

University of Groningen

Relevance of shrinkage versus fragmented response patterns in rectal cancer

Kus Ozturk, Sonay; Graham Martinez, Cristina; Sheahan, Kieran; Winter, Desmond C; Aherne, Susan; Ryan, Éanna J; van de Velde, Cornelis Jh; Marijnen, Corrie Am; Hospers, Geke AP; Roodvoets, Annet Gh

Published in:
Histopathology

DOI:
[10.1111/his.15027](https://doi.org/10.1111/his.15027)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kus Ozturk, S., Graham Martinez, C., Sheahan, K., Winter, D. C., Aherne, S., Ryan, É. J., van de Velde, C. J., Marijnen, C. A., Hospers, G. AP., Roodvoets, A. G., Doukas, M., Mens, D., Verhoef, C., van der Post, R. S., & Nagtegaal, I. D. (2023). Relevance of shrinkage versus fragmented response patterns in rectal cancer. *Histopathology*, 83(6), 870-879. <https://doi.org/10.1111/his.15027>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.




Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Relevance of shrinkage versus fragmented response patterns in rectal cancer

Sonay Kus Ozturk,¹  Cristina Graham Martinez,¹  Kieran Sheahan,² Desmond C Winter,³ Susan Aherne,² Éanna J Ryan,³ Cornelis JH van de Velde,⁴ Corrie AM Marijnen,⁵ Geke AP Hospers,⁶ Annet GH Roodvoets,⁴ Michail Doukas,⁷ David Mens,⁸ Cornelis Verhoef,⁸ Rachel S van der Post¹ & Iris D Nagtegaal¹ 

¹Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands, ²Department of Pathology, ³Department of Surgery, St. Vincent's University Hospital, Dublin, Ireland, ⁴Department of Surgery, ⁵Department of Radiotherapy, Leiden University Medical Centre, Leiden, ⁶Department of Oncology, University Medical Centre Groningen, Groningen, ⁷Department of Pathology and ⁸Department of Surgical Oncology, Erasmus Medical Centre, Rotterdam, The Netherlands

Date of submission 8 May 2023
Accepted for publication 31 July 2023

Kus Ozturk S, Graham Martinez C, Sheahan K, Winter D C, Aherne S, Ryan É J, van de Velde C J H, Marijnen C A M, Hospers G A P, Roodvoets A G H, Doukas M, Mens D, Verhoef C, van der Post R S & Nagtegaal I D

(2023) *Histopathology* 83, 870–879. <https://doi.org/10.1111/his.15027>

Relevance of shrinkage versus fragmented response patterns in rectal cancer

Aims: Partial response to neoadjuvant chemoradiotherapy (CRT) presents with one of two main response patterns: shrinkage or fragmentation. This study investigated the relevance of these response patterns in rectal cancer, correlation with other response indicators, and outcome.

Methods and results: The study included a test ($n = 197$) and a validation cohort ($n = 218$) of post-CRT patients with rectal adenocarcinoma not otherwise specified and a partial response. Response patterns were scored by two independent observers using a previously developed three-step flowchart. Tumour regression grading (TRG) was established according to both the College of American Pathologists (CAP) and Dworak classifications. In both cohorts, the predominant response pattern was fragmentation (70% and 74%), and the scoring interobserver agreement was excellent ($k = 0.85$). Patients with a fragmented pattern presented with significantly higher pathological stage (ypTNM II-IV, 78%

versus 35%; $P < 0.001$), less tumour regression with Dworak ($P = 0.004$), and CAP TRG ($P = 0.005$) compared to patients with a shrinkage pattern. As a predictor of prognosis, the shrinkage pattern outperformed the TRG classification and stratified patients better in overall (fragmented pattern, hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.19–3.50, $P = 0.008$) and disease-free survival (DFS; fragmented pattern, HR 2.50, 95% CI 1.23–5.10, $P = 0.011$) in the combined cohorts. The multivariable regression analyses revealed pathological stage as the only independent predictor of DFS.

Conclusions: The heterogeneous nature of tumour response following CRT is reflected in fragmentation and shrinkage. In rectal cancer there is a predominance of the fragmented pattern, which is associated with advanced stage and less tumour regression. While not independently associated with survival, these reproducible patterns give insights into the biology of tumour response.

Keywords: neoadjuvant chemoradiation treatment, partial response, patterns of response, rectal cancer

Address for correspondence: S Kus Ozturk, Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands. e-mail: sonay.kusozturk@radboudumc.nl

Introduction

Chemoradiotherapy (CRT) is one of the main neoadjuvant treatments in locally advanced rectal cancer management; it facilitates radical surgical resection due to tumour downstaging and decreases the risk of local recurrence.^{1–3} To evaluate the effect of this therapy, resection specimens are assessed for response. Tumour regression grading (TRG) and tumour downstaging are well-known response indicators, that also have been suggested as surrogate outcomes of neoadjuvant therapies.^{4–7}

