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Prognostic value of tumor necrosis in gastrointestinal stromal tumor

A meta-analysis

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Abstract

Background and aims: There is currently no consensus regarding the influence of tumor necrosis on the prognosis of gastrointestinal stromal tumors (GISTs). Therefore, we conducted a meta-analysis to determine the prognostic role of tumor necrosis in patients with GIST.

Methods: PubMed, Embase, and Web of Science electronic databases were searched from their inception to March 2018. Studies reporting data on the relationship between tumor necrosis and GIST prognosis were eligible. The measure of the effect of interest was the odds ratios (ORs) with 95% confidence intervals (CIs). This study has been registered in the Prospero (number CRD42018096036).

Results: In total, 18 studies including 2320 patients were identified. The total odds of tumor necrosis were associated with a poor GIST prognosis (OR = 5.54, 95% CI = 4.39–6.99). Subgroup analysis of different observed outcomes indicated that tumor necrosis was associated with a decreased disease-free survival (OR = 7.08, 95% CI = 4.78–10.49), recurrence-free survival (OR = 3.96, 95% CI = 2.48–6.32), and overall survival (OR = 4.29, 95% CI = 2.02–9.13). In addition, any tumor site, tumor size, follow-up time, ethnicity, different outcomes of GIST, and different degrees of positive staining of immunohistochemical markers subgroups showed a significantly increased risk of a poor prognosis.

Conclusions: Tumor necrosis may likely predict a poorer prognosis for GIST. However, further well-designed prospective studies with large sample size are required in the future.

Abbreviations: BA = biologic aggressiveness, CI = confidence interval, CT = computed tomography, DFS = disease-free survival, GI = gastrointestinal, GIST = gastrointestinal stromal tumor, KIT = kinase inhibitor tyrosine, M/F = male/female ratio, NIH = National Institutes of Health, OR = odds ratio, OS = overall survival, PDGFRA = platelet-derived growth factor receptor alpha, PRISMA = The Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RFS = recurrence-free survival.

Keywords: gastrointestinal stromal tumor, prognosis, tumor necrosis

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor that arises from the gastrointestinal (GI) tract,[1,2] probably originating from the interstitial cells of Cajal. Activating mutations of kinase inhibitor tyrosine (KIT) and less commonly platelet-derived growth factor receptor alpha (PDGFRA) are believed to be pivotal in the molecular pathogenesis of GIST.[3,4] One of the most predominant characteristics of GIST is its malignant potential varying from small lesions with benign behavior to aggressive sarcoma.[5] About 40% tumors in patients with GIST that were localized at the time of detection give rise to metastasis, and 10% to 20% of patients present with overt metastasis.[6,7] To estimate the malignant potential of GIST, several criteria have been proposed to predict the outcome of patients with GIST, including classifications from National Institutes of Health (NIH), the modified NIH, the Armed Forces Institute of Pathology.[8–11] However, even the prognosis of patients according to risk classification can vary. So far, there remains no consensus on the potential factors influencing the prognosis of patients with GIST, excepting for mitotic count, tumor size, tumor site, and tumor rupture, which are included in the existing prognostic criteria. The identification of independent and reproducible prognostic factors may affect therapeutic decisions and influence the performance of clinical work. Other factors such as genotype,[12]

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The authors have no conflicts of interest to disclose.

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immune infiltrates,[13] positive surgical margins,[14] and tumor necrosis may play an important role in the prognosis.

Tumor necrosis, a distinct type of cell death, is usually associated with abnormal processes such as exposure to various toxins or teratogens, infections, trauma, and ischemia.[15] Tumor necrosis was shown to be an independent prognostic factor of soft tissue sarcoma early in 1984 by Costa et al[16] and Trojani et al[17] and was later included in the National Cancer Institute grading and the French Federation of Cancer Centers Sarcoma Group gradings. Trojani et al[17] showed that tumor differentiation, mitosis count, and tumor necrosis were necessary and sufficient to retain all the prognostic information in soft tissue sarcoma in a multivariate analysis. Costa et al[16] reported tumor necrosis to be the single best histopathologic parameter to predict the time to recurrence and the overall survival (OS) of patients with soft tissue sarcoma, as well as the clinical course after recurrence independent of patient age and sex and tumor location and size.

