

I.4. Pathological findings in biopsy specimens**I.4.1. Histological type**

Pathological type	Number	%
Adenocarcinoma	4519	99.80
Neuroendocrine tumor	3	0.10
Transitional cell carcinoma	2	0.00
Other	2	0.00
Uncertain	3	0.10
Total	4529	100

I.4.3. Poorer differentiation

Number	%
W/D	959 21.20
M/D	1664 36.70
P/D	1337 29.50
Uncertain	569 12.60
Total	4529 100

I.5. TNM classification**I.5.1. T stage distribution**

T stage	Number	%
T0	12	0.27
T1a	166	3.73
T1b	78	1.75
T1c	901	20.26
T2a	968	21.77
T2b	771	17.34
T3a	702	15.79
T3b	491	11.04
T4	358	8.05
Total	4447	100

TNM stage followed by 1997 UICC's TNM classification.

I.5.2. N stage distribution

N stage	Number	%
N0	3569	78.80
N1	501	11.06
NX	459	10.13
Total	4529	100

I.4.2. Predominant differentiation

Pathological pattern	Number	%
W/D	1416	31.30
M/D	1972	43.50
P/D	931	20.60
Uncertain	210	4.60
Total	4529	100

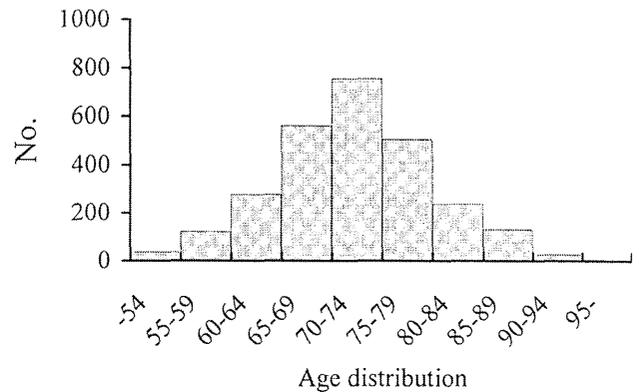
I.5.3. M stage distribution

M stage	Number	%
M0	3243	71.61
M1a	40	0.88
M1b	861	19.01
M1c	63	1.39
MX	322	7.11
Total	4529	100

II. General statistics in clinical T1c-T3N0M0 prostate cancer

II.1. Age distribution

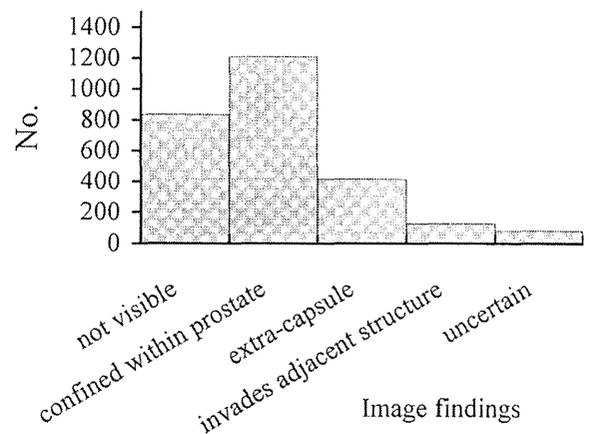
Age range	Number	%
<54	38	1.42
55-59	123	4.61
60-64	279	10.45
65-69	562	21.04
70-74	756	28.30
75-79	506	18.94
80-84	240	8.99
85-89	132	4.94
90-94	27	1.01
95>	8	0.15
Total	2671	100



Cases were divided into age groups by 5 years as indicated. Bars demonstrate the number of cases between equal and over the age on the left lower corner and below the age on the right lower corner of each bar. The numbers below each bar indicates the percentage of cases in each age group among all registered cases.

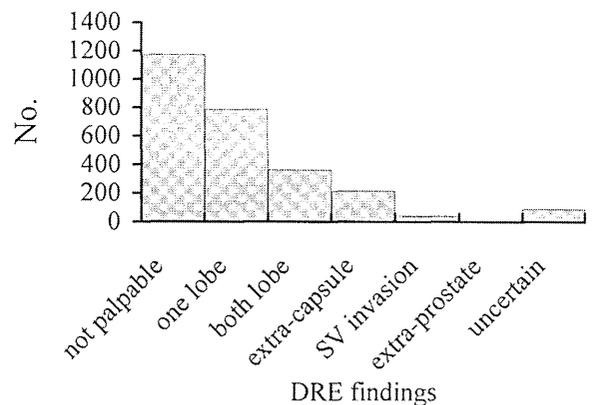
II.2. Findings of image study

Number	%	
Not visible	836	31.87
Confined within prostate	1209	46.09
Extra-capsule	416	15.86
Invades adjacent structure	128	4.88
Uncertain	82	1.30
Total	2671	100



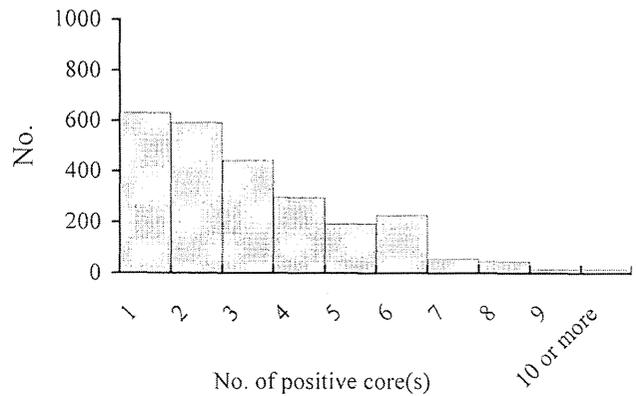
II.3. DRE findings

Number	%	
Not palpable	1174	43.95
One lobe	786	29.43
Both lobe	362	13.55
Extra-capsule	215	8.05
SV invasion	40	1.50
Extra-prostate	5	0.19
Uncertain	89	3.33
Total	2671	100



II.4. Number of cancer positive core(s) in systematic prostate biopsy

Core(s)	Number	%
1	631	25.03
2	592	23.48
3	443	17.57
4	296	11.74
5	192	7.62
6	226	8.97
7	55	2.18
8	46	1.83
9	16	0.64
10 or more	16	0.64
Total	2513	100



*uncertain: 158 patients.

II.5. Correlation between DRE findings and image findings

DRE	Image findings					Total
	Not visible	Confined	Extra-capsule	Invades	Uncertain	
Not palpable	678	409	37	22	28	1174
One lobe	111	510	111	31	23	786
Both lobe	29	204	88	25	16	362
Extra-capsule	5	31	159	15	5	215
SV invasion	1	2	11	25	1	40
Extra-prostate	0	2	0	3	0	5
Uncertain	12	51	10	7	9	89
Total	836	1209	416	128	82	2671

II.6. T stage distribution†

Stage	Number	%
T1c	721	26.99
T2a	794	29.73
T2b	528	19.77
T3a	426	15.95
T3b	202	7.56
Total	2671	100

†T stage followed by 1997 UICC's TNM classification.

II.7. Correlation between Gleason's score† and T stage

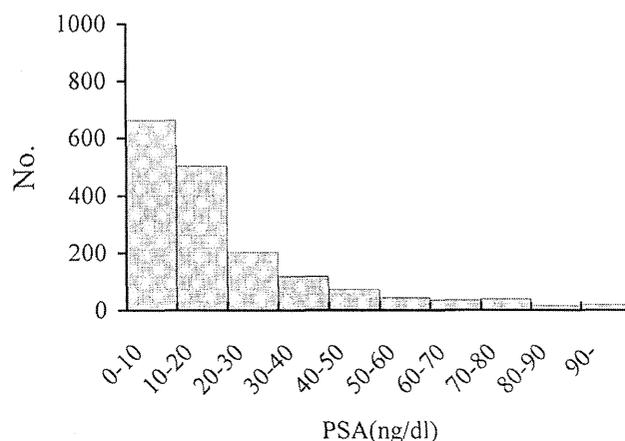
Gleason's score	T stage (1997 UICC)					Total
	T1c	T2a	T2b	T3a	T3b	
2	37	28	16	2	1	84
3	48	50	19	13	3	133
4	51	65	31	16	4	167
5	73	109	70	51	22	325
6	91	109	61	39	22	322
7	93	101	98	88	49	429
8	17	26	25	35	15	118
9	18	24	28	44	18	132
10	5	4	5	4	0	18
Total	433	516	353	292	134	1728

†The Gleason grade was not judged in 943 patients.

