Table 1 Patient characteristics

Age (range) (years)	57 (17–84)
Gender (male/female)	52/38
Primary site	
Maxillary sinus	12
Ethmoid sinus	8
Sphenoid sinus	5
Nasal cavity	62
Other site	3
Tumor type	
Squamous cell carcinoma	22
Adenoid cystic carcinoma	15
Olfactory neuroblastoma	27
Melanoma	14
Others	12
TNM stage	
T	
T1	4
T2	16
T3	9
T4	54
Tx	7
N	
N0	88
N1[a]	3
N2	0
PBT dose schedule ($BED_{3.0}$)	
70 GyE/28 fr (128.3 Gy)	5
70 GyE/35 fr (116.7 Gy)	4
66 Gy/33 fr (110 Gy)	1
65 GyE/26 fr (119.2 Gy)	61
60 GyE/15 fr (140 Gy)	14
60 GyE<	5

fr Fraction, *PBT* proton beam therapy, *BED* biological equivalent dose

[a] All lymph node metastases had located nearby primary tumor.

time was censored at the last confirmed date of survival if the patient was alive. Progression-free survival time was defined from the start of treatment to the first day of confirmation of progressive disease at any site or any cause of death.

Results

Patient characteristics

A total of 112 patients with malignancies of the nasal cavity, paranasal sinuses, or involving the skull base were treated using PBT. For 10 patients, the follow-up duration was 1 year or less, mainly because patients were referred to our institution from hospitals or institutions located far from our institution. Another 12 patients died within 1 year after PBT. Therefore, as for late toxicities, the remaining 90 patients were reviewed in the current study.

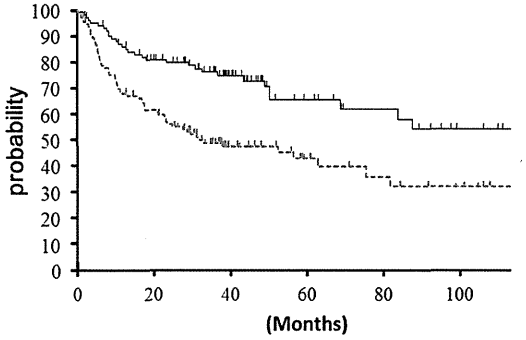

Fig. 1 Overall and progression-free survival for all the 112 patients. *Solid line* indicates overall survival curve; *broken line* indicates progression-free survival curve. With a median follow-up period of 57.5 months, 3-year overall survival and progression-free survival rates were 74.7 % and 48.2 %, respectively, and the 5-year overall and progression-free rates were 64.2 % and 44.5 %, respectively

Median age was 57 years (range, 17–84 years). The major primary site was the nasal cavity ($n = 62$, 69 %). Regarding treatment, 16 patients received surgery before PBT, and 20 patients received induction chemotherapy before PBT. Eleven patients received PBT concurrently with cisplatin, and the remaining patients received PBT alone.

The most common treatment was PBT alone at 65 GyE in 26 fractions. Patient characteristics are listed in Table 1.

Treatment outcome

Median observation period was 57.5 months (range, 12.4–162.7 months). Among 112 patients, the 5-year progression-free and overall survival rates were 44.5 % and 64.2 %, respectively (Fig. 1). A total of 55 patients were confirmed to have tumor progression, consisting of 26, 14, and 15 patients with local, regional, and distant failure, respectively. Eleven patients had not visited for more than 2 years, and we were unable to confirm death. Of these 11, recurrence could not be confirmed in 7 patients.

Late toxicity profile

The toxicity profile is listed in Table 2. Median time to onset of grade 2 or greater late toxicity, except cataract, was 39.2 months (range, 2.7–99.8 months), and 3 patients developed grade 2 or more severe toxicities; the interval from the completion of PBT was more than 5 years. Grade 3 late toxicities occurred in 17 patients (19 %) with 19 events. Grade 3 osteonecrosis caused by exodontia after

Table 2 Late toxicity ($n = 90$)

Grade (CTCAE version 4.0)	1	2	3	4
Hearing loss	1	1	2	0
Nerve disorder[a]	0	1	1	0
Encephalomyelitis infection	0	0	0	2
Cataract	1	1	5	0
Optic nerve disorder	0	4	1	4
Necrosis (other, specify)[b]				
Brain	5	1	1	0
Soft tissue	0	0	1	0
Bone	0	4	2	0

[a] All central nervous system disorders (I–XII) were classified in this category

[b] In-field necrosis induced by PBT was classified in the nearest implication of CTCAE v4.0

PBT was observed in 2 patients. Grade 4 late toxicities occurred in 6 patients (7 %) with 6 events (encephalomyelitis infection 2, optic nerve disorder 4).

Case 1: optic nerve disorder Gr. 4

A 79-year-old man with T4 olfactory neuroblastoma of the nasal cavity received PBT alone. At 42 months after PBT, MRI revealed no evidence of malignancy (Fig. 2). However, he gradually became aware of decreased visual acuity 3 years after treatment, and finally became blind at 51 months after treatment.

Detailed information about patients with grade 4 optic nerve disorder is shown in Table 3.

Case 2: brain necrosis Gr. 1

A 68-year-old man whose disease was T4N0M0 squamous cell carcinoma of the nasal cavity received proton beam therapy with cisplatin. Three months after PBT, MRI revealed no evidence of malignancy, and no toxicity. This finding did not change during long-term follow-up for 24 months at 3-month intervals. However, at 24 months after treatment, an edematous change was found in a frontal lobe, and brain necrosis without symptoms was confirmed

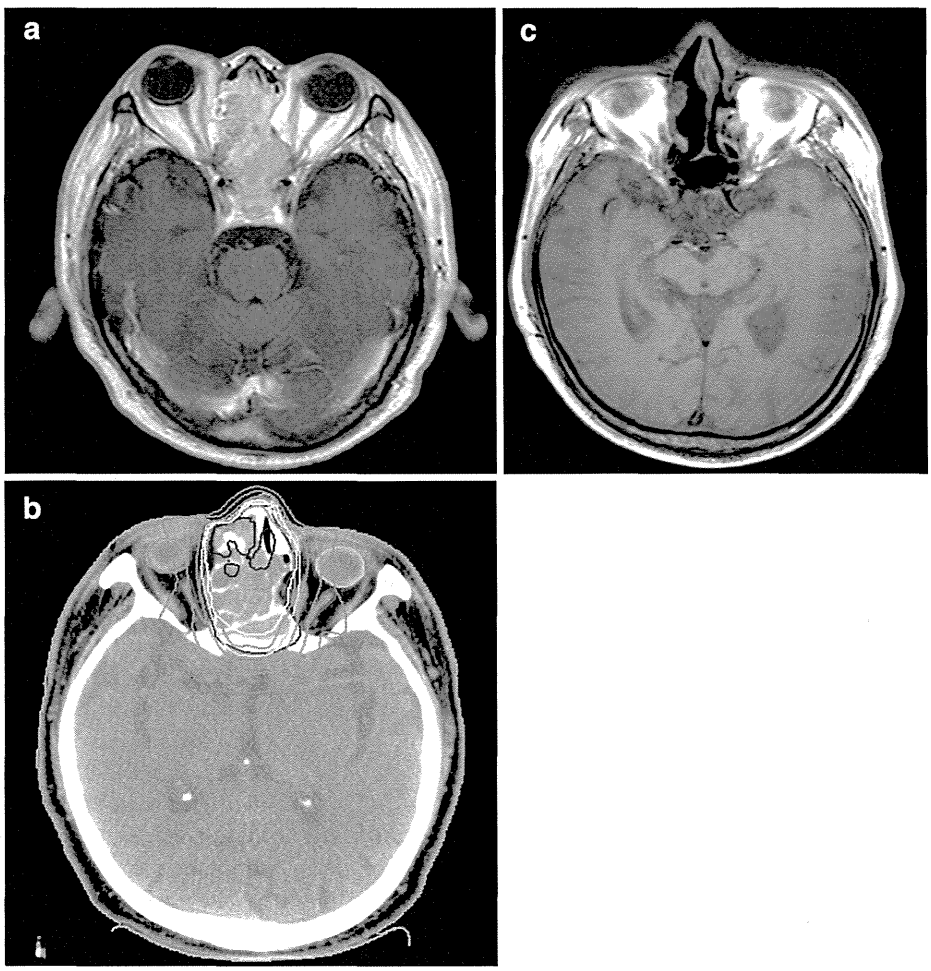

Fig. 2 Optic nerve disorder in a patient treated with proton beam therapy (PBT). **a** Magnetic resonance imaging (MRI) at pretreatment; **b** dose distribution of PBT; **c** MRI at 3 years after treatment. Dose-painting simulation of PBT indicated a maximum dose to the right optic nerve of 61.4 GyE. Although MRI at 3 years after treatment revealed no evidence of malignancy or change in the optic nerve, the patient became blind at 51 months after treatment

