Original Article

Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: a systematic review and meta-analysis

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Background: There are two distinct types of gastric carcinoma (GC), intestinal, more frequently sporadic and linked to environmental factors, and diffuse (undifferentiated) that is highly metastatic and characterized by rapid disease progression and a poor prognosis. However, there are many conflicting data in the literature concerning the association between histology and prognosis in GC. This meta-analysis was performed to provide demonstration if histology according to Lauren classification is associated with different prognosis in patients with GC.

Methods: We searched PubMed, the Cochrane Library, SCOPUS, Web of Science, CINAHL, and EMBASE for all eligible studies. The combined hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) in terms of overall survival (OS) were evaluated.

Results: A total of 73 published studies including 61,468 patients with GC were included in this meta-analysis. Our analysis indicates that GC patients with diffuse-type histology have a worst prognosis than those with intestinal subgroup in all studies (HR 1.23; 95% CI, 1.17–1.29; P<0.0001), in both loco-regional confined (HR 1.21; 95% CI, 1.12–1.30; P<0.0001) and advanced disease (HR 1.25; 95% CI, 1.046–1.50; P=0.014), in Asiatic (HR 1.2; 95% CI, 1.14–1.27; P<0.0001) and Western patients (HR 1.3; 95% CI, 1.19–1.41; P<0.0001), and in those not exposed (HR 1.15; 95% CI, 1.07–1.24; P<0.0001) or exposed (HR 1.27; 95% CI, 1.17–1.37; P<0.0001) to (neo)adjuvant therapy.

Conclusions: Our results indicated that histology might be a useful prognostic marker for both early and advanced GC patients, with intestinal-type associated with a better outcome. This information could be used for stratification purpose in future clinical trials.

Keywords: Gastric cancer (GC); prognostic factor; Lauren classification; diffuse histology; meta-analysis

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Introduction

Despite its incidence in Western countries had a steady decline over the last decade, gastric cancer (GC) still represents one of the major causes of cancer mortality worldwide (1). The prognosis of GC is mostly related to disease extension according to the seventh TNM classification (2). Currently, the clinical or pathological stage is the only validated tool available in the clinical practice to drive treatment decision-making. However, it

must be pointed out that the individual risk of recurrence significantly varies within the same stage, and overall survival (OS) profoundly depends on additional prognostic factors (3,4).

The diffuse and intestinal types of GC describe two histological entities that are different with regard to epidemiology, pathogenesis, biological features and clinical behavior. Currently, there is no difference in the clinical management of these two main histotypes identified by both World Health Organization and Lauren's classification systems (5,6). It is generally recognized that GC with a differentiated histology or intestinal-type shows a better prognosis than individual with a poorly differentiated histology or a diffuse-type (7). However, most available studies were limited by the small sample size and retrospective nature, with consequent methodological limitations and barriers in validating the histotype as an independent prognostic factor.

In this systematic review and meta-analysis, we aimed at clarifying the prognostic value of Lauren's classification in patients with surgically resected GC.

Methods

Search strategy

The search was performed searching the electronic database PubMed, the Cochrane Library, SCOPUS, Web of Science, EMBASE and CINAHL up to December 2015. Searches included the terms *("gastric cancer"* or *"gastric carcinoma")* and *("Lauren"* or *intestinal* or *diffuse)* and *(multivariate* or *multivariable* or *cox regression)* and *(hazard ratio)*. Manual selection of relevant studies was carried out based also on the related articles function. The citation lists of all retrieved articles were analyzed to identify other potentially relevant reports.

Study selection and data extraction

The following criteria for eligibility among studies were set before collecting articles: (I) histology according to Lauren classification was evaluated in primary GC tissue (biopsies or surgical specimen of primary tumor); (II) survival information (median OS) at specific follow-up was reported in the article as HR according to multivariate analysis, after histology classification resulted significantly in univariate analysis; (III) articles were published in English language; (IV) when several articles were published by the same authors or group, the newest or most informative single article was selected. Exclusion criteria were the following: (I) no information on OS was provided; (II) letters to editor/commentary, reviews, and articles published in a book or papers; (III) clinical studies with chemotherapy or concurrent chemoradiotherapy treatment investigating response rates only.

Two authors (FaP and RB) did the search and identification independently, and selection of an article was reached by consensus with a third author (FiP). The following information was extracted from each report by the two authors independently: year of publication, country, patient size, type of study, histology (intestinal *vs.* diffuse disease rates), disease stage (locoregional tumors *vs.* stage IV), surgery (rate), type and rate of (neo)adjuvant therapy, survival data (HRs) and covariates indagates in multivariate analysis.

Statistical analysis

For analysis of survival results, HRs were pooled to provide an aggregate value. In this analysis, all HRs with 95% confidence intervals (CIs) adjusted for the maximum number of covariates (significantly associated with OS in univariate analysis) and available in the articles, were combined for obtaining a prognostic information of diffuse (*vs.* intestinal) histology, independent of other clinicopathological covariates. Subgroup analysis was performed according to race (Asiatic *vs.* non-Asiatic origin, localized *vs.* stage IV disease, and no systemic therapy *vs.* systemic therapy exposure). Data were entered into the Comprehensive Meta Analysis software v 3.3.070 (November 20^{th,} 2014). The Cochran's test was used to assess the heterogeneity of included studies. For heterogeneity tests, $P<0.05$ was considered to indicate significance. If the test of heterogeneity was significant ($P<0.05$ or $I^2>50\%$), the random-effect model was used. Otherwise, the fixed-effect model was used. By convention, an observed HR of >1 implied the worst survival for the group with diffuse histology.

