療法の意義は見出せていないと考えるべきである．このほか，小児の進行期例を対象とした2つの試験があるが，放射線療法の上乗せ効果は示されなかった[19][20]．

以上の結果からは，小児の進行期や完全寛解例における放射線療法の意義は明らかではないものの，2006年のExpert Panel on Radiation Oncology Hodgkin's Work Groupでは，病期によらず少量の放射線療法(10～25.5Gy)を行うことが推奨されている．また，放射線療法を行うことが望ましくないと判断される症例では非交叉耐性レジメンを用いて，フルコースの化学療法を行うことが推奨されており，治療方針決定にあたっては症例ごとの慎重な検討が必要と考える．

4．結節性リンパ球優位型に対する放射線療法

古典的ホジキンリンパ腫に比べ発生頻度(約4～5％)は低く，その病態や治療方針に関してはいまだ不明な点が多いが，一般に予後良好であり治療強度を落とした治療が行われている[21]．一部の報告では，早期例に対し無治療でもよいとの報告があるが，現時点では高齢者や全身状態不良例などの理由以外で無治療を選択するのは時期尚早と考える．本疾患のみを対象にした臨床試験は組まれていないものの，早期で浸潤領域リンパ節数の少ない症例ではIFRTを用いて，30Gy程度を投与するのが妥当と考えられる．また，化学療法の併用に関しても信頼できるデータが少なくその有用性は不明である．

5．新規治療技術の導入

GELA-EORTCガイドラインでは，CT治療計画を用いた3次元治療計画を基本としているが，さらに精度の向上と毒性の軽減を図るため，強度変調放射線療法(intensity-modulated radiotherapy；IMRT)やイメージガイド下放射線療法(image-guided radiotherapy；IGRT)の導入も検討されるべきではある．しかし，安易な導入が治療成績の低下や毒性の増加につながらないよう慎重な姿勢で望まなければならない[22]．とくに，縦隔病変を有する症例におけるIMRTの導入には慎重を要し，ブレオマイシンを含むABVD療法が行われた症例では低線量であっても広範囲に肺野が照射された場合には重篤な肺毒性をひき起こしかねない．

以上，ホジキンリンパ腫における放射線療法の意義と最近の動向を提示した．治療に伴う効果(ベネフィット)と毒性(ハーム)を考慮し，臨床の現場で対応していかなければならない．

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Clinical Trial Note

Accelerated Fractionation versus Conventional Fractionation Radiation Therapy for Glottic Cancer of T1-2N0M0 Phase III Study: Japan Clinical Oncology Group Study (JCOG 0701)

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A randomized Phase III study was started in Japan to demonstrate the non-inferiority of survival of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 glottic cancer. This study began in September 2007, and a total of 360 patients will be accrued from 22 institutions within 4 years. The primary endpoint is 3-year progression-free survival (PFS). The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Key words: laryngeal neoplasms – radiotherapy – dose fractionation – clinical trials – phase III

INTRODUCTION

Accelerated fractionation radiation therapy has considerable benefits in terms of treatment duration and cost compared with conventional fractionation methods. In addition, some reports suggest that increased single radiation dose and shortened treatment time may improve local control (1–7). However, no multi-institutional randomized study has been conducted to show that accelerated fractionation is equivalent to conventional fractionation in terms of efficacy and safety for early glottic cancer. Various types of fractionation methods are performed in clinical practice, and according to the guidelines of the Head and Neck Cancer Disease Site Group in Canada, an optimal fractionation protocol has not yet been established (8). We therefore designed a study, which investigates whether accelerated fractionation radiotherapy is suitable for T1-2N0M0 glottic cancer in terms of survival, feasibility, voice function and safety.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2007 and the study was activated in September 2007. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000819 [http://www.umin.ac.jp/ctr/index.htm].

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PROTOCOL DIGEST OF THE JCOG 0701

Purpose

The aim of this study is to demonstrate the non-inferiority of the efficacy of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 (UICC/TNM, 6th edition) glottic squamous cell carcinoma.

Study Setting

A multi-institutional randomized Phase III study.

Resources

Grants-in-Aid for Cancer Research (17-17, 16-12, 17S-5) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the 3-year progression-free survival (PFS) proportion in all eligible patients. PFS is defined as days from randomization to first evidence of local progression, distant metastasis or death from any cause. In patients alive without events, PFS will be censored at the last visit. The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Overall survival is defined as days from randomization to death from any cause. Local progression-free survival consists of time free from local disease progression or death from any cause, while disease-free survival is defined as duration free of local progression, distant metastasis, secondary cancer or death from any cause. Survival with preserved voice function is defined as days from randomization to first evidence of death from any cause or appearance of voice changes of Grade 3 or more as diagnosed by the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The proportion of treatment completion denotes the percentage of patients whose treatment is completed within the recommended length of time: 51 days for T1 and 53 days for T2 in the conventional radiation arm, and 39 days for T1 and 43 days for T2 in the accelerated radiation arm.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill each of the following criteria: (i) primary tumor site lies within the vocal cords; (ii) the tumor consists of histologically proven squamous cell carcinoma; (iii) the extent of the primary tumor is evaluated as T1 or T2 without impaired cord mobility; (iv) the tumor is clinically staged as N0/M0; (v) radiation therapy can be completed within the recommended duration without interruption due to national holidays; (vi) age between 20 and 80 years; (vii) ECOG performance status of 0 or 1; (viii) no prior surgery or radiation therapy of the larynx; (ix) no prior chemotherapy for any malignancies within 5 years; (x) sufficient organ function; (xi) completed written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) psychosis; (v) treatment with systemic steroids; (vi) history of collagen disease except for rheumatism; (vii) insulin-dependent or poorly controlled diabetes mellitus; (viii) poorly controlled hypertension; (ix) history of severe heart disease, heart failure; (x) myocardial infarction or angina pectoris within the past 6 months.

Randomization

After the confirmation of the inclusion and exclusion criteria by telephone or fax to the JCOG Data Center, the patients are randomized to either conventional radiation arm or accelerated radiation arm, by the minimization method of balancing the arms according to T factor (T1/T2 by UICC/TNM, 6th edition) and institution.

Treatment Method

In conventional radiation arm, conventional fractionation radiotherapy with 2 Gy/fr (1 fr/day and 5 fr/week) is performed 33 times for a total dose of 66 Gy in patients with T1 disease, and 35 times for a total dose of 70 Gy in patients with T2 disease. Irradiation twice daily is permitted, but the maximum number of irradiation sessions per week is limited to five. It is recommended that treatment using the conventional fractionation method is completed within 51 days for T1 disease and 53 days for T2 disease.

In accelerated radiation arm, accelerated fractionation radiotherapy with 2.4 Gy (1 fr/day and 5 fr/week) is delivered 25 times for a total dose of 60 Gy in patients with T1 disease, and 27 times for a total dose of 64.8 Gy in patients with T2 disease. Twice-daily irradiation is prohibited, as is irradiation six or more times per week. Recommended duration of accelerated fractionation radiotherapy is 39 days for T1 disease and 43 days for T2 disease.

In both study arms, the gross tumor volume (GTV) is defined as the GTV of the primary tumor. The clinical target volume (CTV) in T1 disease is the entirety of the vocal cords, while the CTV in T2 disease includes a 1-cm margin surrounding the tumor in addition to the vocal cords. The planning target volume (PTV) is defined as the CTV plus a margin of 0.5-1 cm in the craniocaudal direction and 0.5 cm in the posterioanterior direction.