III. Correlation between PSA and clinicopathological factors in clinical T1c-T3N0M0 prostate cancer

III.1. PSA distribution†

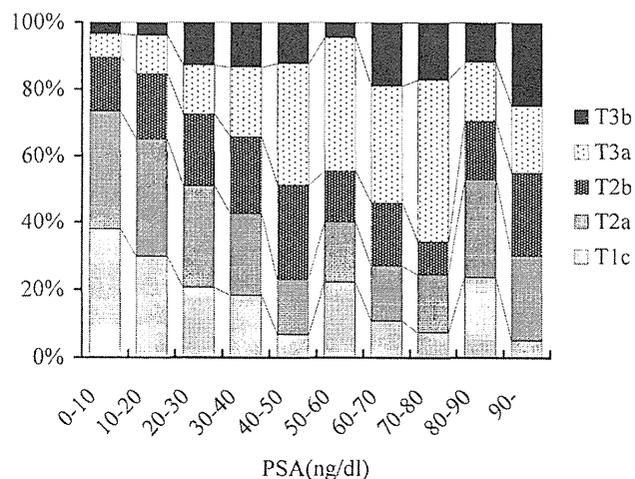
PSA(ng/dl)	Total	%
0-10	663	36.131
10-20	504	27.466
20-30	204	11.117
30-40	120	6.54
40-50	74	4.033
50-60	45	2.452
60-70	37	2.016
70-80	41	2.234
80-90	17	0.926
90>	20	1.09
1725	100	



†Cases were divided into groups of PSA value by 10 ng/mL as indicated. Methods of measurement was Tandem-R as the standard, and include all Tandem-R compatible kits, such as E test TOSOH, CHEMILUMI ACS-PSA, SHIFALITE PSA and LUMIPULSE PSA. Bars demonstrate the number of cases between equal and over the value on the left lower corner and below the value on the right lower corner of each bar. Cases with PSA equal and over 90 ng/mL were counted as a group. The numbers below each bar indicates the percentage of cases in each group among all registered cases.

III.2. Correlation between PSA and clinical T stage

PSA(ng/dl)	T stage					Total
	T1c	T2a	T2b	T3a	T3b	
0-10	251	236	107	46	23	663
10-20	150	178	99	58	19	504
20-30	42	62	44	30	26	204
30-40	22	29	28	25	16	120
40-50	5	12	21	27	9	74
50-60	10	8	7	18	2	45
60-70	4	6	7	13	7	37
70-80	3	7	4	20	7	41
80-90	4	5	3	3	2	17
90>	1	5	5	4	5	20
Total	492	548	325	244	116	1725

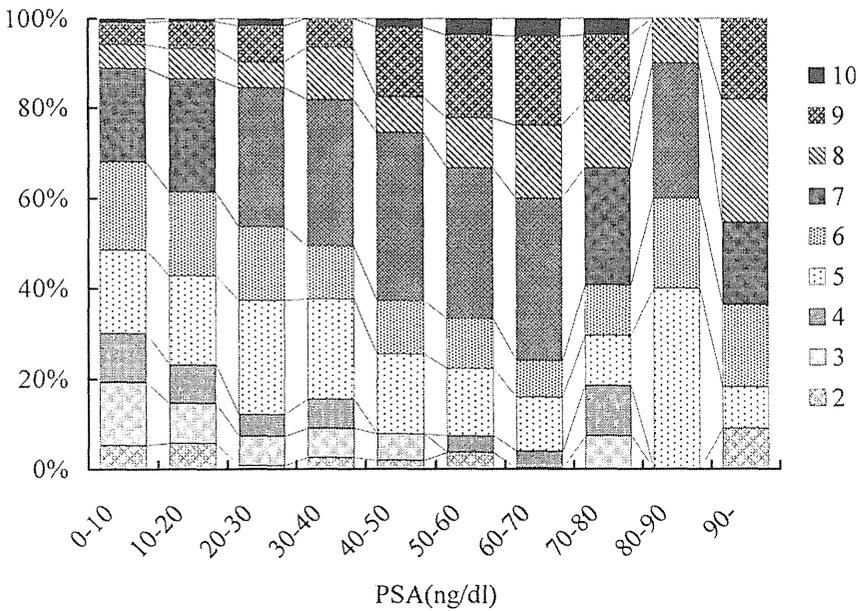


Cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of each T stage among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.

III.3. Correlation between PSA and Gleason's score

PSA(ng/dl)	Gleason's score									Total
	2	3	4	5	6	7	8	9	10	
0-10	24	63	49	83	88	94	24	22	4	663
10-20	19	29	28	65	61	83	22	20	2	504
20-30	1	8	6	31	20	38	7	10	2	204
30-40	2	5	5	17	9	25	9	5	0	120
40-50	1	3	0	9	6	19	4	8	1	74
50-60	1	0	1	4	3	9	3	5	1	45
60-70	0	0	1	3	2	9	4	5	1	37
70-80	0	2	3	3	3	7	4	4	1	41
80-90	0	0	0	4	2	3	1	0	0	17
90>	1	0	0	1	2	2	3	2	0	20
Total	49	110	93	220	196	289	81	81	12	1725

Cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of each Gleason's score among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group. The numbers below each bar indicates the number of cases in each PSA group.

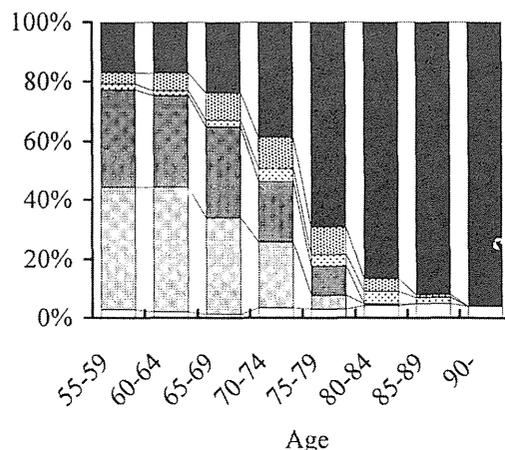


IV. Main initially planned treatment for fresh cases without concomitant malignancy patients in clinical T1c-T3N0M0 prostate cancer

IV.1. Age distribution and treatment

Age range	Treatment						Total
	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	
55-59	3	44	35	2	4	18	106
60-64	5	101	74	4	14	41	239
65-69	6	148	141	10	41	108	454
70-74	21	132	122	27	63	229	594
75-79	12	18	38	15	36	268	387
80-84	8	1	0	8	8	163	188
85-89	5	0	0	2	1	93	101
90>	1	0	0	0	0	24	23
Total	61	444	410	68	167	944	2094

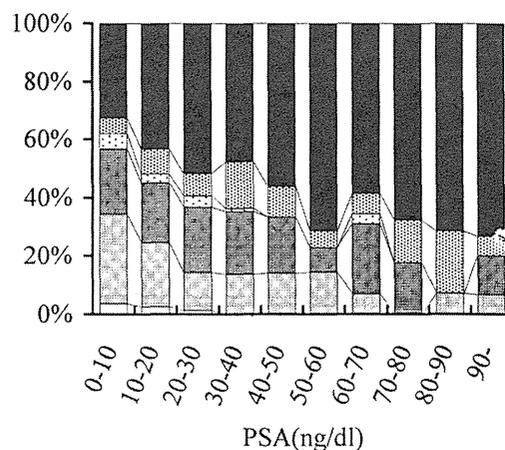
Clinical T1c-T3 cases were divided by age. Bars demonstrate the percentage of adopted treatment among each age group.



