

57–73%)³ and HER2 3+/non-amplified (i.e. false-positive) cases (3% versus 27–43%)³ in salivary duct carcinoma.

As far as the pattern of amplification is concerned, Skalova *et al.* described a homogeneously staining region (HSR) pattern in all amplified cases, while we observed three different patterns of amplification: (i) five cases presented amplified genes arranged as HSR, usually one or two per nucleus; (ii) one case showed multiple scattered single-copy HER2 signals and chromosome 17 polysomy (calculated ratio between HER2 and centromeric probe (CEP) 17 copy number was more than 2 in all tumour nuclei); (iii) two cases showed a pattern of hybridization consistent with double minutes (Figure 1), a very unusual occurrence in breast cancer.⁴

Considering the breast model where the efficiency of herceptin-based therapy is restricted to HER2 3+ or amplified cases⁵ and assuming that in salivary duct carcinoma the biological basis of response to herceptin is the same as in breast cancer, we can anticipate successful use of this drug in salivary duct carcinoma. On the basis of the above-reported findings it might be expected that >50% of such patients could benefit from TKR-inhibitor therapy. However, the high rate of HER2 3+ non-amplified cases (>27%), likely to be unresponsive, necessitates FISH analysis for patient selection. Assessment by FISH is further supported by our preliminary data regarding the relationship between protein expression and the amplification pattern. Despite the presence of a 3+ immunohistochemical score, we found no HER2 protein by immunoprecipi-

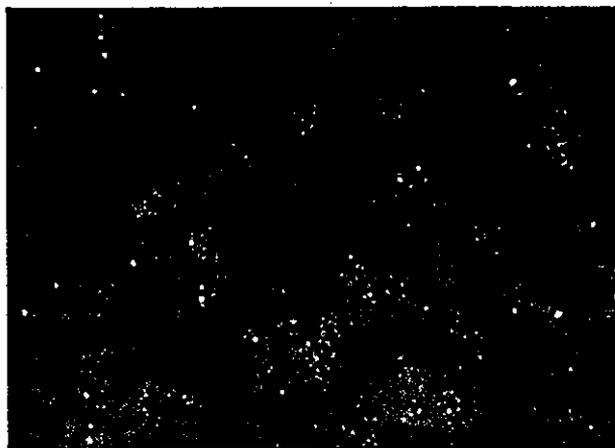


Figure 1. Example of HER2 gene amplification in salivary duct carcinoma (HER2 signals in orange, centromeric probe (CEP) 17 signals in green). Note the pattern of amplification consistent with the presence of double minutes showing multiple clusters of amplified genes scattered over the nucleus.

tation and Western blotting experiments in the two cases carrying double minute-related amplification. If this finding is confirmed by further experiments and since the lack of HER2 protein expression is correlated with an unsuccessful response to herceptin therapy, FISH is likely to become the assessment of choice in this salivary tumour type.

ACKNOWLEDGEMENT

This work was supported by 'AIRC 2001 (Associazione Italiana per la Ricerca sul Cancro)', grant no. 420.198.122.

G P Dagrada
T Negri
E Tamborini
M A Pierotti^{1,2}
S Pilotti²

*Experimental Molecular Pathology,
Department of Pathology and*

¹*Experimental Oncology Department, Istituto Nazionale
per lo Studio e la Cura dei Tumori, Milano, Italy*

²*Senior Co-authors*

1. Skalova A, Starek I, Vanecek T *et al.* Expression of HER-2/*neu* gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence *in-situ* hybridization and immunohistochemistry. *Histopathology* 2003; 42: 348–356.
2. Dagrada GP, Mezzelani A, Alasio L *et al.* HER-2/*neu* assessment in primary chemotherapy treated breast carcinoma: no evidence of gene profile changing. *Breast Cancer Res. Treat.* 2003; 80: 207–214.
3. Pauletti G, Godolphin W, Press MF *et al.* Detection and quantitation of HER-2/*neu* gene amplification in human breast cancer archival material using fluorescence *in situ* hybridization. *Oncogene* 1996; 13: 63–72.
4. Mitelman F. *Catalog of chromosome aberrations in cancer*, 5th ed. New York: Wiley-Liss, 1994.
5. Vogel CL, Cobleigh MA, Tripathy D *et al.* Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J. Clin. Oncol.* 2002; 20: 719–726.

Malignant mixed epithelial and stromal tumours of the kidney: a report of the first two cases with a fatal clinical outcome

Sir: Mixed epithelial and stromal tumour of the kidney (MESTK), a rare benign neoplasm of unknown aetiology, is a recently established entity unifying several neoplasms such as adult mesoblastic nephroma, cystic hamartoma of the pelvis, adult type cystic nephroma,

multilocular renal cysts, and solid and cystic biphasic tumour of the kidney.¹⁻⁴ In cases reported as MESTK, recurrence or fatal outcome has, to date, never been reported. Here, we present two cases of malignant MESTK with local recurrences and fatal outcomes.

The first case was in a 43-year-old Japanese woman, who had undergone radical nephrectomy for a right renal tumour and developed a local recurrent tumour 2 years later. Nine months after extirpation of the recurrent tumour she developed another local recurrence, associated with severe haemorrhage which could not be sufficiently controlled even by three trials of transarterial embolization. The recurrent tumour was found to have invaded adjacent organs allowing only palliative surgery for mass reduction. The patient died 43 months after initial nephrectomy. The second case was in a 31-year-old Japanese woman who had undergone radical nephrectomy for a tumour in the upper pole of the left kidney. Four months after the operation, she developed a local recurrent tumour, accompanied by massive ascites. She died 11 months after nephrectomy.

In case 1, the primary tumour measured approximately 70 mm in diameter, was located mainly near the renal hilus and appeared to consist chiefly of solid components. In case 2 it measured 70 × 70 × 60 mm, was generally well circumscribed and extended beyond the renal capsule. It consisted of solid and cystic components; the former was yellowish and firm and the latter was filled with haematoma.

The primary tumours of both patients were composed of proliferating spindle-shaped cells and epithelial tubular structures of various sizes (Figure 1a). The epithelial components were intermingled with the stromal components throughout the tumours. In case 1, the spindle cells had bright eosinophilic cytoplasm and fusiform nuclei with moderate atypia, formed interlacing bundles and small fascicles with high cellularity (Figure 1b) and infiltrated the renal hilar fat extensively. In case 2, the stromal components were composed of varying numbers of atypical spindle cells with clear cytoplasm that formed fascicles or whorled around the small tubules. No blastema was present. In both cases, the sizes of the epithelial tubular structures were variable, from small tubules reminiscent of normal collecting ducts to cystically dilated ducts lined by cells with a hobnail appearance (Figure 2). All the cells of the epithelial components lacked cytological atypia. It is noteworthy that tubular structures could be seen even in the extrarenally invading part of case 2's tumour and in the recurrent tumour of case 1, confirming that the tubules were not normal structures that had become involved but were integral neoplastic components of the tumours. Mitoses were conspicuous in both cases.

