Outcomes and predictive factors of prostate cancer patients with extremely high prostate-specific antigen level

doi: 10.1007/s00432-014-1681-8

Outcomes and predictive factors of prostate cancer patients with extremely high prostate-specific antigen level

Kouji Izumi[a]*, Wen-Jye Lin[b], Hiroshi Miyamoto[c], Chiung-Kuei Huang[d], Aerken Maolake[a], Yasuhide Kitagawa[a], Yoshifumi Kadono[a], Hiroyuki Konaka[a], Atsushi Mizokami[a], Mikio Namiki[a]

[a]Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

[b]Immunology Research Center, National Health Research Institutes, Zhunan, Miaoli County, Taiwan

[c]Pathology and Urology, Johns Hopkins University School of Medicine, James Buchanan Brady Urological Institute, Baltimore, MD, USA

[d] Department of Medicine, The Warren Alpert Medical School of Brown University, Providence, RI, USA

***Corresponding author:** Address correspondence to Kouji Izumi, M.D. Ph.D.**,** Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan.

Telephone: +81-76-265-2393, Fax: +81-76-222-6726

E-mail: azuizu2003@yahoo.co.jp

The number of tables/figures: 2 tables and 6 figures

Supplementary data: none

Short title: PCa with PSA > 100 ng/mL

Word count: 2369

None of the contributing authors have any conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Summary

Purpose: Prostate-specific antigen (PSA) is a useful biomarker of prostate cancer (PCa). High-risk localized PCa is defined using T stage, Gleason score (GS), and PSA. However, PSA level defining high-risk PCa is at most 20 ng/mL. In PCa patients with high PSA, it is unclear whether PSA itself can be a prognostic factor. **Methods**: Of 642 patients who were diagnosed as PCa, 90 patients with PSA > 100 ng/mL were retrospectively analyzed. Patients were divided into three groups according to PSA level: very high (> 1000 ng/mL), moderately high (200 – 1000 ng/mL), and slightly high (100 – 200 ng/mL). **Results**: There were no significant differences in overall survival or PCa-specific survival (PCaSS) among the three groups. Regardless of PSA level, high M stage and GS significantly reduced PCaSS. When the risk classification was made using M stage and GS (high risk = M1 and GS ≥ 9, low risk = M0 and GS < 9, and intermediate risk = others), PCaSS was significantly different among high-, intermediate-, and low-risk groups with 5-year survival rates of 58.2%, 80.6%, and 100%, respectively. Although there were no differences in treatment performed during the castration-resistant stage,

patients undergoing alternative anti-androgen and zoledronic acid treatment had better PCaSS after being castration-resistant. **Conclusions**: As PSA could not be a prognostic factor in PCa patients with high PSA > 100 ng/mL, the novel risk classification using M stage and GS may help clinicians to predict PCaSS and to plan follow-up schedules after diagnosis.

Key words: Prostate-specific antigen, Prostate cancer, TNM classification, Gleason score, Castration-resistant prostate cancer

Introduction

Prostate-specific antigen (PSA) is useful as a biomarker of disease progression and prognosis in prostate cancer (PCa) patients in addition to TNM classification and Gleason score (GS). High-risk localized PCa is defined using T stage, Gleason score, and PSA; however, PSA level used to define high-risk PCa is at most 20 ng/mL (D'Amico et al. 1998). Nomograms such as the Partin table also focus on PSA < 10 ng/mL for localized PCa (Naito et al. 2005; Partin et al. 2001). Meanwhile, little attention has been paid to patients with high PSA > 100 ng/mL regardless of localized or metastatic disease. PSA screening systems in Western countries, such as the USA and European countries, are well established because of the high prevalence and high mortality rate of PCa (Siegel et al. 2013; Ferlay et al. 2010; Andriole et al. 2009; Schroder et al. 2009). Therefore, PCa patients with high PSA > 100 ng/mL may rarely be found. However, around 25% of PCa patients were found with PSA > 100 ng/mL in Japan (Cooperberg et al. 2009), and probably more PCa patients would be found with high PSA in other Asian and developed countries. For clinicians, PSA is often the earliest information of PCa patients among PCa risk factors because GS is found with PCa diagnosis on biopsy specimens and TNM

classification is determined with radiological examinations after diagnosis of PCa. In such PCa patients with high PSA, clinicians tend to predict poorer prognosis associated with higher PSA; however, it is still unclear whether PSA itself is actually a prognostic factor. As shown in **Fig. 1**, the PCa patient with a PSA level of 4182 ng/mL at diagnosis lived much longer than the patient with a PSA level of 108 ng/mL at diagnosis who died of PCa, in contrast to our initial expectations. In addition, it is unclear which types of treatment after being castration-resistant affect patient prognosis in men with PSA > 100 ng/mL at diagnosis. In this study, we examined whether PSA can predict patient prognosis in PCa patients with high PSA > 100 ng/mL and clarified factors and treatments that affect the survival of such PCa patients.

