Table 5. Multivariate analyses for potential prognostic factors that were significant in univariate analysis

Factor	1995–1999 (n = 98)		2000–2004 (n = 114)		1985–2004 (n = 413)	
	p	Relative Risk	p	Relative Risk	p	Relative Risk
Age (<60 vs. ≥60 years)	0.0028	0.40 (0.22–0.73)*	0.0010	0.36 (0.20–0.66)	<0.0001	0.53 (0.41–0.68)
Performance status (0–2 vs. 3, 4)	0.016	0.47 (0.26–0.87)	0.34	0.78 (0.46–1.31)	0.12	0.82 (0.64–1.06)
B symptom (– vs. +)	0.010	0.33 (0.14–0.77)	—	—	0.18	0.75 (0.49–1.15)
Lactate dehydrogenase (normal vs. high)	0.24	0.71 (0.40–1.26)	0.020	0.55 (0.33–0.91)	0.0001	0.61 (0.47–0.78)
Tumor number (single vs. multiple)	0.0025	0.41 (0.23–0.73)	—	—	0.017	0.74 (0.57–0.95)
CSF dissemination (– vs. +)	—	—	—	—	0.82	1.04 (0.72–1.51)
Whole-brain dose (<40 vs. ≥40 Gy)	—	—	0.0019	0.42 (0.24–0.72)	0.31	0.88 (0.68–1.13)
I.v. chemotherapy (– vs. +)	0.87	1.05 (0.56–1.99)	0.088	1.81 (0.92–3.56)	0.69	1.06 (0.81–1.38)
MTX-containing chemotherapy (– vs. +)	0.082	2.08 (0.91–4.74)	0.52	1.23 (0.66–2.30)	0.0014	1.82 (1.26–2.63)

Abbreviation: CSF, cerebrospinal fluid; i.v., intravenous; MTX, methotrexate.

*Figures in parentheses are 95% confidence intervals.

ber were associated with better survival. In the group treated during 2000–2004, lower age, normal LDH level, and lower whole-brain dose were associated with better survival. When all patients were combined, age, tumor number, LDH level, and use of MTX-containing chemotherapy were significant factors.

Discussion

PCNSL has been increasing and is becoming an important tumor in neuro-oncology. So, it was considered meaningful to survey data on PCNSL in our country every 5 years. Various changes have been noted with regard to patient and tumor characteristics. The reason for the decrease of the proportion of male patients to nearly 50% observed in this study is unknown, and the phenomenon is in contrast to that observed in other studies showing male preponderance.[1,26] Further studies will clarify whether this trend is a universal one. The increase of aged patients may be due to recent better recognition of the disease; previously, aged patients might have remained undiagnosed, but with the recent establishment of managing PCNSL, the proportion of aged patients undergoing biopsy appeared to have increased. The recent increase in the incidence of multiple tumors is striking; it was as high as 55% in the most recent period, whereas it was between 30% and 40% in the two previous periods as well as in most previous reports.[7,21,26,27] Probably, improvement in imaging modalities and techniques, including more frequent use of MRI, has contributed to the improved detection of small tumors.

Regarding treatment, attempts at resection of tumors have decreased, because it is now clear that surgical resection does not contribute to improved prognosis.[3] This was also suggested in the present study. No major changes appeared to have occurred regarding radiotherapy. Shibamoto et al.[28] suggested the possible use of partial-brain radiation for a solitary lesion, but the idea has not yet spread nationwide. To reduce radiation doses by using chemotherapy has not become popular in our country. Increased use of systemic chemotherapy, espe-

cially MTX-based regimens, appears to be a worldwide trend, and it was confirmed in the present study.

Prognosis of PCNSL patients has certainly improved during the last decade. The 5-year survival was 30% in two periods: 1995–1999 and 2000–2004. However, further improvement was not observed in the latter period as compared with the former period, despite the fact that more patients underwent MTX-containing chemotherapy. One reason for this observation may be the higher patient age in the newest period (median: 65 vs. 59 years). In addition, prognosis of patients undergoing MTX-containing chemotherapy appears to be poorer in the newest period than in the preceding period, suggesting that some patients who were not necessarily expected to benefit from MTX-containing chemotherapy were treated with the chemotherapy. Furthermore, patients who did not receive MTX-containing chemotherapy in the most recent period had poorer prognosis. This would suggest that many patients regarded as ineligible for MTX-containing chemotherapy were not in favorable conditions and had poor prognosis. As a result, the increase of patients undergoing MTX-containing chemotherapy in the most recent period did not lead to improved survival when all patients were analyzed.

Age, PS, and tumor multiplicity are well-known prognostic factors for PCNSL,[22,23,27,29] and high LDH level and presence of B symptom or cerebrospinal fluid dissemination may also adversely affect prognosis.[19,22,26,30] The present study with a large number of patients seen between 1985 and 2004 suggested that age and LDH level are the most important prognostic factors followed by tumor number. However, tumor multiplicity was not associated with prognosis in the most recent series; the increase in patients with multiple tumors might be a reason for this discrepancy.

Chemotherapy is being increasingly used in the treatment of PCNSL, as is some advocate deferred radiation therapy in elderly patients.[2,16] Since the questionnaires were sent to radiation oncologists in the present study, all patients had received radiation. To our knowledge, however, very few patients are treated by chemotherapy alone in Japan, and results of the present study appear

to represent the status of treatment for PCNSL in our country. The prognosis of the patients did not differ significantly by the radiation field and total dose. Partial-brain radiation was not associated with decreased survival. Moreover, patients receiving whole-brain doses lower than 40 Gy had better survival than those receiving higher doses; those treated with partial-brain fields are included in the former group. Reni et al.[31] reported that whole-brain doses of 40 Gy or higher were associated with better prognosis, but later the same group found that they did not seem to improve prognosis.[11] The result of the present study would suggest that the whole-brain dose may not be important, and it is not contradictory to the proposal made by Shibamoto et al.[28] that partial-brain irradiation may be considered, especially in patients with a single lesion. With respect to the total radiation dose, Nelson et al.[32] did not find improved survival with the use of 60 Gy versus 50 Gy. Comparing two series of prospective studies, however, Bessel et al.[33] reported that a dose of 45 Gy appeared to be better than 30.6 Gy. In the present study, influence of total radiation dose was not clear when 50-Gy or higher doses were compared with lower doses. It seems difficult to draw any conclusions on optimal radiotherapy from retrospective studies; prospective studies should provide better answers.

There have been no randomized studies showing the benefit of chemotherapy as compared with radiation alone. A small randomized study failed to show the efficacy of CHOP chemotherapy when added to radiotherapy.[34] In the present study, the effect of chemotherapy, especially MTX-containing chemotherapy, was suggested in patients treated between 1995 and 1999 and between 2000 and 2004. The effect of MTX-containing chemotherapy was supported by multivariate analysis of patients seen during the 20-year period. In addition, patients receiving MTX-based regimens had better prognosis than those receiving other regimens in the group

seen during 1995–2004 with ages <70 years and PS 0–2. The discrepancy from the results of the preceding decade may be due to improvement of chemotherapy. Although full details of chemotherapy regimens were not necessarily reported in many patients, especially in the oldest survey, MTX-containing regimens in the oldest period appeared to be less intensive than those used in the more recent periods. Another reason may be improvement of management of patients undergoing chemotherapy. Before 1994, MTX-containing chemotherapy was not popular in our country and neuro-oncologists might not have been familiar with performing it. Shibamoto et al.[30] recently reported an improved survival for patients undergoing radiotherapy alone in the 1990s with a 5-year survival of 18%, but in the present study, patients undergoing MTX-based chemotherapy and radiation had a 5-year survival of around 50% during 1995–2004. The lack of randomized trials regarding the effect of MTX-based regimens is a flaw in neuro-oncology, but at the present time, conducting a randomized study of radiation versus radiochemotherapy may not be possible in view of the results of the present as well as other phase II studies.

