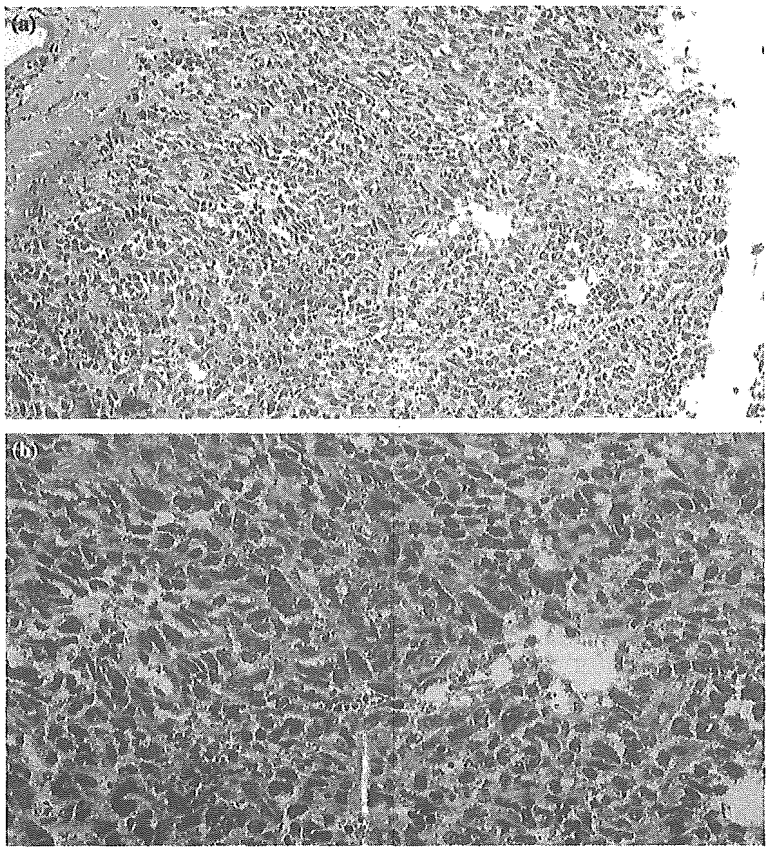

Figure 2. Pathological findings of pituitary biopsy specimen before RT. The primary tumor is composed of monomorphic cells showing mild to moderate nuclear pleomorphism [hematoxylin and eosin, (a) 20×; (b) 40×].

Easy fatigability and hypotension continue from hospitalization day due to lowering of the adrenal cortex function following lowering of the pituitary function. So in October 20, we increased the dose of adrenocortical steroid drug (hydrocortisone, Cortril®) from 20 to 30 mg/m^2. After that, systolic pressure increased up to the normal level. Easy fatigability improved too. The state of mania and disorientation, which appearing after surgery, also became better slightly during her admission.

Postradiation radiological finding

According to MRI in 6 November (on the 2nd day after the completion of RT), regarding the tumor with internal necrosis or cystic component located from clivus to sella turcica and suprasellar region, cystic lesion enlarged slightly but solid lesion itself tended to become smaller, and the enhanced lesion paralleled with left cerebral falx also tended to become better slightly, and hydrocephalus could not be seen.

Reoperation

In 30 March (on the approximately 5th month after the completion of RT), she received transnasal tumor resection to depress intracranial pressure. Its histology revealed that necrotic tissue made up approximately more than half. Tumor had viable cells. Probably

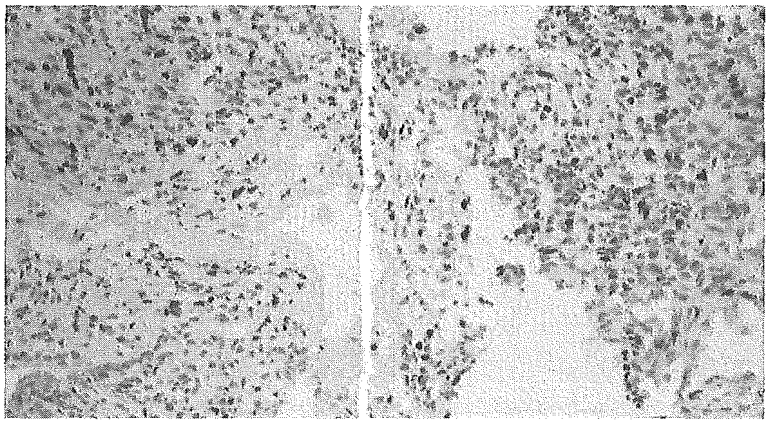

Figure 3. MIB-1 immunostaining of pituitary biopsy specimen before RT, 20×. MIB-1 LI = 24.1%. Proliferation indices were calculated as the percentage of labeled tumor nuclei per total tumor nuclei counted, in the area of greatest tumor labeling.

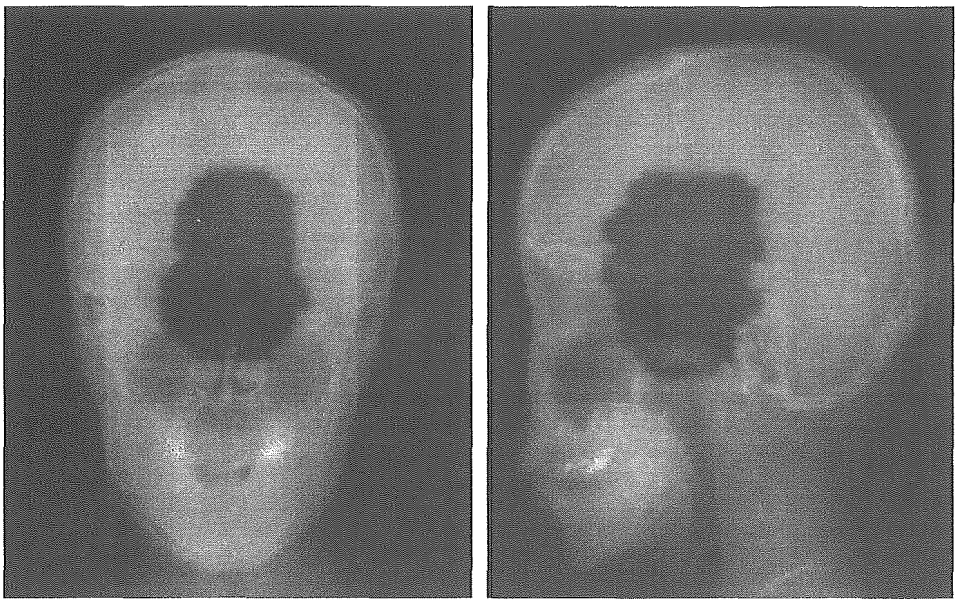

Figure 4. Linacgram (one monitor unit irradiation) in dynamic conical conformal radiotherapy using a c-arm-mounted for the sellar and parasellar area. [(1) anterior-posterior direction; (2) lateral direction.]

approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with degeneration (Figure 5). Immunohistochemically, there was no remarkable change in p53, p21, chromogranin A, PRL, MIB1-LI, and tunnel.