IV.2. PSA and treatment

PSA(ng/dl)	Treatment						Total
	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	
0-10	18	152	110	26	27	161	494
10-20	10	89	83	12	34	175	403
20-30	2	20	35	6	12	80	155
30-40	0	12	19	1	14	42	88
40-50	0	8	11	0	6	32	57
50-60	0	5	3	0	2	25	35
60-70	0	2	7	1	2	17	29
70-80	0	0	6	0	5	23	34
80-90	0	1	0	0	3	10	14
90>	0	1	2	0	1	11	15
Total	30	290	276	46	106	576	1324

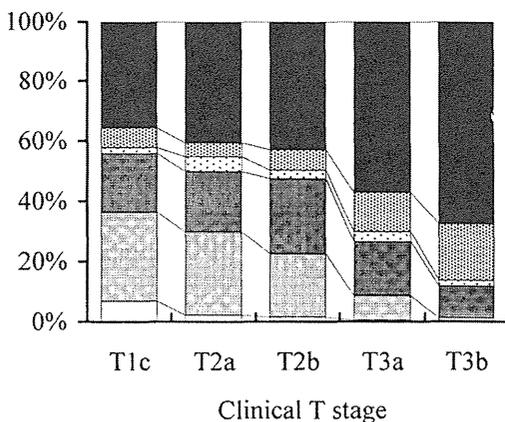
Clinical T1c-T3 cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of adopted treatment among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.



IV.3. Main treatment and clinical T stage†

Initial treatment	T stage					Total
	T1c	T2a	T2b	T3a	T3b	
W/W	39	14	7	2	0	62
RPP	167	173	88	29	2	459
RPP+Hx	110	126	105	63	17	421
Rx	11	31	12	12	3	69
Rx+Hx	37	29	28	46	30	170
Hx	202	255	181	202	108	948
Total	566	628	421	354	160	2129

†Bars demonstrate the percentage of adopted treatment and each stage.

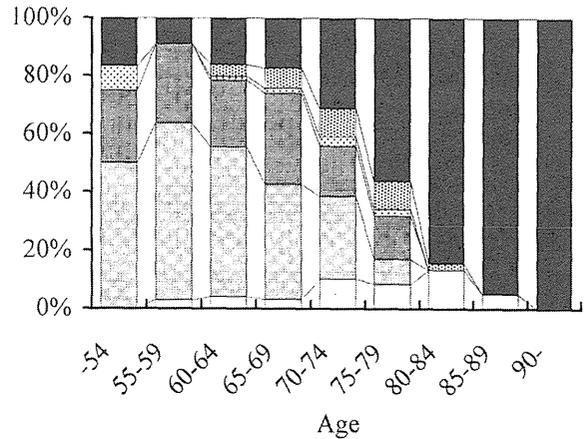


W/W
 RPP
 RPP+Hx
 Rx
 Rx+Hx
 Hx

IV.4. T stage, age and initially planned treatment

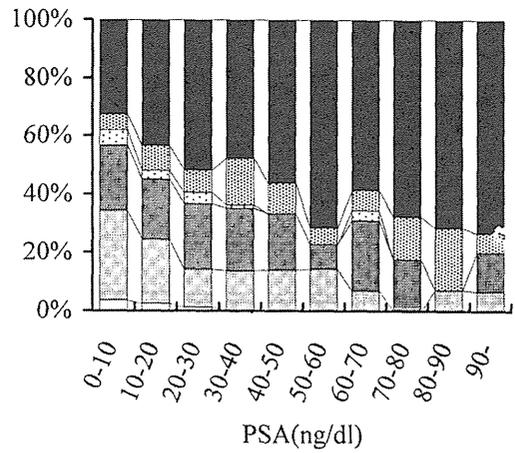
T1c

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	6	3	1	0	2	12
55-59	1	20	9	0	0	3	33
60-64	3	38	17	1	3	12	74
65-69	4	50	40	2	9	22	127
70-74	16	44	27	5	15	49	156
75-79	8	8	14	2	9	53	94
80-84	6	0	0	0	1	38	45
85-89	1	0	0	0	0	19	20
90>	0	0	0	0	0	4	4
Total	39	166	110	11	37	202	565



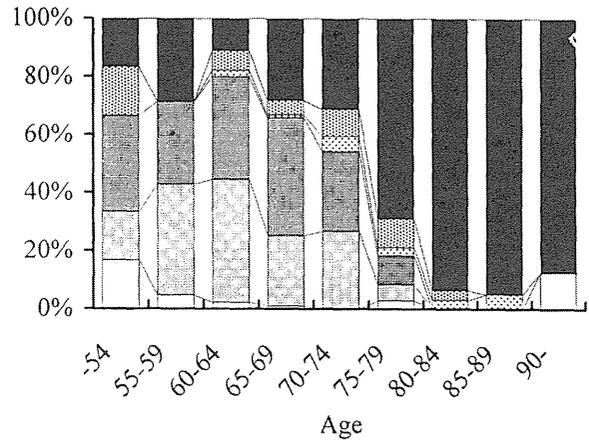
T2a

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	6	3	0	0	0	9
55-59	1	13	13	2	2	4	35
60-64	1	37	18	2	0	4	62
65-69	0	63	36	3	10	25	137
70-74	5	49	44	11	13	70	192
75-79	1	5	11	9	3	82	111
80-84	2	0	0	3	1	41	47
85-89	4	0	0	1	0	27	32
90>	0	0	0	0	0	2	2
Total	14	173	125	31	29	255	627



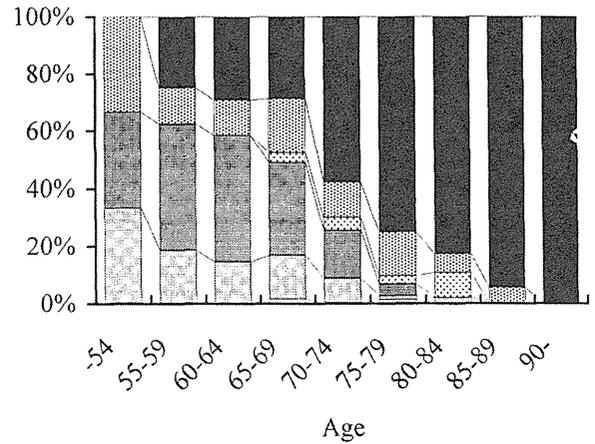
T2b

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	1	1	2	0	1	1	6
55-59	1	8	6	0	0	6	21
60-64	1	19	16	1	3	5	45
65-69	1	25	42	1	5	29	103
70-74	0	31	32	6	11	36	116
75-79	2	4	7	2	7	49	71
80-84	0	0	0	1	1	29	31
85-89	0	0	0	1	0	19	20
90>	1	0	0	0	0	7	8
Total	7	88	105	12	28	181	421



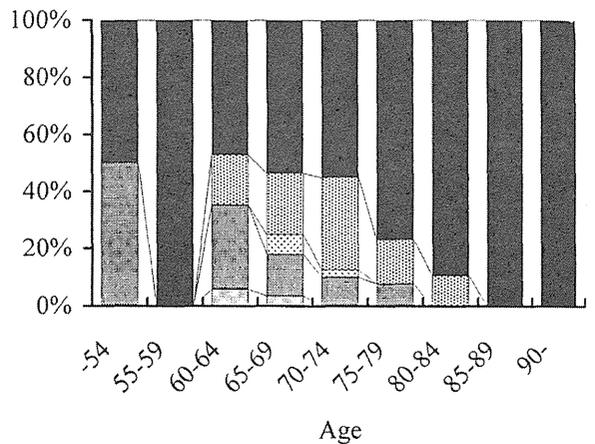
T3a

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	1	1	0	1	0	3
55-59	0	3	7	0	2	4	16
60-64	0	6	18	0	5	12	41
65-69	1	9	19	2	11	17	59
70-74	0	8	15	4	11	52	90
75-79	1	1	3	2	11	54	72
80-84	0	1	0	4	3	38	46
85-89	0	0	0	0	1	17	18
90>	0	0	0	0	0	8	8
Total	2	29	63	12	45	202	353



T3b

age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	0	1	0	0	1	2
55-59	0	0	0	0	0	1	1
60-64	0	1	5	0	3	8	17
65-69	0	1	4	2	6	15	28
70-74	0	0	4	1	13	22	40
75-79	0	0	3	0	6	30	39
80-84	0	0	0	0	2	17	19
85-89	0	0	0	0	0	11	11
90>	0	0	0	0	0	3	3
	0	2	17	3	30	108	160



Clinical T1c-T3b cases were divided by age.
 Correlation between adopted treatment and each stage were plot the percentage of each groups
 Abbreviations are follows: W/W; watchful waiting, RPP; retropubic radical prostatectomy, Hx: hormonal therapy, Rx; irradiation.