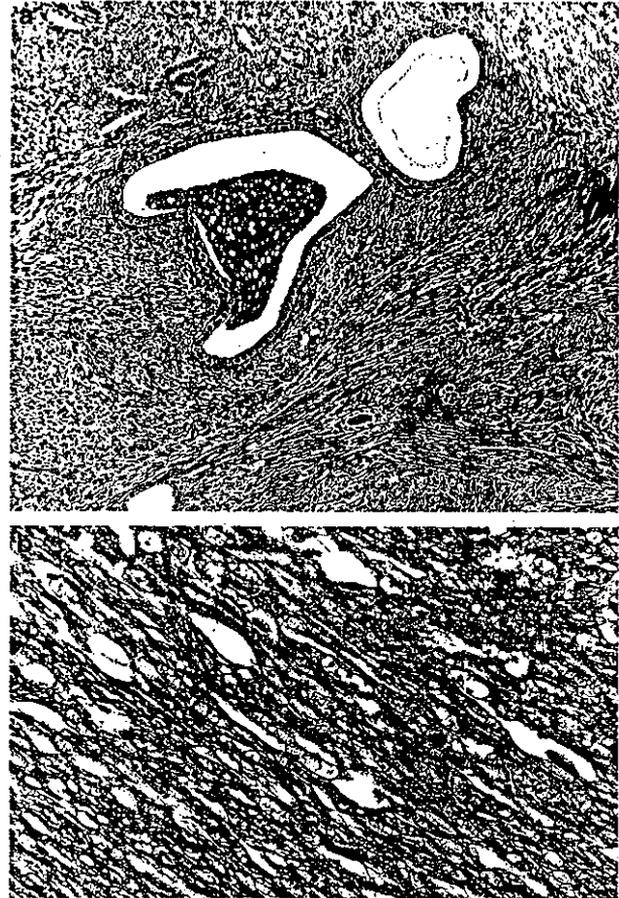


Figure 1. The primary tumour of case 1. a, The tumour is composed mainly of proliferating spindle-shaped cells and epithelial tubular or cystic structures scattered amidst the spindle cells. b, The spindle cells have eosinophilic cytoplasm and fusiform nuclei with moderate atypia and have formed small fascicles with high cellularity. Haematoxylin and eosin.

Immunohistochemically, the spindle cells of both cases were vimentin-positive, and those of case 1 were muscle-specific actin- and α -smooth muscle actin-positive. The cells of the epithelial structures of both cases were cytokeratin- and vimentin-positive and focally epithelial membrane antigen-positive.

The overall histopathological and immunohistochemical findings of these two cases were similar to those of MESTK,² but they consisted of more atypical spindle cells forming interlacing fascicles, bundles and whorling around the tubules with increased numbers of mitotic figures.

The differential diagnoses include leiomyosarcoma, biphasic synovial sarcoma⁴ and related tumours. Although leiomyosarcoma is the most common mesenchymal tumour arising in the kidney, it contains neither neoplastic epithelial components nor entrapped tubules, because its growth is expansive rather than

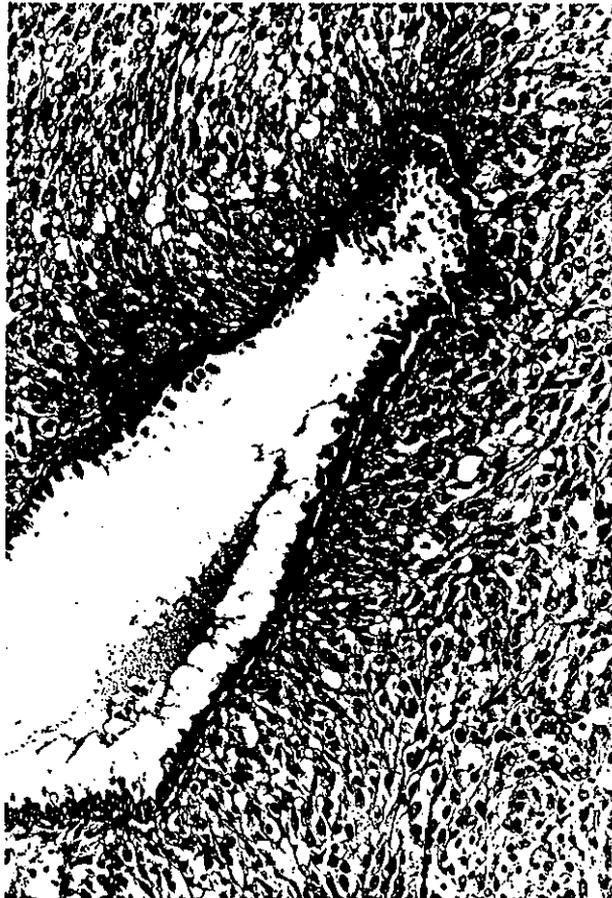


Figure 2. The primary tumour of case 2. Some cystic structures are lined by cells with a hobnail appearance. Haematoxylin and eosin.

infiltrative. Biphasic synovial sarcoma of the kidney is a rare neoplasm that contains both epithelial and stromal components.⁵ Even if typical biphasic synovial sarcomas occur in the kidney, their epithelial cells are usually cuboidal or polygonal and form solid nests and glandular or tubular structures,⁶ whereas the epithelial components in the present two tumours lacked obvious cytological atypia and were considered to be similar to those of the normal collecting ducts.

In conclusion, rarely, MESTK has a malignant histopathological appearance and behaves aggressively. In this situation, this tumour needs to be distinguished from leiomyosarcoma and synovial sarcoma arising in the kidney.

ACKNOWLEDGEMENTS

This study was supported by a Grant-in-Aid for the Second Term Comprehensive 10-Year Strategy for Cancer Control and a Grant-in-Aid for Cancer Research

from the Ministry of Health, Labour and Welfare of Japan.

