表3　口腔癌以外の予防照射領域の1例

部位	CTV1	CTV2
頬粘膜	P	IN（Ⅰ～Ⅲ）
舌・口腔底	P	IN＋CN（Ⅱ～Ⅴ）
声門	P	－
声門上	P	IN＋CN（Ⅱ～Ⅴ）
上咽頭	P	IN＋CN（Ⅰb～Ⅴ、RPLN）
中咽頭		
側壁	P	IN（Ⅰb～Ⅴ）
前壁	P	IN＋CN（Ⅰb～Ⅴ、（RPLN））
下咽頭	P	IN＋CN（Ⅱ～Ⅴ，RPLN）
副鼻腔	P	－

P：Primary tumor＋subclinical region
IN：Ipsilateral lymph node
CN：Contralateral lymph node
RPLN：Retropharyngeal lymph node
CTV：Clinical target volume

表4　通常分割照射における線量制限

脊髄	45Gy以下
脳幹	54Gy以下
耳下腺	平均線量26Gy以下、耳下腺体積の50％は20Gy以下
下顎骨	70Gy以下
網膜	45Gy
視神経・視交叉	50Gy以下

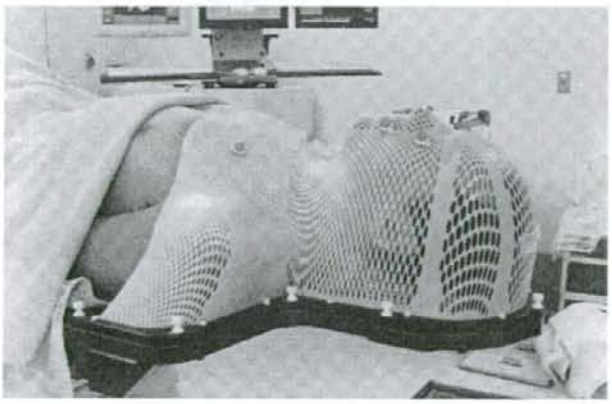

図2　頭頸部用固定具（IMRTでの使用例）

Intensity Modulated Radiation Therapy）。

3）重要臓器OAR（organ at risk）の取扱い

放射線治療では、不可逆性でQOLの低下を招く晩期の有害事象を発生させないために、重要臓器への線量制限を行いながら治療計画を立てなければならない。**表4**に通常分割照射におけるOARの線量制限の1例を記す。

ここ数年の間に、IMRTを用いて耳下腺の被曝線量を軽減させることにより、唾液分泌を保ち口腔内乾燥を減らせるといった報告がみられる[13]。さらに最近では、耳下腺の保護により唾液量は保たれるが、患者の口腔内乾燥といった自覚症状の改善、QOLの改善が相関していないという報告もあり[14]、漿液性の唾液だけではなく粘液性のムコ多糖類が含まれた唾液分泌が自覚症状に大きく影響すると考えられている。つまり、純漿液腺である耳下腺だけでなく、混合腺である顎下腺や舌下腺の保護もQOLを低下させないためには必要となる可能性がある。

4）固定具

放射線治療中の体動を抑え、精確な照射を行うため、通常は症例ごとにオーダーメイドの固定具を作成する（**図2**）。特にIMRTにおいては精度の高い治療計画を行い、また1回の治療時間も30分以上かかることから、固定具の重要性が一層高まっている。

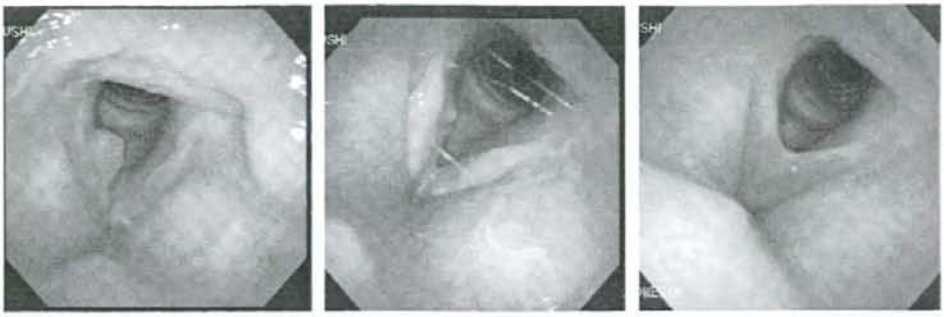

図3　喉頭癌（右声門：T1aN0M0）
左から治療前、治療直後、治療後10週目

IMAGE PREVIEW 参照

部位ごとの癌転移の特徴

1）上咽頭

最も転移しやすい癌である。リンパ節転移は広範で、levelⅡだけでなくⅢ、Ⅳや耳介後部のリンパ節にも転移しやすい。初診時M0であっても骨、肝、肺に遠隔転移が多く、その80%は治療開始1年以内に発生する。局所進行癌で発見されることが多く、早期癌でも解剖学的に手術療法の適応が低い領域であるため、病期によらず放射線治療が第1選択である。照射野が広く、複雑な解剖学的部位と進展方式であること、耳下腺・脳幹・視神経といったOARがPTV（planning target volume）に近接していることから、IMRTの有用性が最も発揮できる領域である。以前は局所再発が多かったが、放射線治療技術の進歩により局所再発より遠隔再発が多くなってきており、化学療法の役割が高まっている。

2）中咽頭

中咽頭は前壁、側壁、後壁、上壁の4亜部位に分類される。発生部位により腫瘍の性格は大きく異なり、治療法、治療成績に大きく影響する。側壁、上壁の頻度は70%程度と高く、前壁、後壁は30%以下と発生頻度は少ない。また後壁の治療成績は他の亜部位に比べ悪い。

