TABLE 2 Results of Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

Case	Age	Sex	Stage factors	Tumor regression	Resolution of bile duct	Biliary drainage	Heat sessions	Chemotherapy regimen	Dose of RT (Gy)	Survival months
1	66	f	T4N2	CR	NC	PTCD	x6, x1	MTX, 5-Fu	54	15.5
2	60	f	T4N2	CR	no stenosis	None	x5, x6	MTX, CDDP, 5-Fu	50, 24	33
3	52	f	T4	CR	CR	Withdrawal of PTCD	x6	CDDP, 5-Fu	56	10
4	57	f	T4	CR	CR	PTCD → metallic stent	x5	MTX, 5-Fu	40	5.5
5	62	m	T4M1	CR	no stenosis	None	x5	MTX, 5-Fu	54	10
6	57	m	T4	PR	CR	PTCD	x5, x3	CDDP, 5-Fu	46	21
7	48	f	T4M1	PR	PR	PTCD → metallic stent	x2	CDDP, VP16	40	16
8	64	f	T4	PR	no stenosis	None	x4	MTX, 5-Fu	40	14
9	41	f	T4M1	PR	PR	Withdrawal of PTCD	x3	MTX, 5-Fu	50	13
10	69	f	T4M1	PR	CR	Withdrawal of PTCD	x5	MTX, 5-Fu	50	13
11	83	f	T4	PR	CR	Withdrawal of PTCD	x4	MTX, 5-Fu	50	12.5
12	69	m	T4N2	PR	no stenosis	None	x5	MTX, 5-Fu	50	10.5
13	62	f	T4N2	PR	no stenosis	None	x6	MTX, 5-Fu	54	7
14	65	f	T4	PR	no stenosis	None	x3	CDDP, 5-Fu	50	8 alive
15	70	m	T4	PR	PR	PTCD→ metallic stent	x4	MTX, 5-Fu	56	6.5
16	72	m	T4M1	PR	PR	None	x5	CDDP, 5-Fu	60	5.5
17	72	m	T4	PR	NC	PTCD	x4	CDDP, 5-Fu	46	5
18	73	m	T4N2	PR	no stenosis	None	x6	CDDP, 5-Fu	50	4.5
19	72	f	T4M1	PR	no stenosis	None	x6	MTX, 5-Fu	50	3
20	68	f	T4	NC	CR	PTCD → metallic stent	x4	MTX, 5-Fu	52	5
21	59	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	50	13.5
22	72	f	T4N2	NC	PR	PTCD → metallic stent	x2	MTX, 5-Fu	42	12
23	65	m	T4	NC	PR	PTCD	x2	MTX, 5-Fu	50	8.5
24	53	f	T4	NC	PR	PTCD	x4	CDDP, 5-Fu	38	6.5
25	55	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	38	6
26	69	f	T4	NC	no stenosis	None	x3	CDDP, 5-Fu	32	4
27	64	m	T4M1	NC	no stenosis	None	x3	MTX, 5-Fu	30	2.5
28	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	8.5
29	72	f	T4	NC	NC	PTCD	x4	MTX, 5-Fu	32	8
30	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	3

RT: radiotherapy; CR: complete response; PR: partial response; NC: no change; PTCD: percutaneous transhepatic cholangiodrainage.

carcinoma cells and degenerative cells were sparsely observed. Carcinoma cells were also detected peripherally. Common bile duct of six cases was not completely obstructed, though it was partly obstructed with debris or necrotic mass. Frequency and degree of hematogenous or lymphogenous metastases were not different from other cases **(Table 3)**.

Complication of TCRT

Treatment complications by TCRT were nausea and vomiting (Grade 1-2, 16 cases), gastritis (Grade 2, 7 cases), leukocytopenia (Grade 2, 4 cases; Grade 3, 2 cases; Grade 4, 1 case), thrombocytopenia (Grade 2, 1 case; Grade 3, 1 case), gastric or duodenal ulcer (Grade 2, 2 cases), fistula due to tumor necrosis (2 cases), and hemobilia from ruptured pseudoaneurysm of the hepatic artery (1 case). These complications were successfully treated conservatively.

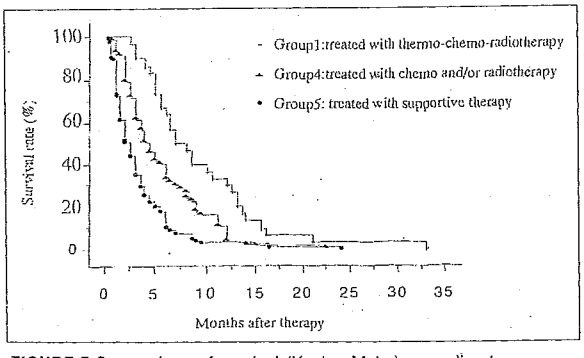


FIGURE 5 Comparison of survival (Kaplan-Meier) according to treatment regimen. There was a significant difference in the survival rate between group 1 and group 4,5 ($p<0.01$).

DISCUSSION

Gallbladder carcinoma carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. The 5-year survival rate following surgery for gallbladder carcinoma has been reported to be between 5 and 13% in the literature (9,10). Such distressing results are due partly to a low resectability rate and late diagnosis but also to certain limitations in the radical removal of the tumors. Therefore, the postoperative recurrence rate is high. Clinical benefit of radical resection for advanced gallbladder carcinoma is still controversial. For advanced gallbladder carcinoma, we have performed TCRT. We have also performed combined resection of the alimentary tract with or without the liver, with adjuvant IORT in some cases, chemotherapy and/or radiotherapy, and supportive therapy for

TABLE 3 Pathological Findings at Autopsy in Patients Treated with Thermo-Chemo-Radiotherapy

ase	Histology	Change of gallbladder wall and tumor: Necrosis	Hyalinization or fibrosis	Scattered degenerative tumor cells	Bile duct	Metastases: Liver	Lung	Lymph node
	well diff. adenoca.	+	++	++	stenosis	++	+	++
	poorly diff. adenoca.	+	++	++	obstructed	+	-	+
	poorly diff. adenoca.	+	++	+	stenosis	++	-	++
	adenosquamous ca.	+	++	+	obstructed	-	-	-
1	well diff. adenoca.	+	+	+	obstructed	+	+	-
5	well diff. adenoca.	+	++	+	stenosis	+	+	+
8	pleomorphic ca.	++	+	+	open	+	+	-
0	well diff. adenoca.	+	++	+	stenosis	+	+	+
1	well diff. adenoca.	++	++	++	stenosis	+	-	-
2	well diff. adenoca.	+	+	+	obstructed	+	+	+
8	well diff. adenoca.	++	++	+	obstructed	+	+	++

well diff. adenoca.: well differentiated adenocarcinoma; poorly diff. adenoca.: poorly differentiated adenocarcinoma; adenosquamous ca.: adenosquamous carcinoma; pleomorphic ca.: pleomorphic carcinoma.

these tumors (4). We analyzed the effectiveness of TCRT for Stage IV gallbladder carcinoma compared with other treatment regimens.

R0-resection was the most beneficial for prolonging survival. However, despite aggressive tumor removal with adjuvant IORT, there was no significant difference in the survival rate between patients treated with R1,2-resection and TCRT.

Most reasons for unresectability for cure in cases without distant metastases are due to the involvement of the hepatoduodenal ligament. Deeply invaded tumors, especially those located in the neck or body of the gallbladder, are apt to spread to the bile duct or the connective tissues in the hepatoduodenal ligament, with encasement of major vessels, or both. Moreover, tumor cells that spread to the ligament often cannot be cleared away completely, even when dissection of the tissue is performed. In nonresected cases, tumor spread to the hepatoduodenal ligament also frequently induces the development of obstructive jaundice which cannot be controlled, resulting in early death from cholangitis. One of the desired strategies for advanced gallbladder carcinoma appears to be control of this involvement of the hepatoduodenal ligament.

Effectiveness of TCRT on nonresctable tumors was surprising. In respect to tumor regression, there were 5 CR cases and 14 PR cases. At autopsy, marked hyalinization or fibrosis with necrosis replaced the gallbladder wall or tumor in almost all cases. Additionally, we observed that biliary obstruction resolved completely in 6, and partially in 9 of 20 patients with obstructive jaundice. TCRT was effective for management of involved hepatoduodenal ligament. In 11 patients, PTCD was able to be removed. Moreover, placement of self-expandable metallic stent into the patency-restored bile duct after TCRT was useful for keeping the longer patent period of the duct.

First of all, we consider why it is effective to combine radiation therapy on chemotherapy with hyperthermia. When the target lesion is heated up to around 42°C, the cancer killing effect of radiation or anticancer drug is enhanced. This fact is well documented by many reports on biological research (11-14). Furthermore, research in the fields of molecular biology and genetics is being conducted actively to clarify the mode of action of hyperthermia (15,16).

There are also many clinical studies that reveal effectiveness of combination treatment of radiation therapy and hyperthermia. In the meantime, European and American researchers are applying microwave therapy to superficial tumors (17) and conducting phase III study to clarify the combined use of hyperthermia (18,19). The effectiveness of thermoradiotherapy for deep-seated tumors has been revealed by prospective randomized studies (16,20). In Japan, the clinical research on hyperthermia is more active than in other countries (21). Especially, stream is RF-capacitive heating for deep-seated tumors. Effective deep heating of chest and upper abdomen with less side effects can be achieved only by RF-capacitive heating equipment (21).

