Table 2: Score distributions and child-parent relationships of the Japanese version of the PedsQL™ Brain Tumor Module

	Number of patients (n)	Mean	SD	Median	Minimum	Floor (%)	Maximum	Ceiling (%)	Differencea	SD	95% CI		ICC
Child-report													
Cognitive Problems	137	69.6	21.9	71.4	0	1.5	100	10.2	5.2	22.5	1.43	9.02	0.49
Pain and Hurt	136	84.4	18.4	91.7	16.7	0.0	100	43.4	3.5	20.5	0.04	7.00	0.41
Movement and Balance	136	83.9	24.6	100.0	0	2.2	100	52.2	13.0	22.9	9.12	16.87	0.64
Procedural Anxiety	136	69.5	30.7	75.0	0	7.4	100	27.9	9.2	27.8	4.45	13.87	0.62
Nausea	136	85.9	21.3	95.0	0	0.7	100	48.5	2.3	19.1	-0.89	5.58	0.65
Worry	136	79.6	23.7	83.3	0	1.5	100	39.0	4.4	30.2	-0.75	9.51	0.18
Parent-report													
Cognitive Problems	140	64.1	22.6	64.3	0	1.4	100	6.4					
Pain and Hurt	165	81.5	19.7	83.3	25.0	0.0	100	41.2					
Movement and Balance	166	70.4	29.3	75.0	0	3.6	100	31.9					
Procedural Anxiety	164	57.2	34.4	58.3	0	13.4	100	21.3					
Nausea	164	84.2	23.0	95.0	0	0.6	100	49.4					
Worry	164	76.5	23.1	75.0	0	1.2	100	29.3					

[a]parent report score subtracted from child report score
CI, confidence interval; ICC, intraclass correlation coefficient

both the child- and parent-reports for children (8-12 years old).

At the retest, two children and two parents answered that the physical condition or lifestyle of the child had changed since responding to the initial questionnaire. We therefore analyzed the retest answers of the remaining 22 children and 27 parents. On comparison of characteristics between the retest and non-retest samples using Fisher's exact test or Student's t-test, observed tendencies for the retest sample were that children were undergoing treatment (n = 17 [61%]; P = 0.008), parents were not mothers (n = 5 [18%]; P = 0.008), and parents were relatively old (average age, 43.5 years old; P = 0.001). No tendency was noted with regard to the initial scores of the retest sample being higher or lower than those of the non-retest sample. In the retest sample, each retest scale score fell in the same range as initial test scale scores (Table 3). The Pain and Hurt scale for the child-report indicated moderate agreement, while the other scales indicated good or high agreement.

Validity

Exploratory factor analyses produced six factors correspondent to each scale (Table 4). Factor-item correlations were between 0.33 and 0.96 in the child-report, and 0.55 and 1.00 in the parent-report.

With regard to known-group differences, the Cognitive Problems scale was sensitive for developmental impairment, the Movement and Balance scale was sensitive for tumor location (supratentorial or infratentorial) and paresis, and the Nausea scale was sensitive for a patient currently undergoing chemotherapy (Table 5). The Cognitive Problems scale was not completely sensitive for having received whole brain irradiation, with a 95% confi-

Table 3: Reliability of the Japanese version of the PedsQL™ Brain Tumor Module

	Cronbach's coefficient alpha					Retest reliability (n = 28)				
			Age group							
	Total (n = 166)	Toddler (n = 26)	Young child (n = 31)	Child (n = 56)	Adolescent (n = 53)	Change	SD	95% CI		ICC
Child-report										
Cognitive Problems	0.83	-	0.73	0.80	0.85	-1.3	15.1	-7.8	5.3	0.67
Pain and Hurt	0.50	-	0.48	0.35	0.57	-1.5	17.3	-9.0	6.0	0.45
Movement and Balance	0.78	-	0.78	0.79	0.75	0.0	14.6	-6.3	6.3	0.77
Procedural Anxiety	0.82	-	0.75	0.85	0.85	1.4	29.3	-11.2	14.1	0.67
Nausea	0.84	-	0.62	0.82	0.93	2.8	18.6	-5.3	10.8	0.74
Worry	0.75	-	0.84	0.60	0.76	-4.3	19.8	-12.9	4.2	0.70
Parent-report										
Cognitive Problems	0.92	-	0.89	0.90	0.93	1.3	13.6	-4.7	7.3	0.76
Pain and Hurt	0.80	0.92	0.77	0.81	0.74	-2.9	13.3	-8.3	2.5	0.82
Movement and Balance	0.91	0.84	0.89	0.89	0.93	1.6	11.3	-3.0	6.2	0.92
Procedural Anxiety	0.96	0.98	0.94	0.95	0.96	-3.7	21.1	-12.4	5.1	0.82
Nausea	0.93	0.86	0.87	0.93	0.94	-1.0	8.2	-4.3	2.4	0.95
Worry	0.86	0.86	0.93	0.69	0.88	-0.3	16.2	-6.9	6.2	0.74

CI, confidence interval; ICC, intraclass correlation coefficient

dence interval from -2.3 to 12.9 in the child-report and from 0.8 to 16.0 in the parent-report.

With regard to presumed hypotheses of convergent and discriminant validity, the Cognitive Problems scale correlated better with the School Functioning scale than with the other three scales, and the Movement and Balance scale correlated better with the Physical Functioning scale than with the other three scales (Table 6). The Procedural Anxiety scale correlated slightly better with the Emotional Functioning scale than with the other three scales, although the difference was trivial. The Procedural Anxiety scale also negatively-correlated better with the Trait Anxiety scale than with the State Anxiety scale and the Worry scale correlated relatively-better with the Emotional Functioning scale than with the other three scales. With regard to scales that correlated particularly well in the parent-report, the Cognitive Problems scale correlated well with the School Functioning scale, Movement and Balance scale correlated well with the Physical Functioning scale, and the Procedural Anxiety and Worry scales correlated relatively well with the Emotional Functioning scale.

Discussion

In the present study, to facilitate the sharing of data across international borders, we developed the Japanese language version of the PedsQL™ Brain Tumor Module and confirmed its feasibility, reliability, and validity. Our fixed forward-backward translation procedure used to develop the survey ensures that the Japanese version conforms to the original both conceptually and linguistically while keeping the Japanese culture in mind.

As the participants in the development of the original PedsQL™ Brain Tumor Module included no children with movement or balance problems, providing essentially no variability in responses to these items, the Movement and

Table 4: Factorial validity of the Japanese version of the PedsQL™ Brain Tumor Module