After the introduction of the initial 5-tier tumour regression grading (TRG) classification by Mandard,⁸ several modifications have been suggested consisting of 3-, 4-, or 5-tiers,^{9–13} based on either tumour percentage or tumour–stroma ratio. In practice, considerable inter-observer variation as well as the wide variation in classifications and definitions hamper a standardized approach. However, both pathologic complete response (pCR) and “no response” classifications are generally straightforward. The “partial response” group display profound heterogeneity, causing poor interobserver agreement.^{14–16} Conflicting results about the clinical relevance of TRG have been reported.^{6,14,17–22}

Previous small rectal cancer studies indicated “shrinkage” and “fragmentation” as two main response patterns after neoadjuvant therapy.^{14,17,23,24} Shrinkage is defined as the downsizing of the residual tumour resulting in a luminal tumour bulk or defined discrete tumour mass. Fragmentation refers to the dissociation of the tumour mass forming different-sized groups spreading randomly into the tumour bed.¹⁴ The presence of a fragmented pattern increases the possibility of tumour in the deeper layers of the bowel, resulting in an advanced ypT stage, more frequent lymph node metastasis, and poor outcome.^{17,23,24} Although the clinical relevance of the pattern of response has been suggested, these terms are fairly new, ill-defined, and have not been used in daily practice yet.

In the present study we investigate response patterns in rectal cancer in four large international multicentre cohorts, focusing on clinical relevance of response patterns compared with well-known response indicators.

Materials and methods

PATIENTS

We included patients with clinical stage I–III rectal cancer receiving long-term CRT and diagnosed with adenocarcinoma not otherwise specified and a partial

response to treatment. Patients with multiple malignancies, tumours other than adenocarcinoma, and specific subtypes (mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma) were excluded. Clinical and follow-up data including demographic features, cTNM staging, locoregional or distant disease recurrence dates, and vital status were retrieved. Follow-up was performed according to national guidelines and trial protocols. Relevant pathologic data including pathological stage were obtained from the institutional pathology databases. The ethical standards of the research Ethics Committee and the Helsinki Declaration of 1964 and later versions were thoroughly met.

The test cohort was retrieved from the local pathology databases of two centres, namely, the Radboud University Medical Centre, the Netherlands, and St. Vincent's University Hospital, Ireland, and patients underwent surgery in the period 2003–2020.

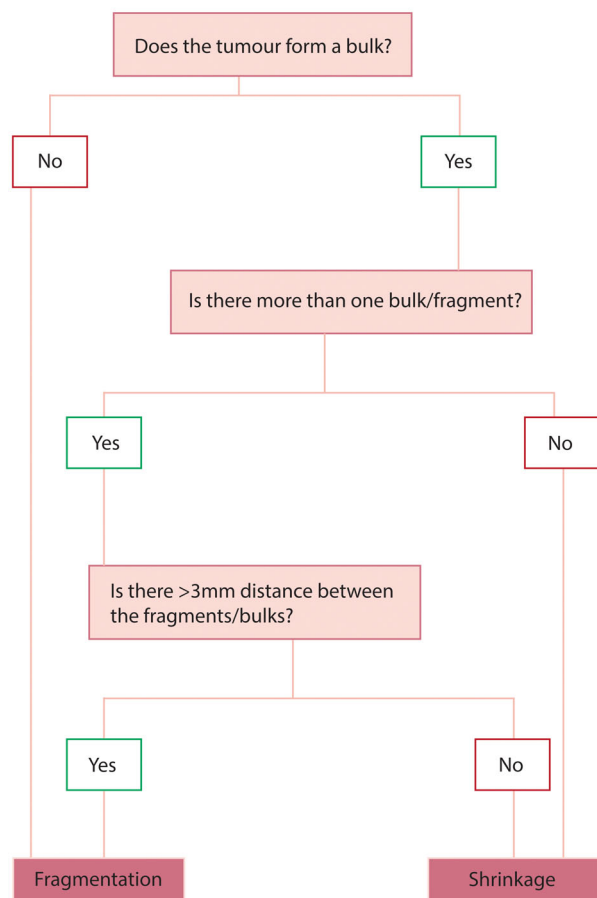
A combined external cohort from the standard arm of the prospective RAPIDO trial (NCT01558921)²⁵ and the Erasmus University Medical Centre, the Netherlands, was used as a validation cohort. All of the patients selected were operated on between 2006 and 2022.

ASSESSMENT OF TUMOUR RESPONSE

After histological review, all tumour representative haematoxylin-eosin (H&E) slides per case were selected and digitized to assess response. Tumour response was assessed in two ways. First, tumour regression was graded by a pathologist (S.K.O.) in the primary tumour slides according to 5-tiered Dworak and 4-tiered Modified Ryan Scheme, as suggested in the AJCC/College of American Pathologists (CAP).⁹ Dense tumoral mass without regressive changes, that is, fibrosis, acellular mucin, was classified as no response. Second, patterns of response were evaluated. Two main response patterns, i.e. tumour shrinkage and fragmentation, were assessed using a previously developed flowchart by two independent observers (S.K.O. and C.G.M.; Figure 1).²⁶ Difficult cases were discussed among the same researchers to reach consensus and, in case of discordance, consultation with an expert gastrointestinal pathologist (I.D.N.) was carried out. After scoring all the tumour slides per case, an overall response pattern was attributed to each rectal cancer.

