# Expression of Hepatocyte Growth Factor in Prostate Cancer May Indicate a Biochemical Recurrence After Radical Prostatectomy

SACHIYO NISHIDA[1,2], YOSHIHIKO HIROHASHI[1], TOSHIHIKO TORIGOE[1], MASANORI NOJIMA[3], RYUTA INOUE[1,2], HIROSHI KITAMURA[2], TOSHIAKI TANAKA[2], HIROKO ASANUMA[4], NORIYUKI SATO[1] and NAOYA MASUMORI[2]

*Departments of [1]Pathology, [2]Urology, [4]Department of Surgical Pathology, Sapporo Medical University School of Medicine, Chuo-ku, Sapporo, Japan; [3]Division of Advanced Medicine Promotion, The Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan*

**Abstract**. *We previously found that prostate cancer stem-like cells (CSCs)/cancer-initiating cells (CICs) express hepatocyte growth factor (HGF) and that the HGF/c-MET proto-oncogene product (c-MET) signal has a role in the maintenance of prostate CSCs/CICs in an autocrine fashion. HGF is, thus, a novel marker for prostate CSCs/CICs. We hypothesized that high expression of HGF might be related to early recurrence of prostate cancer after radical prostatectomy, and the purpose of the present study was to evaluate the relationship between expression of HGF in prostate tissues and biochemical recurrence after radical prostatectomy. One hundred-one patients with prostate cancer who underwent open or laparoscopic radical prostatectomy from November 2008 to October 2011 with an adequate prostate-specific antigen (PSA) follow-up period, were investigated. Immunohistochemical staining of HGF was compared to biochemical recurrence after radical prostatectomy. Patients with tumors exhibiting HGF positivity of 5% or more had a significantly shorter biochemical recurrence-free period than that of patients whose tumor HGF positivity was less than 5% (p=0.001). In multivariate Cox regression, preoperative PSA and HGF positivity were independent predictors of biochemical recurrence following prostatectomy. Our finding suggests a direct link between expression of HGF, a novel prostate marker of CSCs/CICs, and biochemical recurrence after radical prostatectomy in patients with prostate cancer.*

*Correspondence to:* Yoshihiko Hirohashi, MD, Ph.D. or Toshihiko Torigoe, MD, Ph.D., Department of Pathology, Sapporo Medical University School of Medicine, South-1, West-17, Chuo-ku, Sapporo 060-8556, Japan. Tel: +81 116112111 (ext. 2692), Fax: +81 116432310, e-mail: hirohash@sapmed.ac.jp

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Prostate cancer is one of the common and lethal types of cancer in males. The behavior of some cancer types can vary regardless of the Gleason score and other clinicopathological factors. Androgen deprivation is the standard therapy for advanced prostate cancer; however, most patients with an aggressive form of prostate cancer, named castration-resistant prostate cancer (CRPC), experience relapse within a few years after initial treatment, and there is no known effective treatment for CRPC. Recent efforts have thus focused on developing biomarkers that provide clinicians with better ability to identify clinically significant cancer and aid in treatment decisions (1).

Signaling of hepatocyte growth factor (HGF) and its receptor c-MET proto-oncogene product(c-MET) is activated in cancer cells and is related to cancer cell growth, cell motility and matrix invasion (2, 3). HGF/c-MET signaling can therefore reasonably be a target for cancer therapy (4). Furthermore, HGF and its receptor c-MET may play important roles in progression of castration-resistant prostate cancer (CRPC). c-MET expression has been shown to be associated with the emergence of a castration-resistant tumor (5). However, HGF and c-MET have not been associated with biochemical recurrence after radical prostatectomy, that is, after treatment of clinically localized prostate cancer.

Cancer stem-like cells (CSCs)/cancer-initiating cells (CICs) have high tumor-initiating ability and are resistant to chemotherapy and radiotherapy, and they are, therefore, thought to be responsible for cancer recurrence after treatment and for distant metastasis (6, 7). Prostate cancer contains a small population of CSCs/CICs, and we have previously reported successful isolation of prostate

CSCs/CICs from the human prostate carcinoma cell line 22Rv1 by using aldehyde dehydrogenase (ALDH) activity (8). In addition, gene expression analysis revealed that growth factors, including HGF, were overexpressed in prostate CSCs/CICs, whereas the receptor of HGF, c-MET, was expressed in both CSCs/CICs and non-CSCs/CICs at similar levels. Further analysis revealed that HGF secreted from prostate CSCs/CICs had a role in maintenance of prostate CSCs/CICs in an autocrine fashion (9).

