Clinical and Prognostic Significance of HIF-1α, PTEN, CD44v6, and Survivin for Gastric Cancer: A Meta-Analysis

Jing Chen1,2,*, Tao Li3, Qilun Liu3, Haiyan Jiao1,2, Wenjun Yang1,2, Xiaoxia Liu1,2, Zhenghao Huo1,2,6
1 Department of Medical Genetic and Cell Biology, Ningxia Medical University, Yinchuan, China, 2 Key Laboratory of Fertility Preservation and Maintenance (Ningxia Medical University), Ministry of Education, Yinchuan, China, 3 Department of Oncology, General Hospital of the Ningxia Medical University, Yinchuan, China

Abstract

Purpose: This study was to quantitatively summarize published data for evaluating the clinical and prognostic significance of four proteins involved in hypoxia-inducible factor-1 (HIF-1α) regulation of the metastasis cascade.

Methods: Searches were performed using the MEDLINE, EMBASE, Cochrane Library, and Chinese Biomedicine databases without any language restrictions. Studies were pooled and either the summary risk ratio (RR) or odds ratio (OR) was calculated. Potential sources of heterogeneity were sought out via subgroup and sensitivity analyses, and publication bias was also performed.

Results: Seventeen studies evaluated HIF-1α, 20 studies evaluated phosphatase and tensin homolog (PTEN), 20 studies evaluated Survivin, and 16 studies evaluated CD44v6. Our results showed that increased HIF-1α expression was linked to a poor 5-year overall survival (RR = 1.508; 95% confidence interval (CI) 1.318–1.725; P < 0.001). Decreased survival was heavily influenced by advanced tumor invasion (OR = 3.050; 95% CI 2.067–4.501; P < 0.001), lymph node metastasis (1415 patients; OR = 3.486, 95% CI 2.737–4.440; P < 0.001), distant metastasis (OR = 6.635; 95% CI 1.855–23.738; P = 0.004), vascular invasion (OR = 2.368; 95% CI 1.725–3.252; P < 0.001), and dermotenesis (OR = 2.112; 95% CI 1.410–3.163; P < 0.001), tumor size (OR = 1.921; 95% CI 1.395–2.647; P < 0.001), and a higher TNM stage (OR = 2.762; 95% CI 1.941–3.942; P < 0.001). Similarly, aberrant expression of PTEN, CD44v6, and Survivin were also observed in tumors that correlated with poor OS. The higher ORs of death at 5 years were 1.637 (95% CI = 1.452–1.845; P < 0.001), 1.901 (95% CI = 1.432–2.525; P < 0.001), and 1.627 (95% CI = 1.384–1.913; P < 0.001), respectively, with an OR = 2 for the main stratified meta-analyses of clinical factors.

Conclusions: Our findings indicate that HIF-1α/PTEN/CD44v6/Survivin, as measured by immunohistochemistry, can be used to predict the prognosis and potential for invasion and metastasis in Asian patients with gastric cancer. The development of strategies against this subset of proteins could lead to new therapeutic approaches.

Introduction

Gastric cancer is one of the most aggressive tumors and tends to be associated with peritoneal dissemination, lymph node metastasis, and hematogenous metastasis. Although recent advances in its diagnosis and treatment have offered increased long-term survival for patients diagnosed at early stages of gastric cancer, the prognosis of advanced cancer remains dismal, with a 5-year survival rate of only 10–15% [1,2]. A majority of patients with advanced disease die due to complications induced by metastasis but not the primary tumor [3]. Recently, a series of rate-limiting steps have been proposed for tumor cells to become metastatic [4]. The multi-step processes consist of loss of cellular adhesion, local invasion, motility, angiogenesis, intravasation, circulation, extravasation, homing, and the premetastatic niche, and organotropism colonization in specific organs [5]. Therefore, identifying novel markers in the key steps of metastasis will help to predict recurrence and survival for patients in the early stages of gastric cancer.

Hypoxia has been reported to contribute directly to many critical aspects of cancer biology, including angiogenesis, epithelial-mesenchymal transition, invasion, metastasis, stem cell maintenance, energy metabolism, autocrine growth factor signaling, and refractory to targeted therapies [6,7]. The best characterized hypoxia response pathway is mainly mediated through a transcription factor called hypoxia-inducible factor-1 (HIF-1α) [8]. Currently, the number of target genes, which are controlled by HIF-1α, is greater than 1000 and can be divided into the following five categories: transcription factors and histone modifiers; matrix degradation enzymes; receptor, receptor-associated kinases, and transporters; microRNA targets; and cell-adhesion molecules and membrane proteins [9,10]. In addition, routine phase 1 and phase