Table 3 Grade 4 optic nerve disorder in detail

Gender	Age	Primary site	T stage	Treatment		Chiasm and optic nerve volume >50 Gy/(max)	Time to onset	Status	
M	56	Nasal cavity	1	PBT alone	65 GyE/26 fr	0.5 cc/(63.7 GyE)	6Y2M	Alive w/o disease	8Y2 M
F	52	Nasopharynx	4	PBT alone	65 GyE/26 fr	0.2 cc/(65.3 GyE)	4Y3M	Alive w/o disease	6Y2 M
M	79	Nasal cavity	4	PBT alone	65 GyE/26 fr	0.17 cc/(61.4 GyE)	4Y3M	Alive w/o disease	4Y5 M
M	79	Nasal cavity	4	PBT alone	60 GyE/15 fr	0.03 cc/(53.2 GyE)	1Y5M	Died of disease	4Y6 M

M Male, *F* female, *Y* years, *M* months, *PBT* proton beam therapy, *w/o* without

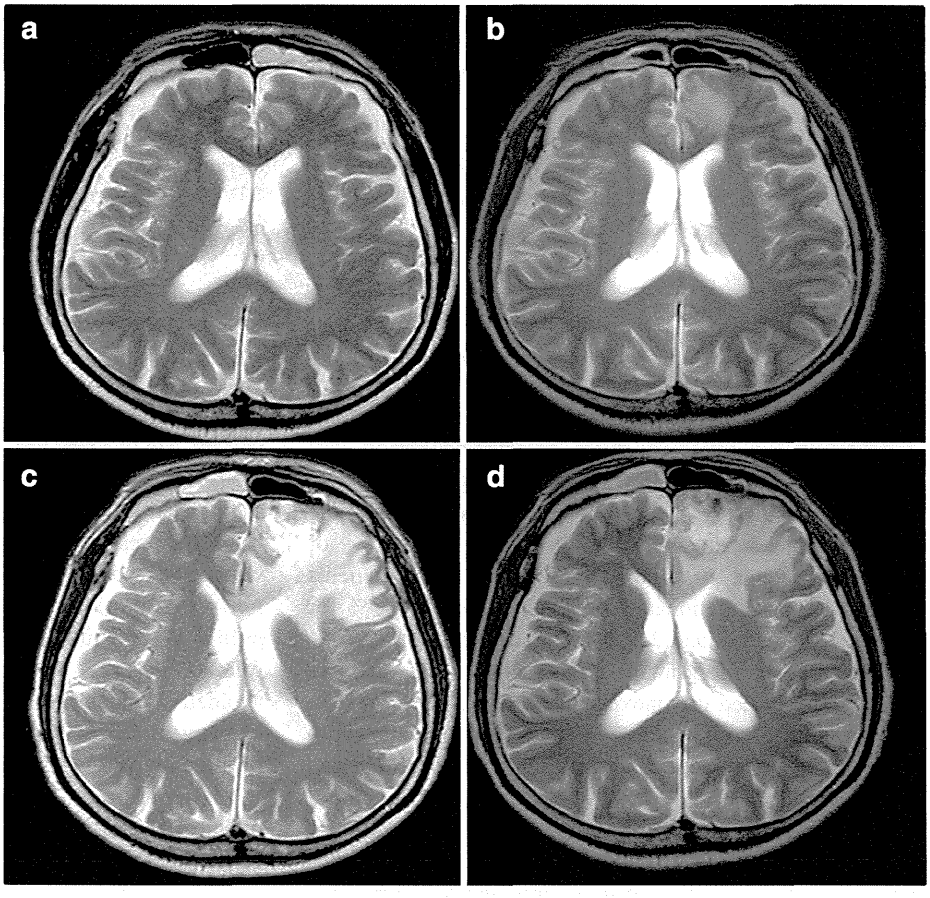

Fig. 3 Brain necrosis in a patient treated with PBT: MRI at pretreatment (**a**), 2 years after treatment (**b**), 2.5 years after treatment (**c**), and 3 years after treatment (**d**). The volume of brain to which was prescribed > 60 GyE was 17.5 cc and maximum dose was 65 GyE. The patient developed no serious symptoms throughout the follow-up period, and he presently remains alive at more than 4 years after treatment

at 30 months after treatment. This late toxicity gradually improved on MRI without additional treatment (Fig. 3).

Univariate analyses

In univariate analysis, T stage (T4 vs. non-T4), sex, age (less than 65 years vs. 65 years or more),induction chemotherapy (on vs. off), concurrent chemotherapy(on vs. off), dose per fraction (≥2.5 Gy vs. <2.5 Gy), and primary site (nasal cavity vs. others) were investigated. However, no significant factors with an impact on the frequency of brain necrosis and optic nerve disorder were identified (Table 4).

Mild to serious optic nerve disorder as late toxicities occurred in seven patients with T4 who had not received induction chemotherapy; these did not occur in patients with T4 who had received induction chemotherapy.

Discussion

This study clarified details of the late toxicity profile of PBT and late toxicity. The several previous reports of late toxicity following radiotherapy for the intracranial region have shown considerable variation in frequency. We

Table 4 Univariate analysis

Total		Brain necrosis			Optic nerve disorder		
		% ≥ Gr. 1	Odds ratio	95 % CI	% ≥ Gr. 2	Odds ratio	95 % CI
T4	54	9.3	1.73	0.32–9.47	14.9	2.53	0.49–13.0
Non-T4	36	5.6			5.6		
Male	52	3.8	0.29	0.60–1.43	11.5	1.46	0.39–5.48
Female	38	13.2			7.9		
65<	66	7.6	0.91	0.19–4.38	10.6	1.36	0.26–7.06
65≥	24	8.3			8.3		
Induction chemotherapy (+)	20	5.0	1.12	0.21–6.03	5.0	0.36	0.04–3.00
(−)	70	8.6			10.0		
Concurrent chemotherapy (+)	11	0.0	–	–	0.0	–	–
(−)	79	8.9			11.4		
≤2.5 Gy/1 fr	76	7.9	1.11	0.14–8.50	9.2	0.64	0.15–2.79
>2.5 Gy/1 fr	14	7.1			14.3		
Nasal cavity	62	6.5	0.60	0.14–2.51	8.1	1.13	0.23–5.47
Others	28	10.7			7.1		
T4	54						
T4 + induction	18	10.5	0.82	0.14–4.99	0.0	–	–
T4 w/o induction	36	11.1			19.4		

consider that a relatively short observation period will result in the underestimation of late toxicity.

Debus et al. [13] reported an incidence of chronic therapy-induced toxicity on median follow-up of 35 months (range, 3 months to 12 years) in 189 patients who underwent fractionated radiotherapy of only 1 % for grades 1–2 toxicity and 2.1 % for grade 3 disease.

With a median follow-up of 56 months, in contrast, Lee et al. [14] reported the unexpected development of severe late complications in 34.6 % of patients receiving hypofractionated stereotactic body radiotherapy (SBRT) as a boost treatment.

In our present data, median time to onset of grade 2 or greater late toxicity except cataract was 39.2 months (range, 2.7–99.8 months). Further, although only 5 patients (5.5 %) had severe late toxicities (≥grade 3) within 3 years after treatment, 17 patients (18.9 %) experienced 20 events during the total follow-up period. Mizoe et al. [15]. reported the late toxicity profile of carbon-ion therapy for their series of head and neck cancer patients of 52 (22 %, 52/236) events of all grades, and four cases of blindness. Previous reports are summarized in Table 5.

With regard to brain necrosis, several investigators [16–18] reported that severe brain injury was usually irreversible, and sometimes fatal. Surgical resection of a focal region of necrosis can be of benefit and may be life saving [19]. On the other hand, little is known about the outcome of mild or intermediate brain injury. In the present study, we found that some cases of mild or intermediate brain necrosis improved spontaneously after a long period.

In our present study, we experienced many events that would not usually be encountered without long-term follow-up, and an adequate understanding of the toxicity profile of PBT in these patients thus requires long-term follow-up. For T4 disease, severe late toxicities might be avoided by induction chemotherapy. We speculate that subsequent decrease in tumor size after PBT might have an positive impact on decrease in irradiation dose to the brain.

As for efficacy, Zenda et al. [10] reported a 5-year overall survival rate with PBT for unresectable carcinoma of the paranasal sinuses of 55.0 %, whereas Hoppe et al. reported a 5-year survival rate of definitive (chemo)radiotherapy for these patients of only 15 %. These results emphasize the ongoing need for considerable improvement in treatment strategies for these conditions.

