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ORIGINAL ARTICLE

Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients

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To compare combination therapy with bicalutamide 80 mg and a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A alone in Japanese men with untreated advanced prostate cancer. A total of 205 patients with stage C/D prostate cancer were randomized to either LHRH-A + once-daily oral bicalutamide 80 mg or placebo. Primary study variables have been reported previously. Secondary variables included: time to achieve prostate-specific antigen ≤4 ng/ml, time-to-treatment failure (TTTF), time-to-disease progression (TTP), overall survival (OS), adverse events and adverse drug reactions. Following combination therapy with bicalutamide 80 mg, there were significant ($P<0.001$) advantages over LHRH-A alone in terms of TTTF and TTP, but the difference in the interim OS was not statistically significant. First-line combination therapy with bicalutamide 80 mg in Japanese patients with advanced prostate cancer offers significant benefits over LHRH-A alone, with respect to TTTF and TTP. Follow-up for OS continues.
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Keywords: clinical trials; advanced prostate cancer; hormone therapy; LHRH-A; bicalutamide

Introduction

Combined androgen blockade (maximum androgen blockade), consisting of an antiandrogen plus either a luteinizing hormone-releasing hormone agonist (LHRH-A) or orchiectomy, is standard care in Japan for patients with advanced prostate cancer.[1,2]

Although the rationale for administering combination therapy is strong, results from individual clinical studies have been mixed.[3] The Prostate Cancer Trialists' Collaborative Group (PCTCG) conducted a meta-analysis of all available randomized trials (27 studies) of combination therapy versus castration alone.[4] The results of this large analysis ($n=8275$) demonstrated a small but statistically significant survival benefit, with the addition of a nonsteroidal antiandrogen (nilutamide or flutamide), to castration monotherapy ($P=0.005$). Conversely, combination therapy with the steroidal antiandrogen cyproterone acetate was associated with a 13% increase in the risk of death ($P=0.04$).

First approved in 1995, bicalutamide is a nonsteroidal antiandrogen. A Phase III study to assess the efficacy of bicalutamide 50 mg combination therapy was initiated in Caucasian men using a flutamide combination regimen, which was considered standard care at that time, as the active comparator.[5] The results demonstrated that bicalutamide 50 mg combination therapy was at least as effective as flutamide combination therapy. In addition, the bicalutamide regimen was better tolerated, with a significantly lower rate of diarrhea ($P<0.001$) and fewer withdrawals due to adverse events.

Using data from the study conducted by Schellhammer *et al.*,[5] together with findings from the PCTCG meta-analysis,[4] a retrospective analysis was recently conducted to indirectly assess the efficacy of bicalutamide 50 mg combination therapy with that of castration alone. This analysis demonstrated that bicalutamide 50 mg combined with castration results in a 20% reduction in the risk of mortality compared with castration alone.[3]

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This estimated benefit is larger than that observed with the other antiandrogens in the PCTCG analysis.

To date, only three studies have investigated combination hormonal therapy in Japanese men with advanced prostate cancer. Two of these studies assessed combination therapy using the steroidal antiandrogen chlormadinone acetate, and one used the nonsteroidal antiandrogen flutamide. Neither of the steroidal antiandrogen studies showed an improvement in overall survival (OS) with combination therapy compared with LHRH-A alone.[6,7] The use of the nonsteroidal antiandrogen flutamide combined with an LHRH-A was studied in 161 Japanese patients.[8] In this unblinded study, combination therapy was superior to LHRH-A monotherapy in terms of reduction of prostate-specific antigen (PSA) level and time to PSA progression.

To further elucidate the effect of adding an antiandrogen to LHRH-A, we initiated a randomized, double-blind, multicenter study. As bicalutamide has good compliance and tolerability findings, it was selected for investigation in this study.[9] In most countries, bicalutamide is given at a dose of 50 mg when used in combination with an LHRH-A. However, based on pharmacokinetic and pharmacodynamic data, the approved dose of bicalutamide in Japanese men is 80 mg per day. We had previously conducted a pilot study of LHRH-A in combination with bicalutamide 80 mg per day, which identified no significant safety concerns.[10] Therefore, we selected the 80 mg dose for our phase III study in Japanese men.[11,12]

Primary efficacy findings (median follow-up 66 weeks) from this phase III study have previously been reported in an interim publication.[9] At 12-weeks following treatment initiation, bicalutamide 80 mg combination therapy significantly improved the proportion of patients achieving PSA levels of $\leqslant 4$ ng/ml compared with LHRH-A alone (79.4 versus 38.6%, respectively; $P<0.001$). Bicalutamide also improved 12-week overall tumor-response rates compared with LHRH-A alone (77.5 versus 65.3%, respectively; $P=0.063$). Importantly, safety was not compromised with the addition of a second therapy (withdrawal rate due to adverse drug reactions 8.8% bicalutamide versus 10.9%, LHRH-A alone).

This is the first double-blind, controlled clinical trial to assess bicalutamide combination therapy versus castration alone, in men with prostate cancer. Here, we report a longer-term analysis of the secondary outcome variables from this study, at a median of 127 weeks. We discuss time to achieve a PSA level of $\leqslant 4$ ng/ml, time-to-treatment failure (TTTF), time-to-disease progression (TTP), OS and the incidence of adverse events and adverse drug reactions. These results were first presented in brief at the American Society of Oncology (ASCO) annual meeting in 2005. Treatment responses subsequent to disease progression, including antiandrogen withdrawal syndrome and responses to second-line bicalutamide 80 mg treatment are also discussed.

Patients and methods

Study design and treatment

Financial sponsorship for this trial was provided by AstraZeneca. The design of this randomized, double-blind, multicenter trial has been reported previously.[9] All patients received LHRH-A (goserelin acetate 3.6 mg or leuprorelin acetate 3.75 mg) by subcutaneous depot injection every 4 weeks. Patients were randomized 1:1 to either oral bicalutamide 80 mg or matching placebo, once daily, using a double-blind method. As the minimum duration of follow-up time exceeded 6 months, the code was broken in September 2002 for ethical reasons. Subsequently, patients in the LHRH-A only group discontinued placebo and received LHRH-A alone, and patients in the bicalutamide 80 mg combination therapy group continued combination therapy in an open-label manner. Combination therapy was continued until November 2003, or until either disease progression or other withdrawal criterion occurred.

If a patient in the combined therapy group experienced disease progression during open-label treatment, bicalutamide was discontinued and the patient was monitored for antiandrogen withdrawal syndrome. Any subsequent therapy was initiated at the investigator's discretion. Patients in the LHRH-A only group who had disease progression were treated at the investigator's discretion, with addition of bicalutamide 80 mg being an option.

Patients

Patients with histologically confirmed, previously untreated advanced (stage C/D) prostate cancer were recruited, February 2000–December 2001, at 49 Japanese centers. Inclusion and exclusion criteria have been described previously.[9] All patients provided written, informed consent before enrolment.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice requirements. The protocol was approved at all participating institutions by an Institutional Review Board. An Independent Data Monitoring Committee was established to conduct annual interim assessments of findings from the study.

Assessments

The primary lesion and metastatic sites were assessed clinically and by appropriate imaging techniques (scintigraphy, computed tomography, magnetic resonance imaging, ultrasound, X-ray) at baseline, 12 weeks and as appropriate. Efficacy assessments were performed, as described previously,[9] and were measured at baseline, weeks 1, 4, 5, 8 and 12 after the start of treatment, and then every 4 weeks until either disease progression or treatment withdrawal. Following this, patients were evaluated annually for progression and survival. Outcome variables were established using the Japanese Urological Association Criteria, edition 2.[13]

Details of adverse events were recorded at each visit and up to 4 weeks after treatment withdrawal. Events for which a causal relationship to the study drug(s) could not be excluded were classified as adverse drug reactions.

Outcome variables and statistical analysis

All patients who received at least one dose of study medication were included in the safety and primary efficacy analyses (intention-to-treat analysis).

The primary study variables were the PSA normalization rate (defined as the proportion of patients with a normal (≤4 ng/ml) PSA level) and overall tumor-response rate (defined as the proportion of patients with a partial response or better) at 12 weeks and the rate of withdrawals due to adverse drug reactions at the time of data cutoff (January 22, 2004). Calculations on the sample size required assumed that these variables would be similar to those observed in previous studies.[9] The percentage of withdrawals due to adverse drug reactions in the combined androgen blockade (CAB) group was considered clinically acceptable if the upper limit of the 95% confidence interval (CI) for the difference between the two treatment groups was <12.5%. Based on these assumptions, the required sample size (90% power, two-sided significance level of 0.05) was 200 patients (100 in each treatment group).

Secondary variables were: time to achieve PSA levels of ≤4 ng/ml; TTTF; TTP; OS; quality-of-life (to be reported elsewhere); and the incidence of adverse events/adverse drug reactions. TTTF was defined as the number of days between the first dose of the study treatment (earliest of LHRH-A or randomized therapy) and the earliest of study treatment withdrawal, disease progression or death. TTP was defined as the number of days between the first dose of study treatment and either disease progression or prostate cancer death. The relapse of primary lesion and/or metastatic sites assessed by imaging techniques, and/or PSA relapse (e.g. increases at three consecutive measurements) were judged to be disease progression.

