Finally, we cannot avoid the greatest disadvantage of RARP: its cost. Bolenz et al.[27] warned that the use of robot technology was increasing without a mature assessment of cost-effectiveness. In the present study, RARP was associated with a 52.7% increase in the total cost compared with ORP. This is an important disadvantage despite its low complication rate and shorter postoperative length of stay, and a justification of this heavy cost pressure on national universal health care insurance would be required in the near future. The cost differences are mainly explained by the official fee for the surgery itself: approximately $4108 for ORP versus $7743 for LRP versus $5978 for MIE-RP versus $9528 for RARP (as of April 2012). Another concern relating to cost is profitability. It is estimated that a single robotic console costs approximately $1.5 million, and a dual-console is $2.25 million. There is also an annual maintenance fee of $150 000.[27,28] Kuwahara[29] estimated that a Japanese hospital needs at least 100 RARP cases annually to balance the profit and loss equation. Considering that there were 12 992 radical prostatectomies in the 2012 DPC database and hearing that Japan would add more than 100 surgical robots, the question of profitability arose. However, because of limited available data, it is difficult to deepen the discussion about cost-effectiveness of RARP in the current study. The data in the present study, however, can contribute to the formation of health care policy involving the future management of surgical robot distribution in Japan.

Some limitations in the present study must be mentioned. First, it is a retrospective, observational study, and patients were not assigned to each radical prostatectomy group randomly but on clinical practice basis. Unobserved confounders could cause biased results, although we exerted our best efforts to reduce the potential bias by incorporating multiple imputation, propensity-score matching, and generalized estimating equations.[15–19] Second, the DPC database lacked some highly interesting variables such as extent of lymph node dissection, nerve-sparing performance, blood loss volume, conversion to open surgery, and postoperative status in urinary incontinence and erectile dysfunction. Anesthesia time was used as one of the outcomes in the present study, however, real surgical time, which was not available from the DPC database, would be more ideal. Third, an administrative claims database might contain some inadequate coding, which could lead to underestimation or overestimation of events. Fourth,

hospitalization duration and cost data largely vary from one country to another, so the generalizability of our findings may be limited. Among developed countries, Japan is famous for its long length of stay.[30] Finally, the hospitals in the DPC database are not sampled randomly and are biased toward those with a large bed volume.[31]

Despite these limitations, our analyses provide up-to-date information for the safety aspect of RARP during the year of its initial introduction in Japan, which was worthwhile for robot-assisted surgery in any field.

In conclusion, the introduction of robotic surgery in Japan has led to dynamic changes in the clinical structure and outcomes of prostate cancer surgery. Based on the retrospective population-based analysis during its initial year, it was observed that RARP would be associated with several favorable safety aspects when compared with three conventional prostatectomies, although it would have the longest anesthesia time and was the most costly.

Abbreviations

CCI	Charlson comorbidity index
DPC	Diagnosis Procedure Combination
ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
LRP	laparoscopic radical prostatectomy
MIE-RP	minimum incision endoscopic radical prostatectomy
ORP	open radical prostatectomy
RARP	robot-assisted radical prostatectomy
RCT	randomized control trial

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Definitions of perioperative complications

Table S2. Detailed background and outcome data after multiple imputation and one-to-one propensity-score matching

ORIGINAL ARTICLE

Improvement of symptoms of aging in males by a preparation LEOPIN ROYAL containing aged garlic extract and other five of natural medicines – comparison with traditional herbal medicines (Kampo)

Hiroaki Nishimatsu[1], Tadaichi Kitamura[2], Daisuke Yamada[1], Akira Nomiya[1], Aya Niimi[1], Motofumi Suzuki[1], Tetsuya Fujimura[1], Hiroshi Fukuhara[1], Tohru Nakagawa[1], Yutaka Enomoto[1], Haruki Kume[1], Yasuhiko Igawa[3], and Yukio Homma[1]

[1]Department of Urology, Faculty of Medicine, University of Tokyo, Tokyo, Japan, [2]Department of Urology, Asoka Hospital, Tokyo, Japan, and [3]Department of Continence Medicine, The University of Tokyo Graduate School of Medicine, Tokyo, Japan

Abstract

"LEOPIN ROYAL®" (LER), a non-prescription health-promoting medication in Japan, is a preparation containing six natural medicines, namely, aged garlic extract, ginseng, oriental bezoar, velvet antler, cuscuta seed and epimedium herb. To determine the effect of LER on symptoms of aging in males, we conducted an open-labeled, randomized clinical trial using Kampo (mainly kamishoyosan) as a control. Forty-nine male patients (age, 62.7 (SD 11.8) years) with mild or more pronounced symptoms of aging were enrolled and randomly assigned to the LER ($n = 24$) or Kampo group ($n = 25$) for 6 months. The Aging Males' Symptoms (AMS) scale and the International Index of Erectile Function with 5 questions (IIEF-5) were tested at baseline, and after 3 and 6 months of administration of the medications. In the AMS scale, the somatic and psychological sub-scores and total score decreased depending on the time course in both groups. However, the decrease in the slope of the LER group was greater than that of the Kampo group. There was a significant difference between the groups and the group and month interaction (G × M), as revealed by a linear mixed model analysis ($p < 0.05$). The IIEF-5 score increased in the LER group ($p = 0.02$ with regard to G × M). In conclusion, the present results indicate that LER is possibly superior to mainly kamishoyosan on the rate of improvement of symptoms of aging, including erectile dysfunction, in males.

