Tumor regression grade (TRG) for gastric cancer and radiological methods on predicting response to perioperative chemotherapy: a narrative review

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Background and Objective: Perioperative chemotherapy has been increasingly practiced on gastric cancer (GC) in Western Countries where two third of the patients have locally advanced disease at diagnosis. The histological and radiological evaluation of the tumor response to chemotherapy are both cornerstones of this multimodal therapy to predict the oncological outcomes. This article aims to review the current tumor regression grade (TRG) classification systems available and give an overview regarding radiological methods on predicting response to therapy.

Methods: A literature search was performed in MEDLINE (PubMed) and Scopus. The terms tumor regression grade, pathologic response, gastric cancer, gastric adenocarcinoma, RECIST 1.1, radiological prediction of response, perioperative, preoperative and neoadjuvant chemotherapy were included. English papers published until December 2021 were reviewed.

Key Content and Findings: Several TRG systems (Dworak, Mandard, Ryan, Becker, and Japanese Gastric Cancer Association-TRG) are available in literature, but none has been widely accepted and indicated by the international guidelines for GC. The response evaluation criteria in solid tumors (RECIST) 1.1 are still the most widely used radiological criteria in clinical trials despite their limitations regarding GC. In fact, the stomach is not a solid organ and its lesions are often not measurables. In order to discriminate responders from non-responders patients to perioperative chemotherapy for GC, all imaging techniques have been evaluated in terms of prediction of tumor response to chemotherapy. Indeed, there is still no clear evidence of superiority of one imaging technique over the others.

Conclusions: An effective histopathological evaluation method of TRG with an independent prognostic role for GC is urgently needed in clinical practice. A 4-tiered system for grading the regression of the primary tumor, associated with a 3-tiered system for the metastatic lymph nodes achieved a good consensus among experienced pathologists. To date, one of the most promising techniques for prediction of TRG is the diffusion weighted imaging (DWI) magnetic resonance imaging (MRI). As futures perspectives, molecular subgroups analysis and radiomics are spreading widely for the evaluation of their predictive prognostic role.

Introduction

Gastric cancer (GC) is still ranking third among the most common malignant tumors in terms of mortality rate. In the last decade, with the progression of the multimodal treatment, patients with early-stage disease (stage I) achieve a cure rate of 90%; nonetheless, patients with locally advanced GC have still a poor prognosis (1). The aim of neoadjuvant chemotherapy for locally advanced GC is to downstage the primary tumor improving the rate of radical surgeries. Since the publication of MAGIC and AIO-FLOT-4 trial results, showing that perioperative chemotherapy improves progression free (PFS) and overall survival (OS), it has progressively become the standard of care for locally advanced GC in Western Countries (2-5).

Pathologically, after neoadjuvant treatment and surgery there are two main methods to assess the residual cancer: tumor-node-metastasis (TNM) and tumor regression grade (TRG). TNM is currently used in the routine clinical practice worldwide and one of its limitations is to be founded on the location instead of the quantity of the residual tumor. Conversely TRG, that is a quantitative approach to describe the residual cancer, could be a strong and effective complement to TNM. Between the existing TRG systems there are two different methods to quantify the regressive changes after neoadjuvant chemotherapy: the estimation of the chemo-induced fibrosis in relation to residual tumor (6,7) or the estimation of the percentage of residual tumor related to the original tumor site (8-11).

However, not all patients have effective respond to perioperative chemotherapy. In non-responder, preoperative chemotherapy could be avoided. Thus, there is a need to identify a method to discriminate responder and non-responder patients.

The aim of this study is to review the different TRG classification systems and the current role of imaging for prediction of response to preoperative therapy in GC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-34/rc).

Methods

As part of this review, a literature search was performed using MEDLINE (PubMed) and Scopus. The terms tumor regression grade, pathologic response, gastric cancer, gastric adenocarcinoma, RECIST 1.1, radiological prediction of response, perioperative, preoperative and neoadjuvant chemotherapy were included. Only papers written in English and published until December 2021 were reviewed. Further details of the literature search are listed in *Table 1*.