In recent years, studies on the possible prognostic factors for GIST reported that tumor necrosis might independently influence the recurrence or survival of patients with GIST.[18–21] However, other studies reported contradictory findings.[22,23] The discordance may be due to small sample sizes and different characteristics among studies. Since GIST is a soft tissue sarcoma,[1] the ability of tumor necrosis to predict the outcome of patients with GIST remained controversial as a result of the inconsistent results of published studies. Thus, tumor necrosis may be a significant prognostic factor for GIST. Therefore, we conducted a meta-analysis to clarify the relationship between tumor necrosis and GIST prognosis.

2. Methods

2.1. Search strategy and selection criteria

Two investigators independently performed a systematic search of the PubMed, Embase, and Web of Science databases (last updated on March 2018), using the following search terms: "gist," "gists," "gastrointestinal stromal tumor," "gastrointestinal stromal tumors" combined with "necrosis." The articles cited in selected articles were also examined to identify additional relevant studies. All studies were carefully evaluated to avoid duplicate data. We included published studies that reported the correlation between tumor necrosis and the prognosis of GIST. The criteria used for the study selection were as follows: participants (P): all patients were required to have morphology compatible with GIST and positive immunostaining for KIT (CD117) or PDGFRA (discovered on GIST-1 [DOG-1]). Recent research showed the PKCθ sensitivity is similar to CD117 and superior to DOG1 sensitivity.[24] Thus, the expression of PKCθ in CD117/DOG1 negative GISTs was added to our diagnostic criteria. Interventions (I) and comparisons (C): comparing the prognosis of GIST with necrosis versus GIST without necrosis. Outcomes (O): recurrence-free survival (RFS), disease-free survival (DFS), OS, and risk classification (high risk level) by the modified NIH. Study design (S): retrospective or prospective study. Enough data for the estimation of odds ratios (ORs) and 95% confidence intervals (CIs). We excluded articles if they were not published in English, did not include sufficient information to calculated ORs and 95% CIs and failed to report a prognosis.

2.2. Data extraction and qualitative assessment

Two investigators independently extracted the required data from all eligible studies. Discrepancies between the 2 investigators were resolved by discussion or consensus with a senior investigator. Descriptive and quantitative data were extracted from each study for the following: first author, year of study recruitment, nation, sample size, tumor site, tumor size, male to female ratio, mean patient ages, percentage of GIST with tumor necrosis, mean follow-up time, and outcomes of patients with tumor necrosis-positive GIST. The measure of the effect of interest was the OR with 95% CI, which were estimated according to the available data if they could not be directly acquired in the included articles. Qualitative assessment was performed for the included articles using the Newcastle–Ottawa Quality Assessment Scale for case–control studies.

2.3. Statistical analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) check list was used as a protocol and guideline for the meta-analysis. To evaluate the prognostic value of tumor necrosis, we extracted or calculated the ORs and corresponding 95% CI for the clinical outcomes observed in the eligible studies. Data on the predictive ability of tumor necrosis were combined across the eligible studies by inverse variance using ORs. A fixed-effects model was used to estimate the pooled ORs and 95% CIs. An OR >1 suggested a worse prognosis for GIST with tumor necrosis. Chi-square-based Q tests were used for checking the heterogeneity assumption, in which a $P > .10$ indicated a lack of heterogeneity among studies. The effect of heterogeneity was quantified using I^2 tests. I^2 values of <25%, about 50%, >75%, respectively, were considered "low," "moderate," and "high." Subgroup analysis was performed for observed clinical outcomes, tumor size, tumor site, follow-up time, and patient ethnicity. Sensitivity analysis was conducted to determine whether exclusion of any studies affected the results. The effect of publication bias on the reported outcomes was assessed graphically by both Egger's and Begg's tests. A $P < .05$ was considered significant statistically. All P values in this study were 2-sided.

