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Original article

Clinicopathological significance and prognostic role of microvessel density in gastric cancer: A meta-analysis

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ABSTRACT

Objective: The aim of this study was to elucidate the clinicopathological significance and prognostic role of microvessel density (MVD) in gastric cancer (GC) through a meta-analysis.
Methods: This meta-analysis included 4094 patients from 26 eligible studies. We investigated the correlation between MVD and clinicopathological characteristics, including survival rate. In addition, subgroup analysis based on microscopic magnification among evaluation criteria of MVD was performed.
Results: High MVD was significantly correlated with worse overall and disease-free survival rates [hazard ratio (HR), 3.028, 95% confidence interval (CI) 2.105–4.357 and HR 2.045, 95% CI 1.530–2.732, respectively]. MVD was significantly increased in GC with diffuse type of Lauren's classification [mean difference (MD) 3.091, 95% CI 0.615–5.567], lymphatic invasion (MD 8.262, 95% CI 3.310–13.214), lymph node metastasis (MD 5.730, 95% CI 2.444–9.016), higher pT stage (pT3-4) (MD 7.093, 95% CI 0.060–14.126) and higher pTNM stage (III–IV) (MD 3.023, 95% CI 0.181–5.865). However, MD of MVD was not significantly different in regard to vascular invasion (MD 7.430, 95% CI 1.015–15.875), tumor differentiation (MD 5.501, 95% CI 1.353–12.355) and tumor size (MD 4.731, 95% CI 2.003–11.465).
Conclusion: Taken together, higher MVD was significantly correlated with worse prognosis. In addition, MVD was significantly higher in GC with aggressive tumor behavior than in GC without aggressive features.

1. Introduction

The prevalence of gastric cancer (GC) is the fifth highest in the world [1]. Recently, the age-standardized incidence and mortality rates of GC have been decreased [2]. In malignant tumor, angiogenesis is related to tumor proliferation and metastasis [3]. Proangiogenic factors, which cause unregulated neovascularization, are produced by GC cells and are involved in tumor growth and metastasis [3,4]. As a result, the estimation of angiogenesis within tumor can be used as a prognostic factor in GC. In malignant tumors, angiogenesis can be investigated through measurement of microvessel density (MVD) or microvessel area, or through quantification of angiogenic molecules or angiogenic receptors in tumor tissues [5]. MVD is related with vascular endothelial growth factor (VEGF), which is an important factor in angiogenesis of GC [3]. MVD represents the degree of angiogenesis and is representatively measured by counting microvessels within a tumor. To detect the microvessels, immunohistochemical (IHC) detection of endothelial markers is necessary. Various antibodies for detecting endothelial cells, such as CD31, CD34, factor VIII, and endocan, have been used in the previous reports [3,6–30]. However, the evaluation criteria for angiogenesis within tumors have not yet been established.

This study aimed the elucidation of the clinicopathological significance and prognostic role of MVD in GC through a meta-analysis. In addition, to define the optimal criteria of the evaluation of MVD in GC, subgroup analysis based on microscopic magnification was performed.

2. Material and methods

2.1. Published studies search and selection criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through August 15, 2017. These databases were searched using the following key words: 'gastric cancer' and 'microvessel density'. The titles and abstracts of all searched articles were screened for exclusion. Review articles were also screened to find additional eligible studies. Articles were included if the study was performed in human GCs and if there was information about the correlation between MVD and clinicopathological characteristics and survival

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rate. Articles were excluded if they were case reports or non-original articles; or if the article was not written in English.

2.2. Data extraction

Data from all eligible studies were extracted by two independent authors. The included data were extracted from each of the eligible studies [3,6–30]: the first author's name, year of publication, study location, number of patients analyzed, and information for the correlations between MVD and clinicopathological characteristics or between high MVD and survival rate. For quantitative aggregation of survival results, the correlation between high MVD and survival rate was analyzed according to the hazard ratio (HR) using one of three methods. In studies not quoting the HR or its confidence interval (CI), these variables were calculated from the presented data using the HR point estimate, log-rank statistic or its *P*-value, and the O-E statistic (difference between the number of observed and expected events) or its variance. If those data were unavailable, HR was estimated using the total number of events, number of patients at risk in each group, and the log-rank statistic or its *P*-value. Finally, if the only useful data were in the form of graphical representations of survival distributions, survival rates were extracted at specified times to reconstruct the HR estimate and its variance under the assumption that patients were censored at a constant rate during the time intervals [31]. The published survival curves were read independently by two authors in order to reduce reading variability. The HRs were then combined into an overall HR using Peto's method [32].

2.3. Statistical analyses

To perform the meta-analysis, all data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, USA). We investigated the correlation between high MVD and survival rate of GC. In addition, according to clinicopathological characteristics and evaluation criteria, a meta-analysis for mean difference (MD) of MVD was performed. Heterogeneity between the studies was checked by the Q and I^2 statistics and expressed as *P*-values. Additionally, sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. In the current meta-analysis, because eligible studies used various diagnostic criteria and population, the application of random-effect model rather than fixed-effect model was more suitable. For the assessment of publication bias, Begg's funnel plot and Egger's test were primarily used. The results were considered statistically significant at $P < 0.05$.