In the present study, we hypothesize that high expression of HGF is related to early recurrence of prostate cancer after radical prostatectomy and investigated the relationship between frequency of prostate CSCs/CICs, which were identified by immunohistochemical staining using an antibody against HGF, and biochemical recurrence after radical prostatectomy.

## Patients and Methods

*Patients*. We reviewed clinical pathology archives of 106 consecutive patients who underwent open or laparoscopic radical prostatectomy and were diagnosed as having localized prostate cancer at Sapporo Medical University Hospital during the period from November 2008 to October 2011. One hundred and one of 106 patients with prostate cancer were followed-up for a minimum of two years. Fifty-one patients were surgically treated with a laparoscopic approach and 50 patients with open approach. Informed consent was obtained from the patients to use surgical specimens remaining after pathological diagnosis for the investigational study, which was approved by the Institutional Review Board for Clinical Research at our university (approval no. 25-36). All hematoxylin- and eosin-stained slides were reviewed, and all of these specimens revealed prostate adenocarcinoma. The median age at operation was 67 years (range=50-78 years). The median follow-up period of patients with no biochemical recurrence was 40 months (range=28-60 months). All hematoxylin- and eosin-stained slides were reviewed, and clinical stage was assigned using the seventh edition of the American Joint Committee on Cancer TNM Staging System for Prostate Cancer (7th edition, 2009) (10).

The patients' characteristics are shown in Table I. Lymph node dissection was performed in all patients. No cases underwent neoadjuvant or adjuvant hormonal therapy.

*Immunohistochemistry and scoring*. Immunohistochemical staining using formalin-fixed paraffin-embedded sections of surgically-resected prostate carcinoma was performed as described previously (11). Goat monoclonal antibody against HGF (R and D Systems, Minneapolis, MN, USA) was used at 1,000-times dilution. The slides were then counterstained with hematoxylin, rinsed, dehydrated through graded alcohols into a nonaqueous solution, and cover-slipped with mounting media. All specimens were reviewed independently using light microscopy in at least five areas at ×400 magnification by investigators who were blinded to clinicopathological data (TT and YH). Tumors presenting at least one HGF-positive cancer cell per high power field were considered to be HGF-positive. The positivity rate and intensity grade were recorded.

Table I. *Characteristics of 101 patients of the study.*

| Characteristics | |
|---|---|
| Median age in years (range) | 67 (50-78) |
| Median body mass index (kg/m$^2$) (range) | 23.5 (18.7-32.7) |
| Median preoperative PSA ng/ml (range) | 6.4 (2.4-46.7) |
| Surgical approach N (%) | |
| Open | 50 (49.5) |
| Laparoscopy | 51 (50.5) |
| Pathological stage N (%) | |
| 2a | 21 (20.7) |
| 2b | 28 (27.7) |
| 2c | 38 (37.6) |
| 3a | 7 (6.9) |
| 3b | 7 (6.9) |
| Positive surgical margins N (%) | 43 (42.5) |
| Positive nodes N (%) | 3 (2.9) |
| Gleason sum N (%) | |
| 6 | 15 (14.8) |
| 7 | 60 (59.4) |
| 8 | 7 (6.9) |
| 9 | 19 (18.8) |

*Statistical analysis*. We investigated the relationships between HGF positivity and other clinicopathological parameters, *i.e.* preoperative PSA, pathological T stage, and Gleason grade, by Fisher's exact tests. Biochemical recurrence-free survival was assessed by the Kaplan–Meier method, and differences between two groups were compared using the log-rank test. Biochemical recurrence after radical prostatectomy was defined as an initial PSA value of 0.2 ng/ml or less followed by subsequent confirmatory PSA value of 0.2 ng/ml or more.

To define HGF overexpression, time-dependent receiver operating characteristic (ROC) curve analysis for biochemical recurrence within 2 years or 5 years after radical prostatectomy was performed using the positivity rate and intensity grade of HGF expression to identify the optimum cut-off point that maximized the sum of sensitivity and specificity (12). Cut-off points of HGF positivity and intensity were defined as the point on the ROC curve closest to the upper left corner. Cox regression analyses were used to assess whether HGF or other conventional factors were associated with biochemical recurrence following prostatectomy. To assess a statistical independence of HGF from the other factors, we perform multivariate Cox regression analysis. However, because the incidence of the event (biochemical recurrence) was very low, we selected a few important variables using the backward elimination methods. In this step, after entering all of the variables assessed by the univariate analysis, the variables were removed one by one if Wald $p>0.1$. SPSS Version 20.0 (IBM, Armonk, NY, USA) was used to perform statistical analyses. All tests were two-tailed and a $p$-value of less than 0.05 was considered statistically significant.

