２．学会誌・雑誌等における論文掲載（福本 巧、具 英成ら）

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
後腹膜脂肪肉腫術後再発に対してスペーサー手術および陽子線照射による2段階治療が奏効した1例	岩崎 寿光，福本 巧，出水 祐介，寺嶋 千貴，藤井 收，小松昇平，松本 逸平，味木 徹夫，不破 信和，具 英成	日本消化器外科学会雑誌. 47(7) 403-409		国内
同時性腸骨転移を伴う肝細胞癌に対し集学的治療を行い長期生存を得た1例	宗 慎一，木戸 正浩，福本 巧，武部 敦志，田中 基文，木下 秘我，蔵満 薫，津川 大介，福島 健司，浦出 剛史，吉田 俊彦，浅利 貞毅，岡崎 太郎，新関 亮，松本 逸平，味木 徹夫，具 英成	癌と化学療法. 41(12)2107-2109		国内
粒子線治療後に局所再発した転移性肝癌の1切除例	吉田 俊彦，武部 敦志，福本 巧，木戸 正浩，田中 基文，蔵満 薫，木下 秘我，津川 大介，福島 健司，浦出 剛史，宗 慎一，味木 徹夫，松本 逸平，新関 亮，岡崎 太郎，浅利 貞毅，後藤 直大，松本 拓，具 英成	癌と化学療法. 41(12) 2071-2073		国内

委託業務題目：「PGAスペーサーの有効性・安全性に関する臨床研究、
c．スペーサー治療研究会での粒子線治療の適応拡大と標準治療法の確立」
機関名：山形大学（医学部 放射線腫瘍学講座）

2．学会誌・雑誌等における論文掲載（根本 健二ら）

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Phase I/II trial of definitive carbon ion radiotherapy for prostate cancer: evaluation of shortening of treatment period to 3 weeks.	Nomiya T1, Tsuji H1, Maruyama K1, Toyama S1, Suzuki H2 Akakura K3, Shimazaki J4, Nemoto K5, Kamada T1, Tsujii H1; Working Group for Genitourinary Tumors	British Journal of Cancer. 110(10):2389-95.	13 May 2014	国際誌

委託業務題目：「PGAスペーサーの有効性・安全性に関する臨床研究、
c．スペーサー治療研究会での粒子線治療の適応拡大と標準治療法の確立」
機関名：国立がん研究センター東病院（粒子線医学開発分野）

1．学会等における口頭・ポスター発表（秋元 哲夫ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
粒子線治療の特徴と今後の展望(口演)	秋元哲夫	福岡(日本臨床腫瘍学会)	2014年7月	国内
Acute toxicities and DVH parameters for organ at risk in proton beam therapy for stage III non-small cell lung cancer	茂木 厚、秋元哲夫、他	米国(American Society for Radiation Oncology)	2014年9月	国外
食道癌に対する化学療法併用陽子線治療の有効性と可能性について	秋元哲夫、他	横浜(日本放射線腫瘍学会)	2014年12月	国内

2．学会誌・雑誌等における論文掲載（秋元 哲夫ら）

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up	Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, Hayashi R, Akimoto T	Int J Clin Oncol	2014年	国内

委託業務題目：「PGAスペーサーの有効性・安全性に関する臨床研究、
c．スペーサー治療研究会での粒子線治療の適応拡大と標準治療法の確立」
機関名：筑波大学（医学医療系 放射線腫瘍学）

1．学会等における口頭・ポスター発表（櫻井 英幸ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
スペーサーを併用した陽子線治療の初期経験	斎藤高，室伏景子，沼尻晴子，水本斉志，大西かよ子，石川仁，福光延吉，粟飯原輝人，奥村敏之，櫻井英幸	横浜（日本放射線腫瘍学会第 27 回大会）	2014. 12. 11-13	国内

2．学会誌・雑誌等における論文掲載（櫻井 英幸ら）

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
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	劔持明，久倉勝治，寺島秀夫，明石義正，櫻井英幸，大河内信弘	日本臨床外科学会雑誌 2014, 75(5):1164-1168.	2014.5	国内

委託業務題目：「PGAスペーサーの有効性・安全性に関する臨床研究、
c．スペーサー治療研究会での粒子線治療の適応拡大と標準治療法の確立」
機関名：脳神経疾患研究所 南東北がん陽子線治療センター

1．学会等における口頭・ポスター発表（中村 達也ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
高齢食道癌に対する陽子線治療の成績(口頭)	小野崇	日本放射線腫瘍学会(JASTRO)第27回学術大会	2014/12/11 ～13	国内
III期非小細胞肺癌に対する陽子線治療の初期治療成績	畑山佳臣	第131回 日本医学放射線学会 北日本地方会	2014/10/24	国内
再発口腔癌に対する動注化学陽子線療法の治療成績	林雄一郎	日本放射線腫瘍学会(JASTRO)第27回学術大会	2014/12/11 ～13	国内
鼻腔癌新鮮例に対する陽子線治療の初期経験	阿左見祐介	第 11 回 日本粒子線治療臨床研究会	2014/10/4	国内
Proton beam therapy for cancer	晴山雅人	International cancer symposium in Sakhalin	2014/10/1-3	国外
食道癌に対する X 線、陽子線を併用した化学放射線治療の治療成績	中村達也	第 68 回 日本食道学会学術集会	2014/7/3-4	国内

委託業務題目：「PGAスペーサーの有効性・安全性に関する臨床研究、
c．スペーサー治療研究会での粒子線治療の適応拡大と標準治療法の確立」
機関名：名古屋市立大学（医学系研究科 放射線医学）

1． 学会等における口頭・ポスター発表（岩田 宏満ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
陽子線治療における基礎生物-RBE・OER に関して-, 招待講演, 口頭発表	岩田宏満	日本放射線影響学会 第 57 回大会	2014/10	国内
Spot scanning 照射法による陽子線治療 -生物学的基礎検討・初期臨床経験-, 口頭発表	岩田 宏満, 荻野 浩幸, 服部 有希子, 橋本 眞吾, 安井 啓祐, 林 建佑, 歳藤 利行, 山田真帆, 馬場二三八, 芝本 雄太, 溝江 純悦	日本放射線種学会第 27 回学術大会	2014/12	国内

2．学会誌・雑誌等における論文掲載（岩田 宏満ら）

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Carbon ion therapy for early-stage non-small-cell lung cancer.	Demizu Y, Fujii O, Iwata H, Fuwa N.	Biomed Res Int.	2014 ;2014 :727962 Epub 2014 Sep 11	国外