T Nakagawa
Y Kanai²
H Fujimoto
H Kitamura
H Furukawa¹
S Maeda³
T Oyama⁴
T Takesaki⁵
T Hasegawa²

Urology and ¹Diagnostic Radiology Divisions,
National Cancer Centre Hospital,
²Pathology Division, National Cancer Centre
Research Institute and
³Department of Pathology, Nippon Medical School
Hospital, Tokyo, and
⁴Urology and ⁵Pathology Divisions, Yamanashi Prefectural
Central Hospital, Yamanashi, Japan

1. Michal M, Syrucek M. Benign mixed epithelial and stromal tumor of the kidney. *Pathol. Res. Pract.* 1998; 194: 445-448.
2. Adsay NV, Eble JN, Srigley JR, Jones EC, Grignon DJ. Mixed epithelial and stromal tumor of the kidney. *Am. J. Surg. Pathol.* 2000; 24: 958-970.
3. Michal M. Benign mixed epithelial and stromal tumor of the kidney. *Pathol. Res. Pract.* 2000; 196: 275-276.
4. Svec A, Hes O, Michal M, Zachoval R. Malignant mixed epithelial and stromal tumor of the kidney. *Virchows Arch.* 2001; 439: 700-702.
5. Argani P, Faria PA, Epstein JI et al. Primary renal synovial sarcoma: molecular and morphologic delineation of an entity previously included among embryonal sarcomas of the kidney. *Am. J. Surg. Pathol.* 2000; 24: 1087-1096.
6. Tumors of uncertain differentiation and those in which differentiation is nonmesenchymal. In Kempson RL, Fletcher CDM, Evans HL, Hendrickson MR, Sibley RK eds. *Tumors of the soft tissues (Atlas of tumor pathology, Third Series, Fascicle 30)*. Washington, DC: Armed Forces Institute of Pathology, 2001; 419-501.

Neuroendocrine carcinoma of the vulva with paraganglioma-like features

Sir: Neuroendocrine tumours (NTs) of the female genital tract are relatively uncommon.¹ Particularly, NTs occurring in the vulva are extremely rare with the few cases reported in the English literature considered as Merkel cell carcinoma (MCC).² Here we document a neuroendocrine vulvar carcinoma with peculiar microscopic, immunohistochemical and ultrastructural features reminiscent of a paraganglioma.

Clinical Data

Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association

CANCER REGISTRATION COMMITTEE OF THE JAPANESE UROLOGICAL ASSOCIATION

Abstract

Background: The purpose of the present paper was to investigate etiology, diagnosis, initial treatment, pathological findings and final outcomes for prostate cancer in Japan.

Methods: From 2001, the Japanese Urological Association initiated computer-based registration of prostate cancer patients in Japan to estimate etiology, diagnosis, initial planned treatment, pathological findings and final outcome.

Results: A total of 173 institutions responded and 4529 patients who were diagnosed with prostate cancer in 2000 were registered. In the first year, background factors, diagnostic procedures and initially planned treatment were recorded. The analysis of these registered cases is presented here. Nearly 30% of the cases demonstrated <10 ng/mL of prostate specific antigen. The six-core biopsy was the most commonly used procedure. The clinical T staging distribution was as follows: T1c, 20.3%; T2a, 21.8%; T2b, 17.3%; T3a, 15.8%; T3b, 11.0%; and T4, 8%. More than 70% of cases were diagnosed as M0. Hormone therapy alone was the initial treatment plan in more than half of the cases.

Conclusion: This is the first report on prostate cancer patients in Japan based on multi-institutional registration. Pathological findings and final outcome will be surveyed later by the Japanese Urological Association. After 5 years, adopted treatment, pathological results and final outcome will be registered.

Key words epidemiology, Japan, neoplasm, prostate.

Introduction

Prostate cancer is known around the world as a disease of elderly men. Parkin *et al.* reported that three-quarters of cases occur in men over 65 years of age.¹ In Japan, although the incidence of prostate cancer has been much less than in American and European countries, it has been sharply rising during the last two decades, a trend also observed in other Asian countries. Even before the introduction of prostate specific antigen (PSA) testing in the early 1990s, incidence rates had been rising in

many countries.^{1–5} Changes from traditional Japanese to more Western lifestyles and nutritional habits have been implicated in the increase in the incidence of prostate cancer in Japan.³ In the early 1990s, the PSA test contributed to the earlier diagnosis of prostate cancer, which is also reflected in the increased incidence. Now, in Japan as in other developed countries, prostate cancer is a large and growing public health problem whose risk factors are essentially unknown.

The precise nature of this problem differs from one country to another because of the wide range of national incidence and, to a much lesser degree, survival profiles that have been reported.^{1,5–8} Recently, however, Nakata *et al.*⁴ reported that the mortality rate of prostate cancer patients in Japan has been increasing as rapidly as the incidence, while in North America the mortality rate has actually declined even in the face of rising incidence.⁹

Correspondence: Hiroyuki Fujimoto MD, Urology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

Email: juacr@nifty.com, juacr@ml.res.ncc.go.jp

Received 28 January 2003; accepted 29 June 2004.

The Japanese Urological Association (JUA) and the Japanese Society of Pathology revised the 2nd edition of *General Rule for Clinical and Pathological Studies on Prostate Cancer* to the 3rd edition in 2001¹⁰ and, in accordance with this new edition, initiated a study to estimate the etiology, diagnosis, initial treatment, pathological findings and final outcomes for prostate cancer in Japan by employing computer-based registration of prostate cancer patients from institutions all over Japan. The registration program has been established by the members of committee for revision of *General Rule for Clinical and Pathological Studies on Prostate Cancer*. Here we report the background data at diagnosis from the initial registration of 4529 patients who were diagnosed pathologically with prostate cancer in 2000.

Methods

Using a CD-ROM program developed by the members of committee for revision of *General Rule for Clinical and Pathological Studies on Prostate Cancer* and the staff of the National Cancer Center, new patients who were diagnosed by pathology to have prostate cancer in 2000 were registered. Age, occupation, race, concomitant malignancy, family history, past history and symptoms were entered as background factors for each prostate cancer patient. The findings from digital rectal examination (DRE), imaging, PSA level, number of cores taken by biopsy, number of positive core(s), histology of the biopsy specimen, Gleason score, 5th tumor, nodes, metastases (TNM) classification (5th edition), diagnostic process and initial treatment plan were also entered. The collected data were analyzed.

Results

One hundred and seventy-three institutions responded and 4529 patients who were diagnosed with prostate cancer in 2000 were registered. Approximately 14 000 new prostate cancer patients were estimated in Japan this year;⁹ therefore, approximately 30% of total cases were covered by this registry.

Background data

The age distribution of patients is summarized in Figure 1. More than one-quarter of all patients were 70–74 years old, and three-quarters were 60–79 years old. The ethnic distribution was as follows: Japanese, 99.56%; non-Japanese Mongolians, 0.29%; and Caucasian, 0.13%. Only 71 patients (1.57%) had a family

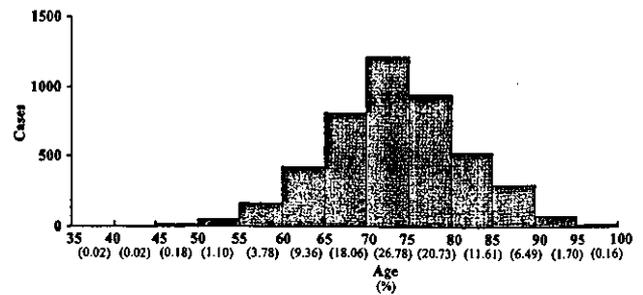


Fig. 1 Age distribution of prostate cancer newly diagnosed in 2000 and registered. Registered cases were divided into 5-year age groups as indicated. Bars indicate the number of cases equal to and above the age on the left lower corner and below the age on the right lower corner of each bar. The numbers below each bar indicate the percentage of cases in each age group among all registered cases.

