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ORIGINAL ARTICLE

Prostate Cancer

Prognostic role of chromogranin A in castration-resistant prostate cancer: a meta-analysis

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We aimed to investigate the prognostic value of chromogranin A (CgA) in castration-resistant prostate cancer (CRPC). We conducted a systematic literature search of PubMed, Web of Science, and EMBASE for citations published prior to September 2017 that described CgA and CRPC and performed a standard meta-analysis on survival outcomes. Our meta-analysis included eight eligible studies with 686 patients. The results were as follows: progression-free survival (PFS) was associated with CgA level (hazard ratio [HR] = 2.47, 95% confidence interval [CI]: 1.47–4.14, $P = 0.0006$); PFS was relative to CgA change (HR = 9.22, 95% CI: 3.03–28.05, $P < 0.0001$); and overall survival (OS) was relative to CgA level (HR = 1.47, 95% CI: 1.15–1.87, $P = 0.002$). When we divided the patients into two groups according to therapy status, the result for OS relative to CgA level was an HR of 1.26 (95% CI: 1.09–1.45, $P = 0.001$) in the first-line hormonal therapy group, and an HR of 2.33 (95% CI: 1.40–3.89, $P = 0.001$) in the second-line hormonal therapy or chemotherapy group. This meta-analysis indicated that a high CgA level had a negative influence on OS and PFS in CRPC patients. In addition, CRPC patients with a rising CgA had a shorter PFS. Further studies are needed to verify the prognostic value of CgA in CRPC.

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Keywords: castration-resistant prostate cancer; chromogranin A; prognosis

INTRODUCTION

Prostate cancer is one of the most prevalent cancers in men worldwide.[1] Androgen-deprivation therapy (ADT) is the most common treatment for metastatic or advanced prostate cancer. Nevertheless, after 18–24 months of response to treatment,[2] most patients develop castration-resistant prostate cancer (CRPC). CRPC is an end-stage disease with a median survival of 9 months to 27 months,[3] but individual survival varies widely.

Despite reaching castration resistance, the androgen receptors (ARs) of prostate cancer cells are considered still active.[4,5] Because of this, several strategies exist to inhibit AR signaling pathways, including enzalutamide, abiraterone acetate, docetaxel, and cabazitaxel and have improved overall survival (OS) in patients with metastatic CRPC.[6–9] However, it should be noted that more effective ADT could increase the incidence of neuroendocrine differentiation (NED) in CRPC. According to the past research, NED is related to tumor progression and poor prognosis.[10]

A study showed that chromogranin A (CgA) levels in immunohistochemical research are clearly elevated in CRPC patients.[11] In addition, plasma CgA levels rose in prostate cancer patients after hormone treatment.[12] CgA is an acidic glycoprotein usually expressed in neuroendocrine cells.[13] It is one of the most widely used sera and tissue markers of NED, which may work for the detection and surveillance of NED in CRPC patients.[14,15] Several studies have demonstrated that high serum CgA levels are related to high-grade,[12] advanced-stage disease and poor prognosis.[12,16]

The purpose of the present study was to summarize and analyze the current evidence regarding the prognostic value of CgA in CRPC patients. To achieve this, we conducted a meta-analysis to assess the literature on this issue.

MATERIALS AND METHODS

Search strategy

A bibliographic search was conducted for all articles before September 2017 by using PubMed, EMBASE, and Web of Science. Different combinations of the following terms were used according to a free-text protocol: chromogranin A, castration-resistant prostate cancer, hormone-refractory prostate cancer (HRPC), neuroendocrine prostate cancer, prognosis or survival, or oncological outcome. We systematically screened the references from all related literature. Two independent investigators (PH and RQG) evaluated the published articles, and disagreements were fully discussed to consensus.

Study selection

The studies were screened in accordance with the following inclusion criteria: (1) research analyzing the relationship between CgA and CRPC or HRPC prognosis; (2) studies that clearly described outcome assessment and presented OS or progression-free survival (PFS); (3) survival outcome that was displayed as a hazard ratio (HR) and corresponding 95% confidence interval (CI) or inclusion of the necessary information to reach an estimated HR and 95% CI by using the methods described by Tierney *et al.*[17] The exclusion criteria were as follows: (1) study was a review, letter, case report, or meta-analysis;

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(2) the data were not available; (3) it was a duplicate publication; (4) the study was not in English.

