HOW I DO IT

Particle Beam Radiotherapy with a Surgical Spacer Placement for Advanced Abdominal Leiomyosarcoma Results in a Significant Clinical Benefit

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Running head: Particle beam with a surgical spacer

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INTRODUCTION

Leiomysarcoma is a rare malignant tumor originating from smooth muscle cells. Because of the limited number of cases, the natural history and optimal treatment have not been clarified. In particular, prognosis of leiomyosarcoma originating from large vessels including the inferior vena cava (IVC) and Aorta is extremely poor. Recent data support an aggressive surgical resection combined with adjuvant chemotherapy as the best treatment option for a leiomyosarcoma from the IVC [1,2]. However, the long-term outcome of curative resections for leiomyosarcoma from large vessels has been disappointing. The five-year survival rates obtained with absolute curative resections were observed to range from 34.8% to 53.3% [1,2]. Hines et al. suggested that radiation therapy after a surgical resection may prolong survival [2]. It should be noted, however, that an absolute curative resection was performed in all of their cases and the effectiveness of chemotherapy and radiotherapy were assessed in the framework of adjuvant therapy. There is no report about the treatment of an unresectable leiomyosarcoma and the overall survival rate.

Particle beam radiotherapy is a new mode of radiotherapy that has an inherent advantage over photon radiotherapy. Particle beams, such as proton and heavier ion beams, show an increase in energy deposition with penetration depth up to a sharp maximum at the end of their range to form the so-called Bragg peak. It thus permits delivery of higher doses of radiation to the tumor, which may lead to profoundly improved tumor eradication. Recent results from major centers have shown the therapeutic superiority of particle radiotherapy for various kinds of malignant tumors [3,4]. However, the application of proton beam radiotherapy for abdominal malignant tumors is restricted because most of them come in contact with the intestine that cannot tolerate the radical dose of particle beams. Several studies have investigated the risk factors related to late gastrointestinal tract disturbance after radiotherapy. Ishikawa et al. assessed that the dosimetric parameter was a very important factor in the occurrence of gastrointestinal bleeding after particle radiotherapy [5]. Gastrointestinal disturbances, such as ulcer formation and colitis, generally occur within several months after the completion of particle radiotherapy. However, the irradiated volume of a marginal tumor is normally limited to make it lower than the maximum dose in order to prevent any toxicity to the nearby gastrointestinal tract. To overcome this limitation, we developed a novel two-step treatment with a surgical spacer placement and subsequent proton beam radiotherapy and achieved a significant clinical benefit for three patients.

METHODS

The treatment strategy is to attempt to keep the intestine away from the irradiation field by spacer placement and to perform proton beam radiotherapy with a curative intent. Eight Gore-Tex sheets (20 cm x 15 cm x 2 mm^2) were superimposed and applied as a spacer to keep safety margin away from the intestine. The spacer was fixed with the retroperitoneum and peritoneum. During the spacer placement surgery, no part of the tumor was resected because it was just a first step to allow proton beam radiotherapy.

PATIENT AND RESULTS

We would show the representative case. A 65-year-old female was diagnosed to have a far advanced leiomyosarcoma measuring 12 x 12 cm that originated from IVC above the level of the aortic bifurcation because of extensive invasion to the unresectable nearby tissues including the spinal cord, the right iliopsoas muscle, right internal and external iliac arteries and the right urinary tract. The tumor did not fulfill the indication for a curative resection due to the poor prognosis of a far advanced leiomyosarcoma. She was then referred to our department to undergo particle beam radiotherapy. Abdominal MRI after the operation showed the spacer maintained a sufficient open space between the tumor and intestines (Fig. 1A-D, asterisk: the huge tumor, arrowhead: Gore-Tex spacer sheets around the tumor)(Fig. 1D operative finding of the spacer replacement). One month later, she underwent proton beam radiotherapy with 70.4 GyE in 16 fractions over 24 days at Hyogo Ion Beam Medical Center (HIBMC). The dose-distribution curve and dose-volume histogram in treatment planning are shown in Fig 2. Due to the spacer, the digestive tract is located entirely outside the irradiated volume (Fig. 2A). Dose-volume histogram of the clinical target volume (CTV) and the intestine. CTV is entirely irradiated with ≥ 90% of the prescribed dose, and the intestine is hardly irradiated (Fig. 2B). Thus, the spacer placement protected the intestines. Acute and late toxicities associated with treatment were evaluated using both the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity score and RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity score [6]. Acute or late treatment-related toxicities were judged as grade 2. An abdominal MRI taken 6 months after the two-step treatment showed the distinct shrinkage of the tumor measuring 6 x 6 cm (Fig. 3A and 3B) and the positron emission tomography scan did not show metastasis to the remote organs throughout the body (data not shown). Since local control is generally defined as no sign of re-growth or new tumors in the treatment volume, this patient was determined to have achieved excellent local control of a far advanced leiomyosarcoma with minimal toxicity. We never remove spacers after particle beam radiotherapy because of the potential surgical risk. We are therefore now developing new spacers made of absorbable mesh.

