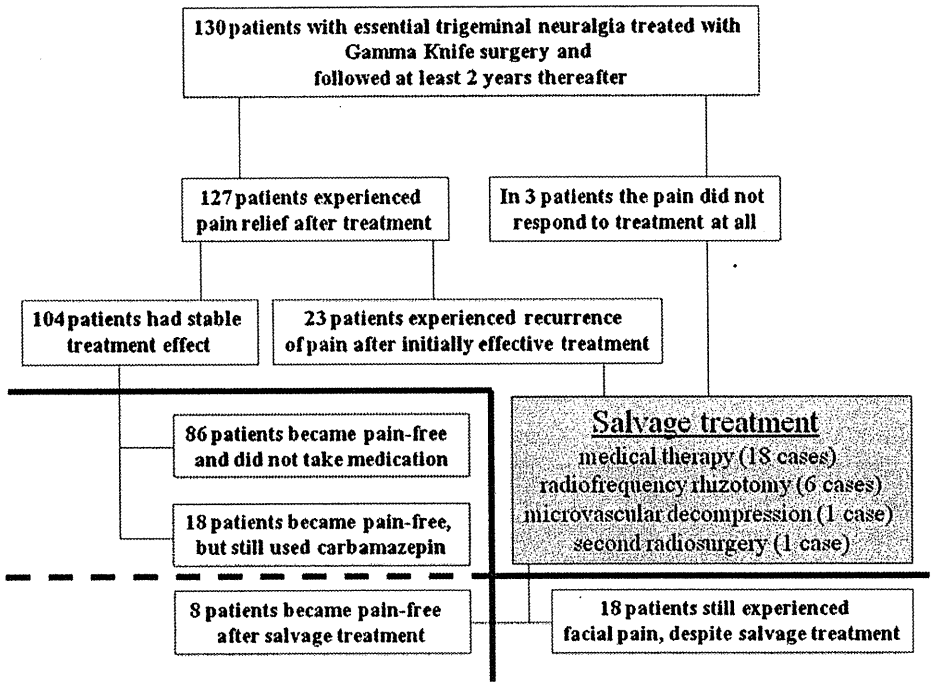

Fig. 6 Schematic representation of the different outcomes after Gamma Knife surgery for essential trigeminal neuralgia in the present series

disease [23, 38, 40], no previous history of failed surgery (particularly, MVD [26]) for trigeminal neuralgia [2–4, 7, 23, 25, 28, 38, 40, 41, 44, 45, 49, 53, 56], fewer number of previous surgeries [6, 21, 23, 53], transient improvement after the latest surgical procedure [21], evidence of the vascular compression of the nerve [38], absence of multiple sclerosis [34, 44, 45, 56], shorter distance between the radiosurgical target on the trigeminal nerve and the brainstem [29, 44], smaller size of the trigeminal cistern [44], and better initial response to radiosurgical treatment [40, 47, 51]. However, for only some variables the prognostic value could be demonstrated more or less consistently. Of note, our previous analyses did not reveal any significant clinical predictor of results of GKS for trigeminal neuralgia [12–17].

Nuances of radiosurgical planning may have a profound impact on treatment success in cases of trigeminal neuralgia [45]. Nevertheless, there is no uniform consensus on the standard technique, and published recommendations on the target selection, number of isocenters, and irradiation dose are somewhat contradictory. Particularly, two different radiosurgical targets are similarly advocated. The first one is located on the root entry zone (REZ) of the trigeminal nerve in the vicinity to the pons ("Pittsburgh target"), whereas another is defined on the retrogasserian part of the nerve ("Marseille target"). Two studies directed on com-

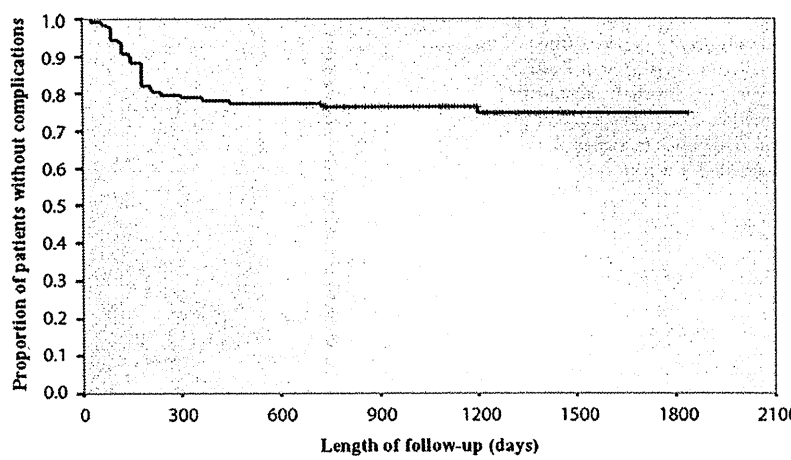

Fig. 7 Kaplan–Meier curve reflecting proportion of facial hypesthesia and/or paresthesia after Gamma Knife surgery for essential trigeminal neuralgia. The median period to development of complication after treatment constituted 6 months

Table 2 Results of Gamma Knife surgery for trigeminal neuralgia in various age groups of patients

Age (years)	Number of patients	Initial pain response to treatment	Recurrence[a]	Excellent outcome[b]	Complications	
					Total	Bothersome
Total	130 (100%)	127 (98%)	23 out of 127 (18%)	86 (66%)	31 (24%)	16 (12%)
less than 50	7 (100%)	6 (86%)	3 out of 6 (50%)	4 (57%)	3 (43%)	–
50–59	17 (100%)	16 (94%)	1 out of 16 (6%)	10 (59%)	3 (18%)	2 (12%)
60–69	50 (100%)	49 (98%)	9 out of 49 (18%)	33 (66%)	13 (26%)	5 (10%)
70–79	33 (100%)	33 (100%)	7 out of 33 (21%)	23 (70%)	8 (24%)	6 (18%)
80 and more	23 (100%)	23 (100%)	3 out of 23 (13%)	16 (70%)	4 (17%)	3 (13%)
χ_{trend}^2	–	4.915	0.489	0.807	0.715	1.019
P value	–	0.0264	NS	NS	NS	NS

[a] Defined as re-appearance of regular pain attacks noted 6 months and more after radiosurgery

[b] Pain and medication free after initial radiosurgery

parison of these targets with regard to outcome actually led to opposite conclusions. Matsuda et al. [32] marked slightly better pain control and a lower complication rate with the use of "Pittsburgh target," but reconsidered such findings later on [33]. In contrast, Park et al. [39] noted some improvements in results and significantly shorter time to pain relief if "Marseille target" was applied. On the other hand, the optimal number of isocenters for delivery of irradiation is not completely clear. In their prospective analysis, Flickinger et al. [6] did not find any advantages of treatment with two isocenters, which in fact was associated with higher complication rate, probably due to increased dose to the nerve. Therefore, at present only one 4-mm isocenter is usually used for management of trigeminal neuralgia. Nevertheless, there are reports that combining two 4-mm isocenters [35], or 4- and 8-mm isocenters [20] in such cases may improve dose delivery and potentially enhance response to treatment. The optimal maximum irradiation dose also requires further clarification. There is a general belief that its increase up to 85–90 Gy is associated with improvement of pain control, but, in fact, in several series the treatment effectiveness did not differ significantly within a range of doses from 70 to 90 Gy [4, 7, 20, 25, 41, 44, 47, 50, 53]. Additionally, the response to GKS in cases of trigeminal neuralgia may be, at least partially, related to radiation-induced functional or structural modifications in the brainstem, but not in the nerve itself [29, 51], and may be significantly influenced by such variables as beam shielding, dose rate, and output factor used for calculation of the dosimetry [7, 29, 31].

