Four year clinical statistics of iridium-192 high dose rate brachytherapy

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Original Article

Four year clinical statistics of iridium-192 high dose rate brachytherapy

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Background: We evaluated the efficacy and complications of high dose rate (HDR) brachytherapy using iridium-192 (^{192}Ir) combined with external beam radiotherapy (EBRT) in patients with prostate cancer.
Methods: Ninety-seven patients underwent ^{192}Ir HDR brachytherapy combined with EBRT at our institution between February 1999 and December 2003. Of these, 84 patients were analysed in the present study. ^{192}Ir was delivered three times over a period of 2 days, 6 Gy per time, for a total dose of 18 Gy. Interstitial application was followed by EBRT at a dose of 44 Gy. Progression was defined as three consecutive prostate-specific antigen (PSA) rises after a nadir according to the American Society for Therapeutic Radiology and Oncology criteria. The results were classified into those for all patients and for patients who did not undergo adjuvant hormone therapy.
Results: The 4-year overall survival of all patients, the nonadjuvant hormone therapy group (NAHT) and the adjuvant hormone therapy group (AHT) was 87.2%, 100%, and 70.1%, respectively. The PSA progression-free survival rate of all patients, NAHT, and AHT was 82.6%, 92.0%, and 66.6%, respectively. Of all patients, the 4-year PSA progression-free survival rates of PSA < 20 and PSA ≥ 20 groups were 100%, and 46.8%, respectively. According to the T stage classification, PSA progression-free survival rates of T1c, T2, T3, and T4 were 100%, 82.8%, 100%, and 12.1%, respectively. Prostate-specific antigen progression-free survival rates of groups with Gleason scores (GS) < 7 and GS ≥ 7 were 92.8% and 60.1%, respectively. Of NAHT, PSA progression-free survival of PSA < 20 was 100% vs 46.8% for PSA ≥ 20, that of T1c was 100% vs 75% for T2, and that of GS < 7 was 100% vs 75% for GS ≥ 7. No significant intraoperative or postoperative complications requiring urgent treatment occurred except cerebellum infarction.
Conclusions: ^{192}Ir HDR brachytherapy combined with EBRT was as effective as radical prostatectomy and had few associated complications.

Key words external beam radiotherapy, high dose rate brachytherapy, iridium-192, prostate cancer.

Introduction

Prostate-specific antigen (PSA) measurement is now widely used in screening of prostate cancer, and the disease rate is increasing in Japan.[1] Both hormone therapy and radical prostatectomy used in the treatment of prostate cancer have many complications, such as bleeding during operation, incontinence, anastomotic stenosis of the urethra, and erectile dysfunction. Therefore, it is necessary to develop new treatment methods that can maintain patients' quality of life (QOL) as much as possible. Good results have been reported with the conventional treatment for localized prostate cancer, radical prostatectomy, which has a 10-year PSA-free survival rate of 75%.[2] However, since this treatment method is associated with a high incidence of complications, such as incontinence and erectile dysfunction, it remains unsatisfactory from the viewpoint of postoperative QOL. With regard to radiotherapy, external radiation using a liniac has generally been performed and various devices have been developed to improve the results or minimize complications. However, there are limits to the effectiveness of external radiation, and the remaining percentage of viable cancer cells as determined by prostate biopsy after radiation range from 40% to 50%.[3] Akakura reported that radical prostatectomy is superior to radiation with regard to both 5-year PSA progression-free survival and cancer-specific survival,[4] whereas recently, good results have been reported with high dose rate (HDR) brachytherapy.[5–7] Brachytherapy was developed for high-dose irradiation only to the prostate and to have less effect on neighboring tissues, such as the rectum and bladder. ^{192}Ir HDR brachytherapy has been performed in more than 10 institutions in Japan since 1991. In Kanazawa University Hospital, 97 patients were treated with ^{192}Ir HDR brachytherapy combined with external beam radiation therapy (EBRT) from February 1999 to December 2003. The present study was performed to examine the usefulness of this treatment method.

