scanning, image fusion, surgical planning, registration for navigation, and updating of navigation images. The progenitor of our system was first described by the Erlangen University group, and that system has been improved stepwise over a number of years.[32] Our system is a fully integrated architecture incorporating such improvements, so is almost functionally equal to the current system in Erlangen. In the first year following installation, we operated mainly on brain tumors, but also other diseases including cerebrovascular and functional diseases. The effectiveness and feasibility of intraoperative MR imaging for these diseases is still controversial.[6,42]

The present study describes the layout and features of our intraoperative MR imaging system, and analyzes our initial experiences of 100 consecutive procedures performed in the first year, and discuss the indications and limitations of this system.

Materials and Methods

I. Features of the operation theater

Figure 1 shows the appearance of our 10.5 × 6.6 m operating room, BrainSUITE®. The walls, floor, and ceiling contain radiofrequency shielding based on aluminum and copper mesh. The high-field-strength (1.5 T) MR imager (Magnetom Symphony; Siemens Healthcare, Erlangen, Germany) consists of a superconductive magnet with a length of 160 cm and an inner bore diameter of 60 cm, and a gradient system with a maximum field strength of 30 mT/m and an effective slew rate of 125 T/m/sec. The performance is equivalent to systems used for diagnostic imaging. An elliptical line (8-m major and 5-m minor axis) is drawn around the scanner to mark the 5-gauss field limit for safety. The operating table is positioned parallel to the scanner during surgery so that the patient's head lies outside the 5-gauss line. Therefore, standard surgical instruments can be used regardless of magnetic properties (ferromagnetic or non-ferromagnetic). The connection between the table and head-holder is a ball-and-socket joint that allows the head-holder orientation to be freely adjusted. When imaging is necessary, the table is rotated manually by 180 degrees about a vertical axis to align it with the scanner bore.

The head-holder has a bivalve shape, consisting of two parts, and contains an 8-channel receiver array. The upper part of the head-holder is sterilized with plasma and placed above the operating field for MR imaging, but is removed during surgery. Rapid automatic image registration is realized with a reference array attached to the upper part of the head-holder. The array contains 14 MR imaging-visible fiducial markers as well as 4 infrared reflector spheres that are continuously tracked by a ceiling-mounted infrared camera. Navigation is accomplished with an error of less than 0.6 mm.

The anesthesia equipment is MR imaging-compatible (Estiva 5; Datex-Ohmeda, Inc., Madison, Wisc., U.S.A.). Inhalation and exhalation ducts are approximately 6 m in length to allow the table to rotate and move into the scanner. The neuro-microscope (NC4 multivision scope; Zeiss, Oberkochen, Germany) is ceiling-mounted outside the 5-gauss line. Navigation-related information is sent to the neuro-microscope so that the configuration of objects (e.g. tumor and pyramidal tract) can be superimposed over the surgical field in the microscope view. Surgical equipment in contact with the patient's body (e.g., scalp clamps, aneurysm clips) must be MR imaging-compatible to prevent burns and image degradation.

II. Patient population

One hundred consecutive patients, 51 males and 49 females aged 13 to 80 years (mean 50.7 years), were treated in the BrainSUITE® at Nagoya Central Hospital between August 2006 and August 2007. Surgeries that were thought to have the potential to benefit from intraoperative MR imaging and navigation were scheduled. Emergency surgeries were not performed. Patients were treated for brain tumors (n = 87, 87%), vascular diseases (n = 11, 11%), and functional diseases (n = 2, 2%). Histological examinations revealed gliomas (n = 38; World Health Organization grade 2 n = 7, grade 3 n = 10, glioblastoma multiforme n = 21), meningioma (n = 14), pituitary adenoma (n = 9), metastatic tumor (n = 9), schwannoma (n = 6), craniopharyngioma (n = 3), germinoma (n = 2), malignant lymphoma (n = 2), epidermoid (n = 1), cavernoma (n = 1), tuberculoid granuloma (n = 1), and arachnoid cyst (n = 1). Craniotomy and tumor removal were performed in 70 patients (70/87), and navigation-based stereotactic biopsy was performed in 17 patients (17/87). Surgery for vascular diseases consisted of clipping for cerebral aneurysms (n = 7; unruptured 6, ruptured 1), superficial temporal artery-middle cerebral artery (STA-MCA) bypass for internal carotid artery occlusion (n = 3), and removal of an arteriovenous malformation (n = 1). Surgery for functional diseases included subthalamic nucleus-deep brain stimulation (STN-DBS) for advanced Parkinson's disease (n = 1), and microvascular decompression (MVD) for trigeminal neuralgia (n = 1). The local ethical committee approved the clinical utilization of intraoperative high-field MR imaging as well as the navigation system, and signed informed consent was

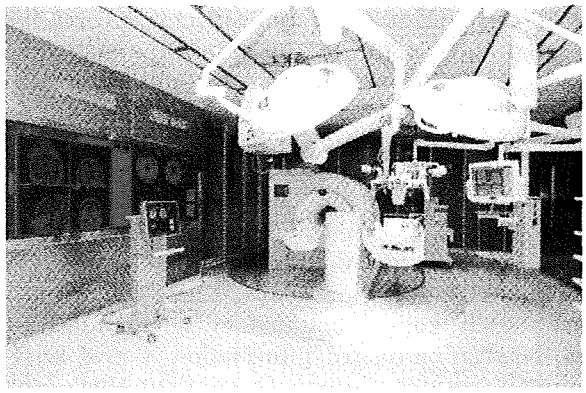

Fig. 1 Photograph showing the integrated intraoperative magnetic resonance imaging and neuro-navigation system (BrainSUITE®): The 50-gauss (*red*) and 5-gauss (*yellow*) lines are marked on the floor. The imager, operating table, and operating microscope are all integrated with the navigation system.

provided by all patients prior to surgery.

III. Brain tumor surgery

Surgical planning was based on multiple sequences of MR images taken 1 or 2 days before surgery. Target lesions and important anatomical structures were coded as colored objects (Fig. 2A). Image fusion was used to integrate and display metabolically interesting areas of gliomas suggested by [^{18}F]fluorodeoxyglucose-PET, [^{11}C]L-methionine-PET, or MR spectroscopy. Diffusion tensor imaging was performed to visualize the major white matter tracts such as the pyramidal tract or optic radiation. Preoperative functional MR imaging was used to identify the primary motor cortex or language centers. On the day of surgery, the first MR imaging was performed after positioning, but before the operation started, to provide a reference for navigation (reference MR image). This process was necessary to ensure a low registration error. The preoperatively coded objects described above were then incorporated through automatic image registration and fusion, a process requiring less than 20 seconds. During craniotomy and microsurgery, standard surgical instruments were utilized. If the tumor was located in or around the pyramidal tract, electrophysiological monitoring such as somatosensory-evoked potential and/or motor-evoked potential (MEP) monitoring was used (Bravo; Nicolet Biomedical, Madison, Wisc., U.S.A.) in combination with diffusion tensor imaging tractography.

Intraoperative MR imaging was performed when the surgeon considered that the goal of surgery had

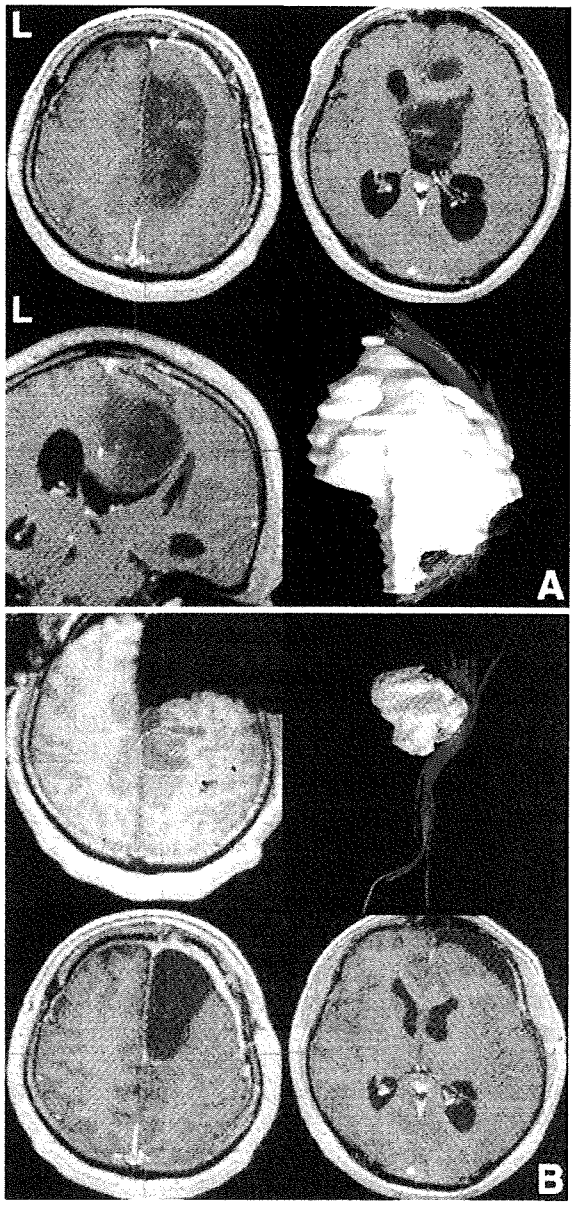

Fig. 2 A 35-year-old male with an anaplastic astrocytoma in the right frontal lobe extending to the third ventricle. A: Preoperative magnetic resonance (MR) images (*upper row*) and surgical planning images (*lower row*) showing the pyramidal tract (*rainbow*) and the tumor (*yellow*). The pyramidal tract was shifted posterior and laterally by the tumor. B: Intraoperative MR images (*upper row*) revealing a tumor remnant (*orange line*) anterior to the pyramidal tract, resulting in resumption of resection, and total removal of the tumor (*lower row*). The patient developed hemiplegia postoperatively, which completely resolved after 1 week (supplementary motor area syndrome).

