesions to quantify the pathologic diagnosis may experience serious respiratory dysfunction. A proportion of the patients who do not have malignant tumors are inevitably overtreated and experience surgical complications.

Stereotactic body radiotherapy (SBRT) has been one of the treatments for Stage I NSCLC in medically inoperable patients. Recently, high local control and survival rates of SBRT were

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reported in several studies (1–7). Onishi *et al.* summarized the results of a Japanese series retrospectively and reported that a pulmonary complication rate of above Grade 2 arose in only 5.4% of patients (1). For the patients who received a dose compatible with the biologic effective dose (BED) of 100 Gy or more, the local control rate was 91.6%. For the patients who were judged to have been operable but who were treated with SBRT, the 5-year overall survival rate was 70.8%, which is equivalent to that achieved in the previously mentioned surgery series (1).

A serious question among radiation oncologists is whether it is ethically justifiable not to give SBRT to those patients who have peripheral lung lesions highly suggestive of lung cancer but who failed to have lung cancer diagnosed pathologically. If SBRT is as safe as image-guided re-biopsy and as effective as surgical resection, it may be ethical to give SBRT to these patients. However, we cannot answer this question, because the risk and benefit have not been compared between elective surgical resection, watchful waiting, and SBRT for small peripheral lung lesions without pathologic confirmation.

We have found in a national survey of SBRT that a small number of patients with the clinical diagnosis of NSCLC are actually treated with SBRT without pathologic confirmation in each institution. The aim of the present study was to evaluate the outcome of SBRT for peripheral small lung lesions that were clinically diagnosed as primary lung cancer without pathologic confirmation in 12 institutions during the past 10 years in Japan.

METHODS AND MATERIALS

Eligibility criteria

Twelve institutions were selected from the member institutions of the Japan Clinical Oncology Group trial, JCOG0403, for which the quality of clinical record and dosimetry accuracy of SBRT had already been evaluated by audit (8). This is a multi-institutional retrospective study using the same eligibility criteria, which were that (a) surgery was contraindicated or refused, (b) the tumor diameter was <50 mm, (c) tumors were highly suggestive of primary lung cancer and diagnosed as Stage I lung cancer clinically but the patients did not have a pathologic diagnosis, and (d) the performance status was 0 to 2 according to World Health Organization guidelines.

Patients

A total of 115 patients who were highly suspected of having lung cancer but who lacked pathologic confirmation of the disease were diagnosed with Stage I lung cancer clinically and treated with SBRT in 12 institutions during the last 10 years in Japan. The patient characteristics are given in Table 1. There were 93 cases of T1N0M0 and 22 cases of T2N0M0 disease. The number of medically operable and inoperable patients was 43 and 72, respectively. Tumor size was recorded at the maximum diameter on the CT scan taken at the start of radiotherapy. The median tumor size was 20 mm (range, 5–45 mm). The median follow-up period was 14 months (range, 1–142 months). There were 11 patients whose follow-up period was <4 months at the time of this analysis.

Diagnosis was based on CT findings and enlargement of the lesion on sequential examination with or without fluorodeoxyglucose (FDG)–positron emission tomography (PET) findings. The tumors were diagnosed as highly suggestive of primary lung cancer by diagnostic radiologists when there was definitive enlargement of the lesion on sequential CT examination and/or positive findings on FDG-PET without any metastatic lesion in the diagnostic evaluation. Several findings such as the configuration of the lung lesion were also used in the diagnosis. Of 72 patients who were examined with FDG-PET, 67 patients had positive findings on FDG-PET. Other clinical history and findings as well as laboratory findings were also used for diagnosis as much as possible to prevent inclusion of patients with metastatic lung tumors or inflammatory or granulomatous lesions in the study population.

Table 1. Characteristics of patients (115 patients)

Characteristic	Value
Age (y)	
Median	77
Range	50–92
Gender (*n*)	
Male	87
Female	28
Tumor size (mm)	
Median	20
Range	5–45
T stage (*n*)	
T1	93
T2	22
Medical condition (*n*)	
Operable	43
Inoperable	72

The reasons for the lack of pathologic confirmation were as follows: (a) bronchoscope- or CT-guided biopsy failed in 59 patients, and these patients refused re-biopsy or surgical resection; (b) 21 patients were not indicated for a biopsy procedure or surgery because of medical complications; (c) 14 patients refused a biopsy procedure as well as surgery even at the initial examination; (d) a biopsy was not indicated in 14 patients because their history of NSCLC was strongly suggestive of the new development of a second primary NSCLC, likely inoperable, and they refused surgery; and (e) a biopsy was not indicated in 7 patients because there was little possibility to confirm the pathology because of the tumor's small size, and these patients refused surgery.

Radiotherapy

All patients underwent irradiation using stereotactic techniques. Three-dimensional treatment planning was performed using non-coplanar static ports or dynamic arcs. Various techniques using breathing control or gating methods and immobilization devices such as a vacuum cushion with or without a stereotactic body frame were used to reduce respiratory internal margins. Appropriate margins were adopted for the clinical target volume and the planning target volume.

A total dose of 30 to 70 Gy at the isocenter was administered in two to 10 fractions. Using a linear-quadratic model, we defined the BED as $nd(1+d/\alpha/\beta)$, with Gray units, where n was the fractionation number, d was the daily dose, and the α/β ratio was assumed to be 10 for tumors. The BED was not corrected with values for tumor doubling time or treatment term. The median BED at the isocenter in this study was 106 Gy (range, 56–141 Gy).