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## REVIEW

# Tumour deposits are a significant prognostic factor in gastric cancer – a systematic review and meta-analysis

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## Tumour deposits are a significant prognostic factor in gastric cancer – a systematic review and meta-analysis

**Aims:** Tumour deposits (TDs) are clusters of cancer cells in the soft tissue that are discontinuous from the primary tumour. In this review we are exploring their relevance for prognosis in patients with gastric cancer.

**Methods and results:** A literature search was performed to identify studies providing data on TDs and prognosis in gastric cancer patients. Eight papers were included in the meta-analysis, which was carried out in terms of risk ratios (RR) and hazard ratios (HR) with 95% confidence interval (95% CI). Of 7445 patients, 1551 had TDs (20.9%). TDs were associated with a

decreased overall survival (OS) in univariate (HR = 2.82, 95% CI = 1.9–4.3) and multivariate analyses (HR = 1.65, 95% CI = 1.3–2.1). TDs were also associated with known prognostic factors such as synchronous metastatic disease (RR = 9.5), invasion depth (RR = 1.8), lymph node metastasis (RR = 1.7), lymphatic invasion (RR = 1.7), vascular invasion (RR = 2.6) and poor differentiation (RR = 1.2).

**Conclusions:** We found a strong indication that TDs are independent predictors of prognosis in patients with gastric cancer; hence, TDs should be included in the staging of gastric cancers.

**Keywords:** gastric neoplasms, prognosis, staging, tumour deposits

## Introduction

Gastric cancer (GC) is the fifth leading cause of cancer mortality worldwide, with a relatively high incidence in eastern countries such as Japan, China or Korea.<sup>1</sup> Currently, the gold standard for GC treatment in most parts of the world is surgery plus chemo(radio)therapy (CRT). This has been standard treatment in Europe and North America for many years, respectively,<sup>2,3</sup> while postoperative chemotherapy is

standard in most Asian countries.<sup>4</sup> A patient's individual treatment selection is based on disease stage, as more advanced stages will require more aggressive treatment, including chemotherapy and/or radiotherapy. Staging is determined by the extent of invasion of the primary tumour, the number of lymph node metastases (LNM) and presence of distant metastases. The current prognostic factors of GC are *HER2* status, residual disease (R0, R1, R2), the tumour site, age, extent of resection and molecular subtype (TNM 8th edition).<sup>5</sup> In colorectal cancer (CRC), tumour deposits (TDs) are included in staging because they have been shown to be an independent prognostic factor.<sup>6–9</sup> Until now, TDs have not been included in GC staging

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due to limited evidence, but are presumably also an independent prognostic factor.<sup>10–16</sup> TDs were first described in 1935<sup>17</sup> in the rectum. Since then, ‘tumour deposits’ have been reported under a variety of other terms, such as ‘extranodal spread’,<sup>18</sup> ‘positive nodules in extranodal soft tissues’<sup>12</sup> and ‘extranodal metastases’.<sup>11,15</sup> With regard to definition their origin is controversial,<sup>10,13–15,18</sup> as some authors consider TDs to be metastatic lymph nodes that have lost their structure, while others consider them to be disseminated cancer cells that originated from the primary tumour. The consensus is that they are discrete tumour foci found in surrounding fat (perigastric in GC) that show no evidence of residual lymph node tissue or continuity with the primary tumour.<sup>15</sup>

Therefore, we assessed the prognostic value of TDs in GC patients by performing a systematic review of published studies to determine whether the TD status influences outcome in GC patients. On the basis of the results, we will discuss whether TDs should be included in future editions of the TNM staging guideline.