Table 1 Sequences and parameters used in BrainSUITE®

	Sequences	TR (msec)	TE (msec)	TI (msec)	FA (°)	FOV (mm)	Thickness (mm)	No. of slices	Parallel imaging	Scan time (min.sec)
Tumors (gliomas)	3D T1WI (3D FLASH)	11	5.2	0	15	282	1.1	160	-	5.06
	3D T1WI (3D MPRAGE)	2160	4.38	1100	15	282	1.1	160	+	3.55
	3D T2WI (3D TSE)	3200	580	0	variable	282	1.1	160	+	4.43
	3D FLAIR (3D TSE)	6000	402	0	variable	282	2.2	64	+	4.50
	DTI (SE-EPI)	7500	99	0	90	320	2.5	50	+	5.39
	CSI	1600	135	0	90	120×120	20.0	1	-	7.41
	fMR imaging (FID-EPI)	3500	50	0	90	192	3.0	35	-	4.16
Pituitary tumors	2D T2WI (2D TSE)	3630	105	0	90	190	1.6	14	+	5.50
	3D T1WI (3D FLASH VIBE)	10	3.65	0	12	190	0.7	128	+	6.32
Vascular diseases	DWI (SE-DWI)	3500	107	0	90	260	5.0	19	+	1.19
	MR angiography (3D TOF)	39	7.1	0	25	240	0.9	40	+	6.05
	PWI (FID-EPI)	230	1000	0	90	40	5.0	10	+	1.28
Functional diseases	2D STIR	8900	92	180	180	230	1.5	25	+	7.18
	3D T1WI (3D FLASH)	11	5.2	0	15	282	1.1	160	-	5.06
	CISS	10.18	5.09	0	70	200	0.8	60	-	5.46

CISS: constructive interference in steady state, CSI: chemical shift imaging, 3(2)D: three(two)-dimensional, DTI: diffusion tensor image, DWI: diffusion-weighted image, EPI: echo planar image, FA: flip angle, FID: free induction decay, FLASH: fast low-angle shot, fMR: functional magnetic resonance, FOV: field of view, MPRAGE: magnetization prepared rapid gradient echo, PWI: perfusion-weighted image, SE: spin echo, STIR: short time to inversion recovery, TE: echo time, TI: time to inversion, TOF: time of flight, TR: repetition time, TSE: turbo spin echo, T1(2)WI: $T_{1(2)}$-weighted image, VIBE: volume interpolated breath-hold examination.

been met, or after a significant brain shift had occurred. Frequently used imaging parameters are shown in Table 1. Contrast enhancement used 0.2 ml/kg of gadolinium. Diffusion tensor imaging was obtained intraoperatively as well.[29] If intraoperative MR imaging indicated incomplete resection, surgical planning was revised with the newly obtained images, and the surgical procedure was resumed under the updated navigation information (Fig. 2B).

IV. Surgery for cerebrovascular and functional diseases

Three-dimensional (3-D) T_1-weighted MR imaging (fast low-angle shot [FLASH], magnetization-prepared rapid gradient-echo), MR angiography, and diffusion-weighted MR imaging were performed before and after clipping surgery. Navigation was employed in some cases, including one complex aneurysm of the anterior communicating artery. Constructive interference in the steady state (CISS) MR imaging was added before and after MVD in a patient with trigeminal neuralgia. Frame-based stereotaxy was performed with a Leksel stereotactic frame (Elekta, Stockholm, Sweden) to treat Parkinson's disease with STN-DBS. 3-D FLASH MR imaging and short time inversion recovery MR imaging were performed after loading the frame for the initial targeting. Microelectrode recording was performed (Lead-Point®; Medtronics, Minneapolis, Minn., U.S.A.) for electrophysiological confirmation. To assure positional accuracy after electrode implantation, 3-D FLASH imaging was acquired with the specific absorption rate limited to 0.1 W/kg or less following the safety guidelines recommended by Medtronics.[37]

V. Data analysis

Each procedure was evaluated with respect to the usefulness of intraoperative images and navigation, technical problems, and patient outcomes. Any effect of intraoperative MR imaging on the surgical strategy was also documented, such as extension of the tumor resection, or correction of the catheter, electrode, or biopsy needle position. The extent of the brain tumor resection was calculated based on manual segmentation of the tumor outline in the planning software. Glioma volume was defined as the volume of increased intensity on T_1-weighted images with contrast medium. Tumor volume for non-enhanced tumors was defined as the area of increased intensity on T_2-weighted images. Subtotal or greater resection was defined as more than 95% of the tumor volume absent postoperatively. We did not use the term total resection for gliomas because of their characteristic infiltrating progression. The postoperative neurological condition of all patients was documented.

Table 2 Modification of surgical strategy by intraoperative magnetic resonance images in BrainSUITE®

	Subgroups	No. of cases		Percentage
		Total	With modification	
Glioma	overall	38	27	71.1
	subtotal resection	22	21	95.4
	partial resection	9	6	66.6
	biopsy	7	0	0
Pituitary tumor	overall	9	4	44.4
	total resection	7	3	42.8
	partial resection	2	1	50
Meningioma	overall	14	2	14.2
	total resection	13	1	7.6
	partial resection	1	1	100
Schwannoma	overall	6	1	16.7
	total resection	5	0	0
	partial resection	1	1	100
Metastatic tumor	overall	9	3	33.3
	total resection	5	1	20
	biopsy/cyst aspiration	4	2	50
Others	overall	11	3	27
	total resection	5	2	40
	biopsy/cyst aspiration	6	1	16.7
Vascular diseases		11	0	0
Functional diseases		2	0	0
Total		100	40	40

Results

Intraoperative MR imaging, including reference MR imaging, was performed 242 times during the 100 procedures. No incident was caused by the ferromagnetic instruments. The period of interruption for each intraoperative MR imaging session was approximately 20 minutes, depending on the imaging sequences. Intraoperative MR imaging affected the surgical strategy in 40 of the 100 cases, most frequently in the glioma group (27/38), and less so in the other tumor group (13/49). These results are summarized in Table 2. The surgical strategy was not modified after intraoperative MR imaging for cerebrovascular or functional diseases, but intraoperative MR imaging confirmed the success of each procedure while the patient was still on the operating table.

I. Glioma surgery

Gliomas (n = 38) were located as follows: frontal lobe, n = 18; temporal lobe, n = 2; parietal lobe, n = 3; occipital lobe, n = 1; frontoparietal lobe, n = 3; frontotemporal lobe, n = 2; temporo-occipital lobe, n = 4; insula, n = 2; thalamus, n = 1; and cerebellum, n = 2. Craniotomy and tumor resection were performed in 31 cases, and navigation-guided biopsy in 7 cases. Intraoperative MR imaging was taken 2 to 5 times (mean 2.8). Intraoperative MR imaging modified the surgical strategy in 27 of the 38 patients. Subtotal or greater resection was achieved in 22 of the 31 cases. Intraoperative imaging revealed tumor remnants in 21 of these 22 cases, resulting in the resumption of surgery. A representative case is shown in Fig. 2. Some tumor was intentionally left to prevent neurological deterioration in 10 cases. Intraoperative imaging contributed to the identification of the optimal location and volume of the intentional remnant in 6 of these 10 cases. Diffusion tensor imaging-based tractography was performed combined with MEP monitoring (employing transcortical and direct white matter stimulation) in 19 cases, and without MEP monitoring in 25 cases. Postoperatively, 5 patients showed transient deterioration of motor functions, but improved to the baseline within 1 day to 2 weeks. One patient experienced wound infarction which required debridement later. One patient with glioblastoma arising from the medial thalamus developed deep vein infarction postoperatively, and suffered from prolonged disturbance of consciousness. This was the most severe complication in the series.

II. Other tumor surgeries

Intraoperative MR imaging was performed 2 to 3

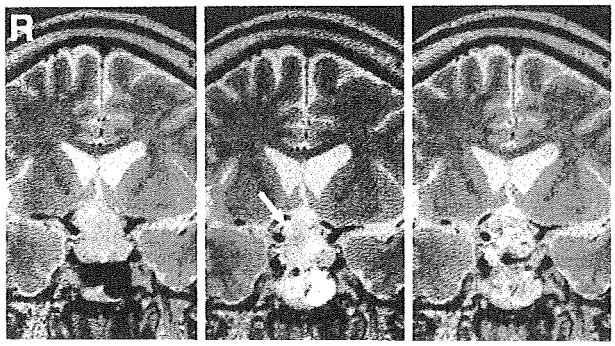

Fig. 3 **A 51-year-old male with a non-functional pituitary adenoma treated through an endoscopic transnasal approach. Preoperative (*left*) and intraoperative magnetic resonance (MR) images (*middle*) revealing a tumor remnant behind the fold of the arachnoid membrane (*arrow*), which was not visible through the endoscope, and final intraoperative MR image (*right*) confirming complete resection.**

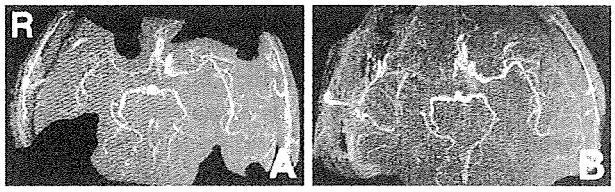

Fig. 4 **A 49-year-old male with right internal carotid artery occlusion treated by right double superficial temporal artery-middle cerebral artery (MCA) anastomoses. Intraoperative magnetic resonance (MR) imaging was taken before and after anastomoses, including MR angiograms (A, B). Immediately following anastomoses, MR angiograms showed good patency of the bypass and improved delineation of vascularity in the MCA area.**

times (mean 2.2). Overall, gross total resection was achieved in 35 of the 39 cases, excluding 10 biopsy cases (Table 2). Intraoperative imaging revealed tumor remnants in 7 patients. Simpson grade 2 or better resection was achieved in all cases of meningioma (n = 14) except for one. Image fusion with the bone window 3-D computed tomography was useful if the tumor was located at the skull base. Pituitary adenomas (n = 9) were treated through a transcranial approach in 4 cases and endoscopic transnasal approach in 5 cases. Total resection was achieved in 7 cases. The endoscope and instruments were used without complications outside the 5-gauss line. Besides 3-D T_1-weighted images, thin slice sagittal and coronal T_2-weighted images were useful to identify tumor remnants (Fig. 3). For schwannoma cases (n = 6), total resection was performed in 5 cases. For metastatic tumors (n = 9), total resection was performed in 5 cases, and biopsy or aspiration of the cyst was performed in the remaining cases. The surgical strategy was frequently modified following intraoperative MR imaging for pituitary adenomas (44.4%) as well as for metastatic tumors (33.3%) as summarized in Table 2.

III. Surgery for cerebrovascular and functional diseases

MR angiography showed good patency of the anastomosis site in all cases of STA-MCA anastomosis (n = 3) (Fig. 4). MR angiography had difficulties in evaluating the vasculature around the clipping site due to artifacts. However, diffusion-weighted imaging was useful to rule out acute ischemic complications.

Microelectrode recording was successfully performed using the ordinary device in the STN-DBS procedure. The magnetic field did not interfere with the recording, and the signal/noise ratio was better than that recorded in a standard operating room. The 3-D T_1-weighted imaging (FLASH) demonstrated correct placement of the electrode. CISS images clearly demonstrated that the decompression was successful after MVD for trigeminal neuralgia.

