Index（UCLA PCI)日本語版作成の試み。日本泌尿器科学会誌　93 巻　659-668、2002年

19.　付表 Appendix

・説明文書・同意書

・Performance status scale　（ECOG）

・毒性規準（NCI-CTC 日本語訳 JCOG 版）（省略）

・薬剤添付文書（省略）

・ケースレポートフォーム一式

・QOL 調査票（SF36 ver2.0 日本語版、UCLA-PCI ver1.3 日本語版）

付表：Performance Status

ECOG の Performance Status（PS）の日本語訳

Performance Status の Grade

Grade	Performance Status
0	全く問題なく活動できる。 発病前と同じ日常生活が制限なく行える。
1	肉体的に激しい活動は制限されるが、歩行可能で、軽作業や座っての作業は行うことができる。例：軽い家事、事務作業
2	歩行可能で自分の身の回りのことはすべて可能だが作業はできない。 日中の50%以上はベッド外で過ごす。
3	限られた自分の身の回りのことしかできない。 日中の50%以上をベッドか椅子で過ごす。
4	全く動けない。自分の身の回りのことは全くできない。 完全にベッドか椅子で過ごす。

この規準は全身状態の指標であり、局所症状で活動性が制限されている場合は、臨床的に判断する。

症例の観察期間は 3.8 年と比較的短いが、PSA 再発を来した症例が 25.1％あり、再発までの期間の中央値は術後 365 日であった。その後の治療法は、内分泌療法 23.2％、放射線療法 20.5％、両者 2.7％、経過観察のみ 22.8％、不明 30.8％であった。また、術後病理病期は pT3 以上 32.6％あり、欧米と同様に術前の臨床病期での under staging が問題と考えられた。予後に関しては、明らかな癌死は 7 名のみであり、極めて良好であった。

D．考察
1）患者登録は各施設の IRB 承認を得なければならないため、本年度は登録症例数が少ないが、今後積極的に患者登録を進めて行きたい。この検討により、PSA 再発症例に対する治療指針が確立されれば、一部の患者においては内分泌療法や放射線療法を避けることによって副作用が回避できるのみならず、最終的には医療費の軽減にもつながるものと期待される。

2）日本人は、欧米に比べ前立腺癌の発症頻度は低いことが知られているが、限局性前立腺癌対する根治術後のアウトカムは欧米のそれとほぼ同等の結果となっている。

E．結論=JCOGにプロトコールの承認を受け、各施設の倫理委員会の承認を得て、患者登録を開始し、7名の患者登録を得た。
2）アウトカム研究として、根治的前立腺摘除術後のPSA再発を来した症例が25.1％あり、そのアウトカムは欧米とほぼ同等である。

F．研究発表
1．論文発表
Yokomizo A, Tobisu K, Kawamoto H, Nihei K, Ishizuka N, Naito S. Randomized Controlled Trial to Evaluate Radiation plus Endocrine Therapy or Endocrine Therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG 0401. *Jpn. J. Clin. Oncol.*, 35:34-36, 2005.

横溝　晃、古賀寛史、此元竜雄、蔦巣賢一、内藤誠二. 早期前立腺がんに対する根治術後のPSA再発症例の統計解析.泌尿器外科　12(8), 881-886, 2004.

2．学会発表
1) Seiji Naito, TREATMENT OF PATIENTS WITH PSA RECURRENCE AFTER REDICAL PROSTATECTOMY. January 25, 2005. The 18th International Symposium of Foundation for Promotion of Cancer Research.

2) 内藤誠二、「早期前立腺がんにおける根治術

後の再発に対する標準的治療法の確立にかんする研究」2005 年 2 月 15 日、がん臨床研究成果発表会（研究者向け）にて発表。

3）横溝　晃、古賀寛史、此元竜雄、内藤誠二、JCOG泌尿器科腫瘍研究グループ。早期前立腺がんにおける根治術後の再発に関するoutcome study、2003年10月22日、第41回日本癌治療学会総会にて発表。

4）本の早期前立腺がん根治手術後の再発に関するアウトカム研究。2005年4月14日、第93回日本泌尿器科学会総会で発表予定。

G．知的財産権の出願・登録状況
1．特許取得　なし
2．実用新案登録　なし。

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takahashi A, Yanase M, Masumori N, et al.	External beam radiation monotherapy for localized or locally advanced prostate cancer.	Jpn. J. Clin. Oncol.	33	73-77	2003
Akaza H, Homma Y, Okada K et al.	Prostate Cancer Study Group. A prospective and randomized study of primary hormonal therapy for patients with localized or locally advanced prostate cancer unsuitable for radical prostatectomy: results of the 5-year follow-up.	BJU Int.	91	33-36	2003
Ito K, Yamamoto T, Ohi M et al.	Natural history of PSA increase with and without prostate cancer.	Urology	62	64-69	2003
Wang L, Habuchi T, Tsuchiya N et al.	Insulin-like growth factor-binding protein-3 gene -202 A/C polymorphism is correlated with advanced disease status in prostate cancer.	Cancer Res.	63	4407-4411	2003
Arai Y, Egawa S, Terachi T	Morbidity of laparoscopic radical prostatectomy: summary of early multi-institutional experience in Japan.	Int. J. Urol.	10	430-434	2003
Namiki S, Tochigi T, Kuwahara M et al.	Health-related quality of life after radical prostatectomy in Japanese men with localized prostate cancer.	Int. J. Urol.	10	643-650	2003
Akakura K, Suzuki H, Ueda T et al.	Possible mechanism of dexamethasone therapy for prostate cancer: suppression of circulating level of interleukin-6.	Prostate	56	106-109	2003

Yokomizo A, Tobisu K, Kawamoto H et al.	Randomized Controlled Trial to Evaluate Radiation plus Endocrine Therapy or Endocrine Therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG 0401.	Jpn. J. Clin. Oncol.	35	34-36	2005
Yamanaka H, Ito K, Naito S et al	Effectiveness of adjuvant intermittent endocrine therapy following neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer.	Prostate	63	56-64	2005
Nishiyama T, Hashimoto Y, Takahashi K.	The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer.	Clin Cancer Res.	10	7121-7126	2004
Akaza H, Usami M, Hinotsu S, et al.	Characteristics of patients with prostate cancer who have initially been treated by hormone therapy in Japan: J-CaP surveillance.	Jpn. J. Clin. Oncol.	34	329-336	2004
Hachiya T, Akakura K, Saito S, et al.	A retrospective study of the treatment of locally advanced prostate cancer by six institutions in eastern and north-eastern Japan.	BJU Int.	95	534-540	2005
Kikuno N, Moriyama-Gonda N, Yoshino T et al.	Blockade of paclitaxel-induced thymidine phosphorylase expression can accelerate apoptosis in human prostate cancer cells.	Cancer Res.	64	7526-7532	2004

External Beam Radiation Monotherapy for Localized or Locally Advanced Prostate Cancer

Atsushi Takahashi[1], Masahiro Yanase[1,2], Naoya Masumori[1], Hiroto Sasamura[1], Toshiro Oda[1], Toshiaki Tanaka[1], Naoki Itoh[1], Taiji Tsukamoto[1], Atsushi Oouchi[3], Masato Hareyama[3], Hiroki Shirato[4], Keiji Takatsuka[2] and Noriomi Miyao[5]

[1]Departments of Urology and [3]Radiology, Sapporo Medical University School of Medicine, Sapporo, [4]Department of Radiology, Hokkaido University School of Medicine, Sapporo, [2]Department of Urology, Sunagawa City Medical Center, Sunagawa, Hokkaido and [5]Department of Urology, Muroran City General Hospital, Muroran, Hokkaido, Japan

Purpose: We report the treatment results and complications of external beam radiation monotherapy for localized or locally advanced prostate cancer patients.
Methods: Fifty-four patients with $T_{1b-3a}N_0(pN_0)M_0$ prostate cancer were treated with external beam radiation monotherapy between 1989 and 2001 at four institutes.
Results: During the 4–122 month follow-up period (median: 25 months), 11 (20%) patients experienced biochemical failure, including one with simultaneous local recurrence. The 2-year actuarial biochemical control rate was 85%. Univariate analysis showed that the clinical T classification ($P = 0.01$), Gleason score ($P = 0.006$), pretreatment PSA ($P = 0.02$) and PSA nadir value ($P = 0.01$) were associated with a higher probability of biochemical failure. Multivariate analysis using the Cox proportional hazards model demonstrated that only the PSA nadir value was a strong predictor of PSA recurrence ($P < 0.01$). Adverse events were mild and tolerable. No severe urinary or bowel complications were observed.
Conclusions: External beam radiation monotherapy is effective for clinically organ-confined prostate cancer with a low incidence of severe complications in a mean follow-up period of 2 years.