Acknowledgments

References

1. Panageas KS, Elkin EB, DeAngelis LM, Ben-Porat L, Abrey LE. Trends in survival from primary central nervous system lymphoma, 1975–1999: a population-based analysis. *Cancer.* 2005;104:2466–2472.

2. DeAngelis LM. Primary central nervous system lymphoma: a curable brain tumor. *J Clin Oncol.* 2003;21:4471–4473.

3. Batchelor T, Loeffler JS. Primary CNS lymphoma. *J Clin Oncol.* 2006; 24:1281–1288.

4. Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). *J Neurooncol.* 1999;43:241–247.

5. Bessell EM, Hoang-Xuan K, Ferreri AJ, Reni M. Primary central nervous system lymphoma: biological aspects and controversies in management. *Eur J Cancer.* 2007;43:1141–1152.

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

7. Blay JY, Conroy T, Chevreau C, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol.* 1998;16:864–871.

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

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

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

11. Reni M, Ferreri AJ, Guha-Thakurta N, et al. 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.* 2001;51:419–425.

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

13. Bessel EM, Graus F, Lopez-Guillermo A, et al. Primary non-Hodgkin's lymphoma of the CNS treated with CHOD/BVAM or BVAM chemotherapy before radiotherapy: long-term survival and prognostic factors. *Int J Radiat Oncol Biol Phys.* 2004;59:501–508.

14. O'Brien PC, Roos DE, Pratt G, et al. Combined-modality therapy for primary central nervous system lymphoma: long-term data from a Phase II multicenter study (Trans-Tasman Radiation Oncology Group). *Int J Radiat Oncol Biol Phys.* 2006;64:408–413.

15. Laack NN, Ballman KV, Brown PB, O'Neill BP. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: results of North Central Cancer Treatment Group (NCCTG) 96-73-51. *Int J Radiat Oncol Biol Phys.* 2006;65:1429–1439.

16. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol.* 2006;24:4570–4574.

17. Kiewe P, Loddenkemper C, Anagnostopoulos I, Reinwald M, Thiel E, Korfel A. High-dose methotrexate is beneficial in parenchymal brain masses of uncertain origin suspicious for primary CNS lymphoma. *Neuro-oncol.* 2007;9:96–102.

18. Herrlinger U, Kuker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. *Ann Neurol.* 2005;57:843–847.

19. Shenkier TN, Voss N, Chhanabhai M, et al. The treatment of primary central nervous system lymphoma in 122 immunocompetent patients: a population-based study of successively treated cohorts from the British Colombia Cancer Agency. *Cancer.* 2005;103:1008–1017.

20. Mathew BS, Carson KA, Grossman SA. Initial response to glucocorticoids: a potentially important prognostic factor in patients with primary CNS lymphoma. *Cancer.* 2006;106:383–387.

21. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. *J Clin Oncol.* 2003;21:4483–4488.

22. Hayabuchi N, Shibamoto Y, Onizuka Y, et al. Primary central nervous system lymphoma in Japan: a nationwide survey. *Int J Radiat Oncol Biol Phys.* 1999;44:265–272.

23. Shibamoto Y, Tsuchida E, Seki K, et al. Primary central nervous system lymphoma in Japan 1995–1999: changes from the preceding 10 years. *J Cancer Res Clin Oncol.* 2004;130:351–356.

24. Kawamura T, Ishiguchi T, Shibamoto Y, et al. Results of primary central nervous system lymphoma treated by radiation and chemotherapy: retrospective analysis of twelve institutions in the Tokai district in Japan, 1995–1999. *Radiat Med.* 2006;24:9–16.

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

26. Ferreri AJM, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol.* 2003;21:266–272.

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

28. Shibamoto Y, Hayabuchi N, Hiratsuka J, et al. Is whole-brain irradiation necessary for primary central nervous system lymphoma? Patterns of recurrence following partial-brain irradiation. *Cancer.* 2003;97:128–133.

29. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol.* 2006;24:5711–5715.

30. Shibamoto Y, Ogino H, Hasegawa M, et al. Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s. *Int J Radiat Oncol Biol Phys.* 2005;62:809–813.

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

32. Nelson DF, Martz KL, Bonner H, et al. 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 Radiat Oncol Biol Phys.* 1992;23:9–17.

33. Bessel EM, Lopez-Guillermo A, Villa S, et al. Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: an analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. *J Clin Oncol.* 2001;20:231–236.

34. Mead GM, Bleehen NM, Gregor A, et al. A Medical Research Council randomized trial in patients with primary central nervous system non-Hodgkin's lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer.* 2000;89:1359–1370.

CLINICAL-PATIENT STUDIES

Secondary anaplastic oligodendroglioma after cranial irradiation: a case report

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Abstract Secondary brain tumors rarely arise after cranial irradiation; among them, meningiomas and glioblastomas are the most common and secondary oligodendroglial tumors the most rare. We present a 48-year-old man who developed an oligodendroglial tumor 38 years after receiving 50 Gy of cranial irradiation to a pineal tumor. He underwent gross total removal of a calcified, ring-enhanced mass in the right temporal lobe. The tumor was histologically diagnosed as anaplastic oligodendroglioma. Our review of previously reported secondary oligodendroglial tumors that developed after cranial irradiation revealed that these rare tumors arose after low-dose cranial irradiation or at the margin of a field irradiated with a high dose. We suggest that secondary oligodendroglial tumors arising after cranial irradiation are more aggressive than primary oligodendrogliomas.

Keywords Secondary brain tumors · Oligodendroglial tumors · Irradiation · Anaplastic oligodendroglioma

Background

The approximate cumulative risk for secondary brain tumors after cranial irradiation is 1–3% [1–4]. Radiation-

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induced secondary oligodendroglial tumors are very rare; to our knowledge, only seven cases have been reported to date [5–11]. We encountered a patient who developed a secondary anaplastic oligodendroglial tumor after radiotherapy (RT) and discuss the development of secondary oligodendroglial tumors after cranial irradiation.

Case report

This 48-year-old man was admitted to Hiroshima University Hospital in March 2005 with progressive vomiting, hiccups, and left-sided hemianopsia. In 1967, at the age of 10, he had undergone irradiation with Co-60 at Hiroshima University Hospital to treat a pineal tumor. The radiotherapeutic regimen delivered 2 Gy (200 rad) per day using alternate bilateral side ports every other day; the total dose was 50 Gy (5,000 rad). The size of the irradiation field was 6 × 6 cm at the isocenter cross-section. The tumor had completely disappeared, and no further events developed until 2005.