Discussion

High-field intraoperative MR imaging has several advantages over low-field MR imaging. The quality of intraoperative images obtained at a high field is almost equal to that of preoperative images, and this leads to more reliable information derived from the visualization of anatomical structures and residual tumor. The higher intrinsic signal/noise ratio with a high field allows us to acquire a higher spatial resolution in a given scan time. Various sequences are available. Diffusion tensor imaging, which is feasible with high-field but is difficult with low-field MR imaging, can visualize the course of subcortical tracts. Obvious disadvantages of high-field MR imaging are the high initial cost, the large space required due to the relatively wide magnetic fringe field, and the necessity for extra safety precautions in the vicinity of the super-conducting magnet.

The best use for the integrated navigation and intraoperative high-field MR imaging system seems to be glioma surgery. In our series of gliomas, the rate

of greater than subtotal resection was 71%, which is almost equal to or better than the rates reported previously.[15,16,25,38] The findings of intraoperative imaging modified the surgical strategy in 71.1% of patients with gliomas, the highest among our cases of brain tumors, indicating that glioma surgery was the best indication.

This system provides three advantages for glioma surgery. Firstly, updating navigation with intraoperative images compensated for the "brain shift" caused by withdrawal of cerebrospinal fluid and/or mass reduction of the tumor. Secondly, high-field MR imaging could provide diffusion tensor imaging-based tractography intraoperatively. Less than 10 minutes was required for both measurement of diffusion tensor imaging and computation of tractography. Artifacts were seen at the surface of the brain, but not at subcortical locations, so this technique was especially useful for visualizing the subcortical tracts. The importance of tractography for the preservation of motor function in gliomas is well known.[12,34] However, brain shift must also be considered. The maximum shift in white matter is reported to range from −8 to +15 mm intraoperatively,[30,31] consistent with our experience. Since our system allowed tractography to be updated intraoperatively, safety was maintained even after the brain shift had occurred. Furthermore, the combination of tractography and MEP monitoring with direct white matter stimulation improved monitoring accuracy.[1,13,14,21] We found that tractography based on intraoperative diffusion tensor imaging localized the pyramidal tract (as identified by direct white matter stimulation) more accurately than preoperative diffusion tensor imaging, and this finding will be reported in detail elsewhere. The occurrence of postoperative transient paresis was probably high in our series, but might reflect our surgical approach nearly to the tumor boundary. Thirdly, our system could fuse navigation with other modalities such as PET and MR spectroscopy, thus improving the accuracy of the histological diagnoses. Gliomas exhibit tumor-heterogeneity to varying degrees, so metabolic information should be used to guide biopsies.[20,26,27] Although image fusion is available for standard navigation, our system is advantageous because we can confirm the position of the collected specimen immediately after the procedure by intraoperative MR imaging. In general, extending glioma resection as far as possible prolongs patient survival.[15,16] Long-term follow up is necessary to reveal whether surgical management with this integrated navigation and intraoperative MR imaging system leads to an improved prognosis.

Considering the indication for other tumors, we believe that pituitary adenomas are also a good indication. The percentage of surgeries modified by intraoperative MR imaging (44.4%) was the second highest following gliomas. Even with endoscopic assistance, tumor remnants are not readily discriminated from the normal pituitary gland. The blind side behind the fold of the arachnoid and the descending sella diaphragm is another problem. Intraoperative MR imaging could identify tumor remnants which indicated further resection, as similarly described previously.[7,33] Metastatic tumors have relatively identifiable boundaries, but some demonstrate infiltrative characteristics so that intraoperative MR imaging was useful to achieve complete resection. Meningiomas, schwannomas, and other extra-axial tumors have a clear margin, so the need for intraoperative imaging was reduced. However, both intraoperative images and navigation were found to be helpful if some of the tumor was intentionally left to preserve functional structures.

Vascular reconstructive surgery is a possible indication. Our results showed good patency of the anastomotic vessels by MR angiography, which confirmed surgical success. We experimentally performed perfusion-weighted imaging before and after anastomosis, using the analysis method previously recommended.[35] Various imaging findings have been reported after vascular reconstructive surgery,[4,8,43,45] but our imaging study in the superacute postoperative period might contribute to the prediction of hyperperfusion syndrome, or to intraoperative control for anesthesia. Further study is necessary to clarify its importance. Intraoperative MR images were less useful in clipping surgery. An important issue was clip-induced artifacts which complicated the evaluation of tiny branches and the residual neck.[42] However, we assumed that intraoperative diffusion-weighted imaging was useful to exclude acute ischemic complications.[22,23] Intraoperative MR imaging provided two advantages for STN-DBS.[6] One advantage was intraoperative visualization of the electrode location, as we were able to accurately locate the electrode by considering the reported artifact patterns.[36] The other advantage involved the higher signal/noise ratio during microelectrode recording due to the radiofrequency shielding. As techniques for directly imaging STN advance in the future, obtaining intraoperative MR images will become more important.[39] Spinal surgery may also be considered as an indication, as reported.[17]

The management of this system raises several issues. Maintenance of safety is very important.[11] To avoid magnetic absorption-related accidents, all staff working in the MR imaging-equipped operating

room must be educated concerning safety. The lines and ducts leading to the patient are potentially troublesome for patient transport, and continuous training is recommended. The limitation of surgical positioning is also important. Although we were able to perform complex approaches such as the anterior petrosal, lateral suboccipital, and transcondyle approaches, positioning limits must be considered. A flexible MR-compatible table that can be bent was recently reported,[18,19] and such improvements are necessary. The cost-benefit ratio must also be considered. The technology of the intraoperative MR imager has continuously progressed, and the importance of intraoperative images is often emphasized.[3,10,19,44] Further study is necessary to elucidate whether such a system improves patient outcomes over the long term. If such a system achieves social recognition, the health insurance system might be revised, and if healthcare providers adopt this technology widely, then further improvement of the cost-benefit ratio should result.

The integration of intraoperative high-field MR imaging and navigation is important for maximizing resection and minimizing complications in brain tumor surgeries, especially for infiltrative tumors such as gliomas. Tumors of the pituitary gland are also a good indication. Intraoperative imaging is not as advantageous for other extra-axial tumors, but still helpful in confirming the success of surgery or in deciding the volume and location of tumors to be intentionally left unresected. The system increases the accuracy and safety of surgery for cerebrovascular or functional diseases, but the indication is somewhat limited. The fully integrated system contributes to smooth workflow during surgery.

Acknowledgments

We would like to thank Mr. T. Nishihata (Department of Radiology, Nagoya Central Hospital) and Ms. H. Ishiguro (Department of Surgical Nursing, Nagoya Central Hospital) who have contributed since the installation, as well as all staff of Nagoya Central Hospital for their help in managing this system. We also thank Mr. Matthew Nielsen (Siemens, Healthcare Sector) for his technical advice regarding intraoperative MR imaging and for his help in the preparation of this manuscript.

References

1) Berman J, Berger MS, Mukherjee P, Henry RG: Diffusion-tensor imaging-guided tracking of fibers of the pyramidal tract combined with intraoperative cortical stimulation mapping in patients with gliomas. *J Neurosurg* 101: 66–72, 2004
2) Black PM, Moriarty T, Alexander E III, Stieg P, Woodard EJ, Gleason PL, Martin CH, Kikinis R, Schwartz RB, Jolesz FA: Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. *Neurosurgery* 41: 831–842, 1997
3) Bradley WG: Achieving gross total resection of brain tumors: intraoperative MR imaging can make a big difference. *AJNR Am J Neuroradiol* 23: 348–349, 2002
4) Calamante F, Ganesan V, Kirkham FJ, Jan W, Chong WK, Gadian DG, Connelly A: MR perfusion imaging in Moyamoya Syndrome: potential implications for clinical evaluation of occlusive cerebrovascular disease. *Stroke* 32: 2810–2816, 2001
5) Darakchiev BJ, Tew JM Jr, Bohinski RJ, Warnick RE: Adaptation of a standard low-field (0.3-T) system to the operating room: focus on pituitary adenomas. *Neurosurg Clin N Am* 16: 155–164, 2005
6) De Salles AA, Frighetto L, Behnke E, Sinha S, Tseng L, Torres R, Lee M, Cabatan-Awang C, Frysinger R: Functional neurosurgery in the MRI environment. *Minim Invasive Neurosurg* 47: 284–289, 2004
7) Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C: Intraoperative magnetic resonance imaging during transsphenoidal surgery. *J Neurosurg* 95: 381–390, 2001
8) Fujimura M, Mugikura S, Shimizu H, Tominaga T: [Diagnostic value of perfusion-weighted MRI for evaluating postoperative alteration of cerebral hemodynamics following STA-MCA anastomosis in patients with moyamoya disease]. *No Shinkei Geka* 34: 801–809, 2006 (Jpn)
9) Gasser T, Ganslandt O, Sandalcioglu E, Stolke D, Fahlbusch R, Nimsky C: Intraoperative functional MRI: implementation and preliminary experience. *Neuroimage* 26: 685–693, 2005
10) Hall WA, Galichich W, Bergman T, Truwit CL: 3-Tesla intraoperative MR imaging for neurosurgery. *J Neurooncol* 77: 297–303, 2006
11) Hall WA, Liu H, Martin AJ, Pozza CH, Maxwell RE, Truwit CL: Safety, efficacy, and functionality of high-field strength interventional magnetic resonance imaging for neurosurgery. *Neurosurgery* 46: 632–641, 2000
12) Kamada K, Sawamura Y, Takeuchi F, Kawaguchi H, Kuriki S, Todo T, Masutani Y, Aoki S, Kirino T: Functional identification of the primary motor area by corticospinal tractography. *Neurosurgery* 56(1 Suppl): 98–109, 2005
13) Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Takano T, Kirino T, Kawahara N, Morita A: Combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. *J Neurosurg* 102: 664–672, 2005
14) Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS: Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending

motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. *J Neurosurg* 100: 369–375, 2004
15) Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 95: 190–198, 2001
16) Laws ER, Shaffrey ME, Morris A, Anderson FA Jr: Surgical management of intracranial gliomas — does radical resection improve outcome? *Acta Neurochir Suppl* 85: 47–53, 2003
17) Mastronardi L, Elsawaf A, Roperto R, Bozzao A, Caroli M, Ferrante M, Ferrante L: Prognostic relevance of the postoperative evolution of intramedullary spinal cord changes in signal intensity on magnetic resonance imaging after anterior decompression for cervical spondylotic myelopathy. *J Neurosurg Spine* 7: 615–622, 2007
18) Matsumae M, Fukuyama H, Ishikawa H, Osada T, Baba T, Mizokami Y, Atsumi H, Ishikawa H, Tsugu A, Tominaga J, Shiramizu H, Shimoda M: Fully functional MR-compatible flexible operating table resolves the neurosurgeon's dilemma over use of intraoperative MRI. *Tokai J Exp Clin Med* 33: 57–60, 2008
19) Matsumae M, Koizumi J, Fukuyama H, Ishikawa H, Mizokami Y, Baba T, Atsumi H, Tsugu A, Oda S, Tanaka Y, Osada T, Imai M, Ishiguro T, Yamamoto M, Tominaga T, Shimoda M, Imai Y: World's first magnetic resonance imaging/x-ray/operating room suite: a significant milestone in the improvement of neurosurgical diagnosis and treatment. *J Neurosurg* 107: 266–273, 2007
20) McKnight TR, Lamborn KR, Love TD, Berger MS, Chang S, Dillon WP, Bollen A, Nelson SJ: Correlation of magnetic resonance spectroscopic and growth characteristics within Grades II and III gliomas. *J Neurosurg* 106: 660–666, 2007
21) Mikuni N, Okada T, Enatsu R, Miki Y, Hanakawa T, Urayama S, Kikuta K, Takahashi JA, Nozaki K, Fukuyama H, Hashimoto N: Clinical impact of integrated functional neuronavigation and subcortical electrical stimulation to preserve motor function during resection of brain tumors. *J Neurosurg* 106: 593–598, 2007
22) Minematsu K, Li L, Fisher M, Sotak CH, Davis MA, Fiandaca MS: Diffusion-weighted magnetic resonance imaging: rapid and quantitative detection of focal brain ischemia. *Neurology* 42: 235–240, 1992
23) Moseley ME, Kucharczyk J, Mintorovitch J, Cohen Y, Kurhanewicz J, Derugin N, Asgari H, Norman D: Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am J Neuroradiol* 11: 423–429, 1990
24) Muragaki Y, Iseki H, Maruyama T, Kawamata T, Yamane F, Nakamura R, Kubo O, Takakura K, Hori T: Usefulness of intraoperative magnetic resonance imaging for glioma surgery. *Acta Neurochir Suppl* 98: 67–75, 2006
25) Nimsky C, Fujita A, Ganslandt O, von Keller B, Fahlbush R: Volumetric assessment of glioma removal by intraoperative high-field magnetic resonance imaging. *Neurosurgery* 55: 358–370, 2004
26) Nimsky C, Fujita A, Ganslandt O, von Keller B, Kohmura E, Fahlbush R: Frameless stereotactic surgery using intraoperative high-field magnetic resonance imaging. *Neurol Med Chir (Tokyo)* 44: 522–533, 2004
27) Nimsky C, Ganslandt O, Buchfelder M, Fahlbusch R: Intraoperative visualization for resection of gliomas: the role of functional neuronavigation and intraoperative 1.5 T MRI. *Neurol Res* 28: 482–487, 2006
28) Nimsky C, Ganslandt O, Fahlbusch R: 1.5T: intraoperative imaging beyond standard anatomic imaging. *Neurosurg Clin N Am* 16: 185–200, vii, 2005
29) Nimsky C, Ganslandt O, Fahlbusch R: Implementation of fiber tract navigation. *Neurosurgery* 58(4 Suppl 2): ONS-292–304, 2006
30) Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R: Intraoperative diffusion-tensor MR imaging: shifting of white matter tracts during neurosurgical procedures — initial experience. *Radiology* 234: 218–225, 2005
31) Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R: Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. *Neurosurgery* 56: 130–137, 2005
32) Nimsky C, Ganslandt O, von Keller B, Fahlbush R: Intraoperative high-field-strength MR imaging: implementation and experience in 200 patients. *Radiology* 233: 67–78, 2004
33) Nimsky C, von Keller B, Ganslandt O, Fahlbusch R: Intraoperative high-field magnetic resonance imaging in transsphenoidal surgery of hormonally inactive pituitary macroadenomas. *Neurosurgery* 59: 105–114, 2006
34) Okada T, Mikuni N, Miki Y, Kikuta K, Urayama S, Hanakawa T, Fushimi Y, Yamamoto A, Kanagaki M, Fukuyama H, Hashimoto N, Togashi K: Corticospinal tract localization: integration of diffusion-tensor tractography at 3-T MR imaging with intraoperative white matter stimulation mapping — preliminary results. *Radiology* 240: 849–857, 2006
35) Ostergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR: High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. *Magn Reson Med* 36: 726–736, 1996
36) Pollo C, Vingerhoets F, Pralong E, Ghika J, Maeder P, Meuli R, Thiran JP, Villemure JG: Localization of electrodes in the subthalamic nucleus on magnetic resonance imaging. *J Neurosurg* 106: 36–44, 2007
37) Rezai AR, Phillips M, Baker KB, Sharan AD, Nyen-

huis J, Tkach J, Henderson J, Shellock FG: Neurostimulation system used for deep brain stimulation (DBS): MR safety issues and implications of failing to follow safety recommendations. *Invest Radiol* 39: 300–303, 2004
38) Schneider JP, Trantakis C, Rubach M, Schulz T, Dietrich J, Winkler D, Renner C, Schober R, Geiger K, Brosteanu O, Zimmer C, Kahn T: Intraoperative MRI to guide the resection of primary supratentorial glioblastoma multiforme—a quantitative radiological analysis. *Neuroradiology* 47: 489–500, 2005
39) Slavin KV, Thulborn KR, Wess C, Nersesyan H: Direct visualization of the human subthalamic nucleus with 3T MR imaging. *AJNR Am J Neuroradiol* 27: 80–84, 2006
40) Steinmeier R, Fahlbusch R, Ganslandt O, Nimsky C, Buchfelder M, Kaus M, Heigi T, Lenz G, Kuth R, Huk W: Intraoperative magnetic resonance imaging with the magnetom open scanner: concepts, neurosurgical indications, and procedures: a preliminary report. *Neurosurgery* 43: 739–747, 1998
41) Sutherland GR, Kaibara T, Louw D, Hoult DJ, Tomanek B, Sanders J: A mobile high-field magnetic resonance system for neurosurgery. *J Neurosurg* 91: 804–813, 1999
42) Sutherland GR, Kaibara T, Wallace C, Tomanek B, Richter M: Intraoperative assessment of aneurysm clipping using magnetic resonance angiography and diffusion-weighted imaging: technical case report. *Neurosurgery* 50: 893–898, 2002
43) Suzuki Y, Negoro M, Shibuya M, Yoshida J, Neguro T, Watanabe K: Surgical treatment for pediatric moyamoya disease: Use of the superficial temporal artery for both areas supplied by the anterior and middle cerebral arteries. *Neurosurgery* 40: 324–330, 1997
44) Truwit CL, Hall WA: Intraoperative magnetic resonance imaging-guided neurosurgery at 3-T. *Neurosurgery* 58(4 Suppl 2): ONS-338–ONS-346, 2006
45) Wityk RJ, Hillis A, Beauchamp N, Barker PB, Rigamonti D: Perfusion-weighted magnetic resonance imaging in adult moyamoya syndrome: characteristic patterns and change after surgical intervention: case report. *Neurosurgery* 51: 1499–1505, 2002

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Commentary

This paper reports on the excellent experience of the authors using intraoperative high field MRI and neuronavigation. All possible applications have been tested and critically reviewed, from glioma surgery, to cerebrovascular procedures, to functional neurosurgery. The conclusion is that the main utility of intraoperative MRI is to solve problems connected with tumor removal: in particular, to ascertain gross total removal of the lesion, and to spare functionally relevant subcortical white matter tracts, such as pyramidal tract, optic pathways and speech related tracts. Very honestly, the authors point out the limitation of this procedure as well: for instance, the difficulties in demonstrating patency of perforators, or sack residuals, in aneurysm surgery, due to the artifacts of the metallic clip that obscure the vision of the surrounding region. Moreover, they suggest that the best results for neurooncology, in term of radical surgery with respect of normal functioning structures, is achieved by the coupling of intraoperative MRI with other monitoring systems, particularly neuronavigation, but also neurophysiological intraoperative testing. Finally, they mention the financial aspect, that in these days is not the least important. It would be nice to organize a prospective work to compare the cost/effect of two different methods to obtain the above mentioned results in glioma surgery (radicality and respect of normal tracts), namely intraoperative MRI and 5-ALA fluorescence, both integrated with neurophysiological monitoring. I do think that the anatomical check (namely MRI) will be at the end superior, but still there is a possible role also for different, less costly, procedures.

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The authors did meaningful and interesting work to provide the initial experiences of high-field 1.5T intraoperative magnetic resonance imaging (iMRI) and neuro-navigation in 100 cases of neurosurgical procedures and to explore its clinical indications and limitations.

The intraoperative imaging is an important tool in modern minimally invasive neurosurgery, and serves to maximize lesion removal and minimize morbidity. The best use of iMRI is for the lesions without identifiable boundaries, located in eloquent areas, deep-seated, and difficult to find and access. Its use can be exemplified in glioma surgery. As we all know, the principle of the glioma surgery is maximal safe tumor resection, however, to realize this aim remains a

challenge to all neurosurgeons. Without intraoperative image guidance, tumor resection, to a high extent, depends on surgeons' experience. Often, the degree of tumor resection is prone to be overestimated and the potential risk of neurological deficit is increased by pursuing greater resection. I agree that glioma surgery is a good indication for iMRI and neuro-navigation.

iMRI and neuro-navigation helps to localize lesion, identify vital neurovascular structures, and detect remnant tumor. However, every coin has two sides, this system is not completely reliable. It is always essential that surgeons must make right and timely judgements intraoperatively. Besides, the high cost limits its wide application. There is less value for tumors with clear margins according to the cost-effectiveness principle. Maybe we can get more benefit from the multimodality use of more techniques, such as the fluoroscope in glioma surgery and intraoperative fluorescein angiography in surgery of cerebrovascular diseases.

Safety and effectiveness is the final goal of surgery. iMRI and neuro-navigation can further this aim, and the authors have provided a meaningful study and obtained good results which has important value in image-guided neurosurgery.

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Int J Clin Oncol (2009) 14:273–274
DOI 10.1007/s10147-009-0922-3

INTRODUCTION TO REVIEW ARTICLES

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Treatment of metastatic brain tumors

Received: June 15, 2009

The number of patients with metastatic brain tumors has been increasing because of advances in less invasive imaging modalities such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), improvements in the treatment of extracranial cancers, and the increase of the elderly population. According to the Central Brain Tumor Registry of the United States, the incidence of primary brain tumors is 16.5 cases per 100000 person-years.[1] On the other hand, cancers are detected in 400 persons per 100000 population and of these individuals, 30% or 40% have metastatic brain tumors. This means that the incidence of metastatic brain tumors is estimated to be seven to nine times as high as that of primary brain tumors.

