Table 2. *Survival in elderly patients undergoing surgery for malignant astrocytic tumour*

Histology	No. of patients	Median survival time (months)	Probability	
Total	88			
Group A	37	8.8		
Group B	26	12.7	NS	
Group C	25	17.6		
Anaplastic astrocytoma	37			
Group A	20	10.3		
Group B	11	13.8	NS	
Group C	6	34.9		
Giloblastoma	51			
Group A	17	6.0	P = 0.0054*	
Group B	15	11.7		P = 0.0024**
Group C	19	16.0		

* Between Group A and B, ** between Groups A and C.

intra-operative navigation system monitoring in Group C (16.0 months, n = 19) compared to B (11.7 months, n = 15), but there was not a statistical significance between the groups (p = 0.5729).

The number of patients with better pre-operative performance status of ECOG 0-2 increased after the introduction of MR imaging. The median survival time of the patients with better pre-operative performance status was significantly longer than that of the patients with lower performance status of ECOG 3-4 (Table 3).

Gross total resection was achieved in more patients after the introduction of MR imaging. The median survival time of patients with gross total resection was significantly longer than that of patients with partial resection or biopsy (Table 3).

More patients had better postoperative performance status after the introduction of MR imaging. The median survival time of patients with better postoperative performance status was significantly longer than that of patients with lower performance status (Table 3).

The overall morbidity was 30.7%. The surgical morbidity was 17.1% and the medical complication rate was 13.6%. The operative mortality was 0%. Functionally significant neurological worsening occurred in eleven patients, which was caused by cerebral vascular damage during the operation in four patients, surgical intervention extending to eloquent areas in four patients, postoperative intraparenchymal haematoma in one patient, status epilepticus following surgery in one patient, and encephalitis following cerebrospinal fluid leakage in one patient. The median survival time of the patients with or without complications was 8.5 months (n = 27) and 13.8 months (n = 61), respectively, with no statistically significant difference.

Table 3. *Effect of neuroimaging methods on outcome in elderly patients*

	No. of patients				Median survival time (months)	Probability
	Group A	Group B	Group C	Total		
Preoperative ECOG						
0–2	14	14	20	48	17.9	P = 0.0013
3–4	23	12	5	40	7.5	
Postoperative ECOG						
0–2	12	17	19	48	17.6	P = 0.0004
3–4	25	9	6	40	5.7	
Extent of removal						
Gross total	8	6	16	30	19.3	P < 0.0001
Partial or biopsy	29	20	9	58	8.5	

Discussion

The present study indicates that the adoption of pre-operative MR imaging and additional imaging modalities was accompanied by a lengthening in survival time after surgery in elderly patients with a malignant astrocytic tumour. Among the factors in this may have been an earlier diagnosis and thus better performance status at surgery, allowing more thorough surgical resection, and better performance status after the initial treatment. Our analysis found that patients with malignant astrocytic tumour aged 60 years or over could survive as long as 17.6 months using current treatment modalities such as MR imaging with functional mapping, intra-operative navigation system, and intra-operative functional mapping under "awake" craniotomy or under generalized anesthesia. Median survival times extend further after the introduction of functional brain mapping and intra-operative navigation system monitoring in patients with glioblastoma, although there was no statistical significance between Group B and C. The lack of the statistical significance may be due to the small patient population (in which patients with tumour in eloquent area are further less). Future evaluation with a larger number of patients would address this important issue. Alternatively, we do not rule out the possibility that multiple factors including the surgeon's experience, awareness of the referring physician, and development of the operative microscope also contributed, at least in part, to the better outcome.

Most previous studies have found that surgical treatment for elderly patients with malignant astrocytic tumour resulted in high mortality and morbidity as well as a high complication rate [2, 4, 13]. In a series of 207 consecutive patients (mean age 53 years), 53 patients over 65 years old had a complication rate of 30.2%, and 20 patients over 70 years old had a complication rate of 50% [4]. Both rates were much higher than the overall complication rate of 25.1%. In a series of 80 patients aged over 65 years who underwent craniotomy for intra-axial tumour, the death rate was 3.8%, and worsening of the neurological state occurred in 16.3% and medical complications in 28.8% [13]. Surgical treatment for elderly patients clearly carries the risk of a worse outcome and a high complication rate. No significant improvement of survival time was found in 40 patients aged over 65 years treated by aggressive surgery plus radiotherapy compared with 88 patients treated by stereotactic biopsy plus radiotherapy [7]. In their series, the optimal treatment with resection plus radiation for elderly patients with glioblastoma resulted in an average survival of 30 weeks. In contrast, our results demonstrate that patients treated by gross total resection had a significantly longer median survival time (19.3 months) than patients with partial resection or biopsy (8.5 months) ($P < 0.0001$). Gross total resection was obtained in more patients after the introduction of MR imaging, suggesting that pre-operative MR imaging with or without functional mapping provides more precise anatomical and/or functional information, and contributes to more thorough surgical resection.

Our study indicates that pre-operative as well as post-operative performance status is also a significant contributing factor for better prognosis. Elderly patients with better performance status (≥ 70 Karnofsky performance status score) treated by maximal resection and definitive radiotherapy had a longer survival time than those treated by palliative radiation and biopsy [10]. Median survival was found to be longer in elderly patients who were more functional [1]. Patients older than 70 years with Karnofsky performance status score of more than 70 may benefit from surgical treatment for malignant astrocytic tumour followed by reduced doses of limited field radiotherapy [11].

We propose, based on the findings of this retrospective study that thorough surgical resection should be considered even in elderly patients with malignant astrocytic tumour if their performance status is good and preoperative evaluation by MR imaging is available.

References

1. Ampil F, Fowler M, Kim K (1992) Intracranial astrocytoma in elderly patients. J Neurooncol 12: 125–130
2. Bernstein M, Parrent AG (1994) Complications of CT-guided stereotactic biopsy of intracranial brain lesion. J Neurosurg 81: 165–168
3. Burger PC, Green SB (1987) Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. Cancer 59: 1617–1625
4. Cabantog AM, Bernstein M (1994) Complication of first craniotomy for intra-axial brain tumor. Can J Neurol Sci 21: 213–218
5. Halperin EC (1995) Malignant gliomas in older adults with poor prognostic signs. Getting nowhere, and taking a long time to do it. Oncology (Huntingt) 9: 229–234
6. Kallio M (1990) Therapy and survival of adult patients with intracranial glioma in a defined population. Acta Neurol Scand 81: 541–549
7. Kelly PJ, Hunt C (1994) The limited value of cytoreductive surgery in elderly patients with malignant glioma. Neurosurgery 34: 62–66
8. Kreth FW, Warnke PC, Scheremet R, Ostertag CB (1993) Surgical resection and radiation therapy versus biopsy and radiation therapy in the treatment of glioblastoma multiforme. J Neurosurg 78: 762–766

9. McLendon RE, Robinson JS Jr, Chambers DB, Grufferman S, Burger PC (1985) The glioblastoma multiforme in Georgia, 1977–1981. Cancer 56: 894–897
10. Mohan DS, Suh JH, Phan JL, Kupelian PA, Cohen BH, Barnett GH (1998) Outcome in elderly patients undergoing definitive surgery and radiation therapy for supratentorial glioblastoma multiforme at a tertiary care institution. Int J Radiat Oncol Biol Phys 42: 981–987
11. Pierga JY, Hoang-Xuan K, Feuvret L, Simon JM, Cornu P, Baillet F, Mazeron JJ, Delattre JY (1999) Treatment of malignant gliomas in the elderly. J Neurooncol 43: 187–193
12. Shinoda J, Sakai N, Murase S, Yaho H, Matsuhisa T, Funakoshi T (2001) Selection of eligible patients with supratentorial glioblastoma multiforme for gross total resection. J Neurooncol 52: 161–171
13. Tomita T, Raimondi AJ (1981) Brain tumors in the elderly. JAMA 246: 53–55
14. Whittle IR, Denholm SW, Gregor A (1991) Management of patients aged over 60 years with supratentorial glioma: lessons from an audit. Surg Neurol 36: 106–111

Correspondence: Toshihiro Kumabe, M.D., Department of Neurosurgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, 980-8574, Japan. e-mail: kuma@nsg.med.tohoku.ac.jp

J Neurosurg (Suppl) 102:171–174, 2005

Gamma knife surgery for hemangioblastomas

MASAO TAGO, M.D., ATSURO TERAHARA, M.D., MASAHIRO SHIN, M.D., KEISUKE MARUYAMA, M.D., HIROKI KURITA, M.D., KEIICHI NAKAGAWA, M.D., AND KUNI OHTOMO, M.D.

Departments of Radiology and Neurosurgery, University of Tokyo Hospital; Department of Radiology, Toho University, Omori Hospital; and Department of Neurosurgery, Kyorin University Hospital, Tokyo, Japan

Object. The authors reviewed their 14-year experience using stereotactic radiosurgery for the treatment of hemangioblastomas and define the role and the proper strategy for radiosurgery of this condition.

Methods. This is a retrospective study of 38 hemangioblastomas in 13 patients. Seven patients had von Hippel–Lindau disease. All patients have undergone at least one follow-up visit. The median and mean tumor volumes were 0.23 cm^3 and 0.72 cm^3 respectively (range 0.004::4.84 cm^3). Twenty-eight tumors received 20 Gy to the margin, and the remainder received 18 Gy. The median clinical follow-up period was 36 months (range 3–159 months).