Materials and Methods

Of 642 patients who were diagnosed as having PCa at Kanazawa University Hospital between January 2000 and December 2010, 90 patients with PSA > 100 ng/mL were retrospectively analyzed with regard to their backgrounds, treatments, and survival. The patients were divided into three groups based on their PSA levels, i.e., very high (VH, > 1000 ng/mL), moderately high (MH, 200 – 1000 ng/mL), and slightly high (SH, 100 – 200 ng/mL).

Overall survival (OS), PCa-specific survival (PCaSS), and castration-resistant PCa (CRPC)-free survival (CFS) were compared among these groups. Three patients for whom the date of being CRPC was unclear were removed from the analysis of CFS. In addition, other risk factors were also examined to determine whether their prognostic significance. In addition, to clarify the better treatment strategy for patients with high PSA, PCaSS after being CRPC was analyzed according to the treatment strategy. CRPC was defined as the status after three continuous elevations of PSA during androgen-deprivation therapy (ADT), including medical or surgical castration with or

without anti-androgen treatment.

Statistical analyses were performed using the commercially available software Prism (GraphPad, San Diego, CA). Comparisons between three groups were performed by one-way ANOVA. Comparisons of tendencies among different groups were performed by chi-square test for trends. Comparisons of survival described as Kaplan–Meier curves were performed by Log-rank test or Log-rank test for trends. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

OS and PCaSS in overall patients

All patients underwent combined androgen blockade consisting of luteinizing hormone-releasing hormone analog and anti-androgen as primary treatment except one patient who was treated with surgical castration alone. OS and PCaSS in all patients are shown in **Fig. 2**, and relatively long survival was estimated; 5-year survival rates of OS and PCaSS were 72.2% and 79.1%, respectively, and 10-year survival rates were 51.5% and 67.7%, respectively.

Patient background, OS, PCaSS, and CFS in each group according to PSA value

Patient backgrounds are shown in **Table 1**. The highest PSA value at diagnosis was 16702 ng/mL. Although there were no differences in age or follow-up time among groups, T, N, and M stages and GS tended to be worse as PSA increased. However, there were no significant differences in OS, PCaSS, and CFS among VH, MH, and SH groups (**Fig. 3**).

OS and PCaSS according to T, N, and M stages and GS

As it was demonstrated that PSA could not be used to predict patient survival when PSA value was higher than 100 ng/mL, other factors were examined to determine whether they

could be used as prognostic factors in this patient cohort. As shown in **Fig. 4**, there were no differences in OS or PCaSS among each T stage or N stage. On the other hand, there were significant differences in both OS and PCaSS among M0, M1b, and M1c stages ($P = 0.0075$ and $P = 0.0048$, respectively). GS could not predict OS, but there were significant differences in PCaSS among each GS group (i.e., GS ≤ 7, GS = 8, and GS ≥ 9, $P = 0.0166$).

Novel risk classification of PCa with PSA > 100 ng/mL

Based on the observations that high M stage and GS worsened PCaSS, a novel risk classification combining M stage and GS was developed to better predict PCaSS. High risk was defined as M1 and GS ≥ 9, low risk was defined as M0 and GS < 9, and intermediate risk was defined as neither high nor low risk. With the exception of one patient for whom the GS was not available, 89 patients were divided into these risk groups; the numbers of patients in the high, intermediate, and low risk groups were 32, 36, and 21, respectively. As shown in **Fig. 5**, PCaSS was clearly distinguished according to risk, and this risk classification was a better predictor of PCaSS than using M stage or GS alone ($P = 0.0039$). Five-year survival rates in the high, intermediate, and low risk groups

were 58.2%, 80.6%, and 100%, respectively, and 10-year survival rates in these groups were 29.1%, 80.6%, and 92.3%, respectively.

Treatments performed and PCaSS after being CRPC

As there was no significant difference in CFS among VH, MH, and SH, treatments performed during CRPC stage were examined to determine whether they affect PCaSS after being CRPC. There were no significant differences in treatments performed among VH, MH, and SH groups (**Table 2**). As shown in **Fig. 6**, although docetaxel (DTX), estramustine phosphate (EMP), and ethinylestradiol (EE) did not improve PCaSS, patients who underwent alternative anti-androgen (AA) and zoledronic acid (ZOL) therapy had significantly better PCaSS after being CRPC than those who did not (P = 0.0088 and P = 0.0137). ZOL is usually administered not when PCa has become castration-resistant but when bone metastasis is found. Therefore, PCaSS from diagnosis was also analyzed; however, ZOL showed no improvement.