Table 1 Findings of local imaging study

	n	(%)
Not visible	1255	27.71
Confirmed within prostate	1580	34.89
Extra-capsule	732	16.16
Invades adjacent structure	685	15.12
Uncertain	277	6.12
Total	4529	100.00

history of prostate cancer in either their father (0.66%), brother (0.82%), or uncle (0.09%). Common occupations of the registered patients were the following: retired (61.29%), office clerks or associate professionals (8.06%), corporate or general managers (6.93%), agricultural, forestry, or fishery workers (6.71%), and professionals or technicians (6.62%). A total of 520 patients (11.48%) had a history of other malignancies.

Initial evaluation

Of all the patients, 71.08% (3219 cases) presented with some symptoms and 339 cases (7.49% of all and 35.17% of metastatic disease) presented with symptoms from metastases.

The most commonly used staging modalities were transrectal ultrasonography (TRUS; 78.32%) and bone scan (73.53%), followed by computed tomography (CT; 66.75%) and magnetic resonance imaging (MRI; 42.77%). The findings from local imaging studies are summarized in Table 1. As expected, local imaging studies yielded better sensitivity (66.17% produced a positive finding) than DRE (58.29% true-positives; Table 2).

Table 2 Findings of digital rectal examination

	<i>n</i>	(%)
Not palpable	1706	37.67
One lobe	1090	24.07
Both lobe	760	16.78
Extra-capsule	481	10.62
Seminal vesicle invasion	113	2.50
Extra-prostate	196	4.33
Uncertain	18.3	4.04
Total	4529	100.00

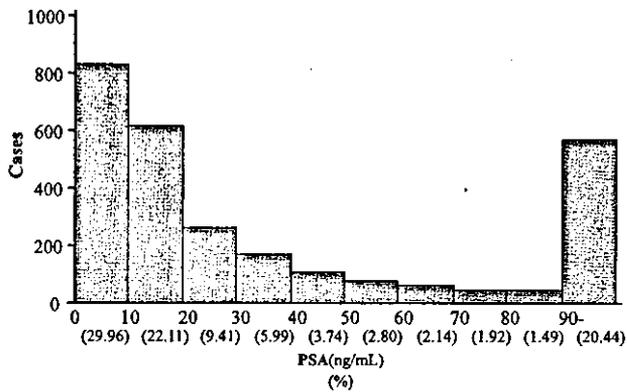


Fig. 2 Distribution of prostate specific antigen (PSA) value of registered cases. Registered cases were divided into groups of PSA value by 10 ng/mL as indicated. The PSA value was measured by Tandem-R and includes all Tandem-R compatible kits, such as *E-test* Tosoh, Chemilumi ACS-PSA, Shifalite PSA and Lumipulse PSA. Bars indicate the number of cases equal to and above the value on the left lower corner and below the value on the right lower corner of each bar. Cases with PSA \geq 90 ng/mL were counted as a single group. The numbers below each bar indicate the percentage of cases in each group among all registered cases.

The PSA level distribution is summarized in Figure 2. Nearly 30% of prostate cancer cases diagnosed in 2000 demonstrated a PSA value of <10 ng/mL.

A summary of the biopsy statistics is shown in Tables 3–5 and Figure 3. Because the same number of cores is usually taken from each lobe, the 5th, 7th, and 9th core samples are supposed to be additional targeted biopsies of suspicious lesions (Table 3). The percentage of biopsies yielding all positive cores was higher for the 6-core than for the 8-core biopsy (Fig. 3). However, the percentage of biopsies yielding only one positive core was higher for the 8-core procedure. A total of 99.8% of tumors were determined pathologically to be adenocarcinoma, followed by neuroendocrine tumors (0.1%). Moderately differentiated adenocarcinoma (43.5%) was

Table 3 Number of adopted biopsy cores

Core(s)	<i>n</i>	(%)
1	5	0.12
2	93	2.30
3	52	1.28
4	264	6.52
5	90	2.22
6	2128	52.52
7	282	6.96
8	616	15.20
9	90	2.22
\geq 10	432	10.66
Total	4052	100

Uncertain, 168 patients.

Table 4 Primary Gleason grade

Gleason grade	<i>n</i>	(%)
1	376	8.30
2	541	11.90
3	1155	25.50
4	695	15.30
5	308	6.80
Uncertain	1454	32.10
Total	4529	100

Table 5 Secondary Gleason grade

Gleason grade	<i>n</i>	(%)
1	251	5.50
2	552	12.20
3	1020	22.50
4	780	17.20
5	312	6.90
Uncertain	1614	35.60
Total	4529	100

the most common differentiation state found in this population, followed by well-differentiated (31.3%) and poorly differentiated adenocarcinomas (20.6%). Gleason grade classification is summarized in Tables 4,5; grade 3 was found to be the most common grade in both primary and secondary dominant tumors.

Initial staging

Clinical T stage of this population is summarized in Figure 4. The clinical T staging distribution is as follows: T1c, 20.3%; T2a, 21.8%; T2b, 17.3%; T3a, 15.8%; T3b, 11.0%; and T4, 8%. Regionally limited lymph node metastases examined mainly by CT were found in 501 cases (11.06%), and 3569 cases

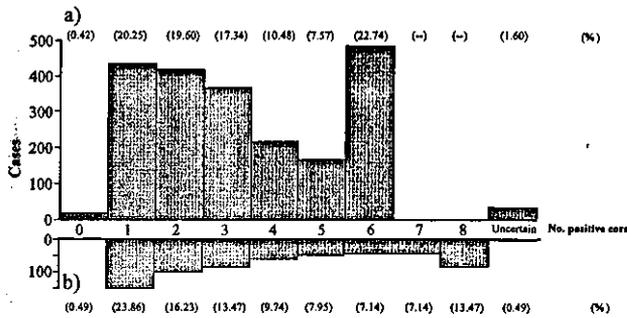


Fig. 3 Number of cancer-positive cores in (a) 6-core biopsy ($n = 2128$) and (b) 8-core biopsy ($n = 616$). Registered cases were divided into groups by number of cancer-positive cores as indicated. Bars indicate the number of cases in each group. The percentage of cases in each group among each subgroup of 6- or 8-core biopsy is indicated over or below the bars.