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Patients and methods

We evaluated the prognosis and complications during the follow-up period in the 84 who could be examined of the 97 patients treated with brachytherapy from February 1999 to December 2003. It was impossible to follow up 13 patients because we could not make contact. The patients' clinical background data are shown in Table 1. Median patient age was 72 years (range 48–81). Of the 84 patients included in this study, 35 (42%) were in clinical stage T1c, 30 (36%) were in T2, 12 (14%) were in T3, and 7 (8%) were in T4. One patient had lymph node (LN) metastasis and no patients had remote metastasis. Median initial PSA values were 10.4 ng/mL (range 3.4–251.6) and median initial prostate volume was 25.0 mL (range 8.9–48.2). Tumors were classified histologically as adenocarcinomas in all patients and median Gleason score (GS) was 7 (range 5–9). Seventy-five (75%) patients underwent neoadjuvant hormone therapy for 1–18 months.

When the probability of lymph node metastasis by Partin nomogram[8] exceeded 5%, we recommended lymphadenectomy (PLND) to the patient, and 24 (24.7%) patients underwent PLND. In the event that lymph node metastasis was confirmed by PLND before brachytherapy, the patients were excluded from the study. The protocol varied at each instituton.[9–11] In our institution, we performed the radiation therapy as follows. The radiation protocol consisted of 18 Gy (6 Gy × three fractions) by brachytherapy. The applicators for brachytherapy were inserted according to transrectal ultrasound (TRUS) guides in the lithotomy position under lumbar anesthesia. The amount of internal irradiation was set to 6 Gy each, and was performed once on one day and twice on the next day. Applicators were removed after the third internal irradiation, and then immediately the urethral catheter was tense for 2 h for the arrest of hemorrhage. The catheter was removed the following day. Conformal EBRT (2 Gy × 22 fractions) was began from 1–2 weeks after brachytherapy. Adjuvant hormone therapy (AHT) was performed in patients who satisfied more than two of the following criteria: clinical stage T3 or T4, GS ≥ 7 and PSA ≥ 20 ng/mL. Thirty-two patients received AHT and 52 patients did not receive AHT. Measurement of PSA was performed every 1–3 months after brachytherapy, and digital rectal examination or TRUS was performed. In the present study, recurrence was defined as three times consecutive elevation of PSA after a nadir, and the day of recurrence was defined as the day on which the first rise of PSA was observed according to the criteria of the American Society for Therapeutic Radiology and Oncology (ASTRO).

The results were classified into the all patients group, patients who underwent AHT, and patients who did not undergo AHT (NAHT). Kaplan–Meier curve analyses were used to calculate overall survival and PSA progression-free survival. Moreover, each group was divided into subgroups according to initial PSA, clinical stage and GS, and PSA progression-free survival was also evaluated. The log–rank test was used for comparisons between subgroups. Two-sided *P*-values of less than 0.05 were regarded as statistically significant data.

Table 1 The background of patients who underwent high dose rate brachytherapy

	All patients	NAHT group	AHT group
Number of cases	84	52	32
Clinical stage			
T1 (n)	35	28	7
T2 (n)	30	23	7
T3 (n)	12	1	11
T4 (n)	7	0	7
Initial PSA			
<20 (n)	58	45	13
≥20 (n)	26	7	19
Gleason score			
<7 (n)	45	27	18
≥7 (n)	39	25	14

AHT, adjuvant hormone therapy; NAHT, nonadjuvant hormone therapy (patients who did not undergo adjuvant hormone therapy); PSA, prostate-specific antigen.