In the present series the treatment strategy was rather uniform with constant use of one 4-mm isocenter for delivery of 90 Gy maximum irradiation dose to the retrogasserian part of the trigeminal nerve at the level of trigeminal incisura. Use of "Marseille target" located at a distance from the brain stem permitted for us to deliver the desired irradiation dose in all cases, whereas beam plugging technique for avoidance of excessive irradiation of the pons was necessary only in patients with narrow cerebellopontine cistern [11–17]. Special emphasis was put on positioning of the nerve in the center of not just 50%, but 80% isodose area, which can be efficiently attained with APS. It provides increase both in average dose and energy delivered to the target, which may influence the results of GKS. In the series of Regis et al. [44], a trend toward treatment failure was noted in cases with lower minimal dose applied to the trigeminal nerve. Massager et al. [31] found that increase of the mean dose to the nerve and amount of delivered radiation energy are associated with better pain response. Our previous study revealed that a greater amount of energy delivered per volume of the trigeminal nerve (so-called, "unit energy") might be associated with earlier onset of treatment effect [14, 15].

On the other hand, targeting accuracy may have a tremendous effect on the outcome of trigeminal neuralgia radiosurgery [9, 51]. While in general MRI provides a good opportunity for localization of the trigeminal nerve, the mean Euclidean deviation of the target was reported to be more than 1 mm in 40% of cases, and more than 1.5 mm in 9% of cases [30]. It is frequently caused by distortion of MR images during their acquisition and/or stereotactic transformation [20, 30]. In fact, the uncertainty of target location with MRI is more than twice of that found on CT [20]. Therefore, from 2002 during radiosurgical management of trigeminal neuralgia, we constantly applied guidance not only with high-resolution MRI, but also with

contrast-enhanced and "bone window" CT. Location of the target on the retrogasserian part of the nerve at the level of trigeminal incisura allows effective three-dimensional evaluation of the distortion artifacts using fused "bone window" CT and MR images and corresponding correction of the isocenter coordinates. Influence of such a technique on the outcome was evaluated previously in the series of patients treated between 1998 and 2002 with Leksell Gamma Knife model B [11–17]. In total, 29 and 14 patients underwent GKS without and with use of fused images, respectively. Initial pain relief (93% vs. 100%) and freedom from pain (63% vs. 86%) were observed more frequently in the latter group, although the differences did not reach statistical significance. It should be additionally noted that if MRI could not be performed for any reason, the retrogasserion target on the trigeminal nerve can be set according to location of the trigeminal incisura on CT [15]. Our limited experience suggests that such an approach may be effectively used in these rare cases instead of the more invasive CT myelocisternography.

Application of the abovementioned treatment principles resulted in generally satisfactory outcome in the present series of patients, who were followed for at least 2 years after radiosurgery. Overall, in 104 cases (80%) pain-free status was attained after initial GKS, and 86 of them were off medication. It corresponds well to previously published results of the centers which similarly used retrogasserion target for radiosurgical management of the essential trigeminal neuralgia (Table 3). Nevertheless, variability of treatment parameters, as well as differences in patients' populations, length of follow-up, and outcome evaluation, significantly complicate comparison of the reported data.

Results of radiosurgery for trigeminal neuralgia are time-related and reported pain relief rate constitutes 60–95% at 1 year, 50–77% at 2 years, 41–70% at 3 years, and 34–66% at 4 years, with possible plateau thereafter [3–5, 7, 10, 18, 19, 21–26, 28, 35, 40, 41, 43, 45, 50, 53, 56]. Meanwhile, the definition of recurrence varies. Since at present the treatment effectiveness in such cases can be explained as a two-stage process with initial blocking of ephaptic transmission and subsequent development of axonal degeneration within the nerve, in our opinion the persistent attacks of facial pain accompanying its general reduction during first months after GKS should not be considered as treatment failure. Such episodes were noted in 48% of our patients, but required no additional treatment, and did not prevent attainment of excellent outcome later on. True recurrence, defined as definite re-appearance of the regular pain attacks after initially effective radiosurgery, was observed in 18% of cases of the present series, but never during the first posttreatment year.

Optimal salvage management of trigeminal neuralgia after failed radiosurgery or pain recurrence remains uncertain, whereas re-irradiation, percutaneous ablative procedures, and MVD had been similarly applied in such cases. In particular, second GKS is frequently recommended for patients with pain recurrence if initial treatment was sufficiently effective. Moreover, even third-time irradiation had been tried in resistant cases [19]. The reported success rate varies from 56% to 94% [1, 4, 5, 18, 19, 23, 25, 35, 41, 54, 56], and in fact may be comparable with the primary treatment [18, 56]. The usually recommended cumulative dose during two GKS sessions for avoidance of the excessive damage to the nerve varies from 120 to 150 Gy [5, 19, 22, 26]. Therefore, if the chosen radiosurgical target is the same as the initial one or located in its vicinity, the irradiation dose should be reduced compared to the previous treatment, usually up to 40–70 Gy [18, 19, 22, 23, 25, 26, 35, 50]. Alternatively, maximal irradiation doses of 80–90 Gy can be applied safely if a new target at a distance from the initial one is selected [1, 5, 34, 54, 56]. Favorable results of re-irradiation may be associated with higher dose to REZ [1] and cumulative dose of more than 130 Gy [5]; therefore, these parameters may be tailored according to the requirements of individual cases. Meanwhile, in the present series re-irradiation at the time of pain recurrence was done only once. Overall, various types of salvage treatment were successful in just eight out of 26 our patients, which probably corresponds to the fact that only 31% of them underwent second surgical intervention, whereas others were treated by medication only. More aggressive management strategy at the time of pain recurrence might be more reasonable in these cases.