No patient died. The survival rate was 84.6% (11 of 13 patients). The actuarial 5- and 10-year survival rates were both 80.8%. The median radiological follow-up period was 35 months (range 7–147 months). Only one tumor increased in volume 24 months after treatment in association with an intratumoral hemorrhage. The tumor control rate was 97.4% (37 of 38 tumors). Actuarial 5- and 10-year control rates were both 96.2%. New lesions and/or those increasing in size outside the irradiated area were discovered in five patients (38.5%). Nine tumors revealed peritumoral contrast enhancement which was seen more frequently in larger tumors with a volume greater than 0.5 cm^3 ($p = 0.0034$).

Conclusions. Gamma knife surgery is a safe and effective method to control hemangioblastomas for as many as 10 years. Higher doses and smaller tumors probably contribute to good outcomes. Recurrence outside the original irradiated area is common. Peritumoral contrast enhancement may be seen in larger tumors. The authors recommend regular imaging follow up and early repeated treatment in the face of new or growing tumors.

KEY WORDS • **stereotactic radiosurgery** • **gamma knife surgery** • **hemangioblastoma** • **von Hippel–Lindau disease**

HEMANGIOBLASTOMAS are rare benign tumors of the central nervous system that usually occur in the posterior fossa or upper cervical spinal cord. Approximately 20% of patients with intracranial hemangioblastoma have VHL disease, and they typically suffer from multiple tumors. Resection is the treatment of choice for most hemangioblastomas; however, their vascularity, critical locations, and multiplicity sometimes make resection a less attractive alternative, particular in patients with VHL disease. Conventionally fractionated radiotherapy has been used for the treatment of residual or unresectable hemangioblastomas. Sung, et al.,[7] reported 10-year survival rates of 56.5 % and 27.3 % in patients who received 40 Gy or more and 36 Gy or less, respectively. They recommended a dose of 45 to 50 Gy over a period of 4.5 to 5 weeks.

Recently, stereotactic radiosurgery has been used for the treatment of hemangioblastomas.[1–5] Although the authors of these few articles documented encouraging outcomes after radiosurgery, the long-term results have not been previously investigated nor have long-term appropriate strategies for the use of radiosurgery been established. In this report, we have undertaken a retrospective review of our 14-year experience and attempted to define the role of GKS and the proper strategy in this disease.

Abbreviations used in this paper: GKS = gamma knife surgery; MR = magnetic resonance; VHL = von Hippel–Lindau.

Clinical Material and Methods

Thirteen patients with 46 hemangioblastomas underwent GKS in a series of 15 treatments at the University of Tokyo Hospital between June 1990 and March 2004. We evaluated all patients (38 tumors), each of whom has undergone at least one follow-up visit (Table 1). There were ten men and three women. There were seven patients with VHL disease. The mean patient age was 43.4 years (range 26–84 years). All patients had undergone between one and four open surgeries before GKS, and diagnoses in all cases had been con-

TABLE 1
Patient characteristics

Characteristic	Value
no. of patients/tumors	13/38
male/female ratio	10:3
mean age in yrs (range)	43.4 (26–84)
VHL disease	7
prior surgery	13
prior conventional radiotherapy	1
tumor location	
cerebellar hemisphere	26
cerebellar vermis	5
brainstem	3
fourth ventricle	2
cervical spine	1
temporal lobe	1
tumor size	
median diameter in mm (range)	7.7 (2.0–21.0)
median volume in cm^3 (range)	0.23 (0.004–4.84)
dose (Gy)	
median max dose (range)	40 (36–40)
median margin dose (range)	20 (18–20)

firmed histologically at the time of GKS. Only one patient had received conventional radiotherapy before GKS, at a dose of 30 Gy. Twenty-six of 38 tumors were located in the cerebellar hemispheres. The median and mean tumor volumes were 0.23 cm^3 and 0.72 cm^3, respectively (range 0.004–4.84 cm^3).

Gamma knife surgery was performed using the Leksell gamma knife models (Elekta Instrument AB, Stockholm, Sweden). Treatment planning was performed using KULA or Leksell GammaPlan (Elekta Instruments AB) and stereotactic computerized tomography or MR images. The treatment protocol calls for the irradiation of the enhanced mass with a margin dose of 20 Gy. In cystic tumors only the mural nodule is targeted. In this series, all tumor margins were covered by the 50% isodose. Twenty-eight tumors received 20 Gy to the margin, and the remainder received 18 Gy.

Clinical and neuroradiological follow up were, in principle, requested 3, 6, and 12 months after the procedure. Afterward, follow-up evaluations were performed every 6 months for 2 years and then annually. We defined tumor control as lack of enlargement of the solid component on MR and/or computerized tomography images, regardless of any change in size of the cystic component.

Actuarial patient survival and tumor control rates were calculated by the Kaplan–Meier method.

The Fisher exact test was used for nonparametric variables. The level of significance is $p < 0.05$.

Results

The median clinical follow-up period was 36 months (range 3–159 months). Only two patients were followed-up for more than 5 years, but 12-year follow-up data were obtained in both of them. Two patients died, 3 and 35 months after the treatment, respectively. The causes of death were primary lung cancer and pleural carcinomatosis from a renal cell carcinoma in a patient with VHL disease. No neurological death was observed. The patient survival

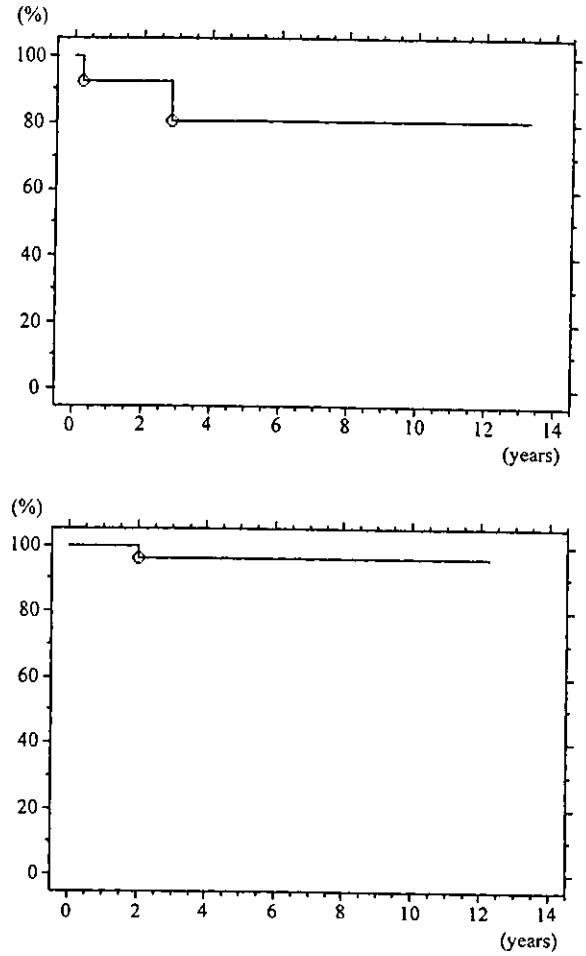

FIG. 1. Kaplan–Meier curves showing survival rate *(upper)* and tumor control rate *(lower)* after GKS for hemangioblastomas.

rate was 84.6% (11 of 13). Actuarial 5- and 10-year survival rates were both 80.8% (Fig. 1 *upper*).

The median radiological follow-up period in 38 tumors in 12 patients was 35 months (range 7–147 months). No neuroimaging studies were available in the patient who died of lung cancer 3 months after GKS. Only one tumor appeared to increase in size at 24 months after the treatment. In this case, intratumoral hemorrhage was revealed on MR images. It was not clear whether the tumor itself had grown. The other 37 tumors were controlled locally. One disappeared, nine regressed, and 27 remained unchanged. The tumor control rate was 97.4% (37 of 38 tumors) at the time of the most recent follow up. Actuarial 5- and 10-year tumor control rates were both 96.2% (Fig. 1 *lower*). Statistical evaluation of the effects of patient characteristics and treatment factors on survival and tumor control was impossible with such a small number of patients. New lesions and/or those increasing in size outside the irradiated area were discovered in five patients (38.5%) during the follow-up period.

Some adverse radiation effects were seen on the follow-up images. Brain edema was shown adjacent to eight tumors in three patients. With the exception of one case, all the tumors with radiation-induced edema also demonstrated peritumoral contrast enhancement. Another two lesions revealed abnormal peritumoral enhancement. These enhance-

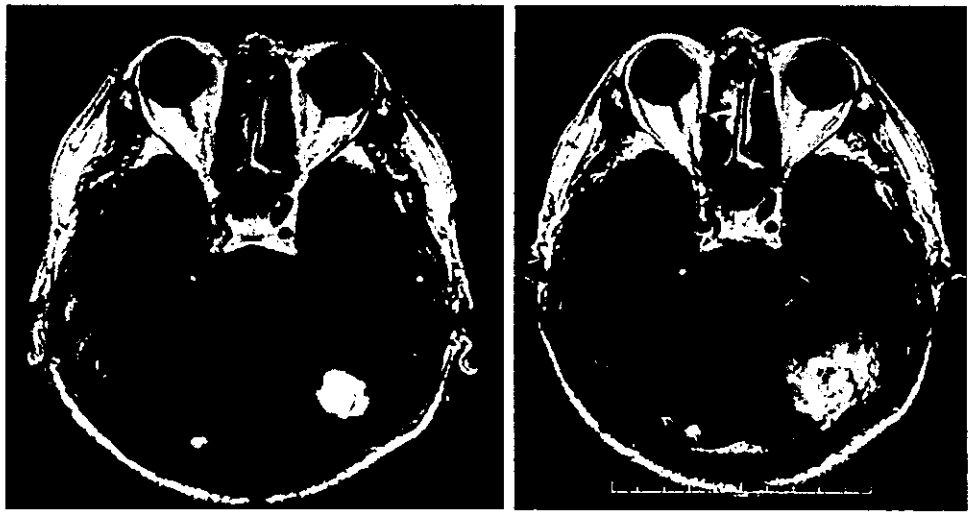

FIG. 2. Magnetic resonance images obtained in a man who underwent a second GKS for two hemangioblastomas in the left cerebellar hemisphere (another lesion is not shown) *(left)*. Two months later, abnormal peritumoral enhancement accompanied by brain edema was recognized, and 2 months later (4 months after GKS), the enhancement enlarged *(right)*.

ments arose between 2 and 6 months (median 3 months) after GKS and improved gradually with conservative management over 2 years (Fig. 2). This change was recognized more frequently in larger tumors (> 0.5 cm^3) than in smaller ones. The difference was statistically significant ($p = 0.0034$). Another possible unwanted change was an increase in the volume of the cystic component, which was noticed in five lesions between 2 and 36 months after GKS. One of these patients underwent an operation to resect the cystic mass. One other patient was transiently symptomatic.

