Table 2 The 1-year and 3-year recurrence-free survival rates according to clinicopathological characteristics in all patients

		% 1-year (mean ± SE)	% 3-year (mean ± SE)	*P*-value
Age				0.146
	≤70 years	76.4 ± 0.01	62.8 ± 0.01	
	>70 years	77.7 ± 0.01	59.4 ± 0.01	
Gender				0.747
	Male	77.3 ± 0.01	61.0 ± 0.01	
	Female	76.0 ± 0.02	62.3 ± 0.02	
Papillary type				0.639
	Yes	77.0 ± 0.01	61.4 ± 0.01	
	No	77.6 ± 0.03	60.3 ± 0.03	
Tumor stalk				0.009
	Yes	78.2 ± 0.01	62.8 ± 0.01	
	No	74.3 ± 0.01	57.8 ± 0.02	
Multiplicity				<0.001
	No	82.7 ± 0.01	66.3 ± 0.01	
	Yes	68.8 ± 0.01	54.0 ± 0.02	
Size				<0.001
	≤3 cm	78.7 ± 0.01	62.8 ± 0.01	
	>3 cm	64.2 ± 0.03	49.8 ± 0.03	
Pathological T category				<0.001
	pTa	81.4 ± 0.01	65.6 ± 0.01	
	pT1	72.5 ± 0.01	56.8 ± 0.01	
Grade				<0.001
	G1/2	78.8 ± 0.01	62.7 ± 0.01	
	G3	69.6 ± 0.02	55.2 ± 0.02	
Intravesical instillation				<0.001
	No Tx	73.1 ± 0.01	56.2 ± 0.01	
	chemoTx	80.3 ± 0.01	64.2 ± 0.01	
	BCG	81.0 ± 0.02	70.3 ± 0.02	

BCG, Bacillus Calmette-Guérin.

tion, the 1- and 3-year recurrence-free survival rates were 73.1% and 56.2%, respectively, in patients without any adjuvant therapy, compared with 80.3% and 64.2% in patients with intravesical chemotherapy, and 81.0% and 70.3% in patients with intravesical BCG therapy (Fig. 1). In multivariate analysis (Table 3), multiple bladder tumors, a tumor size greater than 3 cm, pathological stage T1, tumor grade G3, and the absence of adjuvant intravesical instillation were independent risk factors for tumor recurrence. Recurrence risk was 1.7 times higher for multiple tumors, and 1.5 times higher for tumors greater than 3 cm compared with those equal to or smaller than 3 cm. Intravesical instillations were a protective factor of tumor recurrence since the risk was lower than 1. The risk of recurrence was 0.65 and 0.4 times lower for patients treated with intravesical chemotherapy and BCG instillation, respectively. Patients treated with BCG instillation had significantly less likelihood of papillary type, tumor stalk, solitary, and small size tumor, but greater likelihood of a higher stage and higher grade tumor than those with intravesical chemotherapy or without adjuvant instillation (Table 4). Patients treated with intravesical chemotherapy had significantly less likelihood of a solitary, small size tumor, but greater likelihood of a higher pathological stage and higher grade tumor than those without adjuvant instillation.

In a subgroup of patients with pT1G3, 164, 154, and 163 patients were treated with intravesical chemotherapy, BCG instillation, and without any adjuvant instillation, respectively. The Kaplan–Meier curve indicated that the differences among the groups were significant ($P = 0.039$ for intravesical chemotherapy *vs* BCG instillation, $P = 0.007$ for intravesical chemotherapy *vs* no adjuvant therapy, and $P < 0.001$ for BCG instillation *vs* no adjuvant therapy) (Fig. 2).

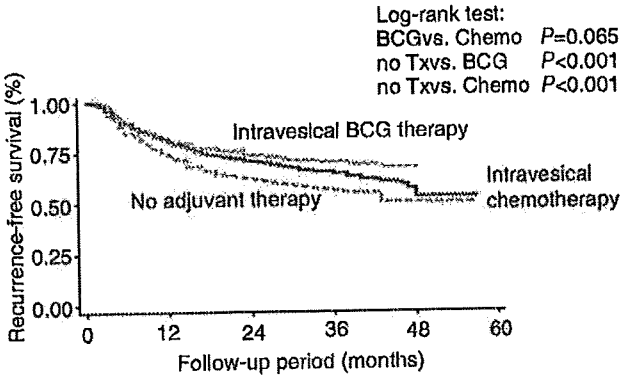

Fig. 1 Kaplan–Meier curves for tumor recurrence in the overall patient population ($n = 3237$) comparing no instillation ($n = 1527$), Bacillus Calmette-Guérin (BCG) instillation ($n = 396$), and chemotherapeutic instillation ($n = 1314$).

Table 3 Univariate and multivariate Cox regression analysis for tumor recurrence in all patients

		Univariate	Multivariate		
		P-value	Hazards ratio	95% CI	*P*-value
Age		0.159			
	≤70 years				
	>70 years				
Gender		0.764			
	Male				
	Female				
Papillary type		0.706			
	Yes				
	No				
Tumor stalk		0.011			
	Yes				
	No				
Multiplicity		<0.001			<0.001
	No		1		
	Yes		1.69	1.50–1.92	
Size		<0.001			<0.001
	≤3 cm		1		
	>3 cm		1.52	1.28–1.80	
Pathological T category		<0.001			<0.001
	Ta		1		
	T1		1.32	1.17–1.50	
Grade		<0.001			
	G1/2		1		0.002
	G3		1.28	1.10–1.50	
Intravesical instillation		<0.001			<0.001
	no Tx		1		
	chemoTx		0.65	0.57–0.74	<0.001
	BCG		0.41	0.33–0.51	<0.001

BCG, Bacillus Calmette-Guérin.

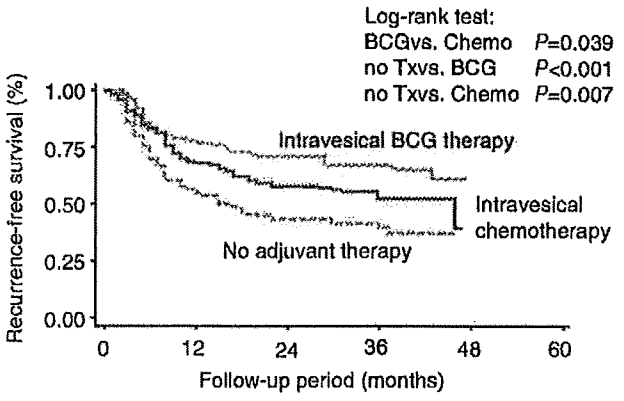

Fig. 2 Kaplan–Meier curve for tumor recurrence in patients with T1G3 ($n = 481$) comparing no instillation ($n = 163$), Bacillus Calmette-Guérin (BCG) instillation ($n = 154$), and intravesical chemotherapy ($n = 164$).

Tumor recurrence in patients treated with intravesical chemotherapy and BCG instillation

We next evaluated the prognostic indicators for tumor recurrence, particularly in patients treated with intravesical chemotherapy, which accounted for 76.8% of the intravesical adjuvant therapy. Intravesical chemotherapy consisted of adriamycin (doxorubicin) in 41, epirubicin in 468, pirarubicin in 680, mitomycin C (MMC) in 120, peplomycin in seven, and tiotepa in one. Overall, an anthracycline chemo-agent was used in 90.5% of the cases of intravesical chemotherapy. When patients treated with an anthracycline chemo-agent were compared with those receiving MMC treatment, Kaplan–Meier curve analysis revealed that the differences among the groups were not significant (Fig. 3).

Kaplan–Meier analysis (Table 5) and univariate Cox proportional hazards regression analysis (Table 6) revealed gender, presence or absence of tumor stalk, tumor multiplicity, tumor size, pathological stage, and tumor grade were significant predictors for tumor recurrence. In multivariate analysis, male gender, multiple bladder tumors, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Female patients had a recurrence risk 0.7 times lower than male patients. Recurrence risk was 1.7 times higher for multiple tumors, and 1.3 times higher for tumors greater than 3 cm compared with those equal to or smaller than 3 cm. Patients with T1 tumor had a recurrence risk 1.3 times higher than those with Ta.

In patients treated with BCG instillation, no clinicopathological factors were associated with tumor recurrence in uni- and multivariate analysis (data not shown).