One major limitation of this study warrants mention. The precision of dose calculations was made uncertain by the internal heterogeneity, which in turn prevented any medical physics analysis of the late toxicity profile. In particular, precise analysis of dosage from the current pencil-beam dosimeter algorithm is not possible [20].

As part of an ongoing physics evaluations, our group is presently conducting further recalculations of treatment plans for patients with fatal late toxicity using Monte Carlo methods.

Table 5 Previous reports of late toxicity

Age (range)					Follow-up period				
Author	Year	Disease	Pt No.	Treatment	Per fraction	Total dose	Median (range)	Late toxicity in detail (%)	
Schulz-Ertner et al.	2005	ACC of skull base	53	24: RT-FSRT/ IMRT boost	–	70 Gy	24 (2–92) M	≥Gr. 3 late toxicity	1.8
				29: RT-CI boost	54 Gy–3 GyEx6	72 GyE	16 (2–60) M		
Uy et al.	2002	Intracranial meningioma	40	25: Ope-IMRT	1.7–2.0 Gy	40–56 Gy	30 (6–71) M	≥Gr. 3 late toxicity	7.5
				15: IMRT					
Debus et al.	2001	Skull base meningioma	189	RT alone	1.8 Gy	56.8 Gy	35 (3–144) M	≥Gr. 3 late toxicity	2.1
Pehlivan et al.	2011	Skull base tumor	62	PBT alone	1.8–2.0 GyE	63–74 GyE	38 (14–92) M	≥Gr. 3 TL toxicity	3.2
								≥Gr. 1 TL toxicity	11.2
Weber et al.	2012	Intracranial meningioma	39	31: Ope-PBT	–	55.5–66.1 GyE	49.3 (11.5–93.3) M	5-year toxicity free survival	84.5
				8: PBT				≥Gr. 3 late toxicity	12.8
Lee et al.	2012	Head and neck cancer	26	EBRT-SBRT	EBRT: 45–50.4 Gy/25–28 fr SBRT: 10–25 Gy/3–5 fr		56 (27.6–80.2) M	≥Gr. 4 late toxicity	3.8
									34.6
								≥Gr. 3 late toxicity	
Mizoe et al.	2012	Head and neck cancer	236	Carbon-ion therapy	3.6 GyE (4GyE)	57.6 GyE (64 GyE)	<60 months	All grade late toxicity	22.0
Present study		Nasal/paranasal malignancies and skull base tumors	90	16: Ope-PBT(+CDDP)	2.0–4.0 GyE	60–70 GyE	59.7 (12.4–169.7) M	≥Gr. 4 late toxicity	6.6
				74: PBT(+CDDP)				≥Gr. 3 late toxicity	21.1

Pt patient, *No* number, *ACC* adenoid cystic carcinoma, *RT* radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *IMRT* intensity modulated radiotherapy, *M* months, *Gr* Grade, *PBT* proton beam therapy, *TL* temporal lobe, *EBRT* external-beam radiotherapy, *SBRT* stereotactic body radiotherapy

In conclusion, the late toxicity profile of proton beam therapy in patients with malignancy involving the nasal cavity, para-nasal sinuses, or skull base was partly clarified. Because late toxicity can occur as late as 5 years after treatment, long-term follow-up is necessary.

Conflict of interest The authors declare that they have no conflict of interest.

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臨床経験

スペーサー挿入術により消化管が近接する腫瘍に陽子線治療を施行した6例

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骨盤内や後腹膜の腫瘍への放射線治療は，消化管が近接し高線量照射が難しい．エックス線治療より線量集中性が良い陽子線治療においても，消化管への線量低減が図り難い．われわれは消化管近接腫瘍への陽子線治療に際し，スペーサーを腫瘍と消化管の間に挿入している．子宮頸癌2例・子宮体癌1例・子宮肉腫1例・S状結腸癌1例・直腸癌1例の計6例に対し，スペーサー挿入後に陽子線治療を施行した．うち1例は同部位への照射歴を有していた．術式は，大網で包んだゴアテックスを腫瘍と消化管の間に固定し，消化管との間にセーフティーマージンを確保するという方法である．1例は小腸を切除したため，腸間膜をスペーサーとして用いた．術後，CTで腫瘍と消化管の間のセーフティーマージンを確認し，消化管近接腫瘍に対する高線量照射を安全に行い得た．

索引用語：スペーサー挿入術，陽子線治療，放射線治療

緒　言

陽子線治療は，1946年にWilsonによって初めて提唱されて以来，悪性腫瘍に対する治療として用いられてきた[1)~6)]．特に，肝細胞癌・肺癌・前立腺癌・頭頸部癌に対する治療で良好な成績が報告されている[7)~9)]．陽子線の特長は，エックス線と比較して高い線量集中性と生物学的効果を有することである[2)~4)6)]．エックス線をはじめとする光子線や中性子線は，体表付近で最も高エネルギーであり，徐々に減衰しながら標的臓器へ向かいそのまま後方に突き抜けるため，標的の周囲の組織にも一定の線量が照射されてしまう．一方，陽子線をはじめとする粒子線は「ブラッグ・ピーク」というエネルギーのピークに一定の深さで到達し，後方にほとんど影響を及ぼさず標的に高線量を照射できる（**Fig. 1**）．

しかし，骨盤内や後腹膜の腫瘍では標的が消化管に近接しており，放射線性腸炎の危険性が高く[10)~15)]，エックス線よりも線量集中性の良い陽子線であっても高線量の照射は困難であり，治療対象は限定される[16)17)]．われわれは，消化管への線量低減を図り，消化管近接腫瘍への陽子線治療の適応を拡大するため，開腹下に再発悪性腫瘍周囲へスペーサーを挿入している．スペーサーにより，近接する消化管への合併症なく再発悪性腫瘍へ陽子線照射を施行した6症例を経験したので，特に1症例の詳細を具体的に供覧しながら論じる．

症　例

症例は，2010年9月から2012年7月までに経験した

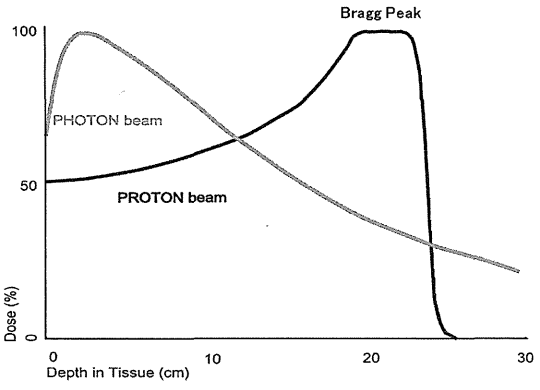

Fig. 1：Dose distribution of photon beam and proton beam in vivo. Proton beam has a Bragg Peak.

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Table 1 : Six cases experienced in our institution.

	Age	Sex	Disease	Site of recurrence	History of radiation	Proton irradiation plan	Complications
Case 1	52	F	Cervical cancer	Inside of pelvis, urinary tract invasion	45 Gy, Inside of pelvis	72.6 GyE / 22 Fr	–
Case 2	57	F	Uterine sarcoma	Inside of pelvis, urinary tract invasion + right lung	–	72 GyE / 18 Fr	–
Case 3	63	F	Endometrial cancer	Para-aortic lymph nodes, aortic invasion	50 Gy, Retroperitoneal lymph nodes	60 GyE / 20 Fr	–
Case 4	44	F	Sigmoid colon cancer	Retroperitoneal lymph nodes, urinary tract invasion	–	60 GyE / 20 Fr	Displacement of spacer
Case 5	53	M	Rectum cancer	Pelvic lymph nodes, external iliac artery invasion	–	69 GyE / 23 Fr	–
Case 6	74	F	Cervical cancer	Inside of pelvis + para-aortic lymph nodes	CCRT, Uterine cervix (primary tumor)	54 GyE / 18 Fr	Displacement of spacer

History of radiation to the recurrent tumors, targets of proton therapy, was found in the case 1 and 3. History of radiation to the primary tumor was found in the case 6. Displacement of the spacer during the course of proton therapy was found in the case 4 and 6. We could irradiate calculated dosage after reexamining the plan for proton therapy in the case 4. We had to stop proton irradiation in the case 6. In other cases, we found no such complications as might disrupt proton radiation.

