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Editorial Comment

Assessing downgrading of locally advanced rectal cancer after chemo-radiotherapy

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Pre-operative chemo/radiotherapy (CRT) is now part of standard care for the treatment of patients with locally advanced rectal cancer.[1] Not only does pre-operative CRT improve local control in comparison to surgery or post-operative CRT but also has the additional advantages of reducing the risk of tumour cell seeding and promoting tumour downstaging, thus facilitating surgery and possibly improving long-term outcome.[2]

Tumour downstaging, namely the comparison of pre-treatment clinical, radiographic or ultrasound T and N stage to post-treatment pathologic stage is frequently used as a measure of tumour response. Although tumour downstaging has been linked to improvements in patient outcome, it is limited to some extent by the accuracy of pre-treatment staging modalities. Moreover, although the ypTNM is recognised as an important prognostic parameter of disease-free survival after pre-operative CRT, it may be suboptimal for describing the changes undergone by the tumour after therapy. For example, a tumour initially staged as cT3 which post-treatment is represented only by small microfoci of residual tumour cells in the subserosa will still be considered ypT3 despite showing significant regressive changes.

An alternative approach to measure tumour response is to grade the histological changes caused by pre-operative CRT. These can vary widely from pathological complete response (pCR), namely the absence of residual tumour cells following therapy, to the lack of any regressive changes. Several tumour regression grading systems have been proposed, the most frequently used based on proposals by Dworak[3] and Mandard,[4] originally described for rectal and oesophageal cancers, respectively. Both systems comprise five distinct tumour regression grades (TRG) and have previously been shown, mostly in retrospective studies, to predict disease-free survival, with patients experiencing a pCR (i.e. Dworak TRG 4 and Mandard TRG 1) benefitting from the most favourable outcome. In addition to these, similar methods based on Mandard's approach including the three-point system published by Ryan and colleagues[5] and the four-point College of American Pathologists (CAP) system (based on Ryan's) used by the American Joint Committee on Cancer (AJCC)[6] are also currently being employed to grade regressive changes following neoadjuvant treatment (Table 1).

In this issue of the *European Journal of Cancer*, Dhadda and colleagues evaluate the prognostic power of the Mandard regression grading system and propose a simplified alternative using a cohort of 158 locally advanced rectal cancer patients.[7] They not only confirm that increasing Mandard score (TRG 1, 2 and 3–5) is related to poorer disease-free and

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Table 1 – Examples of tumour regression grading systems.

Five-point Dworak[3](1997)		Five-point Mandard[4](1994)	Three-point Ryan (modified from Mandard)[5](2005)		Four-point CAP (modified from Ryan)[6](2010)	
TRG 0	No regression	TRG 1	Complete regression; absence of residual cancer and fibrosis extending through the wall	TRG 1	No viable cells; single cells or small groups of cancer cells	TRG 0	No viable cells (complete response)
TRG 1	Dominant tumour mass with obvious fibrosis and/or vasculopathy	TRG 2	Presence of rare residual cancer cells scattered through the fibrosis	TRG 2	Residual cancer outgrown by fibrosis	TRG 1	single cells or small groups of cancer cells (moderate response)
TRG 2	Dominantly fibrotic changes with few tumour cells or groups (easy to find)	TRG 3	Increase in the number of residual cancer cells, but fibrosis still predominant	TRG 3	Significant fibrosis outgrown by cancer; no fibrosis with extensive residual cancer	TRG 2	Residual cancer outgrown by fibrosis (minimal response)
TRG 3	Very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance	TRG 4	Residual cancer outgrowing fibrosis			TRG 3	Minimal or no tumour kill; (extensive residual cancer)
TRG 4	No tumour cells, only fibrotic mass; total regression or response	TRG 5	Absence of regressive changes				

overall survival, but that its effect is still maintained after adjusting for the prognostic impact of the circumferential resection margin, perineural invasion and nodal status. The authors then propose a simplified four-point Mandard tumour regression grading system that, unlike other methods, incorporates the lymph node status into TRG 4.[7]

It is clear that any tumour regression grading system considered for implementation into routine diagnostic pathology should consist of at least three parameters: simplicity, reproducibility and the ability to contribute independent prognostic information above-and-beyond what can be reached with other routinely reported and well-established prognostic features. The simplified four-point Mandard groupings and inclusion of lymph node positivity proposed by Dhadda et al. not only seems to predict disease-free survival in multivariate analysis but also leads to excellent inter-observer agreement between two independent pathologists (kappa = 0.89).

Consensus over the most appropriate tumour regression grading system has not yet been reached and efforts to standardise TRGs for patients with locally advanced rectal cancer founded on a large evidence base should remain a priority. The performance of the proposed system here, and others such as the Dworak, Mandard, and CAP should be compared in the context of large prospective trials to identify the most feasible, reproducible and relevant for patient management. The promising results of the proposed four-point Mandard system described in this paper to improve prognostic risk stratification following pre-operative CRT thus warrant further validation in the prospective setting.

Conflict of interest statement

None declared.

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