Original Article

Single Infusion of Zoledronic Acid to Prevent Androgen Deprivation Therapy-induced Bone Loss in Men With Hormone-naive Prostate Carcinoma

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BACKGROUND: Androgen-deprivation therapy (ADT) decreases bone mineral density (BMD) and increases fracture risk in patients with prostate carcinoma. The authors investigated the effectiveness of a single infusion of zoledronic acid initiated subsequent to ADT on BMD with hormone-naive prostate carcinoma. **METHODS:** Forty men received either a single infusion of zoledronic acid (4 mg intravenously on Day 1) or no infusion during ADT. BMD of the proximal femur and posteroanterior lumbar spine was measured by dual-energy x-ray absorptiometry and urinary N-telopeptide (u-NTx) at 6 and 12 months. **RESULTS:** At baseline, the overall BMDs demonstrated no significant difference in lumbar spine and hip regions. At 6months, mean (±standard error) BMD of the posteroanterior lumbar spine decreased 4.6% ± 1.0% in control patients and increased 5.1% ± 1.2% in patients receiving zoledronic acid, a significant difference ($P = .0002$). At 12 months, the change in BMD between the 2 groups was statistically significantly different at the lumbar region ($P = .0004$), indicating that zoledronate preserved BMD. For u-NTx, bone turnover was statistically significantly decreased in the zoledronate group compared with controls at 6 months ($P < .0001$), but returned to pretreatment levels at 12 months in the zoledronate group. **CONCLUSIONS:** Bone loss begins at 6 months with ADT. A single infusion of zoledronic acid in patients receiving ADT reduces bone mineral loss and maintains BMD at least at 12 months during ADT. Further study is needed to determine the best dosing schedule to prevent ADT-induced bone loss in men with hormone-naive prostate carcinoma. **Cancer 2009;115:3468–74. © 2009 American Cancer Society.**

KEY WORDS: prostate carcinoma, androgen-deprivation therapy, bone mineral density, bisphosphonate.

Current data from the Prostate Strategic Urologic Research Endeavor (CaPSURE) and Surveillance, Epidemiology, and End Results–Medicare database of the United States have demonstrated an increase in

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We thank Yukitoshi Ohta, RT, Erina Sato, CRC, and Mineko Uemae, RT, for helpful data management.

Received: August 11, 2008; **Revised:** January 10, 2009; **Accepted:** January 13, 2009

Published online: May 29, 2009 © 2009 American Cancer Society

DOI: 10.1002/cncr.24404, www.interscience.wiley.com

recent years in the proportion of patients with localized and advanced prostate carcinoma for whom androgen-deprivation therapy (ADT) is being selected.[1,2] Data on the current treatment of prostate cancer in Japan indicate that ADT is chosen to treat localized/advanced prostate cancer in an extremely high proportion of cases.[3]

Testosterone is the primary male hormone and is important in establishing and maintaining the typical male characteristics. Possible adverse effects (AEs) of ADT, in the form of gonadotropin-releasing hormone (GnRH) agonists, are generally related to changing levels of hormones, such as hot flushes, loss of muscle mass, erectile dysfunction, fatigue, anemia, and osteoporosis.

The results of several prospective studies show that a rapid loss of bone mineral density (BMD) occurs within the first 6 to 12 months of ADT.[4,5] The risk of skeletal fracture associated with ADT was recently reported,[6] and it is important to note that a skeletal fracture in a patient with prostate carcinoma is an independent and adverse predictor of survival.[7] Recent studies have shown that bisphosphonates, such as alendronate, pamidronate, risedronate, and zoledronic acid, will maintain the increased BMD in patients on ADT.[8-12] However, the durable or long-term efficacy of zoledronic acid is still unknown.

We investigated the effectiveness of a single infusion of zoledronic acid initiated subsequent to ADT on BMD and biochemical markers of bone turnover in patients with hormone-naive prostate carcinoma. The main focus of this study was to evaluate the near-term effectiveness of a single infusion of zoledronic acid during the 12 months after ADT.

MATERIALS AND METHODS

Patients

Study participants were recruited at Kitasato University Hospital between September 2006 and March 2007. All patients had prostate adenocarcinoma with bone metastasis and did not receive any hormonal therapy (hormone naive) previously. Treatment with GnRH agonist was initiated at study entry in all patients. Men with metabolic bone disease, history of treatment for osteoporosis, a serum calcium level <8.4 mg/dL or >10.6 mg/dL, or a serum creatinine concentration >1.5 mg/dL were also excluded. At the screening visit, BMD of the posteroanterior lumbar spine and proximal femur was determined by dual-energy x-ray absorptiometry (DXA). T score was calculated from a Japanese male reference database.[13] Patients with T score of −2.5 or less were excluded.

Study Design

This study was a randomized, prospective controlled pilot study over 12 months. Eligible patients were simply randomized by random numbers that are readily generated by computer software (Excel version 2003; Microsoft, Redmond, Wash). Forty eligible patients were randomly assigned to receive either zoledronic acid at a dose of 4 mg (Zometa; Novartis Pharmaceuticals Inc, Basel, Switzerland) intravenously on Day 1 only (n = 20) or no treatment (n = 20). The patients received zoledronic acid simultaneously with the initiation of ADT. Patients were evaluated at baseline and at 6 months and 12 months. Serum samples were obtained at each visit and stored at −80°C. BMD was measured by DXA at baseline, 6 months, and 12 months. All patients provided written informed consent.

Safety Assessment

The AEs were monitored every 3 months. Physical examinations and serum creatinine/calcium levels were monitored every 3 months. AEs were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE v.3.0).

Study Endpoints

BMD of the posteroanterior lumbar spine and proximal femur was determined by DXA using a Hologic QDR 4500A/SL densitometer (Hologic Inc, Waltham, Mass) in all patients. The DXA device was standardized and calibrated using the Anthropomorphic Spine Phantom (Hologic Inc). In vivo precision assessment was performed according to the International Society for Clinical Densitometry recommendation.[14] By determining precision error (0.012 g/cm^2) and least significant change (0.034 g/cm^2 at 95% confidence interval [95% CI]), it was

Table 1. Clinical Characteristics of the Patients

Characteristics	Zoledronic Acid Group			Control Group			*P*
	Mean	No.	SD	Mean	No.	SD	
Patients treated		20			20		
Age, y (range)	70.5 (53-81)			70 (60-82)			NS
Serum testosterone, ng/mL	4.08		0.85	4.12		0.63	NS
Body mass index, kg/m^2	23.7		2.23	22.3		2.8	NS
Urinary NTx, nmol BCE/nmol Cr	44.6		35.6	33.2		14.2	NS
Bone mineral density, g/cm^2							
Posteroanterior lumbar spine	1.026		0.23	0.936		0.183	NS
Total hip	0.856		0.138	0.859		0.174	NS
Femoral neck	0.726		0.13	0.719		0.148	NS
T score							
Posteroanterior lumbar spine	−0.23		1.42	−0.41		1.19	NS
Total hip	−0.66		1.11	−0.39		1.30	NS
Femoral neck	−1.06		1.00	−1.14		1.17	NS

SD indicates standard deviation; NS, not significant; NTx, N-telopeptide; BCE, bone collagen equivalents; Cr, creatinine.

confirmed that sufficiently precise assessment was done in our hospital. Serum concentrations of testosterone (SRL Inc., Tokyo, Japan) were measured by radioimmunoassays. Urine concentrations of N-telopeptide (NTx; SRL Inc.) were measured by enzyme immunoassays.

Statistical Analysis

The primary study endpoint was the percentage change in the BMD of the posteroanterior lumbar spine from baseline to Months 6 and 12. Statistical analyses were performed using SPSS statistical software (version 13.0; SPSS Japan Inc., Tokyo, Japan). Values are reported as means ± standard error [SE] unless otherwise specified. All P values were 2-sided, and $P < .05$ was considered statistically significant.

RESULTS

Forty eligible patients were randomly assigned to receive either zoledronic acid (n = 20) or no drug treatment (n = 20). Table 1 lists the baseline characteristics of patients in both groups. All patients were hormone naive and received treatment with a GnRH agonist after study entry.