委託業務題目：「次世代型・体内吸収性スペーサーの開発」
機関名：放射線医学総合研究所 重粒子医科学センター

1．学会等における口頭・ポスター発表（山田 滋ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Treatment of gastrointestinal tumors with particle therapy:口頭	Shigeru Yamada	Shanghai:53rd Annual Meeting of Particle	2014年6月	国外
大腸癌の術後再発に対する重粒子線治療:口頭	山田滋、安田茂雄、山本直敬、磯崎哲朗、塩見美帆、高橋渉、中嶋美緒,原田麻由美、鎌田正、辻井博彦	福岡:第 12 回日本臨床腫瘍学会	2014年7月	国内
消化器癌に対する重粒子線治療の現状と展望:口頭	山田 滋	福岡:第 39 回日本大腸肛門病学会	2014年9月	国内
消化器癌における重粒子線治療:口頭	山田 滋	横浜:第 3 回神奈川大腸がん治療セミナー	2014 年 11 月	国内
放射線治療後の直腸がん術後骨盤内局所再発に対する重粒子線治療の有効性の検討:口頭	山田 滋、磯崎由佳、安西誠、安田茂雄、鎌田正、辻井博彦	横浜:日本放射線腫瘍学会第 27 回	2014 年 12 月	国内
直腸癌局所再発に対する重粒子線治療適応拡大のためのスペーサーの有用性に関する研究:口頭	山田 滋、安西誠、安田茂雄、鎌田正、辻井博彦	神戸:第 4 回スペーサー治療研究会	2015年2月	国内
Particle Radiotherapy for Locally Recurrent Rectal Cancer:口頭	Shigeru Yamada	Seoul:2nd Samsung Colorectal Cancer Center Single Topic Symposium	2015年2月	国外

2．学会誌・雑誌等における論文掲載（山田 滋ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
直腸癌局所再発に対する重粒子線治療	山田滋・磯崎哲朗・磯崎由佳・安西誠・安田茂雄・鎌田正・辻井博彦	臨床外科	2014 年 10 月	国内

委託業務題目：「次世代型・体内吸収性スペーサーの開発」
機関名：獨協医科大学（医学部 放射線治療センター）

1．学会等における口頭・ポスター発表（村上 昌雄ら）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Efficacy of PGA spacer in particle therapy: a novel strategy making temporal space between tumor and adjacent organs	Hiroaki Akasaka, Ryohei Sasaki, Daisuke Miyawaki, Naritoshi Mukumoto, Nor Shazrina Sulaiman, Wang Tian Yuan, Shigeru Yamada, Masao Murakami, Yusuke Demizu, Takumi Fukumoto	Micro-mini & nano dosimetry and prostate cancer treatment workshop	2014年	国外
Interim assessment of clinical prospective ran-domized trial for patients with HCC between proton and carbon-ion radiotherapy	Murakami M, Terashima K, Nishimura K, Demizu Y, Fuwa N	The 15th Asian Oceanian Congress of Radiology	2014年9月	国内

Ⅳ. 研究成果の刊行物・別刷

吸収性スペーサーを用いた体内空間可変粒子線治療の
有用性と安全性の検討
（Ｈ２６－革新的がん－一般－０３０）
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Biology Contribution

Preclinical Evaluation of Bioabsorbable Polyglycolic Acid Spacer for Particle Therapy

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Summary

The authors aimed to evaluate the effectiveness of an implanted nonwoven fabric polyglycolic acid spacer for reducing damage to surrounding tissue from particle beam irradiation. The spacer exhibits excellent properties related to bio-absorbability, bio-compatibility, thickness retention, and water equivalency by physical and animal experiments. This study shows that this novel spacer

Purpose: To evaluate the efficacy and safety of a polyglycolic acid (PGA) spacer through physical and animal experiments.

Methods and Materials: The spacer was produced with surgical suture material made of PGA, forming a 3-dimensional nonwoven fabric. For evaluation or physical experiments, 150-MeV proton or 320-MeV carbon-ion beams were used to generate 60-mm width of spread-out Bragg peak. For animal experiments, the abdomens of C57BL/6 mice, with or without the inserted PGA spacers, were irradiated with 20 Gy of carbon-ion beam (290 MeV) using the spread-out Bragg peak. Body weight changes over time were scored, and radiation damage to the intestine was investigated using hematoxylin and eosin stain. Blood samples were also evaluated 24 days after the irradiation. Long-term thickness retention and safety were evaluated using crab-eating macaques.

Results: No chemical or structural changes after 100 Gy of proton or carbon-ion irradiation were observed in the PGA spacer. Water equivalency of the PGA spacer was equal to the water thickness under wet condition. During 24 days' observation after 20 Gy of carbon-ion irradiation, the body weights of mice with the PGA spacer were

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Conflict of interest: none.

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could be a useful device for particle therapy by making spaces between tumor and adjacent organs.

relatively unchanged, whereas significant weight loss was observed in those mice without the PGA spacer ($P<.05$). In mice with the PGA spacer, villus and crypt structure were preserved after irradiation. No inflammatory reactions or liver or renal dysfunctions due to placement of the PGA spacer were observed. In the abdomen of crab-eating macaques, thickness of the PGA spacer was maintained 8 weeks after placement.

Conclusions: The absorbable PGA spacer had water-equivalent, bio-compatible, and thickness-retaining properties. Although further evaluation is warranted in a clinical setting, the PGA spacer may be effective to stop proton or carbon-ion beams and to separate normal tissues from the radiation field.

Introduction

Particle therapy has emerged as a promising treatment modality, exhibiting more-focused effects on target tissues. Several systematic reviews associated with proton or carbon-ion therapy discuss the extensive use of particle therapy to treat various malignant tumors, including chordoma, ocular melanoma, and prostate cancer (1-3). Although several studies have indicated the efficacy of proton therapy for the treatment of hepatocellular carcinoma (4-6), the utility of proton therapy for other upper abdominal malignant tumors has not been clarified. One possible reason is that it is difficult to deliver curative doses of radiation to treat upper abdominal tumors without damaging adjacent, radiosensitive organs, such as the duodenum, jejunum, and stomach. Another reason seems to be that image guidance in this area is difficult, and organ motion due to breathing or peristalsis may alter the beam range (7, 8).

Previous studies of the treatment of prostate cancer have reported methods involving injection of a layer of hyaluronic acid or other gels to separate prostate and rectum (9-15), although, given the risk of puncture, this approach may not be readily adaptable for treatment of upper abdominal malignant tumors. A method using surgically placed Gore-Tex sheets as a spacer has been reported (16-18). Although this method provides for separation of adjacent organs, the material is not resorbed.