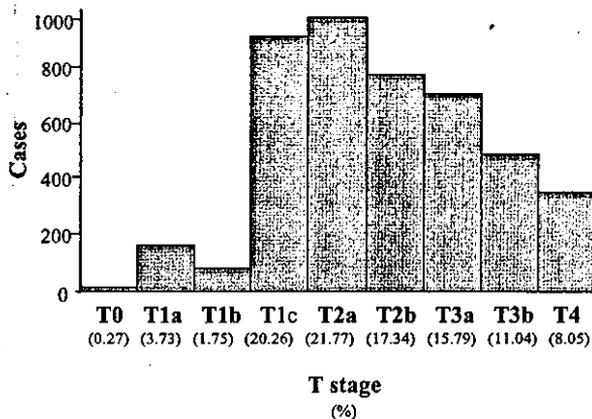


Fig. 4 Distribution of local staging (T staging). Registered cases were divided into groups by local staging as indicated according to the 1997 International Union Against Cancer (UICC) tumor, nodes, metastases (TNM) classification. Bars indicate the number of patients for each T stage. The numbers below each bar indicate the percentage of cases in each age group among all registered cases.

(78.80%) were diagnosed as negative lymph node metastasis.

Distant metastases are detailed in Table 6. More than 70% of patients were negative for distant metastasis.

Initial treatment strategies

Selected plans are summarized in Figure 5. Hormonal therapy alone was chosen for more than half of the cases. Prostatectomy with or without hormonal therapy was planned for 27.4% (1240 cases). Irradiation with or without hormonal therapy was not very common (8.1%). For cases of T1c to T3N0M0 (2671 cases total),

Table 6 M stage

M stage	<i>n</i>	(%)
M0	3243	71.61
M1a	40	0.88
M1b	861	19.01
M1c	63	1.39
MX	322	7.11
Total	4529	100

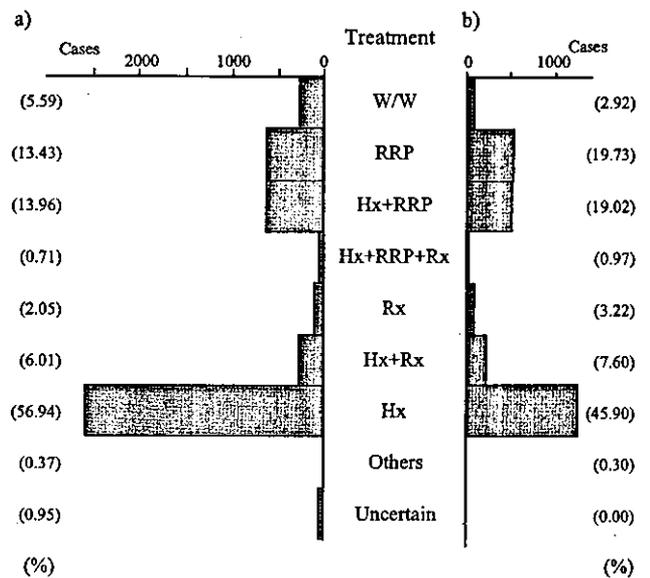


Fig. 5 Initial treatment plan for (a) all registered cases ($n = 4529$) and (b) cases of T1c to T3 without lymph node or distant metastases ($n = 2671$). Registered cases were divided into groups by initial treatment plan, which includes each treatment modality and appropriate combinations, as indicated. W/W, watchful waiting; RRP, retroperic radical prostatectomy; Hx, hormonal therapy; Rx, irradiation. Bars indicate the number of cases in each group. The numbers below each bar indicate the percentage of cases in each group among all registered cases or the subgroup of patient at stage T1c to T3 without lymph node or distant metastases.

45.90% (1226 cases) were scheduled to undergo hormonal therapy without any other additional treatment. Irradiation was not commonly advised for this group (10.8%).

Additional data are summarized in Appendix I-IV.

Acknowledgments

These clinicopathological statistics are the results from a number of institutions in Japan. We are also grateful to Dr E Okajima and Dr K Kawashima (Division of

Urology, National Cancer Center, Tokyo), and Ms M Nakamura, a secretary of cancer registration office, for special efforts to analyze and summarize the data.

This document was established by the Cancer Registration Committee of the Japanese Urological Association. Members of this task force include: Hiroyuki Fujimoto, MD, National Cancer Center Hospital, Tokyo; Tsuneharu Miki, MD, Chair, Cancer Registration Committee of the Japanese Urological Association, Kyoto University of Medicine, Kyoto; Masaru Murai, MD, Keio University School of Medicine, Tokyo; Tomoaki Fujioka, MD, Iwate Medical University School of Medicine, Iwate; Seiji Naitoh, MD, Graduate School of Medical Science, Kyushu University, Kyushu; Tadao Kakizoe, MD, National Cancer Center, Tokyo; Akihiko Okuyama, MD, Graduate School of Medical Science, Kyushu University, Kyushu; Hideyuki Akaza, MD, Institute of Clinical Medicine, University of Tsukuba, Tsukuba; Youichi Mizutani, MD, Kyoto University of Medicine, Kyoto; and Sadao Kamidono, MD, Kobe University School of Medicine, Kobe, Japan.

Member of the Cancer Registration Committee of Japanese Urological Association

This document was established by the Cancer Registration Committee of Japanese Urological Association. Members of this task force include: Hiroyuki Fujimoto, MD, National Cancer Center hospital, Tokyo; Tsuneharu Miki, MD, Chair, Cancer Registration Committee of Japanese Urological Association, Kyoto University of Medicine, Kyoto; Masaru Murai, MD, Keio University School of Medicine, Tokyo; Tomoaki Fujioka, MD, Iwate Medical University School of Medicine, Iwate; Seiji Naito, MD, Graduate School of Medical Science, Kyushu University, Kyushu; Tadao Kakizoe, MD, National Cancer Center, Tokyo; Akihiko Okuyama,

MD, Graduate School of Medicine, Osaka University, Osaka; Hideyuki Akaza, MD, Institute of Clinical Medicine University of Tsukuba, Tsukuba; Youichi Mizutani, MD, Kyoto University of Medicine, Kyoto; Sadao Kamidono, MD, Kobe University School of Medicine, Kobe.

References

- 1 Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. *Eur. J. Cancer* 2001; 37 (Suppl. 8): 4-66.
- 2 Breslow N, Chan CW, Dhom G *et al.* Latent carcinoma of prostate at autopsy in seven areas. *Int. J. Cancer* 1977; 20: 680-8.
- 3 Akazaki K, Stemmermann GN. Comparative study of latent carcinoma of the prostate among Japanese in Japan and Hawaii. *J. Natl Cancer Inst.* 1973; 50: 1137-44.
- 4 Nakata S, Takahashi H, Ohtake N, Takei T, Yamanaka H. Trends and characteristics in prostate cancer mortality in Japan. *Int. J. Urol.* 2000; 7: 254-7.
- 5 Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I. International comparisons. *BJU Int.* 2002; 90: 162-73.
- 6 Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int. J. Cancer* 1999; 80: 827-41.
- 7 Coleman MP, Esteve J, Damieki P *et al.* *Trends in Cancer Incidence and Mortality*. IARC. Scientific Publications no. 121. International Agency for Research on Cancer, Lyons, 1993.
- 8 Whittlemore AS. *Trends in Cancer Incidence and Mortality*. *Cancer Surveys, Vol. 19, 20*. Imperial Cancer Research Fund/Cold Spring Harbor Laboratory Press, New York, 1994.
- 9 The Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1997: estimates based on data from 12 population-based cancer registries. *Jpn J. Clin. Oncol.* 2002; 32: 318-22.
- 10 Japanese Urological Association and The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Prostate Cancer*. Kanehara, Tokyo, 2001.