Magnetic resonance imaging (MRI) revealed a new mass lesion in the right temporal lobe (Fig. 1a). It was ring-enhanced by gadolinium; perifocal edema and a mid-line shift were noted. A computerized tomography (CT) image showed calcification inside the lesion (Fig. 1b). We performed craniotomy and removed the mass totally. Histologically, most of the tumor cells were round and uniform with prominent perinuclear halos and a high nuclear:cytoplasmic ratio; there were mitotic activity and microvascular proliferation (Fig. 2a, b). On microsatellite analysis chromosomes 1p and 19q were intact. Immunohistological examination (Table 1) revealed positivity for S-100, olig-2, glial fibrillary acidic protein (GFAP) (Fig. 2c), phosphatase and tensin homolog (PTEN), and

Fig. 1 MRI and CT brain
scans. (a) T1-weighted
gadolinium-enhanced axial MRI
shows a mass lesion in the right
temporal lobe. The presence of
perifocal edema produced a
right-to-left midline shift. (b)
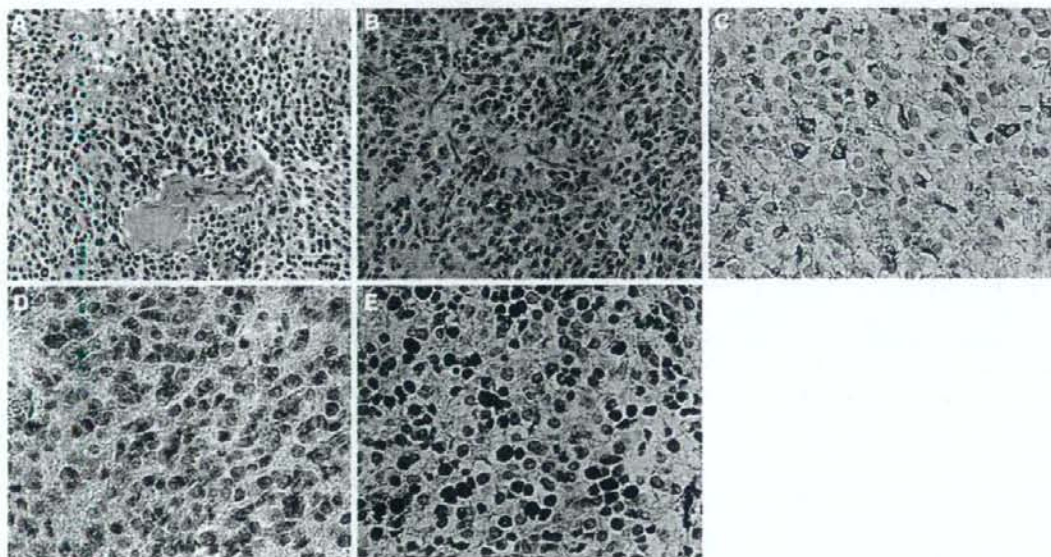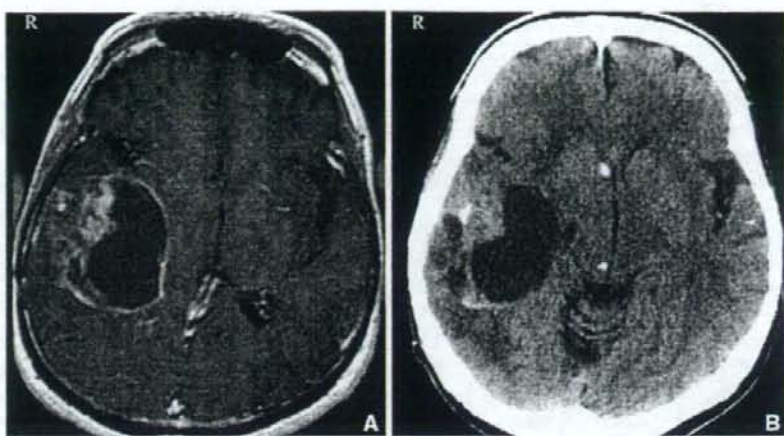Plain CT scan shows
calcification inside the lesion

Fig. 2 Histological findings on the anaplastic oligodendroglioma. (a, b) Most of the tumor cells are round and uniform with prominent perinuclear halos and a high nuclear:cytoplasmic ratio. Note the

mitotic activity and microvascular proliferation. Immunostaining for (c) GFAP, (d) MGMT, (e) MIB-1

O^6-methylguanine DNA methyltransferase (MGMT) (Fig. 2d). Epidermal growth factor receptor (EGFR), p53, multidrug-resistance (MDR), neurofilament, synaptophysin, and bcl-2 were negative. Most of the tumor cells expressed MGMT. The MIB-1 labeling index was 22.1% (Fig. 2e).

Despite previous extended local irradiation (54 Gy) and chemotherapy based on an alkylating agent (ACNU), his tumor recurred 18 months later at the site of the originally treated tumor bed.

Discussion

Compared to normal cells, cancer cells are highly sensitive to ionizing radiation [12], and the development of RT has increased the life span of patients with malignant tumors. However, long-term survivors may experience the sequelae of RT, e.g., vascular occlusion, teleangiectatic dilation, stroke, a decrease in brain weight and size, and hormonal dysfunction after pituitary irradiation [13]. Secondary malignancies are critical post-irradiation complications [1–

Table 1 Materials and methods of immunostaining

Antibody	Dilution	Manufacturer	Method	Result
EGFR (M)	×40	Novo castra	LSAB	Negative
p53 (M)	×150	Novo castra	LSAB	Negative
MDR (M)	×200	Santa-cruz	LSAB	Negative
Neurofilament (M)	Prediluted	Immunotech	ENVISION	Negative
Synaptophysin (R)	×50	DAKO	ENVISION	Negative
bcl-2 (M)	×50	DAKO	LSAB	Negative
MIB-1 (M)	×150	DAKO	LSAB	22.1%
PTEN (M)	×150	Santa-cruz	LSAB	Positive
MGMT (M)	×150	Santa-cruz	LSAB	Positive
GFAP (M)	×150	DAKO	LSAB	Positive
Olig-2 (R)	×100	IBL	LSAB	Positive
S-100 (R)	×500	DAKO	ENVISION	Positive

(M): Mouse anti-human

(R): Rabbit anti-human

EGFR: Epidermal growth factor receptor

MDR: Multidrug resistance

PTEN: Phosphatase and tensin homolog

MGMT: O6-methylguanine DNA methyltransferase

LSAB: labeled streptavidin-biotin

11, 13–16]. Although irradiation destroys cancer cells, it can induce mutations in surrounding normal cells. In some instances the DNA repair mechanisms are incapable of repairing all of the cells with damaged DNA, and some cells with damaged DNA may persist [17]. The pathogenesis of secondary post-RT tumors cannot be determined from their spontaneously occurring antecedents because the primary and secondary tumors are radiographically, pathologically, and clinically indistinguishable. Cahan et al. [15] presented diagnostic criteria for secondary sarcomas arising after irradiation. Although their criteria have been modified, fundamental determinants are: (1) tumors arising within a previously irradiated field or its immediate vicinity, (2) a latency period longer than 6 years, (3) absence of a genetic predisposition, and (4) a histological difference between the primary and secondary tumors. Our patient developed a rare secondary oligodendroglial tumor and fulfilled all of these criteria.

Gliomas, meningiomas, and sarcomas are the most frequently investigated secondary tumors that arise after cranial irradiation. Among secondary gliomas, glioblastomas and anaplastic astrocytomas have the highest incidence rate. In a review of 114 secondary gliomas arising after cranial irradiation, only 4 were oligodendroglial tumors [14]. We reviewed our and 7 previously reported cases in detail (Table 2); 7 (including our case) were males, and 5 had undergone whole cranial irradiation with 24 Gy or less to treat leukemia. The others received more than 50 Gy of cranial irradiation.

When RT is applied via two or more sources, the highest possible dose is delivered to the target lesion at the crossing of the sources. In patients treated with Co-60, tissues at the periphery of the target site are exposed to lower doses [12]. Our study of published images from two patients who had received more than 50 Gy [5, 7] revealed that their secondary tumors arose from the margin of the irradiated field. At his first treatment, our patient had received alternating doses of Co-60 from both sides; the total delivered dose was 50 Gy. Therefore, based on our calculations, his secondary tumor developed in an area that had been exposed to approximately 20 Gy. This finding strengthens our hypothesis that secondary oligodendroglial tumors tend to develop after low-dose irradiation or in the immediate vicinity of a field exposed to high-dose radiation treatment.