We finally investigated publication bias for OS meta-analysis with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau and Egger's bias test (8,9). Moreover, in the presence of publication bias for the primary analyses, we conducted a trim-and-fill-adjusted analysis (10) to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was

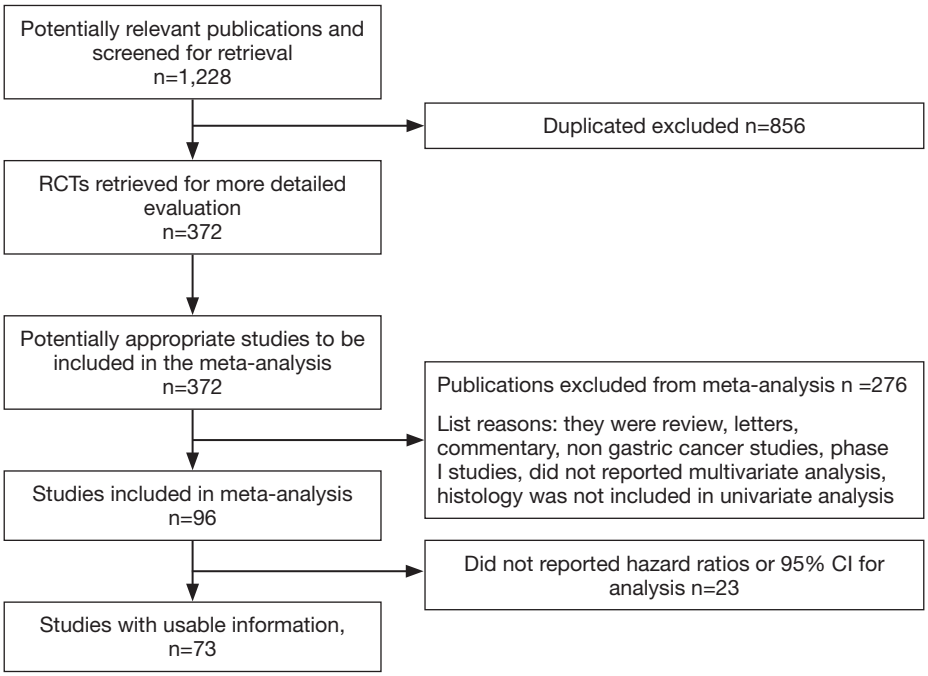

Figure 1 Overview of trials search and selection.

symmetric about the (new) effect size.

Results

A total of 1,228 potentially relevant citations were reviewed (*Figure 1*). Among them, 23 reported OS data as risk ratio or odds ratio or did not report 95% CI for inclusion in the final analysis. Ultimately, 73 studies (*Table 1*) that reported the prognostic value of histology classification for OS were analyzed. The total number of patients included was 61,468, ranging from 41 to 11,189 patients per study (median, 274). The major characteristics are shown in *Table 1*.

In n=7 publications a retrospective analysis of prospective trials was presented, all other publications reported a retrospective analysis of surgically treated series of patients with GC. The majority (n=45) were Asiatic countries publications; the remaining n=28 publication were of Western origin (including n=3 multinational, n=5 US, n=1 Brazilian, n=16 European, n=1 Giordany, n=1 Tunisian and n=1 Turkish series). Surgery of the primary tumor was performed in all patients in n=68 studies. Chemotherapy, plus or minus radiotherapy was offered to many patients except in n=20 publication where no patients received systemic therapy (in n=18 studies this data was not reported). When reported, intestinal histology ranged from 8.5% to 83% of patients, diffuse subtype from 9.8% to 73.5% (only in n=6 studies rates of different histologies were not reported).

Meta-analysis of adjusted hazard ratios (HRs) for OS (all studies)

The effect of histology classification on OS was evaluated in all studies with a total of 61,468 patients analyzed. Overall, the HRs of each study (adjusted for the maximum number of the covariates available and with significant association in univariate analysis) were pooled using a random-effect model, and the final value (HR 1.23; 95% CI, 1.17–1.29; P<0.0001; I^2 38%, P for heterogeneity 0.001; *Figure 2*), indicates that diffuse histology was an indicator of worst prognosis.

Subgroup analysis according to race, stage and systemic therapy

In studies selected for the country (Asiatic *vs.* non-Asiatic countries, only n=2 studies not included for mixed origins) the increased risk of death associated with diffuse histology was similar (HR 1.22; 95% CI, 1.15–1.29; P<0.0001 *vs.* HR 1.28; 95% CI, 1.19–1.38; P<0.0001 according to random