Fragmentation was identified as dissociated tumour groups without a discrete tumour mass or tumours containing fragments at least 3 mm away from the bulk (Figure 2C–F). The remnants in the fragmented pattern were heterogeneous in size. While some cases

DIAGRAM FOR PATTERN OF RESPONSE ASSESSMENT

Figure 1. Flow chart.²⁶

purely consisted of clusters of more than 10 cells (clustered fragmentation), others were composed of fewer than 10 cell groups (scattered fragmentation), or a mixture of different-sized tumour groups (mixed fragmentation).

Shrinkage was characterized by bulk-forming tumour residue without fragments or with fragments within 3 mm of the tumour bulk (Figure 2A, B). The main tumour bulk may reside in the luminal (luminal shrinkage) or deeper layers (irregular shrinkage).

The distribution of residual tumour cells among the layers of the bowel was also assessed. Tumour downstaging was defined as a decrease between the preoperative clinical and postoperative pathological stage.

STATISTICAL ANALYSIS

The two main response patterns were compared according to their baseline characteristics. Pearson's

χ^2 and analysis of variance (ANOVA) tests were used for qualitative and quantitative comparisons, respectively. The correlation between patterns of response and ypTNM was tested with Spearman's ρ rank correlation test. Cohen's kappa coefficient (κ) was used to measure the interobserver agreement rate for the classification of the patterns of response. A κ score of 0.60–0.79 indicated moderate agreement and a κ score above 0.80 was considered strong interobserver agreement.

The interval between surgical resection and death or last follow-up time was defined as overall survival (OS) time. Disease-free survival (DFS) time was defined as the time from surgical resection to disease recurrence and/or death or the last follow-up time. Kaplan–Meier survival curves and log-rank tests were used to visualize OS and DFS. Univariable and multivariable Cox regression analyses were performed to demonstrate survival-associated clinicopathological variables in the test cohort and validation cohort separately. Multivariable analysis was repeated after the combination of two cohorts. $P < 0.05$ was considered statistically significant. Hazard ratios (HRs) and risk ratios (RRs) are presented with a 95% confidence interval (CI).

For all analyses, RStudio (2020) was used. Results were confirmed by a second researcher using SPSS Statistics v25.0 (IBM, Armonk, NY, USA).

Results

TEST COHORT

From the original 283 patients, we excluded patients with special type adenocarcinomas ($n = 36$), pCR ($n = 27$), and no response to CRT ($n = 23$), resulting in the inclusion of 197 patients with partial response.

PATTERNS OF TUMOUR RESPONSE

Fragmentation (70%) was the predominant main response pattern observed in the test cohort. An excellent interobserver agreement was reached ($\kappa = 0.85$) by use of the flowchart in the response pattern evaluation. There was full agreement on tumour response patterns in 183 out of 197 cases (93%). More than half of the shrinkage pattern cases presented with ypTNM I. Advanced stages showed more frequently a fragmented pattern ($P < 0.001$, Table 1). Indeed, there was a significant positive correlation between ypTNM and response patterns (Spearman's rank correlation coefficient,

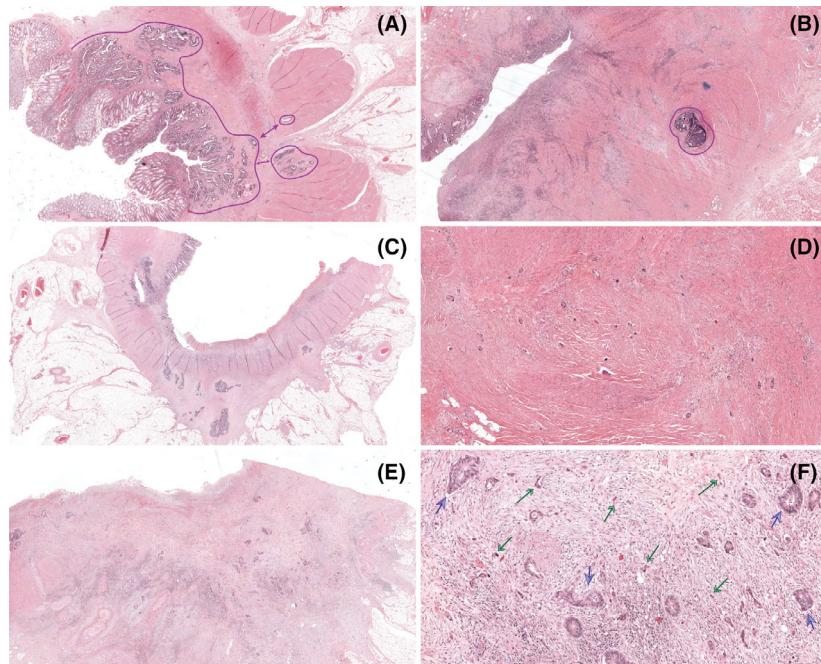


Figure 2. A: Luminal shrinkage, B: Irregular shrinkage, C: fragmented clustered, D: fragmented scattered, E,F: Fragmented mixed (thin arrows indicate scattered, thick arrows indicate clustered component).