The diagnosis of metastatic brain tumors is usually made by MRI. Most of these tumors show isointensity on T1-weighted images (T1WI) and are highly enhanced by gadolinium-diethylenetriaminepentaacetic acid (DTPA). They are usually round-shaped and the central area shows low intensity on T1WI due to necrosis or fluid collection. Multiplicity is another characteristic of metastatic brain tumors; however, some glioblastomas and malignant lymphomas form multiple intracranial enhancing lesions. The final diagnosis should be made by biopsy if possible.

The prognosis of patients with metastatic brain tumors is poor and most of them have been treated only by irradiation of the whole brain. According to a recursive partitioning analysis of 1200 patients enrolled in three Radiation Therapy Oncology Group (RTOG) clinical trials (RTOG 79-16; 85-28; 89-05), patients with metastatic brain tumors could be classified into three groups. Class 1 includes patients with a Karnofsky performance status (KPS) of 70 or less, age less than 65 years,, controlled primary tumor, and no metastases except in the brain. Class 3 includes patients with a KPS below 70, while all other patients are classified as class 2. The median survivals in classes 1, 2, and 3 were 7.1, 4.2, and 2.3 months, respectively.[2]

On the other hand Patchell et al.[3] reported the significance of surgery for brain metastases. They randomized patients with a solitary brain metastasis into two groups, those receiving whole-brain radiotherapy (WBRT) and those receiving WBRT after craniotomy. The median survival of the WBRT group was only 8 weeks, while that of the surgery + WBRT group was 40 weeks; local recurrence appeared in 52% of the WBRT group and in 20% of the surgery + WBRT group.[3]

Stereotactic radiosurgery (SRS) was introduced for the treatment of brain metastases and has now been used for 20 years. A combination of SRS and WBRT showed better local control than WBRT alone, but longer survival compared with that in the WBRT group was obtained in only a limited subset of patients.[4] It is well known that WBRT influences the cognitive function of patients, and the non-inferiority testing of SRS compared with upfront WBRT is ongoing.

The effect of chemotherapy on brain metastases is controversial. It is difficult to conduct clinical trials because most of the patients receive radiotherapy, and the chemotherapeutic agents that would be chosen are commonly used for the primary cancers. Although most brain metastases are considered to be chemoresistant because of the presence of the blood-brain barrier, they sometimes shrink with only the chemotherapy used for the treatment of the primary cancer. Chemotherapy could be an important treatment modality, particularly for recurrent brain metastases after radiotherapy.

No standard therapy for brain metastases has been established yet. Surgical removal is necessary for large tumors, but only a few patients have a chance of undergoing surgery, because of tumor multiplicity and poor performance status. WBRT, SRS, and chemotherapy should be used appropriately to obtain long survival and maintain a good quality of life for the patients. The cooperation of neurosurgeons, oncologists, nursing staff, social workers, and the patient's family is essential for the optimal treatment of metastatic brain tumors.

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References

1. Central Brain Tumor Registry of the United States (CBTRUS) (2008) Statistical report. Primary brain tumors in the United States, 2000–2004. Hinsdale
2. Gaspar L, Scott C, Rotman M, et al. (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37:745–751
3. Patchell RA, Tibbs PA, Walsh JW, et al. (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500
4. Andrews DW, Scott CB, Sperduto PW, et al. (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III result of the RTOG 9508 randomized trial. Lancet 363:1665–1672

Int J Clin Oncol (2009) 14:275–280
DOI 10.1007/s10147-009-0917-0

REVIEW ARTICLE

Yoshitaka Narita · Soichiro Shibui

Strategy of surgery and radiation therapy for brain metastases

Received: June 1, 2009

Abstract Cancer patients with brain metastases have poor prognoses and their median survival time is about 1 year. Surgery with whole-brain radiation therapy (WBRT) has been used in the treatment of single brain metastasis measuring 3 cm or more. Stereotactic radiosurgery (SRS) including the use of the Gamma knife and Cyberknife is widely used for the treatment of small and multiple brain metastases; however, recent clinical studies have revealed that SRS + WBRT is superior to WBRT or SRS alone in terms of survival time and local tumor control rates. Here, surgical indications and the strategy of surgery and radiation therapy are discussed, based on many clinical trials of treatments for brain metastases. To improve the survival rate and quality of life for these cancer patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy with the close cooperation of physicians, surgeons, radiologists, and neurosurgeons, based on accumulated evidence.

Key words Brain metastases · Surgery · WBRT · SRS

Introduction

As cancer treatment has advanced, the survival of cancer patients has been prolonged, and the number of patients who have concomitant brain metastases has been increasing. According to the 11th edition of the Brain Tumor Registry of Japan,[1] the 1-year and 5-year survival rates of 4839 patients with brain metastases registered between 1991 and 1996 were 43.8% and 13.6%, respectively, whereas the corresponding rates for glioblastoma patients were 55.9% and 7.2%. The prognoses of patients with brain metastases and glioblastomas remain poor, showing similar treatment outcomes. Although various combinations of treatments, including surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) have been attempted, the median survival time (MST) of patients with brain metastases is about 1 year, because brain metastases is stage IV cancer and because their prognoses depend largely on the status of the primary focus. In Japan, there are currently about 50 gamma knife and 20 Cyberknife facilities that can easily provide SRS. Patients with multiple metastases or concomitant leptomeningeal metastases, for which WBRT is desirable, are also occasionally treated by SRS only. To improve the survival rate and quality of life (QOL) for these patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy, tailored to the individual needs of patients, based on accumulated evidence in different fields of medical practice (evidence-based medicine; EBM).

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Frequency of patients with brain metastases

According to the Metropolitan Detroit Cancer Surveillance System, brain metastases occurred in 9.6% of approximately 170000 patients diagnosed with cancer from 1973 to 2001.[2] In regard to the primary lesion, the incidence of brain metastases is reportedly 19.9% for lung cancer, 6.9% for melanoma, 6.5% for renal cancer, 5.1% for breast cancer, and 1.8% for colon cancer. A Dutch cohort study (2700 patients) found the incidence of brain metastases over 5 years to be 8.5%, and the incidences by primary lesion site were 16.3% for lung cancer, 7.4% for melanoma, 9.8% for renal cancer, 5.0% for breast cancer, and 1.2% for colon cancer.[3] Thus, approximately 10% of patients who had cancer developed brain metastases. According to Health and Welfare Statistics in Japan, there were 569000 patients with malignant neoplasms in 2001, and it is estimated that more than 50000 develop brain metastases annually. An analysis of autopsy cases revealed a higher frequency of brain metastases; brain metastases were found in 20%–40% of autopsied cancer patients.[4] The number of deaths from malignant neoplasms was approximately 336000 in 2007,

suggesting that there were 60000–120000 patients with brain metastases.[5] The cause of death in cancer patients with brain metastases was reported to be exacerbation of the primary lesion in 50%, and neural death due to brain metastases or leptomeningeal metastases in 30%,[6] suggesting that more than 20000 cases of neural death due to metastatic tumors occur in Japan annually. Considering that the number of annual deaths from primary malignant brain tumors, including glioma, in Japan is approximately 2000, controlling brain metastases is an important goal for neurosurgeons.

According to the 11th edition of the Brain Tumor Registry of Japan[1] based on collected data from mainly neurosurgical facilities, the frequencies of the primary foci in 10071 cancer patients with brain metastases registered between 1984 and 1996 were 52.3% for lung cancer, the highest, followed by breast (8.9%), renal (5.4%), rectal (5.2%), gastric (5.2%), colon (4.1%), head and neck (3.5%), hepatic (2.1%), uterine (1.7%), and thyroid (1.4%) cancers. Pathologically, adenocarcinoma was most frequent, accounting for 58.5%, whereas the frequency of squamous cell carcinoma was 13.5%.

The chief complaints of patients with brain metastases are focal signs including hemiparesis and aphasia (58%), signs of increased intracranial pressure (19%), and complaints without neurological symptoms (10%). Three percent of patients were asymptomatic and those patients were diagnosed by radiological findings.[1]

Prognostic factors

A Radiation Therapy Oncology Group (RTOG) study reviewed about 1200 patients enrolled in clinical trials that used WBRT, and analyzed prognostic factors by recursive-partitioning analysis (RPA) to classify them into RPA classes I-III.[7] Favorable prognostic factors for patients with metastatic brain tumor were Karnofsky performance status (KPS) of 70 or more, no distant metastasis other than brain metastases, controlled primary focus, and age less than 65 years; patients with these factors were considered to represent RPA class I (accounting for 20% of all subjects). KPS less than 70 was a poor prognostic factor, and such patients were categorized as RPA class III (accounting for 15%), whereas other factors were considered to represent RPA class II (accounting for 65%). MSTs were 7.1, 4.2, and 2.3 months for patients in RPA classes I, II, and III, respectively (Table 1). These RPA classes are commonly used when assessing treatment results for brain metastases.

Indications for surgery

Patients with brain metastases often have rapidly progressing neurologic symptoms, necessitating rapid determination of optimal therapeutic strategies. Figure 1 shows the therapeutic strategies used at the National Cancer Center in Japan.