Discussion

As the number of PCa patient with PSA > 100 ng/mL at diagnosis may not be high in many Western countries (Cooperberg et al. 2009), there have been very few studies of the prognosis in patients with such high PSA. However, the number of patients with PSA > 100 mg/mL in other countries should not be neglected. In South Korea, PSA at diagnosis was more than 100 ng/mL in 18.3% of PCa patients, and this is similar to the rate of 25% for Japanese patients with primary ADT (Cooperberg et al. 2009; Jang et al. 2012). Many patients with PSA > 100 ng/mL were found clinically; however, there have been no assessments of the relation between PSA and prognosis in such cases. For example, as shown in **Fig. 1**, it is unclear whether there are any differences in background or prognosis between patients with PSA = 100 ng/mL and PSA = 4000 ng/mL. Compared to previous reports of progression-free survival in patients classified according to clinical stage, CFS in the overall patient cohort in this study was similar to stage III patients and much better than stage IV patients, and OS in the overall patient cohort was between stage III and stage IV patients (Hinotsu et al. 2007). These results indicate that even if PSA at diagnosis is higher than 100 ng/mL, patients still have better survival than stage IV

patients. Interestingly, when patients were divided into three groups according to PSA level, there were no differences in OS, PCaSS, or CFS among groups, indicating that PSA is no longer a prognostic factor at levels beyond 100 ng/mL. Although PSA level is important for prognosis in patients with PSA < 100 ng/mL, especially between 4 and 20 ng/mL, prognosis may reach a plateau in those with PSA >100 ng/mL. This result is consistent with those of a previous study that showed that the hazard ratio of progression in patients with 100 – 500 ng/mL and > 500 ng/mL was similar, compared to patients with PSA < 20 ng/mL as a reference (Kitagawa et al. 2013). In contrast, both M stage and GS were found to be prognostic factors in PCaSS in this study. In the VH group, each T, N, and M stage and GS were significantly higher than those in the SH group. However, prognosis was not significantly different among VH, MH, and SH. This discrepancy may have been due to the variance in patient background. That is, patients with high M stage did not necessarily have high GS in the VH group. The novel risk classification based on the data in this study for patients with PSA > 100 ng/mL clearly distinguished PCaSS among risk groups and solved the problem that PSA is not useful as a prognostic marker. This risk classification was superior to each T, N, and M stage as well as GS for

predicting PCaSS. Previously, the risk classification for patients undergoing primary ADT was developed as Japan Cancer of the Prostate Risk Assessment (J-CAPRA) by Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) and the Japan Study Group of Prostate Cancer (J-CaP) using TNM classification, GS, and PSA at diagnosis. Patients were scored from 0 to12 by J-CAPRA score and progression-free survival rates in each scored patient group were significantly different (Cooperberg et al. 2009). J-CAPRA score is very useful for predicting the outcome and is applicable to patients with both localized and advanced disease. However, scoring may be complicated, especially in T stage and GS. The risk classification in this study may be applicable as simplified for the specific PCa population with PSA > 100 ng/mL with a simple scoring system.

As the high PSA level may affect treatment outcome, the effects of treatment during CRPC on PCaSS were also investigated in this study. DTX was first shown to improve OS of CRPC patients with phase III study, and EMP, EE, AA, and ZOL were reported to contribute to better prognosis (Tannock et al. 2004; Petrylak et al. 2004: Kojima et al. 2004; Ueno et al. 2013; Matsumoto et al. 2013; Izumi et al. 2010). DTX, EMP, and EE did

not improve PCaSS after CRPC. In Japan, DTX was approved for PCa in 2008 and the patient number was relatively low, which may have influenced the outcome. Meanwhile, AA improved PCaSS after CRPC. PSA is downstream of androgen/AR signaling, and a high level of PSA may indicate highly activated androgen/AR signaling. AA using flutamide was reported to decrease the PSA level in 88% of CRPC patients *via* the reduction of adrenal androgens (Narimoto et al. 2010). It is possible that this mechanism functioned well in such high PSA patients. However, this may be biased because only seven patients did not undergo AA due possibly to their poor condition and were moved to DTX treatment immediately. ZOL is administered for patient with bone metastases (M1b) for the reduction of skeletal-related events (Saad et al. 2004). Therefore, the patients given ZOL may be regarded as having more advanced disease. Nevertheless, ZOL improved PCaSS after CRPC. A previous study showed that ZOL improved progression-free survival in patients with GS $\geq$ 8 and suggested that it may have an effect in some advanced patients (Ueno et al. 2013). However, ZOL did not improve PCaSS from the time of diagnosis, and the possibility of bias should also be taken into consideration.

This study had a number of limitations. The small sample size may have prevented determination of the precise statistical significance of differences between groups. Larger prospective studies with longer follow-up periods and data from other ethnic backgrounds are needed to confirm our findings. Moreover, as a variety of anti-neoplastic treatments, including DTX, AA, EMP, EE, and others not described here for CRPC, were performed, some outcomes may not have been impacted only by M stage and GS or by AA and ZOL.