Appendix

I. General statistics

I.1. Background

I.1.1. Races

Race	Number	%
Japanese	4509	99.56
Mongolian (without Japanese)	13	0.29
White	6	0.13
Uncertain	1	0.02
Total	4529	100

I.1.3. Occupation

Occupation	Number	%
Service workers	101	2.23
Transportal and postal related workers	63	1.39
Corporate and general managers	314	6.93
Craft, related trades workers and elementary occupations	165	3.64
Mining labourers	8	0.18
Office clerks and associate professionals	365	8.06
Professionals and technicians	300	6.62
Agricultural, forestry and fishery workers	304	6.71
Sales workers	119	2.63
Protective services workers	14	0.31
Others or retired	1002	22.12
Uncertain	1774	39.17
Total	4529	100

I.2. Symptoms

I.2.1. Urological

Symptoms	Number	%
+	3219	71.08
-	1273	28.11
Uncertain	37	0.82
Total	4529	100

I.3. Staging method and findings

I.3.1. Modality of image study

Number	% in all cases	
CT	3023	66.75
MRI	1937	42.77
Bone scan	3330	73.53
TRUS	3547	78.32

I.1.2. Family history of prostate cancer

	Number	%
Father	30	0.66
Brother	37	0.82
Uncle	4	0.09
Total	71	1.57

I.1.4. Distribution of organs of concomitant malignancy

Organ	Number
Kidney	33
Urothelial	111
Testis	2
Penile	3
Head and neck	34
Lung	50
Esophageal	10
Stomach	107
Colon	120
Liver and gall bladder	19
Pancreas	9
Skin	6
Hematological	8
Sarcoma	3
Breast	1
Uncertain and other	4
Total	520
Negative	4022

I.2.2. Metastatic

Symptoms	Number	%
+	339	7.49
-	4137	91.34
Uncertain	53	1.17
Total	4529	100

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.4.2. 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.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

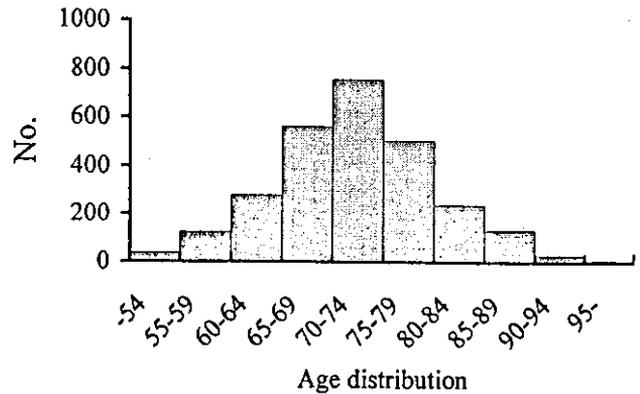
I.5.3. M stage distribution

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

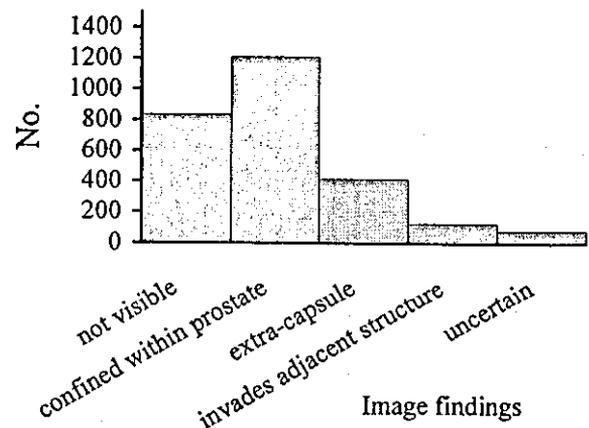
Age range	Number	%
<54	38	1.42
55-59	123	4.61
60-64	279	10.45
65-69	562	21.04
70-74	756	28.30
75-79	506	18.94
80-84	240	8.99
85-89	132	4.94
90-94	27	1.01
95>	8	0.15
Total	2671	100



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.

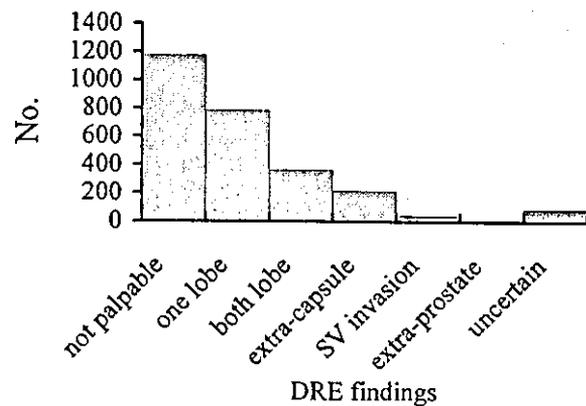
II.2. Findings of image study

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

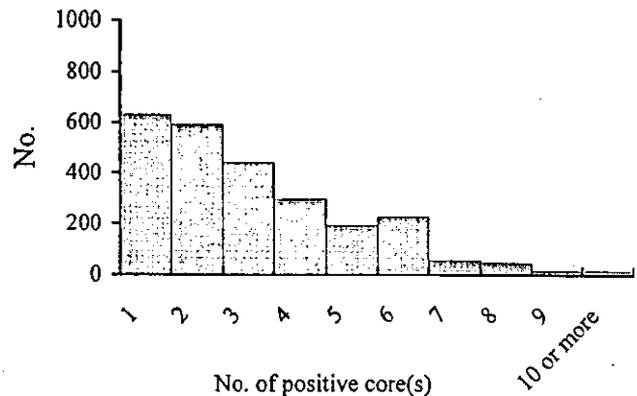
Number	%	
Not palpable	1174	43.95
One lobe	786	29.43
Both lobe	362	13.55
Extra-capsule	215	8.05
SV invasion	40	1.50
Extra-prostate	5	0.19
Uncertain	89	3.33
Total	2671	100