Results

Seventy-seven percent of patients received neo-AHT because many patients were consulted to our hospital after receiving neo-AHT at other institutions. We investigated prognosis irrespective of neo-AHT. Although there have been no previous reports of the effectiveness of neo-AHT, we thought that performing neo-AHT hardly had an effect on the PSA progression-free survival after brachytherapy because most of the prostate cancer tissues provided by radical prostatectomy are still alive after a short duration or neo-AHT.[12] The median observation period of the 84 patients was 20.4 months (range 1–51). Recurrence of PSA occurred in 7 of 32 patients (32%) receiving AHT (Table 1). Of the 52 patients that did not receive AHT, 1 patient had recurrence. Although there was no indication of when LN metastasis was positive, LN metastasis was found in one patient in the present study. He was pointed out about LN metastasis after HDR bachytherapy for reexamining LN specimens for another research. The 4-year overall survival of all patients, the NAHT group, and the AHT group was 87.2%, 100%, and 70.1%, respectively ($P = 0.023$ between NAHT and AHT). All of the patients who died were classified as T4 stage, and all received AHT (Fig. 1). Prostate-specific antigen progression-free survival of all patients, the NAHT group, and the AHT group was 82.6%, 92.0%, and 66.6%, respectively ($P = 0.023$ between NAHT and AHT; Fig. 2). The rates according to initial PSA value are shown in Figure 3. Of all patients, the 4-year PSA progression-free survival of the PSA < 20 group was 100%, while that of the PSA ≥ 20 group was 46.8%. The difference between the two groups was significant ($P < 0.0001$). None of the patients in the NAHT group with PSA < 20 showed recurrence, and the PSA progression-free survival rate of the PSA ≥ 20 group was 50%. The rates according to clinical stage are shown in Figure 3 ($P < 0.019$). In the total patient group, PSA progression-free survival rates of those in stage T1c, T2, T3 (24 months

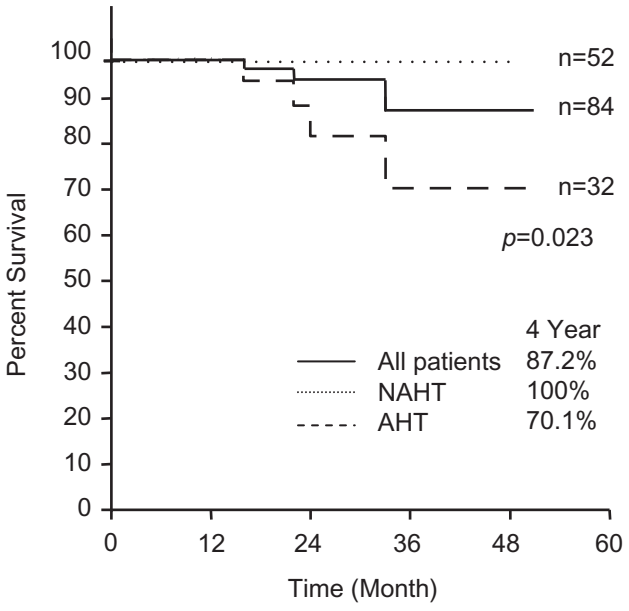

Fig. 1 Kaplan–Meier analysis of overall survival. Percent of overall survival of the patients in all patients, nonadjuvant hormone therapy group and adjuvant hormone therapy group was compared.

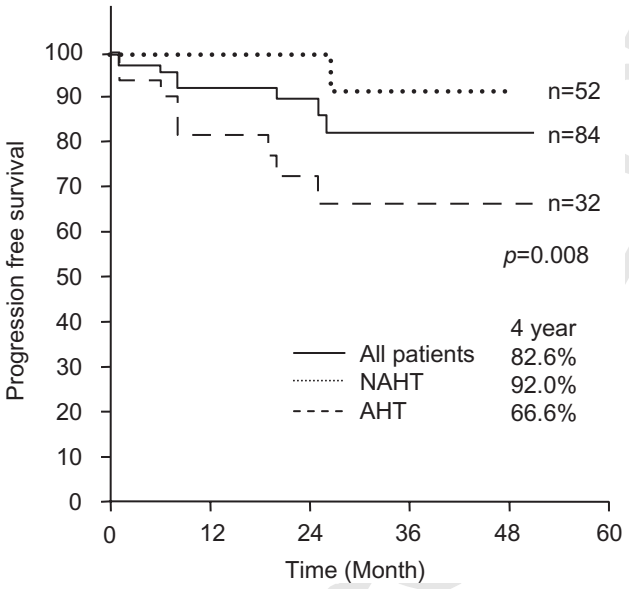

Fig. 2 Kaplan–Meier plot of prostate-specific antigen (PSA) progression-free survival. Percent of PSA progression-free survival of the patients in all patients, nonadjuvant hormone therapy group and adjuvant hormone therapy group was compared. PSA failure is defined as three consecutive PSA rises after a nadir.

