Chronological urodynamic evaluation of changing bladder and urethral functions after robot-assisted radical prostatectomy

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Validation of TNM classification for metastatic prostatic cancer treated using primary androgen deprivation therapy

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Keywords: Prostate cancer; Primary androgen deprivation therapy; metastasis; TNM classification.

Abstract

Purpose: The current tumor–node–metastasis (TNM) classification system has been used for many years. The prognosis of patients with metastatic prostate cancer (mPC) treated using primary androgen deprivation therapy (PADT) was analyzed according to the TNM classification.

Methods: A total of 5,618 cases with lymph node metastases only (N1M0), non-regional lymph node metastasis (M1a), bone metastasis (M1b), and distant metastasis (M1c) were selected from the Japanese Study Group of Prostate Cancer database. Overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS) rates were calculated using Kaplan–Meier analysis. The influence of clinical variables on patient prognosis was evaluated using the Cox's proportional hazard regression model.

Results: The 5-year OS, CSS, and PFS were 76.0, 83.2, and 38.8 % in N1M0, 57.5, 69.0, and 23.0 % in M1a, 54.0, 63.1, and 23.0% in M1b, and 40.0, 51.5, and 16.6% in M1c, respectively. OS, CSS, and PFS worsened as the stages progressed. OS, CSS and PFS were all significantly worse in N1M1b compared with N0M1b. Multivariate analysis revealed that OS and CSS were worse in patients with a Gleason score ≥ 8, and that combined androgen blockade (CAB) treatment provided better OS than non-CAB treatments at any tumor stage. However, OS and CSS were worse in individuals with a prostate-specific antigen > 100 ng/ml only in M1b.

Conclusions: Patient prognosis worsened with stage progression, therefore, current TNM classification

system of mPC for PADT was shown to be trustworthy. Each PC cell that develops bone or lymphoid metastasis may exhibit different characteristics.

Introduction

Prostate cancer is one of the most common cancers in males worldwide [1]. Some reports have suggested that prostate-specific antigen (PSA) screening contributes to the detection of early stage prostate cancer, and hence, the mortality rate from prostate cancer has been decreasing [2]. However, 10-20% of prostate cancer patients are diagnosed with metastatic disease, even today [3]. Androgen deprivation therapy (ADT) is usually selected as the first line therapy for metastatic prostate cancer (mPC). Nevertheless, the effectiveness of ADT is generally not permanent, and treatment selection for castration-resistant prostate cancer (CRPC) can be challenging [4]. The effectiveness of docetaxel [5] and other new drugs [6-8] for CRPC has been reported; however, the improvement in the prognosis of those patients is still not sufficient. The effectivenesses of primary ADT (PADT) are thought to have huge impacts on the prognosis of patients with mPC.

The tumor–node–metastasis (TNM) classification system was published by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), and is used for the staging of malignant tumors, including prostate cancer. The staging determined by the TNM classification system is thought to correlate closely with cancer prognosis; therefore, the staging affects the treatment plan. The

TNM classification system has been revised several times, and the current edition was the seventh. The TNM classification of mPC has not changed since the fourth edition published in 1992. Regional lymph node metastasis is classified to N1, distant lymph node metastasis is classified as M1a, bone metastasis is classified as M1b, and other sites of distant metastasis are classified as M1c [9]. The most common metastatic sites of PC are the bones, and the frequency of metastases to other sites, including the lymph nodes or viscera, is lower [10, 11]. A recent report showed that the prognosis of metastatic CRPC with visceral metastasis was unfavorable [12]. Although the current TNM classification system has been used for many years, no sufficient evaluation of patient prognosis according to the mPC subcategory classified by the TNM system has been performed to date. In Japan, the Japanese Study Group of Prostate Cancer (J-CaP) study, which was performed to evaluate the therapeutic value of PADT for PC, registered 26,000 cases from 2001 to 2003, and the cases were followed up to the present day. In the current study, mPC cases that had been followed up prospectively for over 10 years were extracted from this cohort and analyzed to evaluate the therapeutic value of PADT according to tumor stage determined using the TMN classification system.

Materials and methods

Patients and background

A total of 26,272 patients who started ADT between 2001 and 2003 were registered at 385 institutions

throughout Japan in the J-CaP study [13]. The data collection procedures were approved by the local and central institutional review boards. Of these cases, 5,618 N1M0, M1a, M1b, and M1c cases were included in the current study; however, 359 cases of M1x (an unclear M1 subcategory) were excluded. Generally, the registered cases were updated every 3 months with progression data including survival and disease progression. The patients were followed until September 30, 2014. The patients were diagnosed by prostate biopsy at each institution, and the N and M staging was determined by the results of imaging findings such as bone scintigraphy, magnetic resonance imaging, and computed tomography. The clinical stage was determined based on the fifth edition of the TNM classification published in 1997 [14].

PADT was performed using flutamide, chrolmadinone acetate (CMA), or diethyl stilbestrol (DES) as anti-androgens (AAs), and 1-month or 3-month preparations of goserelin or lauprolide as luteinizing hormone-releasing hormone (LHRH) agonists. LHRH or castration + AA was performed in 3,864 patients (69%), compared with LHRH monotherapy in 519 patients (9%), castration monotherapy in 288 patients (5%), LHRH or castration + short AA in 338 patients (6%), and other treatments in 609 patients (11%). Short AA was defined as AA therapy given between 30 days before and 60 days after the start of LHRH for flare prevention [15]. LHRH analog or castration + AA were classified as CAB, whereas LHRH or castration monotherapy, LHRH or castration monotherapy + short AA and other treatments were classified as non-CAB.

