



NEOADJUVANT THERAPY IN RECTAL CANCER

Tumor response: A complex issue

Prof. Dr. Iris Nagtegaal



RESPONSE: WHY DO WE WANT TO KNOW?

- Prognostic relevance: better response is better outcome
- Alternative endpoint for clinical trials
- Potential for local excision / watchfull waiting
- Risk of lymph node metastases
- Predictive marker for adjuvant therapy



Downstaging
Tumor regression grading

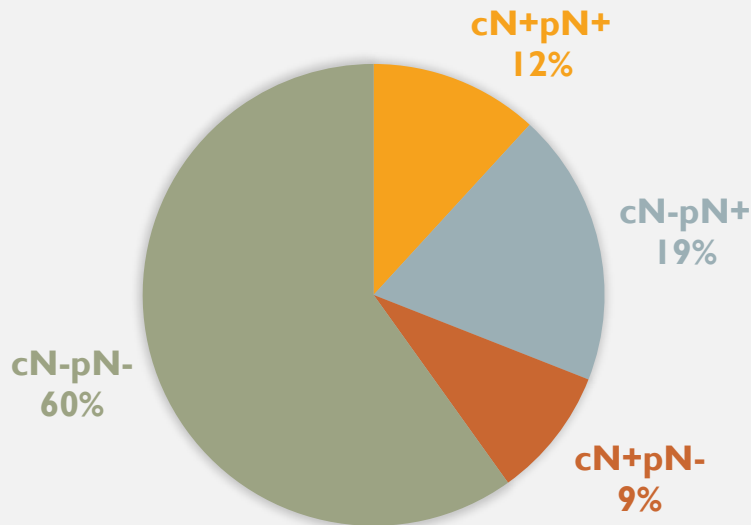
DOWNSTAGING

Based on clinical stage before the start of treatment

European Journal of Surgical Oncology 44 (2018) 1241–1246

Clinical lymph node staging in colorectal cancer; a flip of the coin?

Nelleke P.M. Brouwer^{a,*}, Rutger C.H. Stijns^b, Valery E.P.P. Lemmens^{c,d}, Iris D. Nagtegaal^e,
Regina G.H. Beets-Tan^{f,g}, Jurgen J. Fütterer^b, Pieter J. Tanis^h, Rob H.A. Verhoeven^d,
Johannes H.W. de Wilt^a