Table 1 Characteristics of included studies

Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
An *et al.*, 2010 (11)	Korea	Retrospective series	251	40	91, 6 *vs.* 8.4	Cardia 100	100	No	50.2/45.8	0.951 (0.533–1.698)	Borrmann, pT, pN, LVI
Atmaca *et al.*, 2012 (12)	German	Retrospective analysis of 4 prospective trials	357	18.2	0 *vs.* 100	Proximal GEJ 30%, other 70%	NR	Yes	39/48	1.1 (0.81–1.69)	EGFR, age, type of CT, site, sex, metachronous/ synchronous M+
Ben Ayed-Guerfali *et al.*, 2011 (13)	Tunisian	Retrospective series	79	NR	69 *vs.* 31	Cardia 10, other 90%	100	No	57/43	1.65 (0.346–7.894)	Sex, HP, site, TNM stage, EBV, CIMP, p16, RAR-beta, RASSF1A, DAPK, CDH1
Bani-Hani *et al.*, 2005 (14)	Giordany	Retrospective series	89	33.7	89 *vs.* 11	Upper 3rd-entire stomach 18%, other 82%	100	No	66/34	2.53 (0.89–7.20)	Age, sex, pN, HP, cyclin E, TNM stage, pT, site, G
Becker *et al.*, 2012 (15)	German	Retrospective series	428	33	100 *vs.* 0	Cardias, GEJ 55%; distal 45%	100	Neoadj CT	43.9/25	0.982 (0.786–1.226)	Diameter, LVI, R+, G, TRG, TNM stage
Bian *et al.*, 2012 (16)	China	Retrospective series	222	NR	85 *vs.* 15	Cardia 25%, other 75%	100	No	62/38	1.049 (0.748–1.471)	Sex, age, site, G, pT, pN, M+, TNM stage. QKI expr
Bilici *et al.*, 2010 (17)	Turkey	Retrospective series	238	29.5	100 *vs.* 0	Proximal 16%, distal 84%	100	NR	50/50	0.99 (0.23–1.17)	Age, sex, site, G, size, pT, Borrmann, surgery, pN, cTNM stage, LVI, VI, PNI, M+
Chen *et al.*, 2014 (18)	China	Retrospective series	991	55.3	100 *vs.* 0	Upper 3rd 37.2%, other 62.8%	100	Adj CT (62.4)	44.5/45.9	1.024 (0.883–1.187)	Age, site, gastrectomy, Borrmann, size, morphology, G, LVI, VI, pT, pN, TNM stage, adj CT
Choi *et al.*, 2007 (19)	Korea	Retrospective series	286	NR	85 *vs.* 15	Cardia + body 46%, other 54%	100	NR	36/52	0.83 (0.45–1.53)	Sex, pT, LVI, M+, NDRG2 expr
de Maat *et al.*, 2007 (20)	the Netherlands	Retrospective analysis of a prospective study	137	NR	100 *vs.* 0	NR	100	NR	77/23	1.58 (1.075–2.38)	pN+, pT, TNM stage, D1 *vs.* D2, COX2
Deng *et al.*, 2015 (21)	China	Retrospective series	1,521	38	100 *vs.* 0	Proximal 3rd 45.6%, other 54.4%	100	24.1 neoadj	38/62	1.267 (1.098–1.463)	Age, site, size, pT, pN, n° N+, type surgery, D1 *vs.* D2,

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
Di Bartolomeo *et al.*, 2015 (22)	Italy	Retrospective analysis of a prospective study	346	61	100 *vs.* 0	Proximal 18%, other 82%	100	Adj CT [100]	52/48	1.41 (0.97–2.04)	TNM stage, G, osteopontin, E-caderina, beta catenina, COX2
Eom *et al.*, 2012 (23)	Korea	Retrospective series	448	52.6	100 *vs.* 0	NR	100	No	46.6/41.7	1.03 (0.51–2.10)	Type surgery, pT, pN
Fujitani *et al.*, 2012 (24)	Japan	Retrospective series	70	19.4	100 *vs.* 0	Proximal 40%, other 60%	100	Neoadj CT	28.5/71.5	1.323 (0.635–2.755)	Age, sex, pT, pN, G, R+
Gómez-Martin *et al.*, 2012 (25)	Spain	Retrospective series	148	NR	0 *vs.* 100	NR	NR	Yes (81.8)	50.7/28.3	1.47 (1.01–2.17)	PC, HER2
Gong *et al.*, 2005 (26)	US	Retrospective series	86	25.7	84 *vs.* 16	NR	100	No	61.6/38.4	1. 37 (0.77–2.49)	Stat3, VEGF, MVD, TNM stage, R+, age
Guo *et al.*, 2013 (27)	China	Retrospective series	2,379	65	100 *vs.* 0	Proximal 12%, other 88%	100	NR	55/45	1.182 (1.045–1.336)	Age, size, Borrmann type, LVI, pT, pN
Ha *et al.*, 2013 (28)	Korea	Retrospective series	495	NR	98 *vs.* 2	Upper rd 16%, other 84%	100	Yes adj CTRT [100]	35/59	1.301 (0.834–2.030)	MET, M+, pN, age, sex, G
Hayashi *et al.*, 2008 (29)	Japan	Retrospective series	134	69	100 *vs.* 0	Proximal 24%, other 76%	100	NR	37/63	1.262 (0.668–2.385)	Age, TNM stage, HER1-2-3-4
He *et al.*, 2012 (30)	China	Retrospective series	103	NR	53.3 *vs.* 46.6 (stage III, IV)	Proximal 9.7%, other 90.2%	100	Yes (for advanced stages)	74.7/25.2	2.470 (1.166–5.230)	Kiel stage, Snail
Hsu *et al.*, 2011 (31)	Taiwan	Retrospective series	1,036	NR	46.6 *vs.* 53.7 (stage III, IV)	GEJ 16.4%, 83.5% other	100	Yes [60]	50/37.6	1.450 (1.163–1.806)	Age, size, pT, pN, R+, VI, HP
Hu *et al.*, 2015 (32)	China	Retrospective series	96	NR	25 *vs.* 75 (stage III, IV)	NR	100	No	41.6/58.3	1.311 (0.717–2.396)	CXCR3 expression, age, pT, pN
Jang *et al.*, 2010 (33)	Korea	Retrospective series	11,189	NR	88 *vs.* 12	Upper 3rd 11.3%, other 82.7%	100	No	36.6/52.3	1.085 (0.958–1.228)	Sex, age, size, G, TNM stage, R+, site
Janjigian *et al.*, 2012 (34)	US	Retrospective analysis of 6 clinical trials	381	18.2	0 *vs.* 100	GEJ 36.7, 50.1 other	NR	Yes (1st or 2nd line)	48.2/46.4	1.33 (0.93–2.32)	Age, sex, HER2, PS, CT type, site, stage IV, liver & peritoneal M+
Jun *et al.*, 2009 (35)	Korea	Retrospective series	973	NR	100 *vs.* 0	NR	100	NR	NR	1.540 (0.782–3.032)	Size, G, TNM stage, LVI, VI, PNI