To overcome these anatomical and therapeutic difficulties, and to deliver effective radiation doses to treat upper abdominal tumors, we have developed a nonwoven fabric spacer composed of bio-absorbable suture material. The purpose of this preclinical study was to evaluate the efficacy and safety of the spacer by physical experiments and analyses in animal models.

Methods and Materials

Development and evaluation of a novel absorbable spacer: The polyglycolic acid spacer

The nonwoven spacer was produced with suture material made of a biocompatible synthetic polymeric material, polyglycolic acid (PGA). The process for producing the nonwoven fabric involves entangling threads in 3 dimensions using a needle punching process and other methods (19, 20). The PGA spacer is sterilized by ethylene oxide. After the sterilization, the ethylene oxide was completely removed from the PGA spacer.

The surface of the PGA spacer was examined before and after irradiation using a scanning electron microscope (SEM) (VE-7800; Keyence Japan, Osaka, Japan). Before the examination, the sample was mounted onto metal stubs and then coated with a gold/palladium alloy using a pulse plasma system.

The PGA spacer was analyzed before and after irradiation using a spectrophotometer (FT/IR-4200; Jasco, Easton, MD) with an attached attenuated total reflectance accessory (ATR PRO450-S; Jasco) at room temperature and under the following conditions: wave number range 600-4000 cm^{-1}; scan time 50 seconds; resolution 4 cm^{-1}.

Nuclear magnetic resonance (NMR) analysis was performed to study the structure and status of the PGA spacer before and after irradiation. The sample was prepared by mixing 100 μL of hydrolyzate with 100 μL of 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) and 800 μL of distilled water at room temperature.

The molecular weight of the PGA spacer was determined using a gel permeation chromatography unit consisting of a pump (LC-10ADvp), an injector (SIL-10ADvp), a detector (RID-10A), and an oven (CTO-10ADvp; all from Shimadzu, Kyoto, Japan). The HFIP was used as both the solvent and the eluent. Elution was performed at a temperature of 42°C and at a flow rate of 0.7 mL/min. The columns (KF-803, KF-804, HFIP-806; Showa Denko, Tokyo, Japan) were calibrated with polymethyl methacrylate standards.

The inherent viscosity of the PGA spacer before and after irradiation, calculated from the flow time measurement, was determined in the HFIP solution at 25°C using an Ubbelohde viscometer.

Irradiation

For the spectrophotometric, NMR, weight-average molecular weight, and viscosity examinations, 100 Gy of proton or carbon-ion beams were used for the evaluation of the PGA spacer at the Hyogo Ion Beam Medical Center (HIBMC) (21).

For physical study, a spread-out Bragg peak (SOBP) was established by proton or carbon-ion irradiation at the HIBMC (22). Dose distribution was evaluated using a 150-MeV proton or 320-MeV carbon-ion transmission passing through a ridge filter with a 60-mm width of SOBP. Dose calculations were performed using radiation treatment planning system software (Xio; Elekta, Tokyo, Japan) at the HIBMC. For the evaluation of SOBP shifts, the depth of a median dose of 20-80% distal fall-off from the beam axis was calculated.

For animal studies, mice were exposed to 20 Gy of carbon-ion (290 MeV) radiation using particles accelerated by the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS) (Chiba, Japan) (22). The depth–dose curve of the carbon-ion beam was modified with a range modulator to create a 60-mm-wide SOBP. All examinations were performed in accordance with the guidelines for animal experiments of the NIRS.

Evaluation for water equivalency of the PGA spacer

Water equivalency of the PGA spacer under dry or wet conditions was evaluated using proton or carbon-ion irradiation at the HIBMC. The size of the PGA spacer used in this test was 50 × 50 × 20 mm. The PGA spacer was mounted on the water phantom detector to measure the shift of the depth–dose curve.

Protective effect of the PGA spacer in vivo

Male C57BL/6 mice aged 8 weeks were irradiated with or without the insertion of the PGA spacer. Before each experiment, mice were anesthetized with somnopentyl (0.1 mg/g body weight), administered intraperitoneally. Each mouse was fixed on the board in the supine position with the head at 12 o'clock and the feet at 6 o'clock. The PGA spacer used in this experiment was 20 × 20 × 4 mm. The PGA spacer was surgically inserted between the intestine and the abdominal wall. Two weeks after placement of the spacer, the abdomens of the mice were irradiated using the carbon-ion beam. Weight changes of the mice were observed for 24 days after the irradiation.

To evaluate the protective effect of the PGA spacer, histologic analysis of villi and crypts of the intestine was performed. Seven days after irradiation, the intestines and the placed PGA spacers were removed from the abdomens and fixed in 10% formalin. Next, 2-cm sections of duodenum from each mouse were embedded in paraffin blocks, cut into 4-μm sections, and stained with hematoxylin and eosin.

Evaluation for toxicity of the PGA spacer by blood tests

Tests on blood collected 24 days after carbon-ion irradiation were performed to evaluate potential systemic toxicity associated with placement of the PGA spacer. Half of the blood of each mouse was used for blood cell counts, whereas the other half was centrifuged at 2500 rpm for 10 minutes to obtain serum. All sera were immediately frozen at −80°C and were subsequently evaluated for inflammatory reaction by C-reactive protein; liver toxicity by alanine transferase and lactate dehydrogenase; and renal toxicity by creatinine.

Long-term thickness retention and safety of the PGA spacer in vivo

Male crab-eating macaques (*Macaca fascicularis*, aged 4-6 years) were used to evaluate thickness-retaining properties and bio-absorbable properties of the PGA spacer. The PGA spacer used with the macaques was 30 × 30 × 15 mm and was fixed to the inner abdominal wall to evaluate both thickness retention and adhesion. Serial CT examinations (Auklet TSX-003A; Toshiba, Tokyo, Japan) were performed every week for 12 weeks after the spacer placement. To evaluate for adhesions, abdominal muscles and residual PGA spacer were evaluated by hematoxylin and eosin stain and silver impregnation stain.

Statistics

The data were expressed as the mean ± standard error. A one-way analysis of variance test followed by Bonferroni's post hoc test was used for statistical analysis, and P values of $< .05$ were considered statistically significant.

Results

Characterization of the PGA spacer

A macroscopic feature and an SEM image of the PGA spacer are shown in Figure 1a. The SEM image reveals the nonwoven 3-dimensional structure. The Fourier Transform Infrared Spectroscopy (FT-IR) FT-IR spectra of irradiated and nonirradiated PGA spacers are presented in Figure 1b. The spectral bands were assigned as follows: (*1*) stretching vibration of–C–O–C– at 1050–1200 cm^{-1}; (*2*) deformation vibration of H–C–H at 1415 cm^{-1}; (*3*) stretching vibration of C=O at 1740 cm^{-1}; and (*4*) stretching vibration of H–C–H at 2950 cm^{-1}. No changes were observed in these spectra after 100 Gy of proton or carbon-ion irradiation.

