Assessment of Tumor Regression of Esophageal Adenocarcinomas After Neoadjuvant Chemotherapy

Comparison of 2 Commonly Used Scoring Approaches

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Abstract: Histopathologic determination of tumor regression provides important prognostic information for locally advanced gastroesophageal carcinomas after neoadjuvant treatment. Regression grading systems mostly refer to the amount of therapy-induced fibrosis in relation to residual tumor or the estimated percentage of residual tumor in relation to the former tumor site. Although these methods are generally accepted, currently there is no common standard for reporting tumor regression in gastroesophageal cancers. We compared the application of these 2 major principles for assessment of tumor regression: hematoxylin and eosin–stained slides from 89 resection specimens of esophageal adenocarcinomas following neoadjuvant chemotherapy were independently reviewed by 3 pathologists from different institutions. Tumor regression was determined by the 5-tiered Mandard system (fibrosis/tumor relation) and the 4-tiered Becker system (residual tumor in %). Interobserver agreement for the Becker system showed better weighted κ values compared with the Mandard system (0.78 vs. 0.62). Evaluation of the whole embedded tumor site showed improved results (Becker: 0.83; Mandard: 0.73) as compared with only 1 representative slide (Becker: 0.68; Mandard: 0.71). Modification into simplified 3-tiered systems showed comparable interobserver agreement but better prognostic stratification for both systems (log rank Becker: $P = 0.015$; Mandard $P = 0.03$), with independent prognostic impact for overall survival (modified Becker: $P = 0.011$, hazard ratio = 3.07; modified Mandard: $P = 0.023$, hazard ratio = 2.72). In conclusion, both systems provide substantial to excellent interobserver agreement for estimation of tumor regression after neoadjuvant chemotherapy in esophageal adenocarcinomas. A simple 3-tiered system with the estimation of residual tumor in % (complete regression/1% to 50% residual tumor/ >50% residual tumor) maintains the highest reproducibility and prognostic value.

Key Words: tumor regression, chemotherapy, interobserver variability, esophageal adenocarcinoma

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Neoadjuvant chemotherapy (CTX) or radiochemotherapy, followed by surgery or perioperative treatment, represents the current standard treatment for locally advanced esophageal adenocarcinomas and adenocarcinomas of the gastroesophageal junction.[1,2] This approach has been shown to provide clinical benefit for patients compared with surgery alone; particularly patients with complete or subtotal tumor response show significant improved survival.[1–4]

The effects of preoperative treatment can be determined by histology, and determination of tumor regression (ie, tumor regression grading [TRG]) is now frequently integrated in the pathology reports of resection specimens for these tumors.[5,6] TRG systems for upper gastrointestinal carcinomas refer to the amount of therapy-induced fibrosis in relation to residual tumor (eg, Mandard system)[7] or the estimated percentage of residual tumor in relation to the previous tumor site (eg, Becker, Schneider, or Chirieac system).[8–11] Currently, there is no common standard for processing resection specimens after neoadjuvant treatment and for subsequent reporting of tumor regression for gastrointestinal cancer. It is still a matter of debate which system may provide better results in terms of interobserver agreement or prognostic value. In this study, we compared the application of these 2 major approaches for assessment of TRG in esophageal adenocarcinomas after neoadjuvant CTX especially with regard to the following: (a) interobserver agreement; (b) reliability of assessment of TRG on 1 representative slide or on the whole (previous) tumor area; (c) prognostic discrimination.

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MATERIALS AND METHODS

Case Selection

Hematoxylin and eosin–stained slides from 89 randomly selected resection specimens out of a collection of 280 cases with locally advanced esophageal adenocarcinomas, following neoadjuvant CTX,[12] were used for this study. The patients were treated between 1996 and 2007 in the department of surgery at Klinikum Rechts der Isar der Technische Universität München, Germany. Neoadjuvant treatment consisted of cisplatin-based or oxaliplatin-based and 5-fluorouracil-based CTX (PLF/OLF regime) without additional radiation, according to previously published protocols, including the MUNICON trial. Patients of 60 years or younger and otherwise good health status were also given paclitaxel (T-PLF/OLF).[13,14] Surgery was conducted 2 to 3 weeks after CTX completion. The study protocols of neoadjuvant CTX were approved by the institutional review board at the Technische Universität München. Patient follow-up assessment was performed every 3 months for the first year and at 6-month intervals thereafter. The postoperative pathologic classifications of the tumors used in this study, which were taken from the original pathologic reports are given in Table 1. For comparison, the description of the whole collection of 280 cases, which has already been described in previous studies,[12,15] is given as a supplemental file (S1, Supplemental Digital Content 1, http://links.lww.com/PAS/A215). All resection specimens had been worked up in a standardized manner, which included embedding of the whole tumor bed.[8,15]