$\rho = 0.36$, $P < 0.001$). Residual tumour in deeper layers (muscularis propria: fragmented 96% versus shrinkage 49%, $P < 0.001$ and subserosa: fragmented 71% versus shrinkage 18%, $P < 0.001$) was more common in the fragmented pattern. Patients with a fragmented pattern had less tumour regression in both Dworak ($P = 0.004$), and CAP TRG classifications ($P = 0.005$). Clinical stage ($P = 0.85$) and clinical T stage ($P = 0.13$) were similar among the two main response patterns (Table 1).

PROGNOSIS

The median follow-up time was 56 months (interquartile range [IQR] 36–104) in the test cohort. Patients with a shrinkage pattern had a trend of better OS, although the difference was not significant (5-year; 85% versus 70%, $P = 0.094$). The risk of disease recurrence (RR: 1.14, 95% CI: 0.86–1.51, $P = 0.40$) was similar among the two main response patterns.

In the univariable survival analysis, advanced pathological stage (HR 1.9, 95% CI 1.0–3.6, $P = 0.05$) was an indicator of poor OS and DFS. Absence of downstaging and poor tumour regression according to Dworak and CAP TRGs were also indicators of poor OS (Figure 3). In multivariable regression analyses, none of the aforementioned variables

proved to be an independent prognostic factor of survival.

VALIDATION COHORT

From the original 293 patients in the validation cohort, we excluded 75 patients (13 pCR, 19 no response, and 43 mucinous adenocarcinomas), resulting in 218 patients. Compared to the test cohort, the validation cohort presented less advanced tumours (ypTNM III 32% validation cohort versus 35% test cohort, $P = 0.006$) and a higher prevalence of cases with high tumour regression according to the Dworak classification (TRG 2–3, 86% versus 76%, $P = 0.03$; Table 1). The fragmented pattern remained the predominant pattern and the proportions of shrinkage (26%) and fragmented pattern (74%) were similar to the test cohort ($P = 0.68$). When scoring patterns of response, the interobserver agreement was again excellent ($\kappa = 0.83$).

The validation cohort's median follow-up time was 65 months (IQR 50–85). Patients with a shrinkage pattern had a better OS than those with a fragmented pattern (5-year; 88% versus 72%, $P = 0.045$). Furthermore, patients with a shrinkage pattern had a lower risk of recurrence (RR: 2.37, 95% CI: 1.06–5.28, $P = 0.02$) and a better DFS compared to patients with a fragmented pattern of response (5-year; 80% versus 62%, $P = 0.01$).

Table 1. Clinicopathologic characteristics of the patients

	Test cohort (<i>n</i> = 197)				Validation cohort (<i>n</i> = 218)				<i>P</i> (T versus V)		
	Total	Shrinkage, <i>n</i> = 55 30%	Fragmented, <i>n</i> = 142 70%	<i>P</i>	Total	Shrinkage, <i>n</i> = 56 26%	Fragmented, <i>n</i> = 162 74%	<i>P</i>			
Age, median (min-max)	61	42–80	62	28–81	0.61	60	18–83	63	32–86	0.13	0.66
Gender (%)											
Male	58	31	69	0.69	64	27	73	0.73	0.39		
Female	42	26	74		36	30	70				
Medical centre (%)											
Centre 1	57	29	71	0.94	26	37	63	0.04			
Centre 2	43	27	73		74	22	78				
Clinical stage (%)											
I	5	5	5	0.85	1	2	—	0.27	0.05		
II	18	14	20		17	16	17				
III	77	81	75		82	82	83				
Pathological stage (%)											
I	34	65	22	<0.001	23	55	10	<0.001	0.006		
II	31	15	37		45	20	55				
III	33	20	38		32	25	35				
IV	2	—	3		—	—	—				
Recurrence (%)											
Yes	19	13	21	0.60	23	12	28	0.03	0.50		
No	81	87	79		77	88	72				
Downstaging (%)											
Yes	67	81	62	0.19	61	71	58	0.15	0.46		
No	33	19	38		39	29	42				
Dworak TRG (%)											
TRG1	24	14	27	0.004	14	—	19	<0.001	0.03		
TRG2	64	62	65		74	64	77				
TRG3	12	24	8		12	36	4				
CAP TRG (%)											
Score 1	13	25	8	0.005	12	36	4	<0.001	0.68		
Score 2	71	64	74		75	64	78				
Score 3	16	11	18		13	—	18				

The comparisons that were statistically significant are highlighted with bold.