Clinical neurological deterioration occurred in four patients, including the aforementioned patient with the transient increase in the cyst volume. Another patient, who was treated with GKS for four lesions in two sessions during a 13-year follow up as described previously, experienced transient hydrocephalus due to brain edema with enhancement and was treated conservatively. Symptoms in the other two patients were caused by new or growing tumors that had not been treated with GKS.

Discussion

The findings in our series indicate that GKS can be an effective method for achieving a local tumor control rate of 96.2% at 10 years. Authors of several reports have previously documented the effect of radiosurgery on hemangioblastomas, and the tumor control rate has been between 75% and 100%; however, in none of these studies were the long-term results such as 10-year tumor control rates described.[1–5] Hemangioblastomas are benign, slowly growing tumors so it can be difficult to judge whether the control of a tumor by GKS represents an improvement over the natural course of the untreated disease. In our cases, five patients developed new lesions and/or their lesions increased in size. Nonetheless, all GKS-treated tumors were controlled. Moreover, two patients, who were followed up for more than 12 years, both underwent a second GKS for new tumors, which arose after the initial treatment. These findings suggest that GKS can indeed control the tumors; however, long-term outcomes such as 15-, 20-, or 30-year survival and control rates will require continuing study.

We have summarized the outcomes of previously reported series and this present study in Table 2. Our outcomes are comparable to those reported by Niemelä, et al.,[3] and Chang, et al.[1] The control rates published by Patrice, et al.,[5] Pan, et al.,[4] and Jawahar, et al.,[2] seem to be worse. Patrice, et al., and Jawahar, et al., indicated that a higher radiosurgical dose and a smaller tumor volume significantly contributed to a higher tumor control rate. Chang, et al., also described the importance of higher dose. In conventional radiotherapy, patients who received 40 Gy or more lived longer than those who received 36 Gy or less.[7] The median margin dose in our study and the other two studies with higher control rates was 20 Gy or more, which was higher than in the other studies in which the control rates were lower. An additional factor in the high survival rate in the current series is the relatively low tumor volume.

In our series, peritumoral contrast enhancement was recognized on MR images in nine tumors. This change has not previously been mentioned in any detail. The enhancement was related to tumor volume. The mechanism of this enhancement is not known. Progressive thickening of the intimal layer begins as early as 3 months after GKS.[4,6] Hemangioblastomas have a rich capillary network; thus congestion due to intimal thickening could lead to an increased permeability of neighboring blood vessels.

Our results suggest that good tumor control may be achieved with small lesions and a high dose. On the whole, the development of new lesions or continued tumor growth requiring surgery and the development of complications were all related to larger tumors. The recommended strategy is to choose GKS for smaller tumors. After treatment, we recommend serial imaging follow up every 6 to 12 months to ensure that new or growing lesions may be detected when they are still small.

TABLE 2
*Summary of outcomes after stereotactic radiosurgery for hemangioblastomas**

Authors & Year	No. of Patients/ Tumors	Follow Up in Mos (range)	Technique	Tumor Size (range)		Margin Dose in Gy (range)	Control Rate %			Survival Rate %			
				Mean Diameter (mm)	Mean Volume in cm^3		Overall	2-Yr	5-Yr	10-Yr	Overall	2-Yr	5-Yr	10-Yr
Niemelä, et al., 1996	10/11	43 (13–122)	GKS	13.5 (6–43)		20 (5–35)	100.0	100.0	100.0		80.0	90.0	67.5	67.5
Patrice, et al., 1996	22/38	24.5 (6–77)	GKS or LINAC		0.97 (0.05–12)	15.5 (12–20)	86.2	86.0			81.9	88		
Chang, et al., 1998	13/29	43 (11–84)	LINAC		1.6 (0.07–65.4)	23.2 (18–40)	96.6				92.3			
Pan, et al.,1998	13/20	29 (24–36)	GKS	20 (7.5–55)		18.4 (12–24	69.2				92.3			
Jawahar, et al., 2000	27/29	48 (6–108)	GKS		3.2 (0.36–27)	16.1 (11.7–20)	75.9	84.5	75.2		77.8		75.1	
present study	13/38	36 (3–159)	GKS	7.7 (2.0–21.0)	0.23 (0.004–4.84)	20 (18–20)	97.4	96.2	96.2	96.2	84.6	92.3	80.8	80.8

* LINAC = linear accelerator.

Conclusions

Gamma knife surgery is a safe and effective method to control hemangioblastomas and achieve local tumor control of 96.2% at 10 years. Higher doses and smaller tumors probably contribute to better outcomes. Recurrence outside the original GKS-treated area is common and was seen in five patients (38.5% in this study). Peritumoral contrast enhancement is related to larger tumors and resolves with conservative management. Regular imaging follow up is important so that subsequent treatments, if needed, may be used on smaller lesions, which respond better.

References

1. Chang SD, Meisel JA, Hancock SL, et al: Treatment of hemangioblastomas in von Hippel-Lindau disease with linear accelerator-based radiosurgery. **Neurosurgery 43:**28–35, 1998
2. Jawahar A, Kondziolka D, Garces YI, et al: Stereotactic radiosurgery for hemangioblastomas of the brain. **Acta Neurochir 142:**641–645, 2000
3. Niemela M, Lim YJ, Soderman M, et al: Gamma knife radiosurgery in 11 hemangioblastomas. **J Neurosurg 85:**591–596, 1996
4. Pan L, Wang EM, Wang BJ, et al: Gamma knife radiosurgery for hemangioblastomas. **Stereotact Funct Neurosurg 70 (Suppl 1):** 179–186, 1998
5. Patrice SJ, Sneed PK, Flickinger JC, et al: Radiosurgery for hemangioblastoma: results of a multiinstitutional experience. **Int J Radiat Oncol Biol Phys 35:**493–499, 1996
6. Phillips T: Early and late effects of radiation on normal tissues, in Gutin P, Leibel S, Sheline G (eds): **Radiation Injury to the Central Nervous System.** New York: Raven Press, 1991, pp 37–55
7. Sung DI, Chang CH, Harisiadis L: Cerebellar hemangioblastomas. **Cancer 49:**553–555, 1982

Address reprint requests to: Masao Tago, M.D., Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. email: tago-rad@h.u-tokyo.ac.jp.

科研費研究課題の成果

Cアーム型ライナックを用いた3次元歳差集光原体照射法と治療計画システムの開発

中川恵一*

*東京大学大学院医学系研究科放射線医学講座

2004年 INNERVISION 「インナービジョン」 7月号

科研費研究課題の成果

Cアーム型ライナックを用いた3次元歳差集光原体照射法と治療計画システムの開発

中川恵一*

目的・意義

癌の臨床において，機能や形態を温存できる放射線治療のウェートが確実に高まっている。最近では，脳腫瘍，脳血管奇形などを対象として，1回に大量の放射線量を，微小な患部に集中させる定位放射線治療が急速に普及しつつある。定位放射線治療では，当初，専用装置であるガンマナイフが先行して研究されたが，現在では直線加速器を用いた方法が主流となってきている。直線加速器を用いて定位放射線治療を行う方法は，寝台のアイソセンタ中心の回転と，ガントリの回転を組み合わせるマルチアーク照射法が一般的であるが，直線加速器の機械的精度上，最も誤差の大きい寝台の回転を伴うため，位置的精度は最小の場合でも±1mmと，ガンマナイフのそれより1桁高い。さらに，ガンマナイフでは，半球状に配列された線源から一点に向って細いビームが集中する「歳差集光型」(図1)となっているため，マルチアーク法より線量集中性が高いなど，ガンマナイフの優位性は明らかである。しかし，ガンマナイフは，患者の頭部の上方にヘルメット状に線源を配置する機構を持つため，頭部以外の利用はできないという決定的限界がある。

中等大以上の容積の腫瘍に対する高精度放射線治療では，これまで原体照射が標準的治療技法であった。原体照射は，かつて世界をリードする先端的照射技法であったが，現在では，強度変調放射線治療(Intensity modulation radiotherapy：IMRT)に代表される新世代の治療技法の後塵を拝しており，さらなる改良が望まれてきた。