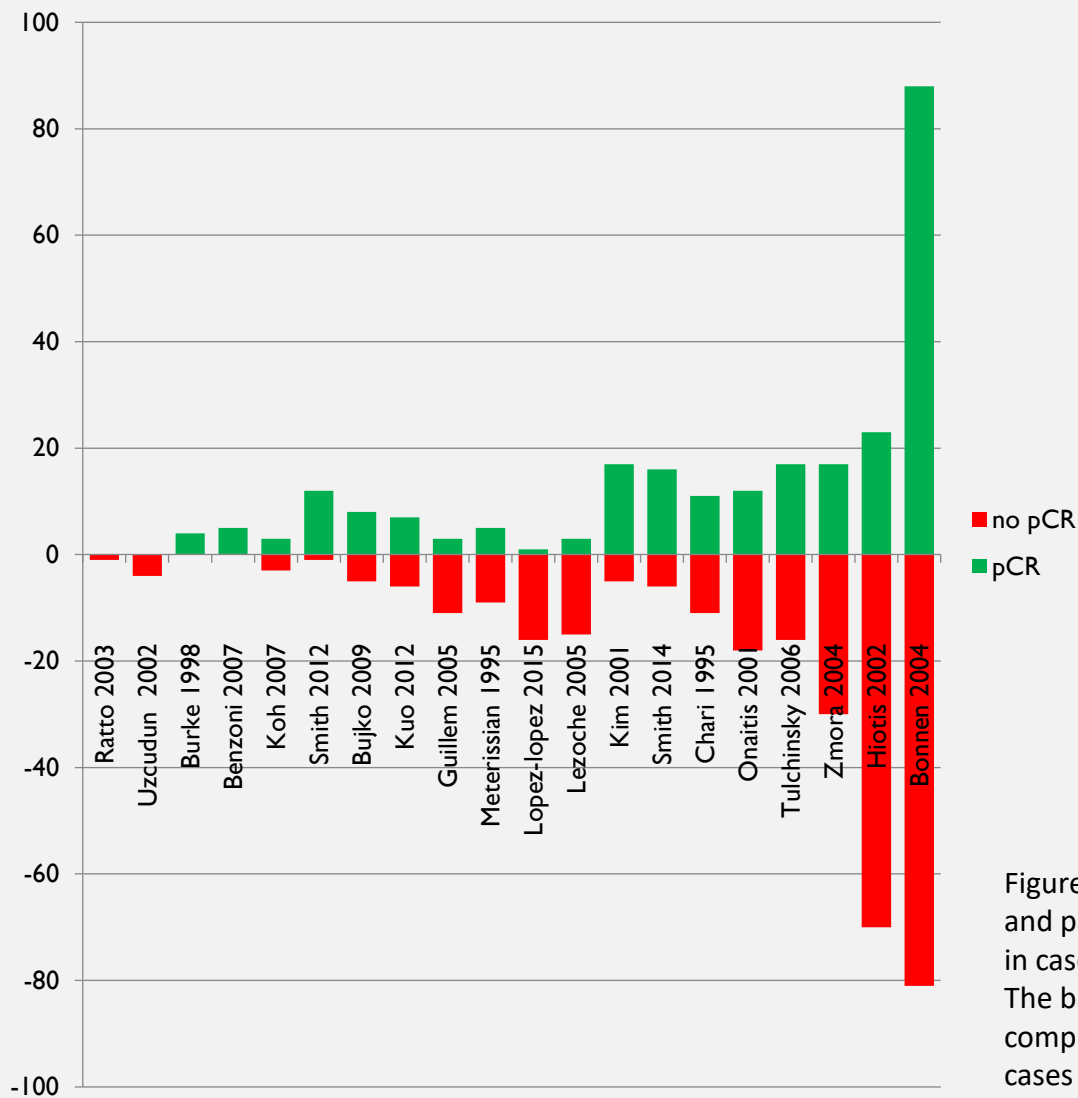
Rectal cancer

$$\text{Sensitivity} = A/(A+B) * 100\% = 38\%$$

$$\text{Specificity} = D/(C+D) * 100\% = 87\%$$

$$\text{PPV} = A/(A+C) * 100\% = 56\%$$

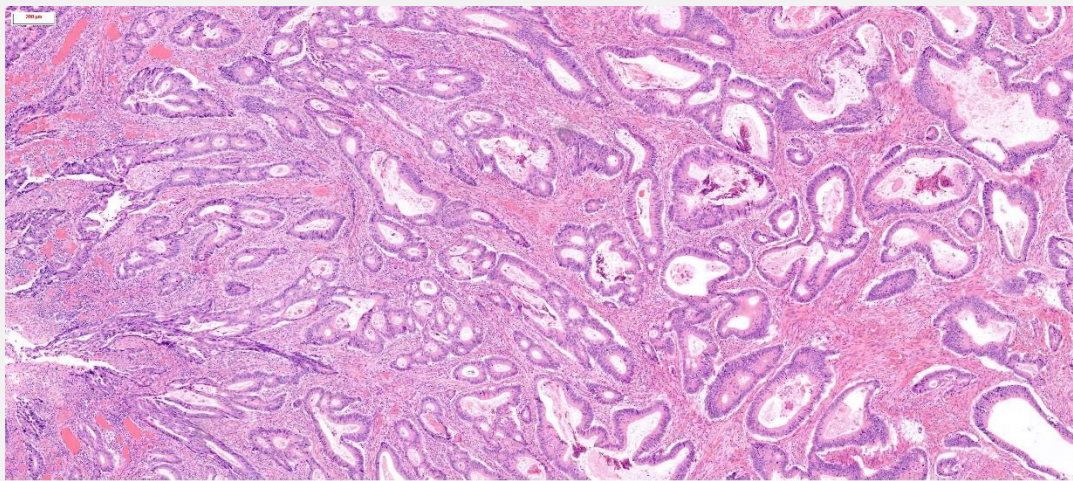
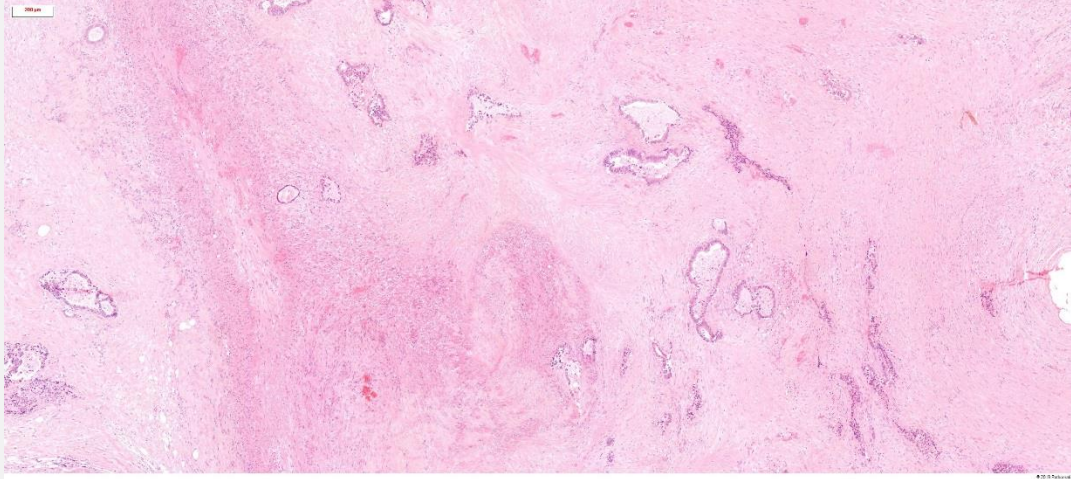
$$\text{NPV} = D/(B+D) * 100\% = 76\%$$



Complete response: the most simple form of downstaging

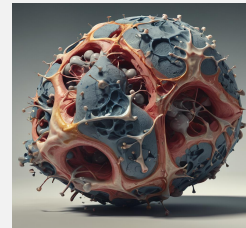
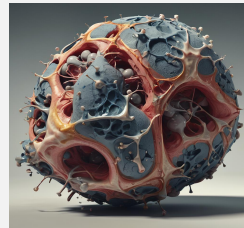
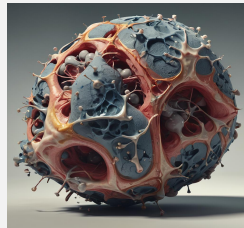
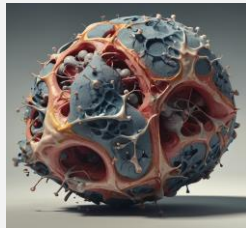
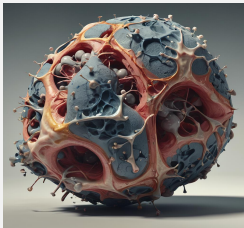
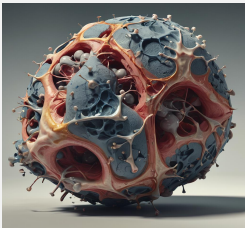
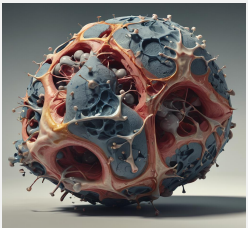
Figure 1. Comparison between clinical complete response and pathological complete response (primary tumour only) in cases with resection after neoadjuvant chemoradiation. The bars represent the total number of cases with a clinical complete response, the green part of the bar represent the cases where the clinical complete response is confirmed by a pathological complete response.

