

RESEARCH ARTICLE

Prognostic Value of Tissue Vascular Endothelial Growth Factor Expression in Bladder Cancer: a Meta-analysis

Yu-Jing Huang, Wei-Xiang Qi, Ai-Na He, Yuan-Jue Sun, Zan Shen, Yang Yao*

Abstract

Objective: The prognostic role of vascular endothelial growth factor (VEGF) in bladder cancer remains controversial. This meta-analysis aimed to explore any association between overexpression and survival outcomes. **Methods:** We systematically searched for studies investigating the relationships between VEGF expression and outcome of bladder cancer patients. Study quality was assessed using the Newcastle-Ottawa Scale. After careful review, survival data were extracted from eligible studies. A meta-analysis was performed to generate combined hazard ratios (HRs) for overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS). **Results:** A total of 1,285 patients from 11 studies were included in the analysis. Our results showed that tissue VEGF overexpression in patients with bladder cancer was associated with poor prognosis in terms of OS (HR, 1.843; 95% CI, 1.231-2.759; $P = 0.003$), DFS (HR, 1.498; 95% CI, 1.255-1.787; $P = 0.000$) and DSS (HR, 1.562; 95% CI, 0.996-1.00; $P = 0.052$), though the difference for DSS was not statistically significant. In addition, there was no evidence of publication bias as suggested by Begg's and Egger's tests except for DFS (Begg's test, $P = 0.221$; Egger's test, $P = 0.018$). **Conclusion:** The present meta-analysis indicated elevated VEGF expression to be associated with a poor prognosis in patients with bladder cancer.

Keywords: Vascular endothelial growth factor - prognosis - bladder cancer - meta-analysis

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Introduction

Bladder cancer is the second most common malignancy of the urinary tract after prostate cancer, with approximately 390 000 new cases annually, and has the sixth highest cancer mortality (Jemal et al., 2011). Despite recent advances in screening and multimodality therapy, the outcome for bladder cancer remains generally poor, emphasizing the need for early detection and prognostic markers. Currently, the most widely studied prognostic factors are related to pathological characteristics of the neoplasm, including tumor size, grade, stage, and vascular invasion (Thieblemont et al., 1996; Kanda et al., 2006; Youssef et al., 2011; van Rhijn, 2012). However, a variety of other potential prognostic markers remain to be further characterized (Kanda et al., 2006).

Angiogenesis, defined as the formation of new blood vessels from existing vasculature, plays an important role in tumor growth and metastasis by providing oxygen, nutrients and growth factors to the cancer cells (Folkman, 1995). Vascular endothelial growth factor (VEGF), a homodimeric glycoprotein with a molecular weight of approximately 45 kDa, is considered to be one of the most important regulators in tumor angiogenesis (Ferrara, 2004). Furthermore, the invasiveness of some tumors

have recently been linked to high levels of VEGF, leading several authors to conclude that an important relationship between VEGF and prognosis exists for bladder cancer (Crew et al., 1997; Inoue et al., 2000; Bernardini et al., 2001; Theodoropoulos et al., 2004; Yang et al., 2004; Zu et al., 2006; Pignot et al., 2009; Shariat et al., 2010; Li et al., 2011). However, conflicting results were showed in other studies regarding the ability of VEGF to predict prognosis in bladder cancer (Suzuki et al., 2005; Nadaoka et al., 2008; Szarvas et al., 2008; Szarvas et al., 2009; Ma et al., 2010; Zaravinos et al., 2012).

Therefore, in this study, we sought to conduct a meta-analysis to estimate the prognostic importance of elevated VEGF expression for survival among patients with bladder cancer.

Materials and Methods

Search strategy

We searched Medline, PubMed, Embase, and the Web of Science using the search terms: ((VEGF or vascular endothelial growth factor) and (cancer or carcinoma) and 'bladder' and 'prognosis'). The last search was updated in November 2012. To expand our search, references of the retrieved articles were also screened for additional studies.

