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Expert Review

Relevant issues in tumor regression grading of histopathological response to neoadjuvant treatment in adenocarcinomas of the esophagus and gastroesophageal junction

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SUMMARY. **Multimodality treatment combining surgery and oncologic treatment has become widely applied in curative treatment of esophageal and gastroesophageal junction adenocarcinoma. There is a need for a standardized tumor regression grade scoring system for clinically relevant effects of neoadjuvant treatment effects. There are numerous tumor regression grading systems in use and there is no international standardization. This review has found nine different international systems currently in use. These systems all differ in detail, which inhibits valid comparisons of results between studies. Tumor regression grading in esophageal and gastroesophageal junction adenocarcinoma needs to be improved and standardized. To achieve this goal, we have invited a significant group of international esophageal and gastroesophageal junction adenocarcinoma pathology experts to perform a structured review in the form of a Delphi process. The aims of the Delphi include specifying the details for the disposal of the surgical specimen and defining the details of, and the reporting from, the agreed histological tumor regression grade system including resected lymph nodes. The second step will be to perform a validation study of the agreed tumor regression grading system to ensure a scientifically robust inter- and intra-observer variability and to incorporate the consented tumor regression grading system in clinical studies to assess its predictive and prognostic role in treatment of esophageal and gastroesophageal junction adenocarcinomas. The ultimate aim of the project is to improve survival in esophageal and gastroesophageal adenocarcinoma by increasing the quality of tumor regression grading, which is a key component in treatment evaluation and future studies of individualized treatment of esophageal cancer.**

KEY WORDS: **esophageal adenocarcinoma, gastroesophageal junction carcinoma, neoadjuvant treatment, tumor tissue response, delphi survey, overall survival.**

INTRODUCTION

Although adenocarcinoma of the esophagus and gastroesophageal junction (EAC) is rare in many parts of the world, its annual incidence has increased to such high levels as 5–10% in Western countries since the 1970s.[1,2] Median survival remains limited, especially in patients with advanced stage disease. Neoadjuvant or perioperative chemotherapy or chemoradiotherapy, followed by surgery, represents the current standard treatment for locally advanced EAC.[3–11] These approaches have been shown to provide clinical benefits for patients compared with surgery alone, especially in patients with complete or subtotal tumor response. Theoretically, there are numerous advantages with this therapeutic approach, such as downstaging of the primary tumor, which may increase tumor resection rate and tumor-free resection margins, facilitation of organ conservation in the form of the option of less extensive surgery and, perhaps most importantly, reduction of micrometastases outside the operative field. One important caution is represented by the fact that previous trials lumped together gastric and gastroesophageal junction cancers.[7,9] Given the observation that the main effects of neoadjuvant therapy seemed to be confined to the junction cancers, the question arises, which effects are truly evidence based in gastric

cancer per se? In fact, ensuing meta-analyses of the available databases suggested a nonsignificant effect on overall survival of corresponding regimens when gastric cancer patients were specifically analyzed.[12] Accordingly, the pivotal question remains virtually unanswered, i.e. which effects do these different chemotherapies and chemoradiotherapy regimens exert on adenocarcinoma (AC) of the esophagus, gastroesophageal junction, and those occurring in the stomach?

It will unavoidably become highly pertinent to offer a robust surrogate marker to be used in exploratory phase 2 clinical trials. Such trial designs are extorted by the complexity and many logistic challenges connected with pivotal phase 3 trials using overall survival as the primary end point. There is an impelling need for the further clinical research in the field of neoadjuvant treatment of EAC, e.g. to better document the magnitude of the effect of adding radiotherapy (and its various modalities) to chemotherapy and the refinement of the chemotherapy regimens. Increased knowledge, e.g. molecular tumor characteristics and genomic subtypes of EAC, will play a central role in future research[13] and mandates to be introduced and eventually integrated as a natural part of the inborn dynamics of a corresponding tumor regression grading (TRG) system.