## Methods

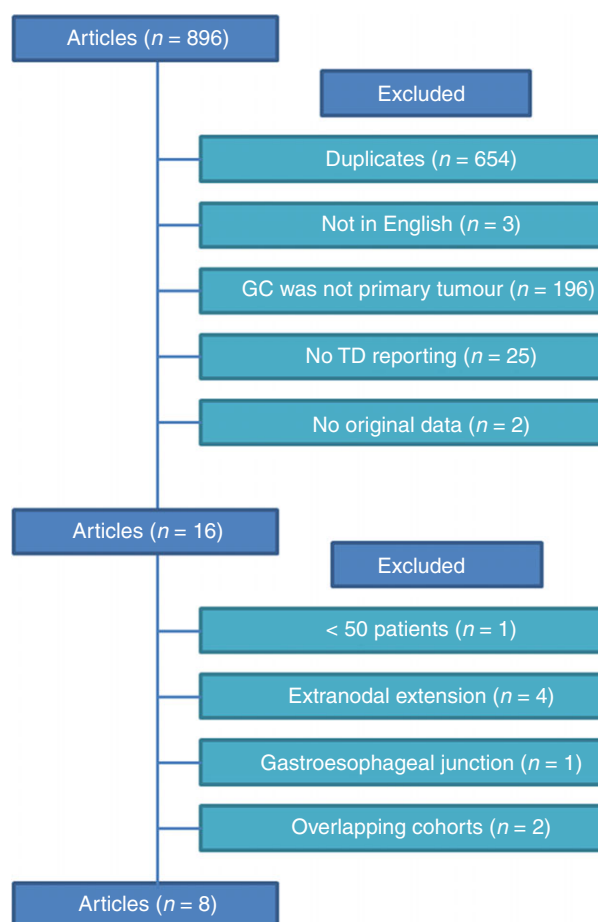
### SEARCH STRATEGY AND SELECTION CRITERIA

A comprehensive literature search was carried out using the Pubmed and Web of Science search engines from commencement to August 2018. The key words used for this search were: ‘tumour deposits’, ‘extranodal metastasis’, ‘extranodal spread’ and ‘prognosis’ or ‘staging’ in combination with ‘gastric cancer’, ‘stomach cancer’, ‘stomach tumour’ or ‘gastric tumour’.

Selection criteria included only original articles published in English which included at least 50 patients (Figure 1). In case of overlapping patient data, the study with the largest number of patients was included in this meta-analysis. Studies that included patients with other primary tumours were excluded. Lastly, studies in which histology was not reviewed for the entire cohort were also excluded, as TD reporting was uncommon in past years and could be under-reported in databases and pathology reports.

### DATA EXTRACTION AND STATISTICAL ANALYSIS

A meta-analysis was performed in terms of hazard ratio (HR) or risk ratio (RR) with 95% confidence interval (CI). The number of patients with and without TDs was obtained from each study. The tumour–node–metastasis (TNM) stage, HR, RR and overall survival (OS) obtained from each study were also extracted and entered in Review Manager version 5.3 (The Cochrane



**Figure 1.** Flowchart showing the article search strategy for the systematic review. The steps followed were identification of papers in the search, selection with eligibility criteria and final inclusion of papers. TDs, tumour deposits; CRT, chemoradiotherapy; RT, radiotherapy; GC, gastric cancer.

Collaboration, Copenhagen: The Nordic Cochrane Centre, 2012). If HR data were not available in a certain study, it was extracted from the Kaplan–Meier curves using the Parmar estimation.<sup>19</sup> The model used was a random-effects model where weighting was performed with the inverse variance. Heterogeneity was measured with  $I^2$ , where a percentage higher than 50% was considered a moderate heterogeneity of the samples. When heterogeneity was found, subanalysis was performed. A logistic regression analysis was also performed in order to investigate the multivariate relationship of pathological risk factors.

### QUALITY ASSESSMENT AND RISK OF BIAS

In order to assess the quality of the reporting in the studies included, we followed the REMARK (REporting recommendations for tumour MARKer prognostic

studies<sup>20</sup>) guidelines specifically focusing on TD reporting (Supporting information, Table S1). Only studies with data on outcome were included and were therefore subjected to quality assessment. Scoring was performed by two independent investigators (C.G.M. and I.D.N.). In case of disagreement, a consensus score was reached. All studies were scored according to these recommendations as 1, reported and 0, non-reported, and items that were not applicable were excluded from the calculation. Nineteen criteria were evaluated from all sections, giving special attention to the Methods section.