In the ^{1}H-NMR spectra of the PGA spacer (Fig. 1c), the signal at 4.92 ppm may be attributed to the methylene proton of the PGA. Because of impurities in the solvent, absorption signals appeared at 4.3-4.7 ppm. No signal changes were observed after the same irradiations.

Analysis of the weight-average molecular weights of the PGA spacer indicated no changes in molecular weight as a result of cutting and cross-linking of the molecular chains (Fig. 1d), and no viscosity changes were observed after the irradiation (Fig. 1e). Together, these results indicate that no

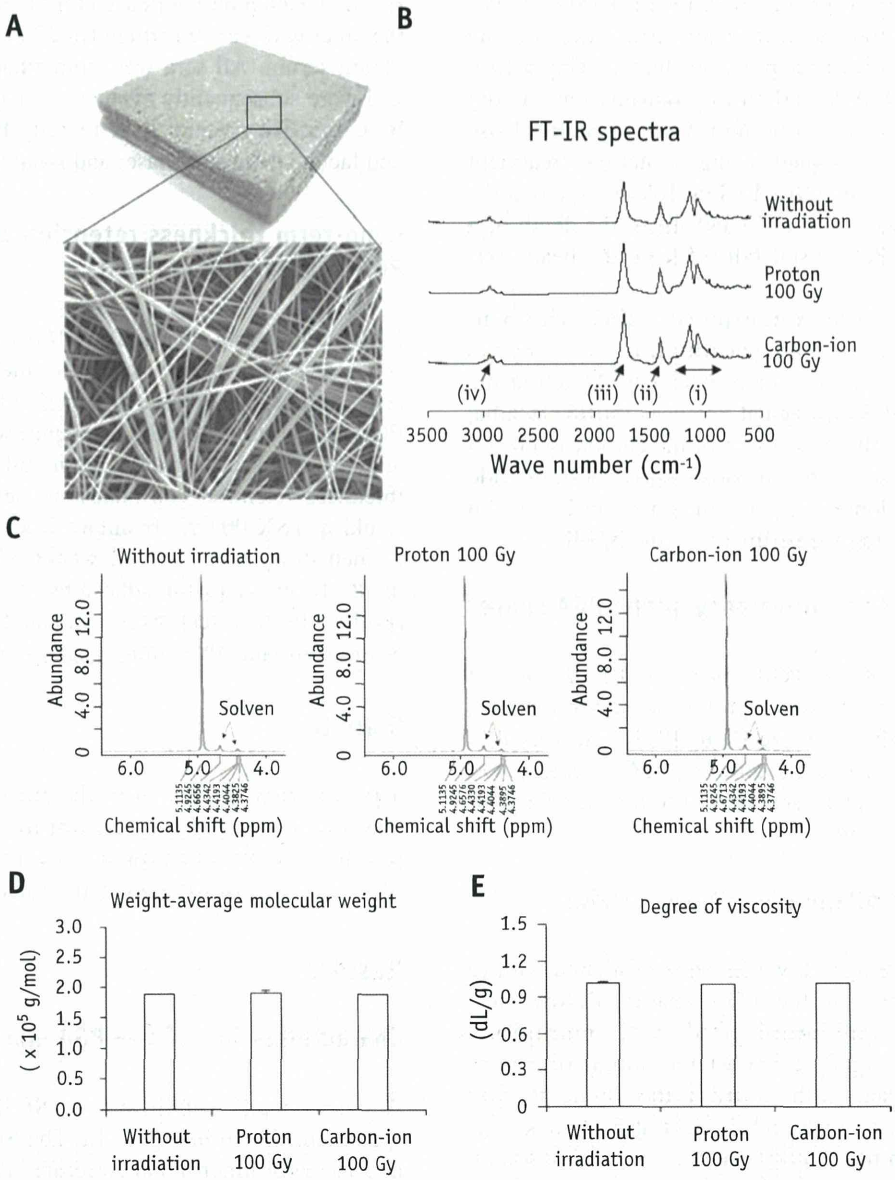

Fig. 1. Physicochemical properties of the polyglycolic acid (PGA) spacer. (a) Scanning electron microscope image (× 50) of the spacer. (b) Fourier Transform Infrared Spectroscopy (FT-IR) spectra. (c) ^{1}H-Nuclear magnetic resonance spectra. (d) Weight-average molecular weight. (e) Inherent viscosity of the HFIP (1,1,1,3,3,3-Hexafluoro-2-propanol) solution of PGA. In all examinations the PGA spacer was analyzed before or after 100 Gy of proton or carbon-ion irradiation.

chemical or structural changes occurred after exposure to high-dose proton or carbon-ion irradiation.

Water equivalency of the PGA spacer

One advantage of the PGA spacer is its water-absorbing properties. The average thickness of the wet PGA spacer placed on a water phantom detector was 21.8 ± 1.5 mm (Fig. 2a and c). When a dry PGA spacer was set, no range shift was observed for the SOBP, whereas when a wet PGA spacer was set, a 21.7 ± 1.5 mm range shift after proton or carbon-ion irradiations (Fig. 2b) was measured. There was a 21.7 ± 1.2 mm range shift after proton or carbon-ion irradiations by radiation treatment planning system calculation (Fig. 2c). These results indicated that the water equivalency of the PGA spacer was equal to the water thickness in the wet condition.

Protective effect of the PGA spacer in vivo

The SOBP setting for the animal experiments is shown in Figure 3. The depth of penetration for mouse abdominal skin surface was set at 3 mm with a binary filter. After exposure to 20 Gy of carbon-ion irradiation, body weights of mice with the PGA spacer were well preserved, whereas mice that did not receive the PGA spacer placement exhibited significant weight loss over a period of 24 days ($P<.05$; Fig. 4a). The histologic analysis indicated severe

