先－３（別　紙）
２４．１．１９

前回改定時の陽子線治療及び重粒子線治療の評価

１．先進医療専門家会議での検討

(1) 評価結果

・悪性腫瘍に対する陽子線治療（固形がんに係るものに限る。）

一次評価結果　総合Ｃ

二次評価結果　先進医療として継続することが妥当

・重粒子線治療（固形がんに係るものに限る。）

一次評価結果　総合Ｃ

二次評価結果　先進医療として継続することが妥当

(2) 課題

①有効性・効率性

・前立腺がん、肺がん、頭頸部がん、肝がん等については、手術等の有効な既存治療も存在するが、これらの既存治療との比較検討結果は示されていない。

・近年普及しつつある IMRT 等の放射線治療との比較が十分に検討されていない。

②技術的成熟度

・放射線治療の専門医等が不足している。また、人材育成を促進した場合も、より普及性の高い IMRT 等と競合する可能性がある。

③普及性

・巨額な建設費を伴う施設の適正配置等、国内整備の在り方に関して更なる検討が必要。

２．中医協での検討

・中医協総会（平成 22 年 1 月 20 日）

先進医療専門家会議での評価結果を踏まえ、保険導入について検討を行ったが、有効性、安全性に加え、効率性等についてもさらなる検討を求める意見が示された。

・中医協総会（平成 22 年 1 月 27 日）

当該技術の実施状況等（参考資料１）を踏まえさらなる検討を行った結果、先進医療で継続することとされた。

３．実施状況

・実施件数推移

件数/年	18 年	19 年	20 年	21 年	22 年	23 年
陽子線	533	678	611	821	1225	1508
重粒子線	453	557	634	779	729	873

・実施施設等で得られたエビデンス（参考資料２）

個々の医療技術が保険適用されるまでの基本的な流れ

臨床研究
研究データの蓄積

通常、保険診療との併用が不可（自由診療）

医療機関からの提案

関係学会
○学会内で合意形成
○要望とりまとめ

関係学会からの提案

先進医療専門家会議
○有効性や安全性等の観点で検討し、総合評価として適否を判断
○安全な実施のため、施設基準を設定

先進医療
保険診療との併用が可能※

○実施医療機関でのデータ蓄積
○定期的な実績報告

（中医協　調査専門組織）
医療技術評価分科会
保険適用の是非について議論

先進医療専門家会議
保険適用の是非について議論

報告

報告

中医協
個々の医療技術の保険導入・点数設定について議論

診療報酬改定

すべて保険適用

保険診療

先進医療専門家会議における粒子線治療に関する検討について

粒子線治療は、陽子線治療が平成 13 年から、重粒子線治療が平成 15 年から保険との併用が承認され、現在はともに先進医療として実施されている。

平成 22 年度診療報酬改定に合わせて、他の技術と同様に、保険導入の適否を含めた再評価が行われた結果、「先進医療として継続することが妥当」と判断された。

検討の概要は以下の通り。

１．現状

（１）粒子線治療は、骨軟部腫瘍、小児がん、悪性黒色腫、前立腺がん、肺がん、頭頸部がん、肝がん等について良好な治療成績を収めている。特に、骨軟部腫瘍、小児がん、悪性黒色腫、頭蓋底腫瘍等については、従来の治療法より成績が良好とされている。

（２）１施設当たりの年間症例数は、陽子線 約 160 件、重粒子線 約 400 件であり※1、着実に増加している。 （※１ 平成 21 年度実績報告より）

（３）実施医療機関は、陽子線 ５施設、重粒子線 ２施設に限られている。

（４）先進医療に係る費用（自己負担）は、１患者につき約 300 万円にのぼる。

２．課題

（１）有効性・効率性

①前立腺がん、肺がん、頭頸部がん、肝がん等については、手術等の有効な既存治療も存在するが、これらの既存治療との比較検討結果は示されていない。

②近年普及しつつある IMRT※2等の放射線治療との比較が十分に検討されていない。

※２ 強度変調放射線治療。腫瘍病巣に最適な線量を照射し、正常組織への線量を大幅に低減することができる照射技術。

（２）技術的成熟度

放射線治療の専門医等が不足している。また、人材育成を促進した場合も、より普及性の高い IMRT 等と競合する可能性がある。

（３）普及性

巨額な建設費を伴う施設の適正配置等、国内整備の在り方に関して更なる検討が必要。

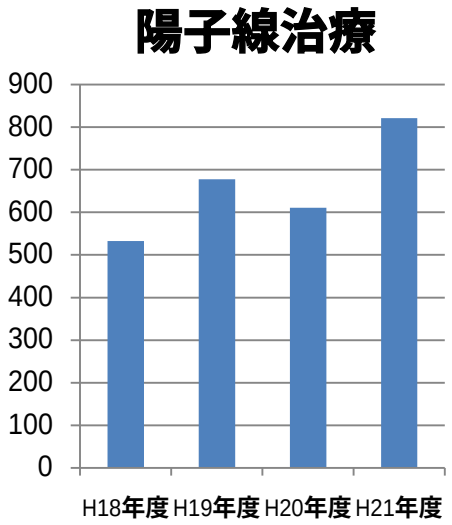
３．評価結果

保険導入については、上記のような課題を踏まえた更なる検討が必要と判断され、粒子線治療については「先進医療として継続することが妥当」と判定された。

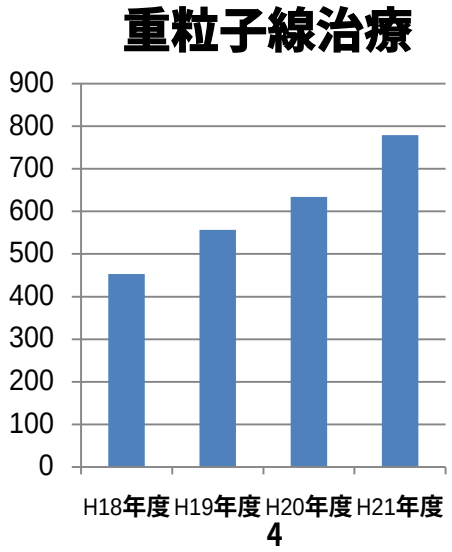
粒子線治療の現況について
(参考資料)

先進医療における粒子線治療の実績

陽子線治療	20年度 (H20.6.30時点)	21年度 (H21.6.30時点)
実施施設数	3施設	5施設
年間実施件数	611件	821件
1件当たり先進医療費用	2,850,879円	2,756,454円
1件当たり保険外併用療養費	215,457円	319,037円



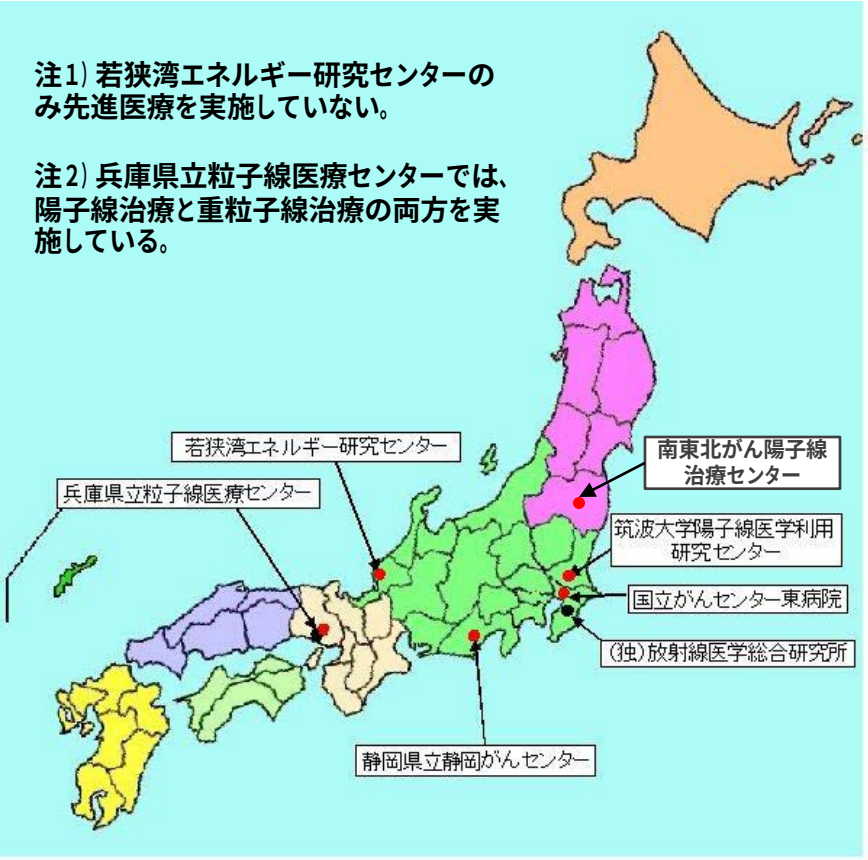
重粒子線治療	20年度 (H20.6.30時点)	21年度 (H21.6.30時点)
実施施設数	2施設	2施設
年間実施件数	634件	779件
1件当たり先進医療費用	3,080,412円	3,023,297円
1件当たり保険外併用療養費	410,507円	341,538円



国内の粒子線施設の現況

注1）若狭湾エネルギー研究センターのみ先進医療を実施していない。

注2）兵庫県立粒子線医療センターでは、陽子線治療と重粒子線治療の両方を実施している。



平成２１年11月時点
出典：(財) 医用原子力技術研究振興財団
http://www.juryushi.org/hospital_jpn/hospital.html
(一部改変)

先進医療実施医療機関 (平成22年1月現在)

陽子線治療	千葉県	国立がんセンター東病院
	兵庫県	兵庫県立粒子線医療センター
	静岡県	静岡県立静岡がんセンター
	茨城県	筑波大学附属病院
	福島県	(財) 脳神経疾患研究所附属南東北がん陽子線治療センター
重粒子線治療	千葉県	(独) 放射線医学総合研究所・重粒子医科学センター病院
	兵庫県	兵庫県立粒子線医療センター