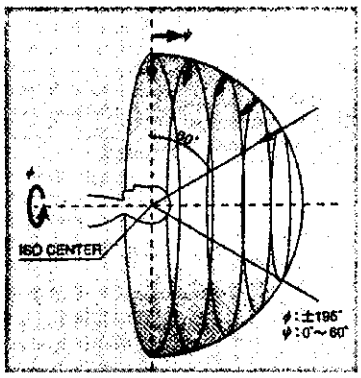

図1　歳差集光照射

方法・成果

本研究では，定位放射線治療や原体照射に関する上記の問題点を解決するため，直線加速器を用いて，ガンマナイフと同様の歳差集光照射に，原体照射機構と組み合わせることにより，「3次元歳差集光原体照射法」を実現した(図2)。これは，直線加速器のガントリをCアームで保持し，ガントリ回転のほかに，Cアームに沿った回転を加える「Cアーム型ライナック」(図3)により，ガンマナイフと同様の集光照射機構を実現させ，これに原体照射における多分割絞りの運動を連動されるものである。照射中に，ビームは円錐状に腫瘍に入射し，各入射角に応じて，多分割絞りが連続的に変化する。これにより，頭部，体幹部を問わず，すべての部位の悪性腫瘍の放射線治療を，ガンマナイフやIMRTを凌ぐ高い精度で行うことができ，放射線治療成績の向上に大きく寄与すると期待される。また，現在，市販の治療計画装置をプラットフォームとして，歳差集光原体照射に対応する治療計画ソフトウエアを開発中である。

歳差集光原体照射での線量分布特性をガンマナイフと比較した結果，線量分布は基本的には類似するが，ターゲット内の均一性は，ガンマナイフが低線量域の等方向性においては歳差集光照射が優れていた。

まとめ(展望)

歳差集光原体照射を可能とする直線加速器はこれまで，国内外を問わず皆無であり，本研究はまったく独創的である。独創的装置はしばしば専用装置となるが，本装置では，通常の直線加速器による治療を完全に包含しており汎用性が高い。また，将来，加速管の小型化が実現した場合には，Cアームの自由度を高めることで，さらなる線量集中性，線量分布の任意性が高まると期待でき，先駆性と発展性に富んでいる。

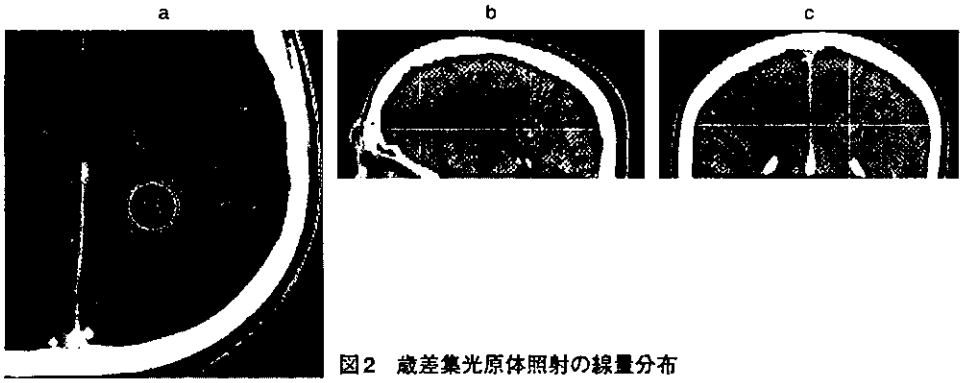

図2　歳差集光原体照射の線量分布

図3　Cアーム型ライナック

＊東京大学大学院医学系研究科放射線医学講座

J Cancer Res Clin Oncol (2004) 130: 351–356
DOI 10.1007/s00432-004-0547-x

ORIGINAL PAPER

Yuta Shibamoto · Emiko Tsuchida · Kaori Seki
Natsuo Oya · Masatoshi Hasegawa · Yukihiro Toda
Mitsuhiro Takemoto · Minako Sumi
Jun-ichi Hiratsuka · Masahiko Oguchi
Masako Hosono · Shigeo Yasuda · Mitsuharu Sougawa
Yoshihisa Kakutoh · Naofumi Hayabuchi

Primary central nervous system lymphoma in Japan 1995–1999: changes from the preceding 10 years

Received: 14 November 2003 / Accepted: 20 January 2004 / Published online: 18 March 2004

Abstract *Purpose*: Previously, we conducted a nationwide survey of primary central nervous system lymphoma (PCNSL) treated between 1985 and 1994 in Japan. In the present study, we conducted further investigations of PCNSL patients treated between 1995 and 1999 to clarify possible changes with time in the clinical features, treatment, and outcome of this disease. *Methods*: Thirteen Japanese institutions were surveyed, and data on 101 patients with histologically-confirmed PCNSL were collected. These data were compared with those of 167 patients treated at the same institutions between 1985 and 1994. *Results*: Regarding patient and tumor characteristics, the proportion of patients with good performance status (PS) was significantly higher in the group treated during 1995–1999 than in that treated during 1985–1994, but other characteristics were not significantly different. Regarding treatment, more patients in the more recent period (66%) received systemic chemotherapy than those in the preceding period (53%, $P = 0.049$). For all patients, including those who did not complete radiotherapy, the median survival time was 17 months and 30 months in patients treated between 1985 and 1994 and those treated between 1995 and 1999, respectively, and the 5-year survival rate was 15% versus 31% ($P = 0.0003$). In both patient groups, higher age and tumor multiplicity were associated with poor prognosis in multivariate analysis. In patients treated between 1995 and 1999, those who received systemic chemotherapy showed significantly better prognosis than those who did not ($P = 0.0049$), but the difference was not significant in multivariate analysis ($P = 0.23$). *Conclusions*: The high survival rates observed in the present survey are comparable with those of recent prospective studies employing intensive chemoradiotherapy. The improvement in prognosis appeared to result, at least in part, from the increase in the proportion of patients with better PS. Since the clinical feature and treatment outcome of patients with PCNSL can thus change with the era, historical control data should not be used in comparing different treatment modalities.

Keywords Brain neoplasm · Lymphoma · Primary CNS lymphoma · Radiotherapy · Chemotherapy

Author affiliations are: Niigata University (ET), Tokyo Women's Medical University (KS), Kyoto University (NO), Gunma University (M Hasegawa), Kurume University (YT, NH), Okayama University (MT), National Cancer Center (M Sumi), Kawasaki Medical School (JH), Cancer Research Institute (MO), Osaka City University (M Hosono), Chiba University (SY), Kansai Medical University (M Sougawa), and Tohoku University (YK)

Y. Shibamoto (✉)
Department of Radiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, 467-8601 Mizuho-ku, Nagoya, Japan
E-mail: yshiba@med.nagoya-cu.ac.jp
Tel.: +81-52-8538274
Fax: +81-52-8525244

Y. Shibamoto · E. Tsuchida · K. Seki · N. Oya · M. Hasegawa
Y. Toda · M. Takemoto · M. Sumi · J. Hiratsuka
M. Oguchi · M. Hosono · S. Yasuda · M. Sougawa
Y. Kakutoh · N. Hayabuchi
JASTRO CNS Lymphoma Study Group, Japan

Introduction

Primary central nervous system lymphoma (PCNSL) is increasing and is becoming one of the most important tumors in neuro-oncology. Radiation therapy has been the standard treatment for PCNSL until recently, but the outcome of patients treated by radiation alone has not necessarily been satisfactory (Shibamoto et al. 1990; Reni et al. 1997; Hayabuchi et al. 1998; Nelson 1999). More recently, the use of high-dose methotrexate (MTX)-containing chemotherapy before radiation appeared to have gained some success in obtaining

long-term survival (Glass et al. 1994; Blay et al. 1998; Brada et al. 1998; Abrey et al. 2000; Ferreri et al. 2000; O'Brien et al. 2000; Reni et al. 2001; Bessel et al. 2001; Caldoni & Aebi 2002; DeAngelis et al. 2002). However, there has been no randomized trial suggesting the superiority of the combined modality treatment over radiation therapy alone, and a recent study by a German group suggested a high rate of progressive disease during treatment with 6 courses of 8 g/m^2 of MTX (Herrlinger et al. 2002). Therefore, the benefit of high-dose MTX appears to remain uncertain. Since the clinical features of PCNSL appear to be changing with time, it may not be reasonable to consider that combined MTX-containing chemotherapy and radiation is superior to radiation alone, by comparing the results of combined treatment with the historical control data in patients treated by radiation therapy alone.

Previously, Hayabuchi et al. (Hayabuchi et al. 1998) conducted a nationwide survey of PCNSL in Japan treated between 1985 and 1994. The findings on 466 patients were previously published. Considering the increasing importance of this disease, we organized a research group consisting of 13 institutions to carry out both retrospective and prospective studies on PCNSL. As a first study of this group, we collected data on PCNSL patients treated between 1995 and 1999 at these institutions. In addition to analyzing these data on 101 patients, we compared the data with those on 167 patients from the previous survey treated between 1985 and 1994 at the same institutions, to investigate changes in the clinical feature, treatment modality, and outcome between these eras.

Materials and methods

Subjects of the present survey were patients with histologically-proven PCNSL who received radiation therapy between 1995 and 1999. Those who did not complete the planned radiotherapy were included. Clinical characteristics, treatment and prognosis of each patient shown in the Results section were asked using a detailed questionnaire. Data on 101 patients were collected from 13 institutions. For comparison, data on 167 patients treated in the preceding 10 years, i.e., between 1985 and 1994, at the same institutions were obtained from the data source of the previous nationwide survey (Hayabuchi et al. 1998) and were analyzed. Data regarding tumor size (maximum diameter at diagnosis and before radiation therapy) was asked for in the present survey, which had not been done in the previous survey. As often happens with such a survey, a number of the items were unanswered by the investigators. Various chemotherapy regimens had been used, and were categorized as follows: (A) cyclophosphamide, vincristine, and prednisolone (COP) or COP plus doxorubicin (CHOP/VEPA); (B) intravenous methotrexate (MTX) alone or MTX-containing regimens. The drugs included in regimen A had often been used in combination with MTX, and such regimens were categorized into this group; (C) cytarabine plus procarbazine; (D) nitrosourea-containing regimens. Some of the drugs in regimen A had been used in combination with nitrosoureas, and such regimens were included in this group. When MTX had been used in combination, the regimen was categorized into group B; (E) cisplatin plus etoposide; and (F) Single use or combination of miscellaneous other agents not included in the above groups. For analysis of treatment results, regimens C–F were grouped together. Differences in patient, tumor, and treatment characteristics between groups were examined by Fisher's exact test.