Follow-up

All enrolled patients are followed-up at least every 6 weeks for the first 6 months and then every 3 months for a duration of 3 years. Laryngeal fiberscope and cervical lymph node exploration by manipulation are carried out at each visit.

Study Design and Statistical Method

This trial is designed to demonstrate that accelerated fractionation radiation therapy is not inferior to the conventional fractionation method in terms of 3-year PFS. If the non-inferiority of accelerated radiation arm is verified, the accelerated fractionation method will be the preferred treatment.

The planned sample size is 360 patients, with 180 cases per arm. We anticipate 3 years of follow-up after 4 years of accrual, ensuring at least 80% power with one-sided alpha of 5% and a non-inferiority margin of 5% for the primary endpoint. This assumes an expected 3-year PFS of 80% in patients treated with the conventional fractionation method, and 85% in those treated with the accelerated fractionation method.

Interim Analysis and Monitoring

We plan on conducting two interim analyses, considering multiplicity according to the method recommended by the Southwest Oncology Group (9). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by the Data Center to evaluate and improve study progress and quality.

Participating Institutions (From North To South)

Sapporo Medical University, Tohoku University, Saitama Cancer Center, National Cancer Center East, National Cancer Center, Tokyo Metropolitan Komagome Hospital, Tokyo Women's Medical University, Tokyo Medical Center, Keio University, Cancer Institute Hospital, University of Tokyo, Kitasato University, Niigata Cancer Center, Yamanashi University, Shinshu University, Aichi Cancer Center, Kyoto University, Osaka University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hiroshima University, Kyushu University.

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Conflict of interest statement
None declared.

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Relationship Between the Response to Treatment and the Prognosis of Patients with Aggressive Lymphomas Treated with Chemotherapy Followed by Involved-field Radiotherapy: Radiographic Assessment

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Objective: We examined the relationship between the response to treatment and prognosis of patients with aggressive lymphoma.
Methods: We reviewed 33 patients with aggressive lymphoma treated with chemotherapy consisting of the CHOP regimen followed by radiotherapy. Twelve patients had Stage I, 13 had Stage II, 6 had Stage III and 2 had Stage IV disease. According to the International Prognostic Index (IPI), 13 had low, 15 had low-intermediate, 2 had high-intermediate and 3 had high IPI. After three to six cycles of chemotherapy, involved-field radiotherapy was performed. We evaluated the response to treatment by computed tomography (CT), magnetic resonance imaging (MRI) and gallium scintigraphy (Ga-67) at the time of completion of chemotherapy and at the time of completion of radiation therapy. The median follow-up period was 48 months (4–80).
Results: The 2-year progression-free survival rates of the patients with Ga-67 positive uptake and Ga-67 negative uptake after completion of chemotherapy were 78 and 26% ($P = 0.009$), respectively. However, there were no statistically significant correlations between progression-free survival and the response after completion of chemotherapy determined by CT ($P = 0.75$) or MRI ($P = 0.19$). The response to treatment at the time of completion of overall treatment was not useful for prediction of prognosis.
Conclusions: Ga-67 positive uptake at the completion of chemotherapy before radiotherapy may be associated with poor prognosis.

Key words: aggressive lymphoma – chemotherapy – radiotherapy – gallium scintigraphy

INTRODUCTION

The treatment policy for aggressive lymphoma is determined based on the International Prognostic Index (IPI) (1), Cotswolds Modification of the Ann Arbor Staging System (2) and patient's condition. Patients with localized aggressive lymphoma can be cured with systemic chemotherapy and/or radiotherapy. The CHOP regimen (consisting of a combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) is generally the first choice for chemotherapy (3) with and without consolidative radiotherapy (4). However, the usefulness of rituximab (anti-CD20 monoclonal antibody) has been reported and R-CHOP (CHOP + rituximab) has been adopted for chemotherapy (5). With these standard treatments, the cure rate of patients with all stages of aggressive lymphoma is about 40%. However, there are limits to predicting the outcome based on IPI score, and further prognostic predictors during treatment leading to early changes in therapy may improve outcome and survival.

With regard to the role of imaging diagnosis of malignant lymphoma, imaging evaluation contributes not only to differential diagnosis but also to the initial staging for determining the optimum treatment strategy and evaluation of the effects of treatment. The International Workshop to Standardize Response Criteria based on computed tomography (CT) have been widely used for response assessment of Non-Hodgkin's lymphoma (NHL) (6). CT and gallium scintigraphy (Ga-67) are generally used for evaluation of the

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effects of treatment in patients with NHL. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are also used in special situations. However, the values of these modalities for clinical usage are still controversial. This raises questions of how best to make use of the results of CT, MRI and Ga-67 to make changes to the treatment strategy.

We evaluated the relationship between the response to treatment evaluated by radiographic imaging and prognosis of patient with aggressive lymphoma.

PATIENTS AND METHODS

We reviewed 33 patients with aggressive lymphoma treated with chemotherapy followed by radiotherapy from 2000 to 2003. The median age of the patients was 64 years (range 20–81), and the male:female ratio was 12:21. Pathological diagnosis was confirmed according to the World Health Organization Classification (7) of lymphoid neoplasms: 26 patients were classified as having lesions of diffuse large B-cell lymphoma, 2 as peripheral T-cell lymphoma, 2 as angioimmunoblastic T-cell lymphoma and 3 as extranodal T-/NK-cell lymphoma (Table 1). Thirteen percent of patients (4/33) were in performance status 2–3, 68% (19/33) had elevated serum lactate dehydrogenase and 21% (7/33) had bulky tumors (>6 cm). According to the Cotswolds modification of the Ann Arbor staging system (2), pretreatment evaluation included history and physical examination, complete blood count, serum chemistry, upper gastrointestinal endoscopy, bone marrow aspiration, CT scan of the neck, chest, abdomen and pelvis, Ga-67, MRI of the primary lesion and ultrasonography of the neck and abdomen. The median follow-up period for all patients was 21 months (range 4–46).

CT was performed with a slice thickness of 5 mm before and after the intravenous injection of contrast medium. MRI was performed with a 1.5-T unit using spin-echo technique. T1-weighted images were acquired axial images. Axial T2-weighted fat-suppressed images were also obtained. Slice thickness was 5 mm with no interslice gap in the axial projection. Thereafter, T1-weighted post gadolinium with fat-suppressed images in axial projections were obtained sequentially. Ga-67 scanning was performed 48–72 h after intravenous injection of 185 MBq ^{67}Ga-citrate. SPECT cameras with medium-energy, general-purpose collimators and three energy peaks of 93, 184 and 296 keV were used. Total-body images in anterior and posterior views were supplemented with appropriate planar views of the thorax and abdomen. After uniformity correction, 10 mm transaxial tomograms were reconstructed using a medium filter.

Treatment

Chemotherapy consisted of the CHOP regimen, including cyclophosphamide at 750 mg/m^2 (Day 1), doxorubicin at 50 mg/m^2 (Day 1), vincristine at 1.4 mg/m^2 (Day 1) and oral prednisolone at 100 mg/day (Days 1–5). Drug doses were reduced by up to 50% in consideration of age and co-morbid illness; full-dose CHOP was applied in 22 patients, 80% CHOP in 9 patients, 70% CHOP in 1 patient and 50% CHOP in 1 patient. Chemotherapy was repeated every 3 weeks. The number of treatment cycles was determined by prognostic factors, such as stage, IPI score and tumor size. In patients in clinical Stages I–II, with IPI score of 0–2, or with non-bulky tumors (≤6 cm), three cycles of CHOP were used. Six cycles were applied in other patients in Stages III–IV, with IPI score of 3–5, or with bulky tumors (>6 cm). Three cycles of CHOP were applied in 24 patients and 6 cycles in 8 patients. One patient received four cycles of treatment because of progressive disease (PD).