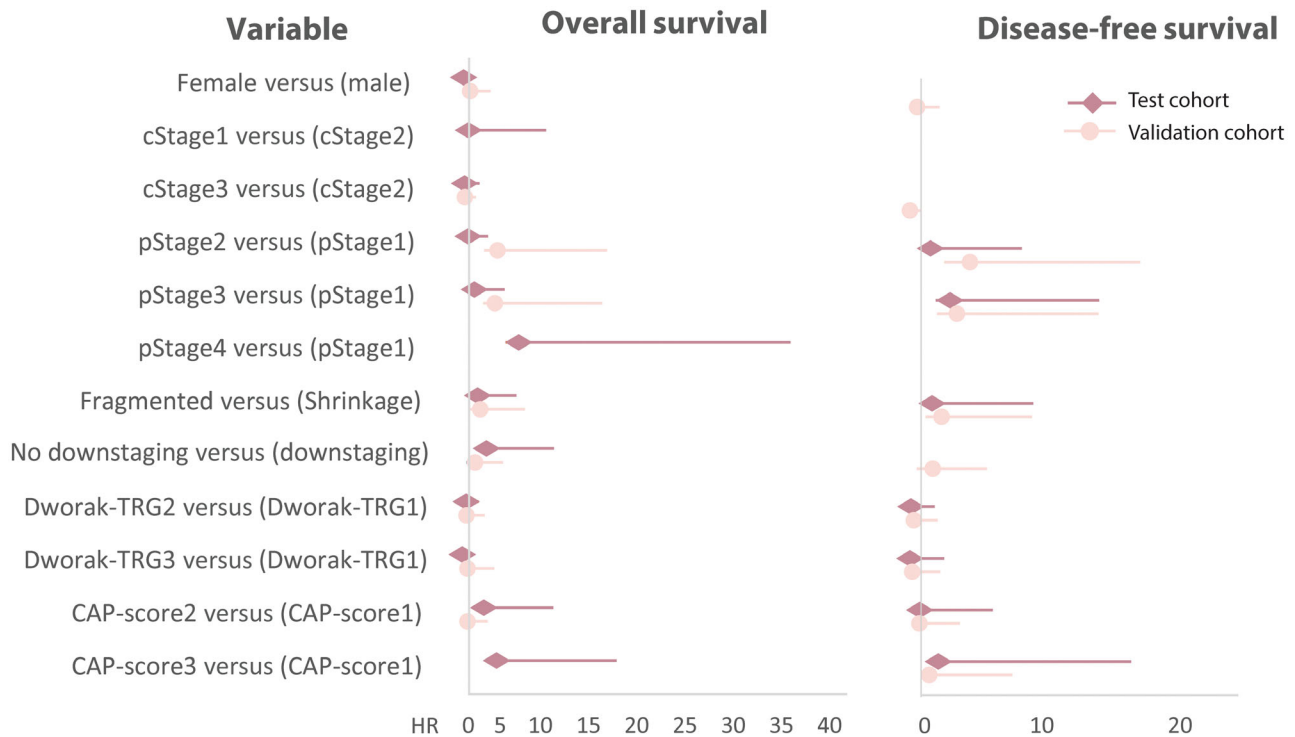


Figure 3. Univariate regression analyses of test and validation cohorts. The reference variable is indicated between brackets (e.g. female versus [male]).

Univariable Cox regression analysis revealed worse OS and DFS rates in patients with a fragmented pattern (HR 2.15, 95% CI 0.99–4.65, $P = 0.05$ and HR 2.75, 95% CI 1.16–6.53, $P = 0.02$, respectively) and advanced ypTNM. Absence of downstaging was also an indicator of poor DFS (Figure 3). Only the ypTNM was an independent prognostic factor of OS (HR 3.14, 95% CI 0.95–10.33, $P = 0.05$) and DFS (HR 3.69, 95% CI 1.31–10.35, $P = 0.01$) in the multivariable regression analyses.

UNIVARIABLE AND MULTIVARIABLE ANALYSES IN THE COMBINED COHORTS

In order to increase the statistical power for the multivariable analysis, both cohorts were pooled together. Patients with a shrinkage pattern had a better OS (5-year; 87% versus 73%, $P = 0.008$; Figure 4) and DFS (5-year; 80% versus 63%, $P = 0.004$; Figure 4B). Neither Dworak nor CAP TRG classifications significantly predicted OS or DFS.

Univariable regression analysis confirmed the poor prognostic effect of the fragmented pattern in OS (HR 2.04, 95% CI 1.19–3.50, $P = 0.008$) and DFS (HR 2.50, 95% CI 1.23–5.10, $P = 0.011$). Advanced

ypTNM and the absence of downstaging were other prognostic indicators associated with worse OS and DFS. Multivariable regression analysis revealed ypTNM as the only significant independent prognostic factor of OS and DFS (Tables 2 and 3).

Discussion

Our study confirms that, following CRT, two major response patterns are observed in rectal cancer. The most frequent pattern is fragmentation. However, shrinkage is associated with more regression, and a better outcome. The strong association with ypTNM limits its impact in the multivariable analysis.

This study is in line with earlier observations in oesophageal cancers, suggesting that there are universal patterns of response in gastrointestinal tract tumours.²⁶ In rectal cancer, we observe a similar, although less pronounced, prognostic impact. A reason behind this might be the relatively favourable life expectancy of rectal cancer compared to oesophageal cancer,^{29,30} even in tumours with a fragmented pattern.