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
Jung *et al.*, 2011 (36)	Korea	Retrospective series	293	38.2	48.8 (stage III) *vs.* 51.2 (stage IV)	Upper 3rd 19.1%, other 80.9%	100	Yes adj CT (62.5)	50/50	1.585 (1.135–2.212)	NLR, TNM stage, surgery, PNI, adj CT
Kulig *et al.*, 2010 (37)	Poland	Retrospective series	1,992	NR	64 *vs.* 36	Proximal 20%, other 80%	100	Yes [69]	68.4/42.6	1.01 (0.87–1.16)	Age, BMI, site, splenectomy, pT, pN, LNR, M+, R+, adj CT
Kunz *et al.*, 2012 (38)	USA	Retrospective SEER database	9,325	NR	88.1 *vs.* 5.4	Esophagus/ cardia 34.3, antrum/body/ fundus 32.8	100	Yes 30.8 (RT 23)	8.5/19.5/71.8 (other)	1.347 (1.264–1.434)	Age, sex, race, SES, site, TNM stage, G, surgery, CT, RT, hospital size, institution, year,
Kawanishi *et al.*, 2000 (39)	Japan	Retrospective series	90	NR	93 *vs.* 7	NR	100	NR	47.7/52.3	1.451 (0.426–4.429)	pN+, pT, peritoneal carcinomatosis, AMFR+, ECD+, AMFR/ECD+
Kim KH *et al.*, 2011 (40)	Korea	Retrospective series	149	65.2	83.2 *vs.* 16.8	Upper 16.1%, other 83.9%	100	Yes adj CT [100]	39.6/46.4	1.137 (0.799–1.617)	Type surgery, LNR, TNM stage, ERCC1 & GSTP1
Kim MA *et al.*, 2005 (41)	Korea	Retrospective series	729	47	90.2 *vs.* 9.8	Cardia 14.4%, 85.6% other	100	NR	37.7/55.4	1.106 (0.866–1.413)	Site, TNM stage, LVI, R+, WHO classification
Koh *et al.*, 2013 (42)	Korea	Retrospective series	143	NR	40 *vs.* 60	GEJ/cardia 15.4%, other 84.6%	100	Yes preop CT [100] + post CT (62.9)	26.5/73.5	1.912 (1.147–3.186)	pN+, M+
Kurokawa *et al.*, 2015 (43)	Japan	Multicentre retrospective study	1,148	62	100 *vs.* 0	Upper 22.2 lower, middle 77.8	100	No	54/46	1.07 (0.86–1.33)	Age, sex, site, pT, pN, adj CT, HER2
Lee HS *et al.*, 2003 (44)	Korea	Retrospective series	329	42	86 *vs.* 14	NR	100	No	37.3/52.8	1.46 (0.80–2.65)	TNM stage, TSG expression
Lee HS *et al.*, 2013 (45)	Korea	Retrospective series	653	51	80.7 *vs.* 9.3	NR	100	Yes adj CT (44.2)	48.7/35.7	1.790 (0.894–3.584)	Tumor deposit, pT, pN+, LVI, VI, PNI
Lee HW *et al.*, 2015 (46)	Korea	Retrospective series	179	96	95 *vs.* 5	Cardia 2.8%, other 97.2%	100	No	54/46	1.579 (0.989–2.521)	Size, pT, pN, p4ebp1
Lee JH *et al.*, 2015 (47)	Korea	Retrospective series	111	74, 9	100 *vs.* 0	Upper-medium 13.5%, other 86.5%	100	Yes adj CT (1.7)	NR	2.216 (0.184–26.632)	Age, sex, D2, PNI, site, size, G, pT
Lee OJ *et al.*, 2009 (48)	Korea	Retrospective series	106	NR	81.1 *vs.* 18.9	Cardia 3.8%, other 96.2%	100	No	41.5/58.5	1.81 (0.38–8.49)	Age, sex, grade, TNM stage, mucin phenotype

Table 1 (*continued*)