(参考) 建設中の施設一覧

陽子線治療	福井県	福井県陽子線がん治療センター (仮称)
	鹿児島県	がん粒子線治療研究センター
重粒子線治療	群馬県	群馬大学重粒子線医学研究センター

先進医療の施設基準

告示番号３３　重粒子線治療（固形がんに係るものに限る。）の施設基準

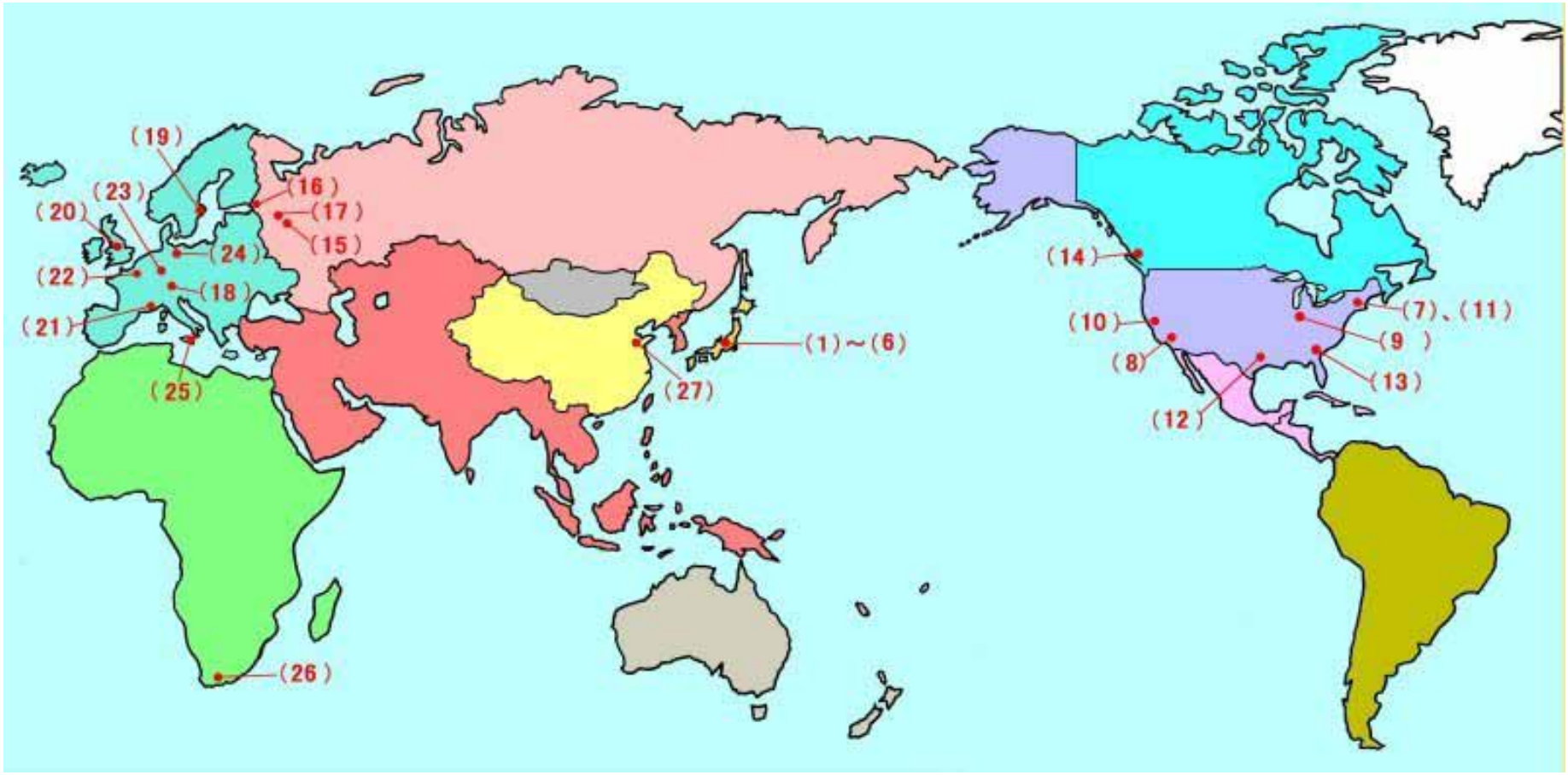
イ　主として実施する医師に係る基準

(1) 専ら放射線科に従事し、当該診療科について十年以上の経験を有すること。
(2) 放射線科専門医であること。
(3) 当該療養について二年以上の経験を有すること。
(4) 当該療養について、当該療養を主として実施する医師又は補助を行う医師として十例以上の症例を実施しており、そのうち当該療養を主として実施する医師として五例以上の症例を実施していること。

ロ　保険医療機関に係る基準

(1) 放射線科を標榜していること。
(2) 実施診療科において、常勤の医師が二名以上配置されていること。
(3) 診療放射線技師が配置されていること。
(4) 医療機器保守管理体制が整備されていること。
(5) 倫理委員会が設置されており、必要なときは必ず事前に開催すること。
(6) 医療安全管理委員会が設置されていること。
(7) 当該療養について十例以上の症例を実施していること。

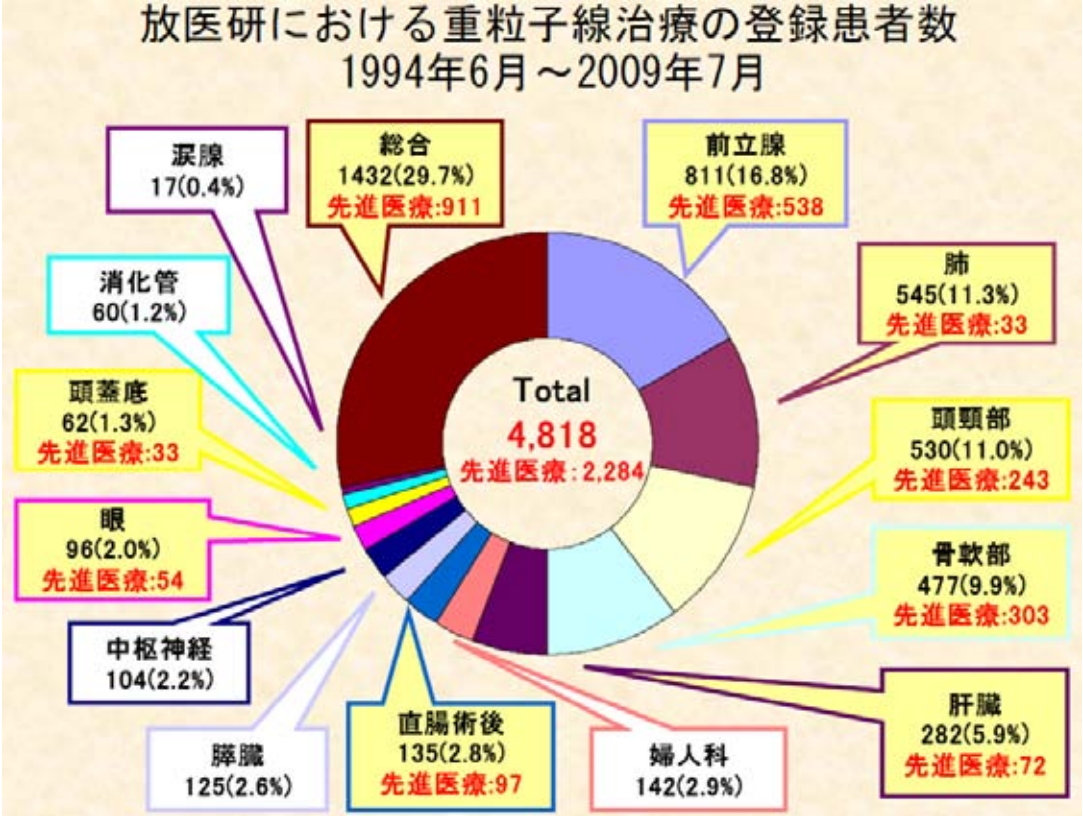
海外の粒子線施設の現況



平成20年2月時点

平成21年11月時点
出典：(財) 医用原子力技術研究振興財団
http://www.juryushi.org/hospital_jpn/hospital.html

重粒子線治療の対象となっているがんの種類



http://www.nirs.go.jp/hospital/result/pdf/200907.pdf

先進医療の実績報告にみられる主ながん種※

- 前立腺がん　約160例
- 肝がん　約120例
- 肺がん　約80例

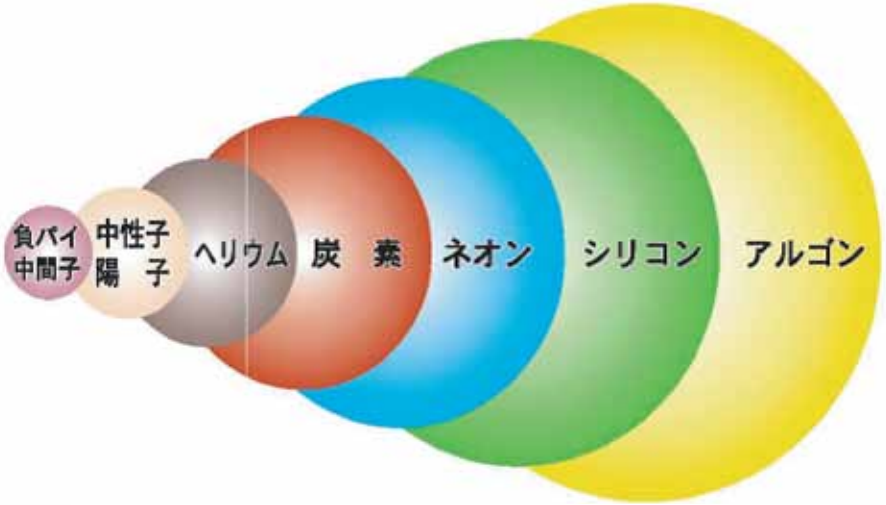
注1）20年7月1日～21年6月30日の期間を対象とした実績報告における症例数。