Statistical analysis

Patients were followed until death or until they withdrew from the study. Events for PFS were determined by clinicians according to rising PSA levels. PSA failure was determined as a PSA level at least 2.0 ng/ml higher and a 25% rise from the nadir level, which was confirmed by a second PSA test at least 4 weeks later. The relationships among demographic data were assessed using chi-squared tests. One-way analysis of variance was performed for comparisons of three or more groups with Tukey's HSD post-hoc test. Pearson's correlation coefficient was used to determine the relationships among age, PSA, and GS. OS, CSS, and PFS were calculated using the Kaplan–Meier method. Events taken into account to calculate OS and CSS were death for any reason and cancer-related deaths, respectively. The events taken into account for the calculation of PFS were PSA failure, clinical failure, and death. Differences among groups were assessed using log-rank tests. The influences of the clinical variables that affected prognosis were evaluated using Cox's proportional hazard regression model. All data analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be statistically significant.

Results

The demographic data available from the database are shown in Table 1. Regarding age, patients with M1b tumors were significantly older than were those in the other groups. PSA levels tended to increase as

the stage progressed. The GS was significantly higher in the M1a group compared with the other groups. There was no significant difference in the proportion of patients that received CAB among groups. After a mean follow-up of 3.3 years 1,923 patients (34.2%) died, of which 1,364 (24.3%) were PC-specific deaths. Figure 1 shows the OS, CSS, and PFS in all groups, as well as the hazard ratios (HRs) analyzed using the Cox hazard model. OS, CSS, and PFS declined as the stage progressed; however, there were no statistically significant differences between M1a and M1b cases. The 5-year OS was 76.0 % in the N1M0, 57.5 % in M1a, 54.0 % in M1b, and 40.0 % in M1c cases (Figure 1A). There was no significant difference in CSS between the M1a and M1b groups. The 5-year CSS was 83.2 % in the N1M0, 69.0 % in M1a, 63.1 % in M1b, and 51.5 % in M1c cases (Figure1 B). There was no significant different in the PFS of patients that received PADT between the M1a and M1b groups. The 5-year PFS was 38.8 % in the N1M0, 23.0 % in M1a, 23.0 % in M1b, and 16.6 % in M1c cases (Figure 1C).

Among the patients in the M1b group, the 2,445 cases of N0M1b and the 1,607 cases of N1M1b were compared. The mean age, PSA, and GS were 74.2 years, 651 ng/ml, and 7.6 in the N0M1b group, compared with 72.5 years old, 1,325 ng/ml, and 8.0 in N0M1b, respectively; the differences between any of these were considered significantl at $p < 0.001$. The 5-year OS was 58.9% [95% confidence interval (CI) 56.3-61.5] in the N0M1b, compared with 46.2 % (95%CI 43.0-49.4) in N1M1b. The 5-year CSS was 69.4 % (95%CI 66.8-72.0) in the N0M1b, compared with 54.8 % (95%CI 51.5-58.1) in the N1M1b. Finally, the 5-year PFS was 28.3 % (95%CI 26.1-30.5) in the N0M1b, and 15.5 % (95%CI 13.3-17.7) in

the N1M1b; the differences between any of these were considered significant at $p < 0.001$.

The effects of age, GS, PSA, and the type of ADT on OS and CSS were analyzed using multivariate analysis. The OS of patients aged > 75 years was shorter than was that of patients aged ≤ 75; however, there was no such differences were observed in M1a cases. The OS of patients with a GS ≥ 8 was worse than was that of individuals with a GS of ≤ 7. The OS of patients with a PSA > 100 ng/ml was significantly worse in only patients with M1b disease; however, the OS of patients with a PSA of ≤ 100 ng/ml was significantly worse in individuals with M1a disease. Conversely, PSA had no effect on the prognosis of patients with N1M0 and M1c disease. The OS of patients treated using CAB was higher than was that of those treated using non-CAB at all stages (Table 2). The CSS of all groups with a GS ≥ 8 was significantly shorter compared with a GS ≤ 7, and CSS were not affected by age in any groups. The CSS of after CAB treatment was significantly higher than that after non-CAB treatments in all groups except M1a. The CSS of patients with M1b disease and a PSA ≥ 100 ng/ml was significantly shorter than those with a PSA < 100 ng/ml; however, there was no significant difference in CSS among the N1M0 and M1c groups. In contrast, CSS in patients with M1a disease was worse in those with a PSA ≥ 100 ng/ml than in those with a PSA < 100 ng/ml (Table 3). There were no significant correlations among age, PSA, and GS in the N1M0, M1a, and M1c groups. However, there were significant correlations between age and GS ($R = -0.58$, $p < 0.001$) and PSA and GS ($R = 0.55$, $p = 0.001$) in the M1b group.