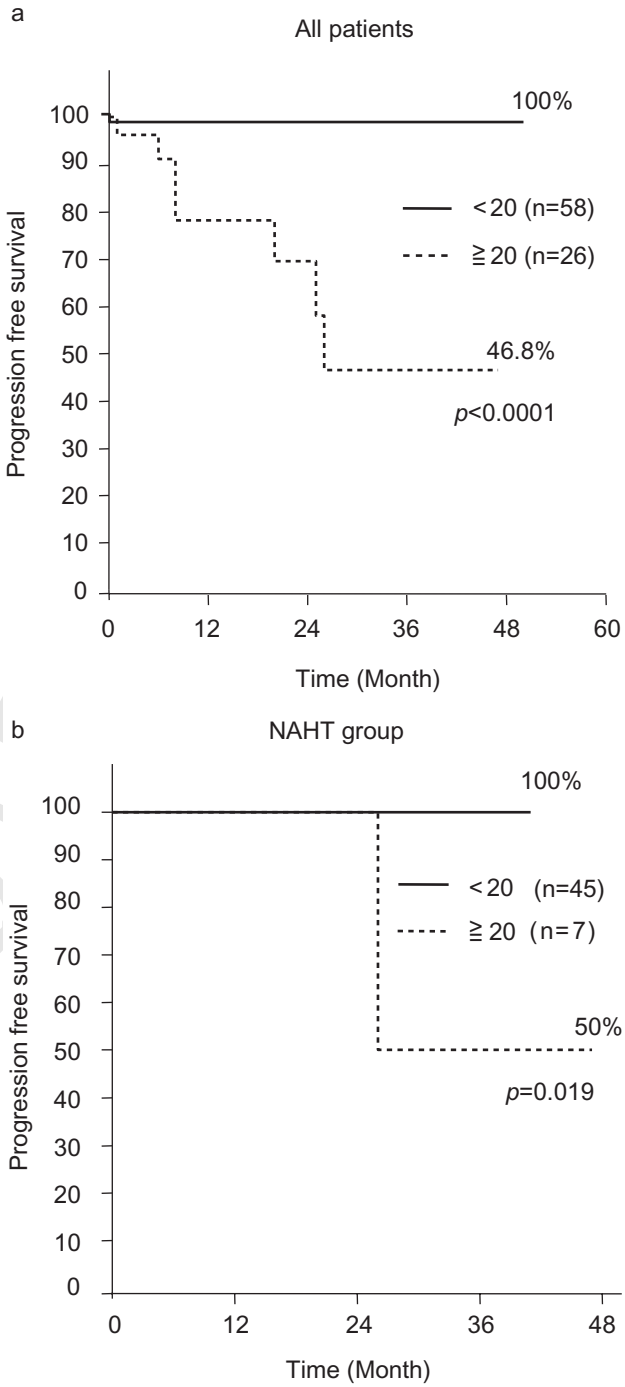

Fig. 3 Kaplan–Meier plots of progression-free survival according to initial prostate-specific antigen (PSA). For both groups, PSA progression-free survival in the cases of initial PSA < 20 was high compared with that of initial PSA ≥ 20.

followed), and T4 (40 months followed) were 100%, 82.8%, 100%, and 12.1%, respectively (Fig. 4). In the NAHT group, the rates for T1c and T2 were 100% and 75%, respectively. The rates classified according to GS are shown in Figure 5. Of all patients, PSA progression-free survival rate of the GS < 7 group was 92.8%, which was not significantly different from that of the GS ≥ 7 group (60.1%). The NAHT group showed the almost same result as all patients.