Department of Oncology, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China *For correspondence: yangyao12@yahoo.com

Table 1. Newcastle-Ottawa Quality Assessment Scale

Selection	
1. Representativeness of the exposed cohort	
a) Truly representative of the average 'bladder cancer patient' in the community (*)	
b) Somewhat representative of the average 'bladder cancer patient' in the community (*)	
c) Selected group of users (e.g. nurses, volunteers)	
d) No description of the derivation of the cohort	
2. Selection of the non exposed cohort	
a) Drawn from the same community as the exposed cohort (*)	
b) Drawn from a different source	
c) No description of the derivation of the non exposed cohort	
3. Ascertainment of exposure	
a) Secure record (e.g. surgical records) (*)	
b) Structured interview (*)	
c) Written self-report	
d) No description	
4. Demonstration that outcome of interest was not present at start of study	
a) Yes (*)	
b) No	
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	
a) Study controls for 'metastasis or micrometastasis' (*)	
b) Study controls for any additional factor (*)	
Outcome	
1. Assessment of outcome	
a) Independent blind assessment (*)	
b) Record linkage (*)	
c) Self-report	
d) No description	
2. Was follow-up long enough for outcomes to occur?	
a) Yes ('2 years') (*)	
b) No	
3. Adequacy of follow-up of cohorts	
a) Complete follow-up - all subjects accounted for (*)	
b) Subjects lost to follow-up unlikely to introduce bias -small number lost '25%' follow up, or description of those lost (*)	
c) Follow up rate < '75%' and no description of those lost	
d) No statement	

A study can be awarded a maximum of one star (*) for each numbered item in the Selection and Outcome categories. A maximum of two stars can be given in Comparability. Underlined and quoted phrases are provided in the scale to allow for adjustment to particular studies

Study selection

Two independent reviewers assessed the eligibility of studies. Abstracts of all candidate articles were read. Articles that could not be categorized based on title and abstract alone were retrieved for full-text review. These articles were independently read and checked for inclusion criteria. Disagreements were resolved through consensus with a third reviewer.

Primary studies that reported data required for meta-analysis were identified and included. Study inclusion/exclusion criteria for primary studies were as follows: (1) proven diagnosis of bladder cancer in humans, (2) VEGF evaluation using tissue-based methods, and (3) correlation of VEGF with overall survival (OS), disease-free survival (DFS) or disease-specific survival (DSS). There was no pre-specified sample size or follow-up period used to determine study inclusion. Only studies

written in English were included. Studies not directly reporting hazard ratios (HRs) were allowed if data were available for statistical estimation. When more than one of the same patient populations was included in several publications, only the most recent or complete study was used to avoid duplication of information.

Quality assessment

Quality assessment was performed in each of the acceptable studies by two reviewers independently using the Newcastle–Ottawa Quality Assessment Scale for cohort studies (Table 1) (Wells et al., 2003). This scale is an eight-item instrument that allows for assessment of patient population and selection, study comparability, follow-up, and outcome of interest. A star system of the NOS (range, 0–9 stars) has been developed for the evaluation. The highest value for quality assessment was 9 stars. Any discrepancies were resolved by a consensus reviewer.

Data extraction

Two investigators extracted data from eligible studies independently, discussed discrepancies and reached consensus for all items. The following information was extracted from each article: (1) basic information from papers, such as first author's name, year of publication; (2) information of study designation, such as study design; (3) demographic data such as inclusion criteria, patient age, sex, and treatment during follow-up; (4) tumor data such as VEGF expression in the primary site, stage, grade, vascular invasion, and metastases; (5) survival data such as OS, DFS and DSS; (6) variables such as number of patients analyzed, method of tissue VEGF measurement, cut-off values for VEGF levels, and geographical district of the patients. The primary data were the HRs and 95% confidence intervals (CI) for survival outcomes, including OS, DFS and DSS.

Statistical analysis

The primary outcome for analysis was survival in patients with high VEGF values as compared to those with low VEGF values. HRs with 95% CIs were reported for individual studies with HR>1 and 95% CI for the aggregated HR not crossing 1 designates a prognostic role of high VEGF. When HRs were not reported in an article, they were calculated to use established methods reported by Parmar et al. (1998).

Forrest plots were undertaken to evaluate the heterogeneity of combined HRs. Statistical assessment was performed using a χ^2 -based test of homogeneity and evaluation of the inconsistency index (I^2) statistic. Heterogeneity was defined as $p<0.10$ or $I^2>50\%$ (Higgins et al., 2003). When heterogeneity was judged between primary studies, a fixed effect model was used for pooled analyses. If not, a random effect model was used (DerSimonian et al., 1986). Egger's test was performed to test for publication bias (Egger et al., 1997).

Statistically significant test was determined by a P-value of less than 0.05 for a summary HR and publication bias. All analyses were carried out using STATA.

