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Microvessel Density in patients with Gastrointestinal Stromal Tumors: a systematic review and meta-analysis

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Abstract

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are considered the most common mesenchymal tumors of the gastrointestinal (GI) tract. Microvessel density (MVD) constitutes a direct method of vascularity quantification and has been associated with survival rates in multiple malignancies.

AIM

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To appraise the effect of microvessel density (MVD) on the survival of patients with GIST.

METHODS

This study adhered to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. Electronic scholar databases and grey literature repositories were systematically screened. The Fixed Effects or Random Effects models were used according to the Cochran Q test.

RESULTS

In total, 6 eligible studies were identified. The Pooled Hazard Ratio (HR) for disease free survival (DFS) was 8.52 (95%CI: 1.69-42.84, $P = 0.009$). The odds ratios of disease-free survival between high and low MVD groups at 12 and 60 mo did not reach statistical significance. Significant superiority of the low MVD group in terms of DFS was documented at 36 and 120 mo (OR: 8.46 $p < 0.0001$ and OR: 22.71 $P = 0.0003$, respectively) as well as at metastases rate (OR: 0.11 $P = 0.0003$).

CONCLUSION

MVD significantly correlates with the HR of DFS and OS rates at 36 and 120 mo. Further prospective studies of higher methodological quality are required.

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal (GI) tract. According to existing literature, the average GIST incidence is estimated at 10 to 15 cases per million, ranging from 4.3 to 22/1,000,000 between different geographical locations^[1,2]. Furthermore, although the age of reported cases spans from 10 to 100 years, the median GIST presentation appears during the mid-60 years of age, with no discrepancies in terms of gender allocation^[1,2].

Based on recent studies, the origin of these tumours can be traced to the interstitial cell of Cajal, a myenteric plexus pacemaker^[2-4]. The most frequent GIST locations are the stomach (55.6%), small (31.8%) and large intestine (6%). Further primary sites include the oesophagus, the omentum, the mesentery and the retroperitoneum^[1-2,5]. Regarding morphological characteristics, GISTs are classified in spindle cell, epithelioid cell and mixed type histological subgroups^[6].

The majority of GISTs have been found to express KIT, a proto-oncogene protein^[7]. Specifically, KIT or c-kit is positive through immunohistochemical staining in almost 95% of all GISTs^[6], while KIT-negative GISTs have been demonstrated to harbour mutations of platelet-derived growth factor receptor-alpha (PDGFRA)^[6,8-9]. Alteration of the function of these receptor tyrosine kinases (RTKs) is considered of major importance

in the GIST oncogenesis, through the RAS-RAF-MAPK and PI3K-AKT-mTOR pathways^[6]. Surgical excision is considered the gold standard treatment for GISTs. However, kinase inhibitor adjuvant therapy (i.e. imatinib and sunitinib) has been introduced for treatment of advanced and metastatic disease^[10–15], improving the overall survival (OS) and time to progression (TTP) rates. Despite this, treatment resistance and disease recurrence rates still remain a significant problem ^[11,13].

To prognose the therapy outcomes, various risk grading systems have emerged, including those proposed by Fletcher *et al*^[16] and Miettinen *et al*^[17]. Several clinical and histopathologic factors been investigated such as tumor size, mitotic activity, anatomical origin, tumor rupture, tumor mutation type, predominant cell type, cellular density, p53, Ki-67, neutrophil to lymphocyte ratio (NLR) and blood vessel invasion^[6,11,13,18–20].

Microvessel density (MVD) assessment technique, based on the original work of Weidner *et al*,^[21] constitutes a direct method of vascularity quantification, since it represents the number of small blood vessels in tumoral tissue. Estimation of the vasculature is achieved through the application of various immunohistochemical endothelium labelling stains, such as cluster of differentiation (CD) 31, CD34, CD105 and von Willebrand Factor (vWF). The correlation between tumoral MVD and overall survival outcome in GIST patients has been extensively researched^[8–9,22–25]. However, to the best of our knowledge, there is still no study assessing overall prognostic value of MVD in these neoplasms.