Tumor regression modifications after preoperative therapy

During the macroscopic pathological evaluation an estimation of specimens is essential to estimate the extent of the tumor bed (the original site of the tumor) and to assure proper embedding for accurate microscopic investigation. The following step is the assessment of the chemo-induced changes into the tumor area under the microscope, which is the real core of the assessment process. Macroscopically residual tumor with ulcerating or infiltrative features or tumor regression signs like scars can be spotted (*Figure 1*). By histology, tumor regression after preoperative treatment is mainly represented by subacute and subchronic inflammation. Those cytotoxic effects usually develop between the end of the preoperative treatment and the surgical resection (12) (*Figure 2*). Microscopically, the morphological chemo-induced changes of the tumor can be described at cellular and stromal level. On the cellular level, several features can be found in the residual neoplastic component: cytoplasmic vacuolization, eosinophilic cytoplasm and marked nuclear atypia, including hyperchromasia, karyorrhexis, pyknosis and enlarged nuclei; oncocytic differentiation and development of neuroendocrine differentiation may be also found. Mitoses are hardly seen in opposition to apoptotic figures (6-8,13-17). Stromal changes embrace modifications like histiocytic reaction with foamy or occasionally hemosiderin-laden macrophages, cholesterol clefts and foreign body

Table 1 The search strategy summary

Items	Specifications
Date of search	4th April, 2022
Databases and other sources searched	EMBASE (PubMed), Scopus
Search terms used	Tumor regression grade, pathologic response, gastric cancer, gastric adenocarcinoma, RECIST 1.1, radiological prediction of response, perioperative, preoperative and neoadjuvant chemotherapy
Time frame	1950–2021
Inclusion and exclusion criteria	Inclusion: written in English
Selection process	Initial selection by Mainardi F and Berardi E then review and amended by Garbarino GM

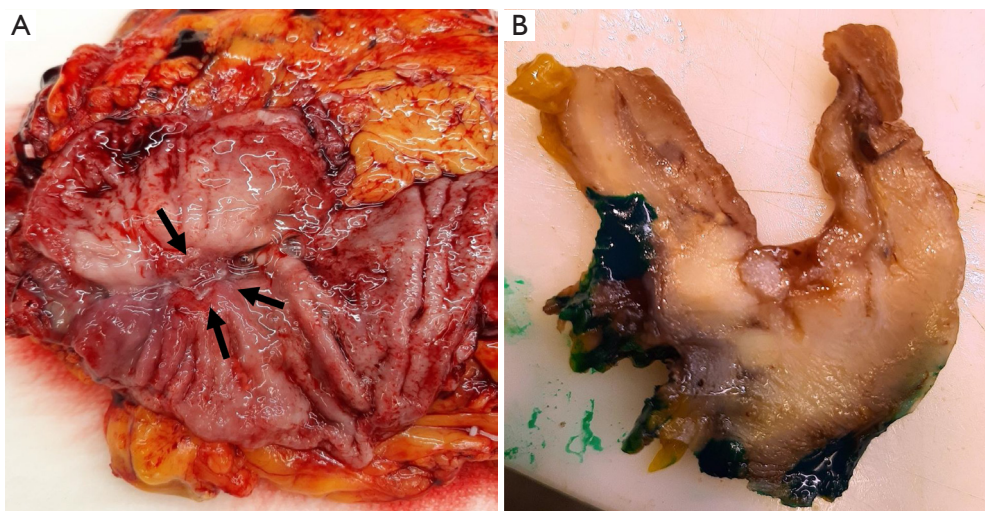RECIST, response evaluation criteria in solid tumors.

Figure 1 Macroscopic pathological evaluation of gastric neoplasia after preoperative chemotherapy. (A) Gross fresh examination of stomach adenocarcinoma with partial response to neo-adjuvant chemotherapy; note the ulcerated residual neoplasia (black arrows). (B) Section of the same tumor after fixation shows the presence dense fibrotic tissue involving the perivisceral fat. (Pictures from archive of Sant'Andrea University Hospital, Sapienza University of Rome).
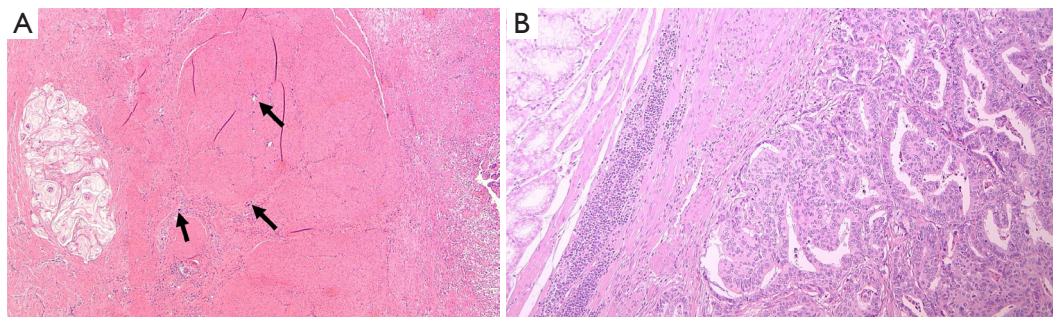