Data extraction

Data from all the included studies were extracted by two reviewers (PH and RQG) independently with a standardized form. The extracted data included the following: author's name, year of publication, country, type of study, the number of patients, median follow-up time, median age, CgA (median value and cut-off point), and oncologic outcomes (OS and PFS). Disagreements were settled by consensus.

Assessment of study quality

Two reviewers (RQG and PH) independently used the Newcastle Ottawa Scale, which was suggested for the evaluation of nonrandomized studies,[18] to assess the quality of the included studies. This scale evaluates four types of risk: patient selection, comparability of high CgA and low CgA groups, comparability of increases and decreases in CgA, and evaluation of outcomes. Any differences were reassessed by all the authors until consensus was reached.

Statistical analyses

We used log[HR] and the variance as the condensed outcome estimate from all studies in the meta-analysis. If no obvious heterogeneity was found among studies (I^2 >50% and P value < 0.1 indicated apparent heterogeneity),[19] the fixed-effects model (Mantel-Haenszel method) was used to pool the consequences; otherwise, we used a random-effects model (DerSimonian and Laird method), which provides more conservative projections than fixed-effects models when heterogeneity exists.[20] When the potential source of heterogeneity was significant, we used subgroup analysis and meta-regression analysis.

A funnel plot was used to assess the publication bias in the included studies, and the statistical assessment of publication bias was done using Egger's test.[21] The data analysis was performed by Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK). $P < 0.05$ was regarded as statistically significant.

RESULTS

Study identification and quality assessment

Figure 1 shows the process of study selection. A total of 405 studies were initially identified from the literature search. After the duplicates were removed, 190 were screened. According to the titles and abstracts, 161 were removed: 59 were not related, 70 were case, series/case reports, and 42 were letters/reviews/comments. After being reviewed in depth, only 9 were deemed fully eligible. Twenty studies were excluded due to inadequate outcomes. Of the 9 studies, one was excluded due to having no relevant data. Finally, eight studies, with a total of 686 CRPC patients, were included in this meta-analysis.[14,15,22–27]

Table 1 summarizes the main features and findings of the included studies.[14,15,22–27] The CRPC patients were from different countries (Italy, America, Germany, and China). The study publication time ranged from 2000 to 2017. For the eight eligible studies, six studies[14,15,22–25] containing 599 patients were carried out to research the influence of CgA level on the OS of CRPC patients, two studies[22,23] containing 83 patients investigated the PFS, and two studies[26,27] including 53 patients were used to research the influence of CgA changes on the PFS of CRPC patients. The quality scores of the included studies ranged from 7 to 9, and these studies are qualified for meta-analysis.

Overall survival

Among the six studies that referred to OS, there was significant heterogeneity observed (I^2 = 51%, Chi^2 = 10.30, P = 0.07; **Figure 2**).

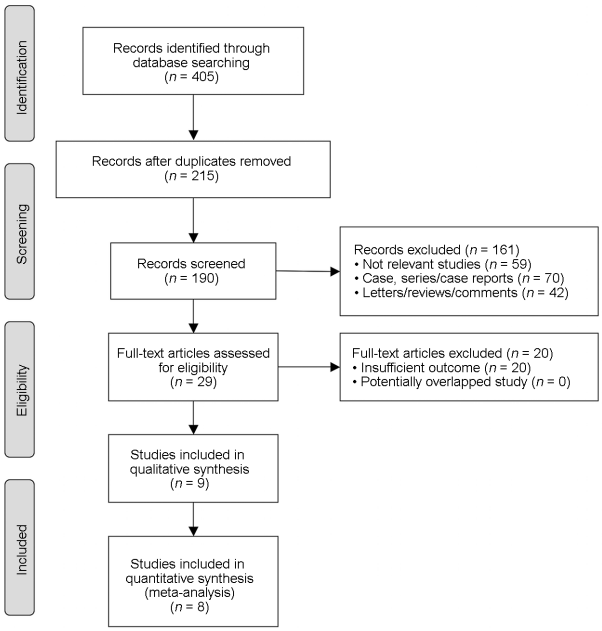

Figure 1: Flow diagram of the study selection.