TABLE 1. Histopathologic Characterization of the Case Collection

Parameter	n (%)
ypT category	
ypT0	7 (8.0)
ypT1	5 (6.0)
ypT2	18 (20.2)
ypT3	58 (65.2)
ypT4	1 (1.1)
ypN category	
ypN0	28 (31.5)
ypN1	17 (19.1)
ypN2	24 (27)
ypN3	20 (22.5)
Distant metastases	
Absent	76 (85.4)
Present	13 (14.6)
Diffentiation (grading)	
G2	32 (36)
G3/G4	53 (59.6)
Resection status	
R0	77 (86.5)
R1	12 (13.4)
TRG original report (Becker)	
TRG1a	7 (7.9)
TRG1b	16 (18)
TRG2	21 (23.6)
TRG3	45 (50.6)
Total	89 (100)

Estimation of Tumor Regression

The slides were reviewed by 3 independent pathologists (E.K., S.T., R.L.) who were unaware of the initial pathologic report. TRG was performed according to the (a) Mandard system,[7] which recognizes 5 histologic TRGs, on the basis of the ratio of vital tumor tissue and fibrosis: TRG1—complete regression (= fibrosis without detectable tumor cells); TRG2—fibrosis with scattered tumor cells; TRG3—fibrosis and tumor cells with preponderance of fibrosis; TRG4—fibrosis and tumor cells with preponderance of tumor cells; TRG5—tumor without changes of regression (Table 2A); and (b) Becker system,[8] in which the grading of the tumor regression is based on the estimation of the percentage of vital tumor tissue in relationship to the macroscopically identifiable tumor bed (previous site of the tumor) and is divided into 4 grades: TRG1a—complete tumor regression without residual tumor; TRG1b— < 10% residual tumor per tumor bed; TGR2—10% to 50% residual tumor; TRG3— > 50% residual tumor cells with or without signs of treatment effect (Table 2B). Histologic examples of different degrees of regression are shown in Figure 1.

For 39 cases, all slides from the completely embedded tumor bed were reviewed. For 50 cases only 1 representative slide was used for estimation of TRG. For comparative final analysis, a definitive TRG was determined for both systems according to the best interobserver agreement (see below).

Statistics

For the statistical procedures SAS V9.2 (The SAS Institute, Cary, NC) and SPSS 21 software (SPSS Inc., Chicago, IL) were used. For categorical methods, simple and weighted κ values were used. Estimation of survival probabilities in patient subgroups by univariate analysis was performed using the Kaplan-Meier method, and the log rank test was used for statistical comparisons. Cox proportional hazard models were used to analyze multivariate relationships of covariates with survival. To determine the effect of each variable on patients' outcome 95% confidence intervals (CI) were used. All tests were 2 sided, and the significance level was set at 0.05. To estimate the goodness-of-fit of each TRG, the Akaike

TABLE 2. TRG Systems Used in This Study

TRG	Criteria
(A) Mandard TRG System	
1	Complete regression (= fibrosis without detectable tissue of tumor)
2	Fibrosis with scattered tumor cells
3	Fibrosis and tumor cells with preponderance of fibrosis
4	Fibrosis and tumor cells with preponderance of tumor cells
5	Tissue of tumor without changes of regression
(B) Becker TRG System	
1a	No residual tumor/tumor bed + CTX effect
1b	< 10% residual tumor/tumor bed + CTX effect
2	10%-50% residual tumor/tumor bed + CTX effect
3	> 50% residual tumor/tumor bed + CTX effect