Survival rates were calculated from the date of starting radiotherapy using the Kaplan-Meier method, and differences in pairs of survival curves were examined by the log-rank test. Multivariate analysis of prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups, and all the parameters were entered as dichotomous variables. All statistical analyses were carried out using a computer program, Stat View Version 5 (SAS institute, Cary, NC, USA).

Results

Table 1 shows patient, tumor, and treatment characteristics in the two groups treated between 1985 and 1994 and between 1995 and 1999. There were more patients with better WHO performance status (PS) score in the group treated between 1995 and 1999 than in the

Table 1 Patient, tumor, and treatment characteristics

Characteristic		1985–1994	1995–1999	*P*
Gender	Male/female	97/70	67/34	0.20
Age (years)	< 60/≥ 60	83/84	53/48	0.71
	Median (range)	60 (15–84)	59(15–84)	
Performance status	0–2/3,4	69/95	60/41	0.0078
Lactate dehydrogenase	Normal/high	49/34	50/30	0.75
B symptom	Yes/no	16/133	11/81	0.83
Phenotype	B/T	75/8	79/6	0.59
Tumor number	Single/multiple	103/63	56/43	0.44
Maximum tumor diameter	At diagnosis	–	3 (1.5–9)	
Median (range) (cm)	Before radiation	–	3 (0–9)	
Radiotherapy	Completed/not completed	158/9	97/4	0.77
Radiation field	Whole brain/partial brain	146/21	92/9	0.43
Spinal radiation	Yes/no	15/152	4/97	0.15
Total dose (Gy)	< 50/≥50	54/113	28/73	0.49
	Median (range)	50 (2–70)	50 (6–80)	
Whole-brain dose (Gy)	< 40/≥40	70/97	42/59	1.0
	Median (range)	40 (0–54)	40 (0–60)	
Chemotherapy	Yes / no	78/70	65/34	0.049

Table 2 Chemotherapy regimens (COP cyclophosphamide, vincristine and prednisone, CHOP/VEPA COP plus doxorubicin)

Regimen	1985–1994	1995–1999
COP, CHOP/VEPA	35 (45%)	25 (38%)
Methotrexate-containing regimens	18 (23%)	27 (42%)
Cytarabine and procarbazine	0	7 (11%)
Nitrosourea-containing regimens	13 (17%)	2 (3%)
Cisplatin and etoposide	8 (10%)	4 (6%)
Miscellaneous drugs	4 (5%)	0

group treated in the preceding 10 years, but the other patient and tumor characteristics did not differ significantly between the two groups. Radiotherapy characteristics were similar between the two groups. During both study periods, more than 85% of the patients were treated with whole-brain irradiation with or without focal boost, and the median total and whole brain doses were 50 Gy and 40 Gy, respectively. Whole spinal irradiation was employed in less than 10% of the patients. On the other hand, more patients seen between 1995 and 1999 received systemic chemotherapy than those seen between 1985 and 1994 (66% vs 53%, $P = 0.049$). Table 2 shows chemotherapy regimens used in the two groups. The use of MTX-containing regimens appeared to be increasing recently. However, a high dose of MTX (>2 g/m^2 per administration) was used in only 14 patients (14% of all patients) treated between 1995 and 1999.

Figure 1 shows overall survival curves for all patients in the two groups. Patients in the present survey had significantly better survival rates than those in the previous survey ($P = 0.0003$); median survival time was 30 vs 17 months, and the 3-year survival rate was 46% vs 24%. The 5-year survival was 31% and 15%, respectively. Table 3 summarizes survival data in the two groups according to potential prognostic factors. In both study periods, patients with ages <60 years, PS 0–2, or a single tumor showed significantly higher survival rates. Patients with normal lactate dehydrogenase (LDH) levels or without B symptom had better prognoses than those with high LDH level or with B symptom, respectively, in the group treated between 1995 and 1999, but not in those treated during 1985–1994.

To analyze the influence of treatment-related factors on outcome, patients who did not complete radiotherapy (and died soon) were excluded. In patients treated between 1985 and 1994, those who received partial-brain radiation, spinal radiation, or whole-brain dose <40 Gy showed better prognoses, but these phenomena were not observed in patients treated between 1995 and 1999. Figure 2 shows survival curves according to the treatment modality, i.e., radiation alone vs radiation plus chemotherapy. In patients treated between 1985 and 1994, the two groups showed similar prognoses. In patients treated between 1995 and 1999, however, those who received radiation plus chemotherapy showed significantly better survival than those who received radiation alone. Among these patients, 61% of the

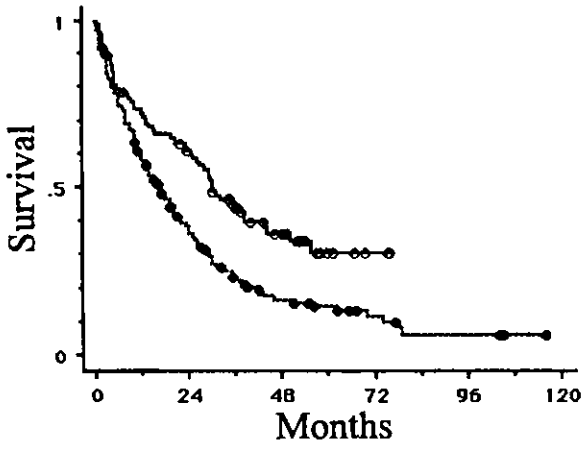

Fig. 1 Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (____O____). The difference was significant ($P = 0.0003$)

patients who received radiochemotherapy were younger than 60 years, but 39% of those treated with radiation alone were younger than 60 years ($P = 0.050$). Similarly, 64% of the patients who received radiochemotherapy had a PS 0–2, but 55% of those treated with radiation had a PS 0–2 ($P = 0.50$). Figure 3 shows survival curves according to the chemotherapy regimens. In patients treated between 1985 and 1994, there was no significant difference in survival curves according to the regimens. On the other hand, there was an overall difference in those treated between 1995 and 1999 ($P = 0.018$). Patients receiving MTX-containing regimens showed better survival than those treated with CHOP/VEPA or COP ($P = 0.0071$).

Multivariate analyses were performed for potential prognostic factors, which were significant in univariate analyses (Table 4). Factors concerning the radiation field and spinal radiation were not included because of the small number of patients in one of the groups. In both patient groups treated during 1985–1994 and 1995–1999, age and tumor number were suggested to be significant prognostic factors. PS and LDH level did not reach statistical significance. The radiation dose to the whole brain and chemotherapy did not prove significant in patients treated between 1985 and 1994, and in those treated between 1995 and 1999, respectively.

Discussion

The most significant finding of this study appears to be that patients treated between 1995 and 1999 showed a significantly better prognosis than those treated between 1985 and 1994. Comparison of the patient and tumor characteristics revealed that there were more patients with better PS between 1995 and 1999 than between 1985 and 1994. This may be due to the earlier diagnosis of the disease in recent years and improvement in gen-

Table 3 Survival data according to potential prognostic factors (MST median survival time in months, 5-YSR 5-year survival rate)

Prognostic factor		1985–1994				1995–1999			
		n	MST	5-YSR(%)	*P*	*n*	MST	5-YSR(%)	*P*
Gender	Male	97	15	8.7	0.13	67	32	31	0.62
	Female	70	22	23		34	28	33	
Age (years)	< 60	83	20	22	0.0057	53	44	45	0.0052
	≥ 60	84	13	6.8		48	23	15	
Performance status	0–2	69	24	18	0.0015	60	37	32	0.024
	3,4	95	11	13		41	12	30	
B symptom	Yes	16	10	7.5	0.30	11	14	18	0.027
	No	133	18	17		81	36	35	
Lactate	Normal	49	22	31	0.17	50	55.5	43	0.0084
dehyrdogenase	High	34	21	5.8		30	20.5	(20)[b]	
Tumor number	Single	103	22	19	0.0021	56	55.5	43	0.0083
	Multiple	63	11	7.9		43	26	17	
Tumor size (cm)[a]	≤ 3 cm	–	–	–	–	51	32	33	0.95
	> 3 cm	–	–	–		41	37	31	
Radiation field	Whole brain	139	17	12	0.026	89	30	31	0.99
	Partial brain	19	35	38		8	35	(33)	
Spinal radiation	Yes	15	31	37	0.042	4	-	(50)	0.69
	No	143	17	13		93	30	30	
Total dose (Gy)	< 50	45	16	22	0.79	24	29.5	26	0.16
	≥ 50	113	18	13		73	36	32	
Whole-brain dose	< 40	61	24	22	0.025	38	32	26	0.83
(Gy)	≥40	97	14	11		59	30	32	
Chemotherapy	Yes	65	18	19	0.63	64	38	40	0.0049
	No	74	19	14		31	25	(14)	

[a] Maximum tumor diameter before radiation
[b] Figures in parentheses are 4-year survival rate