	Child-report (n = 137, 64% of the cumulative variance)						Parent-report (n = 166, 78% of the cumulative variance)					
Cognitive Problems												
It is hard for me to figure out what to do when something bothers me	0.01	**0.45**	-0.06	0.15	0.06	0.15	**0.60**	-0.13	0.11	0.18	-0.01	0.08
I have trouble solving math problems	-0.01	**0.54**	0.25	-0.05	-0.05	-0.21	**0.75**	0.02	0.06	-0.05	-0.03	0.05
I have trouble writing school papers or reports	0.05	**0.82**	-0.02	0.06	-0.02	-0.25	**0.79**	-0.01	0.01	0.08	0.06	-0.13
It is hard for me to pay attention to things	-0.08	**0.63**	-0.07	-0.17	0.14	**0.31**	**0.81**	0.11	-0.09	-0.11	0.03	0.00
It is hard for me to remember what I read	0.04	**0.68**	-0.04	-0.09	0.13	0.18	**0.88**	0.04	-0.02	-0.03	-0.02	-0.04
It is hard for me to learn new things	-0.01	**0.65**	0.10	0.14	-0.21	-0.01	**0.85**	0.04	-0.09	0.01	-0.06	-0.01
I get mixed up easily	0.03	**0.40**	-0.07	0.27	-0.06	0.13	**0.67**	-0.11	0.09	0.03	0.07	0.11
Pain and Hurt												
I ache or hurt in my joints and/or muscles	-0.10	-0.06	-0.02	0.15	-0.05	**0.77**	-0.03	-0.05	0.01	0.05	0.06	**0.82**
I hurt a lot	0.23	0.16	0.11	-0.03	-0.11	**0.39**	-0.01	-0.01	0.04	-0.02	-0.03	**0.94**
I get headaches	-0.04	0.03	-0.08	-0.13	0.05	**0.38**	0.05	0.14	-0.12	-0.04	-0.03	**0.55**
Movement and Balance												
It is hard for me to keep my balance	-0.01	0.06	-0.05	**0.52**	0.20	-0.13	0.01	-0.03	0.08	**0.81**	0.11	-0.04
It is hard for me to use my legs	0.01	-0.05	0.10	**0.85**	-0.08	0.06	-0.01	0.01	-0.05	**1.00**	-0.06	0.01
It is hard for me to use my hands	0.00	0.05	-0.09	**0.87**	0.11	-0.05	0.03	0.06	-0.06	**0.83**	-0.05	0.01
Procedural Anxiety												
Needle sticks (i.e. injections, blood tests, IVs) hurt me	0.02	0.01	**0.72**	-0.14	0.11	-0.03	-0.04	0.01	**0.89**	0.04	0.02	0.03
I get scared when I have to have blood tests	-0.11	0.00	**0.74**	0.12	0.13	-0.13	0.02	0.04	**0.95**	-0.04	0.00	-0.06
I get scared about having needle sticks (i.e. injections, blood tests, IVs)	-0.03	0.10	**0.89**	-0.04	-0.06	0.05	0.01	0.01	**0.98**	-0.03	-0.04	-0.01
Nausea												
I become sick to my stomach when I have medical treatments	**0.46**	-0.16	0.16	-0.02	0.00	**0.34**	-0.02	**0.88**	0.05	-0.05	-0.05	0.04
Food does not taste very good to me	**0.79**	0.10	-0.04	-0.02	0.01	-0.02	-0.01	**0.83**	0.04	0.10	-0.15	0.02

Table 4: Factorial validity of the Japanese version of the PedsQL™ Brain Tumor Module (Continued)

I become sick to my stomach when I think about medical treatments	**0.61**	-0.06	0.01	-0.01	0.11	0.20	0.08	**0.80**	0.06	-0.04	-0.01	0.00
I feel too sick to my stomach to eat	**0.80**	0.06	-0.14	-0.02	0.22	-0.14	-0.01	**0.88**	-0.04	-0.01	0.05	0.04
Some foods and smells make me sick to my stomach	**0.96**	-0.03	0.00	0.04	-0.26	-0.16	0.01	**0.86**	-0.04	0.04	0.10	-0.04
Worry												
I worry about side effects from medical treatments	0.30	-0.06	0.25	0.06	**0.33**	-0.04	-0.05	0.25	0.02	0.02	**0.72**	0.04
I worry about whether or not my medical treatments are working	0.00	-0.01	0.13	0.10	**0.65**	0.08	-0.07	0.01	0.02	0.05	**0.92**	-0.03
I worry that my cancer will come back or relapse	-0.02	0.00	0.06	0.06	**0.79**	-0.05	0.12	-0.16	-0.06	-0.08	**0.81**	0.01

Factor patterns from a principal factor method with promax rotation. Factor loadings of more than 0.30 are bolded.

Balance scale for the child-report was excluded from the original version [16]. Previous studies have shown that problems with movement and balance are important but infrequent in children with brain tumors [4,29]. Although the ceiling effect was relatively high, our version presented score distributions for the child-report including the Movement and Balance scale, which has a standard deviation nearly equal to that of the other scales. With regard to the Pain and Hurt scale, we observed a narrow range and low standard deviation, due in large part to the characteristics of our sample population. Because more than one month had passed since the children's histological diagnosis of a brain tumor, a few children who took part in our study were experiencing pain from intracranial hypertension or postoperative pain.

Several studies have reported on the differences and concordance between the child- and parent-reports. The differences between these reports are dependent on the scales and samples [30,31]. In the present study, scores for all child-report scales were higher than those for the parent-report. Good concordance has been reported for observable domains such as physical activity or symptoms, while poor concordance has been reported for non-observable domains such as depression or social quality of life [32-34]. In the present study as well, good concordance was observed for the Movement and Balance scale, the Procedural Anxiety scale, and the Nausea scale, while poor concordance was observed for the Worry scale, findings which suggest that using the PedsQL™ Brain Tumor Module with both the child- and parent-reports can provide bilateral information. In this manner, we recommend interpretation of both aspects of HRQOL based on the child- and parent-reports.

With regard to obtention of results, only a short amount of time was required to complete the questionnaire, and few missing values were observed, suggesting good feasibility. With regard to children of any age with impairments who were unable to complete their questionnaires on their own (in the present study, those with mental retardation, attention deficit disorder, dyslexia, visual impairment, and paresis), interviewer-delivered administration has been found to help these participants complete the child-report questionnaires. Given that these children made up a non-negligible percentage of our population (17%), the importance of participants having access to interviewer-administration cannot be overstated. Although severe mental retardation hampered one child from completing the child-report questionnaire even with an interviewer's assistance, the child's parents had no problems in completing the parent-report. Persistent disturbance of consciousness in her child hampered one parent from completing the parent-report questionnaire. With regard to the applicable scope of the PedsQL™ Brain Tumor Module, the present findings suggest that this module can be used even on children with severe mental retardation, although not on children with persistent disturbance of consciousness.

Table 5: Known-groups validity of the Japanese version of the PedsQL™ Brain Tumor Module

	Child-report						Parent-report					
	Number of patients (n)	Mean	SD	Difference	95% CI (P)a		Number of patients (n)	Mean	SD	Difference	95% CI (P)a	
Cognitive Problems												
Have received whole brain irradiation												
Yes	54	66.4	23.6	5.3	-2.3	12.9	56	59.1	22.4	8.4	0.8	16.0
No	83	71.7	20.7		(0.168)		84	67.5	22.3		(0.031)	
Experiencing developmental impairment												
Yes	27	57.1	26.7	15.5	6.5	24.5	28	42.2	22.9	27.4	19.1	35.7
No	110	72.7	19.6		(< 0.001)		112	69.6	19.0		(< 0.001)	
Movement and Balance												
Tumor location												
Infratentorial	52	74.7	29.0	15.0	6.6	23.4	67	57.0	28.0	23.2	14.7	31.7
Supratentorial	79	89.7	19.8		(< 0.001)		93	80.2	26.1		(< 0.001)	
Experiencing paresis of hands or legs												
Yes	28	57.7	32.6	32.9	24.2	41.6	35	33.6	24.6	46.7	38.3	55.1
No	108	90.7	16.4		(< 0.001)		131	80.3	21.7		(< 0.001)	
Nausea												
Currently undergoing chemotherapy												
Yes	36	72.1	29.4	18.7	11.2	26.3	46	62.6	27.9	30.0	23.6	36.4
No	100	90.8	14.7		(< 0.001)		118	92.6	13.6		(< 0.001)	

[a]P-value from Student's t test
CI, confidence interval

In addition to good feasibility, our results also suggested sufficient reliability. All scales for both the child- and parent-reports showed retest reliability. With regard to child-report scales, although agreement for the Pain and Hurt scale between the initial test and retest was relatively low compared to that observed for other scales, values were not lower than those for other scales in a systematic review on assessment of pediatric pain [35]. Most scales for the child-report and all scales for the parent-report showed internal consistency reliability coefficients approaching or exceeding the standard of 0.70. For the Pain and Hurt scale for the child-report in particular, the narrow range may result in a lower Cronbach's coefficient alpha. Scales not approaching or meeting the 0.70 standard should be used only for descriptive or exploratory research.