Treatment-related morbidity was limited to facial hypesthesia and/or paresthesia and was noted in 24% of patients, which is within range of its reported incidence, from 7% to 49% [2, 3, 6–8, 10, 18–47, 49–54, 56]. The risk of complication may be increased in cases of salvage radiosurgery, especially after a failed initial one [1, 5, 18, 19, 25, 26, 50, 52, 56].The controversy exists whether a greater irradiation dose results in higher rate of post-treatment facial numbness, since this was shown in some reports [31, 33, 41, 42, 53] but was not proved in others [3, 7, 18, 20, 21, 23, 47, 50]. In fact, sensory disturbances may be caused not by irradiation of the nerve itself, but by accompanied alteration of the brainstem [1, 9, 29]. Meanwhile, it is not clear whether mild-to-moderate facial numbness after radiosurgery for trigeminal neuralgia should be considered as a complication or as side effect corresponding to pain response to treatment. Multiple studies revealed its association with both pain relief and durability of the treatment effect [1, 5, 19, 21–23, 29, 31–34, 41–43, 47, 51, 53, 54]. In the majority of cases, sensory disturbances are well tolerated and not infrequently steadily resolved in time. Unfortunately, in some patients, facial hypesthesia or dysesthesia after radiosurgery for trigeminal neuralgia may

Table 3 Recently published results of Gamma Knife surgery for trigeminal neuralgia with targeting of the retrogasserion part of the trigeminal nerve

Author (year of publication)	Number of patients	Maximal irradiation dose (Gy)	Length of follow-up (months)	Initial pain relief (%)	Satisfactory results on last follow-up		Rate of pain recurrence (%)	Additional salvage surgery[b] (%)	Morbidity	
					Total (%)	Excellent results[a] (%)			Total (%)	Bothersome (%)
Massager et al. (2004) [29]	47	90	Range: 6–42 mean, 16	89	75	64	8	15	34	4
Jursinic et al. (2005) [20]	38[c]	90	Range: 1–40	ND	82	ND	18	ND	34	ND
Regis et al. (2006) [44]	100	Range: 70–90 median, 85	Minimum, 12	94	80	48	34	17	10	0
Massager et al. (2007) [31]	358	Range: 70–90 median, 90	Minimum, 12	ND	84	74	ND	ND	25	3
Dellaretti et al. (2008) [3]	76	Range: 75–90 median: 85	Range: 6–42 mean, 20	99	71	67	27	ND	21	11
Matsuda et al. (2008) [32]	49	Range: 80–90 mean, 89	Mean, 25	82	67	43	17	ND	45	27
Regis et al. (2009) [45]	262	Range: 70–90 median, 85	Minimum, 12	89	58[d]	ND	34	21	17	2
Hayashi (2009) [16]	150[e]	90	More than 24	97	77	ND	ND	10	28	ND
Park et al. (2010) [39]	16	Range: 83–90 median, 85	Minimum, 12 mean, 17	ND	94	44	6	ND	25	0
Present series	130	90	Range: 24–66 mean, 38	98	80	66	18	6	24	12

ND no data

[a] Pain and medication free after initial radiosurgery

[b] Any type of surgery (microvascular decompression, percutaneous ablative procedures, radiosurgery) due to failed GKS or pain recurrence

[c] Patients treated with one 4-mm isocenter

[d] Proportion of pain-free patients at 5 years after treatment

[e] This previously reported series included patients treated both with Leksell Gamma Knife model B and model C with APS

be bothersome, particularly due to lost sensation of the buccal mucosa resulting in trauma with chewing. Numbness, which interfered with the activities of daily life, was observed after GKS in 12% of our patients, and might represent a significant challenge both for treatment and prognosis due to its unknown natural history. Other complications were described previously after radiosurgical management of essential trigeminal neuralgia, including corneal numbness, decrease or loss of the corneal reflex, dry eye syndrome, corneal keratitis, severe deafferentation pain, masseter weakness or trismus, loss of taste (dysgeusia), facial palsy, transient hearing loss, and superior cerebellar artery occlusion [1, 6, 8, 10, 18, 21, 26, 27, 33, 34, 36, 41, 55, 56]. However, their incidence is low and no such cases were noted in the present series.

Conclusions

Radiosurgical management of essential trigeminal neuralgia results in an extremely high rate of initial pain relief, which in the present series was observed in 98% of cases usually within first month after irradiation. Pain recurrence and treatment-associated complications are, however, not uncommon. Overall, 66% of our patients treated with Leksell Gamma Knife model C with APS remained pain- and medication-free at the time of the last follow-up, which

constituted at least 2 years. Outcome after radiosurgical management of the essential trigeminal neuralgia may be influenced by various technical nuances; therefore, it should be preferably done in specialized clinical centers with extensive experience and sufficient expertise in the treatment of this disorder.

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Comments

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This is a review of a retrospective cohort study, in which the authors evaluate a set of prospectively collected data regarding patients with idiopathic trigeminal neuralgia at a large Japanese Medical Center. The study is valuable, since it contributes to a field that is relevant to many neurosurgeons. We realize that SRS, and in particular GKS, has become one of the standard management options for TN in Asia. The authors report an excellent response rate at the time of last follow up. Data are coherent and compatible with the existing literature. However, it remains a worthwhile discussion 1) to see what causes this trend towards this first line management employing SRS vs. non-destructive methods such as MVD and 2) to reconsider whether this is acceptable, given the current evidence of a significantly shorter durability in cases of succesful responses. Current consensus in Europe and the US remains that destructive techniques are offered only as a second option, despite the convenience of SRS as requested per patient demands and more experience with redo SRS (see Huang et al., 2010; Kimball et al., 2010).The discussion part of the study is very well done and deserves particular credit.

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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 2000[1] 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.

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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

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%).

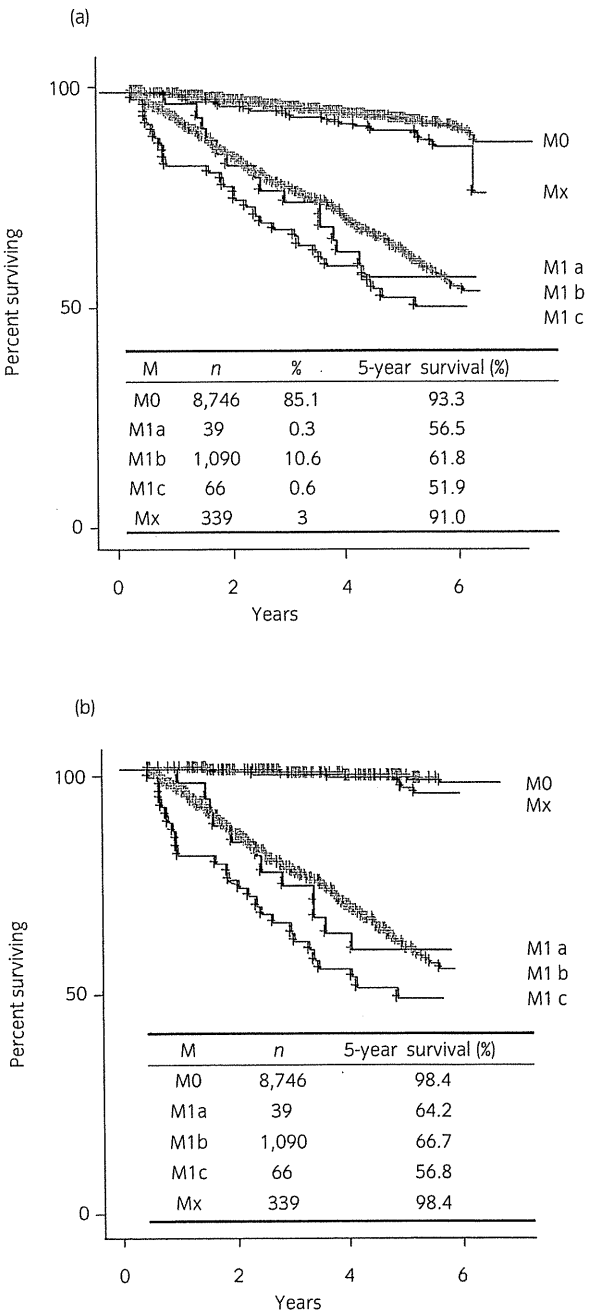

Fig. 1 Kaplan–Meier curves of (a) overall survival and (b) prostate cancer-specific survival according to M stage (n = 10 280).