3. Results

3.1. Baseline study characteristics

The initial searches included 411 records. After further review, 63 articles were assessed for eligibility. Of these, 45 articles were excluded due to insufficient data. Among them, the full text was not available for 8 articles and 37 articles were excluded because they did not include necessary direct or indirect data. The screening process is shown in Figure 1. A total of 18 studies were included in the meta-analysis.[18–23,25–36]

The characteristics of included studies are shown in Table 1. In total, 2320 patients were included in the analysis; of these, 792 patients had GIST with tumor necrosis. All eligible articles were published between 1998 and 2017. The prevalence tumor necrosis positivity rate ranged between 15.0% and 76.9%. Among the clinical outcomes observed in patients with GIST, DFS was observed in 8 studies, RFS in 5 studies, and OS in 2 studies. Two studies described the outcomes using risk classification (high risk) by the modified NIH and 1 study used the biologic aggressiveness score as the prognostic criterion for GIST. For tumor sites, 3 articles focused on gastric, 4 on small intestine, 1 on the rectum, and 1 on GIST out of GI tract (extra GI). Among all the 18 studies, 4 were carried out in the USA, 6 in

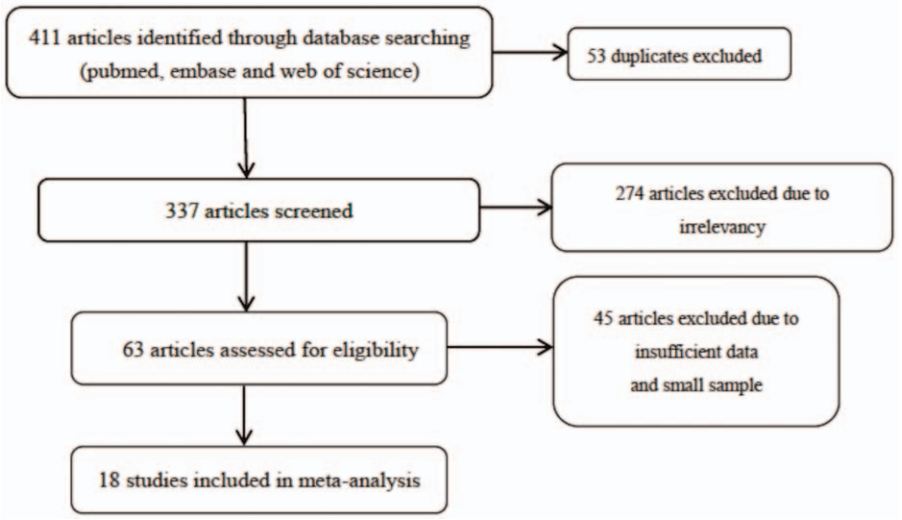

Figure 1. Flow chart of study selection.

China, 2 in Korea, 2 in Japan, 1 in Switzerland, 1 in Italy, 1 in Singapore, and 1 in India. The mean follow-up time ranged from 24 months to 69 months. The mean tumor size was ≤5 cm, 5 to 10 cm, and >10 cm in 3, 8, and 2 studies. The quality of the studies assessed by the Newcastle–Ottawa Quality Assessment Scale ranged from 5 to 8, with scores of 5 in 2 articles, 6 in 5 articles, 7 in 7 articles, and 8 in 4 articles.

3.2. Meta-analysis and subgroup analysis

In the pooled analysis of all 18 studies, the meta-analysis revealed that GIST with tumor necrosis had a significantly poorer prognosis than that in GIST without tumor necrosis (OR = 5.54, 95% CI = 4.39–6.99, $P < .001$) (Fig. 2). This finding indicated a lack of heterogeneity in the pooled analysis ($I^2 = 6.2\%$, $P_{\text{heterogeneity}} = .38$). Subgroup analysis was conducted to

Table 1

Main characteristics of the included studies.