Key words: external beam radiation – localized or locally advanced prostate cancer

INTRODUCTION

Definitive radiation therapy and radical prostatectomy have been considered the standard curative treatment for localized prostate cancer in the USA and Europe (1). In Japan, much attention has also recently been paid to radiation therapy as an alternative primary treatment. This may be due in part to the high success rate and limited adverse effects with recent innovations in radiation techniques. New strategies such as three-dimensional (3-D) conformal therapy and intensity modulated radiation therapy (IMRT) allow conformation to the shape of the prostate and minimize radiation exposure to normal tissue, resulting in a lower incidence of radiation-induced complications (2). In addition, these techniques are expected to permit radiation dose escalation in order to improve local control. Another reason for the attention may be the recent advances in and prevalence of transmission systems such as the Internet,

which can allow patients easily to obtain information about the treatment of prostate cancer around the world. In Japan, there are few reports about radical radiotherapy for localized prostate cancer (3,4). In this paper, we report on the efficacy and adverse effects of external beam radiation therapy alone in localized or locally advanced prostate cancer patients.

PATIENTS AND METHODS

Between 1989 and 2001, 54 patients with T_{1b-3a} prostate cancer were treated with external beam radiation alone at Sapporo Medical University Hospital, Hokkaido University Hospital, Sunagawa City Medical Center and Muroran City General Hospital. No patients received neoadjuvant or adjuvant hormonal therapy before biochemical failure or clinical failure. In principle, patients selected this modality based as their preference.

The external beam radiotherapy was delivered to the prostate using the conventional four-field box (anterior, posterior and right and left laterals) technique in 24 patients. The total dose ranged from 60 to 70 Gy (median, 65 Gy) in 24–30 fractions within 6–7.5 weeks. Thirty patients (56%) were treated with

Table 1. Patients' characteristics

Characteristic	No. of patients (%)
Age (years)	41–81 (mean: 71.3)
Clinical T classification	
T1b/1c	22 (41)
T2a/2b	23 (42)
T3a	9 (17)
Pretreatment PSA (ng/ml)	
≤10.0	16 (30)
>10.0	38 (70)
Gleason score	
≤6	40 (74)
>6	14 (26)
Lymph node dissection	
Yes	32 (59)
No	22 (41)
Type of radiotherapy	
Conventional	24 (44)
Conformal	30 (56)
PSA nadir level	
≤1.0	25 (46)
>1.0	29 (54)
Time to PSA nadir	3.1–55.1 (median: 14.4)
PSA half-life (M)	0.7–9.3 (median: 2.1)

Figure 1. Biochemical progression-free survival rate after external beam radiation for 54 patients with $T_{1b-3a}N_0(pN_0)M_0$ prostate cancer.

conformal techniques. Of these patients, 26 received a total dose of 70 Gy within 7 weeks with 10 MV X-rays in daily fractions of 2 Gy. For four other patients, radiotherapy was performed with 2.5 daily fractions for 6.5 weeks to give a total dose of 65 Gy.

Serum PSA was measured by the Hybritech assay, with a lower limit of detection of 0.2 ng/ml. Biochemical failure was defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel statement (5). Thus, three consecutive rises in PSA after reaching the PSA nadir were regarded as biochemical failure. The date of failure was the midpoint between the nadir and the first of the three rises in PSA. If hormonal therapy was given to patients prior to meeting the above criteria for failure, the patients were considered to suffer from biochemical failure at the time of initiation of hormonal therapy.

Late complications induced by radiation were scored using the Radiation Therapy Oncology Group (RTOG) toxicity scoring system, with grade 1 for minimal symptoms with no requirement of medication, grade 2 for slightly more severe symptoms with a need for medication, grade 3 for complications requiring minor surgical intervention such as transurethral resection, laser coagulation or blood transfusion and grade 4 for requirement of hospitalization and major intervention.
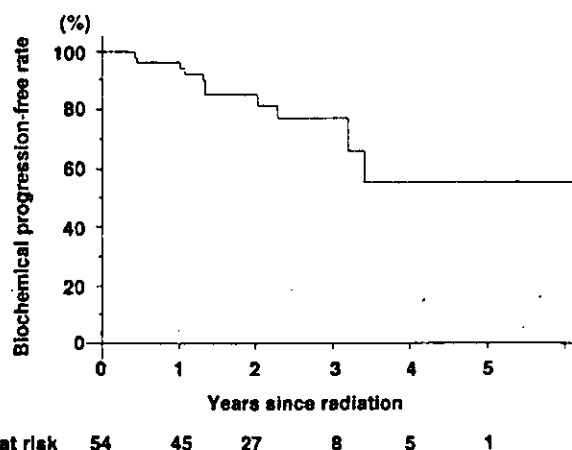
The time to biochemical failure was calculated from the date of completion of radiation to the date of PSA relapse. The biochemical progression-free rate was calculated by the Kaplan–Meier method. The statistical significance of differences was determined by the log rank test. A P-value of <0.05 was considered statistically significant. Multivariate analysis by Cox's proportional hazards model was performed to determine whether any variables independently affected biochemical failure. The variables studied were (1) patient age, (2) clinical T classification (T1b–2b or T3), (3) biopsy Gleason score (3–6 or 7–9), (4) pretreatment PSA (≤10 or >10), (5) total radiation dose, (6) PSA nadir value (≤1.0 or >1.0) and (7) PSA half-life. All analyses were performed using StatView 5.0 for Macintosh (SAS Institute, Cary, NC).

RESULTS

PATIENTS' CHARACTERISTICS

Patients' characteristics are shown in Table 1. The mean age at diagnosis was 71.3 years (range, 41–81 years). Of the 54 patients, 45 (83%) were diagnosed as having clinically localized prostate cancer (T1b–2b). Of all patients, 32 (59%) received staging lymphadenectomy, by which they were proved to be pathologically free of lymph node metastasis. The median pretreatment PSA level was 14.9 ng/ml (range, 1.4–80.5 ng/ml). The median Gleason score was 5 (range, 2–9). The follow-up period ranged from 4 to 122 months with a median of 25 months.

OUTCOME

During the follow-up period, 11 (20%) patients experienced biochemical failure. Of these, one had simultaneous local recurrence. The patient who experienced local recurrence had T3a with Gleason score 7. He received a total dose of 65 Gy in a conventional four-field box. Sixteen months after radiation, he had two consecutive PSA elevations and suffered from a

Table 2. Univariate and multivariate analyses for factors associated with biochemical failure

Variable	Univariate		Multivariate	
	PSA-free survival (%)ᵃ	P value	Hazards ratio	P value
T classification				
T1–2	89.0	0.01	4.15	0.09
T3a	64.8			
Gleason score				
≤6	90.8	0.005	1.62	0.52
>6	69.8			
Pretreatment PSA				
≤10.0	92.9	0.02	3.8	0.25
>10.0	81.0			
PSA nadir level				
≤1.0	95.5	0.01	17.79	0.02
>1.0	73.7			

ᵃAt 2 years.

Table 3. Complication rates of radiation therapy

	Grade				
	0	1	2	3	4
Gastrointestinal					
Conventional ($n = 24$)	12 (50)ᵃ	5 (21)	7 (29)	0	0
Conformal ($n = 30$)	20 (79)	8 (27)	2 (6)	0	0
Genitourinary					
Conventional ($n = 24$)	19 (79)	3 (13)	2 (8)	0	0
Conformal ($n = 30$)	27 (87)	2 (7)	1 (6)	0	0

ᵃNumber of patients (%).

ADVERSE EVENTS

Bowel and urinary toxicities were generally mild and tolerable (Table 3). There was a trend towards reduced toxicity with regard to gastrointestinal toxicity in the conformal radiation group when compared with the conventional radiation group. No grade 3 or higher toxicity was observed in either group.

weak urinary stream due to local recurrence. He received transurethral resection of the prostate and then hormonal therapy. No patients developed distant metastasis.

Of the 11 patients, seven met the criteria of ASTRO and the others underwent hormonal therapy before meeting the criteria because of rapid PSA elevation.

The 2-year actuarial biochemical control rate was 85% (Fig. 1). Of these patients with PSA failure, nine had biochemical failure within 25 months and the other two at 38 and 41 months, respectively. No death due to prostate cancer was observed during the follow-up period.