V.

Institutions that were registered

Institution	Number	Number of patients
University Hospital	31	1159
National Hospital	11	422
General Hospital	131	2984
Total	173	4565?

Thirty three patients in 4565 were deleted because of duplication, insufficient date, etc.

Institution	Number of patients	Institution	Number of patients
Hokkaido		Obama Community Hospital	2
Hokkaido University Graduate School of Medicine	29	Fukui General Hospital	4
Otaru Municipal Hospital	26	Yamanashi Prefecture	
Asahikawa City Hospital	17	Yamanashi Medical University	27
Bibai Rosai Hospital	10	Yamanashi Prefectural Central Hospital	27
Asahikawa Red Cross Hospital	20	Nagano Prefecture	
Kin-Ikyo Chuou Hospital	17	Shinshu University School of Medicine	43
Kushiro City General Hospital	20	Matsumoto National Hospital	51
Jinyukai Hospital	21	Ina Central Hospital	39
Hokkaido Hospital for Social Health Insurance	16	Nagano Red Cross Hospital	58
Muroran City General Hospital	40	Nagano Municipal Hospital	53
Aomori Prefecture		Gifu Prefecture	
Aomori Rosai Hospital	21	Gifu University School of Medicine	19
Iwate Prefecture		Gifu Municipal Hospital	27
Iwate Rousai Hospital	20	Kizawa Memorial Hospital	13
Miyagi Prefecture		Gifu Red Cross Hospital	10
Tohoku University Hospital	21	Shizuoka Prefecture	
Ishinomaki Red Cross Hospital	13	Hamamatsu Medical Center	36
Miyagi Cancer Center	59	Hamamatsu Red Cross Hospital	12
Fukushima Prefecture		Seirei Mikatahara General Hospital	68
Fukushima Medical University Hospital	24	Hamaoka Municipal Hospital	6
Fujita Public Hospital	29	Aichi Prefecture	
Ibaraki Prefecture		Fujita Health University	46
Institute of Clinical Medicine University of	31	TOYOTA Memorial Hospital	15
Tsukuba		Josai Municipal Hospital, City of Nagoya	16
Kitaibaraki Municipal General Hospital	8	Meijo Hospital	13
Hakujuji General Hospital	6	National Chubu Hospital	22
Tochigi Prefecture		Koyo Hospital	7
Rosai Hospital for Silicosis	12	Tottori Prefecture	
Gunma Prefecture		Nozima Hospital	11
Gunma University Hospital	52	Shimane Prefecture	
Gunma Cancer Center	21	Masuda Red Cross Hospital	18
Tatebayashi Kousei Hospital	41	Okayama Prefecture	
Motojima General Hospital	8	Okayama University Graduate School of Medicine and Dentistry	39
Saitama Prefecture		Kawasaki Medical School	71
National Defense Medical College	35	Okayama Central Hospital	40
Koshigaya Municipal Hospital	22	Kurashiki Medical Center	49
Saiseikai Kanagawaken Hospital	36	Kawasaki Hospital	27
Yokoham Rosai Hospital	55	Kurashiki Central Hospital	68
The International Goodwill Hospital	27	Konko Hospital	11
Niigata Prefecture		Hiroshima Prefecture	
Niigata Cancer Center Hospital	64	Kohsei General Hospital	5
Niigata City General Hospital	37	Yamaguchi Prefecture	
Itoigawa General Hospital	5	Yamaguchi University School of Medicine	17
Toyama Prefecture		Tokushima Prefecture	
Toyama Medical and Pharmaceutical University	26	Tokushima Municipal Hospital	21
Toyama Prefectural Central Hospital	16	Tokushima Red Cross Hospital	30
Toyama Red Cross Hospital	16	Oe Kyodo Hospital	17
Asahi General Hospital	3	Kagawa Prefecture	
Kamiichi Welfare Hospital	8	Kagawa Medical University	31
Saiseikai Toyama Hospital	5	Kagawa Prefectural Central Hospital	51
Ishikawa Prefecture		Sanuki Municipal Hospital	12
Kaga Chuoh Hospital	9	Ehime Prefecture	
Fukui Prefecture		National Shikoku Cancer Center	57
Fukui Prefectural Hospital	8	Matsuyama Shimin Hospital	28
		Saiseikai Imabari Hospital	24

Institution	Number of patients	Institution	Number of patients
Matsuyama Red Cross Hospital	37	Nagahama City Hospital	26
Shikoku Central Hospital	8	Kyoto	
Jyuzen General Hospital	17	Kyoto Second Red Cross Hospital	20
Kochi Prefecture		Kyoto Yawata Hospital	2
Hata Kenmin Hospital	13	Saiseikai Kyoto Hospital	29
Fukuoka Prefecture		Hukuchiyama City Hospital	9
Graduate School of Medical Sciences, Kyushu University	35	Osaka	
Kokura National Hospital	13	Wakakusa Hospital	5
Omuta City General Hospital	27	Kinki University School of Medicine	19
Hara Sanshin General Hospital	102	The Center for Cancer and Cardiovascular Diseases, Osaka	90
Yahata City Hospital	10	Osaka Police Hospital	39
Chikushi Hospital Fukuoka University	16	Osaka Kosei-Nenkin Hospital	27
Tagawa Municipal Hospital	4	Higashiosaka City General Hospital	22
Nippon Steel Yawata Memorial Hospital	6	Osaka Seamen's Insurance Hospital	10
Satte General Hospital	9	Osaka Red Cross Hospital	30
Saitama Municipal Hospital	27	Rinku General Medical Center	25
Kawaguchi Municipal Medical Center	29	Izumisano Municipal Hospital	
The Kitasato Institute Medical Center Hospital	22	Ohno Memorial Hospital	9
Saiseikai Kurihashi Hospital	25	Kanbara Hospital	3
Jichi Omiya Medical Center	29	Belland General Hospital	32
Chiba Prefecture		Hyogo Prefecture	
Graduate School of Medicine, Chiba University	32	Kobe National Hospital	17
Matsudo Municipal Hospital	38	Nishiwaki Municipal Hospital	18
Kameda Medical Center	23	Hara Genitourinary Hospital	27
Yatsu Hoken Hospital	19	Ashiya Municipal Hospital	26
Juntendo University Urayasu Hospital	28	Shinsuma Hospital	4
Tokyo		Self Defense Forces Hanshin Hospital	1
Keio University School of Medicine	138	Takayama Clinic	18
Kidney Center, Tokyo Women's Medical University	79	Kakogawa Municipal Hospital	19
Showa University School of Medicine	45	Nara Prefecture	
International Medical Center of Japan	35	Nara National Hospital	6
National Tokyo Medical Center	83	Yamato Takada Municipal Hospital	14
National Cancer Center Hospital	101	Saiseikai Chuwa Hospital	15
Tokyo Metropolitan Ohkubo Hospital	9	Nara Social Insurance Hospital	10
Cancer Institute Hospital	94	Kokuho Central Hospital	9
Toranomon Hospital	100	Ikoma General Hospital	2
Minamitama Hospital	18	Wakayama Prefecture	
Inagi Municipal Hospital	14	Wakayama Rosai Hospital	17
Nagakubo Clinic	36	Hidaka General Hospital	7
Tokyo Medical University Hachioji Medical Center	17	Kinan General Hospital	2
Kosei General Hospital	22	Nagasaki Prefecture	
National Hospital Tokyo Disaster Medical Center	21	Nagasaki University School of Medicine	28
Kanagawa Prefecture		Isahaya Insurance General Hospital	22
Kitasato University	96	Oita Prefecture	
Yokohama City Kowan Hospital	9	Oita National Hospital	16
Yokosuka Kyosai Hospital	40	Nakatsu Daiichi Hospital	21
Kawasaki Municipal Kawasaki Hospital	14	Yamaga General Hospital	3
St. Marianna University School of Medicine Toyoko Hospital	22	Miyazaki Prefecture	
Mie Prefecture		Miyazaki Medical College	21
Faculty of Medicine, Mie University	16	Kenritu Nobeoka Hospital	16
Takeuchi Hospital	32	Kushima City National Health Insurance Hospital	5
Shiga Prefecture		Kagoshima Prefecture	
		Satsumagun Ishikai Hospital	10
		Okinawa Prefecture	
		Okinawa Prefectural Naha Hospital	9

JUA Cancer Registration Statistics**Oncological outcomes of the prostate cancer patients registered in 2004: Report from the Cancer Registration Committee of the JUA**

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Objectives: In 2001, the Cancer Registration Committee of the Japanese Urological Association initiated a data collection of prostate cancer patients into a computer-based database. The aim of the present study is to report the clinical and pathological characteristics and outcomes of prostate cancer patients diagnosed in 2004 in Japan.