After completion of three to six cycles of chemotherapy, involved-field radiotherapy was performed to all patients. The involved field was defined as the regional area including the primary lesion and involved nodes. In patients in Stages III–IV, radiation field was determined by the primary bulky

Table 1. Patients and tumor characteristics

Age (years)	20–81 (median 64)
Sex	
Male	12
Female	21
WHO classification	
Diffuse large B-cell	26
Peripheral T-cell	2
Angioimmunoblastic T-cell	2
Extranodal T-/NK-cell	3
Stage	
I	12
II	13
III	6
IV	2
IPI	
Low	13
Low-intermediate	15
High-intermediate	2
High	3
Primary site	
Waldeyer's ring	12
Lymph node	8
Sinonasal cavity	6
Thyroid	3
Bone	3
Soft tissue	1

NK-cell, natural-killer cell; IPI, International Prognosis Index; WHO, World Health Organization.

lesion. Conventional radiotherapy was used with supervoltage X-rays (4–10 MV). The radiation dose was 30–30.6 Gy given in 17–20 fractions over 4 weeks in patients who achieved complete response (CR) and 40–50 Gy in 20–28 fractions over 4–6 weeks in patients who did not achieve CR.

Response Assessment

CT, MRI and Ga-67 were used for imaging diagnosis of the lesions. Evaluation was performed pretreatment, after chemotherapy within 4 weeks and at the end of radiation therapy within 4 weeks. Post-treatment MRI was omitted in three patients with complete disappearance of primary lesion on CT. The response to treatment was determined by CT and MRI according to the report of an International Workshop to Standardize Response Criteria for NHL (6). CR was defined as complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms. Previously involved nodes or nodal masses on CT or MRI >1.5 cm in largest diameter must regress to <1.5 cm and previously involved nodes/nodal masses of 1.1–1.5 cm must regress to <1.0 cm. Partial response (PR) was defined as a reduction of at least 50% in the sum of the product of the greatest diameters of the six largest dominant nodes or nodal masses with no increase in the size of other nodes and with no new sites of disease. Stable disease (SD) was less than PR but not PD. PD was defined as a 50% increase in the sum of the product of the greatest diameters from the nadir of any previously identified abnormal node for PR and non-responders, or the appearance of any new lesion during or at the end of therapy. Ga-67-based determinations of CR, SD and PD were defined as complete disappearance of accumulation, equal accumulation and increased accumulation as compared with before treatment, respectively.

Statistical Analysis

Survival was measured from the first day of treatment. Death from any cause was included as an event in the overall survival, and any failure and any cause of death were included as events in the progression-free survival. The overall and progression-free survival curves were calculated using the Kaplan–Meier method (8). Differences between the survival rates were tested for statistical significance by the generalized Wilcoxon test. Statistical significance for all analyses was set at $P < 0.05$.

RESULTS

After completion of treatment, 21 patients (64%) achieved CR, 7 patients (21%) achieved PR and 5 patients (15%) developed PD of the 28 patients showing CR and PR, 21 showed no progression, whereas the remaining 7 did show progression. One patient had relapse at local progression and 6 patients showed relapse at lymph nodes outside the area of the primary lesion.

The 2-year overall and progression-free survival rates were 72 and 63%, respectively (Fig. 1). The 2-year progression-free survival rates in patients with IPI scores of 0–1 and 2–4 were 92 and 49%, respectively ($P = 0.001$). The correlation between progression-free survival and response after completion of chemotherapy was stronger with Ga-67 ($P = 0.009$) than CT or MR (Table 2), neither of which showed statistically significant correlations ($P = 0.75$ and $P = 0.19$, respectively). No correlations were found between the response after completion of all treatments and progression-free survival with CT ($P = 0.15$), MRI ($P = 0.77$) or Ga-67 ($P = 0.23$).

The 2-year progression-free survival rate in patients in whom Ga-67 uptake had disappeared at completion of chemotherapy was 80%, whereas that in patients in whom uptake remained was 26% ($P = 0.001$) (Fig. 2).

DISCUSSION

Aggressive lymphomas are a heterogeneous group of diseases that vary with regard to histopathology, clinical behavior in response to therapy and outcome. In contrast to many solid tumors, lymphomas are highly sensitive to chemotherapy and radiotherapy, and approximately 50–60% of patients with aggressive lymphoma achieve prolonged survival and cure (9,10). In the present study, 21 of 33 patients (63%) with aggressive lymphoma achieved disease-free survival for the duration of the study.

The effect of treatment for malignant lymphomas has conventionally been determined based on CT (6). However, there are limitations in assessment of response to therapy by CT (11–15), and Ga-67, FDG-PET and MRI have been reported to be useful for detection of the lesions. MRI is particularly useful in identifying bone and CNS involvement. MRI can suggest leptomeningeal involvement when

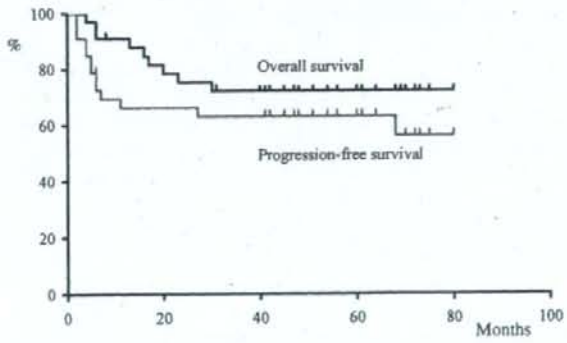

Figure 1. Overall and progression-free survival curves of all patients.

Table 2. Hazard ratios assessing for evaluation of the treatment effect by computed tomography, magnetic resonance imaging and Ga-67 for progression-free survival

Modality	Hazard ratios (95% CI)	*P* value
After chemotherapy		
CT:CR	Reference	
CT:residual	1.0 (0.3–4.7)	0.75
MRI:CR	Reference	
MRI:residual	1.7 (0.6–16)	0.19
Ga-67:CR	Reference	
Ga-67:residual	2.9 (1.7–40)	0.009
After chemotherapy followed by radiation		
CT:CR	Reference	
CT:residual	0.2 (0–1.9)	0.15
MRI:CR	Reference	
MRI:residual	0.5 (0–12)	0.77
Ga-67:CR	Reference	
Ga-67:residual	1.5 (0.5–20)	0.23

CI, confidence interval; CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging; Ga-67, gallium scintigraphy.