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

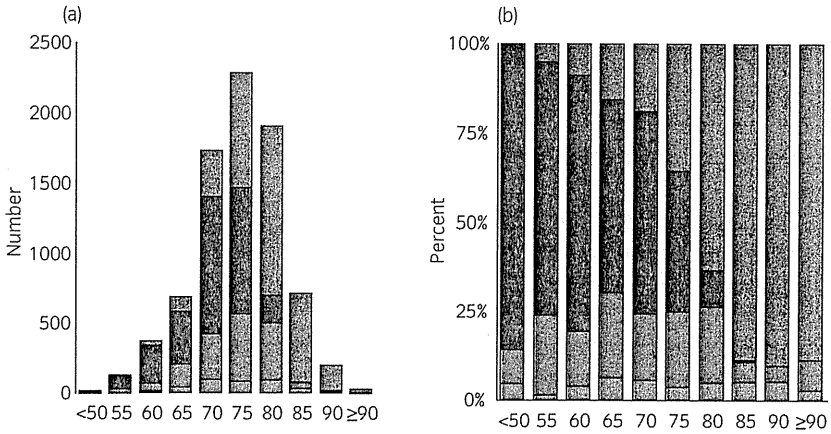

Fig. 2 Age distribution by main treatment modality in patients with T1-4N0M0 prostate cancer ($n = 8424$). (a) Totals and numbers of patients who underwent each treatment modality. (b) Percentages of each treatment by age. Hx, hormone ablation therapy; RP, radical prostatectomy; Rx, radiation therapy; 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) Program[4], 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 Program[4], 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 USA[4]. 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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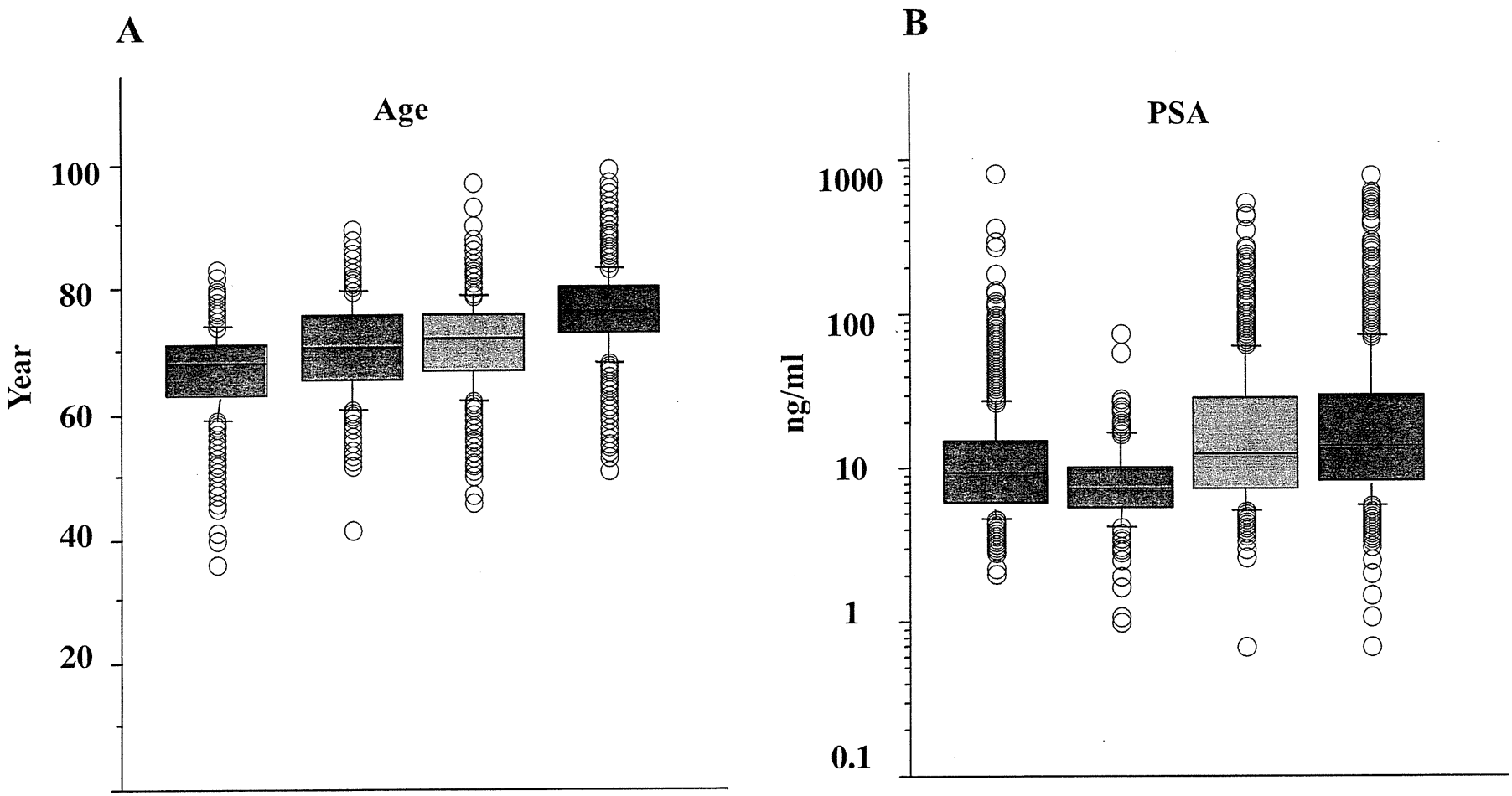
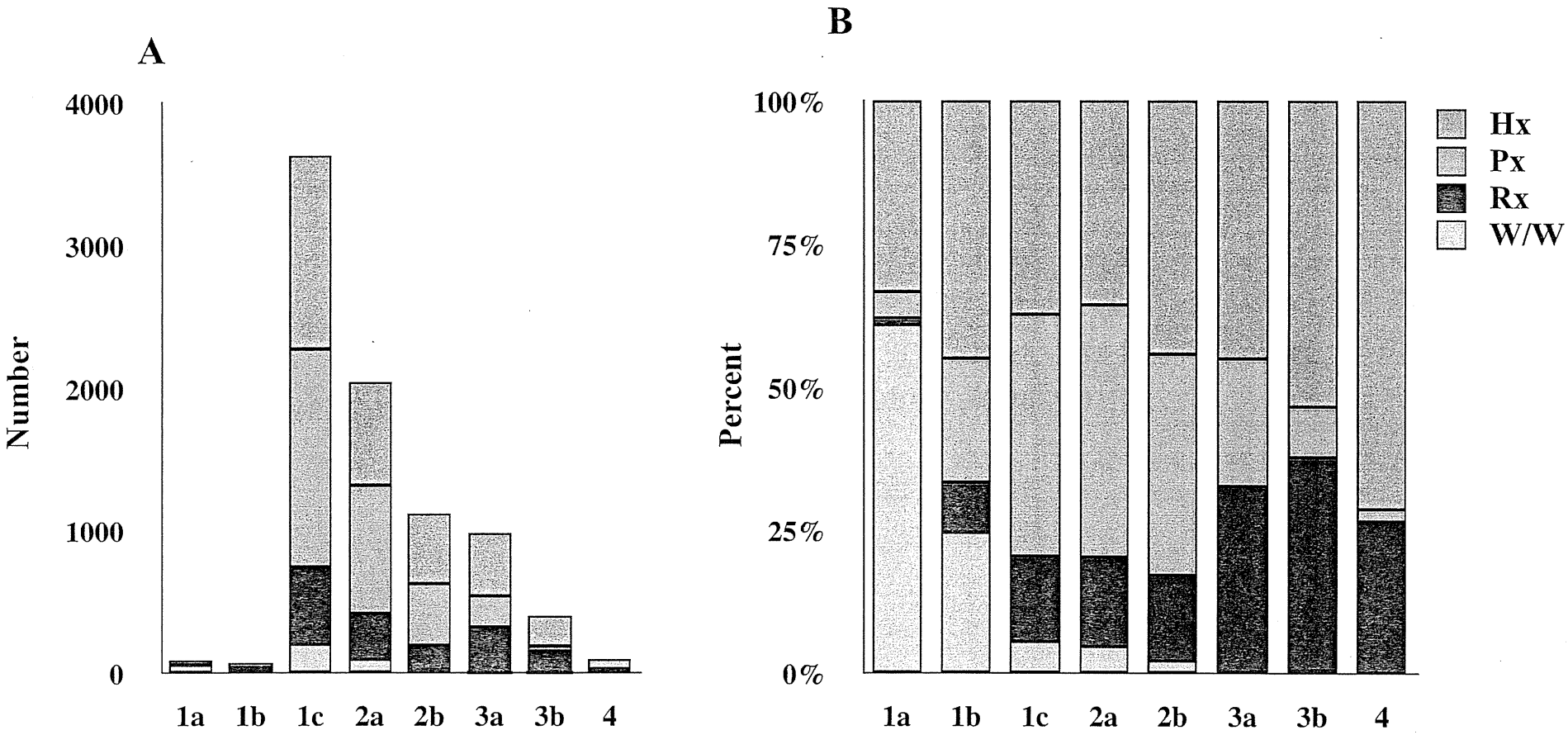
Fig. S1