Table 4 Clinicopathological characteristics in patients treated with intravesical chemotherapy (IVI), Bacillus Calmette-Guérin (BCG) instillation, and no adjuvant therapy

Patients	IVI chemotherapy No. patients (%)	BCG instillation No. patients (%)	No IVI treatment No. patients (%)	*P*-value
	1314	396	1527	
Age				0.853
≤70	671 (51.1)	199 (50.3)	790 (51.7)	
>70 years	643 (48.9)	197 (49.8)	737 (48.3)	
Gender				0.287
Male	1038 (79.0)	323 (81.6)	1239 (81.1)	
Female	276 (21.0)	73 (18.4)	288 (18.9)	
Papillary type				<0.001
Yes	1224 (93.2)	325 (82.1)	1389 (91.0)	
No	69 (5.3)	57 (14.4)	86 (5.6)	
Unknown	21 (1.6)	14 (3.5)	52 (3.4)	
Tumor stalk				<0.001
Yes	925 (70.4)	225 (56.8)	1101 (72.1)	
No	316 (24.1)	143 (36.1)	326 (21.4)	
Unknown	73 (5.6)	28 (7.1)	100 (6.55)	
Multiplicity				<0.001
Yes	588 (44.8)	242 (61.1)	482 (31.6)	
No	690 (52.5)	132 (33.3)	988 (64.7)	
Undetected	14 (1.1)	10 (2.5)	9 (0.6)	
Unknown	22 (1.7)	12 (3.0)	48 (3.1)	
Tumor size				<0.001
<1 cm	369 (28.1)	101 (25.5)	543 (35.6)	
1–3 cm	716 (54.5)	197 (50.0)	768 (50.3)	
>3 cm	180 (13.7)	68 (17.2)	126 (8.25)	
Uncountable	15 (1.1)	13 (3.3)	17 (1.1)	
unknown	34 (2.6)	17 (4.3)	73 (4.8)	
Pathological T category				<0.001
pTa	672 (51.1)	120 (30.3)	859 (56.3)	
pT1	642 (48.9)	276 (69.7)	668 (43.8)	
Grade				<0.001
G1	287 (21.8)	37 (9.3)	458 (30.0)	
G2	817 (62.2)	178 (45.0)	855 (56.0)	
G3	210 (16.0)	181 (45.7)	214 (14.0)	

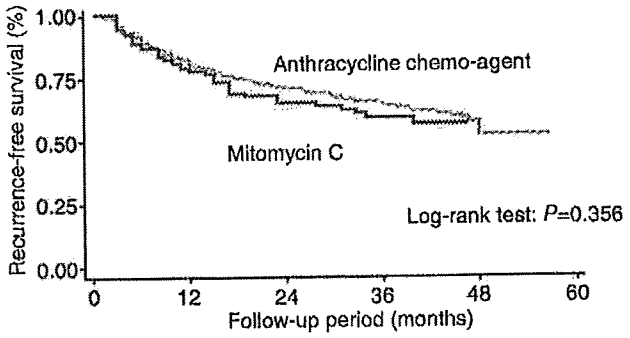

Fig. 3 Kaplan–Meier curve for tumor recurrence in patients treated with adjuvant intravesical chemotherapy comparing an anthracycline chemo-agent and mitomycin C treatment.

Discussion

In the present study, we characterized the clinical outcome of newly diagnosed non-muscle invasive bladder cancer in a large contemporary series of patients from a Japanese bladder cancer registry and determined the predictors for tumor recurrence. Overall, bladder tumor multiplicity, a tumor size greater than 3 cm, pathological stage T1, tumor grade G3, and the absence of adjuvant intravesical instillation were found to independently increase the risk of tumor recurrence. Numerous publications have reported the same prognostic indicators as ours for tumor recurrence in non-muscle invasive bladder cancer.[1–3] Recently, a combined analysis was carried out using data from 2596 non-muscle invasive bladder cancer patients collected from seven European Organization for Research and Treatment of Cancer (EORTC) trials.[4] In the analysis, six clinicopathological risk factors, namely multiplicity, tumor size, prior recurrence rate, pathological stage, concomitant CIS, and tumor grade were determined. Four of the six predictors for tumor recurrence in the present study were shared with their indicators; however, the big difference between their study

Table 5 The 1-year and 3-year recurrence-free survival rates according to clinicopathological characteristics in patients treated with intravesical chemotherapy

		% 1-Year (mean ± SE)	% 3-Year (mean ± SE)	*P*-value
Age				0.695
	≤70 years	79.2 ± 0.02	64.7 ± 0.02	
	>70 years	81.6 ± 0.02	63.4 ± 0.02	
Gender				0.025
	Male	79.2 ± 0.01	62.7 ± 0.02	
	Female	84.6 ± 0.02	69.7 ± 0.03	
Papillary type				0.209
	Yes	80.7 ± 0.01	64.7 ± 0.02	
	No	74.5 ± 0.05	57.6 ± 0.06	
Tumor stalk				0.016
	Yes	82.0 ± 0.01	66.4 ± 0.02	
	No	76.2 ± 0.02	58.9 ± 0.03	
Multiplicity				<0.001
	No	85.6 ± 0.01	69.6 ± 0.02	
	Yes	73.8 ± 0.02	57.5 ± 0.02	
Size				0.004
	≤3 cm	81.8 ± 0.01	65.6 ± 0.02	
	>3 cm	70.7 ± 0.04	55.8 ± 0.04	
Pathological T category				0.002
	pTa	84.0 ± 0.02	68.1 ± 0.02	
	pT1	76.4 ± 0.02	60.1 ± 0.02	
Grade				0.001
	G1/2	82.1 ± 0.01	66.1 ± 0.02	
	G3	71.1 ± 0.03	54.5 ± 0.04	

and ours is that their population has included both primary and recurrent cases. A more homogenous population of patients who initially diagnosed non-muscle invasive bladder tumor was evaluated in our current study.

Overall, 12.2% received BCG instillation in our study. In the subgroup of patients treated with BCG instillation, no clinicopathological factors were associated with tumor recurrence. Kaplan–Meier analysis demonstrated that the recurrence-free survival in the BCG instillation group was significantly higher than that in the intravesical chemotherapy group especially in pT1G3 patients ($P = 0.039$), which was confirmed by others.[11] Furthermore, BCG instillation was significantly selected in patients with multiple, larger, and higher pathological stage tumors, compared with intravesical chemotherapy. These results suggested that BCG instillation was carried out for the prevention of recurrence in a relatively smaller percentage of high risk patients than would have been expected from the current clinical situation.[12,13] One reason for the difference in the percentage of BCG instillations carried out between 1999–2001 and the present is that the current clinical management for non-muscle invasive bladder cancer is highly affected by the guidelines.[14,15]

In our subgroup consisting of the 1314 patients treated with adjuvant intravesical chemotherapy, multivariate analyses demonstrated that male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Only about 10% of the patients were treated with MMC intravesical chemotherapy. Au *et al.* reported that intravesical chemotherapy using a modified 40 mg dose of MMC accompanied by a decrease in urine volume during the procedure and urine alkalinization significantly improved the therapeutic benefit of traditional MMC treatment for the prevention of tumor recurrence.[16] Meanwhile, Huncharek *et al.* have showed that maintenance intravesical chemotherapy reduced tumor recurrence, when compared with a single course of induction chemotherapy.[17] Further study is warranted to prove the therapeutic benefit with these modalities, especially in Japanese patients who have these risk factors for recurrence. In our multivariate analyses, gender is an independent predictor for tumor recurrence in patients treated with adjuvant intravesical chemotherapy but not in overall patients. There has been no study to evaluate the influence of gender for tumor recurrence in a large series of bladder cancer patients treated with intravesical chemotherapy. The exact reason why female patients have better outcome for tumor recurrence than male patients has to be elucidated in a future study.

Frydenberg *et al.* conducted a survey of a population cancer registry that included about 700 newly diagnosed non-muscle invasive bladder cancers between 1990 and 1995 in Victoria of Australia. Logistic regression analysis revealed that tumor grade and pathological T stage were independent factors affecting the risk of recurrence. Less than 10% of the patients received adjuvant intravesical chemotherapy or immunotherapy.[18] Gårdmark *et al.* analyzed the clinical characteristics of about 10 000 newly diagnosed cases of bladder cancer obtained from the Swedish National Bladder Cancer Register between 1997 and 2001.[19] A large number of the patients, even in the high risk group, were still undertreated and they concluded that the survival rate of bladder cancer in Sweden during this period seemed to remain at the levels previously reported for the 1980s. The accumulation of data provided by a large cancer registry is of great importance to understanding the

Table 6 Univariate and multivariate Cox regression analysis for tumor recurrence in patients treated with intravesical chemotherapy

		Univariate	Multivariate		
		P-value	Hazard ratio	95% CI	*P*-value
Age		0.660			
	≤70 years		1		
	>70 years		0.71	0.55–0.91	0.008
Gender		0.030			
	Male		1		
	Female		1.67	1.37–2.03	<0.001
Papillary type		0.706			
	Yes				
	No				
Tumor stalk		0.023			
	Yes				
	No				
Multiplicity		<0.001			
	No		1		
	Yes		1.34	1.03–1.73	0.028
Size		0.005			
	≤3 cm		1		
	>3 cm		1.33	1.09–1.62	0.004
Pathological T category		0.003			
	Ta		1		
	T1		1.33	1.09–1.62	
Grade		0.002			
	G1/2				
	G3				

CI, confidence interval.

trends in the clinical characteristics of the disease and its treatment management, and to providing an opportunity for analysis of the indicators predicting prognosis.[20]

The present study has several limitations. First, the results were obtained from a dataset created by data only from centers participating in the bladder cancer registry. Since all of the centers in Japan do not participate in the cancer registry, the dataset does not include data for all bladder cancers in Japan. However, approximately 180 institutions participate in the cancer registry in Japan and the dataset contained data for approximately 6000 patients so we believe that the results represent an accurate reflection of the characteristics of patients with newly diagnosed bladder cancer and its clinical outcome in the period from 1999 and 2001.[21] Another limitation is that the follow-up period was short. Median follow-up was 24 months and this bias might affect the understanding of true risk factors and the natural course of non-muscle invasive bladder cancer and make us unable to analyze the prediction of tumor progression and survival. In fact recurrence-free survival in our study was somewhat better than that reported in another large series.[3] Several papers pointed out the importance of the use of data from long-term follow-up of non-muscle invasive bladder cancer.[22,23] Further study would be warranted to accumulate long-term follow-up data in the bladder cancer registry.