On the sixth month after RT, tumor around cavernous sinus grew bigger and she became completely blind. In May 24, she received transnasal ventriculo-peritoneal shunt surgery for hydrocephalia. Its histology revealed that it was a fibro-fatty tissue accompanied with bleeding. The tumor cell was hyperchromatic and short of cellularity. Such tumor cell was proliferating with remarkable bleeding necrosis. Although there were many cells that had changed into degeneration and necrosis, viable tumor tissues remained to be seen. The morphology was similar to the previous findings.

Dissemination and death

MRI in 11 June (Figure 6) revealed that band of enhanced lesions in midbrain, pons, medulla, and the surface of bilateral temporal lobe were recognized, which was thought of as meningeal seeding. Enhanced nodule was recognized at the bottom of the left temporal lobe too, which was thought of as metastasis.

At June 22, she died of brain symptom. Survival time from present to death was approximately 10 months.

Discussion

Pituitary carcinomas are rare neoplasms distinguished from invasive adenomas by the presence of craniospinal and/or systemic metastases. Also in our case, intracranial metastases were recognized at 10 months after the onset of symptoms.

In this case, the histological change after RT was thought of as an influence from RT not surgery nor natural course of the tumor. On the approximately 5th month after completing RT, its histology revealed that necrotic tissue made up approximately more than half.

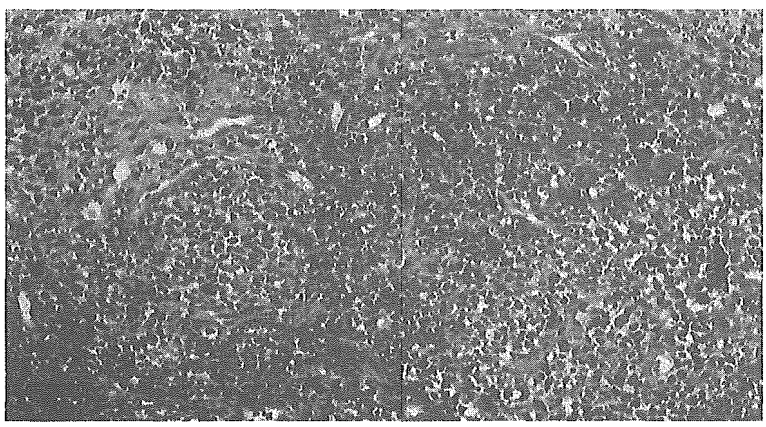

Figure 5. Pathological findings of pituitary biopsy specimen after RT. Necrotic tissue made up approximately more than half. Tumor had viable cells. Probably approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with denaturalization (hematoxylin and eosin).

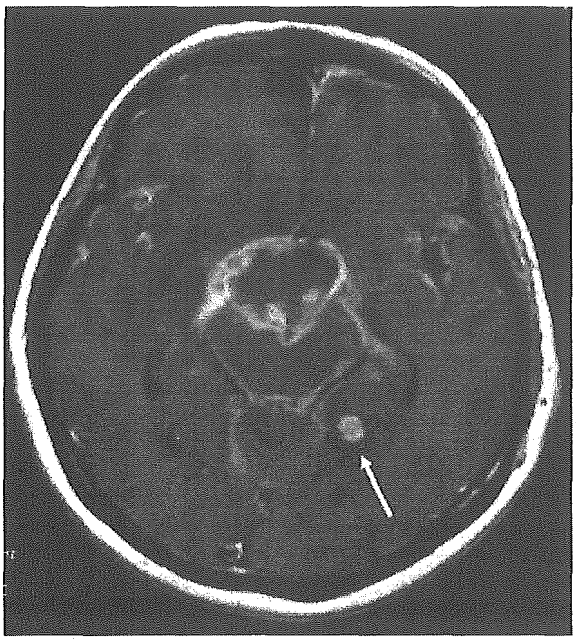

Figure 6. MRI (axial, T1-weighted), with gadolinium enhancement on the 10th month after completing RT. Band of enhanced lesions in midbrain, pons, medulla, and the surface of bilateral temporal lobe were recognized, which was thought of as meningeal seeding. Enhanced nodule was recognized at the bottom of the left temporal lobe too, which was thought of as metastasis (*arrowhead*).

But viable cells were also residual in two-fifth of tumor cells. Additionally we performed tunnel stain in order to detect the presence of plasmotomy and injury of nuclear DNA. In the nucleus of postirradiated cells, tunnel stain remained to be negative. It was confirmed by using tunnel stain that the cells lapsing into apoptosis didn't increase and in other words this state of post irradiation cell wasn't a cell death caused by apoptosis. Necrosis post irradiation occurred but it wasn't confirmed that the phenomenon of apoptosis happen actually.

In our case, serum PRL level before treatment was slightly high. Additionally immunohistochemically, PRL was weakly positive in part of the tumor. Our tumor may be a PRL-producing pituitary carcinoma. Fifty-two cases, which have been reported in the literature published in English to date, include 30% PRL-producing tumors [2]. Pernicone et al. [2] reported that patients with PRL cell tumors presented most commonly with headache and visual field deficits and amenorrhea and galactorrhea were noted in one each out of 7 patients. Our case also presented with amenorrhea, a severe headache, and a narrow visual field.

Expression of the Ki-67 antigen, which occurs during the S, M, and G1 phases of the cell cycle and is demonstrated with the MIB-1 antibody (which detects a nuclear antigen expressed by proliferating cells during the entire cell cycle), was quantified in the primary tumors. Indices of MIB-1 were often high (< 1–40%) in carcinomas [1, 2, 4–7]. The values obtained for our patient indicate above-average labeling for the primary tumor, which correlates well with the rapid growth of the metastasis.

Because such labeling indices do not account for ongoing apoptosis in tumors and are subject to variations in technical interpretation and to sampling errors, they are better used as predictors of tumor behavior for populations of patients, rather than predictors of the behavior of any particular tumor.