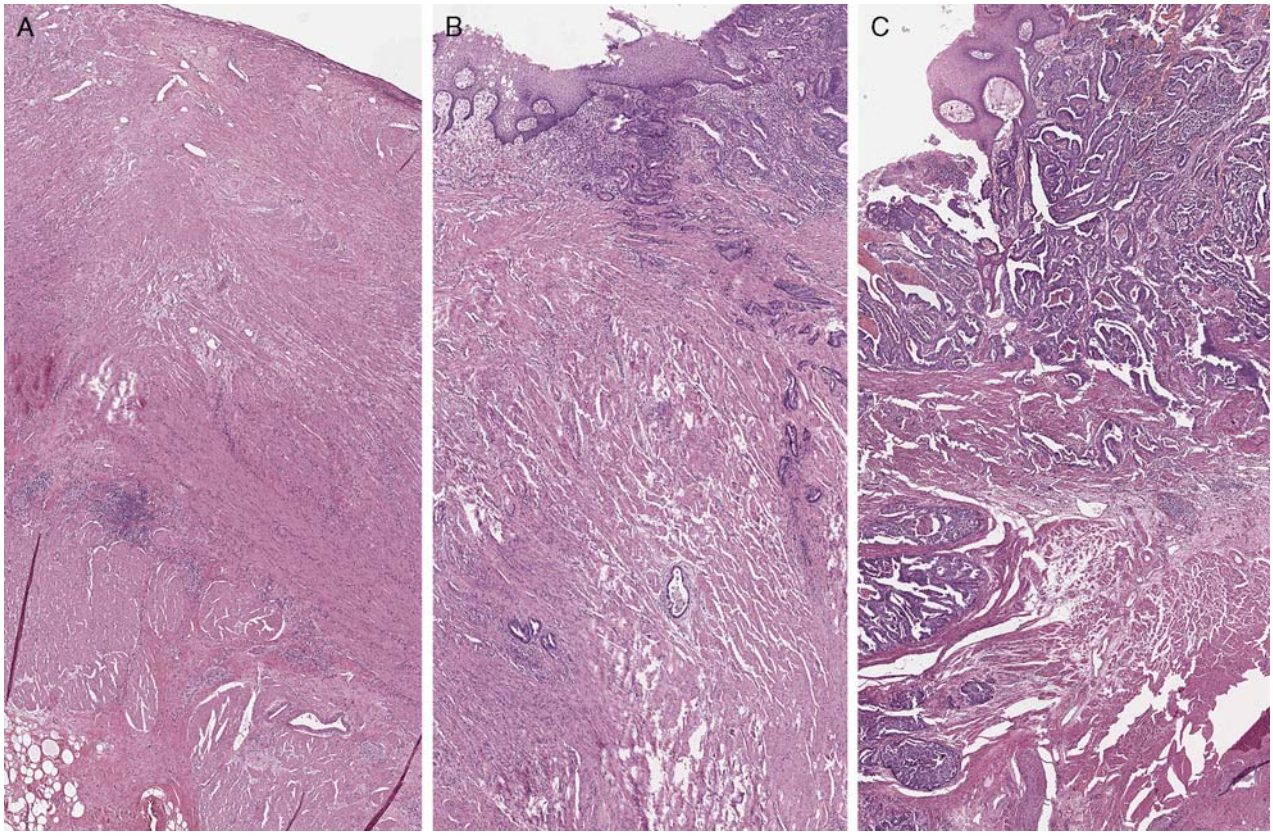

FIGURE 1. Histologic examples of different grades of tumor regression of esophageal adenocarcinomas following neoadjuvant CTX: (A) complete regression; (B) subtotal/partial tumor regression with <50% residual tumor; (C) no regression with >50% residual tumor (hematoxylin and eosin staining).

Information Criterion (AIC) and Schwarz Bayesian Information Criterion (SBC) were used. Both methods adjust the −2 log likelihood statistics for the number of parameters in the model and the number of observations used. Lower values of AIC and SBC indicate superior model fit, with the "best" model showing the lowest values for both.