Figure 2 Example of tumor regression grade. (A) Partial response with scattered neoplastic glands (black arrows) through the fibrotic tissue and muscularis propria. Note the mucin-lake on the left edge (hematoxylin-eosin staining, ×10). (B) Absence of response: neoplastic glands on the right compared to non-neoplastic glands on the left (hematoxylin-eosin staining, ×20). (Pictures from archive of Sant'Andrea University Hospital, Sapienza University of Rome).
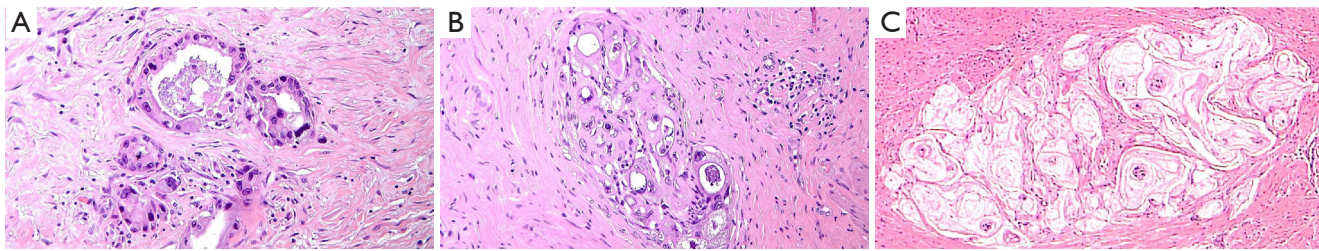
Figure 3 Histologic features of tumor after neoadjuvant chemotherapy. (A,B) High grade atypia in regressive glands surrounded by fibrosis (hematoxylin-eosin staining ×40); (C) Mucinous-Lake findings (hematoxylin-eosin staining ×20). (Pictures from archive of Sant'Andrea Hospital, Sapienza University of Rome).

reactions, and dystrophic calcifications. Unorganized branch of fibrous tissue with following disarray of the physiological structure is frequently observed. The presence of mucinous substance is widely documented, either as mucin lakes with some scattered residual neoplastic cells or as acellular mucin lakes (6,8,14,17-20). The mucous pool should not be regarded as a viable remaining tumor, but the presence of mucin lakes should be promptly followed by a careful search for viable residual tumor cells (*Figure 3*) (13). Vascular changes such as obliterative endarteritis and myxohyaline intimal proliferation in vessels have often been reported (10). Treatment-induced changes such as inflammation and oedema have also been reported in adjacent non-neoplastic tissue. The changes in non-tumor epithelia may be similar to those in neoplastic cells, with condensed chromatin, nuclear pleomorphism and eosinophilia (8,13,14). Such changes in non-tumor tissues may hinder the distinction from true neoplastic changes.

Several histopathologic chemo-induced modifications like calcification, acellular mucinous lakes and the pattern of response (fragmentation *vs.* bulk reduction) have been proved to be linked with patients' prognosis (20-22).

TRG systems

TRG systems categorize the quantity of regressive changes after perioperative chemotherapy with the aim to become an objective histopathologic prognostic tool in clinical practice. As previously mentioned, many histopathological detectable modifications are not frequently observed and are not completely specific for tumor regression after chemotherapy. Thus, the available regression classification systems mainly refer to single parameters, which are better reproducible: the proportion of residual tumor, expressed as a percentage, or the estimated ratio of regressed fibrosis to residual tumor, which is typically based on description. The available TRG systems that are those of Dworak (6), Mandard (7), Ryan (23) Becker (8,24) and Japanese Gastric Cancer Association-TRG (15) are summarized in *Table 2*.