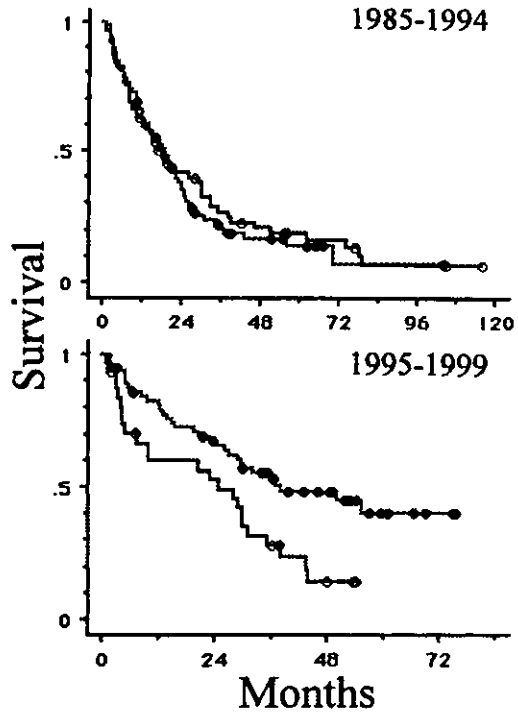

Fig. 2 Survival curves according to the treatment modality. ____O____ : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel, $P = 0.0049$)

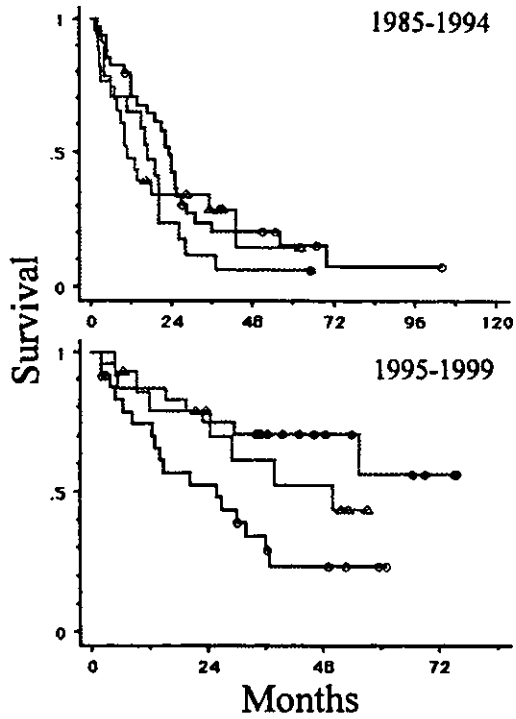

Fig. 3 Survival curves according to chemotherapy regimens. ____O____ : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -Δ- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.32$; lower panel, $P = 0.018$)

Table 4 Multivariate anayses for potential prognostic factors that were significant in univariate analysis

Factor	1985–1994 (n = 154)		1995–1999 (n = 72)	
	P	Relative risk	P	Relative risk
Age (< 60 vs ≥ 60 years)	0.036	1.48 (1.03–2.15)[a]	0.047	2.07 (1.01–4.22)
Performance status (0–2 vs 3,4)	0.13	1.36 (0.92–2.01)	0.13	1.77 (0.85–3.68)
Lactate dehydrogenase (normal vs high)	–	–	0.13	1.70 (0.86–3.34)
Tumor number (single vs multiple)	0.0093	1.67 (1.13–2.45)	0.0032	2.82 (1.42–5.62)
Whole-brain dose (< 40 vs ≥ 40 Gy)	0.22	1.28 (0.86–1.91)	–	–
Chemotherapy (yes vs no)	–	–	0.23	1.53 (0.32–1.31)

[a]Figures in parentheses are 95% confidence intervals

eral care including corticosteroid therapy and less aggressive surgery. Since PS was a significant prognostic factor in univariate analysis, it is suggested that the increase in the proportion of better PS patients may, at least in part, have contributed to the improvement in prognosis in patients treated between 1995 and 1999.

Age, PS, and tumor multiplicity are well-known prognostic factors for PCNSL (Corry et al. 1998; Hayabuchi et al. 1998; O'Brien et al. 2000). The present results of univariate analyses agree with these previous observations, although the influence of PS did not reach a significant level in multivariate analysis. Patients with a high LDH level treated between 1995 and 1999 showed a poorer prognosis than those with a normal LDH level in univariate analysis. However, LDH was not a significant factor in patients treated between 1985 and 1994, as also shown in the multivariate analysis of patients treated between 1995 and 1999. The previous analysis of 466 patients in the nationwide survey suggested an association of high LDH level and poor prognosis in both univariate and multivariate analyses (Hayabuchi et al. 1998), so LDH may be a potential prognostic factor which is certainly weaker than age, PS, and tumor multiplicity. A similar finding was obtained regarding B symptom. In the newer survey, we investigated the influence of tumor size, but it did not appear to have a significant influence on patient outcome.

Regarding the method of radiation therapy, patients who were treated with a partial-brain field showed a better prognosis than those treated with a whole-brain field in the group treated between 1985 and 1994. Shibamoto et al. (Shibamoto et al. 2003) recently discussed the possible benefit of using partial-brain irradiation, especially in patients with a single lesion. Due to the retrospective nature of the present study and the small number of patients who received partial-brain irradiation, no conclusion should be drawn regarding radiation field, but avoiding whole-brain radiation may be a future topic in the treatment of PCNSL. The observation in the earlier period that patients who received spinal radiation and those who received whole-brain doses of less than 40 Gy had a better prognosis are paradoxical, and it is suggested that these observations would represent patient selection bias, which is often seen in retrospective analysis. As has been suggested by previous findings (Nelson et al. 1992; Hayabuchi et al. 1998), a higher dose of radiation did not appear to be associated with survival improvement.

In patients treated between 1985 and 1994, those who received radiation alone and those who received radiation plus chemotherapy showed a similar prognosis. On the other hand, in patients treated between 1995 and 1999, those who received radiation plus chemotherapy had a significantly better prognosis than those who received radiation alone. However, the effect of chemotherapy was not significant in multivariate analysis. Since younger patients were more often treated with combined radiation and chemotherapy, this may be one of the reasons why the effect of chemotherapy was not supported by multivariate analysis. Analysis according to chemotherapy regimens suggested a possible advantage of MTX-containing regimens over conventional CHOP or similar regimens. Several studies have suggested the ineffectiveness of CHOP or similar regimens, especially when given before radiation (Schultz et al. 1996; O'Neill 1999; Mead et al. 2000), although post-radiation CHOP requires further investigation (Shibamoto et al. 1999). The present findings suggest that systemic chemotherapy with weak or moderate intensity may not be beneficial in PCNSL.

The findings of the present study revealed that the treatment outcome for PCNSL varies greatly with the era. Although most of the chemotherapy regimens used were of mild or moderate intensity and only 14% of the patients received high-dose-MTX-containing chemotherapy, the 5-year survival rate of 31% for all patients treated between 1995 and 1999 (including those who did not complete radiotherapy) were equal to that recently reported by the Radiation Therapy Oncology Group (DeAngelis et al. 2002) or those of other series using intensive combined modality treatment including high-dose MTX (Brada 1998; Bessell et al. 2001). Therefore, it appears to be inappropriate to discuss the usefulness of treatment modality by comparing with the historical control data. There have been no major randomized studies, except for a small one (Mead et al. 2000), regarding the benefit of combining chemotherapy with radiation, but to confirm the efficacy of chemotherapy, randomized studies appear to be necessary.

Acknowledgements This study was supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (14030042, 14370276, 14657214). The authors wish to thank Drs. Kumiko Karasawa, Atsushi Nishikawa, Naoto Shikama, Koichi Isobe, and Kuniaki Katsui for valuable help in collecting data.

References

Abrey LE, Yahalom J, DeAngelis LM (2000) Treatment for primary CNS lymphoma: the next step. J Clin Oncol 18:3144–3150

Bessell EM, Graus F, Lopez-Guillermo A, Villa S, Verger E, Petit J, Holland I, Byrne P (2001) CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 50:457–464

Blay JY, Conroy T, Chevreau C, Thyss A, Quesnel N, Eghbali H, Bouabdallah R, Coiffier B, Wagner JP, Le Mevel A, Dramais-Marcel D, Baumelou E, Chauvin F, Biron P (1998) High-dose MTX for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 16:864–871

Brada M, Hjiyiannakis D, Hines F, Traish D, Ashley S (1998) Short intensive primary chemotherapy and radiotherapy in sporadic primary CNS lymphoma. Int J Radiat Oncol Biol Phys 40:1157–1162

Calderoni A, Aebi S (2002) Combination chemotherapy with high-dose MTX and cytarabine with or without brain irradiation for primary central nervous system lymphomas. J Neurooncol 59:227–230

Corry J, Smith JG, Wirth A, Quong G, Liew KH (1998) Primary central nervous system lymphoma: age and performance status are more important than treatment modality. Int J Radiat Oncol Biol Phys 41:615–620

DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ (2002) Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93–10. J Clin Oncol 20:4643–4648

Ferreri AJM, Reni M, Villa E (2000) Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. Ann Oncol 11:927–937

Glass J, Gruber ML, Chef L, Hochberg FH (1994) Preirradiation MTX chemotherapy of primary central nervous system lymphoma: long-term outcome. J Neurosurg 81:188–195

Hayabuchi N, Shibamoto Y, Onizuka Y, JASTRO CNS Lymphoma Study Group members (1999) Primary central nervous system lymphoma in Japan: a nationwide survey. Int J Radial Oncol Biol Phys 44:265–272

Herrlinger U, Schabet M, Brugger W, Kortmann RD, Kuker W, Deckert M, Engel C, Schmeck-Lindenau HJ, Mergenthaler HG, Krauseneck P, Benohr C, Meisner C, Wiestler OD, Dichgans J, Kanz L, Bamberg M, Weller M (2002) German Cancer Society Neuro-Oncology Working Group NOA-03 multi-center trial of single-agent high-dose MTX for primary central nervous system lymphoma. Ann Neurol 51:247–252