FACTORS AFFECTING BIOCHEMICAL RECURRENCE

By univariate analysis, the clinical T classification ($P = 0.01$), Gleason score ($P = 0.006$), pretreatment PSA ($P = 0.02$) and PSA nadir value ($P = 0.01$) were associated with a higher probability of biochemical failure (Table 2). Neither the total radiation dose nor PSA half-life predicted PSA failure in this study.

First, to identify if parameters before radiation can predict PSA failure, multivariate analysis by the Cox proportional hazards model was performed using age, preoperative PSA, clinical T classification and biopsy Gleason score. However, no parameter could predict biochemical failure. Next, when PSA nadir and PSA half-life were included in the multivariate analysis, the PSA nadir value was independently a strong predictor of PSA recurrence ($P < 0.01$). The 2-year actuarial biochemical control rates in patients with PSA nadir values ≤1.0 and PSA nadir values >1.0 were 95.5 and 73.7%, respectively.

DISCUSSION

Radiation therapy already occupies an important position as a curative treatment for organ-confined prostate cancer throughout the world (1), although there have been no prospective randomized trials that directly compared the clinical efficacy of radiation with radical surgery for the disease.

To date, retrospective studies have demonstrated that the 5-year biochemical progression-free rate in external beam radiotherapy alone ranges from 40 to 65% (6–9). A possible explanation for the wide variation in biochemical control may be the selection of different risk groups (i.e. pretreatment PSA, clinical T stage, Gleason score). Indeed, in a multi-institutional analysis of a total of 1765 patients with T1–2, the 5-year biochemical progression-free rate was as high as 65% (6). On the other hand, studies containing higher stage (T3) patients had lower biochemical control rates (7–9). In this study, 11 of the 54 patients (20%) experienced biochemical failure, with the 2-year biochemical control rate being 85%. Of the patients with PSA failure, nine (82%) failed within 25 months, suggesting that biochemical failure occurs relatively soon after treatment. Several studies with longer follow-up periods have also shown that most patients have an increasing risk of biochemical failure within 36 months, but few fail beyond 4 years (7,8). Therefore, despite the short follow-up in this study, our results are likely not to be overestimated. Of the 11 patients with PSA relapse, five had T3a (one with $T_{3a}pN_0M_0$ and four $T_{3a}N_0M_0$). If T3 patients were excluded from analysis, the 2-year biochemical progression-free rate became higher (89%). This finding is consistent with other workers' data (6–9), suggesting that radiation monotherapy for the treatment of clinical T3 prostate cancer does not represent a satisfactory modality. Since recent reports have demonstrated that the combination of androgen deprivation and radiation produced a significant

benefit for locally advanced prostate cancer (10,11), combining the two modalities may seem to be the standard approach for clinical T3 prostate cancer patients. However, at present, when and how long hormonal therapy should be added to radiation therapy remains unclear.

Several studies have demonstrated that the pretreatment PSA level, Gleason score, clinical T stage and PSA nadir level are significantly associated with biochemical failure (12–16). Our study showed that only the PSA nadir level was an independent predictor for PSA recurrence among the several parameters examined. While the importance of the PSA nadir is clear, in the clinical setting it is inconvenient to predict the outcome by the PSA nadir, because it usually takes a long time to determine it (mean: 14 months in this study). Therefore, we tried to examine whether the PSA half-life was a good parameter for predicting PSA recurrence. However, we failed to obtain a positive association between the PSA half-life and biochemical failure. This finding is in agreement with those of Ritter et al. (17) and Zagars and Pollack (18). The latter reported that the PSA half-life was correlated with the pretreatment PSA level, but did not predict disease outcome.

Since the survival outcome and biochemical control for radiation therapy and radical surgery seem to be comparable in localized prostate cancer (19,20), complications have increasingly become an important factor for decision making for treatment selection. Our study showed that radiation-induced complications were generally mild and acceptable. Conformal radiotherapy, especially, had a trend towards less toxicity when compared with conventional therapy. Several other studies support this result (21,22). Recently, investigators at the Memorial Sloan-Kettering Cancer Center reported that high-dose radiotherapy (75 Gy or higher) by 3-D conformal therapy and IMRT could be administered effectively in localized prostate cancer patients without increasing complications (23). In particular, IMRT allowed dose escalation to 81 Gy or higher with a lower incidence of rectal toxicity (grade 2: 2%) than 3-D conformal therapy (grade 2: 14%). Moreover, such ultra-high-dose radiation produced excellent results. Taken together with these results, we expect that these conformal techniques may become the gold standard for treating localized prostate cancer.

In summary, external beam radiation monotherapy is an effective and safe modality for managing clinically localized prostate cancer in Japan. Accumulating data on this modality with regard to survival outcome, complications and assessment of quality of life will help Japanese patients to select appropriate treatment.

Acknowledgement

References

1. Porter AT, Littrup P, Grignon D, Forman, J, Montie JE. Radiotherapy and cryotherapy for prostate cancer. In: Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, editors. Campbell's Urology, 7th ed., vol. 3. Philadelphia: Saunders 1998;2605–27.
2. Zelefsky MJ, Leibel SA, Kutcher GJ, Fuks Z. Three-dimensional conformal radiotherapy and dose escalation: where do we stand? *Semin Radiat Oncol* 1998;8:107–14.
3. Akakura K, Furuya Y, Suzuki H, Komiya A, Ichikawa T, Igarashi T, et al. External beam radiation monotherapy for prostate cancer. *Int J Urol* 1999; 6:408–23.
4. Kitamura K, Shirato H, Suzuki K, Shinohara N, Demura T, Harabayashi T, et al. The relationship between technical parameters of external beam radiation therapy and complications for localized prostate cancer. *Jpn J Clin Oncol* 2000;30:225–9.
5. American Society for Therapeutic Radiology and Oncology. Consensus statement: guideline for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035–41.
6. Shipley WU, Thames HD, Sandler HM, Hanks GE, Zietman AL, Perez CA, et al. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *J Am Med Assoc* 1999;281:1598–604.
7. Kestin LL, Vicini FA, Ziaja EL, Stromberg JS, Frazier RC, Martinez AA. Defining biochemical cure for prostate carcinoma patients treated with external beam radiation therapy. *Cancer* 1999;86:1557–66.
8. Hanlon AL, Hanks GE. Failure patterns and hazard rates for failure suggest the cure of prostate cancer by external radiation. *Urology* 2000;55: 725–9.
9. Aref I, Eapen O, Cross P. The relationship between failure and time to nadir in patients treated with external beam therapy for T1–3 prostate carcinoma. *Radiother Oncol* 1998;48:203–7.
10. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
11. Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of the Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 1997;15:1013–21.
12. Meek AG, Park TL, Oberman E, Wielopolski L. A prospective study of prostate specific antigen levels in patients receiving radiotherapy for localized carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1990;19: 733–41.
13. Hanks GE, Lee WR, Schultheiss TE. Clinical and biochemical evidence of control of prostate cancer at 5 years after external beam radiation. *J Urol* 1995;154:1850–7.
14. Zagars GK, Pollack A, von Eschenback AC. Prognostic factors for clinically localized prostate cancer. *Cancer* 1997;79:1370–80.
15. Critz FA, Levinson K, Williams WH, Holladay DA, Holladay CT. The PSA nadir that indicates potential cure after radiotherapy for prostate cancer. *Urology* 1997;49:322–6.
16. D'Amico AV, Whittington R, Mallkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation or interstitial radiation therapy for clinically localized prostate cancer. *J Am Med Assoc* 1998;280:969–74.
17. Ritter MA, Messing EM, Shanahan TG, Potts S, Chappell RJ, Kinsella TJ. Prostate-specific antigen as a predictor of radiotherapy response and patterns of failure in localized prostate cancer. Group Protocol 85-31. *J Clin Oncol* 1992;10:1208–17.
18. Zagars GK, Pollack A. Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. *Radiother Oncol* 1997;44:213–21.
19. Kupelian P, Katcher J, Levin H, Zippe C, Suh J, Macklis R, et al. External beam radiotherapy versus radical prostatectomy for clinical stage T1–2 prostate cancer; therapeutic implications of stratification by pretreatment PSA levels and biopsy Gleason scores. *Cancer J Sci Am* 1997;3:78–87.
20. Martinez AA, Gonzalez JA, Chung AK, Kestin LL, Balasubramaniam M, Diokno AC, et al. A comparison of external beam radiation therapy versus radical prostatectomy for patients with low risk prostate carcinoma diagnosed, staged and treated at a single institution. *Cancer* 2000;88:425–32.
21. Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. *Lancet* 1999;353:267–72.