DISCUSSION

Three cases of unresectable abdominal leiomyosarcomas originating from the abdominal aorta or the IVC were treated with this two-step treatment and all of those cases achieved local control of the primary tumors. From the viewpoint of the disease-free survival, considerable progress was achieved in all three patients (Table 1). All three patients showed grade 1 dermatitis as an acute toxicity. While two of three patients reported grade 2 dermatitis as a late toxicity. HBMC is the only facility of particle radiotherapy which both proton and carbon ion beams are available all over the world and we have treated patients using either proton or carbon ion beams since 2001. The policy of choosing beam type at HBMC was as follows: carbon ions show a more favorable dose distribution than protons, however, carbon ions can only be delivered from fixed ports, while a 360-degree rotating gantry can be used for protons. Treatment plans for both carbon ion and proton were made basically, and better one was chosen for the patient treatment. This type of approach using surgical displacers plus photon (also called X-ray) beam radiotherapy has been previously employed in other malignancies such as rectal cancer [7,8]. However, several lines of evidence support our novel strategy. Particle beams permit favorable dose distributions with a steep dose fall-off at the field borders, suggesting more precise dose localization can be achieved compared with photon beams [4]. Moreover, the use of photon beam is usually restricted to pelvic tumors due to the deposit in surrounding tissues. In contrast, almost no dose of particle beam is deposited in the normal tissue beyond the Bragg peak. We believe surgical spacer placement can keep safety margin from the intestine and full-dose particle beam radiotherapy can be achieved without serious toxicities only by this first step. Furthermore, previous approach with displacer was utilized for postsurgical adjuvant radiotherapy in principle. The rate of local tumor control and acute or late treatment-related toxicities using surgical displacers plus photon were not presented. Although we need further case-control study, our results strongly indicate that this new strategy might potentially be an effective and innovative therapy for unresectable abdominal malignant tumors.

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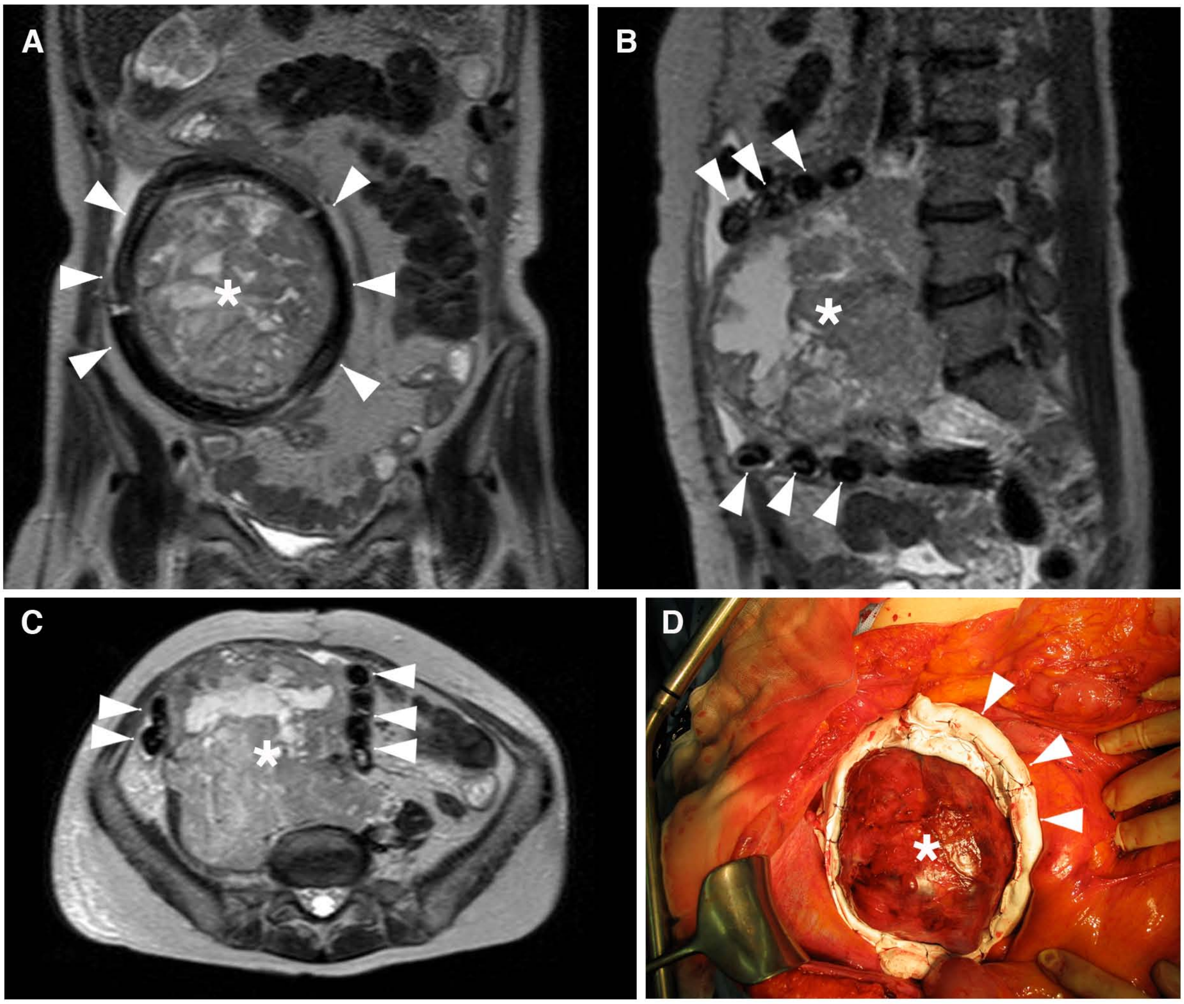
Fig. 1. (**A-C**) Abdominal MRI after the operation for spacer placement. (**D**) The spacer around the tumor using gore-tex sheets. The arrowhead shows the spacer around the tumor, and it maintained a sufficient open space between the tumor and the intestines. The asterisk shows the tumor.