Introduction

With the increasing aging population in Japan, the health-related quality of life (HRQoL) in elderly men has become an important issue. Age-related changes in somatic, psychological and sexual function in men are partially explained by the decline in androgen level, which is known as "Androgen Deficiency in the Aging Male" (ADAM) or "Late-onset Hypogonadism" (LOH). For treatment of the ADAM or LOH, androgen replacement therapy (ART), antidepressants and erectile dysfunction (ED) treatments are used. However, Kampo are often used because of patients' preference to "natural" or "safe" medications. Kampo is based on traditional Chinese medicine (TCM) but adapted to Japanese culture. Currently, 148 Kampo medications are approved for reimbursement in Japan. Kampo and other herbal medicines are different depending on whether or not it is based on TCM theory.

"LEOPIN ROYAL®" (LER) is a unique liquid formula, non-prescription health-promoting medication in Japan, but is not a Kampo. This preparation contains concentrated aged garlic extract (AGE), ginseng extract, oriental bezoar tincture, velvet antler fluid extract, cuscuta seed extract and epimedium herb extract. AGE and ginseng have been reported to be effective against ED in male animal and human [1,2]. Velvet antler, cuscuta seed and epimedium herb have been traditionally used as an aphrodisiac in East Asia [3].

In this study, we determined whether LER could improve the symptoms of aging in males in an open-label, Kampo-treatment controled, randomized clinical trial.

Materials and methods

Participants

Men visiting our hospital with symptoms of aging were invited to enroll into the study. Selection criterion was a score of 27 or more (mild or more) on the Aging Males' Symptoms
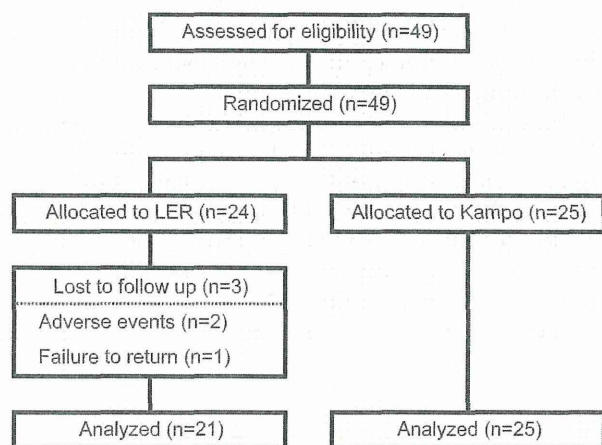
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Figure 1. Flow chart for enrollment of patients and follow-up data.

scale (AMS scale). Traditional pattern for Kampo medicine was not diagnosed. All patients provided informed written consent, and the Institutional Review Board of the University of Tokyo Hospital approved this study.

Eligible participants ($n = 49$, age 62.7 (SD 11.8) years) were enrolled and randomly assigned to the LER ($n = 24$) or Kampo ($n = 25$) group. Participants of each group were treated with LER or Kampo for 6 months according to the approved dosage of each regimen. Three participants in the LER group were lost to follow-up because of adverse events ($n = 2$) and failure to return ($n = 1$). As a result, 46 participants (21 in the LER group and 25 in the Kampo group) completed the study protocol (Figure 1).

Treatments

The LER (manufactured by Wakunaga Pharmaceutical Co., Ltd., Osaka, Japan, Lot no. EA0, F0G, GAB, H0F, etc) was purchased at a pharmacy. The package insert of LER has been described as follows: Ingredient: 2 mL of LER contains 1.8 mL of concentrated AGE, 273 mg of ginseng extract, 0.15 mL of oriental bezoar tincture, 0.03 mL of velvet antler fluid extract, 30 mg of cuscuta seed extract and 5 mg of epimedium herb extract. Dosage: adults 15 years and above; 1 mL (one capsule full), with normal or warm water, twice daily.

AGE contained in the LER is a unique garlic extract manufactured by soaking sliced garlic (*Allium sativum*) cloves in an aqueous ethanol and naturally extracted/aged [4]. Ginseng extract, cuscuta seed extract and epimedium herb extract are extracts of *Panax ginseng* root, *Cuscuta* sp. seed and *Epimedium* sp. herb, respectively, which are extracted with 30% aqueous ethanol and concentrated. Oriental bezoar tincture and velvet antler fluid extracts are alcoholic liquid extracts of *Bos taurus* gallstone and *Cervus* sp. antler in a pre-calcified stage, respectively.