Considering the above, a systematic literature review and meta-analysis of the reported outcomes was designed to estimate the pooled effect of tumor vascularity on survival of GIST patients, based on MVD measurements.

MATERIALS AND METHODS

Study protocol

The present meta-analysis was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions and PRISMA guidelines^[26]. The study was not registered in current electronic databases.

Primary endpoint

The primary endpoint of the present meta-analysis was considered the Hazard Ratio (HR) of Disease-Free Survival (DFS) between low and high MVD measurements in patients suffering from GISTS. Pooled $HR > 1$ denoted a higher risk of death in patients with high MVD, compared to patients with low MVD.

Secondary endpoints

The secondary endpoints included pooled Odds Ratios (ORs) of DFS between high and low MVD measurements, at four specific time points (12, 36, 60 and 120 mo) of follow-up. Moreover, the pooled OR between high and low MVD tumours of the presence of metastases in GIST patients was estimated. A pooled $OR > 1$ suggested superiority of low MVD tumours when compared to respective high MVD tumours, in terms of survival endpoints. On the contrary, concerning the metastases endpoint the opposite applied.

Eligibility criteria

Eligible studies were prospective or retrospective trials with a study population consisting of GIST patients, whose outcomes of interest were reported in English and were retrievable. Specifically, the study design must have incorporated a primary tumor MVD assessment.

Exclusion criteria consisted of studies written in a language other than English, with no endpoint of interest, insufficient survival data and no human studies. Furthermore, studies in the format of a letter, conference abstract, expert opinion or duplicate trials were not incorporated in the meta-analysis.

Literature search

A systematic literature search in electronic scholar databases (Medline, CENTRAL, Scopus and Web of Science) and grey literature repositories (OpenGrey.eu and medRxiv) was performed to identify eligible studies. The last search date was

December 2022. The literature search included the following search keywords: 'gist', 'gastrointestinal stromal tumor', 'stromal tumor', 'mvd', 'microvessel density' and 'microvascular density'.

Study selection and data collection

The first step of screening included removing duplicate entries. Subsequently, titles and abstracts of the remaining studies were assessed based on the inclusion criteria. A full text review of accepted entries was then performed, to validate consistency with the eligibility criteria. The electronic database screening, study selection, data extraction as well as methodological and quality assessment were performed in duplicate and blindly by two independent investigators (K.P. and P.K.). To reach consensus, disagreements were resolved by mutual revision and discussion. If discrepancies were not resolved, the opinion of a third investigator (K.D) was considered.

The Newcastle-Ottawa Scale (NOS)^[27] was utilized to perform rigorous quality and methodological evaluation of eligible studies. NOS evaluates non-RCT trials in certain endpoints, such as selection and comparability of study groups and confirmation of the exposure. Each included study was rated with a score ranging from 0 to 9. Cohen's κ statistic was also calculated.

Statistical analysis

Data analysis and statistical computations were performed using Cochrane Collaboration RevMan version 5.3 and IBM SPSS version 23. The primary and secondary endpoints were reported in the form of HR and OR, respectively. Results of the analyses were presented with the corresponding 95% Confidence Interval (95%CI).

If eligible trials did not directly provide the HR or OR in the article results, they were estimated based on the algorithm proposed by Parmar *et al*^[28] and Tierney *et al*^[29]. Specifically, required data for the meta-analysis of trials endpoints were reconstructed from the Kaplan-Meier (KM) curves provided^[30]. The precision of extracted coordinates was enhanced through utilization of a digitizing software (Digitizelt)^[31].

If included trials did not provide the mean and Standard Deviation (SD) of continuous variables, they were estimated from the median and the Interquartile Range

(IR) based on the algorithm described by Hozo *et al*^[32]. Given a sample size of >25, the mean was considered equal to the median. For a sample of <70, the SD was regarded as IR/4. In the other case, the SD was calculated as IR/6.

The statistical method applied was Mantel-Haenszel (MH) and the Inverse Variance (IV) for OR and HR, respectively. Both the Fixed Effects (FE) and Random Effects (RE) model were calculated. The final model that was estimated was based on the Cochran Q test. If statistically significant heterogeneity was present (Q test $P < 0.1$), then the RE model was applied. A further quantification of the heterogeneity was performed through the calculation of I². Statistical significance was considered at the level of $p < 0.05$.