Table 2. Main Characteristics and Results of the Included Studies

Article & publication year	Study design	Country	Treatment	Number of patients (M/F)	Age(y) low/high	Tumor grade	Study subtype	VEGF detection method	Survival analysis	Hazard ratios	cut-off level	Number with high VEGF	Conclusion
Zaravinos et al. 2012	C	Greece	S	77(68/9)	72.12	NR	6 of 9	VEGF-A mRNA	OS, DSS	Estimated	Median	40	Negative
Li et al. 2011	R	China	S	93(82/11)	67	42/51	7 of 9	VEGF-C Antibody	OS, DSS	Estimated	50% staining	37	Positive
Pignot et al. 2009	R	France	S	84(67/17)	68	0/84	6 of 9	VEGF-A mRNA	OS, DFS	Report	mRNA value of 3	55	Positive
Herrmann et al. 2007	R	Germany	S	262(NR)	62	NR	5 of 9	VEGF-D Antibody	OS, DFS	Estimated	25% staining	98	Indeterminate
Yang et al. 2004	R	China	Multi-treatment	161(NR)	58	63/98	5 of 9	VEGF-C Antibody	OS	Estimated	10% staining	88	Positive
Theodoropoulos et al. 2004	R	Greece	Multi-treatment	93(71/22)	68	75/18	7 of 9	NR	OS, DFS	Estimated	Median	46	Positive
Zu et al. 2006	R	China	Multi-treatment	45(NR)	58	29/16	5 of 9	VEGF-C Antibody	DFS	Estimated	50% staining	26	Positive
Nadaoka et al. 2008	R	Japan	NR	72(NR)	66.46	122/97	4 of 9	NR	DSS, DFS	Reported	10% staining	44	Negative
Szarvas et al. 2008	R	Hungary	S	107(NR)	71.6	57/56	5 of 9	NR	DSS	Reported	Median	54	Negative
Suzuki et al. 2005	R	Japan	Multi-treatment	87(75/12)	66.6	33/54	5 of 9	VEGF-C Antibody	DSS	Reported	10% staining	36	Negative
Shariat et al. 2010	R	Canada	S	204(NR)	NR	NR	6 of 9	NR	DSS	Estimated	Median	175	Positive

Summary table of studies included in meta-analysis. Study design is described as case-controlled (C) or retrospective (R). Treatment describes whether the patients received curative surgical resection (S). Tumour grade was most often described using the WHO classification, but occasionally other systems were utilized. Study quality is listed using the results of the Newcastle–Ottawa questionnaire (Table 1); NR, not reported

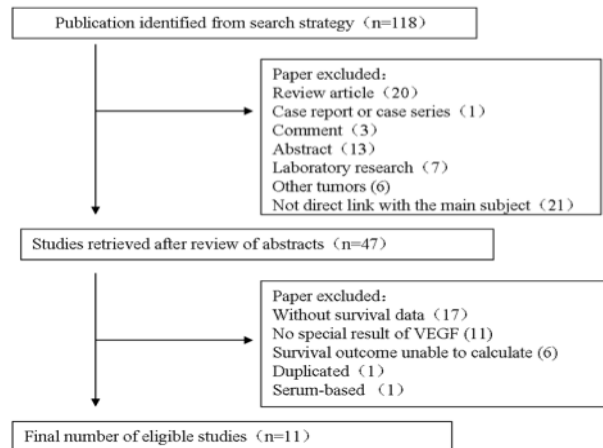


Figure 1. Flow Chart of the Meta-analysis

Results

Study identification and eligibility

An electronic search yielded 118 articles, of which 71 were excluded on the basis of their abstracts. We then screened the remaining 47 articles in full text. Upon further review, 17 articles were eliminated on the basis of without survival data, 11 articles were excluded because there is no special result of VEGF, and 6 articles were eliminated due to inadequate data for calculation. We also excluded a previous study with data overlap and a study investigating the association of serum VEGF level with survival. The selection process and reasons for exclusion have been summarized in Figure 1. From the 11 studies that were included (Bernardini et al., 2001; Theodoropoulos et al., 2004; Yang et al., 2004; Suzuki et al., 2005; Zu et al., 2006; Herrmann et al., 2007; Nadaoka et al., 2008; Szarvas et al., 2008; Pignot et al., 2009; Shariat et al., 2010; Li et al., 2011; Zaravinos et al., 2012), a total of 1285 patients were analyzed. The characteristics of the selected studies are presented in Table 2.