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Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
Marano *et al.*, 2015 (49)	Italy	Retrospective series	274	53	100 *vs.* 0	Upper 28.1%, other 71.9%	100	No	54.7/39.7	1.074 (0.76–1.63)	Age, site, G, AJCC TNM version
Martinho *et al.*, 2013 (50)	Brazil	Retrospective series	152	62.3	82.2 *vs.* 17.7 (stage III, IV)	Proximal 10.5%, other 89.5%	100	NR	65/35	1.56 (0.74–3.28)	Sex, size, WHO classification, pN, LVI, VI, PNI, RKIP
Matsubara *et al.*, 2008 (51)	Japan	Retrospective series	87	NR	0 *vs.* 100	NR	100	Yes (first line)	46/54	1.71 (1.08–2.70)	IGFR, PS
Min *et al.*, 2015 (52)	China	Retrospective series	215	NR	100 *vs.* 0	Cardia 20%, other 80%	100	NR	69.3/19.5	1.324 (0.839–2.088)	Sex, age, size, site, G, VI, pT, pN, TNM stage , peritoneal carcinomatosis, G3BP1
Nagashima *et al.*, 2005 (53)	Japan	Retrospective series	55	NR	36 *vs.* 64	NR	No	Yes	55/45	1.695 (1.159–2.487)	Molecular phenotype, TNM stage, PS, macroscopic type, age
Orditura *et al.*, 2014 (54)	Italy	Retrospective series	41	22	100 *vs.* 0	Gej 100%	100	Yes neoadj CTRT [100]	46/54	1.41 (0.46–4.27)	G, pT, pN, clinical response, TRG, TNM stage, LNR, stage/response
Otsuki *et al.*, 2011 (55)	Japan	Retrospective series	106	48	58 *vs.* 42	NR	100	NR	44/56	1.1 (0.46–2.7)	pT, pN, vimentin RNA
Park KW *et al.*, 2014 (56)	Korea	Retrospective series	154	NR	100 *vs.* 0	NR	100	NR	NR	1.165 (0.843–1.608)	LNR, TNM stage, type surgery, NFKB, VEGF
Park S *et al.*, 2015 (57)	Korea	Retrospective series	4,282	35.8	100 *vs.* 0	Upper third 13.4%, other 86.6%	100	Yes adj CT except pT1N0	44/56	1.498 (1.019–2.202)	Age, G, site, pT, pN, VI
Pinheiro, 1999 (58)	the Netherlands	Retrospective series	1,543	NR	65 *vs.* 35	Cardia 21%, other 79%	100	NR	83/13	1.44 (1.2–1.7)	Age, site, TNM stage, surgery
Qiu *et al.*, 2014 (59)	China	Retrospective series	838	NR	90 *vs.* 10	36% proximal, 56% distal	100	Adj CT [70]	33.9/51	1.440 (1.004–2.066)	Age, sex, TNM stage, HER2, G
Reim *et al.*, 2013 (60)	German	Retrospective series	1,767	77	75 *vs.* 25	Upper not GEJ 37.2%, other not GEJ 62.8%	100	Yes neoadj CT 19, adj CT 6.6	43.8/34.7	1.245 (1.084–1.432)	TNM stage, pT, pN, M+, R+, age, LVI, LNR, G
Rodríguez Santiago *et al.*, 2005 (61)	Spain	Retrospective series	183	43	100 *vs.* 0	Superior 17.5%, other 82.5%	100	Yes adj CT if pN+	47.5/35	2.45 (1.37–4.37)	Age, sex, pT, LNR, site

Table 1 (*continued*)

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Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
Rosa *et al.*, 2014 (62)	Italy	Retrospective series	936	NR	82.4 *vs.* 17.6	Upper third 19.1%, other 80.9%	100	Yes periop CT 2.9 & adj CT 38.5	48/42.9	1.34 (0.86–1.73)	TNM stage, site, year, nodes retrieved, complications, multivisceral resections, R+
Sawaki *et al.*, 2012 (63)	Japan	Retrospective analysis of a prospective study	101	18.6	0 *vs.* 100	GEJ 3.9%, other 96.1%	15.7	Yes first line CT ± trastuzumab [100]	72.5/9.8	3.24 (1.08–9.70)	Treatment arm, sex stage, age, site, measurable disease, n° lesions, n° M+ sites, visceral M+, surgery, previous CT, HER2 status
Shen *et al.*, 2014 (64)	China	Retrospective series	909	70	97.6 *vs.* 2.4	Cardia 34%, other 66%	100	Yes adj CT [32]	42.5/57	1.15 (0.79–1.68)	Age, sex, platinum regimen, POU5F1P1 rs10505477
Shim HJ *et al.*, 2011 (65)	Korea	Retrospective series	174	NR	0 *vs.* 100	GEJ-cardia 6.3%, other 93.7%	55.7	Yes 3rd line CT [100]	58.6/23.6	1.02 (0.62–1.69)	PS, albumin, G, DCR first line, DCR second line, PFS 2nd line
Shim JH *et al.*, 2014 (66)	Korea/USA	Retrospective series	2,187	>72	94.2 *vs.* 5.8	Upper third 13%, other 87%	100	No	47/36	1.25 (0.83–1.66) US, 1.25 (0.9–1.66) Korea	Site, sex, n° N+, n° N, pT
Shimoyama and Kaminishi, 2003 (67)	Japan	Retrospective series	123	NR	92 *vs.* 8	NR	100	NR	46/54	5.8 (1.5–23.3)	Angiogenin, pT, pN
Shinmura *et al.*, 2014 (68)	Japan	Retrospective series	271	NR	100 *vs.* 0	NR	100	NR	NR	1.662 (0.871–3.298)	pT, pN, AURKA, TNK2
Sierra *et al.*, 2003 (69)	Spain	Retrospective series	156	37.3	75 *vs.* 25	Proximal 18%, other 82%	100	Yes adj CT [37]	40/60	2.78 (1.47–5.25)	TNM stage, LNR, M+, type of lymphadenectomy
Stiekema *et al.*, 2013 (70)	the Netherlands	Retrospective series	132	53	100 *vs.* 0	Upper third 18%, other 82%	100	Yes neoadj CT or CTRT 57 adj CT or CTRT 36	47/53	2.317 (1.188–4.519)	pT, pN, adj CT, R+
Stiekema *et al.*, 2015 (71)	the Netherlands	Retrospective series	409	18 and 11	100 *vs.* 0	Proximal 3%, other 97%	100	Yes neoadj CT 23 + adj CTRT 9	54/46	1.31 (1.03–1.68)	Age, sex, site, type surgery, n° N+, pT, pN, adj CT, neoadj CT, adj CTRT
Sun *et al.*, 2015 (72)	China	Retrospective series	265	19-feb	15 *vs.* 85 (stage II–IV)	NR	100	No	49/51	1.574 (1.081–2.292)	PDH expression, age, size, pT, TNM stage, pN+, LVI, G
Takashima *et al.*, 2014 (73)	Japan	Pooled analysis of two phase III trials	319	NR	0 *vs.* 100	NR	27.9	Yes 2nd line CT [100]	51/49	1.03 (0.8–1.315)	Trial enrollment, sex, age, PS, Borrmann type, surgery, target lesions, peritoneal carcinomatosis, n° M+ sites