Additionally, proof of the validity of our results was evidenced on several points. The fixed scale-development methods of the present study ensured the content validity and the results ensured construct validity through factorial, known-groups, and convergent and discriminant validity. Our study was the first to clarify the module's factor structure, which had not been confirmed in the original version or other translations of the PedsQL™ Brain Tumor Module. Each scale was sensitive for medical variables and treatment status within the scope of the assumption. The 95% confidence interval of the Cognitive Problems scale for the child-report with regard to having undergone whole brain irradiation spanned across zero. Variations in age at undergoing radiation and time since radiation treatment in our sample might reduce between-group differences. In addition to whole brain irradiation,

other factors related to cognitive function exist, such as intracranial surgery [5] and hydrocephalus [36], and consideration of these factors may be recommended in clinical investigations into cognitive problems. All scales have been confirmed to correlate better with theoretically predicted scales than with the non-predicted scales, albeit by a trivial difference. We were not surprised by our observation of correlations between non-predicted pairs, because all scales of PedsQL™ Brain Tumor Module and PedsQL™ Generic Core Scales are domains of HRQOL.

One limitation to our study warrants mention. Our sample population did not include children with tumors diagnosed less than one month prior to administration of the questionnaire, which may limit the generalizability of the findings. Future studies and analyses are needed to explore the sensitivity and responsibility of the PedsQL™ Brain Tumor Module and factors related to the child-parent discordance for the Worry scale.

Conclusions

We developed the Japanese version of the PedsQL™ Brain Tumor Module and confirmed its feasibility, reliability, and validity. This module is the only validated instrument suitable for evaluating brain tumor-specific HRQOL in children. High feasibility may decrease loss of patients to follow-up even in prospective studies. Using this module to assess primary and secondary endpoints may be useful in enabling future studies to become more sensitive to the interplay of disease- and treatment-specific effects. Further, descriptive or exploratory studies can identify high-risk groups of children with tumors as well as survivors of brain tumors, and thereby develop nursing intervention regimens based on individual risk level. Use of the PedsQL™ Brain Tumor Module in clinical trials and studies may help to improve HRQOL in children with brain tumors.

Table 6: Convergent and discriminant validity of the Japanese version of the PedsQL™ Brain Tumor Module

	The PedsQL™ Generic Core Scales				STAIC	
	Physical Functioning	Emotional Functioning	Social Functioning	School Functioning	State Anxiety	Trait Anxiety
Child-report	(n = 134)				(n = 106)	
Cognitive Problems	0.61	0.56	0.62	0.70	-0.45	-0.51
Pain and Hurt	0.46	0.62	0.47	0.43	-0.34	-0.54
Movement and Balance	0.77	0.49	0.69	0.61	-0.17	-0.31
Procedural Anxiety	0.50	0.53	0.52	0.52	-0.21	-0.41
Nausea	0.57	0.42	0.32	0.38	-0.29	-0.14
Worry	0.50	0.59	0.44	0.44	-0.39	-0.42
Parent-report	(n = 166)					
Cognitive Problems	0.43	0.43	0.57	0.79		
Pain and Hurt	0.50	0.52	0.20	0.54		
Movement and Balance	0.76	0.52	0.52	0.48		
Procedural Anxiety	0.37	0.38	0.18	0.28		
Nausea	0.35	0.50	0.02	0.30		
Worry	0.21	0.53	0.30	0.28		

STAIC, the State-Trait Anxiety Inventory for Children

Competing Interests
The authors declare that they have no competing interests.

Authors' contributions
IS, AH, RN, YI, and KK conceptualized the rationale and design of the study. IS, AH, TY, AM, KI, NS, RN, YI, and KK conducted scale development. AH, TY, AM, KI, YS, KS, NS, TK, MT, and RN coordinated participants and settings in each institution. IS and AH presented this study to families and collected data. IS and KK conducted statistical analyses and interpreted the data. IS, RN, YI, and KK drafted the manuscript. All authors read and approved the final manuscript.

Acknowledgements
This work was supported by a Grant-in-Aid for Pediatric Cancer Treatment and Research from the Children's Cancer Association of Japan 2008 and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (No. 18-14) 2008.

Author Details
[1]Department of Family Nursing, Graduate School of Health Sciences and Nursing, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, [2]Children's Cancer Association of Japan, 1-3-12 Asakusabashi, Taito-ku, Tokyo 111-0053, Japan, [3]Division of Pediatric Neuro-Oncology, Department of Neuro-Oncology/Neurosurgery, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka-shi, Saitama 350-1298, Japan, [4]Department of Neurosurgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan, [5]Department of Pediatrics, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, [6]Department of Neurosurgery, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo 060-8648, Japan, [7]Department of Neurosurgery, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan, [8]Departments of Neurosurgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan, [9]Department of Neurosurgery, Kurume University School of Medicine, Asahimachi 67, Kurume-shi, Fukuoka 830-0011, Japan, [10]Department of Neuro-Oncology/Neurosurgery, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka-shi, Saitama 350-1298, Japan and [11]Department of Pediatrics, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

Received: 4 November 2009 Accepted: 14 April 2010
Published: 14 April 2010

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doi: 10.1186/1477-7525-8-38
Cite this article as: Sato *et al.*, Development of the Japanese version of the Pediatric Quality of Life Inventory™ Brain Tumor Module *Health and Quality of Life Outcomes* 2010, **8**:38

Neurol Med Chir (Tokyo) 50, 713～719, 2010

Standard Therapy for Glioblastoma— A Review of Where We Are

Ryo NISHIKAWA

Department of Neuro-Oncology/Neurosurgery, International Medical Center, Saitama Medical University, Saitama

Abstract

Glioblastoma is the most common primary malignant brain tumor in adults and is a challenging disease to treat. The current standard therapy includes maximal safe surgical resection, followed by a combination of radiation and chemotherapy with temozolomide. However, recurrence is quite common, so we continue to search for more effective treatments both for initial therapy and at the time of recurrence. This article will review the current standard of care and recent advances in therapy for newly-diagnosed and recurrent glioblastomas, based on the most authoritative guidelines, the National Cancer Institute's comprehensive cancer database Physician Data Query (PDQ®), and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology™ for central nervous system cancers (V.1.2010), to elucidate the current position and in what direction we are advancing.

Key words: glioblastoma, standard therapy, chemotherapy, temozolomide, clinical trial

Definition of Standard Therapy

Standard therapy is the treatment that experts agree is appropriate, accepted, and widely used, and is also called best practice and standard of care.[14] Health care providers are obligated to provide patients with standard therapy. Physicians are not allowed to provide patients with non-standard therapy without explaining the reason why standard therapy will not be provided and obtaining informed consent. Every clinical trial should have a convincing scientific basis to indicate that testing the treatment is worthwhile, and the patients should be informed that the test treatment is not a standard therapy, which is requisite from an ethical point of view. The Institutional Review Board (IRB) will examine the protocols, case report forms, and related documents from both scientific and ethical points of view. In randomized phase 3 studies, the control arms are always standard therapies of the diseases.

Standard Therapy for Glioblastoma in Physician Data Query (PDQ®)

PDQ® is the National Cancer Institute's comprehensive cancer database, and is the most authoritative guideline.[15] PDQ® is written in an itemized manner, so needs some commentary and explanations (Table 1).

Table 1 Standard therapy for glioblastoma in PDQ®

Surgery plus radiation therapy for elderly glioblastoma patients
No additional benefit from brachytherapy added to external-beam radiation therapy and carmustine (BCNU)
BCNU-impregnated polymer (Gliadel wafer) implanted during initial surgery
Radiation therapy and concurrent chemotherapy with temozolomide

PDQ®: Physician Data Query.