Analysis of publication bias through visual inspection of symmetry of funnel plots (Supporting information, Figure S1) was carried out. As the capacity to detect this bias was limited by the small number of studies included, the potential publication bias found in the funnel plots should be treated with considerable caution.

#### ETHICAL STANDARDS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation at Radboudumc and with the Helsinki Declaration of 1964 and later versions.

## Results

#### SEARCH RESULTS

A total of 896 papers were identified by searching in Pubmed and Web of Science databases. Duplicates and studies that did not meet the inclusion criteria were excluded (Figure 1). Three studies had overlapping patient data,<sup>12,21,22</sup> thus we included the study with the largest patient group.<sup>12</sup> We excluded studies with extranodal extension of lymph node metastasis<sup>12,23–25</sup> and a study with junction cancers<sup>26</sup> because it included patients with cancer in the gastro-oesophageal junction. Lastly, one study was excluded<sup>18</sup> because of insufficient number of cases without capsule rupture. Finally, eight studies were included for meta-analysis (Table 1), comprising 8431 patients who did not have neoadjuvant treatment.

#### QUALITY OF THE REPORTING

Eight studies were included in the meta-analysis to correlate TD presence with patient overall survival<sup>10–16,27</sup> and with other prognostic factors such as lymph node metastasis (LNM) and invasion depth. For lymph

vessel invasion (LVI) only five could be included,<sup>11,13,14,16,27</sup> and only four for vascular invasion (VI).<sup>11,14,16,27</sup> The median reporting of the studies calculated by a modified version of the REMARK guideline table was 66.9%, ranging from 44.4% to 77.8% (Supporting information, Table S1).

#### PROGNOSTIC IMPACT OF TDS

Of the eight studies, the mean frequency of TDs was 20.9%, ranging from 10.6% to 36.7% (Table 1). When TDs were present, overall survival was significantly decreased in the univariate (HR = 2.82, 95% CI = 1.87–4.28) and multivariate analysis (HR = 1.65, 95% CI = 1.30–2.11) (Figure 2). Considerable heterogeneity was observed between the studies ( $I^2 = 96%$  in univariate and  $I^2 = 41%$  in multivariate analyses), which could be explained by differences at the TNM stage. When studies were grouped according to different proportion of T1–3 versus T4 patients, the heterogeneity disappeared ( $I^2 = 13%$ ) (Supporting information, Figure S2). The quality of reporting did not correlate with the magnitude of HR (Spearman's  $r = 0.14$ ;  $P = 0.75$ ).