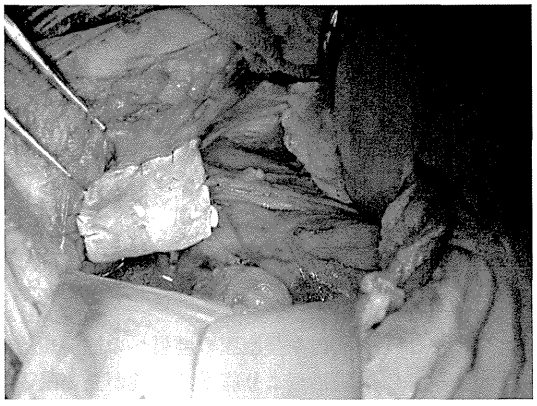

Fig. 2 : Operative findings show that the gore-tex sheet is placed at the anterior aspect of the recurrent tumor.

子宮頸癌2例・子宮体癌1例・子宮肉腫1例・S状結腸癌1例・直腸癌1例の計6例で，再発部位は骨盤底1例・後腹膜リンパ節2例・骨盤リンパ節1例・骨盤内＋傍大動脈リンパ節1例・肺＋骨盤内1例であった（**Table 1**）．いずれの症例も，術前のCTでは照射部位に消化管が近接しており，陽子線照射による消化管障害を回避できないと判断され，開腹下で腫瘍と消化管の間にスペーサーを挿入した（**Fig. 2**）．症例3は再発部位へのエックス線照射歴を有していた．スペーサー挿入術の術式は，折り畳んだゴアテックスを腫瘍と消化管の間に挿入し周囲の結合織と糸針で密に固定し，さらに大網で覆いセーフティーマージンを確保するという方法を標準としているが，症例2では小腸を切除したため腸間膜をスペーサーとして用いた．大網は距離を確保しボリュームを得るために，胃への脈管を切離して右あるいは左の胃大網動静脈を茎とするようデザインした．スペーサーを挿入することで，再発腫瘍と消化管との間に充分なマージンが確保され，高線量の陽子線の照射が可能となった（**Fig. 3a～c**）．以下に具体的な1症例を提示する．

症例1：52歳，女性．

現病歴：子宮頸癌Stage Ⅲbに対して広汎子宮全摘術＋膀胱尿管新吻合術を施行した．術後4カ月で骨盤底再発に対し，放射線45Gyを照射したが，血球減少傾向が強く継続が困難であった．

既往歴：13歳からてんかんで内服加療中．

治療経過：初回手術から2年後，骨盤底腫瘍の再増大を認めた．前述の経過のため他臓器への影響が少な

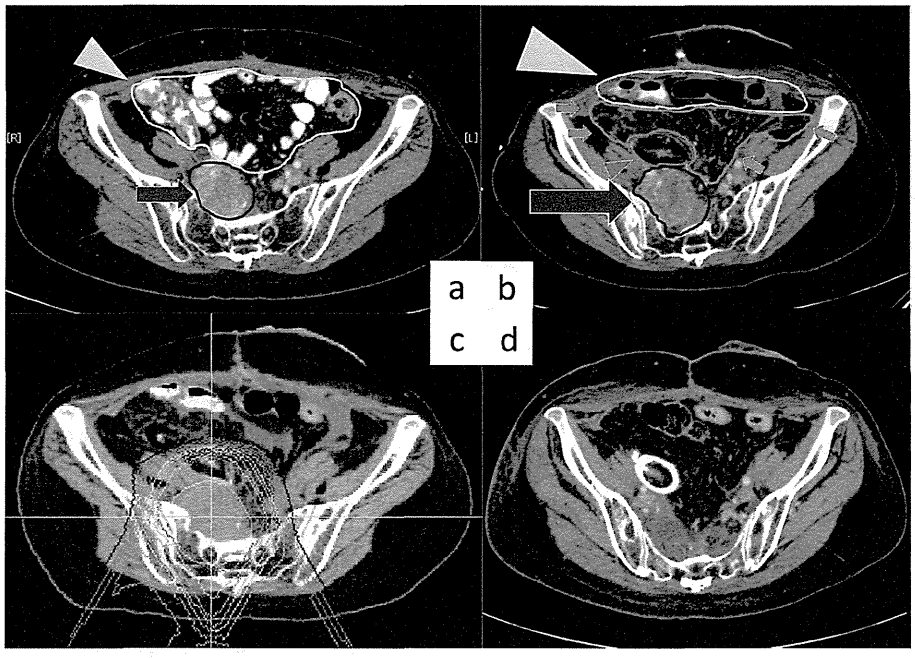

Fig. 3a : Abdominal CT before the operation shows the recurrent tumor (arrow) to be located very close to the gastrointestinal tract (arrow head).

b : The sufficient spacer between the tumor (arrow) and the gastrointestinal tract (arrow head) was obtained with the gore-tex sheet (small arrow head) and the greater omentum (small arrows) in CT.

c : Dose distribution curve of proton beam in treatment planning of the patient. Margin by the spacer has been secured between the tumor and the intestinal tract.

d : Abdominal CT four months after proton beam therapy shows the reduction of the recurrent tumor.

い陽子線治療を考慮したが，骨盤底の再発腫瘍近傍に小腸が落ち込んでおり安全な照射は困難であったため，スペーサー挿入術を施行した．仙骨前面の腫瘍の周囲を剥離し，数回折りたたんで10mm以上の厚みを持たせたゴアテックスシートを大網で被覆し，再発腫瘍前面に挿入し，周囲の組織と密に固定した．術後のCTで標的とする再発腫瘍と消化管の間に充分なマージンがあることを確認し，スペーサー挿入から17日後より陽子線治療72.6GyE/22Frを施行した（**Fig. 3a～c**）．陽子線治療後のCTでは明らかな腫瘍の縮小を認め，有効な局所制御効果が得られた（**Fig. 3d**）．

結　果

いずれの症例も，術前のCTでは陽子線照射予定部位に消化管が近接しており，他臓器への影響の少ない陽子線であっても消化管障害を回避できないと判断した．そこで，開腹下で腫瘍と消化管の間にスペーサーを挿入した．スペーサー挿入により，再発腫瘍と消化管との間に充分なマージンが確保され，高線量の陽子線の照射が可能となった．

スペーサー挿入術を施行した6例のうち，1例はスペーサーの移動により陽子線の照射計画を見直すこととなった．また，1例はスペーサーの移動により陽子線照射を中止した．その他4例は予定通りの照射を完遂することができた．いずれの症例も放射線性腸炎を含む明らかな合併症は認めなかった．

考　察

子宮頸癌・子宮体癌・子宮肉腫・大腸癌の再発に対して，各々のガイドライン上では可能な限り外科的切除が推奨されているが，切除不能例においては放射線治療も選択肢の一つとされ，長期生存症例など多数の報告がなされている[18)~20)]．

悪性腫瘍に対する放射線治療において，骨盤内腫瘍

や後腹膜腫瘍では消化管が近接しており，放射線照射による消化管障害が問題となる[10][11]．消化管に放射線照射が行われた際の有害事象は，消化管運動障害・出血性変化・潰瘍・狭窄・瘻孔形成等多岐にわたり，放射線性腸炎と称され治療に難渋する[10][12]．

筑波大学の陽子線治療は，1983年から開始され，近年は年間300例を超えている[7]~[9][21][22]．しかしながら，照射部位に消化管が近接している場合には，エックス線と比較して周囲への影響が少ない陽子線であっても放射線性腸炎の危険性から治療対象は限定されてきた[16][17]．われわれは，この難点を解決するため，2010年からスペーサー挿入術を施行している．

スペーサーにはシート状のゴアテックスと大網を主に用いた．数回折りたたんで10mm以上の厚みを持たせたゴアテックスシートを大網で被覆した上，再発腫瘍前面に挿入し，周囲の組織と密に固定した．

スペーサーにティッシューエクスパンダーを使用する方法は以前から報告されているが，放射線照射終了後に抜去が必要である[23][24]．スペーサーにティッシューエクスパンダーやゴアテックス等の人工物を使用する場合には消化管との癒着や摩擦による障害が問題となると考え[25][26]，われわれは大網でゴアテックスを被覆することでゴアテックスと消化管の接触を低減し，加えて大網もスペーサーの一部として更なる厚みをもたせることで腫瘍と消化管との間に充分なセーフティーマージンを確保することができた．症例2のように，腸間膜と大網をスペーサーとすることで，人工物は使用せず自家組織のみで充分なセーフティーマージンを確保できた症例も経験し，新たなスペーサーの作成の展望となると考えた．

術後のCTで標的とする再発腫瘍と消化管の間に充分なマージンがあることを確認し，陽子線照射を施行した．陽子線照射により標的病変に対して有効な局所制御効果が得られ，放射線性腸炎をはじめとする重篤な合併症は認めなかった．しかしながら，長期予後に関しては現段階では明らかではなく，今後の更なる症例の蓄積が必要である．