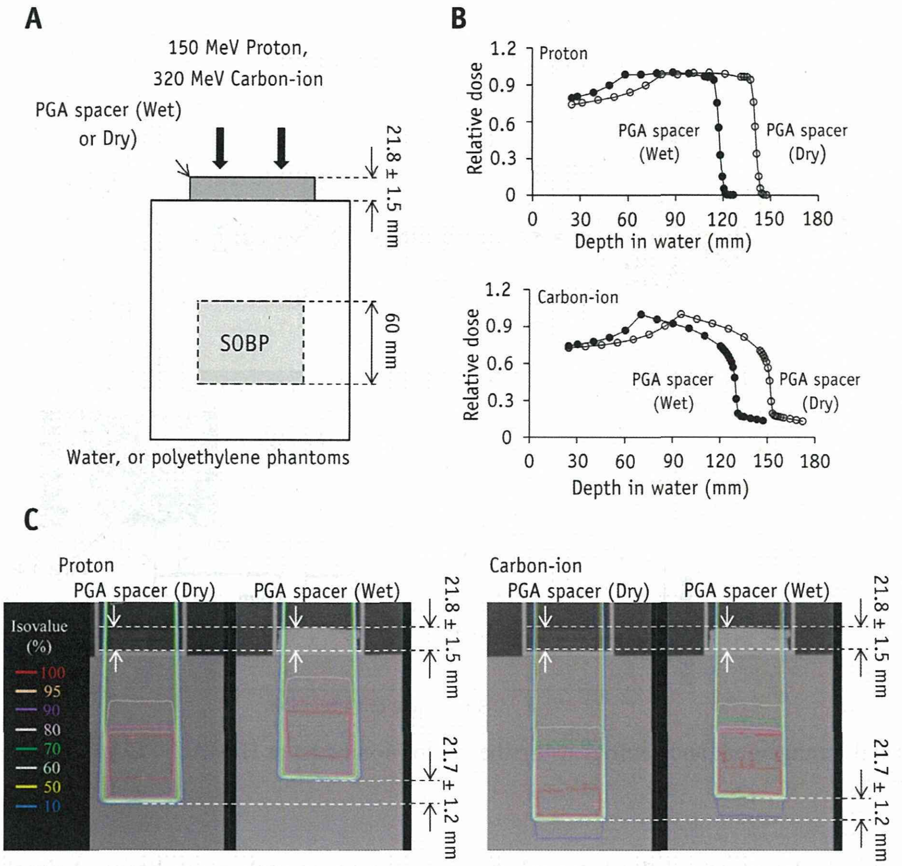

Fig. 2. Phantom study using a water phantom detector at HIBMC. (a) Schema of the experimental settings. (b) Results of measured profile curves for proton and carbon-ion beams, indicating the direction parallel to the beam axis. (c) Results of calculated dose distribution in a longitudinal plane on the beam axis for the proton and carbon-ion beams, with a dry or a wet spacer. PGA = polyglycolic acid; SOBP = spread-out Bragg peak.

damage to the villi and crypts in the intestines of mice that received 20 Gy of carbon-ion irradiation, compared with mice that were not irradiated. Conversely, degradation was not observed in the villi and crypts of intestines for those mice with inserted PGA spacers over a period of 7 days after the irradiation (Fig. 4b). Additionally, evaluation of villi lengths indicated no significant change for mice that had received the spacer ($P<.05$; Fig. 4c).

Toxicity

Although blood samples exhibited slightly elevated white blood cell counts for mice that had received the PGA spacers, no C-reactive protein (CRP) elevation was observed, suggesting that spacer placement did not induce any inflammatory reaction. In addition, there was no liver or renal dysfunction (Table 1).

Long-term thickness retention and safety of the PGA spacer in vivo

Long-term thickness retention and safety were evaluated in crab-eating macaques. At 8 weeks after placement of the spacer, 90% (13.5 mm) of the original thickness was preserved (Fig. 5a). Serial abdominal CT images revealed that thickness was stable until 8 weeks, and then decreased over 12 weeks (Fig. 5b). Figure 5c indicates minimal adhesion of the spacer to the abdominal wall. Infiltration of inflammatory cells was not observed.

Discussion

The focus of this study was to evaluate properties of a bio-absorbable PGA spacer for particle therapy. Spacer placement is a promising method designed to allow for increased tumor dose, while limiting exposure to adjacent organs. Previous attempts have been made to use bio-compatible agents as spacers. Prada et al (9, 10) reported injecting 3-7 mL of hyaluronic acid (HA) into perirectal fat before rectal radiation therapy in high-dose or low-dose brachytherapy. Results of their study indicated that the injected HA did not migrate or change in shape for almost a year. Similarly, Wilder et al (11) reported that cross-linked hyaluronic gel could safely and effectively reduce the mean rectal dose. However, Daar et al (12) reported degradation of HA within weeks of radiation exposure. Using a different

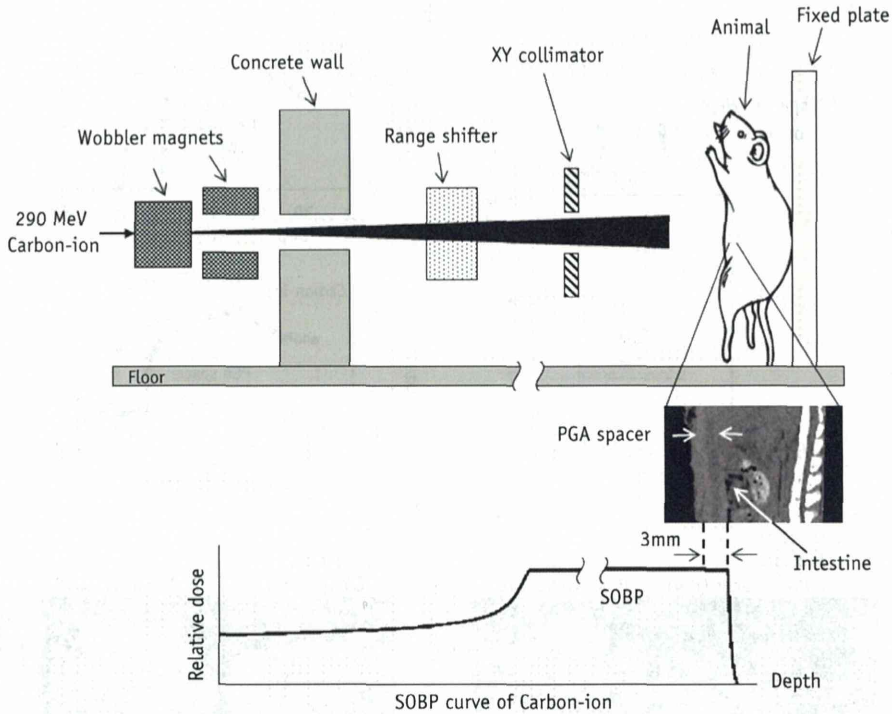

Fig. 3. Experimental arrangement and settings using the carbon-ion beam at HIMAC. PGA = polyglycolic acid; SOBP = spread-out Bragg peak.

approach, Susil et al (13) demonstrated the potential efficacy of a synthetic polyethylene glycol–based hydrogel (DuraSeal; Confluent Surgical, Waltham, MA) as a prostate–rectum spacer. Additionally, Pinkawa et al (14) reported similar results after injection of a different spacer gel (SpaceOAR System; Augmenix, Waltham, MA), whereas Noyes et al (15) demonstrated that, using human collagen, the increased separation between the prostate and rectum resulted in a significant decrease in radiation exposure to the rectum during intensity modulated radiation therapy and was associated with no rectal toxicities. In all of these studies, however, the methods or agents reported were limited to prostate–rectum separation and could be difficult to use in other locations.