3）下咽頭

下咽頭は梨状陥凹、咽頭後壁、輪状軟骨後部の3亜部位に分けられる。梨状陥凹が約7割と最も多く、次いで輪状軟骨後部、咽頭後壁となっている。下咽頭癌は頭頸部癌の中でも手術、放射線治療いずれでも予後不良の癌といわれている。頸部リンパ節転移の頻度が高く、遠隔転移も頭頸部癌の中では上咽頭癌について多いとされている。そのため早期で発見される割合は少なく、stageⅠ、Ⅱは下咽頭癌全体の20%であるが、内視鏡技術の進歩により今後高まる可能性が高い。

放射線治療法の進歩により、早期下咽頭癌では80%を超える局所制御率が報告されている。しかし、生存率はいまだ不良で、遠隔転移が多いことと、重複癌の合併率が高いことなどによる。ルビエールリンパ節から頸部食道まで病巣が進展する可能性があり、照射野は広範に設定する必要がある。放射線治療によりCRとならなければ、救済手術を考慮する[15,16]。

4）喉頭

喉頭癌は頭頸部癌の中で発生頻度が最も高い。喉頭は声門上部、声門部、声門下部の3つの亜部位に分けられる。声門癌、声門上癌ともに放射線単独治療が標準治療となっている。表在性の癌（Tis）であれば、経内視鏡的手術（stripping/laser）でもQOLを下げずに治癒できると考える。声門下癌の発生頻度は低い。

①声門癌

声門部に発生する声門癌（図3）は喉頭癌全体の6～7割を占める。嗄声により早期に診断されることが多く、リンパ節転移はまれで、T1/2では3%以下である。5年局所制御率は放射線治療単独でⅠ期80～95%、Ⅱ期70～80%である。声門を中心とした5×5～6×6cmの照射野でⅠ期66Gy/33分割、Ⅱ期70Gy/35分割が標準的である。満足できる治療成績が得られており、晩期の有害事象も軽微で標準的治療が確立されているといえる。しかし、全治療日数43日以下、1回線量2.25Gy以上、総線量65Gy以上で、T2の局所制御率向上との報告がある[17]。

T2声門癌では、1回線量2Gy以下では5年局所制御

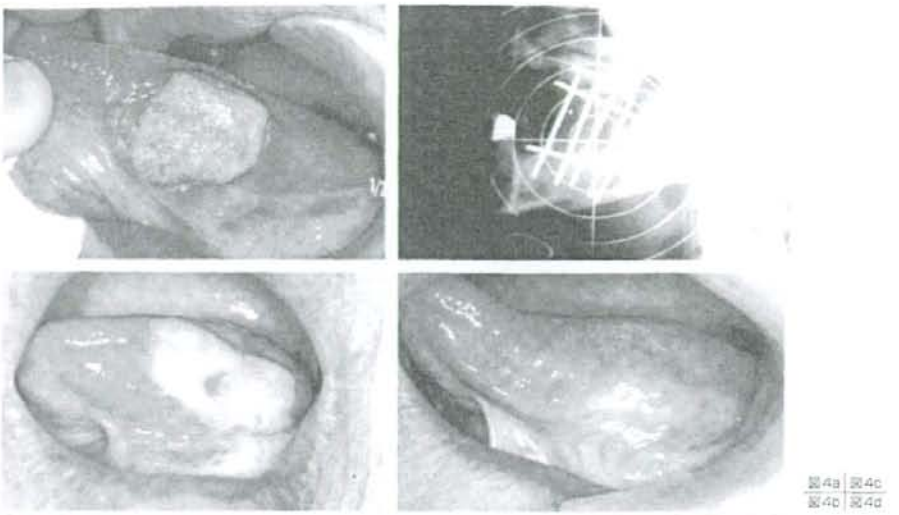

図4a | 図4c
図4b | 図4d

図4　舌癌：T2N0M0
セシウム針による組織内照射（70Gy）
a：治療前
b：治療10日後
c：セシウム針刺入写真
d：治療3年後

IMAGE PREVIEW 参照

率が不良（68％／82％）との報告もあり[8]、治療期間の短縮を目指した1回線量2Gyと2.4Gyの無作為試験が現在本邦で行われ[9]、さらなる治療の進歩が期待される。

②声門上癌

リンパ節転移のリスクが高く、頸部の予防的照射が必要となる。

5）口腔

口腔は、上・下口唇、頬歯槽溝、頬粘膜、上・下歯肉、臼後三角、硬口蓋、口腔底、舌前2/3からなる。早期口腔癌のリンパ節転移のリスクは口唇：5％、口腔底：10～20％、舌：25～30％、頬粘膜：10～20％である。治療法は放射線治療が選ばれることが多いが、病巣がきわめて小さく、辺縁が明瞭で、舌実部や舌辺縁の前方に局在する症例に対しては部分切除を選択する場合もある。

小線源治療

IMRTなど外部照射の進歩が急速になされているが、線量集中性と顎骨障害や粘膜潰瘍、唾液腺障害などのすべてにおいて小線源治療が勝っており、究極の動態追跡照射的放射線治療といえる。

実際の治療術式はイリジウム針やセシウム針線源を用いた低線量率連続組織内照射が主体となる。厚みのある腫瘍に対しては外部照射を先行した後に組織内照射を行う。LDR（低線量率組織内照射）では60～70Gy/6～7日が標準治療とされる。30～40Gyの外部照射を併用する場合は組織内照射60Gy前後となる。セシウム針は2002年より供給停止となっている。高線量率の線源によるRALS（remote after loading system）を用いた分割組織内照射は医療従事者の被曝がまったくなく、患者管理の点でも今後主流になると考えるが、あまり普及していない。