In a large series of pituitary tumors, including noninvasive and invasive adenomas as well as carcinomas, Thapar et al. [4] reported significant differences in MIB-1 mean LI. Aside from considerable case-to-case variations, these authors established a cutoff value of 3% to separate indolent adenomas from ones exhibiting more aggressive behavior. This threshold is generally viewed as a reliable indicator of clinical outcome [4].

Abnormal accumulation of p53 protein was not observed in our case. The p53 tumor suppressor gene is thought to play a role in the development or evolution of adenohypophysial neoplasms. Deletion of one gene copy and/or mutation of the remaining copy interferes with its normal suppressive activity and has been found to occur in a variety of neoplasms, including colorectal, brain, breast, lung, bone, soft tissue, testis, and bladder tumors [8, 9]. A recent study from a laboratory demonstrated p53 overexpression in most pituitary carcinomas [10]. Pituitary carcinoma lacking accumulation of p53 protein is very rare, only three such cases being previously reported, but may occur in the absence of p53 accumulation [11].

Pituitary carcinomas are associated with a poor prognosis. They often undergo extensive dissemination, exhibit a poor response to radiation and chemotherapy, and result in death within 1 year of diagnosis. The literature further suggests that patients with systemic disease have poorer survival than those with craniospinal spread. Clinically non-functionally pituitary carcinomas occasionally demonstrated synchronous presentation [12, 13] but otherwise exhibited intervals to metastasis ranging from 2 months [14] to 148 months [15]. The survival times after initial presentation also varied widely. The longest surviving patient reported was still alive 72 months after diagnosis of the metastasis [16], but several patients survived 6 months or less after the onset of metastasis [17, 18]. Once metastases occurred, the new carcinomas were rapidly fatal; the mean survival period was 2.6 years in patients with craniospinal metastases, usually to the subarachnoid space or dura, and 1 year in those with extraneural spread, usually to liver, bone, and lung [3]. In our case, survival time from present to death was approximately 10 months and survival from the onset of dissemination to death was a few weeks, which was shorter than most of previous reports.

The only pituitary carcinomas previously demonstrated in radionuclide scans included one GH-secreting tumor and two prolactin-secreting tumors [19–21]. In our case, the PET study before treatment revealed that no uptake was detected in the pituitary carcinoma. We surmise that because in our case the tumor had a lot of liquid and interstitial component, that is, necrotic and cystic component and little material part according to histopathology, in the PET the uptake of the tumor was remarkably lower than that of surrounding normal brain tissue.

Pituitary carcinomas can follow unpredictably indolent or fulminant courses. Tailoring appropriate therapy

for individual patients can therefore be difficult. Cytotoxic chemotherapy in setting has been reported by others but has demonstrated limited success in controlling tumor growth or hormonal hypersecretion. Because no standard regimen exists, a number of drugs have been tested, in a variety of combinations. No objective response was achieved in the majority of cases. RT generally provides only palliation. In our case, because the lesion was confined to the pituitary without systemic metastasis and the patient compliance was poor, the patients did not receive chemotherapy.

In our pituitary carcinoma, MIB-1 LI was relatively high (24.1%), pathologically approximately 2/5 of tumor cells were viable cells even after RT (60 Gy in 30 fractions) and survival time was very short (approximately 10 months). Probably this was not independent.

References

1. Roncaroli F, Schithauer BW, Young WF et al.: Silent corticotroph carcinoma of the adenohypophysis. A report of five cases. Am J Surg Pathol 27: 477–486, 2003
2. Pernnicone PJ, Scheithauer BW, Sebo TJ et al.: Pituitary carcinoma: a clinicopathologic study of 15 cases. Cancer 79: 804–812, 1997
3. Pernicone PJ, Scheithauer BW: Invasive pituitary adenoma and pituitary carcinoma. In: Thapar K, Kovacs K, Acheithauer BW, et al. (eds) Diagnosis and Management of Pituitary Tumors. Humana Press, Totowa, NJ, pp 369–385
4. Thapar K, Kovacs K, Scheithauer BW et al.: Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. Neurosurgery 35: 1012–1017, 1994
5. Knosp E, Kitz K, Perneczky A: Proliferation activity in pituitary adenomas: measurement by monoclonal antibody ki-67. Neurosurgery 25: 927–930, 1989
6. Gaffey TA, Scheithauer BW, Lloyd RV et al.: Corticotroph carcinoma of the pituitary: a clinicopathological study. Report of four cases. J Neurosurg 96: 352–360, 2002
7. McCutcheon IE, Pieper DR, Fuller GN et al.: Pituitary carcinoma containing gonadotropins: treatment by radical excision and cytotoxic chemotherapy: case report. Neurosurgery 46: 1233–1240, 2000
8. Barker SJ, Markowitz S, Fearon ER et al.: Suppression of human colorectal carcinoma cell growth by wild-type p53. Science 249: 912–915, 1990
9. Bartek J, Bartkova J, Vojtesek Z et al.: Aberrant expression of the p53 oncoprotein is a common feature of a wide spectrum of human malignancies. Oncogene 6: 1699–1703, 1991
10. Thapar K, Scheithauer BW, Kovacs K et al.: p53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. Neurosurgery 38: 765–777, 1996
11. Kumar K, Macaulary RJ, Kelly M et al.: Absent p53 immunohistochemical staining in a pituitary carcinoma. Can J Neurol Sci 28: 174–178, 2001
12. Myles ST, Johns RD, Curry B: Clinicopathological conference: carcinoma of the pituitary gland with metastases to bone. Can J Neurosurg 64: 588–593, 1986
13. Nudleman KL, Choi B, Kusske JA: Primary pituitary carcinoma: a clinical pathological study. Neurosurgery 16: 90–95, 1985
14. Saadeh IK, Houlston RS, Ellison DW et al.: Carcinoma of the pituitary in aaasociation with pulmonary stenosis and microcepaly. J Intern Med 235: 183–184, 1994
15. Epstein JA, Epstein BS, Molho L et al.: Carcinoma of the pituitary gland with metastases of the spinal cord and roots of the cauda equina. J Neurosurg 21: 846–853, 1964
16. O'Brien DP, Phillips JP, Rawluk DR et al.: Intracranial metastases from pituitary adenoma. Br J Neurosurg 9: 211–218, 1995
17. Kuroki M, Tanaka R, Yokoyama M et al.: Subarachnoid dissemination of a pituitary adenoma. Surg Neurol 28: 71–76, 1987
18. Sakamoto T, Itoh Y, Fushimi S et al.: Primary pituitary carcinoma with spinal cord metastasis: case report. Neurol Med Chir (Tokyo) 30: 763–767, 1990
19. Walker JD, Grossman A, Anderson JV et al.: Malignant prolactinoma with extracranial metastases: a report of three cases. Clin Endocrinol (Oxf) 38: 411–419, 1993
20. Hurel S, Harris PE, Greenman Y, Woolf P, Coniglio J et al.: Remission of acromegaly caused by pituitary carcinoma after surgical excision of growth hormone-secreting metastasis detected by 111-indium pentetreotide scan. J Clin Endocrinol Metab 81: 1628–1633, 1996