Patients with a single metastasis measuring 3 cm or more, those with smaller tumors such as cerebellar neoplasms associated with severe neurologic symptoms due to cerebral edema, or those with multiple tumors with advanced neurologic symptoms in whom prompt improvement of neurologic symptoms is expected from surgery, undergo

Table 1. RPA classification and prognoses (MST) of cancer patients with brain metastases

Class I	KPS ≧70, age <64 years Controlled primary tumor No extracranial metastases
Class II	KPS ≧70 but other than class I
Class III	KPS <70

	n	Class I MST (months)	Class II MST (months)	Class III MST (months)
WBRT[7]	1176	7.1	4.2	2.3
SRS[16]	265	14.0	8.2	5.3
WBRT + SRS[16]	295	15.2	7.0	5.5
OPE + WBRT[10]	125	14.8	9.9	6.0

RPA, Recursive partitioning analysis; KPS, Karnofsky performance status; MST, median survival time; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; OPE, operation

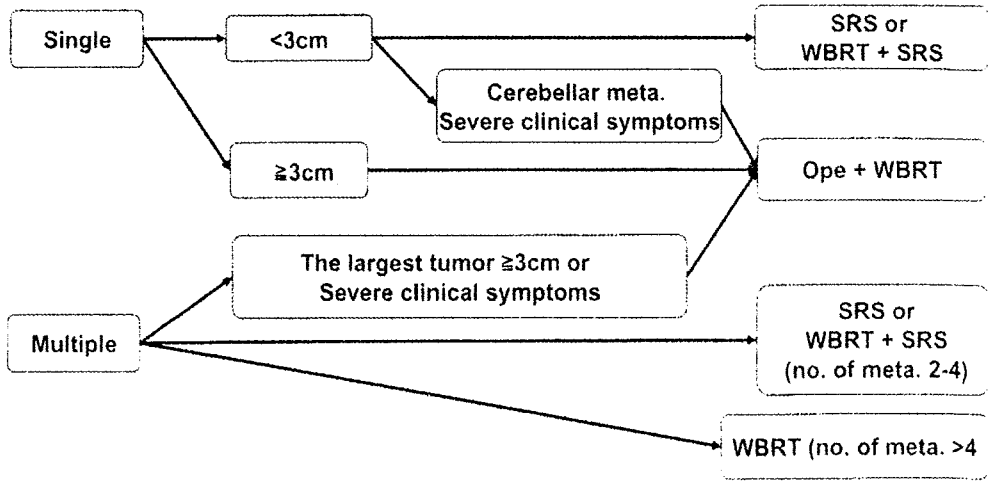

Fig. 1. Surgical and radiotherapy treatment of brain metastases (*meta*). *SRS*, Stereotactic radiosurgery; *WBRT*, whole-brain radiation therapy; *ope*, operation

craniotomy for tumor resection within 1 week of diagnosis and WBRT beginning 8 days after surgery, if possible. MST after WBRT without surgery is approximately 6 months, and therefore surgical candidates have a vital prognosis of at least 6 months. Considering that the MST of patients with brain metastases is approximately 1 year, it is critical to prevent worsening of neurologic symptoms and performance status (PS) in patients undergoing surgery.

Patients who have large cystic lesions in the eloquent area and those with poor PS or poor prognoses who are not good candidates for craniotomy for tumor resection under general anesthesia may undergo palliative insertion of an Ommaya reservoir for cystic tumor management. Removing the fluid content via the Ommaya reservoir to reduce the cyst prior to radiotherapy may effectively alleviate neurologic symptoms. Patients with a metastasis to the mesencephalic aqueduct, brainstem, or cerebellum, and those with obstructed cerebrospinal fluid (CSF) absorption resulting from carcinomatous meningitis may develop acute hydrocephalus. In these patients, endoscopic third ventriculostomy or ventriculoperitoneal shunt may ameliorate impaired consciousness.

Radiotherapy following surgery

According to the Brain Tumor Registry of Japan,[1] among 3793 patients with lung cancer who underwent surgery between 1981 and 1996, radiotherapy was added to the treatment protocol in 41.5%, whereas surgery alone was employed in 58.5%. Although surgery alone is a common therapeutic option in Japan, the 1-year survival rate was 50.9% for surgery combined with radiotherapy and 38.7% for surgery alone, showing better outcomes with the former treatment modality. Because approximately half of the patients undergoing surgery alone subsequently suffer recurrence,[5] the addition of radiotherapy is necessary. In patients with brain metastases, surgery combined with WBRT is the standard treatment worldwide. This strategy is based on the following findings. Patchell et al.[8] carried out a randomized controlled trial (RCT) of surgery + WBRT (36 Gy/12 fractions) vs surgery alone in patients with a single metastasis, and found that the MST was 10 months in the surgery + WBRT group and 3.75 months in the surgery-alone group. The local recurrence rates were 20% and 52%, respectively, and postoperative KPS was also more favorable in the surgery + WBRT arm. Similarly, Vecht et al.[9] reported that surgery combined with WBRT prolonged survival. On the other hand, a randomized study comparing surgery + WBRT (50.4 Gy) to surgery alone showed both local recurrence (10% vs 46%, respectively) and recurrence at other sites (14% vs 37%, respectively) to be significantly less frequent in patients given surgery + WBRT, although there was no significant intergroup difference in MST.[5] Based on the results of these RCTs, surgery combined with WBRT has become the standard treatment for a single brain metastasis. Agboola et al.[10] reported that MSTs with surgery + WBRT were 14.8, 9.9, and 6.0 months for patients in RPA classes I, II, and III (Table 1).

In Japan, postoperative local irradiation has commonly been applied to the site of tumor resection at various facilities. Indeed, until 2002, the National Cancer Center also employed focal radiation therapy (FRT) at 50 Gy in patients with a single tumor. However, there have been no RCTs comparing FRT and WBRT as modes of postoperative radiotherapy. At present, in consultation with radiologists and medical oncologists regarding the optimal postoperative radiotherapy, WBRT at 37.5 Gy (15 fractions/3 weeks) is generally used for patients in RTOG RPA class I postoperatively. In patients in RTOG RPA class II or III who have a poor prognosis due to their general condition, WBRT at 30 Gy (10 fractions/2 weeks) is applied, with the goal of an early return home if possible. An analysis of the mode of recurrence in 109 patients who underwent FRT at 50 Gy ($n = 58$) or WBRT at 30 Gy ($n = 51$) postoperatively at the National Cancer Center demonstrated the absence of recurrence in 43% and 59% of patients given FRT and WBRT, respectively. Thus, recurrence was less frequent in patients given WBRT than in those given FRT. The rates of recurrence at the site of surgery were 12% and 14%, respectively, showing no marked difference. However, recurrence in areas other than the surgical site was slightly more frequent after FRT (33%) than after WBRT (12%). Metastases to the spinal cord occurred in 3% and 4% of patients given FRT or WBRT, respectively, and the incidences of carcinomatous meningitis were 9% and 12%, respectively, showing no marked differences in dissemination of tumors between the two groups.

In 180 patients who underwent craniotomy for tumor resection combined with radiotherapy between 1990 and 2005 in the Neurosurgery Division at the National Cancer Center, MST was 12.3 months. In 47 patients with pulmonary adenocarcinoma, MST was 15.1 months, and the 5-year survival rate was 15.0%. MST and the 5-year survival rate in 18 patients with squamous cell carcinoma of the lung were 14.9 months and 23.2%, respectively, while the corresponding figures were 13.8 months and 32.5%, respectively, in 29 patients with breast cancer.

Surgical complications

The most important issue in the surgical treatment of brain metastases is to avoid deterioration of PS. Even if there is only a possibility that paralysis may be ameliorated by long-term rehabilitation training, partial resection should be employed rather than risking the exacerbation of paralysis due to total resection, and radiotherapy should be used to address possible residual tumor, given its anticipated efficacy.

Paek et al.,[11] who reviewed 208 patients treated surgically, reported that 1.9% died within 30 days, and that postoperative neurologic deterioration occurred in 6%. Systemic complications, including pneumonia, urinary infection, and venous thrombosis occurred in 13.9% of the patients.

In a series of 152 patients who underwent craniotomy for tumor resection between 2000 and 2006 at the National Cancer Center, complications occurred in 6 (3.9%). Exacerbation of paralysis occurred in 2 patients (1.3%) due to postoperative hematoma and in 1 (0.7%) due to tumor resection. One patient (0.7%) developed a surgical wound infection and another, spinal fluid leakage. Sudden cardiopulmonary arrest following suboccipital craniotomy occurred in 1 patient with a cerebellar metastasis from lung cancer. It was speculated that the cardiopulmonary arrest in this patient was attributable to circulatory volume loss due to the use of mannitol at the time of craniotomy, as the patient had had severe intracranial hypertension preoperatively and dehydration had been exacerbated by mannitol or glycerol before surgery. This patient was successfully resuscitated and craniotomy was performed again 1 week later, with successful tumor resection; the patient was discharged without neurologic abnormalities. This case provided a warning regarding the risk of mannitol use in dehydrated patients. There was one death (0.7%) within 30 postoperative days. This patient was elderly (80 years) and was found to have concomitant carcinomatous meningitis at autopsy.

Radiotherapy for patients not suitable for surgery

WBRT is the standard radiotherapy for patients who are not good candidates for surgery, usually with a radiation dose of 30 Gy (3 Gy × 10 fractions/2 weeks). This procedure is reported to exert a therapeutic effect equal to WBRT at 40 Gy (2 Gy × 20 fractions).[12] WBRT at 30 Gy has been widely employed because it requires only a short treatment period. However, irradiation at 37.5 Gy using a lower dose for each fraction (2.5 Gy × 15 fractions/3 weeks) has also been used in many clinical studies, conducted after the RTOG 9508 study, to reduce adverse reactions to irradiation. On the other hand, reported adverse reactions to WBRT include leukoencephalopathy and progressive dementia, ataxia, and incontinence due to radiation-induced necrosis, occurring in approximately 10% of patients.[13,14] SRS using Lekshell Gamma knife (Elekta; Stockholm, Sweden), Cyberknife (Accuray; Sunnyvale, CA, USA), X-knife (Radionics; Burlington, VT, USA), or Linear accelerator (Linac) (Elekta; Stockholm, Sweden) radiosurgery is also useful for treating tumors with diameters of 3 cm or less. In Japan, SRS alone is widely used for single lesions. Serizawa et al.[15] reported that an MST of 9.0 months was achieved in 521 patients who underwent gamma knife radiosurgery. Sneed et al.,[16] reported that MSTs with SRS alone were 14.0, 8.2, and 5.3 months for patients in RPA classes I, II, and III (Table 1).

Although there has been no RCT comparing SRS and WBRT, the Japanese Radiation Oncology Study Group (JROSG) carried out an RCT in patients who had four or fewer brain metastases measuring 3 cm or less to compare WBRT + SRS (65 patients) and SRS alone (67 patients).[17] The 1-year survival rate and MST were 38.5% and 7.5 months, respectively, in the WBRT + SRS group, and 28.4% and 8.0 months, respectively, in the SRS-alone group, respectively, showing no marked differences between the two groups. The frequencies of neural death due to brain metastases were 19.3% and 22.8%, respectively. The respective incidences of new lesions at 1 year and the rates of recurrence of brain metastases, including local recurrence, were 41.5% and 46.8% in the WBRT + SRS group, and 63.7% and 76.4% in the SRS-alone group, demonstrating significantly lower rates with the combination of WBRT and SRS. Additional stereotactic irradiation was required in 10 patients in the combined treatment group and 29 in the SRS-alone group. However, additional stereotactic irradiation was actually performed in 9 and 19 patients, respectively; salvage therapy could not be conducted in all patients with tumor recurrence. The mean memory test score (maximum score, 30 points) on the mini-mental state examination (MMSE) in patients who survived for more than 1 year was 27.0 (range, 23–30) in the combined group and 28.0 (range, 18–30) in the SRS-alone group, showing no significant difference between the two groups. Thus, SRS combined with WBRT did not increase the incidence of dementia as compared with SRS alone. In the randomized RTOG 9508 study, patients who had three or fewer metastatic foci measuring 4 cm or less in greatest dimension underwent WBRT (37.5 Gy/15 fractions) combined with SRS (164 patients, including 92 patients with a single tumor) or WBRT alone (167 patients, including 94 patients with a single tumor).[6] Among those with a single metastasis, MST was 6.5 months in the WBRT + SRS group and 4.9 months in the WBRT-alone group, showing a significant intergroup difference ($P = 0.039$). KPS at 6 months was well maintained or improved in 43% and 27% of the patients in the WBRT + SRS and WBRT-alone groups, respectively, showing significantly better results for the combined irradiation group. The response rate at 3 months and the local control rate at 1 year were also superior in the combined irradiation group, indicating the usefulness of additional SRS in patients with a single tumor. In patients with two to three metastatic foci, MST was 5.8 months after combined irradiation and 6.7 months after WBRT alone, showing no significant difference.