This is the first report showing the reduced meaning of PSA at diagnosis when the value is more than 100 ng/mL and the concise and useful risk classification of patients with PSA > 100 ng/mL. In addition, AA and ZOL may bring about better outcomes in CRPC patients with PSA > 100 ng/mL. These findings may help clinicians to predict PCaSS and to plan appropriate follow-up schedules after diagnosis.

Conflict of interest

None declared.

Reference

Andriole GL, Crawford ED, Grubb RL, 3rd, et al. (2009) Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 360:1310-9.

Cooperberg MR, Hinotsu S, Namiki M, et al. (2009) Risk assessment among prostate cancer patients receiving primary androgen deprivation therapy. J Clin Oncol 27:4306-13.

D'Amico AV, Whittington R, Malkowicz SB, et al. (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280:969-74.

Ferlay J, Parkin DM, Steliarova-Foucher E. (2010) Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 46:765-81.

Hinotsu S, Akaza H, Usami M, 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 37:775-81.

Izumi K, Kadono Y, Shima T, et al. (2010) Ethinylestradiol improves prostate-specific antigen levels in pretreated castration-resistant prostate cancer patients. Anticancer Res 30:5201-5.

Jang JY, Kim YS. (2012) Is prostate biopsy essential to diagnose prostate cancer in the older patient with extremely high prostate-specific antigen? Korean J Urol 53:82-6.

Kitagawa Y, Hinotsu S, Shigehara K, et al. (2013) Japan Cancer of the Prostate Risk Assessment for combined androgen blockade including bicalutamide: clinical application and validation. Int J Urol 20:708-14.

Kojima S, Suzuki H, Akakura K, et al. (2004) Alternative antiandrogens to treat prostate cancer relapse after initial hormone therapy. J Urol 171:679-83.

Matsumoto K, Tanaka N, Hayakawa N, et al. (2013) Efficacy of estramustine phosphate sodium hydrate (EMP) monotherapy in castration-resistant prostate cancer patients: report of 102 cases and review of literature. Med Oncol 30:717.

Naito S, Kuroiwa K, Kinukawa N, et al. (2008) Validation of Partin tables and

development of a preoperative nomogram for Japanese patients with clinically localized prostate cancer using 2005 International Society of Urological Pathology consensus on Gleason grading: data from the Clinicopathological Research Group for Localized Prostate Cancer. J Urol 180:904-9; discussion 909-10.

Narimoto K, Mizokami A, Izumi K, et al. (2010) Adrenal androgen levels as predictors of outcome in castration-resistant prostate cancer patients treated with combined androgen blockade using flutamide as a second-line anti-androgen. Int J Urol 17:337-45.

Partin AW, Mangold LA, Lamm DM, et al. (2001) Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 58:843-8.

Petrylak DP, Tangen CM, Hussain MH, et al. (2004) Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-20.

Saad F, Gleason DM, Murray R, et al. (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 96:879-82.

Schroder FH, Hugosson J, Roobol MJ, et al. (2009) Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 360:1320-8.

Siegel R, Naishadham D, Jemal A. (2013) Cancer statistics, 2013. CA Cancer J Clin 63:11-30.

Tannock IF, de Wit R, Berry WR, et al. (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-12.

Ueno S, Mizokami A, Fukagai T, et al. (2013) Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study. Anticancer Res 33:3837-44.

Figure legends

Fig 1. Cases with PSA > 100 ng/mL

PSA at diagnosis in Case 1 and Case 2 was more than 4000 and around 100 ng/mL, respectively. Generally, prognosis of Case 1 with higher T and N stage than Case 2 seemed to be worse than that of Case 2. However, survival time of Case 1 was much longer than that of Case 2. CAB = combined androgen blockade, ZOL = zoledronic acid, AA = anti-androgen, EMP = estramustine phosphate.

Fig 2. OS and PCaSS in overall patients

Five-year survival rates of OS and PCaSS were 72.2% and 79.1%, respectively, and 10-year survival rates were 51.5% and 67.7%, respectively.

Fig 3. OS, PCaSS, and CFS in VH, MH, and SH

Based on PSA at diagnosis, patients were divided into very high (VH, > 1000 ng/mL, n = 21), moderately high (MH, 200 – 1000 ng/mL, n = 37), and slightly high (SH, 100 – 200 ng/mL, n = 32) groups. However, there were no significant differences in OS, PCaSS, or CFS among VH, MH, and SH groups (P = 0.2381, P = 0.7742, and P = 0.1909, respectively).