The first point is the treatment of glioblastoma (GBM) in the elderly population. Since the landmark European Organization for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) study published in 2005, the standard therapy for GBM has been post-operative adjuvant radiotherapy with concomitant and adjuvant temozolomide (TMZ) (so-called Stupp's regimen).[25] However, the patients eligible for this study were aged from 18 to 70 years, so the standard therapy for GBM patients aged over 70 years remains undetermined. Because the frequency of severe adverse events of TMZ is less than 10%, and the pharmacokinetic profile of TMZ is not age-dependent, investigators surmise that Stupp's regimen would be applicable for elderly patients, but this notion has not actually been proven yet.

A randomized phase 3 study comparing postoper-

ative supportive care and postoperative radiation therapy plus supportive care was performed for GBM patients over 70 years old.[10] The median survival time was 29.1 weeks for the 39 patients who received radiation therapy plus supportive care and 16.9 weeks for the 42 patients who received only supportive care. The hazard ratio of death in the radiation therapy arm was 0.47 (95% confidence interval [CI] 0.29–0.76; p = 0.002). This study was discontinued prematurely at the first interim analyses, because the radiotherapy plus supportive care arm was superior to the only supportive care arm with a preset boundary of efficacy. Post-operative radiotherapy resulted in a robust improvement in survival in elderly patients with GBM, and is now the standard therapy for this population. To prove that a full dose of 60 Gy/30 fractions was necessary for elderly GBM patients, a randomized study of patients 60 years and older comparing post-operative radiotherapy of 60 Gy/30 fractions (standard course) and 40 Gy/15 fractions administered over the course of 3 weeks (short course) was performed. Overall survival (OS) was similar for the two groups; 5.1 months for the standard course arm, and 5.6 months for the short course arm (p = 0.57).[22] Although there was concerns about the power of the study, which was discontinued prematurely at the first interim analysis when 100 patients were recruited, the results showed the outcomes of the two arms were statistically equivalent, so the short course of radiotherapy seemed to be the reasonable treatment option for elderly patients with GBM.

Deterioration of cognitive function is a well known adverse effect of radiotherapy, especially in the elderly population. Treatment with only TMZ, without radiotherapy, may be equivalent in OS and would provide better health-related quality of life (QoL), which is a reasonable hypothesis to be tested in elderly GBM patients. Three randomized phase 3 studies for elderly GBM patients are on-going: a three-arms study by the Nordic Clinical Brain Tumor Group assessing the efficacy of short course radiotherapy and only TMZ arms with standard course radiotherapy of 60 Gy; a study by the German Neuro-Oncology Working Group simply testing the efficacy of only TMZ treatment versus the standard course of radiotherapy, and the study by NCIC and EORTC aiming at the assessment of the additive effect of TMZ to short course radiotherapy. Three institutes from Japan, Kitano Hospital, Hiroshima University, and the International Medical Center, Saitama Medical University are members of the international study group for the NCIC/EORTC study, CE.6. Conclusions from these studies will decide if only TMZ is equivalent to radiotherapy, and provides better QoL, and if concomitant and adjuvant TMZ with short course radiotherapy would be valuable for elderly GBM patients.

The second point in PDQ® is evaluation of the efficacy of brachytherapy for GBM. A randomized cooperative study showed no additional benefit from brachytherapy added to external-beam radiation therapy and carmustine (BCNU) (NIH Trial 87-01).[23] Interstitial brachytherapy is one of the techniques to deliver high doses of irradiation to the tumor beds. Stereotactic radiotherapy is another high-dose local radiotherapy technique, which also failed to show survival advantage compared to external beam irradiation in a phase 2 study by the Radiation Therapy Oncology Group (RTOG 0023).[4] Because of the highly invasive nature of GBM, however high the irradiated dose is, the effect of radiotherapy would be limited as the irradiated field is restricted to the enhanced lesion.

The third point in PDQ® is the evaluation of BCNU-impregnated polymer (Gliadel® wafer) implanted during surgeries. A multicenter randomized double-blinded controlled trial with 240 patients with high-grade glioma including 207 GBM and 21 anaplastic glioma reported significantly longer OS for patients who had Gliadel® wafer placed intraoperatively (13.8 months for Gliadel® wafers vs. 11.6 months for placebo; HR 0.73, 95% CI 0.56–0.95; p = 0.0018).[32] However, a subanalysis of 207 GBM patients could not show significantly longer survival with Gliadel® wafer (13.1 months in the Gliadel®-treated group and 11.4 months in the placebo-treated group, p = 0.08). The spacial and temporal distribution of BCNU released from the polymer was calculated by a mathematical simulation model.[31] The penetration depth of BCNU from a polymer was estimated to be 0.5 cm. The penetration depth was defined as the average distance measured from the surface of a polymer at which the drug concentration is 1% compared to that of the polymer surface. The distance of penetration is short because BCNU has a high transvascular permeability and, therefore, is very easily absorbed into the systemic circulation. BCNU molecules, being lipid-soluble and very permeable, enter the bloodstream before they can travel far. Together with the short half life of BCNU (1.5 hours), the short distance of penetration would limit the efficacy of the therapy.

The last point in PDQ® is radiation therapy and concurrent chemotherapy. A randomized study performed by EORTC and NCIC was a landmark of GBM treatment. Radiation therapy plus TMZ followed by 6 months of adjuvant TMZ in patients with newly diagnosed GBM demonstrated a statistically significant survival advantage over simple

radiotherapy.[25] The median OS was 14.6 months with radiotherapy plus TMZ and 12.1 months with only radiotherapy (HR 0.63, 95% CI 0.52 to 0.75; $p < 0.001$). The treatment is relatively safe and well tolerated. The combined treatment regimen consists of concomitant and adjuvant TMZ with radiotherapy. While the dose of TMZ for adjuvant phase is 150–200 mg/m^2 for 5 days every 4 weeks, TMZ of 75 mg/m^2 is administered daily during the concomitant phase with radiotherapy. The rationale for the small dose and continuous administration of TMZ with radiotherapy are radiosensitization induced by TMZ and chemosensitization by O^6-methylguanine-deoxyribonucleic acid-methyltransferase (MGMT) depletion induced by TMZ. Radiosensitivity enhancement of tumor cells by TMZ was shown in vitro and in vivo. The enhancing effect involves inhibition of deoxyribonucleic acid (DNA) repair leading to increased mitotic catastrophe.[11] MGMT depletion induced by protracted TMZ schedules was shown in the peripheral blood mononuclear cells. MGMT decreased significantly after 7, 14, and 21 days of treatment with low-dose and protracted TMZ administration, thus resulting in autosensitization to TMZ.[27] MGMT is the key enzyme to determine the sensitivity for TMZ. In the clinical setting, promoter methylation of MGMT is one of the factors contributing to better outcomes for GBM patients treated by TMZ.[9]

In the combined treatment arm with TMZ and radiotherapy, patients with GBM with methylated MGMT promoters showed significantly better OS than those with unmethylated MGMT promoters.[9] In the only initial radiotherapy arm, patients with methylated MGMT promoter also showed improvement in OS. This was expected because more than 70% of the patients in the radiotherapy arm received chemotherapy, most likely with an alkylating agent at progression, and 60% of these patients received TMZ at progression. When progression-free survival (PFS) was analyzed, so eliminating second-line therapies as a confounding factor, PFS was only prolonged in patients with methylated MGMT promoters who were treated with radiotherapy plus TMZ. However, a close look at the Kaplan Meyer survival curves of patients in the radiotherapy arm with methylated or unmethylated MGMT promoters finds that the PFS of patients with methylated MGMT promoter showed slightly longer survival than that of patients with unmethylated MGMT promoter. In another set of patients who received radiotherapy without any alkylating agents, MGMT promoter methylation was predictive of response to radiotherapy and good prognosis.[21] Although the mechanism of radiation resistance by MGMT activation is not clear, methylated MGMT promoter may be a surrogate marker of as yet unidentified processes, other than TMZ resistance, that contribute to the overall aggressive biology of GBM. Furthermore, cancer-associated DNA methylation may affect the expression of many CpG island-associated genes including MGMT, either modifying sensitivity to radiation or resulting in less aggressive phenotype.[18]

Is ACNU Only a Memory?