注2）当該期間の報告症例数は計779症例。

※ 固形がんであれば、先進医療として保険併用が可能。
（現行の先進医療では、がんの種類について特段の限定をしていない）

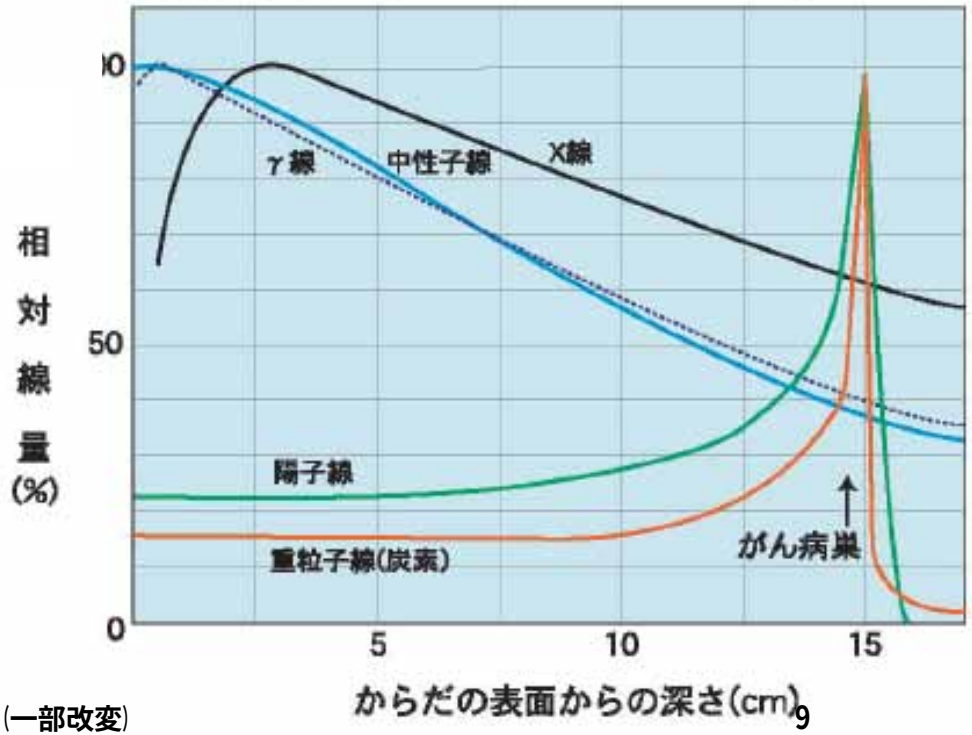
【参考】粒子線治療とは

■粒子の大きさ



電子よりも重い粒子を加速器で高速に加速したものを重粒子線という。重粒子線は、中性子線、陽子線、重イオン（炭素、ネオン等のイオン）線等に分けられる。

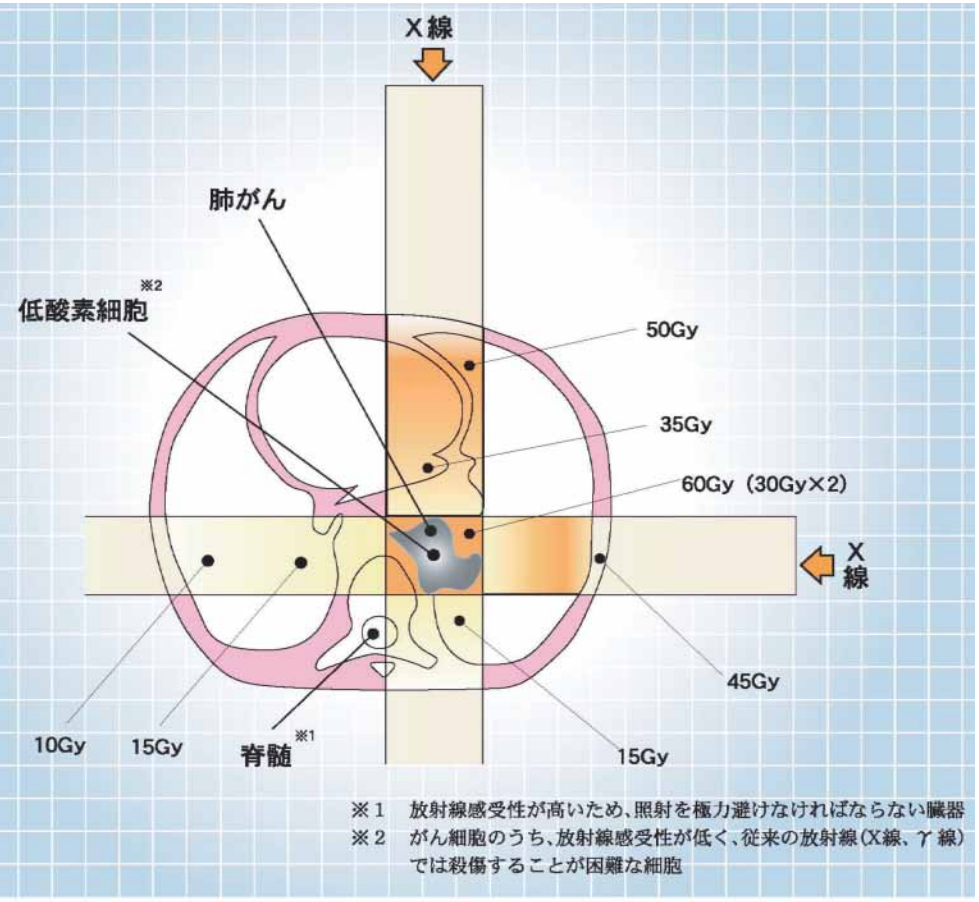
■各種放射線の生体内における線量分布



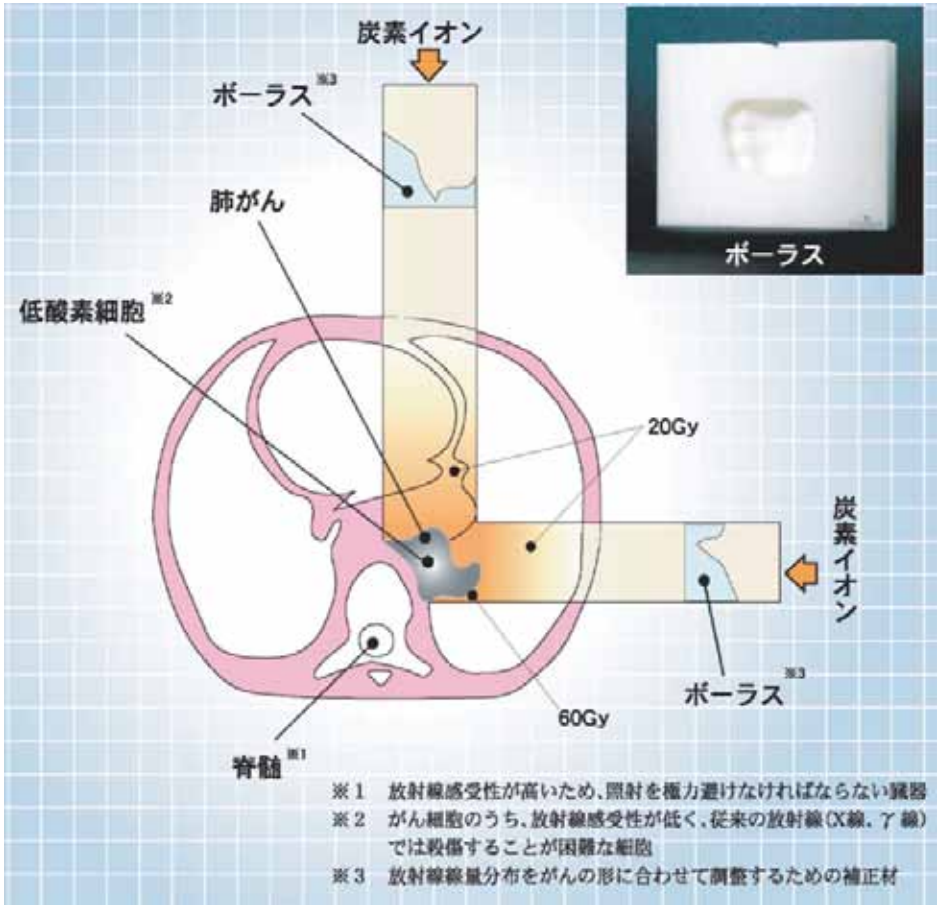
出典：http://www.nirs.go.jp/info/report/pamphlet/pdf/himac-d.pdf （一部改変）
独立行政法人放射線医学総合研究所「HIMAC　重粒子線がん治療装置」パンフレットより

【参考】従来法との比較

■従来の放射線治療（X線2門照射の場合）



■重粒子線治療（炭素イオン水平垂直2門照射の場合）



出典：http://www.nirs.go.jp/info/report/pamphlet/pdf/himac-d.pdf （一部改変）
独立行政法人放射線医学総合研究所「HIMAC 重粒子線がん治療装置」パンフレットより

Feasibility of Proton Beam Therapy for Chordoma and Chondrosarcoma of the Skull Base

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ABSTRACT

We explored the general feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base. Clinical records and treatment-planning data of patients with the pathological diagnosis of chordoma or chondrosarcoma were examined. Proton beam therapy was administered for gross tumor mass as well as microscopic residual disease after surgery. The prescribed dose was determined to maximize the coverage of the target and to not exceed predefined constraints for the organs at risk. Eight cases of chordoma and eight cases of chondrosarcoma were enrolled. The median tumor volume was 40 cm^3 (range, 7 to 546 cm^3). The prescribed dose ranged from 50 to 70 Gy (relative biological effectiveness [RBE]), with a median of 63 Gy RBE. The median follow-up duration was 42 months (range 9 to 80 months). The overall survival rate was 100%, and the local control rate at 3 years of chordoma and chondrosarcoma were 100% and 86%. None of the patients developed radiation-induced optic neuropathy, brain stem injury, or other severe toxicity. Proton beam therapy is generally feasible for both chordoma and chondrosarcoma of the skull base, with excellent local control and survival rates.

KEYWORDS: Proton beam, radiotherapy, skull base, chordoma, chondrosarcoma

Chordoma and chondrosarcoma of the skull base are rare tumors. The combined incidence of these tumors of the skull base in the United States is reported to be 0.03 per 100,000 population. Chordoma is a tumor arising from the remnants of the notochord. About half of these tumors occur at the sacrococcygeal synchondrosis, and ~30 to 40% occur at the spheno-occipital synchondrosis.[1] Chondrosarcomas originate from primitive mesenchymal cells or from the embryonic rests of the cartilaginous matrix. This neoplasm may arise in any bone, and the most common sites of origin are the pelvis and extremities. About 5% of all chondrosarcomas occur at the skull base.[2] Although chordomas and chondrosarcomas have distinct histological features, the clinical presentation and treatment strategies for these tumors occurring at the skull base are similar, and the treatments remain challenging, in contrast to those for these tumors arising at other sites.[3,4]

Similar to the case for such tumors arising at other sites, surgical removal is the primary curative option.[5]

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Skull Base 2011;21:201–206.

Received: November 28, 2010. Accepted: January 10, 2011. Published online: March 25, 2011.
DOI: http://dx.doi.org/10.1055/s-0031-1275636.
ISSN 1531-5010.

However, the complex bony structures of the skull base and the surrounding critical organs may not allow complete resection of these tumors.[6] Therefore, adjuvant treatments need to be considered both for the remaining gross tumor mass and for microscopic tumor cells around the primary tumor as adjuvant treatment; about half of the patients receive postoperative radiotherapy according to reports from several institutes.[7]

Proton beam therapy has been reported to be useful for adjuvant treatment of tumors of the skull base, reportedly yielding excellent outcomes.[8] The main advantageous effect of a proton beam are the protons' physical feature of the Bragg peak, which provides excellent conformity of the irradiation field. The physical rationale of the treatment was tested at select institutes between the 1970s and 1990s.[9,10] At the same time, more reliable dose constraints for normal tissues at the skull base for protons rather than the doses known to be acceptable for photon treatment were explored.[10–13] These dose constraints for organs at risk surrounding a tumor were then used at individual institutes. Apparently, the developed dose constraints enabled escalation of the target dose in proton beam therapy, whereas the target dose in photon treatment is usually compromised with historically accepted dose constraints for the surrounding organs.

After these revisions of the prescription method of proton beam therapy, few data have been published on the outcomes of this treatment for skull base tumors. Furthermore, the reproducibility of the results among institutes has also not been assessed. Therefore, it was considered that reproducible or better outcomes of treatment planning with objectively established parameters should be tested before general application of the treatment. Furthermore, preferential selection of proton beam therapy over other newly developed techniques of radiotherapy needs to be assessed more clearly with appropriate selection of subjects suitable for the treatment, because comparable clinical outcomes of other advanced radiotherapeutic techniques are emerging for certain types of skull base tumors.[14,15]

METHODS

The data of consecutive patients who underwent proton beam therapy for chordoma or chondrosarcoma of the skull base from July 2003 through November 2008 were retrospectively reviewed. All patients had a histopathologically confirmed diagnosis of chordoma or chondrosarcoma based on previous surgery or biopsy. The eligibility for surgical resection of the patients referred to our institute was estimated by experienced neurosurgeons or head and neck surgeons. In patients eligible for surgery, the tumor was removed to the maximum extent possible before proton beam therapy.

The gross tumor volume (GTV) was defined as the gross extent of the tumor observed on computed tomography (CT) or magnetic resonance imaging (MRI). The clinical target volume (CTV) was defined as the GTV plus a margin of 5 to 8 mm. The planning target volume (PTV) was determined to be the same as the CTV. Critical organs around the target were also delineated on the planning CT images. Taking into account the relative biological effect of a proton beam, the dose was reported in Gy (relative biological effectiveness [RBE]), which was equivalent to the physical dose in Gy multiplied by 1.1. We adopted unique constraints for critical organs in the proton beam therapy, according to a previous report from the proton beam therapy institute. The dose to the optic nerves and chiasma were constrained to 60 Gy RBE. The maximum doses covering 0.9 cm^3 of the brain stem ($D_{0.9}$) and the center of the brain stem were limited to less than 67 Gy RBE and 60 Gy RBE, respectively.[10] The prescribed dose was defined as the dose that covered 90% of the GTV. An attempt was made to deliver more than 50 Gy RBE to the PTV. According to the dose constraints and predefined homogeneity value for PTV, the maximum dose to the PTV was within 105% of the prescribed dose and was 70 Gy RBE. Every patient was treated by the conventional fractionated schedule, at 1.8 Gy RBE/fraction. The treatment was not combined with photon beam therapy in any of the patients. During the treatment session, the head and neck were immobilized by thermoplastic shells. Orthogonal fluoroscopy was performed before every treatment session to verify the localization.

Patients were seen at our institute or by the local physician after the treatment and were monitored for survival, disease progression, and development of adverse events. The patterns of failure and response of the irradiated tumors were examined by MRI, CT, and positron emission tomography performed every 3 to 6 months. The images were compared with the baseline images obtained before the treatment planning. Local progression was defined as increase of the tumor volume as compared with the pretreatment volume or the appearance of new lesions in the CTV. Toxicities were scored according to the Common Toxicity Criteria, version 3.0, of the National Cancer Institute.

The end points analyzed were the overall survival rate and the local control rate. All events were measured from the first day of the proton beam therapy to the last day of follow-up. The overall survival rates and the actual local progression-free rates were calculated using the Kaplan-Meier approach. All the statistical analyses were performed using the PASW 17 (IBM, Chicago, IL).

RESULTS

The characteristics of the patients and the tumors are shown in Table 1. Nine patients presented with diplopia

Table 1 Characteristics of the Patients and Tumors

Characteristics	Value
Age, median (range)	38 (9–78)
Gender (*n*): male/female	10/6
Histological type: chordoma/chondrosarcoma/mesenchymal chondrosarcoma	8/5/3
Previous treatment (*n*): surgery/chemotherapy/none	13/2/2
Pretreatment symptom (*n*): diplopia/pain/diminished visual acuity/facial nerve palsy	9/3/2/2
Gross tumor volume (cm^3), median (range)	40 (7–546)
Clinical target volume (cm^3), median (range)	113 (39–667)

Table 2 Characteristics of Tumor Extension

Tumor Location	Number of Patients (%)
Clival invasion	11 (61%)
Parasellar extension	8 (44%)
Sphenoid sinus invasion	10 (55%)
Suprasellar extension	7 (38%)
Petrous bone invasion	10 (55%)
Occipital bone invasion	7 (38%)
Frontal bone invasion	3 (18%)
Cervical spine	5 (27%)

before treatment and two with decreased visual acuity. The tumor extents are illustrated in Table 2. The tumors mainly involved the clivus, sphenoid sinuses, and petrous bone. Except for the tumors arising from the cervical spine, the tumors presented with extension to more than seven sites.

The delivered radiation doses are shown in Figs. 1 and 2. The mean dose to the GTV and mean dose to the CTV were 63 Gy RBE (range, 50 to 70 Gy RBE) and 60 Gy RBE (range, 48 to 69 Gy RBE). The D_{95} was lower than the mean dose to the GTV (median, 57 Gy RBE, range 41 to 70 Gy RBE) and to the CTV (median, 47 Gy RBE, range 28 to 62 Gy RBE). There were two patents with a lower prescribed dose (50 Gy RBE). The doses in these patients were selected taking into account the risk of radiation-induced optic neuropathy. One patient had a mesenchymal chondrosarcoma arising from the frontal bone. The posterior margin abutted on the optic nerves and optic chiasma. Considering his age and the scant information on the potential response of the tumor to radiotherapy, the dose to the tumor was limited to the dose constraint for the optic nerve as accepted for ordinary photon beam therapy. The other patient with the lower dose to the target also had mesenchymal chondrosarcoma. In an attempt to preserve the visual acuity on both sides, 50 Gy RBE was also selected as a constraint for the optic nerves by the patient. The mean and $D_{0.9}$ dose to the brain stem were 27 Gy RBE (range, 0 to 48 Gy RBE) and 45 Gy RBE (range, 0 to 63 Gy RBE). The median dose to the optic nerve was 43 Gy RBE (range, 0 to 67 Gy RBE). The median dose to the cochlea was 27 Gy RBE (range, 0 to 69 Gy RBE).