Since the preparation of indistinguishable placebo against LER is difficult, we designed an open-labeled, mainly kamishoyosan (Kampo group) controled, randomized trial. We decided to prescribe kamishoyosan ($n = 20$, *Jia Wei Xiao Yao San* in Chinese), which is used for somatic symptoms of LOH, to patients assigned to the Kampo group. However, the following Kampo medications were prescribed according

to patient's symptoms or needs; hangekoubokuto ($n = 1$, *Ban Xia Hou Pu Tang*), saikokaryukotsuboreito ($n = 1$, *Cai Hu Jia Long Gu Mu Li Tang*), hochuekkito ($n = 1$, *Bu Zhong Yi Qi Tang*), goshajinkigan ($n = 1$, *Niu Che Shen Qi Wan*) and hachimijiogan ($n = 1$, *Ba Wei Di Huang Wan*).

Evaluation of symptoms of aging in males

Participants were evaluated using the AMS scale, the International Index of Erectile Function with 5 questions (IIEF-5), the ADAM questionnaire and the Self-Rating Questionnaire for Depression (SRQ-D) at the time of enrollment (baseline), and after 3 and 6 months of treatment. The AMS scale is a HRQoL scale for aging male and was developed by Heinemann et al. in Germany [5,6]. The scale consists of 17 items to obtain the degree of each symptom on a scale of 1–5, and is able to measure for three-dimension sub-scores (somatic, psychological and sexual) and total score (the sum of three sub-scores). Severity of symptoms in the total score is defined in the following four categories; severe (score 50+), moderate (37–49), mild (27–36) and no (≤ 26). The IIEF-5 developed by Rosen et al. [7] is a diagnostic tool for ED, and consists of five items of five degrees. ED severity is classified in the following five categories; severe (score ≤ 7), moderate (8–11), mild to moderate (12–16), mild (17–21) and no ED (22–25). The ADAM questionnaire developed by Morley et al. [8] is a screening test for ADAM, and consists 10 items to obtain yes/no answers. A positive result on the questionnaire is defined as an affirmative answer ("yes") to questions 1 or 7 or any 3 other questions. The SRQ-D is a screening test for masked depression, and developed by Abe et al. [9] in Japan. The questionnaire consists of 18 items of four degrees, and the total score is calculated as the sum of each question score except questions 2, 4, 6, 8, 10 and 12. Depression severity is classified in the following three categories; masked depression (score 16+), borderline depression (11–15) and no depression (≤ 10).

Endocrinologic tests

Some of the subjects underwent endocrinologic tests at baseline and after 6 months of treatment for serum testosterone, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and estradiol (E2). Serum testosterone and free testosterone levels were measured by coated tube radioimmunoassay (Mitsubishi Chemical Medience Corp., Tokyo, Japan), FSH, LH and PRL were measured by fluorescent enzyme immunoassay (Tosoh Corp., Tokyo, Japan), and E2 was measured by chemiluminescent enzyme immunoassay (Fjirebio Inc., Tokyo, Japan).

Statistical analysis

To compare the differences of time courses between the two treatment groups, we used a linear mixed model analysis adjusted for the baseline and age, with group and month interaction ($G \times M$). Difference from the baseline in each group was compared by paired *t*-tests with the Bonferroni correction. The baseline characteristics of the subjects were compared between the two groups by the Mann–Whitney

U-test and *t*-test. All tests were performed with a two-sided α level of 0.05 and analyzed using the Statistical Package for the Social Sciences (SPSS) 16.0J (SPSS Japan Inc., Tokyo, Japan).

Results

The baseline characteristics of the subjects are shown in Table 1. Age, interval of administration, categories of the AMS scale (total score), IIEF-5, SRQ-D and ADAM questionnaire were comparable between the LER and Kampo groups. However, the mean psychological sub-score in AMS scale of the LER group was significantly lower than that of the Kampo group (Table 2).

Table 2 shows scores of the AMS, IIEF-5, SRQ-D and ADAM questionnaire after 3 and 6 months of treatment. The somatic sub-score in the AMS scale significantly decreased after 3 and 6 months in both the treatment groups. However, the decrease slope for the LER group was greater than that in the Kampo group, and there was a significant difference between the treatment groups (G) and the group and month interaction (G × M), as revealed by the linear mixed model

Table 1. Baseline characteristics of subjects.