Following disease progression and discontinuation of bicalutamide in the combination group, no change in PSA or reduced PSA levels were described as antiandrogen withdrawal responses. Among patients who had disease progression following LHRH-A alone, and were subsequently given bicalutamide 80 mg in an open-label fashion, a ≥50% reduction in PSA levels constituted a response to second-line combination treatment.

The Cox proportional hazards model was used to analyze the time-to-event data. In addition, time to achieve PSA ≤4 ng/ml, TTTF and TTP were compared between the treatment groups using the log-rank test.

Results

Patient demographics and dispositions

Patients ($n=205$) were randomized to either bicalutamide 80 mg combination therapy ($n=102$) or LHRH-A alone ($n=103$). Two patients in the LHRH-A only arm withdrew before therapy. As reported previously, patient demographics for the two treatment groups were well matched (Table 1).

Treatment was discontinued early in 54/102 patients who received bicalutamide 80 mg combination therapy, and in 78/101 of the patients who received LHRH-A alone (Figure 1). Only one patient, who received combination therapy, could be not followed-up for efficacy.

Efficacy variables

Here, we report the effect of bicalutamide on the secondary efficacy variables of the study at a median follow-up of 127 weeks (Table 2).

Table 1 Patient demographics at baseline

Characteristic	*Bicalutamide 80 mg combination therapy*, n (%)	*LHRH-A alone*, n (%)
N	102 (100)	101 (100)
Age (years)		
<75	53 (52.0)	50 (49.5)
≥75	49 (48.0)	51 (50.5)
PSA (ng/ml)		
<60	40 (39.2)	37 (36.6)
≥60	62 (60.8)	64 (63.4)
Histopathological class		
Well	3 (2.9)	6 (5.9)
Moderate	52 (51.0)	55 (54.5)
Poor	47 (46.1)	40 (39.6)
Clinical stage		
C/D1	59 (57.8)	57 (56.4)
D2	43 (42.2)	44 (43.6)
Disease stage		
T2	3 (2.9)	1 (1.0)
T3	83 (81.4)	77 (76.2)
T4	16 (15.7)	23 (22.8)
Nodal stage		
N0	74 (72.5)	63 (62.4)
N1	28 (27.5)	38 (37.6)
Metastatic status		
M0	59 (57.8)	58 (57.4)
M1	43 (42.2)	43 (42.6)
Lesion of metastases		
Bone	40 (39.2)	40 (39.6)
Lymph node	28 (27.5)	38 (37.6)
Other	2 (2.0)	3 (3.0)
LHRH-A		
Goserelin acetate	77 (75.5)	79 (78.2)
Leuprorelin acetate	25 (24.5)	22 (21.8)
Performance status		
0, 1	99 (97.1)	99 (98.0)
2	3 (2.9)	2 (2.0)

Abbreviations: LHRH-A, luteinizing hormone-releasing hormone agonist; PSA, prostate-specific antigen.

Time to achieve a prostate-specific antigen level of ≤4 ng/ml. Time to achieve a PSA level of ≤4 ng/ml was significantly shorter with bicalutamide 80 mg combination therapy than with LHRH-A alone (8.1 weeks versus 24.1 weeks, respectively; hazard ratio (HR) 3.96; 95% CI 2.77–5.66; $P<0.001$) and occurred in 96/102 (94.1%) patients in the combination therapy arm and 59/101 (58.4%) patients in the LHRH-A only arm ($P<0.001$).

Time-to-treatment failure. Time-to-treatment failure was significantly longer with bicalutamide 80 mg combination therapy than with LHRH-A alone (Figure 2). Treatment failure occurred in 54/102 (52.9%) patients at a median of 117.7 weeks in the combination therapy group and in 78/101 (77.2%) patients at a median of 60.3 weeks in the LHRH-A only group (HR 0.54; 95% CI 0.38–0.77; $P<0.001$).

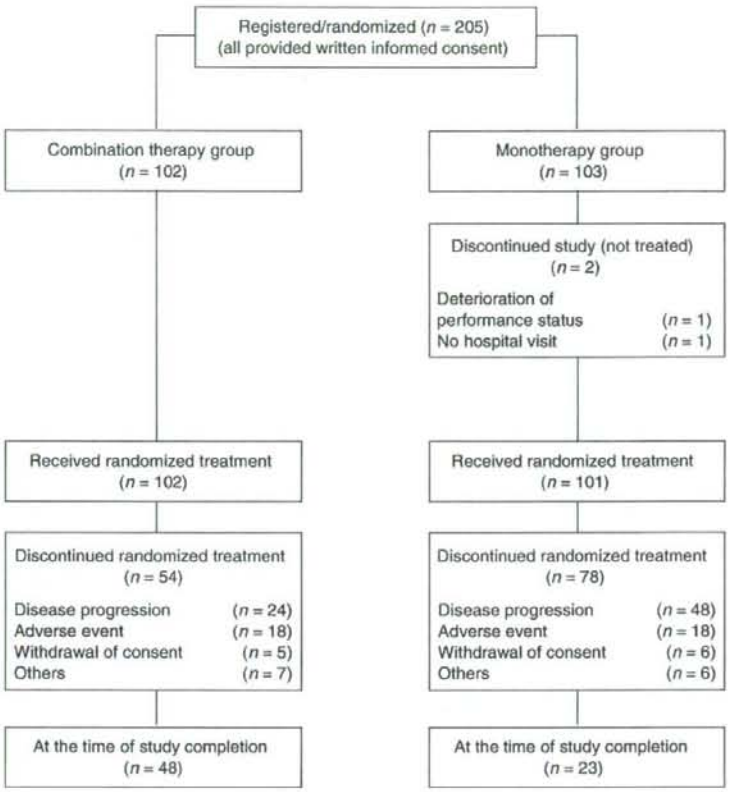

Figure 1 Outline of trial.

Table 2 Efficacy findings: bicalutamide 80 mg in combination with LHRH-A

Secondary efficacy variable	*Bicalutamide 80 mg combination therapy*	*LHRH-A alone*	*Log-rank test (P-value)*
N	102	101	
No. of patients with PSA ⩽4 ng/ml	96	59	
Median time to PSA ⩽4 ng/ml, weeks (range)	8.1 (2.9–91.6)	24.1 (3.1–119.7)	<0.001
No. of patients with treatment failure	54	78	
Median time to treatment failure, weeks (range)	117.7 (2.9–186.9)	60.3 (3.1–185.1)	<0.001
No. of progression events	30	57	
Time to progression, weeks (range)	Not yet reached (0.1–188.1)	96.9 (7.1–190.1)	<0.001
No. of deaths	13	18	
Time to mortality, weeks (range)	Not yet reached (8.3–202.0)	Not yet reached (8.1–190.1)	Not significant

Abbreviations: LHRH-A, luteinizing hormone-releasing hormone agonist; PSA, prostate-specific antigen.

Time to disease progression. Overall, disease progression occurred in 30/102 (29.4%) and 57/101 (56.4%) patients in the combination therapy and LHRH-A only groups, respectively. Patients in the combination therapy group benefited from a significantly longer TTP than patients in the LHRH-A alone group (HR 0.40; 95% CI 0.26–0.63; $P<0.001$; Figure 3). The median TTP in the LHRH-A group was 96.9 weeks; the median TTP has yet to be reached in the combination group.

Time-to-disease progression among patients with different stages of prostate cancer was investigated as part of an exploratory analysis. A greater effect was seen in bicalutamide 80 mg combination therapy versus LHRH-A alone in the 99 patients with stage C locally advanced disease (134.1 weeks versus median TTP not yet reached, $P<0.001$; Figure 4).

Overall survival. To date, 13/102 (12.7%) patients in the bicalutamide 80 mg combination group and 18/101 (17.8%) in the LHRH-A only group have died. The disease-specific survival findings were similar for the treatment groups (Figure 5).

Exploratory analysis of combined PSA data from the treatment groups demonstrated a significantly lower disease-specific mortality rate among patients who

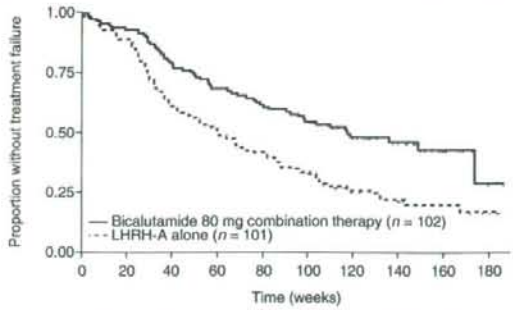

Figure 2 Time-to-treatment failure in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.54; 95% CI 0.38–0.77; $P<0.001$; bicalutamide 80 mg combination therapy events = 54 (52.9%); LHRH-A alone events = 78 (77.2%); LHRH-A, luteinizing hormone-releasing hormone agonist.

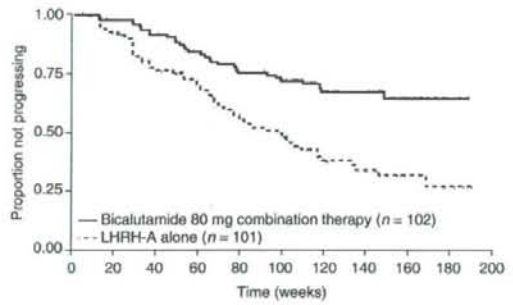

Figure 3 Time to disease progression in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.40; 95% CI 0.26–0.63; $P<0.001$; bicalutamide 80 mg combination therapy events = 30 (29.4%); LHRH-A alone events = 57 (56.4%); LHRH-A, luteinizing hormone-releasing hormone agonist.