Study	Nation	Sample size	Tumor necrosis(n)	Age (mean, years)	M/F	Tumor site	Tumor size (mean, cm)	Follow-up (mean, month)	Outcome	OR	LCI	UCI	Adjustments
[36]	Korea	31	14	48 (23–95)	15/16	Small intestine	4.7	NA	DFS	11.92	2.18	65.15	NO
[31]	USA	31	9	58 (31–82)	8/23	Extra GI	13.6	24	RFS	11.90	1.85	76.53	Cellularity
[25]	Japan	140	36	60 (28–78)	76/64	Gastric	5.7	NA	OS	5.28	1.92	14.52	Ulceration, cell type, nuclear atypia, cellularity
[28]	USA	68	30	61 (33–96)	34/35	Any	NA	26	OS	3.30	1.06	10.27	NA
[22]	Switzerland	18	5	60 (41–81)	11/7	Small intestine	5.4	69	DFS	8.25	0.80	85.56	NA
[23]	Japan	22	10	55 (37–74)	9/13	GI tract	6.8	NA	RFS	1.40	0.26	7.60	NO
[19]	USA	50	11	60 (34–84)	25/25	Gastric	4.4	36	DFS	25.00	2.56	243.75	NA
[35]	Italy	61	17	60 (23–86)	29/32	GI tract	5.3	35	DFS	8.89	2.19	36.10	NO
[27]	Taiwan–China	39	30	61 (20–86)	21/18	Any	5.9	NA	DFS	4.00	0.79	20.38	Age, size
[34]	China	29	11	52 (32–72)	14/45	Rectum	4.0	NA	DFS	4.55	0.92	22.63	Adjacent invasion, pleomorphism
[21]	Singapore	171	77	59 (27–92)	93/78	Any	NA	40	RFS	3.66	1.69	7.96	Locally advanced disease, tumor perforation, pleomorphism
[33]	China	114	67	59 (15–82)	67/47	Any	7.0	NA	RFS	3.95	1.61	9.72	NO
[32]	China	332	104	58 (13–88)	200/112	Any	NA	60	High risk(NIH)	7.68	4.54	12.99	NA
[29]	India	121	68	48 (8–83)	94/27	Any	10.7	27	DFS	4.52	1.64	12.47	NO
[18]	Korea	113	17	56 (20–83)	62/51	Small intestine	NA	NA	RFS	4.71	1.76	12.60	Tumor size, mitosis, genotype
[26]	China	129	97	56 (23–86)	65/64	GI tract	7.9	NA	High risk(NIH)	10.41	3.39	32.02	NO
[30]	USA	111	67	62 (24–92)	69/42	Small intestine	5.5	36	BA score (4)	2.03	0.84	4.95	NA
[20]	China	740	122	59 (20–91)	368/372	Gastric	NA	33	DFS	7.62	4.47	13.00	Age, gender, tumor location, tumor size, mitosis

BA = biologic aggressiveness, CI = confidence interval, DFS = disease-free survival, GI = gastrointestinal, M/F = male/female ratio, NA = not available, NIH = National Institute of Health, NO = none, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival.