In 2000, the Japan Clinical Oncology Group (JCOG) brain tumor study group was discussing how to initiate clinical studies for brain tumors in Japan. One of the foci of the discussion was the standard therapy for GBM at that time. 1-(4-Amino-2-methyl-5-pirimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) was widely used based on a small randomized study in Japan in the 1980s.[26] The response rate was better in the combined treatment arm with ACNU and radiotherapy (47.5% in the combined treatment arm, 13.5% in the simple radiotherapy arm), but the OS was not significantly different (median OS was 14 months and 12 months, respectively). Although the combined therapy with ACNU and radiotherapy was promising, a randomized phase 3 study had not been performed. Nevertheless, without a phase 3 study, the combination of ACNU and radiotherapy was adapted as the standard therapy for malignant gliomas in Japan. The brain tumor study group of JCOG considered this as the community standard of GBM therapy that was made the starting point.

The JCOG 0305 study was a randomized phase 2 study comparing two combined-treatment protocols, ACNU with radiotherapy and procarbazine (PCZ) plus ACNU with radiotherapy. In the PCZ plus ACNU arm, PCZ was administered before ACNU aiming to deplete MGMT and to enhance the chemosensitivity to ACNU.[24] When the phase 2 study cleared a preset boundary of efficacy, the phase 3 study would begin, which was the original design. However, an interim analysis revealed there was no survival advantage of the test arm. This study was discontinued and did not proceed to phase 3. The control arm, ACNU with radiotherapy, achieved a median OS of 16.6 months for GBM, which should have been the basic data for the clinical trials for GBM thereafter in Japan. In 2005, the results of the combination of TMZ and radiotherapy were published as previously mentioned, and the combination of TMZ and radiotherapy became the standard therapy of GBM worldwide. No randomized comparison of ACNU and TMZ has been considered so far, based on the following reasoning.

The HR for death in the radiotherapy plus TMZ arm was 0.63 (95% CI 0.52–0.75; $p < 0.001$).[25] Meta-analysis evaluating the effectiveness of nitrosoureas (mainly BCNU) found the HR was 0.85 (95% CI 0.78–0.91; $p < 0.0001$). Considering the 95% CI, nitrosoureas were not thought to be as good as TMZ. The OS and PFS for GBM patients treated with concomitant and adjuvant TMZ with radiotherapy were 14.6 months and 6.9 months, respectively, whereas those with ACNU and radiotherapy were 16.6 months and 5.1 months based on the JCOG study, respectively. The better OS with ACNU and radiotherapy in Japan was possibly related to salvage therapies including repeat surgeries and stereotactic radiosurgeries, and to elaborate supportive care. The better OS with ACNU treatment was not due to better tumor control by ACNU because the PFSs were similar. Another retrospective report comparing BCNU and TMZ also showed that PFS was not significantly different between the two groups.[29] Severe adverse events (CTCAE grade 3 or higher) are more frequent in ACNU-treated patients than in TMZ-treated patients; leucopenia in 39% and 3% of the patients, respectively.

As the next step, the JCOG brain tumor study group has just started a randomized phase 2 study comparing a combination therapy of interferon-β plus TMZ with radiotherapy and a combination therapy of TMZ with radiotherapy, considering the latter as the standard therapy for GBM (JCOG 0911). This strategy is based on data showing the sensitizing effect of IFN-β for TMZ was possibly due to attenuation of MGMT expression via induction of the protein p53.[16]

When GBM Recurs

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ is available on-line (http://www.nccn.org). The guideline for central nervous system cancers (V.1.2010) states surgical resection should be considered first if recurrent or progressive tumors are resectable. Systemic chemotherapies are indicated if allowed by the performance status of the patients.

Bevacizumab with or without chemotherapy is the first in the list of possible second line chemotherapies for GBM (Table 2). As we learn more about the biology of GBM and its aberrant signaling pathways, the neuro-oncology community has begun to investigate the role of molecular targeted therapies. The angiogenesis pathways and their associated antiangiogenic agents are the most promising topic recently. Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), was first approved in combination with chemotherapy for colorectal, lung, and breast cancers. Despite initial reluctance to evaluate bevacizumab in patients with brain tumors because of concerns with intracranial hemorrhage, the combination of bevacizumab and irinotecan was studied in a single-arm phase 2 study for recurrent GBM.[30] The response rate was 57%, and PFS at 6 months was 46%. These results compared quite favorably with historical data of response rate of 8% and PFS at 6 months of 21% by TMZ for recurrent GBM.[34] To clarify the contribution of irinotecan, a large phase 2 study randomized 167 patients with recurrent GBM to either single agent bevacizumab or bevacizumab plus irinotecan. The response rates were 28% in the single treatment arm with bevacizumab and 38% in the combination arm of bevacizumab plus irinotecan, and the PFS at 6 months was 43% and 50%, respectively.[8] Curiously enough, the randomized design of the trial was not designed to compare outcomes in the two treatment groups, but to evaluate their superiority to the historical results of salvage chemotherapies, 15% of PFS at 6 months, without bias in treatment assignment. Bevacizumab is usually well tolerated, with the most common adverse effects being hypertension and minor bleeding, such as epistaxis. Intracranial hemorrhage occurred in less than 4% of patients and was severe in only approximately 1% of patients.

Table 2 The second-line chemotherapies for recurrent glioblastoma in NCCN guideline

Bevacizumab with/without chemotherapy
Temozolomide
Nitrosourea or PCV
Cyclophsphamide
Platinum-based regimens

NCCN: National Comprehensive Cancer Network; PCV: procarbazine, lomustine, and vincristine.

Individual infiltrative tumor cells tend to grow along preestablished normal cerebral vasculature, so there is no need for tumor-associated angiogenesis from the tumor cells in the central core. Indeed, there is at least a theoretical concern that inhibiting malignant glioma angiogenesis may have little effect on the infiltrative component of the disease and so little impact on the overall survival of the patient. Furthermore, recent laboratory evidence suggests that inhibition of VEGF may actually increase the invasive nature of tumor cells.[19] There seems to be a proinvasive adaptation to anti-angiogenic therapy, as suggested by magnetic resonance imaging in a subset of GBM patients who developed multifocal

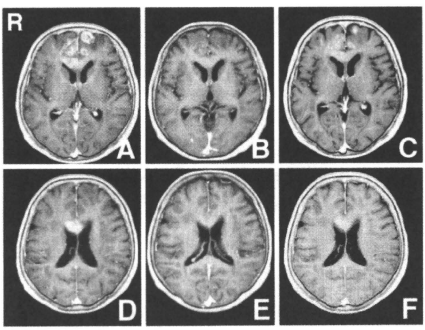

Fig. 1 Initial (A, D) and two follow-up magnetic resonance images 3 days (B, E) and 10 days (C, F) after bevacizumab treatment of a 68-year-old female patient with glioblastoma showing the heterogeneously enhanced tumor regressed 3 days after bevacizumab treatment, but reappeared 7 days later.

recurrence of tumors during the course of therapy with bevacizumab.[6,13,17] The infiltrative tumor cells are most often responsible for clinical relapse and ultimately the death of patients with gliomas. Early results from phase 2 trials showed that incorporation of bevacizumab into the standard initial treatment for newly diagnosed GBM increased median PFS, but prolongation of OS is still unclear. Two large phase 3 trials for newly diagnosed GBM are currently randomizing patients to standard radiotherapy and TMZ with or without bevacizumab.

A unique advantage of bevacizumab is the ability to decrease peritumoral edema. Patients treated with bevacizumab often have decreased corticosteroid dependence secondary to neutralization of VEGF, a known vascular permeability factor. Vascular permeability is decreased in and around the tumor, so decreasing both cerebral edema and the uptake of gadolinium within the tumor. An illustrative case (Fig. 1) showed marked decrease of enhancement on MRI after three days of bevacizumab administration. The decrease in enhancement was not due to tumor shrinkage as the enhancement was regained 7 days later (Fig. 1). As such, the remarkable radiographic response rates and PFS by bevacizumab should be interpreted cautiously.