In conclusion, patients with multiple tumors, a tumor size greater than 3 cm, tumor grade G3, or pathological T1 tumors were at greater risk, whereas those treated with intravesical BCG instillations had a decreased risk of tumor recurrence in the overall patient population. In patients treated with intravesical chemotherapy, male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Further study of datasets created from longer follow-up data is warranted in order to analyze tumor progression and disease survival.

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Prospective Evaluation of Selection Criteria for Active Surveillance in Japanese Patients with Stage T1cN0M0 Prostate Cancer

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Objective: Selection criteria for active surveillance (AS) program of localized prostate cancer remain to be standardized. The purpose was to evaluate the validity of selection criteria and investigate the feasibility of this AS program.

Methods: Patients meeting the criteria (i) stage T1cN0M0, (ii) age 50–80, (iii) serum prostate-specific antigen (PSA) ≤20 ng/ml, (iv) one or two positive cores per 6–12 systematic biopsy cores, (v) Gleason score ≤6, and (vi) cancer involvement in positive core ≤50% were enrolled and encouraged to start AS for at least 6 months during the period between January 2002 and December 2003. PSA was measured bimonthly for 6 months and every 3 months thereafter. Trigger of treatment recommendation was PSA-doubling time (PSADT) of ≤2 years or pathological progression at re-biopsy. Primary endpoint was '%PSADT > 2y', which was defined as the proportion of patients who showed PSADT assessed at 6 months >2 years out of all the patients who chose AS. Point estimate of '%PSADT > 2y' was expected to be >80%.

Results: One hundred and eighteen patients opted for AS and 16 chose immediate treatment at enrollment. PSADT for the initial 6 months based on four measurements could be assessed in 106 patients. Intent-to-treat analysis of '%PSADT > 2y' was 71.2% (84/118, 95% CI: 62.1–79.2). Pathological progression rate at 1-year re-biopsy was 33%. Fifty-four (46%) patients remained on AS for maximal observation of 54 months. General health-related QOL in patients undergoing AS was not impaired.

Conclusions: The primary endpoint, '%PSADT > 2y', did not meet the pre-specified decision criteria. Further prospective study with revised program and endpoint is needed.

Key words: active surveillance – prostate cancer – PSA-doubling time

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INTRODUCTION

Widespread use of prostate-specific antigen (PSA) testing in Japan has resulted in a marked increase in the incidence of 'favorable risk' cancer, as has been seen in Western countries. Subsets of prostate cancers detected by PSA screening, however, might not have adversely affected patients' life span if they were to remain undetected. Etzioni et al. (1) estimated over-diagnosis rates under PSA screening in Caucasian and African-American men as 18–44%, but the rate still remains unclear in Japanese men. Minimal cancer (tumor volume <0.5 ml, organ-confined, no Gleason pattern 4 or 5) was found in 31.6% in the first round and 42.6% in the second round (4-year interval) in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), Section Rotterdam (2). In contrast, Loeb et al. (3) detected only 5–10% of clinically insignificant cancer in their longitudinal prostate-cancer screening study. To avoid over-treatment without compromising lifetime, active surveillance (AS) with selective delayed intervention seems a practical treatment option for favorable risk patients, although selection criteria remain to be standardized.

Selection criteria so far published were based on biopsy features and PSA levels at diagnosis, although they have not yet been validated in a prospective trial (4,5). Organ-confined cancers with tumor volume >0.5 ml of Gleason score ≤ 6 have been considered as indolent or clinically unimportant. This standard, however, was arbitrarily defined (6). What is clinically more important is tumor growth velocity. The only way so far applicable for the prediction of tumor growth velocity is to utilize PSA kinetics. In men with untreated prostate cancer, serum PSA appears to increase exponentially over time (7). Therefore, PSA-doubling time (PSADT), calculated using log-linear regression, may be an appropriate measure of cancer growth.

In this study, we have prospectively evaluated the selection criteria for AS with selective delayed intervention in patients with favorable risk prostate cancer using PSADT that was calculated with four consecutive PSA points for 6 months as a primary endpoint.

PATIENTS AND METHODS

This was a multi-center prospective non-randomized study. Seven cancer center hospitals and six university hospitals participated in this study. The institutional review board of each participating institution approved the study protocol and all the patients gave written informed consent.

Study Population and Enrollment Criteria

Patients with newly detected stage T1cN0M0 prostate cancer harboring the biopsy features described subsequently were enrolled during the period between January 2002 and December 2003. In order to be eligible for the study, participants should have met the following criteria: (i) age ranging between 50 and 80, (ii) initial serum PSA being ≤ 20 ng/ml, (iii) number of positive core being one or two per 6–12 systematic biopsy cores, (iv) Gleason score being ≤ 6 and (v) $\leq 50\%$ cancer involvement in any of the positive cores. Patients who had past history of cerebral infarction, unstable angina, diabetes uncontrollable with insulin, severe hypertension or suffered myocardial infarction within 6 months were excluded from this study. In the first step, candidate patients in whom the biopsy criteria of (iii), (iv) and (v) were confirmed by the central pathologist were asked to give their written consent to participate in this study. Then the patients were encouraged to start AS for at least 6 months according to the program described subsequently. Those who did not want to opt for AS immediately started treatments including radical prostatectomy (RP), external beam radiation (EBRT) and androgen-deprivation therapy (ADT).

The AS Program

In patients who opted for the AS program, serum PSA was monitored every 2 months for 6 months and every 3 months thereafter. Those who showed PSADT of ≤ 2 years (y) after 6 months were recommended to start aggressive treatment. After the initial checkpoint, patients undergoing AS were recommended to start treatment when either PSADT assessed with all PSA measurements or PSADT assessed with PSA points measured within 1 year was ≤ 2 years. The patients who remained on AS for 1 year were recommended to undergo re-biopsy and those who did not fit the initial pathology criteria were also recommended to start aggressive treatment.

PSA Assay and PSADT

All PSA determinations were made centrally using the Tandem-R monoclonal immuno-radiometric assay (Hybritech Inc., San Diego, CA, USA). PSADT was assessed with the assumption that PSA changed with time in simple exponential fashion, which was precisely described elsewhere (8). PSADT was calculated as the natural log of 2 divided by the slope, if PSA values were distributed on the y-axis of a scatter plot and time on the x-axis. It was a line function that fitted the PSA values over time and the PSA slope was calculated using least-squared regression. Outlier of PSA values was excluded from regression calculation when clinical manifestation of prostate inflammation was apparent. These calculations were performed with the software specifically developed for this study.

When an unnatural increase in serum PSA was found during AS, re-measurement of PSA was allowed within 3 months. Then, the principal investigator, the secretary of the study office and the duty doctor discussed whether the pending PSA value could be omitted from the PSADT evaluation.

Histopathological Review

In addition to the eligibility criteria (iii), (iv) and (v) described earlier, the maximal tumor length was recorded for all positive cores by the central pathologist. For radical prostatectomy specimens, stepwise serial sections were made and subjected to thorough pathological review. Pathological T-stage was described according to the UICC TNM-classification 1997 (9).

QOL Assessment

The patient-reported health-related quality of life (HRQOL) was assessed at the time of registration and 1 year later. General HRQOL was evaluated with the Japanese version RAND SF-36 (10), and disease-related QOL was assessed with the Japanese version UCLA Prostate Cancer Index (UCLA PCI) (11). Each scale of SF-36 was standardized to the Japanese population normative values, with a mean score of 50 and an SD of 10. The function and bother scores of urinary, bowel and sexual domains of UCLA PCI were calculated according to the scoring instructions (12).

Endpoints and Sample Size

Primary endpoint was '%PSADT > 2y' defined as a proportion (%) of AS patients showing PSADT >2 years at the initial 6-month assessment out of all the patients who opted for AS at registration. The secondary endpoints were defined as follows: (i) proportion (%) of AS patients who met the initial pathology criteria at the time of re-biopsy, (ii) proportion (%) of the non-organ-confined rate in patients who chose radical prostatectomy as an initial strategy, (iii) adverse events in patients who chose aggressive treatment as an initial strategy, (iv) impairment of HRQOL in AS patients and other treatment patients, (v) overall survival of AS patients and other treatment patients and (vi) metastasis-free survival of AS patients and other treatment patients. The planned sample size was 100 patients who opted for AS, which was determined based on the precision of estimate to give the width of 95% confidence intervals for '%PSADT > 2y' within 10%.

Follow-up

The local progression in AS patient was examined with digital rectal examination (DRE) and transrectal ultrasonography at least twice per year and at the suspicion because of rising PSA. Chest X-ray, CT scan or MRI for abdominal/pelvic cavity and bone scintigraphy were performed at least once every two years to rule out the presence of metastasis.