HISTOLOGICAL TUMOR RESPONSE RATES AND ITS CLINICAL RELEVANCE

TRG systems for EAC aim to categorize the amount of regressive changes, referring to the amount of therapy-induced fibrosis in relation to residual tumor cells or the estimated percentage of residual tumor cells in relation to fibrosis (see Table 1).[14–22] The prognostic significance of histological response to chemotherapy and chemoradiotherapy has been investigated for a variety of different malignancies, among others for EAC. The Response Evaluation Criteria in Solid Tumors (RECIST) is the gold standard for evaluation of tumor response, but it requires the presence of a measurable lesion.[23] Given the fact that resectable EAC does not always have measurable lesions, the use of RECIST is not a valid option for clinical EAC research. Tumor regression can also be evaluated histologically in the resected specimens by assessing the grade of viable tumor cells in relation to fibrosis in the tumor, the so-called TRG. Previous research has not shown a strong correlation between the radiologically detected reduction of the primary tumor volume and the histological TRG.[24] In esophageal cancer patients, it has repeatedly been reported that histological TRG is a better surrogate endpoint for survival compared with the RECIST response rate.[16,17,20,21,24]

Numerous studies have investigated the prognostic relevance of histological TRGs in esophageal squamous cell carcinoma and EAC. It is interesting to note that in patients with subtotal and partial histological regression (i.e. Mandard 2 and 3; Becker 1b and 2), an intermediate outcome was found placed between patients with complete and absent histological regression.[25] It is therefore not appropriate to generally merge the different TRG tiers together into a simplified two-tiered classification scheme with 'responders' and 'nonresponders', as such a maneuver might be unable to reflect the particular impact of subtotal and partial tumor regression, as shown in EAC.[26]

Mandard *et al*.[14] were first to describe a method for TRG, which successfully predicted outcomes. In their study on esophageal cancer patients, most of whom had squamous cell carcinoma receiving neoadjuvant chemoradiotherapy, the grade of TRG strongly correlated with disease-free survival. Chirieac and coworkers confirmed,[15] in a study based on mainly ACs originating from the distal esophagus or gastroesophageal junction, that post-therapy TRG reliably predicted disease-free and overall survival. In these studies, two different TRG systems (a 5 scale and a 4 scale) were applied. Nevertheless, depending on the case composition and the statistical models used, histological TRG has repeatedly been found to be an independent prognostic marker for survival in EAC.[16,27] This evidence suggests that histological TRG is a valid surrogate endpoint variable with relevance for overall survival in trials of multimodality treatment of EAC patients.

ISSUES IN THE ASSESSMENT OF PATHOLOGIC RESPONSE

Significant regressive changes may result in complete disappearance of malignant cells and replacement of the tumor by fibrous or fibro-inflammatory granulation tissue. Signs of resorption, like histiocytic reaction with foamy and sometimes hemosiderin-laden macrophages, cholesterol deposits and foreign body reaction, as well as dystrophic calcifications, can also be seen. In this context, it should be pointed out that the presence of foamy histiocytes has particularly been shown to more specifically reflect tumor regression due to cytotoxic treatment, while stromal changes like fibrosis and granulating inflammation can also be observed in untreated carcinomas, probably following endogenous tumor necrosis. A frequent finding in ACs with large extracellular mucin component prior to exposure to neoadjuvant therapy is the presence of acellular mucin lakes after therapy. These should not be considered as representing viable residual tumors as more focused research is needed to elucidate whether acellular mucin pools represent a sign of histological regression or not.[28] It needs to

Table 1 Existing tumor regression grade systems for esophageal and gastroesophageal junction adenocarcinoma