A couple of successful regimens suggested low dose and continuous TMZ administration as a rechallenge was effective for recurrent disease.[20,33] Due to its usage as the first-line treatment of GBM, TMZ has been no longer considered by many investigators to be a reasonable choice for patients with recurrent GBM. However, alternative schedules of TMZ addressing different pathophysiological mechanisms could be effective even after progression during standard TMZ regimens.[33] There are several rationales supporting TMZ rechallenge. Firstly, there may be a benefit from alternative modes of action, such as antiangiogenic properties of a metronomic regimen. Secondly, as MGMT is inactivated after each reaction of removal of methyl bases (suicide enzyme), exposure to continuous and low-dose TMZ depletes MGMT activities. Thirdly, the schedule of temozolomide permits a greater drug exposure than the conventional schedule of 5 days every 28 days, with comparable or even lower toxicities.

A "one week on/one week off" scheme (150 mg/m^2 at days 1–7 and days 15–21, in a 28-day cycle) has been associated with considerable efficacy and was tolerated by patients. Another alternative is an intensified three out of four weeks approach (75–100 mg/m^2 at days 1–21, in a 28 day cycle). This regimen may yield similar results with respect to efficacy, but a higher rate of toxicity, specifically lymphopenia and infection, has been reported. Another regimen is a metronomic administration of TMZ, 20 mg daily.

The third optional treatment for recurrent GBM is regimens containing nitrosoureas, such as procarbazine, lomustine, and vincristine (PCV) chemotherapy. A randomized trial by the Medical Research Council Brain Tumour Working Party showed no benefit to PCV chemotherapy for newly diagnosed GBM.[12] However, PCV has certain activity, especially for malignant glioma with oligodendroglial component.[3,28] Therefore, this regimen may be important for recurrent GBM.

Cyclophosphamide is among the list of possible chemotherapies for recurrent GBM. However, the reference cited in the NCCN guideline is a report of recurrent anaplastic astrocytomas, and the efficacy of cyclophosphamide for recurrent GBM is not known.[5] Lastly, platinum-based regimens are reported to show modest activities for recurrent GBM.[1,2,7]

On-going Phase 3 Trials for Future Revision of the Standard Therapy

Table 3 shows four on-going randomized phase 3 confirmatory trials for GBM. Another schedule of TMZ administration (RTOG 0525), additive effect of bevacizumab (RTOG 0825, AVAglio), and also possible additive effect of cilengitide, integrin $\alpha v\beta 5$ inhi-

Table 3 Three on-going randomized phase 3 studies for newly diagnosed glioblastoma

Regimen	Organized by	Number of patients
Stupp's regiman with/without bevacizumab	Roche (AVAglio)	920
Stupp's regimen with/without bevacizumab	RTOG 0825	720
Stupp's regimen with/without cilengitide for patients with methylated MGMT promoter status	Merck Serono (CENTRIC)	504
Stupp's regimen vs. adjuvant dose-dense (3-1) temozolomide	RTOG 0525	834

MGMT: O^6-methylguanine-deoxyribonucleic acid-methyltransferase.

bitor, for MGMT promoter methylated GBM (CENTRIC) are to be tested for newly diagnosed patients. In conclusion, the survival of patients with GBM continues to improve, albeit more slowly than we would like. Various new agents are currently under study, singly and in combination. Improved understanding of the complex biology of GBM may allow for more rational and effective therapy selection for patients, further extending survival in the years to come.

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Address reprint requests to: Ryo Nishikawa, M.D., Department of Neuro-Oncology/Neurosurgery, International Medical Center, Saitama Medical University, 1397 Yamane, Hidaka, Saitama 350-1298, Japan.
e-mail: rnishika@saitama-med.ac.jp

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(8)788–794
doi:10.1093/jjco/hyq044
Advance Access Publication 20 April 2010

Clinical Outcomes of Stereotactic Brain and/or Body Radiotherapy for Patients with Oligometastatic Lesions

Tetsuya Inoue[1,*], Norio Katoh[1], Hidefumi Aoyama[1], Rikiya Onimaru[1], Hiroshi Taguchi[1], Shunsuke Onodera[1], Satoshi Yamaguchi[2] and Hiroki Shirato[1]

[1]Department of Radiology, Hokkaido University Graduate School of Medicine and [2]Department of Medical Physics, Hokkaido University Graduate School of Medicine, Sapporo, Japan

*For reprints and all correspondence: Tetsuya Inoue, Department of Radiology, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: t-inoue@med.hokudai.ac.jp

Received November 30, 2009; accepted March 11, 2010

Objective: Several recent studies have shown that oligometastatic disease has curative potential, although it was previously considered to signal a patient's last stage of life. Stereotactic body radiotherapy has been available for extra-cranial metastases in addition to stereotactic cranial radiotherapy for brain metastases. The aim of the present study was to retrospectively evaluate the clinical outcomes of stereotactic radiotherapy for patients with oligometastatic lesions.

Methods: Between 1999 and 2008, 41 patients with five or fewer detectable metastases were treated with stereotactic radiotherapy at our institution. The treated oligometastatic lesions were in the brain, lung and adrenal glands.

Results: With a median follow-up period of 20 months, the 3-year overall survival, progression-free survival, local control and distant control rates were 39%, 20%, 80% and 35%, respectively, and the respective 5-year rates were 28%, 20%, 80% and 35%. The median survival time was 24 months. According to interval to recurrence, the 3- and 5-year overall survival rates were 19% and 10%, respectively, for patients with <12 months ($n=18$), compared with 53% and 40% for those with ≥ 12 months ($n=23$) ($P=0.006$).

Conclusions: Precise stereotactic radiotherapy was effective in controlling oligometastatic lesions for patients with a median survival time of 24 months. Interval to recurrence may impact the overall survival rate and should be included in the stratification criteria in a prospective randomized trial to investigate the benefits of stereotactic radiotherapy for patients with oligometastases.

Key words: oligometastases – stereotactic body radiotherapy – stereotactic radiotherapy – radiosurgery

INTRODUCTION

Most patients who have had any recurrent or metastatic sites of cancer are considered to be in their last stage of life. However, stereotactic cranial radiosurgery (SCRS) and stereotactic cranial radiotherapy (SCRT) have been shown to be useful for prolonging useful life in patients with solitary or oligo brain metastases with or without whole brain radiotherapy (WBRT) (1,2). The treatment outcomes are related to the number of metastases and the presence or absence of extra-cranial disease (3). A Phase III study has suggested that SCRS with WBRT results in better survival than WBRT alone for patients with a single brain metastasis or patients with tumors > 2.0 cm in diameter (4). These studies have shed light on the possibility of improving treatment outcomes by using high-dose local radiotherapy with or without whole-body cancer treatment in patients with extra-cranial metastasis.

Stereotactic body radiotherapy (SBRT) with high local dose has been applied to extra-cranial diseases such as peripheral Stage I non-small cell lung cancer (NSCLC) and has been reported to provide excellent local control (LC) and survival compatible with surgery (5,6). Recently, indications for SBRT have been extended to include lung metastases (7–9), liver metastases (10,11), adrenal gland metastases (12,13), spinal metastases (14–16), and others (17). Excellent LC has been reported in these reports, but the clinical benefits of SBRT for extra-cranial metastasis are yet to be determined. In most of these studies, SBRT was used for patients with fewer than five metastatic sites or for those in the clinical state of so-called oligometastasis (18).