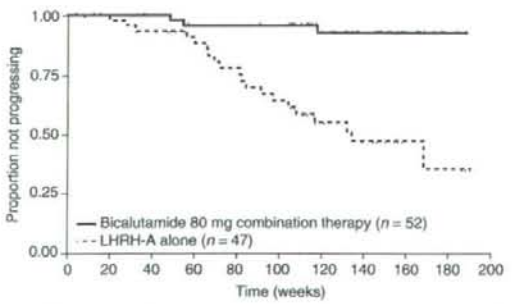

Figure 4 Time to disease progression among patients with stage C prostate cancer. $P<0.001$; bicalutamide 80 mg combination therapy events = 3 (5.8%); LHRH-A alone events = 20 (42.6%); LHRH-A, luteinizing hormone-releasing hormone agonist.

achieved a PSA level $\leqslant 4$ ng/ml at 12 weeks, compared with patients who did not (HR 0.15; 95% CI 0.06–0.38; $P<0.001$; Figure 6).

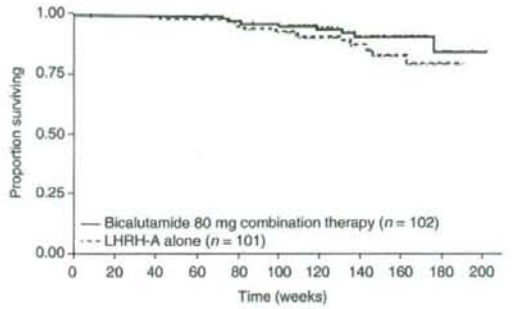

Figure 5 Disease-specific survival in patients receiving bicalutamide 80 mg combination therapy or LHRH-A alone. Median follow-up: 127 weeks; hazard ratio 0.63; 95% CI 0.26–1.54; $P=0.314$; bicalutamide 80 mg combination therapy events = 8 (7.8%); LHRH-A alone events = 13 (12.9%); LHRH-A, luteinizing hormone-releasing hormone agonist.

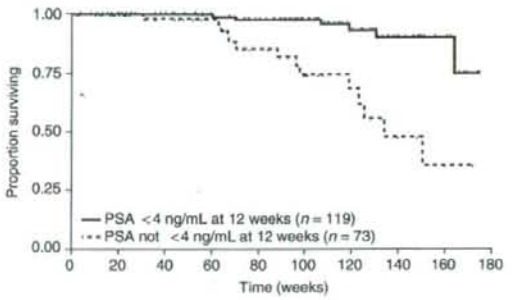

Figure 6 Disease-specific survival for patients achieving PSA levels of $\leqslant 4$ ng/ml at 12 weeks versus those not achieving PSA levels of $\leqslant 4$ ng/ml at 12 weeks. Hazard ratio 0.15; 95% CI 0.06–0.38; $P<0.001$; PSA, prostate-specific antigen.

Responses subsequent to disease progression

Eighteen patients consented to undergo follow-up for antiandrogen withdrawal syndrome: seven (38.9%) had a reduced/unchanged PSA after discontinuing bicalutamide. The median time to response in these seven patients was 6.9 weeks and the effect lasted for a median of 58.1 weeks.

Among patients who received LHRH-A only, before relapse, 31/40 (77.5%) experienced decreased PSA levels after adding bicalutamide 80 mg (i.e. $\geqslant 50\%$ reduction in PSA following relapse). The median times to, and duration of, response with second-line bicalutamide 80 mg combination therapy were 4.1 weeks and 39.6 weeks, respectively.

Tolerability

Bicalutamide 80 mg combination therapy had a tolerability profile similar to LHRH-A alone (Table 3). Withdrawals due to adverse drug reactions were comparable: 8.8% (9/102) of patients in the combination therapy group withdrew, whereas 10.9% (11/101) in the LHRH-A only group (95% CI on difference: −10.7–6.4).

Table 3 Incidence of most common (>10% in either group) adverse events (AEs) and adverse drug reactions (ADRs) among patients with advanced prostate cancer receiving either bicalutamide 80 mg combination therapy or LHRH-A alone

	Bicalutamide 80 mg combination therapy (n = 102)		*LHRH-A alone (n = 101)*	
	AEs (%)	*ADRs (%)*	*AEs (%)*	*ADRs (%)*
Any	93.1	66.7	93.1	65.3
Any serious	29.4	2.0	25.7	8.9
Nasopharyngitis	28.4	1.0	25.7	1.0
Hot flushes	17.6	16.7	33.7	32.7
Back pain	15.7	2.0	12.9	3.0
Increased blood LDH	11.8	6.9	7.9	3.0
Anemia	10.8	8.8	6.9	5.9
Increased blood ALP	10.8	10.8	5.9	5.0
Increased blood ALT	7.8	2.9	13.9	9.9
Increased blood AST	7.8	3.9	12.9	10.9
Constipation	6.9	1.0	11.9	1.0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; LHRH-A, luteinizing hormone-releasing hormone agonist.
Two patients in the bicalutamide 80 mg combination therapy group had an adverse drug reaction of breast pain and one patient in this arm had nipple swelling.

Discussion

This trial is the world's first double-blind controlled study to directly compare bicalutamide plus LHRH-A versus LHRH-A alone in men with prostate cancer.

Once-daily bicalutamide 80 mg in combination with LHRH-A provided superior efficacy to LHRH-A alone in terms of time to achieve PSA levels of ⩽4 ng/ml, TTTF and TTP. Notably, the median TTP has still not been reached among patients receiving bicalutamide 80 mg combination therapy, but was 96.9 weeks among men in the LHRH-A only arm. Additionally, the differences in TTTF and TTP between the two treatment groups were greater than those observed in an earlier analysis,[9] indicating that the advantage seen with bicalutamide 80 mg combination therapy has become more pronounced with increased follow-up.

These findings are supported by those reported in an earlier interim analysis from this study, which showed that at 12 weeks, patients receiving bicalutamide 80 mg combination therapy are significantly more likely to achieve PSA levels of ⩽4 ng/ml and have higher overall tumor-response rates than those receiving LHRH-A alone.[9]

An exploratory analysis revealed that the effect of bicalutamide 80 mg therapy on TTP is most pronounced in patients with locally advanced disease (stage C). The baseline characteristics of the two treatment groups were well balanced among patients with stage C disease. This suggests that although combination therapy using bicalutamide 80 mg has the potential to benefit all patients with advanced/locally advanced disease, the benefit over castration alone is greatest for patients with locally advanced tumors without spread to the lymph nodes or elsewhere.

There was no significant difference between the bicalutamide 80 mg combination therapy arm and the LHRH-A only arm in terms of OS/disease-specific survival at this analysis. This was not unexpected, as the mortality rates remain low in both treatment arms. Long-term follow-up of patients will be continued to show if there is any correlation between the choice of treatment and a reduced risk of death. Findings from an additional exploratory analysis of this data suggest that this is likely to be the case. The exploratory analysis revealed an association between levels of PSA ⩽4 ng/ml at 12 weeks and a lower risk of death caused by prostate cancer. This, taken alongside the primary trial finding that bicalutamide 80 mg combination therapy significantly improves the proportion of patients achieving PSA levels of ⩽4 ng/ml at 12 weeks relative to LHRH-A alone, demonstrates that bicalutamide 80 mg combination therapy has strong potential to improve survival. The likelihood that bicalutamide 80 mg combination therapy can improve OS versus castration alone is further supported by the findings from a recent indirect analysis by Klotz *et al*.[3] In this analysis, bicalutamide 50 mg plus LHRH-A was associated with a 20% reduction in mortality risk compared with LHRH-A alone.

Most patients with advanced prostate cancer who initially respond to combination therapy with an antiandrogen plus castration will, ultimately, experience disease progression. However, following subsequent withdrawal of antiandrogen therapy, some patients will experience a decrease in serum PSA levels and develop an antitumor response. This well-recognized phenomenon is referred to as the antiandrogen withdrawal syndrome and has also been described for patients who have received other nonsteroidal antiandrogens.[14–16] Indeed, a PSA response following withdrawal of nonsteroidal antiandrogen therapy (including with bicalutamide) typically occurs in approximately 15–36% of patients, and is characterized by a ⩾50% decrease in PSA for 4–7 months.[17,18] In this trial, 39% of patients had a PSA response (no change or a decrease in PSA levels) following discontinuation of bicalutamide 80 mg, and responses lasted for a median of 58 weeks. One explanation of why the PSA response rate following bicalutamide withdrawal was higher in this study, than in others, is that our definition of response was different to that used in other studies.

In those men who experienced disease progression following first-line LHRH-A alone, 78% (31/40) responded to the addition of bicalutamide 80 mg treatment. The efficacy of second-line bicalutamide 80 mg combination therapy in men with prostate cancer could suggest that combination therapy should only be used following initial therapy with castration alone. However, the median duration of response to second-line bicalutamide 80 mg was 40 weeks, and the median TTP following LHRH-A alone was 97 weeks, indicating a combined total TTP of 137 weeks. In contrast, based on current findings, the median TTP in patients receiving first-line bicalutamide 80 mg combination therapy is expected to be greater than the median TTP of 137 weeks calculated for patients receiving delayed bicalutamide 80 mg combination therapy (to date, <50% of patients have experienced progression). Therefore, we would expect bicalutamide 80 mg combination to be more effective as a first-line approach than as a second-line approach.