The reason for use of PGA to make nonwoven fabric spacer is that PGA is one of the most widely studied polymers and has excellent mechanical properties (19, 20) and biological affinity (23, 24). Historically, PGA has played a central role in surgery since its development as the first synthetic absorbable suture material in 1962 (25). Under physiologic conditions, PGA is degraded by certain enzymes, especially those with esterase activity (26, 27). The degradation product, glycolic acid, is nontoxic and can enter the tricarboxylic acid cycle, after which it is excreted as water and carbon dioxide. Part of the glycolic acid is also excreted in urine (25, 26).

Efficacy and safety of the PGA spacer was intensively tested in this study. As seen in Figure 2, the PGA spacer exhibited water equivalency after irradiation by either proton or carbon-ion beam. Animal experiments (Fig. 4) indicated that use of the PGA spacer prevented weight loss after abdominal carbon-ion beam irradiation. Histologic analysis also showed prevention of villi loss in the intestine, whereas blood tests revealed no toxic reactions (Table 1). An optimal spacer should have thickness-retaining properties and water equivalency in accordance with clinical situations. In particle therapy, because treatment protocols take 2-7 weeks (3, 6), a spacer that keeps its thickness for that period of time seems ideal. The PGA spacer retained more than 90% of thickness for 8 weeks and seems to be adaptable for many different protocols. These findings together suggest that the PGA spacer might become a useful device in particle therapy; however, further evaluations in experimental settings or in clinical settings seem to be necessary.

Among several upper abdominal malignant tumors, pancreatic cancer has the poorest prognosis (28, 29). Although chemoradiation must be considered to achieve locoregional control, grade 3 or higher toxicity has been observed in approximately 20-40% of patients who received preoperative chemoradiation (30). Recently, Terashima et al (31) reported successful results combining gemcitabine with proton therapy to treat locally advanced pancreatic cancer. In that study they reported 1-year freedom from local progression and overall survival rates of 81.7% and 76.8%, respectively. These results were speculated to be brought by a total dose of 67.5 Gy relative biological effectiveness (RBE) to the

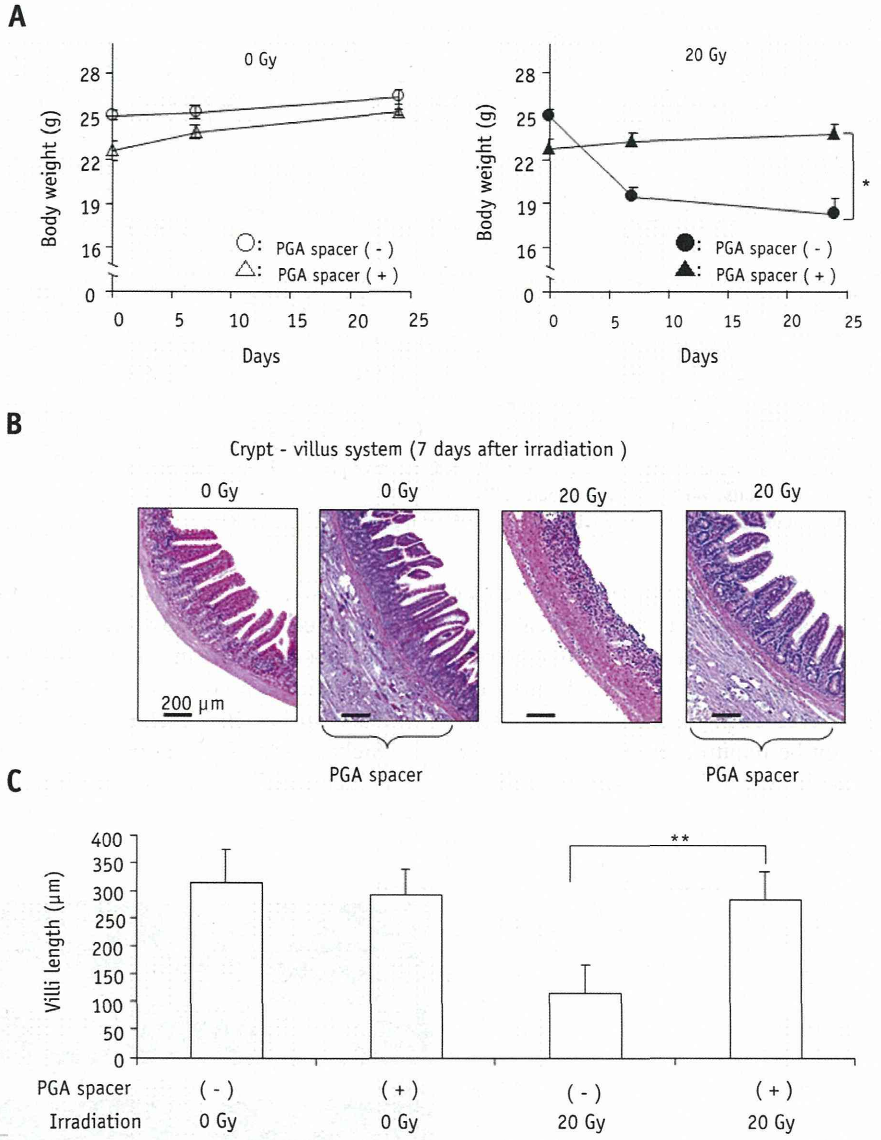

Fig. 4. Protective effect of the polyglycolic acid (PGA) spacer. (a) Effect of carbon-ion irradiation on the body weight of mice with or without PGA spacer. Each plot represents the mean ± standard error of body weight of 3 mice in each group. (b) Hematoxylin and eosin–stained transverse sections of small intestinal villi. Representative images of small intestinal villi of unirradiated and irradiated mice. The irradiated samples were obtained 7 days after exposure to a carbon-ion beam. All scale bars indicate 200 μm. (c) Statistical analyses corresponding to villi length. Data are expressed as mean values ± standard error. *$P<.05$; **$P<.001$.

major part of the planning target volume (2.7 Gy[RBE] per fraction), while simultaneously limiting the dose to the gastrointestinal tract to a total 45 Gy(RBE) (1.8 Gy [RBE] per fraction), suggesting that the planning target volume dose was higher compared with results of other studies (32, 33). However, approximately 10% of the patients subsequently developed grade 3 or higher gastric ulcers, several months after completing the therapy (34). In such cases, surgical placement of a PGA spacer between the pancreas and stomach might be an effective option to reduce the gastrointestinal toxicities with keeping the same dose to the tumors. However, disadvantages of receiving a surgical procedure should be carefully taken into account for the placement of the PGA spacer.