Both the poor interobserver agreement in TRG and its discrepancies with ypTNM^{4,27,28} hamper clinical

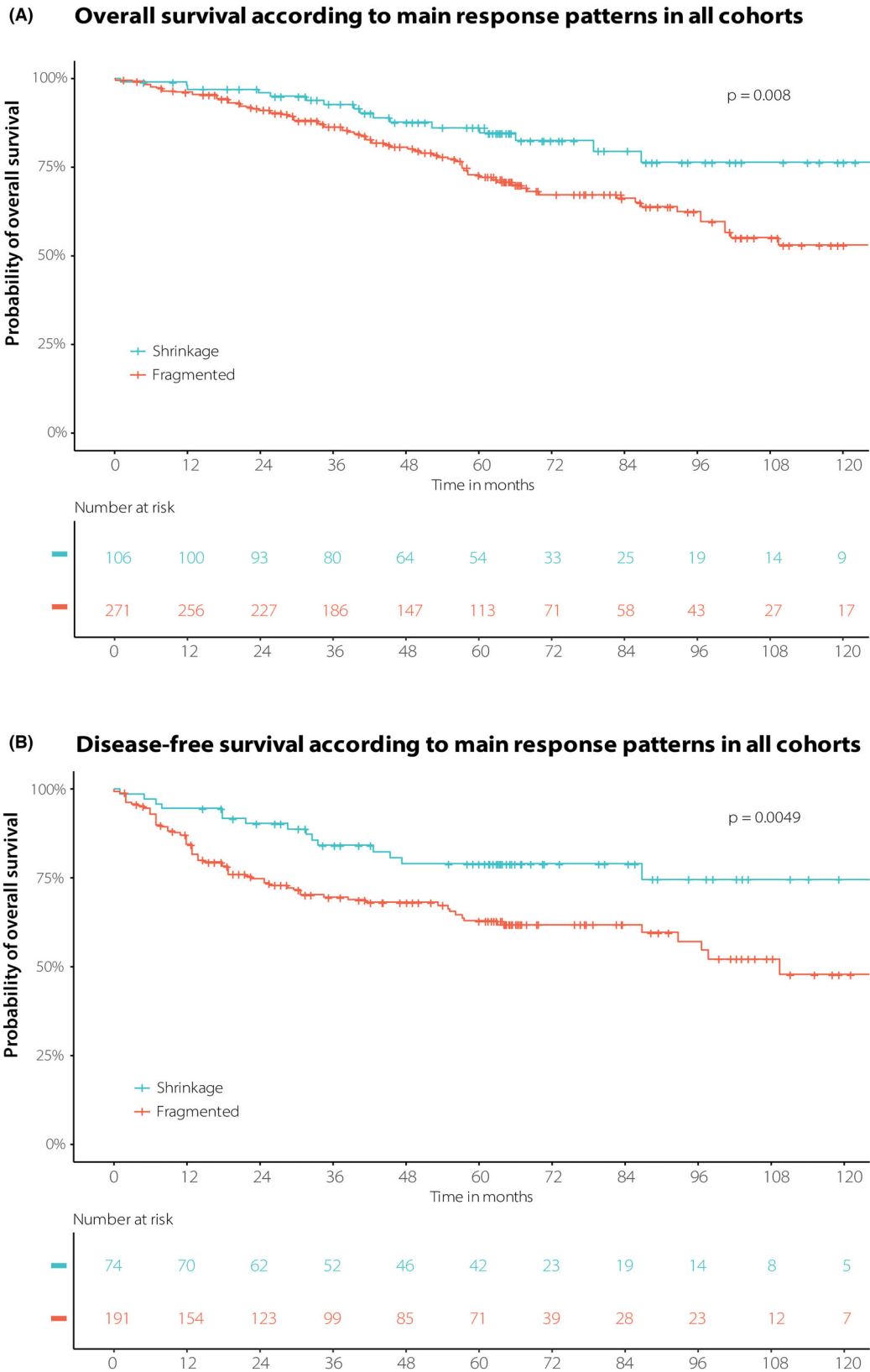


Figure 4. A,B: Overall survival and disease-free survival curves according to two main response patterns in combined cohorts.

Table 2. Univariate and multivariate analysis to identify risk factors of overall survival in combined cohorts

Covariate	n	Univariate analysis		Multivariate analysis	
		HR	95% CI	HR	95% CI
Gender					
Male	180	1.00			
Female	112	0.74	0.46–1.19		
Cohort					
Test	197	1.00			
Validation	180	0.90	0.60–1.37		
Clinical stage					
I	5	1.00			
II	45	1.79	0.23–13.55		
III	212	1.01	0.13–7.30		
Pathological stage					
I	107	1.00		1.00	
II	140	1.79	0.99–3.24	1.90	0.83–4.35
III	121	2.11	1.17–3.82	1.73	0.68–4.40
IV	4	7.73	1.75–34.08	—	—
Response pattern					
Shrinkage	106	1.00		1.00	
Fragmentation	271	2.04	1.19–3.50	1.82	0.87–3.79
Downstaging					
Yes	165	1.00		0.63	0.33–1.19
No	96	1.85	1.12–3.05	1.00	
Dworak TRG					
TRG1	68	1.00			
TRG2	262	0.67	0.40–1.11		
TRG3	47	0.48	0.22–1.04		
CAP TRG					
Score 1	49	1.00		1.00	
Score 2	278	1.48	0.76–2.88	0.85	0.36–2.02
Score 3	50	2.45	1.10–5.48	1.01	0.34–2.98

The comparisons that were statistically significant are highlighted with bold. HR, hazard ratio; CI, confidence interval.