The mean percentage changes in BMD of the posteroanterior lumbar spine, the total hip, and the femoral neck differed significantly between groups (Fig. 1). At 6 months, the mean (±SE) BMD of the posteroanterior lumbar spine decreased 4.6% ± 1.0% from baseline in control men and increased 5.1% ± 1.2% from baseline in men given zoledronic acid ($P = .0002$). At 12 months, the mean (±SE) BMD of the posteroanterior lumbar spine decreased 8.2% ± 1.8% from baseline in the control men and increased 3.5% ± 0.8% from baseline in the men receiving zoledronic acid ($P = .0004$). The between-group differences in percent change from baseline to 6 months and to 12 months were 9.7% (95% CI, 7.0%-12.4%) and 11.7% (95% CI, 9.6%-13.4%), respectively.

At 6 months, the mean (±SE) BMD of the total hip decreased 2.2% ± 0.5% from baseline in the controls and increased 1.1% ± 0.7% from baseline in the treatment group ($P = .0025$). At 12 months, the mean (±SE) BMD of the total hip decreased 4.6% ± 1.0% from baseline in controls and increased 1.1% ± 0.6% from baseline in those given zoledronic acid ($P = .0008$). The between-group differences in percent change from baseline to 6 months and to 12 months were 3.3% (95% CI, 2.2%-4.4%) and 5.7% (95% CI, 4.6%-6.9%), respectively.

At 6 months, the mean (±SE) BMD of the femoral neck decreased 0.7% ± 0.1% from baseline in the controls and increased 1.8% ± 0.8% from baseline in the treatment group ($P = .0063$). At 12 months, the mean (±SE) BMD of the femoral neck decreased 1.8% ± 0.4% from baseline in controls and increased 5.1% ± 1.3% from baseline in

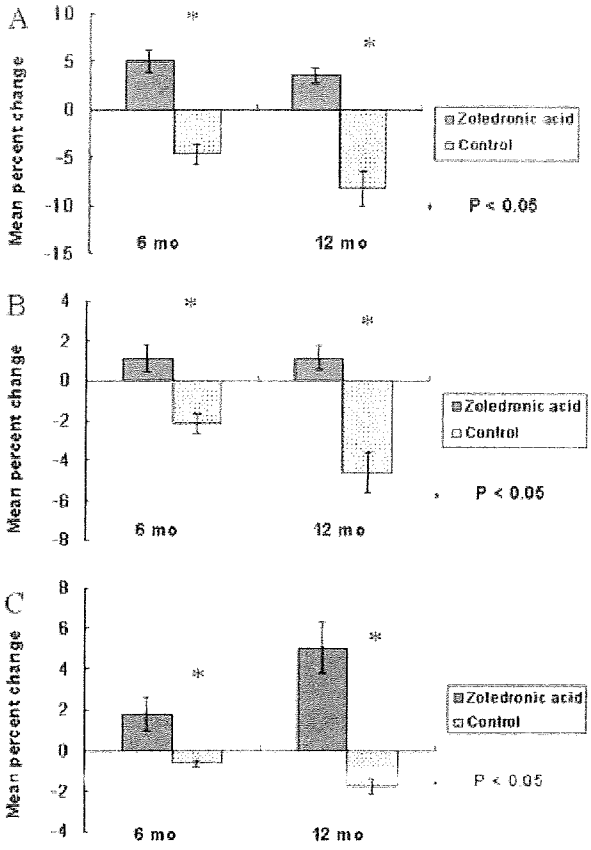

FIGURE 1. Geometric mean percent changes from baseline for bone mineral density for the (A) lumbar spine, (B) total hip, and (C) femoral neck are shown. *P* values are between-group comparisons of the percentage change from baseline to 12 months after treatment.

those given zoledronic acid ($P = .0393$). The between-group differences in percent change from baseline to 6 months and to 12 months were 2.5% (95% CI, 1.3%-3.7%) and 6.9%.(95% CI, 4.6%-9.2%), respectively.

Changes from baseline to 6 months in urine NTx differed significantly between the groups (Fig. 2). Mean (±SE) urine NTx increased by 70.3% ± 15.7% in control men and decreased by 9.5% ± 10.8% in the zoledronic acid group, a statistically significant difference ($P < .0001$). At 12 months, the mean (±SE) urine NTx increased 63.9% ± 14.3% from baseline in the control group and increased 19.7% ± 19.3% from baseline in the zoledronic acid group; these differences did not reach statistical significance ($P = .0703$).

AEs related to treatment in each group were never higher than grade 3 (using NCI-CTCAE v.3.0). Neither

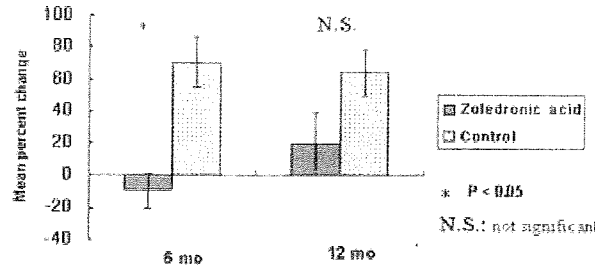

FIGURE 2. Geometric mean percent changes from baseline for urine N-telopeptide are shown. *P* values are between-group comparisons of the percentage change from baseline to 12 months after treatment.

azotemia nor osteonecrosis of the jaw was reported in either group.

DISCUSSION

The incidence and mortality of prostate carcinoma is rapidly increasing in Japan. In 2000, the Japanese Urological Association (JUA) launched a system for registering patients who were newly diagnosed with prostate carcinoma at institutions authorized by the JUA. The compilation results of 2000 were published and surprisingly indicated that primary ADT was used in 40% of patients with T1c disease and in >50% of patients with T2 disease.[3]

Conversely, the US National Cancer Institute Physician Data Query and American Urological Association guidelines do not recommend hormonal therapy for treatment of localized prostate carcinoma. However, CaPSURE surveillance data have demonstrated that in recent years the use of ADT has increased for patients with all stages of prostate carcinoma.[1] Furthermore, several randomized controlled trials show an overall survival benefit of neoadjuvant ADT as well as adjuvant ADT, and this combination treatment has had a large impact.[15-17] Thus, ADT for prostate carcinoma is being adopted and the number of patients undergoing ADT may increase worldwide in the future. However, among men surviving at least 5 years after the diagnosis of prostate carcinoma, 19.4% of those who received ADT had skeletal fractures, and there was a statistically significant relationship between the number of doses of GnRH received during the 12 months after diagnosis and subsequent risk of fracture.[18] In addition, the occurrence of skeletal-related events (SREs), including fractures, contributes

significantly to the cost of care for patients with advanced prostate carcinoma.[19] The average total cost of treatment was €13,051/patient over the 24-month follow-up period, which includes an average cost of €6973/patient to treat SREs. Treatment of SREs more than doubled total treatment costs, and these data suggest that bisphosphonates can reduce SREs and healthcare costs.

Recent studies have shown that bisphosphonates, such as alendronate, pamidronate, risedronate, and zoledronic acid, will maintain the increased BMD in patients on ADT.[8-12] Greenspan et al reported the effect of the oral bisphosphonate alendronate given orally (70 mg) once weekly on BMD, and markers of bone turnover in patients with nonmetastatic prostate carcinoma recently initiating ADT or receiving ADT for ≥6 months evaluated in a prospective, randomized, double-blind, placebo-controlled, partial crossover trial.[20] In patients treated with alendronate, BMD increased over 12 months by 3.7% ($P < .001$) at the spine and 1.6% ($P = .008$) at the femoral neck. Conversely, patients in the placebo group had losses of 1.4% ($P = .045$) at the spine and 0.7% ($P = .081$) at the femoral neck. At 12 months, the difference between the 2 groups was 5.1% ($P < .001$) at the spine and was 2.3% ($P < .001$) at the femoral neck.

Intravenous bisphosphonates also increase BMD in GnRH agonist–treated men.[8,10-12] To our knowledge, Smith et al were the first to assess the effect of zoledronic acid on BMD during ADT for nonmetastatic prostate carcinoma.[8] Patients with prostate carcinoma (no metastases) who were beginning ADT were randomly assigned to receive zoledronic acid at a dose of 4 mg or placebo intravenously every 3 months for 1 year. The mean BMD in the lumbar spine increased by 5.6% in patients receiving zoledronic acid and decreased by 2.2% in those given placebo (mean difference, 7.8%; $P < .001$). The mean BMD of the femoral neck, trochanter, and total hip also increased in the zoledronic acid group and decreased in the placebo group after 1 year of therapy.