Authors	Complete or near complete tumor regression	Partial or no tumor regression	Number of grades
Mandard *et al*.[14]	Grade 1: Complete regression Grade 2: Presence of rare residual cancer cells scattered through the fibrosis	Grade 3: Increase in the number of residual cancer cells but fibrosis still predominate Grade 4: Residual cancer outgrowing fibrosis Grade 5: Absence of regressive changes	5
Chirieac *et al*.[15]	Grade 1: No residual carcinoma Grade 2: 1–10% Residual carcinoma	Grade 3: 11–50% Residual carcinoma Grade 4: >50% Residual carcinoma	4
Schneider *et al*.[16]	Grade 1: No residual carcinoma Grade 2: 1–10% Residual carcinoma	Grade 3: 11–50% Residual carcinoma Grade 4: >50% Residual carcinoma	4
Meredith *et al*.[17]	Grade 1: No residual carcinoma	Grade 2: Partial response: change in T or N stage from preoperative EUS or greater than 50% reduction in size of tumor compared pre- and postoperatively Grade 3: No response: no change in tumor stage compared to preoperative EUS stage and postoperative pathology stage	3
Ryan *et al*.[18]	Grade 1: No viable cancer cells or single cancer cells or small groups of cancer cells	Grade 2: Residual cancer outgrown by fibrosis Grade 3: Significant fibrosis outgrown by cancer or extensive residual cancer with no fibrosis	3
Donahue *et al*.[19]	Grade 1: No residual carcinoma Grade 2: Near-complete: microscopic focus of viable tumor cells in an otherwise necrotic specimen with no tumor remaining in resected lymph nodes	Grade 3: No response: macroscopic residual viable tumor at primary site and/or positive lymph nodes	3
Kim *et al*.[20]	Grade 1: No residual carcinoma Grade 2: Residual tumor <1 cm in greatest dimension and limited to mucosa or submucosa with no nodal involvement or cancer in primary and microscopic neoplastic cells in a single regional node	Grade 3: No response: all other tumors.	3
Donington *et al*.[21]	Grade 1: No vital residual tumor cells at primary site	Grade 2: Any residual tumor cells at primary site.	2
Barbour *et al*.[22]	Grade 1: Major response: <10% residual viable tumor cells	Grade 2: >10% Residual viable tumor cells	2

be emphasized that tumor regression often follows a centrifugal pattern in the native tumor so even if the superficial or peripheral tumor has completely regressed, residual tumor cells may be found in the central areas of the tumor bed, respectively.

Another common feature of the proposed histological TRG systems (Table 1) is that they are based on an estimation of the percentage of vital tumor tissue in relation to the macroscopically identifiable tumor bed, which is virtually impossible to define with adequate accuracy. Clinical EAC trials offer the opportunity to evaluate the histologic TRG of the resected tumor and, due to the increasing use of neoadjuvant treatment, this can now be done in a much larger scale. Theoretically, the information obtained by the histological TRG could have many implications and clinical applications and relevance some of which are summarized below:

1. The correlation of histologic response to survival could contribute to a more accurate estimation of the patient's individual prognosis.
2. Based on the results of the tumor's in vivo chemotherapy or chemoradiotherapy sensitivity, more efficacious therapeutic regimens could be chosen in the postoperative setting.
3. The identification and clinical evaluation of specific histological tumor characteristics or biomarkers that are related to low or no tumor regression (in biopsy specimens) to neoadjuvant treatment harbors the potential to guide the clinician to proceed directly to surgical resection without further delay.
4. Histologic TRG can form the basis for the sample size calculation of phase 2 randomized clinical trials to explore novel avenues among the current chemotherapeutic regimens and those in the pipeline.

THE RELEVANCE OF LYMPH NODE STATUS

The clinical, as well as the pathological, lymph node status is an important prognostic parameter in EAC and an independent predictor of survival.[22,29,30] The number of involved nodes, subdivided from N0 to N3, plays a pivotal role in the 8th edition of AJCC/UICC staging of cancers of the esophagus and gastroesophageal junction. This system, however, does not take into account the location of involved nodes, which may be a problem since the distribution