Risk of bias across studies

To estimate the publication bias of included studies, the funnel plot of the primary outcome was visually inspected. Regarding the primary outcome, Egger's test was also performed.

RESULTS

Study selection

Through the above-mentioned search algorithm (Figure 1), 994 citations were retrieved (Medline: 412, Web of Science: 526, Scopus: 31, CENTRAL: 1, OpenGrey.eu: 15, medRxiv: 9). The next step included the removal of 340 duplicate records. A total of 654 records underwent title and abstract screening, resulting in the exclusion of 631 entries (17 reviews/ meta-analyses, 2 conference abstracts, 4 paediatric studies, 608 irrelevant records). Examination of compliance with eligibility criteria extended to the full text articles of the previously accepted records. In total, 5 studies with inadequate survival data and 12 irrelevant studies were excluded. Subsequently, 6 studies^[8-9,22-25] were included in the present meta-analysis.

Study characteristics

Table 1 summarizes the characteristics of included studies. Regarding study type, all trials had a retrospective design. Furthermore, all except one trial^[9] were single centre,

with sample size ranging from 53 to 124. More specific information regarding the analysis and total specimen sample are reported in Table 1. Mean patient age and gender allocation are also displayed in Table 1. Mean follow-up period extended from 2.5 years in the study by Waengertner *et al*^[24], up to 81.7 mo in the study by Takahashi *et al*^[23].

Concerning the MVD assessment method that was applied, the majority of included trials described the use of light microscopy and immunochemistry, implementing the technique proposed by Weidner *et al*^[21] (Table 2). Exceptions to this were trials by Imamura *et al*^[8] and Waengertner *et al*^[24] which reported the application of a modified Horak technique and Chalkley method, respectively. Despite the fact that the majority of eligible trials used CD31 antibodies, Zhao *et al*^[25] utilized the CD34 antibody. Heterogeneity was identified in the reported level of magnification. More specifically, the applied magnification spanned from 40X up to 400X. Furthermore, non-uniformity was discovered in the number of spots examined, which ranged from 3 to 10 spots. Only two trials^[8-9] confirmed blinded estimation of microvessel density by two independent observers, and none provided information about the existence of separate count for intratumoral and peritumoral vessels. All researchers except Zhao *et al*^[25] included the MVD cut-off value in their study articles.

Table 3 summarizes the data regarding the risk classification of included tumours. Moreover, the localization of GISTs included: 9 in the oesophagus, 284 in the stomach, 127 in the small intestine and 28 in the anatomic area of the colon and rectum. According to Table 4, only the study group of Chen *et al* recorded tumor complications like necrosis (37%) and haemorrhage (72.6%). Table 4 incorporates histopathologic characteristics, such as the mitotic count and the tumor size of included GISTs. From the eligible trials, tumor cell type categorization was performed in only 3^[8,24-25] studies. In total, 29 epithelioid, 222 spindle and 25 mixed tumours were identified. Finally, inconsistent data were provided by the included trials in terms of the operation performed and chemotherapy type administered.

Risk of bias within studies

Regarding the assessment based on the NOS scale, most studies achieved a 5-star score. The trial by Chen *et al*^[22] was an exception, as it appointed a 6 star score. Inter-rater agreement was estimated to be in a very good level (Cohen's k statistic: 86.8%, $p < 0.001$)

Primary endpoint

Data regarding the HR of DFS were extracted from 4 studies (Figure 2). Meta-analysis of these data showed a statistically significant ($P = 0.009$) hazard ratio of DFS (HR: 8.52, 95%CI: 1.69-42.84), in favour of the low MVD group. Since heterogeneity was significant (Q test $p < 0.001$, $I^2 = 90\%$), a RE model was applied.