Fig 4. OS and PCaSS according to T, N, and M stage and GS

T, N, and M stage and GS were examined to determine whether they can be used as prognostic factors in patients with PSA > 100 ng/mL. There were no differences in OS or PCaSS among each T and N stage ($P = 0.0535$ and $P = 0.2884$ with T stage, respectively, and $P = 0.2381$ and $P = 0.1530$ with N stage, respectively). On the other hand, there were significant differences in both OS and PCaSS among each M stage ($P = 0.0075$ and $P = 0.0048$, respectively). GS could not predict OS ($P = 0.1273$). However, there were significant differences in PCaSS among each GS group ($P = 0.0166$).

Fig 5. Novel risk classification of PCa with PSA > 100 ng/mL

High risk was defined as M1 and GS ≥ 9, low risk was defined as M0 and GS < 9, and intermediate risk was defined as neither high nor low risk. The numbers of patients in the high, intermediate, and low risk groups were 32, 36, and 21, respectively. PCaSS was clearly distinguished according to risk, and this risk classification showed better prediction of PCaSS than using M stage or GS alone ($P = 0.0039$). Five-year survival rates in high, intermediate, and low risk groups were 58.2%, 80.6%, and 100%, respectively, and 10-year survival rates were 29.1%, 80.6%, and 92.3%, respectively.

Fig 6. Treatments performed and PCaSS after being CRPC

Although docetaxel (DTX), estramustine phosphate (EMP), and ethinylestradiol (EE) did not improve PCaSS ($P = 0.9936$, $P = 0.3699$, and $P = 0.4685$, respectively), patients who underwent alternative anti-androgen (AA) and zoledronic acid (ZOL) therapy had significantly better PCaSS after being CRPC than those who did not ($P = 0.0088$ and $P = 0.0137$). However, ZOL did not improve PCaSS from the time of diagnosis ($P = 0.1092$).

Table 1. Patient backgrounds

		VH	MH	SH	*P*
n		21	37	32	
Median age, yr		73 (60 – 86)	75 (52 – 92)	74.5 (50 – 95)	0.9909
Median PSA, ng/mL		3349 (1018 – 16702)	281 (203 – 979)	138 (102 – 197)	< 0.0001
T	1, 2	2	8	5	0.0315
	3	5	15	19	
	4	14	14	8	
N	0	4	20	16	0.0264
	1	17	17	16	
M	0	1	11	24	< 0.0001
	1b	15	21	7	
	1c	5	5	1	
GS	6, 7	2	9	15	0.0184
	8	5	12	3	
	9, 10	14	16	14	
	NA	1	0	0	
Median FU, days		988 (10 – 4165)	1424 (29 – 4218)	1390 (7 – 4612)	0.3409
CRPC Dev	yes	11	22	13	0.2932
	no	10	15	19	

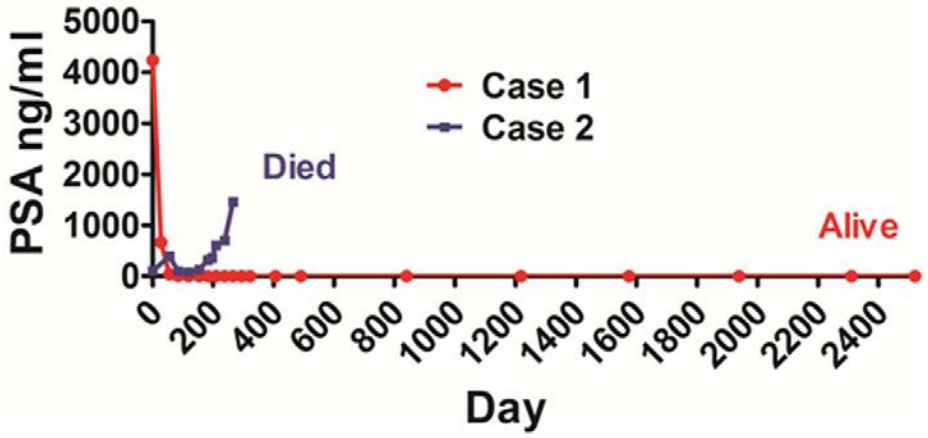
VH = very high, MH = moderately high, SH = slightly high, GS = Gleason score, NA = not available, FU = follow-up, CRPC Dev = castration-resistant prostate cancer development. Values in parentheses indicate range.

Table 2. Treatment performed in CRPC patients

		VH	MH	SH	*P*
DTX	yes	3	7	2	0.5613
	no	8	15	11	
ZOL	yes	7	15	4	0.0841
	no	4	7	9	
EMP	yes	7	16	7	0.522
	no	4	6	6	
EE	yes	3	9	2	0.2749
	no	8	13	11	
AA	yes	10	19	11	0.8953
	no	1	3	2	

DTX = docetaxel, ZOL = zoledronate, EMP = estramustine phosphate, EE = ethinylestradiol, AA = alternative anti-androgen. Other abbreviations are the same as in Table 1.