Methods: Overall, 11 385 patients from 239 institutions were registered into the database. After excluding 1105 patients because of insufficient data, duplication or insufficient follow up, 10 280 patients were eligible for the analysis. Most of them (10 198, 99.2%) were Japanese and 1195 (11.6%) had metastatic disease at the time of diagnosis. The mean and median follow up was 53.2 months and 61.5 months, respectively.

Results: The 5-year overall and prostate cancer-specific survival rate was 89.7% and 94.8%, respectively. The 5-year prostate cancer-specific survival rate of M0 and M1 disease was 98.4% and 61.1%, respectively. For 8424 cases of organ-confined or regional disease, Japanese urologists used as the initial treatment hormone ablation therapy alone (3360, 39.9%), radical prostatectomy (3140, 38.1%), radiation therapy (1530, 18.2%) and watchful waiting (394, 4.7%) including active surveillance or palliative observation.

Conclusions: This is the first large population report of survival data in Japanese prostate cancer patients. In Japan, the disease population, survival period with metastatic disease and ratio of patients having hormone ablation therapy differ from those in Western countries.

Key words: epidemiology, Japanese, prostate neoplasm, registration, survival.

Introduction

In the 1990s, prostate-specific antigen (PSA) testing became widespread in Japan, as in the USA and Europe. The incidence of prostate cancer in Japan also appears to be rising. There is no doubt that PSA screening contributes to earlier diagnosis of prostate cancer. Whether earlier detection of the prostate cancer in Japanese men helps reduce prostate cancer-specific mortality is unknown as a result of the lack of detailed information about Japanese prostate cancer patients.

In 2001, the Japanese Urological Association (JUA) initiated a study to estimate the etiology, diagnosis, initial treatment, pathological findings and final outcomes of prostate cancer using computer-based registration of prostate

cancer patients from institutions all over Japan. In 2005, we published the initial report on the registered 4529 prostate cancer patients diagnosed in 2000¹ and the estimated etiology, diagnosis and initial planned treatment were analyzed. In 2010, detailed information including the main treatment modality used, adjuvant therapies used and survival of prostate cancer patients diagnosed in 2004 was collected to assess the current situation of prostate cancer in Japan.

Methods**Patients and treatments**

In 2010, data on patients diagnosed with prostate cancer in 2004 were collected, along with 5-year survival data and radical prostatectomy pathology results. Incidental cancer found within specimens removed during radical cystoprostatectomy for bladder cancer and transitional cell carcinoma of the prostate concomitant with bladder cancer were excluded from this registry. In all, 11 385 patients were

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registered from 239 institutions. Excluded from the analysis were 37 duplications (only one record was removed and the patient remained in the registry), six patients because of insufficient data and 1062 patients with less than 180 days of follow up, leaving 10 280 patients included in the analysis.

Variables

Pathological staging was based on the fifth edition of the TNM classification and the third edition of the General Rule for Clinical and Pathological Studies on Prostate Cancer (2001).² For the PSA analysis, only cases measured with the Tandem-R kit PSA assay ($n = 4567$, 44.4%) were included to avoid statistical scatter. The definition of PSA failure was determined based on the clinician's judgement.

Survival data were analyzed according to the main treatment modality and the M stage. The initial main treatment modalities used were categorized into four groups: hormone ablation therapy alone (Hx), radical prostatectomy (RP) with or without neoadjuvant hormone treatment (NHT), radiation therapy (Rx) with or without NHT and watchful waiting (W/W) including active surveillance or palliative observation irrespective of the intent. Characteristics and outcomes from the four treatment groups were analyzed separately.

Analysis of progression-free survival was not possible as a result of difficulties in timing recurrence correctly. In some RP cases, adjuvant therapy was initiated just after the operation on the basis of the pathological findings. In addition, there were substantial differences in how post-Rx PSA failure was defined. For these reasons, the exact timing of recurrence was not able to be determined for a sizable number of patients, whom we consequently described as having "stable disease." Therefore, we had no other choice but to focus on the mortality rate, overall survival (OS) and prostate cancer-specific survival (PCSS).

Statistical methods

For statistical analysis, Student's *t*-test was used for analysis of intergroup differences in means and the χ^2 -test was used for intergroup comparisons. Survival data was analyzed by the Kaplan–Meier method.

Results

Overall data

The registered patients' characteristics including age, PSA, Gleason score and TNM classification were summarized according to the main initial treatment modality (see Table S1, supporting information). In the 10 280 patients, the number of the patients treated by Hx, RP, Rx and W/W was 4934 (49.8%), 3212 (31.5%), 1605 (10.4%) and 485 (4.7%), respectively. The 44 patients were treated by other modalities.

There were statistically significant differences among patients in different treatment groups. Patients treated with RP were the youngest (median age 68.0 years), with patients treated with Hx on average approximately 8.5 years older (median age 76.0 years). Overall, median PSA at diagnosis was 13.0 ng/mL, but the median PSA within the W/W group was 7.3 ng/mL, which was the lowest. Median Gleason score was 7 among Hx, RP and Rx groups, and 6 in W/W patients. Approximately 50–60% of each group was staged as T1c or T2 disease. In contrast, 11.5% of patients presented with metastatic disease at the time of diagnosis.

The 5-year OS and PCSS of all 10 280 patients was 98.7% and 94.8%, respectively. Figure 1 shows the Kaplan–Meier curves according to M stage. Bony disease (M1b) comprised the majority of M1 patients. The 5-year OS and PCSS was 61.8% and 66.7%, respectively. In M1 disease, there was a significant correlation between survival and Gleason score ($P < 0.001$).

T1-4N0M0 prostate cancer

There were 8424 patients with T1-4N0M0 prostate cancer. The distribution and proportion of clinical T (cT) stage and age by treatment group are shown in Figure 2. Interestingly, in Japan more than 30% of patients received Hx as the main treatment modality across all cT stages. Even for cT1 or cT2 disease, RP, Hx and Rx were carried out in approximately 50%, 30% and 20% of the cases, respectively. The age distribution differed dramatically across treatment groups. For patients less than 75 years-of-age, RP was widely used. Rx was carried out at similar rates (approximately 20%) in patients up to 80 years-of-age. Hx was the major treatment in patients over 80 years-of-age.

OS and PCSS in T1-4N0M0 disease by treatment group were shown to be 97.6% and 99.6% in RP, 95.6% and 98.5% in Rx, 96.4% and 99.7% in W/W and 88.9% and 97.7% in Hx. Five-year PCSS for patients without metastatic disease was excellent (98.4%).

Distribution of age and PSA in patients with T1-4N0M0 prostate cancer according to treatment was shown in Figure S1. Figure S2 shows cT distribution and the main treatment adopted in these patients. Figure S3 shows overall and prostate cancer-specific survival by main treatment adopted in these patients.

Radical prostatectomy

RP was carried out in 3212 patients (see Table S2, supporting information). Overall, 96.2% of RP patients had radical prostatectomy through the retropubic approach, and 89% had an open procedure. Concerning neurovascular bundle preservation, 70.4% of the patients received RP without nerve preservation. Lymph node dissection was carried out in 91% of the patients with mainly limited obturator lymph node dissection (71.6%).