Israeli et al assessed the benefit of zoledronic acid in patients with pre-existing bone loss. Patients were randomized to receive zoledronic acid at a dose of 4 mg or placebo intravenously every 3 months when initiated during the first year of ADT in patients with locally advanced prostate carcinoma.[11] Although all patients receiving zoledronic acid in their study experienced increases in lumbar spine and total hip BMD, patients with low baseline T scores (−1 or less and −2 or greater) experienced a greater magnitude of increase in lumbar spine BMD than patients with normal baseline T scores (more than −1) (5.8% vs 4.4%, respectively). A similar difference in the magnitude of NTx suppression was observed. Zoledronic acid–treated patients with low baseline T scores experienced greater NTx suppression than patients with normal baseline T scores (−82.7% vs −58.4%, respectively). These results suggest that patients with pre-existing bone loss may experience a greater benefit of zoledronic acid treatment.

In patients with hormone-refractory metastatic prostate carcinoma, frequent treatment with zoledronic acid (4 mg every 3 weeks) reportedly decreases the risk of SREs.[21]

Patients with hormone-refractory prostate carcinoma and a history of bone metastases were randomly assigned to a double-blind treatment regimen of intravenous zoledronic acid at a dose of 4 mg, zoledronic acid at a dose of 8 mg (subsequently reduced to 4 mg; 8/4), or placebo every 3 weeks for 15 months. The median time to first SRE (defined as pathologic bone fractures, spinal cord compression, surgery to bone, radiation therapy to bone, or a change of antineoplastic therapy to treat bone pain) was 321 days for patients who received placebo, was not reached for patients who received zoledronic acid at a dose of 4 mg ($P = .011$ vs placebo), and was 363 days for those who received zoledronic acid at a dose of 8/4 mg ($P = .491$ vs placebo). Given the results of this study, zoledronic acid (4 mg every 3-4 weeks) was approved to treat patients with hormone-refractory prostate carcinoma metastatic to bone, and this treatment remains the only known effective schedule to prevent SRE complications in patients with metastatic prostate carcinoma.

The results of the current study demonstrate that a single infusion of zoledronic acid within the first 12 months of ADT prevents bone loss and increases BMD in men with hormone-naive prostate carcinoma. Compared with the control group, zoledronic acid significantly increased lumbar spine and femoral neck BMD by 11.7% and 5.7%, respectively ($P = .0004$ and $P = .0008$, respectively). A single infusion of zoledronic acid can provide a durable effect for the hormone-naive patient for at least 12 months after ADT. When initiating ADT for hormone-naive patients with prostate carcinoma, the simultaneous use of a single infusion of zoledronic acid

might have not only bone health but also compliance advantages for ADT-induced osteoporosis, because the most significant BMD loss occurs within 12 months after ADT therapy in these men.

The findings of the current study demonstrated that urinary NTx returned to the pretreatment levels at the 12-month follow-up in the zoledronate group. If the changes in the urinary NTx levels indicate BMD loss in advance, an annual infusion of zoledronate might be a lower dosage in this patient population, and an infusion every 6 months will be favorable to maintain urinary NTx levels.

Our results are consistent with the results of previously published studies,[10,12] although we evaluated only hormone-naive patients (using zoledronic acid with simultaneous ADT) and consistent timing of follow-up of BMD every 6 months. However, these results do not justify less frequent administration of zoledronic acid to prevent SREs in patients with hormone-naive prostate carcinoma, because the study was powered to demonstrate a significant change in BMD, but was not powered to assess the impact on the risk of SREs.

The prognosis of primary ADT performed in patients with prostate carcinoma is quite good, and 50% of patients were alive after primary ADT at 10-year follow-up in a Japanese population.[3] Thus, we must take care of not only cancer control but also the patient's bone health based on a probably long life span for these men.

Conclusions

A single infusion of zoledronic acid increased BMD and decreased urine NTx levels in hormone-naive patients with prostate carcinoma. These effects were durable within 12 months after the initiation of ADT. However, urinary NTx returned to pretreatment levels at 12 months, and further study is needed to clarify the optimal regimen of therapy, as well as its long-term efficacy.

Conflict of Interest Disclosures

Supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare, Japan.

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International Journal of Urology (2008) 16, 410–412 doi: 10.1111/j.1442-2042.2008.02230.

Case Report

Alternative approach in the treatment of adrenal metastasis with a real-time tracking radiotherapy in patients with hormone refractory prostate cancer

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Abstract: Patients with an adrenal tumor usually undergo laparoscopic adrenalectomy. However, an alternative treatment approach might be needed in some patients with adrenal metastasis from malignancy or with severe complications. Real-time tracking radiotherapy (RTRT) with a gold marker is considered one of the feasible treatment options because this system can reduce the adverse effects of organ movement such as that in the adrenal gland or kidney. A 64-year-old patient with hormone refractory prostate cancer presented with clinically isolated adrenal metastasis. The patient underwent RTRT treatment with an implanted gold marker in the right adrenal metastasis. There were no adverse events. Although disease progression with elevated prostate-specific antigen occurred 8 months later, there was no further growth of the right adrenal metastasis before he died. From our experience, RTRT with an implanted gold marker might be feasible for the treatment of isolated adrenal metastasis from malignancies including prostate cancer.

Key words: adrenal metastasis, prostate cancer, real-time tracking radiotherapy system.

Introduction

Although laparoscopic adrenalectomy has become the standard approach for the treatment of benign adrenal tumors, management of adrenal metastases from malignancy remains controversial. Recently, a real-time tracking radiotherapy (RTRT) system has been developed to treat malignancies originating from moving organs such as the lung or prostate. In the present report, we describe the first patient who underwent RTRT with an implanted gold marker to treat an isolated adrenal metastasis of hormone refractory prostate cancer.

Case report

A 60-year-old patient with a brain tumor and multiple lung tumors was referred to our hospital in June 2001. The patient had previously undergone an open adrenalectomy for a left adrenal tumor with primary aldosteronism in 1991. At admission, the serum prostate-specific antigen (PSA) value was 98.6 ng/mL (0–4 ng/mL) and the patient was suspected to have multiple metastases that originated from prostate cancer. Pathological evaluation of transrectal prostate biopsy demonstrated adenocarcinoma, Gleason score 4 + 4. The patient had no metastases to the bone or lymph node. The patient received gonadotropin-releasing hormone and underwent surgical resection of the brain tumor. Although the disease status had been well controlled with hormonal treatment for 28 months, a computed tomography (CT) scan of the abdomen revealed a tumor in the right adrenal gland in October 2003. The serum PSA value was elevated to 45.8 ng/mL, even though the patient received sufficient antiandrogen therapy with maximal androgen blockade at that time. We therefore diagnosed that the right adrenal mass might be a metastasis from hormone refractory prostate cancer. The patient received salvage hormonal therapy with glucocorticoid in addition to maximal androgen blockade. Although the serum PSA value was transiently decreased by salvage hormonal therapy, the serum PSA value was again increased to 324.3 ng/mL in August 2005. An abdominal CT showed the enlargement of the right adrenal mass (67 × 33 mm). The patient had no signs of metastases to other organs including the brain, lung, bone and lymph nodes at that time. Based on these findings, we supposed that local treatment with systemic hormonal therapy would be needed and that RTRT with a gold marker to this lesion might be appropriate because this approach is considered less invasive than laparoscopic adrenalectomy in this disease status. We thoroughly informed the patient and family regarding this treatment approach and written informed consent was obtained. As the first step, a radiopaque gold marker, 2.0 mm in diameter, was inserted in the adrenal mass under CT guidance. Then, a dose of 48 Gy (6 Gy × 8 fraction) was irradiated to the right adrenal mass using the RTRT system. This system consisted of four sets of diagnostic X-ray imaging equipment, image processor units, a trigger control unit, and a dual-photon conventional linear accelerator with multileaf collimators. The linac was gated to irradiate the tumor only when the internal marker was located within the region of the planned coordinates relative to the isocenter (Fig. 1). There were no adverse events during radiotherapy. After 6 months, the serum PSA value gradually declined to 67.4 ng/mL and the right adrenal mass was also reduced to 42 × 21 mm in size. Although disease progression with PSA elevation occurred 8 months later, the tumor of the right adrenal gland did not show any signs of growth before the patient died of bone metastasis in February 2007 (Figs 2,3).

Discussion

We report a patient who showed good control of adrenal metastasis from hormone refractory prostate cancer using RTRT with an implanted gold marker. In general, laparoscopic adrenalectomy is a feasible treatment approach for an adrenal tumor because of its minimally invasive quality. However, this application against isolated adrenal metastases from malignancy remains controversial. Moinzadeh and Gill[1] reported 31 patients who underwent 33 laparoscopic resections for adrenal malignancy including 26 metastatic lesions. Although

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Received 14 February 2008; accepted 16 November 2008.