Quality assessment

Quality assessment using the Newcastle–Ottawa Scale was performed on all 11 studies included for meta-analysis. Of note, there was no study attempting to control for important prognostic factors that may have confounded the association of high VEGF with survival. The NOS scores of 1-3, 4-6 and 7-9 were defined as low, intermediate and high-quality studies, respectively. Our NOS results showed that the median overall score was 5

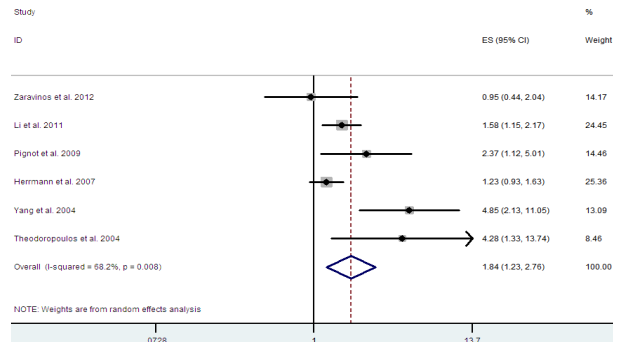


Figure 2. Random-effects Model of Hazard Ratio (95% confidence interval) of OS Associated with High VEGF Levels Versus Low Levels

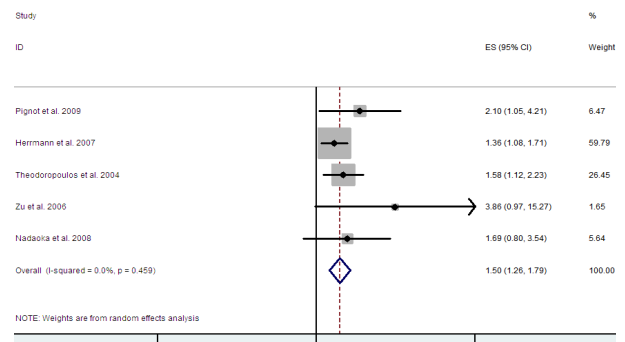


Figure 3. Fixed-effects Model of Hazard Ratio (95% confidence interval) of DFS Associated with High VEGF Levels Versus Low Levels

(range 4 to 7), which indicated that the quality of included trials was acceptable.

Overall survival

The pooled hazard ratio for OS showed that high VEGF level was significantly associated with OS (HR, 1.843; 95% CI, 1.231-2.759; $P = 0.003$; Figure 2). There was significant heterogeneity ($P = 0.008$, $I^2 = 68.2%$, $\chi^2 = 15.71$), and the pooled HR for OS was performed by using the random-effects model.

Disease-free survival

The pooled hazard ratio for PFS showed that high VEGF level was significantly associated with DFS (HR, 1.498; 95% CI, 1.255-1.787; $P = 0.000$; Figure 3). No significant heterogeneity was found ($P = 0.459$, $I^2 = 0.0%$, $\chi^2 = 3.63$), and the pooled HR for DFS was performed by using the fixed-effects model.

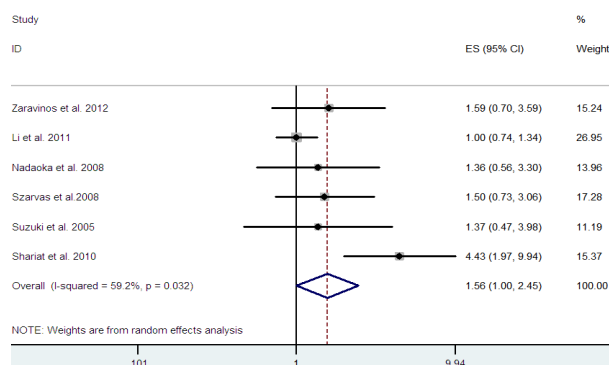


Figure 4. Random-effects Model of Hazard Ratio (95% confidence interval) of DSS Associated with High VEGF Levels Versus Low Levels

Disease-specific survival

The pooled hazard ratio didn't show significant difference in DFS between VEGF over expression group with VEGF low expression group (HR, 1.562; 95% CI, 0.996-1.00; $P = 0.052$; Figure 4). There was significant heterogeneity ($P = 0.032$, $I^2=59.2$, $\chi^2=12.24$), and the pooled HR for DFS was performed by using the random-effects model.

Publication bias

There was no evidence for significant publication bias in OS (Begg's test, $P = 0.133$; Egger test, $P = 0.149$) and DSS (Begg's test, $P = 1$; Egger test, $P = 0.140$) studies. However, according to DFS, Begg's test indicated no publication bias among these studies regarding risk ratio ($P = 0.221$), but Egger's test indicated a publication bias ($P = 0.018$).