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Country	Type of study	N pts	Follow up (months)	Stage (I–III *vs.* stage IV) (%)	Site	Primary surgery (%)	Ct (%)	Intestinal/ diffuse (%)	OS HR (diffuse *vs.* intestinal)	Variables used in MVA
Tan *et al.*, 2011 (74)	Various	Retrospective series	518	33, 56, 39, 36*	74 *vs.* 26	NR	100	Yes adj CT [16]	48.8/35.3	0.81 (0.50–1.32)	Intrinsic genomic subtypes, G
Verlato *et al.*, 2015 (75)	Italy	Retrospective series	568	106	100 *vs.* 0	NR	100	No	61/39	1.91 (1.09–3.36)	Hospital, age, sex, site, pT, pN, D2 *vs.* D3
Wang BB *et al.*, 2011 (76)	Korea	Retrospective series	3,018	NR	85 *vs.* 15	Upper 11.87%, other 88%	100	NR	44/56	1.131 (1.012–1.358)	Sex, age, past history, family history, site, number lesions, M+, R+, D1-2-3, type of resection, G, Borrmann type, pT, pN, n° N dissected
Wang L *et al.*, 2003 (77)	USA	Retrospective series	86	25.7	73.6 *vs.* 16.3	NR	100	No	61.6/38.4	0.9 (0.5–1.8)	TNM stage, Sp1, R+, age, sex
Wang X *et al.*, 2013 (78)	China	Retrospective series	866	NR	73.8 *vs.* 26.2	Upper 15.9%, other 84.1%	100	NR	61.8/34.3	1.152 (0.897–1.480)	Age, sex, site, size, G, pT, pN, R+, TNM stage, PLA2G2A expression
Wu CW *et al.*, 2006 (79)	Taiwan	Retrospective analysis of a prospective study	221	94.5	100 *vs.* 0	12.6 % upper, other 87.4% other	100	No	NR	1.20 (0.80–1.80)	Age, D1 *vs.* D3, sex, site, Borrmann type, pT, pN, spleen/pancreas removed, type surgery, transfusions
Wu X *et al.*, 2010 (80)	China	Retrospective series	962	26.4	100 *vs.* 0	NR	100	NR	NR	1.036 (0.786–1.366)	Age, sex, TNM stage, site, IL17A and F genotype
Xu *et al.*, 2012 (81)	China	Retrospective series	929	35	97.5 *vs.* 2.5	Fundus or cardia 38.7%, other 61.3%	100	No	41.9/58.1	1.181 (0.945–1.474)	Age, sex, size, TNM stage, SOD2 rs4880
Yao *et al.*, 2004 (82)	USA	Retrospective series	86	25.9	72 *vs.* 28	Proximal 23%, other 77%	100	No	66/44	0.78 (0.36–1.68)	SP1, VEGF, TNM stage, R+, G, age
Ye training cohort, 2013 (83)	Various	Retrospective series	81	NR	75 *vs.* 25	NR	100	No	52/48	1.11 (0.63–1.92)	Age, sex, size, TNM stage, MDM2 expression
Ye testing cohort, 2013 (83)	Various	Retrospective series	368	NR	86 *vs.* 14	NR	100	Yes adj CT (23.2)	57/43	0.98 (0.75–1.26)	Age, sex, size, TNM stage, MDM2 expression
Ye validation cohort, 2013 (83)	Various	Retrospective series	357	NR	97.2 *vs.* 2.8	NR	100	Yes adj CT (37.5)	41/59	0.68 (0.49–0.96)	Age, sex, size, TNM stage, MDM2 expression

*, follow up of different cohorts; °, analysis of three different cohorts in the same publications. OS, overall survival; PFS, progression-free survival; LNR, lymphnode ratio; GEJ, gastro-esophageal junction; n pts, number of patients; HR, hazard ratio; MVA, multivariate analysis; NR, not reported; CT, chemotherapy; RT, radiotherapy; G, grade; R+, margin resection positive; TNM, tumor node metastasis; VEGF, vascular endothelial growth factor; pT, pathological tumor stage; pN, pathological nodal stage; n° N+, number of node positive; D, lymphadenectomy extension; M+, metastases; LVI, lymphovascular invasion; PNI, perineural invasion; VI, vascular invasion; PS, performance status; DCR, disease control rate; HER, human epidermal receptor; HP, helicobacter pylori.

