CNS Germ Cell Tumors: Pattern of Failure and Effects of Radiation Volume

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This retrospective study was conducted to evaluate local control and overall survival after radiotherapy for patients with intracranial germ cell tumors and to investigate the influence of irradiated field on treatment outcome. Thirty-two patients with surgically confirmed or suspected primary intracranial germ cell tumors (GCT) treated at the Division of Therapeutic Radiology and Oncology, Chiang Mai University, Chiang Mai, Thailand between January 1988 and December 1999 were reviewed. Seven patients were not included in the analysis of treatment outcome and survival due to incompleteness of radiation treatment or death before the end of treatment. The median follow up time of 39.5 months (range from 2.3 months to 136.1 months). Median age at diagnosis was 16.5 years with 23 males and 9 females. Patients were irradiated to the primary tumor with an adequate margin in 7 patients, to the whole brain with a cone down boost in 8 patients. Craniospinal irradiation (CSI) was performed in 10 patients. For the 25 evaluable patients, 5 year overall survival was 86.4%. Five-year disease free survival was 72.9%. Five year overall survival rates were 83.1% and 90.0% for the germinoma and nonbiopsied group. (p-value = 0.6052). Routine prophylactic CSI was not given with a spinal only failure rate of 33.3%. Five-year overall survival were 85.7%, 87.5%, 85.7% for CSI, whole brain irradiation with boost and local field irradiation (p-value = 0.9037). Five-year disease free survival were 85.7%, 72.9%, 85.7% for CSI, WBRT, and local field (p-value = 0.6403). This retrospective study suggests that definitive radiation therapy is effective in controlling germinoma, and cure rates are excellent with irradiation alone. Craniospinal irradiation can eliminate the risk of relapse especially in patients who had incomplete diagnostic craniospinal evaluation.

Keywords: *CNS Germ cell tumor, Radiotherapy, Pattern of failure*

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Intracranial germ cell tumors (GCT) are rare. They represent 0.5-2.5% of all intracranial tumors[1,2]. Although they are more common for unknown reasons in Japan where they account for approximately 4% of CNS neoplasms[3].

The behaviour of these tumors is highly dependent on the histology. In the past, diagnosis of the disease has been made radiologically due to the difficulty of biopsy and the risk of tumor seeding by biopsy[4]. However, new techniques have allowed neurosurgeons to biopsy safely so that most recommend that a tissue diagnosis be obtained prior to treatment[2,5].

The optimal radiation treatment volume is controversial. Because of the infiltrating and disseminating nature of the disease, whole brain or craniospinal irradiation have often been recommended[6,7,8], while others believe spinal prophylaxis is necessary only for nongerminoma germ cell tumor[2] or reserve adjuvant spinal irradiation for patients with CSF dissemination[1,9].

It is unlikely to be possible to conduct a prospective randomized study for these rare neoplasms. Therefore, the authors have retrospectively analyzed their experience to evaluate local control and overall

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survival after radiotherapy and to investigate the influence of the irradiated field on outcome.

Material and Method

Patients

A retrospective study was performed in the Division of Therapeutic Radiology and Oncology, Chiang Mai University, Chiang Mai, Thailand. Thirty-two patients treated for confirmed or suspected primary intracranial germ cell tumors between January 1988 and December 1999 were reviewed. A pathologic tissue diagnosis was obtained in 15 patients. All of them were germinomas. Seventeen unbiopsied patients were presumed to have germ cell tumors based on clinical presentation and neuroradiographic imaging of tumor in the pineal or suprasellar region. These patients received a trial of 20 Gy limited volume irradiation followed by repeat imaging. All of them had a good response to irradiation and were presumed to be germinomas. Patients' records were reviewed with respect to age, gender, location of tumor, CSF cytology, myelography or spinal MRI, type of surgery, radiation field and doses, dates and site of failure, date of last follow-up, and date and cause of death. Disease free survival and overall survival were calculated from date of diagnosis. The median follow-up time of the present study was 39.5 months (range from 2.3 months to 136.1 months).

Treatment

Seventeen unbiopsied patients had a shunting procedure. Surgical excision was performed in 8 patients and biopsy in 7 patients (Table 1).

Radiosensitivity assessment was undertaken in all cases in which a histological diagnosis had not been done with repeat radiological studies after a dose of 20 Gy to the tumor region.