Clinically, oligodendroglial tumors are sensitive to RT [18], whereas astrocytic tumors are resistant. In rats, high-dose irradiation selectively induced apoptosis in oligodendroglial, but not astrocytic cells and led to optic neuropathy [19]. This suggests that astrocytic cells that survive high-dose irradiation can develop into high-grade astrocytoma over the long term and that oligodendroglial tumors may develop after the delivery of lower doses (<24 Gy) of irradiation.

It remains unknown whether the features of primary and secondary oligodendroglial tumors are identical. Histologic analysis showed that radiation-induced meningiomas tended to behave more aggressively [16]. The course of four previously reported secondary oligodendroglial tumors was aggressive, and the prognosis of the three other patients was not described (Table 2). Studies of patients with oligodendroglial tumors indicated that a loss of chromosome 1p and 19q was indicative of high sensitivity to chemo- and radiotherapy and that these patients had a better probability of survival [20–22]. Reports of secondary oligodendroglial tumors after cranial irradiation did not address allelic loss. Chromosomes 1p and 19q were intact in our patient; this may explain why his secondary oligodendroglial tumor recurred within 18 months of adjuvant therapy. In addition, our immunohistological examination revealed increased MGMT expression, which reduces the toxicity of alkylating agents by rapidly reversing the formation of adducts at the O^6 position of guanine, thereby averting the formation of lethal cross-links. Thus, MGMT activity is a major mechanism of resistance to alkylating drugs [23, 24].

The presence of intact chromosome 1p and 19q and the increased expression of MGMT in our patient suggest that his type of secondary oligodendroglial tumors was more aggressive than the primary type. The level of MGMT expression should be investigated not only in secondary oligodendroglial tumors, but also in secondary astrocytic tumors and glioblastomas.

Table 2 Secondary oligodendroglial tumors after cranial irradiation

Author, year	Age at RT (years)	Sex	Primary diagnosis	Chemotherapy	Radiation dose (Gy)	Latency (years)	Secondary diagnosis	Surgery	Postoperative irradiation (Gy)	Chemotherapy	Outcome
Zuccarello et al., 1986	32	M	Meningioma	No	56	10	Oligodendroglioma/glioblastoma	Total	No	–	Died. Postoperative complication
Fontana et al., 1987	6	M	Leukemia	Yes	24	11	Glioblastoma/oligodendroglioma multifocal	Biopsy	30.5	–	Died. 7 months after RT
Huang et al., 1987	26	M	Pituitary adenoma	No	66	12	Anaplastic oligodendroglioma	Subtotal	No	–	No data
Palma et al., 1988	3	M	Leukemia	Yes	24	11	Oligoastrocytoma	Subtotal	40	–	Died. 13 months after surgery
Corn.B et al., 1993	12	F	Leukemia	Yes	20	16	Malignant oligodendroglioma	Subtotal	No	Lomustine/procarbazine/vincristine	Died. 16 months after surgery
Panigrahi et al., 2003	7 2 years with minimal	M	Leukemia	Yes	5.4	7	Anaplastic oligoastrocytoma neurodeficiency	Tumor	resected	No	Palliative
Tannover et al., 2006	5	M	Leukemia	Yes	18	9	Anaplastic oligoastrocytoma	Total	No	-	No data
Present case, 2008	10	M	Pinealoma	No	50	38	Anaplastic oligoastrocytoma	Total	54	ACNU/vincristine	Recurrence. 18 months after surgery

Conclusion

We described a patient with a secondary oligodendroglial tumor that developed after cranial irradiation. We postulate that these tumors develop after low-dose cranial irradiation or at the margin of a radiation field exposed to high-dose treatment. As secondary oligodendroglial tumors tend to be highly aggressive, optimal treatment strategies must be developed.

References

1. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M (2005) Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab 90:800–804
2. Al-Mefty O, Kersh J, Routh A, Smith R (1990) The long-term side effects of radiation therapy for benign brain tumors in adults. J Neurosurg 73:502–512
3. Ron E, Modan B, Boice JJ et al (1988) Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med 319:1033–1039
4. Tsang R, Laperriere N, Simpson W, Brierley J, Panzarella T, Smyth H (1993) Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. Cancer 72:2227–2233
5. Zuccarello M, Sawaya R, deCourten-Meyers G (1986) Glioblastoma occurring after radiation therapy for meningioma: case report and review of literature. Neurosurgery 19:114–119
6. Fontana M, Stanton C, Pompili A et al (1987) Late multifocal gliomas in adolescents previously treated for acute lymphoblastic leukemia. Cancer 60:1510–1518
7. Huang C, Chiou W, Ho D (1987) Oligodendroglioma occurring after radiation therapy for pituitary adenoma. J Neurol Neurosurg Psychiat 50:1619–1624
8. Palma L, Vagnozzi R, Annino L, Ciapetta P, Maleci A, Cantore G (1988) Post-radiation glioma in a child. Case report and review of the literature. Childs Nerv Syst 4:296–301
9. Corn B, Curtis M, Lynch D, Gomori J (1994) Malignant oligodendroglioma arising after radiation therapy for lymphoma. Med Pediatr Oncol 22:45–52
10. Panigrahi S, Das M, Stagler D et al (2003) Development of secondary anaplastic oligoastrocytoma after matched unrelated bone marrow transplantation in a child with acute myeloid leukemia. Acta Haematol 109:196–198
11. Tanriover N, Ulu M, Sar M, Uzan M (2007) Anaplastic oligoastrocytoma: previous treatment as a possible cause in a child with acute lymphoblastic leukemia. Childs Nerv Syst 23:469–473
12. Kisileva E, Goldobenko G, Kanaev S (1996) Radiation therapy of malignant tumors. Medicina, Moscow, (in Russian)
13. Stelzer K (2000) Acute and long-term complications of therapeutic radiation for skull base tumors. Neurosurg Clin North Amer 11:597–604
14. Ellen EM (1999) Radiation-induced tumors. In: Berger MS, Wilson CB (eds) Gliomas, 1st edn. Saunders, Philadelphia, pp 724–735
15. Cahan W, Woodward H, Higinbotham N (1948) Sarcoma arising in irradiated bone: report of eleven cases. Cancer 1:3–29
16. Rubinstein A, Shalit M, Cohen M (1984) Radiation-induced cerebral meningioma: a recognizable entity. J Neurosurg 61:966–971
17. Verheyde J, Benotmane MA (2007) Unraveling the fundamental molecular mechanisms of morphological and cognitive defects in the irradiated brain. Brain Res Rev 53:312–320
18. Louis D, Ohgaki H, Wiestler O, Kleihues P (2006) WHO classification of tumours of the central nervous system. IARC Press, Lyon
19. Nagayama K, Kurita H, Nakamura M et al (2005) Radiation-induced apoptosis of oligodendrocytes in the adult rat optic chiasm. Neurol Res 27:346–350
20. Cairncross J, Ueki K, Zlatescu M et al (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 90:1473–1479
21. Ino Y, Betensky R, Zlatescu C et al (2001) Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. J Clin Cancer Res 7:839–845
22. Smith J, Perry A, Borell T et al (2000) Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol 18:636–645
23. Spiro T, Liu L, Majka S, Haaga J, Willson J, Gerson S (2001) Temozolomide: the effect of once- and twice-a-day dosing on tumor tissue levels of the DNA repair protein O6-alkylguanine-DNA-alkyltransferase. Clin Cancer Res 7:2309–2317
24. Tolcher A, Gerson S, Denis L (2003) Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. Br J Cancer 88:1004–1011

2217 Value of Chemotherapy with ECF in Advanced Esophageal Cancer Treated with Endoscopic Guided High Dose Rate Intraluminal Brachytherapy (EGHDRILBT)

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Purpose/Objective(s): There were 132 patients with Stage III/IV esophageal cancer and advanced metastatic disease or poor performance scores entered into this prospective study and results analyzed. All patients had near total or total dysphagia at presentation.