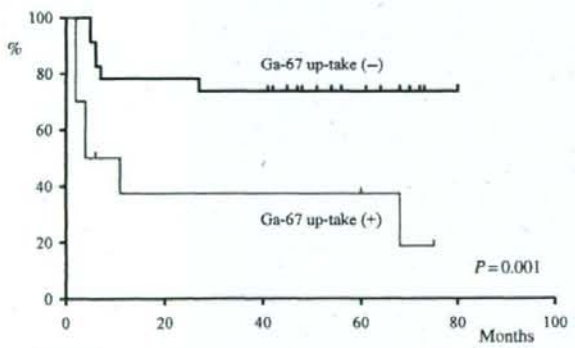

Figure 2. Progression-free survival curves according to the findings of gallium scintigraphy after completion of chemotherapy. Ga-67, gallium scintigraphy.

gadolinium has been used. MRI can also be used to identify bone marrow involvement (16). In contrast, CT and MRI often show a residual mass, which may not be neoplastic. In clinical CR patients treated with chemotherapy and/or radiation, only 10–18% of residual masses detected by CT and/or MRI are viable tumors (17,18). In patients whose residual masses were detected by CT or MRI, it was difficult to discriminate between a viable tumor, necrosis and fibrosis. The response to treatment of aggressive lymphoma is heterogeneous, even in patients with the same histological findings. Ga-67 and FDG-PET findings are indicators of cancer cell viability and can be used to monitor the response of the tumor cells in each patient to the particular course of chemotherapy received. In Hodgkin's lymphoma and aggressive or highly aggressive lymphoma, Ga-67 and FDG-PET may prove particularly useful in detecting residual disease (11–15,19–21). It has previously been shown that Ga-67 performed at the end of chemotherapy is superior to CT in patients with both Hodgkin's lymphoma and NHL for monitoring the response to treatment (12,22,23).

After patients have completed the entire planned treatment regimen, reevaluation should be done to determine the response to therapy. Achieving complete remission to therapy is the most important single prognostic factor in patients with NHL. Salvage treatment, such as high-dose therapy and autologous or allogeneic bone marrow transplantation, can sometimes cure disease in patients who fail to respond to initial therapy (24). In the relationship between treatment effect and prognosis, patients who responded to chemotherapy earlier are predisposed to accomplish a higher CR rate (25,26). Kaplan et al. (11) reported Ga-67 imaging to be an excellent indicator of residual viable tumors early during chemotherapy in 37 patients with diffuse large B-cell lymphoma. At follow-up, 59% of the patients who were Ga-67 positive halfway through therapy died, whereas in the group of negative patients only 20% died due to disease progression. Front et al. (12) compared the disease-free survival between patients with positive or negative Ga-67 and CT scan. CT findings were not predictive of outcome in contrast to Ga-67 imaging. In the present study, the correlation between progression-free survival and response after completion of chemotherapy was stronger in determination by Ga-67 than by CT.

The value of FDG-PET in the assessment of lymphoma has been investigated. FDG-PET combines the advantages of nuclear medicine techniques, such as Ga-67, as an indicator of tumor viability with improved resolution and higher sensitivity, and these advantages lead to higher lesion detection efficiency. Prognosis is grave for patients in whom the persistence of accumulation was seen with FDG-PET after one cycle of chemotherapy for Hodgkin's and NHL (15,27,28). On the other hand, in case the accumulation disappeared after one cycle of chemotherapy, the recurrence rate was reduced. Similarly, early interim FDG-PET is an accurate and independent predictor of progression-free survival and overall survival (29–35). All studies published to date suggested increased sensitivity of FDG-PET as compared with other imaging modalities, including Ga-67, when used for lymphoma staging (36–39). Such findings provide rationale for incorporating FDG-PET into revised response criteria for malignant lymphoma (40–42). PET is strongly recommended before treatment for patients with routinely FDG-avid, potentially curable lymphomas to better delineate the extent of disease. In addition, FDG-PET is essential for the post-treatment assessment of diffuse large B-cell lymphoma and Hodgkin's lymphoma (42). Although it has been shown that Ga-67 and FDG are both useful agents and that they show similar behavior in lymphoma after treatment, FDG-PET costs significantly higher and possesses more complicated logistics than Ga-67. Just now Ga-67 scan

should be used as an alternative for PET in hospitals where it has not been set up.

The results of the present study suggest that FDG-PET and Ga-67 scintigraphy are an efficient method for predicting the outcome of individual patients with aggressive lymphoma. Patients with abnormal FDG-PET or Ga-67 uptake after chemotherapy may need to receive additional treatment modifications. Effort is now being made to improve the outcome in patients who do not achieve CR, including modification of dose intensity, use of autologous stem cell transplantation and multiple new agents. Further studies are required to determine whether early selection with FDG-PET or Ga-67 increases survival in patients who do not show an early response to treatment.

Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Brain**

SPINAL RECURRENCE FROM INTRACRANIAL GERMINOMA: RISK FACTORS AND TREATMENT OUTCOME FOR SPINAL RECURRENCE

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Purpose: To analyze retrospectively the risk factors of spinal recurrence in patients with intracranial germinoma and clinical outcomes of patients who developed spinal recurrence.

Methods and Materials: Between 1980 and 2007, 165 patients with no evidence of spinal metastases at diagnosis were treated with cranial radiotherapy without spinal irradiation. The median follow-up in all 165 patients was 61.2 months (range, 1.2–260.1 months).

Results: After the initial treatment, 15 patients (9.1%) developed spinal recurrences. Multivariate analysis revealed that large intracranial disease (≥4 cm) and multifocal intracranial disease were independent risk factors for spinal recurrence. Radiation field, total radiation dose, and the use of chemotherapy did not affect the occurrence of spinal recurrences. Of the 15 patients who experienced spinal recurrence, the 3-year actuarial overall survival and disease-free survival (DFS) rates from the beginning of salvage treatments were 65% and 57%, respectively. In the analysis, presence of intracranial recurrence and salvage treatment modality (radiotherapy with chemotherapy vs. radiotherapy alone) had a statistically significant impact on DFS. The 3-year DFS rate in patients with no intracranial recurrence and treated with both spinal radiotherapy and chemotherapy was 100%, whereas only 17% in patients with intracranial recurrence or treated with radiotherapy alone ($p = 0.001$).

Conclusion: Large intracranial disease and multifocal intracranial disease were risk factors for spinal recurrence in patients with intracranial germinoma with no evidence of spinal metastases at diagnosis. For patients who developed spinal recurrence alone, salvage treatment combined with spinal radiotherapy and chemotherapy was effective in controlling the recurrent disease. © 2008 Elsevier Inc.

Germinomas, Spinal recurrence, Radiation, Chemotherapy.

INTRODUCTION

Intracranial germinomas represent 0.5–2.5% of all intracranial tumors and are more common in Japan than in Western countries (1–5). These tumors occur primarily in the pineal or neurohypophyseal regions and most often affect teenagers and young adults. In contrast to intracranial nongerminomatous germ cell tumors, germinomas are one of the most radiosensitive tumors known and are curable by radiotherapy alone (1, 5–13). Although radiotherapy has been the standard treatment for intracranial germinoma for many years, agreement on the optimal management of these tumors has not been reached. One of the major controversies in the management of intracranial germinoma is the use of craniospinal irradiation in patients with no evidence of spinal metastases at diagnosis (14–18).

Recently, several reports have indicated that the incidence of spinal recurrence was found to be too low to warrant routine spinal irradiation. With modern imaging procedures, the proportion of patients presenting with spinal disease at the time of diagnosis is low, and the risk of secondary spinal seeding in germinoma did not exceed 15% in a large series (8, 19, 20). However, the risk factors for spinal recurrence in patients with no evidence of spinal metastases at diagnosis have not been well documented. Moreover, there is minimal information

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regarding the outcomes of salvage treatment for patients who developed spinal recurrence. In the current study, we reviewed a retrospective and multi-institutional series of 165 patients with intracranial germinoma who had no evidence of spinal metastases at diagnosis and evaluated the risk factors for spinal recurrence and treatment outcomes for patients who developed spinal recurrences after the initial treatment.