Mead GM, Bleehen NM, Gregor A, Bullimore J, Shirley D, Rampling RP, Trevor J, Glaser MG, Lantos P, Ironside JW, Moss TH, Brada M, Whaley JB, Stenning SP (2000) A Medical Research Council randomized trial in patients with primary central non-Hodgkin's lymphoma. Cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Cancer 89:1359–1370

Nelson DF (1999) Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). J Neuro-Oncol 43:241–247

Nelson DF, Martz KL, Bonner H, Nelson JS, Newall J, Kerman HD, Thomson JW, Murray KJ (1992) Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radial Oncol Biol Phys 23:9–17

O'Brien P, Roos D, Pratt G, Liew K, Barton M, Poulsen M, Olver I, Trotter G (2000) Phase II multicenter study of brief single-agent MTX followed by irradiation in primary CNS lymphoma. J Clin Oncol 18:519–526

O'Neill BP, O'Fallon JR, Earle JD, Colgan JD, Earle JD, Krigel RL, Brown LD, McGinnis WL (1999) Primary central nervous system non-Hodgkin's lymphoma (PCNSL): survival advantages with combined initial therapy? A final report of the North Central Cancer Treatment Group (NCCTG) study 86–72–52. Int J Radiat Oncol Biol Phys 43:559–563

Reni M, Ferreri AJM, Garancini MP, Villa E (1997) Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature. Ann Oncol 8:227–234

Reni M, Ferreri AJ, Guha-Thakurta N, Blay JY, Dell'Oro S, Biron P, Hochberg FH (2001) Clinical relevance of consolidation radiotherapy and other main therapeutic issues in primary central nervous system lymphomas treated with upfront high-dose MTX. Int J Radiat Oncol Biol Phys 51:419–425

Schultz C, Scott C, Sherman W, Donahue B, Fields J, Murray K, Fisher B, Abrams R, Meis-Kindblom J (1996) Preirradiation chemotherapy with cyclophosphamide doxorubicin, vincristine, and dexamethazone for primary CNS lymphomas: initial report of Radiation Therapy Oncology Group protocol 88–06. J Clin Oncol 14:556–564

Shibamoto Y, Tsutsui K, Dodo Y, Yamabe H, Shima N, Abe M (1990) Improved survival rate in primary intracranial lymphoma treated by high-dose radiation and systemic vincristine-doxorubicin-cyclophosphamide-prednisolone chemotherapy. Cancer 65:1907–1912

Shibamoto Y, Sasai K, Oya N, Hiraoka M (1999) Systemic chemotherapy with vincristine, cyclophosphamide, doxorubicin and prednisolone following radiotherapy for primary central nervous system lymphoma: a phase II study. J Neurooncol 42:161–167

Shibamoto Y, Hayabuchi N, Hiratsuka J, Tokumaru S, Shirato H, Sougawa M, Oya N, Uematsu Y, Hiraoka M (2003) Is whole-brain irradiation necessary for primary central nervous system lymphoma? Patterns of recurrence following partial-brain irradiation. Cancer 97:128–133

特集 固形腫瘍の新しい治療

小児固形腫瘍・脳腫瘍の放射線治療

角 美奈子 国立がんセンター中央病院放射線治療部

要旨

放射線治療の技術的進歩としての三次元放射線治療（Three-dimensional conformal radiotherapy:3D-CRT）について，その構成要素および治療計画について紹介する．さらに，応用としての脳腫瘍や軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．

Key Words

radiation therapy
three-dimensional conformal radiotherapy
clinical trial
pediatric

0386-9806/04/¥100/頁/JCLS

はじめに

放射線治療の歴史は1895年のレントゲンによるX線の発見に始まるとされる．その後の放射線生物学・物理学の研究の発展と治療技術・装置の開発により，悪性腫瘍治療の3本柱のひとつとして広く応用されている．その特徴としては，①機能・形態の温存，②治療対象部位の制限が少ない，③合併症を有する患者や高齢者など対象患者の制限が少ない，の3点があげられている．しかし，これらの特徴はさらなる局所制御率の向上と有害反応の軽減があってこそ，臨床においてその有用性を発揮すると考えられる．

本稿では，放射線治療の技術的進歩として三次元放射線治療（Three-dimensional conformal radiotherapy，以下3D-CRTと略す）について述べる．さらに，その応用としての脳腫瘍や，軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．

三次元放射線治療計画

3D-CRTとは，放射線腫瘍医の追究する理想をCTやMRI，PETなどの放射線診断学と治療装置に関するテクノロジーの進歩が支え，実現した治療方法といえよう．その応用と成果は重

要臓器に囲まれた，従来の二次元放射線治療では正常組織の有害反応ゆえに，放射線治療にとって困難の多かった領域，脳腫瘍・頭頸部腫瘍や骨盤腫瘍などの治療で，まずその成果が報告され，諸臓器の治療でその応用が進行している．

3D-CRTとは，永田らによれば[1]“薄い間隔で撮像された複数のCT画像に基づいて，正確なターゲット領域とリスク臓器体積（organs at risk volume）の幾何学的配置を決定する．それらを画像処理した種々の三次元画像を用いたうえで，適切な三次元線量計算に基づき正確な放射線治療計画を行う”と定義している．従来の放射線治療が“照射方向と照射野辺縁の設定をしてからターゲット内の線量分布を確認する”のに対し，“ターゲットと関連正常臓器の輪郭を設定してから，計算された三次元画像を利用することによって，照射方向や照射門数を決定する”ように，治療計画は大きな変化をとげた．

さらに，強度変調放射線治療（Intensity-Modulated Radiotherapy：IMRT）では“ターゲットの内部の詳細な照射線量と各種関連リスク臓器の詳細な容積線量を定義（prescribe）した後に，治療計画装置によって最適な照射方法を決定する”こととなり，望ましい線量分布の実現が，治療計画装置の進歩により可能となりつつある．

もっとも重要であるターゲットの決定において，治療計画を施行する放射線腫瘍医間における認識の差異を最小化するために，国際的な用語の統一が行われてきた．現在使用されているICRU Report 62[2]による表記では表1に示す用語が使用されている．放射線治療にかかわるターゲットの決定においては，ICRU Report 62に従い対象を決定していくが（図），その容積はGTV＜CTV＜ITV＜PTVの順に大きくなり，対象とする疾患やその組織型・分化度，臨床病期などにより異なる設定が必要となった．たとえば，聴神経腫瘍など良性腫瘍や動静脈奇形，転移性脳腫瘍に対する定位放射線照射においては，CTVはGTVに限りなく近づくこととなる．ターゲットの決定において重要な役割を果すのは画像診断であり，CTやMRI，PETにとどま

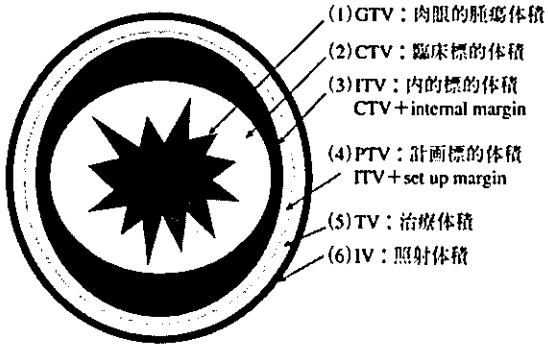

図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定

表1　放射線治療にかかわるターゲットの決定

GTV：Gross Tumor Volume 肉眼的腫瘍体積	画像や触診で明らかに腫瘍が存在すると判断される領域の体積
CTV：Clinical Target Volume 臨床標的体積	GTV＋顕微鏡的進展範囲
ITV：Internal Target Volume 内的標的体積	CTVに臓器移動に対するmarginを加えた標的体積 CTV＋IM
PTV：Planning target volume 計画標的体積	ITVに患者およびビームの位置合わせに関する不正確さを考慮した領域 ITV＋SM

IM：internal margin：呼吸移動や腸管のガスによる影響など体内臓器の移動にかかわるmargin
SM：set up margin：毎回の治療における設定誤差にかかわるmargin

らずMolecular ImagingやFunctional Imagingの応用で腫瘍の浸潤・残存範囲や正常組織の機能を考慮した治療計画の可能性が実現されている．

治療計画の選択においては，従来は治療計画を行って線量分布を計算し（forward planning），その比較により最適治療計画を選択していた．近年，線量を設定したあとに治療計画を最適化するinversed planningが実現している．治療計画の比較には，線量分布図以外に容積線量ヒストグラム（Dose-Volume Histogram:DVH）が使用され，ターゲットや周囲の重要なリスク臓器の全容積中の照射線量が表示されている．TCP（tumor control probability）やNTCP（normal tissue complication probability）の計算も可能である．

3D-CRTは，ターゲットへの線量の集中を可能とし有害反応の軽減をもたらしうるが，総線量の増加により局所制御率の向上が望みうる領域においては，局所制御率をも期待させることとなった．3D-CRTには日本で開発された原体照射や，定位放射線照射，non-coplanar固定多門三次元照射，わが国で開発された歳差運動照射，アメリカで開発されたCyber-knifeなども含まれる．森田ら[3]によれば原体照射とは，“光子線ないし粒子線ビームを用いた二次元ないし三次元方向からの回転運動照射で，どの照射方向から見ても照射野形状がターゲット形状に一致している照射法”と定義されている．CT-simulator，治療計画装置，照射野形状を作成するためのマルチリーフコリメーター（Multi-leaf Collimator:MLC）を搭載した治療装置とネットワークの構築により，原体照射は可能となり，多くの施設に普及している．non-coplanar固定多門三次元照射は，体軸と垂直な方向以外から照射する三次元照射方法で，体軸にそって重要な臓器がとりまくように存在する脳腫瘍や骨盤内腫瘍では，リスク臓器体積の照射線量の軽減に有用である．