Statistical Analysis

This study was designed to evaluate the validity of our selection criteria for AS. Point estimate of the primary endpoint was expected to be >80% for validating the selection criteria. The point estimates and 95% confidence intervals calculated by the exact method were carried out for proportions. For QOL analysis, subscale scores were compared with the Japanese population normative values and differences of subscale scores within patients were assessed. The Student's *t*-test and paired *t*-test were carried out accordingly in QOL analysis for exploratory purpose.

RESULTS

Participants

One hundred and thirty-four patients were enrolled into this study, and 118 chose the AS program and 13 chose RP, 2 chose EBRT and 1 chose ADT as an initial treatment. Table 1 shows clinical and pathological characteristics of each treatment group.

PSADT in AS Patients and Primary Endpoint

Among 118 patients who chose the AS program, 7 changed the treatment strategy immediately after registration and 5 patients missed at least 1 PSA determination during the first 6 months. Therefore, PSADT at 6 months was completely calculated in 106 AS patients. Fortunately, there was no unnatural increase in PSA possibly due to prostate inflammation during the initial 6-month evaluation, although it was found in 11 patients thereafter. Distribution of PSADT at 6 months in the 106 patients is shown in Fig. 1. Twenty-two patients showed PSADT to be <2 years, whereas 59 patients showed PSADT to be >10 years or negative PSA slope. On the basis of the intent-to-treat analysis, the primary endpoint, '%PSADT > 2y' at 6 months, was 71.2% (95% CI: 62.1–79.2%).

Prediction of 'Rapid Riser'

Among 106 AS patients in whom PSADT at 6 months was completely calculated, 22 (20.8%) patients were so-called rapid risers (PSADT ≤2 years) as described earlier. In order to analyse the proportion of rapid riser in the setting of more stringent criteria, one more condition could be added to the original criteria. Either one of following conditions could be added: (i) PSA density <0.15, (ii) maximum tumor length <3 mm, (iii) initial PSA <10 ng/ml or (iv) only one positive core per 6–12 systematic cores. Distribution of PSADT ≤2 years, 2 years <PSADT <10 years and PSADT ≥10 years under the four sets of criteria was compared (Table 2). Distribution of PSADT, however, did not prove to be statistically different between any of the subgroups and the original AS cohort, and the proportion of rapid risers under more stringent condition was not reduced.

Table 1. Baseline data in each treatment group

	AS	RP	EBRT	ADT	Total
Age					
50–59	5	0	0	0	5
60–69	51	6	0	0	57
70–74	44	6	1	0	51
75–80	18	1	1	1	21
Initial PSA (ng/ml)					
<10	95	11	1	1	108
≥10	23	2	1	0	26
Mean	7.2	7.1	11.2	4.6	7.3
Core no. at biopsy					
6	37	5	0	0	42
7–8	33	7	1	1	40
9–10	21	2	1	0	24
11–12	27	1	0	0	28
Positive core no.					
1	91	10	1	1	103
2	27	3	1	0	31
Gleason sum					
5	13	2	0	0	15
6	105	11	2	1	119
Max. % cancer					
Mean	13.6	9.4	16.8	11.1	13.5
Median	11.2	9.0	16.8	11.1	11.1
Max	46.7	35	23.3	11.1	46.7
Max. tumor length (mm)					
<3	103	12	1	1	117
≥3	15	1	1	0	17
Mean	1.6	1.5	2.5	1.0	1.6
Median	1.4	1.5	2.5	1.0	1.5
Max	5.8	3.5	3.5	1.0	5.8

One patient who chose EBRT at registration underwent RP soon after registration.
ADT: androgen-deprivation therapy
AS: active surveillance
PSA: prostate-specific antigen
RP: radical prostatectomy
EBRT: external beam radiation

The 6-Month PSADT Versus the 12-Month PSADT

For 99 patients undergoing AS for ≥1 year including 12 patients who wanted to remain on AS in spite of short PSADT at 6 months (≤2 years), the initial 6-month PSADT was compared with the 12-month PSADT that was assessed using all PSA determinations for 1 year after registration, as shown in Fig. 2. Eight of the 12 patients who wanted to remain on AS in spite of short PSADT (PSADT ≤2 years) at 6 months showed the 12-month PSADT to be >2 years.

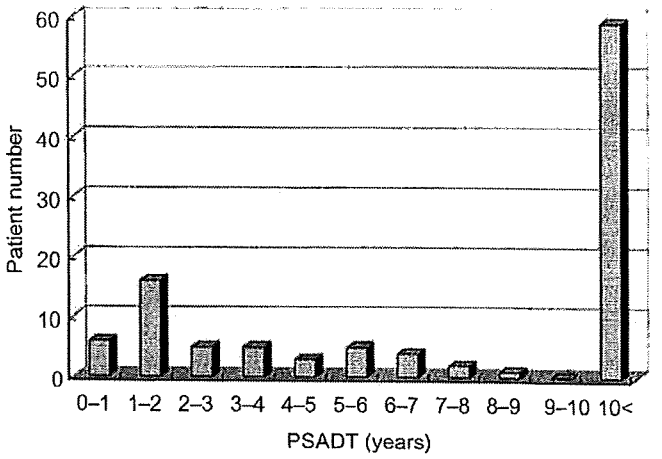

Figure 1. Distribution of the initial 6-month prostate-specific antigen doubling time (PSADT). PSADT >10 years or those which showed negative slope is categorized as PSADT >10 years.

In contrast, among 58 patients with PSADT estimated at 6 months being >10 years ('stable PSA'), only two patients showed PSADT <2 years at 12 months.

Re-biopsy

As a rule of the present study, re-biopsy was recommended to the patients who remained on AS for 1 year and showed PSADT >2 years at the 12-month evaluation, although a few wanted to continue AS in spite of short PSADT. Sixty-six out of 99 patients who remained on AS at least for 1 year agreed to undergo re-biopsy. Among the 66 patients, four patients wanted to remain on AS in spite of PSADT <2 years. The pathological evaluation revealed that 44 out of 66 patients (66.7%, 95% CI: 54.0–77.8) were eligible for the pathological selection criteria again, including 25 patients in whom the second-round biopsy turned negative. Among the 22 patients who did not meet the criteria, three or more positive cores were found in 15 patients, Gleason score ≥7 was observed in 13 and >50% cancer occupation in a positive core was found in 7 as shown in Table 3. There was no association of PSADT with the aggressive findings. Two of four who had PSADT <2 years showed the aggressive findings and the remaining two met the pathological criteria again. After confirmation of deviation from the pathological criteria at re-biopsy, 15 of 22 patients immediately underwent treatment (10: RP; 3: EBRT with or without ADT; 1: seed implantation; 1: ADT) and showed no clinical recurrence until 31 October 2006. In contrast, seven patients wanted to continue AS despite the aggressive pathological findings at re-biopsy. Six remained on AS uneventfully, whereas one patient who started ADT 1 year later showed re-elevation of PSA on 31 October 2006.

Prostatectomy Specimens

Thirteen patients chose RP as the initial treatment and one patient who chose EBRT at registration underwent RP

Table 2. Distribution of the initial 6-month PSADT in subgroups that fit the original selection criteria or that with one additional restriction

PSADT at 6 months	Original criteria (%)	Additional restriction (%)			
		Initial PSA <10	PSAD ≤0.15	One positive core	Max. length <3 mm
Rapid	22 (20.8)	18 (21.7)	10 (23.8)	17 (20.5)	21 (22.6)
Intermediate	25 (23.5)	23 (27.7)	12 (28.5)	20 (24.1)	21 (22.6)
Stable	59 (55.7)	42 (50.6)	20 (47.6)	46 (55.4)	51 (54.8)
Patient number	106	83	42	83	93

Rapid: PSADT was ≤2 years; intermediate: PSADT was between 2 years and 10 years; stable: PSADT was ≥10 years.
PSADT: prostate-specific antigen doubling time

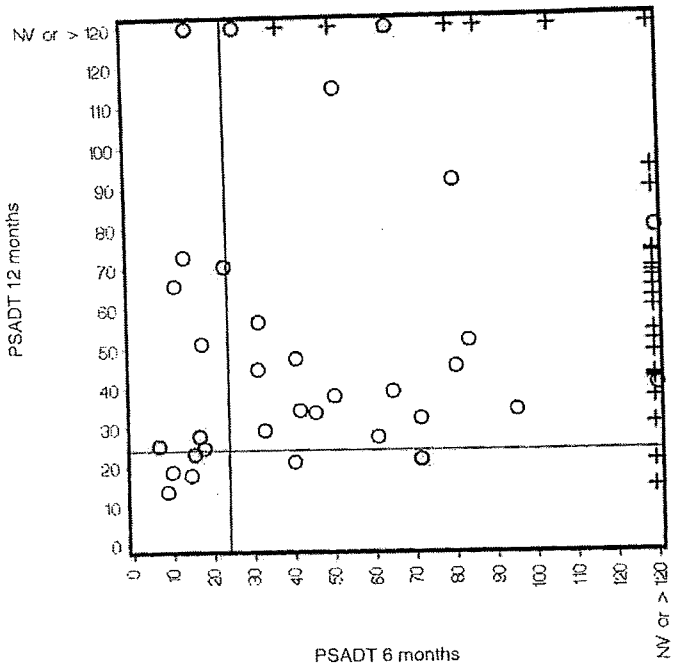

Figure 2. Comparison of the 6-month with the 12-month PSADT in 99 patients who remained on active surveillance (AS) for at least 1 year. '+' indicates PSADT >10 years. 'O' indicates PSADT ≤10 years.