Discussion

The current M stage of PC has been determined using the fourth edition of the TNM classification system since 1992 [9]. The effects of treating mPC using PADT, according to subgroups separated by M stage, have not been evaluated in detail. In the current study, the prognosis and factors that influence PADT for mPC in subgroups defined by the current TNM classification were analyzed. The most common metastatic site of PC was the bone in 84 % of the aggregate results from 74,826 PC cases in the United States [10]. In the current study, M1b was the metastatic category of 78% of cases in the TNM classification, which was likely the result of a high frequency of bone metastasis, consistent with previous reports. The mean patient age was higher in the M1b group compared with the other subcategories, with the peak age of 70–74 years. The PSA level at diagnosis increased with stage progression. The mean GS was significantly higher in the M1a group than in other groups. OS and CSS deteriorated as the tumor stage progressed; however, there was no significant difference between M1a and M1b. The trends in PFS were the same as those in OS and CSS. As such, the efficacy of PADT was considered to affect the prognosis of the patients. Patients with M1c disease, including visceral metastasis, had the worst prognosis. Previous reports showed that PC patients with extensive metastasis had poor prognosis [16], and that the poor prognosis of CRPC was also reported to be highly affected by liver and lung metastasis, in that order of decreasing influence, regardless of other metastases including bone [12]. In the current study, multivariate analysis revealed that OS was significantly higher in patients treated using CAB

compared with than non-CAB, with HRs 0.63–0.75 in all subcategories except M1a.

Patients aged > 75 years had poor OS in all stages; however, there was no significant difference in CSS among any age groups. Patients with a GS ≥ 8 had significantly worse OS and CSS in all stages. OS and CSS were also significantly worse in patients with M1b disease and a PSA ≥ 100 ng/ml. CSS was also worse in M1a patients with a PSA < 100 ng/ml. However, PSA level had no significant effect on patients with other stage disease. A significant correlation between PSA level and the frequency of bone metastasis was reported previously [17, 18]. In addition, there was no significant correlation between PSA level and the metastatic pattern, except for bone metastasis, in a previous report [11]. Patients with M1a disease subtype and systemic lymph node metastasis had different characteristics from those with M1b disease and bone metastasis, such as higher GS, the absence of correlation between PSA and disease prognosis such as OS or CSS, and a low effect of CAB as the PADT. M1a is categorized as systemic lymph node metastasis, and we did not analyze how many cases with M1b disease had systemic lymph node metastasis in the current study. When patients with N0M1b and N1M1b disease were compared, OS, CSS, and PFS were significantly worse in the N1M1b group compared with N0M1b, regardless of the higher age in the N1M1b group.

PC is a complex multifaceted and biologically heterogeneous disease [19]; therefore, each PC cell may have different characteristics, react differently to treatment, and have favorable sites and patterns that support its metastatic proliferation, such as hematogenous or lymphogenous metastasis. The prognosis of

patients in the current study became poor as the tumor stage progressed from N1M0 to M1c; however, both the chronological extension and metastatic pattern should be considered to better understand the mPC status of individual patients. The current data did not contain detail regarding the metastatic site; therefore, we did not analyze the prognosis according to the detailed metastatic site. Different patient prognoses depending on the metastatic sites and extension have been reported [12, 16]. The detailed metastatic sites were reported as PUL (pulmonary), OSS (osseous), HEP (hepatic), BRA (brain), LYM (lymph nodes), MAR (bone marrow), PLE (pleura), PER (peritoneum), SKI (skin), and OTH (other) in TNM ver. 3 [20]. These evaluations were not adopted in the current version of the TNM classification. Nevertheless, these expressions may be convenient for evaluating detailed prognosis according to the metastatic site.

In the current study, the prognosis of in M1a-c mPC treated using PADT was a mean OS of 6.9 years, a mean CSS of 8.3 years, a mean PFS of 3.5 years; the 3-year, 5-year, and 10-year survival rates were 68 %, 53 %, and 34 %, respectively. Reports from western countries have reported that the 5-year and 10-year survival rates of patients with mPC were 23 % and 7 %, respectively (SWOG8894; mean age 70.2 years) [21], and that the mean OS of patients with mPC treated using CAB was 2.8–3.0 years [22]. The mean age of J-CaP patients with M1a-c disease was 73.4 years, which was higher than the age of comparable patients in previous reports from western countries. Therefore, Japanese patients with mPC treated using PADT had a better prognosis than did those from western countries. Ethnic differences regarding the

effects of ADT have been reported previously [23], and a large-scale study reported that CSS was higher in Japanese PC patients treated using PADT compared with those in the United Stated [24].

The present study has some limitations. Because of missing information of some unregistered subcategories such as 359 cases of M1x, and so not all patients with mPC in the cohort were enrolled. In addition, the treatment and follow-up plans were not unified because the treatment decision-making and follow-up schedules were at the discretion of each hospital and the detailed treatment regimens were not registered. The evaluations of NM classification were performed using imaging diagnoses; therefore, the staging results may be scattered because of differences in the imaging diagnostic capabilities of each hospital and no central review of the imaging. The GSs in the current study were not reviewed by central pathologist and not influenced by the current ISUP (the International Society of Urological Pathology) classification published in 2005 because the registration period was from 2001 to 2003 [25]. Scattering may also be possible because local pathologists diagnosed GS. During the follow-up period, novel drugs for PC became available, such as zoledronic acid in 2002 for the management of bone metastasis, which may have improved the prognosis of patients with mPC [26]. Docetaxel, which has improved the prognosis of CRPC, became available in Japan in 2008 [5]. The recently released new drugs for CRPC, such as abiraterone [6], enzalutamide [7] and cabazitaxel [8], were likely to have had little influence on the current study. Patient prognosis may improve as novel treatments are released. The J-CaP database includes a huge number of cases and long-term follow-up from patients that are registered at various

hospitals all over Japan. Therefore, the results of the current are considered to represent the true clinical prognosis of mPC treated using PADT in Japan, regardless of the limitations described above.