We used a random-effects model to pool the HR and relevant 95% CIs. As shown in **Figure 2**, the combined HR of these studies indicated that a low CgA level is related to longer OS in CRPC patients (HR = 1.31, 95% CI: 1.15–1.50, $P < 0.0001$). However, there was still some remaining heterogeneity (I^2 = 51%, Chi^2 = 10.30, P = 0.07; **Figure 2**), so we conducted a subgroup analysis according to the therapy received. One group, which included 3 studies, received the first-line hormonal therapy;[14,15,24] the other received the second-line hormonal therapy or chemotherapy.[22,23,25] For the first-line hormonal group, the studies showed that a low CgA level was related to better OS in CRPC patients (HR = 1.26, 95% CI: 1.09–1.45, P = 0.001), and for the second-line hormonal group, the studies indicated that low CgA level also meant better OS in CRPC patients (HR = 2.33, 95% CI: 1.40–3.89, P = 0.001; **Figure 3**). In addition, there was no heterogeneity in either group (the first-line hormonal therapy group: I^2 = 23%, Chi^2 = 2.61, P = 0.27; or the second-line hormonal therapy or chemotherapy group: I^2 = 19%, Chi^2 = 2.47, P = 0.29; **Figure 3**).

Progression-free survival

PFS data were reported in four studies. Two studies investigated PFS of high CgA versus low CgA. The results demonstrated that the PFS for CRPC with high CgA is shorter than that for CRPC with low CgA (HR = 2.47, 95% CI: 1.47–4.14, P = 0.0006), and no significant heterogeneity was observed (I^2 = 0, Chi^2 = 0.14, P = 0.71; **Figure 4**). Two other studies investigated PFS of increasing or decreasing CgA. The results demonstrated that the increasing CgA results in shorter PFS in CRPC patients, (HR = 9.22, 95% CI: 3.03–28.05, $P < 0.0001$), and no significant heterogeneity was observed (I^2 = 0, Chi^2 = 0.54, P = 0.46; **Figure 5**).

Publication bias

We use a funnel plot of the meta-analysis results to evaluate the publications. No apparent publication bias was found in this meta-analysis (**Supplementary Figure 1**). Egger's test showed that there was no apparent publication bias for OS or PFS.

Table 1: Characteristics and quality score of the included studies

Study	*Country*	*Type of study*	*Patients (n)*	*Renal insufficiency*	*Proton-pump inhibitor (%)*	*Median follow-up (month)*	*Median age (year)*	*Median CgA*	*CgA group (n)*	*Treatment*	*Outcome*	*Quality score*
Berruti *et al.*[14]	Italy	Retrospective	108	No	No	24.4	74	17.3 U l^{-1}	53 (<17.6 U l^{-1}) 45 (≥17.6 U l^{-1})	ADT (LHRH analogue)	OS	8
Matei *et al.*[15]	Italy	Retrospective	47	NA	NA	32	66	25 U l^{-1}	27 (<36 U l^{-1}) 20 (≥36 U l^{-1})	ADT (LHRH analogue)	OS	7
Conteduca *et al.*[22]	Italy	Retrospective	35	No	No	12.2	75	174 ng ml^{-1}	10 (<120 ng ml^{-1}) 17 (120–360 ng ml^{-1}) 8 (≥360 ng ml^{-1})	ADT (new AR antagonist/ enzalutamide)	PFS, OS	8
Burgio *et al.*[23]	Italy	Retrospective	48	No	No	21.7	73	235.5 ng ml^{-1}	16 (<120 ng ml^{-1}) 16 (120–360 ng ml^{-1}) 16 (≥360 ng ml^{-1})	ADT (CYP17 blocker/ abiteraterone)	PFS, OS	9
Taplin *et al.*[24]	America	Prospective	321	No	NA	35.23	70	12 U l^{-1}	161 (≤12 U l^{-1}) 160 (>12 U l^{-1})	ADT (antiandrogen, LHRH analogue, surgical castration, estrogen, progesterone agent)	OS	7
Berruti *et al.*[25]	Italy	Retrospective	40	No	NA	NA	NA	NA	22 (<20 U l^{-1}) 18 (≥20 U l^{-1})	ADT (2nd line) or chemotherapy	OS	7
Von Hardenberg *et al.*[26]	Germany	Prospective	53	NA	16 (30.8)[a]	34	71.3	1st BW: 132 ng ml^{-1} 3rd BW: 160 ng ml^{-1}	9 (CgA fall) 43 (CgA rise)	Chemotherapy (docetaxel)	PFS, OS	8
Dong *et al.*[27]	China	Retrospective	34	NA	No	19	69.5	115.86 ng ml^{-1}	17 (CgA fall) 17 (CgA rise)	ADT (CYP17 blocker)	PFS	8