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum (18), who hypothesized that LC of oligometastases may yield improved systemic control and prolonged survival. Niibe et al. (19–21) have also reported the state of oligometastasis/oligo-recurrence. They suggested that some oligometastasis/oligo-recurrence patients could survive for as long as the patients with primary cancer only, and thus these patients must be treated curatively. Improvements in diagnostic modalities have facilitated early detection of small metastatic lesions, both intra-cranial and extra-cranial, and have provided a sound rationale for Hellman and Weichselbaum's hypothesis. Recent clinical research has shown that some patients with recurrence or distant metastases can expect long-term survival after SBRT and SCRT (7–11,19–23). It remains uncertain whether these results are due to selection bias or some positive effect of SBRT and SCRT. A prospective randomized trial should be undertaken to answer this question, but prognostic factors to stratify the patients are not yet well understood.

In this study, we retrospectively analyzed our experience with SBRT and/or SCRT/SCRS for patients with oligometastases.

PATIENTS AND METHODS

Patient Characteristics

A database of patients who received SBRT and SCRT/SCRS at our institution was used to select the patients whose primary sites were treated by surgery or definitive radiation therapy between 1995 and 2007. There were 41 patients who had five or fewer detectable oligometastatic lesions at the time of SBRT and/or SCRT and had been treated with SBRT and/or SCRT/SCRS between 1999 and 2008. Diagnosis of the oligometastatic lesions was based on whole-body computed tomography (CT) and brain magnetic resonance imaging (MRI) findings. Fluorodeoxyglucose-positron emission tomography was performed as needed. The oligometastatic lesions were diagnosed by diagnostic radiologists during the diagnostic evaluation.

The treatment methods for the primary sites were surgery in 23 patients and definitive radiotherapy in 18. Definitive radiotherapy consisted of conventional radiotherapy in 8 patients and SBRT in 10.

There were seven patients who had previously been treated by SBRT and/or SCRT/SCRS to oligometastatic sites prior to receiving surgery or radiotherapy at their primary sites. The treatment time interval between the surgery/definitive radiation therapy to the primary sites and the initial SBRT and/or SCRT/SCRS to oligometastatic sites ranged from 1 to 4 months (median 2 months) in these seven patients. In the other 34 patients, the median treatment interval time from primary sites to oligometastatic sites was 21 months (range 0–121 months). We defined the treatment interval time from primary sites to oligometastatic sites as interval to recurrence. In this study, all analyses started from the day of SBRT and/or SCRT/SCRS to oligometastatic sites.

The patient characteristics are given in Table 1. There were 22 men and 19 women, and the median age was 66 years (range 30–82 years). The primary cancers consisted of lung cancer, head and neck cancer, breast cancer, colorectal cancer, renal cell carcinoma, renal pelvic cancer, hepatocellular carcinoma, thymic cancer and apocrine gland cancer. The study patients were separated into a favorable group (breast, colorectal, renal, thymic and apocrine gland cancer) and others, according to Rusthoven et al. (10). The primary histology was mainly adenocarcinoma. The number of oligometastatic tumors was mainly one or two tumors; there were only two patients who had three oligometastatic tumors and only one patient who had five. The sites involved with the oligometastatic lesions were the brain, lung and adrenal gland. Lung and adrenal gland metastases were treated by SBRT. There were no patients with oligometastatic liver metastases treated by SBRT at our institution. Fourteen patients were treated by chemotherapy as an adjuvant therapy or as a treatment for recurrence or metastases. No chemotherapy was administered during the treatment for oligometastases. No patients underwent surgical removal of the metastatic lesions.

There were 24 patients who had single or multiple brain metastases. Brain metastases were treated by SCRT or SCRS. According to the recursive partitioning analysis, 5, 18 and 1 patients were classified as Class I, Class II and Class III, respectively.

SCRT/SCRS Technique

Fifteen of 24 patients were treated by SCRT alone, five by SCRS alone and four by SCRS with WBRT for their brain metastases. The patients who received WBRT were randomly assigned to the group of SCRS with WBRT by the clinical trial of the Japanese Radiation Oncology Study Group (JROSG 99-1) (2). These patients were treated with 6- or 10-MV photons using a linac-based stereotactic system and were immobilized by a thermoshell in SCRT and a stereotactic frame in SCRS. The gross tumor volume (GTV) was defined based on MRI and CT images. A 1–3-mm

Table 1. Patient characteristics (41 patients)

Characteristics	Value
Age (years)	
Median	66
Range	30–82
Gender (*n*)	
Male	22
Female	19
Primary cancer (*n*)	
Lung	25
Head and neck	6
Breast	3
Colorectal	2
Liver	1
Renal	1
Renal pelvic	1
Thymic	1
Apocrine gland	1
Primary histology (*n*)	
Adenocarcinoma	23
Squamous cell carcinoma	6
Thyroid cancer	2
Large cell carcinoma	2
Others	8
Treatment for primary cancer (*n*)	
Resection	23
SBRT	10
Conventional radiation therapy	8
Sites involved with oligometastatic disease (no. of tumors)	
Brain	33
Lung	22
Adrenal gland	5
Number of oligometastatic tumors (*n*)	
1	27
2	11
3	2
4	0
5	1
Number of oligometastatic involved organs (*n*)	
1	37
2	4

SBRT, stereotactic body radiotherapy.

margin was added to the GTV to create the planning target volume (PTV). Treatment was prescribed to the 100% isodose line, with the 80–90% isodose line covering the PTV. A total dose of 15–25 Gy was administered in one fraction for SCRS, and a total dose of 20–40 Gy was administered in four fractions for SCRT. A total dose of 30 Gy was administered in 10 fractions for WBRT.

SBRT Technique

All patients with lung metastases and 10 patients with primary lung cancer received SBRT as the definitive radiotherapy. They received real-time tumor-tracking radiotherapy (RTRT). The RTRT system has been described in detail elsewhere (24,25). In brief, 1.5–2.0-mm gold markers were implanted near the tumor by means of image-guided procedures. CT scans were taken with the patients holding their breath at the end of normal expiration. The GTV was contoured in axial CT images. The clinical target volume (CTV) was defined three dimensionally as the GTV on CT with a 6–8-mm margin for primary lung cancers and was considered to be equal to the internal target volume. We treated adrenal gland metastases using the RTRT system. The CTV was defined as the GTV on CT with a 3-mm margin for adrenal gland metastases and with a 5-mm margin for lung metastases. The PTV was three dimensionally defined as the CTV plus a 5-mm margin with optimal reduction near the organ at risk.

Treatment was prescribed to the 100% isodose line covering the PTV within the 80% isodose line. Patients were treated with 4-, 6- or 10-MV photons. SBRT was delivered by using multiple non-coplanar static ports. A total dose of 48 Gy was administered in eight fractions in patients with adrenal gland metastases. A total dose of 35–60 Gy was administered in four or eight fractions in patients with lung metastases or primary lung cancer, respectively.

Statistical Analysis

LC was defined as no progression of the tumor in the CTV, and marginal recurrence was counted as local failure in this study. Follow-up of the patients was based on clinical examination in the outpatient clinic and/or periodic radiological examination. In principle, radiological examinations such as chest X-ray, whole-body CT and brain MRI were performed once every 3–4 months, but the frequency strongly depended on the clinical situation. The overall survival (OS) and progression-free survival (PFS) rates were calculated from the day of SBRT and/or SCRT/SCRS to oligometastatic sites using the Kaplan–Meier method.

Possible prognostic factors were as follows: age, gender, primary cancer, primary histology, treatment for primary cancer, sites involved with oligometastatic disease, number of oligometastatic tumors and the treatment interval time from primary sites to oligometastatic sites (defined as interval to recurrence). The log-rank test was used to calculate the statistically significant differences. A value of $P < 0.05$ was considered to be statistically significant. Significant variables on univariate analysis (UVA) were tested with

multivariate analyses (MVA). MVA was performed using a Cox proportional hazards regression model.

RESULTS

Local Tumor Response and Distant Metastases

The median follow-up period was 20 months (range 1–111 months). The 3- and 5-year LC rates were each 80%, and the 3- and 5-year distant control (DC) rates were each 35% (Fig. 1).