結　語

陽子線治療の標的とする再発悪性腫瘍に消化管が近接する6例に対してスペーサー挿入術を施行した．それぞれの症例の状況に応じて大網で被覆したゴアテックスや腸間膜，また大網そのものをスペーサーとして用いた．スペーサー挿入後に陽子線治療を行うことにより，消化管近接腫瘍に対して高線量の放射線を照射することが可能となった．

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SURGICAL SPACER INSERTION FOR PROTON BEAM THERAPY TO THE NEAR-GASTROINTESTINAL TUMOR—REPORT OF SIX CASES—

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High-dose rate radiotherapy for pelvic and retroperitoneal tumors is difficult due to the proximity of the gastrointestinal tract. Dose reduction to the gastrointestinal tract is difficult even for Proton beam therapy, which has better dose concentration than x-ray therapy. On the occasion of proton beam therapy to near-gastrointestinal tract tumors, we insert a spacer between the tumor and the gastrointestinal tract. We treated a total of six cases, including two cases of cervical cancer, each one case of endometrial cancer, uterine sarcoma, sigmoid colon cancer, and rectal cancer. Of these six cases, one had a history of radiation to the primary tumor, with proton beam therapy for a recurrent tumor after the spacer insertion. In this operation, gore-tex was wrapped by greater omentum in order to ensure safety margin and fixed between a recurrent tumor and the gastrointestinal tract. In one case, we used mesentery as a spacer because we had resected the small intestine. After the operation, we confirmed the safety margins between the recurrent tumor and the gastrointestinal tract by using CT, and safely achieved high-dose rate radiation to near-gastrointestinal tract tumors.

Key words : surgical spacer insertion, proton beam therapy, radiotherapy

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Review Article

Carbon Ion Therapy for Early-Stage Non-Small-Cell Lung Cancer

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Carbon ion therapy is a type of radiotherapies that can deliver high-dose radiation to a tumor while minimizing the dose delivered to the organs at risk; this profile differs from that of photon radiotherapy. Moreover, carbon ions are classified as high-linear energy transfer radiation and are expected to be effective for even photon-resistant tumors. Recently, high-precision radiotherapy modalities such as stereotactic body radiotherapy (SBRT), proton therapy, and carbon ion therapy have been used for patients with early-stage non-small-cell lung cancer, and the results are promising, as, for carbon ion therapy, local control and overall survival rates at 5 years are 80–90% and 40–50%, respectively. Carbon ion therapy may be theoretically superior to SBRT and proton therapy, but the literature that is currently available does not show a statistically significant difference among these treatments. Carbon ion therapy demonstrates a better dose distribution than both SBRT and proton therapy in most cases of early-stage lung cancer. Therefore, carbon ion therapy may be safer for treating patients with adverse conditions such as large tumors, central tumors, and poor pulmonary function. Furthermore, carbon ion therapy may also be suitable for dose escalation and hypofractionation.

1. Introduction

Carbon ion therapy, also known as carbon ion radiation therapy, is a type of radiotherapies that is categorized as particle therapy. While photons are used for conventional radiotherapy, beams with completely different characteristics (such as protons and carbon ions) are used in particle therapy. Heavy ion radiotherapy is a synonym of carbon ion therapy in current clinical practice.

At present, approximately 40 particle therapy centers are available worldwide. Only 8 have carbon ion therapy facilities (4 in Japan, 2 in Germany, 1 in China, and 1 in Italy), and the remainder have proton therapy facilities (current information available at the website of the Particle Therapy Co-Operative Group: http://www.ptcog.ch/). This disparity is likely to exist because proton therapy facilities are smaller and have lower installation costs and operating costs. For example, installation costs approximately 70 million USD for proton facilities are compared with approximately 140 million USD for carbon ion facilities. Furthermore, rotating gantries are basically only available for proton therapy facilities; Heidelberg Ion Beam Therapy Center (HIT), Germany, is the only institution that possesses a rotating gantry which can be used for carbon ion therapy.

2. History of Carbon Ion Therapy

The history of particle therapy began with proton therapy at Lawrence Berkeley Laboratory, 1954 [1]. After the trials with several types of particle therapy, including neutron, pion, helium ion, and neon ion, carbon ion therapy started at the National Institute of Radiological Sciences (NIRS), Japan, 1994 [2]. Among the various types of ion species, carbon ions were chosen for therapy because the biologically expressed dose distribution is assumed to be superior to other types of ion species. Additionally, the amount of high-linear energy transfer (LET) components is assumed to be sufficient to ensure a benefit by controlling radioresistant tumors. The details of physical and biological characteristics of carbon ion therapy are described below. Excellent clinical outcomes

Table 1: Comparison of the physical aspects of protons and carbon ions.

	Protons	Carbon ions
Rotating gantry	Available	Not available (fixed portals only)
Penumbra	Inferior	Superior
Range	Longer	Shorter

from NIRS led to the subsequent carbon ion therapy facilities, such as Gesellschaft für Schwerionenforschung, Germany, 1997; Hyogo Ion Beam Medical Center (HIBMC), Japan, 2002; Institute of Modern Physics, China, 2006; HIT, Germany, 2009; Gunma University Heavy Ion Medical Center, Japan, 2010; Centro Nazionale di Adroterapia Oncologica (CNAO), Italy, 2012; and Saga Heavy Ion Medical Accelerator, Tosu, Japan, 2013. Among these carbon ion therapy centers, HIBMC, HIT, and CNAO also have proton therapy facilities. More than 13,000 patients have been treated with carbon ion therapy around the world as of the end of 2013. Several carbon ion therapy facilities are under construction or in the planning phase worldwide, primarily in Japan.

3. Physical Characteristics of Carbon Ion Therapy

Photons consist of waves of light and do not possess an electric charge or mass, whereas charged particles such as protons and carbon ions possess electric charge and mass (Figure 1). Photons emit maximal energy near the body surface; this energy decreases gradually and passes through the entire thickness of body structures. In contrast, charged particles emit a relatively low dose near the body surface and deposit their maximum energy just before stopping in the deep interior of the body, an effect known as the Bragg peak. By modifying this peak according to the position and size of the tumor into a spread-out Bragg peak (SOBP) [3], it is possible to deliver high-dose radiation to a tumor while minimizing the dose delivered to the organs at risk (Figure 2).

Although both proton therapy and carbon ion therapy are charged particle therapies, there are slight differences in their physical characteristics. With respect to monoenergetic beams, carbon ion therapy shows a superior penumbra compared with proton therapy and low-dose leakage (<10%) on the distal side of the Bragg peak, unlike proton therapy (due to nuclear spallation reactions) (Figure 3). However, the latter issue does not impact practice because two or more portals are typically used in a clinical setting. The largest difference in the mechanical aspects of these approaches is the availability of a rotating gantry, which can rotate 360 degrees and allows the tumor to be irradiated from arbitrary angles. Table 1 shows a comparison between protons and carbon ions at HIBMC.

4. Biological Characteristics of Carbon Ion Therapy

Carbon ions, which are classified as high LET radiation, show a high ionization density and a high rate of DNA damage caused by the direct action of radiation. Carbon ions are likely to induce DNA double-strand breaks, which are difficult to repair and frequently lead to cell death [4]. Thus, carbon ions have the following biological characteristics and are expected to be effective even for photon-resistant tumors. First, they have a high relative biological effectiveness (RBE), showing

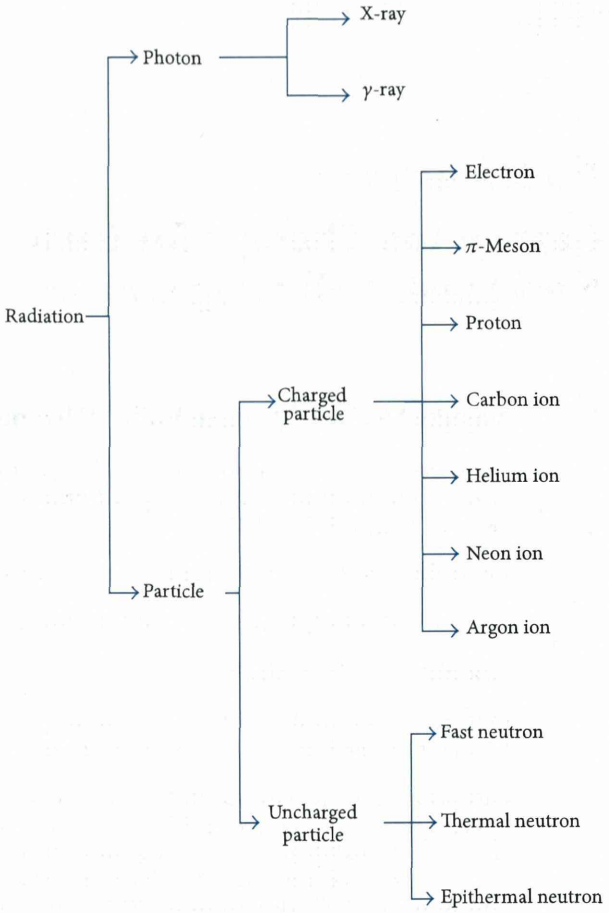


Figure 1: Types of radiation.