Conclusion

In the current study, the prognoses of patients with mPC was subcategorized according to the TNM classification system and treated using PADT in the J-CaP database were analyzed. The prognosis worsened as the stage progressed, therefore, current TNM classification system of mPC for PADT was shown to be trustworthy; however, there were no significant differences in OS, CSS, and PFS between M1a and M1b disease. Each PC cell that develops bone metastasis or lymphoid metastasis may have different characteristics. CAB was more effective for the treatment of mPC than was non-CAB in our database.

Conflict of interest We declare no conflicts of interest

References

1. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, Bray F (2012)

International variation in prostate cancer incidence and mortality rates. Eur Urol 61:1079-1092

2. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M et al (2012) Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 366:981-990

3. Fujimoto H, Nakanishi H, Miki T, Kubota Y, Takahashi S, Suzuki K, Kanayama HO, Mikami K, Homma Y (2011) Oncological outcomes of the prostate cancer patients registered in 2004: report from the Cancer Registration Committee of the JUA. Int J Urol 18:876-881

4. Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD (2004) Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. Endocr Relat Cancer 11:459-476

5. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I et al (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512

6. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Jr., Saad F et al (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005

7. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND et al (2012) Increased survival with enzalutamide in prostate cancer after

chemotherapy. N Engl J Med 367:1187-1197

8. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L et al (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147-1154

9. Beahrs OH, Henson DE, V.P.Henson R, B.J.Kennedy (eds.) (1992) Manual for staging of cancer fourth edition. Philadelphia: J.B.Lippincott Company: 181-186

10. Gandaglia G, Abdollah F, Schiffmann J, Trudeau V, Shariat SF, Kim SP, Perrotte P, Montorsi F, Briganti A, Trinh QD et al (2014) Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. Prostate 74:210-216

11. Vinjamoori AH, Jagannathan JP, Shinagare AB, Taplin ME, Oh WK, Van den Abbeele AD, Ramaiya NH (2012) Atypical metastases from prostate cancer: 10-year experience at a single institution. AJR Am J Roentgenol 199:367-372

12. Pond GR, Sonpavde G, de Wit R, Eisenberger MA, Tannock IF, Armstrong AJ (2014) The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol 65:3-6

13. Akaza H, Usami M, Hinotsu S, Ogawa O, Kagawa S, Kitamura T, Tsukamoto T, Naito S, Hirao Y, Murai M et al (2004) Characteristics of patients with prostate cancer who have initially been

treated by hormone therapy in Japan: J-CaP surveillance. Jpn J Clin Oncol 34:329-336

14. Fleming ID, Cooper JS, Henson DE (eds.) (1997) American Joint Committee on Cancer (AJCC). AJCC cancer staging manual. 5th edition. Philadelphia: J.B.Lippincott: 181-186

15. Hinotsu S, Akaza H, Usami M, Ogawa O, Kagawa S, Kitamura T, Tsukamoto T, Naito S, Namiki M, Hirao Y et al (2007) Current status of endocrine therapy for prostate cancer in Japan analysis of primary androgen deprivation therapy on the basis of data collected by J-CaP. Jpn J Clin Oncol 37:775-781

16. Eisenberger MA, Blumenstein BA, Crawford ED, Miller G, McLeod DG, Loehrer PJ, Wilding G, Sears K, Culkin DJ, Thompson IM, Jr. et al (1998) Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339:1036-1042

17. Pal RP, Thiruudaian T, Khan MA (2008) When is a bone scan study appropriate in asymptomatic men diagnosed with prostate cancer? Asian J Androl 10: 890-895

18. Lai MH, Luk WH, Chan JC (2011) Predicting bone scan findings using sPSA in patients newly diagnosed of prostate cancer: feasibility in Asian population. Urol Oncol 29: 275-279

19. Shtivelman E, Beer TM, Evans CP (2014) Molecular pathways and targets in prostate cancer. Oncotarget 5:7217-7259

20. Beahrs OH, Henson DE, V.P.Henson R, Myers MH (eds.) (1988) Manual for staging of cancer, third edition. Philadelphia: J.B.Lippincott: 177-182

21. Tangen CM, Faulkner JR, Crawford ED, Thompson IM, Hirano D, Eisenberger M, Hussain M (2003) Ten-year survival in patients with metastatic prostate cancer. Clin Prostate Cancer 2:41-45

22. Collette L, Studer UE, Schroder FH, Denis LJ, Sylvester RJ (2001) Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. Prostate 48:29-39