The complications are shown in Table 2. No significant intraoperative or postoperative complications requiring

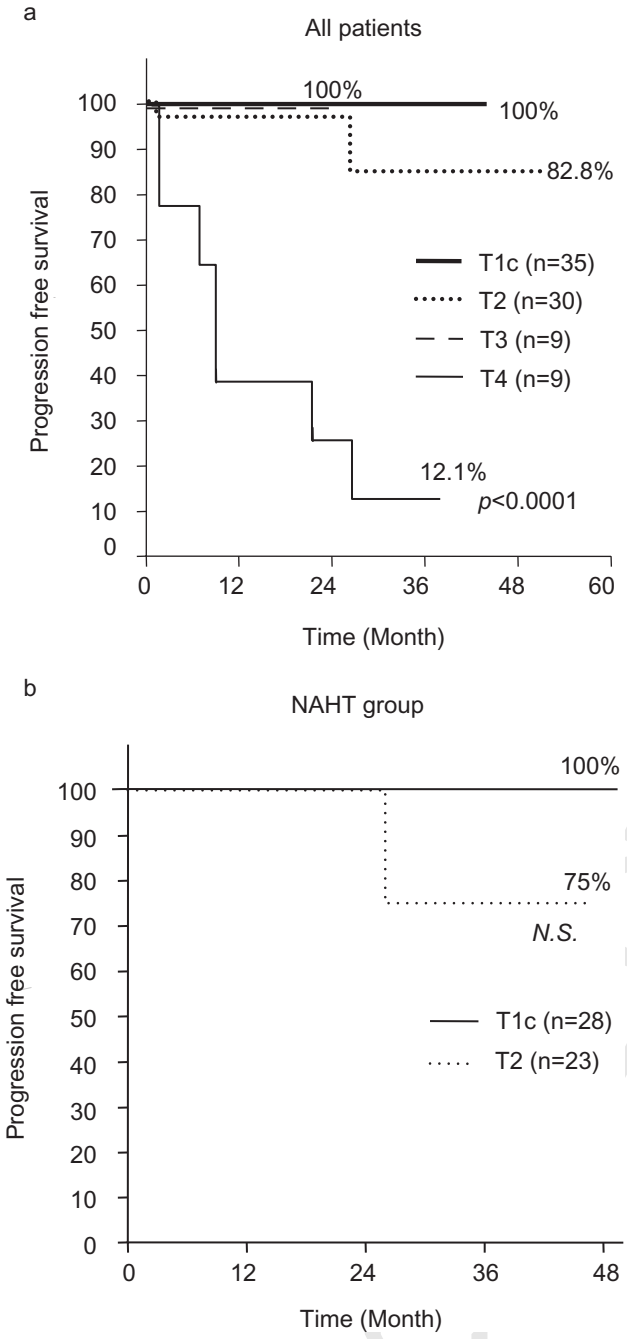

Fig. 4 Kaplan–Meier plots of progression-free survival according to clinical stage. There was no significant difference between T1 cases and T2 cases in all patients and nonadjuvant hormone therapy groups. N.S., not significantly different.