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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。

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。

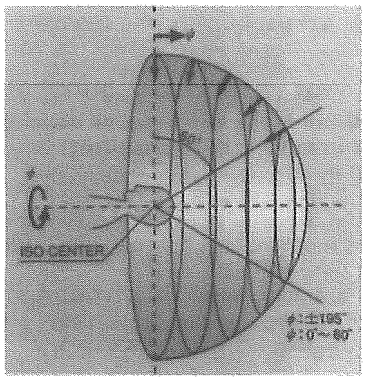

図1　歳差集光照射

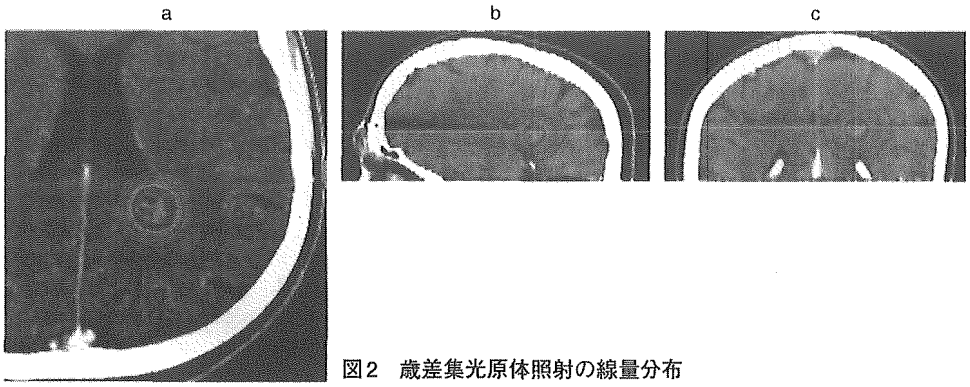

図2　歳差集光原体照射の線量分布

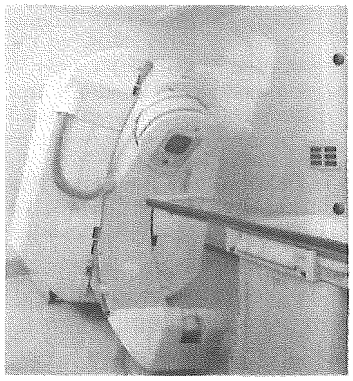

図3　Cアーム型ライナック

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ORIGINAL PAPER

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

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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

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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

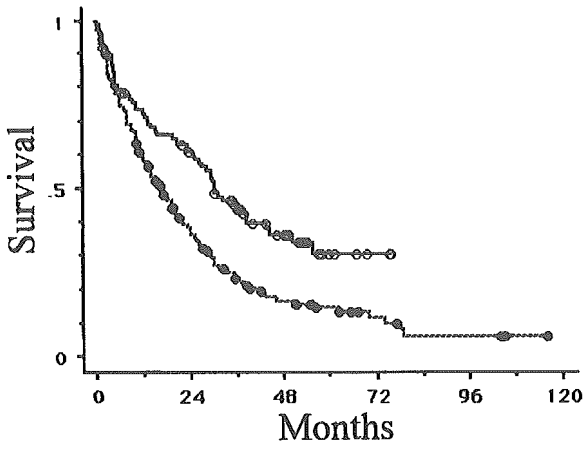

Fig. 1 Survival curves for patients with primary central nervous system lymphoma treated between 1985 and 1994 (- - -●- - -) and for those treated between 1995 and 1999 (_____O_____). The difference was significant ($P = 0.0003$)

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 dehyrdogenase	Normal	49	22	31	0.17	50	55.5	43	0.0084
	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 (Gy)	< 40	61	24	22	0.025	38	32	26	0.83
	≥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

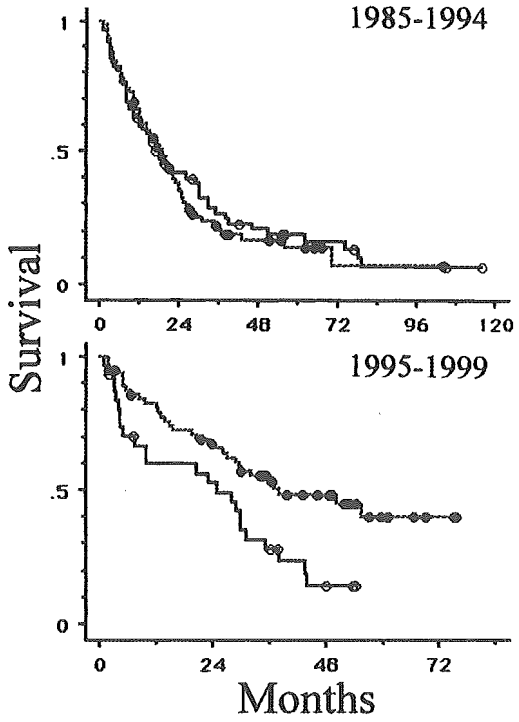

Fig. 2 Survival curves according to the treatment modality. _____O_____ : patients treated with radiation alone, - - -●- - - : patients treated with radiation and chemotherapy. The difference was significant in the group of patients treated between 1995 and 1999 (upper panel, $P = 0.63$; lower panel,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

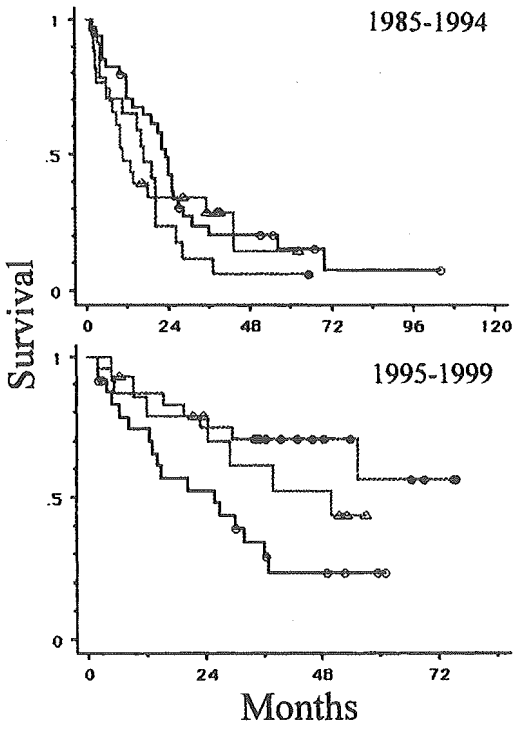

Fig. 3 Survival curves according to chemotherapy regimens. _____O_____ : cyclophosphamide, vincristine, prednisolone ± doxorubicin, - - -●- - - : methotrexate-containing regimens, - - -Δ- - - : other regimens. The difference among the curves was significant in the group of patients treated between 1995 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.