Materials/Methods: An EGHDRILBT to a dose of 18 Gy in 3 fractions on alternate days as per IAEA protocol was given to relieve dysphagia. Thirty-four of these patients who had advanced metastatic disease but were in a good general condition received further chemotherapy with ECF regimen 2-3 weeks after completion of HDRILBT. Patients were followed at regular intervals to assess for dysphagia relief and quality of life.

Results: The majority os the patients were men (101 vs. 31); with lesions located mainly in the lower third (81/132) or GE junction (24/132). Pathology was mainly adenocarcinoma (90/132) that were poorly differentiated (60/132). Seventy-four patients presented with metastatic disease while 87 had nodal metastasis. Patients who received additional ECF were younger ($p < 0.001$) and in better performance status than those who received EGHDRILBT alone.

More than 90% patients experienced relief of dysphagia by at least 1 grade (mostly 2 grades) within 4-6 weeks of EGHDRILBT. The mean dysphagia-free survival (DFS) was 182 days for HDRILBT group and 232 days for patients who received additional ECF ($p = 0.2954$). The mean overall survival (OS) for the EGHDRILBT group was 155 days and 266 days for patients who received additional chemotherapy with ECF ($p = 0.0010$). On univariate analysis, performance status ($p = 0.0041$) impacted on OS but not on DFS ($p = 0.09571$). On multivariate analysis, treatment length ($p = 0.02003$) and additional ECF chemotherapy ($p = 0.0007$) impacted on OS while additional ECF chemotherapy alone impacted on the DFS ($p = 0.0462$). There was no effect of any of the other 13 prognostic variables analyzed on OS or DFS. Eleven strictures (EGHDRILBT alone- 7, EGHDRILBT + ECF- 4; mean time to occurrence 130 and 135 days, respectively) were seen in the whole group which were successfully dilated. Four fistulae due to progressive disease (mean time to fistulae 148 days) were seen (all received EGHDRILBT alone). No other complications were recorded in the study.

Conclusions: An EGHDRILBT is an effective, safe, and quick method of palliation of dysphagia in esophageal cancer with metastatic disease and/or poor performance status. Most patients experience significant relief of dysphagia within 4-6 weeks of treatment. Additional chemotherapy with ECF after EGHDRILBT improves OS and DFS and should be offered to patients with metastatic disease and with good performance scores wherever possible. The incidence of complications with EGHDRILBT is low and additional chemotherapy after HDRILBT does not increase the incidence of complications.

2218 Radiation Therapy for Esophageal Cancer in Japan: Preliminary Results of the Patterns of Care Study 2003-2005

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Purpose/Objective(s): To evaluate and to improve the quality of radiation therapy (RT), the Patterns of Care Study (PCS) was repeatedly conducted in Japan during the past 15 years. The purpose of this study is to reveal the current status of RT for esophageal cancer in Japan according to the PCS and also show the comparable data with the United States (US) and other countries.

Materials/Methods: A national survey of 33 facilities including both academic (17) and nonacademic (16) institutions was conducted using the original two-stage cluster sampling. Detailed information was accumulated on 310 patients with thoracic esophageal cancer treated with RT between 2003 and 2005. Patients with lower Karnofsky Performance Status (KPS) score (<60), with double cancer or with distant organic metastases were excluded.

Results: Median age was 67 years. Eighty-eight percent (88%) were male and 12% were female. Nineteen percent (19%) were detected by screening and 23% had no complaint with swallowing. Median KPS score was 80. Fifty-five percent (55%) had the main lesion in midthoracic esophagus and 26% had in lower-esophagus. Fourteen percent (14%) had Stage I disease, 19% had Stage IIA, 9% had Stage IIB, 52% had Stage III, and 4% had Stage IV disease. Median tumor length was 5 cm and 98% had squamous cell carcinoma histology. All patients received external beam RT and high energy machine with >= 6MV was used for 92%. A CT-based planning was used for 84%. Brachytherapy was used for 6%. A total of 71% received chemotherapy and 23% received surgery. Preoperative chemoradiation therapy (CRT) was used for 9%, 5-FU (96%), and CDDP (77%) were the main agents for chemotherapy. Median total dose of external RT was 60 Gy for all patients, 40 Gy for preoperative CRT, and 60 Gy for definitive CRT. In definitive CRT patients, 16% received less than equal 55 Gy and 18% received more than 65 Gy. In nonsurgery patients, median initial longitudinal field size was 17 cm. Lower neck irradiation was used for 34% and upper abdominal irradiation was for 35%. A total of 87% were treated as in-patients during RT and 25% received central venous nutrition support. There were 86% patients who completed the planned treatment. Treatment outcome was evaluable in 77% of the patients and residual tumor was not found in 47% at the farnishment of the treatment. Grade 2 or more toxicities were observed in 21%. Overall 2-year survival rate was 55%. Significant variables for overall survival in univariate analysis include Stage (0-IIb vs. III-IV, 68% vs. 44%; $p = 0.001$), tumor length (<= 5cm vs. 5cm<, 63% vs. 43%; $p = 0.001$) and institutions (academic vs. non-academic, 63% vs. 46%; $p = 0.016$).

Conclusions: High total external radiation dose was commonly and consistently used for definitive CRT in Japan. Considerable differences were observed in patient and tumor characteristics and RT administration between US and Japan.

Quality of Life of Extremely Long-Time Germinoma Survivors Mainly Treated with Radiotherapy

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Abstract

Purpose: To assess the quality of life (QOL) of extremely long-time survivors with germinoma mainly treated with radiotherapy. **Patients and Methods:** We enrolled 52 of 68 patients who received radiotherapy between 1968 and 1995 at our hospital. They were 41 males and 11 females; the tumor location was pineal in 20, neurohypophyseal in 15, pineal and neurohypophyseal in 11 patients; in 6 it was located in another region. All underwent radiotherapy; the median dose was 48.2 (range 40.0–60.2) Gy. The median follow-up period was 226 (range 0–448) months. The clinical outcome and QOL were evaluated retrospectively. **Results:** In 6 patients, the tumor recurred; 6 other patients developed second tumors while in complete remission from the first tumor. The main cause of 12 deaths was complications due to primary tumor invasion, the initial treatment, or tumor recurrence rather than tumor progression. The 10-, 20-, and 30-year actuarial survival rate was 83.6, 77.5, and 64.2%, respectively. Of 44 patients, 6 were married and 3 males with solitary pineal tumors were fathers. Among 32 patients, 14 had, or had not, graduated from high school; the other 18 went on to higher education. Twenty-one patients had no occupation; 7 of 11 formerly employed patients had left their jobs. **Conclusion:** Radiotherapy delivered between 1968 and 1995 to patients with germinoma yielded satisfactory outcomes but a decline in the QOL. Copyright © 2009 S. Karger AG, Basel

The introduction of more effective treatments has improved the rate and length of survival of children with cancer [1, 2]. Since the 1960s, patients with germinoma, one of the primary brain tumors that frequently affect children, adolescents and young adults, have been given a good prognosis because radiotherapy led to the disappearance of the tumor [3–5]. Although various modalities, including chemotherapy, were developed in the mid-1990s to avoid the late adverse effects of radiotherapy [6, 7], little is known regarding the quality of life (QOL) of extremely

long-time germinoma survivors primarily treated with radiotherapy. Therefore, we retrospectively analyzed their clinicopathological status and identified social problems encountered by these individuals.