## Results

*Expression of HGF in human prostate cancer tissues*. HGF-positive cells were detected in 45 out of the 101 cases (Figure 1). In 45 positive cases, the median cell positivity rate was 5% (range=1-50%). Time-dependent ROC curve

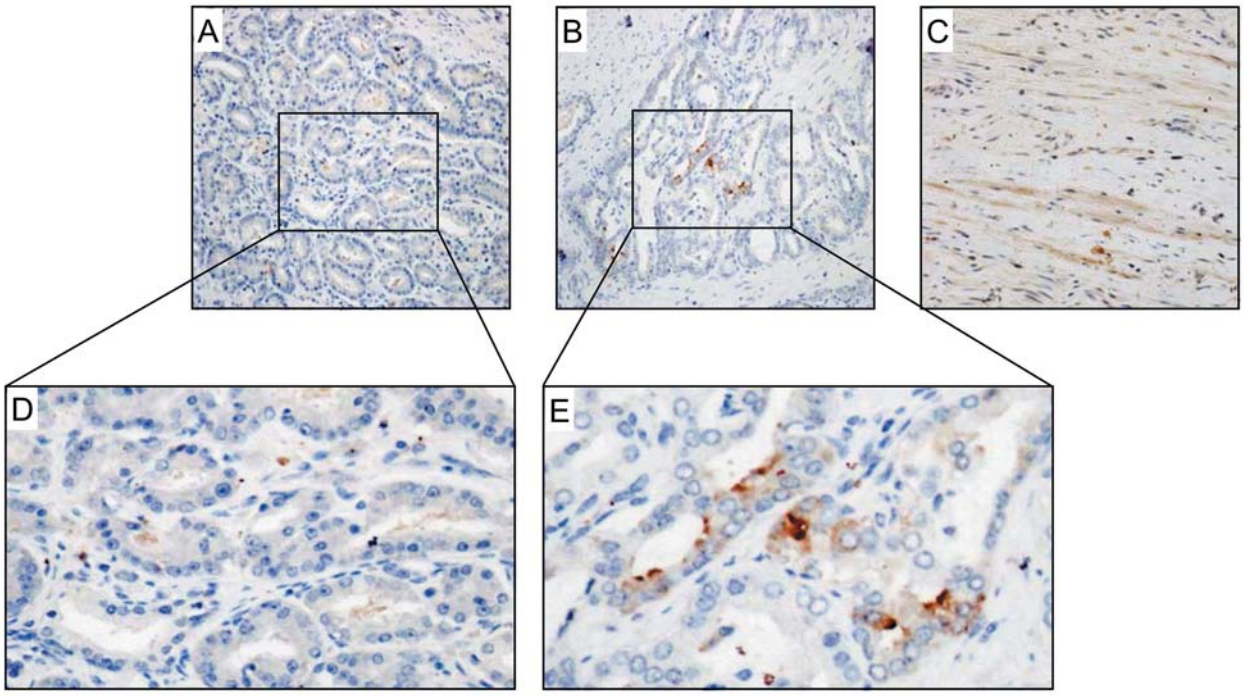


Figure 1. *Representative immunohistochemical staining of hepatocyte growth factor (HGF): negative HGF expression in tumor cells shown in (A) and (D), positive HGF expression in tumor cells shown in (B) and (E), and positive HGF expression in fibroblasts shown in (C). Original magnification ×100.*

analysis for biochemical recurrence within 2 years demonstrated excellent discrimination of HGF-positivity rate (AUC=0.756), with sensitivity and specificity of 72.7% and 81.1%, respectively. The AUC for biochemical recurrence within 2 years was higher than that for within 5 years (data not shown). Using the optimum cut-off of 5% to define overexpression, there was a significantly larger number of patients with biochemical recurrence in the group with HGF staining of 5% or more than in the group with HGF staining of less than 5% (Table II). Hereafter, cases with an expression rate of 5% or more are denoted as HGFP≥5% and those with an expression rate of less than 5% are denoted as HGFP<5%.