METHODS AND MATERIALS

Patient characteristics

A retrospective review of medical records between 1980 and 2007 identified 240 patients with documented intracranial germinoma treated by radiotherapy at the Department of Radiology, University of the Ryukyus Hospital, Kyushu University Hospital, Shinshu University Hospital, Chiba University Hospital, Yamanashi University Hospital, or the International Medical Center of Japan. Of these, 75 patients having spinal metastases at diagnosis or treated with spinal irradiation were excluded, and a total of 165 patients with no evidence of spinal metastases at diagnosis and treated with cranial radiotherapy without spinal irradiation were subjected to this analysis. With regard to the 75 patients treated with spinal irradiation, 68 patients had no evidence of spinal metastases at diagnosis. The majority of these 68 patients were treated with routine craniospinal irradiation regardless of their disease status between 1980 and 1995, and the disease characteristics of these 68 patients, such as the tumor size and the number of tumor, were not significantly different compared with those of 165 patients treated without spinal irradiation.

Table 1 indicates the patient and treatment characteristics of all 165 patients. All patients were evaluated by computed tomography or magnetic resonance imaging (MRI) scans before initial treatment. One hundred and two patients (62%) were diagnosed pathologically; the remaining 63 patients (38%) were diagnosed clinically as having germinoma by clinical and neuroradiologic signs, as described previously (6, 9, 26). For the assessment of spinal metastases at diagnosis, 81 patients (49%) were evaluated by spinal MRI and the remaining 84 patients were evaluated by cerebrospinal fluid cytology or cerebrospinal fluid tumor markers. Forty patients (24%) had multifocal tumors involving more than one intracranial site, and serum human gonadotropin levels were elevated in 34 (21%) patients, who as a group had a median human gonadotropin value of 44 mIU/mL (range, 15–251 mIU/mL). Patients with human gonadotropin levels greater than 100 mIU/mL had pathologically verified germinomas. No patients had elevated alpha-fetoprotein or carcinoembryonic antigen titer.

Radiotherapy

Details of radiotherapy method were described as previously (21). In brief, radiotherapy was administered using a ^{60}Co teletherapy unit (4 patients), or a 4-, 6-, or 10-MV linear accelerator, and daily fraction sizes of 1.8–2.0 Gy for the primary tumor 5 days per week were mostly used. In most cases, treatment fields were determined using conventional X-ray simulators. For some cases, in an effort to spare normal brain from the high-dose volume of irradiation, computed tomography simulators were also used to boost the primary disease site. Localized-field irradiation was defined as a partial brain field covering the primary tumor with a generous margin, but not including the third ventricle and lateral ventricles.

One hundred three patients (62%) were treated using a radiation field encompassing the whole brain with or without a boost, 42 patients with the whole ventricle with or without a boost, and 20 patients with a localized-field smaller than the whole ventricle (Table 2). The total dose to the primary site ranged from 24 to 59.5 Gy (median, 48.5 Gy), with 7 patients (4%) receiving total doses of >55 Gy because we previously lacked a consensus regarding optimal doses for these tumors, especially for large tumors. Whole-brain doses ranged from 19.5 to 44 Gy (median, 30 Gy), whole-ventricle doses ranged from 24 to 40 Gy (median, 25.2 Gy), and localized-field doses ranged from 24 to 55.8 Gy (median, 40 Gy).

For patients with spinal recurrences, spinal radiotherapy with or without cranial radiotherapy was administered. The method of spinal radiotherapy was described as previously (22). In brief, spinal irradiation was supplemented using a posteroanterior field with single doses of 1.6–2.0 Gy per fraction and five fractions per week.

Table 1. Patient and treatment characteristics (n = 165)

Characteristic	No. of patients
Age (median, 17 y)	
<20 y	109 (66)
≥20 y	56 (34)
Gender	
Female	38 (23)
Male	127 (77)
KPS	
≥70	128 (78)
<70	27 (16)
Unknown	10 (6)
Tumor location	
Pineal	65 (39)
Neurohypophyseal	46 (28)
Thalamus or basal ganglia	14 (9)
Multifocal	40 (24)
No. of tumor	
Single	125 (76)
Multifocal	40 (24)
Maximal tumor size (cm)	
<4	131 (79)
≥4	34 (21)
Serum hCG level	
Normal	131 (79)
High	34 (21)
Pathology	
Verified	102 (62)
Unverified	63 (38)
Spinal MRI evaluation at diagnosis	
Yes	81 (49)
No	84 (51)
Total radiation dose (Gy)	
≤50	131 (79)
>50	34 (21)
Treatment field	
WB/WV ± B	145 (88)
Local	20 (12)
Chemotherapy	
Yes	75 (45)
No	90 (55)

Abbreviations: KPS = Karnofsky performance status; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; WB/WV = whole brain/whole ventricle; B = boost.

Data in parentheses are percentages.

Chemotherapy

Seventy-five patients (45%) received systemic chemotherapy with a total of one to six courses (median, three courses) during the initial treatment to reduce the total number of radiation doses

Table 2. Radiation field, total radiation dose, and incidences of intracranial and spinal recurrences according to the treatment modality

Treatment modality	Radiation field	Total radiation dose (range) (Gy)	No. of pts.	No. of low-risk group for SR*	No. of intracranial recurrence	No. of spinal recurrence
RT alone						
	WB ± B	50 (38–59.5)	77	18	1	5
	WV ± B	45 (40–52)	4	0	2	1
	Local	48 (24–55.8)	9	0	3	2
	Total	50 (24–59.5)	90	18 (20%)	6 (7%)	8 (9%)
RT + CT						
	WB ± B	49 (30–55)	26	10	2	4
	WV ± B	30 (24–50)	38	15	1	3
	Local	30 (24–40)	11	0	1	0
	Total	40 (24–50)	75	25 (33%)	4 (5%)	7 (9%)
Total		48.5 (24–59.5)	165	43 (26%)	10 (6%)**	15 (9%)**

Abbreviations: RT = radiotherapy; CT = chemotherapy; WB = whole brain; WV = whole ventricle; B = boost; SR = spinal recurrence; MRI = magnetic resonance imaging.

* Defined as patients with spinal MRI stage negative, small tumor (<4 cm), unifocal tumor, and treatment with WB or WV.

** Four patients developed both intracranial and spinal recurrences.

or radiation fields (Table 2). In patients with radiotherapy alone (median total dose, 50 Gy), 77 of 90 patients (86%) were treated with whole-brain irradiation with or without boost, whereas in patients with radiotherapy and chemotherapy (median total dose, 40 Gy), only 35% of the patients (26 of 75 patients) were treated with whole brain irradiation with or without boost. In the current study, we did not intend to use chemotherapies to reduce the risk of spinal recurrences for these patients. Of 75 patients, 71 patients (95%) received chemotherapy before radiotherapy; 2 patients during radiotherapy and the remaining 2 patients after radiotherapy. All patients received cisplatin or carboplatin in combination with other agents. The most commonly used regimen was a combination of cisplatin and etoposide (35 patients), and the next most common was a combination of carboplatin and etoposide (28 patients). Nine patients received a combination of ifosfamide, cisplatin, and etoposide and 3 patients received a combination of cisplatin and methotrexate. The remaining 1 patient received cisplatin-vinblastine-bleomycin combination therapy. Cycles were usually repeated every 3–4 weeks. Cisplatin and etoposide therapy consisted of cisplatin (20 mg/m^2) and etoposide (60 mg/m^2) for 5 consecutive days (Days 1–5) (23). In the carboplatin and etoposide therapy group, carboplatin (450 mg/m^2) was given on Day 1 and etoposide (150 mg/m^2) was given for 3 consecutive days (Days 1–3) (24). The ifosfamide, cisplatin, and etoposide regimen consisted of iphosphamide (900 mg/m^2), cisplatin (20 mg/m^2), and etoposide (60 mg/m^2) for 5 consecutive days (25); the combination of cisplatin and methotrexate regimen consisted of 50 mg/m^2 of cisplatin on Day 1 with 3 mg of intrathecal methotrexate twice during initial treatment. The cisplatin-vinblastine-bleomycin regimen consisted of cisplatin (20 mg/m^2) for 5 consecutive days (Days 1–5), vinblastine (4–6 mg/m^2) on Days 1 and 8, and bleomycin (10–15 mg/m^2) on Days 1, 8, and 15 (26).