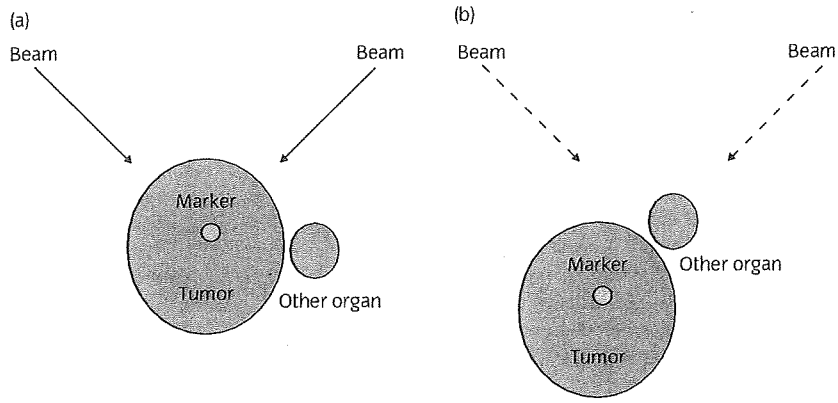

Fig. 1 Schema of the real-time tracking radiotherapy system. A radiopaque gold marker is inserted into the target organ. a) Radiotherapy is done only when the position of the marker is within the planned area. b) Radiotherapy is not done.

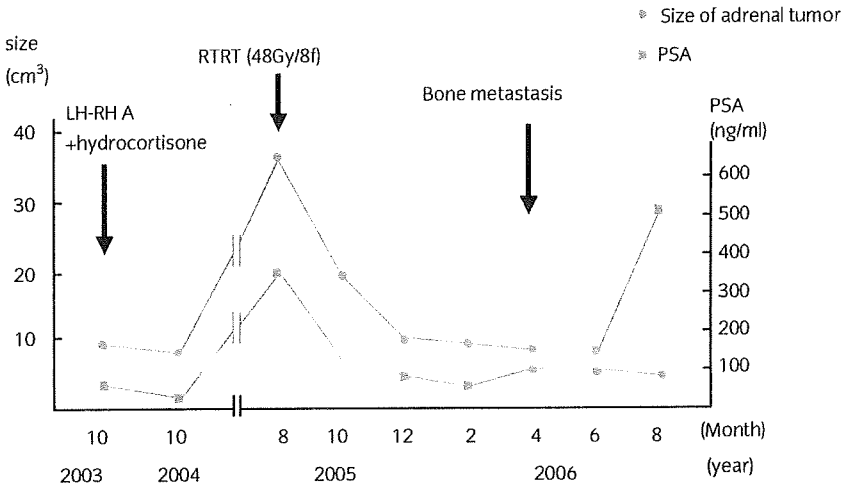

Fig. 2 Serum prostate-specific antigen (PSA) value and the size of the adrenal tumor after real-time tracking radiotherapy (RTRT) with an implanted gold marker. Adrenal size was calculated using computed tomography and the equation: tumor size = largest diameter × smallest diameter × smallest diameter ×1/2 (mm^3). LH-RH A, luteinizing hormone–releasing hormone agonist.

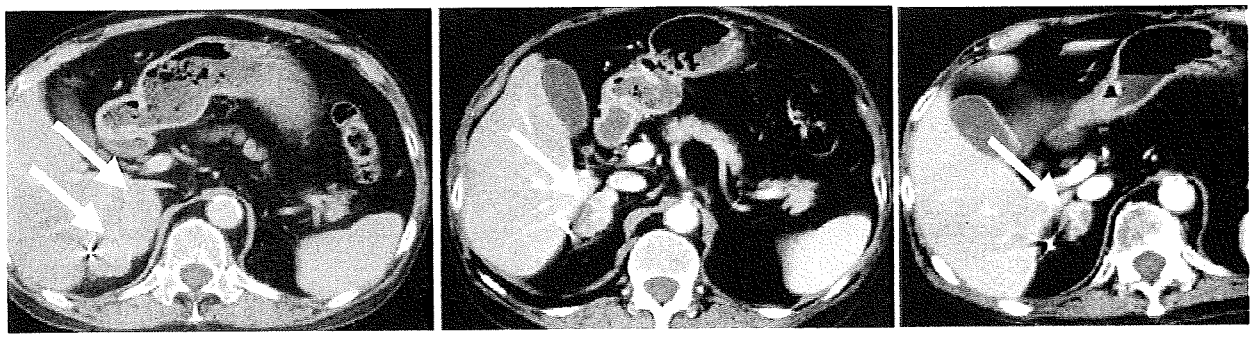

Fig. 3 Reduction of adrenal mass demonstrated by computed tomography.

there was no surgical mortality, severe complications occurred in four patients (13%) and local recurrence was noted in seven patients (23%). Furthermore, Brunt[2] showed that the overall conversion rate was 8.7% in patients undergoing laparoscopic resection of adrenal metastases. Although laparoscopic adrenalectomy was, at first, considered one of the treatment options for isolated adrenal metastasis, we judged that this treatment approach was not feasible because of the evidence presented above as well as the patient's preference to avoid such surgery.

Thus, we considered the application of radiation to isolated adrenal metastasis because hormone refractory prostate cancer is considered relatively radio-sensitive. However, radiotherapy to the adrenal gland is not common. Administering radiation to this organ is considered difficult and complicated because it is a moving organ surrounded by radio-sensitive organs including the duodenum, and the small and large intestines. Recently, a novel technique of radiotherapy, RTRT with an implanted gold marker, has been developed and physical aspects of this

system have been described in detail previously.[3] Prostate, lung and bladder cancers have been treated with the RTRT system for better targeting (Fig. 1).[4,5] In the case of a prostate cancer patient, this system is applied with intensity-modulated radiation therapy to reduce the morbidity.[6] Based on this evidence, this technique was applied to treat adrenal metastasis of hormone refractory prostate cancer in the present case. Adverse events such as diarrhea, intestinal perforation, and bleeding around the adrenal gland were not observed. The size of the tumor gradually decreased over an 18-month period.

Whether treatment of clinically isolated adrenal metastasis alters the natural history of stage IV disease remains controversial.[7] Sarela *et al.* reported that the overall estimated actuarial survival at 5 years after adrenalectomy for metastasis was 29% with a median survival of 28 months and it should be offered to patients with favorable tumor biology.[8] Mercier *et al.*reported that adrenalectomy can provide long-term survival in patients with isolated adrenal metastasis from non-small cell lung cancer.[9] Further studies are required to confirm whether our strategy can contribute to improving the prognosis of patients with metastatic adrenal malignancy.

In conclusion, RTRT with an implanted gold marker for adrenal metastasis from hormone refractory prostatic cancer was safe and feasible. This radiation system offers an alternative treatment option for adrenal malignancy.

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Jpn J Clin Oncol 2009;39(8)502–508
doi:10.1093/jjco/hyp053

Health-related Quality of Life using SF-8 and EPIC Questionnaires after Treatment with Radical Retropubic Prostatectomy and Permanent Prostate Brachytherapy

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Received February 8, 2009; accepted May 1, 2009; published online May 28, 2009

Objective: The health-related quality of life (HRQOL) after treatment of prostate cancer is examined using a new HRQOL tool. HRQOL, based on the expanded prostate cancer index composite (EPIC) and SF-8 questionnaires, was prospectively compared after either a radical retropubic prostatectomy (RRP) or a permanent prostate brachytherapy (PPB) at a single institute.

Methods: Between October 2005 and June 2007, 96 patients were treated by an RRP and 88 patients were treated by a PPB. A HRQOL survey was completed at baseline, and at 1, 3, 6 and 12 months after treatment, prospectively.

Results: The general HRQOL in the RRP and PPB groups was not different after 3 months. However, at baseline and 1 month after treatment, the mental component summary was significantly better in the PPB group than in the RRP group. Moreover, the disease-specific HRQOL was worse regarding urinary and sexual functions in the RRP group. Urinary irritative/obstructive was worse in the PPB group, but urinary incontinence was worse in the RRP group and had not recovered to baseline after 12 months. The bowel function and bother were worse in the PPB group than in the RRP group after 3 months. In the RRP group, the patients with nerve sparing demonstrated the same scores in sexual function as the PPB group.