22. Michalski JM, Purdy JA, Winter K, Roach M III, Vijayakumar S, Sandler HM, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000;46:391–402.

23. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001;166:876–81.

A prospective and randomized study of primary hormonal therapy for patients with localized or locally advanced prostate cancer unsuitable for radical prostatectomy: results of the 5-year follow-up

H. AKAZA[1], Y. HOMMA[2], K. OKADA[3], M. YOKOYAMA[4], M. USAMI[5], Y. HIRAO[6], T. TSUSHIMA[7], Y. OHASHI[8], Y. ASO[9] and the Prostate Cancer Study Group

Departments of Urology, [1]Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, [2]University of Tokyo, [3]Nihon University, [4]Toranomon Hospital, Tokyo, [5]Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [6]Nara Medical University, Kashihara, Nara, [7]Okayama University, Okayama, [8]Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo, and [9]Fujieda Municipal General Hospital, Fujieda, Shizuoka, Japan

OBJECTIVE

To evaluate the effect of primary hormonal therapy for patients with localized and locally advanced prostate cancer.

PATIENTS AND METHODS

Patients with stage T1b-T3 prostate cancer who were not scheduled for radical prostatectomy were allocated into two groups: group 1 (73 men) received luteinizing hormone-releasing hormone (LHRH) agonist monotherapy and group 2 (78 men) received LHRH agonist and chlormadinone acetate. Patients were followed using serum prostate specific antigen levels, prostate size and the detection of distant metastasis for 5 years.

RESULTS

The median (range) follow-up was 78 (63-87) months. The 5-year progression-free survival rate was significantly higher in group 2 (68%) than in group 1 (47%). However, the overall and cause-specific survival rate at 5 years were similar in both groups, at 72% and 93% in group 1, and 64% and 89% in group 2, respectively.

CONCLUSION

The overall survival rates of the both groups were no different from that of the normal Japanese population of the same age group. Although this study did not include an untreated group, i.e. watchful waiting, these results might indicate the usefulness of primary hormonal therapy in controlling localized and locally advanced prostate cancer. The 5-year observation period is still short and the study is continuing to determine the 10-year survival.

KEYWORDS

primary hormonal therapy, LHRH agonist, localized, locally advanced prostate cancer

INTRODUCTION

Radical prostatectomy is considered the 'gold standard' for treating localized and some cases of locally advanced prostate cancer. However, there are patients for whom radical prostatectomy is not an option for various reasons, e.g. those who are a poor risk for surgery, have a relatively short life-expectancy or who do not wish to undergo surgery. Primary hormonal therapy might be an option for such patients.

Since 1993 we have conducted a prospective randomized study of the effect of primary hormonal therapy on patients with T1b-T3 prostate cancer who were not scheduled for radical prostatectomy. We compared the effect of LHRH agonist monotherapy (group 1) with the concomitant use of an LHRH agonist and the steroidal antiandrogenic agent chlormadinone acetate (CMA) (group 2). In our initial report [1], the 2-year progression-free survival (PFS) of group 2 was significantly higher than that of group 1, which suggested an additive effect of CMA with LHRH agonist. In this report, we present the 5-year follow-up results.

PATIENTS AND METHODS

Patients with T1b, T1c, T2a, T2b or T3 prostate cancer (1997 TNM classification [2]) who were not scheduled for radical prostatectomy for various reasons [1] were enrolled. Cancer stages were determined using biopsy, ultrasonography and/or CT. Bone scintigraphy and/or CT were used to determine the absence of distant metastasis before enrolment. Examinations before treatment confirmed a serum testosterone level of ≥1 ng/mL and a performance status of grade 0-3 [3]. Written consent to participate in the study was obtained from all patients before initiating treatment.

Between February 1993 and March 1995, 178 patients were enrolled at the participating institutions; they were randomly allocated to two groups using the dynamic balancing method to ensure equal distributions of cancer stage and grade of histological differentiation among the groups. Patients in group 1 were given LHRH agonist monotherapy (leuprorelin acetate depot, 3.75 mg monthly) and those in group 2 LHRH agonist plus CMA (100 mg/day) for the first 2 years. Treatment after the 2-year follow-up was subject to change according to physician or patient preference. Of the 90 patients allocated to group 1 and of the 88 allocated to group 2, 17 and 10 were excluded from

analysis because of ineligibility or protocol violation, respectively, as previously reported [1]. Thus the analysis included 73 patients in group 1 and 78 in group 2.

In the initial 2 years serum levels of PSA and testosterone were measured using the Delfia PSA (Wallac Oy, Finland) and a radioimmunoassay, respectively, before and after 12 weeks of treatment, and then at 3-month intervals. After 2-years of follow-up, PSA was measured at each institution using the individual assay kit chosen. Prostate size was measured using TRUS or CT, and bone scintigraphy and/or CT was used to detect distant metastasis.

Recurrence was defined as the identification of any of three clinical features, i.e. imaging findings confirming distant metastasis, an increase of PSA level by ≥25% of nadir values, or an increase in prostate size by ≥25% of nadir values from bidimensional measurements.

Student's t-test or the Mann–Whitney U-test was used, depending on data type, to assess differences. Survival and PFS were analysed using the Kaplan-Meier method, and the results assessed using the log-rank test and the generalized Wilcoxon test; $P < 0.05$ was considered to indicate significance.

RESULTS

The median (range) follow-up was 78 (63-87) months; the characteristics of the patients are shown in Table 1. Over 40% of patients were staged T3 in both groups, and 11% and 17% of patients were diagnosed as poorly differentiated in group 1 and 2, respectively.

There was recurrence in 39 and 23 patients in group 1 and 2, respectively; among these patients, distant metastasis was confirmed in 12 and 11 in group 1 and 2, respectively (Table 1). The 5-year PFS rate was 47% in group 1 and 68% in group 2; there was a significant difference between the groups (Fig. 1a). Twenty-four patients in group 1 and 26 in group 2 died during the follow-up; of these, four in group 1 and six in group 2 died from prostate cancer (Table 1). The overall survival rate at 5 years was 72% and 64% (Fig. 1b) and the cause-specific survival rate 93% and 89%, respectively (Fig. 1c). The overall survival rate of both groups was no different from that of the normal Japanese population of the same age group (Fig. 1b).

Variable	Group 1	Group 2
Number	73	78
Age, years (SD)	76.1 (6.7)	75.2 (6.4)
Clinical stage, n		
T1b,c	9	11
T2a	13	14
T2b	20	16
T3	31	37
Histological differentiation, n		
Well	26	27
Moderate	39	38
Poor	8	13
Pretreatment PSA level, ng/mL		
mean (SD)	52.4 (103.5)	151.5 (742.4)
median (range)	22.7 (0.6-711)	22.4 (0.8-6350)
5-year outcome, n		
Alive	49	52
Dead	24	26
Prostate cancer death	4	6
Other cancer death	7	3
Not cancer death	13	17
Recurrence	39	23
Distant metastasis	12	11
Elevation of PSA level or increase in prostate size	27	12

TABLE 1
The characteristics of the patients and the 5-year outcome

The serum testosterone levels of group 2 were significantly lower than those of group 1 in first 2 years (Fig. 2).

DISCUSSION

In Japan, primary hormonal therapy is commonly chosen for treating localized prostate cancer; even in the USA, 12.7% of 2216 patients with T2 prostate cancer received hormonal therapy alone [4]. However, because there is no clear evidence that it is effective, the use of primary hormonal therapy for localized prostate cancer is controversial. In the European Association of Urology Guidelines for Prostate Cancer, hormonal therapy is listed as an option for patients with T1b–T2b disease [5]. However, other Practice Guidelines for prostate cancer do not recommend hormonal therapy for patients with T1-T2 cancers [6].

The present study was conducted to clarify the effect of primary hormonal therapy on patients with T1b-T3 disease for whom radical treatment, e.g. surgery or radiation, was not indicated. At the 5-year follow-up, 10 of 151 patients died from prostate cancer, and

the 5-year cause-specific survival rate was 90%. Even though 45% of patients had T3 disease, this survival rate seems very high. However, because the mean age of the patients at enrolment was 76 years, 40 patients died from other causes, e.g. other cancers, pneumonia or cardiovascular disease. This may be one of the reasons why there were so few deaths from prostate cancer. The overall survival rate at 5 years was ≈70%; this rate was no different from that of the normal Japanese population of the same age group [7] (Figs 1b,c). Although the present study did not include an untreated group, i.e. watchful waiting, these results might indicate the utility of primary hormonal therapy in controlling localized and locally advanced prostate cancer.