TUMOR REGRESSION GRADING

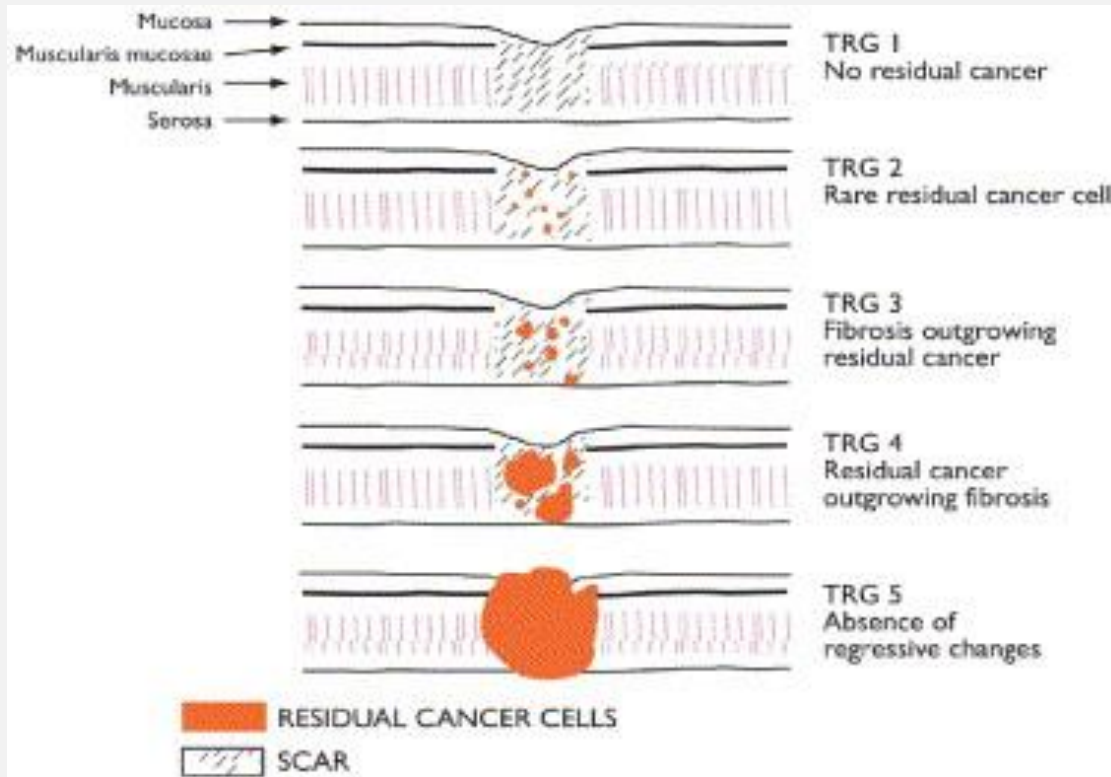


BUT WE CANNOT DO IT!

1. Different classification schemes
2. Different stage grouping methods
3. Poor interobserver variability
4. Also present in patients not treated with neoadjuvant therapy



THE ORIGIN OF TRG SYSTEMS



Tumor cells difficult to find

Tumor cells easy to find

Obvious fibrosis/vasculopathy

Mandard, 1994; adapted by Dworak, 1997 for rectal cancer

DIFFERENT CLASSIFICATION SCHEMES

DOI:10.1093/jnci/dju248
First published online September 23, 2014

© The Author 2014. Published by Oxford University Press. All rights reserved.
For Permissions, please e-mail: journals.permissions@oup.com.