The treatment protocol of TCRT was established and its effectiveness was evidenced by a series of research reports published by Sugimachi and his colleagues. They treated esophageal carcinoma with combination of radiotherapy and chemotherapy and additionally with 6 sessions of intracelial heating. They demonstrated significant improvement in the clinical effectiveness and 5-year survival ratio (22). Furthermore, they applied chemoradiotherapy and TCRT in a randomized control study before operation of esophageal carcinoma. Their phase III study revealed that clinical and histopathological effects were superior in TCRT to chemoradiotherapy (23).

This study established the treatment protocol of TCRT for advanced gallbladder carcinoma, comparing it with four other treatment modalities, and clarifying its effectiveness. We prefer TCRT for patients whose tumors have invaded the hepatoduodenal ligament in place of an aggressive surgical approach.

REFERENCES

1 **Nimura N, Hayakawa L, Maeda S, et al:** Combined portal vein and liver resection for carcinoma of the biliary tract. Br J Surg 1991; 78:727-731

2 **Donohue JH, Nagorney DM, Grant CS, et al:** Carcinoma of the gallbladder. Arch Surg 1990; 125:237-241.

3 **Arcangeli G, Cividalli A, Nervi C:** Tumor control and therapeutic gain with different schedules of combined heat and radiation. Int J Radiat Oncol Biol Phys 1983; 9:1125-1134.

4 **Okamoto A, Tsuruta K, Isawa T, Kamisawa T, Tanaka Y:** Treatment of T3 and T4 carcinoma of the gallbladder. Int Surg 1996; 81:130-135.

5 **American Joint Committee on Cancer:** TNM classification of malignant tumors. 5th Edition. Philadelphia: Wiley-Liss, Inc., 1997.

6 **Hiraoka M, Jo S, Akuta K, Nishimura Y, Takahashi M, Abe M:** Radiofrequency capacitive hyperthermia for deep-seated tumors. II. Effects of thermoradiotherapy. Cancer 1987; 60:128-135.

7 **Kamisawa T, Isawa T, Koike M, Tsuruta K, Okamoto A:** Hematogenous metastases of pancreatic ductal carcinoma. Pancreas 1995; 11:345-349.

8 **Appendix A Grading of Toxicity:** Manual of oncologic therapeutics. Philadelphia: J.B. Lippincott, 1989.

9 **Cubertafond PA, Cucchiaro G:** Surgical treatment of 724 carcinomas of the gallbladder. Results of the French Surgical Association Survey. Ann Surg 1994; 219:275-280.

10 **Oertli D, Herzog U, Tondelli P:** Primary carcinoma of the gallbladder: operative experience during a 16 year period. Eur J Surg 1993; 159:415-420.

11 **Dewey WC, Hopwood LE, Saporeto LA, et al:** Cellular response to combination of hyperthermia and radiation. Radiology 1977; 123:463-471.

12 **Overgaard J:** Simultaneous and sequential hyperthermia and treatment of an experimental tumor and its surrounding normal tissue in vivo. Int J Radiat Oncol Biol Phys 1980; 6:1507-1517.

13 **Rhee JG, Kim TH, Song CW:** Changes in acidity of mouse tumor by hyperthermia. Int J Radiat Oncol Biol Phys 1984; 10:393-399.

14 **Song CW:** Effect of local hyperthermia and blood flow and microenvironment: a review. Cancer Res 1984; 44:4721-4730.

15 **Ohnishi K, Ohnishi T:** Heat-induced p53-dependent signal transduction and its role in hyperthermic cancer therapy. Int J Hyperthermia 2001; 17:415-427.

16 **Harima Y, Nagata K, Harima K, et al:** Bax and Bcl-2 protein expression following radiation therapy versus radiation plus thermoradiotherapy in stage IIIB cervical carcinoma. Cancer 2000; 88:132-138.

17 **Stewart JR, Gibbs FA Jr:** Hyperthermia in the treatment of cancer. Perspectives on its promise and its problems. Cancer 1984; 54:2823-2830.

18 **Valdagni R, Amichetti M:** Report long-term follow-up in a randomized trial comparing radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys 1993; 28:163-169.

19 **Vernon CC, Hand JW, Field SB, et al:** Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized control trials. Int J Radiat Oncol Biol Phys 1998; 40:289-295.

20 **Van der Zee, Gonzalez D, Van Rhoon GC, Van Dijk JDP, Van Putten WLJ, Hart AAM:** Comparison of radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective randomized multicenter trial. Lancet 2000; 335:1119-1125.

21 **Matsuda T:** Cancer treatment by hyperthermia, radiation and drugs. London, Washington DC: Taylor&Francis, Inc., 1993.

22 **Sugimachi K, Matsuda H, Ohno S, et al:** Long term effects of hyperthermia combined with chemotherapy and irradiation of the treatment of patients with carcinoma of the esophagus. Surgery Gynecol Obstet 1988; 167:319-323.

23 **Kitamura K, Kuwano H, Watanabe M, Toh Y, Matsuda H, Sugimachi K:** Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. J Surg Oncol 1995; 60:55-58.

Eur Spine J (2006) 15: 216–222
DOI 10.1007/s00586-005-0979-2

ORIGINAL ARTICLE

Taku Saito
Taiji Kondo
Takahiro Hozumi
Katsuyuki Karasawa
Atsushi Seichi
Kozo Nakamura

Results of posterior surgery with intraoperative radiotherapy for spinal metastases

Received: 16 September 2004
Revised: 15 April 2005
Accepted: 27 May 2005
Published online: 13 August 2005

T. Saito (✉) · T. Kondo · T. Hozumi
Department of Orthopaedic Surgery,
Tokyo Metropolitan Komagome Hospital,
3-18-22 Hon-Komagome, Bunkyo-ku,
Tokyo, 113-6877, Japan
E-mail: tasaitou-tky@umin.ac.jp
Tel.: +81-3-58008656

K. Karasawa
Department of Radiation Oncology, Tokyo
Metropolitan Komagome Hospital,
Tokyo, Japan

A. Seichi · K. Nakamura
Department of Orthopaedic Surgery,
University of Tokyo, Tokyo, Japan

Abstract *Object*: Spinal cord compression from spinal metastasis represents a substantial clinical problem. Complete resection of spinal metastases is difficult in many cases, and conventional surgical decompression of the spinal cord with or without instrumentation often results in unsatisfactory neurological recovery and local recurrence, even if combined with external radiotherapy. To increase rates of local control and improve neurological recovery in such cases, we introduced decompressive surgery combined with intraoperative radiotherapy (IORT) for the treatment of spinal metastasis in 1992. We report the results of neurological recovery and local control in cases that received surgery with IORT. *Methods*: Between November 1992 and December 2001, 133 cases (117 patients) were treated using IORT at Tokyo Metropolitan Komagome Hospital. The 79 cases (74 patients) that received posterior spine surgery only for spinal paresis due to spinal metastasis were reviewed. *Results*: Improvement of at least one level according to Frankel's classification was attained in 68 cases (86%). Of the 58 patients unable to walk preoperatively, 45 patients (78%) regained walking ability postoperatively. Rate of local recurrence was 2.5%. *Conclusions*: IORT, combined with posterior surgery and FERT, might be one of the effective methods for local control of spinal metastasis and neurological improvement, especially in cases with progressive and multi-level lesions.

Keywords Spinal metastasis · Intraoperative radiotherapy · Decompressive surgery · Local control

Introduction

Incidence of spinal metastasis is about 30% in patients with cancer at time of death [12, 19], and about 5% of cancer patients are estimated to develop neurological deficit as a result of spinal metastases [2]. Recent advances in oncological therapy are increasing the duration that patients with metastases can expect to live, and effective treatment is required to control both spinal metastases and associated neurological symptoms. However, results of surgical intervention are often unsatisfactory. Conventional surgical decompression of the spinal cord with or without instrumentation often results in local recurrence. Surgery combined with external radiotherapy often does not completely control the disease, particularly if the tumor is radioresistant. In addition, treatment of progressive neurological symptoms during or after external radiotherapy is difficult, as conventional decompressive surgery does not achieve satisfactory neurological recovery.

To increase rates of local control and improve neurological recovery of such patients, we introduced decompressive surgery combined with intraoperative radiotherapy (IORT) for the treatment of spinal metastasis in 1992. We report the results for neurological recovery and local control in patients who received surgery with IORT.

Materials and methods

Between November 1992 and December 2001, a total of 133 cases (117 patients) were treated using IORT at Tokyo Metropolitan Komagome Hospital. To determine rates of neurological improvement in patients with spinal metastasis, we reviewed 79 cases (74 patients) that received:

- posterior spine surgery (excluding anterior spine surgery);
- for spinal paresis (excluding patients who received surgery for intractable pain or cauda equina paresis);
- due to spinal metastasis (excluding primary spinal tumors).

Patients comprised 48 men and 26 women, with a mean age of 61.4 years (range, 42–85 years).