Due to the high heterogeneity level, further statistical investigation was performed. The first step included a sensitivity analysis for the effect of each study separately. The overall heterogeneity level was not affected by any study. Meta-regression (Supplementary Material Tables) for the variables sample size, age and follow-up duration did not identify any statistically significant factor. Subgroup analysis regarding the number of study centres and the antibody used were identical to the above-mentioned sensitivity analysis. Analysis of studies implementing the Weidner MVD assessment method showed a statistically significant hazard ratio. Similarly, exclusion of the two studies which did not report blinded MVD evaluation did not influence heterogeneity. Further explanatory analyses (Supplementary Material Tables) included meta-regression of the primary outcome with the number of spots examined, the percentage of high-risk tumours, gastric and small intestine tumours, large size tumours (≥ 5 cm) and spindle cell malignancies. A significant correlation was not confirmed with any of the previously mentioned variables.

Secondary endpoints

In total, 3 studies provided data concerning the comparison between high and low MVD groups for DFS at 12 mo (Figure 3). Meta-analysis of these data showed no statistically significant difference ($P = 0.13$) of DFS (OR: 1.91, 95%CI: 0.83-4.41) at 12 mo between the two study groups. However, a statistically significant difference ($p < 0.001$) of DFS (OR: 8.46, 95%CI: 3.54-20.19) in favour of the low MVD group was estimated at

36 mo. Although there was no difference ($P = 0.58$) of DFS rates (Figure 4) at 60 mo (OR: 2.31, 95%CI: 0.12-44.82), the low MVD group displayed a higher ($P = 0.0003$) DFS rate (Figure 3) at 120 mo (OR: 22.71, 95%CI: 4.11-125.57).

Finally, two studies provided data concerning the development of metastases (Figure 3). Meta-analysis of these data showed a statistically significant ($P = 0.0003$) lower ratio of metastases (OR: 0.11, 95%CI: 0.03-0.36) in the low MVD group. Heterogeneity was not significant in this analysis (Q test $P = 0.29$, $I^2 = 10$).

Risk of bias across studies

Visual inspection of the funnel plot suggested that studies by Wang *et al*^[8] and Waengertner *et al*^[23] lie beyond the 95%CI limits. Based on Egger's test, there was no statistically significant publication bias ($P = 0.517$). Exclusion of the above-mentioned trials resulted in a statistically significant HR (7.71 95%CI: 4.02-14.8, $p < 0.001$) in favour of the low MVD group, though with a limited degree of heterogeneity (Q test $P = 0.64$, $I^2 = 0\%$).

DISCUSSION

Since GISTs are the most frequently occurring parenchymal neoplasms of the GI tract, research is focused on improving prognosis, introducing novel chemotherapeutic agents and refining current surgical approaches^[11-15,33]. Since a few decades ago conventional chemotherapy and radiotherapy did not yield satisfactory results, a R0 resection of the tumor was considered the only therapeutic option for adequate long-term survival^[33]. The discovery of the c-kit proto-oncogene mutation and ligand independent activation of the KIT receptor tyrosine kinase in GISTs, resulted in subsequent development of the tyrosine kinase inhibitors imatinib and sunitinib. This led to the onset of targeted molecular therapy of these neoplasms^[11,13,33]. In a cohort study by Guller *et al*^[34], the Surveillance, Epidemiology and End Results database was screened, with 5,138 GIST patients included. Data analysis revealed that recent advancements in treatment resulted in a significant increase in survival rates of both

metastatic (3-year OS: 54.7%, cancer-specific survival: 61.9%) and non-metastatic disease (3-year OS: 88.6%, cancer-specific survival: 92.2%)[34].

It must be noted that despite the above-mentioned novelties, the mortality rate – particularly for the metastatic group – remains high. As a result, various risk grading tools have been developed to quantify the risk and provide accurate prognosis regarding survival endpoints. The study group of Fletcher *et al* proposed the use of primary tumor size and mitotic count as grading parameters, which classified GISTs in four successive categories based on risk of aggressive behaviour^[16]. Due to a discrepancy in the metastatic risk between gastric and intestinal GISTs of different grading scores, the primary tumor location was also incorporated ^[17]. Exporting data from the SSG XVIII trial and using the Z9001 study as a validation tool, Joensuu *et al* suggested that high tumor mitotic count, non-gastric location, large size and tumor rupture were significantly and independently related to a suboptimal recurrence-free survival (RFS)^[18].