The median follow-up period for the study patients was 42 months (range, 9 to 80 months). At the time of the analysis, all the patients were alive. One mesenchymal chondrosarcoma recurred at 23 months after the proton beam therapy in the CTV, which was delivered at a dose of 50 Gy RBE. Another two cases

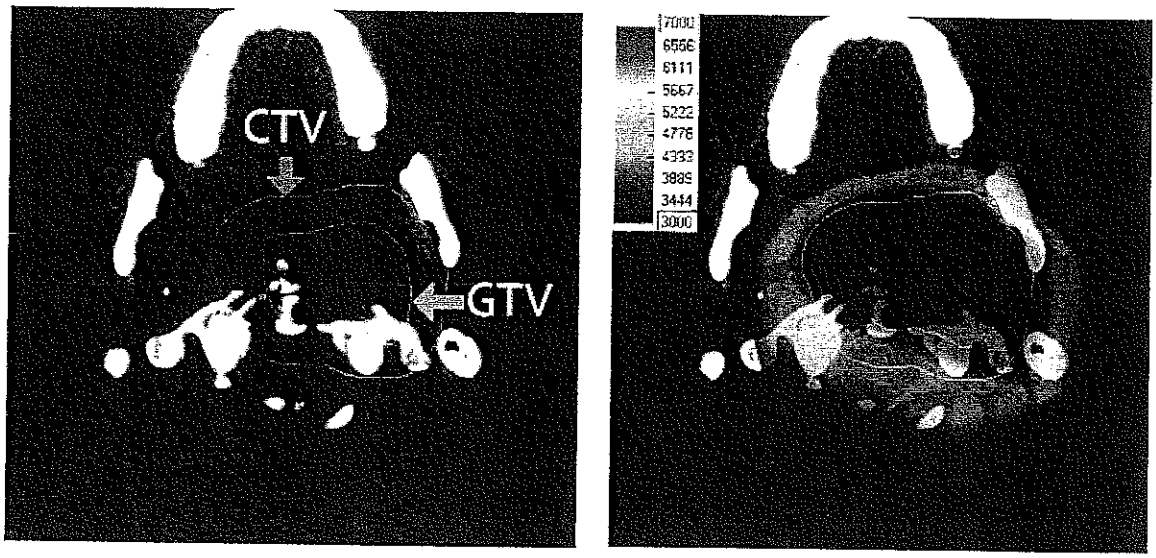

Figure 1 Delivered dose to target volumes and organs at risk. CTV, clinical target volume; GTV, gross tumor volume.

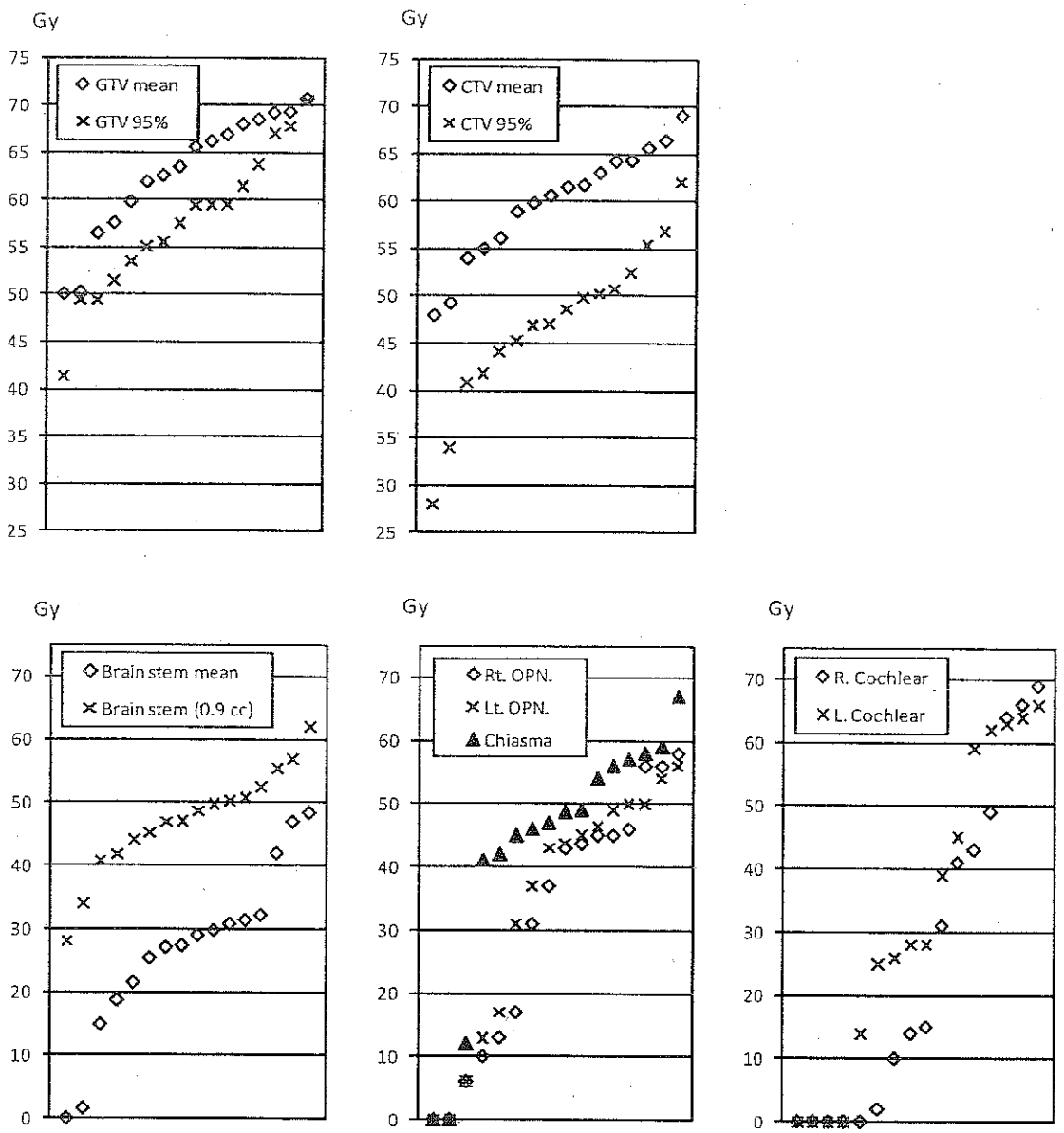

Figure 2 Dose distribution in a case of chondrosarcoma. The gross tumor volume (GTV) and clinical target volume (CTV) were irradiated with a mean dose of 56 Gy and 50 Gy, respectively. High-dose area in brain stem was limited at the surface.

recurred in the CTV at 55 months and 71 months after the treatment. One patient underwent reconstruction surgery for the vertebrae immediately after the proton beam therapy with 60 Gy RBE to the GTV. The tumor was found in the CTV, but not within the GTV. Another patient presented with a recurrent lesion at the center of the GTV, which was delivered 60 Gy RBE. The patient underwent stereotactic radiosurgery for the tumor, which measured 5 mm in diameter.

No patient developed radiation-induced optic neuropathy. There was a patient with variations in the visual acuity during the follow-up period. Because of the frequent intervention for cataract and the normal optic nerve findings throughout the observation period, the perturbations of the visual acuity were not regarded as being attributable to the radiation neuropathy.

There were no patients with symptoms of brain stem radiation necrosis, such as ataxia, weakness, and dysarthria. Deterioration of ocular motion was not observed in any of the patients at the time of the analysis. In the eight patients who presented with diplopia, the symptom improved after the treatment. Grade 2 serous otitis was observed in six patients. Among these, three patients showed persistent disease for more than 3 months. Five patients showed petrous bone destruction by the tumor, and in three of these patients, more than 60 Gy RBE had been delivered to the cochlear systems.

DISCUSSION

Proton beam therapy for chordoma and chondrosarcoma is known to be one of the best options to decrease the

probability of recurrence after surgical removal. Excellent local control and survival rates have been reported from the United States and Europe from 1989 to 2001 (Table 3). The treatment targets in these reports consisted of the clinical target volume with addition of a significant margin to the remnant tumor. Because microscopic tumor cells around the tumor need to be treated in the postoperative setting, this expanded treatment target volume is large and irregular in shape and frequently involves the critical organs at the skull base (i.e., central nervous system, sensory organs, and cranial nerves). Nevertheless, the prescribed doses are markedly higher than the dose constraints for the critical organs. Proton beam therapy is considered the ideal method for dose-gradient irradiation to irregular-shaped targets among critical organs. Even though the number of subjects was small, the inclusion of larger tumors in the present study, as compared with that in previous reports of proton beam therapy, with adequate 3-year disease control rates lends support to the concept of use of proton beam therapy for the disease.

There are several reports of excellent long-term control rates of chordomas and chondrosarcomas with stereotactic radiotherapy and radiosurgery. These reports indicate identical outcomes with stereotactic treatment as with proton beam therapy in selected cases. However, the tumor volumes in these reported cases were smaller than those in patients treated by proton beam therapy, and unfavorable control rates were noted for larger tumors. The irradiated targets in these cases were the gross tumors alone. In this limited-volume irradiation, microscopic residual tumor cells around the primary nests were not irradiated. On the other hand, repeated treatment may be possible in the event of the tumor arising in different parts of the skull base. The differences in the target volume and size of the tumors treated may cause difficulties in comparison of the treatment outcomes between the modalities. However, at least the eligibility of large tumors for treatment may be an advantage in proton beam therapy.

The present series included subjects with extensive invasions to skull base structures. Except for the lesion arising from the cervical vertebrae, all the lesions caused destruction of the petrous bone or suprasellar part of the sphenoid. Additionally, most patients presented with ocular symptoms or visual disturbances, suggestive of encasement or involvement of the cranial nerves by the tumor. Even proton beams could not provide the dose gradient needed at the microscopic border between the tumor and the surrounding organs. Consequently, most patients needed to be given comparable or equivalent doses to the dose constraints for critical organs. Except for two cases of chondrosarcoma, we introduced experimental dose constraints for the optic nerves and brain stem. These were almost identical to the dose constraints reported from experienced high-volume proton beam therapy institutes, but higher than the doses generally accepted for photon beam treatment.[16] Among 32 optic nerves, 10 were delivered a dose identical to the constraint dose, 50 to 60 Gy RBE. Absence of radiation-induced optic neuropathy in our case series with a median follow-up duration of 36 months suggests that the experimental constraint dose is feasible. Our results also suggested the feasibility of using the dose constraint for the brain stem. Terahara et al. reported that the incidence of brain stem injury was associated with the volume irradiated with a certain dose.[11] The constraint dose for $D_{0.9}$ implemented in our study according to their report allowed us to deliver a higher dose to the target than that to the whole brain stem.

Although the treatment-related morbidity rate in the present study was acceptable, there were six patients who developed grade 2 otitis after proton beam therapy. There have been few reports of otitis following proton beam therapy, although the adverse effect has been reported following radiotherapy for nasopharyngeal

Table 3 Reported Outcomes of Skull Base Chordoma and Chondrosarcoma

Study	Munzenrider et al 1999[10]	Austin-Seymour et al 1989[11]	Hug et al 1999[12]	Noël et al 2001[9]	Present Study
Number of patients	621	68	58	67	16
Mean volume (range), mL	NA	45 (2–282)	*	28 (1–125)	40 (7–546)
Mean dose (range)	(66–83)	69 (57–76)	71 (65–79)	67 (60–70)	63 (50–70)
Follow-up (range)	41 (1–254)	34 (17–152)	33.2 (7–75)	29 (4–71)	42 (9–80)
Histology: Ch/Cn	375/246	40/28	33/25	49/18	8/8
Local control					
	Ch: 5 y 98%	5 y 82%	Ch: 3 y 67%	Ch: 3 y 85%	Ch: 3 y 100%
	Cn: 5 y 73%		Cn: 3 y 94%	Cn: 3 y 71%	Cn: 3 y 86%
Overall survival					
	Ch: 5 y 80%	5 y 80%	Ch: 3 y 87%	Ch: 3 y 75%	Ch: 3 y 100%
	Cn: 5 y 48%		Cn: 3 y 100%	Cn: 3 y 88%	Cn: 3 y 100%

*, cases more than 25 mL. Ch, chordoma; Cn, chondrosarcoma; NA, not applicable.

tumors. One reason it has not been reported as an adverse effect of proton beam therapy is that the disease has not yet been recorded as a severe event according to the toxicity criteria. Another reason is the anatomic site of the tumors in previously reported series. Chondrosarcomas in a half of the present subjects tended to arise from the off-axis part of the skull base as compared with chordomas.[2] Therefore, they are likely to occupy the eustachian tube and the auric media. The dose-effect relationship with otitis in the patients with nasopharyngeal tumors suggested an increase risk of the symptom with a dose of 70 Gy delivered to the auric media. In the present study, the otitis media developed in patients who had more than 60 Gy delivered to the auric media. Establishment of a method to predict the risk of otitis after proton beam therapy will be necessary for improving the quality of life.