N0症例においても、約3割に頸部リンパ節転移が生じるといわれている。そのため厳重な経過観察により早期のリンパ節転移を発見し、すみやかに頸部郭清術を行うべきである（**図4**）。

まとめ

早期頭頸部癌に対する放射線治療成績は、ほぼ上記に示したとおりである。推奨される治療法は日本放射線腫瘍学会のガイドラインに記載されている。しかし、頸部リンパ節領域の照射範囲、併用化学療法など、各施設間で治療方針により違いがみられる。放射線治療計画のモニタ上で、CTの断面像にGTV（gross tumor volume）、CTV、OARをマウスで実際に囲んでいると、放射線を当てて制御すべき病巣部分と、照射外の機能温存・保護すべき部分を明確にしないといけないことにあらためて気がつく。

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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.

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.

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.

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)	Intra-cranial 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	L1-3	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; FE = 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

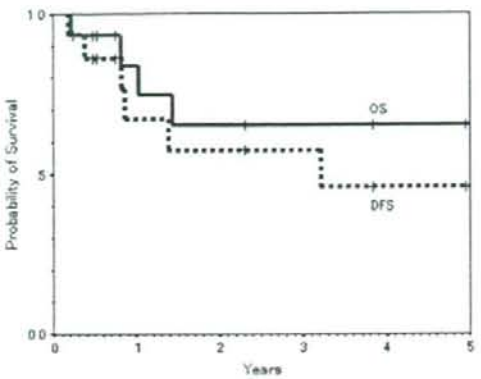

Fig. 1. Actuarial overall survival (OS) and disease-free survival (DFS) for all 15 patients with intracranial germinoma who developed spinal recurrence from the beginning of salvage treatment.

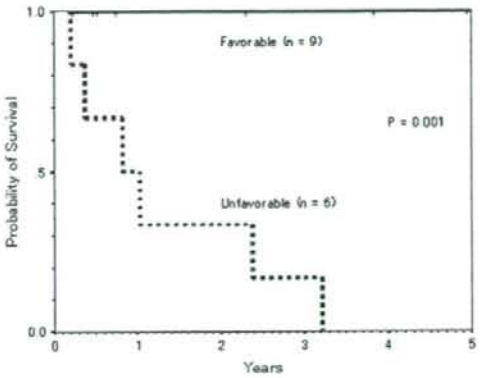

Fig. 2. Actuarial disease-free survival rates from the beginning of salvage treatment according to the presence of intracranial recurrence and treatment modality in patients with intracranial germinoma who developed spinal recurrences.

(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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CLINICAL INVESTIGATION **Lung**

STEREOTACTIC BODY RADIOTHERAPY FOR PRIMARY LUNG CANCER AT A DOSE OF 50 GY TOTAL IN FIVE FRACTIONS TO THE PERIPHERY OF THE PLANNING TARGET VOLUME CALCULATED USING A SUPERPOSITION ALGORITHM

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Purpose: To retrospectively analyze the clinical outcomes of stereotactic body radiotherapy (SBRT) for patients with Stages 1A and 1B non–small-cell lung cancer.

Methods and Materials: We reviewed the records of patients with non–small-cell lung cancer treated with curative intent between Dec 2001 and May 2007. All patients had histopathologically or cytologically confirmed disease, increased levels of tumor markers, and/or positive findings on fluorodeoxyglucose positron emission tomography. Staging studies identified their disease as Stage 1A or 1B. Performance status was 2 or less according to World Health Organization guidelines in all cases. The prescribed dose of 50 Gy total in five fractions, calculated by using a superposition algorithm, was defined for the periphery of the planning target volume.

Results: One hundred twenty-one patients underwent SBRT during the study period, and 63 were eligible for this analysis. Thirty-eight patients had Stage 1A (T1N0M0) and 25 had Stage 1B (T2N0M0). Forty-nine patients were not appropriate candidates for surgery because of chronic pulmonary disease. Median follow-up of these 49 patients was 31 months (range, 10–72 months). The 3-year local control, disease-free, and overall survival rates in patients with Stages 1A and 1B were 93% and 96% ($p = 0.86$), 76% and 77% ($p = 0.83$), and 90% and 63% ($p = 0.09$), respectively. No acute toxicity was observed. Grade 2 or higher radiation pneumonitis was experienced by 3 patients, and 1 of them had fatal bacterial pneumonia.

Conclusions: The SBRT at 50 Gy total in five fractions to the periphery of the planning target volume calculated by using a superposition algorithm is feasible. High local control rates were achieved for both T2 and T1 tumors.

Stereotactic body radiotherapy, Lung cancer, Superposition algorithm.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) for patients with early non–small cell lung cancer (NSCLC) is now being investigated in prospective studies (1, 2). Historically, numerous clinical trials of lung tumor treatment were carried out with dose calculation by using the Clarkson algorithm or without heterogeneity correction.

We have carried out SBRT since 2001 with dynamic conformal arc therapy calculated by using the multigrid (MG) superposition algorithm (3). In this retrospective study, we analyzed the clinical outcomes of patients with Stage 1 NSCLC who were irradiated with a dose of 50 Gy total in five fractions to the periphery of the planning target volume (PTV), calculated by using the superposition algorithm.