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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

Pro-Gastrin–Releasing Peptide as a Factor Predicting the Incidence of Brain Metastasis in Patients with Small Cell Lung Carcinoma with Limited Disease Receiving Prophylactic Cranial Irradiation

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BACKGROUND. Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis with an effect on overall survival in patients with small cell lung carcinoma (SCLC). In spite of multidisciplinary intensive treatment approaches, many patients still experience brain metastasis. The authors retrospectively analyzed the characteristics of the first failure event due to brain metastasis (FBM) in patients treated with PCI.

METHODS. Between January 1990 and April 2004, 71 patients with limited disease SCLC were treated with PCI after completing systemic treatment at the National Cancer Center Hospital (Tokyo, Japan). Univariate and multivariate analyses were used to identify factors related to FBM and survival.

RESULTS. The FBM and overall incidence of brain metastasis (OBM) were 16.9 % (12 of 71) and 26.8% (19 of 71), respectively. Median time to progressive disease and median survival were 8.4 months and 21.6 months, respectively. Elevation of pro-gastrin–releasing peptide (Pro GRP) level before PCI was found to be a significant predictive and prognostic factor for FBM, OBM, and survival on multivariate analysis ($P = 0.007$, $P = 0.025$, and $P = 0.009$, respectively).

CONCLUSIONS. An elevated Pro GRP level before PCI was found to be significantly related to FBM and survival, and should be considered before PCI is performed. *Cancer* **2005;104:811–6.** © *2005 American Cancer Society.*

KEYWORDS: prophylactic cranial irradiation, small cell lung carcinoma, limited disease, predictive factor, pro-gastrin–releasing peptide.

Small cell lung carcinoma (SCLC) accounts for approximately 20% of all lung carcinomas.[1] Although SCLC rapidly develops distant metastasis, it is very sensitive to chemoradiotherapy, unlike non-SCLC. Limited disease SCLC is clinically confined to the hemithorax, and chemoradiotherapy is the standard treatment. In patients with limited disease SCLC, chemotherapy combined with thoracic radiotherapy yields complete remission (CR) rates of 50–85%, with a median survival time of 12–20 months.[2–4] The 5-year survival rate is reported to be 26% for patients who have CR.[4] Because chemoradiotherapy reduces the risk of intrathoracic disease recurrence, distant metastasis in the brain has been the main cause of disease recurrence. Although only 10% of patients have brain metastasis at the time of diagnosis, the cumulative incidence at 2 years is > 50%.[5,6] As many as 73% of patients develop clinically apparent central nervous system metastases before death,[7,8] and even higher rates are documented in autopsy series.[9] The brain is the initial site of disease recurrence in 5–

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33% of patients, and is the only site of disease recurrence in ≤ 20% of patients.[10,11]

Although several randomized trials of prophylactic cranial irradiation (PCI) have attempted to reduce the risk of brain metastasis and to improve survival, to our knowledge its role in the management of patients with SCLC has remained controversial according to the results of each trial.[12–14]

Recently, the metaanalysis of these trials comparing PCI with no-PCI found that PCI led to a small but significant absolute reduction in mortality (5.4%), and that PCI not only significantly reduced the risk of brain metastasis, but also improved both overall survival (OS) and disease-free survival among patients with SCLC in CR.[15] These results suggest that PCI should be considered as a part of the standard treatment for patients with limited disease SCLC who achieved CR or good partial remission (PR).

Although PCI was performed for patients who achieved CR or good PR as part of the combined treatment that consisted of chemotherapy and thoracic radiotherapy, brain metastasis occurred in 4–24% of the treated patients.[6,12–14] Whole-brain irradiation (WBRT) for brain recurrence was often difficult because these patients had already received PCI to the whole brain. Therefore, we should strictly consider PCI for patients who could achieve a true CR, as assessed with diagnostic imaging. In addition, we should be careful to follow the patients who have a high risk of brain recurrence after PCI.

To our knowledge, there are no previous reports that describe the characteristics of patients with brain metastasis after PCI. In the current study, we analyzed retrospectively predictive factors for brain metastasis in patients with limited disease SCLC treated with PCI.

MATERIALS AND METHODS

Patients

A total of 71 patients with limited disease SCLC were treated with PCI after chemoradiotherapy for primary disease between January 1990 and April 2004 at the National Cancer Center Hospital (Tokyo, Japan). Fifty-four patients were male, and the median age was 62 years old (range, 40–75 years).

Histologic or cytologic examination confirmed the diagnosis of SCLC in all patients. Before the initiation of systemic treatment, staging was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and brain, as well as radionuclide bone scanning and bone marrow aspiration and biopsy. Limited disease was defined as being limited to one hemithorax, mediastinal, hilar, or supraclavicular area, which could be encompassed within a reasonable single radiation portal. Patients with pleural effusion found on chest films or CT scan were excluded.

Tumor response was classified in accordance with the World Health Organization (WHO) criteria.[16] After systemic treatment, including thoracic radiotherapy, PCI was administered to patients with CR or good PR according to the results of chest radiography and CT or MRI scans of the head, chest, and abdomen.

Thoracic Radiotherapy

The majority of patients (n = 55 [77.5%]) received accelerated twice-daily thoracic radiotherapy comprised of 45 gray (Gy) in 1.5-Gy fractions. The remaining patients (n = 16 [22.5%]) received once-daily radiotherapy, 50 Gy in 2-Gy fractions. Radiotherapy was performed 5 days per week, excluding weekends and holidays. Sixty of the 71 patients received concurrent chemoradiotherapy, which began on Day 2 of the first cycle of combination chemotherapy as cisplatin (80 mg/m^2, Day 1) plus etoposide (100 mg/m^2, Days 1, 2, and 3). The other patients received sequential thoracic radiotherapy after the forth cycle of chemotherapy.