*Associations between expression rates of HGF and clinicopathological variables*. Kaplan–Meier plots and log-rank tests showed that patients with prostate cancer with HGFP ≥5% had a significantly shorter biochemical recurrence-free period than did patients with HGFP<5% (Figure 2) ($p<0.001$). Univariate analysis demonstrated that HGF positivity predicted biochemical recurrence ($p<0.05$). Furthermore, multivariate Cox regression with/without the backward elimination method suggested that preoperative PSA and HGF positivity were independent predictors of

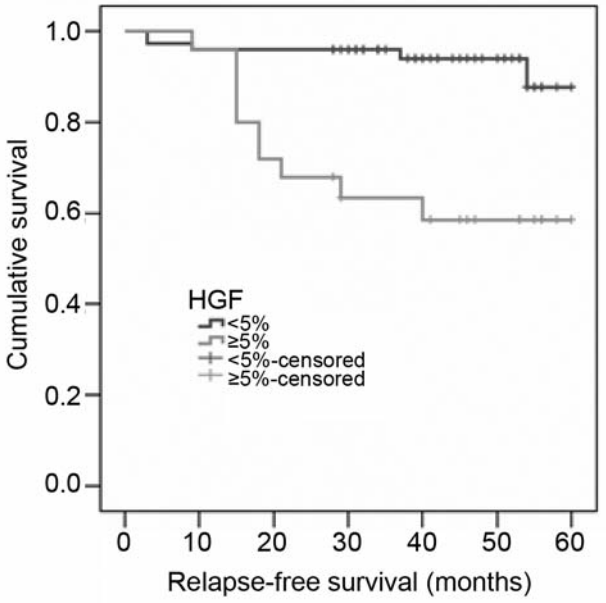


Figure 2. *Kaplan–Meier curve for rates of biochemical recurrence of prostate cancer after radical prostatectomy according to hepatocyte growth factor (HGF) expression status. Patients with HGF ≥5% had a significantly shorter biochemical recurrence-free period than did patients whose tumors exhibited HGF<5% (p<0.001).*

Table II. *Hepatocyte growth factor (HGF) expression and pathological factors in patients underwent radical prostatectomy*

| | | HGFP <5% | | 5% or more | | Total | |
|---|---|---|---|---|---|---|---|
| | | Mean (N) | SD (%) | Mean (N) | SD (%) | N | *p*-Value |
| | N | 76 | | 25 | | | |
| Age (years) | | 66.3 | 6.1 | 62.9 | 6.5 | | 0.021 |
| BMI (kg/m$^2$) | | 23.7 | 2.6 | 23.7 | 2.3 | | 0.988 |
| Preoperative PSA | | 8.8 | 6.4 | 9.4 | 5.7 | | 0.663 |
| Stage | 2a | 15 | 14.8% | 6 | 21.9% | 21 | |
| | 2b | 21 | 27.0% | 7 | 25.5% | 28 | |
| | 2c | 33 | 42.4% | 5 | 18.2% | 38 | |
| | 3a | 3 | 3.9% | 4 | 14.6% | 7 | |
| | 3b | 4 | 5.1% | 3 | 10.9% | 7 | 0.742 |
| Surgical margins | – | 44 | 59.5% | 12 | 48.0% | 56 | |
| | + | 30 | 40.5% | 13 | 52.0% | 43 | 0.357 |
| Gleason sum | 6 | 12 | 14.0% | 3 | 9.4% | 15 | |
| | 7 | 44 | 51.2% | 16 | 50.0% | 60 | |
| | 8 | 7 | 8.1% | 0 | 0.0% | 7 | |
| | 9 | 13 | 15.1% | 6 | 18.8% | 19 | 0.796 |
| Biochemical recurrence within 2 years | | 3 | | 8 | | | |
| Biochemical recurrence rate (2 years/1000person-year) | | 1.70 | | 14.98 | | | |
| Biochemical recurrence within 5 years | | 5 | | 10 | | | |
| Biochemical recurrence rate (5 years/1000 person-year) | | 1.58 | | 11.07 | | | |
| Median follow-up period (months) | | 40.5 | | 40 | | | |

PSA: Prostate-specific antigen; MBI: body mass index.

biochemical recurrence following prostatectomy (Table III). Gleason score was not selected as a statistically independent predictor of biochemical recurrence in multivariate analysis.