	LER (*n* = 21)	Kampo (*n* = 25)	*p* Value
Age – years, mean (SD)	61.9 (11.4)	63.7 (12.5)	0.61†
Range	37–85	40–84	
Interval of administration – day, mean (SD)	181 (15.5)	184 (35.7)	0.68†
AMS scale (total score) categories – no. (%)			
Severe (score 50+)	7 (33%)	12 (48%)	
Moderate (score 37–49)	10 (48%)	9 (36%)	0.38‡
Mild (score 27–36)	4 (19%)	4 (16%)	
No (score ≤26)	0 (0%)	0 (0%)	
IIEF-5 categories – no. (%)			
Severe (score ≤7)	16 (76%)	16 (64%)	
Moderate (score 8–11)	4 (19%)	4 (16%)	
Mild to moderate (score 12–16)	1 (5%)	3 (12%)	0.26‡
Mild (score 17–21)	0 (0%)	2 (8%)	
No ED (score 22–25)	0 (0%)	0 (0%)	
SRQ-D categories – no. (%)			
Masked depression (score 16+)	3 (14%)	5 (20%)	
Borderline depression (score 11–15)	7 (33%)	5 (20%)	0.80‡
No (score ≤10)	11 (52%)	15 (60%)	
ADAM questionnaire			
Positive (''yes'' to question 1 or 7 or any 3 other questions) – no. (%)	21 (100%)	25 (100%)	

The *p* values were calculated by *t*-test† or Mann–Whitney *U*-test‡ to compare between the groups.
LER, LEOPIN ROYAL®; AMS, Aging Males' Symptoms; IIEF-5, International Index of Erectile Function with 5 questions; SRQ-D, Self-Rating Questionnaire for Depression; ADAM, Androgen Deficiency in Aging Males; ED, erectile dysfunction.

Table 2. Time courses of scores related symptoms of aging in males.

	Treatment group	Score – mean (SD)			*p* Value	
		Baseline	3 months	6 months	G	G × M
AMS scale						
Somatic sub-score	LER	20.4 (5.1)	15.2 (4.1)*	13.8 (4.1)*	<0.01	<0.01
	Kampo	22.4 (5.1)	21.3 (5.5)*	20.0 (5.2)*		
Psychological sub-score	LER	10.6 (3.9) †	8.5 (3.1)	8.0 (2.8)*	<0.01	0.047
	Kampo	13.2 (4.4)	13.0 (3.9)	12.7 (3.4)		
Sexual sub-score	LER	15.5 (5.0)	15.2 (4.0)	14.5 (3.9)	0.47	0.79
	Kampo	15.6 (3.5)	14.8 (4.0)*	14.4 (3.7)*		
Total score	LER	46.5 (11.4)	38.9 (8.9)*	36.2 (8.5)*	<0.01	0.048
	Kampo	51.2 (12.1)	49.0 (12.4)*	47.0 (11.4)*		
IIEF-5 score	LER	5.6 (3.3)	8.4 (6.1)*	7.5 (5.7)	0.041	0.019
	Kampo	6.5 (5.1)	6.7 (4.6)	6.4 (5.0)		
SRQ-D score	LER	10.3 (5.4)	8.8 (4.5)	9.0 (5.2)	0.50	0.55
	Kampo	9.9 (5.9)	9.3 (5.5)	9.0 (5.2)		
ADAM questionnaire	LER	21 (100%)	19 (90%)	20 (95%)		
Positive – no. (%)	Kampo	25 (100%)	24 (96%)	24 (96%)		

The *p* values were calculated by the linear mixed model analysis adjusted for the baseline and age to compare between the treatment groups (G) and the group and month interaction (G × M).
†*p* < 0.05 compared between the two groups at the baseline by *t*-test.
*p < 0.05 compared with the baseline in each group by paired *t*-tests with the Bonferroni correction.
LER, LEOPIN ROYAL®; AMS, Aging Males' Symptoms; IIEF-5, International Index of Erectile Function with 5 questions; SRQ-D, Self-Rating Questionnaire for Depression; ADAM, Androgen Deficiency in Aging Males.

Table 3. Endocrinologic values before and after treatments of LER and Kampo.

	Treatment Group	Serum level – mean (SD)			*p* Value
		n	Baseline	6 months	
Testosterone (ng/mL)	LER	18	3.28 (2.03)	3.44 (2.08)	0.51
	Kampo	14	3.60 (0.82)	3.80 (0.75)	0.17
Free testosterone (pg/mL)	LER	18	7.89 (3.73)	9.32 (6.08)	0.24
	Kampo	11	7.67 (3.28)	6.99 (3.38)	0.10
FSH (mIU/mL)	LER	17	13.0 (12.7)	12.8 (10.8)	0.66
	Kampo	15	11.0 (5.1)	10.9 (4.6)	0.77
LH (mIU/mL)	LER	16	5.41 (5.06)	5.31 (4.45)	0.85
	Kampo	11	6.70 (4.24)	6.28 (3.59)	0.48
PRL (ng/mL)	LER	13	7.56 (3.62)	8.10 (7.49)	0.83
	Kampo	12	4.85 (1.52)	4.93 (0.76)	0.89
E2 (pg/mL)	LER	5	36.0 (32.4)	32.8 (28.6)	0.18
	Kampo	10	15.8 (3.4)	16.4 (3.0)	0.44