Importantly, in our trial, combination of bicalutamide 80 mg with LHRH-A did not lead to a rise in toxicity or withdrawals compared with LHRH-A alone. The rates of

withdrawal due to adverse drug reactions were also similar for the two treatment groups. As in the earlier analysis, the most common adverse events, occurring with similar incidence in both treatment arms, were nasopharyngitis and hot flushes. Although the reason for the relatively high incidence of nasopharyngitis is not clear, the incidence of nasopharyngitis that was attributed to adverse drug reactions was very low (1.0% in both groups). Less than 7% of patients in the bicalutamide 80 mg combination therapy group had gastrointestinal symptoms (constipation 6.9%, nausea 5.9% and diarrhea 4.9%), which was comparable to that observed in the LHRH-A only arm (11.9, 3.0 and 4.0%, respectively). The incidence of gastrointestinal adverse events among patients receiving bicalutamide 80 mg was lower than predicted from studies with bicalutamide 50 mg combination therapy in Caucasians,[5] but reflected the low incidence reported in the earlier analysis of our study.[5,9] As expected from previous studies of hormonal combination therapy,[19] the incidences of breast pain and gynecomastia were also low, occurring in only three men in the bicalutamide 80 mg combination group, and in no men in the LHRH-A alone group.

The tolerability profile of bicalutamide makes it an attractive agent for use in hormonal combination regimens, particularly as the profile is favorable compared with other antiandrogens.[17,20] Compared with bicalutamide, flutamide carries a higher risk of gastrointestinal events and hepatotoxicity; nilutamide is associated with delayed adaptation to darkness, alcohol intolerance and interstitial pneumonitis; and steroidal antiandrogens carry a risk of hepatotoxicity, cardiovascular events, reduced sexual potency and adverse serum lipid changes.

In summary, among Japanese men with advanced prostate cancer, first-line treatment with a combination of bicalutamide 80 mg and an LHRH-A provides significant efficacy benefits over LHRH-A alone, without increasing the incidence of adverse events or reducing tolerability. Patients continue to be followed for OS.

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*Values in parentheses represent the number of enrolled patients.

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The Outcome of Prostate Cancer Screening in a Normal Japanese Population with PSA of 2–4 ng/ml and the Free/Total PSA Under 12%

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Objective: No previous study has reported the numbers of prostate cancer (PC) patients existing among a normal Japanese population with prostate-specific antigen (PSA) < 4 ng/ml. The aim of this study was to elucidate the performance of %free PSA as a screening tool for a normal Japanese population with PSA of 2–4 ng/ml and to examine the characteristics of cancer detected using this criterion.
Methods: We conducted a prospective, multi-center study to evaluate the performance of %free PSA among a normal Japanese population. We decided on a %free PSA cutoff value of 12% according to the preliminary results. A total of 5548 consecutive screening volunteers aged 50–79 years were enrolled in the project. Men with total PSA > 4 ng/ml, or men with total PSA of 2–4 ng/ml and %free PSA of ≤12% were indicated to undergo 12 core biopsies.
Results: There were 826 (14.9%) men with PSA of 2–4 ng/ml. Among them, those with %free PSA of ≤12% numbered 100 (12.1%). Forty-nine out of 100 men (49%) received biopsy, and 16 PC patients were detected. Among 10 patients undergoing radical prostatectomy, seven were associated with extra-prostatic extension (pT3) or high-grade cancer (Gleason score ≥ 8).
Conclusions: We confirmed the ability of %free PSA and demonstrated that there are considerable numbers of PC patients among the normal Japanese population with PSA of 2–4 ng/ml. We ascertained that cancers detected in this study had a variety of tumor characteristics, including those of an aggressive nature.

Key words: prostate cancer – screening – PSA – %free PSA

INTRODUCTION

Prostate-specific antigen (PSA) is useful in the early detection, clinical staging and post-treatment monitoring of prostate cancer (PC). PSA is widely utilized in PC screening, and a cutoff value of 4 ng/ml has long been applied (1). The efficacy of PSA as a screening tool has been established; however, PSA screening is associated with unnecessary biopsies. Several investigators in the USA and Europe reported the results that examined the ability of the free-to-total PSA ratio (%free PSA) as a screening tool against the normal population with PSA between 4 and 10 ng/ml (2) or <4 ng/ml (3,4).

Catalona et al. (5) reported that when a %free PSA cutoff value of 15% was used as a criterion for biopsy, 54% of cancers would have been detected, compared with 33% of non-PCs undergoing biopsy in normal American men with PSA of 2.51–4 ng/ml. Eventually, a higher %free PSA cutoff could not be applicable in terms of selecting true cancer patients, and leads to low specificity.

The data from Thompson et al. (6) show that PC was detected in 23.9% of normal American controls with PSA of

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2.1–3 ng/ml and in 26.9% of those with a PSA of 3.1–4 ng/ml in the PC Prevention Trial (PCPT). Although Asian people have a low incidence of PC compared with the people of the USA or Europe, little is known about the incidence of PC in the normal Japanese population, especially those with PSA of 2–4 ng/ml.

In Japan, the cutoff value of 4 ng/ml has dominantly been accepted and utilized in PC screening. Based on these reports regarding the ability of %free PSA and the results of the PCPT, we expected to detect significant number of PC patients with PSA of 2–4 ng/ml by taking %free PSA selection in Japan.

Therefore, we conducted a prospective, multi-center study for PC screening. The aim of this study was to investigate the performance of %free PSA as a screening tool for a normal Japanese population with PSA ranging from 2 to 4 ng/ml. Moreover, we examined the characteristics of the cancer detected using this criterion.

PATIENTS AND METHODS

Study Design

We have carried out a preliminary PSA screening program in Miyagi prefecture, Japan in 2001 and 2002 and performed prostate biopsy in men with PSA over 4 ng/ml. We also evaluated both the free and total PSA values in all men. We analyzed 39 men with PSA 4–10 ng/ml who received prostate biopsy. Figure 1A shows the distribution of the value of %free PSA with 12 PC and 27 non-PC men in this preliminary study. (It is significant that the mean value of %free PSA with PC men is lower compared with that with non-PC men.) When a %free PSA cutoff value was set at 12%, the sensitivity and the specificity were 58.3 and 77.8%, respectively, which appeared eligible (Fig. 1B, AUC date not shown).

From 2003, we started the Northern Japan %free PSA Screening Project.

The indication for biopsy was expanded, which is PSA over 4 ng/ml or PSA ranging from 2 to 4 ng/ml with selection using %free PSA. Based on the preliminary results obtained from men with PSA 4–10 ng/ml, we experimentally decided on a %free PSA cutoff value of 12%. Four facilities participated in this co-operative prospective project, and a total of 11 communities located in Hokkaido and the Tohoku district (northern part of Japan) were enrolled. Male volunteers, 50- to 79-year old, participated in the project and received PSA testing along with ordinary health checks held by the community. Digital rectal examinations (DREs) were not performed in the community screening and thus were not used as an indication for biopsy.

PSA Analysis

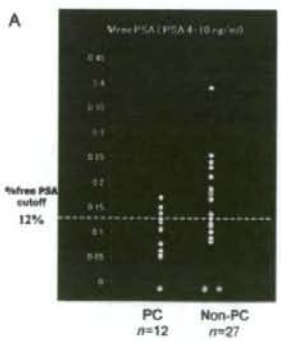
Serum samples were collected in each community and total and free PSA values (Architect®, Abbott, USA) were measured 3–5 h after the collection. The value of %free PSA was then calculated. Men with a total PSA of >4 ng/ml, or men with total PSA ranging from 2 to 4 ng/ml and %free PSA of ≤12% were indicated to undergo subsequent biopsy.

Prostate Biopsy

Our project unified the biopsy method. Each staff urologist of four facilities performed DRE and transrectal ultrasound (TRUS)-guided systematic biopsy and collected 12 cores of the prostate. The central pathologist of the project made a diagnosis based on the biopsy specimens, and the Gleason scores of the detected cancers were also evaluated.

Statistics

Statistical analyses were performed using an unpaired *t*-test on the Stat View program and values of $P < 0.05$ were considered statistically significant.



B

F/T	Sens. (%)	Spes. (%)
0.08	41.7	100
0.09	41.7	92.6
0.1	41.7	92.6
0.11	58.3	85.2
0.12	**58.3**	**77.8**
0.13	75.0	74.1
0.14	83.3	51.9
0.15	91.7	48.1
0.16	91.7	48.1
0.17	100	29.6

Figure 1. (A) A dot plot shows an individual %free cutoff value. * versus ** $P < 0.01$. (B) Percent-free PSA cutoff value, sensitivity and specificity obtained from men with PSA 4–10 ng/ml. When a cutoff value is 12%, sensitivity and specificity show an eligible performance. PC, prostate cancer; Sens., sensitivity; Spes, specificity; PSA, prostate-specific antigen.