Although there was no significant difference between the groups in survival, the 5-year PFS rate in group 2 was significantly higher than that of group 1. Serum testosterone levels after treatment were significantly lower in group 2 than in group 1, indicating that CMA enhances the testosterone-decreasing effect of the LHRH agonist. The LHRH agonist suppresses LH secretion from the pituitary gland by down-regulating LHRH receptors [8]. Steroidal antiandrogen suppresses LHRH

FIG. 1.

Survival curves for a, progression-free; b, overall; and c, cause-specific survival, in group 1 (red dashed line) and group 2 (green solid line). There was a significant difference in a, (P = 0.0068, log-rank test; P = 0.0130, generalized Wilcoxon test). In b and c the survival curve for the normal Japanese population at 76 years old is shown as the light red dotted line.
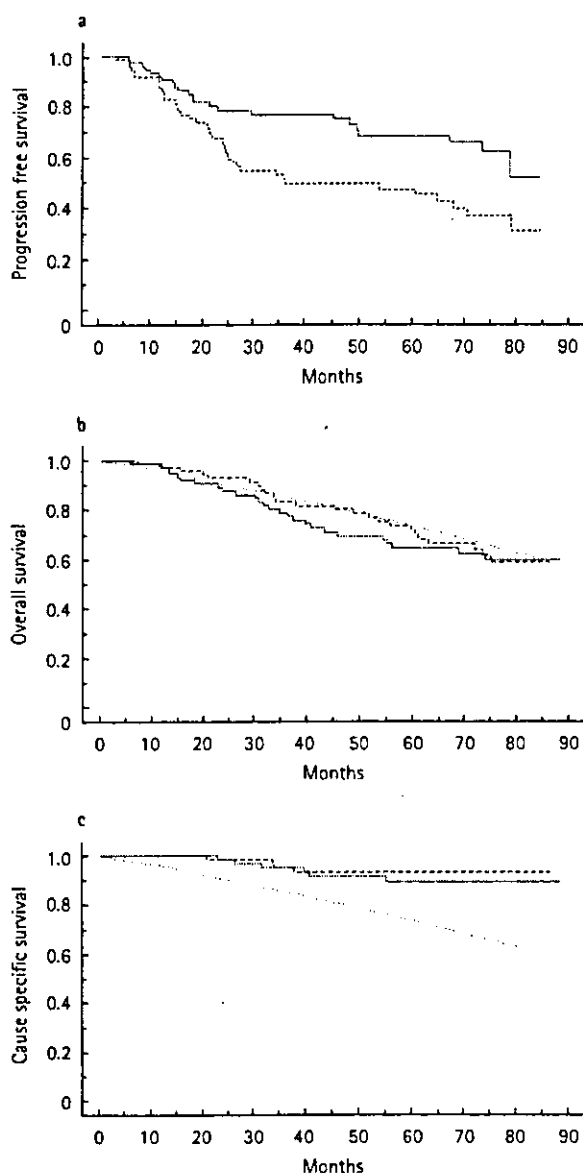
secretion from the hypothalamus and LH secretion from the pituitary gland by negative feedback via progesterone receptors [9]. Thus, the combination of LHRH agonist and CMA might have a more potent effect in decreasing testosterone than LHRH agonist monotherapy. Kotake *et al.* [10] reported no significant difference in PFS between LHRH agonist monotherapy and a LHRH agonist plus CMA in patients with advanced prostate cancer. These results might indicate that a reduced testosterone level enhanced by combined CMA and LHRH agonist is insufficient to improve the survival of patients with advanced cancer. Such disease might require maximum androgen blockade to prevent adrenal androgenic action [11,12].

The bicalutamide Early Prostate Cancer Program [13], which is investigating the efficacy of hormone therapy for localized prostate cancer, is currently underway. In the near future, the use of primary hormonal therapy for localized prostate cancer may become established.

The present results suggest that primary hormonal therapy is useful in patients with T1b-T3 prostrate cancer who are unsuitable for radical therapy. However, the 5-year follow-up is still short, and the effect of combined therapy using LHRH agonist and CMA on survival remains unclear; the study is continuing to determine the 10-year survival rate.

35

Hospital (Kiichiro Ito), Sumitomo Hospital (Toshiaki Yoshioka), Osaka Rosai Hospital (Susumu Miyoshi), Nara Medical University (Yoshihiko Hirao), Nara Prefectural Nara Hospital (Shoji Samma), Wakayama Medical University (Toshiaki Shinka), Youka Hospital (Shoudou Wataru), Okayama University Graduate School of Medicine and Dentistry (Hiromi Kumon), Okayama Red Cross Hospital (Katsuyoshi Kondou), Kawasaki Medical School (Masaaki Morioka), Fukuyama National Hospital (Satoru Matsuki), Yamaguchi University School of Medicine (Katsusuke Naito), Faculty of Medicine, Kagawa Medical University (Yoshiyuki Kakehi), The University of Tokushima School of Medicine (Susumu Kagawa), Ehime University School of Medicine (Masayoshi Yokoyama), Matsuyama Red Cross Hospital (Tsuneo Shiraishi), National Shikoku Cancer Center (Yoshiteru Sumiyoshi), Kochi Municipal Hospital (Hirohide Iriguchi), Graduate School of Medical Sciences, Kyushu University (Seiji Naito), Kyushu Kosei-Nenkin Hospital (Hiroo Yagi), Japan Red Cross Society, Nagasaki Atomic Bomb Hospital (Yasuyuki Kusaba), Nagasaki Municipal Hospital (Tanetoshi Hara), Kumamoto University School of Medicine (Shoichi Ueda).

REFERENCES

1 Akaza H, Homma Y, Okada K et al. Early results of LH-RH agonist treatment with or without chlormadinone acetate for hormonal therapy of naive localized or locally advanced prostate cancer: a prospective and randomized study. Jpn J Clin Oncol 2000; 30: 131–6

2 Sobin LH, Wittekind Ch eds. TNM Classification of Malignant Tumors, 5th edn. New York: John Wiley & Sons, Inc, 1997

3 Japanese Urological Association and The Japanese Society of Pathology eds.
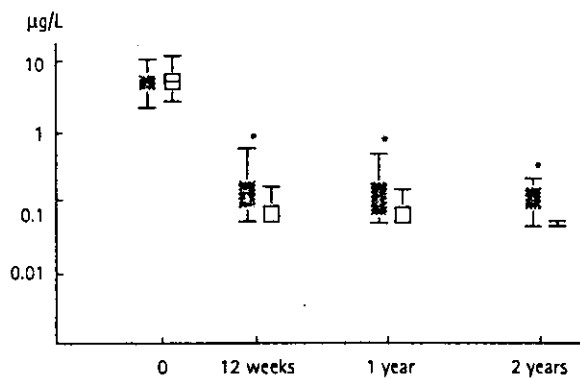

FIG. 2.
The serum testosterone levels with time in group 1 (green boxes) and group 2 (open boxes). The central line is the median, the box the interquartile range and the bars the SEM. *P < 0.01.

General Rule for Clinical and Pathological Studies on Prostate Cancer. 3rd edn. Tokyo: Kanahara, 2001

4 Harlan LC, Potosky A, Gilliland FD et al. Factors associated with initial therapy for clinically localized prostate cancer: Prostate Cancer Outcomes Study. J Natl Cancer Inst 2001; 93: 1864–71

5 Aus G, Abbou CC, Pacik D et al. EAU Guidelines on Prostate Cancer. Eur Urol 2001; 40: 97–101

6 Baker LH, Bahnson RR, Hanks GE et al. NCCN Practice Guidelines for Prostate Cancer. Oncology 2000; 14: 111–9

7 Statistics and Information Department. Minister's Secretariat, Ministry of Health and Welfare 18th Life Table. Kousei No Shihyo 1997; 44: 30–9

8 Chodak GW. Luteinizing hormone-releasing hormone (LHRH) agonists for treatment of advanced prostatic carcinoma. Urology 1989; 33 (Suppl. 5): 42–4

9 de Voogt HJ. The position of cyproterone acetate (CPA), a steroidal anti-androgen, in the treatment of prostate cancer. Prostate Suppl 1992; 4: 91–5

10 Kotake T, Usami M, Akaza H et al. Goserelin acetate with or without

antiandrogen or estrogen in the treatment of patients with advanced prostate cancer; a multicenter randomized, controlled trial in Japan. Jpn J Clin Oncol 1999; 29: 562–70

11 Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA, Eisenberger MA. Complete androgen blockade for prostate cancer: what went wrong? J Urol 2000; 164: 3–9

12 Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer. an overview of the randomized trials. Lancet 2000; 355: 1491–8

13 See WA, McLeod D, Iversen P, Wirth M. The bicalutamide Early Prostate Cancer Program. Demography. Urol Oncol 2001; 6: 43–7

Correspondence: H. Akaza, Department of Urology, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba-city, Ibaraki 305-0006, Japan. e-mail: akazah@md.tsukuba.ac.jp

Abbreviations: CMA, chlormadinone acetate; PFS, progression-free survival.