The initial field included the primary tumor volume with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was tumor involvement).

Chemotherapy

All patients received cisplatin combination chemotherapy. After concurrent chemoradiotherapy, 34 patients received 3 cycles of cisplatin plus etoposide, 17 patients received CODE therapy (cisplatin at a dose of 25 mg/m^2 weekly for 6 weeks; vincristine at a dose of 1 mg/m^2 during Weeks 2, 4, and 6; and doxorubicin at a dose of 40 mg/m^2 and etoposide at a dose of 80 mg/m^2 for 3 days during Weeks 1, 3, and 5), and 9 patients received 3 cycles of cisplatin (60 mg/m^2, Day 1) plus irinotecan (60 mg/m^2, Days 1, 8, 15). In patients treated with sequential radiotherapy, five patients received four cycles of cisplatin plus etoposide, four patients received four cycles of cisplatin plus irinotecan, and two patients received four cycles of cisplatin containing combination chemotherapy, optimized for each patient.

Prophylactic Cranial Irradiation

All patients who achieved CR (n =40 [56.3%]) or good PR (n = 31 [43.7%]) were treated with PCI. The median time between the initiation of systemic induction treatment and the initiation of PCI (duration) was 3.7 months (range, 2.6–7.5 months).

The target volume was the entire intracranial site. Individual shaped ports with multileaf collimators

were used to define the irradiation target volume. Patients were treated using a megavoltage linear accelerator with 4–6 megavolt (MV) photons. Treatment was delivered with equally weighted right and left lateral fields, with the dose calculated on the central ray at mid-separation of the beams.

Of the 71 patients who received PCI, the majority of patients (52 of 71 [73.2%]) received 25 Gy in 2.5-Gy fractions daily, 12 patients received 30 Gy in 2-Gy fractions daily, 6 patients received 24 Gy in 1.5-Gy fractions twice daily, and 1 patient received 36 Gy in 2-Gy fractions daily. All PCI was performed a total of 5 days per week. The treatment was administered with a linear accelerator of 6 MV (n = 53 patients) or 4 MV (n = 18 patients). The median follow-up time after PCI was 16.3 months (range, 1.4–113.6 months).

Statistical Analysis

The first failure event due to brain metastasis (FBM) was defined as brain metastasis as a first event after PCI, and the overall incidence of brain metastasis (OBM) was defined as the overall incidence of brain metastasis found throughout the clinical course after PCI. Clinical and laboratory variables before PCI were chosen by considering possible factors indicated by our own experience. We determined the predictive factors for FBM and OBM using both univariate (Pearson chi-square test/Fisher exact test) and multivariate analysis.

Before PCI, 9 categorized variables for multivariate analysis were selected, as follows: gender (male vs. female), age (< 60 vs. ≥ 60 years), response to systemic treatment (CR vs. good PR), time between the start of systemic treatment and the start of PCI (duration: < 4 months vs. ≥ 4 months), hemoglobin level (< 10 g/dL vs. ≥ 10 g/dL), lactate dehydrogenase level (≤ 229 U/L vs. > 229 U/L), C-reactive protein (≤ 0.1 mg/dL vs. > 0.1 mg/dL), neuron-specific enolase (NSE) (≤ 10 ng/mL vs. > 10 ng/mL), and pro-gastrin–releasing peptide (Pro GRP) (≤ 46 pg/mL vs. > 46 pg/mL).

Time to progressive disease (PD) was measured from the first day of PCI until PD or the last day of follow-up without PD, and OS time was measured from the first day of PCI until death or the last day of follow-up. Median time to PD and median OS were estimated using the Kaplan–Meier method. Prognostic factors were evaluated by multivariate analysis. All statistical analyses were performed using SPSS version 12.0J (SPSS Inc., Chicago, IL).

RESULTS

Incidence of Brain Metastasis

FBM and OBM were observed in 16.9% (12 of 71; 95% confidence interval [95% CI], 8.2–17.3%) and 26.8% (19 of 71; 95% CI, 16.5–27.3%) of patients, respectively. Nine patients with FBM had multiple brain metastases and the others had solitary lesions. Among these patients, six were reirradiated with WBRT or stereotactic multiarc radiotherapy, five were treated with systemic chemotherapy, and one received best supportive care. The median times to FBM and OBM were 9.4 months (range, 1.1–23.5 months) and 12.0 months (range, 1.1–92.9 months), respectively. In univariate analysis, an elevated Pro GRP level was found to be significantly related to FBM and OBM (Table 1) (P = 0.007 and P = 0.029, respectively). Using a complete dataset from

TABLE 1
Univariate Analyses of Pretreatment Variables for FBM and OBM

Variables	No. of patients	No. of FBM	P value	No. of OBM	P value
Gender			0.27		0.99
Male	54	11		15	
Female	17	1		4	
Age (yrs)			0.71		
≥ 60	38	7		11	0.66
< 60	33	5		8	
Energy (MV)			0.99		0.36
4	18	3		3	
6	53	9		16	
Total dose (Gy)			0.99		0.08
≤ 25	58	10		13	
> 25	13	2		6	
Hyperfraction			0.27		0.33
Twice daily	6	2		3	
Once daily	65	10		16	
Response			0.63		0.70
Good PR	31	6		9	
CR	40	6		10	
Duration (mos)[a]			0.61		0.86
≥ 4	25	5		7	
< 4	46	7		12	
Hemoglobin level (g/dL)			0.75		0.79
< 10	43	8		12	
≥ 10	28	4		7	
LDH level (U/L)			0.99		0.99
> 229	6	1		1	
≤ 229	65	11		18	
CRP level			0.75		0.50
> 0.1 mg/mL	42	8		10	
≤ 0.1 mg/dL	29	4		9	
NSE level (ng/mL)			0.63		0.99
> 10	8	2		2	
≤ 10	59	10		16	
Pro GRP level (pg/mL)			0.007		0.029
> 46	12	5		5	
≤ 46	37	2		4	

FBM: first failure event due to brain metastasis, OBM: overall incidence of brain metastasis, MV: megavolt; Gy: grays; PR: partial remission, CR: complete remission; LDH: lactate dehydrogenase, CRP: C-reactive protein; NSE: neuron- specific enolase; Pro GRP: pro-gastrin-releasing peptide.
[a] Duration indicates the time between the initiation of systemic induction treatment and the initiation of prophylactic cranial irradiation.