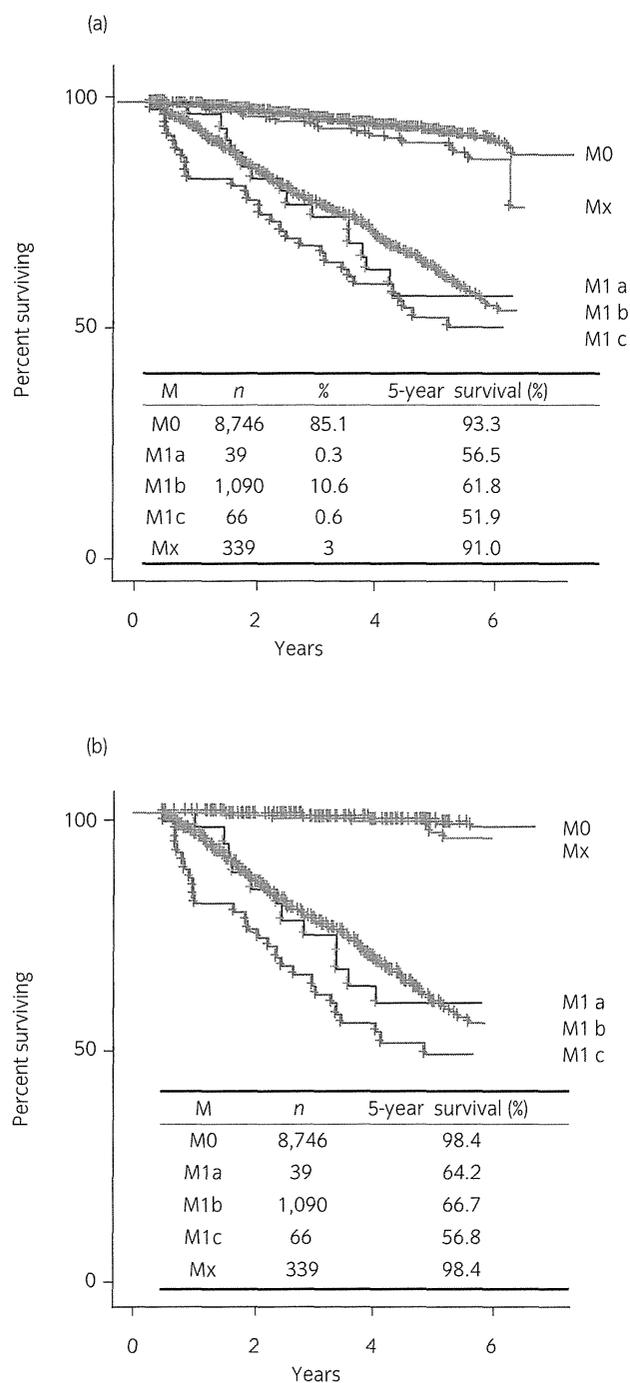


Fig. 1 Kaplan–Meier curves of (a) overall survival and (b) prostate cancer-specific survival according to M stage ($n = 10\ 280$).

The outcomes of 3200 RP patients according to NHT duration are summarized (see Table S3, supporting information). Because of uncertain NHT status, 12 patients were excluded. In the RP with NHT group ($n = 1164$), most pathological parameters including node metastasis (pN) and surgical margin status (ew) were better than in those patients without NHT ($n = 2045$; $P < 0.001$), except for seminal vesicle invasion (sv). However, the survival status of RP

with NHT group did not differ from the RP without NHT group. The disease-free rate and prostate cancer death rate in the RP group within this observation period of approximately 5 years was approximately 70–75% and less than 1%, respectively.

Hormonal therapy alone

In this registration series, 4934 patients were treated with Hx alone (see Table S4, supporting information). In these patients, 3582 patients (72.6%) had non-metastatic disease (M0) and 1061 patients (21.5%) had bony metastasis (M1b). The combination of luteinizing hormone-releasing hormone (LH-RH) analogs with non-steroidal anti-androgen drugs were used in the majority of the Hx patients (67.4%). In M0 disease, 25% of patients received monotherapy with LH-RH analogs or surgical castration, and 67.4% patients were treated with maximum androgen blockade (MAB). Estrogen or estramustine phosphate therapy as the initial Hx was rare for M0 disease. For M1b disease, 82% of patients received MAB and 14.4% of patients received estrogen or estramustine phosphate as the initial treatment. The 5-year PCSS in patients with M0 disease was 93.3% and in M1b patients, it was 71.2%. In M0 patients, 8.4% of the patients died of other causes, which seemed to be higher when compared with patients treated with other modalities.

Curative radiation for prostate cancer

Rx as a radical treatment was used for 1554 patients. There were 28 patients who received particle radiotherapy and 27 patients were treated by uncertain modality. Excluding these patients, the characteristics of the 1499 patients are summarized (see Table S5, supporting information). Radiation therapy was classified as external beam radiation therapy with Liniac (EBRT; $n = 1241$), brachytherapy (BT; $n = 210$) or a combination (BT + EBRT; $n = 48$). Median age in EBRT was 72.9 years and median PSA was 15.0 ng/mL. In contrast, that in BT was 70.0 years and median PSA was 7.30 ng/mL. When compared with EBRT patients, BT patients were younger and had lower PSA, Gleason scores and earlier stage disease. The median PSA level in patients who received EBRT was 15.0 ng/mL, higher than in RP patients. In 1241 EBRT patients, 88.6% received radiation to the prostate only and the median dose in EBRT was 70 Gy. No cancer deaths were observed in patients who received BT and BT + EBRT. In the EBRT group, 5-year PCSS was 98.3% (see Table S6, supporting information).

Watchful waiting

In this registry, W/W included active surveillance, deferred treatment and palliative observation. At the time of registration, 72.4% of patients were maintained on watchful

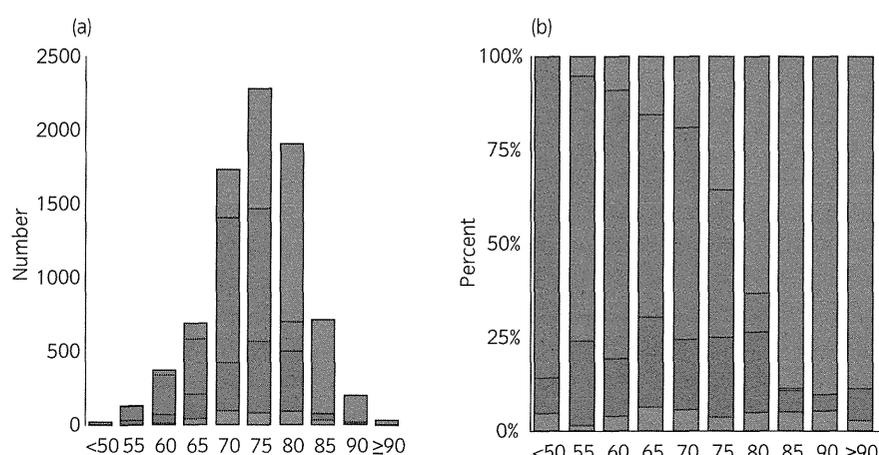


Fig. 2 Age distribution by main treatment modality in patients with T1-4N0M0 prostate cancer ($n = 8424$). (a) Totals and numbers of patients who underwent each treatment modality. (b) Percentages of each treatment by age. Hx, hormone ablation therapy; RP, radical prostatectomy; Rx, radiation therapy; W/W, watchful waiting.

Number of the patients by age and main treatments

	<50	50-55<	55-60<	60-65<	65-70<	70-75<	75-80<	80-85<	85-90<	≥90
Hx	0	7	34	108	329	815	1207	637	184	31
RP	18	94	269	675	982	899	198	4	0	0
Rx	2	30	58	166	326	485	409	41	9	3
W/W	1	2	15	45	100	86	96	37	11	1

waiting. In the W/W group, 0.62% of the patients died of prostate cancer. The incidence was similar to that in the RP patients (see Table S7, supporting information).

Discussion

The present report is the first large-scale study of the characteristics and survival of prostate cancer patients in Japan based on multi-institutional registry data. The estimated number of newly diagnosed prostate cancer patients in Japan in 2005 was 42 997.³ This registry seems to cover approximately one-quarter of newly diagnosed prostate cancer in Japan. With regard to prostate cancer incidence and mortality, ethnic differences between American or European and Asian men are well known. Understanding the actual situation of Japanese prostate cancer patients is indispensable to addressing many clinical issues regarding prostate cancer treatment.