Ten patients were treated with a Cobalt-60 machine and 22 patients were treated on 6MV linear accelerators. Treatment fields ranged from a local field (primary tumor plus 2 centimeters margin) to craniospinal irradiation. Seven patients were excluded from the analysis of treatment outcome and survival; five of them did not complete their radiation treatment due to poor compliance and two died before the end of treatment. For the 25 evaluable patients; 7 patients were irradiated to the primary tumor with 2-centimeters margins, 8 patients were treated to the whole brain with boost, and the other 10 patients received craniospinal radiotherapy. Treatment characteristics are summarized in Table 2.

Results

Patients

There were 23 males and 9 females. Age range at diagnosis was 2-64 years, with a median of 16.5 years. Among the 26 pineal tumor patients, 22 patients were males and 4 were females, whereas for the 6 suprasellar tumor patients, there were 5 females and 1 male (Table 1). Tumor location and gender ratios are listed in Table 3.

Spinal staging

Cerebrospinal fluid cytology was performed in 11 patients and was positive in 1 patient. Spinal MRI and myelography revealed spinal involvement in only 1 of the 6 patients studied (Table 4).

Pattern of relapse

There were 7 recurrences in the 25 evaluable patients. Two patients had relapse confined to the primary site (following local RT to primary tumor in 1 patient, the other patient received craniospinal RT).

The other five patients had spinal failure only. None of these patients had had spinal irradiation (two of them had been treated with local RT and the other 3 patients received whole brain RT with boost to primary site). Therefore 5 of 15 patients (33%) treated without spinal radiation had spinal relapse. Conversely, none of the 10 patients who had craniospinal RT had spinal relapse. The authors also analysed the pattern of relapse in 2 subgroups of patients (the biopsied versus unbiopsied) as shown in Table 5. Distribution of treatment approaches was equally divided among the biopsied and non-biopsied patients. Local failure occurred in 2 of the non-biopsied patients and spinal relapse in one. Spinal relapse occurred in 4 biopsied

Table 1. Patients characteristics

Age:	Median 16.5	Range (2-64)
Sex:	Male	= 23
	Female	= 9
Histology:	Verified	= 15
	Unbiopsied	= 17
Tumor site:	Pineal	= 26
	Suprasellar	= 6
Type of surgery:	VP shunt (unbiopsied)	17
	Biopsy	= 7
	Removal tumor	= 8

Table 2. Treatment characteristics

Evaluable Patients (n = 25)	No. of Patients		
	Local RT (n = 7)	WBRT with boost (n = 8)	CSI (n = 10)
Germinoma (n = 13)	3	5	5
Unbiopsied (n = 12)	4	3	5

Table 3. Tumor site, gender ratio and median age

Histology	Tumor site	Male:Female	Median age (range)
Germinoma	Pineal	9:10	16.0 (11-27)
	Suprasellar	1:5	13.5 (7-24)
Unbiopsied	Pineal	13:14	17.0 (64)
	Suprasellar	-	-

Table 4. Spinal staging of patients

Investigation	No. Cases	No. positive
Myelography	1	-
Spinal MRI	5	1
CSF cytology	11	1

Table 5. Pattern of recurrence in 13 Germinoma patients and 12 unbiopsied patients

RT field	No. of case		Local failure		Spinal Failure		Local + spinal failure	
	Germ*	Unbx**	Germ	Unbx	Germ	Unbx	Germ	Unbx
Local RT	3	4	-	1	2	-	-	-
WBRT with boost	5	3	-	-	2	1	-	-
CSI	5	5	-	1	-	-	-	-

* Germ = Germinoma
** Unbx = Unbiopsied

patients. Table 6 summarizes all the details and outcome of 25 evaluable patients.

Survival

Six of the 25 evaluable patients expired: all from prognosis of their germ cell tumors. All of them were pineal region tumors. The 5-year overall survival rate was not significantly different between the germinoma and non-biopsied group (83.1% vs 90%, p = 0.6052). The 3-year overall survival was 85.7%, 87.5%, and 85.7% for CSI group, WBRT with boost group and local field radiotherapy, respectively (p = 0.9037). The 3-year disease free survival rate was 85.7%, 72.9% and 85.7% for CSI group, WBRT with boost group and local field radiotherapy, respectively (p = 0.6403). Overall survival and disease free survival is illustrated in Fig. 1-3.

Discussion

The present retrospective study has confirmed the excellent results of radiation therapy alone in the management of histologically verified or suspected primary intracranial germ cell tumors.