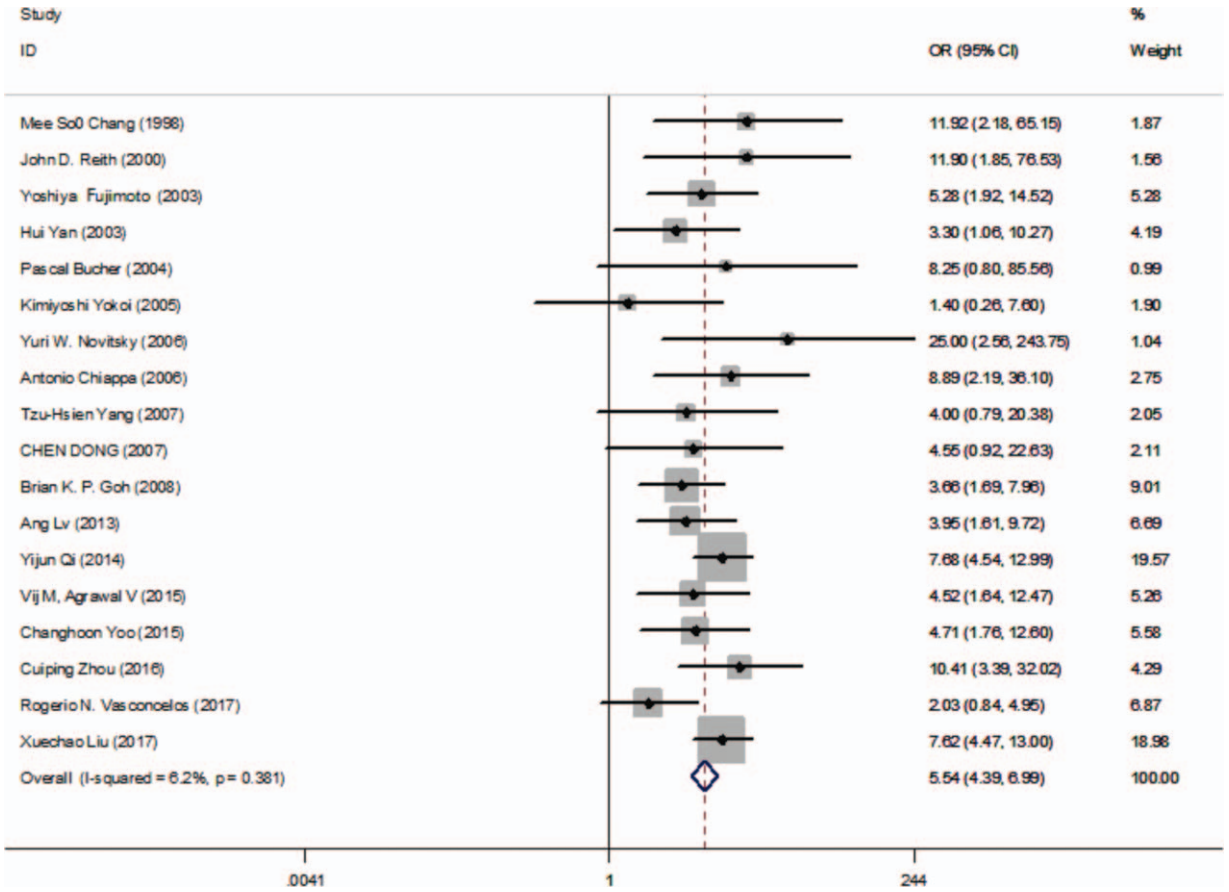

Figure 2. Pooled ORs on the association of tumor necrosis with GIST prognosis. GIST = gastrointestinal stromal tumor, OR = odds ratio.

assess the influence of different outcomes observed in studies, patient ethnicity, follow-up time, tumor site, and tumor size, as shown in Table 2. DFS, RFS, and OS were reported in different studies. Moreover, (high) risk classification according to NIH 2008 classification was also used as an indicator for the prognosis of GIST. Studies describing DFS (OR = 7.08, 95% CI = 4.78–10.49, $I^2 = 0.0\%$), RFS (OR = 3.96, 95% CI = 2.48–6.32, $I^2 = 0.0\%$), OS (OR = 4.29, 95% CI = 2.02–9.13, $I^2 = 0.0\%$) indicated that tumor necrosis was significantly associated with a reduced DFS, RFS, and OS. Among them, tumor necrosis was most related to a reduced DFS, least to RFS, and OS was between them. Tumor necrosis was also related to a high risk according to the NIH 2008 classification (OR = 8.11, 95% CI = 5.04–13.06, $I^2 = 0.0\%$). Mean tumor size was evaluated by 13 articles. Studies where mean tumor size was ≤5 cm (OR = 9.28, 95% CI = 3.29–26.18, $I^2 = 0.0\%$), 5 to 10 cm (OR = 4.23, 95% CI = 2.78–6.43, $I^2 = 16.2\%$), or >10 cm (OR = 5.64, 95% CI = 2.32–13.75, $I^2 = 0.0\%$) indicated that tumor necrosis could predict a poor prognosis for GIST of any tumor size. However, for tumors ≤5 cm, the impact of necrosis on GIST prognosis was greater than that of tumors ranging from 5 cm to 10 cm and tumors >10 cm. Studies on GIST at any site (OR = 5.14, 95% CI = 3.66–7.22, $I^2 = 0.0\%$,), GI tract (OR = 6.48, 95% CI = 2.98–14.09, $I^2 = 50.6\%$), gastric (OR = 7.41, 95% CI = 4.67–11.77, $I^2 = 0.0\%$), small intestine (OR = 3.75, 95% CI = 2.07–6.79, $I^2 = 29.6\%$) indicated that tumor necrosis could predict a poor prognosis for GIST at any site. In addition, the risk of poor prognosis for gastric GIST with tumor necrosis was higher than that of GIST of small intestine. Due to the lack of reports on the rectum and extra GI, 2 studies were not included the subgroup analysis. Mean follow-up times ranging from 24 months to 36 months were found in 7 studies and >36 months in 3 studies. Analysis of follow-up times of 24 to 36 months (OR = 5.54, 95% CI = 3.84–7.97, $I^2 = 40.1\%$) and >36 months (OR = 6.14, 95% CI = 4.01–9.42, $I^2 = 28.7\%$) indicated a poorer outcome for GIST with a follow-up time >24 months; with increasing follow-up time, the impact of tumor necrosis on GIST also increased. Two ethnicities were included in the pooled analysis: 12 included Asian and Pacific Islands patients, while 6 studies included Caucasian patients. Tumor necrosis predicted a poor prognosis for GIST in both the Asian and Pacific (OR = 5.86, 95% CI = 4.54–7.57, $I^2 = 0.0\%$) and Caucasian (OR = 4.25, 95% CI = 2.43–7.42, $I^2 = 35.3\%$) groups. Subgroup analysis of these ethnicities revealed that people in Asian and Pacific Islanders who had GIST with tumor necrosis may have a worse outcome than that of Caucasians. Moreover, subgroup analyses on immunohistochemical staining showed a higher impact of tumor necrosis to prognosis of GIST in the groups where a higher rate of positive immunohistochemical staining was found for CD117 (>90%) (OR = 6.23, 95% CI = 4.22–9.19, $I^2 = 0.0\%$), CD34 (>50%) (OR = 6.86, 95% CI = 4.52–10.40, $I^2 = 0.0\%$), and S100 (>20%) (OR = 6.00, 95% CI = 3.27–15.15, $I^2 = 45\%$). Contrary results were found in subgroup of lower rate of immunohistochemical staining for smooth muscle actin (SMA) (≤30%) (OR = 6.82, 95% CI = 2.71–17.19, $I^2 = 33\%$).