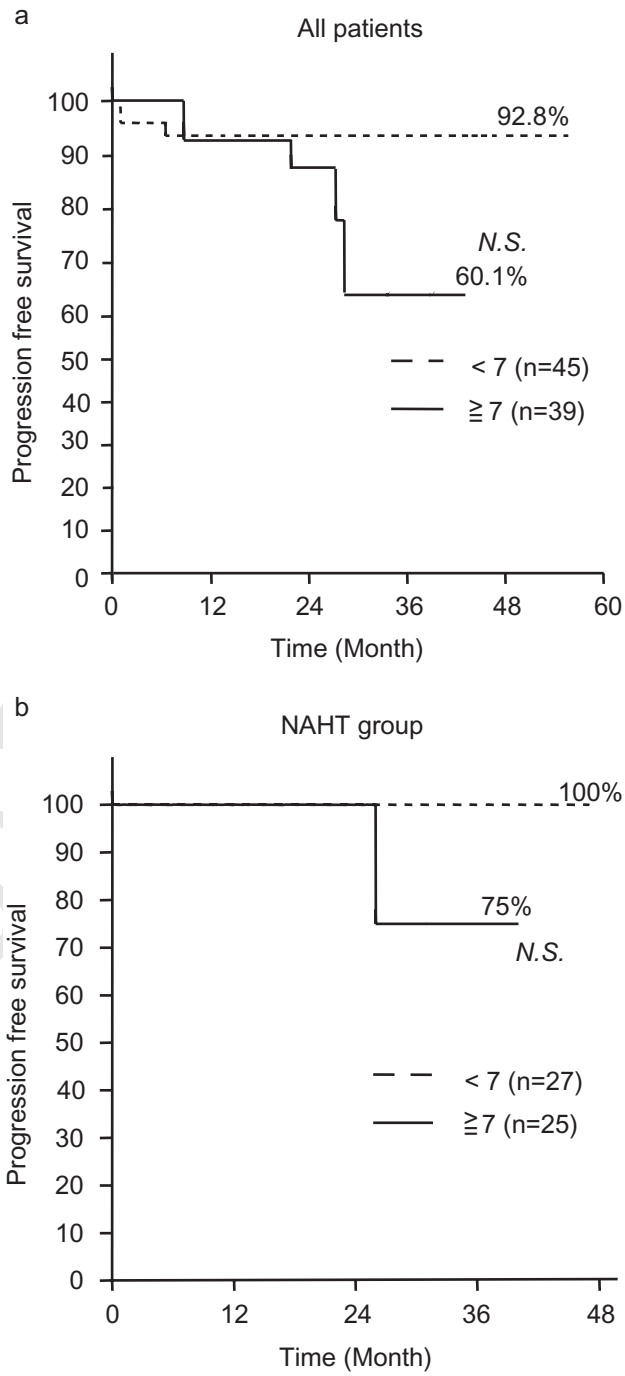

Fig. 5 Kaplan–Meier plots of prostate-specific antigen (PSA) progression-free survival according to Gleason score (GS). PSA progression-free survival in the cases of GS < 7 was high compared with that of GS ≥ 7. N.S., not significantly different.

urgent treatment occurred, except in one patient with prior atrial fibrillation and a cerebral infarction that had occurred 6 months previously merged with cerebellar infarction during the treatment described here. The most common complication was urination trouble (8.2%) such as dysuria and urinary retention. The incidence of incontinence was 4 of 97 cases (4.1%). Two cases (2.1%) needed transfusion by bleeding from the prostate after removing the applicators. Although a in one case, perforating the peritoneum caused the blood pressure to fall, the patient felt better after sufficient infusion and receiving catecholamine. One postoperative ileus case and one delirium case were observed.

Table 2 The major complications in the treatment are indicated

Complication	Number of cases
Urinary retention	8 (9.5%)
Incontinence	4 (4.8%)
Blood transfusion	2 (2.4%)
Ileus	1 (1.2%)
Delirium	1 (1.2%)
Cerebellum infarction	1 (1.2%)
Perforating peritoneum	1 (1.2%)

No significant intraoperative or postoperative complications requiring urgent treatment occurred except cerebellum infarction.

Discussion

In the present study, we confirmed the usefulness of ^{192}Ir HDR brachytherapy-boosted EBRT. Although the observation period was short, PSA recurrence was observed in 8 of 84 patients; 6 of these cases were classified as T4. Risk factors before radiotherapy for PSA-free survival have been reported to be GS, initial PSA, and clinical stage.[13–15] Especially, PSA progression-free survival rate was high in the GS < 7 and PSA < 20 cases. We also investigated the NAHT group to exclude effect of hormone therapy. As we expected, these rates in the NAHT group were very good during the 4-year follow-up period. The PSA progression-free survival of William Beaumont Hospital Royal Oak,[16] performed according to a protocol similar to our institution, was reported 67%. However, further longer-term follow up is still necessary.

Since AHT eventually affects the prognosis of patients, we classified the patients by presence of AHT and compared prognosis. We gave AHT to the high risk patients who satisfied more than two of the following criteria: stage T3 or T4, GS ≥ 7 and PSA ≥ 20 ng/mL in order to make risk of recurrence lower. We gave AHT to 38% of patients in the present study. We expected AHT to improve the patients prognosis. However, the PSA progression-free survival rate in the AHT group was still poor. The reason for this result was especially due to the performance to the patients with stage IV disease, and local-relapsed patients after hormone therapy. In fact, the high risk patients who were treated with AHT except stage IV and local-relapsed patients still have good prognosis for 2 years after brachytherapy (Fig. 4). Combination of brachytherapy and AHT for high risk patients might improve the prognosis.