Primary tumor sites comprised: breast ($n=13$); lung ($n=12$); colon ($n=9$); thyroid ($n=7$); prostate ($n=7$); kidney ($n=6$); liver ($n=5$); multiple myeloma ($n=4$); malignant lymphoma ($n=3$); pharynx ($n=3$); stomach ($n=1$); esophagus ($n=1$); bladder ($n=1$); uterus ($n=1$); parotid gland ($n=1$); pancreas ($n=1$); malignant melanoma ($n=1$); leiomyosarcoma of the thigh ($n=1$); squamous cell carcinoma of the external genitalia ($n=1$); and unknown ($n=1$).

Surgery was performed in the following vertebrae: cervical ($n=3$); cervicothoracic ($n=7$); thoracic ($n=60$); and thoracolumbar ($n=9$).

Metastases were assessed using the surgical classification system for spinal tumors proposed by Tomita et al. [17] (Fig. 1). In the current study, types 6 and 7 progressive and multi-level lesions were common.

Simulation study and in vivo measurement

Simulation studies were undertaken to determine dose distribution in IORT, particularly to estimate irradiated dose in the spinal cord. Dose distributions for a human vertebra and phantom are presented in Fig. 2. In vivo measurements were also performed several times to confirm actual irradiated doses using a small film (GAF CHROMIC film type MD-55; Nuclear Associates, NY,

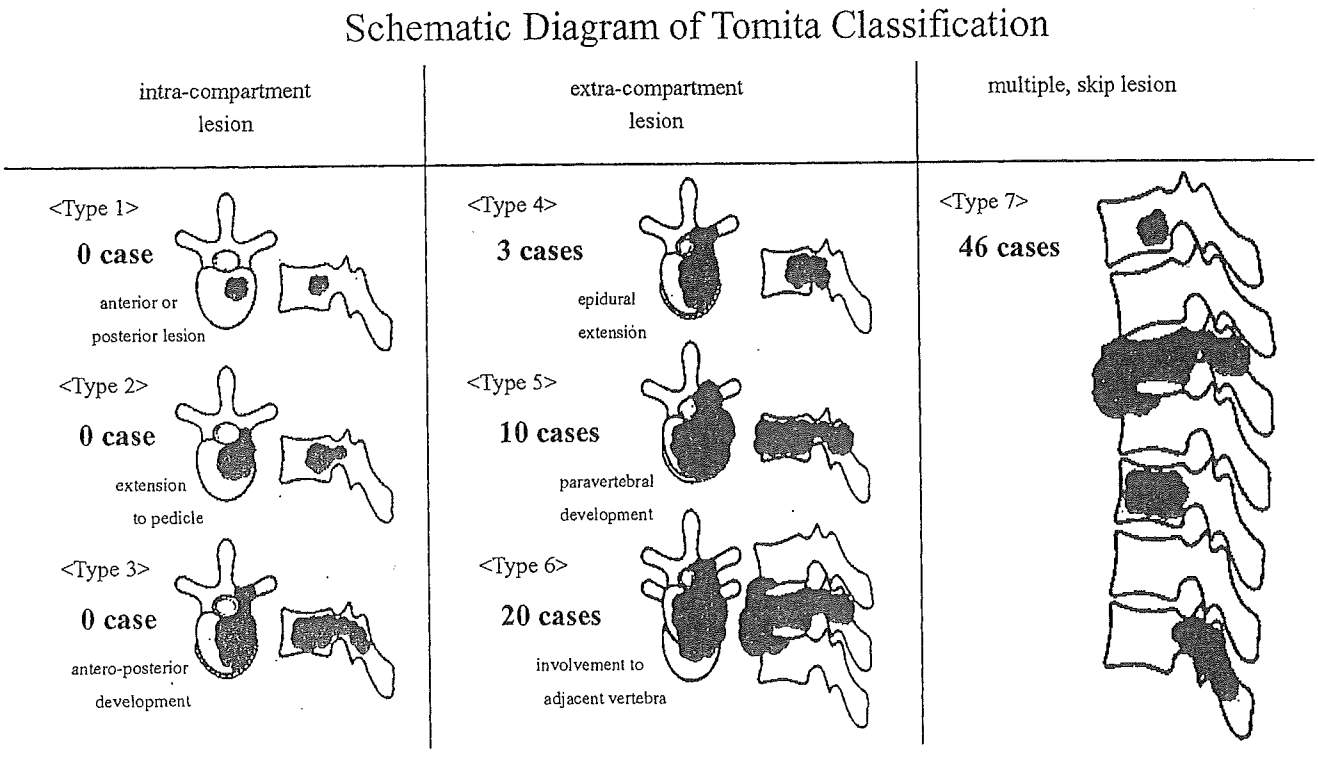


Fig. 1 Schematic diagram of surgical classification for vertebral tumors proposed by Tomita et al. [17] In the current study, metastatic lesions were extensive in many cases

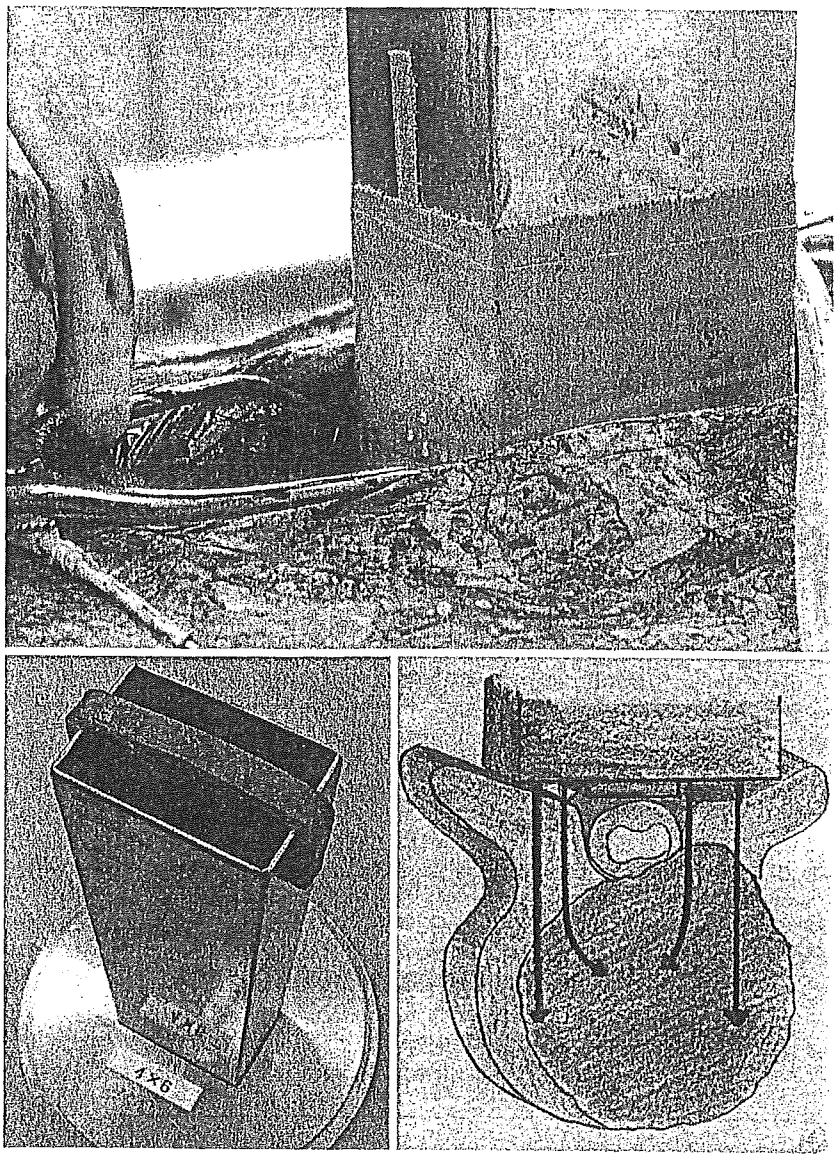


Fig. 2 Representation of electron beam when lead shielding is used to protect the spinal cord (*left*). Dose distribution for *cone size* 4 × 6 cm, *energy* 16 MeV, *shield width* 10 mm, *shield thickness* 5 mm

USA) for dose measurement. Dose of IORT in these measurements was 20 Gy.

Percentage dose in the spinal cord was 10–25% (equivalent to 2–8 Gy of fractionated external radiotherapy (FERT)) with a lead shield, and 90% (equivalent to 84 Gy of FERT) without lead shielding. In FERT, radiation myelopathy reportedly occurs in 0.2–0.5% of cases with irradiation at 50 Gy, and in 50% of cases at 68–73 Gy [6, 8, 9, 15]. Lead shielding is effective and absolutely indispensable for preventing radiation myelopathy.

Irradiated dose in vertebral tumors varies with location. Simulation studies indicated that percentage dose is minimized at the posterior edge of the vertebrae. In vivo measurements showed that the range of irradiated doses at the posterior edge is approximately 6.3 Gy (mid) to 35 Gy (lateral edge) in FERT.