#### TDS AND HISTOLOGICAL RISK FACTORS ASSOCIATION

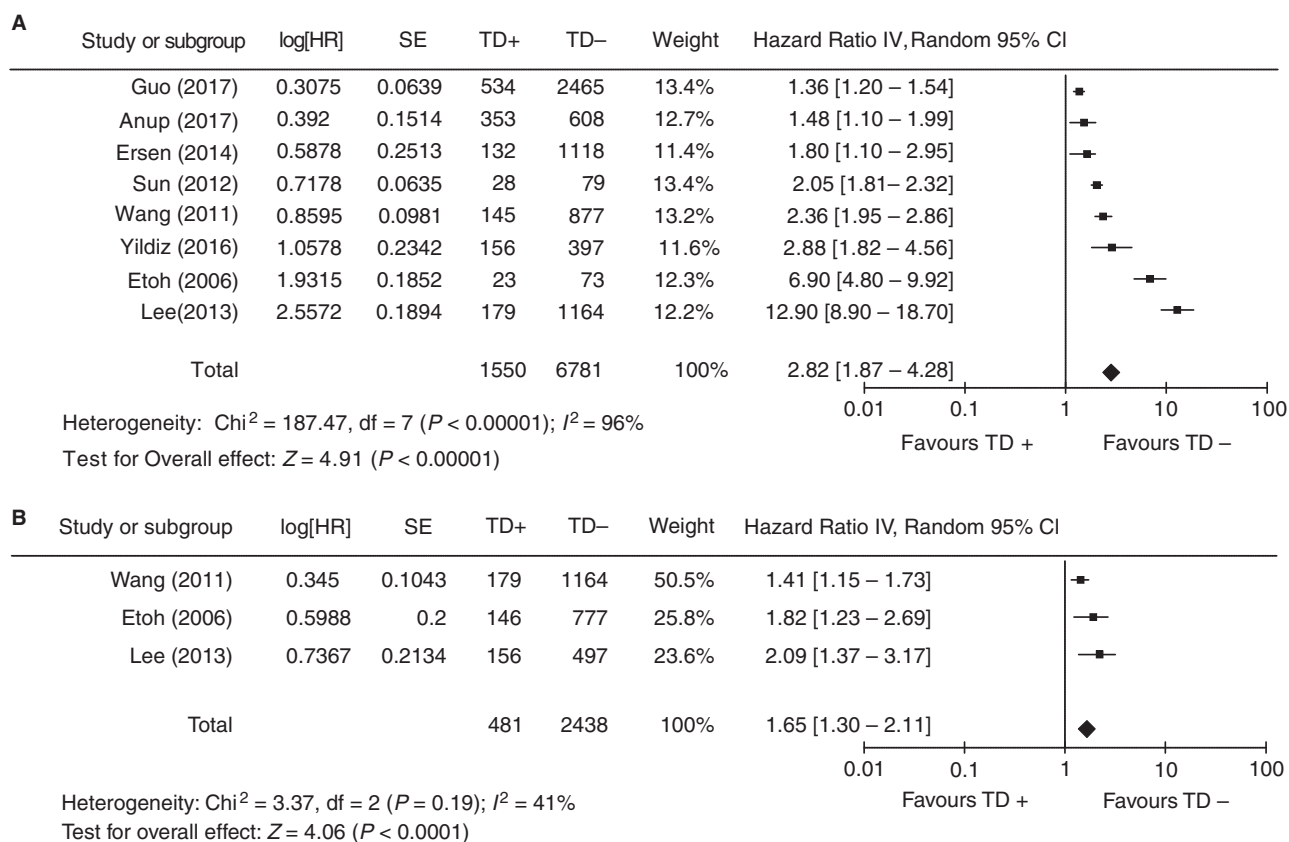
TDs occurred more frequently in tumours with a higher T-category (T3/T4 versus T1/T2: RR = 1.82, 95% CI = 1.39–2.37) and T4 versus T1/T2/T3; RR = 2.24, 95% CI = 1.62–3.09), LNM (RR = 1.71, 95% CI = 1.37–2.14), LVI (RR = 1.70, 95% CI = 1.29–2.24), VI (RR = 2.64, 95% CI = 1.21–5.74) and presence of metastases (RR = 9.50, 95% CI = 2.79–32.33) (Figure 3). Heterogeneity was found to be high (93–99%) among all comparisons. When studies were grouped according to different proportions of T1–3/T4 patients in each study,  $I^2$  (heterogeneity) was 0% for the T-category; it decreased substantially for LVI (from 94% to 49%) and reduced slightly for LNM and VI. Therefore, subgrouping by T category only explained invasion depth and LVI heterogeneity. The other pathological risk factor comparisons could not be explained by this subgrouping or by sample size or study populations. In spite of the high heterogeneity, the direction of the effect in the forest plots was broadly consistent.

When analysing the histological grade of the tumour, we found that poorly differentiated tumours (high-grade tumours) had a higher risk of presenting with TDs (RR = 1.23, 95% CI = 1.10–1.38) (Supporting information, Figure S3A). High heterogeneity