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

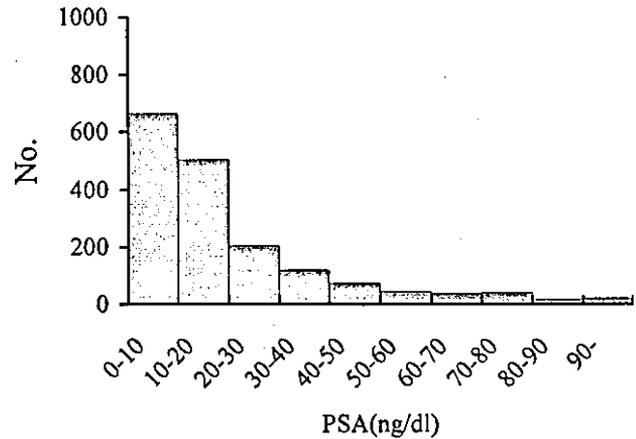
Gleason's score	T stage (1997 UICC)					Total
	T1c	T2a	T2b	T3a	T3b	
2	37	28	16	2	1	84
3	48	50	19	13	3	133
4	51	65	31	16	4	167
5	73	109	70	51	22	325
6	91	109	61	39	22	322
7	93	101	98	88	49	429
8	17	26	25	35	15	118
9	18	24	28	44	18	132
10	5	4	5	4	0	18
Total	433	516	353	292	134	1728

†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†

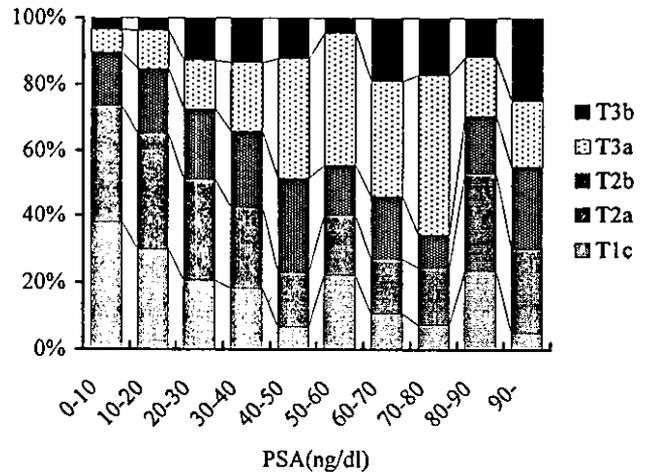
PSA(ng/dl)	Total	%
0-10	663	36.131
10-20	504	27.466
20-30	204	11.117
30-40	120	6.54
40-50	74	4.033
50-60	45	2.452
60-70	37	2.016
70-80	41	2.234
80-90	17	0.926
90>	20	1.09
1725	100	



†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

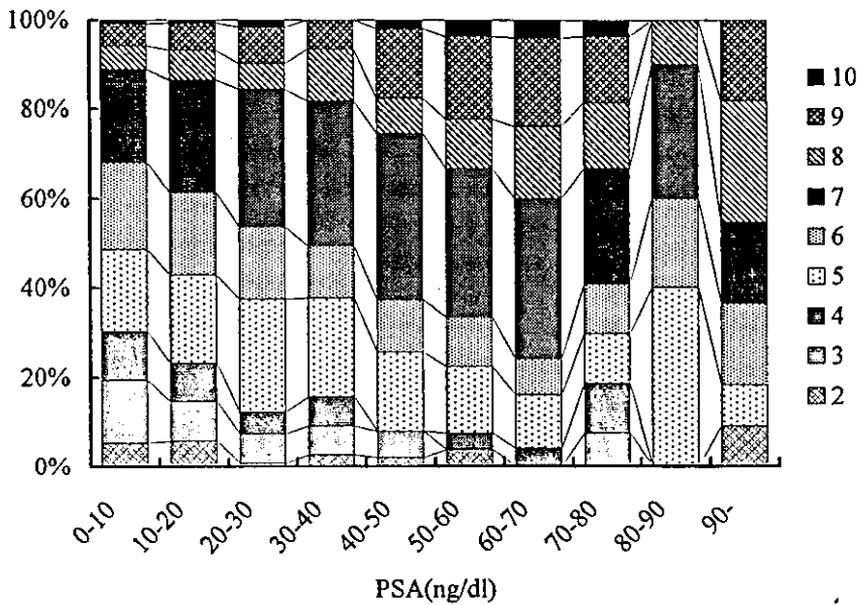


Cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of each T stage among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.

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.

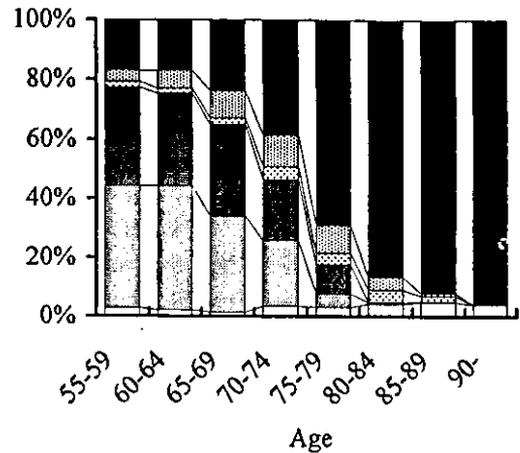


IV. Main initially planned treatment for fresh cases without concomitant malignancy patients in clinical T1c-T3N0M0 prostate cancer

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

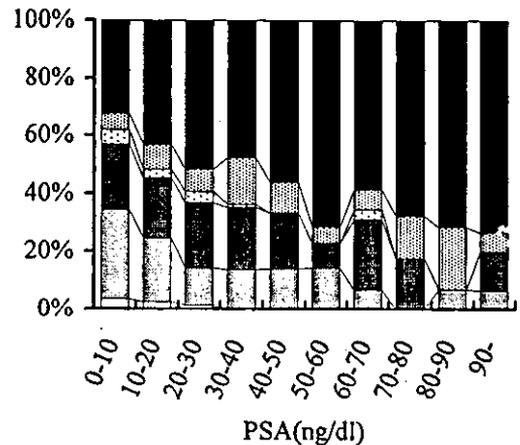
Clinical T1c-T3 cases were divided by age. Bars demonstrate the percentage of adpoted treatment among each age group.



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

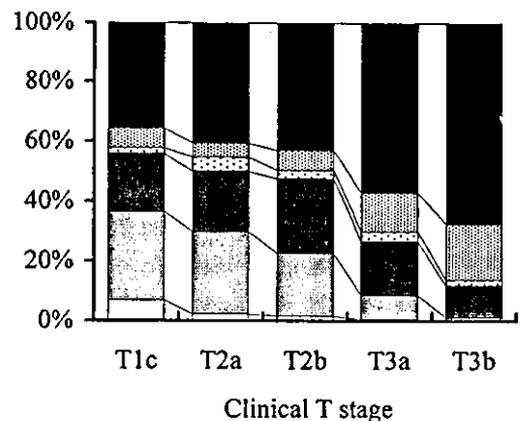
Clinical T1c-T3 cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of adpoted treatment among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.