Based on the results of various prior clinical studies, WBRT combined with SRS might be considered to be a feasible standard treatment for a single metastasis.[6,17] However, in Japan, gamma knife radiosurgery alone is often used to treat patients with three to four lesions measuring 3 cm or less in diameter. On the other hand, when medical oncologists describe the above evidence to patients, an increasing number of patients choose gamma knife treatment after WBRT.

In patients with many (five or more) lesions and those who have concomitant leptomeningeal metastases, there is no evidence supporting the propriety of SRS treatment alone, and WBRT is therefore necessary.

When considering the mode of radiotherapy for brain metastases, it is necessary to look at clinical trials that use neurocognitive function as an endpoint, in addition to the survival period and the recurrence rate. There may be

future alterations in the standard treatment, as further evidence is accumulated.

Clinical studies of brain metastases in Japan

Although SRS is associated with more frequent recurrence in untreated areas than WBRT, it is advantageous in that the treatment time is shorter and anorexia and general malaise are mild, in contrast to symptoms seen during or immediately after WBRT. The efficacy of SRS, however, lacks corroborative evidence, in contrast to WBRT, as discussed above. Many patients, however, express concern about irradiation applied to normal brain tissue, believing that it induces progressive dementia. In this regard, the Japan Clinical Oncology Group (JCOG)-Brain Tumor Group started an RCT in 2006 to compare the efficacies of surgery combined with WBRT and surgery combined with additional salvage radiation therapy with SRS for residual tumors in patients with four or fewer brain metastases, using the overall survival period, incidence of dementia (proportion of patients showing worsening of MMSE results), and maintained QOL (proportion of patients with no deterioration of PS) as endpoints. This is a noninferiority study. If it is demonstrated that the test treatment (surgery + additional SRS) is not inferior to the standard treatment (surgery + WBRT) in terms of overall survival, the test treatment is regarded as being more useful. As noted above, WBRT combined with SRS is considered to be the standard treatment for patients suitable for SRS. The actual situation is that SRS alone, performed with a gamma knife or other systems, is employed without careful consideration, for fear of adverse reactions to WBRT. The above JCOG trial and various other clinical investigations, seeking to reduce adverse events and to enhance the efficacy of irradiation, are ongoing.

Recurrence after surgery and radiotherapy

There is no standard treatment for recurrence after surgery combined with WBRT or after radiotherapy. Patients undergo magnetic resonance imaging (MRI) studies every 2–3 months after treatment, and if recurrence is detected, surgery or SRS with a gamma knife will be performed. The therapeutic outcomes of operable patients are not necessarily poor. In patients with recurrence, MST after the second surgery is reportedly 11.5 months,[19] whereas MST after surgery in patients with recurrence after gamma knife radiosurgery is 11.1 months.[20] In a study reported before 1990, when additional gamma knife treatment was not available, patients with recurrences after WBRT at 30 Gy received another WBRT at 25 Gy. Therapeutic efficacy was achieved in 42% of these patients, and MST was 5 months, although there was no detailed discussion of safety.[21]

It is unclear whether these post-treatments achieve better survival or better QOL. The most suitable treatment should be chosen for recurrent cases, based on the patient's general condition, neurologic symptoms, and prognosis.

Leptomeningeal metastases or carcinomatous meningitis

In patients diagnosed with leptomeningeal metastases, MST is 3–6 months.[22] Intrathecal administration of methotrexate (MTX) or cytarabine (Ara-C) is a common treatment strategy. Ommaya reservoir insertion is often employed under local anesthesia to reduce the burden on the patient during lumbar puncture and to achieve intraventricular drug administration. Among the complications of this procedure, rates of extraventricular insertion, postoperative infection, and postoperative bleeding[23] are reportedly 3%–12%, 2%–9% and 1%–3%, respectively. Because postoperative deaths have also been reported, caution is required in selecting this procedure. In our hospital, patients with suspected leptomeningeal metastases undergo lumbar puncture and CSF cytology. Once a definitive diagnosis has been obtained, MTX is given intrathecally by lumbar puncture. When the CSF cell count decreases in response to intrathecal MTX, Ommaya reservoir insertion is carried out to allow intraventricular MTX administration. In patients with neurologic symptoms but no prior radiotherapy, WBRT is added. However, the MST of patients (n = 22) treated with MTX via an inserted Ommaya reservoir at our hospital was only 4 months, a poor outcome.

Use of steroids and anticonvulsants

When using steroids for cerebral edema due to brain metastases, attention should be paid to possible adverse reactions such as gastrointestinal bleeding, hyperglycemia, peripheral edema, mental symptoms including a depressive state and insomnia, osteoporosis, and infectious diseases including oral candidiasis.[24] In patients with paralysis, attention to pulmonary embolism due to deep venous thrombosis (DVT) is necessary. If DVT is suspected, the patient should undergo pelvic computed tomography (CT) and ultrasonography, and prophylactic treatment such as warfarinization or inferior vena cava filter placement should be administered.

Pneumonia resulting from decreased immunocompetence due to steroid therapy is common. It should be kept in mind that *Pneumocystis carinii* pneumonia (PCP) may occur in patients on prolonged steroid therapy or in those of advanced age. Patients treated at our hospital who developed PCP, presumably because of prolonged steroid therapy for malignant glioma, had received the equivalent of 15 mg or more prednisolone. From this experience, we have found that trimethoprim-sulfamethoxazole is effective prophylaxis for PCP.

Convulsive seizures occur in 20%–40% of patients with brain tumors, and it may be surprising that there is as yet no evidence showing a prophylactic effect of antiepileptic drugs on these seizures. In a study of valproic acid and placebo administration in patients with brain tumors (90% had brain metastases) with no history of convulsive seizures,[25] 35% and 24%, respectively, developed convulsions during the mean observation period of 7 months, indicating

that valproic acid exerted no prophylactic effect. The American Academy of Neurology (AAN) reviewed 12 previous studies and concluded that there was no distinct prophylactic effect of antiepileptic drugs on convulsive seizures. Thus, the AAN does not recommend regular administration of antiepileptic drugs to patients who have no history of convulsive seizures.[26]

Phenytoin, phenobarbital, and carbamazepine activate the hepatic enzyme cytochrome P450, thereby enhancing the metabolism of various concomitantly used molecular-targeting drugs and anticancer drugs such as nitrosourea (ACNU), MTX, irinotecan (CPT), and adriamycin (ADM), consequently lowering their blood concentrations. Thus, caution is necessary in continuing systemic chemotherapy.[27] In patients who have convulsive seizures and those at high risk for such seizures because of multiple lesions and other factors, medication should begin with a drug that does not activate P450 (e.g., valproic acid or zonisamide), but caution is necessary, as the anticonvulsant drug itself can cause bone marrow suppression.

Conclusions

MST in patients with brain metastases is only about 1 year. In the treatment of brain metastases, it is necessary to maintain the patient's QOL and activities of daily living. For this purpose, the therapeutic strategy should be decided with the close cooperation of internists, surgeons, radiologists, and neurosurgeons, taking into account the patient's clinical history, PS, neurologic findings, tumor size, number of lesions, control of the primary focus, and prognosis.

Conflict of interest

No author has any conflict of interest.

References

1. Brain Tumor Registry of Japan (2003) Report of Brain Tumor Registry of Japan (1969–1996) 11th edition. Neurol Med Chir (Tokyo) 43 (Suppl):i-vii, 1–111
2. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 22:2865–2872
3. Schouten LJ, Rutten J, Huveneers HA, et al. (2002) Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 94:2698–2705
4. Soffietti R, Ruda R, Mutani R (2002) Management of brain metastases. J Neurol 249:1357–1369
5. Narita Y, Shibui S (2008) Diagnosis and treatment for brain and spinal metastases (in Japanese). Gan To Kagaku Ryoho (Cancer and Chemotherapy) 35:2301–2306
6. Andrews DW, Scott CB, Sperduto PW, et al. (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363:1665–1672
7. Gaspar L, Scott C, Rotman M, et al. (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37:745–751
8. Patchell RA, Tibbs PA, Regine WF, et al. (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280:1485–1489
9. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 33:583–590
10. Agboola O, Benoit B, Cross P, et al. (1998) Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiat Oncol Biol Phys 42:155–159
11. Paek SH, Audu PB, Sperling MR, et al. (2005) Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery 56:1021–1034; discussion 1034
12. Borgelt B, Gelber R, Kramer S, et al. (1980) The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 6:1–9
13. DeAngelis LM, Delattre JY, Posner JB (1989) Radiation-induced dementia in patients cured of brain metastases. Neurology 39:789–796
14. Sundaresan N, Galicich JH, Deck MD, et al. (1981) Radiation necrosis after treatment of solitary intracranial metastases. Neurosurgery 8:329–333
15. Serizawa T, Saeki N, Higuchi Y, et al. (2005) Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol. Acta Neurochir (Wien) 147:721–726
16. Sneed PK, Lamborn KR, Forstner JM, et al. (1999) Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys 43:549–558
17. Aoyama H, Shirato H, Tago M, et al. (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295:2483–2491
18. Stafinski T, Jhangri GS, Yan E, et al. (2006) Effectiveness of stereotactic radiosurgery alone or in combination with whole brain radiotherapy compared to conventional surgery and/or whole brain radiotherapy for the treatment of one or more brain metastases: a systematic review and meta-analysis. Cancer Treat Rev 32:203–213
19. Bindal RK, Sawaya R, Leavens ME, et al. (1995) Reoperation for recurrent metastatic brain tumors. J Neurosurg 83:600–604
20. Vecil GG, Suki D, Maldaun MV, et al. (2005) Resection of brain metastases previously treated with stereotactic radiosurgery. J Neurosurg 102:209–215
21. Cooper JS, Steinfeld AD, Lerch IA (1990) Cerebral metastases: value of reirradiation in selected patients. Radiology 174:883–885
22. Demopoulos A (2004) Leptomeningeal metastases. Curr Neurol Neurosci Rep 4:196–204
23. Sandberg DI, Bilsky MH, Souweidane MM, et al. (2000) Ommaya reservoirs for the treatment of leptomeningeal metastases. Neurosurgery 47:49–54; discussion 54–5
24. Hempen C, Weiss E, Hess CF (2002) Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? Support Care Cancer 10:322–328
25. Glantz MJ, Cole BF, Friedberg MH, et al. (1996) A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. Neurology 46:985–991
26. Glantz MJ, Cole BF, Forsyth PA, et al. (2000) Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 54:1886–1893
27. Vecht CJ, Wagner GL, Wilms EB (2003) Interactions between antiepileptic and chemotherapeutic drugs. Lancet Neurol 2:404–409

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 5, pp. 1415–1419, 2009

0360-3016/09/$ see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.12.063

CLINICAL INVESTIGATION **Brain**

STEREOTACTIC RADIOTHERAPY FOR INTRACRANIAL NONACOUSTIC SCHWANNOMAS INCLUDING FACIAL NERVE SCHWANNOMA

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Purpose: Although the effectiveness of stereotactic radiosurgery for nonacoustic schwannomas is currently being assessed, there have been few studies on the efficacy of stereotactic radiotherapy (SRT) for these tumors. We investigated the long-term outcome of SRT for nonacoustic intracranial nerve schwannomas.