Patients and Methods

Between 1968 and 1995, 68 germinoma patients underwent radiotherapy at Hiroshima University Hospital. By March 2006, we had lost contact with 16 patients primarily due to their leaving the Hiroshima area. Of the remaining 52 patients, 40 visited our hospital at least once a year after treatment; 12 died at our or affiliated hospitals between 1972 and 2006. After acquiring prior informed consent from the patient or legal representative, we retrospectively investigated the posttreatment course of the 52 patients by evaluating clinical information contained in their medical records and reviewing imaging studies. Event-free and overall survival rates were calculated with the Kaplan-Meier method and measured from the date of pathological diagnosis or the start of radiotherapy [8]. We also surveyed these patients or their caregivers regarding their academic and occupational careers, and their marital and social status.

Patient characteristics are listed in table 1. Until the introduction in 1976 of computed tomography (CT) at our hospital, pneumoencephalography followed by test irradiation with 20 Gy was the primary tool to diagnose germinoma. The introduction of magnetic resonance imaging (MRI) in 1988 facilitated the clear localization and assessment of the characteristics of the tumors. The most frequent site of the tumors in the 52 patients included in this study (41 males and 11 females) was the pineal or neurohypophyseal region. In 11 patients, these tumors developed synchronously in the pineal- and neurohypophyseal region.

Irradiation therapy was delivered 5 times/week using ^{60}Co teletherapy units (8 cases) or 10 MV X-rays generated by a linear accelerator (44 cases); the typical daily dose to the primary brain tumor was 1.8 or 2.0 Gy. Both the treatment volume and radiation dose changed over time. Whole brain irradiation using the cone down method was performed almost routinely until 1991; the median local dose to the tumor lesion was 50.2 Gy. Whole spine irradiation with a median dose of 25.0 (20.0–30.0) Gy was additionally delivered to 7 patients for prophylaxis. Starting in 1992, germinoma patients received 40-Gy irradiation to the whole ventricle field with the administration, 4 times/week, of CBDCA (100 mg/m²/body surface) [9]. By March 2006, the follow-up period ranged from 0 to 448 months (median 226 months; table 1).

Results

In the course of 12–108 months after the initial therapy, 6 patients suffered tumor recurrence in the primary tumor region (n = 2), the spinal cord (n = 2), and the optic nerve (n = 1); in one patient, the entire wall of the ventricle was involved diffusely in tumor recurrence. Three patients underwent a second course of radiotherapy, one patient received chemotherapy, and 2 underwent concurrent chemo- and radiotherapy. All recurrent lesions disappeared after these salvage treatments (table 2).

Table 1. Patient characteristics

Sex	
Male	41
Female	11
Age at diagnosis, years	
Range	7–32
Median	14.2
Diagnostic imaging	
PEG	7
CT	22
MR	23
Diagnosis	
Pathological	41
Response to radiation	11
Location	
Pineal	20
Neurohypophyseal	15
Pineal + neurohypophyseal	11
Basal ganglia	3
Other	3
Treatment	
Radiation only (46.2–60.2 Gy/median 50.2 Gy)	42
Radiation (40.0 Gy) + 4 times weekly CBDCA (100 mg/m^2)	10
Radiation apparatus	
^{60}Co	8
Linac	44
Follow-up periods, months	
Range	0–448
Median	226

PEG = Pneumoencephalography.

Second tumors developed more than 84 months after the initial treatment in 6 patients without recurrence of the primary tumor. Four of these patients had received alternating doses of irradiation from both sides; the four-field technique was not used. The pathological diagnosis of the 6 second tumors was high-grade glioma (n = 4), atypical meningioma (n = 1), and cavernous angioma (n = 1); all developed within the irradiated field (table 2; fig. 1 and 2).

Table 2. Neuro-oncological follow-up

Recurrence	6[1]
Clinical course after recurrence	
Death with recurring tumor	2
Suicide*	1
Death with deterioration of QOL**	2
Alive with schizophrenia	1
Death	12
Causes of death	
Uncontrolled recurring tumor	2
Adrenal failure without tumor	3
Second tumor	3
Suicide*	1
Syringobulbia	1
Gradual deterioration after caregiver's death**	2
Patients that withdrew from their family and social circle	2
Second tumor after treatment	6[2]

Single and double asterisks indicate same cases.
[1] Recurrence 108, 85, 96, 12, 22, 101 months after treatment.
[2] Recurrence 182, 84, 456, 206, 181, 359 months after treatment (2 glioblastomas multiforme, 1 anaplastic astrocytoma, 1 anaplastic oligoastrocytoma, 1 atypical meningioma, 1 cavernous angioma).

Twelve patients died during the follow-up period; 2 of uncontrolled recurrent tumor, and the remaining 10 died despite complete remission of their primary or recurrent germinoma. The 10 deaths were attributable to adrenal failure (n = 3), glioma as a second tumor (n = 3), gradual deteriorations after the caregiver's death (n = 2), suicide (n = 1), and syringobulbia (n = 1) [10]. Adrenal failure was characterized by slight fever lasting for a few days followed by sudden-onset cardiac arrest. Two patients completely lost touch with their family more than 20 years after treatment (table 2).

Figure 3 shows the cause-specific event-free and actuarial event-free survival rates. These rates appear discordant because 4 patients died of adrenal failure or syringobulbia, and 9 experienced serious events including the development of second tumors, or were lost from follow-up without recurrence.

Figure 4 shows cause-specific and actuarial survival rates. The actuarial survival rate at 10-, 20-, and 30 years was 83.6, 77.5, and 64.2%, respectively. The 2
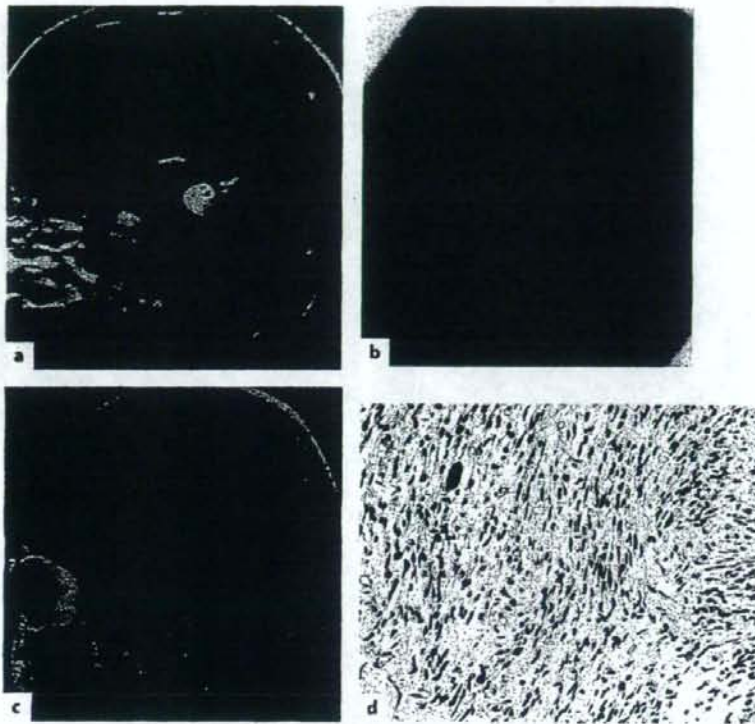
Fig. 1. A 20-year-old man. **a** T_1-weighted gadolinium-enhanced MRI showing 2 lesions in the pineal and neurohypophyseal region. The histological diagnosis was germinoma. **b** Radiation field at the two-field technique. The tumor disappeared completely after 54.0-Gy irradiation. **c** T_1-weighted gadolinium-enhanced MRI revealed a cerebellar tumor that developed 84 months after treatment. **d** Pathological study of surgical materials indicated anaplastic astrocytoma (HE stain).

graphs are dissimilar due to death by suicide, development of glioma as a second tumor, and death of the caregiver.