[a]The percentage of patients taking proton pump inhibitors. NA: not available; CgA: chromogranin A; ADT: androgen deprivation therapy; AR: androgen receptor; CYP17: cytochrome P-450c17; LHRH analogue: luteinizing hormone-releasing hormone analogue; BW: blood withdrawal; OS: overall survival; PFS: progression-free survival

DISCUSSION

In this article, we reviewed the published studies regarding the prognostic value of CgA for CRPC patients and performed a standard meta-analysis to investigate the prognostic value of CgA for CRPC. The results from our meta-analysis of 8 studies comprising 686 patients indicated that having a high CgA level is an independent predictor of worse OS and PFS for CRPC patients and that an increase in CgA is also an independent predictor of worse PFS.

In 1984, O'Connor and Bernstein[28] first reported that CgA might be a potential biomarker of pheochromocytoma. Since then, many studies have assessed the clinical impact of CgA in various neuroendocrine tumors.[29,30] High serum CgA levels are relative to the NED of CRPC,[31] which indicates a poor prognostic factor for CRPC patients and may be associated with the increasing degree of differentiation and resistance to endocrine therapy. In general, NED is expressed in high-grade and advanced-stage prostate cancer, particularly after ADT.[31,32] Some studies indicated that CgA also had a prognostic value in patients treated with luteinizing hormone-releasing hormone (LHRH) analogs and chemotherapy.[14,32] In addition, the sensitivity and specificity of CgA are higher than those of neuron-specific enolase (NSE), because NSE is only located in the cytoplasm and only after NED cells death can NSE be released into the circulating system.[33,34] To date, CgA seems to be the most sensitive marker used to evaluate NED in the general population.[12,33,35,36] Elevated serum levels of CgA are said to be related to late-stage CRPC.[12] Sciarra *et al.*[37] reported an increase in circulating CgA levels in patients with metastatic prostate cancer after 24-month ADT. In addition, Berruti *et al.*[14] indicated that elevated CgA in CRPC was related to prognosis.

For any meta-analysis or systematic review, an exploration of the potential influencing factors of heterogeneity is necessary, especially when there is obvious heterogeneity. In our analysis, we found that there was significant heterogeneity for OS. Fan *et al.*[38] reported that chemotherapy rather than abiraterone acetate might be a better choice for CRPC patients with high CgA levels. We also divided the studies containing OS into two groups based on the therapy received. One group was treated with first-line hormonal therapy, and the other group was treated with second-line hormonal or chemotherapy. Then, we conducted subgroup analysis, and the outcomes showed no significant heterogeneity. According to the subgroup analysis outcomes, we believed that the elevation of CgA was correlated with shorter OS. Isshiki *et al.*[16] showed that CgA levels higher than 49 ng ml^{-1} were related to a shorter survival, and Berruti *et al.*[25] reported that a higher CgA indicated a shorter survival. In addition, Taplin *et al.*[24] showed that a CgA greater than 9.5 U l^{-1} was correlated with reduced OS. Prostate cancer with marked endocrine features is prone to be more invasive and poorly differentiated.[39,40] It is said that NED cells are differentiated from the common pluripotent stem cell population.[41] Stem cells play a vital role in CRPC and might contribute to hormonal therapy and chemotherapy resistance.[42,43] Some studies also found that neuroendocrine cells can produce a large number of regulatory peptides, which can modulate the exocrine prostate cells.[44,45] Several studies reported that a high serum CgA level was related to NED in prostate cancer and resistance to ADT.[16,22,23,46] We theorized that due to the absence of ARs, the AR-targeted therapies were ineffective, and the clinical outcome was influenced. In addition, Mazzucchelli *et al.*[47] reported that NED cells might stimulate neoangiogenesis, which could be related to the aggression of prostate cancer.