Table 2

Subgroup analysis.

Subgroup	OR	95% CI	*P* for overall effect	I^2 statistics	*P* for heterogeneity	No. of included studies
Group on different outcomes						
High risk	8.11	5.04–13.06	<.001	0.00%	.63	2
DFS	7.08	4.78–10.49	<.001	0.00%	.86	8
RFS	3.96	2.48–6.32	<.001	0.00%	.57	5
OS	4.29	2.02–9.13	<.001	0.00%	.55	2
Group on tumor size						
≤5 cm	9.28	3.29–26.18	<.001	0.00%	.46	3
5–10 cm	4.23	2.78–6.43	<.001	16.20%	.30	8
>10 cm	5.64	2.32–13.75	<.001	0.00%	.37	2
Group on tumor site						
Gastric	7.41	4.67–11.77	<.001	0.00%	.46	3
Small intestine	3.75	2.07–6.79	<.001	29.60%	.23	4
Group on follow-up time						
24–36 months	5.54	3.84–7.97	<.001	40.10%	.12	7
>36 months	6.14	4.01–9.42	<.001	28.70%	.29	3
Group on human race						
Asian and Pacific islands	5.86	4.54–7.57	<.001	0.00%	.59	12
Caucasian	4.25	2.43–7.42	<.001	35.30%	.17	6
Group on CD117(+) ≧90%	6.23	4.22–9.19	<.001	0.00%	.70	4
Group on CD34(+) ≫50%	6.86	4.52–10.40	<.001	0.00%	.51	4
Group on SMA(+)						
>30%	4.62	2.28–9.36	<.001	0.00%	.95	2
≦30%	6.82	2.71–17.19	<.001	33.00%	.22	2
Group on S100(+)						
>20%	6.00	2.37–15.15	<.001	45.00%	.18	2
≦20%	4.98	2.46–10.08	<.001	0.00%	.87	2

CI = confidence interval, DFS = disease-free survival, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival, SMA = smooth muscle actin.

3.3. Sensitivity analysis

To assess whether any 1 study had a dominating effect on the summary effect size or heterogeneity, each study was excluded and repeated analyses were conducted. The pooled ORs were not significantly influenced by the omission of any single study.

3.4. Publication bias

Egger's test revealed no evidence of publication bias (Fig. 3). The shape of the funnel plots showed no obvious asymmetries.

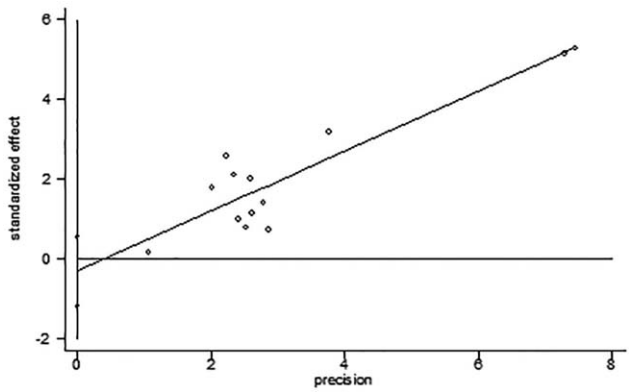

Figure 3. Funnel pots by Egger's test.