In the current study, we demonstrated the features of tumors and the prescription and outcomes of treatment. The present report including subjects with tumors showing local extension and adequate local control rates indicates the advantages of proton beam in the treatment of skull base tumors. We observed a few local recurrences in cases treated with lower doses, but no case of severe toxicity. It could be interpreted that further improvement of the treatment may be expected with dose escalation to the target and with establishment of more predictive dose constraints for organs at risk in the skull base region.

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Original Article

High-Dose Proton Therapy and Carbon-Ion Therapy for Stage I Nonsmall Cell Lung Cancer

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BACKGROUND: A study was undertaken to evaluate the clinical outcome of particle therapy for stage I nonsmall cell lung cancer (NSCLC). **METHODS:** From April 2003 to April 2007, 80 patients with stage I NSCLC were treated with proton therapy or carbon-ion therapy (57 with proton therapy and 23 with carbon-ion therapy) using 3 treatment protocols. In the first protocol, 80 gray equivalents (GyE) of proton therapy was given in 20 fractions, and the second proton therapy protocol used 60 GyE in 10 fractions. For carbon-ion therapy, 52.8 GyE was given in 4 fractions. After achieving promising preliminary results for the first protocol, the authors started to use the second proton therapy protocol to shorten the overall treatment time. Carbon-ion therapy was started in 2005, and thereafter, both proton and carbon-ion therapy plans were made for each patient, and the 1 that appeared superior was adopted. Patient age ranged from 48 to 89 years (median, 76 years). Thirty-seven patients were medically inoperable, and 43 refused surgery. Forty-two patients had T1 tumors, and 38 had T2 tumors. **RESULTS:** The median follow-up period for living patients was 35.5 months. For all 80 patients, the 3-year overall survival, cause-specific survival, and local control rates were 75% (IA: 74%; IB: 76%), 86% (IA: 84%; IB: 88%), and 82% (IA: 87%; IB: 77%), respectively. There were no significant differences in treatment results among the 3 protocols. Grade 3 pulmonary toxicity was observed in only 1 patient. **CONCLUSIONS:** Proton therapy and carbon-ion therapy are safe and effective for stage I NSCLC. Further investigation of particle therapy for stage I NSCLC is warranted. ***Cancer* 2010;116:2476–85.** © *2010 American Cancer Society.*

KEYWORDS: proton therapy, carbon-ion therapy, nonsmall cell lung cancer, stage I, hypofractionated high-dose irradiation.

Lung cancer is the leading cause of cancer related-death in Japan. For stage I nonsmall cell lung cancer (NSCLC), surgical resection has been the standard treatment, and has yielded 5-year overall survival rates of approximately 60%.[1] However, because of medical inoperability caused by a variety of diseases, high age, poor respiratory function, or patient refusal, surgery is not indicated for a considerable proportion of patients with stage I NSCLC. In recent years, the use of x-ray stereotactic radiotherapy has been spreading worldwide as a new treatment modality for stage I NSCLC.[2-5] High local control rates and 5-year survival rates of around 70% have been reported.[2,3] Some studies reported that dose escalation to the target volume improved the probability of local control and overall survival.[6,7] Proton and carbon-ion beam irradiation can theoretically produce a superior dose distribution to the target using the sharp distal falloff of the Bragg peaks produced by these techniques compared with that produced by photon irradiation.[8,9] In addition, carbon-ion beams have high relative biological effectiveness, so a therapeutic gain can be expected.[10] Therefore, particle therapy can potentially deliver a higher dose to the primary tumor, leading to improved local tumor control, while simultaneously decreasing the irradiated volume and doses delivered to the surrounding critical organs such as normal lung tissue, heart, esophagus, spinal cord, and mediastinum.

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DOI: 10.1002/cncr.24998, **Received:** July 10, 2009; **Revised:** August 24, 2009; **Accepted:** August 24, 2009, **Published online** March 11, 2010 in Wiley InterScience (www.interscience.wiley.com)

In April 2001, the Hyogo Ion Beam Medical Center became the first institution in the world to provide both proton therapy and carbon-ion therapy.[11] General practice of proton therapy began in April 2003, and carbon-ion therapy was started in April 2005.[12-14] In the present study, we analyzed the safety and efficacy of high-dose proton therapy and carbon-ion therapy applied to stage I NSCLC at the Hyogo Ion Beam Medical Center.

MATERIALS AND METHODS

Study Design, Patient Eligibility, and Characteristics

This was a clinical study based on protocols determined by the particle therapy committee of Hyogo prefecture. The eligibility criteria were as follows: 1) histologically confirmed primary NSCLC staged as IA or IB (T1 or T2, N0M0: tumor ≤3 cm in greatest dimension [T1], or tumor >3 cm in greatest dimension or infiltration of the main bronchus at a distance from the carina of ≥2 cm [T2], no regional lymph node metastasis [N0], and no distant metastasis [M0]) by the International Union Against Cancer 2002 staging system using computed tomography (CT) scans, bone scans, brain magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose (FDG) positron emission tomography (PET); 2) medical inoperability or refusal of surgical resection; 3) World Health Organization performance status ≤2; 4) no history of previous lung cancer; 5) no prior chest radiotherapy or chemotherapy; and 6) written informed consent. In general, patients were deemed to be medically inoperable when they had poor pulmonary function (vital capacity <75% or ratio of forced expiratory volume in 1 second to forced vital capacity <60%), a history of major cardiovascular diseases, severe diabetes mellitus, advanced age (≥80 years old), or other debilitating conditions that preclude surgery. The treatment protocols have been evaluated by the committee every other year and subjected to minor modifications whenever necessary. The patient number was expected to be at least 35 for each protocol to evaluate toxicity and efficacy. In May 2007, a revision of 1 of the protocols (from 60 gray equivalents [GyE] to 66 GyE in 10 fractions) was planned after 37 patients had accrued at the time of a minor update to the system (improvement of the respiratory gating system), so the data before this date were analyzed in this article, together with the data for the other ongoing protocols. From April 2003 to April 2007, 80 stage I NSCLC patients were treated with proton therapy or carbon-ion therapy at the Hyogo Ion Beam Medical Center. Of these patients, 42 had stage IA (T1N0M0), and 38 had stage IB (T2N0M0) disease. Patient and tumor characteristics are summarized in Table 1.

Treatment Protocols

The 3 treatment protocols proposed by the protocol committee were approved by the institutional review board. The first proton therapy protocol, 80 GyE delivered in 20 fractions, was set on the basis of earlier experiences at the National Cancer Center East (Kashiwa, Japan).[15] After evaluating acute and medium-term toxicity in 15 patients, the second proton therapy protocol using 60 GyE in 10 fractions was started. This protocol was used to shorten the overall treatment time and was based on a protocol used at the Proton Medical Research Center in Tsukuba, Japan.[16] However, even after establishing the second protocol, the first protocol was also used in 5 patients with a lesion close to the mediastinum or large vessels; in these patients, the maximum dose to the esophagus was limited to ≤65 GyE and that to the trachea, main bronchus, and large vessels to ≤76 GyE. The carbon-ion therapy protocol, 52.8 GyE in 4 fractions, was defined according to the protocol used at the National Institute of Radiological Sciences in Chiba, Japan.[17] All radiation doses were delivered to the center of the tumor. All irradiation was given once a day, 5 days a week. The policy for selecting beam type was based partly on the availability of the particle beams (between April 2003 and March 2005, only proton therapy was available). In April 2005, carbon-ion therapy became available, and thereafter, treatment plans for both proton therapy and carbon-ion therapy were made for every patient. Then, the dose-volume histograms were compared, and a more suitable modality (proton therapy or carbon-ion therapy) was determined and actually used for each patient. Chemotherapy was not included in these protocols.

Proton Therapy, Carbon-Ion Therapy, and Treatment Systems

The accelerator complex at the Hyogo Ion Beam Medical Center consisted of 2 ion sources, 2 types of linear accelerators, and a synchrotron (Mitsubishi Electric Corporation, Kobe, Japan). The patients were treated with 150-MeV proton beams and 320-MeV carbon-ion beams. The beam ranges were adjusted by a fine degrader. The spread-out Bragg peaks of the proton and carbon-ion beams were produced using bar-ridge filters. A respiratory gating irradiation system developed at the National Institute of Radiological Sciences in Chiba[18] was used for all

Table 1. Patient and Tumor Characteristics

Characteristics	Proton		Carbon	Total
	80 GyE/20 Fr	60 GyE/10 Fr	52.8 GyE/4 Fr	
No. of patients	20	37	23	80
Age, median y (range)	75 (48-87)	78 (57-87)	75 (54-89)	76 (48-89)
Sex, men/women	13/7	30/7	14/9	57/23
PS 0/1/2	10/7/3	20/11/6	12/10/1	42/28/10
Reason for nonsurgical treatment				
Refusal of surgery	10	19	14	43
Medical inoperability[a]	10	18	9	37
Pulmonary	7	6	6	19
Cardiovascular	3	6	2	11
Severe diabetes mellitus	1	4	0	5
Age	0	2	1	3
Others	0	2	0	2
Clinical stage				
T1N0M0 stage IA	6	21	15	42
T2N0M0 stage IB	14	16	8	38
Longest tumor diameter, median mm (range)	32 (16-45)	31 (11-70)	25 (12-50)	30 (11-70)
Histology, AD/SQ/others	11/8/1	21/15/1	15/4/4	47/27/6
Smoking history (+/−)	14/6	31/6	15/8	60/20

GyE indicates gray equivalents; Fr, fractions; PS, performance status; AD, adenocarcinoma; SQ, squamous cell carcinoma.
[a]Some patients had 2 or more reasons for medical inoperability.

patients to irradiate the beam during the exhalation phase. Patient set-up was performed daily by subtraction of the 2 sets of orthogonal digital radiographs before irradiation. The translation and rotation of the patient detected by the positioning system were compensated for by adjustment of the treatment couch. The setup was continued until the bony landmarks on the digitally reconstructed radiographs agreed within 1 mm. Biological effects of both proton therapy and carbon-ion therapy at the Hyogo Ion Beam Medical Center were evaluated in vitro and in vivo, and the relative biologic effectiveness (RBE) values for proton and carbon-ion irradiation at the Hyogo Ion Beam Medical Center were determined to be 1.1 and 2-3.7 (depending on the depth in the spread-out Bragg peaks), respectively.[19] Because all tissues are assumed to have almost the same RBE for proton or carbon ions, doses expressed in GyE are directly comparable to photon doses.

Treatment Planning

The radiation treatment plans were performed using a CT-based 3-dimensional treatment planning system (FOCUS-M, CMS, St. Louis, Mo and Mitsubishi Electric Corporation). Each patient was immobilized with a custom-made thermoplastic cast (Kuraray Shell Fitter F, Kuraray Trading Co., Osaka, Japan), and 2-mm-thick CT images were taken during the exhalation phase with a respiratory gating system. The lesions under the lung window were taken as the gross tumor volume (GTV), and the clinical target volume (CTV) was defined as the GTV plus a margin of 5 mm in all directions. The planning target volume (PTV) was defined as the CTV plus a setup margin of 5 mm and an internal margin of 1 to 4 mm depending on the stability of respiration under the respiratory gating system. A desirable treatment plan was defined as 1 that covered the PTV with $\geq$95% of the prescribed dose; however, such plans were frequently unable to reduce the doses to organs at risk. So, treatment planning to encompass 95% of the CTV with $\geq$95% of the prescribed dose was sought. The doses were calculated on the basis of the pencil beam algorithm. Adequate beam parameters, including beam energy, spread-out Bragg peak width, and degrader thickness, were selected with FOCUS-M. One to 4 portals were planned in both the proton and carbon-ion treatments.