定位放射線照射（stereotactic irradiation:STI）とは，小病変に対し多方向から放射線を集中させる方法であり，通常の放射線治療に比較し周囲正常組織の線量を極力減少させつつ，病巣に高線量を集中させる治療である．定位放射線治療は，ガンマナイフに代表される1回で照射する定位手術的照射（stereotactic radiosurgery:SRS）と，分割して照射する定位放射線治療（stereotactic radiotherapy:SRT）に大別される．定位的であるという条件としては，①患者あるいはそれに固定された座標系において照射中心を固定精度内に納めるシステムであること，②定位型手術枠または着脱式固定具を用いた方法であること，③固定装置の照射中心精度が1～2 mm以内であること，④治療中を通じて上記固定精度を保つこと，などが考えられている．脳以外の体幹部定位放射線治療に関しては，①照射装置の照射中心精度が±1 mm以内であること，②治療セットアップの精度が左右，背腹方向それぞれに±5 mmを保ち，頭尾方向に±10 mmを保つ機能を有することが，体幹部定位放射線照射研究会から提言されている．

ガンマナイフは201個のCo^{60}より出るγ線がその中心に集束するよう設計されている．頭部固定用のLeksell stereotactic frameを用い，機械的精度を0.1 mmとする高精度の放射線治療である．SRSは一般放射線治療用の直線加速器（Linac）を用いることにより普及し，より均一な線量分布や大きな照射野が可能となった．Lars Leksellらの治療体積が小さければ逆比例して耐容線量が上り，高線量1回投与が可能となる[4]という理論がSRSの裏づけとなっている．よってその特徴を活かすためにも，対象病変は3 cm以下とされる場合が多い．

SRTは分割照射により治療可能比（正常組織の耐容線量/腫瘍の致死線量）が高まるという放射線生物学のLQ（linear quadratic）モデルを背景としている．1回線量や照射回数などの治療

スケジュールが腫瘍により適切に設定可能であるが，精度がSRSより劣る可能性があり，さまざまな工夫が精度管理のためになされている．

定位放射線照射の治療成績は，局所制御において手術と同等と考えられている．有害反応はFlickingerら[5]の動静脈奇形に関する検討より，その発生頻度が照射部位によることが明らかとなり，照射部位や脳神経との位置関係により1回線量の低減が推奨されている．脳転移の治療は，全脳照射と手術に加え定位放射線照射の登場により，その選択の多様性と妥当性に関する検討がさまざまに行われている．

脳腫瘍の三次元放射線治療計画

小児の脳腫瘍ではAstrocytoma星細胞腫がもっとも多く，ついでMedulloblastoma髄芽腫，上衣腫やGerm Cell Tumorが続く．小児の脳腫瘍においては，手術や化学療法の併用による集学的治療の一環として放射線治療が応用されるが，遅発性放射線反応の軽減が重要な課題である．神経機能と神経内分泌機能の発達への影響を軽減するために，照射体積と照射線量の最適化をめざした試みがなされている．

Children's Oncology Group（COG）のLow-

表2　Intergroup Rhabdomyosarcoma Study Groupの臨床試験における横紋筋肉腫の放射線治療Guidelines

臨床試験	総線量	1回線量/ターゲット/タイミング	化学療法と結果
IRS I (1972～78)	age＜3yrs＝40 Gy age＜6yrs and＜5 cm＝50 Gy age＞6 yrs or＞5 cm＝55 Gy age＞6 yrs and＞5 cm＝60 Gy	1.5～2.25 Gy/Fr/day whole muscle bundle or tumor＋margin no difference in local control Immediately:Groups I and II Week 6:Groups III and IV	VAC, VA, VACA Overall 5-year survival 55%
IRS II (1978～84)	Group I＝no RT. Group II＝40-45 Gy. Group III：age＜6yrs and＜5 cm＝40-45 Gy age＞6 yrs or＞5 cm＝45-50 Gy age＞6 yrs and＞5 cm＝50-55 Gy	1.5～2.25 Gy/Fr/day GTV＋2 cm Week 0:Group II Week 6:Groups III and IV	VAC, VA, VadrC-VAC Overall 5-year survival 63% Botryoid89%, Embryonal 68%, Alveolar 52%, Other 55%
IRS III (1984～88)	Grp I FH-no RT. Grp I UH/II-41.4 Gy. Group III varied by age, size but all＜50.4 Gy.	GTV＋2 cm Day 0:PM with CN palsy, BOS erosion, intracranial extension. Week 2:Group II FH/Group III orbit and H/N. Week 6:all others	VAC, VA, VadrC-VAC, VAadr CDDP/VP16 VadrC-VAC＋CDDP Overall 5-year survival 71%
IRS IV (1991～97)	Group I, Stage 1/2-no RT. Group I, Stage3/II-41.4 Gy CRT. Group III randomized to 50.4 Gy CRT vs 59.4 Gy HRT（1.1 Gy BID）	GTV＋2 cm Day 0:PM with CN palsy, BOS erosion, intracranial extension. Week 12:all others	VA, VAC, VAI, VIE Overall 3-yr FFS 77% No difference in local control with CRT vs HRT.
IRS V (1999～04)	Experimental dose reductions for selected patients: Group I alveolar/undifferentiated 36 Gy Group II N0:36 Gy Group III orbit/eyelid:45 Gy Group III second look surgery negative margins:36 Gy microscopically＋margins:41.4 Gy Group III requiring 50.4Gy: volume reduction to initial GTV＋5 mm at 36 Gy if N0, and at 41.4 Gy if N＋	GTV＋2 cm Day 0:PM with intracranial extension only Week 3:low risk, week 12:intermediate, week 15:high risk	Low risk:VA, VAC Intermediate Risk: VAC vs VAC/VTC

Grade Glioma に対する臨床試験においては[6,7]，3D-CRT が応用され線量分布の改善による遅発性放射線反応の軽減が図られている．小児の Glioma の治療においては，発達への影響を考慮して放射線治療の適応を躊躇する傾向にあったが，3D-CRT による正常組織への影響の軽減によって，放射線治療のより積極的な応用が検討されており，今後の臨床試験結果が注目される．

Medulloblastoma の集学的治療においては，Craniospinal Irradiation（CSI）が標準治療であり，high risk 群で 36 ～ 40 Gy，average risk 群で 18 ～ 24 Gy 程度の CSI と，54 Gy 前後の後頭蓋窩への照射が組み合せて施行されている．Children's Cancer Group（CCG）で施行された CCG9892 では，化学療法の併用により CSI の線量を低減する臨床試験が施行され，その効果が確認された[8]．その後の CCG9961 では average risk 群では，化学療法併用で 23.4Gy の CSI と 54 ～ 55.8 Gy の後頭蓋窩への照射が施行された．さらに COG では，average risk 群で CSI の線量の低減とともに，3D-CRT を応用して原発巣への追加照射の照射野を，後頭蓋窩より腫瘍床＋margin へ限局する臨床試験が提案されている．総線量や照射野以外に考慮されるべき放射線治療因子として，治療期間の延長が治療効果に与える影響が delCharco らにより報告されている[9]．5 年後頭蓋窩制御率が照射期間 45 日以内で 89％であったのに対し，45 日を超えると 68％と低下し（$p = 0.01$），5 年無再発生存率が照射期間 45 日以内で 76％であったのに対し，45 日を超えると 43％と低下していた（$p = 0.004$）．放射線治療の中断の治療効果への影響は，International Society of Paediatric Oncology（SIOP）と United Kingdom Children's Cancer Study Group（UKCCSG）の臨床試験でも指摘されており[10]，今後臨床試験を検討する際に十分認識すべきと考える．

軟部組織腫瘍の三次元放射線治療計画

横紋筋肉腫の治療は，1970 年代より集学的治療が積極的に進められており，臨床試験の結果により治療成績の改善が進められてきた分野の一つである．表 2 に，Intergroup Rhabdomyosarcoma Study Group により計画されてきた集学的治療の経過を示す[11-15]．放射線治療は，化学療法の併用薬剤の変化とともに総線量の軽減が図られた．一方で，IRS-Ⅳでは Group Ⅲにおいて，50.4 Gy の通常分割照射と 59.4 Gy の多分割照射（1.1 Gy を 1 日 2 回照射）が比較検討された．Donaldson らの報告では[16]，failure-free survival（FFS）および overall survival（OS）と

表 3　IRS-V 放射線治療 Guidelines による正常組織の耐容線量と DVH による評価

正常組織		通常照射による上限	DVH
頭部	脳	全脳 3 歳未満 23.4Gy	不要
		全脳 3 歳以上 30.6Gy	不要
	左右網膜		必要
	左右視神経	46.8Gy	必要
	視神経交叉	46.8Gy	必要
	下垂体		必要
	角膜	41.4Gy	不要
	水晶体	14.4Gy	不要
	涙腺	41.4Gy	不要
	蝸牛		必要
頸部	甲状腺		必要
胸部	肺	両肺 14.4Gy	必要
	心臓	全心臓 30.6Gy	必要
腹部	肝臓	全肝 23.4Gy	必要
	腎臓	両側で 14.4Gy	必要
	消化管	一部 45Gy	不要
	全腹—骨盤	30Gy（1.5Gy/回）	不要
骨盤	膀胱		必要
	直腸		必要
脊髄	脊髄	45Gy	必要

この耐容線量は化学療法と併用した場合の有害事象の増強することが考慮されていない．大量化学療法併用時の耐容線量はさらに低いことが予想され，両側腎，肝臓全体，両側肺，全脳，脊髄，心臓全体への照射の場合はさらに 5 Gy 程度低い線量を上限とすることが望ましいと考えられる