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 adpoted treatment and each stage.

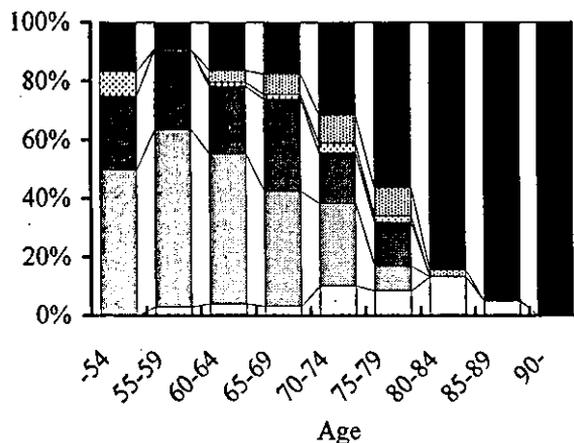


□ W/W □ RPP ■ RPP+Hx
 ▨ Rx ▨ Rx+Hx ■ Hx

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

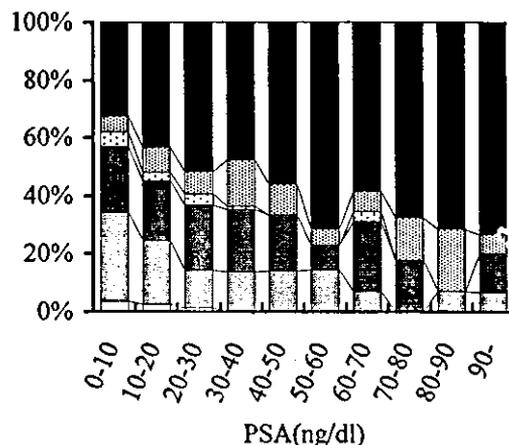
T1c

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



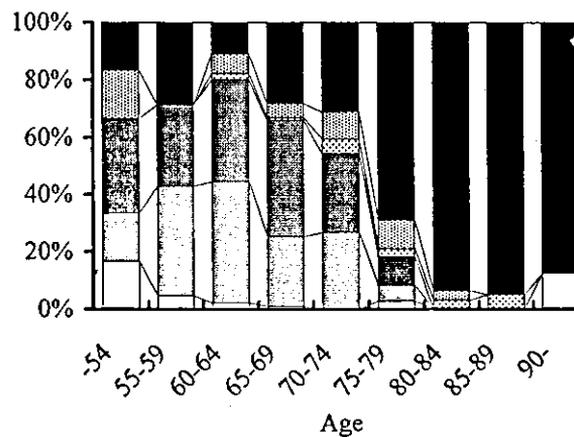
T2a

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



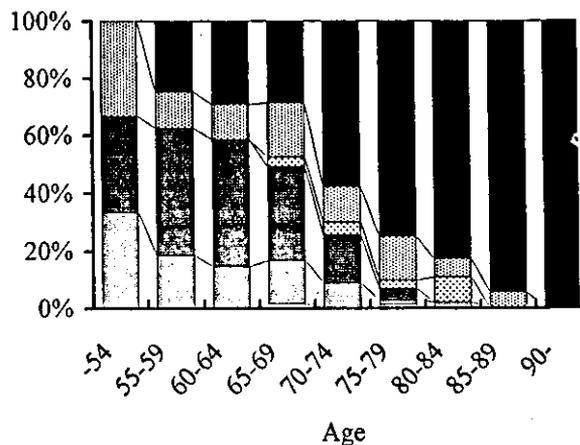
T2b

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



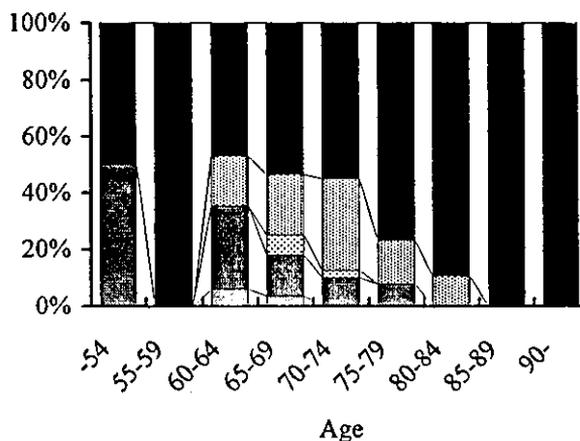
T3a

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 Tsukuba	31	TOYOTA Memorial Hospital	15
Kitaibaraki Municipal General Hospital	8	Josai Municipal Hospital, City of Nagoya	16
Hakujuji General Hospital	6	Meijo Hospital	13
Tochigi Prefecture		National Chubu Hospital	22
Rosai Hospital for Silicosis	12	Koyo Hospital	7
Gunma Prefecture		Tottori Prefecture	
Gunma University Hospital	52	Nozima Hospital	11
Gunma Cancer Center	21	Shimane Prefecture	
Tatebayashi Kousei Hospital	41	Masuda Red Cross Hospital	18
Motojima General Hospital	8	Okayama Prefecture	
Saitama Prefecture		Okayama University Graduate School of Medicine and Dentistry	39
National Defense Medical College	35	Kawasaki Medical School	71
Koshigaya Municipal Hospital	22	Okayama Central Hospital	40
Saiseikai Kanagawaken Hospital	36	Kurashiki Medical Center	49
Yokoham Rosai Hospital	55	Kawasaki Hospital	27
The International Goodwill Hospital	27	Kurashiki Central Hospital	68
Niigata Prefecture		Konko Hospital	11
Niigata Cancer Center Hospital	64	Hiroshima Prefecture	
Niigata City General Hospital	37	Kohsei General Hospital	5
Itoigawa General Hospital	5	Yamaguchi Prefecture	
Toyama Prefecture		Yamaguchi University School of Medicine	17
Toyama Medical and Pharmaceutical University	26	Tokushima Prefecture	
Toyama Prefectural Central Hospital	16	Tokushima Municipal Hospital	21
Toyama Red Cross Hospital	16	Tokushima Red Cross Hospital	30
Asahi General Hospital	3	Oe Kyodo Hospital	17
Kamiichi Welfare Hospital	8	Kagawa Prefecture	
Saiseikai Toyama Hospital	5	Kagawa Medical University	31
Ishikawa Prefecture		Kagawa Prefectural Central Hospital	51
Kaga Chuoh Hospital	9	Sanuki Municipal Hospital	12
Fukui Prefecture		Ehime Prefecture	
Fukui Prefectural Hospital	8	National Shikoku Cancer Center	57
		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	Bellland 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

日本臨牀 第63巻・第2号(平成17年2月号)別刷

特集：前立腺癌

局所進行前立腺癌に対するホルモン療法と
手術療法の併用療法

藤元博行