Follow-up Evaluation and Statistical Analysis

After particle therapy, the patients were observed at 1.5, 3, 4.5, 6, 9, and 12 months during the first year, at intervals of 3 months in the second year, and at 6-month intervals in the third year and thereafter. Regular follow-up studies included chest and upper abdominal CT scans and tumor

Table 2. Treatment Characteristics and Dose Volume Analyses

Characteristics	Proton		Carbon	Total
	80 GyE/20 Fr	60 GyE/10 Fr	52.8 GyE/4 Fr	
No. of patients	20	37	23	80
No. of portals, 1/2/3/4	12/8/0/0	5/31/1/0	0/8/14/1	17/47/15/1
PTV volume, cm^3 (median)	26.5-243.9 (84.8)	22.9-211.0 (61.8)	16.4-290.6 (43.2)	16.4-290.6 (62.8)
V20 lung[a] (%)	5.0-24.0 (8.0)	5.0-17.0 (8.0)	3.0-13.0 (7.0)	3.0-24.0 (8.0)
BED10[b] (GyE)	112	96	122.5	

GyE indicates gray equivalents; Fr, fractions; PTV, planning target volume; BED, biological effective dose.
[a]Percentage of lung volume receiving >20 GyE.
[b]Calculated by linear-quadratic formalism assuming an alfa/beta ratio of 10 GyE.

marker examinations. Brain MRI and FDG-PET were usually performed once or twice per year, or whenever necessary. PET was used to evaluate distant metastases as well as local tumor status, especially when recurrence was suspected within the shadow of radiation fibrosis. Biopsy for a suspected local recurrence was performed only when no definite conclusions could be drawn from imaging studies. Local responses to particle therapy were classified according to the modified World Health Organization response evaluation criteria.[20] As it was difficult to distinguish the residual tumor tissue from radiation fibrosis, the tumors were regarded as locally controlled when there was no expansion of shadows in the irradiated area. Regional lymph node recurrence was not included in local recurrence. The overall survival, cause-specific survival, local-control, and disease-free survival rates were calculated using the Kaplan-Meier method. Differences between pairs of Kaplan-Meier curves were examined by the log-rank test. Values of $P < .05$ were considered to be statistically significant. Statistical analyses were carried out with StatView Version 5 (SAS Institute, Cary, NC). Toxicities were evaluated with the Common Terminology Criteria for Adverse Events version 3.0.

RESULTS

Treatment Characteristics

The proton therapy protocol involving 80 GyE in 20 fractions, that involving 60 GyE in 10 fractions, and the carbon-ion therapy protocol involving 52.8 GyE in 4 fractions were delivered to 20, 37, and 23 patients, respectively. A summary of the treatments is shown in Table 2.

Survival and Local Control

All patients were observed for a minimum of 1.5 years or until death. The median duration of follow-up was 35.5 months (range, 18-66 months) for living patients and 30.5 months (range, 4-66 months) for all patients. For all 80 patients, the 3-year overall and cause-specific survival rates were 75% (95% confidence interval [CI]: 64%-86%; stage IA: 74%; IB: 76%) and 86 % (95% CI, 77%-95%; IA: 84%; IB: 88%), respectively. Local recurrence occurred in 15 patients (IA: 5; IB: 10), and 4 patients with stage IB disease developed local recurrence after 2 years. Local recurrence was confirmed by biopsy in 2 patients, autopsy in 1, and surgical resection in 1. The 3-year local control and disease-free survival rates were 82% (95% CI, 72%-92%; IA: 87%; IB: 77%) and 54% (95% CI, 43%-68%; IA: 67%; IB: 46%), respectively. For the protocols involving 80 GyE/20 fractions of proton therapy, 60 GyE/10 fractions of proton therapy, and 52.8 GyE/4 fractions of carbon-ion therapy, the 3-year overall survival rates were 90%, 61%, and 86%, and the 3-year local control rates were 83%, 81%, and 86%, respectively (Fig. 1). There were no significant differences in the treatment results among the 3 protocols.

Figure 2 shows overall and disease-free survival rates according to medical operability for all patients treated with particle therapy (n = 80) and for those treated with proton therapy (n = 57). When all patients were analyzed, the operable patients had better survival rates than the medically inoperable patients ($P = .028$), although disease-free survival did not differ significantly. For the 43 operable patients treated with proton therapy or carbon-ion therapy, the 3-year overall survival and local control rates were 83% and 88%, respectively. Figure 3 shows overall survival, local control, and disease-free survival rates according to stage for all patients (n = 80, Fig. 3A) and for those treated with proton therapy (n = 57, Fig. 3B). There were no significant differences between stage IA and IB patients, although disease-free survival tended to be better in stage IA patients when all patients were analyzed ($P = .055$). Figure 4 shows overall survival, local control, and disease-free survival curves according to

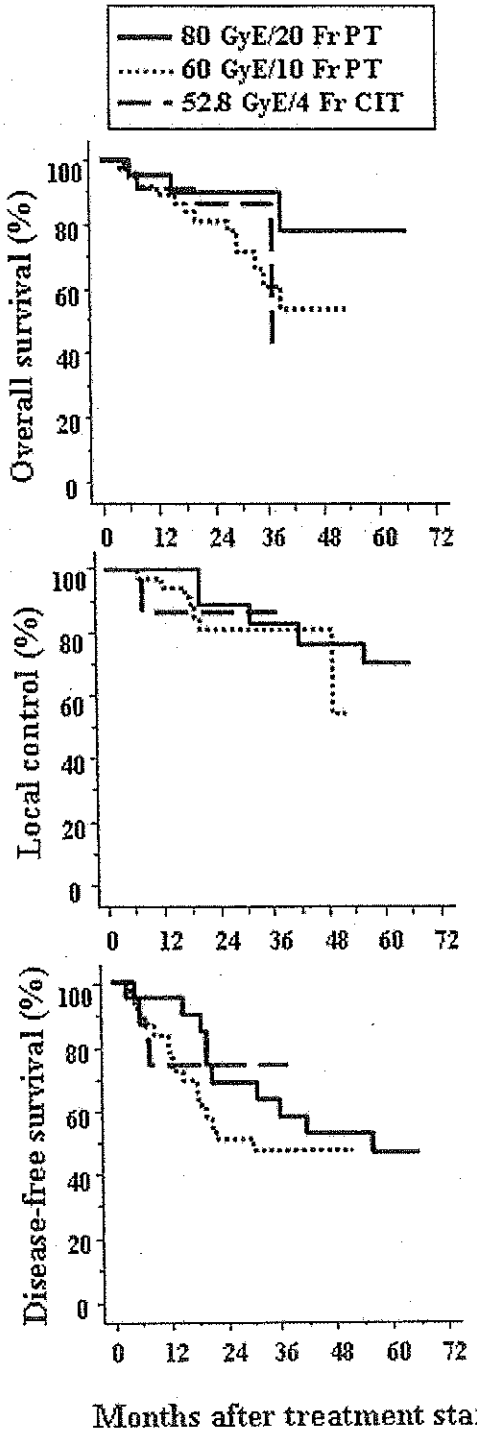

Figure 1. Overall survival, local control, and disease-free survival curves are shown according to protocols involving 80 gray equivalents (GyE)/20 fractions (Fr) of proton therapy (PT), 60 GyE/10 Fr of proton therapy, and 52.8 GyE/4 Fr of carbon-ion therapy (CIT). There were no significant differences in the treatment results among the 3 protocols.

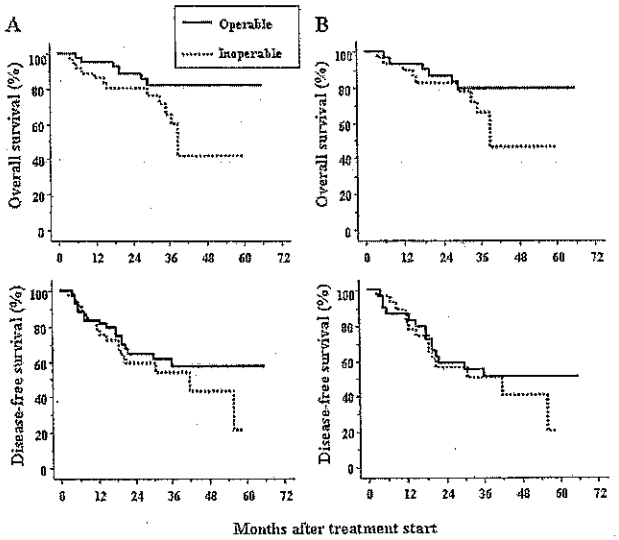

Figure 2. Overall and disease-free survival curves are shown according to medical operability for all patients (n = 80) treated with particle therapy (A: P = .028 and .34, respectively) and for those (n = 57) treated with proton therapy (B: P = .10 and .50, respectively).

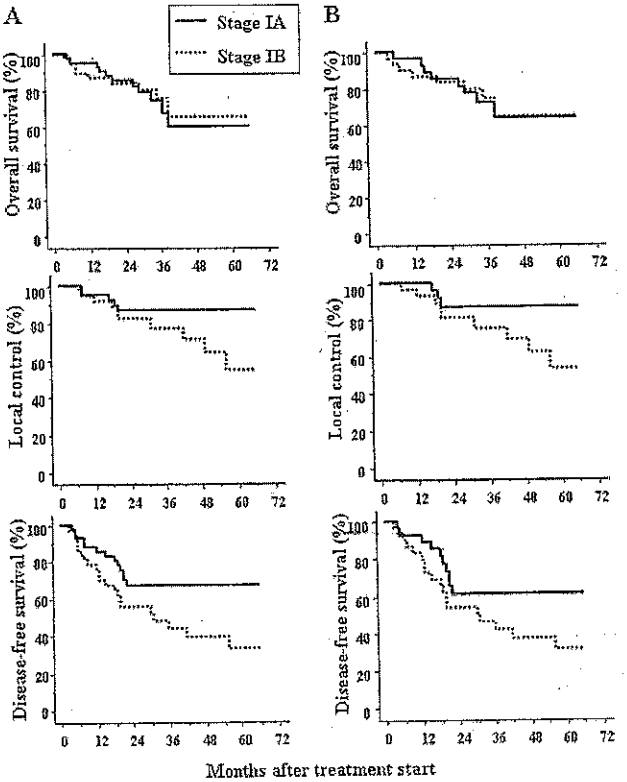

Figure 3. Overall survival, local control, and disease-free survival curves are shown according to stage treated with particle therapy (A: n = 80) and treated with proton therapy (B: n = 57). There were no significant differences between stages IA and IB.

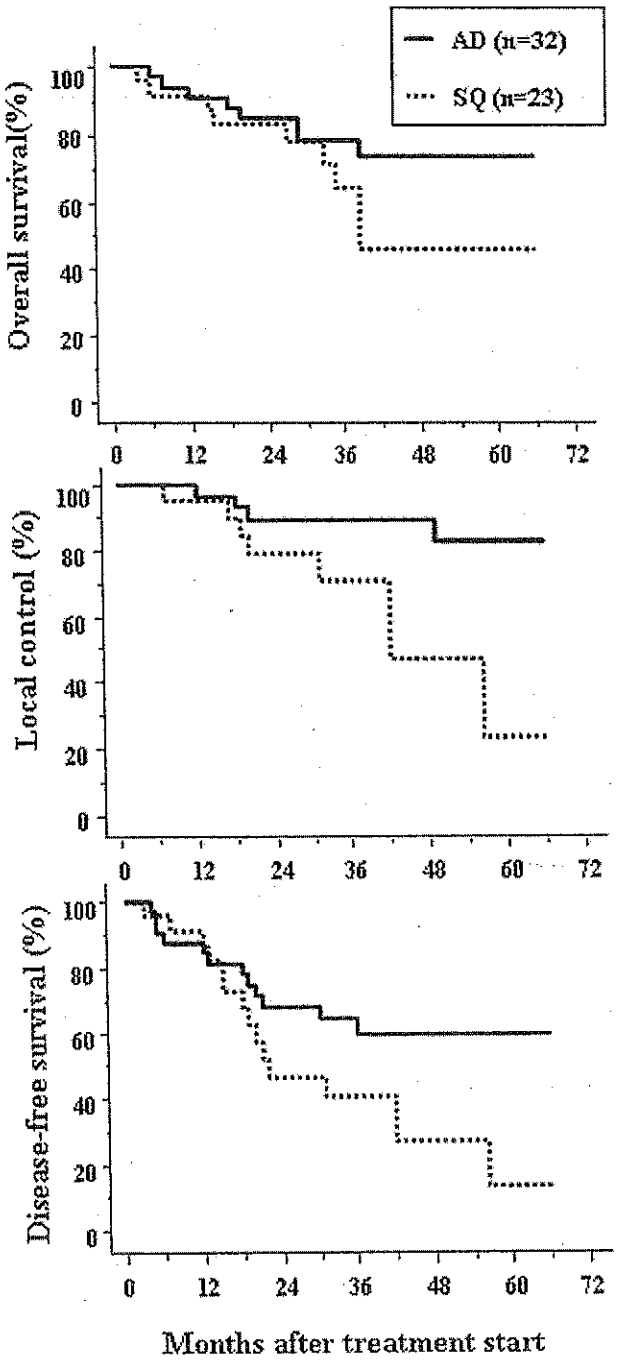

Figure 4. Overall survival, local control, and disease-free survival curves are shown for patients treated with proton therapy according to histology. Patients with adenocarcinoma (AD) had a higher local control rate than those with squamous cell carcinoma (SQ) ($P = .022$), although the overall and disease-free survival rates were not different ($P = .19$ and .061, respectively).

histology in patients treated with proton therapy. The local control rates were higher for adenocarcinoma than for squamous cell carcinoma ($P = .02$). Fourteen patients (7 each with stage IA and IB disease) developed hilar and/or mediastinal lymph node metastases, and 1 of them also had a lung metastasis. In addition, another 12 patients developed distant metastases.