Table 6. Results of 25 evaluable patients

Pts.	RT field	Spinal staging (Results)	Germ*** or Unbx****	Local failure	Spinal failure	Local + spinal failure
1	Local field	ND**	Unbx	-	-	-
2	Local field	ND	Unbx	1	-	-
3	Local field	ND	Unbx	-	-	-
4	Local field	ND	Unbx	-	-	-
5	Local field	CSF cytology (-)	Germ	-	1	-
6	Local field	ND	Germ	-	1	-
7	Local field	ND	Germ	-	-	-
8	WBRT + Boost*	CSF cytology (-)	Unbx	-	1	-
9	WBRT + Boost	ND	Unbx	-	-	-
10	WBRT + Boost	Myelography (-)	Unbx	-	-	-
11	WBRT + Boost	CSF cytology (-)	Germ	-	1	-
12	WBRT + Boost	ND	Germ	-	-	-
13	WBRT + Boost	Spinal MRI (-)	Germ	-	1	-
14	WBRT + Boost	CSF cytology (-)	Germ	-	-	-
15	WBRT + Boost	CSF cytology (-)	Germ	-	-	-
16	CSI	CSF cytology (-)	Unbx	-	-	-
17	CSI	ND	Unbx	-	-	-
18	CSI	CSF cytology (-) Spinal MRI (-)	Unbx	-	-	-
19	CSI	ND	Unbx	-	-	-
20	CSI	ND	Unbx	1	-	-
21	CSI	CSF cytology (-)	Germ	-	-	-
22	CSI	CSF cytology (+)	Germ	-	-	-
23	CSI	Spinal MRI (-)	Germ	-	-	-
24	CSI	CSF cytology (-) Spinal MRI (-)	Germ	-	-	-
25	CSI	CSF cytology (-) Spinal MRI (+)	Germ	-	-	-

* WBRT = Whole brain radiotherapy
** ND = Not done
*** Germ = Germinoma
**** Unbx = Unbiopsied

Edwards et al[10] have shown that only 33% of pineal region tumors in 36 children under the age of 18 years were germinomas, and it has been suggested that radiotherapy is not an appropriate initial treatment for most pineal tumors other than germinomas[11]. Thus, it is important to have the pathological confirmation of tumors where possible. In the present study, the percentage of patients diagnosed by pathological confirmation was 47%, and the authors needed to know the actual pattern of care and the natural history for intracranial germ cell tumors to reduce unnecessary/ inappropriate irradiation for those young patients.

The radiation fields necessary for optimal control continue to be debated[12-14]. Aoyama et al suggested that craniospinal irradiation may not be required, but local irradiation alone without the inclusion of ventricles is not recommended due to low relapse-free survival rate. However, their study reconfirmed that craniospinal irradiation effectively achieve a 10-year relapse-free survival rate (90%)[15]. Wolden et al reported a retrospective study of 48 patients with surgically confirmed or suspected primary intracranial germ-cell tumors and suggested treating with whole ventricular fields plus a boost for all localized tumors[16]. Many series have shown good results without spinal irradiation[12,17,18], although less than whole brain radiotherapy has been associated with a 15% incidence of intracranial recurrence[14,19].

In the authors' experience, craniospinal irradiation is well tolerated and there was no increase in