The *p* values were calculated by paired *t*-test.
LER, LEOPIN ROYAL®; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; E2, estradiol.

analysis. The declines in the psychological sub-score and the total score in the AMS scale of the LER group were greater than those in the Kampo group, and the *p* values of G and G × M were less than 0.05. The IIEF-5 score increased in the LER group, and G and G × M showed significant differences. There was no inter-group difference in sexual sub-score in the AMS scale, SRQ-D and ADAM questionnaire. The serum levels of hormones showed no significant change in either group (Table 3).

Adverse events were noted in two cases of the LER group (epigastric discomfort and skin rash); no causal relationship of epigastric discomfort with LER was established, and that of skin rash with LER remains unclear.

Discussion

In the present study, somatic and psychological symptoms of aging in males showed greater improvement in the LER group than in the Kampo group. Further, only those subjects who were treated with LER reported an improvement in ED, as measured by the IIEF-5.

Kampo medications have been often used in male patients with LOH-related symptoms. Saikokaryukotsuboreito has been reported to be effective for eugonadal patients with LOH-related symptoms [10]. In the cases of severe nervousness, anxiety or irritation, Yokkansan (*Yi Gan San*) and keishikaryukotsuboreito (*Gui Zhi Jia Long Gu Mu Li Tang*) are used. Hachimijiogan, goshajinkigan and hochuekkito are used for ED. Kamishoyosan and hangekoubokuto are known to be medications for females, but these medicines are also used for males with somatic symptoms such as hot flashes and sweating abnormalities [11].

The LER formulation used in this study contains six crude extracts. AGE is one of the extracts that has several pharmacological actions. Kasuga et al. [1] have reported that AGE significantly enhanced sexual behaviors (mounting and intromission) and spermatogenesis in mice with testicular hypogonadism induced by warm water treatment. Nitric oxide (NO) is a trigger to increase blood flow into the corpus cavernous at erection. Morihara et al. [12] indicated that AGE temporarily increased NO production in the plasma of mice, and that the amelioration of NO induced by AGE was due

to constitutive activation of NO synthases. Flow-mediated dilation (FMD) is known to reflect NO-mediated endothelial function. AGE was reported to increase the FMD in patients with coronary artery disease [13] and acute hyperhomocysteinemia induced by an oral methionine challenge in healthy subjects [14]. AGE also has effects on psychological stress. Kyo et al. [15] found a protective effect of AGE on damaged immune function caused by psychological stress induced by a communication box. Psychologically stressed mice showed decreased immune functions, which was restored by AGE. In addition, AGE has been reported to have anti-aging effects on the Senescence-accelerated mice (SAM); AGE extended survival and improved the learning and memory impairment of the SAM [16].

Panax ginseng is an important herbal medicine and is frequently blended in Kampo medications considered tonics. Jang et al. [2] performed a systematic review based on randomized clinical studies of red ginseng and provided evidence suggestive of the effectiveness of red ginseng in the treatment of ED. Ginseng has several pharmacological actions. Gillis [17] reported that the antioxidant and organ-protective actions of ginseng are linked to enhanced NO synthesis in the endothelium of the lung, heart, and kidney and in the corpus cavernosum, and that the enhanced NO synthesis could contribute to ginseng-associated vasodilation and perhaps also to an aphrodisiac action of the root.

Traditionally, the epimedium herb (Ikariso in Japanese, *Yinyanghuo* in Chinese), cuscuta seed (Toshishi, *Tusizi*) and velvet antler (Rokujo, *Lurong*) have been used as an aphrodisiac in East Asia [3]. Makarova et al. [18] reported that oral administration of a lipid-based suspension of *Epimedium koreanum* extract improved erectile function (intromissions and ejaculation) in aged rats. It is well known that icariin is an active ingredient in *Epimedium* sp. The pharmacological actions of icariin on erectile function have been reported to be mediated by the inhibition of cGMP-specific phosphodiesterase 5 (PDE5) *in vitro* [19], expression of NO synthase in castrated rats [20] and increment of serum testosterone levels in cyclophosphamide-treated rats [21].

The flavonoids extracted from the Semen Cuscutae have been reported to increase the weight of testis, epididymis, pituitary gland, stimulated testosterone and LH secretion in

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male rats [22], and reversed the reduction of testosterone level and expression of androgen receptor gene in kidney-yang deficient mice [23]. Velvet antler has been reported to increase the weight of testis and prostate in castrated rats [24]. Oriental Bezoar (Goo, *Niuhuang*) is a dried gallstone of *Bos taurus domesticus* Gmelin, and is widely used in cardioactive over-the-counter (OTC) drugs in Japan [25].