Complications

Table 3 summarizes adverse events according to stage. Symptomatic radiation pneumonitis (grade 2 or higher) was noted in 10 (13%) patients. Only 1 patient who had very poor respiratory function and interstitial pneumonitis before irradiation developed grade 3 radiation pneumonitis; he received steroids and needed continuous oxygen inhalation. Most of these symptomatic grade 2 or 3 radiation pneumonitis cases occurred within 3 to 5 months after the start of irradiation. Symptomatic dermatitis was noted in 13 patients (16%; grade 2 in 10 and grade 3 in 3). For grade 3 dermatitis, which was seen in 4% of cases, wound care for skin ulcers (debridement, wound bed preparation, moist wound healing, etc.) was required. The other main toxicities observed were a grade 2 rib fracture without the presence of cancer in 18 (23%) and grade 2 fibrosis of soft tissue of the thoracic wall in 5 (6%). Most of these toxicities were late toxicities that were seen after 6 months.

DISCUSSION

During the last 10 years, x-ray stereotactic radiotherapy for stage I NSCLC has made marked progress. Favorable results with x-ray stereotactic radiotherapy are accumulating for stage I NSCLC, and x-ray stereotactic radiotherapy is becoming an indispensable treatment modality for patients who refuse surgery or are medically inoperable. An alternative to and possibly better treatment option than x-ray stereotactic radiotherapy is particle radiotherapy, and a comparison among these treatment modalities should be performed with respect to physical dose distribution and biological effectiveness.[8-10] As our facility does not perform x-ray stereotactic radiotherapy, we could not directly compare the dose distribution of particle radiotherapy with that of x-ray stereotactic radiotherapy. Generally speaking, unnecessary irradiation of the mediastinum and contralateral lung can be minimized with particle radiotherapy; the dose conformity at the target site may be better for x-ray stereotactic radiotherapy when using noncoplanar beams.[21-23] The relatively large

Table 3. Complications Related to Particle Therapy

Adverse Event	Proton				Carbon		Total	
	80 GyE/20 Fr		60 GyE/10 Fr		52.8 GyE/4 Fr			
No. of patients	20		37		23		80	
Stage IA/IB	6	14	21	16	15	8	42	38
Radiation pneumonitis								
Grade 2	0	3	3	1	1	1	13%	
Grade 3	0	1	0	0	0	0		
Dermatitis								
Grade 2	1	3	1	3	0	2	16%	
Grade 3	0	3	0	0	0	0		
Rib fracture, grade 2	2	7	3	3	1	2	23%	
Soft tissue, grade 2	0	2	0	2	0	1	6%	

GyE indicates gray equivalents; Fr, fractions.
The toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.

scattered doses at the penumbra, as compared with those produced by x-rays and carbon beams, may be a disadvantage of proton therapy, but conversely it may reduce the risk of marginal recurrence. Regarding dose conformity, most investigators of x-ray stereotactic radiotherapy prescribed its doses to 95% of the PTV volume ($D95_{PTV}$) to be higher than 95%,[2,24] but we planned to prescribe a $D95_{CTV}$ of >95% in the present study, because T2 tumors >5 cm were often treated. Therefore, the target coverage might have been worse in the present study compared with the published data concerning x-ray stereotactic radiotherapy. However, this disadvantage may be improved by more strict treatment planning. In proton therapy, the dose distribution will become superior to that of x-ray stereotactic radiotherapy when noncoplanar beams become available in the near future. Indeed, this is now under investigation in Japan (S. Murayama, personal communication).

The doses of proton therapy and carbon-ion therapy were expressed in GyE so that they were comparable to those used in x-ray stereotactic radiotherapy; the differences in biological effects may be discussed with respect to the doses in Gy for x-ray stereotactic radiotherapy and GyE for proton therapy and carbon-ion therapy.[10,19,25-27] However, carbon-ion therapy is more efficient against hypoxic tumor cells than x-ray radiation. The biological effects of proton irradiation have not been completely clarified, and many clinicians think that the clinical RBE of proton irradiation is higher than 1.1. This needs to be confirmed in clinical studies in the near future. Nevertheless, it is possible that the biological effects of both proton therapy and carbon-ion therapy are higher than those expected from the doses. Interestingly, the local control rates for squamous cell carcinomas obtained by proton therapy were worse than those for adenocarcinoma (Fig. 4). A similar trend was also observed for carbon-ion therapy, although the difference was not significant because of the small number of patients. This is in contrast to the general observations for x-ray radiotherapy.[28] The reason for this is unknown, but during carbon-ion therapy performed at the National Institute of Radiological Sciences, Chiba, squamous cell carcinomas tended to show lower local control rates than melanomas and adenoid cystic carcinomas.[29] During proton therapy and carbon-ion therapy performed for head and neck cancer at the Hyogo Ion Beam Medical Center, a similar trend was also experienced.[30] The differences in radiosensitivity shown by histology should also be investigated further, and more studies are necessary to prove whether these observations are correct. At present, it may be concluded that particle radiotherapy is efficacious against adenocarcinoma, which may not be sufficiently responsive to conventional radiotherapy. We are conducting a laboratory experiment to examine whether the sensitivity to particle therapy is different between adenocarcinoma and squamous cell carcinoma.

The 3 protocols we used were chosen by following those of previous investigators who reported favorable outcomes.[15-17] Linear-quadratic (LQ) formalism is not well applicable to hypofractionated radiation schedules,[31] but if calculated using LQ formalism, a dose of 80 GyE separated into 20 fractions is nearly equal to 52.8 GyE separated into 4 fractions, assuming an alfa/beta ratio of 10 GyE. Therefore, the 2 doses of proton therapy and carbon-ion therapy used in the present study may only be slightly higher than those commonly used in x-ray stereotactic radiotherapy, such as 48 Gy delivered in 4 fractions.[2,24] Conversely, the 60 GyE dose regimen, which was separated into 10 fractions, appears to be lower than

Table 4. Representative Reported Results of Particle Therapy and X-Ray Stereotactic Radiotherapy

Study	Therapy	No. of Patients (IA/IB)	Total Dose	Fraction Size	Dose Specification	Treatment Outcome	Median Follow-up (mo)
Miyamoto 2007[32]	CIT	50 (29/21)	72 GyE	8 GyE	PTV >90%	5-year OS: 50%; 5-year LC: 95%; no grade 3+ toxicity	59
Miyamoto 2007[17]	CIT	79 (42/37)	52.8 or 60 GyE	13.2 or 15 GyE	PTV >90%	3-year OS: 78%; 3-year LC: 98%; no grade 3+ toxicity	39
Bush 2004[33]	PT	68 (29/39)	51 or 60 GyE	5.1 or 6 GyE	NR	3-year OS: 44%; 3-year LC: 74%; toxicity: NR	30
Nihei 2006[15]	PT	37 (17/20)	70-94 GyE	3.5-4.7 GyE	NR	2-year OS: 84%; 2-year LC: 80%; RP grade 3: 8%	24
Onishi 2007[2]	XSRT	257 (164/93)	30-84 Gy	4.4-35 Gy	Marginal dose >80%	3-year OS: 57%; 3-year LC: 80%; RP above grade 2: 5.4%	38
Baumann 2009[34]	XSRT	57 (40/17)	45 Gy	15 Gy	67% isodose of the PTV	3-year OS: 60%; 3-year LC: 92%; RP grade 3: 2%	35
Timmerman 2006[35]	XSRT	70 (35/35)	60 or 66 Gy	20 or 22 Gy	Marginal dose 80%	2-year OS: 55%; 2-year LC: 95%; RP grade 3-4: 14%	33
This study 2010	PT	57 (27/30)	80 or 60 GyE	4 or 6 GyE	CTV >95%	3-year OS: 73%; 3-year LC: 81%; RP grade 3: 2%	40
This study 2010	CIT	21 (14/7)	52.8 GyE	13.2 GyE	CTV >95%	2-year OS: 87%; 2-year LC: 86%; RP grade 3: 0%	24

CIT indicates carbon-ion therapy; GyE, gray equivalents; PTV, planning target volume; OS, overall survival rate; LC, local control rate; PT, proton therapy; NR, not reported; RP, radiation pneumonitis; XSRT, x-ray stereotactic radiotherapy; Gy, grays; CTV, clinical target volume.

these doses. Table 4 summarizes the results of particle therapy and x-ray stereotactic radiotherapy from other institutions.[2,15,17,32-35] Although the patient numbers for each protocol are not sufficiently high, our data seem to be comparable to the previously reported results for particle therapy. In addition to the paucity of data on particle therapy, some of the reported results on proton therapy are preliminary, and other studies are retrospective, with various fractionation schedules; therefore, optimal treatment protocols are still under investigation. Our data would serve as a basis for further refinement of treatment protocols. Results on carbon-ion therapy have only been reported from the National Institute of Radiological Sciences in Chiba, Japan.[19,32] The group has been investigating various fractionation schedules (from 18 to only 1 fraction, recently). We adopted their 4-fraction protocol, and have observed favorable outcome. Carbon-ion therapy is available in only 3 institutions in the world, so optimal treatment schedules need to be further investigated in the future. The overall results with respect to 2- and 3-year local control and survival rates appear roughly comparable to those reported for x-ray stereotactic radiotherapy. However, it should be noted that larger tumors are included in the present study; nevertheless, the results obtained in the present study were similar to those reported for x-ray stereotactic radiotherapy. Tumors >5 cm in diameter are not indicated for x-ray stereotactic radiotherapy, but they can be treated with proton therapy or carbon-ion therapy with considerable expectation of local control.

Pulmonary toxicity was modest in both proton therapy and carbon-ion therapy in the present study. This is not surprising, considering the dose distribution of proton and carbon ions. It should be noted that even in patients with large tumors >5 cm in diameter, no grade ≥3 toxicities developed, indicating the safety of the treatment.[36] Conversely, rib fracture and dermatitis (grade ≥2) were frequently seen in patients treated from April 2003 to December 2004; most of these patients were treated with only 1 portal to obtain enough spread-out Bragg peaks. The dose delivered to the skin and rib rose to about 70% to 100% of the isocenter dose in these cases. Thereafter, we used 2 or more portals and rarely observed such complications. Thus, this problem can be solved by using multiple portals. In view of the acceptable toxicity in the present study, we have been using a new proton therapy protocol involving 66 GyE given in 10 fractions since May 2007. The other proton therapy protocol of 80 GyE in 20 fractions and the carbon-ion therapy protocol of 52.8 Gy in 4 fractions are still under evaluation until higher patient numbers have accrued.

Tumor motion is always a problem in high-precision radiotherapy. Proton therapy provides sharp distal falloff of radiation doses compared with carbon-ion therapy, but in the lung tissue this falloff is somewhat obscured. Carbon-ion beams have a smaller penumbra

than proton beams,[37,38] which influences treatment planning. Thus, special attention needs to be paid to tumor motion, and we treated all patients with the respiratory-gating system. Our treatment system does not use a currently spreading image-guidance system using CT, so image-guided particle therapy should be a topic of future investigation, especially for stereotactic treatment. In addition, 4-dimentional CT evaluation should also be a future topic.