**Table 1.** Overview of the characteristics of the included studies

Study	Origin of cohorts	Period time	Tumour categories	Number of patients	% TDs
Anup <i>et al.</i> <sup>10</sup>	Fuzhou (China)	Jan 2005–Dec 2010	I–IV	1250 (264)*	10.6
Ersen <i>et al.</i> <sup>27</sup>	Izmir (Turkey)	Jan 1999–Dec 2010	I–IV	96	24.0
Etoh <i>et al.</i> <sup>11</sup>	Tokyo (Japan)	Jan 1993–Dec 1996	I–IV	1023	14.3
Guo <i>et al.</i> <sup>12</sup>	Tianjin (China)	Mar 2003–Dec 2011	I–IV	961	36.7
Lee <i>et al.</i> <sup>14</sup>	Seoul (South Korea)	Jan 2004–Dec 2004	I–IV	653	23.9
Sun <i>et al.</i> <sup>13</sup>	Shenyang (China)	Jan 1980–Mar 2010	I–IV	2998	17.8
Wang <i>et al.</i> <sup>15</sup>	Guangzhou (China)	Jan 1994–Dec 2006	I–IV	1343	13.3
Yildiz <i>et al.</i> <sup>16</sup>	Eskisehir (Turkey)	2010–2015	I–IV	107	26.2
All studies				7445	20.9

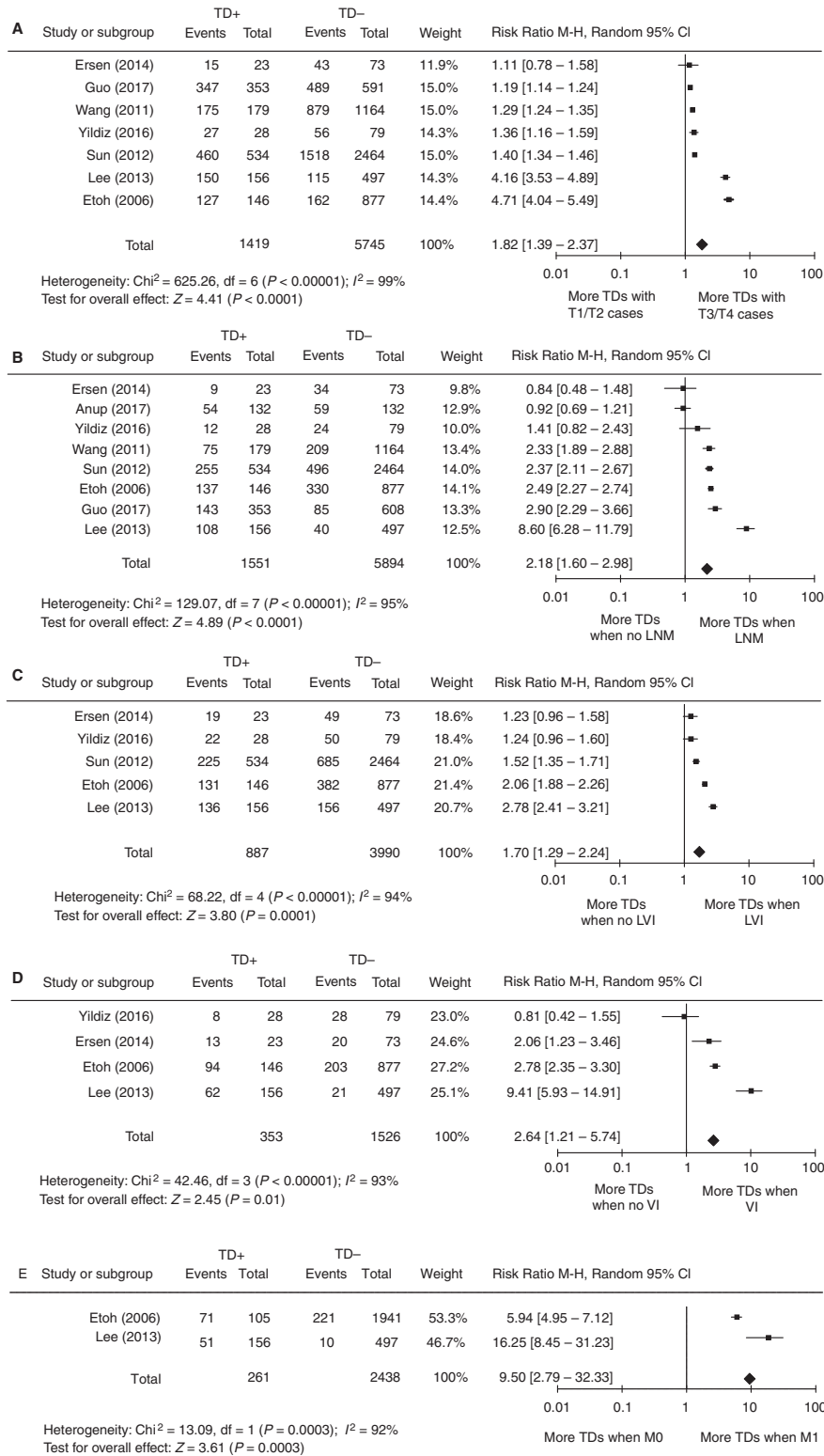
\*The incidence of TDs was determined using 1250 patients, but the rest of the calculations are based on 264 patients (case-cohort design, matched for tumour category).