	RP	W/W	Rx	Hx
n	3,140	394	1,530	3,360
mean	67.0	71.8	71.0	76.0
media	68.0	72.0	72.0	76.0
SD	6.03	7.25	6.64	6.15

	RP	W/W	Rx	Hx
n	1,254	170	643	1,647
mean	15.4	9.35	29.4	31.6
media	9.15	7.18	12.4	13.5
SD	31.3	8.12	50.2	59.9

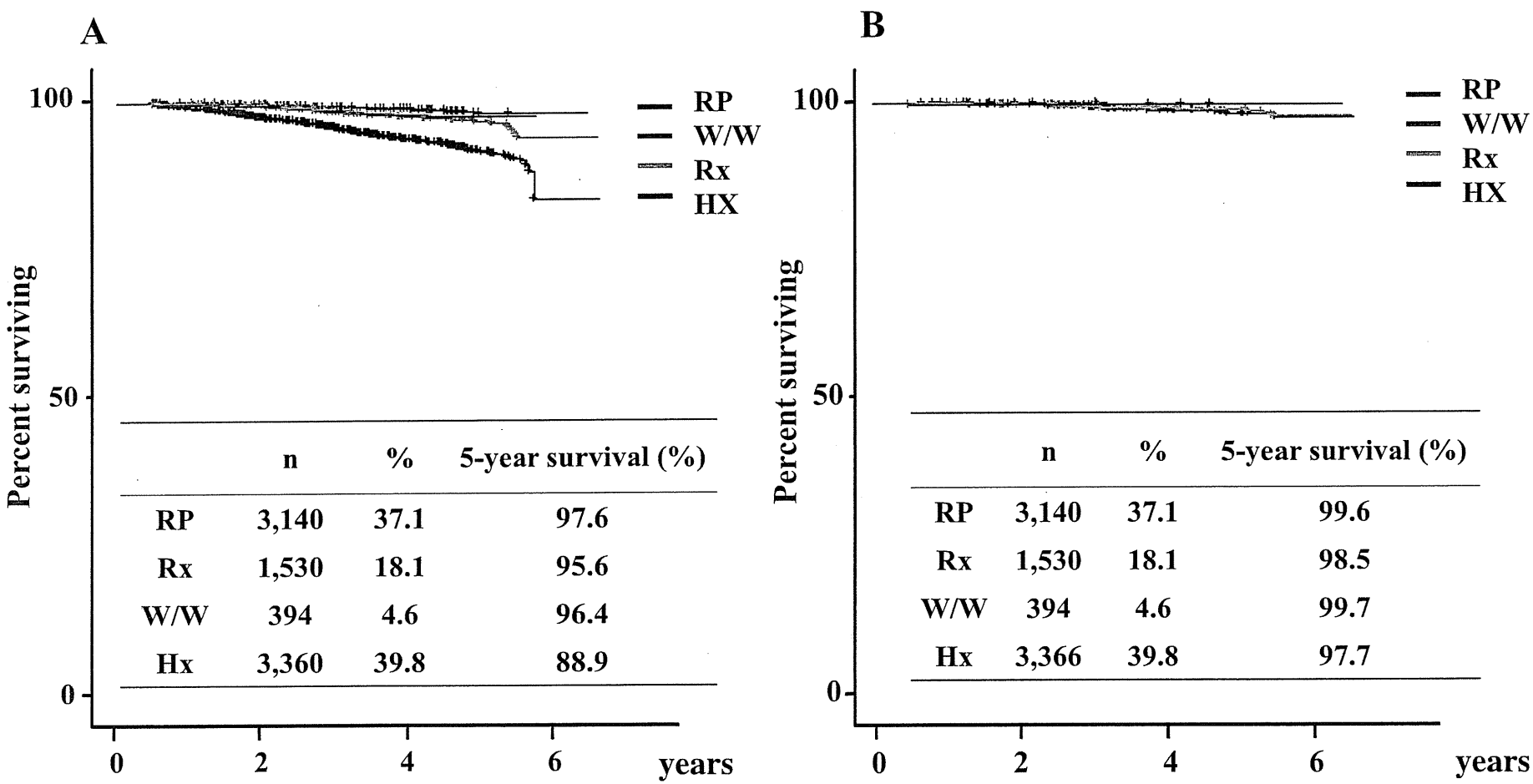
Fig. S2



Number of the patients by cT and main treatments

	1a	1b	1c	2a	2b	3a	3b	4
Hx	29	31	1,352	727	493	440	212	67
RP	4	15	1,532	899	431	218	35	2
Rx	1	6	541	319	167	318	148	25
W/W	53	17	200	95	24	2	2	0