Table 3. Univariate and multivariate analysis to identify risk factors of disease-free survival in combined cohorts

Covariate	n	Univariate analysis		Multivariate analysis	
		HR	95% CI	HR	95% CI
Gender					
Male	115	1.00			
Female	65	0.97	0.57–1.64		
Cohort					
Test	85	1.00			
Validation	180	1.31	0.79–2.15		
Clinical stage					
I	1	—			
II	30	1			
III	149	0.46	0.26–0.80		
Pathological stage					
I	72	1.00		1.00	
II	108	3.67	1.79–7.53	3.69	1.31–10.35
III	83	3.42	1.63–7.18	2.09	0.64–6.85
Response pattern					
Shrinkage	74	1.00		1.00	
Fragmentation	191	2.50	1.23–5.10	1.36	0.66–2.79
Downstaging					
Yes	110	1.00		0.58	0.29–1.15
No	69	2.12	1.16–3.90	1.00	
Dworak TRG					
TRG1	36	1.00			
TRG2	195	0.68	0.34–1.36		
TRG3	34	0.59	0.22–1.55		
CAP TRG					
Score 1	34	1.00			
Score 2	198	1.19	0.51–2.52		
Score 3	33	1.92	0.73–5.05		

The comparisons that were statistically significant are highlighted with bold. HR, hazard ratio; CI, confidence interval.

decision-making. By application of response patterns, we can link response to the stage and the presence of residual tumour cells in deeper layers of the bowel wall. In this study, as well as in oesophageal carcinoma,²⁶ we have shown that implementing our definition and the three-step flowchart classification provided a more reliable and reproducible classification of response patterns, thus solving a practical issue with response classification. Moreover, its clinical relevance is consistent with the previous literature.^{17,23,24,26}

Understanding response to treatment is important on several levels, directly, to determine further treatment strategies but also, indirectly, to understand underlying biological processes. Both pathological and clinical/radiological examinations generally lead to a straightforward diagnosis in case of pCR and no response. However, the evaluation of partial response remains problematic due to the variation and irreproducibility of the methodologies used.^{8–13,21,24,25} On the other hand, partial responders are heterogeneous in terms of outcome. Therefore, there is an urgent need to define solid strategies to improve decision-making and differentiate the poor prognostic subgroups in partial response diagnosis. From that point of view, tumour response patterns may be a strong candidate to investigate tumour behaviour in partial responders.

To the best of our knowledge, there is no explanation yet as to why some tumours shrink while others break into fragments. Indeed, Graham Martinez *et al.* observed a difference in stromal immune cell populations between shrinkage and fragmented patterns in rectal cancer patients.³¹ Yet, more research is needed to provide valuable information about tumour biology behind these patterns. With the increasing trend for organ preservation in both oesophageal and rectal cancer, there is an urgent need for understanding tumour response, and reliable prediction of downstaging and residual tumour. It might be interesting to compare presurgical radiologic findings of two main response patterns and even to make an effort to establish a radiological classification based on these patterns, to guide the extent of surgical treatment. Since patients with a fragmented pattern might not be cured by local excision, it is essential to identify those patients early and treat them accordingly. This should be the next step in predictive research.

Our study had a retrospective nature that may cause bias in case selection. However, including international cohorts and validating our findings with an external cohort strengthen our results.

In conclusion, we confirmed the reproducibility and replicability of the classification for patterns of

response in rectal cancer. This classification can be easily implemented in clinical practice in addition to routinely used regression schemes. Patients with a shrinkage pattern presented with a favourable overall and DFS in rectal adenocarcinoma cohorts. These patterns provide insight in the heterogeneity of tumour response and form the basis for future novel treatment strategies.

Author contributions

S.K.O. and C.G.M. performed the research. S.K.O., C.G.M., R.S.P., and I.D.N. designed the research study. S.K.O., C.G.M., K.S., S.A., M.D., and D.M. collected the data. S.K.O. and C.G.M. analysed the data. S.K.O. wrote the article. All authors provided critical feedback on the article.

Acknowledgements

This study was supported by a KWF programme grant (KWF 2016-2-10602).

Conflict of interest

All authors declare that they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Wiegering A, Isbert C, Dietz UA *et al.* Multimodal therapy in treatment of rectal cancer is associated with improved survival and reduced local recurrence—a retrospective analysis over two decades. *BMC Cancer* 2014; **14**: 816.
2. Sineshaw HM, Jemal A, Charles R *et al.* Changes in treatment patterns for patients with locally advanced rectal cancer in the United States over the past decade: an analysis from the National Cancer Database. *Cancer* 2016; **122**: 1996–2003.
3. Glynne-Jones R, Wyrwicz L, Tiret E *et al.* Clinical practice guidelines rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2017; **28**: 22–40.
4. Nagtegaal ID, Glynne-Jones R. How to measure tumour response in rectal cancer? An explanation of discrepancies and suggestions for improvement. *Cancer Treat. Rev.* 2020; **84**: 101964.