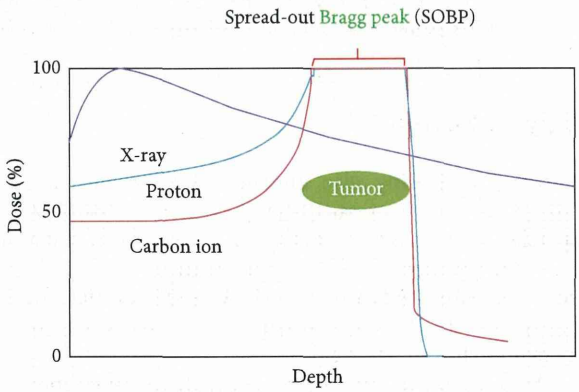


Figure 2: Dose distributions of X-rays, protons, and carbon ions.

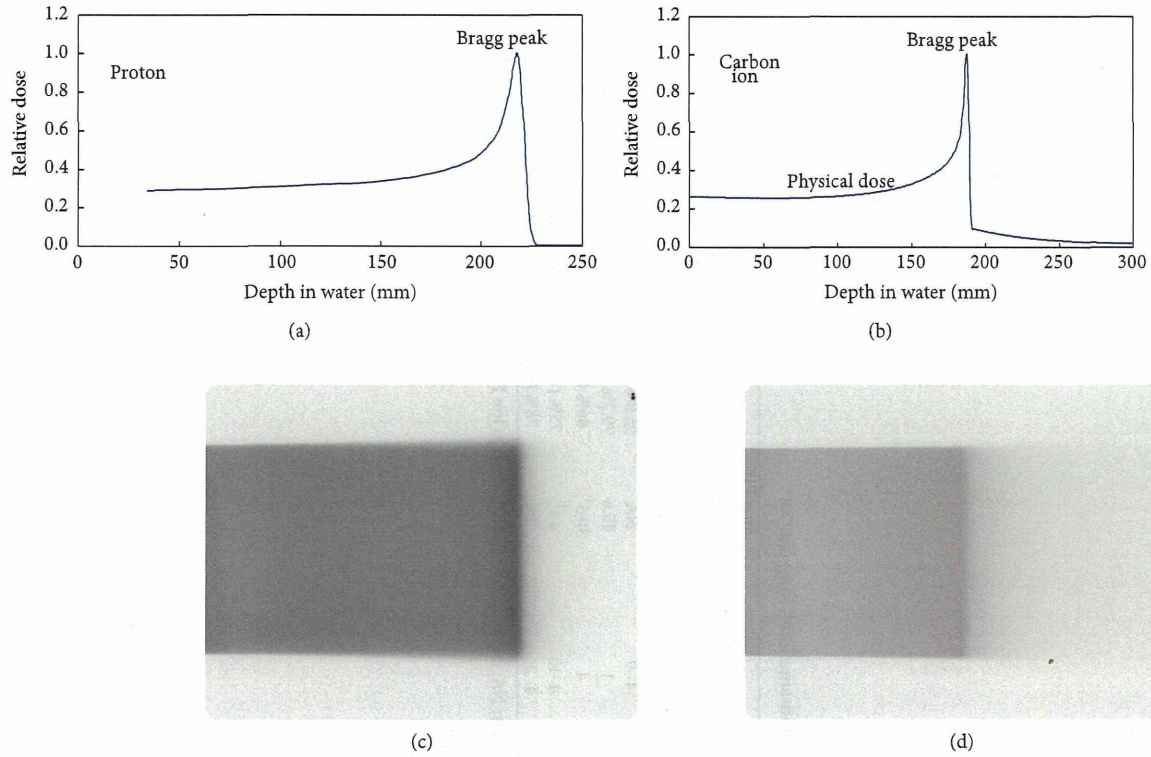


FIGURE 3: Differences in the dose distributions of proton ((a), (c)) and carbon ion ((b), (d)) monoenergetic beams ((a), (b) calculated and measured depth-dose curves; ((c), (d)) film densitometry).

1.2- to 3.5-fold greater biological effects compared with equal physical doses of photons, depending on the position of the SOBP. Second, they have a low oxygen enhancement ratio (OER), meaning that they are effective for treating photon-resistant hypoxic cells. Third, they are less dependent on the cell cycle, suggesting that they may be effective for treating photon-resistant late-S phase cells. The modes of carbon-ion-induced cell death and inactivation include apoptosis, necrosis, autophagy, premature senescence, accelerated differentiation, delayed reproductive death of progeny cells, and bystander cell death [4].

In addition to the excellent local effects, carbon ion therapy may suppress the metastatic potential of cancer cells. Based on *in vitro* and *in vivo* experiments, Ogata et al. suggested that carbon ion irradiation suppresses metastatic potential even at low doses, whereas photon irradiation promotes cell migration and invasive capabilities at a lower dose level [5]. They also provided preclinical evidence that carbon ion therapy is potentially superior to conventional photon therapy in preventing effects on metastases of irradiated malignant tumor cells. An *in vitro* study conducted by Akino et al. investigated the effects of carbon ion irradiation on the metastatic capacity in association with gene expression of non-small-cell lung cancer (NSCLC) cells [6]. The results showed that carbon ion irradiation effectively suppressed the metastatic potential of NSCLC cells. Carbon ion irradiation also had different effects on gene expression, and the down-regulation of a gene that is overexpressed in the majority of primary NSCLC was induced by carbon ion irradiation.

Notably, protons are classified as low LET radiation, and their biological effects are considered to be nearly the same as those of photons (RBE = 1.1) [7].

5. Carbon Ion Therapy for Early-Stage Non-Small-Cell Lung Cancer

Surgical resection with lobectomy has been the standard treatment of choice for early-stage NSCLC: overall survival (OS) rates at 5 years for stages I and II disease are 70% and 40–50%, respectively [8–10]. However, radiotherapy is an option for patients who are not suitable for surgery or refuse it. Recently, stereotactic body radiotherapy (SBRT) using photons has been increasingly used for such patients [11–14]. Another type of high-precision radiotherapy for early-stage NSCLC is particle therapy, including proton therapy [15–20] and carbon ion therapy [17, 19–25]. In this special issue, we focus on carbon ion therapy, and additional reports describe the details of SBRT and proton therapy.

Studies analyzing carbon ion therapy for early-stage NSCLC are summarized in Table 2. Only two Japanese institutions have published these data sets: NIRS [21–25] and HIBMC [17, 19, 20]. In terms of treatment system, NIRS uses horizontal and vertical fixed portals with semicylindrically shaped rotary capsule set on a treatment couch to reduce the disadvantage of unavailability of rotating gantry, whereas HIBMC uses horizontal, vertical, and 45-degree oblique fixed portals. Respiratory-gated irradiation systems are employed

Table 2: Studies of carbon ion therapy for early-stage non-small-cell lung cancer.

Author	Institute	Year	Number of patients	Age (years)	Number of lesions	T1	T2	Total dose [Gy (RBE)]	Number of fractions	Median FU (months)	Local control	Overall survival	Toxicity (≥grade 3)
Miyamoto et al. [21]	NIRS	2003	81	Mean 72	82	41	41	59.4–95.4	9–18	52.6	76% (5-yr)	42% (5-yr)	Lung 3.7%
Miyamoto et al. [22]	NIRS	2007	50	Mean 74.1	51	30	21	72	9	59.2	94.7% (5-yr)	50.0% (5-yr)	Skin 2%
Miyamoto et al. [23]	NIRS	2007	79	Mean 74.8	80	42	37	52.8–60	4	38.6	90% (5-yr)	45% (5-yr)	0%
Sugane et al. [24]	NIRS	2009	28	Mean 82*	29	12	17	52.8–72	4–9	NA	95.8% (5-yr)	30.7% (5-yr)	0%
Takahashi et al. [25]	NIRS	2014	151	Mean 73.9	151	91	60	36–50	1	45.6	79.2% (5-yr)	55.1% (5-yr)	0%
Iwata et al. [17]	HIBMC	2010	23	Median 75	23	15	8	52.8	4	30.5†	86% (3-yr)	86% (3-yr)	0%
Iwata et al. [19]	HIBMC	2013	27	Median 75‡	27	0	27	52.8–68.4	4–10	44†	75% (4-yr)§	55% (4-yr)§	Lung 7%, skin 7%‖
Fujii et al. [20]	HIBMC	2013	41	Median 76	41	26	15	52.8–70.2	4–26	39	78% (3-yr)	76% (3-yr)	Lung 5%, skin 4%

Gy: gray; RBE: relative biological effectiveness; FU: follow-up; NIRS: the National Institute of Radiological Sciences; yr: year; NA: not available; HIBMC: Hyogo Ion Beam Medical Center.