23. Fukagai T, Namiki TS, Carlile RG, Yoshida H, Namiki M (2006) Comparison of the clinical outcome after hormonal therapy for prostate cancer between Japanese and Caucasian men. BJU Int 97:1190-1193

24. Cooperberg MR, Hinotsu S, Namiki M, Carroll PR, Akaza H (2014) Trans-Pacific Variation in Outcomes for Men Treated With Primary Androgen Deprivation Therapy for Prostate Cancer. BJU Int doi: 10.1111/bju.12937

25. Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL (2005) The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 29:1228-1242

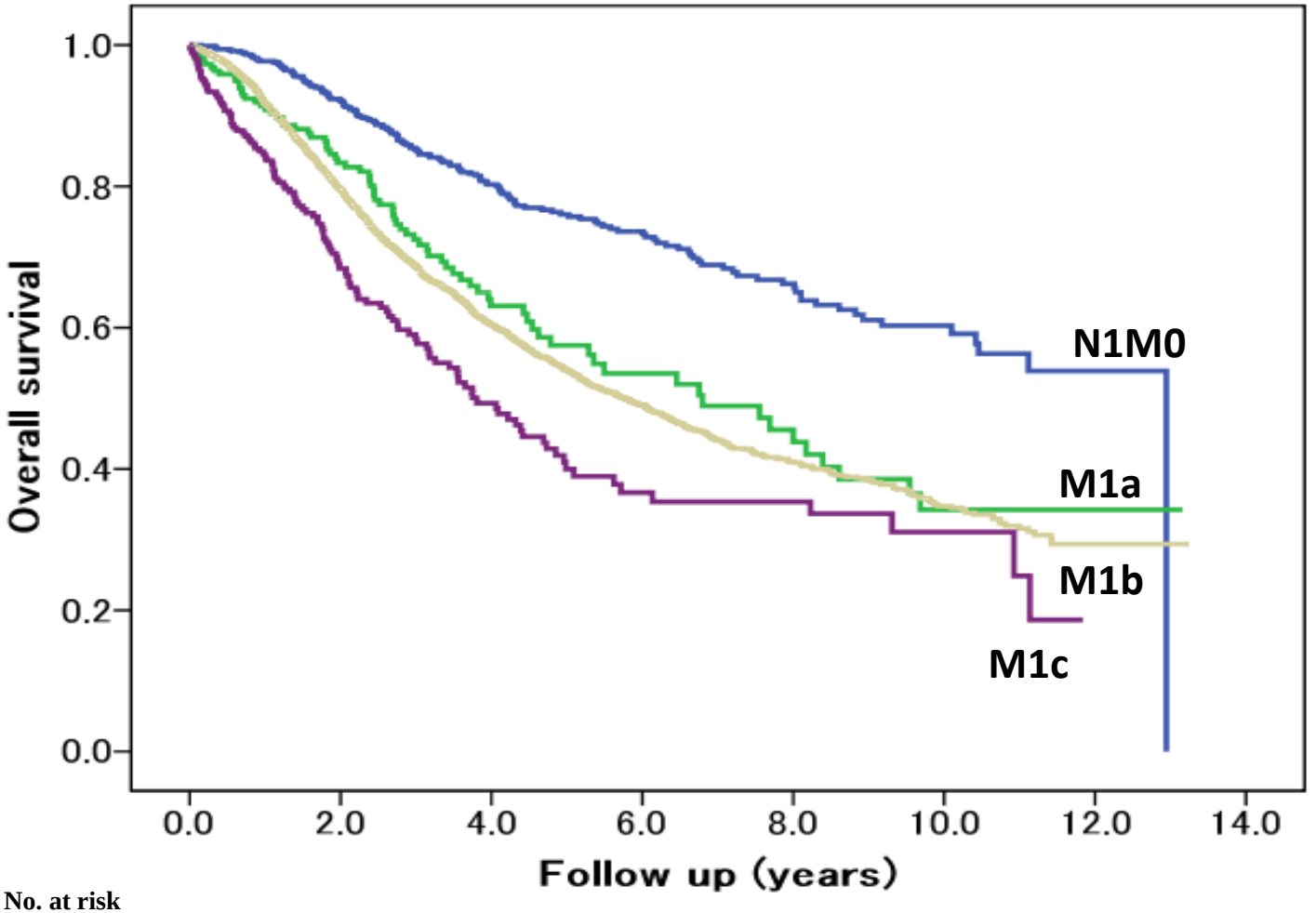
26. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Zheng M (2004) Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst

96:879-882

Figure Legends

Fig. 1.The prognosis of metastatic prostate cancer patients treated using primary androgen deprivation therapy. A, overall survival (OS); B, cancer-specific survival (CSS); C, progression-free survival (PFS). CI, confidence interval; HR, hazard ratio.