A linear–quadratic model was used for dose conversions between IORT and FERT, using biological effective dose (BED):

$$BED = D(1 + d/\alpha/\beta),$$

where D is the total dose, d single fraction dose, and α/β differs for each tissue. In the current study, α/β was three for spinal cord, a late-responding tissue, and ten for vertebral tumor, an early responding tissue [3]. Single fraction dose in FERT was 2 Gy.

IORT procedures

Indications for surgical intervention comprised neurological deficit and intractable pain not expected to be controlled by external radiotherapy or chemotherapy.

Surgery was not indicated for patients displaying high surgical risk, particularly patients in poor general condition with poor prognosis due to poorly controlled primary lesions or metastases involving vital organs. If neurological status of a patient was worse than Frankel classification C (unambulatory) and progression was rapid, emergency surgery was performed.

If a tumor was expected to be hypervascular, preoperative embolization was performed to minimize intraoperative bleeding.

After posterior decompression (laminectomy and resection of epidural metastatic tumor where possible) and control of bleeding, patients were covered with sterile cloth and transferred from the operating room to the radiotherapy room (about 80 m). In the radiotherapy room, an appropriately sized sterile electron cone with a lead shield was connected to the electron beam generator, and placed precisely in the surgical field so that the beam covered the tumor, while the lead shield protected the spinal cord (Fig. 3). An electron beam was generated using a Microtron (Hitachi, Tokyo, Japan). Energy utilized depended on the depth of the lesion. Mean energy in this study was 15.9 MeV (range, 11–20 MeV). Mean dose of IORT was 20.7 Gy (range, 15–25 Gy). All IORT procedures took 40–50 min in the single case, including transfer, preparations and so on. The patients were carefully monitored continuously during transfer and IORT by experienced anesthesiologists.

After IORT, patients were transferred back to the operating room. Internal fixation with instrumentation and posterolateral fusion with allograft was performed if necessary. A spinal instrument made of titanium (CD HORIZON or TSRH; Medtronic Sofamor Danek, Minneapolis, USA) was used because of the reduced interference with postoperative magnetic resonance imaging (MRI).

External radiotherapy

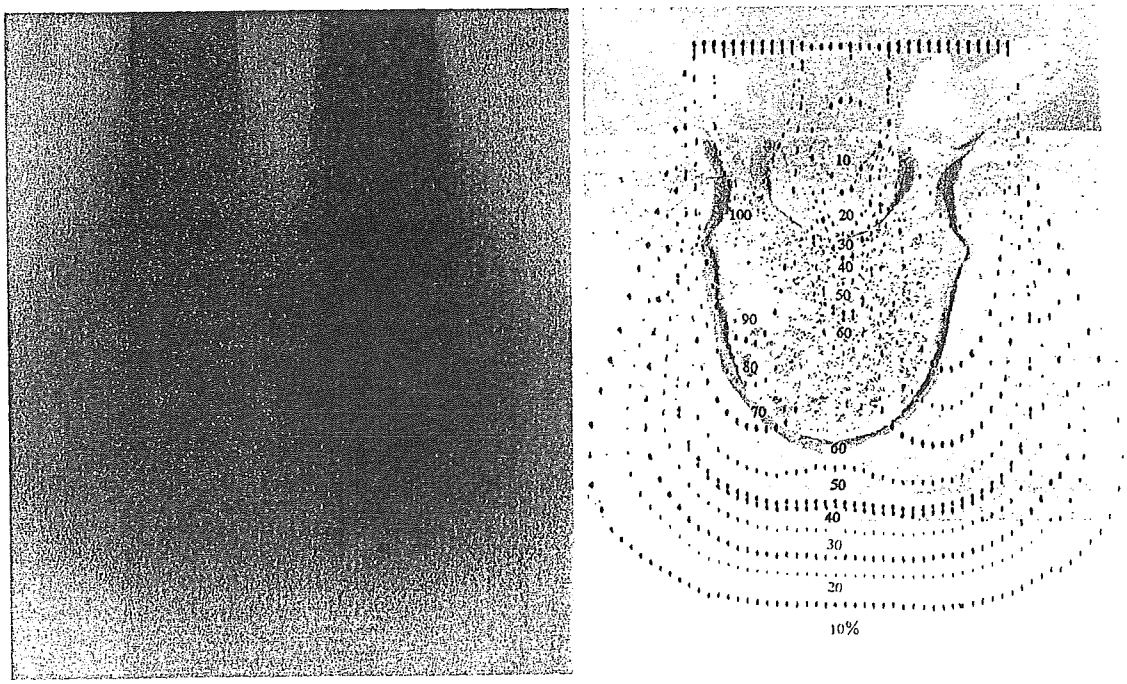
In addition to IORT, external radiotherapy was performed postoperatively in 34 cases, and preoperatively in 20 cases. Mean dose was 36 Gy (range, 12–60 Gy). Single fraction dose was generally 2 Gy.

In principle, if a patient did not receive preoperative radiotherapy, external radiotherapy at a dose of approximately 30 Gy was recommended after wound suture removal to increase local control. The dose of 30 Gy in addition to IORT was selected based on the tolerance dose of the spinal cord. However, consensus regarding optimum doses for such applications has yet to be reached.

Chemotherapy

The decision to perform adjuvant chemotherapy rested with the physicians who had managed the primary

Fig. 3 Photographic (*above*) and schematic (*right below*) representation of intraoperative radiotherapy. Lead shielding to protect the spinal cord was connected to the electron beam generator (*left below*)



lesions. Of the 45 patients who received adjuvant chemotherapy, 12 received preoperative chemotherapy only, 15 received postoperative chemotherapy only, and 18 received both preoperative and postoperative chemotherapy. Chemotherapy was administered for breast cancer ($n=13$), lung cancer ($n=9$), colon cancer ($n=4$), renal cancer ($n=4$), malignant lymphoma ($n=3$), hepatoma ($n=2$), multiple myeloma ($n=2$), prostate ($n=1$), pancreas ($n=1$), stomach ($n=1$), esophagus ($n=1$), malignant melanoma ($n=1$), leiomyosarcoma of the thigh ($n=1$), squamous cell carcinoma of the external genitalia ($n=1$), and adenocarcinoma of the parotid gland ($n=1$).

Hormone therapy was administered for five patients with prostate cancer and two patients with breast cancer.

Clinical evaluation

Neurological function was evaluated using Frankel's classification system [4], as follows:

a complete motor and sensory loss;
b complete motor loss but some sensation preserved;
c some motor power preserved but of no functional use;
d useful motor power including walking with or without aids;
e no neurological symptoms.

Follow-up examinations, including plain radiography and enhanced MRI of the operated site, were performed every 3 months to detect local recurrence.

Results

For 57 patients, mean survival was 10.4 months after IORT (range, 2 weeks to 63 months). The remaining 17 patients were still alive after a mean follow-up period of 20 months (range, 1–65 months). Second surgery with IORT was undertaken in four cases for further spinal metastasis, and in one case for local recurrence.

Posterior decompression was performed without instrumentation in 33 cases, and with instrumentation in 46 cases. Mean duration of surgery was 5 h 10 min (range, 2 h 20 min to 9 h). Mean blood loss was 934 ml (range, 100–4340 ml).

No cases demonstrated immediate neurological deterioration. Neurological improvements according to Frankel's classification are presented in Fig. 4. At least one level of improvement was attained in 68 cases (86%). Of the 58 patients unable to walk preoperatively, 45 (78%) regained walking ability postoperatively. Mobility was improved in six of the 13 patients who did not regain ambulation, but was not improved in seven patients who experienced deteriorated general condition (Fig. 4).

Postoperatively, 66 patients were ambulatory. Of these, 64% were ambulatory by 6 months after surgery, and 36% remained ambulatory by 1 year after surgery. Mean duration of maintained walking ability was 10.3 months (range, 1–65 months). Causes of recurrent loss of walking ability comprised: deterioration of general condition (including metastasis to other organs, $n=30$), other spinal metastases ($n=13$), bone metastasis in lower extremities ($n=2$), radiation myelopathy ($n=1$),

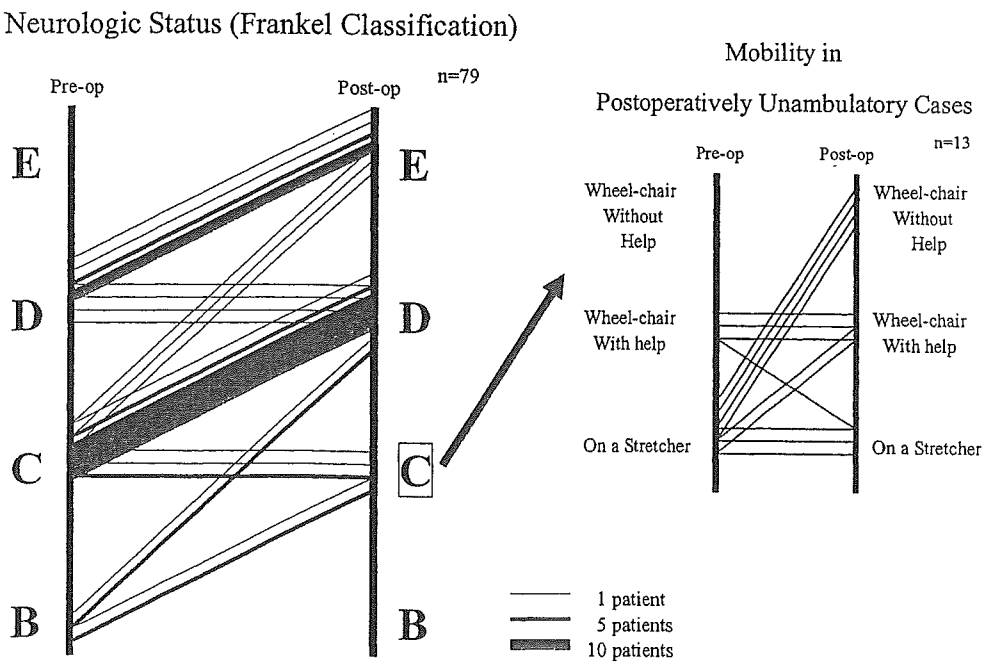


Fig. 4 Neurological improvement according to Frankel's classification. At least one level of improvement was attained by 86% of all patients

local recurrence ($n=2$), and compression fracture and kyphotic changes in the operated vertebra ($n=3$). Patients with compression fracture and kyphotic changes to the operated vertebra displayed metastasis in the thoracic vertebrae and were treated without instrumentation.