Criticisms of TRG

The main issues on histopathologic evaluation of TRG are intra-and inter-observer variability and lack of uniform protocol. The Mandard and Dworak TRG grading systems showed a low interobserver-agreement among expert gastrointestinal pathologists for rectal cancer with kappa values of 0.28 and 0.35, respectively. For gastric and gastroesophageal junction cancers, Becker's TRG achieved the higher interobserver-agreement (kappa value =0.52). Whereas Mandard and the Japanese grading systems showed kappa values of 0.44 and 0.28, respectively (12). Another crucial limitation of TRG is the over-evaluation of the tumor response even in patients underwent to upfront surgery. Smyth *et al.* reported a 18% rate of TRG 2–3 (based on Mandard TRG) in patients that did not receive any preoperative chemotherapy (25). A robust and widely accepted TRG system is still needed for gastrointestinal malignancies after neoadjuvant therapy. To overcome the drawbacks and limitations of existing TRG systems in GC, a Delphi survey among international experts proposes a 4-level system for grading regression in the primary tumor, combined with a 3-level system for metastatic lymph nodes. In this system, based mainly on Becker's TRG, grade 1 corresponds to complete response (no residual tumor), grade 2 to subtotal regression (<10% residual tumor), grade 3 to partial regression (10–50% remaining tumor), and grade 4 to minimal/absent regression (>50% residual tumor). The response in metastatic lymph nodes was classified as: 'a' (complete), 'b' (partial) or 'c' (no response) (26).

Table 2 Summary of TRG systems

Regression grade	Relation between tumor and fibrosis			Proportion of residual tumor	
	Mandard	Dworak	Ryan	Becker	JGCA
Complete	TRG1; no residual cancer cell, total fibrosis	TRG4; no tumor cells, only fibrotic mass		TRG1a; 0% residual tumor	TRG3; 0% residual tumor
Subtotal	TRG2; rare residual cancer cells, scattered through the fibrosis	TRG3; difficult to find tumor cells microscopically, which scattered in fibrotic tissue	TRG1; no or rare residual cancer cells	TRG1b; <10% residual tumor	TRG2; 1–33% residual tumor
Partial	TRG3; more residual cancer cells, but outgrown by fibrosis	TRG2; easy to find tumor cells microscopically, with dominantly fibrotic changes	TRG2; more residual cancer cells	TRG2; 10–50% Residual tumor	TRG1b; 34–66% residual tumor
No response	TRG4; residual cancer cells outgrowing fibrosis TRG5; absence of regressive changes	TRG1; dominant tumor mass with obvious fibrosis TRG0; no regression	TRG3; residual cancer cells outgrowing fibrosis or no regression	TRG3; >50% residual tumor	TRG1a; >67% residual tumor TRG0; 100% residual tumor

TRG, tumor regression grade; JGCA, Japanese Gastric Cancer Association.

The main innovation of this classification system is the incorporation of lymph node regression, which provides a complementary prognostic tool.

Prognostic significance of TRG

Pathological complete response (pCR) has been proved to have a better prognosis compared to poor or incomplete response (3,27,28). Koh *et al.* have proved that patients with pCR had significantly better PFS than patients with non-pCR according to Mandard TRG system (29). Patients with pCR showed a significantly better PFS and OS compared with those with TRG2 to TRG5 (5 years PFS: 68.7% *vs.* 32.2% (P=0.002); and 5 years OS: 72.7% *vs.* 31.4% (P=0.002) (29). These results agree with the review of Tomasello *et al.* that showed that patients achieving a major pathologic response (pCR or near pCR with few residual cells) after preoperative chemotherapy have more than 50% decrease in the risk of death (27). In the same way, both Mandard and Becker TRG systems have been proved to be independent prognostic factors for survival in multivariate analysis (24,30). Controversially Smyth *et al.* did not demonstrate an independent effect of Mandard TRG on survival in the MAGIC trial (25). Despite the known association between pCR and improved survival, evidence of a linear relationship between the degree of response to chemotherapy and OS is still lacking in the literature. In a single-center cohort of 168 patients with GC treated with preoperative chemotherapy, Mansour