*80 years and older only.

†The median follow-up periods for all patients including both proton and carbon ion groups.

‡The median age for all patients including both proton and carbon ion groups.

§Values determined by reading graphs.

‖The rate for all patients including both proton and carbon ion groups.

at both institutions to minimize respiratory movements of the tumor and reduce treatment volume.

The NIRS group has published 5 reports. Miyamoto et al. started a phase I/II trial of carbon ion therapy for stage I NSCLC using 18-fraction regimens based on their years of experience with fast neutron therapy, which is also high LET radiation [21]. They conducted a dose escalation study from 59.4 to 95.4 Gy (RBE). (The particle beam dose is reported in Gy (RBE), which is defined as the physical dose multiplied by the RBE of the protons or carbon ions.) Then, they moved to 9-fraction regimens, with dose escalation from 68.4 to 79.2 Gy (RBE). The 5-year local control (LC) rates of the 18- and 9-fraction regimens were 64% and 84%, respectively (76% for all patients). The hypofractionated regimens showed much better LC. Grade 2 radiation pneumonitis occurred at a rate of 2/3 at the 79.2 Gy (RBE) dose level in 9-fraction regimens; therefore they concluded that 72 Gy (RBE), a dose 10% below 79.2 Gy (RBE), in 9 fractions was recommended regimen for a phase II study. The phase II study treated 50 patients with 51 lesions and showed an excellent 5-year LC rate of 94.7% without grade 3 or greater radiation pneumonitis [22]. The 5-year OS and cause-specific survival (CSS) rates were 50.0% (IA 55.2%; IB 42.9%) and 75.7% (IA 89.4%; IB 55.1%), respectively. Patients with stage IA disease showed significantly better OS and CSS compared to those with stage IB. Next, they conducted an additional phase II study using a regimen of 4 fractions during 1 week [23]. Seventy-nine patients with 80 lesions were treated with a fixed dose of 52.8 Gy (RBE) for stage IA and 60 Gy (RBE) for stage IB. The 5-year LC and OS rates were 90% (T1 98%; T2 80%) and 45% (IA 62%; IB 25%), respectively. No grade 3 or greater toxicities were detected. Although the patients treated in this study were approximately 10 years older than the patients treated by surgery, carbon ion therapy achieved impressive results. Therefore, Sugane et al. next focused on 28 patients aged 80 years and older (median 82 years, range 80–86 years) with stage I NSCLC who underwent carbon ion therapy with 52.8–72 Gy (RBE) in 4–9 fractions [24]. Outcomes were focused on the effectiveness of carbon ion therapy in treating their lung cancer and the impact on their activity of daily life (ADL). Pulmonary function was determined to be too poor for tumor resection by the referring surgeons in 16 patients, and 7 patients refused due to advanced age and poor systemic conditions. Five patients suffered from other diseases, including cardiovascular disease. The 5-year LC and OS rates were 95.8% and 30.7%, respectively. No grade 3 or greater toxicities occurred and no patients started home oxygen therapy or had decreased ADL. In their latest report, Takahashi et al. showed the preliminary results of a phase I/II trial as a dose escalation study using a single fraction [25]. The initial total dose was 28 Gy (RBE) and escalated in increments of 2 Gy (RBE), up to 50 Gy (RBE). For 151 patients treated with 36–50 Gy (RBE), the 5-year LC and OS rates were 79.2% and 55.1%, respectively. No grade 3 or greater toxicities were observed.

The HIBMC group has published 3 reports. HIBMC was established as the first institution in the world that could use both carbon ion therapy and proton therapy, 2001, and more than 6,100 patients have been treated as of the end of 2013. Thus, our studies include the results of both carbon ion therapy and proton therapy; however, here we describe only carbon ion therapy findings. At HIBMC, 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; thereafter, treatment plans for both proton therapy and carbon ion therapy were made for every patient. Then, the dose-volume histograms were compared, and the more suitable modality (proton therapy or carbon ion therapy) was determined and used for each patient. Iwata et al. reported the clinical outcome of carbon ion therapy for 23 patients with stage I NSCLC [17]. The protocol of 52.8 Gy (RBE) in 4 fractions was employed according to the NIRS study [23]. The 3-year LC and OS rates were 86% and 86%, respectively. No grade 3 or greater toxicities were observed. In the second report by Iwata et al. [19], their hypothesis was that particle therapy might be superior to SBRT in T2 (>3 cm) patients because it is rather difficult to treat T2 tumors with SBRT. Twenty-seven patients with T2 tumors were treated with 52.8–68.4 Gy (RBE) in 4–10 fractions. The 4-year LC and OS rates were 75% and 55%, respectively. Severe radiation pneumonitis (grade 3) was noted in 2 patients (7%). Both had T2b (>5 cm) disease and idiopathic pulmonary fibrosis with very poor respiratory function. They concluded that particle therapy was well tolerated and effective for T2N0 M0 NSCLC. The most recent report by Fujii et al. included 41 patients treated with 52.8–70.2 Gy (RBE) in 4–26 fractions [20]. The 3-year LC and OS rates were 78% and 76%, respectively. Severe radiation pneumonitis (grade 3) was observed in 2 patients (5%). In this study, they retrospectively compared the clinical outcomes of carbon ion therapy with those of proton therapy for stage I NSCLC and found no significant difference between the two groups.

Overall, the results of carbon ion therapy for early-stage NSCLC are promising and similar to those of SBRT or proton therapy in terms of LC, OS, and late toxicity. This result is not entirely expected because carbon ions are high LET radiation and could be expected to yield better outcomes. Grutters et al. reported a meta-analysis that compared the effectiveness of radiotherapy with photons, protons, and carbon ions for stage I NSCLC [26]. They concluded the following. (1) The corrected pooled 2- and 5-year OS estimates were 53% and 19%, respectively, for conventional radiotherapy; 70% and 42%, respectively, for SBRT; 61% and 40%, respectively, for proton therapy; and 74% and 42%, respectively, for carbon ion therapy. (2) The OS for patients treated with conventional radiotherapy was significantly shorter than that of patients receiving SBRT, proton therapy, or carbon ion therapy at both 2 and 5 years. (3) SBRT, proton therapy, and carbon ion therapy did not have significantly different 2- or 5-year OS rates. (4) The occurrence of severe adverse events (grades 3–5) was infrequent for all treatment modalities. From the literature currently available, it is difficult to claim that carbon ion therapy provides clinical outcomes that are superior to those of other high-precision radiotherapies such as SBRT and proton therapy.

Therefore, it is reasonable to examine the potential advantages of carbon ion therapy. It is unquestionable that