One patient displayed disseminated intravascular coagulation (DIC), and two developed postoperative pneumonia. These patients died 16–18 days postoperatively. No cases of surgical wound infection were encountered.

One patient displayed neurological improvement temporarily after surgery, followed with neurological deterioration into the preoperative status 3 months later. We could not find any substantial cause of this neurological deterioration and diagnosed as radiation myelopathy. The patient had received both preoperative external radiotherapy (60 Gy) and second IORT for metastasis in an adjacent vertebra.

Discussion

Surgery for spinal metastasis involves posterior decompression, posterior decompression with stabilization, and anterior resection or decompression with reconstruction. In many cases, tumor resection is incomplete and local recurrence may occur. Surgery combined with external radiotherapy may improve the therapeutic ratio, but outcomes remain somewhat unsatisfactory. IORT was applied in our series to minimize local recurrence. The IORT has previously been used to manage pancreatic, bladder, and colorectal cancer and malignant brain tumors. However, no reports of IORT used to manage spinal metastasis in a large series of patients have previously been published from other institutions [16].

The comparison of neurological results with the literature is difficult because of the many various factors, such as kinds of primary tumor, stages of progress and therapeutic histories. Moreover, concepts and indications are very different in each surgical method. For example, the anterior method is usually intended as total resection of metastatic lesion. The results of the anterior method are good, but its indication is usually limited to single and intra-compartment lesion. On the other hand, the posterior method is usually intended as decompression of the spinal cord, and its indication includes progressive and multi-level lesions. As for clinical evaluation, duration of walking ability is very important, nevertheless duration of walking ability was not mentioned in many previous reports of other surgical methods. Frankel's classification is the only means for comparison, because neurological improvement was evaluated merely according to Frankel's classification. Rates of neurological improvement according to Frankel's classification in previous reports of these surgical methods have been approximately 30–40% in posterior decompression, 50–70% in posterior decompression and stabilization combined with external radiotherapy, and 70–80% in the anterior method [1, 5, 11, 13, 14, 18]. The 86% rate of neurological improvement achieved in the current study is not worse at least, considering that many patients displayed progressive and multi-level lesions. In particular, rate of local recurrence in the current study was 2.5%, representing an excellent result compared to previous reports (20–30%) [7, 10]. Because quantifying the effects directly attributable to IORT is difficult in the present study, the following study is required for revealing the conditions that need IORT and the appropriate indication of IORT.

Radiotherapy is necessary in the treatment of spinal metastasis, as radical excision is impossible in many cases. However, total dose is limited by the tolerance dose of the spinal cord. The common dose limit is about 45 Gy, and radiation myelopathy reportedly occurs with the following frequencies in FERT: 0.2–0.5% at 50 Gy; 5% at 57–61 Gy; and 50% at 68–73 Gy [6, 8, 9, 15]. In single IORT of 20 Gy, irradiated dose to the spinal cord is 2–8 Gy (in FERT equivalents). In cases where preoperative external radiotherapy has been administered, dose of IORT should be determined carefully with consideration of total dose. When postoperative external radiotherapy is performed, total dose might be decreased out of consideration for the irradiated dose in IORT (we recommend 30 Gy for most cases). In the current study, one case of radiation myelopathy was encountered. The patient had received high-dose preoperative external radiotherapy (60 Gy) and second IORT for metastasis in an adjacent vertebra. Lead shielding represents an effective preventative measure, but risk of radiation myelopathy should always be considered when performing IORT.

All IORT procedures, especially transfer from the operating room to the radiotherapy room, would increase the infection risk. The most important prophylaxis of infection is to perform all procedures smoothly and quickly, for which cooperation and training of all staff are necessary. Careful covering during transfer and thorough irrigation of the surgical field are also important for prophylaxis of infections. Fortunately, there were no cases of surgical wound infection in these 79 cases.

Two patients displayed local recurrence postoperatively. Primary tumor sites for the two cases were lung and malignant lymphoma, and both cases were treated using adjuvant chemotherapy and external radiotherapy. Both cases displayed large and progressive lesions, and recurrent growth to adjacent vertebrae and the paravertebral area.

Three patients regained ambulation postoperatively, then lost walking ability again due to compression fracture and kyphotic changes in vertebrae that underwent operation without instrumentation. Although no significant differences were observed between results for patients with or without instrumentation, we now add stabilization with instrumentation for all cases of metastases in thoracic vertebrae.

Conclusion

The IORT, combined with posterior surgery and FERT, might be one of the effective methods for local control of spinal metastasis and neurological improvement, especially in cases with progressive and multi-level lesions. This procedure has to be examined for its appropriate indication in the following study.

Acknowledgements The submitted manuscript does not contain any information regarding medical devices or drugs. No funds were received in support of this work and no benefits in any form have been or will be received from commercial parties related directly or indirectly to the subject of this manuscript.

References

1. Bauer HC (1997) Posterior decompression and stabilization for spinal metastases. Analysis of sixty-seven consecutive patients. J Bone Joint Surg Am 79:514–522
2. Black P (1979) Spinal metastasis: current status and recommended guidelines for management. Neurosurgery 5:726–746
3. Eric JH (2000) Radiobiology for the radiologist, 5th edn. Lippincott Williams & Wilkins, Baltimore, pp 397–418
4. Frankel HL, Hancock DO, Hyslop G et al (1969) The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. Paraplegia 7:179–192
5. Hatrick NC, Lucas JD, Timothy AR et al (2000) The surgical treatment of metastatic disease of the spine. Radiother Oncol Sep 56:335–339
6. Jeremic B, Djuric L, Mijatovic L (1991) Incidence of radiation myelitis of the cervical spinal cord at doses of 5500 cGy or greater. Cancer 68:2138–2141
7. Manabe S, Tateishi A, Abe M et al (1989) Surgical treatment of metastatic tumors of the spine. Spine 14:41–47
8. Marcus RB, Million RR (1990) The incidence of myelitis after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 19:3–8
9. McCunniff A, Liang MJ (1989) Radiation tolerance of the cervical spinal cord. Int J Radiat Oncol Biol Phys 16:675–678
10. Missenard G, Lapresle P, Cote D (1996) Local control after surgical treatment of spinal metastatic disease. Eur Spine J 5:45–50
11. Nicholls PG, Jarecky TW (1985) Evaluate posterior decompression by laminectomy for malignant tumors of the spine. Clin Orthop 201:210
12. Ortiz Gomez JA (1995) The incidence of vertebral body metastases. Int Orthop 19:309–311
13. Rompe JD, Hopf CG, Eysel P (1999) Outcome after palliative posterior surgery for metastatic disease of the spine—evaluation of 106 consecutive patients after decompression and stabilisation with the Cotrel-Dubousset instrumentation. Arch Orthop Trauma Surg 119:394–400
14. Sapkas G, Kyratzoulis J, Papaioannou N et al (1997) Spinal cord decompression and stabilization in malignant lesions of the spine. Acta Orthop Scand Suppl 275:97–100
15. Schultheiss TE, Kun LE, Ang KK et al (1995) Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 31:1093–1112
16. Seichi A, Kondoh T, Hozumi T et al (1999) Intraoperative radiation therapy for metastatic spinal tumors. Spine 24:470–473
17. Tomita K, Kawahara N, Baba H et al (1997) Total en block spondylectomy. Spine 22:324–333
18. Wetzel FT, Phillips FM (2000) Management of metastatic disease of the spine. Orthop Clin North Am 31:611–621
19. Wong DA, Fornasier VL, MacNab I (1990) Spinal metastases: the obvious, the occult, and the impostors. Spine 15:1–4