Fig 1



Case	PSA (ng/mL)	TNM	GS	Treatment	FU (days)	Status
1	4182	T3bN1M1c	4+4=8	CAB-ZOL	2521	Alive
2	108	T2bN0M1c	5+4=9	CAB-AA-EMP-ZOL	244	Died

Fig 2

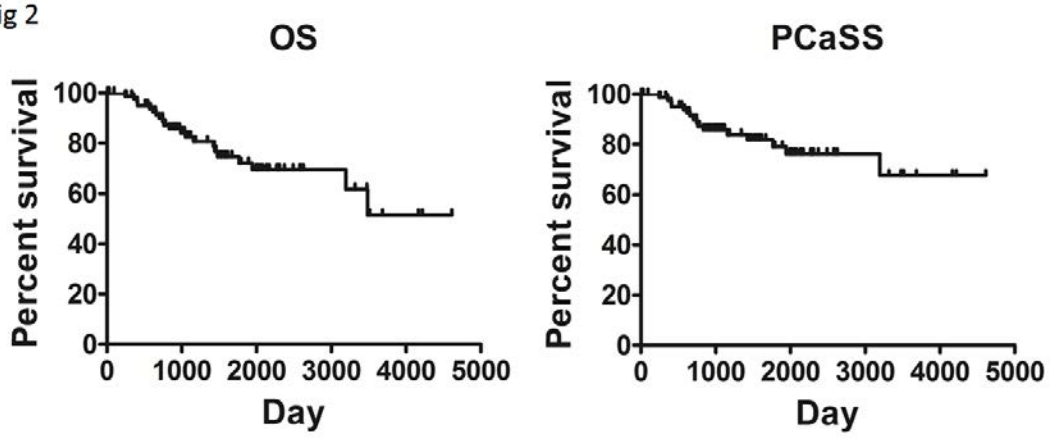


Fig 3

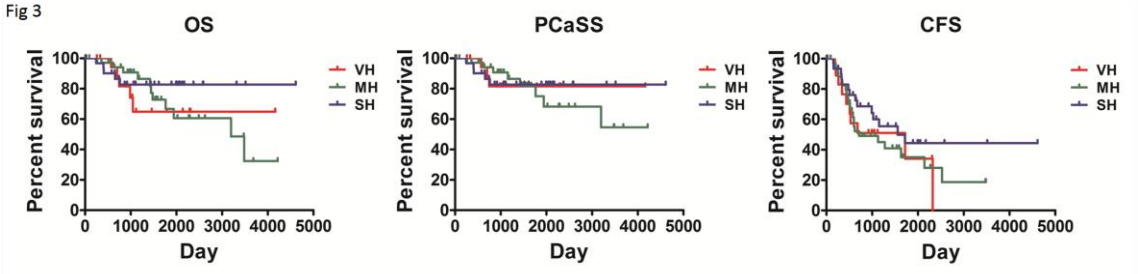


Fig 4

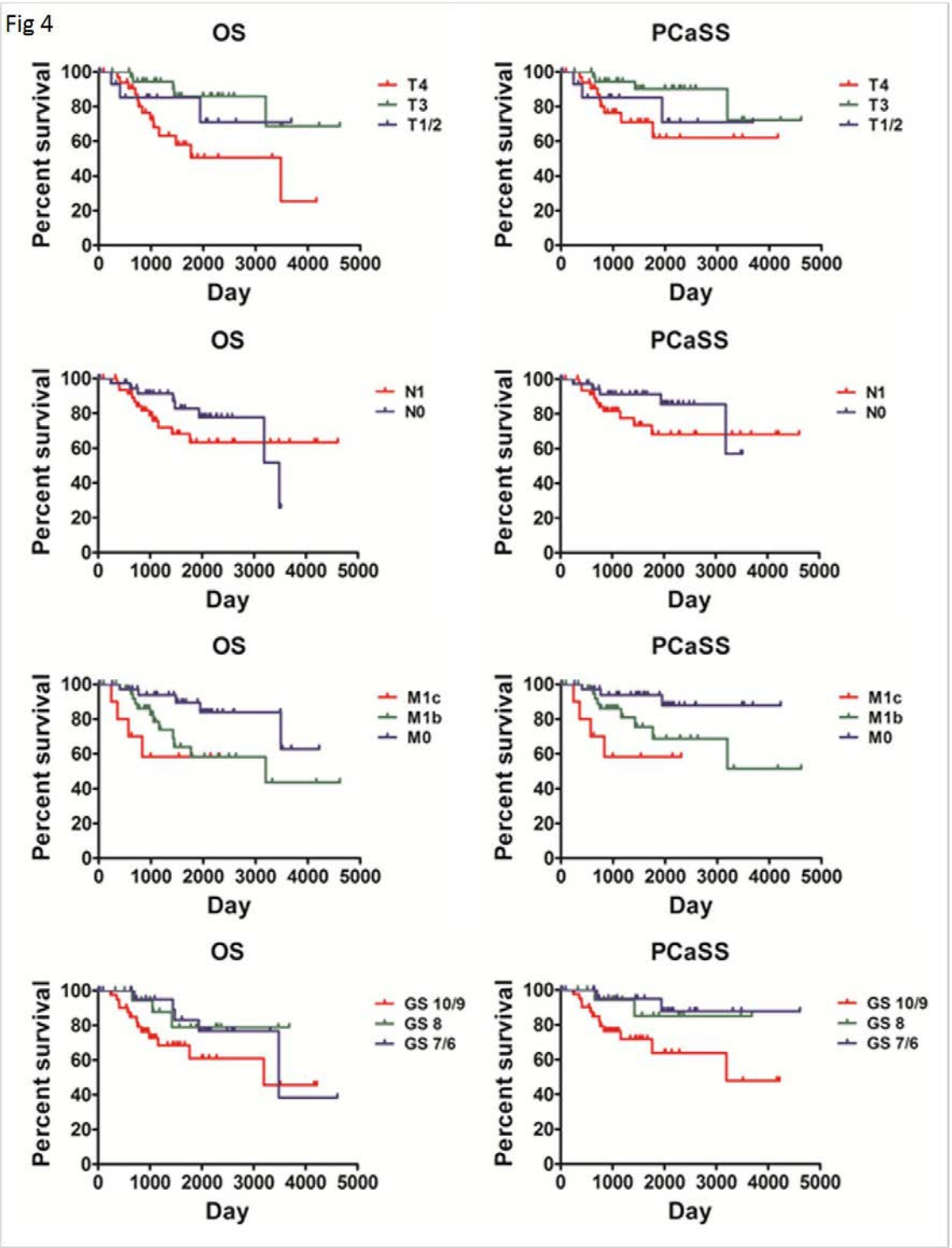

OS
PCaSS
Percent survival
Day
0
1000
2000
3000
4000
5000
20
40
60
80
100
T4
T3
T1/2
N1
N0
M1c
M1b
M0
GS 10/9
GS 8
GS 7/6