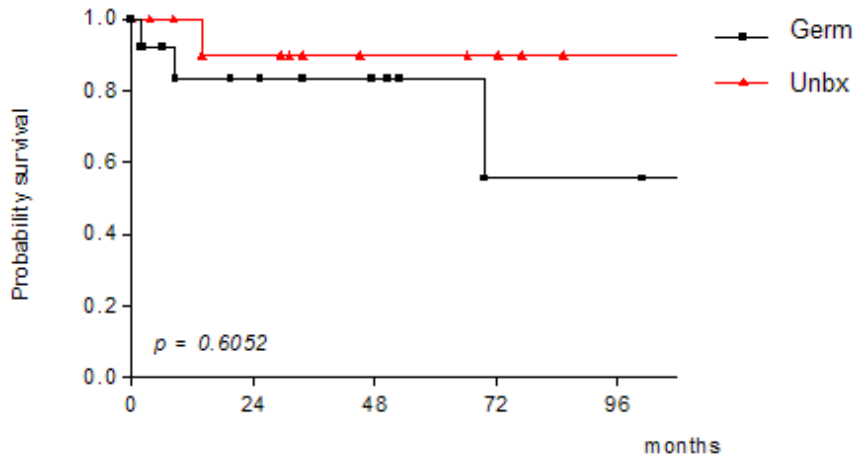

Fig. 1 Overall survival: Germinoma vs non-biopsied group

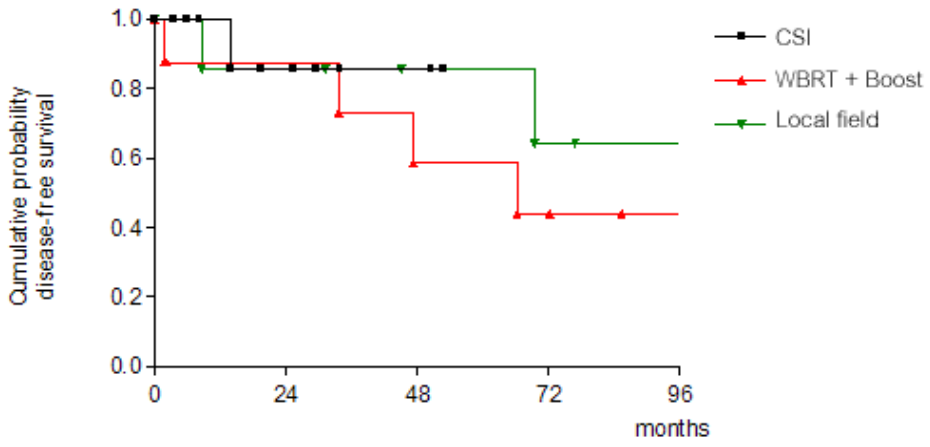

Fig. 2 Disease Free Survival in each radiation field

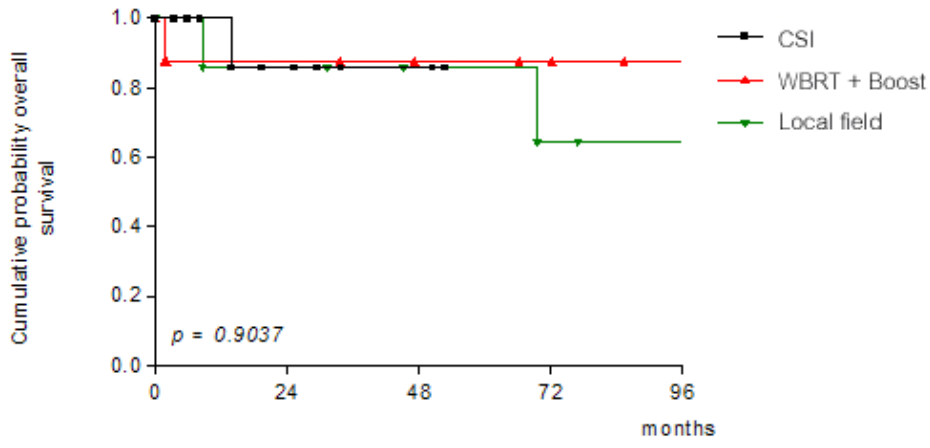

Fig. 3 Overall survival in each radiation field

late radiation toxicity when compared with local field treatment. Using whole neuraxis radiotherapy, the authors have had no spinal drop metastasis in patients treated. For the CSI group, three-year overall survivals and disease free survivals for the CSI group were both 85.7%. A relapse in the spinal canal was observed in 33.3% (5/15) of patients who were not treated with craniospinal irradiation. These results suggest that craniospinal irradiation is associated with the prevention of spinal relapse, although the number of patients in the present study was too small to find a statistically significant difference between CSI and other radiation fields. Linstadt et al[12] have reviewed the results of treatment for germinoma with or without spinal RT. The incidence of spinal failure was 8% versus 23% for histologically verified tumors, but for unverified lesions 11% versus 9% for patients treated with and without spinal RT, respectively. For the present study, the incidence of spinal failure was 0% (0/5) versus 50% (4/8) for germinomas patients who were treated with and without craniospinal RT, and for the unbiopsied group was 0% (0/5) versus 14% (1/7), respectively (Table 5). The good results of the unbiopsied group suggest that where surgery is contraindicated, the use of a 20 Gy trial of radiation with reimaging and completion of RT as for a germinoma can still lead to good results for radioresponsive tumors (presumably germinomas). This data does not give information on this approach for tumors which turn out to be non-radioresponsive on the test as these were not included in this analysis.