Fig. S3


A
100
50
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Percent surviving
RP
W/W
Rx
HX
n % 5-year survival (%)
RP 3,140 37.1 97.6
Rx 1,530 18.1 95.6
W/W 394 4.6 96.4
Hx 3,360 39.8 88.9
0 2 4 6 years
B
100
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Percent surviving
RP
W/W
Rx
HX
n % 5-year survival (%)
RP 3,140 37.1 99.6
Rx 1,530 18.1 98.5
W/W 394 4.6 99.7
Hx 3,366 39.8 97.7
0 2 4 6 years

Table S1 Characteristics of the registered patients

Characteristic	Total (n = 10 280)†		Hx (n = 4934)		RP(n = 3212)		Rx (n = 1605)		W/W (n = 485)		P
	n	%	n	%	n	%	n	%	n	%	
Age (years)											<0.0001
≤35	3	0.03	2	0.04	3	0.09	0	0.00	0	0.00	
40	5	0.05	1	0.02	3	0.09	0	0.00	1	0.21	
45	18	0.18	2	0.04	14	0.44	2	0.12	0	0.00	
50	166	1.61	29	0.59	97	3.02	34	2.12	5	1.03	
55	446	4.34	85	1.72	279	8.69	60	3.74	18	3.70	
60	1171	11.39	248	5.03	693	21.58	174	10.84	50	10.29	
65	2006	19.51	543	11.01	999	31.10	343	21.37	114	23.46	
70	2750	26.75	1201	24.34	916	28.52	508	31.65	109	22.43	
75	2348	22.84	1595	32.33	205	6.38	426	26.54	116	24.07	
80	90	0.88	890	18.04	4	0.12	44	2.74	49	10.08	
85	311	3.03	281	5.70	0	0.00	11	0.69	18	3.70	
90	59	0.57	53	1.07	0	0.00	1	0.06	5	1.03	
≥95	6	0.06	4	0.08	0	0.00	2	0.12	0	0.00	
Mean/median	71.93/72.06		75.43/76.01		66.96/67.96		71.03/72.00		72.30/72.98		
PSA (Tandem-R) ng/mL	n = 4 565		n = 2379		n = 1291		n = 669		n = 217		<0.0001
0–10<	1790	39.21	661	27.78	701	54.30	271	40.51	152	70.05	
10–20<	1088	23.83	510	21.44	369	28.58	160	23.92	46	21.20	
20–30<	425	9.31	236	9.92	109	8.44	66	9.87	14	6.45	
30–40<	198	4.34	122	5.13	39	3.02	37	5.53	0	0.00	
40–50<	144	3.15	89	3.74	29	2.25	25	3.74	1	0.46	
50–60<	107	2.34	68	2.86	7	0.54	30	4.48	2	0.92	
60–70<	79	1.73	56	2.35	8	0.62	15	2.24	0	0.00	
70–80<	75	1.64	63	2.65	3	0.23	8	1.20	1	0.46	
80–90<	57	1.25	42	1.77	5	0.39	10	1.49	0	0.00	
90–100<	33	0.72	25	1.05	4	0.31	4	0.60	0	0.00	
100–1000<	429	9.40	257	10.80	16	1.24	43	6.43	1	0.46	
≥1000	136	2.98	139	5.84	1	0.08	0	0.00	0	0.00	
Mean/median	147.4/13.00		263.79/21.00		16.56/9.10		32.36/12.90		10.96/7.30		
Gleason score											<0.0001
≤5	1381	13.43	533	10.80	524	16.31	195	12.15	123	25.31	
6	2562	24.92	956	19.38	997	31.04	394	24.55	200	41.15	
7	3266	31.77	1546	31.33	1076	33.50	535	33.33	100	20.58	
8	1191	11.59	693	14.05	290	9.03	190	11.84	15	3.09	
9	1449	14.10	953	19.31	239	7.44	238	14.83	15	3.09	
10	199	1.94	134	2.72	27	0.84	35	2.18	2	0.41	
Median	7		7		7		7		6		
TNM classification											
T											<0.0001
0	5	0.05	3	0.06	1	0.03	0	0.00	0	0.00	
1a	136	1.32	37	0.75	4	0.12	2	0.12	89	18.31	
1b	88	0.86	42	0.85	15	0.47	6	0.37	23	4.73	
1c	3858	37.53	1492	30.24	1571	48.91	550	34.27	226	46.50	
2a	2197	21.37	849	17.21	912	28.39	326	20.31	105	21.60	
2b	1336	13.00	698	14.15	441	13.73	170	10.59	26	5.35	
3a	1357	13.20	796	16.13	221	6.88	333	20.75	3	0.62	
3b	773	7.52	565	11.45	39	1.21	165	10.28	3	0.62	
4	451	4.39	396	8.03	2	0.06	47	2.93	1	0.21	
X	77	0.75	56	1.13	6	0.19	6	0.37	10	2.06	
N											<0.0001
0	9237	89.85	4057	82.23	3173	98.79	1558	97.07	411	84.57	
1	684	6.65	627	12.71	12	0.37	38	2.37	4	0.82	
X	358	3.48	250	5.07	27	0.84	9	0.56	71	14.61	
M											<0.0001
0	8746	85.08	3582	72.60	3165	98.54	1562	97.32	398	81.89	
1a	39	0.38	34	0.69	1	0.03	4	0.25	0	0.00	
1b	1090	10.60	1061	21.50	5	0.16	20	1.25	4	0.82	
1c	66	0.64	62	1.26	0	0.00	3	0.19	0	0.00	
X	339	3.30	195	3.95	41	1.28	16	1.00	84	17.28	

†A total of 43 cases were treated with other modalities. Hx, hormone ablation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; Rx, radiation therapy; W/W, watchful waiting.