This was a preliminary study using the PGA spacer in healthy animals. It was not evaluated in a clinical setting. Although the PGA spacer was nontoxic and the degree of adhesion was minimal, it might be possible that its adhesion properties may be different in the presence of malignant tumors. It may also prove more difficult to perform the surgery to implant the spacer around a real tumor. We are

Table 1 Blood test analyses 24 days after carbon-ion irradiation

Parameter	0 Gy		20 Gy	
	Without PGA spacer	With PGA spacer	Without PGA spacer	With PGA spacer
Inflammatory reaction				
CRP (ng/mL)	8.9 ± 0.4	9.8 ± 1.1	9.9 ± 1.0	9.2 ± 0.7
Blood cell count				
WBC (1/mL)	2700 ± 300	5200 ± 815	2000 ± 681	3400 ± 700
RBC (× 10^4/mL)	882 ± 12	847 ± 15	622 ± 119	777 ± 19
Plt (× 10^4/mL)	100.6 ± 15.8	95.3 ± 7.9	92.4 ± 37.3	138.2 ± 26.5
Liver function				
ALT (IU/L)	17.7 ± 0.9	21.0 ± 2.1	29.3 ± 3.5	25.0 ± 2.1
LDH (IU/L)	218.3 ± 32.9	464 ± 116	325.3 ± 77.7	328.3 ± 15.4
Renal function				
CRE (mg/dL)	0.1	0.1	0.1	0.1

Abbreviations: ALT = alanine transferase; CRE = creatinine; CRP = C-reactive protein; LDH = lactate dehydrogenase; PGA = polyglycolic acid; Plt = platelets; RBC = red blood cells; WBC = white blood cells.
Data are expressed as mean ± standard error. n=3 in CRP, WBC, RBC, Plt, ALT, LDH, and CRE.

now evaluating the safety and efficacy of the PGA spacer using tumor-bearing rats, and we will initiate clinical trials to further evaluate the efficacy and safety of this material. Another limitation is that the spacer was tested only near the abdominal walls of crab-eating macaques. In clinical situations, a spacer might be required in other areas of the abdomen. In such cases, careful observation will be necessary, but the thickness-retention and adhesion data presented in this study will be an important help.

In conclusion, this is the first report that we know of describing a nonwoven fabric PGA spacer. The absorbable PGA spacer had water equivalent, bio-compatible, and thickness-retaining properties. Although further evaluation is warranted in a clinical setting, the PGA spacer may be

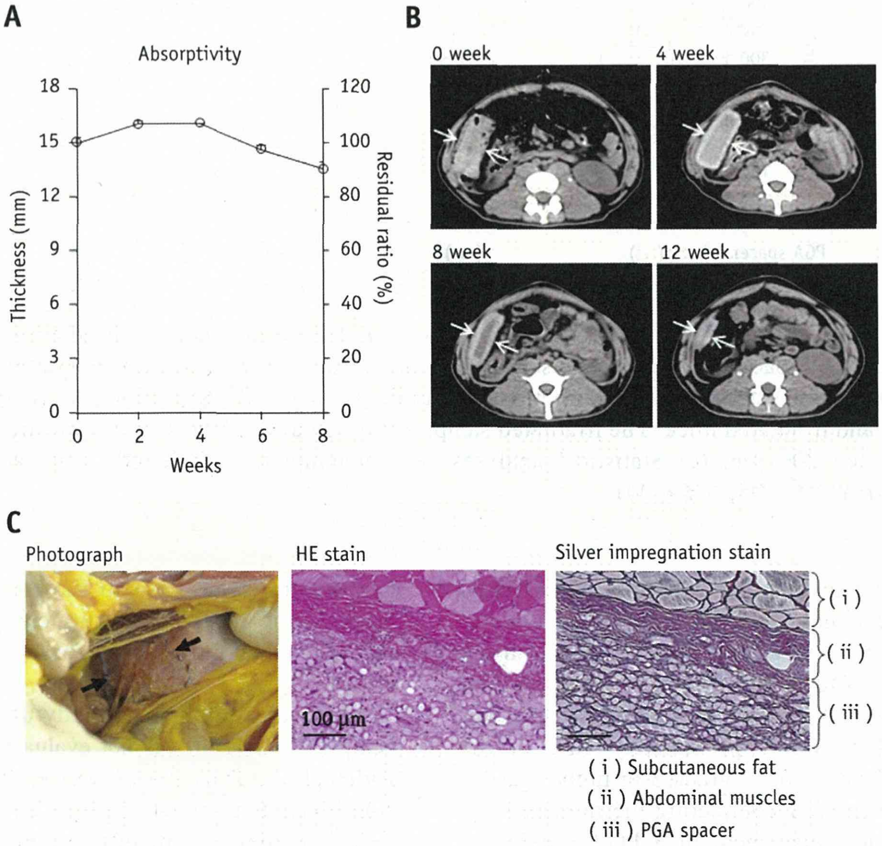

Fig. 5. (a) Evaluation of thickness-retaining properties of the polyglycolic acid (PGA) spacer. Error bar indicates standard error. (b) Serial CT images of inserted PGA spacer in the crab-eating macaques' abdomen. (c) Macroscopic and microscopic features of the inserted PGA spacer at 12 weeks. All scale bars indicate 100 μm

effective to stop proton or carbon-ion beams and to separate normal tissues from the radiation field.