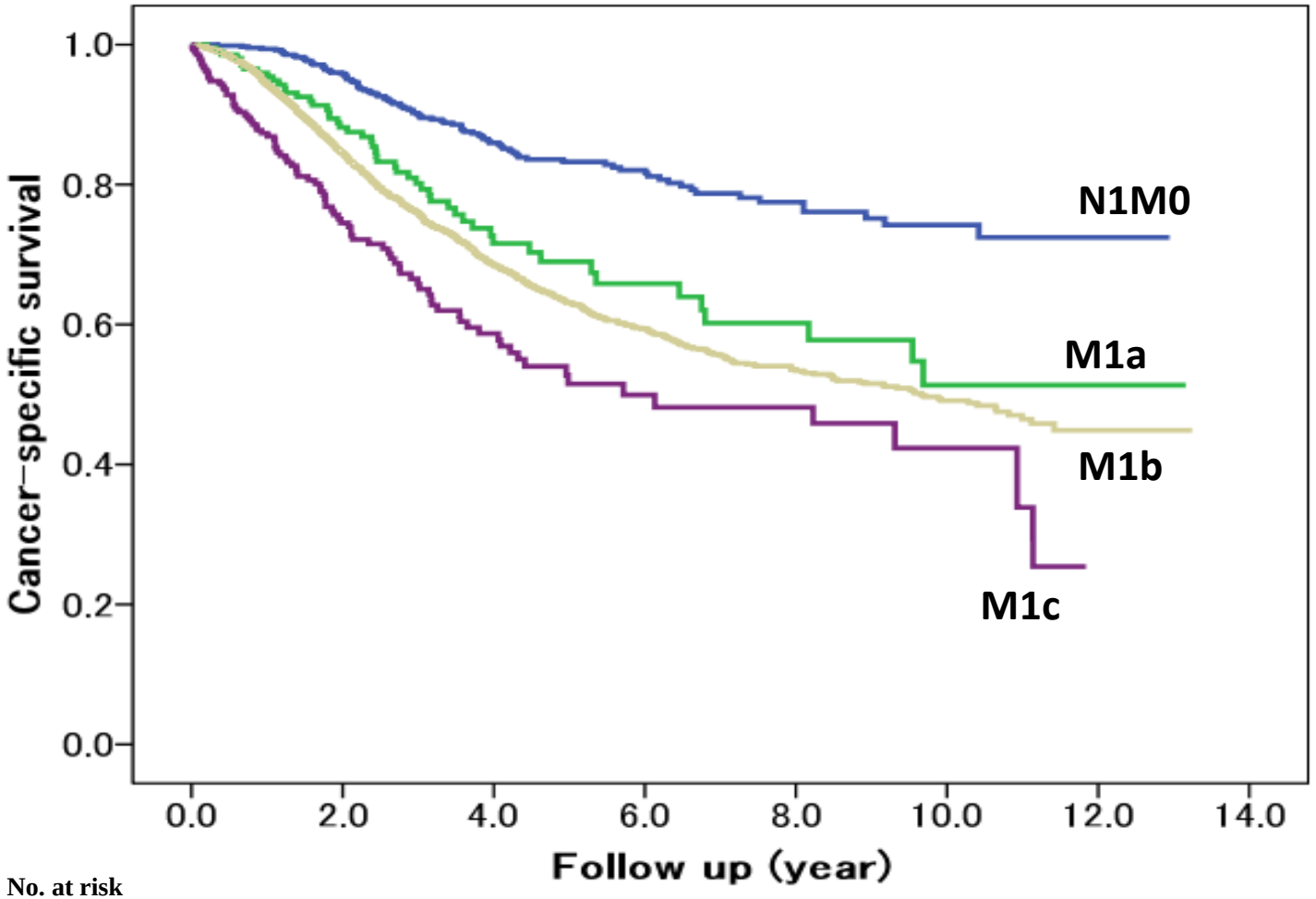
A



No. at risk							
N1M0	730	496	309	187	112	57	13
M1a	224	136	66	37	26	13	2
M1b	4386	2479	1246	632	326	169	25
M1c	278	127	66	29	22	8	

	N1M0	M1a	M1b	M1c
5 –year OS (95%CI)	76.0% (72.1-79.9)	57.5% (48.8-66.2)	54.0% (52.0-56.0)	40.0% (32.1-47.9)
OS, HR (95%CI)	Reference	1.966 (1.498-2.581)	2.200 (1.864-2.595)	3.181 (2.509-4.033)
	0.453 (0.384-0.535)	0.893 (0.711-1.121)	Reference	1.446 (1.203-1.739)