Besides these grading tools, various independent tumor histopathological factors have been studied for their prognostic value. Specifically, GISTs with an epithelioid or mixed cell type have been associated with a significantly lower 5-year recurrence free survival, when compared with the respective spindle cell tumours (23% *vs* 49%)[35]. Moreover, according to Martin *et al*, high tumor cellularity was characterized as a significant poor RFS prognostic factor^[36]. Overexpression of Ki67, a nuclear marker abundant in proliferating cells, was found to have an increased incidence in the high risk group^[19]. On the contrary, expression levels of p53 in GISTs were not significantly associated with clinical outcomes^[37-38]. A pooled analysis from Luo *et al* showed that an elevated neutrophil to lymphocyte ratio was associated ¹⁴ with decreased DFS/RFS (HR: 2.18, 95% CI: 1.30-3.67) ^[20]. Furthermore, blood vessel invasion in the primary tumor was suggested as a predictor of liver metastasis and an aggressive behaviour ^[39].

Angiogenesis in GISTs is considered of the utmost importance for the neoplasm growth and metastasis process^[8]. Proliferation of tumor vasculature is achieved *via* the paracrine release of angiogenic molecules and growth factors from tumor and stromal

cells^[8]. In a recent study by Zhao *et al*, the altered expression and secretion of proliferating and angiogenic agents like PI3K, Akt, PTEN, MMP9 and VEGF were directly associated with the DFS in GIST patients^[25]. Regarding VEGF, higher serum VEGF values were found in GIST patients when compared to healthy controls, while a positive VEGF expression rate was found in high risk groups^[9]. A considerable number of clinical trials have correlated high VEGF levels with poor prognosis^[9,23,25,40]. Another angiogenic factor, PDGF, has been related to GIST vasculogenesis at both theoretical and clinical levels^[41-42]. As tumor angiogenesis often progresses through a hypoxic drive, researchers have correlated the expression levels of respective markers (e.g. HIF-1 α) with survival outcomes^[22,43]. Finally, vasculogenic mimicry (VM) which is a novel pattern of angiogenesis and defined as the formation of fluid conducting channels by highly invasive and dysregulated tumor cells, has also been studied in GISTs^[44-45]. MMP-2 and MMP-9 were found to be contributing factors in VM; a significant association between VM, a high mitotic rate and liver metastases was confirmed^[44].

Microvessel density is a direct method of quantifying and assessing intratumoral vasculature, and consequently angiogenesis potential. Due to the above-mentioned correlation between tumor vascularity and clinicopathological endpoints, various trials investigated GIST MVD. According to Imamura *et al*^[8] and Waengertner *et al*,^[24] a statistically significant difference of survival rates in favour of low MVD GISTs was reported. Furthermore, Wang *et al*^[9] stated that higher MVD values were found in high mitotic count and recurrence groups. Similar results were published by Zhao *et al*, where a significant hazard ratio for DFS was found^[25]. A retrospective study by Takahashi *et al* suggested that while high MVD displayed a significant relationship with liver metastases, it did not influence the survival outcome at 10 years ^[23].

The results of our meta-analysis validated the significance of the MVD value effect on survival. Specifically, higher intratumoral MVD measurements were associated with a lower DFS rate at 36 and 120 mo of follow-up. These were not confirmed at the intermediate endpoints of 12 and 60 mo. The enhanced malignant potential of high

vascularized GISTs was also depicted by the significant association among metastatic rate and MVD values.

The usefulness of these results involve extensive approaches in the clinical outcome prognosis^[8-9,23,25,43]. Consolino *et al* showed that in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), imatinib-resistant tumors had an increased vessel density and permeability, with these attributes significantly correlated with MVD and MDD, respectively^[46]. Contrast enhanced endoscopic ultrasound has also demonstrated the ability to assess GIST vascularity, and subsequently, malignant potential^[47]. Furthermore, since MVD is a direct tumor vasculature marker, it has been used as an indicator of the angiogenesis inhibition, as well as the overall response to novel medical treatment^[48].