RESULTS

Scoring Results

For the 3 participants the concordance rates were 58.4%, 56.2%, and 38.2% (mean 50.9%) for the Mandard TRG system and 69.7%, 83.1%, and 77.5% (mean 76.7%) for the Becker TRG system. When analyzing the whole tumor bed the rates were 71.8%, 59.0%, and 53.8% (mean 61.3%) for the Mandard system and 87.0%, 76.9%, and 74.0% (mean 79.3%%) for the Becker system; when using only 1 representative slide for TRG estimation the rates were 58.0%, 44.0%, and 26.0% (mean 42.7%) for the Mandard system and 80.0%, 78.0%, and 60.0% (mean 72.7%) for the Becker system. The tables with the comparison of the participants are given in detail as supplemental files (S2, Supplemental Digital Content 2, http://links.lww.com/PAS/A216). The comparison of the definitive TRGs determined as described above showed a highly significant correlation between the Mandard and the Becker score ($\chi^2 < 0.001$); however, there were some discrepancies in the "intermediate" TRGs Mandard 2 to 4 and Becker 1b and 2 (Table 3). The concordance rate of the consent TRG and the TRG of the initial report was 82% (73/89).

Interobserver Agreement

Overall, average interobserver agreement for the 5-tiered Mandard system was 0.36 (κ) and 0.62 (weighted κ). For the 4-tiered Becker system it was 0.64 (κ) and 0.78 (weighted κ). Evaluation of the whole embedded tumor site showed improved results (Becker: κ = 0.72/weighted κ = 0.83; Mandard: 0.51/0.73) as compared with only 1 representative slide (Becker: 0.55/0.68; Mandard: 0.21/0.49). The results of these analyses are given in detail as supplemental files (S3, Supplemental Digital Content 3, http://links.lww.com/PAS/A217).

Modification Into 3-Tiered Systems

Following the data of our own findings and of others regarding the prognostic impact of a simplified 3-tiered TRG,[15,16] we performed a separate analysis with both methods of estimation of TRG modified into

TABLE 3. Comparison Between TRGs (Consent) According to Mandard and Becker ($\chi^2 < 0.001$)

	TRG According to Becker				
	1a	1b	2	3	Total
TRG according to Mandard					
1	7	0	0	0	7
2	0	12	2	0	14
3	0	2	13	3	18
4	0	0	6	36	42
5	0	0	0	8	8
Total	7	14	21	47	89

3-tiered systems (for Mandard: TRG1 vs. TRG2 + TRG3 vs. TRG4 + TRG5; for Becker: TRG1a vs. TRG1b + TRG2 vs. TRG3). This resulted in improved concordance rates, with 85.4%, 76.4%, and 70.8% (mean 77.5%) for the modified Mandard system and 88.8%, 86.5%, and 78.7% (mean 84.7%) for the modified Becker system (S1, Supplemental Digital Content 1, http://links.lww.com/PAS/A215). Average interobserver agreement was also enhanced for both systems: for the modified Mandard system it was $\kappa = 0.61$/weighted $\kappa = 0.67$; for the modified Becker system it was $\kappa = 0.74$/weighted $\kappa = 0.77$ (S3, Supplemental Digital Content 3, http://links.lww.com/PAS/A217).

Survival Analysis

For survival analysis, the definitive TRGs for both systems were determined according to the best interobserver agreement. Both systems had prognostic impact for overall survival (log rank Becker: $P = 0.047$; log rank Mandard: $P = 0.053$). The modified 3-tiered TRGs showed superior prognostic stratification for both systems (log rank modified Becker: $P = 0.015$; log rank modified Mandard: $P = 0.03$; Fig. 2). Other prognostic relevant factors in univariate analysis were ypT category ($P = 0.003$), ypN category ($P = 0.001$), distant metastases ($P = 0.001$), tumor differentiation (grading, $P = 0.004$), and resection status ($P < 0.001$). The modified TRGs, but not the original 5-tiered or 4-tiered scores were also independent prognostic factors for overall survival in this case collection (modified Becker: $P = 0.011$, hazard ratio = 3.07 [95% CI, 1.3-7.3]; modified Mandard: $P = 0.023$, hazard ratio = 2.72 [95% CI, 1.5-6.4]; Table 4). The AIC and BIC values of the 2 systems were comparable (modified Mandard: 222/227; modified Becker: 222/226).