B



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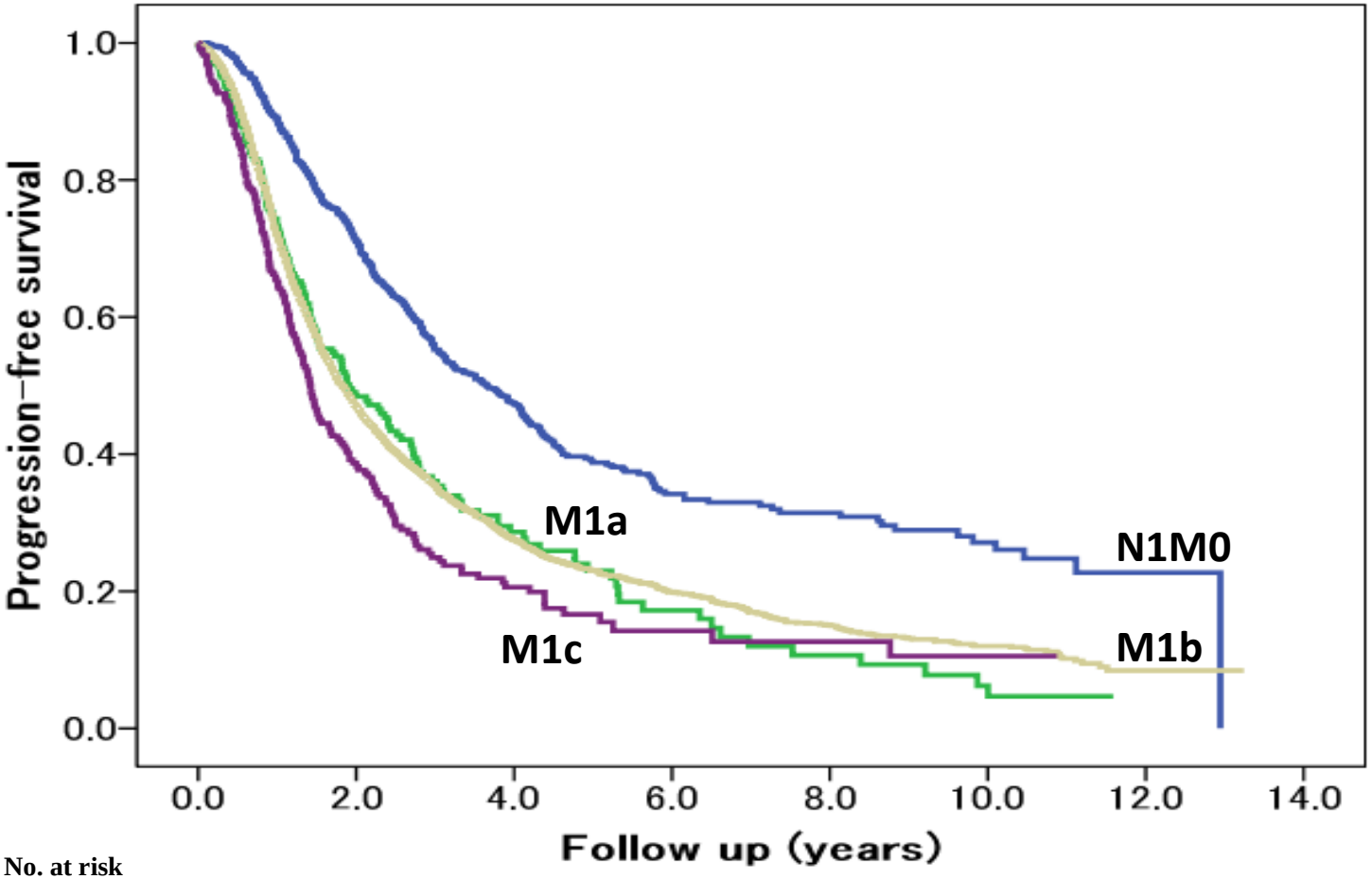
M1b	4386	2479	1246	632	326	169	25
M1c	278	127	66	29	22	8	

	N1M0	M1a	M1b	M1c
5 –year CSS (95%CI)	83.2% (79.7-86.7)	69.0% (60.7-77.3)	63.1% (61.1-65.1)	51.5% (43.2-59.8)
CSS, HR (95%CI)	Reference	2.120 (1.508-2.982)	2.582 (2.091-3.187)	3.930 (2.948-5.240)
	0.386 (0.313-0.477)	0.821 (0.62-1.087)	Reference	1.521 (1.229-1.881)

C



No. at risk							
N1M0	730	388	192	89	56	29	7
M1a	224	81	34	14	8	4	
M1b	4386	1539	627	285	139	76	9
M1c	278	77	31	9	7	1	

	N1M0	M1a	M1b	M1c
5 –year PFS (95%CI)	38.8% (34.3-43.3)	23.0% (15.9-30.1)	23.0% (21.4-24.6)	16.6% (11.1-22.1)
PFS, HR (95%CI)	Reference	1.838 (1.518-2.226)	1.796 (1.608-2.006)	2.308 (1.934-2.755)
	0.556 (0.498-0.621)	1.023 (0.868-1.207)	Reference	1.279 (1.104-1.482)