Table 3. Pathological findings of re-biopsy at 1 year after AS and deviation rates from the selection criteria

Pathological criteria						Deviation rate (%)
Number of positive core	0	1	2	3	4 or more	
Patient number	25	13	13	12	3	22.7
% Cancer/ positive core	0	1–25	25–50	50–75	75–100	
Patient number	25	28	6	5	2	10.6
Gleason score	No score	5	6	7	8–10	
Patient number	25	2	28	9	4	19.7

Number of patients who deviated each pathology criterion was divided with number of AS patients who agreed with re-biopsy ($n = 66$).

immediately after enrollment. Non-organ-confined cancer, positive surgical margins and peri-neural invasion were found in 1, 3 and 4 patients, respectively. There was no lymphatic, vascular and seminal vesicle invasion. Invasion to the bladder wall, the urethral mucosa and the rectal wall were also not found (data not shown).

HRQOL in AS Patients

Baseline HRQOL was measured in 128 patients (AS: 114; RP: 11; EBRT: 2; ADT: 1). As to the general HRQOL measured with SF-36, the physical functioning, bodily pain and vitality scores in patients who chose the AS program were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student's t-test) as shown in Fig. 3A. There was no difference in the baseline scores of both SF-36 and UCLA-PCI between those who remained on AS and those who started other treatment within 1 year. HRQOL of 1 year after AS was measured in 95 patients, and the subscale scores of SF-36 were not statistically different from the baseline scores. Bodily pain, vitality and mental health scales in patients remaining on AS for 1 year were better than the age-adjusted Japanese population normative values ($P < 0.05$, Student's t-test), as shown in Fig. 3B. In AS patients, however, the urinary function, sexual function and bowel bother scores measured with UCLA-PCI were worse than the baseline scores ($P < 0.05$, paired t-test).

Follow-up after Registration

Of all participants, neither manifestation of metastasis nor cancer death was observed until 31 October 2006, and three died of other disease and five did not turn up for follow-up. Of the 118 patients who chose AS, 54 (46%) remained on AS for maximal observation of 54 months, with 3-year actuarial AS-remaining rate being 48.9%. The reasons for

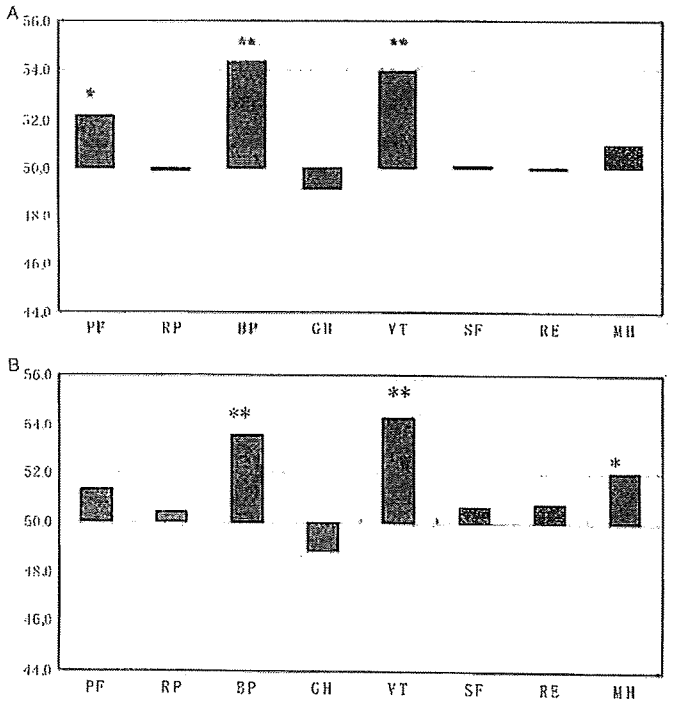

Figure 3. (A) Norm-based scoring of general health-related quality of life (HRQOL) at registration assessed with SF-36 in patients who chose AS. $*P < 0.001$, $**P < 0.0001$. (B) Norm-based scoring of general HRQOL 1 year after AS. PF, physical function; RP, role physical; BP, bodily pain; GH, general health perception; VT, vitality; SF, social function; RE, role emotional; MH, mental health. $*P < 0.05$, $**P < 0.01$.

leaving AS in the 64 patients were as follows: PSADT ≤2 years in 17, pathology progression in 16 and change in T-stage (T1c–T2a) in one. The remaining 30 patients have left AS either due to patient's preference ($n = 15$), co-morbidities ($n = 8$) or for some unknown reason ($n = 7$). Among the 15 patients who wanted to leave the AS program without PSA rise or progression, eight complained of aggravating difficulty in urinary voiding due to accompanying benign prostate hyperplasia (BPH), resulting in undergoing cancer treatment (RP: 4; EBRT: 1; ADT: 1) or transurethral resection of BPH ($n = 2$). Of 16 patients who chose immediate treatment, 15 have been alive without metastasis and one died of lung cancer. Through the observation period, no serious adverse event has been observed in both the AS program group and those who chose immediate treatment.

DISCUSSION

This is the first prospective study on AS in Japanese patients with prostate cancer detected only with PSA elevation. Until the time we started this study, AS had not yet been generally accepted treatment option in Japan, where a randomized study comparing AS with non-AS could hardly been accepted. We therefore designed this study as a phase II setting to assess the validity and feasibility of our AS program. We enrolled 118 AS patients from 13 institutions, which was fewer than the expectation from viewpoint of the most current urology practice. In the early 2000s, however, the annual average number of stage T1cN0M0 patients newly treated at a university hospital or a cancer center hospital in Japan was estimated to be 20–40. Among them, 10–20% of stage T1c might have met the Hopkins pathology criteria for indolent cancer. Under these circumstances, the number of enrollment and those opting for AS suggests high motivation of participants in this study.

PSADT assessed with four serial measurements for 6 months was used as the primary endpoint in this study, although it was a surrogate for survival endpoint. In the calculating PSADT, one critical issue to be solved is how we should handle unnatural surges possibly due to prostate inflammation. Particularly, the number of PSA determinants was relatively small; the influence of measurement error upon estimation of PSADT would be strong. In this study, there was fortunately no unnatural increase in PSA during the initial 6-month evaluation, which might have influence on the primary endpoint. As to the point estimate of '%PSADT > 2y', it was expected to be >80% when this study was designed under the following backgrounds. In 43 untreated cases including 15 non-organ-confined cancers at Stanford University series, 79% showed PSADT to be >2 years (7). In 48 Japanese untreated localized cancers (T1-3N0M0 including 40% of Gleason score ≥7), 71% showed PSADT to be >2 years (13). Our previous retrospective study in 78 Japanese untreated patients (T1N0M0: 53, T2-3N0M0: 25) found that 91% showed PSADT >2 years (14). On the basis of these retrospective studies, although all were small in size, we expected '%PSADT > 2 y' to be ≥80% for the validation of the selection criteria because candidate patients with this selection criteria harbored more favorable biopsy features than those described earlier.

'%PSADT > 2 y'did not reach 80%, and the selection criteria were not validated. We, however, do not consider that major revision of the selection criteria is needed. In the next study, we rather consider that the primary endpoint should be assessed after a longer period (≥1 year) of observation. Comparison of the 6-month PSADT with the 12-month PSADT in the present AS patients strongly suggests the possibility of overestimation as to PSADT estimated at 6 months. The Toronto AS experience demonstrated that the optimal time to determine whether to start a definitive treatment was 2.3 years after starting AS in most of the cases (15,16). In D'Amico et al.'s (17) PSA velocity study, most of the cohort were followed for median of >5 years prior to prostatectomy, but cancer-death rate at 7 years was only 1.75% in Gleason score ≤6 patients. These data warrant a prospective study of AS in which 1–2 years are allowed for observing PSA kinetics. It also remains undetermined whether the critical point of recommendation to start treatment should be PSADT ≤2 years or PSADT ≤3 years. The Toronto AS program has recently revised the timing of

treatment recommendation from PSADT ≤2 years to PSADT ≤3 years (16).

The present study demonstrates the limitation of the current systematic biopsy with regard to select low-risk cancers. The upgrading rate (19.7%) was slightly higher than that (12.9%) seen in the Johns Hopkins series (18). Under-estimation of biopsy has also been demonstrated in the patients who chose RP immediately after registration. These results indicate the necessity to incorporate re-biopsy into AS program, although patients who opt for AS seem to be reluctant to undergo re-biopsy.