The incidence of metastatic prostate cancer at the initial registration was 11.6% in the present study. In the USA, 6.5% were distant stage according to the report from the 1990–2000 database of the Surveillance, Epidemiology and End Results (SEER) Program⁴, suggesting the incidence of metastatic disease is higher in Japan than in the USA. However, the incidence was 21.3% from the Japanese registration data in 2000.¹ Compared with the data from 2000, the ratio of distant disease in 2004 was reduced by half. However, the number of the distant diseases in 2000 ($n = 964$) was almost the same as that in 2004 ($n = 1195$).

In the report derived from the 1973–2000 database of the SEER Program⁴, 5- and 10-year PCSS were approximately 99% and 95%, respectively. Two-thirds of patients were

diagnosed with well or moderately differentiated localized or regional prostate cancer. Among these patients, 5- and 10-year PCSS were approximately 100%. In the present study, 5-year PCSS was 94.8%, which resembles the SEER data from 1995. The PCSS of localized or regional prostate cancer was 98.4%, similar to the SEER data. Five-year PCSS of patients with bony metastasis in Japan was 66.7%, which was better than the 27–37% 5-year PCSS in the USA⁴. The reason why Japanese patients with bony metastasis showed a longer survival period than American patients is uncertain.

The main treatment used for non-metastatic prostate cancer patients in Japan was quite different from that in the USA. In the USA, approximately half of prostate cancer patients received surgery and more than one-third underwent Rx.⁵ In Japan, Hx comprised of 39.9% of the initial main treatment, even for non-metastatic prostate cancer. One of the reasons for the high rate of Hx might be the relatively advanced age at diagnosis. Another reason might be the high rate of health insurance coverage and indifference about erectile dysfunction. In the present study, the most frequent treatment for non-metastatic prostate cancer in patients less than 70-years-old was RP (62.5%). Essentially, for patients younger than 70-years-old, Japanese urologists might choose treatments in agreement with major guidelines published by the National Comprehensive Cancer Network and the European Association of Urology, among others.

Concerning the administration of Hx medications, MAB therapy was recommended for stage D2 prostate cancer.⁶ However, in Japan, 65% of patients with non-metastatic disease received MAB therapy and 25% of them received

LH-RH analogs or surgical castration as monotherapy. The 5-year PCSS of non-metastatic prostate cancer patients in Japan showed excellent results, even in the W/W group. The OS of patients with Hx seemed to be lower than that with other modalities. The patients undergoing Hx are relatively older.

In the present series, detailed data on RP was analyzed. In 2004, open retropubic RP (89.6%) with obturator lymph node dissection (71.6%) was the most common procedure. Interestingly, just 20% of patients received nerve-sparing operations in Japan. In high-volume hospitals in the USA, most radical prostatectomy seems to be carried out using the nerve-sparing technique. For most Japanese men, there might be less concern about sexual function when compared with American men.

The pathological results were sorted by NHT duration, because they might be affected by NHT status. Similar to the data from many randomized controlled studies of NHT^{7,8} most pathological findings were improved by longer NHT, except for seminal sv and pN. However, there was no remarkable improvement in prognosis despite longer NHT as previously reported. However, these data came from non-randomized, non-historically controlled patients.

Additionally, the present study might be the largest population study of Rx in Japan. In past years, the trends and patterns of Rx in Japan were reported by the patterns of care study (PCS).^{9,10} The age, PSA, Gleason score and radiation dose in the EBRT group of the present study were similar to PCS data. The median PSA of 15.0 ng/mL in the EBRT patients was higher than that of the patients treated with RP. Japanese urologists seemed to select EBRT for treating localized advanced disease. The EBRT group in the registry had a disease-free rate of 58% and a stable disease rate of 22.7%. Recently, higher dose radiation has been recognized to contribute to better cancer control. In 2004, 11.0% of the patients received 72 Gy and 11.4% patients received 76 Gy EBRT. Nearly 50% of patients underwent 68 Gy EBRT. Recently, relatively high dose EBRT in combination with NHT was attempted using the intensity modulated radiotherapy technique.

In conclusion, this is the first report of survival data involving one-quarter of newly diagnosed prostate cancer patients in Japan. In Japan, the patient population, survival period with metastatic disease and the ratio of patients receiving Hx differ from Western countries. Also noteworthy is the reduction in the ratio of metastatic prostate cancer at diagnosis, which was 11.6% in 2004, approximately half the rate in 2000. However, the total number of newly diagnosed patients with metastatic prostate cancer in 2004 was almost same as that in 2000. In terms of localized (cT2 or earlier stage) prostate cancer, Hx was used as the main treatment in 36.7% of Japanese patients. The 5-year survival of patients with localized prostate cancer was excellent irrespective of the main treatment used. Five-year OS and PCSS

of patients with M1b disease were superior to that in the USA.

Acknowledgments

These clinicopathological statistics are the results from a number of institutions in Japan (see Appendix I, supporting information). We are grateful for the cooperation of many Japanese urologists. This document was created by the Cancer Registration Committee of the Japanese Urological Association.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Distribution of age (A) and PSA (B) in patients with T1-4N0M0 prostate cancer ($n = 8424$) according to treatment. RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.

Fig. S2 cT distribution and the main treatment adopted in patients with T1-4N0M0 prostate cancer ($n = 8424$). The graph A shows totals and numbers of patients who underwent each treatment modality. The graph B shows percentages of each treatment by clinical stage. RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.

Fig. S3 Kaplan–Meier curves of overall survival (A) and prostate cancer-specific survival (B) by main treatment

adopted in patients with T1-4N0M0 prostate cancer ($n = 8224$). RP, radical prostatectomy; Rx, radiation therapy; Hx, hormone ablation therapy; W/W, watchful waiting.

Table S1 Characteristics of the registered patients.

Table S2 Characteristics of 3212 radical prostatectomy patients.

Table S3 Outcome of 3200 radical prostatectomy cases with or without neoadjuvant hormonal therapy.

Table S4 Outcome of 4934 patients treated with hormone ablation therapy alone.

Table S5 Characteristics of patients treated with radiation therapy as the main treatment.

Table S6 Outcome of patients treated with radiation therapy as the main treatment.

Table S7 Outcome of 485 patients treated with watchful waiting.

Appendix I Statistics from various institutions in Japan.

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Original Article: Clinical Investigation

Clinical outcome of tumor recurrence for Ta, T1 non-muscle invasive bladder cancer from the data on registered bladder cancer patients in Japan: 1999–2001 report from the Japanese Urological Association

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Objective: To characterize the clinical outcome in a large contemporary series of Japanese patients with newly diagnosed Ta, T1 non-muscle invasive bladder cancer who underwent transurethral bladder tumor resection with or without intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) therapy.

Methods: We developed a database incorporating newly diagnosed non-muscle invasive bladder cancer data and outcomes from a Japanese bladder cancer registry between 1999 and 2001 and identified a study population of 3237 consecutive patients who had complete data based on pathological features. Median patient age was 69.9 years.

Results: The 1-year, 3-year, and 5-year overall recurrence-free survival rates were 77.0%, 61.3%, and 52.8%, respectively. In multivariate analyses, the multiplicity of bladder tumors, 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. Overall, 1710 patients (52.8%) received intravesical instillation; chemotherapy in 1314 (76.8%) and BCG treatment in 396 (23.2%). In patients treated with intravesical chemotherapy in which an anthracycline chemo-agent was used in 90.5% of the cases, multivariate analyses demonstrated that male gender, multiple bladder tumors, a tumor size greater than 3 cm, and pathological stage T1 were associated with tumor recurrence.

Conclusions: The accumulation and analysis of data from the Japanese National Bladder Cancer Registry made it possible to determine the clinical characteristics, management trends, and survival rates for the period studied. Further study with a dataset created from longer follow-up data would be warranted to analyze tumor progression and disease survival.

Key words: bladder, carcinoma, non-muscle invasive, recurrence, transitional cell.