Complications of brachytherapy such as incontinence are relatively infrequent as compared with radical prostatectomy. The most common complication was urinary retention or dysuria, but in all cases, patients felt better after receiving an α_1-blocker and/or detaining the urethral catheter for a short term, and there were no cases in which QOL was decreased for a long time. The main cause of dysuria was thought to be that the applicators passed near an urethra, the urethral around was enlarged, and an urethra was suppressed when we implanted applicators into the prostate. In particular, these complications occurred mainly in the early period of this therapy. Then we diminished these complications in therapeutic anaphase by devising a method of implant. The cases of incontinence have been treated by medication of anticholinergic drugs, and all were slight. In the case of peritoneal perforation, we used applicators of conventional length and penetrated the bladder, and perforated the peritoneum due to the short height of the patient. We believe this complication could be avoided by doing puncture while considering the height of the patient more carefully.

Our results indicated that ^{192}Ir HDR brachytherapy is as effective and as radical prostatectomy and a less invasive form of therapy for prostate cancer. Moreover, it is expected to be associated with marked improvements in patients' QOL in the perioperative period. Now we are investigating it with regard to long-term complications such as erectile dysfunction, incontinence, and diarrhea.

Since the initial report of seeding according to TRUS by Holm, brachytherapy has become one of the main methods used for treatment of prostate cancer because of its reduced incidence of complications and high degree of effectiveness.[17] Now, permanent seeding brachytherapy for prostate cancer is the most common form in the United States. In Japan, permanent ^{125}I prostate implants were approved for clinical use in July 2003, and therapy using such implants has recently been performed in some institutions. As it is much less invasive than HDR brachytherapy and is possible to apply on a day-surgery basis, it is expected to become the standard method of brachytherapy in Japan. However, patients indicated for ^{125}I seeding therapy are generally in the low risk group (PSA < 10 and GS < 7) and this method is less effective in the high risk group (PSA ≥ 10 or GS ≥ 7).[18] In fact, it has been reported that ^{125}I seeding showed good tumor control for small tumors with good differentiation, but that this source is not suitable for tumors with capsule penetration or lower differentiation.[19,20] On the other hand it is thought that HDR brachytherapy is effective for prostate cancer discovered after TUR-P and local advanced prostate cancer by devised insertion of applicators to seminal vesicle and so on. Furthermore, we think that combining AHT can raise curative effect for local advanced cancer. Compared to seeding therapy, HDR brachytherapy has strong antineoplastic effects. Serdar Deger *et al*. reported that combined HDR brachytherapy with ^{192}Ir was an alternative treatment option especially for patients with clinical T3 prostate cancer.[21] They reported that progression-free survival for clinical stage T3 patients was 65% at 5-year follow up. Moreover, local control of clinical T3 tumors was reported to be 85% at 10-year follow up.[22]

The use of brachytherapy has increased in Japan. Although permanent ^{125}I prostate implants have been introduced, especially in some institutions, we will also examine ^{192}Ir HDR brachytherapy as a possible treatment modality for prostate cancer.

Conclusions

We analysed 84 cases treated with ^{192}Ir HDR brachytherapy in Kanazawa University Hospital. Although the observa-

tion period was short, brachytherapy appeared to be as effective as radical prostatectomy, but with comparatively few complications. Moreover, we think that it is still more effective to carry out combined HDR brachytherapy and AHT for local advanced prostate cancer.