The Scandinavian randomized trial did not indicate any significant impairment of HR-QOL at 5 years in the watchful waiting arm (19). Similarly, in the present study, any of the SF-36 subscales was not impaired after 1 year of AS. Although 54% of the patients left the AS program and started therapy to the prostate with maximal observation of 4.5 years, 14% stopped AS due to aggravation of physical condition unrelated to prostate cancer. In particular, it should be noted that 7% of AS patients left AS due to voiding difficulty caused by accompanying BPH.

In conclusion, the results obtained here together with those in similar AS programs being conducted in North America and Europe warrant a prospective analysis of AS program in Japanese patients with modified protocol in which selection criteria and primary endpoint are revised.

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Conflict of interest statement

None declared.

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Image of the Month

A Case of Locally Advanced Prostate Cancer in the Transition Zone

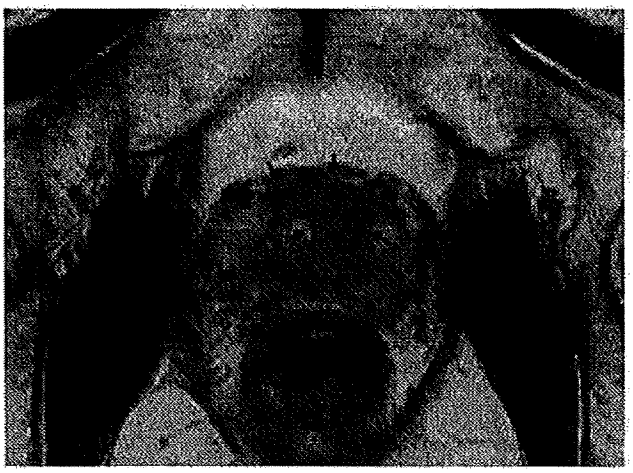

Figure 1.

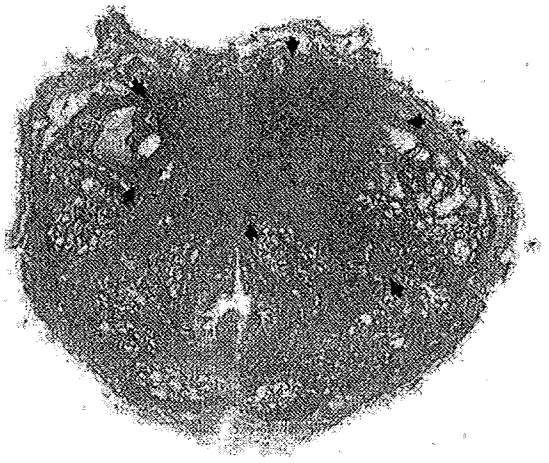

Figure 2.

A 65-year-old man was referred to our hospital for the further evaluation and treatment of prostate cancer. On '3-Tesla' magnetic resonance imaging, an irregular low-intensity tumor, located mainly in the transition zone was demonstrated on T2-weighted imaging. The tumor extended slightly out of the prostate capsule on the ventral side (Fig. 1). We decided to undergo surgical resection for cure, although it is T3N0M0, Stage III, and could be a candidate for nonsurgical treatment. Therefore, we performed modified radical prostatectomy, preserving the bilateral neurovascular bundles.

Histological examination revealed a moderately differentiated adenocarcinoma that located mainly in the transition zone and involving the peripheral zone of the left lobe (Fig. 2; a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org). The cancer cells expanded beyond the prostatic capsule ventrally, but the surgical margin was negative. Six months after surgery, the patient is doing well without any sign of recurrence, urinary incontinence or erectile dysfunction. The serum prostate-specific antigen level is under 0.1 ng/ml.

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Survival of Metastatic Germ Cell Cancer Patients Assessed by International Germ Cell Consensus Classification in Japan

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Background: As a risk classification system of metastatic germ cell tumors, the International Germ Cell Consensus (IGCC) classification was proposed in 1997 and has received broad approval. Since the IGCC classification was based on patients treated between 1975 and 1990, we aimed to investigate whether survival has improved for more recently treated Japanese patients.

Methods: We analyzed 296 patients with metastatic germ cell tumors treated at seven hospitals in Japan between 1990 and 2001. These cases are classified as good, intermediate or poor prognosis groups by the IGCC classification. The 5-year progression-free and the 5-year overall survivals were calculated for each prognosis group.

Results: The median follow-up period of all patients was 53 months. In 227 non-seminomatous germ cell tumor cases, the 5-year progression-free survival (95% confidence interval) for good ($n = 55$), intermediate ($n = 106$) and poor ($n = 66$) prognosis was 96% (91–100), 71% (62–80) and 52% (39–65) ($P < 0.001$), respectively. The 5-year overall survival was 94% (88–100), 81% (73–89) and 61% (49–73) ($P < 0.001$), respectively. In 69 seminoma cases, the 5-year progression-free survival for good ($n = 64$) and intermediate ($n = 5$) prognosis was 78% (67–89) and 80% (45–100) ($P = 0.98$), respectively. The 5-year overall survival was 90% (82–99) and 80% (45–100) ($P = 0.49$), respectively.

Conclusions: There was a trend of increase in survival for any risk groups and, in particular, large increase in survival for patients with a poor prognosis. This increase is most likely attributed to more effective chemotherapy regimens and more extensive care in the experienced institutes.

Key words: chemotherapy – etoposide – IGCC classification – prognosis – germ cell tumor

INTRODUCTION

Since the introduction of cisplatin-based chemotherapy in the 1970s, long-term cure rates of patients with metastatic germ cell tumors have increased up to 80% (1). Progress in cancer chemotherapy regimens such as etoposide, granulocyte-colony stimulating factor (G-CSF) and high-dose chemotherapy with stem cell support have also positively affected cure rates. To further improve treatment outcome, patients with a poor prognosis should be identified at initial diagnosis and treated with a more intensive strategy. The International Germ Cell Consensus (IGCC) classification that was proposed in 1997 has received broad approval as a means of stratifying risk groups (2).

The IGCC classification reviewed germ cell tumors with metastasis in over 5000 patients treated between 1975 and 1990 in 10 European and American countries. However,

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treatment approaches have changed since the 1990s: such as the BEP regimen (3) as standard first line chemotherapy and the use of G-CSF. Therefore, treatment outcome should be substantially improved among those treated in 1990 or later. We analyzed 296 patients with metastatic germ cell tumors who underwent treatment at seven hospitals in Japan between 1990 and 2001 and assessed whether survival has improved according to the IGCC classification in comparison with that by International Germ Cell Cancer Collaborative Group (IGCCCG).

PATIENTS AND METHODS

The study included 296 men admitted to seven hospitals in Japan, National Cancer Center Hospital, Tohoku University Hospital, Kyoto University Hospital, Tsukuba University Hospital, Sapporo Medical University Hospital, Kyushu University Hospital and Kyoto Prefectural University Hospital, between 1990 and 2001. There were 286 patients with metastatic testicular tumor and 10 with extragonadal germ cell tumors (EGCT).

Of the 286 testicular tumor patients, 279 were treated with high orchiectomy and chemotherapy, and three were treated with chemotherapy without orchiectomy. Four were treated with high orchiectomy, but died before chemotherapy. The 10 cases with EGCT were treated with chemotherapy. Most patients received platinum-based primary combination chemotherapy. A total of 141 patients had post-chemotherapy residual tumor excised surgically. Fifteen patients received additional radiation therapy.

As first line chemotherapy for 292 patients, 127 (43%) were treated by BEP (bleomycin, etoposide and cisplatin) or PEP (peplomycin, etoposide and cisplatin), 72 (25%) by EP (etoposide and cisplatin), 52 (18%) by PVB (cisplatin, vinblastine and bleomycin) or PVP (cisplatin, vinblastine and peplomycin), 15 (5%) by VAB-6 (vinblastine, actinomycin D, bleomycin, cyclophosphamide and cisplatin), 5 (2%) by VIP (etoposide, ifosfamide and cisplatin) or VeIP (vinblastine, ifosfamide and cisplatin), and 14 (5%) by other chemotherapy. Thus, 206 (71%) received first line chemotherapy containing etoposide.

Comparisons of different groups were made using the Student's *t*-test or the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. Disease progression-free survival and overall survivals were estimated by Kaplan and Meier plots and stratified by IGCC classification. Differences of survivals between groups were tested using the log-rank test. P value <0.05 were considered statistically significant.

RESULTS

Patient age ranged from 16 to 73 years (median 30 years and mean 31.7 years). The median follow-up time was 53 months, ranging from 0 to 169 months (Table 1). Among the 10 cases with EGCT, three had mediastinal primary disease and seven had retroperitoneal primary disease.

Non-Seminomatous Germ Cell Tumor

There were 227 patients with non-seminomatous germ cell tumor (NSGCT) and their ages ranged from 16 to 65 years (median 28 years and mean 29.9 years). Main histology was embryonal carcinoma (40%), teratoma (15%), seminoma (15%), yolk sac tumor (11%) and choriocarcinoma (8%). According to the IGCC classification, 55 (24%) were classified as good prognosis group, 106 (47%) as intermediate prognosis and 66 (29%) as poor prognosis. The median follow-up time was 50 months, ranging from 0 to 169 months from the initiation of treatment (Table 1). Disease progression occurred in 67 (30%) patients, 45 (20%) died of disease and 3 (1%) died of other disease. In the 67 patients with disease progression, the period of relapse was 0 month (no complete response) in 19 (28%) patients, 1–12 month in 23 (34%), 13–24 month in 10 (15%), 25–36 month in 3 (5%), 37–60 month in 4 (6%) and more than 60 month in 3 (5%).