ELSEVIER

NATURAL HISTORY OF PSA INCREASE WITH AND WITHOUT PROSTATE CANCER

KAZUTO ITO, TAKUMI YAMAMOTO, MASARU OHI, HIROYUKI TAKECHI, KOHEI KUROKAWA, KAZUHIRO SUZUKI, AND HIDETOSHI YAMANAKA

ABSTRACT

Objectives. To investigate the natural history of prostate-specific antigen (PSA) increase in men with and without prostate cancer to clarify the probability of cancer-related PSA increase.

Methods. Between 1986 and 2001, 504 men aged 79 years or younger with baseline PSA levels of 4.0 ng/mL or less and a PSA increase greater than 4.0 ng/mL on consecutive screening were enrolled in this study. The types of PSA increase were classified as "non-cancer-related PSA increase," "suspicious cancer-related PSA increase," and "cancer-related PSA increase." The probability of a "cancer-related PSA increase" was investigated and stratified by baseline PSA levels and elapsed years until the PSA level increased to greater than 4.0 ng/mL.

Results. The probability of a "non-cancer-related increase," "suspicious cancer-related PSA increase," and "cancer-related PSA increase" was 57%, 15%, and 28%, respectively. The PSA velocity before the PSA increase was not significantly different between those with and without prostate cancer. A "non-cancer-related PSA increase" was observed in 92% of those with a PSA increase within 2 years of baseline PSA ranges of 2.0 ng/mL or less. Regardless of elapsed years until a PSA increase to greater than 4.0 ng/mL, a "suspicious cancer-related PSA increase" or "cancer-related PSA increase" was observed in almost one half of those with baseline PSA levels of 2.1 to 4.0 ng/mL.

Conclusions. Intensive serial observations should be recommended before undergoing biopsy for those with a PSA increase within 2 years of a baseline PSA range of 0.0 to 2.0 ng/mL. It may be difficult to distinguish between those with and without cancer using only subsequent total PSA measurements for the remaining cases, and prostate biopsy should be recommended at present. UROLOGY 62: 64–69, 2003. © 2003 Elsevier Inc.

Prostate-specific antigen (PSA) velocity (PSAV) has not been used in clinical settings, because of uncertainties concerning the physiologic and non-cancer-related variability. Several studies have demonstrated that various physiologic conditions and subclinical prostatic inflammatory diseases can cause rapid PSA fluctuations in the short term.[1-4] However, no study has investigated the natural history of PSA increase with and without prostate cancer during long-term observation. Recently, two large population-based screening studies demonstrated that the possibility of PSA progression was strongly related to the baseline PSA range.[5,6] Therefore, it would be very important to clarify what percentage of cases that show increasing PSA levels greater than 4.0 ng/mL may not be a result of prostate cancer, and how and when a cancer-related PSA increase would occur.

MATERIAL AND METHODS

Between April 1986 and December 2001, 21,324 men aged 79 years or younger underwent PSA measurements in a population-based study of screening for prostate cancer in Gunma Prefecture, Japan. All men were invited by letter, including a fact sheet on screening for prostate cancer from the local government, and decided to participate in this screening on the basis of this information. A total of 19,792 men (92.8%) had initial PSA levels of 4.0 ng/mL or less. Of these 19,792 men, 8576 participants (43.3%) screened twice or more were candidates for this study. All PSA measurements were performed using E-test Tosoh II assay by AIA-600 machine (Tosoh, Tokyo, Japan) at one center. Serum PSA levels were measured using frozen serum (−70°C) between 1986 and 1991. Digital

(A)

PSA (ng/ml)

4.0

Time

(B)

PSA (ng/ml)

Bx

Bx-last PSAV

4.0

Base-last PSAV

Time

(C)

PSA (ng/ml)   Bx

Bx-last PSAV

4.0

Base-last PSAV

Time

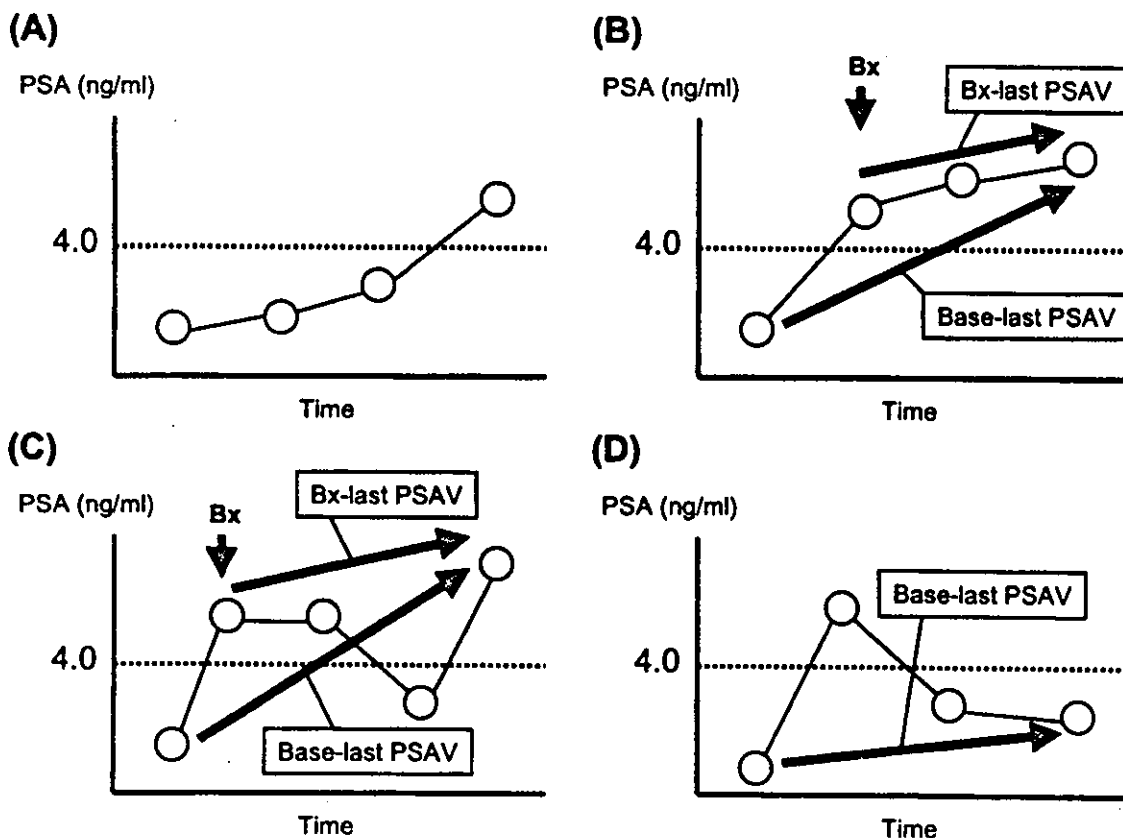**(D)**

PSA (ng/ml)

Base-last PSAV

4.0

Time

FIGURE 1.   *Various patterns of PSA change: (A) PSA increase only at last screening, (B) continuous PSA increase to greater than 4.0 ng/mL in last two or more subsequent screenings, (C) PSA change in last three screenings in the order of increase, decrease, and increase, (D) PSA at last screening of 4.0 ng/mL or less.*

rectal examination-guided four-core biopsy was recommended before 1991 for men with abnormal findings on digital rectal examination and/or with prostatic acid phosphatase levels greater than 3.0 ng/mL. Transrectal ultrasound-guided systematic sextant biopsy and two sets of transition zone biopsies were usually recommended in 1992 and 1993 for men with PSA levels greater than 6.0 ng/mL and/or abnormal findings on the digital rectal examination or transrectal ultrasonography, in 1994 through 1999 for men with PSA levels greater than 4.0 ng/mL, and in 2000 and 2001 according to age-specific reference ranges (greater than 3.0 ng/mL for 64 years or younger, 3.5 ng/mL for 65 to 69 years old, and 4.0 ng/mL for 70 to 79 years old). Alternatively, men who did not have any additional examinations, including prostate biopsy after informed consent on the probability of having prostate cancer, were followed up by annual or 3-month PSA measurements.