Conclusions: This prospective study revealed the differences in the HRQOL after an RRP and PPB. Disease-specific HRQOL is clarified by using EPIC survey. These results will be helpful for making treatment decisions.

Key words: quality of life – EPIC – SF-8 – radical retropubic prostatectomy – permanent prostate brachytherapy

INTRODUCTION

There are many treatment choices for localized prostate cancer, especially low-risk patients. The treatment outcomes between radical retropubic prostatectomy (RRP) and radiotherapy for low-risk localized prostate cancer are the same by recently published retrospective studies (1,2). Therefore, the decision of treatment depends on the patient's or the oncologist's preference. However, it is difficult for patients to decide which treatment should be selected. In Japan, permanent prostate brachytherapy (PPB) was started at 2003 and this treatment is now rapidly expanding (3,4). So decision of treatment is made more difficult. One consideration in the treatment selection is the quality of life (QOL) after treatment, and the QOL is a very important factor for patients. Previously, we reported the QOL comparing RRP and PPB (5). In our study, the disease-specific QOL in prostatectomy was worse than in brachytherapy, especially the urinary and sexual functions, although the general health-related QOL (HRQOL) recovered by 3 months following a prostatectomy. Our reports were used for UCLA-PCI (6), so disease-specific QOL after PPB was not

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explained exactly. Recently, new disease-specific QOL, expanded prostate cancer index composite (EPIC) (7,8), was developed to make up for the disadvantage of UCLA-PCI. However, there have so far been very few reports describing the QOL using EPIC in Japanese subjects, especially in regard to a prospective study. In this study, we evaluated the QOL after RRP and PPB using EPIC.

PATIENTS AND METHODS

Between October 2005 and June 2007, RRP was performed in 114 patients and PPB in 88 patients at our hospital. The indications for PPB were limited in the patients with low and intermediate risk. If the prostate-specific antigen (PSA) level was between 10 and 20 ng/ml or the primary Gleason pattern was 4 among intermediate risk, additional external beam radiotherapy (EBRT) was recommended and considered. Androgen deprivation therapy (ADT) was not used except for volume reduction. The patients treated with PPB received 145 Gy to the prostate with an I-125 seed using a modified peripheral loading technique via a transrectal ultrasound guided transperineal approach (3). Until December 2005, we performed PPB by the pre-planning method and after January 2006, by the intra-operative planning method.

On the other hand, the indications for RRP were patients with any risk but aged 75 years or younger. Clinical stage T3 was also indicated for surgery but the Gleason score and PSA level were carefully considered and informed to the patients. The nerve-sparing technique was performed if the patient wanted to preserve sexual function. The indications for a nerve-sparing procedure depended on the pre-operative (number and Gleason score of the positive biopsy cores, PSA level or patient preference) and intra-operative factors, prioritizing cancer control. The RRP was performed using Walsh's technique by two staff urologists or under their supervision. ADT was not used for neoadjuvant and adjuvant settings. The patients who indicated RRP or PPB selected their own therapy themselves after we informed each therapy.

We measured the general and disease-specific HRQOL using two types of instruments. The general HRQOL was assessed with the Japanese version of Medical Outcome Study 8-Items Short Form Health Survey (SF-8) (9). The SF-8 is an HRQOL assessment consisting of eight scales and generates two summary measures, a physical component summary (PCS) and a mental component summary (MCS). The disease-specific HRQOL was assessed with the EPIC, a 50-item questionnaire that quantifies the prostate cancer-specific HRQOL in eight separate domains (10). In this study, domains of hormone function and bother were omitted because there were few patients with ADT and ADT was used for neoadjuvant setting only. All patients were informed of their cancer diagnosis before being asked to complete the HRQOL questionnaires. No interviews were conducted. The questionnaires were administered at five time points. The baseline survey was conducted within 1 week before surgery and PPB. The follow-up survey was conducted in person at the scheduled study visits at 1, 3, 6 and 12 months after treatment. This study was approved by the Institutional Review Board in our hospital. Written informed consent was obtained from all patients before the initiation of treatment.

QOL scores were shown as mean scores with standard deviation. PCS and MCS are calculated by weighting each SF-8 item using the norm-based scoring method. All scales of the SF-8 above and below 50 were above and below the average in the general Japanese population. All scores of EPIC were linearly transformed to a scale of 0 (lowest) to 100 (highest). Each group comparison was made using the Mann–Whitney U-test and χ^2 test. Two-tailed P values of <0.05 were considered statistically significant. SPSS software ver.16.0J (Tokyo, Japan) was used for all statistical analyses.

RESULTS

Eight patients in RRP were disagreed for this study. The surveys were performed for 96 and 88 patients who underwent RRP and PPB, respectively. The average answer rate of each survey was 82.1% in RRP and 89.1% in PPB. Background of each group is shown in Table 1. The median age of the RRP and PPB groups was 66 and 69 years, respectively. As for the age, the RRP group was younger than the PPB group. As for the clinical stage and PSA level, the PPB group had a lower stage and a lower average PSA level. In addition, the Gleason score was lower in the PPB group. ADT was performed in 13 patients from the PPB group and in 3 patients from the RRP group. All of these patients discontinued hormone therapy after either RRP or PPB. Nerve-sparing surgery was performed in 12 patients. Six patients added EBRT after PPB. After 12 months, five patients demonstrated recurrence in RRP and no patient in PPB. The former was PSA failure only (PSA $>$ 0.2 ng/ml) (Table 1). However, the general and disease-specific QOL among the patients with recurrence or EBRT were the same as in patients without the recurrence or EBRT. We therefore included all cases in this analysis.

The SF-8 scores are listed in Table 2. There is a significant difference for the baseline QOL scores in physical function, role physical, social functioning, role emotional and mental health among each group. These baseline scores were worse in the RRP group than in the PPB group. In the RRP group, the QOL scores at 1 month were worse than the baseline score in physical functioning, role physical, body pain, vitality and social functioning. These worse scores recovered until 3 months except body pain. The score of body pain recovered at 6 months. The scores of role physical, general health, role emotional and mental health improved over the baseline after 6 and 12 months. In the PPB group, the QOL scores in role physical and social functioning at 1 month were worse than the baseline score. These scores recovered until 3 months. The mental health improved above the

Table 1. Patient characteristics for a radical retropubic prostatectomy and permanent prostate brachytherapy

	RRP	PPB	*P* value
Number	96	88	
Age (years)			
Median	66	69	0.008
Range	51–79	52–84	
Clinical stage			
T1	59	64	0.034
T2	31	24	
T3	6	0	
PSA (ng/ml)			
Median	9.0	6.3	<0.001
Range	1.3–60.3	2.0–22.3	
Gleason score			
≤6	18	41	<0.001
7	34	43	
≥8	44	4	
ADT	3	13	0.005
Nerve sparing	12	—	
EBRT	—	6	
Recurrence at 12 months	5	0	0.037

RRP, radical retropubic prostatectomy; PPB, permanent prostate brachytherapy; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; EBRT, external beam radiotherapy.

baseline at 12 months. Comparing the RRP and PPB groups, there were significant differences in all scores except for general health at 1 month after treatment. These QOL scores were better in the PPB group than in the RRP group. The general health was the only same score at 1 month in both groups. After 3 months, some QOL scores were remained worse in RRP but there were no significant differences at 6 months between the RRP and PPB groups.

The SF-8 scores for PCS and MCS are summarized in Table 3. The score of PCS in RRP was worse than in PPB at 1 month, but recovered until 3 months. The baseline difference in MCS scores was significantly worse and continued to 1 month after surgery. It was recovered at 3 months. The MCS score in the high-risk RRP group was poor in comparison to the low- to intermediate-risk group; however, the difference was not significant.