As for PFS, we found that both the high CgA level and increasing CgA indicated poor PFS. Von Hardenberg *et al.*[26] reported that an

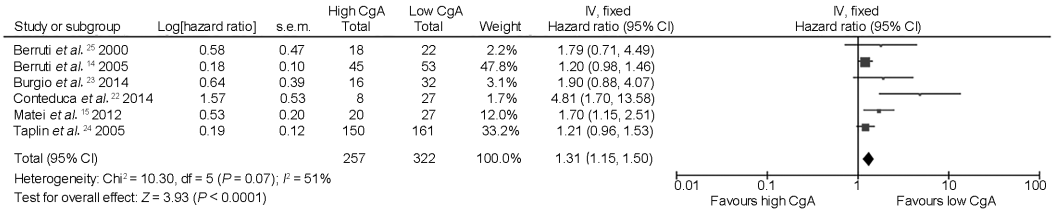

Figure 2: Forest plot comparing OS in patients with high CgA level versus those with low CgA level. OS: overall survival; CI: confidence interval; df: degree of freedom; CgA: chromogranin A; s.e.m.: standard error of the mean; IV: inverse variance methods.

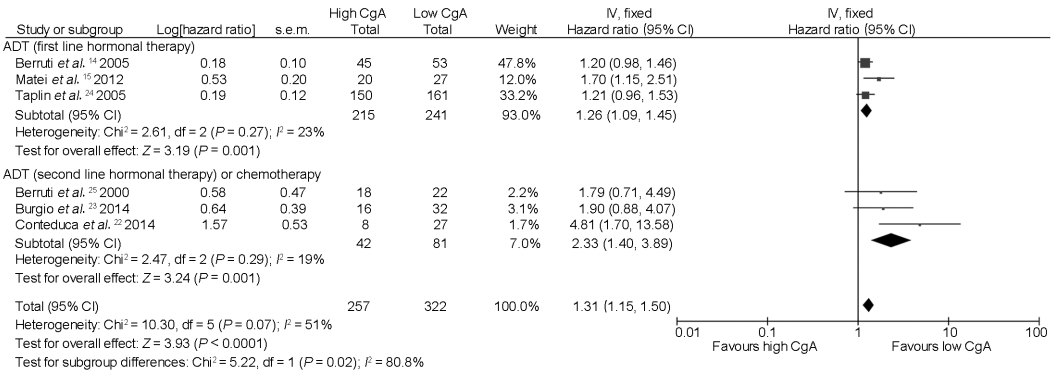

Figure 3: Forest plot comparing OS in patients with high CgA level versus those with low CgA level in different subgroups. OS: overall survival; CI: confidence interval; df: degree of freedom; CgA: chromogranin A; s.e.m.: standard error of the mean; IV: inverse variance methods.

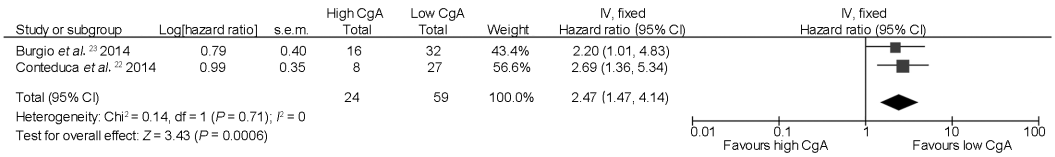

Figure 4: Forest plot comparing PFS survival in patients with high CgA level versus those with low CgA level. PFS: progression-free survival; CI: confidence interval; CgA: chromogranin A; df: degree of freedom; s.e.m.: standard error of the mean; IV: inverse variance methods.