Conclusion

In conclusion, the present study confirms the excellent results obtained with radiotherapy for CNS germ cell tumors and radioresponsive pineal tumor. In the absence of adequate spinal staging, use of craniospinal irradiation eliminates the risk of relapse. In the present study, even with negative spinal staging, without craniospinal irradiation, 5 out of 15 patients relapsed, but these numbers are too small to state categorically that craniospinal irradiation can be safely omitted, even in these cases.

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เนื้องอกสมองชนิดเจิร์มเซลล์: รูปแบบของการกลับเป็นซ้ำของโรคและขอบเขตของการฉายรังสี

อิ่มใจ ชิตาพนารักษ์, วิชาญ หล่อวิทยา, พิมพ์ขวัญ กำเนิดศุภผล, ไบรอัน กอส, จูดิธ ฟอร์ด

การศึกษาย้อนหลังฉบับนี้ มีจุดประสงค์เพื่อประเมินการควบคุมโรคเฉพาะที่และอัตราการรอดชีวิตในผู้ป่วยเนื้องอกสมองชนิดเจิร์มเซลล์ หลังจากได้รับการรักษาด้วยวิธีการฉายรังสี โดยจะประเมินบทบาทของขอบเขตของการฉายรังสีที่มีต่อผลการรักษา สามารถรวบรวมผู้ป่วย ที่มีผลพยาธิวิทยายืนยันหรือมีผลการตรวจของรังสีที่เข้ากันได้กันกับเนื้องอกสมองชนิดเจิร์มเซลล์ได้ทั้งหมด 32 ราย มีผู้ป่วย 7 ราย ที่ไม่สามารถทำการวิเคราะห์ผลการรักษาและอัตราการรอดชีวิตได้เนื่องจากฉายรังสีไม่ครบหรือเสียชีวิตก่อนจบการรักษา หลังจากติดตามผลการรักษาไปประมาณ 39.5 เดือน (2.3-136.1 เดือน) โดยมีค่ากลางของอายุผู้ป่วย 16.5 ปี เป็น เพศชาย 23 ราย เพศหญิง 9 ราย มีผู้ป่วย 7 รายได้รับการฉายรังสีที่บริเวณเนื้องอกและขอบเขตโดยรอบ, 8 ราย ได้รับการฉายรังสีทั้งศีรษะและ 10 รายได้รับการฉายรังสีตลอดแนว ตั้งแต่ศีรษะถึงไขสันหลัง

ในผู้ป่วย 25 ราย ที่สามารถประเมินผลการรักษาได้ พบว่ามีอัตราการรอดชีวิตที่ 5 ปี เป็น 86.4%, มีระยะปลอดโรคที่ 5 ปี 72.9%, ในผู้ป่วยที่มีผลพยาธิสภาพยืนยันว่าเป็นชนิดเจอร์มิโนม่า มีอัตราการรอดชีวิตที่ 5 ปี 83.1% เทียบกับกลุ่มที่ไม่ทราบผลพยาธิสภาพเป็น 90% ซึ่งพบว่าไม่แตกต่างกัน (ค่า p-value 0.6052) เมื่อพิจารณาถึงขอบเขตของการฉายรังสีพบว่ากลุ่มที่ฉายตลอดแนวตั้งแต่ศีรษะถึงไขสันหลัง มีอัตราการอยู่รอดที่ 5 ปี เท่ากับ 85.7%, กลุ่มที่ฉายทั้งศีรษะ 87.5% และกลุ่มที่ฉายครอบคลุมเฉพาะก้อนเนื้องอก 85.7% (ค่า p-value 0.9037) ในการศึกษานี้พบว่า การที่ไม่ได้ฉายตลอดแนวตั้งแต่ศีรษะจนถึงไขสันหลังเพื่อเป็นการป้องกัน ตั้งแต่ต้นนั้น ทำให้ผู้ป่วยมีโรคกลับเป็นซ้ำที่บริเวณไขสันหลังสูงถึง 33.3%

โดยสรุปการศึกษานี้พบว่าการฉายรังสีเพียงอย่างเดียว สามารถควบคุมโรคเนื้องอกสมองชนิดเจิร์มเซลล์ได้เป็นอย่างดี และมีอัตราการหายขาดของโรคค่อนข้างสูง วิธีการฉายรังสีป้องกันตลอดแนวตั้งแต่ศีรษะถึงไขสันหลังสามารถลดความเสี่ยงในการกลับเป็นซ้ำได้โดยเฉพาะในกลุ่มผู้ป่วยที่ไม่ได้ทำการตรวจวิเคราะห์ว่ามีการกระจายของโรคตามแนวไขสันหลังมาก่อน