Table 1 Patient's background grouped by M stage

Characteristic	N1M0	M1a	M1b	M1c
Number	730	224	4386	278
Age, mean (±SD)*	72.6 (±8.2)	71.6 (±7.5)	73.6 (±8.2)	71.6 (±8.3)
<60, n (%)	43 (5.9%)	12 (5.4%)	223 (5.1%)	22 (7.9%)
60–64, n (%)	70 (9.6%)	26 (11.6%)	377 (8.6%)	26 (9.4%)
65–69, n (%)	121 (16.6%)	43 (19.2%)	673 (15.3%)	51 (18.3%)
70–74, n (%)	191 (26.2%)	64 (28.6%)	1064 (24.3%)	72 (25.9%)
75–80, n (%)	165 (22.6%)	47 (21.0%)	1009 (23.0%)	66 (23.7%)
80–85, n (%)	88 (11.5%)	21 (9.4%)	627 (14.3%)	27 (9.7%)
>85, n (%)	52 (7.1%)	11 (4.9%)	413 (9.4%)	14 (5.0%)
PSA, mean (±SD)**	278.5(±869.0)	607.9(±1402.9)	940.5(±2150.8)	1473.6(±2757.6)
<20, n (%)	140 (19.2%)	25 (11.2%)	583 (13.3%)	30 (10.8%)
20–100, n (%)	271 (37.1%)	56 (25.0%)	1028 (23.4%)	67 (24.1%)
100–500, n (%)	235 (32.2%)	91 (40.6%)	1309 (29.8%)	72 (25.9%)
>500, n (%)	84 (11.5%)	52 (23.2%)	1466 (33.4%)	109 (39.2%)
GS, mean(±SD)***	7.7 (±1.4)	8.2 (±1.4)	7.7 (±1.4)	7.8 (±1.3)
<6, n (%)	103 (16.2%)	21 (10.8%)	573 (15.4%)	31 (12.8%)
7, n (%)	184 (29.0%)	39 (20.0%)	1039 (27.9%)	69 (28.4%)
8, n (%)	116 (18.3%)	31 (15.9%)	761 (20.4%)	56 (23.0%)
9–10, n (%)	634 (13.2%)	104 (53.3%)	1355 (36.3%)	87 (35.8%)
Criteria of hormone therapy#				
CAB, n (%)	484 (66.3%)	155 (69.2%)	3045 (69.4%)	180 (64.7%)
Non CAB, n (%)	246 (33.7%)	69 (30.8%)	1341 (30.6%)	98 (35.3%)

SD: standard deviation, PSA: prostate specific antigen, GS: Gleason score, CAB: combined androgen brockade

* Age; N1M0 vs M1b, M1a vs M1b, M1b vs M1c; $p < 0.05$

**PSA; N1M0 vs M1b, N1M0 vs M1c, M1a vs M1c, M1b vs M1c; $p < 0.05$

***Gleason score; N1M0 vs M1a, M1a vs M1b, M1a vs M1c, $p < 0.05$

chi-square test; $p = 0.167$

Table 2. Multivariate analysis of factors that impact on overall survival in patients at different stages

Factor	N1M0				M1a				M1b				M1c			
	n (%)	HR	95% CI	*p* value	n (%)	HR	95% CI	*p* value	n (%)	HR	95% CI	*p* value	n (%)	HR	95% CI	*p* value
Age				0.046				0.524				<0.001				0.007
<75	364 (57.5)	Ref.			123 (63.0)	Ref.			1980 (53.1)	Ref.			146 (60.0)	Ref.		
≥75	269 (42.5)	1.41	1.007–1.981		72 (37.0)	1.17	0.718–1.919		1748 (46.9)	1.27	1.138–1.414		97 (40.0)	1.72	1.162–2.542	
GS				0.026				0.003				<0.001				0.003
≤7	287 (45.3)	Ref.			60 (30.8)	Ref.			1612 (43.2)	Ref.			100 (41.2)	Ref.		
≥8	346 (54.7)	1.5	1.050–2.132		135 (69.2)	2.5	1.361–4.586		2116 (56.8)	1.53	1.369–1.718		143 (58.8)	1.85	1.226–2.788	
PSA				0.782				0.03				<0.001				0.789
<100	356 (56.2)	Ref.			68 (34.9)	Ref.			1325 (35.5)	Ref.			80 (32.8)	Ref.		
≥100	277 (43.8)	1.05	0.747–1.472		127 (65.1)	0.57	0.348–0.947		2403 (64.5)	1.47	1.306–1.662		163 (67.1)	0.95	0.625–1.430	
Teatment				0.016				0.12				<0.001				0.023
Non-CAB	222 (35.1)	Ref.			131 (67.2)	Ref.			1124 (30.2)	Ref.			87 (35.8)	Ref.		
CAB	411 (64.9)	0.66	0.469–0.925		64 (32.8)	0.82	0.644–1.052		2604 (69.8)	0.75	0.666–0.837		156 (64.2)	0.63	0.423–0.937	

HR: hazard ratio, CI: confidence interval, GS: Gleason score, PSA: prostate specific antigen, CAB: combined androgen blockade

Table 3. Multivariate analysis of factors that impact on cancer specific survival in patients at different stages

Factor	N1M0			M1a			M1b			M1c		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age			0.784			0.584			0.742			0.097
<75	Ref.			Ref.			Ref.			Ref.		
≥75	0.94	0.605–1.460		0.837	0.443–1.582		0.98	0.858–1.115		1.479	0.931–2.348	
GS			0.003			0.001			<0.001			0.001
≤7	Ref.			Ref.			Ref.			Ref.		
≥8	2.06	1.283–3.308		4.582	1.899–11.053		1.67	1.455–1.913		2.331	1.409–3.857	
PSA			0.616			0.020			<0.001			0.788
<100	Ref.			Ref.			Ref.			Ref.		
≥100	0.894	0.578–1.384		0.486	0.264–0.894		1.670	1.440–1.937		0.936	0.579–1.513	
Teatment			0.006			0.254			<0.001			0.009
Non-CAB	Ref.			Ref.			Ref.			Ref.		
CAB	0.548	0.355–0.845		0.702	0.383–1.289		0.76	0.661–0.868		0.544	0.344–0.861	

HR: hazard ratio, CI: confidence interval, GS: Gleason score, PSA: prostate specific antigen, CAB: combined androgen blockade