To compare proton therapy and carbon-ion therapy, we evaluated both of the plans. When dose distributions were compared, there were many cases in which low dose areas had spread into the surrounding normal lungs during the proton therapy planning. This was apparently because of the relatively large penumbra of proton beams.[37,38] The dose distribution of a single beam appears to be better in carbon-ion therapy than in proton therapy. However, the beam directions are limited to 3 fixed positions in carbon-ion therapy, whereas proton therapy can use a rotational gantry. The high positioning accuracy achieved by irradiating patients in a supine position was also an advantage of proton therapy. Therefore, carbon-ion therapy appeared to be advantageous for tumors that could be readily treated with the fixed 3 portals. Therefore, we will continue to make treatment plans for both proton therapy and carbon-ion therapy and try to choose the superior method in further studies.

In conclusion, proton therapy and carbon-ion therapy appeared to yield treatment outcomes comparable or possibly superior to those obtained by x-ray stereotactic radiotherapy for stage I NSCLC. The role of proton therapy versus carbon-ion therapy should be clarified in future studies. Optimal doses and fractionation schedules should be further investigated. It should also be clarified whether particle radiotherapy is more efficacious than x-ray stereotactic radiotherapy for T2 tumors and whether radiosensitivity differs with tumor histology. Stereotactic proton therapy using a noncoplanar beam arrangement should be established in the near future.

CONFLICT OF INTEREST DISCLOSURES

This work was supported by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

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先－３（別紙）
参考資料２－３
２４．１．１９

粒子線治療の費用対効果に関する過去の報告のまとめ

日本放射線腫瘍学会　粒子線治療アドホック委員会抄訳作成

＜陽子線治療＞

１．　がんの陽子線治療：臨床的利点の可能性と費用対効果（Proton Therapy of Cancer：Potential clinical advantages and cost-effectiveness）.

リンドクヴィスト、カロリンスカ研究所　Lundkvist J, et al. Karolinska Institutet, Stockholm.

Acta Oncologica 2005; 44：850 -861.;

【要旨】

陽子線治療は、通常の放射線治療に比較して、多くのがん患者に対して臨床的に優位性を提供するかもしれない。しかし、陽子線治療施設の建設費用が高いために、陽子線治療費が通常放射線治療よりも高い。したがって、医学的な効果が、高額な費用に見合うかどうかは、重要である。我々は、４種の癌；左乳癌、前立腺癌、頭頸部癌、小児髄芽腫に関して、費用対効果分析を行った。マルコフ・コーホートシミュレーションモデルをそれぞれの癌種に対して作り、放射線治療を実施された患者の生活をシミュレーションした。コストと「生活の質に関して調整した生存年数(QALYs: 質調整生存年)を主計測項目とした。結果として、陽子線治療は、適切なリスクグループを選ぶことで、費用に見合う効果が得られることが示された。上記４種のがんに関して、陽子線治療で得られる１QALY あたりの平均費用(cost-effectiveness ratio)は、約 10130 ユーロであった。仮に、得られる QALY が 55000 ユーロだとすると、一陽子線治療施設で治療すると仮定した 925 名の４種のがん患者の治療によって、年間に 2.08 千万ユーロ（QALY の総価値　－　総費用）の~~年間~~総利益が得られる。よって、このことは、陽子線治療装置への投資は、費用対効果が良いことを示唆している。しかし、データ不足やそれによる仮定の不確実さがあるので、この結果は注意して解釈されなければならない。

文献１　表 A.　QALY 算出に用いた有害事象のコストと効用値のモデル、および陽子線治療と X 線治療の相対リスクを示す。過去の文献から割り出された値では、乳癌、前立腺癌、頭頸部癌、髄芽腫すべてにおいて、陽子線治療で相対リスクが低下している。

項目	従来のX線治療でのリスク	年間コスト(€)	効用値低下率	相対リスク**** （X 線治療を１とした場合の陽子線でのリスク）
乳癌				
虚血性心疾患増加	43%[1]	初年度 6466，次年度以降 616　*	10%	0.24
他の心血管系疾患増加	27%[1]	初年度 4265，次年度以降 796*	20%	0.24
放射線肺臓炎	14%*	1706*	-	0.04
前立腺癌				
前立腺癌関連死	2.5%（15 年間）	-	-	0.8
軽度放射線腸管障害	14%*	105.2*	7%*	0.6
重度放射線腸管障害	4%*	1774.9*	7%*	0.6
軽度放射線泌尿器障害	9%*	242.2*	7%*	0.6
重度放射線泌尿器障害	0.5%*	571.3*	7%*	0.6
頭頸部癌				
総死亡率	16%(8 年間) *****	-	-	0.76
歯科処置	-	初年度 1608.7、次年度以降 271.7	-	-
髄芽腫				
放射線二次癌による死亡	0.11%**	-	-	0.48
心臓病や他因死	0.056%**	-	-	0.77
聴力低下	13%	5054*	18%	0.12
IQ 低下	4.25 点	2448***		0.12
甲状腺機能低下	33%	114*	10%	0.12
成長ホルモン不足	18.7%	19 歳まで 13478、その後 1348***	20%	0.12
骨粗鬆症	2.4%	50 歳以降 363 ***	2%	0.12
致死的でない癌	0.32%	19565*	-	0.12

1.　一般人との比較。心疾患のリスクは放射線治療後１０年以降の生涯リスク。
* １事象毎あるいは１年のみ
** １事象毎、診断後 10～20 年間
*** １年毎、生涯に渡り
****陽子線治療対従来 X 線治療
*****平均値。診断後数年間が高い。

文献１　表 B. 陽子線と従来 X 線治療との比較

	乳癌[1]	前立腺癌	頭頸部癌	髄芽腫	計
年間患者数	300	300	300	25	925
Δ 費用*	5920.0	7952.6	3887.2	-23646.5	
Δ QALY*	0.1726	0.297	1.02	0.683	
費用/QALY	34290	26776	3811	費用削減	
総費用差(€) **	1.8M	2.4M	1.2M	-0.6M	4.7M
総 QAL 差**	51.8	89.1	306.0	17.1	464.0

1. 心疾患のリスクが高いグループを治療したと仮定。

*患者一人あたり、陽子線治療 ― 従来 X 線治療。

** １年間治療された総患者に対して。

２．　小児髄芽腫の陽子線治療の費用対効果 (Cost-effectiveness of proton radiation in the treatment of childhood medulloblstoma), Lundkvist J, et al. Karolinska Institutet, Stockholm. Cancer 103; 793-801, 2005

背景：放射線治療は髄芽腫治療で重要な位置を占めているが、多くの患者が晩期障害のリスクを伴っている。陽子線治療は、従来の放射線よりも有害事象のリスクを減らせる可能性がある一方、コストが高くなる。この研究は、小児の髄芽腫の治療における陽子線治療と従来のＸ線治療の費用対効果の比較することを目的とした。

方法：マルコフシミュレーションモデルを使って放射線治療の結果を評価した。５歳の髄芽腫の患児を経過観察した。患児は、聴力低下、知能低下、甲状腺機能低下、成長ホルモン低下、骨粗鬆症、心臓病、二次がんなど多様な合併症のリスクがある。患者は、死亡のリスクもあり、通常の死、腫瘍再発による死、治療関連心臓疾患による死、治療関連二次がんによる死、他の治療関連死のリスクグループに分類された。モデル内のパラメーター決定のために文献がレビューされた。

結果：モデルとなった症例に関する解析では、陽子線治療は、23600 ユーロの費用削減になり、患者あたり QALY(Quality-adjusted life-years,QOL 質調整生存年)が 0.68 延長することがわかった。解析は、IQ 低下と成長ホルモン低下の減少が、費用削減に一番大きく貢献し、費用対効果にとって重要であることが示された。

結果：陽子線治療は、小児髄芽腫の治療において、適切な患者選択をすることによって、従来の放射線治療に比べて、費用対効果が優れ、費用削減効果もあることが示された。しかし、長期生存の研究は少なく、放射線治療の長期成績に関するさらなる情報収集が必要である。

文献２　表 A. 患者 100 人あたりの放射線誘発有害事象

変数	聴力低下	甲状腺機能低下	骨粗鬆症	成長ホルモン不足	非致死的二次がん	致死的事象
従来の X 線治療	11.9	16.3	0.4	17.1	1.2	1.91
陽子線治療	1.4	2.7	0.1	2.0	0.7	0.38
差	10.5	13.6	0.3	15.1	0.5	1.53

＊過去の報告から、患児の QOL が陽子線治療で改善が期待できる 100 人当たりの人数。

文献２　表 B. 5 歳の髄芽腫を基本例として計算した費用と結果

変数	陽子線治療	従来の放射線治療	差
放射線治療費用（€）	10217.9	4239.1	5978.8
副作用費用(€)	4231.8	33857.1	－29625.3
総費用（€）	14449.7	38096.2	－23646.5
LYG	13.866	13.600	0.266

QALY	12.778	12.095	0.683
LYG: 生存年数の延長　；　QALY: 生活の質（QOL）質調整生存年			

＊それぞれの有害反応に対する薬剤費や、有害反応による患者の能力低下による生産性の低下を考慮すると、陽子線治療のほうが対費用効果も優れていることがわかった。

＊一つの陽子線治療施設が、髄芽腫だけで施設を維持するためには、年間１１０例の髄芽腫を治療する必要がある。

＊しかし、仮に髄芽腫だけの治療で施設維持が不可能であって、費用節約(cost-saving)にならなくても、陽子線治療は明らかに対費用効果が優れている(cost-effective)。

文献２　表 C. 費用と活動性の差：陽子線治療と従来 X 線治療

費用発生源	費用の差（€）	効用値の差
全体の差	-23646.5	0.683
放射線治療	5978.8	-
知能指数低下	-12206.9	-
聴力低下	-2735.5	0.057
成長ホルモン不足	-14263.2	0.367
甲状腺機能低下	-202.0	0.009
骨粗しょう症	-18.3	0.001
致死的＋非致死的二次がん	95.6	0.021
他の致死的有害事象	-	0.230

参考資料

髄芽腫への放射線治療による内分泌機能障害発生率に関する陽子線治療の従来 X 線治療への優位性（米国臨床腫瘍学会 ASCO 2010 より）

線種	施設・出典	解析対象数	内分泌障害発生頻度（%）
X 線	Ribi, eta al. Zurich University Neuropediarics, 2005, 36(6), 357-65	51	31 (61%)
X 線	Yasuda, et al. 北海道大学 Jpn J Clin Oncol, 38(7), 486-492	16	8 (50%)
陽子線	Yock et al. Massachusetts General Hospital ASCO Proceedings, 2010	59	17 (29%)

＜炭素線治療＞

文献３．直腸癌再発に対する炭素イオン放射線治療の費用対効果(Cost-effectiveness of carbon ion radiation therapy for local recurrent rectal cancer)

モバラキ、大野、山田、櫻井、中野.　群馬大学、放医研

Mobaraki A, Ohno T, Yamada S, Sakurai H, Nakano T.

Gunma University & NIRS

Cancer Science 101: 1834 – 1839, 2010.

[要旨]　診断、再発治療、経過観察、患者移動、補完療法、合併症、入院に関して個々の患者２５名について検討。患者は、直腸の腺癌の原発部の再発に対して根治的手術のみを行い摘出不能の骨盤再発を起こしている。治療は炭素線治療あるいは、３次元原体照射＋化学療法＋温熱療法の比較を行った。２年生存率は、炭素線で８５％、化学放射線治療で５５％であった。平均的な費用は、炭素線治療で４８０万３９４６円、従来治療法で４６１万１１００円であった。炭素線の incremental cost-effectiveness ratio (ICER)を調べると、１％の生存率増加を期待するのに６４２８円の増加であった。必要入院期間は炭素線で３７日、化学放射線治療で６６日であった。炭素線治療は、費用対効果の優れた治療方法であると結論された。

文献３．表. 局所直腸癌再発への従来化学放射線治療と重粒子線治療の増分費用効用比

治 療 方	著者	年	症	５年生	５年局所	再再発に	無病生存	1%生存率増

法			例数	存率（%）	制御率（%）	よる費用(¥)	率のICER(¥)	加あたりのICER(¥)
従来治療法	Willet et al	1991	30	27	38	1752218	10424	12205
	Bussierses et al	1996	73	31	29	1337219	20300	16343
	Valentini et al.	1999	47	22	31	1429441	16769	9271
	Wing et al	2000	107	30	50	2305550	6323	15066
平均			64	27.5	37	1706107	13454	13221
炭素線	Tsujii et al	2008	90	42.8	19.5	936770		

ICER, Incremental cost-effective ratio （増分費用効果比）