METHODS AND MATERIALS

Eligibility criteria

The retrospective study population consisted of patients who had undergone SBRT with intent to cure at either the Tokyo Metropolitan Hiroo General Hospital (Tokyo, Japan; from Dec 2001 to Nov 2004) or the Ofuna Chuo Hospital (Kamakura, Japan; from Feb 2005 to May 2007).

All patients underwent appropriate staging studies identifying their disease as Stage IA or IB. Histopathologic or cytologic confirmation of cancer was required by using either biopsy or cytologic examination in Group A. For cases without histopathologic or cytologic confirmation, *i.e.*, Group B, tumor marker level increase or standardized uptake value positivity on fluorodeoxyglucose positron emission tomography (FDG-PET) was required. As a tumor marker, we monitored carcinoembryonic antigen (<5.0 ng/mL), carbohydrate antigen 19–9 (<40 U/mL), sialyl lex-i antigen (<40

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U/mL), squamous cell carcinoma related antigen CYFRA cytokeratin 19 fragment (<1.5 ng/mL), and CYFRA (<3.4 ng/mL) levels. In all subjects, performance status was 2 or less according to World Health Organization guidelines. Patients with previous radiation to the lung or mediastinal region were excluded.

Treatment methods

Our techniques for immobilization and planning have been described in detail (4–6). We performed 10-arc dynamic conformal stereotactic radiotherapy with or without additional static conformal ports. The three-dimensional radiation treatment planning system (XiO, Version 4.2 or 4.3; CMS, St. Louis, MO) was used at both institutions. Radiation doses were calculated by using an MG-superposition algorithm with heterogeneity correction. The prescribed dose was 10 Gy/fraction × five (50 Gy total) to the PTV periphery. Gross tumor volume was defined as the visible tumor on computed tomography (CT) images using a CT number window level of −600 and width of 1,500. All series equated the gross tumor volume to the clinical target volume (CTV). To account for breathing motion–induced changes in tumor position, a long-scan-time CT (LSTCT; 6–8 s/slice) was performed to delineate the internal target volume (ITV) directly (5). For the PTV, individualized treatment margins of 6–8 mm were applied around the ITV. The treatment dose was prescribed to the periphery of the PTV, which corresponded to 80% of the maximum dose (Fig. 1).

Evaluation

All patients were followed up monthly on an outpatient basis with chest X-ray examinations during the first 6 months. Follow-up CT scans were performed at 1 and 3 months after SBRT and thereafter at 3-month intervals during the first 2 years, even in the absence of clinical symptoms. Subsequently, follow-up interviews and CT scans were obtained at 4–6-month intervals. Our follow-up procedures were previously described in detail (6). If there was a possibility that local treatment or systemic therapy would be required for suspected tumor recurrence, FDG-PET was performed to assess the extent of locally recurrent lesions and detect distant metastases. Biopsy or surgery was performed, if necessary. Toxicity was graded using Version 3 of the National Cancer Institute-Common Toxicity Criteria.

Statistical analysis

Follow-up started from the date of the first SBRT to determine median follow-up and time-to-event estimates as outcome data. Control and survival rates were calculated by using Kaplan-Meier analysis with SPSS 15.0 (SPSS Inc., Chicago, IL). Log-rank test was used to compare control or survival between the subsets of patients analyzed. Differences were regarded as statistically significant at $p < 0.05$.

RESULTS

One hundred twenty-one patients with primary NSCLC were treated with SBRT. Eight of these patients were treated without histopathologic or cytologic confirmation, tumor marker level increase, or positive findings on FDG-PET. Twenty-eight patients were treated for postoperative recurrence or with palliative intent, and 31 were treated on an irregular schedule (*i.e.*, reduced total dose of 40 Gy or 10 fractions) because their tumors were located in the central lung or near critical organs or because of poor pulmonary function. Therefore, 63 patients were included in this analysis and 58 were excluded. Patient characteristics are listed in Table 1. In Groups A and B, 30 and 8 patients had Stage 1A, and 22 and 3 had Stage 1B, respectively. Forty-nine patients were not appropriate candidates for surgery because of chronic pulmonary disease, advanced age, or other chronic illnesses, whereas the remaining 14 were surgical candidates but had chosen SBRT although their physicians and the authors fully explained that surgery is the standard therapy for these stages.

Median follow-up for the 49 living patients was 31 months (range, 10–72 months). Local recurrence developed in 2 Group A and 1 Group B patient. The 3-year local control, regional recurrence-free, distant metastasis-free, and disease-free survival rates in patients with Stages 1A and 1B were 93% and 96% ($p = 0.86$; Fig. 2), 82% and 94% ($p = 0.37$), 87% and 89% ($p = 0.35$), and 76% and 77% ($p = 0.83$; Fig. 3), respectively.

The 3-year overall survival (OAS) rates were 90% and 63% ($p = 0.09$; Fig. 4), and 3-year cause-specific survival (CSS) rates were 100% and 81% ($p = 0.10$; Fig. 5) in patients with Stages 1A and 1B, respectively. The 3-year OAS rates

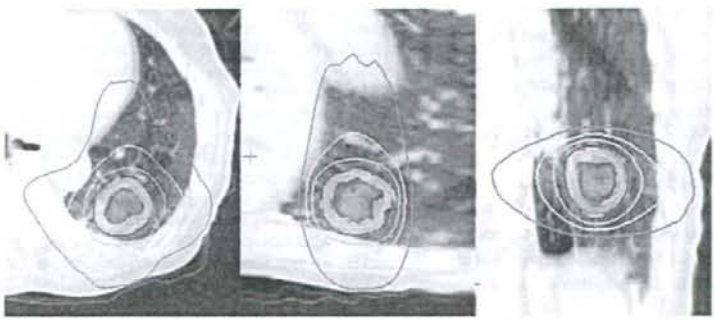

Fig. 1. Axial, sagittal, and coronal images of treatment planning computed tomography (CT). The inner area enclosed by a bold line corresponds to the internal target volume (ITV) directly visualized by long-scan-time CT. The outer area enclosed by a bold line corresponds to the planning target volume derived from the ITV and a 6–8mm margin. The isodose lines from outer to inner represent 20%, 40%, 60%, and 80% of the maximal dose.