Introduction

Transurethral bladder tumor resection (TUR-BT) with or without intravesical therapy is the primary treatment modality in individuals with

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non-muscle invasive Ta, T1 bladder cancer. Some patients with risk factors, such as a high grade, lamina propria infiltration, multiplicity, a large tumor, and concomitant carcinoma *in situ* (CIS) still have a lifelong frequency of multiple recurrences and a probability of stage progression.^{1–4} To date, several contemporary single center series of patients treated with intravesical chemo- or immunotherapy after TUR-BT for Ta, T1 non-muscle invasive bladder cancer have been published to evaluate the prognostic indicators for tumor recurrence in Japan.^{5–8} These studies had relatively small patient populations and single center bias. Data compiled from multiple institutions may offer the benefit of understanding and generalizing the diagnosis, patient selection, staging, pathological evaluation, treatment, and follow-up protocol. In addition, a contemporary series of a large number of patients with Ta, T1 non-muscle invasive bladder cancer has the potential benefit of identifying bladder cancer recurrence as an outcome measure.

We developed a database incorporating comprehensive non-muscle invasive bladder cancer data and outcomes from data collected by multiple centers in Japan in retrospective fashion under the program of the Japanese National Bladder Cancer Registry. The aim of the present study was to characterize the clinical outcome in a large contemporary series of Japanese patients with newly diagnosed Ta, T1 non-muscle invasive bladder cancer who underwent TUR-BT with or without

intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) therapy for preventing tumor recurrence. In addition, we determined the association of established clinical and pathological characteristics with tumor recurrence.

Methods

Patient population

Data sets from multiple centers in Japan were collected in retrospective fashion under the program of the Japanese National Bladder Cancer Registry. The Registry was sponsored by the Japanese Urological Association. The registration included the background of newly diagnosed bladder cancer patients, their clinical and pathological characteristics, and their 3-year clinical outcome after the initial diagnosis. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Ultimately we developed a database incorporating newly diagnosed non-muscle invasive bladder cancer data and outcomes between 1999 and 2001.

A total of 4036 patients with newly diagnosed non-muscle invasive bladder cancer (Ta, T1) N0M0 who were treated with initial TUR-BT from the database were identified. Exclusion criteria included the main histological component of non-urothelial carcinoma ($n = 37$), a non-curative operation was carried out ($n = 703$), the presence of a concomitant CIS ($n = 32$), or incomplete data ($n = 27$). We identified a study population of 3237 consecutive patients for whom there were complete data sets based on pathological features. After complete tumor resection, intravesical chemotherapy or BCG treatment was carried out in 1314 (40.6%) or in 396 (12.2%) patients, respectively for the purpose of preventing bladder tumor recurrence.

Clinical outcomes

Pathological specimens were reviewed by the genitor-urinary pathologist at each institution. Pathological staging and grading were classified according to the 2nd and 3rd edition of the General Rule for Clinical and Pathological Studies on Bladder Cancer.^{9,10} In the study we combined the pT1a and pT1b according to the 2nd edition and treated them as pT1. Recurrence was defined as a new tumor appearing in the bladder after initial clearance. Tumor progression was not analyzed in the present study because of the shorter follow-up period of our study. The time until tumor recurrence was calculated as the time from TUR-BT to the date of the first documented bladder tumor recurrence. Patients who had not experienced bladder tumor recurrence were censored at the last follow-up. Patients who died before bladder cancer recurrence were censored at the time of death.

Statistical analysis

Bladder tumor recurrence-free survival curves were constructed using the Kaplan–Meier method, and were compared with the log-rank test. Cox proportional hazards regression analysis was used to assess the prognostic indicators for recurrence. A P -value less than 0.05 was considered to indicate statistical significance. These analyses were carried out with the STATA version 7.0 statistical software package (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics of overall patient population

Of the 3237 patients (Table 1), 80.3% were men with a median age of 69.9 years (mean; 68.3, range, 18–103). Multiple tumors were found in

Table 1 Clinicopathological characteristic in all patients ($n = 3237$)

	No. patients (%)
Age (years)	
≤ 70	1660 (51.3)
> 70	1577 (48.7)
Gender	
Male	2600 (80.3)
Female	637 (19.7)
Papillary type	
Yes	2938 (90.8)
No	212 (6.6)
Unknown	87 (2.7)
Tumor stalk	
Yes	2251 (69.5)
No	785 (24.3)
Unknown	201 (6.2)
Multiplicity	
Yes	1312 (40.5)
No	1810 (55.9)
Undetected	33 (1.0)
Unknown	82 (2.5)
Tumor size	
< 1 cm	1013 (31.3)
1–3 cm	1681 (51.3)
> 3 cm	374 (11.6)
Uncountable	45 (1.4)
Unknown	124 (3.8)
Pathological T category	
pTa	1651 (51.0)
pT1	1586 (49.0)
Grade	
G1	782 (24.2)
G2	1850 (57.2)
G3	605 (18.7)
Intravesical treatment	
Chemotherapy	1314 (40.6)
BCG	396 (12.2)
No treatment	1527 (47.2)

BCG, Bacillus Calmette-Guérin.

1312 cases (40.5%) and a tumor size greater than 3 cm was observed in 374 (11.6%). Disease was grade 1 in 24.2%, 2 in 57.2%, and 3 in 18.7%. Pathological tumor stage was Ta in 51% and T1 in 49%. There were 608 TaG1, 919 TaG2, 124 TaG3, 174 T1G1, 931 T1G2, and 481 T1G3 cases, respectively. Tumor grade was significantly associated with pathological stage ($P < 0.001$). A total of 1710 patients (52.8%) received intravesical instillation, consisting of chemotherapy in 1314 and BCG treatment in 396.

Tumor recurrence in overall patient population

The 1-year, 3-year, and 5-year overall recurrence-free survival rates were calculated to be 77.0%, 61.3%, and 52.8%, respectively. Kaplan–Meier analysis (Table 2) and univariate Cox proportional hazards regression analysis (Table 3) revealed the presence or absence of tumor stalk, tumor multiplicity, tumor size, pathological stage, tumor grade, and with or without adjuvant intravesical therapy to be significant predictors of tumor recurrence. According to the intravesical instilla-

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

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

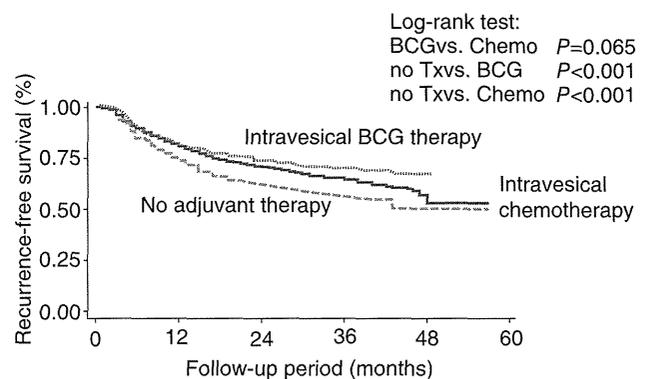


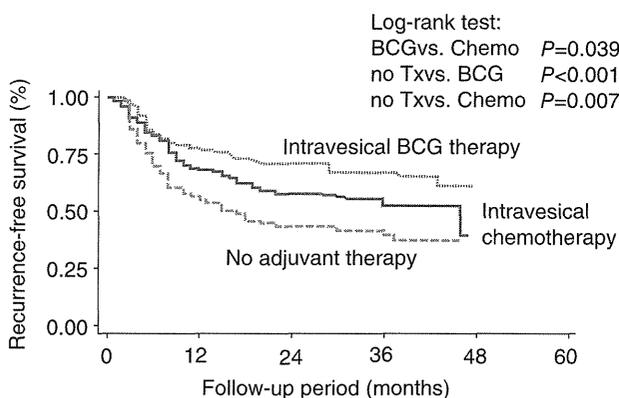
Fig. 1 Kaplan–Meier curves for tumor recurrence in the overall patient population ($n = 3237$) comparing no instillation ($n = 1527$), Bacillus Calmette-Guérin (BCG) instillation ($n = 396$), and chemotherapeutic instillation ($n = 1314$).

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).

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			0.002
	G1/2		1		
	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, plomycin 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).