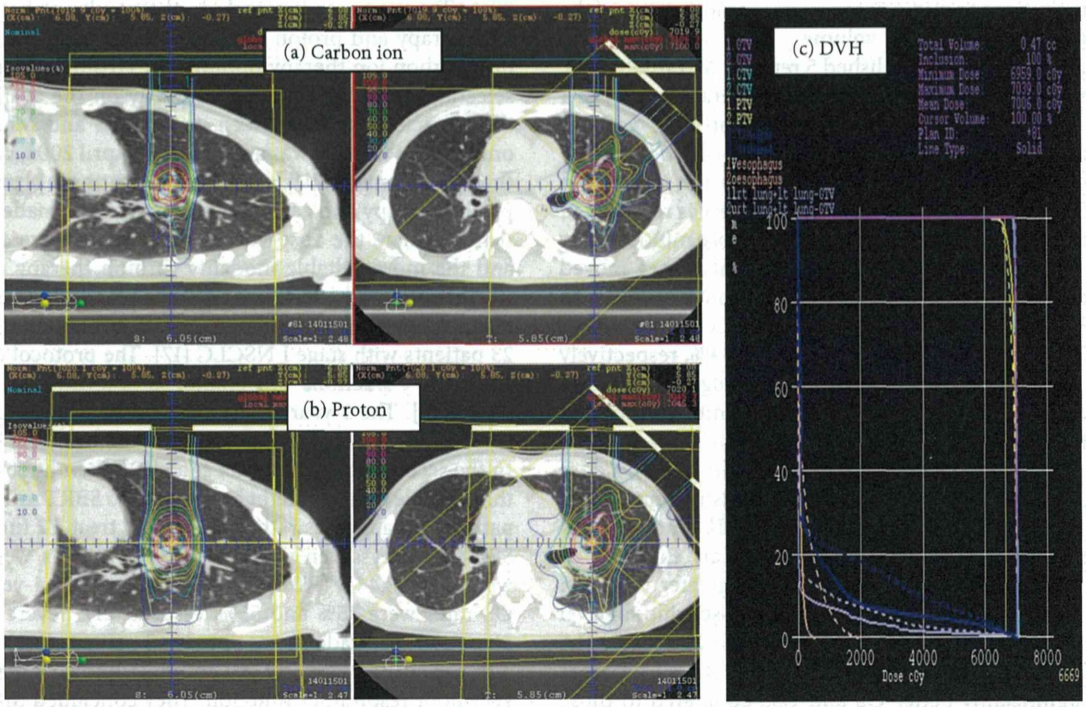
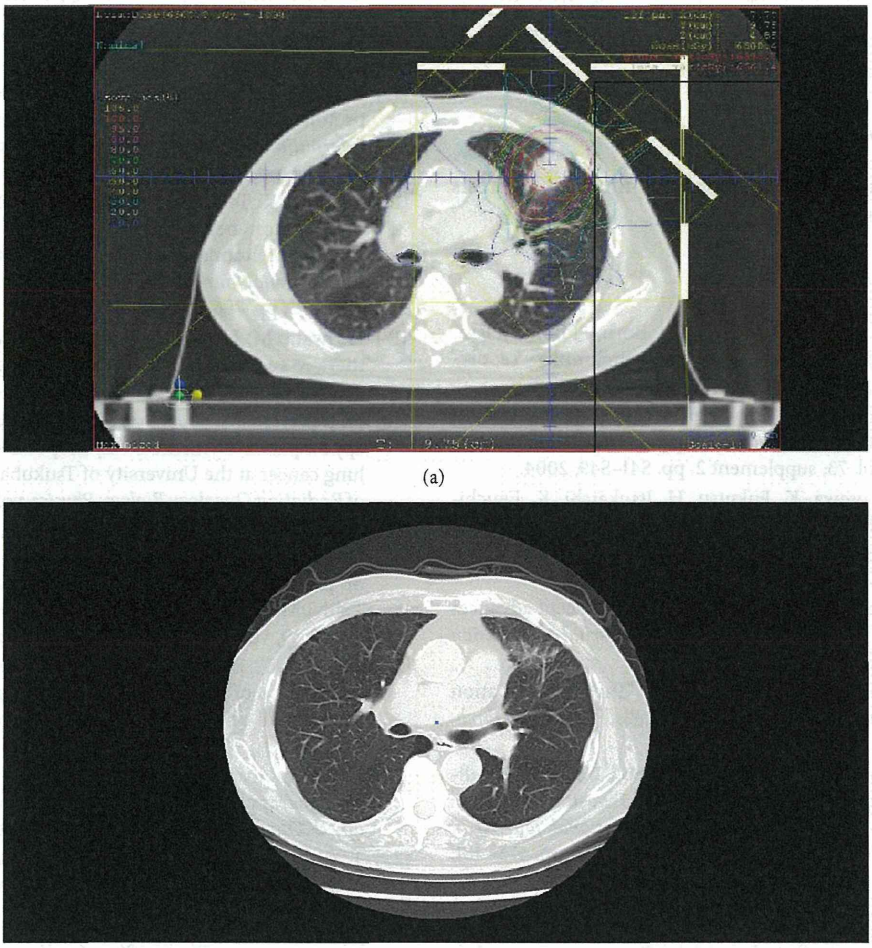


FIGURE 4: Comparison of the carbon ion (a) and proton (b) treatment plans for central-type T1aN0M0 non-small-cell lung cancer. The solid and dashed curves represent the carbon ion treatment plan and proton treatment plan, respectively, in the dose-volume histogram (DVH) (c). The carbon ion was selected for this patient.

carbon ion therapy shows a better dose distribution than SBRT in terms of the low-dose irradiated volume of the lung [27], but less is known about comparing carbon ion therapy with proton therapy. From our experience at HIBMC, where we routinely make both carbon ion and proton therapy plans for each patient, carbon ion therapy demonstrates a better dose distribution in most patients with early-stage lung cancer. A representative comparison of carbon ion therapy and proton therapy plans for central-type T1aN0M0 NSCLC is shown in Figure 4. In this case, it is possible for carbon ion therapy to reduce the doses to the lung, left main bronchus, and esophagus while achieving an equal coverage of target volumes as proton therapy. This superiority of carbon ion therapy to SBRT and proton therapy in dose distribution leads to several possible benefits. First, carbon ion therapy could be safer for treating patients with adverse conditions such as large tumors (e.g., T2), central tumors, or poor lung function. When treating large or central tumors, relatively large volumes of the lung, main bronchus, trachea, and esophagus, for example, are irradiated, and it is therefore preferable to avoid unnecessary irradiation as much as possible. When treating patients with poor lung function due to chronic obstructive pulmonary disease or interstitial pneumonitis, it is crucial to keep the lung dose as low as possible. Second, carbon ion therapy may be suitable for dose escalation and hypofractionation. Dose escalation would be warranted to improve local control, and the superb dose distribution of carbon ion therapy is advantageous in terms of safety. Hypofractionation is beneficial for both patients and health professionals because of the shortening of overall treatment time. However, from the perspective of radiation biology, a larger fraction size leads to an increase in late toxicities, and a smaller fraction number weakens the merits of fractionated irradiation by allowing the reoxygenation and redistribution of the cell cycle. Basic research studies have shown that carbon ion therapy shows low OER and low dependency on the cell cycle (see the chapter of biological characteristics of carbon ion therapy); therefore, the above biological disadvantages would not be the case. In fact, the NIRS group has successfully reduced the number of fractions and reached an ultimate single-fraction regimen, up to a total dose of 50 Gy (RBE) [21–23, 25]. Conversely, SBRT using 54 Gy in 3 fractions revealed a relatively high rate (16.4%) of ≥grade 3 late toxicities [13].

Figure 5 demonstrates a case of an 83-year-old male with peripheral-type T2aN0M0 NSCLC. Surgical resection and chemotherapy were contraindicated for this patient because of advanced age, poor lung function, chronic renal failure, and diabetes mellitus. He was treated with 66 Gy (RBE) of carbon ion therapy in 10 fractions (Figure 5(a)). The patient's acute reaction consisted only of grade 1 dermatitis. Five months later, the tumor showed a complete response, and grade 1 radiation pneumonitis was observed (Figure 5(b)). He is alive without recurrence 9 months after carbon ion therapy.



(a)

(b)

FIGURE 5: A patient with peripheral-type T2aN0M0 non-small-cell lung cancer that was treated with 66 Gy (RBE) of carbon ion therapy in 10 fractions. (a) Dose distribution. (b) A computed tomography image 5 months after carbon ion therapy.

6. Future Perspective

To further improve treatment outcomes, new irradiation technologies such as layer-stacking [28] and scanning [29, 30] are emerging. Although conventional passive beam irradiation benefits from relatively simple treatment planning requirements, one disadvantage of conventional beam irradiation is the significantly excessive dose delivered to the normal tissues along the entrance to the target. Layer-stacking and scanning to a greater extent can reduce this excessive dose, but it is challenging to adopt these technologies to moving targets such as lung tumors. If the day comes when these technologies are available in the clinical settings, carbon ion therapy will be the more effective and safer treatment option for early-stage NSCLC.

The progress of other treatment modalities such as SBRT, proton therapy, radiofrequency ablation, cryoablation, and less invasive surgery for early-stage NSCLC is also likely. It will be crucial to choose an appropriate modality for each case with careful consideration.

7. Conclusions

Carbon ion therapy for early-stage NSCLC has shown promising results and may be theoretically superior to other high-precision radiotherapy approaches such as SBRT and proton therapy in both physical and biological aspects. However, the currently available literature does not show a statistically significant clinical difference among these treatment options. Carbon ion therapy demonstrates a better dose distribution than SBRT (and even proton therapy) in most cases of early-stage lung cancer; thus, carbon ion therapy may be safer for treating patients with adverse conditions such as large tumors (e.g., T2), central tumors, and poor pulmonary function. Carbon ion therapy may also be suitable for dose escalation and hypofractionation. Prospective randomized

controlled trials are warranted to elucidate whether there is truly no difference in clinical outcomes among SBRT, proton therapy, and carbon ion therapy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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