Table 1. The Northern Japan %free PSA Project (2003–04)

PSA	No. of screening	No. of biopsy	PC (PPV%)
0–1.99	4337 (78.1%)	—	—
2–4	826 (14.9%)		
F/T > 12%	726 (87.9%)	—	—
F/T ≤ 12%	100 (12.1%)	49	16 (32.7%*)
4.01–10	310 (5.6%)	218	79 (36.2%**)
10.01–	75 (1.4%)	65	43 (66.2%)
Total	5548	332 (6%)[#]	138 (2.5%[##])

One hundred men (12.1%) showed a %free PSA of ≤12% among 826 men with PSA of 2–4 ng/ml. Sixteen cancer patients were identified in 49 men who received 12 core biopsies. PC, prostate cancer; PPV, positive predictive value; PSA, prostate-specific antigen; F/T, free/total. [#]Total biopsy rate, [##]cancer detection rate, * versus **not significant ($P = 0.38$).

RESULTS

A total of 5548 consecutive screening volunteers aged 50–79 years were enrolled and analyzed in the Northern Japan %free PSA Screening Project in 2003 and 2004 (Table 1). Men with PSA ranging from 2 to 4 ng/ml numbered 826 (14.9%). Among them, those with a %free PSA of ≤12% comprised 100 (12.1%). Forty-nine out of 100 men (49%) received TRUS-guided systematic biopsy, and 16 PC patients were detected. The positive predictive value (PPV) was 32.7%. Fifty-one men did not undergo biopsy mostly because of individual refusal. All men with PSA over 4 ng/ml were also indicated to undergo systematic biopsy. A total of 218 men received biopsy and 79 cancer patients were detected in this category. The PPV of men with PSA ranging from 4.01 to 10 ng/ml was 36.2%. Statistically significant difference of PPV was not observed between the group of men with PSA ranging from 2 to 4 ng/ml and 4.01 to 10 ng/ml. Overall cancer detection rate was 2.5% in this project.

The characteristics of patients with PSA of 2–4 ng/ml, detected by %free PSA, are demonstrated in Table 2. Retropubic radical prostatectomy (RRP) was performed in 10, watchful waiting in 3, external beam radiation therapy and androgen ablation therapy in 1 patient, respectively (one patient's data are not available). Among 10 patients undergoing RRP, seven were associated with extra-prostatic extension (pT3) or high-grade cancer (Gleason score ≥8), and two showed PSA failure within 24 months after surgery. These pathological diagnoses of extirpated specimens were made by local pathologists of each facility.

DISCUSSION

In this study, we initiated a prospective multi-center PSA screening program and especially investigated how many PC patients exist in a normal Japanese population with a PSA range of 2–4 ng/ml by utilizing %free PSA and also examined the characteristics of these cancers. Our project is the first study to target PC patients among a normal Japanese population with PSA between 2 and 4 ng/ml.

With regard to deciding on a cutoff %free PSA value for this category, we experimentally chose 12% according to the preliminary PSA screening results. Our choice was associated with eligible sensitivity and specificity obtained from

Table 2. Patients characteristics detected by %free PSA

Case	Age	tPSA	fPSA	%free PSA	No. of positive core	TNM	GS	Therapy
1	75	2.5	0.03	0.12	3	T3	4 + 3	AAT
2	70	2.51	0.21	0.084	1	T1c	3 + 3	RRP pT2pN0M0 Gleason 3 + 3
3	74	2.63	0.3	0.114	4	T1c	3 + 4	RT
4	64	2.72	0.27	0.099	1	T1c	4 + 4	RRP pT2bpN0M0 Gleason 4 + 4
5	60	2.8	0.16	0.06	1	T2a	3 + 3	WW
6	82	3	0.34	0.11	6	T2c	3 + 4	WW
7	65	3.03	0.3	0.1	1	T1c	3 + 3	RRP pT2pN0M0 Gleason 4 + 4
8	76	3.06	0.25	0.082	1	T1c	4 + 4	RRP pT2bpN0M0 Gleason 4 + 4
9	71	3.1	0.29	0.094	2	T2c	3 + 4	RRP pT2cpN0M0 Gleason 3 + 4
10	72	3.29	0.31	0.094	1	T1c	3 + 3	WW
11	61	3.55	0.38	0.107	3	T1c	3 + 4	RRP pT2cpN0M0 Gleason 3 + 4
12	53	3.8	0.152	0.04	6	T3	4 + 4 (+5)	RRP pT3pN0M0 Gleason 4 + 4
13	66	3.8	0.29	0.08	1	T1c	4 + 3	RRP pT3bpN0M0 Gleason 5 + 4
14	71	3.84	0.33	0.086	4	T1c	4 + 4	RRP pT3apN0M0 Gleason 4 + 3
15	65	3.92	0.42	0.107	N/A	N/A	N/A	N/A
16	56	3.93	0.38	0.097	4	T2a	3 + 4	RRP pT3apN0M0 Gleason 4 + 3

Seven patients underwent prostatectomy, exhibiting extra-prostatic extension and/or aggressive carcinoma components. TNM, tumor–node–metastasis; GS, Gleason score; WW, watchful waiting; RRP, retropubic radical prostatectomy; RT, radiation therapy; AAT, androgen ablation therapy; N/A, not available.

Table 3. Results of the PC screenings for normal population with PSA <4 ng/ml

Author	PSA (ng/ml)	Biopsies done	Biopsy cores	Detection rates (%) (PC/biopsy)	Country
Catalona et al. (4)	2.51–4	368	6 or more	15 (54/368)	USA
Djavan et al. (3)	2.5–4	273	8	24.2 (66/273)	Austria
Babaian et al. (9)	2.5–4	151	11	24.5 (37/151)	USA
Schroder (8)	2–4	2350	N/A	22.3 (524/2350)	Europe (ERSPC)
Pelzer et al. (7)	2.6–4	559	10–15	20.2 (113/559)	Austria
Thompson et al. (6)	2.1–4	675	6 or more	24.7 (167/675)	USA (PCPT)
Present study	2–4 and %fPSA ≤ 12	49	12	32.7 (16/49)	Japan

Nearly 20–25% of cancer detection rates against normal population with PSA < 4 ng/ml have been reported thus far from the USA and Europe.
ERSPC, European Randomized Study of Screening for Prostate Cancer; PCPT, Prostate Cancer Prevention Trial.

biopsied men with PSA of 4.01–10 ng/ml. We assumed that the data of the men with a PSA between 4.01 and 10 ng/ml would, to some extent, serve as an eligible source to determine the appropriate %free PSA cutoff for biopsy in Japanese men with a PSA between 2 and 4 ng/ml. In fact, we had little data on the percentage of PCs in a normal Japanese population with low PSA levels. As the 12% cutoff was not verified yet, a future comprehensive survey is expected to be conducted for normal Japanese men with PSA of 2–4 ng/ml.

There are several PSA screenings for normal populations with PSA < 4 ng/ml in the USA and Europe. The results of these studies are summarized in Table 3. Pelzer et al. (7) reported that 559 screening volunteers with PSA of 2.6–4 ng/ml received prostate biopsy in Austria, and the cancer detection rate was 20.2%. They also evaluated the efficacy of %free PSA in the group and showed a significantly higher cancer detection rate when the %free PSA cutoff value was <15%. It has been established that nearly 20–25% of PC patients exist in this category in the USA or Europe (3–9). In Japan, Kobayashi et al. (10) examined the utility of the PSA–α1-antichymotripsin (ACT) complex and %free PSA for Japanese patients presenting lower urinary tract symptoms and PSA levels of 2–4 ng/ml. They reported that PSA–ACT was more specific than %free PSA and achieved a cancer detection rate of 23.3% on 6–10 core biopsies; however, the group consisted of symptomatic patients and not normal volunteers.

In the present study, 16 cancers were detected from 49 biopsies (32.7%) using a cutoff value of 12 as the %free PSA in this normal group with PSA of 2–4 ng/ml. The cancer detection rate of 32.7% is almost identical to that of PSA with 4.01–10 ng/ml in this study. We think that our cutoff value of 12% is feasible in this regard; moreover, we are confident that there are a considerable number of PC patients among healthy Japanese men with PSA between 2 and 4 ng/ml.

It has been argued whether PCs detected by means of %free PSA in the low PSA range have an aggressive nature (5,11,12). Catalona et al. (5) reported that all men with cancer spreading beyond the prostate showed a %free PSA value of <15%. Meanwhile, Pepe et al. (12) reported that a %free PSA cutoff is not useful for the preoperative staging of patients with PC. Our study revealed that the patients detected have a variety of tumor characteristics. Although the sample size of this study was small and the significance difficult to ascertain, we confirmed that seven patients out of 16 detected men had high-grade cancers (pT3 and/or Gleason score ≥8). Our results are likely to support the idea that lower PSA levels do not always lead to mild tumor characterization, especially in cases with a lower %free PSA value. We could not explain the mechanisms by which the number of significant cancers was high with poor characteristics. It is possible that the low PSA level itself and/or low %free PSA may influence the pathophysiology of an aggressive nature in these patients. Ongoing studies are investigating comparisons of pathological features of cancers detected in the subjects with PSA of 2–4 ng/ml and >4 ng/ml.

There seems to be an overt racial or environmental difference in PC prevalence between Japanese and Americans or Europeans. Previous reports examined all men with PSA of 2 (2.5)–4 ng/ml (3–9); meanwhile, our study investigated only 12.1% (100 of 826) within this category. The cancer detection rate was 20–25% and 32.7%, respectively. Furthermore, the co-investigators (M.K., T.T. and S.K.) previously carried out PC screening both in Japan and China and reported that the cancer incidence and prevalence were higher in Japan (13). It is plausible that not only genetic but also epigenetic or environmental factors may affect the prevalence of PC because the lifestyle in Japan is more similar to that in the USA or Europe compared with that in China. Cross-cultural comparative studies of the cancer detection rate, using common screening indications, will certainly contribute to elucidating the problem.