of metastatic lymph nodes may vary with tumor location, tumor histology, tumor invasion depth, and tumor response to neoadjuvant treatment.[31,32] Interestingly, studies have demonstrated that after neoadjuvant therapy, not only does the frequency of lymph node metastases decrease, but there is also a change in the distribution of lymph node metastases.[31,33] However, the planning of neoadjuvant therapy (e.g. extent of radiation field) and surgical approach often depends on the distribution pattern of nodal metastases. Some argue that metastases in relatively distant lymph nodes represent stage IV disease, while others endorse the phenomenon of 'skip metastases' (i.e. N3 stations affected without corresponding growth at the N1 and/or N2 locations), which do not necessarily correlate with an unfavorable prognosis.[34–41] After neoadjuvant therapy, many studies report a response at the primary tumor and/or the lymph nodes. This is of clinical importance since complete N0 lymph node status after neoadjuvant therapy seems to predict long-term survival. Interestingly, for esophageal cancer, it has been shown that the presence of regressive changes in lymph node metastasis may have an impact on patients' long-term outcomes.[42] This suggests that tumor regression may have occurred at a nodal level after neoadjuvant therapy and that corresponding responses do not necessarily occur concomitantly and to the same extent in the primary tumor. In this context, it is important to recognize that clinical assessment of N-stage is burdened by a low specificity. Important to know also is that different neoadjuvant regimens might affect lymph nodes in different ways, as exemplified by outcomes in centers using solely chemoradiotherapy as opposed to those practicing only chemotherapy.[35] Another issue to take into consideration for the variation in lymph node yields and the interpretation of the presence of regressive changes or not is the involvement of different pathologists.

Given the fact that histological TRG after neoadjuvant chemotherapy or chemoradiotherapy is observed in lymph node metastases and that the presence of lymph node metastases is a strong indicator of poor outcome in esophageal cancer, the morphological lymph node status mandates to be incorporated in a future comprehensive TRG classification system.

HOW TO MOVE FORWARD?

Obviously, a variety of different histological TRG systems (Table 1) have been proposed for EAC in the literature, and if one adds the different ways of processing the specimen, e.g. the number of cross tissue sections, it is virtually impossible to compare the respective response rates to the different available chemotherapy and chemoradiotherapy regimens. This illustrates one of the major problems in the investigation of histologic response after neoadjuvant therapy in patients with EAC. In addition, none of these systems has carefully assessed the true value of adding a structured assessment of concomitant lymph nodes. Both pathologists and clinicians must work on the standardization of specimen processing and the reporting of TRG. A careful workup of histology, and standardized reporting of TRG within trials and studies, will accordingly help to further strengthen the evidence of the value of TRG in multimodality treatment of EAC. The process, which has previously been initiated by our group concerning gastric cancer,[43] is as follows:

- To define and invite a significant group of international expert pathologists and surgical oncologists with a particular interest in EAC;
- To initiate and finalize a structured review (Delphi process) of available classification systems aiming to grade and specify the pros and cons of respective systems;
- To comprehensively review the available histological TRG systems for EAC and, from this process, assess the need and feasibility of modifying an already available system or, if necessary, generate a novel system, to avoid the drawbacks and limitations of some and take advantage of others;
- To specify the details for the disposal of the surgical specimen to allow for a secure, adequate, and standardized histopathological assessment;
- To define the details of the agreed histological TRG classification system for EAC including the resected lymph nodes;
- To define and detail the further process for the validation of the agreed TRG classification system;
- To complete a scientifically robust inter- and intra-observer variability study for the consented histological TRG classification system;
- To incorporate the consented histological TRG system in clinical studies to assess its predictive and prognostic role; and
- To work for the implementation of the agreed system in national registers and large prospective studies to increase comparability between studies and ultimately improve esophageal cancer care and survival.

CONCLUSION

In view of the high number of available TRG systems, it has to be a prioritized project that an international and interdisciplinary commission, including in the first step expert pathologists, reaches a multidisciplinary consensus on TRG reporting in EAC. The Delphi process will focus on reaching international consensus for a standardized TRG assessment system, rather than creating a new system. Critical issues, such

as inter- and intra-observer variability, the definition of the tumor bed, and distinction of tumor fibrosis from regressive fibrosis, must be addressed through individual and institutional projects. Molecular tumor characteristics and tumor cell mutational profiles are likely to be important prognostic factors and key elements in future individual treatment designs as to why a continuous process will be operational to streamline a corresponding classification system. However, the current scientific knowledge does not permit a compound TRG system to be defined. Histological TRG is an important piece of the puzzle in treatment evaluation, and the aim of this project is to improve the quality and accuracy of TRG. Finally, the international TRG assessment system should be a mandatory variable in national registers of esophageal cancer and in the Esophagectomy Complication Consensus Group ESODATA study to create widely adopted standards and to improve the quality of future research and, ultimately, survival of EAC.

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