The marital status was examined in 44 of the 52 patients; of the other patients, one died just after radiotherapy, 5 also died at the age of younger than 18 years, and 2 were already married at the time of undergoing the initial treatment. Six patients got married during the follow-up period; however, 3 divorced and the other 3 patients with solitary pineal tumors were fathers (table 3).

We evaluated the academic and occupational careers of 32 patients; they had undergone radiotherapy at an age younger than 16 years and survived until the age
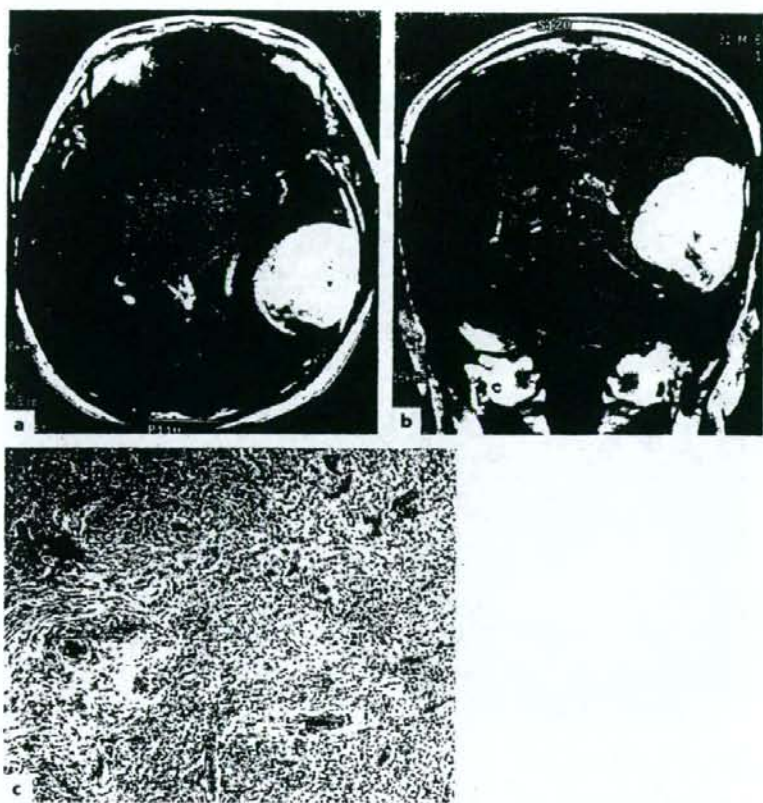
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Fig. 2. A 14-year-old boy. **a, b** At 206 months after 51.6-Gy irradiation of a pineal tumor, T_1-weighted gadolinium-enhanced MRI showed a mass attached to the posterotemporal dura. **c** The histological diagnosis was atypical meningioma (HE stain).

of 18 or older. Of these, 3 graduated from junior and 3 from senior high school, 8 graduated from a special needs senior high school, 10 from community college, and 8 were university graduates. Of these patients, 21 had no occupation and 7 of the remaining 11 patients left their jobs at an age older than 30 years because of recent memory disturbance or dyscalculia (table 3).
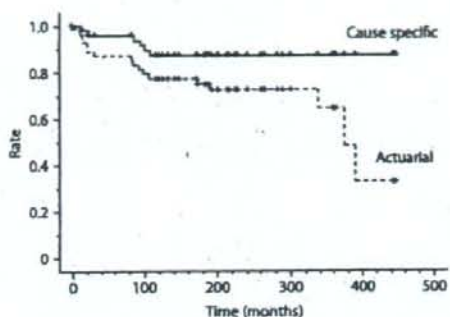
Fig. 3. Cause-specific event-free and actuarial event-free survival rates.
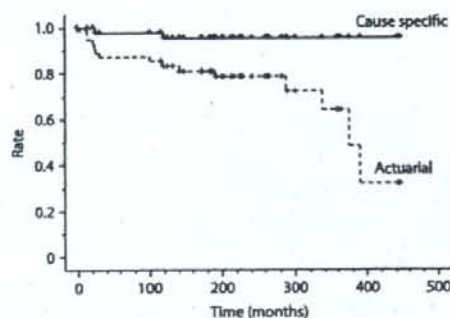

Fig. 4. Cause-specific and actuarial survival rates.

Representative Case

This 21-year-old man (fig. 5) presented with headache and upgaze palsy in 1985. CT showed a calcified tumor in the pineal region with obstructive hydrocephalus. A biopsy specimen of the tumor yielded a histological diagnosis of germinoma. The tumor disappeared completely after 52-Gy radiotherapy. After graduating from the university in 1987, he was licensed as an architect by the Japanese National Board. In 1995, at the age of 31 years, he experienced frequent episodes of recent memory loss and dyscalculia and was forced to resign at the age of 36. He currently lives with his parents who help him with his daily activities.

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Table 3. Marital and career status

| Marital status (n = 44)	
Married	6 (3 with pineal, 3 neurohypophyseal tumors)
Divorced	3
Fathers	3 (all with solitary pineal tumors)
Academic career and occupation (n = 32)	
Graduated from junior high school	3
Graduated from senior high school	3
Graduated from a special-needs senior high school	8
Graduated from community college	10
Graduated from university, or more	8
Left their occupation at the age of over 30 years	7
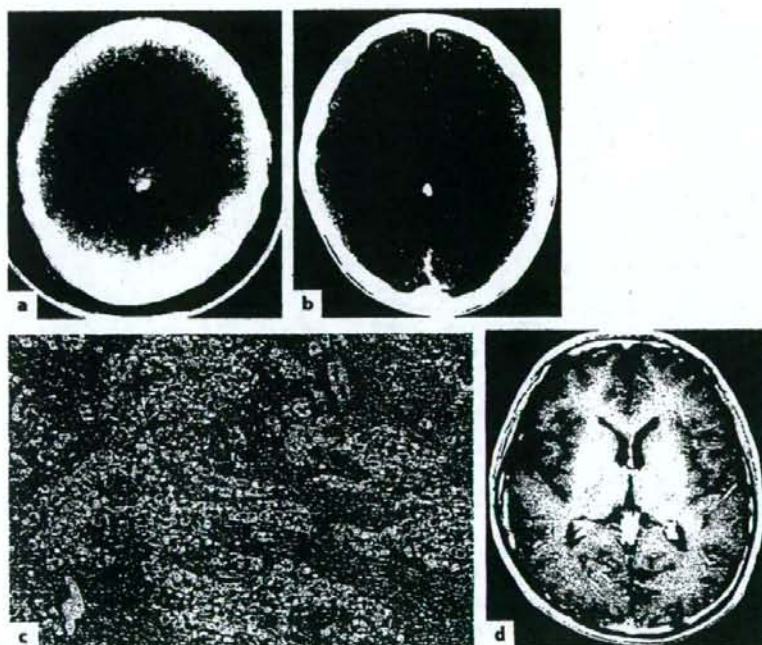
Fig. 5. Representative case. **a** CT performed on admission showed a pineal tumor. **b** After irradiation, CT revealed disappearance of the tumor. **c** Pathological examination of surgical materials revealed germinoma (HE stain). **d** MRI obtained in 2006 when the patient was 42 years old. There was brain atrophy with no tumor recurrence..

Discussion

Germinomas are radiosensitive radiocurable tumors; they account for 0.5–2.5% of all primary brain tumors [3, 5, 7]. They frequently affect children, adolescents, and young adults, and they develop primarily in the pineal or neurohypophyseal region, or synchronously in both regions [5, 7, 10–12]. Some earlier reports addressed the QOL of patients treated with irradiation; the median follow-up duration in most of these reports was less than 15 years [7, 11, 12, 13]. Ours is the first analysis of the QOL of patients surviving longer than 15 years.