There are some limitations in this study. First, the sample size is too small to achieve significance. The percentage of men in this category (PSA 2–4 ng/ml) was 14.9%, which is almost identical to that reported in the USA (8); however, men undergoing biopsy comprised less than half in this project, resulting in the relatively small number. The main reason was the patients' refusal of biopsy, so we must pay attention in this regard to continue the project. Second, the cutoff value of 12% has not been verified yet. It is naturally

estimated that several PC patients potentially exist in the group with PSA of 2–4 ng/ml and %free PSA over 12%. A comprehensive survey is needed to be performed in this category. Third, we cannot definitely determine the efficacy of our screening system and the characterization of the cancer detected because the follow-up period is not sufficient thus far. Ongoing studies (the Northern Japan %free PSA Screening Project) are investigating the effects of screening and may overcome these problems.

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Conflict of interest statement

None declared.

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A randomized clinical trial of suspension technique for improving early recovery of urinary continence after radical retropubic prostatectomy

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Study Type – Therapy (RCT)
Level of Evidence 1b

OBJECTIVE

To evaluate, in a prospective, single-blind, randomized trial, the safety and efficacy of a suspension technique for improving early recovery of continence after radical retropubic prostatectomy (RRP).

PATIENTS AND METHODS

We randomly assigned 60 men with clinically localized prostate cancer to RRP; 30 were treated with the suspension technique and the remaining 30 were not. All patients had RRP by the same surgeon followed by early catheter removal on the third day after RRP. The primary outcome measures were the interval to recovery of continence, and the positive margin rates. The continence status was evaluated by a third party using validated questionnaires at baseline before RRP and at 4 and 7 days, and 2 weeks, 1, 3, 6 and 12 months after RRP.

RESULTS

The suspension technique resulted in significantly greater continence rates at 1, 3 and 6 months after RRP of 53% vs 20%, 73% vs 47% and 100% vs 83%. Kaplan-Meier curves also showed that patients in the suspension group had a significantly earlier recovery of continence than in the no-suspension group; the median (95% confidence interval) interval for recovery was 31 (12–74) days in the suspension group and 90 (65–150) days in the no-suspension group (log rank test, $P = 0.002$). The groups had no significant differences in their histological status.

CONCLUSIONS

The suspension technique had a significant effect on the earlier recovery of urinary continence within 6 months after RRP, without compromising the oncological outcome of RRP.

KEYWORDS

prostate cancer, prostatectomy, urinary continence, suspension technique, randomized trial

INTRODUCTION

Radical prostatectomy (RP) is commonly used to treat patients with clinically confined prostate cancer and a life-expectancy of ≥10 years [1]. Recently, many surgeons reported exceedingly low complication rates during and after retropubic RP (RRP) [2,3]. In the last decade, experienced surgeons have directed their efforts to decrease transfusion rates, decrease hospital stay, shorten the period of urinary catheterization, and improve continence and potency rates after RRP [4]. However, incontinence after RRP remains of great concern for most patients. Although urinary continence at ≥1 year after RRP is preserved in >90% of patients at most major medical centres [5–8], several studies have shown that the quality of life (QoL) is compromised by incontinence rates of 30–83% during the first 3 months after surgery [5,6]. This variation has been attributed to different definitions of continence, surgeon experience, and variations in surgical technique. The use of validated patient questionnaires has improved the standardization of the definition of continence and eliminated physician bias. In addition, a prospective randomized clinical trial needs to avoid the bias from surgeon experience and variations in surgical technique.

Several groups [9–11] suggested a prominent role for the puboprostatic ligaments in the maintenance of continence after RRP, as they support the urethra in maintaining its position in the pelvic floor. Some advocate placing a suture to attach the ligated dorsal vein to the pubic symphysis [12], while others preserve the puboprostatic ligaments before apical resection [9–11]. We developed these procedures into a simple suspension technique of vesico-urethral anastomosis by placing two sutures that are anchored to the puboprostatic ligaments, preserving those anterior attachments to the pubic bone [13,14]. However, Katz *et al.* [15] recommended a wide resection of bladder neck and cutting the puboprostatic ligaments to decrease bladder neck and apical positive margins.

We conducted a prospective, randomized clinical trial to compare the efficacy in terms of earlier recovery of continence after RRP and the safety of using a suspension technique in RRP, with no suspension used in a control group, in men with clinically localized prostate cancer. In this trial, validated patient questionnaires were used to

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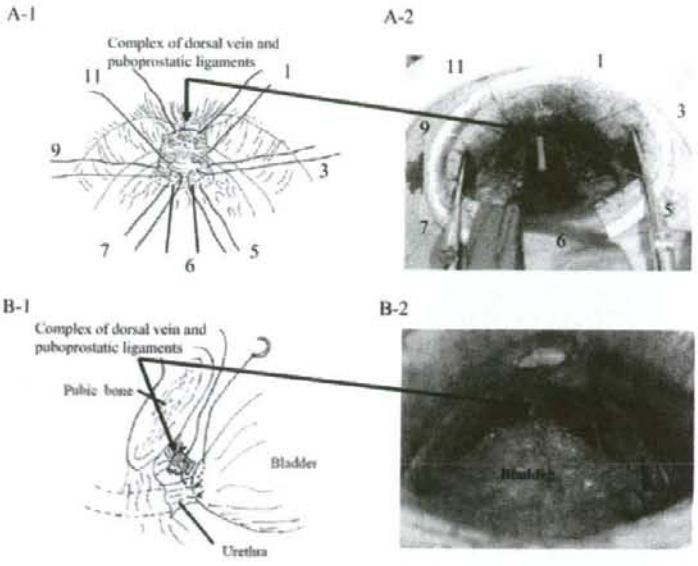
FIG. 1. The suspension technique: A-1 and A-2, seven anastomotic sutures are placed through the mucosa of the urethra. B-1 and B-2, two sutures at the 1 and 11 o'clock positions were anchored to the ligated complex, including both the dorsal vein and the puboprostatic ligaments, to suspend the vesico-urethral anastomosis (lateral view).



evaluate continence by a third party, and a recent series of 60 consecutive patients who had RRP by the same surgeon was analysed.

PATIENTS AND METHODS

This study was a prospective, single-blind, randomized clinical trial of a suspension technique during RRP for localized prostate cancer. The study protocol was approved by the Kurume University School of Medicine ethics committee, and the study was conducted in accordance with the declaration of Helsinki. Patients with a clinical stage of T1 or T2 prostate cancer who were considered for RRP were recruited to participate in this clinical trial at Kurume University Hospital from July 2005 to February 2006. All patients provided written informed consent. Patients were excluded if they had: previous TURP, suprapubic prostatectomy, or local radiotherapy or hormonal therapy; insulin-dependent diabetics (to avoid the possibility that diabetic neuropathy affects the continence); or a history of neurological disease.

Eligible patients were randomized equally into the two groups, having RRP with or without the suspension technique. Randomization was by a blocked stratified procedure, where each block consisted of two treatment assignments with two strata, two age groups (<65, ≥65 years), and two groups with different baseline clinical stages (T1, T2). Before RRP, each patient had a standard evaluation, including taking a careful history, a DRE, TRUS, serum PSA determination, routine blood tests, transrectal biopsies under TRUS guidance, a chest X-ray, pelvic CT, MRI and a radioisotope bone scan. Clinical stages were determined according to the 2002 TNM classification. All participants were unaware of whether they had a suspension procedure or not. Double-blinding was deemed unnecessary because the investigator (who also performed the RRP) had no influence in determining the key evaluation factor, the assessment of continence.

All RRP was done the same surgeon (M.N.) who used a modification of both the anatomical technique described by Walsh and the 'bunching' technique described by Myers, with an attempt at bilateral nerve-sparing whenever feasible [16,17]. All patients also had a limited pelvic lymphadenectomy. The pelvic lymph nodes were submitted for permanent section, with no frozen-section analysis. The neurovascular bundles were preserved unilaterally or bilaterally, depending on the patient's wishes, and the potency status before RRP, favourable Gleason scores, clinical stage and intraoperative assessment of the gland were recorded. The suspension technique was done as reported previously [13,14]; briefly, the puboprostatic ligaments that attach the prostate to the symphysis pubis were not divided before apical resection and were included in the bunching complex. After the ligating the complex, including both the dorsal vein complex and the puboprostatic ligaments, this complex was sharply divided anteriorly from the prostate with a safe distance (1–2 mm), and the urethra was defined and divided. After the apical dissection was completed and the anterolateral pedicles were controlled, Denonvilliers' fascia was incised and seminal vesicles were released as the dissection progressed laterally, to liberate the base of the prostate. After removing the prostate, the bladder neck was reconstructed by completely everting the mucosa and sutured outward with a running 4-0 absorbable suture around the edge. The bladder neck was narrowed to ≈1 cm, for convenient passage of a 20 F catheter. Anastomotic sutures of 3-0 absorbable polyglactin were placed at the 1, 3, 5, 6, 7, 9 and 11 o'clock positions through the full thickness of the urethra, including the mucosa and muscularis of the bladder neck, ensuring mucosa-to-mucosa anastomosis. The sutures at the 1 and 11 o'clock positions were anchored to the ligated complex including both the dorsal vein complex and the puboprostatic ligaments, to suspend the vesico-urethral anastomosis (suspension technique). The difference between the suspension and no-suspension techniques was only the placing of two sutures into the ligated complex (Fig. 1). During the procedure, a portable head-light (PeriLux LED, Hodies, Australia) was used to improve illumination of the surgical field and magnifying loupes (×2.5) were used to allow better visualization of anatomical details. Blood loss was measured by weighing all blood in the gauze and from a suction device during surgery, and the time from skin incision to closure of the wound was defined as the surgical duration. The retropubic space and vesico-urethral anastomosis were drained with a closed suction device at the end of the procedure.