5. Valentini V, Coco C, Picciocchi A *et al.* Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. *Int. J. Radiat. Oncol. Biol. Phys.* 2002; **53**: 664–674.
6. Moureau-Zabotto L, Farnault B, De Chaisemartin C *et al.* Predictive factors of tumor response after neoadjuvant chemoradiation for locally advanced rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2011; **80**: 483–491.
7. Rullier A, Laurent C, Capdepon M, Vendrely V, Bioulac-Sage P, Rullier E. Impact of tumor response on survival after radiochemotherapy in locally advanced rectal carcinoma. *Am. J. Surg. Pathol.* 2010; **34**: 562–568.
8. Mandard AM, Dalibard F, Mandard JC *et al.* Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. *Cancer* 1994; **73**: 2680–2686.
9. Protocol for the Examination of Resection Specimens From Patients With Primary Carcinoma of the Colon and Rectum [Internet]. College of American Pathologists. Version 4.2.0.2. [June 2022]; Available at: https://documents.cap.org/protocols/ColoRectal_4.2.0.2.REL_CAPCP.pdf?_gl=1*1edeqt1*_ga*NDExMzAyNjUyLjE2OTE5MjM2NDc.*_ga_97ZFJSQQOX*MTY5MTkyMzYONy4xLjEuMTY5MTkyNDk2Ny4wLjAuMA
10. 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.
11. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int. J. Colorect. Dis.* 1997; **12**: 19–23.
12. Ryan R, Gibbons D, Hyland JMP *et al.* Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005; **47**: 141–146.
13. Rödel C, Martus P, Papadopoulos T *et al.* Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J. Clin. Oncol.* 2005; **23**: 8688–8696.
14. Gosens MJEM, Klaassen RA, Tan-Go I *et al.* Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. *Clin. Cancer Res.* 2007; **13**: 6617–6623.
15. 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.
16. Trakarnsanga A, Gonen M, Shia J *et al.* Comparison of tumor regression grade systems for locally advanced rectal cancer after multimodality treatment. *J. Natl. Cancer Inst.* 2014; **106**: 1–6.
17. Acenero MJF, Munoz LE, Varela JS *et al.* Prognostic influence of histopathological regression patterns in rectal adenocarcinoma receiving neoadjuvant therapy. *J. Gastrointest. Oncol.* 2017; **8**: 49–54.
18. Bouzourene H, Bosman FT, Seelentag W, Matter M, Coucke P. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. *Cancer* 2002; **94**: 1121–1130.
19. Losi L, Luppi G, Gavioli M *et al.* Prognostic value of Dworak grade of regression (GR) in patients with rectal carcinoma treated with preoperative radiochemotherapy. *Int. J. Colorectal Dis.* 2006; **21**: 645–651.
20. Bedrosian I, Rodriguez-Bigas MA, Feig B *et al.* Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma. *J. Gastrointestinal. Surg.* 2004; **8**: 56–63.
21. Pucciarelli S, Toppan P, Friso ML *et al.* Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. *Dis. Colon Rectum* 2004; **47**: 1798–1807.
22. Topova L, Hellmich G, Puffer E *et al.* Prognostic value of tumor response to neoadjuvant therapy in rectal carcinoma. *Dis. Colon Rectum* 2011; **54**: 401–411.
23. Perez RO, Habr-Gama A, Smith FM *et al.* Fragmented pattern of tumor regression and lateral intramural spread may influence margin appropriateness after TEM for rectal cancer following neoadjuvant CRT. *J. Surg. Oncol.* 2014; **109**: 853–858.
24. Hav M, Libbrecht L, Geboes K *et al.* Prognostic value of tumor shrinkage versus fragmentation following radiochemotherapy and surgery for rectal cancer. *Virchows Arch.* 2015; **466**: 517–523.
25. Nilsson PJ, van Etten B, Hospers GAP *et al.* Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer—the RAPIDO trial. *BMC Cancer* 2013; **13**: 279.
26. Graham Martinez C, Kus Ozturk S, Al-Kaabi A *et al.* Shrinkage versus fragmentation response in neoadjuvantly treated esophageal adenocarcinoma: significant prognostic relevance. *Histopathology* 2022; **80**: 982–994.
27. Swellengrebel HAM, Bosch SL, Cats A *et al.* Tumour regression grading after chemoradiotherapy for locally advanced rectal cancer: a near pathologic complete response does not translate into good clinical outcome. *Radiother. Oncol.* 2014; **112**: 44–51.
28. Duldulao MP, Lee W, Streja L *et al.* Distribution of residual cancer cells in the bowel wall after neoadjuvant chemoradiation in patients with rectal cancer. *Dis. Colon Rectum* 2013; **56**: 142–149.
29. Lordick F, Mariette C, Hausterman K *et al.* Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2016; **27**: 50–57.
30. Glynne-Jones R, Wyrwicz L, Tiret E *et al.* Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2017; **28**: 22–40.
31. Graham Martinez C, Barella Y, Kus Ozturk S *et al.* The immune microenvironment landscape shows treatment-specific differences in rectal cancer patients. *Front. Immunol.* 2022; **13**: 1011498.