et al. found that the degree of histologic response did not independently predict disease-specific survival (31). Other studies that evaluated the prognostic value of Becker's TRG, Mandard's TRG, and the Japanese Gastric Cancer Association TRG showed a prognostic effect in univariate analysis, without confirming the prognostic value of any of these TRGs in multivariate analysis (32-40). Xu *et al.* also showed that histologic type, Lauren classification, vascular or lymphatic invasion, ypN, and post-surgical pathologic stage were significantly associated with survival, but unfortunately, TRG and pathologic T category were not found to be independent factors for OS and disease-free survival (DFS) in patients after perioperative chemotherapy (41). Conversely, Lombardi *et al.* proved by multivariate analysis that Becker TRG, lymph node ratio and tumor size were independent prognostic factors for DFS and disease specific survival (42). This difference among studies may be due to the difference of anatomical location, the selection of survival index and the tumor type (38). In addition to the status and evaluation of the primary tumor, one of the goals of neoadjuvant chemotherapy is the eradication of metastatic and micro-metastatic disease that may have spread to the lymph nodes (36,39). Nodal stage has also been established as an independent survival predictor in several articles (31-33,41). The clinical application of TRG, as an independent prognostic value in GC, is still ambiguous. Some authors deny that a marked histological response to treatment indicates improved survival, while others
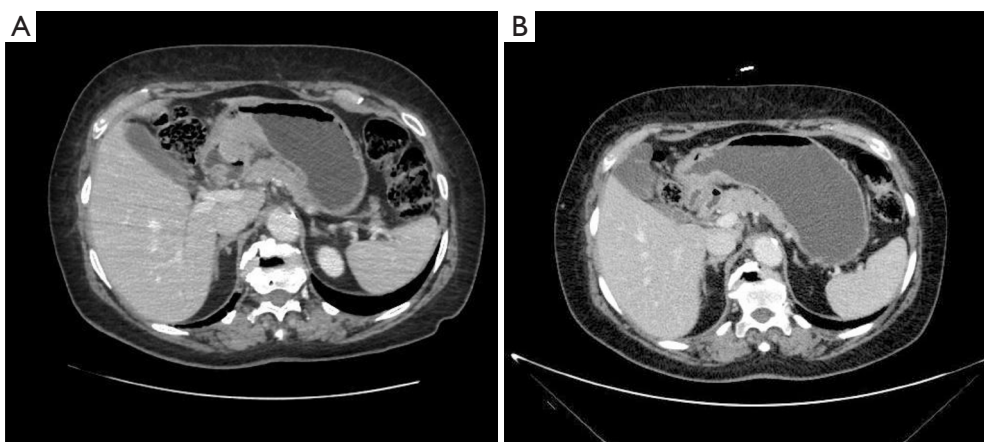
Figure 4 Portal phase CT scan of lesser curvature gastric tumor. (A) Before preoperative chemotherapy; (B) 14 days after the last cycle of preoperative chemotherapy. CT, computed tomography.

believe that pathological TRG has a role as a prognostic marker (31,41,42). Indeed, an internationally and widespread accepted tumor regression grading system for gastrointestinal malignancies following neoadjuvant chemotherapy is still required, as mentioned by the European Society for Medical Oncology Clinical Practice Guidelines on GC (4). The achievement of a critical predictive and prognostic factor could lead to a better selection of patients who may benefit from a neoadjuvant treatment. Conversely, for non-responder patients to preoperative chemotherapy, alternative therapeutic strategies should be identified.

Radiological evaluation and prediction of tumor response

Since 2009, the majority of papers investigating cancer response to neoadjuvant treatments are using the response evaluation criteria in solid tumors (RECIST 1.1): complete response, partial response, stable disease, or progressive disease (43). However, RECIST have several limitations regarding GC. Firstly, the criteria were developed for solid tumors and the stomach is not a parenchymatous organ. Gastric lesion is defined as non-measurable by RECIST because it requires the presence of a measurable lesion, which is often not the case in GC (44). Moreover, RECIST response criteria seem to underestimate histological gastric tumor response compared to the adapted Choi criteria, which appear to better predict survival of these patients (45).

In 2017, the Italian Gastric Cancer Research Group (GIRCG) proposed the maximum tumor diameter reduction rate on computed tomography (CT) scan as a simple, useful and reproducible radiological index to predict TRG after neoadjuvant therapy (46). The key to this technique is to distend the stomach with air or water until the gastric folds appeared mostly flat at the tumor site (*Figure 4*).

Regarding other morphologic techniques, Ang *et al.* attempted to evaluate the value of contrast-enhanced ultrasound (CEUS) in patients with locally advanced GC. Despite a sensitivity of 62.9% and a specificity of 56.3%, CEUS was not significantly more accurate than RECIST criteria (P=0.663) (47).