The results of the EPIC are listed in Table 4. For the baseline score, there was significant difference in urinary incontinence, bowel function and sexual bother between the RRP and PPB groups. These scores were worse in the RRP group at baseline. At 1 month, the urinary incontinence and sexual function were more worsen in RRP. However other scores

Table 2. SF-8 scores of patients undergoing a radical retropubic prostatectomy and permanent prostate brachytherapy

	RRP	PPB	*P* value (RRP vs. PPB)
PF			
Baseline	48.3 ± 6.4	50.3 ± 5.4	0.040
1-month	44.9 ± 6.0*	49.4 ± 5.7	<0.001
3-month	49.1 ± 5.5	49.3 ± 5.8	0.670
6-month	49.9 ± 5.6	49.7 ± 5.2	0.455
12-month	49.9 ± 6.5	49.8 ± 5.6	0.620
RP			
Baseline	46.4 ± 8.5	50.1 ± 6.9	0.002
1-month	41.5 ± 10.2*	48.5 ± 6.9*	<0.001
3-month	48.3 ± 6.6	49.8 ± 6.3	0.066
6-month	50.2 ± 5.6*	49.6 ± 5.5	0.317
12-month	49.9 ± 5.7*	50.1 ± 5.3	0.908
BP			
Baseline	56.6 ± 6.7	54.3 ± 8.3	0.100
1-month	50.1 ± 8.2*	52.8 ± 7.9	0.041
3-month	53.9 ± 7.4*	53.8 ± 8.3	0.832
6-month	55.5 ± 6.4	55.5 ± 6.0	0.904
12-month	55.4 ± 6.4	56.9 ± 5.3	0.164
GH			
Baseline	50.6 ± 6.2	50.8 ± 4.9	0.883
1-month	48.8 ± 7.3	49.8 ± 5.4	0.405
3-month	51.1 ± 5.6	49.6 ± 6.4	0.111
6-month	52.0 ± 5.6	51.1 ± 5.0	0.248
12-month	52.9 ± 5.7*	51.8 ± 5.3	0.149
VT			
Baseline	52.7 ± 6.2	52.6 ± 6.0	0.731
1-month	49.9 ± 6.9*	52.3 ± 5.5	0.039
3-month	52.8 ± 4.7	52.5 ± 6.2	0.866
6-month	53.4 ± 5.0	52.7 ± 5.5	0.475
12-month	53.4 ± 5.3	53.9 ± 5.0	0.535
SF			
Baseline	45.9 ± 10.7	51.3 ± 6.6	0.002
1-month	41.5 ± 9.1*	47.5 ± 8.1*	<0.001
3-month	46.7 ± 8.8	49.7 ± 7.7	0.018
6-month	48.7 ± 8.2	49.3 ± 7.1*	0.785
12-month	49.5 ± 7.9	50.9 ± 6.5	0.302
RE			
Baseline	45.6 ± 8.9	50.1 ± 6.2	0.001
1-month	43.6 ± 10.6	50.0 ± 5.7	<0.001
3-month	48.0 ± 7.6	49.8 ± 6.9	0.031

Continued

Table 2. *Continued*

	RRP	PPB	*P* value (RRP vs. PPB)
6-month	50.3 ± 5.5*	49.9 ± 6.8	0.931
12-month	50.5 ± 5.8*	51.4 ± 4.6	0.453
MH			
Baseline	45.7 ± 7.7	51.3 ± 5.9	<0.001
1-month	47.4 ± 7.7	52.2 ± 5.3	<0.001
3-month	51.3 ± 6.3*	52.7 ± 5.5	0.141
6-month	51.9 ± 5.5*	52.5 ± 5.4	0.579
12-month	52.9 ± 5.9*	54.0 ± 4.3*	0.388

PF, physical functioning; RP, role physical; BP, body pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.
*$P < 0.05$ (baseline vs. 1-, 3-, 6- and 12-month).

Table 3. Summary scores of SF-8 between radical retropubic prostatectomy and permanent prostate brachytherapy

	RRP	PPB	*P* value (RRP vs. PPB)
PCS-8			
Baseline	51.3 ± 6.4	50.7 ± 5.9	0.576
1-month	44.8 ± 6.8*	48.4 ± 5.8*	0.001
3-month	49.5 ± 5.4	49.2 ± 5.7	0.874
6-month	50.8 ± 5.0	50.1 ± 5.0	0.280
12-month	50.4 ± 5.4	50.4 ± 5.0	0.943
MCS-8			
Baseline	44.2 ± 9.1	50.0 ± 5.7	<0.001
1-month	45.1 ± 8.0	50.2 ± 5.8	<0.001
3-month	48.6 ± 7.1*	50.8 ± 5.8	0.067
6-month	50.0 ± 5.9*	50.1 ± 5.6	0.808
12-month	50.8 ± 5.5*	52.0 ± 4.4*	0.353

PCS-8, physical component summary; MCS-8, mental component summary.
*$P < 0.05$ (baseline vs. 1-, 3-, 6- and 12-month).

were worse from baseline, there was no significant difference between RRP and PPB. The urinary incontinence in RRP was recovered after 3 months, but it was worse than in the PPB group until 12 months. The urinary irritative/obstructive score at 1 month was worse from baseline in both groups, but in the RRP group, the score was recovered after 3 months and better than baseline. On the other hand, in the PPB group, the score was remained worse until 6 months and it was significant comparing the RRP group. The urinary bother at 1 month was also worse in both groups from baseline. In the RRP group, it was recovered until 3 months, but

Table 4. EPIC scores of patients undergoing a radical retropubic prostatectomy and permanent prostate brachytherapy

	RRP	PPB	*P* value (RRP vs. PPB)
Urinary irritative/obstructive			
Baseline	92.6 ± 11.6	96.6 ± 7.8	0.058
1-month	86.6 ± 13.6*	81.7 ± 19.3*	0.410
3-month	95.8 ± 5.9	87.4 ± 14.5*	<0.001
6-month	97.3 ± 5.2*	91.4 ± 9.3*	<0.001
12-month	96.8 ± 6.5	94.5 ± 9.0	0.205
Urinary incontinence			
Baseline	94.7 ± 11.8	99.0 ± 5.1	0.004
1-month	45.2 ± 30.9*	93.4 ± 13.6*	<0.001
3-month	72.9 ± 24.2*	96.0 ± 9.8*	<0.001
6-month	81.2 ± 20.8*	93.2 ± 11.9*	<0.001
12-month	84.7 ± 19.6*	95.3 ± 12.0*	<0.001
Urinary function			
Baseline	93.8 ± 10.2	96.8 ± 12.1	0.001
1-month	58.4 ± 25.6*	85.2 ± 17.9*	<0.001
3-month	76.8 ± 18.2*	91.2 ± 17.8*	<0.001
6-month	85.7 ± 15.2*	93.0 ± 9.8*	0.001
12-month	88.2 ± 14.3*	94.0 ± 11.5*	0.001
Urinary bother			
Baseline	90.7 ± 12.2	94.8 ± 8.9	0.096
1-month	80.0 ± 15.9*	83.7 ± 15.6*	0.108
3-month	92.8 ± 8.7	86.5 ± 12.8*	0.004
6-month	94.0 ± 9.1	88.8 ± 12.0*	0.002
12-month	94.3 ± 9.4	93.2 ± 9.3	0.187
Bowel function			
Baseline	90.4 ± 10.8	94.8 ± 7.4	0.009
1-month	85.8 ± 13.8	85.8 ± 13.3*	0.902
3-month	89.6 ± 12.8	86.5 ± 12.5*	0.040
6-month	92.9 ± 8.4	87.7 ± 11.7*	0.002
12-month	92.5 ± 9.0	90.0 ± 9.7*	0.047
Bowel bother			
Baseline	97.3 ± 5.3	98.7 ± 2.9	0.150
1-month	94.6 ± 7.3*	94.3 ± 8.3*	0.764
3-month	97.0 ± 7.2	93.9 ± 10.3*	0.007
6-month	98.1 ± 3.9	94.7 ± 7.8*	0.001
12-month	97.1 ± 6.9	96.7 ± 4.6*	0.096
Sexual function			
Baseline	28.4 ± 21.7	24.0 ± 22.1	0.276
1-month	4.6 ± 9.1*	16.3 ± 16.3	<0.001
3-month	5.7 ± 11.3*	20.3 ± 18.2	<0.001

Continued

Table 4. *Continued*

	RRP	PPB	*P* value (RRP vs. PPB)
6-month	5.0 ± 9.6*	23.2 ± 21.3	<0.001
12-month	6.5 ± 12.3*	23.6 ± 21.4	<0.001
Sexual bother			
Baseline	85.0 ± 20.6	91.9 ± 16.7	0.016
1-month	83.8 ± 27.0	92.4 ± 13.3	0.479
3-month	82.0 ± 26.6	88.1 ± 17.7	0.511
6-month	85.5 ± 21.8	88.0 ± 16.3	0.996
12-month	83.4 ± 25.2	88.3 ± 17.8	0.772

EPIC, expanded prostate cancer index composite.
*$P < 0.05$ (baseline vs. 1-, 3-, 6- and 12-month).

in the PPB group, it remained worse until 6 months significantly. Bowel function and bother were worse in the PPB group at 3 and 6 months than in the RRP group significantly. Bowel function in PPB at 12 months was worse than baseline and RRP group. The sexual function and sexual bother in the RRP group were worse than in the PPB group until 12 months. The sexual function did not recover in the RRP group. In the PPB group, the sexual function and bother did not change in the PPB group. Moreover, no significant factor correlated with the EPIC score and the EPIC did not correlate with SF-8.