The drain was removed on the next day after RRP if the drain volume was <100 mL. The gravity cystogram was routinely done on the second day after RRP. In brief, the bladder was filled with 150–200 mL of contrast medium until the patient reported a sense of fullness and discomfort. Several films of the bladder and vesico-urethral junction were taken in anteroposterior, lateral and oblique projections. Films were also obtained after manipulating the urethral catheter and after emptying the bladder, in an attempt to detect potential extravasation. The urethral catheter was removed 3 days after RRP if there was no or only minimal extravasation on the cystogram [13]. If there was significant extravasation was on the initial cystogram, the urethral catheter was retained and a second cystogram for deciding catheter removal was taken 3–5 days after the initial cystogram in the hospital. Patients were usually discharged from the hospital 7 days after RRP, as defined in the clinical pathway.

For the histopathological examination, the RRP specimens were processed with sections cut at 3-mm intervals, as previously reported [16]. The specimens were delivered fresh, then weighed, measured and grossly inspected. The outer surface of the gland was thoroughly inked with different colours to maintain the orientation of the specimen. The prostate base and apex were defined as the proximal third and distal 5 mm portions of the prostate, respectively. An entire apical block of the prostate, including apical and urethral margins, was removed by a single transverse section perpendicular to the urethra and 5 mm in greatest vertical dissection at the midline. This tissue block then was serially sectioned at 3-mm intervals in parasagittal planes that were perpendicular to the initial transverse incision and parallel to the distal segment of the urethra. The specimen was pathologically classified according to the 2002 TNM system and the following definitions were used to determine the pathological status of the primary tumour: (i) organ-confined disease, tumour confined to the prostate; (ii) positive surgical margins (PSMs), indicated as any cancer in contact with the inked surface of the prostate; (iii) extraprostatic extension, tumour that penetrated through the prostate capsule reaching the inked margins; (iv) seminal vesicle invasion, any invasion of the seminal vesicle wall by tumour cells; and (v) nodal disease, presence of prostate cancer lymph node metastases.

Patients were interviewed by a research nurse using a Japanese version [17] of the University of California, Los Angeles, Prostate Cancer Symptom Index at baseline, and at 4 and 7 days, and 2 weeks, 1, 3, 6 and 12 months after RRP. The Japanese version questionnaire was validated in Japan to be as useful as the original version [18]. Patient responses to these survey items were collected by a data manager at our institution, and who was independent of the operating surgeon. The definition of continence was based on patient responses to three questionnaire items, selected to reflect the range of incontinence severity: (i) Over the past 4 weeks, how often have you leaked urine?; (ii) Which of the following best describes your urinary control during the last 4 weeks?; and (iii) How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks ('4 weeks' in the three items was modified to '24 h' during 1 month after RRP). Continence was defined as the answer of 'Not at all' to (i), 'Total control' to (ii) and 'No pad' to (iii), respectively, and the day on which continence was recovered was recorded.

The sample size was chosen to detect a difference of >30 days in the time to recovery of continence after RRP between suspension and no suspension, with a SD of 40 days, 80% power and the $\alpha = 0.05$ significance level. The sample size was estimated based on the previous clinical trial [13,14]. These calculations and values required the enrolment of 50 men, and this was increased to a target enrolment of 60 to account for a potential discontinuation rate of up to 20%. Data were entered into a computer database with a security system by one research nurse, and then analysed using commercial software. The differences in the mean values among the various groups were assessed using the chi-square test or one-way ANOVA. The primary outcome of interest was the interval before the return of urinary continence after RRP, and the association of this outcome variable with the surgical technique of suspension was assessed using Kaplan–Meier plots, with the log-rank statistic to test for differences in the curves. To minimize and control for selection bias we constructed a Cox proportional hazards model for the interval to continence. Variables considered for this model included surgical technique (suspension or no suspension), age at surgery, body mass index (BMI), baseline PSA level, clinical tumour stage, intraoperative blood loss and duration of surgery, prostate volume, Gleason score, seminal vesicle invasion, PSMs and pathological stage. Test results were considered significant at $P < 0.05$.

RESULTS

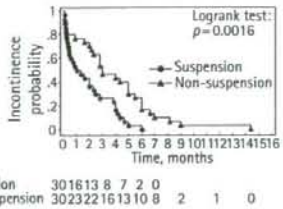
In all, 71 patients were scheduled to undergo open RRP for clinically localized prostate cancer at our institution from July 2005 to February 2006. Of the 71 patients who were screened for eligibility, 60 satisfied all eligibility criteria and agreed to participate in the trial, and were randomized to receive the suspension technique (30) or no suspension (30) during RRP. All of the randomized patients completed the study. There was no significant difference between the groups in the preoperative baseline demographics or the clinical characteristics of the patients. In addition, there was no significant difference in prostate volume, surgical duration and blood loss between the groups (Table 1). No patients had symptoms of urinary incontinence before RRP.

There were no complications during RRP in either group of patients. The median catheterization time was similar in both groups. The rate of urinary retention after catheter removal was 13% (four of 30) and 3% (one of 30) in the suspension and the no-suspension groups, respectively. Those patients with urinary retention were treated with simple catheter replacement for 1 or 2 days. There was no patient with urinary retention after hospital discharge (>7 days). In the median follow-up of 14.2 (12–19) months, no clinical signs of pelvic abscess, urethral stricture or urinoma developed in any patient.

The two groups had no significant differences in their pathological status; in the suspension group, PSM were detected in none and 40% of patients with pT2 and pT3, respectively. In the no-suspension group, PSM were found in 3% and 33%, respectively (Table 2). There was no significant difference between the groups in the frequency of PSMs.

The continence rates at the various follow-up times are shown in (Table 3). The suspension technique resulted in significantly greater continence rates at 1, 3 and 6 months after RRP, although the rates at 12 months were not significantly affected. Kaplan–Meier curves show that the patients in the

FIG. 2. Kaplan-Meier curves showing that the patients in the suspension group had a significantly earlier return of continence than in the no-suspension group (log-rank test, P = 0.002). The median (95% CI) time to recovery in the suspension group was 31 (12–74) days and in the no-suspension group was 90 (65–150) days.



suspension group had a significantly earlier return of continence than those in the no-suspension group (log-rank test, $P = 0.002$; Fig. 2). The median (95% CI) interval to recovery of continence in the suspension group was 31 (12–74) days and in the no-suspension group was 90 (65–150) days. A Cox proportional hazards regression analysis was used to determine risk factors for incontinence after RRP (Table 4). In both the univariable and multivariable analysis, no suspension technique ($P = 0.005$) and age at surgery ($P = 0.035$) were the only significant risk factors for the recovery of continence after RRP. Other factors, including BMI, PSA level, clinical stage, intraoperative blood loss, duration of surgery, prostate weight, Gleason score, seminal vesicle invasion, PSM and pathological stage were insignificant.

DISCUSSION

In the present randomized trial, the suspension technique led to a significantly earlier recovery of continence than in the controls, with median intervals of 31 and 90 days. The suspension technique also resulted in significantly greater continence rates at 1, 3 and 6 months after RRP of 53% vs 20%, 73% vs 47% and 100% vs 83%, although the rate at 12 months were not significantly different. These results are considered reliable, as they were obtained in a randomized and prospective trial, with all RRPs by the same surgeon. This differs from other published studies in which the surgical technique and the patient outcome were usually evaluated retrospectively, and the procedures were often performed by different surgeons from the same institution [2]. Comparative evaluations, ideally by the same

TABLE 1 Clinical data of the 60 men with localized prostate cancer (30 in each group)

Characteristic mean (SD), median (range) or *n* (%)	Suspension	No suspension
Age, years	66.9 (6.5)	66.6 (5.3)
	69 (52–76)	68 (50–75)
BMI, kg/m²	22.7 (2.3)	23.4 (2.4)
	22.7 (16.6–26.1)	23.4 (16.6–29.7)
Clinical T stage		
T1c	13 (43)	14 (47)
T2a	13 (43)	12 (40)
T2b	4 (13)	4 (13)
PSA level before RRP, ng/mL		
	10.6 (6.2)	10.6 (5.8)
	8.9 (4.1–26.0)	8.8 (3.1–26.5)
Intraoperative blood loss, mL		
	429 (223)	517 (354)
	360 (105–1020)	440 (85–1517)
Operative duration, min		
	158 (25)	161 (36)
	154 (120–225)	157 (110–260)
Removal of catheter, days		
	3.1 (0.3)	3.7 (3.2)
	3 (3–4)	3 (3–20)
Prostate weight, g	28.8 (9.4)	34.0 (18.6)
	26.5 (17.4–49.8)	30.2 (11.5–106.6)

TABLE 2 Positive surgical margin rate according to pathological stage

Variable	Number with PSM/total (PSM rate, %)	
	Suspension	No suspension
Pathological stage		
pT2a	0/7 (0)	0/14 (0)
pT2b	0/4 (0)	0/4 (0)
pT2c	0/5 (0)	1/4 (3)
pT3a	10/13 (37)	5/6 (17)
pT3b	2/2 (7)	2/2 (7)
PSM rates		
In pT2	0	33
In pT3	40	33

TABLE 3 Continence rates in 60 men after RRP

Time after RRP	N continent/n available (rate, %)		
	Suspension	No suspension	*P* (chi-square)
4 days	3/24 (13)	2 (8)	0.669
1 week	7/30 (23)	5 (18)	0.561
2 weeks	11/30 (37)	5 (17)	0.093
1 month	16/30 (53)	6 (20)	0.029
3 months	22/30 (73)	14 (47)	0.034
6 months	30/30 (100)	25 (83)	0.020
12 months	30/30 (100)	29 (97)	0.313

surgeon with the same skill, are needed to determine whether the suspension technique provides equal or better outcomes than the no-suspension technique. More experience and more subtle changes in skill might have contributed to the improved outcomes. Another reason is that physician-based assessments of urinary continence and patient-reported outcomes differ. Litwin *et al.* [18] assessed urinary continence in men with prostate cancer using the University of California Los Angeles Prostate Cancer Symptom Index, and identified a significant difference in the physician and patient assessments of urinary QoL (21% vs 97%).