診療
臨床放射線 51 296-301, 2006

Bellyboard使用による前立腺照射時の臓器移動の減少

川上睦美* 唐澤克之* 原田耕作* 羽生菜穂子* 木口由梨絵*

はじめに

最近10年程度の期間に日本でも前立腺癌の罹患率は上昇の一途をたどり，現在では最も多く罹患する癌の中に入りつつある[1]。日本における前立腺癌の治療として，以前には手術もしくは内分泌療法が主として用いられてきたが，1990年代より，放射線治療もその治療オプションとして位置づけられてきた[2]。また，2003年から始められた，放射性ヨウ素粒子（^{125}Iシード線源）を埋め込む小線源治療がホットなトピックスである[3]。しかし外部照射の症例もそれに劣らず増加中であり，我々の施設でも年間数十例の根治的な外部照射を行っている。

前立腺癌の根治に必要な線量は一般的にそのリスク分類によると考えられている。すなわち，低リスク群では70～72Gy，中リスク群は76～78Gy，高リスク群ではそれ以上の線量もしくは補助内分泌療法を併用するということが提唱されている[4]。

また日本においては，欧米と比較して，長年の間多くの施設において放射線治療に内分泌療法が併用されてきた。そして内分泌療法併用時の局所制御に必要とされる放射線線量は60～70Gyと解釈されてきた[5) 6)]。つい最近になり，EBMの普及および患者のQOL意識の向上から，内分泌療法の安易な併用を避ける傾向が出てきたこともあり，あらためて放射線治療単独での局所制御を期待されるようになってきている。

したがって，これまで内分泌療法併用により比較的低い線量でも治癒していた感のあった前立腺癌に対し，従来に比べ少なくとも10Gy程度の線量増加が必要と考えられるようになった[7]。しかし，周囲の正常臓器すなわち，膀胱と直腸，中でも直腸は耐容線量が約70Gyであり，70Gyを超えた線量増加には直腸出血等の危険を伴うことが予想される[8]。

そこで我々は，線量増加を施行するにあたり，腹臥位（prone position）を採用して，前立腺および精嚢と直腸を最も分離して照射できる体位とすることにした。しかし，これでは腹部臓器の呼吸性移動により，前立腺の動きが大きくなるため，この対策としてベリーボード（belly-board）を使用した。

今回我々は，bellyboardの使用が，果たして前立腺の治療中の臓器移動を減少させるか，またその動きは背臥位（supine position）の場合と比較して劣らないか，について検討する目的で実際の患者について，その治療計画時に3体位，すなわち，1）supine position，2）prone positionでbellyboardなし，3）prone positionでbellyboardあり，で呼吸による前立腺の臓器移動について検討した。

* M. Kawakami, K. Karasawa, K. Harada, N. Hanyu, Y. Kiguchi 都立駒込病院放射線科
〔索引用語：前立腺癌，照射体位，ベリーボード〕

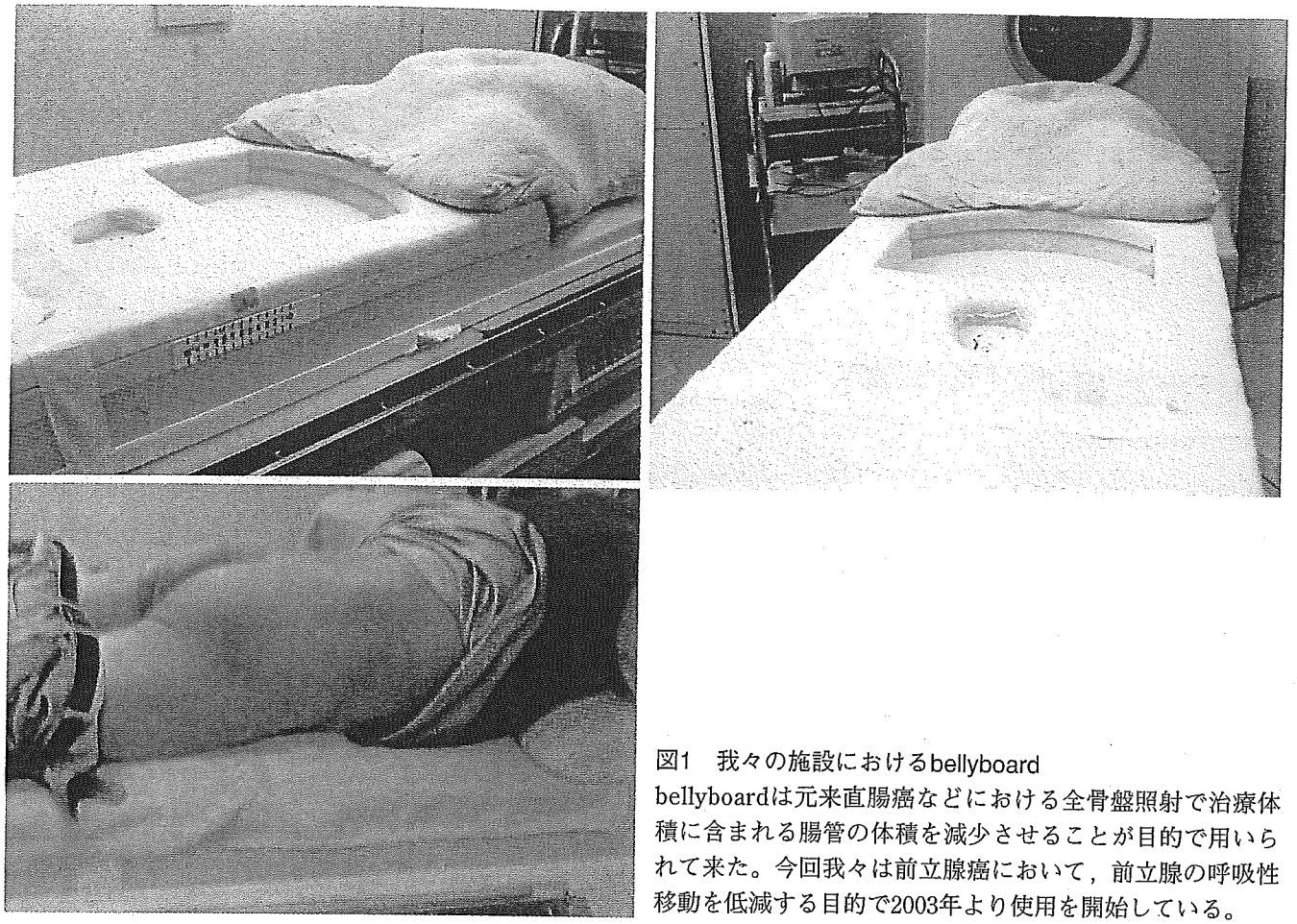


図1　我々の施設におけるbellyboard
bellyboardは元来直腸癌などにおける全骨盤照射で治療体積に含まれる腸管の体積を減少させることが目的で用いられて来た。今回我々は前立腺癌において，前立腺の呼吸性移動を低減する目的で2003年より使用を開始している。

1. 対　象

2004年5月～8月までに当科で放射線治療を行った前立腺癌患者6例（平均年齢74.3歳±5.4歳）。病期分類はstage II：T1c 3名，stage III：T3a 1名，T3b 1名，T3c 1名であり全例に総線量72Gyの外照射を行った。

2. 方　法

内部を造影剤（ガストログラフィン）で満たしたバルーンカテーテルを尿道に挿入し軽く固定し，1）背臥位，2）bellyboardなしの腹臥位，3）bellyboardありの腹臥位の三体位にて，まず膀胱頸部の呼吸性移動を透視上で観察し，次に最大吸気時および最大呼気時のX線撮影を行った。X線フィルム上，膀胱頸部の偏移距離を計測した。

図1は当科で使用しているbellyboardを示す。

3. 結　果

図2は症例4における三体位での吸気時，呼気時の膀胱頸部の偏移を示したものである。背臥位とbellyboardを用いた腹臥位においては呼吸性移動がほとんど見らなかった。bellyboardを用いない腹臥位では膀胱頸部が大きく偏移していた。他の症例でも同様の傾向を示した。

表1は各症例の各体位における膀胱頸部の変位を計測した結果を示したものである。

左右，背腹および頭尾方向の平均移動距離は，背臥位では0.17±04.1mm，1.83±0.98mm，1.5±0.55mm，bellyboardなしの腹臥位で0.5±1.22mm，10.33±4.27mm，3.17±1.60mm，およびbellyboardを用いた腹臥位で0.17±0.41mm，3.0±3.69mm，0.33±0.82mm，三方向への平均移動距離はそれぞれ2.58±0.43mm，11.1±4.05mm，3.07±3.75mmであった。bellyboardなしの腹臥