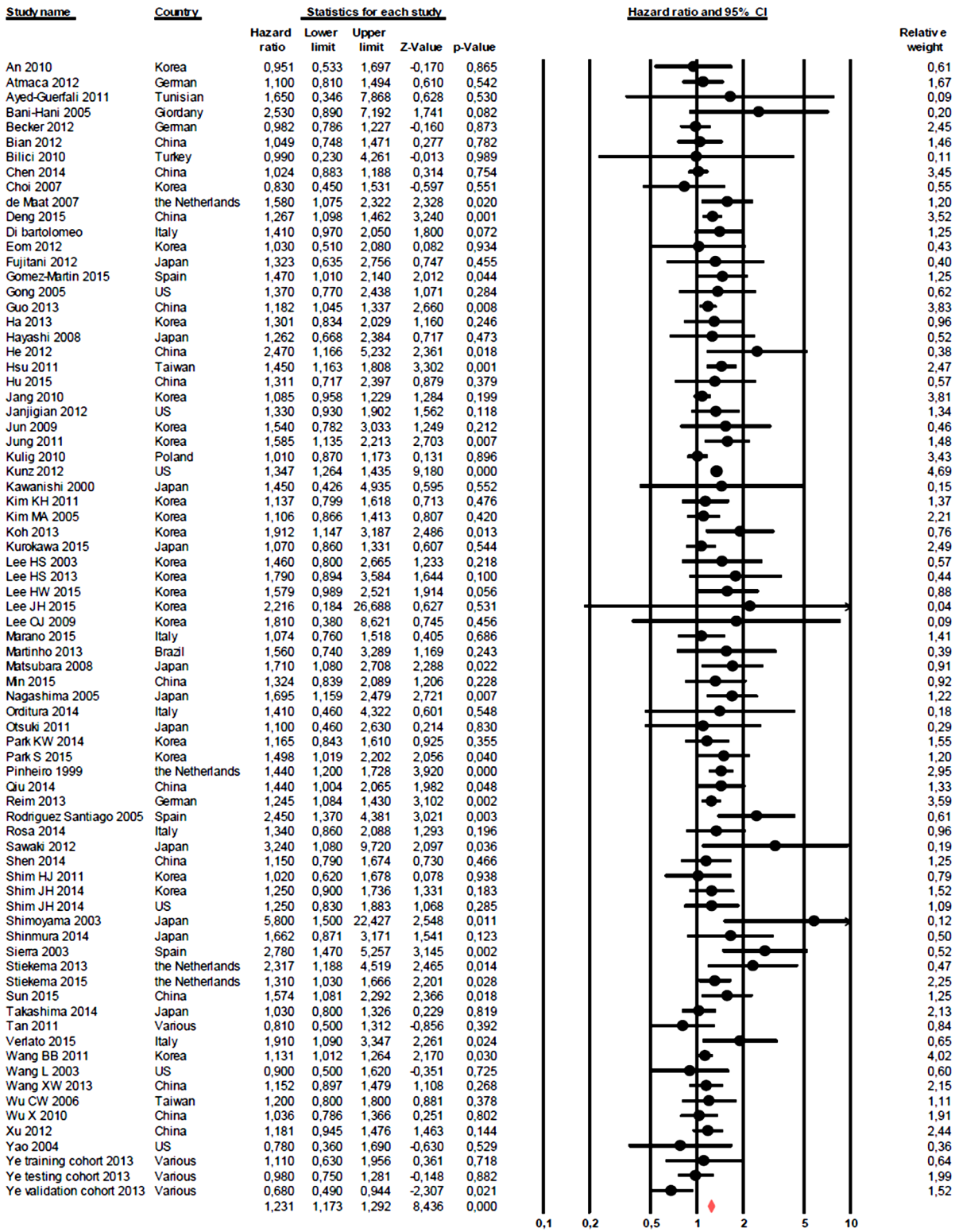

Figure 2 Meta-analysis (forest plot) of 73 studies assessing overall survival of diffuse vs intestinal histology in gastric cancer.

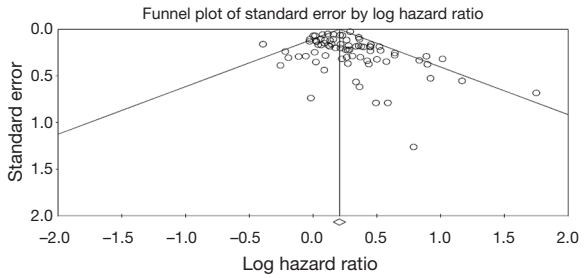

Figure 3 Funnel plot for publication bias (all studies included) of overall survival meta-analysis.

effect model).

The combined HR according to the stage of disease (stage I–III in all tumors *vs.* stage IV disease only) was statistically significant. In fact, a poorer prognosis was observed for both stage I–III and more advanced stages GCs (n=25 *vs.* n=7 studies) with diffuse histology (HR 1.21; 95% CI, 1.12–1.3; P<0.0001 *vs.* HR 1.25; 95% CI, 1.04–1.5; P=0.014 according to random effect model).

In patients exposed to systemic therapy (either for early or advanced disease), the results were similar, with diffuse histology associated with adverse prognosis (HR 1.27; 95% CI, 1.17–1.37; P<0.0001). Similar results were observed in studies that not included patients treated with systemic therapy (HR 1.15; 95% CI, 1.07–1.24; P<0.0001 according to random effect model).

Publication bias

Both Begg's and Egger's test were significant for publication bias (*Figure 3*). Given the publication bias observed, we calculated the Trim-and-Fill-adjusted analysis. With this analysis, 16 missing studies based on a random effects model (according to trim and fill method), put to the left side of the mean effect, are calculated for a final HR 1.18 (95% CI, 1.12–1.24). Finally, the overall result remains unchanged after the one-study-removed procedure, so no dominant study was included.