Of the 8576 men, 573 (6.7%) with PSA levels greater than 4.0 ng/mL at least once in subsequent screenings were enrolled in this study. The follow-up period ranged from 1 to 14 years (mean ± SD 6.0 ± 3.3, median 6).

We classified the types of PSA increase as "non-cancer-related PSA increase," "suspicious cancer-related PSA increase," and "cancer-related PSA increase," according to the patterns of PSA change, the presence or absence of histologically confirmed prostate cancer, biopsy status, and various types of PSAV (Fig. 1 and Table I). The types of PSAV calculated in this study were the PSA change between the baseline PSA measurement and the last follow-up measurement (PSAV$_{base-last}$), the PSA change between immediately before and at the first instance of a PSA increase to greater than 4.0 ng/mL

(PSAV$_{(t-1)-t}$), the PSA change between the baseline PSA measurement and the PSA increase to greater than 4.0 ng/mL for the first time (PSAV$_{base-t}$), and the PSA change between the most recent biopsy and the last follow-up (PSAV$_{Bx-last}$).

The baseline PSA ranges were divided into three groups: 0.0 to 1.0, 1.1 to 2.0, and 2.1 to 4.0 ng/mL. We defined individuals whose PSA levels increased gradually from a lower to a higher PSA range but less than 4.0 ng/mL as different cases. For example, if a man had a PSA level of 0.0 to 1.0 ng/mL at the first measurement, 1.1 to 2.0 ng/mL at the second measurement 3 years after the initial screening, and greater than 4.0 ng/mL at a third measurement 5 years after the initial screening, he would be defined as two different cases as follows: a case with baseline PSA levels of 0.0 and 1.0 ng/mL and with a PSA increase to greater than 4.0 ng/mL at a 5-year interval and a case with baseline PSA levels of 1.1 to 2.0 ng/mL and a PSA increase greater than 4.0 ng/mL at a 2-year interval. Men who had a two-phase PSA increase with interval PSA levels of 4.0 ng/mL or less for more than 4 years were also defined as two different cases. Thus, 714 cases were classified into types of PSA increase. Of these, 504 (70.6%) could be classified as having a "non-cancer-related PSA increase," "suspicious cancer-related PSA increase," and "cancer-related PSA increase," according to the criteria (Fig. 1 and Table I).

If the screening interval between immediately before and at the time of the PSA increase to greater than 4.0 ng/mL for the first time was more than 1 year, the interval PSA levels were calculated on the assumption that the PSA levels had changed over time in a simple exponential fashion to estimate the elapsed years until a PSA increase to greater than 4.0 ng/mL.

Classification of type of PSA increase according to the pattern of PSA change, biopsy status, presence of cancer, and PSAV

Type of PSA Increase	Pattern of PSA Change in Figure 1	Biopsy at PSA Increase	Cancer Detection	PSAV Type	PSAV Cutoff (ng/mL/yr)
Cancer-related increase	A-D	Yes	Yes	—	—
Suspicious cancer-related increase	B	Yes	No	Bx-last	≥1.0
		No	—	Base-last	≥0.2
	C	Yes	No	Bx-last	≥1.0
		No	—	Base-last	≥0.2
	D	No	—	Base-last	≥1.0
Non-cancer-related increase	A-C	Yes (at last follow-up)	No	—	—
	B	Yes	No	Bx-last	<1.0
		No	—	Base-last*	<0.2
	C	Yes	No	Bx-last	<1.0
		No	—	Base-last†	<0.2
	D	·Yes	No	—	—
		No	—	Base-last	<1.0
Not classified	A	No	—	—	—

KEY: PSA = prostate-specific antigen; PSAV = PSA velocity; Bx-last = between screening at most recent biopsy and last follow-up; Base-last = between baseline PSA measurement and last follow-up.
* Continuous PSA decrease must have been observed after having the highest PSA level.
† Last PSA level must have decreased compared with most recent PSA increase.

Differences were considered significant when P was <0.05 using Student's *t* test, Welch's *t* test, or the chi-square test.

RESULTS

The percentage of cases with a "non-cancer-related increase," "suspicious cancer-related PSA increase," and "cancer-related PSA increase" was 56.9%, 14.9%, and 28.2%, respectively. Prostate biopsies were performed at least once in 60.6% (174 of 287) and 16% (12 of 75) of cases classified as "non-cancer-related PSA increase" and "suspicious cancer-related PSA increase," respectively. Table II shows the detailed clinical findings for those with the different types of PSA increase. The PSA levels at the last follow-up and the $PSAV_{base-last}$ were significantly greater in the following order: "cancer-related PSA increase," "suspicious cancer-related PSA increase," and "non-cancer-related PSA increase" (P <0.05). The $PSAV_{base-t}$ and $PSAV_{(t-1)-t}$ were not significantly different between "non-cancer-related PSA increase" and "cancer-related PSA increase."

Of the 193 cases with a screening interval between immediately before and at the time of PSA increase to greater than 4.0 ng/mL of more than 1 year, 117 (61%) may have increased their interval PSA levels to greater than 4.0 ng/mL 1 or more years before their PSA increase to greater than 4.0 ng/mL at the actual screening. The correlation of the three types of PSA increase with the baseline PSA levels was investigated, stratified by the elapsed years until the PSA level was expected to

increase to greater than 4.0 ng/mL (Table III). Of the 189 cases with a PSA increase within 2 years, the percentage with a "non-cancer-related PSA increase" increased if the baseline PSA range was lower (P = 0.0002, chi-square test). In cases with a PSA increase to greater than 4.0 ng/mL after a 3 to 4-year interval, the probability of a "cancer-related PSA increase" was not significantly different among cases with baseline PSA levels of 0.0 to 1.0, 1.1 to 2.0, and 2.1 to 4.0 ng/mL. Regardless of the baseline PSA level, the probability of a "cancer-related PSA increase" or "suspicious cancer-related PSA increase" was relatively high (between 41% and 45%) in cases with a PSA increase greater than 4.0 ng/mL after 5 or more years.

COMMENT

Some studies have reported on PSA fluctuations in men without prostate cancer. Komatsu et al.[1] reported that 36% of cases with baseline PSA levels less than 4.0 ng/mL had a 20% or more PSA increase after an average of 80 days. Riehmann et al.[3] investigated the effects of biologic and intra-assay variation on the PSA change in cases without prostate cancer and demonstrated that the biologic variation was 55%, about fourfold higher than the inter-assay variation. Prestigiacomo and Stamey[4] also demonstrated the possibility of intra-individual physiologic variation after 2 to 3 weeks in men with PSA levels of 4.0 to 10.0 ng/mL. They demonstrated that the mean coefficient of variation was low at 10.5% between assays compared with that of

66

TABLE II. *Clinical findings in men with different types of PSA increase*

Variable	Type of PSA Increase			Statistical Significance[†]
	"Non-Cancer-Related PSA Increase"	"Suspicious Cancer-Related PSA Increase"	"Cancer-Related PSA Increase"	
Patients (n)	287	75	142	
Age at baseline PSA measurement (yr)				
Range	49–79	54–77	44–77	SCPI > NCPI
Mean ± SD	64.5 ± 5.1	65.9 ± 4.8	65.4 ± 5.5	
Median	64	66	65	
Baseline PSA level (ng/mL)				
Range	0.35–4.04	0.98–4.02	0.02–4.09	SCPI > NCPI, CPI
Mean ± SD	2.31 ± 0.96	2.76 ± 0.79	2.40 ± 0.93	
Median	2.33	2.83	2.51	
PSA levels at increase (ng/mL)				
Range	4.10–35.1	4.10–9.54	4.10–64.5	CPI > NCPI > SUSP
Mean ± SD	5.87 ± 3.26	5.20 ± 1.31	7.43 ± 8.43	
Median	4.83	4.71	5.11	
PSA level at last-follow-up (ng/mL)				
Range	0.40–14.8	4.15–23.2	3.79–73.5	CPI > SCPI > NCPI
Mean ± SD	4.02 ± 2.25	6.31 ± 3.16	9.50 ± 10.9	
Median	3.91	5.53	6.27	
Screening interval (yr)				
Range	1–12	1–12	1–11	SCPI, CPI > NCPI
Mean ± SD	1.4 ± 1.1	1.7 ± 1.7	1.7 ± 1.4	
Median	1	1	1	
Elapsed time until PSA increase >4.0 ng/mL[*] (yr)				
Range	1–13	1–12	1–13	CPI > NCPI
Mean ± SD	4.1 ± 2.6	4.1 ± 3.0	4.7 ± 3.0	
Median	3	3	4	
$PSAV_{base-last}$ (ng/mL/yr)				
Range	−0.61–4.80	0.09–2.49	0.08–12.24	CPI > SCPI > NCPI
Mean ± SD	0.38 ± 0.66	0.59 ± 0.48	1.42 ± 1.97	
Median	0.19	0.45	0.81	
$PSAV_{base-t}$ (ng/mL/yr)				
Range	0.04–10.80	0.13–3.00	0.16–12.24	NCPI, CPI > SCPI
Mean ± SD	1.35 ± 1.74	0.86 ± 0.68	1.28 ± 1.63	
Median	0.77	0.64	0.78	
$PSAV_{(t-1)-t}$ (ng/mL/yr)				
Range	0.06–16.3	0.13–6.2	0.09–17.6	NCPI, CPI > SCPI
Mean ± SD	2.40 ± 2.63	1.22 ± 0.97	2.12 ± 2.75	
Median	1.40	1.09	1.32	