For patients with spinal recurrences, the chemotherapy regimens described here were administered to patients who received both radiotherapy and chemotherapy as a salvage treatment.

Statistical analysis

The median follow-up time of all 165 patients was 61.2 months (range, 1.2–260.1 months), and no patients were lost to follow-up.

Table 3. Clinical data on 15 patients with spinal recurrence (at initial treatment)

Pts. no.	Age	Gender	Pathologic confirmation	Serum hCG	KPS (%)	Primary tumor site	Maximal tumor size (cm)	Total radiation dose	Radiation field	Use of CT	CT regimen (initial Tx)
1	20	Male	Yes	Normal	100	P+N	2	30	WV	Yes	EP
2	15	Male	Yes	Normal	60	P	5	50	WB+L	No	—
3	27	Male	Yes	Elevated	100	P	3	50	WV+L	Yes	CBDCA+VP16
4	27	Male	No	Normal	100	P	2	46	WB+L	No	—
5	12	Female	Yes	Elevated	90	N	4.5	40	WB+L	Yes	EP
6	10	Female	No	Elevated	100	P+N	4	40	L	No	—
7	2	Female	Yes	Normal	40	P	2.5	20	L	No	—
8	17	Female	Yes	Normal	100	N+D	3	40	WB+L	No	—
9	20	Male	Yes	Normal	90	P+N+D	3	50	WB+L	Yes	CBDCA+VP16
10	16	Male	Yes	Normal	100	P	5	50	WB+L	No	—
11	18	Female	No	Normal	100	P	1.5	50	WB+L	No	—
12	30	Male	Yes	Elevated	100	P+D	4.5	50	WV	Yes	CBDCA+VP16
13	13	Male	No	Normal	100	N+D	4	59.5	WB+L	Yes	CDDP+MTX
14	14	Male	No	Normal	90	N+Pons	4.5	48.5	WB+L	Yes	CDDP+MTX
15	14	Male	Yes	Normal	90	P+N	4	50	WV	No	—

Abbreviations: hCG = human chorionic gonadotropin; KPS = Karnofsky performance status; CT = chemotherapy; Tx = therapy; P = pineal; N = neurohypophyseal; D = dissemination; WB = whole brain; WV = whole ventricle; L = local; EP = cisplatin and etoposide; EP = cisplatin and etoposide; CBDCA = carboplatin; VA-16 = etoposide; MTX = methotrexate.

Table 4. Clinical data on 15 patients with spinal recurrence (at spinal recurrence)

Pts. no.	Age at spinal recurrence	Spinal recurrence site	Intracranial recurrence	Spinal radiation field	Spinal radiation dose (Gy)	Intracranial RT	CT after spinal recurrence	CT regimens after spinal recurrence	No. of cycles of CT	Site of re-recurrence after salvage Tx	Outcome	Follow up
1	24	C2-3	No	WS	30.6	No	Yes	ICE	3	—	NED	46.0 Mo
2	18	Th8-9	No	WS+L	45	No	Yes	ICE	4	—	NED	27.7 Mo
3	28	Th4	Yes	WS+L	30.6	Yes (24 Gy)	Yes	ICE	3	Intracranial	Dead	9.8 Mo
4	43	LI-3	No	WS+L	46	No	Yes	ICE	5	—	NED	193.9 Mo
5	18	Multiple	Yes	WS+L	46	Yes (20 Gy)	Yes	EP	3	Intracranial	AWD	69.6 Mo
6	13	Multiple	No	WS	36.3	No	Yes	CBDCA+VP16	3	—	NED	6.3 Mo
7	2	Multiple	Yes	WS	30.6	No	No	-	-	Intracranial, Spinal	Dead	2.1 Mo
8	24	L2	Yes	WS+L	44	Yes (18 Gy)	Yes	CBDCA+VP16	3	Intracranial	AWD	78.0 Mo
9	25	C5-Th2	No	WS+L	45	No	Yes	ICE	3	—	NED	59.4 Mo
10	17	Multiple	No	WS	24	No	No	-	-	Spinal	Dead	10.3 Mo
11	18	Th6-7, L4	No	WS	30	No	Yes	CBDCA+VP16	3	Intracranial	Dead	87.0 Mo
12	30	Multiple	No	WS	30	No	Yes	CBDCA+VP16	3	—	NED	2.8 Mo
13	14	Multiple	No	WS	33	No	Yes	CBDCA+VP16	3	—	NED	5.6 Mo
14	15	Multiple	No	WS	20	No	No	-	-	Spinal	Dead	17.1 Mo
15	15	Th12-S3	No	WS+L	45	No	Yes	CBDCA+VP16	3	—	NED	8.9 Mo

Abbreviations: RT = radiotherapy; CT = chemotherapy; Tx = therapy; C = cervival spine; Th = thoracic spine; L = lumbar spine; WS = whole spine; L = localized field; ICE = ifosphamide, cisplatin, and etoposide; PE = cisplatin and etoposide; CBDCA = carboplatin; VP-16 = etoposide; NED = no evidence of disease; AWD = alive with disease; Mo = months.

For the assessment of risk factors for spinal recurrence, the chi-square test and logistic regression analysis were used to investigate the relationship between variables and the occurrence of spinal recurrence. For the assessment of treatment outcomes for patients who developed spinal recurrence, overall and disease-free survival (DFS) rates were calculated actuarially according to the Kaplan-Meier method (27) and were measured from the beginning of salvage treatment. Differences between groups were estimated using the log–rank test (28). A probability level of 0.05 was chosen for statistical significance, and statistical analysis was performed using the SPSS software package (version 11.0; SPSS, Inc., Chicago, IL).

RESULTS

After the initial treatment, 10 patients (6%) developed intracranial recurrence and 15 patients (9.1%) developed spinal recurrences (Table 2). The median duration from the date of initial treatment to the date of spinal recurrence was 16.8 months (range, 2.4–199.2 months). Patient and disease characteristics in 15 patients with spinal recurrence were listed in Tables 3 and 4.