Table 1. Patient and tumor characteristics

	Group A	Group B
Patients (*n*)	52	11
Age (y)	78 (56–91)	78 (66–87)
Gender		
Men	32	8
Women	20	3
Operability		
Operable	13	1
Inoperable	39	10
T Classification		
T1	30	8
T2	22	3
Histologic type		
Adenocarcinoma	35	
Squamous cell cancer	14	
Unclassified NSCLC	3	
Tumor marker		4
SUV positive		9

Abbreviations: NSCLC = non–small-cell lung cancer; SUV = standardized uptake value.

were 91% and 77% ($p = 0.31$), and the 3-year CSS rates were 91% and 94% ($p = 0.66$) in operable and inoperable patients, respectively. Eight and five recurrences were identified in patients with Stage 1A and Stage 1B, respectively (Fig. 6).

All patients were treated, and no acute toxicity was observed. Grades 2 and 3 radiation pneumonitis were identified in 1 and 2 patients, respectively. The Grade 2 pneumonitis occurred 4 months after SBRT; the patient was given oral steroid therapy, and pneumonitis resolved by 6 months. One of the patients with Grade 3 who developed pneumonitis 1 month after SBRT was given oral steroid therapy and pneumonitis resolved by 6 months. In the remaining patient, pneumonitis developed 3 months after SBRT. Although oral steroid and oxygen therapies initially provided relief, the patient developed fatal bacterial pneumonia 8 months after SBRT at the site of radiation pneumonitis. We considered SBRT to have possibly contributed to the events leading to the death (Grade 5).

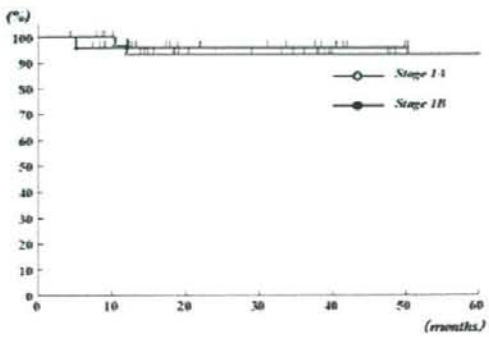

Fig. 2. Local control rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

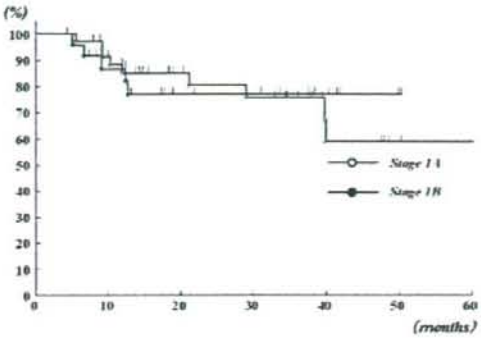

Fig. 3. Disease-free rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

DISCUSSION

A number of prospective Phase II studies have been conducted exploring SBRT treatment of patients with lung tumors. In the Radiation Therapy Oncology Group (RTOG) 0236 study of patients with inoperable primary lung cancer, the prescribed dose was 60 Gy in three fractions at the PTV periphery (2). In the Japan Clinical Oncology Group (JCOG) 0403 protocol, the total dose of 48 Gy at the isocenter in four fractions was prescribed for patients with T1N0M0 primary lung cancer (1).

Relationship between tumor size and total SBRT dose

Some reports (7–9) have shown the local control rate of T1 tumors to be significantly higher than that of T2 tumors with SBRT. Baumann *et al.* (7) treated 141 patients with 30–48 Gy/two to four fractions. They found local failure to be more frequent for T2 (13%) than T1 tumors (3%). Onimaru *et al.* (8) treated 41 patients with 40 Gy/four fractions or 48 Gy/four fractions. A significant difference was seen in local control between patients with T1 and T2 tumors and between 40 and 48 Gy. They also showed a significant difference in

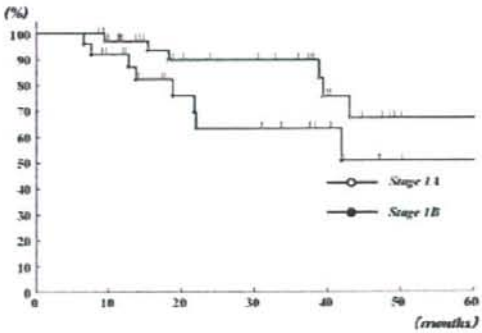

Fig. 4. Overall survival rates for patients with Stages 1A ($n = 38$) and 1B ($n = 25$) treated with stereotactic body radiotherapy.