## Discussion

There is a need for more accurate biomarkers to predict the prognosis of patients with prostate cancer, especially for those with intermediate-grade tumors. Few markers that reliably predict treatment failure (*e.g.* PSA recurrence after surgery) have been reported. Recently, heterochromatin protein 1γ (HP1γ) was reported as a marker of treatment failure (13). To the best of our knowledge, this is the first study in which the relationships between expression of putative CSCs/CICs markers and the most clinically relevant features of prostate cancer were evaluated. Our findings suggest that CSCs/CICs are linked to more aggressive behavior of prostate cancer.

HGF is a paracrine factor produced by cells of mesenchymal origin, while the HGF receptor, c-MET, is expressed by epithelial and endothelial cells (14). HGF plays important roles in the progression of many invasive and metastatic types of cancer (15). The interaction between tumor cells and their surrounding stromal environment remains a crucial factor governing tumor invasion and metastasis. HGF and its receptor c-MET may play important roles, in the progression of CRPC. Serum HGF levels are higher in patients with metastatic prostate cancer than in those with localized tumors or benign lesions (16), and high HGF levels have been associated with poorer outcomes (17). HGF further induces cell invasion associated with stem cell features (18); that is, c-MET was considered to be important for patients with CRPC. In our previous study, we showed that both prostate CSCs/CICs and fibroblasts secrete HGF and that HGF has a role in the maintenance of prostate CSCs/CICs in autocrine and paracrine fashions (9). In this study, there was no difference in immunohistochemical c-MET expression in prostate specimens with and without biochemical recurrence (data not shown), and we demonstrated a relationship between early recurrence after radical prostatectomy and HGF positivity. We, therefore, found a role for the expression of HGF in predicting treatment failure. Our results indicate that the existence of prostate CSCs/CICs has a strong influence on biochemical recurrence after radical prostatectomy, and early treatment targeting prostate CSCs/CICs after radical prostatectomy may, therefore, be important for preventing recurrence.

Preclinical studies have shown that c-MET and HGF are highly expressed in advanced prostate cancer and are associated with disease progression. It has recently been reported that c-MET inhibitors demonstrated antiproliferative efficacy when combined with androgen ablation therapy for

Table III. *Univariate and multivariate analysis for predicting biochemical recurrence of prostate cancers.*

| Factor | Univariate analysis | | | | Multivariate analysis with all items | | | | Multivariate analysis with backward elimination started with all items | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95%CI | | | | 95%CI | | | | 95%CI | |
| | *p*-Value | HR | Lower | Upper | *p*-Value | HR | Lower | Upper | *p*-Value | HR | Lower | Upper |
| 2-year RFS | | | | | | | | | | | | |
| Age (per 1-year increase) | 0.884 | 1.01 | 0.92 | 1.11 | 0.055 | 1.18 | 1.00 | 1.40 | **0.039** | 1.2 | 1.0 | 1.3 |
| BMI (per 1kg/m2 increase) | 0.813 | 1.03 | 0.82 | 1.29 | 0.504 | 1.13 | 0.80 | 1.59 | | | | |
| Preoperative PSA (per 1 ng/ml increase) | **0.009** | 1.07 | 1.02 | 1.12 | **0.003** | 1.17 | 1.06 | 1.30 | **0.001** | 1.2 | 1.1 | 1.3 |
| Pathological T stage (per 1-category increase) | 0.108 | 1.53 | 0.91 | 2.57 | 0.716 | 1.16 | 0.52 | 2.61 | | | | |
| Positive margin*s vs*. negative margins | 0.057 | 3.63 | 0.96 | 13.69 | 0.059 | 4.03 | 0.95 | 17.11 | 0.089 | 3.3 | 0.8 | 13.3 |
| Gleason sum (per 1 increase) | 0.582 | 1.18 | 0.65 | 2.14 | 0.743 | 0.85 | 0.33 | 2.20 | | | | |
| HGF≥5% | **0.002** | 8.58 | 2.27 | 32.40 | 0.001 | 18.36 | 3.41 | 98.73 | **0.001** | 17.1 | 3.4 | 86.7 |
| Open *vs*. laparoscopy | 0.719 | 1.24 | 0.38 | 4.08 | 0.263 | 2.226 | 0.548 | 9.042 | | | | |
| 5-year RFS | | | | | | | | | | | | |
| Age (per 1-year increase) | 0.529 | 1.03 | 0.95 | 1.11 | **0.024** | 1.15 | 1.02 | 1.29 | **0.015** | 1.14 | 1.03 | 1.26 |
| BMI (per 1kg/m2 increase) | 0.823 | 1.02 | 0.84 | 1.24 | 0.815 | 1.03 | 0.80 | 1.33 | | | | |
| Preoperative PSA (per 1 ng/ml increase) | **0.023** | 1.06 | 1.01 | 1.11 | **0.003** | 1.13 | 1.04 | 1.23 | **0.001** | 1.13 | 1.05 | 1.22 |
| Pathological T stage (per 1-category increase) | 0.071 | 1.51 | 0.97 | 2.36 | 0.677 | 1.15 | 0.60 | 2.18 | | | | |
| Positive margin*s vs*. negative margins | 0.160 | 2.11 | 0.75 | 5.94 | 0.142 | 2.31 | 0.76 | 7.03 | | | | |
| Gleason sum (per 1 increase) | 0.459 | 1.21 | 0.73 | 2.01 | 0.93 | 0.97 | 0.46 | 2.05 | | | | |
| HGF ≥5% | **0.001** | 6.62 | 2.26 | 19.40 | **<0.001** | 13.29 | 3.46 | 51.04 | **<0.001** | 14.28 | 3.88 | 52.54 |
| Open *vs*. laparoscopy | 0.671 | 0.799 | 0.284 | 2.247 | 0.999 | 0.999 | 0.321 | 3.114 | | | | |