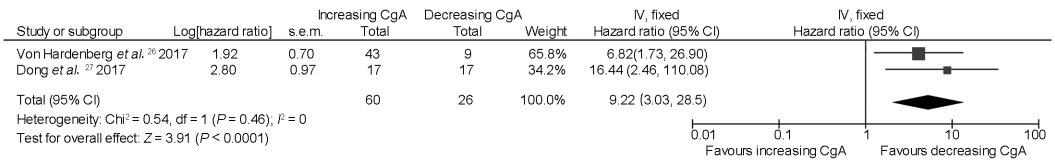

Figure 5: Forest plot comparing PFS according to CgA change. PFS: progression-free survival; CI: confidence interval; df: degree of freedom; CgA: chromogranin A; s.e.m.: standard error of the mean; IV: inverse variance methods.

early high CgA rise could predict the poor outcome of patients independently from PSA. The high increase may be due to expression of a subclone of small cell/neuroendocrine transformation for prostate cancer cells. Conteduca *et al.*[22] believed that high serum CgA levels were associated with shorter OS and shorter clinical PFS, according to the treatment outcome of 35 CRPC patients treated with enzalutamide. Burgio *et al.*[23] showed that high serum CgA levels might predict shorter clinical PFS and indicated a trend for shorter OS in CRPC patients treated with abiraterone. From these studies, we see that high CgA levels and increasing CgA indicated poor prognosis.

To the best of our knowledge, this is the first time that a comprehensive and standard meta-analysis has assessed the predictive role of CgA levels in CRPC. However, several limitations should be considered. First, the number of patients enrolled is not large. Second, among the eight studies, the cut-off values of CgA were different, which may cause bias. Third, there were only four studies that used PFS: two of them used CgA levels, and another included CgA change, which might accidentally increase the risk of random error. Thus, more research is needed to further verify our results. Fourth, studies reported that renal insufficiency and drugs that affect gastric acid secretion may have an effect on CgA levels.[48–52] However, not all the included studies presented the relative information, which may affect the quality of this article. We hope that follow-up studies on CgA pay more attention to these important factors. Fifth, despite the well-acknowledged advantages of meta-analysis, the outcomes were influenced by the quality of the selected studies and the reporting bias that papers with significant outcomes are published more frequently than those with null or nonsignificant results is unavoidable.[43] Finally, in our analysis, most of the included studies were performed on European populations, restricting the generalizability of the discovery.

Notwithstanding these limitations, we should remember that CgA could be widely available, and it is a simple, renewable, and low-cost biomarker. Thus, it may be implemented on a large scale in clinical practice.

CONCLUSIONS

In conclusion, notwithstanding the limitations of this meta-analysis, it seems that CgA has an impact on OS and PFS in CRPC patients. The CRPC patients with high CgA levels have worse OS and PFS. In addition, increasing levels of CgA also indicate worse PFS. These findings indicate that CgA is a good predictive and surveillance tool for CRPC. More large-scale and standardized investigations should be carried out.

AUTHOR CONTRIBUTIONS

PH reviewed articles, performed statistical analyses, made figures and tables, and drafted the manuscript. RQG checked articles, performed statistical analyses, revised figures and tables, and drafted the manuscript. GS performed statistical analysis. KWY helped with data collection and drafted the manuscript. LZ made figures and tables and helped to draft the manuscript. XSL conceived the study, had full access to all the data in the study, took responsibility for the integrity of the data and the accuracy of the data analysis, and revised the manuscript. KZ took part in critical revision and manuscript editing. LQZ conceived the study, helped to draft the manuscript, revised manuscript, and reviewed manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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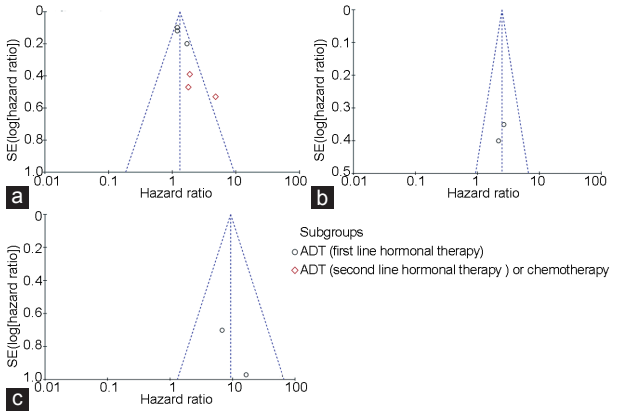

Supplementary Figure 1: Funnel plot for the assessment of potential publication bias: (**a**) OS with CgA level in subgroups; (**b**) PFS with CgA level; (**c**) PFS with CgA change. SE: standard error; ADT: androgen-deprivation therapy; OS: overall survival; CgA: chromogranin A; PFS: progression-free survival.