Concerning sexual function and bother, the effect of nerve sparing was examined. In the RRP group, if nerve sparing was performed, sexual function was worse than baseline but recovered gradually better than in the non-nerve-sparing group. However, the nerve-sparing group did not recover to the baseline at 12 months. On the other hand, sexual bother was worse in the nerve-sparing group than in the non-nerve-sparing group, although it was not significant. Comparing the PPB group, the sexual function after treatment was the same in the nerve sparing, although baseline score was better in the RRP group. Sexual bother was also worse in each group but there was no significant difference (Table 5).

DISCUSSION

The assessment of the treatment for prostate cancer was made, not only regarding the duration of survival, but also the HRQOL. Therefore, the HRQOL after treatment becomes important and there are many QOL reports after treatment of prostate cancer, i.e. RRP, EBRT or PPB (11–15). Litwin et al. (11) reported the QOL after both RRP and PPB. He reported the general QOL to be the same in both groups but that urinary function was better in the PPB group. Moreover, sexual function was better in the PPB group but bowel function was worse. Other investigators reported the same results (12–15). Previously, we reported the results of QOL after RRP and PPB (5). In that study, our results in the

Table 5. EPIC scores in patients undergoing a radical retropubic prostatectomy with/without nerve sparing and permanent prostate brachytherapy

	RRP		PPB	*P* value	
	Nerve sparing	Without		A	B
Sexual function					
Baseline	45.9 ± 21.7	26.4 ± 21.0	24.0 ± 22.1	0.057	0.512
1-month	10.8 ± 11.8	4.0 ± 8.7	16.3 ± 16.3	0.615	<0.001
3-month	18.3 ± 24.7	4.0 ± 5.2	20.3 ± 18.2	0.337	<0.001
6-month	14.9 ± 22.7	3.6 ± 5.2	23.2 ± 21.3	0.245	<0.001
12-month	23.3 ± 24.4	3.6 ± 5.0	23.6 ± 21.4	0.798	<0.001
Sexual bother					
Baseline	93.8 ± 8.8	84.1 ± 21.3	91.9 ± 16.7	0.730	0.013
1-month	70.8 ± 28.2	84.6 ± 27.0	92.4 ± 13.3	0.142	0.643
3-month	71.5 ± 31.7	83.7 ± 25.7	88.1 ± 17.7	0.064	0.880
6-month	79.5 ± 23.3	86.2 ± 21.7	88.0 ± 16.3	0.268	0.757
12-month	81.3 ± 26.0	83.8 ± 25.2	88.3 ± 17.8	0.238	0.941

A, nerve sparing vs. PPB; B, without nerve sparing vs. PPB.

RRP patients were the same as those of the other investigators (11–15). Most of investigators, including us, had used UCLA-PCI for disease-specific QOL. For urinary function, the UCLA-PCI focused mainly on urinary incontinence. Therefore, urinary irritability might have been underestimated. Moreover, bowel function in UCLA-PCI does not include rectum bleeding and irritability, and there are few item numbers in it. Because of these contents, disease-specific QOL in RRP was inferior to PPB. Because of these disadvantages, EPIC is developed for QOL after treatment. Recently, the QOL survey varied from the UCLA-PCI to the EPIC (16–18). The EPIC contained more questions for urinary and bowel functions, including, for example, urinary and bowel irritation, than UCLA-PCI. The results from the EPIC were emphasized for urinary and bowel functions. However, there are a few reports of QOL using EPIC. In this study, we used EPIC for disease-specific QOL. To our knowledge, this report is the first report of longitudinal results using EPIC in Japanese.

The RRP group was worse about urinary function even if EPIC was used. However, urinary irritative had worse in PPB and urinary incontinence had worse in RRP among urinary function. A difference in urinary irritative is a major difference of EPIC from UCLA-PCI. As for the difference in incontinence and irritative, incontinence was bigger. So, urinary function in RRP was worse than PPB. These results indicated that different problem existed in RRP and PPB and emphasized these differences. On the other hand, bowel function was worse in PPB than RRP. Among bowel function, pain, frequency and diarrhea were factors of worse function but bleeding was not a factor in PPB. This point became clear for the first time by using EPIC. Our previous

study using UCLA-PCI did not become clear in these points. On the other hand, sexual function and bother were the same between EPIC and UCLA-PCI scores.

Frank et al. (16) reported the disease-specific QOL after RRP, PPB and EBRT by using EPIC. In their study, PPB had a significantly worse bowel function and bother than RRP (19). Although the RRP had significantly worse urinary incontinence than the PPB, the PPB had more urinary irritation than the RRP. The PPB had a significantly better sexual function than the EBRT or RRP. However, their report was a cross-sectional study, and QOL survey was performed at only one point after treatment. So, their report did not clear about the change of QOL. On the other hand, Ferrer et al. (18) reported the longitudinal QOL after treatment by using EPIC. They examined QOL before and after treatment (1, 3, 6, 12 and 24 months). They reported that the RRP group had worse EPIC sexual summary and urinary incontinence scores compared with the PPB group, and the RRP group had significant better EPIC urinary irritation scores than PPB. Moreover, they reported the change of QOL after treatment. The change of their QOL scores was the same as our results. Other investigators reported the same results.

In this study, we used SF-8 for general HRQOL. SF-8 consisted of only eight questions and obtained the same results as SF-36. General HRQOL and disease-specific QOL are simultaneously analyzed. Because EPIC has too much questions, 50 items, SF-8 is often linked to EPIC. Our report is the first report of longitudinal results using SF-8 in Japanese, to our knowledge. According to SF-8, PCS was worse after 1 month in the RRP group, but the PPB group did not change. PCS in the RRP group was recovered until 3 months after treatment. Therefore, it was thought that the PCS score improves as urinary incontinence is restored. On the other hand, MCS at baseline in RRP was significantly worse than PPB, and this worse score continued until 1 month. After all, MCS scores were the same in both groups at 3 months. In RRP, there were more advanced stage and higher PSA and Gleason score compared with PPB. It was thought that these worse clinical factors and the attitude for operation influenced worse MCS score at baseline in RRP and patients with RRP felt stress. The MCS score tended to be poor in the high-risk group but no significant difference was observed. After treatment, MCS score recovered in the RRP group because patients with RRP felt free of stress. Sahai et al. (19) reported that there was no significant difference in PCS, but the MCS score showed a significant increase after surgery. In their study, surgery was laparoscopic upper urinary tract surgery. Surgery was influenced to MCS, even though it was different from RRP.

In this study, the PPB group had better QOL compared with the RRP group, except for urinary irritative and bowel function. However, there are some limitations associated with our study. There were some differences in the backgrounds between RRP and PPB. This study is a prospective study but not a randomized study. Indeed, the PPB group tended to have a high age and the RRP group included more high-risk patients. If there are many high-risk patients, then recurrence and the need to perform additional treatment would also increase, thus influencing the QOL. However, because this study focused on the outcomes only up until 12 months from the start of treatment, only a few patients with recurrence were thus observed and they did not affect the results. Second, this survey was only up until 12 months and the observation period was thus short. The results of the QOL may therefore change during the long-term follow-up. Recently, Namiki et al. (20) reported the QOL after 5 years. In their report, the urinary function in RRP continued to recover gradually but never returned to baseline after 5 years. Long-term follow-up of QOL is needed in both groups.

Despite these limitations, the change and difference in the QOL up until 12 months became clear in this study. This difference in disease-specific QOL has become more clearer by using EPIC. These results and other published results will therefore be useful and provide important information when selecting the optimal treatments for localized prostate cancer, although long-term observation is necessary.