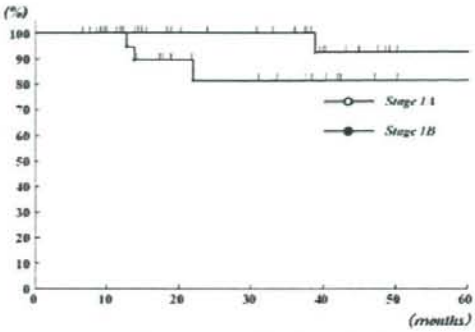

Fig. 5. Cause-specific survival rates for patients with Stages 1A (n = 38) and 1B (n = 25) treated with stereotactic body radiotherapy.

local control between 40 and 48 Gy in patients with Stage IB, but not those with Stage IA. Koto *et al.* (9) treated patients with 45 Gy/three fractions or 60 Gy/eight fractions. The 3-year local control rates were 77.9% (T1) and 40.0% (T2). However, the 3-year local control rate was as high as 96% for both T1 and T2 tumors in our series. These findings suggest that higher doses may contribute to better local control.

Analysis of the biologically effective dose

Table 2 lists methods, treatment factors, and results obtained in this analysis. The biologically effective dose assuming α/β ratios of 10 Gy (BED10) for 50 Gy total in five fractions was 141 Gy. A Japanese multi-institutional retrospective survey showed that a BED10 greater than 100 Gy resulted in significantly better survival and local control than a BED10 less than 100 Gy when SBRT was used to control Stage I NSCLC (10). The range of BED10 in the studies by Onimaru *et al.* (8) and Koto *et al.* (9), which suggested different control rates by tumor volumes, as mentioned, were 80–106 Gy and 105–113 Gy, respectively. These results suggested their treatment regimens to be effective in patients with T1 tumors, while failing to provide adequate control of T2 tumors. Therefore, a BED10 of 100 Gy seems sufficient to control T1 tumors. However, a BED10 greater than 120 Gy, possibly as high as 140 Gy, may be required to control T2 tumors.

PTV definition

Other factors that influence local control are the definition of PTV and the calculation algorithm used. In planning CT, we directly delineate the visualized ITV on an LSTCT (6–8 s/slice) with respiratory motion reduced to less than 10 mm with or without abdominal pressure (5). Recently, we delineated the visualized ITV on a maximum intensity projection image fused with planning CT for more precise visualization (11). Then we added 6–8 mm as a margin to generate the PTV. We adjusted the dose distribution to ensure that 80% of the maximum dose encompassed the PTV. As a result, a prescribed dose of 50 Gy total in five fractions to the

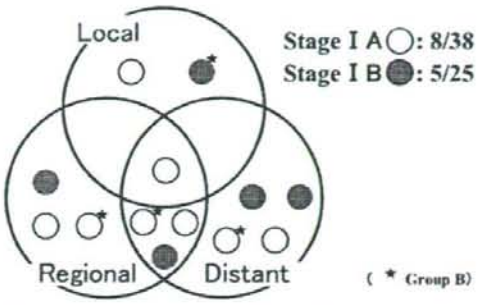

Fig. 6. Recurrence distribution. Eight and five recurrences were identified in patients with Stages 1A (n = 38; white circle) and 1B (n = 25; black circle), respectively. Two (one each, Stages 1A and 1B) were only local recurrences. Three (Stage 1A, one; Stage 1B, two) were only regional recurrences. Four (Stage 1A, two; Stage 1B:, two) were only distant metastases. Three (Stage 1A, two; Stage 1B, one) had combinations of regional recurrence and distant metastases. The other patient (Stage 1A) had combinations of local, regional, and distant recurrence or metastasis. Circles with * indicate cases without pathologic confirmation (Group B).

PTV periphery essentially corresponds to D95 (the minimal dose delivered to 95% of the target volume; data not shown). Giraud *et al.* (12) showed that the CTV margin must be increased to 8 and 6 mm for adenocarcinoma and squamous cell carcinoma to cover 95% of microscopic extension, respectively. However, in our series, the ITV visualized by using LSTCT or maximum intensity projection does not include a CTV margin. We use a CT scanner and a linear accelerator installed in the same treatment suite that share a common table/couch (13). For every treatment, we identify the isocenter position by means of LSTCT with a 2-mm thickness and 1-mm pitch and set it to the isocenter position of the linear accelerator automatically. Therefore, setup error is very small. We then add 6–8 mm as a CTV margin plus a setup margin to the ITV to generate the PTV.

Calculation algorithm and SBRT

In previous SBRT studies, tissue heterogeneity has often not been accounted for during dose calculation. Heterogeneity correction was not used in RTOG 0236 (2). Recently, the RTOG physics committee released recommendations for appropriately accounting for heterogeneity in a planning system. The RTOG 0618 will require calculation taking heterogeneity into account. In the JCOG 0403 study, tissue heterogeneity was accounted for in the dose calculation, and the Clarkson or convolution algorithm was used. However, novel algorithms using the dose kernel of model-based calculation with shapes expanded to correspond with heterogeneity around the calculation point, such as the superposition algorithm, lead to more precise simulation than conventional algorithms (14, 15).

Haedinger *et al.* (16) compared the pencil-beam and collapsed-cone (CC) algorithms for SBRT. They showed that

Table 2. Protocols for stereotactic body radiotherapy

	Our Study	RTOG0236 (2)	JCOG0403 (1)	Onimaru *et al.* (8)	Koto *et al.* (9)
n	63	—	—	41	31
Prescribed dose (Gy/fractions)	50/5	60/3	48/4	40–48/4	45/3; 60/8
Reference point	PTV periphery	PTV periphery	Isocenter	Isocenter	Isocenter
Calculation algorithm	SP	PB	CL/Conv	CL/SP	BPL
Heterogeneity	Yes	No	Yes	Yes	Yes
Dose at isocenter (Gy/fractions)	62.5/5	67–100/3	48/4	40–48/4	45/3; 60/8
BED10 at isocenter	141	211–426	106	80–106	113/105
3-y LC in T1 (%)	93	—	—	67	78
3-y LC in T2 (%)	96	—	—	31	40

Abbreviations: RTOG = Radiation Therapy Oncology Group; JCOG = Japan Clinical Oncology Group; PTV = planning target volume; BED10 = biologically effective dose assuming α/β ratios of 10 Gy; LC = local control; SP = superposition; PB = pencil-beam; CL = Clarkson; BPL = Batho power low; Conv = convolution.

the average PTV dose coverage decreased by 7.1% and the monitor units calculated to achieve the prescribed dose were 5.4% greater with the CC algorithm. Kunieda *et al.* (17), studying nine small lung tumors, showed that the isocenter dose obtained by using the Fast Fourier Transform convolution algorithm was 7–12% higher than the dose obtained by using the MG-superposition algorithm.