As shown in Table 5, the incidence of spinal recurrences was significantly higher in patients with primary large (≥4 cm) tumor at initial diagnosis than those without large tumors. Concerning the maximal tumor size, a cutoff size of 4 cm was used because the incidences of spinal recurrence increased as the tumor size increased, especially to 4 cm or larger (Table 6). Also, the incidence of spinal recurrence was significantly higher in patients with primary multifocal tumor at initial diagnosis compared with those without multifocal tumors. No significant differences were seen with respect to other factors, such as radiation field, total radiation dose, and the use of chemotherapy (Table 5). Of these 40 multifocal primary tumors, 18 tumors were bifocal (pineal and neurohypophyseal), and 3 of 18 patients (17%) with these bifocal germinoma had spinal recurrence after the initial treatment. Multivariate analysis revealed that large intracranial disease and multifocal intracranial disease each were independent risk factors for spinal recurrence (Table 5). We were able to define a low-risk group for spinal recurrence as patients with spinal MRI stage negative, small tumor (<4 cm), unifocal tumor, and treatment with whole-brain or whole-ventricle irradiation (Table 2). None of these 43 patients (0%) in the low-risk group developed spinal recurrence, whereas 15 of 122 patients who did not meet the criteria of the low-risk group (12%) developed spinal recurrence.

Regarding the 15 patients who experienced spinal recurrences, the 3-year actuarial overall survival and DFS rates from the beginning of salvage treatments were 65% and 57%, respectively (Fig. 1). The median total dose to the recurrent spinal disease for all 15 patients was 33 Gy (range, 24–46 Gy), and the total doses of salvage cranial radiotherapy for 3 patients ranged from 18 Gy to 24 Gy (Table 4). These 3 patients had intracranial recurrences at lesions initially treated with doses of 20–24 Gy, and the recurrent diseases extended to the margins of initial boost radiation field. In the analysis, the presence of intracranial recurrence and salvage treatment modality (radiotherapy with chemotherapy vs. radiotherapy alone) had a statistically significant

Table 5. Univariate and multivariate analysis of various potential prognostic factors for spinal recurrence in patients with intracranial germinoma

Variable	No. of pts.	No. of spinal recurrence	Univariate	Multivariate	
			p value	RR (95%CI)	*p* value
Tumor size					
<4 cm	131	7 (5%)	< 0.001	0.141 (0.043–0.462)	0.001
≥4 cm	34	8 (24%)			
Tumor number					
Single	125	8 (6%)	0.033	0.230 (0.070–0.761)	0.016
Multifocal	40	7 (18%)			
Gender					
Female	38	5 (13%)	0.320	—	—
Male	127	10 (8%)			
Pathology					
Verified	102	11 (11%)	0.335	—	—
Unverified	63	4 (6%)			
Spinal MRI at diagnosis					
Yes	81	6 (7%)	0.460	—	—
No	84	9 (11%)			
Total radiation dose					
≤50 Gy	131	13 (10%)	0.470	—	—
>50 Gy	34	2 (6%)			
Serum hCG					
Normal	131	11 (8%)	0.542	—	—
High	34	4 (12%)			
KPS					
≥70%	128	13 (10%)	0.660	—	—
<70%	27	2 (7%)			
Unknown	10				
Radiation field					
WB/WV	145	13 (9%)	0.880	—	—
Local	20	2 (10%)			
Age					
<20 y	109	10 (9%)	0.897	—	—
≥20 y	56	5 (9%)			
Use of chemotherapy					
Yes	75	7 (9%)	0.920	—	—
No	90	8 (9%)			

Abbreviations: MRI = magnetic resonance imaging; hCG = human chorionic gonadtropin; KPS = Karnofsky performance status; WB/WV = whole brain/whole ventricle; RR = relative risk; CI = confidence intervals.

impact on DFS (Table 7). All 3 patients treated with spinal radiotherapy alone died of the disease and all 4 patients with intracranial recurrence died of the disease or were alive with the recurrent disease during the period of this analysis.

Concerning intracranial recurrence and treatment modality, we defined the favorable-prognosis group as patients with no intracranial recurrence who were treated with both spinal radiotherapy and chemotherapy, and the unfavorable-prognosis group as patients with intracranial recurrence or those treated with radiotherapy alone. Four of 9 patients from the favorable risk group and 3 of 6 patients from the unfavorable risk group had spinal MRI evaluation at the time of initial diagnosis. The 3-year DFS rate in the favorable prognosis group was 100%, but only 17% in unfavorable prognosis group ($p = 0.001$, Fig. 2). No patients in the favorable risk group developed late complications, such as neurocognitive dysfunctions, vascular pathology, or leukoencephalopathy after salvage treatments.

Table 6. Incidences of spinal recurrence according to the maximal tumor size

Maximal tumor size	No. of pts.	No. of pts. with spinal recurrence
<2 cm	35	1 (3%)
≤2 cm <4 cm	96	6 (6%)
≥4 cm	34	8 (24%)
Total	165	15 (9%)

DISCUSSION

The current study indicated that large intracranial disease and multifocal intracranial disease at initial diagnosis were independent risk factors for spinal recurrence in patients with intracranial germinoma with no evidence of spinal metastases at diagnosis. Concerning the primary tumor size, several reports have indicated that tumor size is an independent prognostic factor for these tumors (6, 29, 30). Shibamoto *et al.* indicated that a tumor size <3 cm was associated with a better prognosis in patients with intracranial germinoma

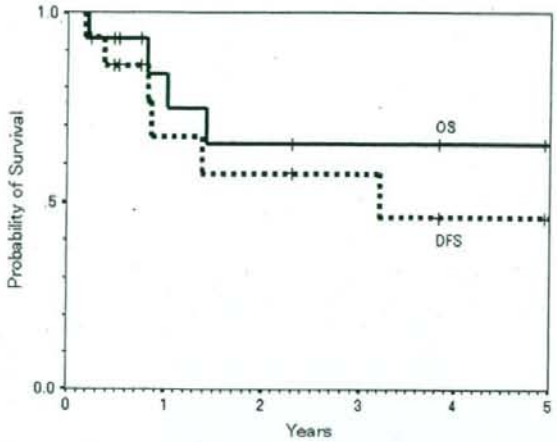

Fig. 1. Actuarial overall survival (OS) and disease-free survival (DFS) for all 15 patients with intracranial germinoma who developed spinal recurrence from the beginning of salvage treatment.

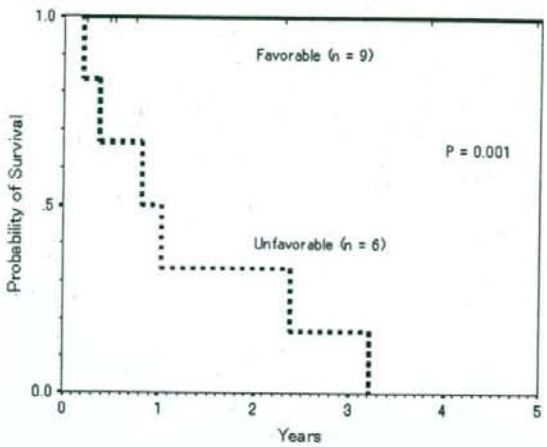

Fig. 2. Actuarial disease-free survival rates from the beginning of salvage treatment according to the presence of intracranial recurrence and treatment modality in patients with intracranial germinoma who developed spinal recurrences.

(30). Shirato *et al.* treated 51 patients with intracranial germinoma, and of 4 patients with more than 4-cm tumor, 1 patient (25%) had a spinal recurrence (6). In the current study, the incidence of spinal recurrence was significantly higher in patients with intracranially large tumor than those without large tumors, and large primary tumor was found to be an independent risk factor for spinal recurrence. These results suggest that craniospinal irradiation appears to be appropriate in patients with large primary tumors, even if there is no evidence of spinal metastases at diagnosis.