3. Results

The current meta-analysis primarily included 337 reports from the database search. Among them, 269 studies were excluded due to insufficient or no information. Other studies were excluded because they involved other diseases (n = 23), used non-English language (n = 43) and animals or cell lines (n = 79), and were non-original articles (n = 6). In addition, one study was excluded due to duplication of the population. Finally, 26 studies were included in this meta-analysis (Fig. 1 and Table 1). The present study included 4094 GC patients from the eligible studies.

To elucidate the prognostic role of MVD, a meta-analysis was performed, investigating the correlation between high MVD and survival rate. High MVD was significantly correlated with worse overall and disease-free survival rates (HR 3.028, 95% CI 2.105–4.357 and HR 2.045, 95% CI 1.530–2.732, respectively Fig. 2). Next, the correlation between MVD and clinicopathological parameters was investigated. The MVD was significantly higher in diffuse type than in intestinal type of Lauren's classification (MD 3.091, 95% CI 0.615–5.567; Table 2). The values of MVD in GCs with lymphatic invasion and lymph node metastasis were significantly higher than those in tumors without lymphatic invasion (MD 8.262, 95% CI 3.310–13.214) and lymph node metastasis (MD 5.730, 95% CI 2.444–9.016). In addition, high pT stage (pT3 and pT4) was significantly correlated with high MVD (MD 7.093, 95% CI 0.060–14.126). The MVD of tumor with pTNM stage III and IV was significantly higher than that of tumor with pTNM stage I and II (MD 3.023, 95% CI 0.181–5.865). There was no significant mean difference of MVDs between tumors with vascular invasion and those without (MD 7.430, 95% CI 1.015–15.875). The mean difference of MVDs was not significantly differed between poorly differentiated and well- and moderately differentiated subgroups (MD 5.501, 95% CI 1.353–12.355). Between GCs with large and small tumor size, there was no significant difference of MVD (MD 4.731, 95% CI 2.003–11.465).

4. Discussion

In malignant tumors, the angiogenesis is an important factor during progression of tumor and is associated with prognosis [3–5]. The evaluation for MVD using IHC can be useful for determining angiogenesis degree and prognosis of GC. However, it is controversial whether high MVD is significantly correlated with aggressive behaviors and worse prognosis [3,6,7,13,14,16,20,22,25,26,28,29]. The present study is the first, to the best of our knowledge, meta-analysis of the clinicopathological significance and prognostic role of MVD in GC.

In GCs, many reports have suggested that high MVD was significantly correlated with reduced survival of GC patients [3,6–30]. However, some studies have reported no significant correlation between high MVD and worse prognosis in GCs. In addition, the detailed information about the correlation between high MVD and clinicopathological parameters. In the current study, the mean differences of MVDs were evaluated between MVD and clinicopathological parameters, including survival. There were significant differences of MVDs in comparisons of lymphatic invasion, lymph node metastasis, depth of tumor, and pTNM stage. Therefore, our data supported that MVD was significantly correlated with aggressive tumor behaviors. In addition, high MVD and worse survival showed positive correlation. However, between GCs with large and small tumor size, there was no significant difference of MVD. In early GC (EGC) with mucosa or submucosa invasion, the value of MVD was significantly lower than in advanced GC. However, Cabuk et al. reported that the value of MVD was significantly higher in the low stage than in the high stage of GC [33]. The debated results might be caused by different evaluation criteria or different immunohistochemical methods. Eligible studies used the various evaluation methods and criteria for the measurement of MVD in GC. Factors affecting the MVD assessment include microscopic magnification, the number of the evaluated fields, and the method of estimation. Individual study can be insufficient to reach a conclusion of the clinicopathological significance of MVD from different methods. Therefore, this meta-analysis can be useful for understanding these matters.

The measurement of MVD is basically conducted by counting microvessels within tumor through several microscopic fields. Therefore, the value of MVD might be mainly affected by microscopic magnification. At first, the measurement of MVD has been introduced at the ×200 magnification [34]. However, other studies have reported results measured by the mean value of several ×400 magnification fields. Variable methods result in discordant MVD values between microscopic magnifications. The reason for these results may be the more concentrated hot spot in higher magnification. Hot spot is represented by the most abundant vascularization in the tumor. Even in the hot spot, vascular structures can be unevenly distributed. Therefore, higher microscopic magnification can focus on more central vascularized area, compared to lower microscopic magnification. The microscopic magnification ×200 was widely used in the evaluation of MVD. In the present study, among variables, subgroup analysis based on microscopic magnification was performed. There were controversial results in some clinicopathological parameters. Between microscopic