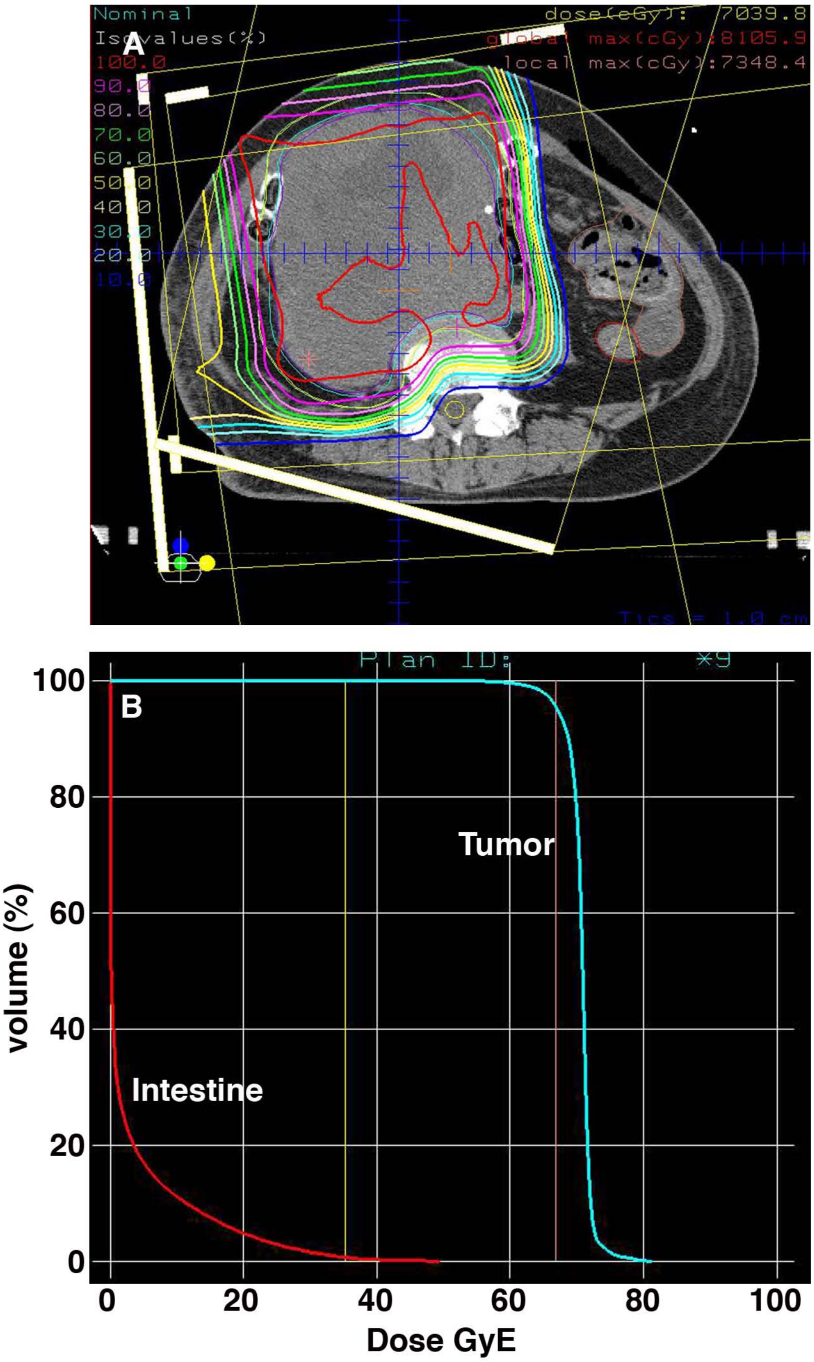
Fig. 2. (**A**) Treatment strategy for proton beam radiotherapy with a total dose of 70.4 GyE in 16 fractions. Isodose curves demonstrate 100% of the prescribed dose at the center and decreasing by 10% of the dose from the inside out. Due to the spacer, the digestive tract is located entirely outside the irradiated volume. (**B**) Dose-volume histogram of the clinical target volume (CTV) and the intestine. CTV is entirely irradiated with $\geq$ 90% of the prescribed dose, and the intestine is hardly irradiated.