Table 2 lists clinical and pathological features in the three groups of NSGCT patients. There was no statistically

Table 1. Pathological characteristics and International Germ Cell Consensus (IGCC) classification of 296 patients

	All patients	NSGCT	Seminoma
No. of patients	296	227	69
Median (range) age (years)	30 (16–73)	28 (16–65)	36 (22–73)
Primary tumor site			
Right testis	143	114	29
Left testis	138	101	37
Bilateral testis	1	0	1
EGCT	10	9	1
Unknown	4	3	1
Main histology (%)			
Seminoma	103	34 (15)	69 (100)
Embryonal carcinoma	90	90 (40)	–
Teratoma	34	34 (15)	–
Yolk sac tumor	25	25 (11)	–
Choriocarcinoma	19	19 (8)	–
Unknown	25	25 (11)	–
IGCC classification (%)			
Good	119	55 (24)	64 (93)
Intermediate	111	106 (47)	5 (7)
Poor	66	66 (29)	–
Median (range) follow-up (months)	53 (0–169)	50 (0–169)	57 (0–168)

NSGCT, non-seminomatous germ cell tumor; EGCT: extragonadal germ cell tumor.

significant difference among the three groups in primary tumor site, T classification or main histology. There was statistically significant difference in AFP ($P < 0.001$), HCG ($P < 0.001$), LDH ($P < 0.001$), N classification ($P = 0.002$), M classification ($P < 0.001$) and first line chemotherapy ($P = 0.047$).

The 5-year progression-free survival and overall survival (95% confidence interval) were, respectively, 96% (91–100) and 94% (88–100) for the good prognosis group, 71% (62–80) and 81% (73–89) for the intermediate prognosis, and 52% (39–65) and 61% (49–73) for the poor prognosis (Fig. 1). There was statistically significant difference both in progression-free and overall survivals among the three groups ($P < 0.001$).

Seminoma

The ages of seminoma patients were between 22 and 73 years (median 36 years and mean 37.4 years). Of the 69 patients with seminomatous tumors, 64 (93%) were classified as good prognosis group and 5 (7%) as intermediate prognosis. The median follow-up time was 57 months from the start of treatment. Disease progression occurred in 14 (20%) patients, 6 (9%) died of disease and 1 (1%) died of other disease. In the 14 patients with disease progression, the period of relapse was 0 month (no complete response) in 2 (14%) patients, 1–12 month in 10 (72%) and 25–36 month in 2 (14%).

Table 3 lists clinical and pathological features in the two groups of seminoma patients. There was no statistically significant difference between the two groups in primary tumor site, T classification or first line chemotherapy. There was statistically significant difference in N classification ($P = 0.044$) and M classification ($P < 0.001$).

There was no statistically significant difference in progression-free survival between the good and intermediate prognosis groups ($P = 0.982$): 5-year progression-free survival (95% confidence interval) of 78% (67–89) and 80% (45–100), respectively (Fig. 2). The 5-year overall survivals were 90% (82–99) and 80% (45–100), respectively, with no statistically significant difference ($P = 0.490$).

DISCUSSION

Current surgical remedies combined with chemotherapy using the BEP regimen can cure 80% of all metastatic germ cell tumors (3). This strategy gained widespread acceptance in the late 1980s. In addition, to reduce the side effect of lung toxicity, peplomycin are sometimes administered instead of bleomycin in Japan. For subsequent relapses or tumors that persist despite BEP therapy, the effects of ifosfamide, paclitaxel and more recently, gemcitabine and irinotecan, are being confirmed (4).

The pre-therapeutic prognosis of relapses and persistent disease is gaining greater importance since physicians can devise more effective initial therapeutic strategies. Several traditional classification methodologies have been proposed, as typified by the Indiana classification. Each had advantages and disadvantages, and a universal classification method has not been established. Against this background, the IGCC classification was proposed based on 5202 prognostic analyses of metastatic germ cell cancers conducted in Europe and North America (2).

In Japan, some prognostic analyses of metastatic germ cell cancers have been attempted at several institutions (5), but not using the IGCC classifications for large numbers of patients. We therefore investigated the applicability of the IGCC classification to Japanese patients with metastatic germ cell tumors in a multi-institutional study.

The risk distributions of patients with seminoma were almost identical between the IGCCCG report and the present study. However, fewer NSGCT patients had a good prognosis and more had an intermediate to poor prognosis in the present study than in the IGCCCG report. Whereas the IGCCCG study consisted of 56%, 28% and 16% groups with a good, intermediate and poor prognosis, respectively, the prognostic distribution of our patients was 24%, 47% and 29%, respectively. These figures suggest that fewer testicular tumors are diagnosed early in Japan compared with those in Europe and North America. In addition, whereas the ratios of EGCT patients in the IGCCCG report were 13% of seminoma patients and 6% of non-seminoma patients, our study included 1% and 4%, respectively, of such patients. Furthermore, our series had only 3 (1%) patients with mediastinal primary tumor, whereas the original IGCCCG report had 3% of such cases. The improved survival of the poor risk group may be partly attributable to this lower percentage of EGCT, especially to the fewer cases of mediastinal primary tumor.

The IGCCCG and the present reports do not significantly differ that the group with seminoma had a good prognosis. However, 5-year progression-free survival values were better for our patients with an intermediate prognosis than those of such patients described in the IGCCCG report (80% versus 67%; Table 4). We did not identify any significant difference in prognosis between the groups with good and intermediate prognoses. Although our study included relatively fewer patients, the prognosis of those with seminoma requires further study, including an analysis of other prognostic factors and parameters.

The prognosis of all prognostic groups of NSGCT patients was better in the present study than in the IGCCCG report. The present study showed that 5-year progression-free and overall survival rates for the good prognosis group was 96% and 94%, respectively, whereas IGCCCG study found 89% and 92%, respectively. Similarly for the poor prognosis group, these values were, respectively, 52% and 61% in the current study, and 41% and 48% in the IGCCCG report (Table 4).

Our patients seemed to have a better overall prognosis than those in the IGCCCG report. Several reasons might account for this. Firstly, etoposide became available in Japan during 1987 and BEP became the first line chemotherapy

Table 2. Clinical characteristics of non-seminomatous germ cell tumor patients

	Good prognosis	Intermediate prognosis	Poor prognosis	*P* value
No. of patients	55	106	66	
Mean age ± SD (years)	30.7 ± 6.4	30.1 ± 10.5	29.0 ± 7.9	0.119
Primary tumor site				0.846
Right testis	29 (53)	56 (53)	29 (44)	
Left testis	24 (43)	45 (42)	32 (48)	
Extragonadal	1 (2)	4 (4)	4 (6)	
Unknown	1 (2)	1 (1)	1 (2)	
AFP (ng/ml)				<0.001
<UPN	18 (33)	21 (20)	20 (30)	
UPN-1000	37 (67)	42 (40)	12 (18)	
1000—10 000	—	43 (40)	12 (18)	
>10 000	—	—	22 (34)	
HCG (IU/l)				<0.001
<UPN	16 (29)	18 (17)	13 (20)	
UPN-5000	39 (71)	69 (65)	27 (41)	
5000–50 000	—	19 (18)	4 (6)	
>50 000	—	—	22 (33)	
LDH (IU/l)				<0.001
<UPN	28 (51)	9 (9)	3 (5)	
UPN-1.5 × UPN	27 (49)	12 (11)	10 (15)	
1.5 × UPN-10 × UPN	—	85 (80)	45 (68)	
>10 × UPN	—	—	6 (9)	
Unknown	—	—	2 (3)	
T classification				0.169
T1	19 (35)	41 (40)	24 (39)	
T2	10 (19)	15 (15)	8 (13)	
T3	4 (7)	6 (6)	10 (16)	
T4	2 (4)	0	3 (5)	
TX	19 (35)	40 (39)	17 (27)	
N classification				0.002
N0	13 (24)	13 (13)	15 (24)	
N1	13 (24)	14 (14)	6 (10)	
N2	21 (39)	27 (26)	14 (22)	
N3	4 (7)	42 (41)	24 (39)	
NX	3 (6)	6 (6)	3 (5)	
M classification				<0.001
M0	29 (54)	33 (32)	6 (10)	
M1a	25 (46)	69 (68)	20 (32)	
M1b	0	0	36 (58)	
Main histology				0.113
Embryonal	28 (51)	43 (41)	19 (28)	
Teratoma	10 (18)	16 (15)	8 (12)	
Seminoma	7 (13)	18 (17)	9 (14)	
Yolk sac tumor	3 (5)	10 (9)	12 (18)	