DISCUSSION

Histopathologic TRG has been shown to provide important prognostic information for patients with locally advanced gastroesophageal carcinomas after preoperative CTX. Whereas for gastric and rectal cancers data about an independent prognostic impact of TRG are divergent,[17–20] the most consistent reports have been published on esophageal carcinomas. In various studies it has been shown that TRG and lymph node statuses are the most important prognostic factors for both adenocarcinoma and squamous cell carcinomas.[4,15,16] This led to proposals of alternative staging systems and the suggestion for the implementation of TRG into the forthcoming AJCC/UICC staging system by several authors.[10–12,16,21]

In the present study we investigated the 2 main approaches for estimation of tumor regression by using 2 commonly used TRG systems as examples. One concept of grading of tumor regression is the estimation of the amount of residual tumor in correlation to fibrosis—often in a descriptive manner, such as the Mandard system.[7] Other TRG systems, such as the Becker grading system,[8]

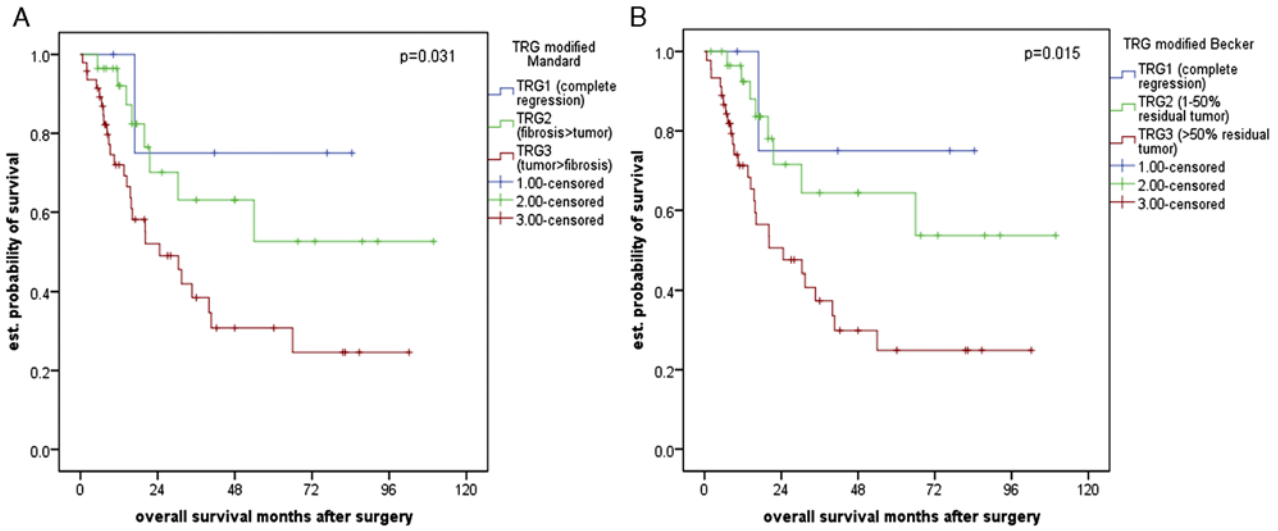

FIGURE 2. Survival analysis: (A) modified TRG according to Mandard, 3-tiered (see also Donohoe et al[16]); (B) modified TRG according to Becker, 3-tiered (see also Chirieac et al[4] and Langer et al[15]).

TABLE 4. Multivariate Analysis for Overall Survival

Parameter	HR	95% CI	*P*
Including modified Mandard score			
ypT category	1.87	0.84-4.15	0.12
ypN category	1.48	1.06-2.08	0.02
Distant metastases	2.18	0.75-6.35	0.15
Differentiation	1.31	0.65-2.61	0.45
Resection status	1.51	0.62-3.68	0.37
TRG (modified Mandard)	2.72	1.15-6.44	0.02
Including modified Becker score			
ypT category	1.887	0.854-4.17	0.12
ypN category	1.517	1.08-2.132	0.02
Distant metastases	2.372	0.792-7.104	0.12
Differentiation	1.197	0.584-2.454	0.62
Resection status	1.412	0.565-3.532	0.46
TRG (modified Becker)	3.071	1.286-7.33	0.01