There are two reports on the effect of LER, containing crude extracts of these natural products, on ED. Ushijima et al. [26] indicate a spermatogenesis-enhancing effect of LER on mice with testicular hypogonadism induced by warm water treatment, and Yaguchi et al. [27] reported that, of the 16 patients with unidentified complaints, one with ED showed a complete response to LER administration for 4 weeks.

In this study, even though the symptoms of aging in male were improved by LER administration, there was no change in the serum androgen level. As described above, the active ingredients in epimedium herb and cuscuta seed have been reported to have a serum testosterone increasing action in animal experiments. However, there is no report on the optimal doses of the action in human. As the dosage of the herbal medicines was not enough, a significant increase in serum testosterone may have not been observed during LER treatment. It has been reported that serum testosterone level does not correlate with erectile function and hypogonadism symptoms [28–31]. The effect of LER may be due to mechanisms other than androgen, for example, peripheral vasodilation by promoting NO synthesis.

Conclusion

Although this study is an open-labeled trial, our data indicate that LER is a safe medication and possibly superior to mainly kamishoyosan on the improvement of somatic and psychological symptoms of aging including ED for elderly male patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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RESEARCH ARTICLE

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Long-term results of radical prostatectomy with immediate adjuvant androgen deprivation therapy for pT3N0 prostate cancer

Yuzuri Tsurumaki Sato[1], Hiroshi Fukuhara[1*], Motofumi Suzuki[1], Tetsuya Fujimura[1], Tohru Nakagawa[1], Hiroaki Nishimatsu[1], Haruki Kume[1], Teppei Morikawa[2], Masashi Fukayama[2] and Yukio Homma[1]

Abstract

Background: Radical prostatectomy is used to treat patients with clinically localized prostate cancer, but there have been few reports of its use in locally advanced disease. We evaluated the long-term results of radical prostatectomy and immediate adjuvant androgen deprivation therapy in Japanese patients with pT3N0M0 prostate cancer.

Methods: We retrospectively reviewed 128 patients with pT3N0M0 prostate cancer who underwent radical prostatectomy at our institute from 2000 to 2006. All pT3N0 patients were treated with adjuvant androgen deprivation therapy shortly after radical prostatectomy. Immediate adjuvant androgen deprivation therapy was continued for at least 5 years. Twenty-three were excluded because of preoperative hormonal therapy, missing data, or others. Death from any cause, death from prostate cancer, clinical recurrence and hormone-refractory biochemical progression were analyzed by Kaplan-Meier graphs. Relative risks of progression were estimated using Cox proportional hazards models with 95% confidence intervals.

Results: The 10-year hormone-refractory biochemical progression-free survival rate was 88.3% and the cancer-specific survival rate was 96.3% after a median follow-up period of 8.2 years (range 25.6-155.6 months). Higher clinical stage (p = 0.013), higher Gleason score at biopsy (p = 0.001), seminal vesicle invasion (p = 0.003) and microlymphatic invasion (p = 0.006) were predictive factors for hormone-refractory biochemical progression by univariate analyses. Multivariate analyses identified Gleason score at biopsy (p = 0.027) and seminal vesicle invasion (p = 0.030) as independent prognostic factors for hormone-refractory biochemical progression. None of the patients with clinical T1 cancers (n = 20), negative surgical margin (n = 12), or negative perineural invasion (n = 11) experienced hormone-refractory biochemical progression.

Conclusions: Radical prostatectomy with immediate adjuvant androgen deprivation therapy may be a valid treatment option for patients with pT3N0M0 prostate cancer.

Keywords: Adjuvant androgen deprivation therapy, Pathological T3, Prognosis, Prognostic factor, Prostate cancer, Radical prostatectomy

Background

Tumor cell penetration of the prostatic capsule or invasion of the seminal vesicle is recognized as locally advanced prostate cancer of pathological T3N0. Patients with pT3N0 prostate cancers have the potential to suffer from disease relapse, and radical prostatectomy alone

may fail to achieve a cure. The introduction of prostate specific antigen (PSA) assays means that more patients now undergo radical prostatectomy at earlier stages. However, pT3 disease still occurs in 25–58% of clinical T1 and T2 prostate cancer patients [1-4]. Although the management of patients with pT3 prostate cancer remains controversial, some reports recommend the use of adjuvant therapies in these patients [5-9]. Few studies have reported treatment outcomes of pT3 cancers, but some clinico-pathologic factors, such as higher Gleason score, higher

* Correspondence: hfukuhara-jua@umin.ac.jp
[1]Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Full list of author information is available at the end of the article

PSA level and seminal vesicle invasion are considered to be prognostic factors associated with poorer outcome [10-13]. However, to the best of our knowledge, there have been few reports of pT3N0 patients treated with adjuvant hormonal therapy, and more outcome data and accurate information are needed for these patients. We therefore analyzed clinical data from patients with pT3N0 prostate cancer to obtain detailed information and long-term outcome data. Importantly, a pathologic diagnosis of pT3N0M0 cancer is not necessarily accurate in patients who have undergone preoperative therapy, and this study therefore only included patients who had not received any preoperative treatment.