Our follow-up study (median period 224 months) of extremely long-time survivors showed that the primary cause of death or severe posttreatment events rendering the QOL unsatisfactory was not germinoma progression but various kinds of complication. Our findings alert to the need for monitoring the development of second tumors by MRI, for certain replacement of oral adrenocorticosteroid therapy, and for maintaining a lifestyle that protects against the occurrence of adrenal failure or suicide in patients who are alive more than 20 years after undergoing irradiation therapy.

Our finding that 6 patients developed a second tumor after radiotherapy to treat their germinoma is important. Of the 4 patients whose second tumors were high-grade gliomas, 3 with glioblastoma died and the other patient with an anaplastic oligodendroglioma required additional treatment to address the recurrent tumor [14]. All 4 neoplasms arose in an area of the brain parenchyma that had been exposed to alternating doses of irradiation from both sides [14]. Current radiotherapeutic techniques, e.g. three-dimensional irradiation and intensity-modulated irradiation therapy minimize the extent of brain injury induced by irradiation.

Most of the survivors in our study population remained unmarried and did not have a regular job. Others resigned at the age of approximately 30 years due to sequelae attributable to their initial treatment. These individuals remain financially unstable and experience difficulties finding caregivers after the death of their parents; their gradual deterioration after the related caregiver's death was a main cause of death. Our findings indicate that long-term cancer survivors, including germinoma survivors, need a supportive social system that includes follow-up and long-term care.

In the past 10 years, regimens have been introduced that involve volume- and field-reduced radiotherapy with chemotherapy to address germinoma [6, 7]. Controversy surrounds the issue of whether these treatments are superior to irradiation from the point of view of tumor control. Studies are underway to evaluate how these therapies lessen the incidence and degree of pituitary impairment [15] or intelligence decline [16], and how they protect against the occurrence of second tumors [14], suicide [11], or withdrawal of these patients from their family and social circle.

Acknowledgements

References

1 Bhatia S, Landier W: Evaluating survivors of pediatric cancer. Cancer J 2005;11:340–354.

2 Curry HL, Parkes SE, Powell JE, Mann JR: Caring for survivors of childhood cancers: the size of the problem. Eur J Cancer 2006;42:501–508.

3 Jennings MT, Gelman R, Hochberg F: Intracranial germ-cell tumors: natural history and pathogenesis. J Neurosurg 1985;63:155–167.

4 Kageyama N: Ectopic pinealoma in the region of the optic chiasm. Report of five cases. J Neurosurg 1971;35:755–759.

5 Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, Seto T: Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg 1997;86: 446–455.

6 Buckner JC, Peethambaram PP, Smithson WA, Groover RV, Schomberg PJ, Kimmel DW, Raffel C, O'Fallon JR, Neglia J, Shaw EG: Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. J Clin Oncol 1999;17:933–940.

7 Sawamura Y, Shirato H, Ikeda J, Tada M, Ishii N, Kato T, Abe H, Fujieda K: Induction chemotherapy followed by reduced-volume radiation therapy for newly diagnosed central nervous system germinoma. J Neurosurg 1998;88:66–72.

8 Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.

9 Allen JC, Walker R, Luks E, Jennings M, Barfoot S, Tan C: Carboplatin and recurrent childhood brain tumors. J Clin Oncol 1987;5:459–463.

10 Sugiyama K, Uozumi T, Arita K, Kiya K, Kurisu K, Sumida M, Harada K: Clinical evaluation of 33 patients with histologically verified germinoma. Surg Neurol 1994;42:200–210.

11 Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, Harms D, Göbel U: Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol 1999;17:2585–2592.

12 Ogawa K, Shikama N, Toita T, Nakamura K, Uno T, Onishi H, Itami J, Kakinohana Y, Kinjo T, Yoshii Y, Ito H, Murayama S: Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients. Int J Radiat Oncol Biol Phys 2004;58: 705–713.

13 Shibamoto Y, Takahashi M, Sasai K: Prognosis of intracranial germinoma with syncytiotrophoblastic giant cells treated by radiation therapy. Int J Radiat Oncol Biol Phys 1997;37:505–510.

14 Doskaliyev A, Yamasaki F, Kenjo M, Shrestha P, Saito T, Hanaya R, Sugiyama K, Kurisu K: Secondary anaplastic oligodendroglioma after cranial irradiation: a case report. J Neurooncol 2008; 88:299–303.

15 Aida T, Abe H, Fujieda K, Matsuura N: Endocrine functions in children with suprasellar germinoma. Neurol Med Chir (Tokyo) 1993;33:152–157.

16 Merchant TE, Sherwood SH, Mulhern RK, Rose SR, Thompson SJ, Sanford RA, Kun LE: CNS germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation. Int J Radiat Oncol Biol Phys 2000;46:1171–1176.

17 Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H: Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. Eur J Cancer 1998;34:104–110.

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中 咽 頭

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■ はじめに

　頭頸部癌は，機能温存，形態温存という放射線治療の特徴を最大限に生かせる部位である。特に中咽頭は摂食，構音，嚥下などの重要な機能をもち，大部分の腫瘍が，放射線感受性の高い扁平上皮癌である。以上の点より，中咽頭癌においては，放射線治療が予後改善と QOL の改善に重要な役割を持つ。中咽頭癌に対しては，CDDP を用いた化学放射線療法が一般的であるが，最新のトピックスとしては，1) IMRT（強度変調放射線治療），2) HPV（パピローマウイルス），3) 分子標的治療，などが挙げられよう。

❶ 中咽頭癌について

　中咽頭癌の TNM 分類は口腔領域癌と同じである（表1）。腫瘍サイズが2cm 以内か4cm 以内かで T1，T2，T3 が分類される。リンパ N ステージに関しては，他の頭頸部癌と共通である。

表1　中咽頭癌に対する TNM

T1：	<= 2cm
T2：	> 2 to 4cm
T3：	> 4cm
T4：	Adjacent structures
N1：	Ipsilateral single <= 3cm
N2：	Ipsilateral single > 3 to 6cm
	Ipsilateral multiple <= 6cm
	Bilateral, contralateral <= 6cm
N3：	> 6cm

　喫煙や飲酒との関連性については従来より指摘されていたが，近年 Human papilloma virus（HPV）ウイルスとの関連性が注目されている。

　発症年齢的には 60 〜 70 歳代で最多であり，95% が扁平上皮癌である。

　初期症状は局所の疼痛ないしは，頸部リンパ節腫脹である。特に舌根由来では，局所症状が出現しにくいために進行して発見されることや，原発不明頸部リンパ節転移で見つかることが多い。

　一般的に予後は，側壁（扁桃）や上壁（口蓋垂，軟口蓋下面）由来が前壁（舌根），後壁由来より良好とされるが，上壁原発の中には 66 〜 70Gy の外照射単独で制御困難な症例もある。

　頸部リンパ節転移の頻度は，側壁（扁桃）が 60 〜 70% で反対側への転移頻度は 10 〜 15% である。扁桃由来以外は両側性リンパ節転移が多く，舌根：7 〜 80%，上壁：40 〜 50%，後壁：50 〜 70% である。

　放射線治療中の喫煙の悪影響については，Browman らの報告[1] があり，低酸素による局所制御率の低下はもとより，粘膜炎等の有害事象の悪化は明らかであり，照射期間および前後の禁煙は不可欠である。

❷ 中咽頭癌に対する放射線治療

1）照射法

　中咽頭癌における患者固定の基本はシェル固定である。原則的に下顎を進展させた状態で，口腔内は義歯を外し，可能な限り上顎口腔粘膜を照射範囲よ