which was used in this study, as well as the Chirieac,[4] Schneider,[9] or Rizk[11] systems, use the percentage of residual tumor in the previous tumor site (the tumor bed) as basis for the TRG. In line with other authors,[22,23] we could demonstrate that both concepts provided substantial to excellent interobserver agreement for the estimation of tumor regression after neoadjuvant CTX and radiochemotherapy in esophageal cancers. In these previous studies, however, only 1 single system has been investigated. Only Mirza et al[24] compared 2 different grading systems case by case (for gastric carcinomas and adenocarcinomas of the gastroesophageal junction), and in agreement with our findings they reported comparable results with substantial interobserver agreement for both systems and a slight advantage of the percentage-based estimation of tumor regression.

A reason for the higher rate of disagreement for the Mandard score may be the existence of difficulties in the assessment of the relative amount of fibrosis. This has been debated to show lack of reproducibility in a recent work by Chetty et al,[25] who investigated the level of interobserver agreement among expert gastrointestinal pathologists for TRG in rectal cancer following neoadjuvant radiochemotherapy. In this study, 17 pathologists applied various regression grading systems for gastrointestinal cancers (eg, the Mandard[7] or the TRG according to the Royal College of Pathologists[26]) on selected slides of tumors, which resulted in unsatisfactory interobserver agreement for all TRG systems. The authors of this paper concluded that there was a need for a simple, reproducible regression grading system with clear criteria and a standardized workup of the resection specimen favoring the assessment of the complete tumor bed as basis for the estimation of TRG. The results of our study confirm these suggestions as we could demonstrate a better interobserver agreement for the cases in which the whole tumor bed was evaluated in multiple slides, in contrast to the subgroup of cases in which only 1 selected slide was analyzed. Moreover, we could show that a modification of both the 5-tiered Mandard score and the 4-tiered Becker score not only resulted in statistically superior rates for interobserver agreement (eg, there were disagreements for the distinction of Mandard score 2 and 3, and 4 and 5, which were then merged to 1 TRG in the modified system) but also in achievement of a better prognostic impact of TRG. In previous studies we already have used a modified Becker score, which originally was developed for gastric cancer and which has been applied for TRG in esophageal cancers in our institute as well.[15] By correlation of the TRGs with clinical outcome we could demonstrate that in the large cohort of esophageal adenocarcinomas from the Technische Universität Munich, from which the cases of the present study had been randomly selected, a 3-tiered TRG (complete regression—partial regression; ie, < 50% residual tumor and no regression) shows improved prognostic value over the original Becker score with 4 grades.[12,15] In contrast to gastric cancer,[27] there is evidence that even small tumor residuals are associated with a more unfavorable outcome, comparable to the prognosis for partial tumor regression (ie, Becker grade 2; 10% to 50% residual tumor). Therefore, a 3-tiered TRG may not only show better interobserver agreement but also enhanced prognostication in clinical management. Similar observations have been made by others,[5,23] and recently, Donohoe et al[16] described the superiority of an identically modified Mandard score over the original 5-tiered grading system and showed an improved prognostic value of this 3-tiered system compared with other commonly used TRGs in a comprehensive study on a large number of cases. In contrast to our study, however, the TRG systems, which were compared with the modified Mandard system in this study, had not been modified or simplified, and the comparison was not done by reviewing the slides of the cases but by a retrospective analysis of the histopathologic reports in the majority of cases. We consider our approach of case-by-case comparison and TRG estimation by 3 independent pathologists as a major strength of our study. In contrast to other works with similar study design,[23,25] we did not invite external pathologists for participation. The 3 investigators in our study, however, have been trained and working in different locations before joining the current affiliation. The study was conducted within the first year at the new institute so a significant in-house bias should be unlikely.

In summary, we could demonstrate that both principles—estimation of the relation of fibrosis to residual tumor versus residual tumor in %—for the assessment of tumor regression after neoadjuvant treatment in esophageal adenocarcinomas provide substantial to excellent interobserver agreement, with a slight superiority of the "residual tumor %"–based TRG system. It is noteworthy that TRG should be assessed after histologic evaluation of the whole embedded tumor bed and not of 1 representative slide. In line with previous published studies,[23] a simplified 3-tiered system (complete regression/1% to 50% residual tumor/ > 50% residual tumor) shows the best reproducibility and prognostic value. TRG according to this system can be recommended to be part of every standard pathology report of esophageal adenocarcinomas following neoadjuvant treatment.