Methods
We retrospectively reviewed 128 patients with pT3N0M0 out of a total of 431 patients with prostate cancer who underwent radical prostatectomy at our hospital from January 2000 to December 2006. These patients were selected because immediate adjuvant hormonal therapy was applied in patients with pT3N0M0 prostate cancer during this period. Twenty-three patients were excluded from the analysis; four because of incomplete data, 12 because they had received preoperative hormonal therapy and seven because they had received bicalutamide only or estramustine as hormonal therapy. Data from the remaining 105 patients were analyzed. Bilateral obturator lymph nodes were dissected in all patients at radical prostatectomy. Immediate adjuvant androgen deprivation therapy was started within 12 weeks of radical prostatectomy. Undetectable PSA levels or PSA nadir were not required to be confirmed following radical prostatectomy. Clinical diagnosis was defined according to the 2009 TNM guidelines based on a digital rectal examination (DRE), transrectal ultrasonography, biopsy results, computed tomography scans and/or magnetic resonance imaging, and bone scintigraphy. All specimens were reviewed by a single pathologist. After radical prostatectomy, patients were followed-up at 1-month intervals for the first 3 months following surgery, then at 3-month intervals for 5 years, and finally at 3–6-month intervals thereafter. Follow-up examinations included measurement of PSA levels, and a DRE, computed tomography scan, magnetic resonance imaging or bone scintigraphy in the event of suspected disease recurrence. Immediate adjuvant therapy included surgical orchiectomy, administration of luteinizing hormone-releasing hormone (LHRH) analogs, and combined androgen blockade consisting of orchiectomy or an LHRH analog together with anti-androgens. Immediate adjuvant androgen deprivation therapy was continued for at least 5 years after radical prostatectomy. Salvage additive or altered hormonal therapies were initiated when the PSA level rose rapidly by >0.4 ng/ml, or when it rose consistently by >0.2 ng/ml for more than three consecutive visits. Salvage additive or altered hormonal therapy included: 1) combined androgen blockade consisting of orchiectomy or LHRH analog with bicalutamide; 2) suspension of bicalutamide to confirm the effects of anti-androgen withdrawal; 3) estramustine; and 4) dexamethasone.

Hormone-refractory biochemical progression was defined as a PSA level >0.2 ng/ml despite the above hormonal therapies. Clinical recurrence was defined as recognizable disease relapse on imaging examination. Clinical recurrence was treated by salvage radiation therapy. This study was approved by the Ethics Committee, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo.

The study end points were death from any cause, death from prostate cancer, clinical recurrence, and hormone-refractory biochemical progression. These end points were analyzed by plotting Kaplan-Meier graphs and comparing them according to each clinicopathologic factor using log-rank tests. Relative risks for hormone-refractory biochemical progression according to each clinicopathologic factor were estimated using the Cox proportional hazards models with 95% confidence intervals. All statistical analyses were performed using JMP version 9 (SAS Institute, Cary, NC, USA) and differences were considered statistically significant at $p < 0.05$. The following clinicopathologic factors were evaluated: age at radical prostatectomy, preoperative PSA level, preoperative T stage (clinical stage), Gleason score of the biopsy specimen, seminal vesicle invasion (representing stage pT3b), surgical margin of operation specimen, microlymphatic invasion, microvascular invasion, perineural invasion, and Gleason score.

Results
The clinical and pathological data for all 105 patients are shown in Table 1. The median age at surgery was 67.0 years and the median preoperative PSA level was 15.1 ng/ml (range 3.5–160.7, with lower and upper quartile values of 8.18 and 24.9). The median number of lymph nodes removed was 7.0 (range 2–19). A total of 43% of patients were underestimated preoperatively as having stage T1 (n = 20; 19.0%) or T2 (n = 25; 23.8%) tumors. Regarding the Gleason score at biopsy, 38 (36.2%) patients had a score of ≥8. Seminal vesicle invasion (pT3b) was detected in 42 patients (40.0%). Microlymphatic and microvascular invasions were detected in 33 (31.4%) and 51 (48.6%) patients, respectively. Immediate adjuvant androgen deprivation therapy consisted of androgen suppression with orchiectomy (n = 17), LHRH analog (n = 64), combined androgen blockade with orchiectomy or LHRH analog and bicalutamide or other anti-androgens (n = 24). Three patients changed their hormonal therapies during follow-up because of adverse events.