Fogliata *et al.* (15) indicated that algorithms based on pencil-beam convolutions showed a systematic deficiency in managing the presence of heterogeneous media. Conversely, "advanced" algorithms in which electron transport is considered indicated good agreement with respect to the Monte Carlo simulation observed. In particular, CC and MG-superposition indicated fairly similar results for the normal lung model. The MG-superposition for XiO is substantially a CC algorithm implementing a speed utility in which the convolution is performed on a coarse grid when no gradients in density of fluence are present (3, 15).

Miften *et al.* (18) reported that the MG-superposition model predicts a dose closer to that of the Monte Carlo simulation, and it estimates the dose build-down and build-up near tissue interfaces and penumbra broadening more precisely than the Clarkson model (18), which overestimates the dose in the lung. Therefore, the actual doses at the PTV periphery are underestimated when calculated using the Clarkson algorithm, and this may result in inadequate dose distribution at the PTV periphery. In the MG-superposition algorithm, a density-scaling method based on O'Connor's theorem (19) is used to scale the kernels by calculating the average density along the straight-line path between the dose deposition and the interaction voxels (3). However, differences in the calculated dose of 10% or more among various algorithms have been reported (14, 20). For this reason, the MG-superposition algorithm is preferred to the Fast Fourier Transform convolution or Clarkson algorithm, which can result in underdosage of the lung tumor by almost 10% (3, 14, 18).

We have used the MG-superposition algorithm for the XiO radiation treatment planning system in planning SBRT of the lung since 2001. Our protocol involves prescribing a dose to the periphery of the PTV. Therefore, the dose we administered was apparently higher than the corresponding dose calculated by using the Clarkson algorithm, and the dose distribution at the PTV periphery is more sufficient.

Dose–volume and toxicity in SBRT

Radiation pneumonitis higher than Grade 1 was observed in 3 patients (5%) in this series. The toxicity rate was low (10, 21, 22), and SBRT seemed to be feasible. However, 1 patient developed fatal bacterial pneumonia associated with radiation pneumonitis. Four patients in the study by Timmerman *et al.* (2) also experienced fatal bacterial pneumonia, and they concluded that their regimen should not be used for patients with tumors near the central airways because of excessive toxicity. In the patient with Grade 5 toxicity in our study, a tumor 5.3 cm in diameter was located at the periphery of the left segment 6 and showed extensive attachment. We speculate that this was a relatively large tumor located not far from the central area, which might have caused the fatal toxicity.

Survival in Stage I primary lung cancer

The 3-year OAS and CSS rates were 90% and 100% in patients with Stage 1A and 63% and 81% in patients with Stage 1B. The 3-year OAS and CSS rates in operable patients were 91% and 91%, and those in inoperable patients were 77% and 94%, respectively. In the study by Nagata *et al.* (23), the 3-year OAS rates in patients with Stages 1A and 1B were 83% and 72%, respectively. In the study by Uematsu *et al.* (24), the respective 3-year OAS rates in patients with Stage 1 and operable patients were 66% and 86%. In the investigation conducted by Onishi *et al.* (10), the 3-year OAS rate in patients with a BED10 greater than 100 was 88%. These SBRT results are consistent among different studies. Conversely, The Japanese Joint Committee of Lung Cancer Registry investigated prognosis in 6,644 patients who underwent resection for non–small-cell cancer histologic type (25). The 5-year survival rates for patients with clinical Stages 1A (n = 2,423) and 1B (n = 1,542) were 72% and 50%, and the 3-year survival rates for those with clinical Stages 1A (n = 2,423) and 1B (n = 1,542) were 82% and 63%, respectively. According to these results, the outcomes of SBRT may be equivalent to those of surgery. Of course, longer follow-up and more experience with SBRT are needed. In conducting prospective trials comparing survival in operable patients undergoing

SBRT vs. surgery, many other factors will be considered, including pain, length of hospital stay, cost-effectiveness, recurrence site, and salvage therapy with local and systemic therapy.

Significance of omission of mediastinal treatment in SBRT

The role of mediastinal lymph node dissection (MLND) in the staging and treatment of patients with NSCLC remains controversial. In a prospective randomized trial, significantly higher survival rates after MLND were indicated in comparison to mediastinal lymph node sampling in patients with Stage 1 NSCLC (82% vs. 57%) (25). Conversely, Izbicki *et al.* (26, 27) reported that MLND did not influence disease-free survival or OAS in patients with NSCLC. A randomized breast cancer study found that internal mammary node (IMN) removal did not improve survival. The IMN dissection confirmed IMN metastases in 20.5% of patients. However, only 4% of patients had IMN recurrence in the no-dissection group (28, 29).