On the other hand, the association of CT scan with endoscopy or endoscopic ultrasonography (EUS) for prediction of GC response to preoperative chemotherapy, resulted in a significant correlation with histopathological response and OS (48,49).

An evident disadvantage of morphological imaging is that it takes time for gross changes in the tumor to manifest themselves. In contrast, metabolic changes precede anatomical changes. Therefore, molecular imaging can play a predominant role in predicting tumor response to preoperative chemotherapy much earlier during treatment.

18F-fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (18F-FDG PET/CT) is widely used to evaluate the response to chemotherapy of several kinds of tumors. Nonetheless, there is still controversy about the pathological response prediction value of 18F-FDG PET/CT in patients treated with neoadjuvant chemotherapy (50-54).

Morgagni *et al.*, in a recent study, recruited 71 patients from 6 Italians centers with noncardia-GC treated with

preoperative chemotherapy to better define the usefulness of 18F-FDG PET/CT in predicting pathological tumor response evaluated by Becker TRG and survival (55). Unfortunately, 18F-FDG PET/CT failed to demonstrate its usefulness in predicting cancer regression. In fact, the metabolic response of 54 patients, ranging from 0% to 70%, did not permit to reliably forecast pathologic tumor regression and survival rates were affected by metabolic response (55).

To date, one of the most promising techniques in the evaluation of preoperative therapy for gastric adenocarcinoma is the diffusion weighted imaging (DWI) magnetic resonance imaging (MRI). Indeed, it represents a radiation free value-adding technique and, when compared to 18F-FDG PET/CT, it seems to be more accurate in predicting TRG (56).

Future perspectives

Nowadays, the correct selection of patients for upfront surgery or a perioperative treatment represents one of the most debated points in the field of multimodal approach for gastric malignancies. Both The Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG) classified GC in molecular subtypes, showing distinct clinical outcomes and different responses to perioperative chemotherapy for each class (57,58).

Regarding the prediction of treatment response in relation to microsatellite instability (MSI) status, a post hoc analysis of the MAGIC trial validates the poor reaction to chemotherapy in MSI patients (59). In fact, for patients undergoing prior surgery, there was no difference in OS between the microsatellite stability (MSS) and MSI/MRD (mismatch repair-deficient) groups. In addition, MSI patients showed an increased risk of mortality (HR 2.18, 95% CI: 1.08–4.42) when treated with perioperative chemotherapy, questioning its role in this subgroup of patients (59). On the other hand, patients with low microsatellite instability (MSI-L), MSS and/or MMRP (mismatch repair-proficient) may benefit from a radical resection after preoperative chemotherapy (60).

A recent study by Kohlruss *et al.* aimed to determine the prognostic and predictive significance of Epstein-Barr virus positivity (EBV+) and high microsatellite instability (MSI-H) subgroups in patients undergoing preoperative chemotherapy (61). The authors analyzed 760 adenocarcinomas of the stomach and esophago-gastric junction, demonstrating that MSI-H and EBV+ are not predictive of tumor response to preoperative chemotherapy, but are predictors of a better prognosis. Regarding MSI, MSI-H patients have a favorable prognosis regardless of chemotherapy, while MSI-L patients have a good response to chemotherapy and poor survival when undergoing upfront surgery. These results suggest that MSI-L patients may be ideal candidates for preoperative chemotherapy.

Together with molecular subgroups analysis, another emerging diagnostic tool in the field of precision medicine is radiomics.

Radiomics has already proven effective for predicting the response to treatment of different types of cancer through a variety of imaging modalities (62-64). With regard to GC, CT-based radiomics has already been tested as a potential preoperative prognostic biomarker (65). CT-based radiomics prior to treatment could provide important information on the response rate to preoperative chemotherapy, improving patient selection for multimodal treatment of GC (66-69).

Conclusions

An effective histopathological evaluation method of TRG with an independent prognostic role is urgently needed in clinical practice. A 4-tiered system for grading the regression in the primary tumor, combined with a 3-tiered system for the metastatic lymph nodes achieved a good consensus among experienced pathologists. Diffusion-weighted MRI seems to be one of the most promising imaging techniques for prediction of TRG. As future perspectives, determination of EBV, microsatellites, and/or MMR statuses on the endoscopic biopsies, as well as radiomics features on the CT scan at the time of diagnosis could help to predict the response rate to preoperative therapy and tailor the best approach for each patient with GC.

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