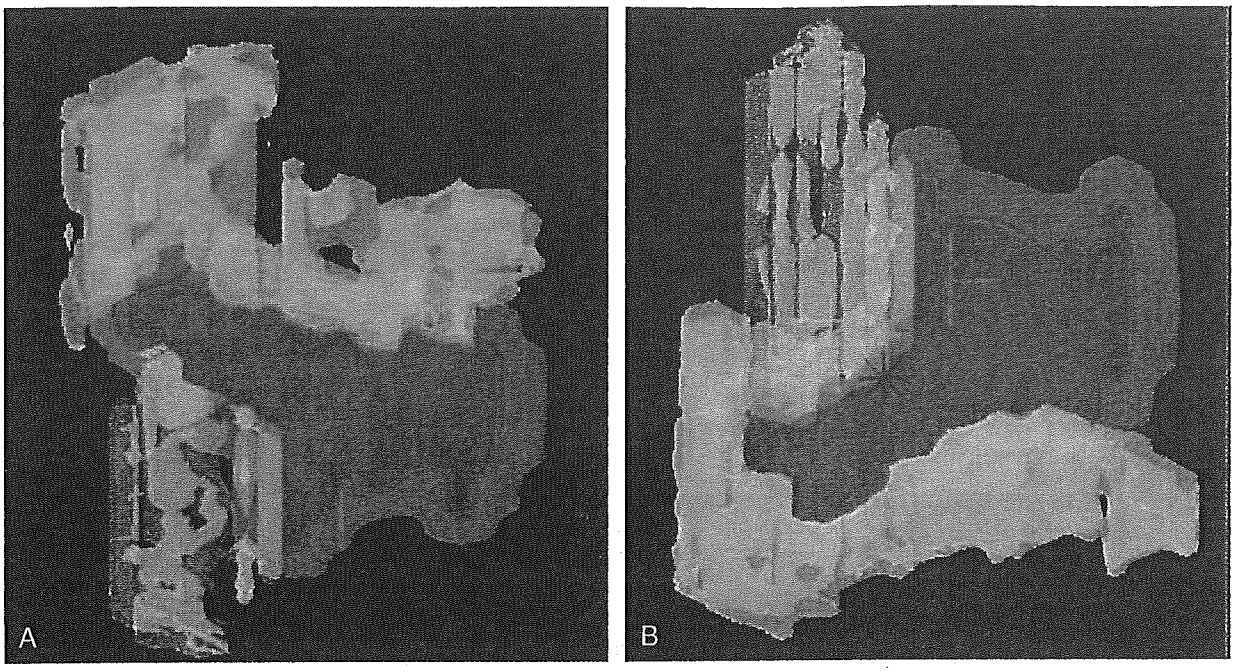


図3　proneとsupineにおけるtarget volumeの形状とorgans at riskとの位置関係を示したもの
prone positionのほうがよりRectumをスペアしていることがわかる。

位での偏移距離は背臥位に比べ有意に大きかったが（p=0.004），これはbellyboardを用いることにより明らかに減少していた（p=0.014）。

4. 考　察

前立腺癌の治療体位として，supineがよいか，proneがよいかについては，以前より様々な議論が行われてきた[9-12]。proneを支持するグループによれば，proneのほうがよりよく精嚢と直腸を分離できて，直腸への線量が減らせ，前立腺への線量が増加できるという意見である[11) 12)]。一方，supineを支持するグループによれば，proneは腹部臓器の呼吸性移動の影響を強く受け，正確に放射線が照射されないという意見である[9-10]。実際2004年のASTROの前立腺癌の外部照射に関するパネルディスカッションでもproneとsupineで治療する施設のポリシーが分かれていた。

bellyboardは元来，直腸癌などの全骨盤照射時に骨盤内の小腸を，骨盤外に逃がすものとして開発されたものである[13]。それを今回前立腺癌治療時に，腹部臓器，特に腸管の呼吸性移動の前立腺への影響を回避する目的で使用してみた。

今回の我々の実験結果では，このbellyboardを使用することによってprone positionであっても，前立腺の呼吸性移動が低減することがわかった。よってsupineおよびprone position両者の好都合な点を兼ね備えた方法であることが示唆された。

図3はprone positionとsupine positionにおけるtarget volume〔clinical target volume（CTV）とplanning target volume（PTV）〕と直腸，膀胱の関係であるが，prone positionにおいてより側方からTarget volumeと直腸がよく分離できることがわかる。これはZelefskiが指摘しているのと同等であった。我々は斜めよりのCrossfire法にて治療を開始し，途中から側方対向二門照射法に変更して，直腸への線量低減に努めている。すなわち，32Gy分の線量を側方より投与するが，その間に3回cone downを行い，最後の2回（72Gyから）は完全に直腸をビームからはずすように照射している。そのようにして治療計画した，線量体積ヒストグラムをprone positionとsupine positionでそれぞれ図4に示す。直腸の最大線量が約3Gy prone positionの方が左にシフトしているのがわかる。同様に直腸の高線量域も約3Gy分左にシフトしている。すなわち，prone positionのほうが，より多くの線量を許容する傾

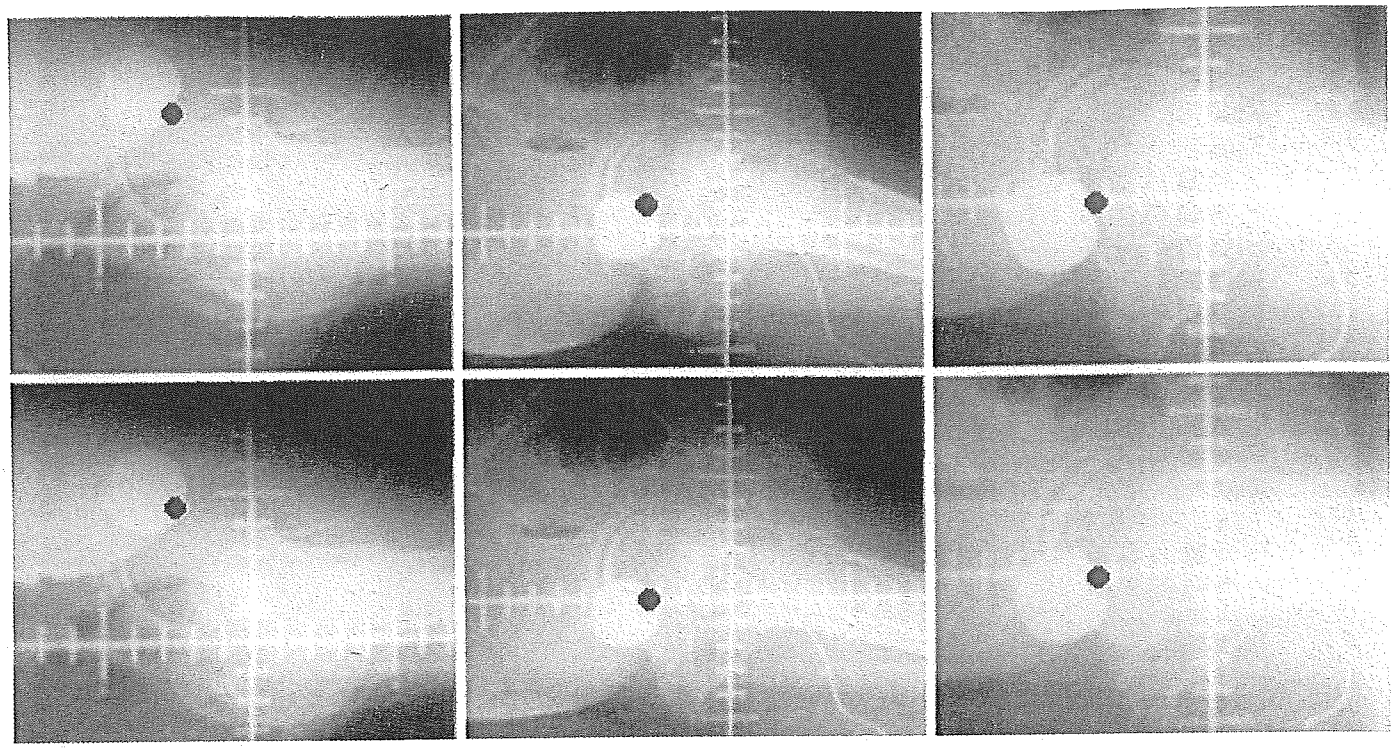


図2　吸気時と呼気時においてX線写真を撮像し，膀胱頸部の変位を測定（同一患者の3つの体位での比較）
supineとbellyboardを使用したproneでは呼吸性の移動がほとんど認められないのに対し，bellyboardを使用しないproneでは呼吸により膀胱頸部が大きく変位している。