Continued

Table 2. *Continued*

	Good prognosis	Intermediate prognosis	Poor prognosis	*P* value
Choriocarcinoma	1 (2)	9 (9)	9 (14)	
Unknown	6 (11)	10 (9)	9 (14)	
First line chemotherapy				0.047
BEP or PEP	29 (53)	51 (48)	29 (45)	
EP	12 (22)	21 (20)	12 (19)	
PVB or PVP	8 (14)	17 (16)	18 (28)	
VAB-6	0	9 (9)	4 (6)	
VIP or VeIP	0	3 (3)	0	
Other	2 (4)	3 (3)	1 (2)	
Unknown	4 (7)	1 (1)	0	
(Died before chemotherapy)	0	1	2	
Mean follow-up ± SD (months)	55.4 ± 30.8	62.4 ± 40.3	53.8 ± 48.0	0.144

Numbers in parentheses are percentages.
SD, standard deviation; UPN, upper limit (normal), AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; BEP, bleomycin, etoposide and cisplatin; PEP, peplomycin, etoposide and cisplatin; EP, etoposide and cisplatin; PVB, cisplatin, vinblastine and bleomycin; PVP, cisplatin, vinblastine and peplomycin; VAB-6; vinblastine, actinomycin D, bleomycin, cyclophosphamide and cisplatin; VIP, etoposide, ifosfamide and cisplatin; VeIP, vinblastine, ifosfamide and cisplatin; IGCC, International Germ Cell Consensus.

thereafter. Second, G-CSF became available in Japan during 1991 and its use has allowed chemotherapy to continue without extending the dosage interval. Furthermore, experienced urologists usually diagnose, administer chemotherapy, excise post-chemotherapy residual mass and perform post-treatment follow-up in Japan. These might be partly involved in the improved survival of our patients. In this study there was a significant difference in the first line chemotherapy for NSGCT, but the reason is not clarified because this is a multi-institutional retrospective study.

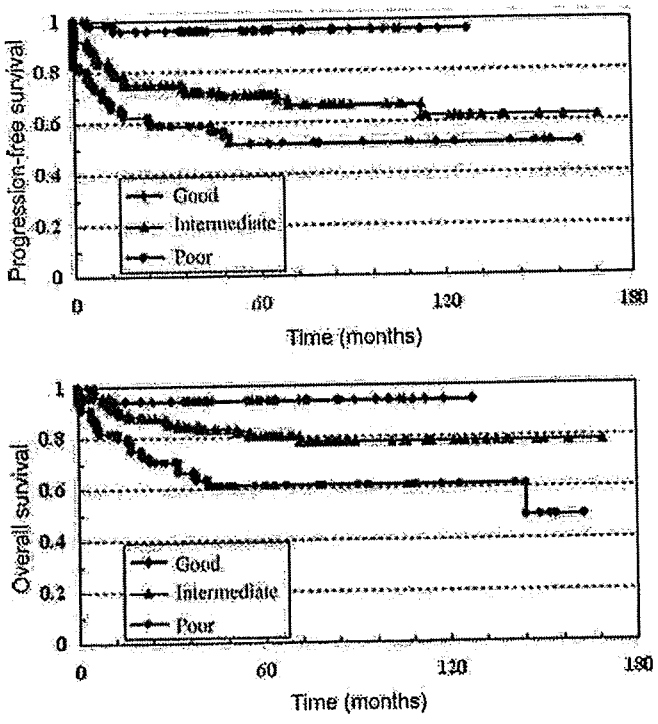

Figure 1. Progression-free and overall survivals in non-seminomatous germ cell tumor patients by IGCC classification. There were significant differences both in progression-free survivals ($P < 0.001$) and overall survivals ($P < 0.001$).

Whereas the IGCCCG report described patients in Europe and North America between 1975 and 1990, we considered patients treated between 1990 and 2001. That is, approximately 40% of the patients described in the IGCCCG report were treated before the widespread use of BEP. Currently available treatments for germ cell cancers are more effective than those administered at the time of the IGCCCG report. Einhorn (6) reported that the survival of patients with a 'poor' prognosis treated with BEP in 2002 was 10% higher than that of corresponding patients in the IGCCCG report. Muramaki et al. (7) reported that the 5-year overall survival of NSGCT patients significantly increased from 72.8% during 1978–1989, to 83.6% during 1990–2001. Similarly, a meta-analysis of NSGCT patients treated after 1989 indicated that the 5-year survival for good ($n = 1087$), intermediate ($n = 232$) and poor ($n = 456$) prognosis groups was 94%, 83% and 71%, respectively, and that the survival of patients with a poor prognosis increased remarkably (8). Therefore, the prognosis of NSGCT patients with a 'poor' prognosis considerably differs between now and before 1989. Compared with before 1989, more patients with a serious general status and major metastasis can be saved using appropriate chemotherapy. This progress might be reflected in the statistical data.

To target intensive treatment strategies for patients with a very poor prognosis, subgroups of such patients have been identified among those with a poor prognosis. Mazumdar et al. (9) identified the rate at which the tumor markers of human chorionic gonadotropin (HCG) and alpha-fetoprotein

Table 3. Clinical characteristics of seminoma patients

	Good prognosis	Intermediate prognosis	*P* value
No. of patients	64	5	
Mean age ± SD (years)	37.4 ± 9.9	38.0 ± 8.8	0.889
Primary tumor site			0.934
Right testis	26 (40)	3 (60)	
Left testis	35 (54)	2 (40)	
Bilateral testis	1 (2)	0	
Extragonadal	1 (2)	0	
Unknown	1 (2)	0	
T classification			0.296
T1	14 (22)	2 (40)	
T2	20 (32)	0	
T3	8 (13)	2 (40)	
T4	3 (5)	0	
TX	18 (28)	1 (20)	
N classification			0.044
N0	1 (2)	0	
N1	7 (11)	0	
N2	17 (27)	0	
N3	35 (55)	3 (60)	
NX	3 (5)	2 (40)	
M classification			<0.001
M0	43 (68)	0	
M1a	20 (32)	0	
M1b	0	5 (100)	
First line chemotherapy			0.839
BEP	16 (26)	2 (40)	
EP	24 (38)	3 (60)	
PVB or PVP	9 (14)	0	
VAB-6	2 (3)	0	
VIP	2 (3)	0	
Other	8 (13)	0	
Unknown	2 (3)	0	
(Died before chemotherapy)	1	0	
Mean follow-up ± SD (months)	58.6 ± 39.4	59.5 ± 45.3	0.642

Numbers in parentheses are percentages.
SD, standard deviation.

(AFP) decline during the first two cycles of chemotherapy as an important risk factor, especially in patients with a poor prognosis. Kollmannsberger et al. (10) developed a regression tree using visceral metastasis, primary site and abdominal mass as risk factors for patients with a poor prognosis. This tree classified five subgroups that differed in terms of 2-year survival ranging from 49% to 84%. Using a similar tree procedure, Dijk et al. (11) developed a new tree

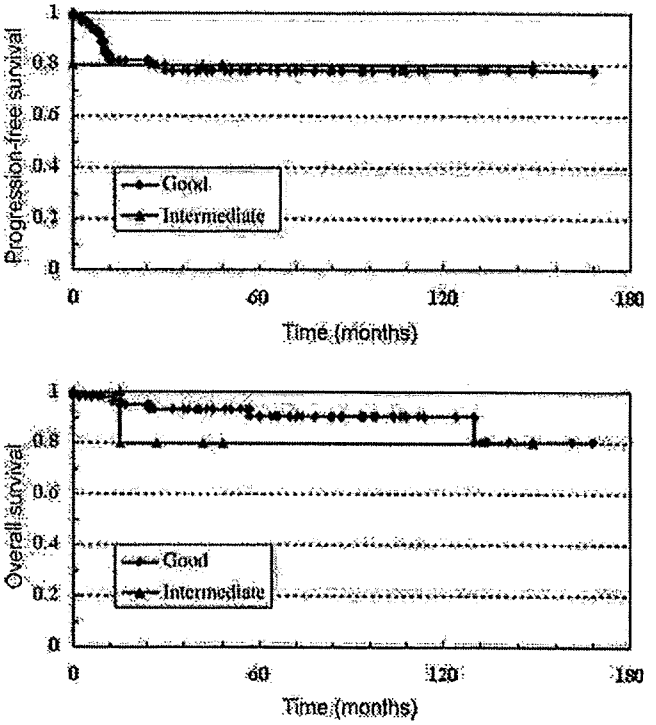

Figure 2. Progression-free survival and overall survival in seminoma patients by IGCC classification. There was no significant difference between the 2 groups.

Table 4. Five-year progression-free and overall survivals in International Germ Cell Cancer Collaborative Group (IGCCCG) report and present study

	NSGCT		Seminoma	
	IGCCCG	Present study (95% CI)	IGCCCG	Present study (95% CI)
Good prognosis group				
5-year progression-free survival (%)	89	96 (91–100)	82	78 (67–89)
5-year overall survival (%)	92	94 (88–100)	86	90 (82–99)
Intermediate prognosis group				
5-year progression-free survival (%)	75	71 (62–80)	67	80 (45–100)
5-year overall survival (%)	80	81 (73–89)	72	80 (45–100)
Poor prognosis group				
5-year progression-free survival (%)	41	52 (39–65)		
5-year overall survival (%)	48	61 (49–73)		

CI, Confidence interval.