TABLE 2
First Progressive Disease Sites after PCI

Site	No. of patients	% of all patients
Local failure (inside the thorax)	20	28.2
Distant metastasis[a]	26	36.6
Abdominal organ	7	9.9
Bone	9	12.7
Spinal cord	1	1.4
Brain	12	16.9
Total	46	64.8

PCI: prophylactic cranial irradiation.
[a] Three patients had more than one progressive disease site in distant metastasis.

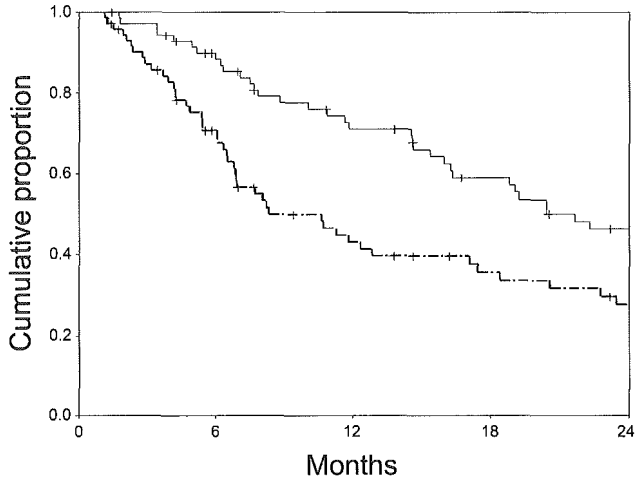

FIGURE 1. Kaplan–Meier analysis of time to disease progression (dotted line) and overall survival (solid line).

49 patients, a multivariate logistic regression model disclosed that an elevated Pro GRP level was a significant predictive factor for both FBM (hazard ratio [HR], 12.5; 95% CI, 2.00–77.9 [$P = 0.007$]) and OBM (HR, 5.89; 95% CI, 1.25–27.7 [$P = 0.025$]).

Time to Progressive Disease and Survival

In the current series, the majority of patients (46 of 71 [64.8%]; 95% CI, 53.7–65.4%) experienced PD in their clinical courses. The first sites of PD are listed in Table 2. The median time to PD and the median survival time were 8.4 months (95% CI, 3.9–12.8 months) (Fig. 1)and 21.6 months (95% CI, 14.1–29.2 months) (Fig. 1), respectively. A multivariate Cox regression model indicated that elevated Pro GRP level before PCI was a prognostic factor (HR, 2.97; 95% CI, 1.31–6.75 [$P = 0.009$]).

DISCUSSION

It is suggested that PCI eradicates subclinical brain metastasis that is protected from cytotoxic drugs by the blood-brain barrier as a pharmacologic sanctuary.[17] A recently reported metaanalysis of seven prospectively randomized trials demonstrated both an OS and disease-free survival advantage for patients with limited disease SCLC who received PCI compared with patients who did not receive PCI.[15] However, the metaanalysis included various trials and often insufficient systemic chemotherapy regimens, different PCI techniques, and a mixed population of patients with limited and extensive disease.[12–15] Therefore, Kotalik et al.[18] found there was insufficient evidence to make a definitive recommendation in terms of the total dose, fractionation, indication, and timing of PCI according to this metaanalysis.

In the current study, 16.9% of patients had brain metastasis as a first site of failure, which is consistent with previous reports of 4–24%.[6,12–14] The salvage treatment for brain metastasis after PCI would be restricted by the number of brain metastases, patient condition, and previous irradiation. To our knowledge, no report has described the predictive or prognostic factors for outcomes after PCI. Therefore, our results could provide useful information concerning the indication of PCI and close follow-up in patients with limited disease SCLC with CR or good PR who received intensive multidisciplinary treatment.

We found that elevated Pro GRP level before PCI was a significant predictive factor for FBM and for OBM ($P = 0.007$ and $P = 0.025$, respectively). The other pretreatment variables such as clinical and laboratory parameters had no influence on FBM or OBM. Among tumor markers, NSE is known to have a high false-positive rate due to hemolysis, whereas Pro GRP is a stable and reliable tumor marker for SCLC.[19] In addition Pro GRP is found to have higher specificity than NSE, and its serum level was frequently elevated at an earlier stage compared with that of the NSE level in patients with SCLC at the time of diagnosis.[20,21] It is reported that Pro GRP reflects tumor volume and the effect of treatment more sensitively than does NSE, and that it is useful in detecting PD because Pro GRP levels increase before disease recurrence becomes evident.[19,21,22] From the results of the current study, the elevation of Pro GRP before PCI might reflect the existence of residual viable tumor cells after a series of induction treatments, even if CR or good PR is indicated by imaging. A PCI would be recommended for patients with limited and extensive disease SCLC with CR.[15] However, PCI might not be sufficiently beneficial for decreasing the incidence of brain metastasis in patients with an elevated Pro GRP level. Therefore, by the completion of whole therapy, we should completely eliminate residual subclinical intracranial

and/or extracranial disease that causes the brain recurrence.

Several evidence-based guidelines for limited disease SCLC described uncertainty in terms of the optimal regimen, schedule of drug administration, duration of chemotherapy, and maintenance chemotherapy.[23,24] Although there is a guideline that recommends a maximum of six cycles of chemotherapy,[23] the trend in clinical trials and practice, including the current study, has been to use only four cycles of cisplatin-based chemotherapy. In patients with CR with elevated Pro GRP after four cycles of chemotherapy, two additional cycles of chemotherapy might be possible to eliminate tumor cells, to normalize Pro GRP levels, and to reduce the risk of brain recurrence.

A previous study suggested that there may be a dose-response relation for PCI, and that higher doses were more effective in reducing the risk of brain metastasis.[14] If currently ongoing trials that compare 25 Gy in 10 fractions with 36 Gy in 18 fractions[18] indicate the superiority of high-dose PCI, this will be another option to optimize the PCI procedure for controlling the subclinical disease at pharmacologic sanctuary.

The previous WHO criteria for evaluation of tumor response[11] did not consider the value of tumor markers. However, the Response Evaluation Criteria in Solid Tumors (RECIST) include tumor markers for assessment of CR.[25] Serum laboratory methods more accurately evaluate the evidence of viable tumor cells, and have a complementary role to the imaging studies when macroscopic tumor disappears or residual scar remains. In SCLC, tumor markers are well correlated to the response and tumor volume,[19,21,22] as was observed with Pro GRP in the current study. Therefore, CR according to the RECIST guidelines might be more appropriate in the evaluation of patients with SCLC for PCI.