Methods and Materials: Seventeen patients were treated between July 1994 and December 2006. Of these patients, 7 had schwannomas located in the jugular foramen, 5 in the trigeminal nerve, 4 in the facial nerve, and 1 in the oculomotor nerve. Radiotherapy was used as an initial treatment without surgery in 10 patients (59%) and after initial subtotal resection in the remaining patients. The tumor volume ranged from 0.3 to 31.3 mL (mean, 8.2 mL). The treatment dose was 40 to 54 Gy in 20 to 26 fractions. The median follow-up period was 59.5 months (range, 7.4–122.6 months). Local control was defined as stable or decreased tumor size on follow-up magnetic resonance imaging.

Results: Tumor size was decreased in 3 patients, stable in 13, and increased in 1 after SRT. Regarding neurologic symptoms, 8 patients (47%) had improvement and 9 patients were unchanged. One patient had an increase in tumor size and received microsurgical resection at 32 months after irradiation. No patient had worsening of pre-existing neurologic symptoms or development of new cranial nerve deficits at the last follow-up.

Conclusions: SRT is an effective alternative to surgical resection for patients with nonacoustic intracranial nerve schwannomas with respect to not only long-term local tumor control but also neuro-functional preservation.

Stereotactic radiotherapy, Facial nerve, Trigeminal nerve, Schwannoma.

INTRODUCTION

Schwannomas of the intracranial nerves account for about 10% of all brain tumors, and they are generated in the eighth nerve in about 90% of cases. Nonacoustic intracranial nerve schwannomas arise from the trigeminal nerve (V) in 0.8% to 8% of cases (1, 2), the jugular foramen (IX/X/XI) in 2.9% to 4% (3, 4), and the facial nerve (VII) in 1.9% (5, 6).

The standard treatment has been total removal via microsurgery. However, surgical total resection is often associated with the development of new neurologic deficits, and incomplete resection often results in tumor regrowth, which requires additional therapy. Sarma *et al.* (7) reported their experience with microsurgery in 46 cases of nonacoustic nerve schwannomas (trigeminal nerve in 26, jugular foramen in 9, facial nerve in 7, hypoglossal nerve in 3, and trochlear nerve in 1). They found that new cranial nerve deficit developed after surgery in 11 patients (24%), cerebrospinal fluid leaks in 5 (11%), meningitis in 3 (7%), and vasospasm requiring angioplasty in 1 (2%), with temporary hemiparesis in 2 cases and permanent hemiparesis in 1 case. Of the patients, 5 (28%) had improvement in pre-existing neurologic deficit.

On the basis of the effectiveness of radiation therapy for acoustic schwannomas, stereotactic radiosurgery (SRS) with a Gamma Knife or linear accelerator–based system has been applied to nonacoustic schwannomas, and an excellent local control rate and few adverse effects have been reported (8–14). Pollock *et al.* (8) administered SRS (12–20 Gy; mean tumor volume, 8.9 mL [range, 0.2–17.6 mL]) with a Gamma Knife to 23 patients (trigeminal nerve in 10, jugular foramen in 10, hypoglossal nerve in 2, and trochlear nerve in 1). The local control rate was 96% during the follow-up period (median, 43 months; range, 12–111 months), and new neurologic deficits developed in 3 cases (12%). Mabanta *et al.* (9) reported on 18 patients (trigeminal nerve in 7, jugular foramen in 9, and facial nerve in 2) who were treated

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Conflict of interest: none.

Received Aug 21, 2008, and in revised form Dec 31, 2008. Accepted for publication Dec 31, 2008.

with linear accelerator radiosurgery (10–15 Gy; mean tumor volume, 5.5 mL [range, 0.7–15.4 mL]). The rate of tumor control was 100%, with worsening of pre-existing nerve VII palsy in 1 case and new-onset hearing loss in 2 cases.

Recent advances in image-guided radiotherapy have made it possible to use fractionated radiotherapy with stereotactic accuracy. Acoustic schwannomas are known to be well treated with fractionated stereotactic radiotherapy (SRT), and there is a lower rate of late adverse effects with this method than with SRS (15). Considering that acoustic schwannomas are often treated with SRT rather than SRS because of the expectation of reducing the late adverse effects, patients with nonacoustic schwannomas such as facial nerve schwannomas would be good candidates for SRT.

Supported by our experience with acoustic schwannomas (15, 16), we have performed SRT for nonacoustic intracranial nerve schwannomas since 1994. In this study we assessed the outcomes of SRT for patients with nonacoustic intracranial nerve schwannomas who were treated at our institution. To our knowledge, this is the largest series to date on the use of SRT for nonacoustic intracranial schwannoma.

METHODS AND MATERIALS

Between July 1994 and December 2006, 17 patients with nonacoustic intracranial nerve schwannomas were treated with SRT at our institution. There were 7 men and 10 women. The median age was 47 years (range, 20–75 years). Of the patients, 5 had schwannomas of the trigeminal nerve (V), 7 of the lower cranial nerves (IX/X/XI) (so-called jugular foramen schwannomas), 4 of the facial nerve (VII), and 1 of the oculomotor nerve (III). There was no patient who was diagnosed with neurofibromatosis.

The tumor volume at the start of radiotherapy ranged from 0.3 to 31.3 mL (mean, 8.2 mL). Surgical total resection had been performed as the initial treatment until 2000, but starting in April 2000, SRT was selected as the initial treatment in principle regardless of tumor size, site, age, and so on, because the effectiveness of SRT for intracranial schwannomas was gradually being clarified. Only 1 patient, who received SRT at December, 2006, had been initially treated by surgery at December, 1987. Of 17 patients, 6 had surgical resection as the initial treatment and radiotherapy was administered for residual or relapsed tumors. One patient had received craniotomy and biopsy before radiotherapy. Consequently, the period between surgery and radiotherapy varied from 0.9 to 228.2 months (median, 7.3 months).

The median total dose was 50 Gy (range, 40–54 Gy) given in 25 fractions in 6 weeks. Radiotherapy was administered 4 days per week with 2 Gy per fraction by use of a thermoplastic fixation device in principle. The fraction size was changed when the stereotactic boost was administered described as follows: One patient received an additional irradiation of 4 Gy in 1 fraction after 44 Gy in 22 fractions and two patients received 10 Gy in 4 fractions after 44 Gy in 22 fractions as a stereotactic boost at the end of the schedule via a direct traumatic fixation device (16).

The treatment planning was based on thin-slice computed tomography (CT) scans. Since October 1998, we have used magnetic resonance imaging (MRI) for planning in addition to CT scan. Five patients in the initial stage were treated without the use of MRI. The images from MRI and CT were overlapped on the computer, and the outline of the target and the organs at risk was enclosed. In principle, the clinical target volume margin was 1 mm and the planning target volume margin was 2 mm. The margin had been slightly modified by the therapeutic radiologist's judgement according to the tumor size, location, and surgical findings. The prescribed dose was given at the isocenter, and the planning target volume was covered by 80% to 90% of the prescribed dose. Conformity indices were not commonly used in the 1990s and were not able to be analyzed in this study. Three-dimensional treatment planning was performed by use of FOCUS and XiO systems (CMS Inc., Maryland Heights, MO).

Informed consent was obtained from all patients. Local tumor control was defined as stable or decreased tumor size on follow-up MRI after the last day of radiotherapy. The tumor volume was measured by use of contrast-enhanced T1-weighted MRI images.

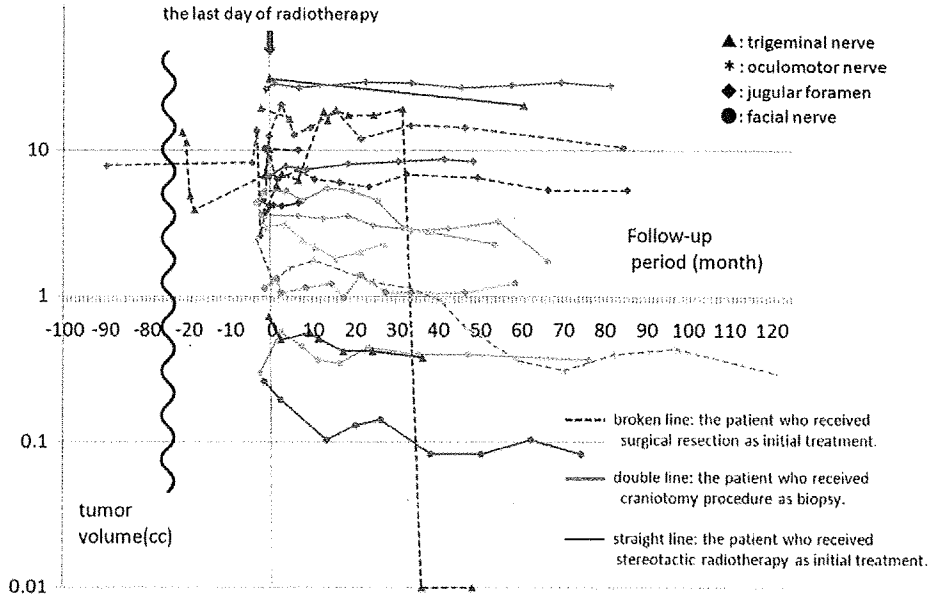

Fig. 1. Transition of tumor volume before and after stereotactic radiotherapy.