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症例報告

後腹膜脂肪肉腫術後再発に対してスペーサー手術および陽子線照射による2段階治療が奏効した1例

岩崎　寿光[1)]　福本　　巧[1)]　出水　祐介[2)]　寺嶋　千貴[2)]
藤井　　收[2)]　小松　昇平[1)]　松本　逸平[1)]　味木　徹夫[1)]
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症例は53歳の男性で，脱分化型後腹膜脂肪肉腫およびその局所再発に対して，3回の開腹手術が施行された．3回目の手術では腫瘍が大動脈に浸潤・固着し，外科切除不能であったため，遺残腫瘍に対する粒子線治療を希望して来院した．腫瘍は小腸と近接しており，そのままでは粒子線による根治的照射は不可能であったため，スペーサー留置手術の後，粒子線照射を併用する2段階治療を計画した．まず，開腹下にスペーサーを留置し腫瘍と近接消化管の間に最低1 cmの距離を確保した．術後1か月より陽子線70.4 GyE/32 Frの照射を開始した．腫瘍は緩徐に縮小し，治療後22か月の現時点では腫瘍は縮小を維持し，再発も認めていない．根治的切除が困難な後腹膜脂肪肉腫に対して本療法は有望な治療手段になりえると考えられた．

キーワード：後腹膜脂肪肉腫，スペーサー，陽子線照射

はじめに

後腹膜脂肪肉腫は後腹膜腫瘍の10～20%を占め[1)2)]，比較的まれな疾患である[3)]．自覚症状を有しないことが多く，診断時には巨大化していることが多い．治療は外科手術が唯一の根治的治療であるが，根治切除率は12～32%と低く，術後の再発率も高い[4)]．

陽子線や炭素イオン線（重粒子線）を用いた粒子線治療は従来の放射線治療に比べ，高い線量集中性と生物学的効果を有するために根治的照射が可能であり，頭頸部・肺・前立腺の悪性腫瘍に対して良好な治療成績が報告されている．一方，腹部の悪性腫瘍では照射による消化管障害の危険性が高く，治療対象が限定される．この弱点を克服するべく我々は第1段階として開腹下にスペーサーを留置することで腫瘍と消化管を離し，第2段階として粒子線照射を行う2段階治療を考案した．

今回，我々は切除不能脱分化型脂肪肉腫再発症例に対して，スペーサー留置・粒子線照射という2段階治療が奏効した症例を経験した．本治療法は腹部難治性固形腫瘍に対する新たな根治的治療戦略となりえると考えられた．

症　例

患者：53歳，男性

〈2014年1月22日受理〉別刷請求先：岩崎　寿光　〒650-0017　神戸市中央区楠町7-5-2　神戸大学大学院肝胆膵外科

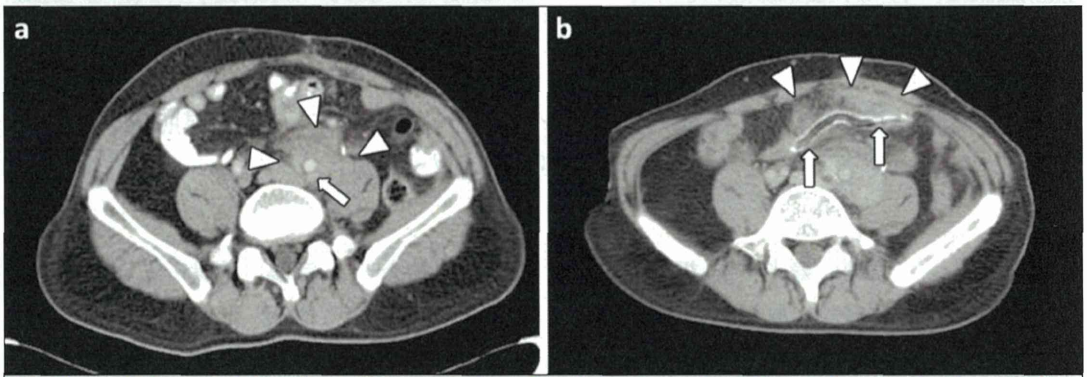

Fig. 1 a: Abdominal CT at the initial consultation showed the tumor located ventral to the lumbar vertebra (arrowheads) encasing the left common ileac artery (arrow). b: Abdominal CT after the operation showed the Goretex sheets (arrows) retaining a sufficient distance between the tumor and the small intestine (arrowheads).

主訴：腹部膨満感

家族歴：特記事項なし．

既往歴：高血圧症，急性肝炎，胆嚢結石症（保存的加療）．

現病歴：2007年6月，前医にて後腹膜巨大脂肪肉腫に対して切除術が施行された（手術所見：腫瘍は主に左腎腹側に位置し，下行結腸間膜と左尿管に固着していた．病理組織学的検査所見：Dedifferentiated liposarcoma．20×15×10 cm．一部に低悪性度脂肪肉腫や悪性組織球腫様細胞の混在を認めた）．

術後2か月に施行したPETにて下行結腸・左腎に近接した後腹膜に再発病巣を認め，再手術が施行された（手術所見：腫瘍浸潤のため，残存腫瘍とともに下行結腸・左腎を合併切除した．病理組織学的検査所見：低悪性度脂肪肉腫．左腎・下行結腸への浸潤を認めた）．術後，外来にて経過観察されていたが，2010年6月の腹部造影CTにて腹部大動脈周囲に約8 cmに渡る再発腫瘍を認めたため，再々手術が施行された（手術所見：腫瘍径は約10 cmで周辺臓器，血管との境界は不明瞭であった．腹部大動脈から左総腸骨動脈に頭尾方向7 cmに渡って強く固着していた．腫瘍の大部分は摘出可能であったが，腫瘍と大動脈固着部は剥離不能であり，腫瘍は遺残した．術後の放射線照射を想定して，腫瘍部に“silver clip”をマーカーとして留置された）．2010年8月，腹部造影CTで腫瘍の再増大を認めたため同年9月，兵庫県立粒子線医療センターを受診した．

初診時検査所見：血清クレアチニン値が，1.32 mg/dlと軽度上昇していたが，その他に異常所見は認めなかった．

腹部造影CT所見：腰椎腹側に境界不明瞭な最大横径55 mmの腫瘍を認めた．腫瘍は左総腸骨動脈を取り囲んでおり，腫瘍左側では左腸腰筋への浸潤が疑われた．腸間膜を隔てた腫瘍の腹側には小腸を認め，腫瘍に近接していた（Fig. 1a）．

腫瘍に対して粒子線による根治的照射を計画した場合，腫瘍腹側の小腸には耐容線量以上の線量が照射されるため根治照射は不可能であった．そのため開腹にてスペーサー留置術を行い，腫瘍と小腸の距離を確保の上（Fig. 1b），二期的に粒子線照射を行う2段階治療の方針とした．

2010年10月，開腹スペーサー留置術を施行した．既知の再発巣以外には，転移・播種病巣は認めなかった．腫瘍はS状結腸間膜を背側から押し上げるように存在していた．背側からの照射が可能となるように腫瘍とS状結腸の間を剥離し，10×20 cmのGore-tex mesh（日本ゴア株式会社製）計3枚を腫瘍と腸管との距離を最低1 cmとするように留置，固定した（Fig. 2）．

手術後1か月の2010年11月より兵庫県粒子線医療センターにおいて治療を開始した．同施設では陽子線と炭素イオン線のいずれもが照射可能である．炭素イオン線は照射角度が制限される（垂直方向を0°と