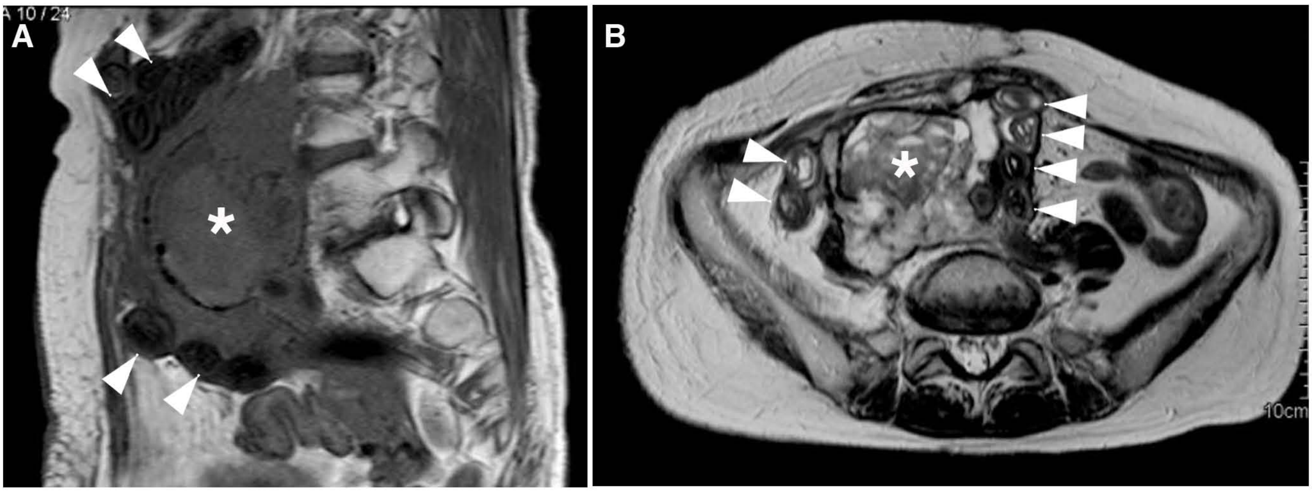
Fig. 3. (**A, B**) Abdominal MRI 6 months after the two-step treatment. The arrowhead shows the spacer. The asterisk shows the distinct shrinkage of the tumor.

TABLE 1 Three cases of abdominal leiomyosarcoma treated with two-step treatment

Age, Sex	Tumor origin	Tumor size (cm)	Protocol (GyE/Fr)	Disease-free survival
62, Male	Abdominal aorta	13 x 13	Proton 80.0/32	406 days
65, Female	Inferior vena cava	12 x 12	Proton 70.4/16	276 days
59, Male	Thoraco-abdominal aorta	10 x 7	Carbon 70.4/16	700 days


A
B
C
D


A
Nominal
Isovalues(%)
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
dose(cGy): 7039.8
global max(cGy):8105.9
local max(cGy):7348.4
B
Plan ID:
Tumor
Intestine
volume (%)
Dose GyE
0
20
40
60
80
100


A 10 / 24
A
*
B
*
10cm