Funding

This study was supported in part by a Grant-in Aid Cancer Research (17-10) from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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Int Urol Nephrol (2009) 41:581–586
DOI 10.1007/s11255-008-9467-z

UROLOGY - ORIGINAL PAPER

Adverse prognostic impact of capsular incision at radical prostatectomy for Japanese men with clinically localized prostate cancer

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Received: 19 June 2008 / Accepted: 21 August 2008 / Published online: 11 September 2008

Abstract
Objectives The objective of this study was to evaluate the significance of capsular incision (CI) at radical prostatectomy (RP) for men with prostate cancer.
Materials and methods This study included 267 men who underwent RP without neoadjuvant therapy and were pathologically diagnosed as having organ-confined disease. CI was defined as exposing benign or malignant glands at the inked margin without documented extraprostatic extension.
Results Pathological examinations identified CI in 53 RP specimens (19.9%), while CI was not detected in the remaining 214 specimens (80.1%). The locations of CIs in RP specimens from these 53 patients were as follows: 39 (73.6%) at the apex, 11 (20.0%) at the anterior site, 4 (7.5%) at the posterior site and 12 (22.6%) at the bladder neck. The incidence of CI was significantly affected by surgical procedure, preoperative serum PSA and microvenous invasion in RP specimen. During the observation period of this study, biochemical recurrence occurred in 10 (18.9%) of the 53 with CI and 20 (9.3%) of the 214 without CI, and the biochemical recurrence-free survival in patients with CI was significantly poorer than those without CI. Furthermore, of several factors examined, biochemical recurrence was significantly associated with preoperative serum PSA, Gleason score, perineural invasion and capsular incision, among which only preoperative serum PSA appeared to be an independent predictor of biochemical recurrence.
Conclusions Despite the lack of independent significance, the presence of CI has an adverse impact on biochemical outcome in patients undergoing RP for clinically localized prostate cancer.

Keywords Capsular incision · Prognosis · Prostate cancer · Radical prostatectomy

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Introduction

With recent advances in anatomical knowledge and improvements in surgical technique, radical prostatectomy (RP) has been widely accepted as the mainstay of treatment for patients with clinically organ-confined prostate cancer [1]. To date, a number of studies have identified factors associated with disease recurrence after RP, of which a positive surgical margin, the only factor that can be modified by surgical technique, is regarded as one of the greatest potential risk factors for disease recurrence following RP [2]. Considering the dramatic migration toward earlier stage detection of prostate cancer in recent years, a positive surgical margin, which is still

reported in approximately 20–40% of patients in contemporary RP series [2–4], may frequently occur by iatrogenic capsular incision of tumor tissue even when cancer is confined to the prostate.

Capsular incision is usually defined as exposing benign or malignant glands at the inked surgical margin without histologically documented extraprostatic extension, and its significance has not yet been well characterized [5]. Although several studies have presented data on patients with capsular incision [5–13], only a few studies have addressed the prognostic outcome of patients with capsular incision, and these findings remain controversial [5–10]. Accordingly, in order to clarify the prognostic significance of capsular incision at RP, we retrospectively reviewed the clinicopathological outcomes in 267 Japanese men with clinically localized prostate cancer who underwent RP according to whether capsular incision was detected or not in RP specimens.

Materials and methods

Between April 2000 and June 2006, 571 men diagnosed as having clinically organ-confined prostate cancer were treated at our institution with either open RP (RRP) or laparoscopic RP (LRP). Of these 571, this study included 145 and 122 undergoing RRP and LRP, respectively, who had not received any neoadjuvant therapies, were diagnosed as having pathologically organ-confined disease, and were followed for longer than 12 months after RP. Prior to surgery, prostate cancer was diagnosed histopathologically using specimens obtained from systematic transrectal ultrasound-guided needle biopsy and/or transurethral resection of the prostate. The staging procedures included digital rectal examination, transrectal ultrasonography, serum prostate-specific antigen (PSA) assay, pelvic computed tomography, and bone scan.

At our institution, it was basically based on the decision of each patient whether LRP or RRP would be selected. RRP was performed based on the procedure described by Walsh [14] in combination with that modified by others [15], while the surgical procedure for LRP used in this series generally followed the methods described by Guillonneau et al. [16]; the details of our technique have previously been reported [17]. In addition, five well-experienced surgeons in laparoscopic surgery were involved in LRP as an operator; however, RRP tended to be performed by less experienced surgeons, including residents in training. In this series, all pathological examinations were performed by a single pathologist according to the 2002 TNM classification system. The surface of the resected specimen was inked, fixed, and whole-mount step sections were cut transversely at 3-mm intervals from the apex of the prostate to the tips of the seminal vesicles. Capsular incision was defined as follows: iatrogenic incisions into the prostate resulting in the presence of benign or malignant glands at the inked surgical margins without histological evidence of extraprostatic extension. We subdivided the location of capsular incision into apex, posterior site, anterior site, and bladder neck.

Patients were postoperatively followed by periodic measurement of serum PSA at least every 3 months for the first 2 years and every 6 months thereafter. Biochemical recurrence was defined as PSA persistently greater than 0.2 ng/ml. Irrespective of pathological findings suggesting a poor prognosis, none of the patients received any adjuvant therapies until their serum PSA levels reached 0.4 ng/ml or greater.

All statistical analyses were performed using Statview® 5.0 software (Abacus Concepts, Berkeley, CA, USA). Differences between the two groups were evaluated using Chi-square, unpaired t or Mann–Whitney U tests. The probability of freedom from biochemical recurrence was estimated using the Kaplan–Meier method. The prognostic significance of certain factors was assessed by the Cox proportional hazards regression model. Probability (P) values less than 0.05 were considered significant.

Results

In this series, 53 (19.9%) of 267 RP specimens were diagnosed as having capsular incision, while capsular incision was not noted in the remaining 214 specimens (80.1%). As shown in Table 1, despite the lack of significant differences in age, pathological stage, Gleason score, lymphatic invasion, and perineural invasion between patients with and without capsular incision, there were significant differences in surgical procedure, preoperative serum PSA value, and microvenous invasion between these two groups.

Table 1 Comparison of characteristics between patients with and without capsular incision who underwent radical prostatectomy

Variables	Capsular incision		
	Negative (n = 214)	Positive (n = 53)	P value
Age (years)[a]	67.9 ± 6.3	69.7 ± 4.9	0.084
Preoperative PSA (ng/ml)[a]	9.0 ± 5.9	11.5 ± 8.8	0.040
Surgical procedure			0.017
RRP	124	21	
LRP	90	32	
Pathological stage			0.059
pT2a	34	2	
pT2b	127	34	
pT2c	53	17	
Gleason score			0.10
6 or less	70	10	
7	138	39	
8–10	6	4	
Lymphatic invasion			0.81
Negative	157	38	
Positive	57	15	
Microvenous invasion			0.034
Negative	198	44	
Positive	16	9	
Perineural invasion			0.18
Negative	86	16	
Positive	128	37	

PSA Prostate-specific antigen, *RRP* open radical prostatectomy, *LRP* Laparoscopic radical prostatectomy

[a] Values are expressed as mean ± standard deviation

Table 2 summarizes the status of capsular incision in 53 RP specimens which were positive for capsular incision. Of these 53 specimens, 11 (20.8%) and 42 (79.2%) were diagnosed as having solitary and multiple positive capsular incision, respectively; however, there was no significant difference in the number of capsular incision between patients undergoing RRP and those undergoing LRP. The locations of capsular incision in the 53 specimens were as follows: 39 (73.6%) at the apex, 11 (20.8%) at the anterior site, 4 (7.5%) at the posterior site, and 12 (22.6%) at the bladder neck. There were no significant differences in the incidence of capsular incision at the apex, anterior site, and posterior site between the RRP and LRP groups, while the incidence of capsular incision at the bladder neck in the LRP group was significantly greater than that in the RRP group.

During the observation period of this study (median, 40 months), biochemical recurrence developed in 30 patients (12.7%) consisting of 10 (18.9%) of the 53 with capsular incision and 20 (9.3%) of 214 without capsular incision. As shown in Fig. 1, the biochemical recurrence-free survival in patients with capsular incision was significantly poorer than those without capsular incision. We then evaluated the impact of several clinicopathological factors on time to biochemical recurrence using the Cox proportional hazard model (Table 3). Of several factors examined by univariate analysis, biochemical recurrence was significantly associated with preoperative serum PSA, Gleason score, perineural invasion, and capsular incision, among which only preoperative serum PSA appeared to be an independent predictor of biochemical recurrence on multivariate analysis.

Discussion

A number of recent studies have reported the potential impact of surgical technique on cancer control in patients undergoing RP for prostate cancer [18, 19]. Of several factors identified as prognostic predictors following RP, surgical margin status is the only factor that can be affected by surgical technique