Besides GIST, MVD assessment has been extensively researched as a means of solid tumor vasculature quantification. Researchers have attempted to identify and estimate the presence of a correlation between microvessel density and survival outcomes in malignancies of the prostate^[49], cervix^[50], ovaries^[51], breast^[52], pancreas^[53], kidney^[54] and lung^[55]. Moreover, in two recent meta-analyses from our study group concerning cutaneous melanoma and patients with differentiated thyroid cancer, high intratumoral MVD was related to poor survival outcomes^[56-57]. According to current literature, the majority of studies validate the presence of a significant correlation between intratumoral MVD and prognosis in solid tumors^[58]. However, a discrepancy exists since a minority of publications question the significance of the above-mentioned correlation^[58].

Heterogeneity of various clinicopathological endpoints (survival, metastasis, local recurrence, response to treatment, *etc.*) in the reported results has been widely attributed to certain methodological variations^[58]. Among these, selection of the hot-spot examination technique is the most important, due to the variability rates and dependence on the assessor training and experience ^[59-60]. Furthermore, the MVD assessment technique includes various modifications, such as Weidner's hot-spot method^[21], the lumen method^[61], Chalkley's method^[62] and the computerized image

analysis system^[63]. Another field of methodological diversity is considered the selection of the endothelial marker, where a variety of choices such as pan-endothelial cell markers (CD31, CD34, vWF) and selective for the activated endothelium factors (CD105) are described. Finally, technical discrepancies are also reported in other methodological fields, such as type of fixative, vasculature estimation, the MVD cut-off value, level of magnification and overall field size^[58]. Our study highlighted this heterogeneity; the use of different assessment methods and definitions of high and low MVD tumours prohibited the calculation of a pooled cut-off point.

Certain limitations should be taken into consideration, prior to appraising results of the present meta-analysis. Firstly, significant levels of heterogeneity were identified; despite conducting explanatory analyses, the validity of study conclusions may be compromised. Furthermore, all eligible studies were designed using a retrospective methodology and included a small sample size, thus allowing the introduction of bias. Moreover, diversity among included studies regarding methodological characteristics of the MVD assessment technique should be also acknowledged. The implementation of different assessment methods and different cut-off points prohibited the strict definition of high and low MVD GISTs. Furthermore, heterogeneity in terms of tumor location, risk classification, histopathological characteristics and cell subtype jeopardized the significance of our outcomes. Inconsistency in surgical or medical treatment could also be an influencing factor on survival endpoints. Finally, since in most trials the raw survival data had to be extracted and reconstructed from the provided Kaplan-Meier curves, a certain amount of bias was introduced, although this procedure has been extensively described and applied in the literature.

CONCLUSION

To the best of our knowledge, the present study is the first attempt to provide an overall estimation of the impact of MVD on survival rates of GIST patients. According to the pooled results of the meta-analysis, GIST allocation between high and low MVD values significantly influenced the DFS hazard ratio. Moreover, high MVD GISTs

demonstrated a statistically significant lower DFS at 36 and 120 mo of follow-up, while no difference was found at 12 and 60 mo. Moreover, high MVD tumours were associated with a significantly higher rate of metastases. ¹ Based on the above-mentioned results and given several limitations, further studies with a larger sample size and adequate methodology are required.

ARTICLE HIGHLIGHTS

Research background

Several clinical and histopathologic factors have been investigated as prognostic indicators of survival in patients with gastrointestinal stromal tumours (GISTs).

Research motivation

Microvessel density (MVD) has been extensively applied as a direct method of tumour vascularity assessment.

Research objectives

This meta-analysis attempted to estimate the pooled effect of tumoral vascularity based on MVD assessment on the survival of patients with GISTs.

Research methods

The present meta-analysis adhered to the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

Research results

Low vascularized tumours were associated with improved pooled disease-free survival. GISTs with lower MVD values displayed a reduced risk of metastases.

Research conclusions

MVD is significantly associated with the survival outcomes of GIST patients.

Research perspectives

Further prospective randomized controlled trials are required to delineate the exact correlation between MVD and prognosis outcomes in GIST patients.

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