The possible mechanisms of urinary incontinence after RP include damage to the pelvic floor and urethral sphincter, damage to pelvic floor innervation, and loss of anterior urethral support. Various surgical techniques, including bladder neck preservation [11,19], intussusception of the bladder neck [20], puboprostatic ligament-sparing [10] and suspension of the vesico-urethral anastomosis [12–14] have been used to improve the early return of continence after RRP. Conflicting reports were published about the effect of bladder neck preservation on continence after RRP.

Selli *et al.* [19] and Deliveliotis *et al.* [11] found that preserving the bladder neck offered an earlier return of continence after RRP, but Poon *et al.* [21] did not. These reports were not randomized trials, and the surgeons were not the same, except in the report of Selli *et al.* In a randomized trial in which the surgeon, pathologist and interviewer were the same throughout, Srougi *et al.* [22] concluded that bladder neck preservation during RRP does not improve urinary continence, and that it might compromise cancer control. Walsh and Marschke [20] did not address bladder neck preservation; their technique instead used intussusception of the bladder neck with Lembert sutures, to prevent the bladder neck from pulling open as the bladder fills. They reported that 82% of the 54 men were continent at 3 months after RRP with intussusception of the bladder neck, vs 54% of 64 men who had RRP without intussusception, but that study was limited because their significantly greater continence rate at 3 months was compared with their previous report. If injuries to the bladder neck, the puboprostatic ligament and urethral sphincter are minimal, the continence mechanism will recover gradually. Therefore, a combination of anterior urethral support, e.g. the suspension technique, and puboprostatic ligament-sparing seems a promising concept in establishing the early recovery of continence after RRP. However, the previously described suspension technique was more concerned with only anterior support of the urethra by anchoring the anastomosis to the pubic bone [12]. Puboprostatic ligaments support the strained external urethral sphincter and preserve the urethra in its normal place in the pelvic floor. Therefore, their anatomical and morphological stability seems to be important in postoperative continence. Lowe [10] reported that preserving the anterior urethral ligamentous attachments was recommended for earlier recovery of continence after RRP, with high continence rates (49% at 1 month and 80.4% at 3 months) after surgery. The premise that suspension is effective could be based on the pubo-urethral continuity of the puboprostatic ligaments. We used both puboprostatic ligament-sparing and suspension techniques in the suspension group.

Analysis	Hazard ratio (95% CI)	*P*
Univariable		
Age at surgery (continuous)	1.055 (1.008–1.104)	0.021
BMI (continuous)	1.037 (0.922–1.166)	0.548
Serum PSA (continuous)	1.019 (0.973–1.066)	0.425
Clinical stage (T2/T1c)	1.079 (0.631–1.845)	0.780
Suspension (no/yes)	2.347 (1.342–4.098)	0.003
Blood loss (continuous)	1.000 (0.999–1.001)	0.692
Duration of surgery (continuous)	1.007 (0.998–1.015)	0.145
Prostate weight (continuous)	1.007 (0.984–1.030)	0.576
Gleason score (continuous)	1.057 (0.735–1.520)	0.765
Seminal vesicle invasion (yes/no)	1.883 (0.584–6.061)	0.290
PSM (yes/no)	1.096 (0.636–1.879)	0.741
Pathological stage (pT3/pT2)	1.244 (0.732–2.114)	0.421
Multivariable		
Suspension (no/yes)	2.337 (1.282–3.906)	0.005
Age at surgery (continuous)	1.049 (1.003–1.096)	0.035

TABLE 4
Cox proportional hazards analysis of risk factors for incontinence after RRP

In the present study, factors such as age, BMI, preoperative PSA level, clinical stage, intraoperative blood loss, duration of surgery, prostate weight, Gleason score, pathological stage, PSMs and surgical technique, all mentioned in previous studies as affecting the continence status after RRP, were analysed using Cox proportional hazards regression models. In both the univariable and multivariable analysis, not using the suspension technique and age at surgery were the only significant risk factors for the recovery of continence after RRP. Eastham *et al.* [23] reported similar results; they found that the risk of urinary incontinence after RRP is related to age and sensitive to the surgical technique used.

Complete removal of the cancer remains the goal of RRP; modifications to the surgical technique of RRP must not compromise the pathological outcome. Most investigators agree that the prostate apex is the most frequent site of PSM after RP. The PSM rate in pT2 prostate cancer for open RP is 2.7–14%, with a decreasing trend during the last decade [15]. In the present study, the pT2 PSM rates were 0% for the suspension group and 3% for the no-suspension group.

The present study has some limitations; there were relatively few patients and the study was conducted in one institution, although it was a prospective and randomized trial. Clinical trials with more patients at several institutions are necessary to confirm the effect of the suspension technique on the early recovery of continence and the oncological outcome after RRP.

The earlier recovery of continence has a clear and positive effect on the patient's QoL, as urinary incontinence is the symptom that bothers most patients after RRP, and undermines their conviction of having chosen this form of treatment. The present prospective randomized study shows that the suspension technique had a significant effect

on the earlier recovery of urinary continence within 1–6 months after RRP, without hindering the oncological outcome. This technique could be used in laparoscopic and/or robotic RP, and could result in earlier continence after surgery.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **(R)RP**, (retropubic) radical prostatectomy; **BMI**, body mass index; **PSM**, positive surgical margin; **QoL**, quality of life.

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Gene expression Profiles of Lysophosphatidic Acid-Related Molecules in the Prostate: Relevance to Prostate Cancer and Benign Hyperplasia

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OBJECTIVE. To elucidate gene expression profiles of lysophosphatidic acid (LPA)-related molecules in cancer, pre-cancerous lesion, and benign hyperplasia of the prostate.

MATERIALS AND METHODS. Prostate tissue samples were surgically obtained from 10 patients with localized prostate cancer and seven patients with invasive bladder cancer. Cancer cells and the corresponding stromal cells from normal prostate, high grade intraepithelial neoplasia (HGPIN), benign hyperplastic glands were isolated by laser capture microdissection. mRNA levels of three LPA receptors, LPA1, LPA2, LPA3, two LPA-synthesizing enzymes, autotaxin (ATX), acylglycerol kinase (AGK), and a LPA-degradation enzyme, prostatic acid phosphatase (PAP), were quantitatively assessed. The expression levels of the same genes were also determined in three human prostate cancer cell lines LNCaP, PC-3, and DU-145.

RESULTS. LPA1 mRNA level was significantly decreased in HGPIN and cancer epithelia when compared to the benign glands. LPA3 mRNA level was elevated in cancer epithelia compared to benign glands. LPA3, AGK, and PAP were predominantly expressed in LNCaP cells while LPA1 and ATX gene expressions were found in PC-3 and Du-145 cells. In BPH, AGK was abundantly expressed in the stroma while PAP was predominant in epithelial cells.

CONCLUSIONS. By acting via LPA3, LPA may play an important role in the development of prostate cancer. Switching of LPA receptor expression from LPA3 to LPA1, may be involved in prostate cancer progression and/or androgen independence. LPA may also play a key role in the development of benign prostatic hyperplasia. *Prostate 69: 283–292, 2009.* © 2008 Wiley-Liss, Inc.

KEY WORDS: **LPA; prostate cancer; benign prostate hyerplasia; autotaxin; laser capture microdissection**

INTRODUCTION

The prostate requires a constant supply of circulating androgen for its normal function. Paradoxically however, diseases of the prostate such as prostate cancer and benign prostatic hyperplasia (BPH) occur in an androgen diminished environment [1] raising the possibility that androgens alone may not be sufficient, though necessary, in the onset of prostate diseases. Indeed, accumulating evidence supports the existence of non-androgenic factor(s) that appear to promote growth of the androgen stimulated prostate [2–5].

One such non-androgenic factor relevant to prostatic growth and pathogenesis is lysophosphatidic acid (LPA) [6,7]. LPA is a potent lipid mediator that evokes an array of cellular processes including proliferation, prevention of apoptosis, cell migration, smooth muscle contraction, and tumor cell motility and invasiveness [8,9]. LPA has been detected in various biological fluids

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