Survival

The 3-year OS and PFS rates were 39% and 20%, respectively; and the respective 5-year rates were 28% and 20% (Fig. 2). The median survival time (MST) was 24 months. Patients with adrenal gland metastasis had an MST of 15 months.

Age, primary histology and the number of oligometastatic tumors were not found to be statistically significant prognostic factors for the OS rate; however, gender, primary cancer, treatment for primary cancer, oligometastatic lung disease and interval to recurrence were statistically significant prognostic factors for the OS rate in the UVA shown in Table 2.

The OS of female patients was significantly longer than that of male patients ($P = 0.01$), and the OS of patients who had undergone resection for primary cancer was significantly longer than those of others ($P = 0.0006$). For patients with primary cancer from favorable primary sites ($n = 8$), the 3- and 5-year OS rates were both 86%, compared with 27% and 17%, respectively, for patients with primary cancer from other primary sites ($n = 33$, $P = 0.02$). We separated the patients into two groups according to interval to recurrence of <12 or ≥ 12 months ($n = 18$, 23, respectively). The 3- and 5-year OS rates were 19% and 10%, respectively, for those with an interval to recurrence of <12 months, compared with 53% and 40%, respectively, for those with an interval to recurrence of ≥ 12 months (Fig. 3; $P = 0.006$). For patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$), the 3- and 5-year OS rates were both 63%, compared with 22% and 14%, respectively, for patients with only brain/adrenal metastases ($n = 25$) (Fig. 4; $P = 0.009$). MVA showed no statistically significant prognostic factors for the OS rate.

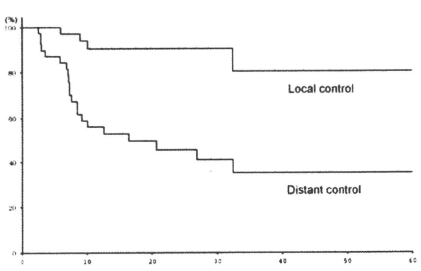

Figure 1. Kaplan–Meier actuarial local control and distant control rate.

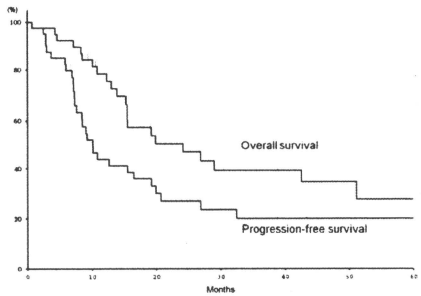

Figure 2. Kaplan–Meier actuarial overall survival (OS) and progression-free survival rate.

Table 2. UVA and MVA for OS rate

Variables	*P* value	
	UVA	MVA
Age		
<65 years	0.72	
Gender		
Female[a]	0.01*	0.72
Primary cancer		
Favorable[a]	0.02*	0.37
Primary histology		
Adenocarcinoma	0.84	
Treatment for primary cancer		
Resection[a]	0.0006*	0.26
Sites involved with oligometastatic disease		
Brain	0.09	
Lung	0.009*	0.47
Adrenal gland	0.09	
Number of oligometastatic tumors		
Single metastasis	0.47	
Interval to recurrence		
≥12 months[a]	0.006*	0.52

UVA, univariate analysis; MVA, multivariate analysis; OS, overall survival.
*Significant ($P < 0.05$).
[a]These variables were favorable predictors for overall survival rate on UVA.

Long Survivors

Four 5-year survivors consisted of two with lung adenocarcinoma, one with renal pelvic cancer and one with thymic cancer. One patient with lung adenocarcinoma had one brain metastasis treated by SCRT, whereas the other patient with lung adenocarcinoma had one brain metastasis treated by SCRS with WBRT and one lung metastasis treated by SBRT. The patient with renal pelvic cancer had two lung metastases treated by SBRT, and the patient with thymic cancer had one lung metastasis treated by SBRT.

Toxicities

Adverse effects were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0. Grade 2 complications occurred in four patients (9.8%), radiation necrosis of the brain occurred in three patients and intercostal neuralgia occurred in one patient. No other adverse effects of Grade 2 or more were observed.

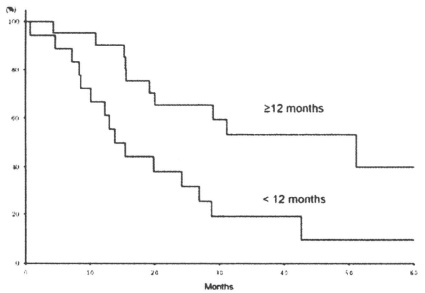

Figure 3. Kaplan–Meier curve of OS rates for patients with interval to recurrence of <12 months ($n = 18$) and ≥ 12 months ($n = 23$). Significant statistical difference was found ($P = 0.006$) between the two groups.

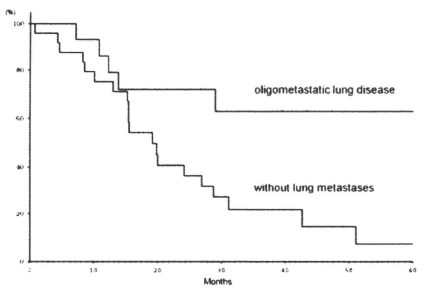

Figure 4. Kaplan–Meier curve of OS rates for patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$) and only brain/adrenal metastases ($n = 25$). Significant statistical difference was found ($P = 0.009$) between the two groups.

DISCUSSION

In this study, the OS rates at 3 and 5 years were 39% and 28%, respectively, and the MST was 24 months, which is equivalent to that in the study of oligometastases previously published, as follows. Milano et al. (22) reported the results of a Phase II trial using SBRT to a dose of 50 Gy in 10 fractions in the treatment of oligometastatic disease with 4-year OS, PFS, LC and DC rates of 28%, 20%, 60% and 25%, respectively. Patients with breast cancer fared significantly better with respect to OS, PFS, LC and DC rates (26), and those with adrenal metastases had significantly worse OS, LC and DC rates (13).

Rusthoven et al. (9,10) have recently reported the results of multi-institutional Phase I/II trials of SBRT for lung and liver metastases. The actual LC rate at 1 and 2 years after SBRT for oligometastatic lung tumors were 100% and 96%, respectively, and the MST was 19 months. The actual in-field LC rates at 1 and 2 years after SBRT for oligometastatic liver tumors were 95% and 92%, respectively, and the MST was 20.5 months. The primary tumor site was significantly predictive of survival. Primary tumors of the lung and ovary as well as non-colorectal gastrointestinal malignancies were found to be associated with poorer survival compared with breast, colorectal, renal, carcinoid and gastrointestinal stromal tumors as well as sarcoma.

Flannery et al. (23) have reported long-term survival in patients with synchronous solitary brain metastasis from NSCLC treated with radiosurgery. The MST was 18 months, and the 1-, 2- and 5-year actuarial OS rates were 71.3%, 34.1% and 21%, respectively. For patients who underwent definitive thoracic therapy, the 5-year actuarial OS rate was 34.6% compared with 0% for those who had non-definitive therapy. The Karnofsky performance status (KPS) also significantly impacted the OS rate.

SBRT and SCRT have been applied for the treatment of metastatic lesions recently; however, conventional radiotherapy remains a standard option for the treatment of metastatic lesions. Andrews et al. (4) reported the result of a Phase III study that compared WBRT with or without SCRS for brain metastases. This study showed WBRT with SCRS improved survival for patients with single brain metastasis or patients with tumors > 2.0 cm in diameter. To our knowledge, there has been no study that compared SBRT with conventional radiotherapy for extra-cranial metastases.

It is important to find prognostic factors related to long-term survival after definitive therapy such as SBRT and SCRT for oligometastatic lesions. According to the studies described above, KPS, the primary tumor site and the oligometastatic site can be predictive of survival. Low KPS, a primary tumor site such as the lung and adrenal metastasis were found to be associated with lower survival in the