4. Discussion

Due to the sensitivity of selective imatinib therapy and common tumor recurrence after complete surgical resection,[37,38] identifying the significant prognostic factors is important for individualized risk classification. The influence of tumor necrosis on the prognosis of GIST has been demonstrated in recent years. However, literature regarding the relationship between tumor necrosis and GIST prognosis is inconclusive. The present meta-analysis demonstrated that the presence of tumor necrosis, as part of either preoperative computed tomography (CT) or pathologic findings, predict a poorer prognosis for GIST regardless of tumor site, tumor size, follow-up time, or patient ethnicity. It may enable clinicians to generate more accurate schemes to determine individual imatinib therapy.

Subgroup analysis of different outcomes indicated that tumor necrosis could influence the DFS, OS, RFS, and the risk classification of GIST (by NIH 2008). Tumor necrosis was most related to DFS, RFS was least related, and OS was between them. Patients with GIST with tumor necrosis had an approximately 7-fold increased risk of disease progression, including disease metastasis, recurrence, and death, and 4-fold increased risk of recurrence compared with those in patients with GIST without tumor necrosis. In addition, subgroup analysis indicated that tumor necrosis was most related to the NIH 2008 risk classifications. Thus, tumor necrosis could be used as a potential factor to distinguish between high-risk GIST and non-high-risk GIST; however, this requires confirmation in future studies. In the subgroup meta-analysis on tumor size, the impact of tumor necrosis to GIST prognosis for tumors <5 cm was higher than that of tumors >5 cm, which means in GIST <5 cm, the

prognostic role of tumor necrosis needs more attention. Liu et al[20] reported that tumor necrosis was associated with a larger tumor size ($P < .01$), a higher mitotic count, tumor rupture, and the presence of nuclear atypia. As larger tumor size, especially >10 cm, indicates aggressive behavior, the impact of tumor necrosis on the GIST prognosis may probably be weakened, which leads to increased awareness of tumor necrosis for tumors <5 cm. In the present study, no correlation between tumor necrosis and mitotic count, tumor rupture and nuclear atypia were identified due to the lack of corresponding information. Further studies are needed to clarify the relationship between tumor necrosis and other predictors. In subgroup analysis of tumor sites, GIST at any site with tumor necrosis had a poorer prognosis than that of tumor necrosis-negative GIST. However, compared to that in small intestine GIST, the impact of tumor necrosis in gastric GIST was greater, suggesting that tumor necrosis in gastric GIST may need more attention. Subgroup analysis also revealed that a longer follow-up time (>36 months) could increase the risk of a poorer prognosis in patients with tumor necrosis-positive GIST. In a study including 2459 patients, Joensuu et al[5] reported estimated 5 and 15-year RFS rates for GIST treated with surgery alone of 70.5% and 59.9%, respectively, indicating that a short follow-up time could lead to underestimates regarding the poor clinical outcome of patients with GIST. This could explain the result of this subgroup analysis. Subgroup analysis of patient ethnicity indicated an increased impact of tumor necrosis on the prognosis of GIST among Asian and Pacific Islander patients compared to that in Caucasians (ORs: 5.86 vs. 4.25). This difference may be caused by the inconsistent level of medical care service between the 2 regions. Moreover, we found a higher impact of tumor necrosis to the prognosis of GIST in the groups with higher rate of positive immunohistochemical staining of CD117, CD34, S100, and in the group with lower rate of SMA (+). Because of limited data, other important markers such as DOG1, protein kinase C-theta, and programmed death ligand (PDL)-1 were not analyzed in this meta-analysis. The reason for this observation remained unclear. In another research by Blakely et al,[39] expression of PDL-1 was associated with tumor necrosis, as well as tumor behavior and clinical outcomes of various tumor types, which may reveal a potential correlation between tumor necrosis and other immunohistochemical markers.

Tumor necrosis, characterized by the presence of dead cells in the form of anucleate "ghost cells" with preservation of the tissue architecture, has been established as a prognostic factor for a variety of malignancies. Sengupta et al[40] reported that tumor necrosis was retained as an independent predictor of outcome for clear cell and chromophobe renal cell carcinoma and suggested that it be incorporated into prognostic models for more accurate risk estimation. In the report by Hiraoka et al[41] including 348 patients with pancreatic duct carcinoma, histologic necrosis was a simple, accurate, and reproducible predictor of postoperative outcome. In another study on colorectal cancer based on 343 patients, tumor necrosis was associated with cancer-specific survival. However, the impact of tumor necrosis on colorectal cancer may be due to its close associations with the host systemic and local inflammatory responses.[42] In addition, a review by Gkogkou et al[43] also reported tumor necrosis to be an independent prognostic factor affecting therapeutic decisions in nonsmall cell lung carcinoma.