**Figure 2.** The impact of TDs on patient outcome, measured by overall survival with a univariate analysis (A) and multivariate analysis (B). SE, standard error; TDs, tumour deposits; CI, confidence interval; IV, inverse variance.

could again be partially explained by T category (when corrected,  $I^2$  decreased from 79% to 51%). Analysis of histological Laurén subtypes<sup>28</sup> gave

diverse individual study results in TD subtype prevalence. No specific subtype was found to have a higher prevalence in our meta-analysis (RR = 1.05, 95%



**Figure 3.** Association between TDs and histological risk factors. **A**, Correlation between TDs and higher tumour categories (T1/T2 versus T3/T4). **B**, Correlation between TDs and LNM. **C**, Correlation between TDs and LVI. **D**, Correlation between TDs and VI. **E**, Correlation between TDs and metastasis (M1). TDs: tumour deposits; LNM, lymph node metastasis; LVI, lymph vessel invasion; VI, vascular invasion; M0, non-metastatic; M1, metastatic.

CI = 0.77–1.44) (Supporting information, Figure S3B). Heterogeneity could not be explained, although two studies had consistent effects on the forest plot.

## Discussion

In this systematic review and meta-analysis on TDs in GC, eight studies were included, with a total of 7445 patients and a mean TD incidence of 20.9%. Presence of TDs was associated with poor outcome in univariate analysis (HR = 2.82). To understand more clearly the importance of TDs as an independent prognostic factor, a multivariate analysis was performed on survival which showed a HR of 1.65, with a 95% CI from 1.30 to 2.11 (Figure 2). These correlations suggest that TDs are also an independent poor prognostic factor, as in these studies the effect was corrected for other risk factors such as invasion depth, LNM, LVI and VI. Furthermore, TDs correlated with known poor prognostic factors such as synchronous metastatic disease (RR = 9.50), LNM (RR = 1.71), LVI (RR = 1.70), VI (RR = 2.64) and invasion depth (RR = 1.82–2.24). This evidence further supports our contention that TDs could be an informative trait when staging a patient's disease progression, and therefore should also be included in GC staging.

Most studies did not report Laurén's histological subtypes of tumours; therefore, we cannot draw conclusions on incidence of TDs in different subtypes. Upon analysis of the studies that included the Laurén classification, we did not observe any association between subtype and TD prevalence. Poorly differentiated tumours more often presented TDs (RR = 1.23), which is consistent with previous literature<sup>29</sup> where it was stated that a higher histological grade (undifferentiated tumours) are correlated with higher T categories, and therefore with worse prognosis.

Although TDs in CRC have been included in the TNM classification since 1997, their prognostic value in other cancers such as GC is still debated. Many individual studies have reported TDs to be an independent prognostic factor in GC but, to the best of our knowledge, there is no meta-analysis to group these findings and demonstrate their significance. A recent study<sup>30</sup> which included a review on the impact of TDs in GC highlighted the undeniable prognostic impact of TDs and the need to conform a strategy for staging and treatment. Therefore, our results can only be compared to those in which TDs have been demonstrated to be an independent prognostic factor, such as for CRC. A recent meta-analysis of TDs in CRC included more than 10 000 patients<sup>31</sup>

with a mean TD prevalence of 22%, very similar to our results, i.e. 21%. When the authors assessed the relation between TDs and other risk factors they found associations with presence of LNM, distant metastasis and extramural vascular invasion. With the available information from the studies we included, we were able to establish associations with TD presence and LNM, tumour invasion depth, LVI, VI, histological grade and especially metastasis, showing that TDs are certainly associated with poor outcome.