Discussion

According to Lauren's classification, GC is categorized as intestinal- and diffuse types (5). Although the Lauren classification system was developed in 1965, it is still widely accepted and employed by pathologists and oncologist, and represents a simple, reproducible and robust classification approach. Intestinal-type GC is more prevalent in men and older people and is associated with chronic inflammation: as a consequence of Helicobacter Pylori-related atrophic gastritis in the antrum, and as a result of reflux in the gastroesophageal junction. Diffuse-type GC is more prevalent in younger people and women, with the absence of a pathogenetic role of inflammation and strong relationship with cell adhesion dysfunction—even as part of hereditary syndromes in germline *CDH1* mutated patients. Clinically, the two histotypes of GC have a different pattern of metastatic spread, with more frequent peritoneal involvement in diffuse cancers (84). Currently, the management of patients with GC is mostly dependent on prognostic assessment based on clinical and pathological stage, while histology still needs to be validated as a prognostic or even predictive factor in patients with GC. As a consequence, treatment algorithms and clinical trials have not been tailored on histotype yet.

In this meta-analysis, we explored whether histology, according to Lauren classification, retains an independent prognostic significance in GC. To our knowledge, this is the first meta-analysis to address this issue. The final pooled analysis showed that diffuse histology, as literature data previously suggested, is confirmed as an independent prognostic factor in multivariate analysis in more than 60,000 patients with resected, localized or advanced GC. In the global population, the risk of death was increased by 23%, and this increased risk was not altered by race, stage (locally advanced *vs.* metastatic) and exposure to chemotherapy. As for now, this represents the most updated systematic on this topic. Liu *et al.* (7), previously, conducted a meta-analysis examining the survival outcomes among patients with diffuse *vs.* intestinal histology. They found a better 5-year OS for patients treated with surgery compared with radiotherapy. A major limitation of their study was that they used adjusted and unadjusted odds ratios that do not take into account adjustment for common clinicopathological variables as our paper did.

In patients with GC, the clinical experience suggests a significant variability of outcomes and responsiveness to treatments. The heterogeneity of GC is related to several factors such as epidemiology, pathogenesis, and disease biology. Prognostic and predictive factors beyond disease stage (3,4) are clearly needed, and histotype could be proposed as a surrogate marker of disease biology. A 3-group classification was previously proposed according to histology and tumor site, namely "proximal non-diffuse", "diffuse", and "distal non-diffuse" types (85,86). It was shown that the subtypes have distinct gene expression profiles. Moreover,

the TCGA study showed the presence of four genomic subtypes [namely, EBV-positive, microsatellite instable, Genome Stable and Chromosomal Instability (87)]. It must be pointed out that microsatellite instable GC is mainly represented by non-diffuse distal cancers while genome stable by intestinal-type ones and chromosomal instability by diffuse-type ones. Thus, there seems to be a good correlation between histology and biology within the TGCA dataset.

The clinical relevance of these data will hopefully allow the distinction in managing each subtype separately. While increasing our knowledge of biological heterogeneity of GC, the goal is to use the distinct biologic subtypes as prognostic and predictive biomarkers to improve patients' management and outcome. However, limited work has been done to create a consensus about the several published subtypes, and their clinical applicability is still difficult due to limited widespread of technologies and costs. Some tools are nowadays implemented for estimating patients' outcome, such as nomograms. One example in GC is the nomogram developed by Kattan *et al.* (88), where the predictions were based on the following established prognostic factors: patient's age and gender, tumor size, depth of tumor invasion, percentage of positive and negative nodes and, notably, tumor primary location and histology. Based on these data and our results, histology may be already used as a simple, costless and easy stratification factor in clinical trials for patients with homogeneous disease stage. It may be also used with predictive purposes when assessing the efficacy of newer drugs. Notably, it was already shown that HER-2 amplification is mostly found in intestinal-type and proximal cancers (89), while FGFR2 amplification is typical of diffuse tumors (90), and even anti-angiogenic drugs may be more effective in intestinal-type GC (91).

A limitation of this review, as with any review or meta-analysis, is publication bias. Publication bias occurs when negative results (negative histology results in our case), which are often not published, are excluded. Analyses of efficacy by histologic subtype may not be reported for several reasons: the histology data were not collected; analyses were not performed because the study was inadequately powered or because historical evidence suggested such analyses were not important; analyses were performed but results were negative (and/or inconsistent across other endpoints) and therefore not reported; or results of analyses were positive but not reported because it was unclear how to interpret the findings. However, heterogeneity was moderate (I^2 =38%), and it has been taken in account through a random effect model analysis. Also, even if publication bias was somewhat significant with Begg's and Egger's tests, the leave-one-out procedure, excluded any "dominant" study. Furthermore, sensitivity analysis adjusting for race, use of systemic therapy or stage did not modify the overall result substantially. Finally, the trim-and-fill procedure found that putting 16 asymmetric studies on the left of the mean effect of the funnel plot; the final results remained substantially unaltered. A second limitation is the use of the Lauren instead World Health Organization classification, that split adenocarcinomas in papillary, tubular mucinous, poorly cohesive and mixed forms. Only two papers included into classification of diffuse types poorly cohesive or signet ring cases, and aim of paper was the validation of prognostic significance of Lauren's subtypes, that is still controversial.

On the contrary, major strengths of this paper are the comprehensive search strategy, careful selection of studies, the attempt of subgroup analyses, and the use of survival outcome that consider HRs adjusted for common confounders.

Many biomarkers are being evaluated to establish prognostic or predictive factors in GC, and several have been identified for their potential key role, but their clinical use remains controversial. In this scenario, the prognostic role of histology seems to confirm a valid prognostic indicator and will play a significant role in future clinical trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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