Response to neoadjuvant therapy (Core)

Several grading systems for histopathological primary tumour response to neoadjuvant therapy have been applied to treated gastrointestinal carcinomas. These include the Mandard,[1] Becker,[2] Japanese Gastric Cancer Association[3] and College of American Pathologists (CAP)[4]/American Joint Committee on Cancer (AJCC)[5] tumour regression grading schemes.[6,7] While the Mandard system[1] is based on the fibrosis/tumour ratio (Table 4), the four-tiered Becker system[2] uses the estimated percentage of residual tumour in relation to the (assumed) pre-therapy tumour size (Table 5). The CAP modified Ryan grading system,[8] which is also referred to by the AJCC Staging System 8th edition,[5] is shown in Table 6.

Table 4: Mandard tumour regression grading system.[1]

Description	**Tumour Regression Score**
Complete regression: fibrosis without detectable tumour	1
Fibrosis with rare, scattered residual cancer cells	2
Fibrosis and tumour cells with a predominance of fibrosis	3
Fibrosis and tumour cells with predominance of tumour cells	4
No signs of regression	5

Table 5: Becker Tumour Regression Grading System.[2]

Description	**Tumour Regression Score**
No residual carcinoma	1
1-10% residual carcinoma	2
11-50% residual carcinoma	3
>50% residual carcinoma	4

Table 6: College of American Pathologists modified Ryan tumour regression grading system.[4]

Description	**Tumour Regression Score**
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumour regression (poor or no response)	3

Reproduced with permission from Ryan R et al (2005). Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 47(2):141-146.[8]

Although many studies have evaluated and compared these grading schemes in assessing treatment response in gastrointestinal carcinomas after neoadjuvant therapy,[6,9-11] there is no consensus on the optimal method to stratify tumour regression. In addition, the inter- and intra-observer variability is high for most grading schemes.[6,7] Nevertheless, response to neoadjuvant therapy should be

reported, as assessment of histological tumour regression may provide valuable prognostic information and may impact on the choice of postoperative therapy.[6] Patients with complete tumour regression of the primary cancer have significantly better overall survival compared to patients with residual adenocarcinoma.[6] As there is currently no consensus, the CAP grading system,[4] which is a modified Ryan scheme,[8] is recommended by the Carcinoma of the Stomach Dataset Authoring Committee. The CAP grading system assesses the residual tumour cells rather than treatment-associated fibrosis.[8]

The presence of lymph node metastasis is one of the most important prognosticators in gastrointestinal carcinomas, but a consensus method to determine tumour regression in lymph nodes has not been established. Furthermore, so far only a few studies have demonstrated that regressive changes in lymph node metastasis were associated with patient outcome.[6] Therefore, tumour regression should only be graded in the primary tumour at present.

If there is no tumour visible on macroscopic examination, the entire assumed tumour bed should be processed into paraffin blocks in order to correctly stage tumours and evaluate treatment response. However, there is no standard protocol for grossing specimens with macroscopically visible residual carcinoma. Most pathologists gross these specimens like those without preoperative treatment. Routine cytokeratin immunohistochemistry (IHC) is not recommended, but it may be helpful, if available, when the specimen is morphologically suspicious for residual viable tumour. According to the UICC[12]/AJCC[5] 8th edition Staging Manuals, acellular mucin pools, necrosis, and degenerative/ reactive changes without viable tumour cells after treatment should be interpreted as negative for tumour.

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