Table S2 Characteristics of 3212 radical prostatectomy patients

Characteristic	Total (n = 3212)†		No NHT (n = 2045)		≤6 m NHT (n = 356)		6–12 m NHT (n = 724)		>12 m NHT (n = 75)		P
	n	%	n	%	n	%	n	%	n	%	
Age											0.15
40–44	3	0.09	1	0.05	1	0.28	1	0.14	0	0	
45–49	14	0.44	9	0.44	2	0.56	3	0.41	0	0	
50–54	97	3.02	68	3.33	4	1.12	22	3.04	3	4	
55–59	279	8.69	169	8.26	24	6.74	74	10.22	10	13.33	
60–64	693	21.58	433	21.17	86	24.16	161	22.24	12	16	
65–69	999	31.10	634	31.00	110	30.90	225	31.08	24	32	
70–74	916	28.52	579	28.31	107	30.06	203	28.04	24	32	
75–79	205	6.38	146	7.14	22	6.18	35	4.83	2	2.67	
80–84	4	0.12	4	0.20	0	0.00	0	0.00	0	0	
Mean/median	67.0/68.0		67.1/68.0		67.2/68.0		66.8/68.0		66.5/67.0		
PSA (Tandem-R; ng/mL)											<0.0001
0–10<	701	54.30	478	60.74	77	55.00	132	40.49	12	16	
10–20<	369	28.58	213	27.06	36	25.71	109	33.44	11	14.67	
20–30<	109	8.44	59	7.50	12	8.57	34	10.43	4	5.33	
30–40<	39	3.02	13	1.65	6	4.29	18	5.52	2	2.67	
40–50<	29	2.25	12	1.52	3	2.14	14	4.29	0	0.00	
50–60<	7	0.54	3	0.38	2	1.43	2	0.61	0	0.00	
60–70<	8	0.62	3	0.38	0	0.00	4	1.23	1	1.33	
70–80<	3	0.23	0	0.00	2	1.43	1	0.31	0	0.00	
80–90<	5	0.39	3	0.38	0	0.00	1	0.31	1	1.33	
90–100<	4	0.31	0	0.00	0	0.00	4	1.23	0	0.00	
≥100	17	1.32	3	0.38	2	1.43	7	2.15	5	6.67	
Mean/median	16.2/9.0		12.8/8.2		15.2/8.90		22.6/10.9		66.6/13.4		
Gleason score											<0.0001
≤5	536	16.69	367	17.95	70	19.66	83	11.46	13	17.33	
6	997	31.04	721	35.26	102	28.65	158	21.82	16	21.33	
7	1076	33.50	616	30.12	108	30.34	318	43.92	28	37.33	
8	290	9.03	179	8.75	31	8.71	71	9.81	9	12.00	
9	239	7.44	111	5.43	34	9.55	83	11.46	8	10.67	
10	27	0.84	19	0.93	4	1.12	4	0.55	0	0.00	
Median	7		6		7		7		7		
T classification											<0.0001
1a	4	0.12	3	0.15	0	0.00	1	0.14	0	0	
1b	15	0.47	8	0.39	2	0.56	5	0.69	0	0	
1c	1566	48.75	1112	54.38	164	46.07	263	36.33	27	36.00	
2a	907	28.24	590	28.85	112	31.46	187	25.83	18	24.00	
2b	440	13.70	260	12.71	51	14.33	116	16.02	13	17.33	
3a	220	6.85	60	2.93	14	3.93	133	18.37	13	17.33	
3b	39	1.21	7	0.34	11	3.09	17	2.35	4	5.33	
4	2	0.06	1	0.05	0	0.00	1	0.14	0	0	
X	6	0.19	4	0.20	2	0.56	0	0.00	0	0	
Approach											<0.0001
Retropubic	3091	96.23	1952	95.45	343	96.35	713	98.48	74	96.7	
Open	2878	89.60	1686	82.44	330	92.70	709	97.93	72	96.00	
Laparoscopic	164	5.11	139	6.80	21	5.90	7	0.97	1	1.33	
Lap-assisted	49	1.53	36	1.76	5	1.40	6	0.83	2	2.67	
Perineal	86	2.68	77	3.77	4	1.12	3	0.41	1	1.33	
NVB preservation											<0.0001
Bilateral	186	5.79	107	5.23	35	9.83	38	5.25	5	6.67	
Hemi-lateral	384	11.96	301	14.72	23	6.46	49	6.77	4	5.33	
None	2262	70.42	1355	66.26	256	71.91	588	81.22	60	80.00	
LND											0.0003
Carried out	2926	91.10	1872	91.54	229	64.33	676	93.37	69	92.00	
Not carried out	268	8.34	162	7.92	55	15.45	45	6.22	5	6.67	
Extent of LND											0.0012
obt	2301	71.64	1489	72.81	222	62.36	538	74.31	47	62.67	
obt + int iliac	105	3.27	58	2.84	24	6.74	20	2.76	3	4.00	
obt + ext iliac	189	5.88	128	6.26	19	5.34	40	5.52	2	2.67	
obt, int + ext iliac	196	6.10	132	6.45	19	5.34	38	5.25	7	9.33	
int iliac	44	1.37	17	0.83	3	0.84	18	2.49	5	6.67	
ext iliac	18	0.56	11	0.54	3	0.84	3	0.41	1	1.33	

†A total of 12 cases showed uncertain neoadjuvant hormonal therapy (NHT) status. ext, external; int, internal; LND, lymph node dissection; NVB, neurovascular bundle; obt, obturator; PSA, prostate-specific antigen.

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

	No NHT ($n = 2045$)		≤6 m NHT ($n = 356$)		6–12 m NHT ($n = 724$)		>12 m NHT ($n = 75$)		P
	n	%	n	%	n	%	n	%	
pT									<0.0001
0	32	1.56	20	5.62	111	15.33	15	20.00	
2a	444	21.71	88	24.72	163	22.51	22	29.30	
2b	775	37.90	130	36.52	247	34.12	20	26.66	
3a	569	27.82	74	20.79	95	13.12	8	10.67	
3b	166	8.12	27	7.58	50	6.91	8	10.67	
4	29	1.42	8	2.25	20	2.76	2	2.67	
Gleason score									<0.0001
≤5	253	12.37	43	12.08	88	12.15	4	5.33	
6	463	22.64	53	14.89	88	12.15	7	9.33	
7	901	44.06	115	32.30	251	34.67	16	21.33	
8	176	8.61	32	8.99	53	7.32	5	6.67	
9	175	8.56	44	12.36	78	10.77	8	10.67	
10	11	0.54	6	1.69	8	1.10	1	1.33	
ew									<0.0001
(+)	696	34.03	92	25.84	98	13.54	16	21.33	
(–)	1265	61.86	250	70.22	571	78.87	56	74.67	
cap									<0.0001
(+)	674	32.96	97	27.25	129	17.82	9	12.00	
(–)	1310	64.06	246	69.10	560	77.35	61	81.33	
ly									<0.0001
(+)	546	26.70	90	25.28	70	9.67	10	13.33	
(–)	1395	68.22	253	71.07	610	84.25	61	81.33	
v									<0.0001
(+)	219	10.71	30	8.43	34	4.70	4	5.33	
(–)	1716	83.91	307	86.24	643	88.81	67	89.33	
pn									<0.0001
(+)	1013	49.54	154	43.26	284	39.23	17	22.67	
(–)	910	44.50	185	51.97	402	55.52	52	69.33	
sv									0.0417
(+)	161	7.87	30	8.43	52	7.18	7	9.33	
(–)	1839	89.93	311	87.36	643	88.81	64	85.33	
br									<0.0001
(+)	20	0.98	7	1.97	19	2.62	0	0.00	
(–)	1429	69.88	277	77.81	561	77.49	59	78.67	
pN									0.3379
0	1597	78.09	249	69.94	619	85.50	55	73.33	
1	54	2.64	11	3.09	14	1.93	1	1.33	
Salvage Therapy									<0.001
none	2025	99.02	330	92.70	658	90.88	71	94.67	
Hx	138	6.75	9	2.53	39	5.39	1	1.33	
Rx	53	2.59	9	2.53	26	3.59	3	4.00	
Hx·Rx	24	1.17	5	1.40	0	0.00	0	0.00	
Survival status									0.0611
NED	1548	75.70	259	72.75	544	75.14	54	72.00	
Alive with disease	439	21.47	87	24.44	163	22.51	21	28.00	
Stable disease	127	6.21	35	9.83	62	8.56	7	9.33	
PSA/clinical failure	301	14.72	49	13.76	93	12.85	13	17.33	
Progressive disease	11	0.54	3	0.84	8	1.10	1	1.33	
Died of prostate cancer	2	0.10	3	0.84	3	0.41	0	0.00	
Died of other causes	45	2.20	6	1.69	14	1.93	0	0.00	