RFS: Recurrence-free survival; MBI: body mass index; PSA: prostate-specitic antigen; HGF: hepatocyte growth factor; HR: hazord ratio; CI: conficdence interval. Bold indicates statistically significant difference.

advanced prostate cancer (19). Furthermore, targeting the c-MET pathway with rilotumumab, a fully human monoclonal antibody against HGF, in combination with mitoxantrone and prednisone (MP), is a potentially viable therapeutic option in CRPC, and a double-blinded, randomized phase II study for patients with CRPC has been performed (20). Unfortunately, rilotumumab combined with MP did not show a treatment advantage in patients with CRPC. Since, HGF–c-MET signaling has important role for self-renewal of CSCs/CICs, c-Met inhibitor treatment might be better to be started for high risk patients just after radical prostatectomy to eradicate remaining CSCs/CICs before they start to differentiate into non-CICs/CICs. Inhibition of c-MET has potency in blocking stem cell-like transition and is therefore a promising tool for targeted-therapy of prostate cancer.

There are several limitations to our study. Firstly, there are the limitations inherent to any retrospective study. Secondly, open or laparoscopic radical prostatectomy was performed by many surgeons. The relatively high margin-positive rate may be due to immature technical skills. Thirdly, immunohistochemistry has inherent limitations such as reproducibility and reliability. Since it is difficult to stain and correctly evaluate old specimens, specimens used in our study were limited to ones obtained in the period from 2008 to 2011. Finally, the follow-up period was relatively short because of the limitation for specimens. Related to this problem, because the incidence of the biochemical recurrence was very low, the reliability of the result of multivariate regression analysis is relatively unsatisfactory. In addition, although the predictability should have been validated in an independent cohort, it could not be performed with small samples. Further investigation is therefore needed.

In summary, the results of this study indicate a direct link between expression of prostate CSC/CIC markers and biochemical recurrence after radical prostatectomy in patients with prostate cancer. Our data support the current CSC hypothesis for prostate cancer, which suggests that therapeutic targeting of CSCs/CICs in prostate cancer is a future possibility.

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## Conflicts of Interest

The Authors declare no conflict of interest.

## References

1 Punnen S, Cooperberg MR, D'Amico AV, Karakiewicz PI, Moul JW, Scher HI, Schlomm T and Freedland SJ: Management of biochemical recurrence after primary treatment of prostate cancer: a systematic review of the literature. European urology *64*: 905-915, 2013.

2 Humphrey PA, Zhu X, Zarnegar R, Swanson PE, Ratliff TL, Vollmer RT and Day ML: Hepatocyte growth factor and its receptor (c-MET) in prostatic carcinoma. The American journal of pathology *147*: 386-396, 1995.

3 Kasai S, Sugimura K, Matsumoto K, Nishi N, Kishimoto T and Nakamura T: Hepatocyte growth factor is a paracrine regulator of rat prostate epithelial growth. Biochemical and biophysical research communications *228*: 646-652, 1996.