表1　体位による膀胱頸部の変位（mm）

	supine				prone bellyboardなし				prone bellyboardあり			
	r-l	a-p	c-c	3DD	r-l	a-p	c-c	3DD	r-l	a-p	c-c	3DD
case 1	1	2	1	2.45	0	10	3	10.44	0	3	0	3.00
case 2	0	2	2	2.83	3	6	4	7.81	1	2	0	2.24
case 3	0	0	2	2.00	0	8	2	8.25	0	3	0	3.00
case 4	0	2	1	2.24	0	12	6	13.42	0	10	2	10.20
case 5	0	3	1	3.16	0	8	2	8.25	0	0	0	0.00
case 6	0	2	2	2.83	0	18	2	18.11	0	0	0	0.00
Average	0.17	1.833	1.5	2.58	0.5	10.33	3.167	11.05	0.17	3	0.33	3.07
Std Dev.	0.41	0.983	0.55	0.43	1.22	4.274	1.602	4.05	0.41	3.69	0.82	3.75

r-l：左右方向，a-p：前後方向，c-c：頭尾方向，3DD：3次元変位，Std Dev：標準偏差

文 献

1) がんの臨床統計 (Cancer Statistics in Japan-2003). がんの統計編集委員会編, 財団法人がん研究振興財団 (Foundation for Promotion of Cancer Research), 2003
2) 唐澤克之：前立腺癌. 癌放射線治療, 篠原出版新社, 2002
3) Hirokawa Y：Advances in brachytherapy；focusing on the permanent implant for early prostate carcinoma. Gan To Kagaku Ryoho 30：2056-2061, 2003
4) Zelefsky MJ et al：Prostate Cancer, (in) Perez CA et al ed；Principles and Practice of Radiation Oncology. p1692-1762, Lippincott, Philadelphia, 2004
5) Shimizu T et al：Conformation radiotherapy of carcinoma of the prostate. Nippon Igaku Hoshasen Gakkai Zasshi 52：993-1000, 1992
6) Karasawa K et al：Rotational 3D-conformal radiation therapy (conformation therapy) combined with hormone therapy for the treatment of stage B2/C prostate cancer in Japanese men. Int J Radiat Oncol Biol Phys 56：208-212, 2003
7) Pollack A：The prostate, (in) Cox JD, Ang KK ed；Radiation Oncology 8th ed. p620-680, Mosby, 2003
8) Lawton CA et al：Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate；analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 21：935-939, 1991
9) Weber DC et al：Patient positioning in prostate radiotherapy；is prone better than supine?. Int J Radiat Oncol Biol Phys 47：365-371, 2000
10) Kitamura K et al：Three-dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. Int J Radiat Oncol Biol Phys 53：1117-1123, 2002
11) Zelefsky MJ et al：The effect of treatment positioning on normal tissue dose in patients with prostate cancer treated with three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 37：13-19, 1997
12) McLaughlin PW et al：The effect of patient position and treatment technique in conformal treatment of prostate cancer. Int J Radiat Oncol Biol Phys 45：407-413, 1999
13) Bertelrud K et al：Bellyboard device reduces small bowel displacement. Radiol Technol 62：284-287, 1991
14) Uematsu M et al：Interfractional movements of the prostate detected by daily computed tomography (CT) -guided precise positioning system with a fusion of CT and linear accelerator (FOCAL) unit. Int J Radiat Oncol Biol Phys 54：s13, 2002

Summary

Reduction of organ motion during 3D-CRT for prostate cancer using Bellyboard

Much debate has been discussed on the position of the body in the conformal radiotherapy of prostate cancer. While prone position can reduce high dose rectal volume near seminal vesicles, it is more influenced by respiratory motion compared with supine position. We have been using bellyboard to reduce prostate motion owing to respiration. We evaluated the difference.

Methods：Six patients with prostate cancer were examined. The patients were taken orthogonal XP films inhaled and exhaled in 1. supine position, 2. prone position without bellyboard and 3. prone position with bellyboard. The deviation of bladder neck was measured.

Results：The average motions in x (right-left), y (anterior-posterior), z (cranio-caudal) direction for position1. were 0.2±0.41mm, 1.8±0.98mm, 1.5±0.55mm, position2. 0.5±1.22mm, 10.3±4.27mm, 3.2±1.60mm and those for position 3. were 0.2±0.41mm, 3.0±3.69mm, 0.3±0.82mm, respectively. The average 3-dimensional motion for position 1. was 2.6±0.43mm, position 2. 11.1±4.05mm and position 3. 3.1±3.75mm. Prone position was significantly more influenced by respiratory motion ($p=0.004$), however, the use of bellyboard significantly reduced the prostate potion ($p=0.014$).

Conclusion：Though the number of evaluated patients is small, bellyboard appears to reduce prostate motion during radiotherapy for prostate cancer. Since rectum and prostate locate in close proximity, this reduction of prostate motion might improve the therapeutic ratio.

Mutsumi Kawakami et al
Department of Radiology
Tokyo Metropolitan Komagome Hospital

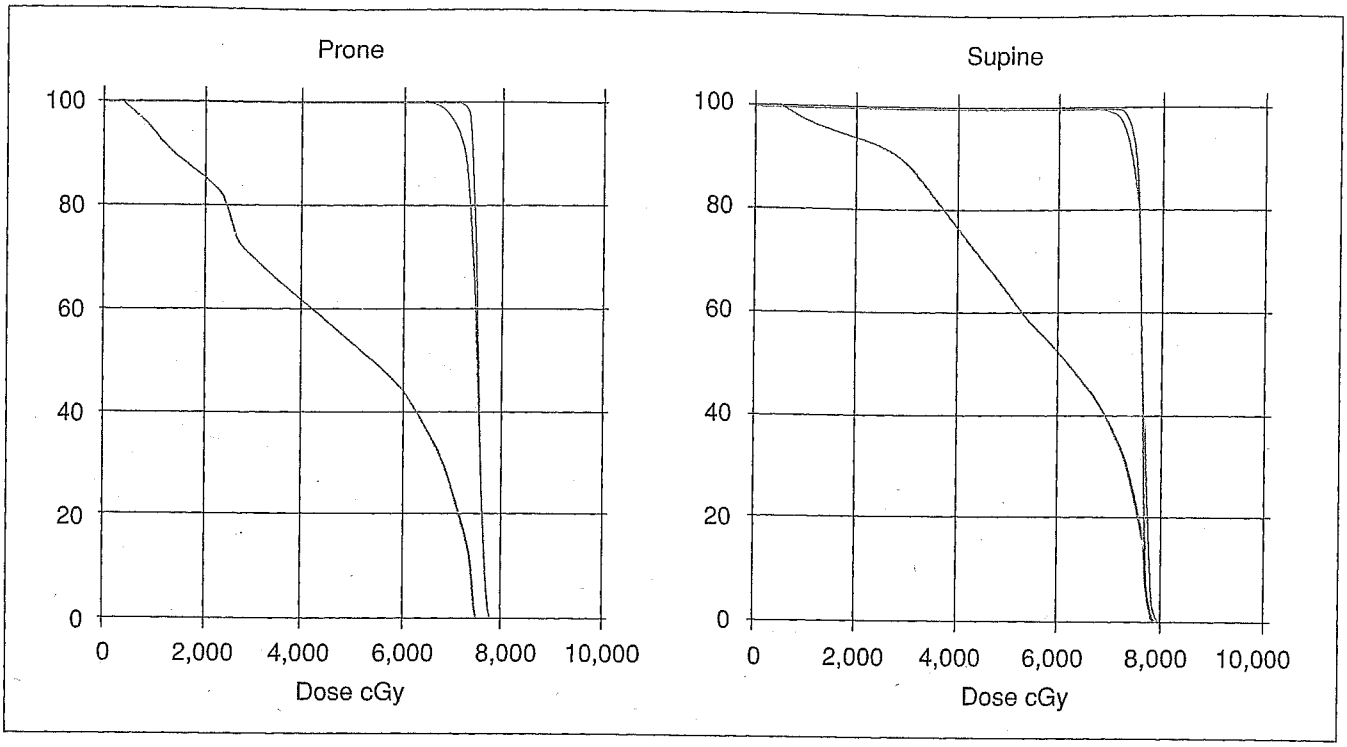


図4　同症例のdose volume histogram
prone positionにおいてよりRectumのDVHが左に寄っていることがわかる。以上より，前立腺の呼吸性移動を考慮にいれなければ，prone positionの方がより直腸の線量を低減させる可能性があることが示唆された。
赤：CTV，緑：PTV，青：直腸壁

向にあることが示唆される。

setup errorに関しては，当院での結果では，supineでもbellyboardを用いたproneでも，90%以上の照射で±5mm以内であることがわかっており，信頼度の高い照射法であることが示唆されている。

また考えなければならないこととしては，Supineでは，intrafractionalのmotionの他に，interfractionalの臓器移動がある。この点については，Uematsuらが，指摘しているように[14]，毎回の放射線治療前にCTを撮像することにより，前立腺は約半数の症例で最大の変位が15mm以上前後に移動することがわかっている。これは無視できない変位であり，そのためアメリカでは，IMRTなどの高精度放射線治療を行う際には，放射線治療室内で毎回の治療時に超音波診断装置を用いて前立腺の位置を確認することなどをしてから治療をしており，治療中の呼吸性移動は少ないものの，かなり大変なworkloadを必要とされる。

一方，proneの場合，恥骨の上（後方）に常に前立腺が存在しており，interfractionalのerrorが生じにくい。唯一頭に入れておく必要があるのが，膀胱の状態で，膀胱が空虚になると，前立腺は恥骨の上を下から上へとすべる様に移動する。よって患者に指導して，常に尿が貯まった状態で放射線治療を行うことが，前立腺位置の固定と，放射線を受ける膀胱壁の体積の減少を齎し，好都合である。

現在までの約1年半の間に約30例の中リスクおよび高リスクの前立腺癌症例に対して76Gyの総線量を使用しているが，特に有害事象の増加はなく，またまだ経過観察期間は短いものの早期のPSA再発は認められていない。

結論として，前立腺癌の放射線治療時にbellyboardを用いてproneで照射することにより，治療中の前立腺の呼吸性移動を減ずることができた。我々の方法は簡便であり，なおかつIMRT等の高度なテクニックを必要とせずに，76Gy程度までは安全に線量増加が可能であることが示唆された。今後引き続き症例を重ねて検討していく予定である。