Key: PSA = prostate-specific antigen; PSAV = PSA velocity; $PSAV_{base-last}$ = PSAV between baseline PSA measurement and last follow-up; $PSAV_{base-t}$ = PSAV between baseline PSA measurement and PSA levels >4.0 ng/mL for first time; $PSAV_{(t-1)-t}$ = PSAV between immediately before and at the time of PSA level >4.0 ng/mL for first time; NCPI = non-cancer-related PSA increase; SCPI = suspicious cancer-related PSA increase; CPI = cancer-related PSA increase.
[*] Years between baseline PSA measurement and PSA level >4.0 ng/mL for first time.
[†] Results of pairwise comparisons by Student's t test or Welch's t test.

23.5% for physiologic variation.[4] In the present study, 97.2% (279 of 287) and 86.8% (249 of 287) of cases with a "non-cancer-related PSA increase" had a more than 20% and a more than 40% PSA increase, respectively (data not shown). Therefore, inter-assay variation and physiologic variation may not be the main causes of non-cancer-related PSA increases. Nadler et al.[7] investigated the prevalence of inflammation and benign prostatic hyperplasia in men with a serum PSA increase in their large-scale screening study. They demonstrated that the prevalence of acute prostatic inflammation was greater in cases with a PSA increase than in those without a PSA increase. In the present study, 59% (169 of 287) of the "non-cancer-related PSA increase" cases may have been caused by prostatic inflammation, because a spontaneous PSA decrease to less than 4.1 ng/mL at the last follow-up or prostatic inflammation on the biopsy specimen was found.

TABLE III. *Relationship between types of PSA increase and baseline PSA levels according to estimated elapsed years until PSA level increased to greater than 4.0 ng/mL for first time*

	Estimated Elapsed Years Until PSA Level Increased to >4.0 ng/mL for First Time								
	1–2			3–4			5+		
Baseline PSA Range (ng/mL)	Non-Cancer-Related PSA Increase	Suspicious Cancer-Related PSA Increase	Cancer-Related PSA Increase	Non-Cancer-Related PSA Increase	Suspicious Cancer-Related PSA Increase	Cancer-Related PSA Increase	Non-Cancer-Related PSA Increase	Suspicious Cancer-Related PSA Increase	Cancer-Related PSA Increase
0.0–1.0	14 (100)	0 (0)	0 (0)	4 (80)	0 (0)	1 (20)	19 (56)	2 (6)	13 (38)
1.1–2.0	19 (86)	2 (9)	1 (5)	20 (56)	4 (11)	12 (33)	36 (55)	9 (14)	20 (31)
2.1–4.0	75 (49)	32 (21)	46 (30)	62 (56)	14 (13)	35 (32)	38 (59)	12 (19)	14 (22)
Total	108 (57)	34 (18)	47 (25)	86 (57)	18 (12)	48 (32)	93 (57)	23 (14)	47 (29)

KEY: PSA = prostate-specific antigen.
Data presented as number of cases, with the percentage in parentheses.

We demonstrated that a PSA increase within 2 years from baseline PSA levels of 0.0 to 2.0 ng/mL may be a "non-cancer-related PSA increase" with high probability. On the other hand, almost one half of the PSA increase from baseline PSA levels of 2.1 to 4.0 ng/mL may be a "cancer-related PSA increase" or "suspicious cancer-related PSA increase," regardless of the elapsed time. The $PSAV_{base-t}$ and $PSAV_{(t-1)-t}$ were not significantly different between a "cancer-related PSA increase" and "non-cancer-related PSA increase," so it would be difficult to distinguish between cases with and without prostate cancer by the findings on serial PSA changes.

There are some flaws in the classification of PSA increase types in this study. First, only 61% of cases classified as having a "non-cancer-related PSA increase" had prostate biopsy performed. However, the median $PSAV_{base-last}$ was low at 0.19 ng/mL/yr. Furthermore, almost one half of cases had a spontaneous decrease to less than 4.0 ng/mL and most of the remaining cases with PSA levels of 4.0 ng/mL or greater at last follow-up had a $PSAV_{base-last}$ of less than 0.5 ng/mL/yr. Therefore, the validity of cases classified into "non-cancer-related PSA increase" should be high.

Second, 14.9% (75 of 504) of cases were classified as having a "suspicious cancer-related PSA increase." The PSA levels at last follow-up and the $PSAV_{base-last}$ in cases with a "suspicious cancer-related PSA increase" were significantly lower than those in cases with a "cancer-related PSA increase" and significantly greater than those in cases with a "non-cancer-related PSA increase." The clinical characteristics were intermediate between "non-cancer" and "cancer-related PSA increase." Therefore, this classification may be admitted in such an observation study.

Finally, 29.4% (210 of 714) of cases could not be classified as any type of PSA increase according to

the criteria indicated in Table I. The PSA levels at increase in those eliminated cases were not significantly different from those classified as "non-cancer-related PSA increase" and "suspicious cancer-related PSA increase," but were significantly lower than those classified as "cancer-related PSA increase." The mean $PSAV_{base-t}$ and $PSAV_{(t-1)-t}$ were significantly lower than those in cases classified as having a "non-cancer-related PSA increase" (data not shown). No specific features were found for their PSA and PSAV; therefore, excluding those 210 cases likely did not lead to bias in this study.

We could demonstrate the natural history of PSA increases with and without prostate cancer. Currently, there are a number of cases that have had their own PSA history; therefore, these findings would be very useful to determine the risk of having prostate cancer in combination with the data on PSA progression.[5,6]

CONCLUSIONS

A PSA increase to greater than 4.0 ng/mL within 2 years may be a "non-cancer PSA increase" in those with baseline PSA levels of 2.0 ng/mL or less. Therefore, careful observations should be recommended before undergoing biopsy. The possibility of a "cancer-related PSA increase" may be relatively high in those with a PSA increase after 3 or more years of measurements or with a baseline PSA range of 2.1 to 4.0 ng/mL. Therefore, prostate biopsy should be recommended at that time.

REFERENCES

1. Komatsu K, Wehner N, Prestigiacomo AF, et al: Physiologic (intra-individual) variation of serum prostate-specific antigen in 814 men from a screening population. Urology 47: 343–346, 1996.
2. Roehrborn CG, Pickens GJ, and Carmody T III: Variabil-

– 98 –

ity of repeated serum prostate-specific antigen (PSA) measurements with less than 90 days in a well-defined patient population. Urology 47: 59–66, 1996.

3. Riehmann M, Rhodes PR, Cook TD, *et al*: Analysis of variation in prostate-specific antigen values. Urology 42: 390–397, 1993.

4. Prestigiacomo AF, and Stamey TA: Physiological variation of serum prostate specific antigen in the 4.0 to 10.0 ng/ml range in male volunteers. J Urol 155: 1977–1980, 1996.

5. Crawford D, Chia D, Andriole GL, *et al*: PSA testing interval, reduction in screening intervals: data from the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. J Urol 167(suppl): 99–100, 2002.

6. Ito K, Yamamoto T, Ohi M, *et al*: The possibility of re-screening intervals of more than one year in men with PSA levels of 4.0 ng/ml or less. The Prostate (in press).

7. Nadler RB, Humphrey PA, Smith DS, *et al*: Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. J Urol 154: 407–413, 1995.