Several authors reported many prognostic factors of clinical and laboratory parameters for patients with SCLC.[26] Almost all the analyses in the previous reports showed pretreatment factors before the initiation of systemic therapies. We analyzed pretreatment parameters for patients with CR or good PR receiving PCI. In our study, most of the laboratory parameters fell within normal limits before PCI, except for Pro GRP as a prognostic factor.

Local failure occurred in approximately one-half of the patients with disease recurrence, in addition to distant failure. The Southwest Oncology Group reported the pattern of failure in 114 patients with limited disease SCLC treated with cisplatin plus etoposide and concomitant thoracic radiotherapy followed by PCI. Local failure and distant metastasis occurred in 49% and 35% of patients, respectively.[27] These results also suggested that the main cause for disease recurrence was local or distant failure. Therefore, it is crucial to develop new drugs or regimens for improving local and distant control, which achieve a high rate of CR without elevation of tumor markers such as Pro GRP before PCI.

The results of the current study demonstrate that elevation of Pro GRP before PCI is a significant predictive factor for the first failure event due to brain metastasis. With regard to the indication of PCI, the assessment of clinical response according to RECIST might be evaluated more accurately using Pro GRP together with conventional imaging studies.

REFERENCES

1. Morita T, Sugano H. A statistical analysis of lung cancer registered in the annual of pathological autopsy cases in Japan between 1958 and 1987, with special reference to the characteristics of lung cancer in Japan. *Acta Pathol Jpn.* 1990;40:665–675.
2. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580 patient Southwest Oncology Group data base. *J Clin Oncol.* 1990;8:1563–1574.
3. Arriagada R, Kramar A, Le Chevalier T, De Cremoux H. Competing events determining relapse-free survival in limited small-cell lung carcinoma. *J Clin Oncol.* 1992;10:447–451.
4. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med.* 1999;340:265–271.
5. Komaki R, Cox JD, Whitson W. Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. *Cancer Treat Rep.* 1981;65:811–814.
6. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst.* 1995;87:183–190.
7. Hirsh FR, Paulson OB, Hansen HH, Larsen SO. Intracranial metastases in small cell carcinoma of the lung. Prognostic aspects. *Cancer.* 1983;51:529–533.
8. Eagan RT, Frytak S, Lee RE, Creagan ET, Ingle JN, Nichols WC. A case for preplanned thoracic and prophylactic whole brain radiation therapy in limited small cell lung cancer. *Cancer Clin Trials.* 1981;4:261–266.
9. Newman SJ, Hansen HH. Frequency, diagnosis, and treatment of brain metastases in 249 consecutive patients with bronchogenic carcinoma. *Cancer.* 1974;33:492–496.
10. Borgelt BB, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys.* 1980;6:1–9.
11. Rosen ST, Makuch RW, Lichter AS, et al. Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer: potential benefit restricted to patients with complete response. *Am J Med.* 1983;74:615–624.

12. Maurer LH, Tulloh M, Weiss RB, et al. A randomized combined modality trial in small cell carcinoma of the lung: comparison of combination chemotherapy-radiation therapy versus cyclophosphamide-radiation therapy effects of maintenance chemotherapy and prophylactic whole brain irradiation. *Cancer.* 1980;45:30–39.
13. Hansen HH, Dombernowsky P, Hirsh FR, Hansen M, Rygard J. Prophylactic irradiation in bronchogenic small cell anaplastic carcinoma. A comparative trial of localized versus extensive radiotherapy including prophylactic brain irradiation in patients receiving combination chemotherapy. *Cancer.* 1980;46:279–284.
14. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of multicentre randomized trial. United Kingdom Coordination Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer.* 1997;33:1752–1758.
15. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med.* 1999;341:475–484.
16. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer.* 1981;147:207–214.
17. Hansen HH. Should initial treatment of small cell carcinoma include systemic chemotherapy and brain irradiation? *Cancer Chemother Rep.* 1973;4:239–241.
18. Kotalik J, Yu E, Markman BR, Evans WK. Cancer Care Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2001; 50:309–316.
19. Yamaguchi K, Aoyagi K, Urakami K, et al. Enzyme-linked immunosorbent assay of pro-gastrin-releasing peptide for small cell lung cancer patients in comparison with neuron-specific enolase measurement. *Jpn J Cancer Res.* 1995;86: 698–705.
20. Takada M, Kusunoki Y, Masuda N, et al. Pro-gastrin-releasing peptide (31-98) as a tumor marker of small-cell lung cancer: comparative evaluation with neuron-specific enolase. *Br J Cancer.* 1996;73:1227–1232.
21. Okusaka T, Eguchi K, Kasai T, et al. Serum levels of pro-gastrin-releasing peptide for follow-up of patients with small-cell lung cancer. *Clin Cancer Res.* 1997;3:123–127.
22. Sunaga N, Tsuchiya S, Minato K, et al. Serum pro-gastrin-releasing peptide is a useful marker for treatment monitoring and survival in small-cell lung cancer. *Oncology.* 1999; 57:143–148.
23. Laurie SA, Logan D, Markman BR, Mackay, JA, Evans WK. Practice guideline for the role of combination chemotherapy in the initial management of limited-stage small-cell lung cancer. *Lung Cancer.* 2004;43:223–240.
24. Simon GR, Wagner H. Small cell lung cancer. *Chest.* 2003; 123:259S–271S.
25. Therasse P, Arbuck AG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000;92:205–216.
26. Yip D, Herper PG. Predictive and prognostic factors in small cell lung cancer: current status. *Lung Cancer.* 2000;28:173–185.
27. Thomas CR, Giroux DJ, Janaki LM, et al. Ten year follow up of Southwest Oncology Group 8269: a phase □□□□ trial of concomitant cisplatin-etoposide and daily thoracic radiotherapy in limited small-cell lung cancer. *Lung Cancer.* 2001; 33:213–219.

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

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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

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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

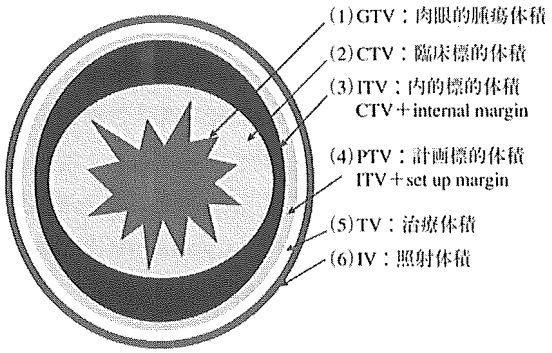

図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定

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