In SBRT, we ruled out mediastinal lymph node involvement by using enhanced CT and PET-CT. However, the respective accuracy, sensitivity, and specificity of CT were reported to be 70%, 69%, and 69%, and even those of PET/CT were only 85%, 84%, and 84% for evaluating preoperative nodal staging (30). Konaka *et al.* (31) retrospectively reviewed data from 171 patients undergoing resection of peripheral clinical T1N0M0 carcinoma smaller than 2 cm in diameter. Lymph node metastases were noted in 18% of patients (6% N1, 12% N2) and were more frequently associated with tumors 1.5–2.0 cm than with those less than 1.5 cm in diameter (31). Therefore, more frequent mediastinal metastasis was suspected in patients with clinical T2N0M0. In our study, 3-year regional recurrence-free rates in patients with Stages 1A and 1B were 82% and 94%, respectively. After a longer follow-up, more frequent hilar and mediastinal metastasis may occur. Therefore, we must pay close attention to future results, keeping in mind that pathologic metastasis does not always induce visible metastasis, as in the study of IMN dissection in patients with breast cancer (28, 29).

Diagnosis of primary lung cancer and indications for SBRT

We analyzed 11 patients without histopathologic or cytologic confirmation who were given a diagnosis of primary lung cancer based on tumor marker level increase and/or standardized uptake value positivity on FDG-PET (Group B). In Group B, local recurrence alone, regional recurrence alone, both regional and distant metastasis, and distant metastasis alone occurred in 1 patient each. One patient died of primary lung cancer. These rates were not substantially different from those of Group A. However, indications for SBRT in patients lacking histopathologic or cytologic confirmation are controversial. In Group B patients, we attempted transbronchoscopic lung biopsy and/or CT-guided biopsy, but were unable to confirm the malignancy because of failure to obtain an adequate biopsy specimen. Currently, the numbers of very early-stage lung cancers detected by means of CT screening are increasing (32). They include small and ground glass opacity lesions, which are difficult to confirm by means of biopsy. Lagerwaard *et al.* (33) reported outcomes of SBRT for patients with Stage 1 NSCLC. Pathologic confirmation of malignancy was obtained in only 31% of their patients. Patients lacking pathologic confirmation were required to have a new or growing lesion that showed CT characteristics of malignancy and FDG-PET uptake before being accepted for SBRT, and the probability of malignancy was calculated retrospectively (34, 35). Methods of diagnosis or criteria for identifying primary lung cancer other than histopathologic or cytologic confirmation may be needed in the future.

CONCLUSION

The SBRT for primary lung cancer with a dose of 50 Gy total in five fractions to the periphery of the PTV calculated by using a superposition algorithm is feasible. The results of this study indicate that high local control rates are achievable for T2 and T1 tumors and the 3-year OAS rate with SBRT may be equivalent to that of surgery.

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BRACHYTHERAPY

Prediction of seed migration after transperineal interstitial prostate brachytherapy with I-125 free seeds

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ABSTRACT

PURPOSE: The present study was undertaken to determine the incidence and predictors of seed migration after transperineal interstitial prostate brachytherapy using I-125 free seeds.

METHODS AND MATERIALS: Between September 2004 and November 2007, 158 patients who underwent transperineal interstitial prostate brachytherapy as monotherapy for clinical T1/T2 carcinoma of the prostate gland were reviewed. Implants had been performed with standard techniques. All 158 patients underwent followup radiographs (orthogonal chest radiographs, a kidney–ureter–bladder radiograph, and a posteroanterior pelvic radiograph) to assess the presence of seed migration at 3 months after transperineal interstitial prostate brachytherapy. Patient characteristics and treatment status were recorded. Univariate and multivariate analyses were performed to identify predictors of seed migration.

RESULTS: Seed migration occurred in 35 of 158 patients (22.2%). Univariate analyses revealed that preoperative prostate volume estimated by transrectal ultrasound, the number of needles, the number of seeds implanted, and the presence or absence of pubic arch interference (PAI) were significantly associated with seed migration. These results indicated that larger prostate glands were more likely to have seed migration. However, the absolute difference in prostate size was not overly impressive (22.4 vs. 26.3 cm^3). Multivariate analysis revealed that the number of seeds implanted and the presence or absence of PAI were significant predictors of seed migration.

CONCLUSION: The number of seeds implanted and the presence or absence of PAI provide the most predictive information on seed migration.

Keywords: Brachytherapy; I-125; Migration; Prostate cancer; Seed

Introduction

Seed migration is a common side effect of transperineal interstitial prostate brachytherapy (1–6). The incidence of seed migration is reported to be between 0.7% and 55%, and the most frequent site of seed migration is the lung (1–4). Pulmonary seed migration is thought to occur by a mechanism in which seeds implanted or eroded into the periprostatic venous plexus migrate hematogeneously to the iliac veins, right heart, and finally the lungs.

Seed migration has some potential adverse effects. For example, a decreased dose to the prostate due to a great loss of radioactive seeds from their intended position could be possible (7). Seed embolization could have a serious effect on various organs, such as the heart (2, 3). There may be a risk of developing a secondary malignancy, such as lung cancer, after radioactive seed embolization. Although no cases of a secondary malignancy after radioactive seed embolization have been reported to our knowledge, the followup period has not been long enough to draw any conclusions.

To avoid these potential adverse effects, it is important to predict the occurrence of seed migration and to reduce its incidence after transperineal interstitial prostate brachytherapy. The present study was undertaken to determine the incidence and predictors of seed migration after transperineal interstitial prostate brachytherapy using I-125 free seeds.

Methods and materials

From September 2004 to November 2007, 159 consecutive patients underwent transperineal interstitial prostate

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