The median follow-up period was 98.7 months (range 25.6–155.6). During the follow-up period, eleven patients

(10.5%) experienced hormone-refractory biochemical progression. Seven patients experienced clinical recurrence and received salvage radiation therapy to clinically recurrent foci. Three (2.9%) patients died of prostate cancer and eight (7.6%) died of other causes. The 5- and 10-year cancer-specific survival rates were 98.1 and 96.3%, respectively. The 5- and 10-year hormone-refractory biochemical progression-free survival rates were 94.3 and 88.3%, with 5- and 10-year clinical recurrence-free survival rates of 96.0 and 93.0%, respectively. The 10-year estimated overall survival rate was 85.7%.

Table 2 shows the hormone-refractory biochemical progression-free survival rates calculated from Kaplan-Meier graphs, according to each clinicopathologic parameter. Univariate analyses using Cox proportional hazard models indicated that higher clinical stage (p = 0.013), higher Gleason score at biopsy (p = 0.001), seminal vesicle invasion (p = 0.003) and microlymphatic invasion (p = 0.006) were predictive factors for hormone-refractory biochemical progression (Table 2). Multivariate analyses

Table 1 Patient characteristics (n = 105)

Parameter		n	(%)
Age, years (median 67.0)	<65	37	35.2
	≥65	68	64.8
PSA, ng/ml [median 14.3 (2.4 − 160.7)]	<10	35	33.3
	10~20<	36	34.3
	20~50<	23	21.9
	≥50	11	10.5
Clinical stage	T1	20	19.0
	T2	25	23.8
	T3	59	56.2
	T4	1	1.0
Gleason score at biopsy	5~6	34	32.4
	7	33	31.4
	≥8	38	36.2
Seminal vesicle invasion	−	63	60.0
	+	42	40.0
Surgical margin	−	12	11.4
	+	93	88.6
Microlymphatic invasion	−	72	68.6
	+	33	31.4
Microvascular invasion	−	54	51.4
	+	51	48.6
Perineural invasion	−	11	10.5
	+	94	89.5
Gleason score at prostatectomy	5~6	16	15.2
	7	54	51.4
	≥8	35	33.3

identified Gleason score at biopsy and (p = 0.027) seminal vesicle invasion (p = 0.030) as independent prognostic factors for hormone-refractory biochemical progression (Table 2).

Discussion

Despite widespread use of PSA measurement, pT3N0M0 prostate cancer still occurs in 25–58% of clinical T1 and T2 prostate cancer patients [1-4]. In the current study, about half of the patients (43%) were also understaged preoperatively as having organ-confined disease. Although pT3N0M0 prostate cancer is not rare, there have been few reports of treatment outcomes in these patients. The optimal postsurgical management for patients with such unfavorable pathological features remains questionable. We therefore analyzed clinical data from patients with pT3N0M0 prostate cancer to obtain detailed information and long-term outcome data.

The patients in this study achieved 5- and 10-year cancer-specific survival rates of 98.1 and 96.3%, respectively, and 5- and 10-year hormone-refractory biochemical progression-free survival rates of 94.3 and 88.3%, respectively. In a previous study, Inagaki et al. reported 1- and 3-year biochemical progression-free survival rates of 53.7 and 34.1% in 106 patients with pT3N0M0 prostate cancer treated with radical prostatectomy alone, after a mean follow-up of 1.5 years [10]. Delongchamps et al. and Briganti et al. reported 5-year biochemical progression-free survival rates of 48 and 45.0% in 147 and 500 patients with pT3N0M0 prostate cancer, respectively, treated with radical prostatectomy alone, after median follow-up periods of 5 and 3.9 years [11,12]. Thompson et al. reported 10-year metastasis-free survival rates and overall survival rates of 61 and 66% in 211 patients with pT3N0M0 prostate cancer treated with radical prostatectomy, even after salvage radiotherapy [5]. Single-modality therapy involving surgery alone might be of limited use in patients with stage pT3N0M0 prostate cancer, and a multimodal approach may be more beneficial. Three studies found that adjuvant radiotherapy after radical prostatectomy reduced the risk of subsequent biochemical recurrence in randomized clinical trials [5-7]. Thompson et al. reported a survival benefit of adjuvant radiotherapy, with a 10-year estimated survival rate of 74% in 214 patients with pT2-3 N0 prostate cancer treated with adjuvant radiotherapy, compared with 66% in 211 cases treated with surgery alone, after median follow-up period of 12.5 years [5,6]. This cohort included patients with pT3N0 and pT2N0 with positive surgical margins, and patients were allowed to receive salvage hormonal therapy during the follow-up period. Regarding the combination of radical prostatectomy and adjuvant hormonal therapy, Dorff et al. reported favorable outcomes in an interim report of a prospective randomized trial of 481