A total of 12 cases were excluded as a result of uncertain neoadjuvant hormonal therapy (NHT) status. ew, surgical status; Hx, hormone ablation therapy; NED, no evidence of disease; pN, node metastasis; PSA, prostate-specific antigen; Rx, radiation therapy; sv, seminal vesicle invasion.

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

M classification	M0 ($n = 3582$)		M1a ($n = 34$)		M1b ($n = 1061$)		M1c ($n = 62$)		Mx ($n = 195$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Type of hormone ablation therapy										
LH-RH analog	3210	89.6	29	85.3	910	85.8	52	83.9	163	83.6
Surgical castration	202	5.6	3	8.8	102	9.6	9	14.5	7	3.6
Anti-androgen (non-steroid)	2326	64.9	27	79.4	803	75.7	49	79.0	120	61.5
Chlormadinone acetate	314	8.8	1	2.9	94	8.9	6	9.7	18	9.2
Estrogen (DES)	73	2.0	5	14.7	156	14.7	8	12.9	4	2.1
Estramustine phosphate (EST)	21	0.6	2	5.9	76	7.2	1	1.6	2	1.0
Steroid	1	0.0	0	0.0	4	0.4	1	1.6	0	0.0
Combination										
LH-RH or surgical castration alone	904	25.2	4	11.8	115	10.8	6	9.7	55	28.2
Anti-androgen alone	173	4.8	0	0.0	21	2.0	4	6.5	25	12.8
MAB	2413	67.4	24	70.6	723	68.1	44	71.0	109	55.9
MAB + DES	40	1.1	2	5.9	77	7.3	0	0.0	2	1.0
MAB + EST	10	0.3	1	2.9	39	3.7	0	0.0	2	1.0
MAB + DES + EST	3	0.1	1	2.9	31	2.9	1	1.6	0	0.0
Anti-androgen + DES	4	0.1	0	0.0	4	0.4	0	0.0	0	0.0
Anti-androgen + EST	2	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Other	33	0.9	2	5.9	49	4.6	7	11.3	2	1.0
Survival status										
Alive	3090	86.3	19	55.9	648	61.1	35	56.5	167	85.6
Stable disease	2733	76.3	11	32.4	354	33.4	16	25.8	146	74.9
PSA/clinical failure	208	5.8	3	8.8	125	11.8	11	17.7	12	6.2
Progressive disease	159	4.4	5	14.7	205	19.3	7	11.3	9	4.6
Died of prostate cancer	96	2.7	12	35.3	306	28.8	24	38.7	8	4.1
Died of other causes	300	8.4	3	8.8	63	5.9	3	4.8	18	9.2

LH-RH, luteinizing hormone-releasing hormone; MAB, maximum androgen blockade; PSA, prostate-specific antigen.

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

Method	EBRT (*n* = 1241)		BT (*n* = 210)		BT + EBRT (*n* = 48)		*P*
	n	%	*n*	%	*n*	%	
Age (years)							<0.001
<50	0	0.00	1	0.48	0	0.00	
50–54	17	1.37	9	4.29	1	2.08	
55–59	33	2.66	15	7.14	3	6.25	
60–64	114	9.19	35	16.67	14	29.17	
65–69	260	20.95	47	22.38	11	22.92	
70–74	407	32.80	65	30.95	10	20.83	
75–79	364	29.33	32	15.24	9	18.75	
80–84	35	2.82	5	2.38	0	0.00	
85–90	8	0.64	1	0.48	0	0.00	
Mean/median	71.74/72.9		68.6/70.0		67.9/67.1		
PSA (Tandem-R) ng/mL							<0.001
0–10<	172	13.86	71	33.81	14	29.17	
10–20<	134	10.80	15	7.14	5	10.42	
20–30<	59	4.75	4	1.90	1	2.08	
230–40<	31	2.50	1	0.48	4	8.33	
40–50<	21	1.69	1	0.48	0	0.00	
50–60<	27	2.18	1	0.48	1	2.08	
60–70<	10	0.81	1	0.48	2	4.17	
70–80<	8	0.64	0	0.00	0	0.00	
80–90<	10	0.81	0	0.00	0	0.00	
90–100<	3	0.24	0	0.00	0	0.00	
100–200<	21	1.69	1	0.48	0	0.00	
≥200	16	1.29	0	0.00	0	0.00	
Mean/median	36.52/15.00		11.26/7.30		18.42/9.78		
Gleason score							<0.001
≤5	154	12.41	38	18.10	4	8.33	
6	242	19.50	114	54.29	12	25.00	
7	442	35.62	45	21.43	21	43.75	
8	160	12.89	7	3.33	4	8.33	
9	214	17.24	6	2.86	5	10.42	
10	28	2.26	0	0.00	2	4.17	
Median	7		6		7		
T classification							<0.001
1a	2	0.16	0	0.00	0	0.00	
1b	6	0.48	0	0.00	0	0.00	
1c	357	28.77	138	65.71	22	45.83	
2a	249	20.06	47	22.38	10	20.83	
2b	134	10.80	18	8.57	8	16.67	
3a	315	25.38	4	1.90	4	8.33	
3b	145	11.68	1	0.48	4	8.33	
4	29	2.34	2	0.95	0	0.00	
x	4	0.32	0	0.00	0	0.00	
N classification							0.178
N0	1200	96.70	208	99.05	48	100.00	
N1	20	1.61	0	0.00	0	0.00	
Risk classification							<0.001
Low	62	5.00	51	24.29	1	2.08	
Intermediate	142	11.44	31	14.76	12	25.00	
High	719	57.94	23	10.95	18	37.50	
NA	318	25.62	105	50.00	17	35.42	

n = 1499. There were 28 patients who received particle radiotherapy and 27 patients who were treated by uncertain modality that were excluded. BT, brachytherapy; EBRT, external beam radiotherapy; NA, not assessed; PSA, prostate-specific antigen.