REFERENCES

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
3. Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: a FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;13:1715–1721.
4. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer*. 2005;103: 1347–1355.
5. Chang F, Deere H, Mahadeva U, et al. Histopathologic examination and reporting of esophageal carcinomas following preoperative neoadjuvant therapy: practical guidelines and current issues. *Am J Clin Pathol*. 2008;129:252–262.
6. Thies S, Langer R. Tumor regression grading of gastrointestinal carcinomas after neoadjuvant treatment. *Front Oncol*. 2013;3:262.
7. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73:2680–2686.
8. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer*. 2003;98:1521–1530.
9. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. *Ann Surg*. 2005;242:684–692.
10. Swisher SG, Hofstetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). *Ann Surg*. 2005;241:810–817; discussion 7-20.
11. Rizk NP, Venkatraman E, Bains MS, et al. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. *J Clin Oncol*. 2007;25:507–512.
12. Langer R, Becker K, Zlobec I, et al. A multifactorial histopathologic score for the prediction of prognosis of resected esophageal adenocarcinomas after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2014;21:915–921.
13. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol*. 2007;8:797–805.
14. Bader FG, Lordick F, Fink U, et al. Paclitaxel in the neoadjuvant treatment for adeno carcinoma of the distal esophagus (AEG I). A comparison of two phase II trials with long-term follow-up. *Onkologie*. 2008;31:366–372.
15. Langer R, Ott K, Feith M, et al. Prognostic significance of histopathological tumor regression after neoadjuvant chemotherapy in esophageal adenocarcinomas. *Mod Pathol*. 2009;22:1555–1563.
16. Donohoe CL, O'Farrell NJ, Grant T, et al. Classification of pathologic response to neoadjuvant therapy in esophageal and junctional cancer: assessment of existing measures and proposal of a novel 3-point standard. *Ann Surg*. 2013;258:784–792; discussion 92.
17. Schmidt T, Sicic L, Blank S, et al. Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas. *Br J Cancer*. 2014;110:1712–1720.
18. Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol*. 2005;23:8688–8696.
19. Shia J, Guillem JG, Moore HG, et al. Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome. *Am J Surg Pathol*. 2004;28:215–223.
20. Rosenberg R, Nekarda H, Zimmermann F, et al. Histopathological response after preoperative radiochemotherapy in rectal carcinoma is associated with improved overall survival. *J Surg Oncol*. 2008;97:8–13.
21. Barbour AP, Jones M, Gonen M, et al. Refining esophageal cancer staging after neoadjuvant therapy: importance of treatment response. *Ann Surg Oncol*. 2008;15:2894–2902.
22. Fareed KR, Ilyas M, Kaye PV, et al. Tumour regression grade (TRG) analyses in patients with resectable gastro-oesophageal adenocarcinomas treated with platinum-based neoadjuvant chemotherapy. *Histopathology*. 2009;55:399–406.
23. Wu TT, Chirieac LR, Abraham SC, et al. Excellent interobserver agreement on grading the extent of residual carcinoma after preoperative chemoradiation in esophageal and esophagogastric junction carcinoma: a reliable predictor for patient outcome. *Am J Surg Pathol*. 2007;31:58–64.
24. Mirza A, Naveed A, Hayes S, et al. Assessment of histopathological response in gastric and gastro-oesophageal junction adenocarcinoma following neoadjuvant chemotherapy: which scoring system to use? *ISRN Pathol*. 2012;2012:519351.
25. Chetty R, Gill P, Govender D, et al. International study group on rectal cancer regression grading: interobserver variability with commonly used regression grading systems. *Hum Pathol*. 2012;43:1917–1923.
26. Bateman AC, Jaynes E, Bateman AR. Rectal cancer staging post neoadjuvant therapy—how should the changes be assessed? *Histopathology*. 2009;54:713–721.
27. Becker K, Langer R, Reim D, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. *Ann Surg*. 2011;253: 934–939.