Fig 5

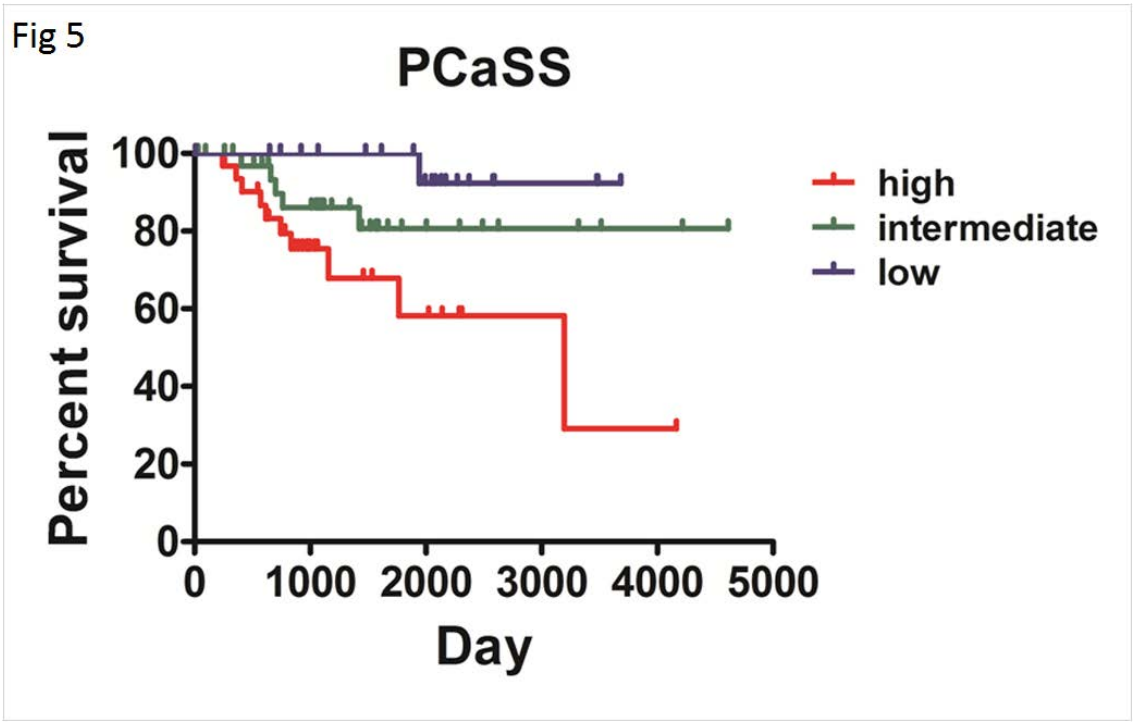
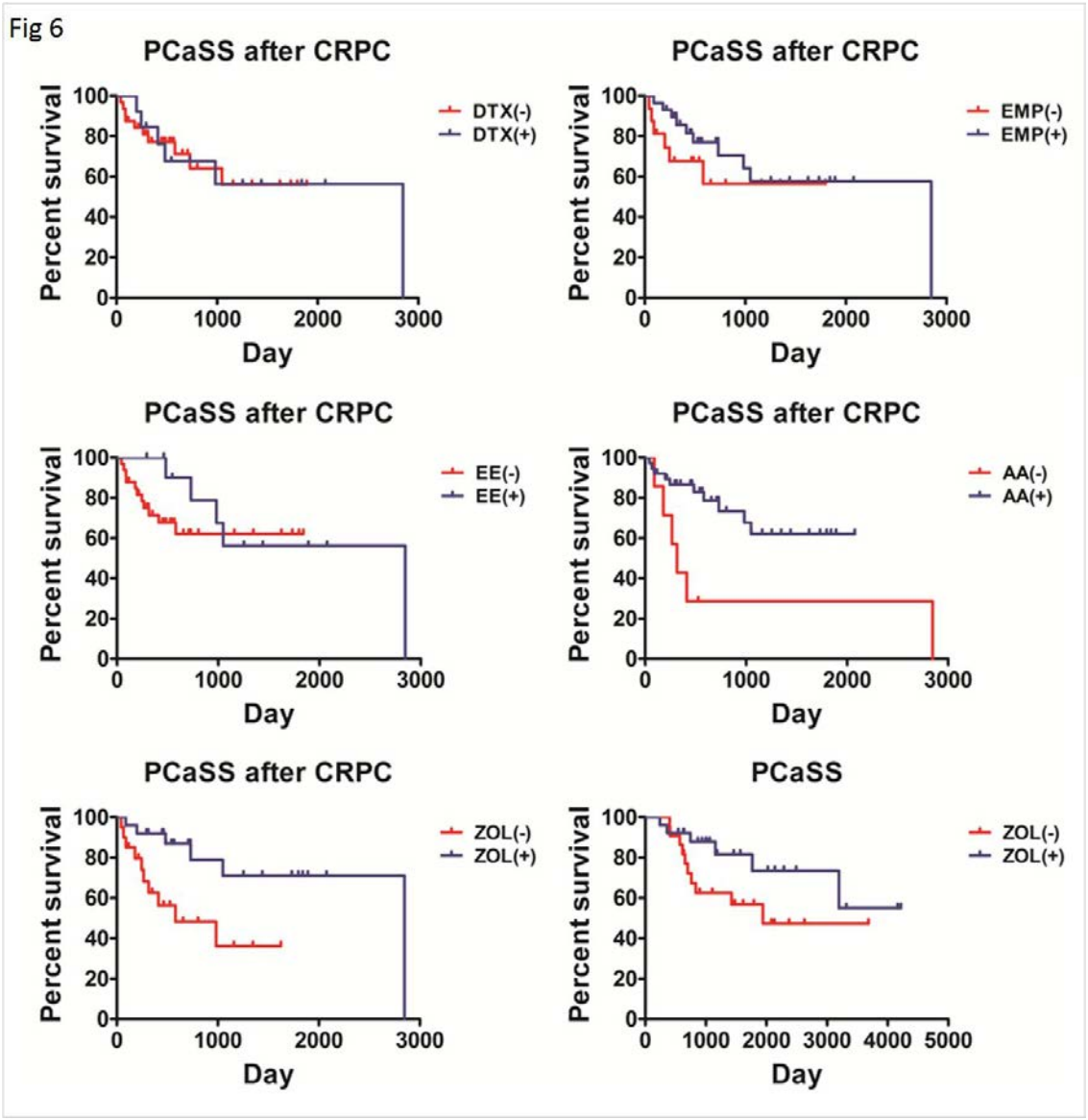

PCaSS
Percent survival
100
80
60
40
20
0
0
1000
2000
3000
4000
5000
Day
high
intermediate
low

Fig 6


PCaSS after CRPC
Percent survival
Day
DTX(-)
DTX(+)
PCaSS after CRPC
Percent survival
Day
EMP(-)
EMP(+)
PCaSS after CRPC
Percent survival
Day
EE(-)
EE(+)
PCaSS after CRPC
Percent survival
Day
AA(-)
AA(+)
PCaSS after CRPC
Percent survival
Day
ZOL(-)
ZOL(+)
PCaSS
Percent survival
Day
ZOL(-)
ZOL(+)