The mechanisms by which tumor necrosis results in a poor prognosis in GIST are still unclarified. One hypothesis is that rapid cell proliferation outgrowing the vasculature leads to hypoxic conditions in tumors, causing subsequent tumor cell death and promoting metastatic cascade.[44,45] The presence of necrosis histologically reflects intratumoral hypoxia, which is a common feature of human cancers.[41] Areas of hypoxic tumor tissue are resistant to treatment and associated with a poor clinical prognosis due to the capacity of hypoxia to drive genomic instability and alter DNA damage repair pathways.[46] Hypoxia induces a transcription program mediated by hypoxia-introducible factor-1α, which could promote aggressive tumor phenotypes.[47] In addition, tumor necrosis is directly associated with both an attenuation of local infiltration of inflammatory cells and the presence of systematic inflammatory response.[48] Inflammatory processes including the local accumulation of products of cyclooxygenase activity[49] and the local production of nitric oxide[50] could promote cell proliferation and death at the sites of inflammation, which are related to hypermethylation of the promoter regions in tumor-suppressor and proapoptotic genes.[51] Following the acquisition of genetic limitations in apoptotic pathways, the resultant increase in necrotic cell death leads to the release of cellular contents, which in turn promote cell growth and cancer progression.[52] Coagulative necrosis within the primary tumor may comprise the tumor vasculature, thereby facilitating the systematic dissemination of malignant cells.[53]

This study has several limitations. First, a limited number of studies were included in this meta-analysis due to the lack of relevant studies. Second, in other studies, tumor necrosis was categorized as absent; minimal (necrotic areas not exceeding 15% of the tumor); moderate (necrotic tissue 15%–50% of the tumor); and massive (necrosis over 50% of the tumor).[16] The definition of tumor necrosis was not clear for each of the included studies and the relationship between the degree of necrosis and GIST prognosis was not analyzed in this meta-analysis. Third, previous studies have showed a significant relation between prognosis of GIST and tumor size, tumor site, mitotic count, tumor rupture, microenvironment,[39] and some blood parameters such as combination of high neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, neutrophil-to-white blood cell ratio, and low lymphocyte-to-white blood cell ratio.[54] However, because of limited data (the included original articles only showed mean tumor size and mean mitotic count), the exact relationship between tumor necrosis and other predictors such as mitotic count and tumor size were not assessed in this study. Correlation between tumor necrosis and blood parameters was not assessed either. Further studies of large sample sizes are needed to identify whether tumor necrosis is an independent factor for a poor GIST prognosis. A fourth limitation was that we could not obtain information regarding the main confounders from most of the studies, especially the main known predictors for GIST such as mitosis, tumor size, and tumor site. We could only extract the adjustments for 6 of 18 studies as shown in Table 1. Therefore, this result should be considered with some caution according to potential confounding. Finally, the definitions of the oncological outcome were not consistent between the 18 articles. Therefore, we conducted subgroup analysis, which indicated that tumor necrosis was associated with decreased DFS, RFS, as well as OS. Besides these, the results of our study may help to define the prognostic role of necrosis in GIST and may be useful in clinical work, especially in clinical consultation.

In conclusion, the presence of tumor necrosis, as part of either preoperative CT or pathologic findings, could predict a significantly poorer prognosis in patients with GIST. In addition,

the presence of tumor necrosis present in GIST could predict a poor DFS, OS, and RFS for GIST regardless of tumor site, tumor size, follow-up time, or patient ethnicity. In addition, the value of tumor necrosis in risk classification (predicting a high risk level) in the NIH 2008 classification may make it an important factor to distinguish between high risk GIST and non-high risk GIST.

Author contributions

Y.Z., M.Y., and L.X. conceived together the study. All authors contributed to the research and development process that resulted in this article. M.Y. and L.X.; Y.Z., X.W., W.Z., Y.C., R.Z., and Q.W.; and L.D. performed data extraction, analysis, and interpretation of data. M.Y. wrote the manuscript under the guidance of Y.Z. All of authors read the manuscript and approved the final manuscript.

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