4 Cecchi F, Rabe DC and Bottaro DP: Targeting the HGF/Met signaling pathway in cancer therapy. Expert Opin Ther Targets *16*: 553-572, 2012.

5 Knudsen BS and Edlund M: Prostate cancer and the met hepatocyte growth factor receptor. Advances in cancer research *91*: 31-67, 2004.

6 Park CY, Tseng D and Weissman IL: Cancer stem cell-directed therapies: recent data from the laboratory and clinic. Molecular therapy: the journal of the American Society of Gene Therapy *17*: 219-230, 2009.

7 Hirohashi Y, Torigoe T, Inoda S, Takahashi A, Morita R, Nishizawa S, Tamura Y, Suzuki H, Toyota M and Sato N: Immune response against tumor antigens expressed on human cancer stem-like cells/tumor-initiating cells. Immunotherapy *2*: 201-211, 2010.

8 Nishida S, Hirohashi Y, Torigoe T, Kitamura H, Takahashi A, Masumori N, Tsukamoto T and Sato N: Gene expression profiles of prostate cancer stem cells isolated by aldehyde dehydrogenase activity assay. The Journal of urology *188*: 294-299, 2012.

9 Nishida S, Hirohashi Y, Torigoe T, Inoue R, Kitamura H, Tanaka T, Takahashi A, Asanuma H, Masumori N, Tsukamoto T, and Sato N: Prostate cancer stem-like cells/cancer-initiating cells have an autocrine system of hepatocyte growth factor. Cancer science *104*: 431-436, 2013.

10 Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A: AJCC Cancer Staging Manual. 2010.

11 Kitamura H, Torigoe T, Hirohashi Y, Asanuma H, Inoue R, Nishida S, Tanaka T, Fukuta F, Masumori N, Sato N and Tsukamoto T: Prognostic impact of the expression of ALDH1 and SOX2 in urothelial cancer of the upper urinary tract. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc *26*: 117-124, 2013.

12 Heagerty PJ, Lumley T and Pepe MS: Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics *56*: 337-344, 2000.

13 Slezak J, Truong M, Huang W and Jarrard D: HP1gamma expression is elevated in prostate cancer and is superior to Gleason score as a predictor of biochemical recurrence after radical prostatectomy. BMC Cancer *13*: 148, 2013.

14 Rubin JS, Bottaro DP, and Aaronson SA: Hepatocyte growth factor/scatter factor and its receptor, the c-met proto-oncogene product. Biochimica et biophysica acta *1155*: 357-371, 1993.

15 Peruzzi B and Bottaro DP: Targeting the c-Met signaling pathway in cancer. Clinical cancer research : an official journal of the American Association for Cancer Research *12*: 3657-3660, 2006.

16 Naughton M, Picus J, Zhu X, Catalona WJ, Vollmer RT and Humphrey PA: Scatter factor-hepatocyte growth factor elevation in the serum of patients with prostate cancer. The Journal of urology *165*: 1325-1328, 2001.

17 Humphrey PA, Halabi S, Picus J, Sanford B, Vogelzang NJ, Small EJ and Kantoff PW: Prognostic significance of plasma scatter factor/hepatocyte growth factor levels in patients with metastatic hormone- refractory prostate cancer: results from cancer and leukemia group B 150005/9480. Clinical genitourinary cancer *4*: 269-274, 2006.

18 van Leenders GJ, Sookhlall R, Teubel WJ, de Ridder CM, Reneman S, Sacchetti A, Vissers KJ, van Weerden W and Jenster G: Activation of c-MET induces a stem-like phenotype in human prostate cancer. PloS one *6*: e26753, 2011.

19 Verras M, Lee J, Xue H, Li TH, Wang Y and Sun Z: The androgen receptor negatively regulates the expression of c-Met: implications for a novel mechanism of prostate cancer progression. Cancer research *67*: 967-975, 2007.

20 Ryan CJ, Rosenthal M, Ng S, Alumkal J, Picus J, Gravis G, Fizazi K, Forget F, Machiels JP, Srinivas S, Zhu M, Tang R, Oliner KS, Jiang Y, Loh E, Dubey S and Gerritsen WR: Targeted MET inhibition in castration-resistant prostate cancer: a randomized phase II study and biomarker analysis with rilotumumab plus mitoxantrone and prednisone. Clinical cancer research: an official journal of the American Association for Cancer Research *19*: 215-224, 2013.

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