As with all meta-analyses, the main drawback is the publication bias, as studies that show negative or insignificant results are less likely to be published. Another limitation is that we identified a number of papers in non-English language which could not be used in the meta-analysis. A major disadvantage is that only Asian papers are included, which potentially indicate that it may not be applicable to the global population. This is not surprising, as in western countries locally advanced tumours (with proven higher prevalence of TDs) are treated with neoadjuvant therapy. However, we did not find any reports including data from patients presenting TDs after neoadjuvant CRT treatment. Conversely, as these are patient groups that have not been treated with post-operative CRT, we were able to establish the true prognostic impact of TDs. Lastly, we believe that there might be a risk of bias in reporting on the prevalence of TDs. This could be due to the fact that TDs may have been reported in older studies as lymph node metastasis or vessel infiltration, and could potentially mean that TDs might be even more prevalent than estimated, which highlights the necessity of TDs reporting.

The need to include TDs in gastric cancer staging is indisputable, but the next step would be to discuss where they should be included. Unfortunately, there is no consensus with respect to the origin of TDs and many hypotheses have been explored, especially in CRC. In the first hypothesis, TDs are thought to originate from extranodal extension of LNM,<sup>32,33</sup> and would therefore be metastatic LNs that have lost their LN characteristic shape and structures and are, hence, mislabelled as TDs when in fact they are LNs. In the second hypothesis, TDs are thought to originate from (lympho)vascular invasion or perineural invasion, where cancer cells depart from the primary tumour and then disseminate into the surrounding soft tissues.<sup>32</sup> This might occur through lymph vessels, blood vessels or nerves, as well as through seeding in the fat tissue. As stated in a study for TDs in rectal cancer, the aggressive

characteristics of TDs and their success in disseminating through different pathways suggest they could be a satellite focus for systemic dissemination.<sup>33</sup> Thirdly, it is thought that they could be continuous to the primary tumour, and that this could be seen when cutting deeper into the tissue, as occurs with extramural invasion when cutting tangentially.<sup>34</sup> Lastly, in cases where patients have been treated pre-operatively, TDs are thought to be remnants of disease after therapy, and their significance is still being discussed.<sup>35</sup>

With the information from the studies we included and the correlation we observe with poor prognostic factors, we are inclined to believe that the second hypothesis might be the most factual hypothesis. Some of the studies included<sup>10,13,15</sup> even provided a TNM adjustment for their cases, and found that patients with TDs had similar survival curves to those patients without TDs but with N3, M1<sup>15</sup> or T4 staging.<sup>10,13</sup> Another study<sup>14</sup> proposed they should be included in the N-category not because of their origin, but because in their cohort, TD+ patient survival behaved more like that of pN1 patients. A possibility would be to include TD reporting separately, as is done with LVI and VI, where a simple binary outcome could be added. Having the recent experience of including TDs in CRC we believe that it should not, in any case, be included only when LNM is absent, as TDs have been shown to provide additional information in the presence of lymph node metastases.

In conclusion, this meta-analysis shows poor GC prognosis when TDs are present. They are associated with many other pathological risk factors and have proved to be an independent prognostic factor, although they are still not included in staging for GC. Because of this, we propose that TDs be reported and, as stated above, should be considered an independent prognostic factor.

## Conflicts of Interest

The authors declare no conflicts of interest.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Table including quality of reporting traits as described in the REMARK guideline.

**Figure S1.** Visual inspection of symmetry of funnel plots of the studies included in the meta-analysis.

**Figure S2.** Forest plot showing the subgrouping according to similar proportion of higher T- categories (T1–3 versus T4 patients) for overall survival HR UV analysis.

**Figure S3.** Forest plots showing association between TDs and higher tumour histological grade and (A) the Laurén diffuse TD subtype, (B) in relation to TD presence.