Discussion

Inducing angiogenesis is one of the hallmarks of cancer (Hanahan et al., 2011), and VEGF, as one of the most important regulators in tumor angiogenesis (Ferrara, 2004), has been thought to be valuable of predicting poor outcome of survival in several cancers, such as lung cancer (Zhan et al., 2009), hepatocellular carcinoma (Schoenleber et al., 2009), gastric cancer (Chen et al., 2011), ovarian cancer (Yu et al., 2012), and osteosarcoma (Qu et al., 2012). However, the prognostic value of VEGF in bladder cancer was undetermined. Yang et al. (2004) and Theodoropoulos et al. (2004) both announce the association between VEGF over expression and poor outcome of patients with bladder cancer. Then several following studies supported their results (Zu et al., 2006; Pignot et al., 2009; Shariat et al., 2010; Li et al., 2011). However, several other studies demonstrated that the level of VEGF expression did not predict outcomes for patients with bladder cancer (Suzuki et al., 2005; Nadaoka et al., 2008; Szarvas et al., 2008; Zaravinos et al., 2012). As a result, the role of VEGF expression in bladder cancer is still not well defined.

Meta-analysis is useful to integrate results from independent studies for a specified outcome. Pooled results from the combining relevant studies are statistical powerful, and make it possible to detecting effects that may be missed by individual studies. This meta-analysis

presents combined results from 11 studies of 1285 patients and reveals that tissue VEGF over expression are associated with prognosis in terms of OS (HR, 1.843; 95% CI, 1.231-2.759; $P = 0.003$), DFS (HR, 1.498; 95% CI, 1.255-1.787; $P = 0.000$) and DSS (HR, 1.562; 95% CI, 0.996-1.00; $P = 0.052$), though the difference in DSS was not statistically significant. Additionally, significant heterogeneity was found in OS ($P = 0.008$, $I^2 = 68.2\%$, $\chi^2=15.71$) and DSS ($P = 0.032$, $I^2=59.2$, $\chi^2=12.24$), but not for DFS ($P = 0.459$, $I^2 = 0.0\%$, $\chi^2=3.63$). Thus, a random effect model was used in combining OS and DSS.

There were several potential sources of heterogeneity among the studies. First, Studies might differ in the characteristics of included patients (age, histological type, tumor grade, stage, tumor size, treatment received, and the duration of follow-up). Furthermore, in some studies, patients were excluded because of insufficient tissue source, insufficient clinical data or insufficient survival data. All of these could potentially lead to selection bias or recruitment bias. Second, language also induces a bias, as positive results tend to be published in English in international journals. Although our search was not restricted, all the studies included were written in English. Third, the differences of methodology and cut-off values among included studies also were sources of heterogeneity and caused selection biases potentially. The variability of IHC techniques, which we could not avoided, may prevent tissue VEGF measurements from standardization. Although four studies chose the median VEGF level as the cut-off value, values varied among studies obviously. Additionally, the heterogeneity in tissue samples cannot be ignored. Fourth, observers in some studies were not blinded to the outcome data, which contributed to information bias.

Publication bias is another problem that we should consider in the present meta-analysis. In order to minimize publication bias, we did the literature search as completely as possible, using PubMed and EMBASE databases, screening references of the retrieved articles, and looking over posters from the annual meetings of the European Society of Medical Oncology and the American Society of Medical Oncology. However, missing some data was unavoidable. In our study, we did not adopt abstracts because data were not available in abstracts. In addition, positive results have more tendencies to be accepted by journals, other than negative results. What's more, negative results are often not submitted for review by journals. Therefore, publication bias was still detected for DFS.

Several important limitations need to be considered when interpreting our analysis. First and important of all, significant heterogeneity between studies existed indeed. Second, this meta-analysis relied on published trials rather than individual patient data (IPD), and meta-analyses based on published data tend to overestimate the predictive effects of VEGF compared with individual patient data analyses. In addition, it precludes a more comprehensive analysis such as adjusting for baseline factors and other differences that existed between the trials from which the data were pooled. Third, original studies included in our analyses almost were retrospective studies (10/11) with 1

case-controlled study, providing a lower level of evidence. And furthermore, publication bias was detected even we expanded our search to the best of our ability. Finally, the small number of included patients negated the possibility of exploring possible sub-group analyses and explored heterogeneity among study populations.

In the conclusion, this meta-analysis for the first time demonstrated that high levels of VEGF are associated with a poor prognosis in patients with bladder cancer. However, one should be cautious when interrupting these results due to the limitations of our studies. Further high-quality studies are still needed to confirm these results.

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