References

1 Hinotsu S, Akaza H. Zenritsusengan no ekigaku. *Jap. J. Clin. Urol.* 2003; **57**: 151–6.
2 Hull GW, Rabbani F, Abbas F *et al.* Cancer control with radical prostatectomy alone in 1000 consecutive patients. *J. Urol.* 2002; **167**: 528–34.
3 Dugan TC, Shipley WU, Young RH *et al.* Biopsy after external beam radiation therapy for adenocarcinoma of the prostate: correlation with original histological grade and current prostate specific antigen levels. *J. Urol.* 1991; **146**: 1313–16.
4 Akakura K, Isaka S, Akimoto S *et al.* Long-term results of a randomized trial for the treatment of Stages B2 and C prostate cancer: radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities. *Urology* 1999; **54**: 313–18.
5 Syed AM, Puthawala A, Sharma A *et al.* High-dose-rate brachytherapy in the treatment of carcinoma of the prostate. *Cancer Control* 2001; **8**: 511–21.
6 Vicini F, Vargas C, Gustafson G, Edmundson G, Martinez A. High dose rate brachytherapy in the treatment of prostate cancer. *World J. Urol.* 2003; **21**: 220–8.
7 Stromberg J, Martinez A, Gonzalez J *et al.* Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. *Int. J. Radiat. Oncol. Biol. Phys.* 1995; **33**: 161–71.
8 Partin AW, Kattan MW, Subong EN *et al.* Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997; **277**: 1445–51.
9 Kasahara K, Inoue K, Karashima T *et al.* High-dose rate iridium-192 brachytherapy combined with external beam radiotherapy for localized prostate cancer. *Nippon Hinyokika Gakkai Zasshi* 2001; **92**: 572–8.
10 Saito S, Momma T, Dokiya T, Murai M. Brachytherapy for prostate cancer in Japan. *Int. J. Urol.* 2001; **8**: S22–7.
11 Egawa S. Brachytherapy for prostate cancer: permanent seed implantation versus HDR temporary brachytherapy. *Jap. J. Urol. Surg.* 2004; **17**: 293–9.
12 Kitagawa Y, Koshida K, Mizokami A *et al.* Pathological effects of neoadjuvant hormonal therapy help predict progression of prostate cancer after radical prostatectomy. *Int. J. Urol.* 2003; **10**: 377–82.
13 Lee WR, Hanks GE, Schultheiss TE, Corn BW, Hunt MA. Localized prostate cancer treated by external-beam radiotherapy alone: serum prostate-specific antigen – driven outcome analysis. *J. Clin. Oncol.* 1995; **13**: 464–9.
14 Zagars GK, Pollack A, Kavadi VS, von Eschenbach AC. Prostate-specific antigen and radiation therapy for clinically localized prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 1995; **32**: 293–306.
15 Pisansky TM, Kahn MJ, Rasp GM, Cha SS, Haddock MG, Bostwick DG. A multiple prognostic index predictive of disease outcome after irradiation for clinically localized prostate carcinoma. *Cancer* 1997; **79**: 337–44.
16 Grills IS, Martinez AA, Hollander M *et al.* High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. *J. Urol.* 2004; **171**: 1098–104.
17 Holm HH, Juul N, Pedersen JF, Hansen H, Stroyer I. Transperineal 125iodine seed implantation in prostatic cancer guided by transrectal ultrasonography. *J. Urol.* 1983; **130**: 283–6.
18 Martinez AA, Pataki I, Edmundson G, Sebastian E, Brabbins D, Gustafson G. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. *Int. J. Radiat. Oncol. Biol. Phys.* 2001; **49**: 61–9.
19 Ragde H, Blasko JC, Grimm PD *et al.* Brachytherapy for clinically localized prostate cancer: results at 7- and 8-year follow-up. *Semin. Surg. Oncol.* 1997; **13**: 438–43.
20 Weyrich TP, Kandzari SJ, Jain PR. Iodine 125 seed implants for prostatic carcinoma. Five- and ten-year follow-up. *Urology* 1993; **41**: 122–6.
21 Deger S, Boehmer D, Turk I *et al.* High dose rate brachytherapy of localized prostate cancer. *Eur. Urol.* 2002; **41**: 420–6.
22 Kovacs G, Galalae R, Loch T *et al.* Prostate preservation by combined external beam and HDR brachytherapy in nodal negative prostate cancer. *Strahlenther. Onkol.* 1999; **175** (Suppl. 2): 87–8.