Table 7. Univariate analysis of various potential prognostic factors for disease-free survival in patients with intracranial germinoma who developed spinal recurrence

Variable	No. of pts.	3-year DFS (%)	*p* Value
Salvage treatment modality			
RT and CT	12	76	0.002
RT alone	3	0	
Presence of intracranial recurrence			
Yes	4	0	0.018
No	11	71	
Age			
<20 y	10	40	0.127
≥20 y	5	75	
Spinal radiation dose			
<40 Gy	9	38	0.163
≥40 Gy	6	75	
Pathology			
Verified	10	49	0.370
Unverified	5	67	
KPS			
≥70%	13	57	0.378
<70%	2	0	
Initial serum hCG level			
Normal	11	65	0.437
High	4	38	

Abbreviations: RT = radiotherapy; CT = chemotherapy; KPS = Karnofsky performance status; hCG = human chorionic gonadotropin; DFS = disease-free survival.

Concerning the number of primary tumors, several authors have recommended craniospinal irradiation for multifocal tumors (19, 31). Lindstadt *et al.* recommended that patients with documented subependymal or subarachnoid metastases presumably are at higher risk for leptomeningeal failure and recommended craniospinal irradiation for these patients (19). Dalttoli *et al.* advocated that craniospinal irradiation should be administered to patients with disease involving more than one intracranial site, demonstrated meningeal seeding, or positive cerebrospinal fluid cytology (31). In the current study, the incidence of spinal recurrence was significantly higher in patients with intracranially multifocal tumor at initial diagnosis than those without intracranially multifocal tumors. Moreover, the multivariate analysis revealed that multifocal primary tumor was found to be an independent risk factor for spinal recurrence. These results suggest that craniospinal irradiation appears to be appropriate in patients with multifocal tumors even if there is no evidence of spinal dissemination at the time of initial diagnosis.

However, optimal management of primary intracranial pineal and neurohypophyseal (bifocal) germinomas still remains controversial (3, 32, 33). Shibamoto *et al.* advocated that when the disease extends along the ventricular walls or is present in both pineal and neurohypophyseal regions, craniospinal irradiation should be considered, taking the patient's age into account (3). Conversely, Lafay-Cousin *et al.* suggested that bifocal germinoma can be considered a locoregional rather than a metastatic disease (33). The definition as either located or disseminated diseases has major implications on required treatment and its associated late morbidity. Moreover, the pathogenesis of such bifocal lesion is contested and the optimal management remains controversial. In the current study, 3 of 18 patients (17%) with bifocal germinoma had spinal recurrences. From our results, bifocal germinoma may

have some potential to metastasize and we advocate that patients with bifocal germinoma should be treated with craniospinal irradiation, taking the patient's age into account.

Although the optimal radiotherapy dose to the primary tumor is still unclear, recent findings have suggested that intracranial germinomas can be generally be cured with doses of between 40 and 50 Gy (3, 5, 6, 9, 20). In the current study, doses greater than 50 Gy were not associated with a decreased risk of spinal recurrence (Table 5). Therefore, doses of 40–50 Gy appear to be appropriate for the primary tumor. Concerning the optimal radiation dose required for the control of microscopic disease, most authors have recommended doses of 25–30 Gy for microscopic disease (7, 10, 13, 34). In the current study, we found that intracranial recurrences occurred with lesions treated at doses of 20–24 Gy in 3 patients, and that total doses of 24 Gy or less may be insufficient for microscopic diseases. Recently, Shibamoto *et al.* recommended a lower craniospinal dose of 20–24 Gy, because similar results were obtained for patient groups with positive or negative cytology (20). Schoenfeld *et al.* indicated that radiotherapy alone with low-dose prophylactic craniospinal irradiation (usually 21 Gy at 1.5 Gy per fraction) cured almost all patients with localized intracranial germinoma with rare complications (17). Further studies are needed to determine whether even lower doses can suffice for the control of microscopic disease.

Recently, to reduce the total radiation doses, the combination of chemotherapy and low-dose radiotherapy has being increasingly investigated (25, 26). The approach of delivering reduced-dose limited-field radiotherapy after a complete response to chemotherapy appears to be meritorious. However, our results indicated that chemotherapy was not associated with decreased risk of spinal recurrences (Table 5). Therefore chemotherapy alone appears to be insufficient to eradicate the microscopic spinal diseases, and spinal radiotherapy is recommended as a prophylactic treatment for spinal recurrence.

Concerning the treatment results for spinal recurrence, our results indicated that presence of intracranial recurrence and treatment modality (radiotherapy with chemotherapy vs. radiotherapy alone) each had a statistically significant impact on DFS. In particular, considering both the presence of intracranial recurrence and the treatment modality, the 3-year DFS in patients with no intracranial recurrence and treated with radiotherapy and chemotherapy was 100%, whereas only 17% in patients with intracranial recurrence and/or treated with radiotherapy alone ($p = 0.001$). Although there have been few reports describing the treatment results of spinal recurrences from intracranial germinoma, recent reports with unusual cases have indicated the efficacy of radiotherapy combined with chemotherapy for spinal tumors (35, 36). Merchant *et al.* treated 8 patients with intracranial germinoma who relapsed after treatment with primary chemotherapy. Of these 8 patients, 2 had spinal recurrences (tumor cells detected by MRI or cytologic evidence of cerebrospinal fluid involvement) and both were successfully treated with combination chemotherapy and radiotherapy (35). Tosaka *et al.* experienced a patient with spinal recurrence from intracranial germinoma who was successfully treated with 24 Gy spinal radiotherapy and several courses of systemic chemotherapy containing carboplatin, etoposide, and iphosphamide, with no recurrences after 1 year (36). Our results indicated that 3-year DFS in patients treated with radiotherapy and chemotherapy was significantly higher than that in patients treated with radiotherapy alone ($p = 0.002$). These results indicated that in patients with spinal recurrence alone, radiotherapy with chemotherapy was effective in controlling the recurrent diseases and should be recommended as a salvage treatment for these recurrent tumors.

Conversely, our results indicated that the patients with intracranial recurrences or treated with radiotherapy alone had a poor prognosis. For patients with intracranial recurrence, most patients have already received approximately 30–50 Gy to the brain and only insufficient radiation doses can be applied to the recurrent intracranial disease. In the current study, total doses of salvage cranial radiotherapy for 3 patients with intracranial recurrence were 18–24 Gy, which appeared to be insufficient for controlling the recurrent intracranial diseases, and all 3 patients were dead or alive with recurrent disease despite salvage therapies. Therefore, from our results, the optimal initial treatment at diagnosis is necessary to reduce the risk of intracranial recurrence (37–39). Concerning treatment modalities, our results indicated that 3 patients treated with spinal radiotherapy alone all died of the disease. Therefore spinal radiotherapy alone appears to be insufficient to control the recurrent spinal diseases.

In conclusion, our results indicated that large intracranial tumor and multifocal intracranial tumor were independent risk factors for spinal recurrence in patients with intracranial germinoma with no evidence of spinal metastases at initial diagnosis, and craniospinal irradiation appears to be appropriate for these patients. Our results also indicated that for patients who developed spinal recurrences alone, a combination of radiotherapy and chemotherapy was effective in controlling recurrent spinal diseases, and should be recommended as a salvage treatment for these recurrent tumors. However, this study is a retrospective study with a various treatment regimens, and further prospective studies are required to confirm our results.

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