ARTICLE |

Comparison of Tumor Regression Grade Systems for Locally Advanced Rectal Cancer After Multimodality Treatment

Atthaphorn Trakarnsanga, Mithat Gönen, Jinru Shia, Garrett M. Nash, Larissa K. Temple, José G. Guillem, Philip B. Paty, Karyn A. Goodman, Abraham Wu, Marc Gollub, Neil Segal, Leonard Saltz, Julio Garcia-Aguilar, Martin R. Weiser

Table 1. Definition of tumor regression grading systems*

Tier	Mandard (five-tier)	AJCC	Dowrak/Rödel (five-tier)	MSKCC	Mandard (three-tier)	Dowrak/Rödel (three-tier)
TRG 0	-	No residual tumor cells	No regression	-	-	-
TRG 1	No residual cancer cells	Single cell or small group of cells	Fibrosis <25% of tumor mass	100% Tumor response	No residual cancer cells	Complete regression
TRG 2	Rare cancer cells	Residual cancer with desmoplastic response	Fibrosis 25%-50% of tumor mass	86%-99% Tumor response	Rare cancer cells or fibrosis outgrowing residual cancer	Fibrosis 25%-99% of tumor mass
TRG 3	Fibrosis outgrowing residual cancer	Minimal evidence of tumor response	Fibrosis >50% of tumor mass	≤85% Tumor response	Residual cancer outgrowing fibrosis or absence of regression	Fibrosis <25% of tumor mass or no regression
TRG 4	Residual cancer outgrowing fibrosis	-	Complete regression	-	-	-
TRG 5	Absence of regressive change	-	-	-	-	-

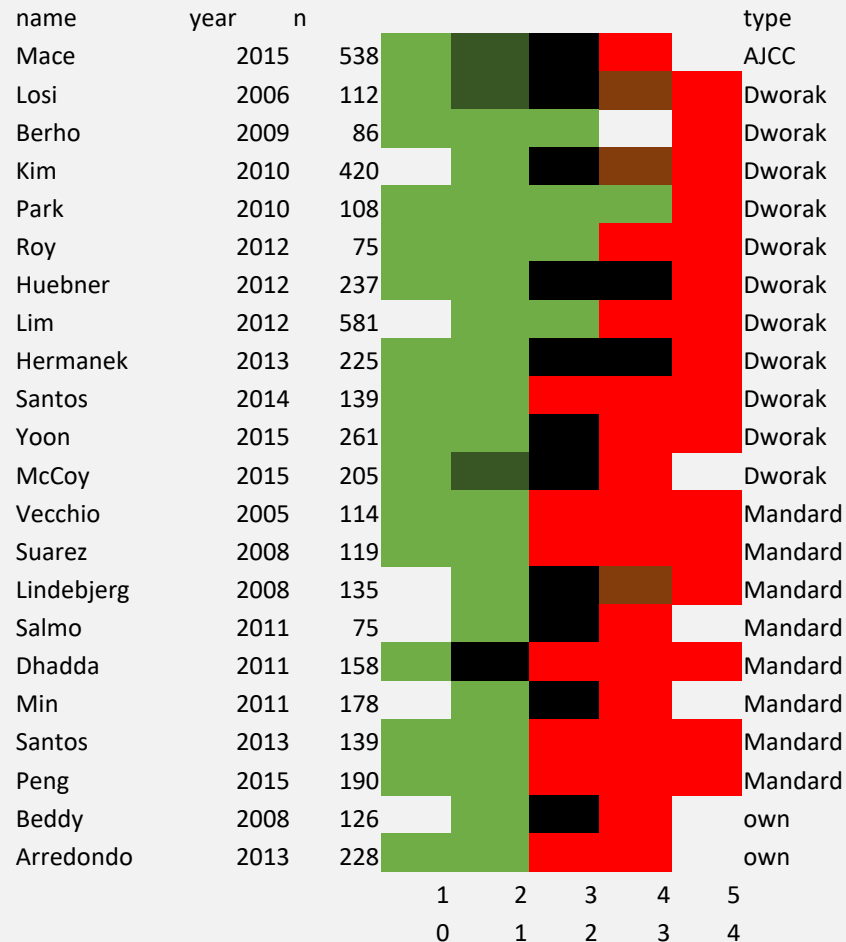
* AJCC = American Joint Committee on Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center; TRG = tumor regression grade.

DIFFERENT CLASSIFICATION

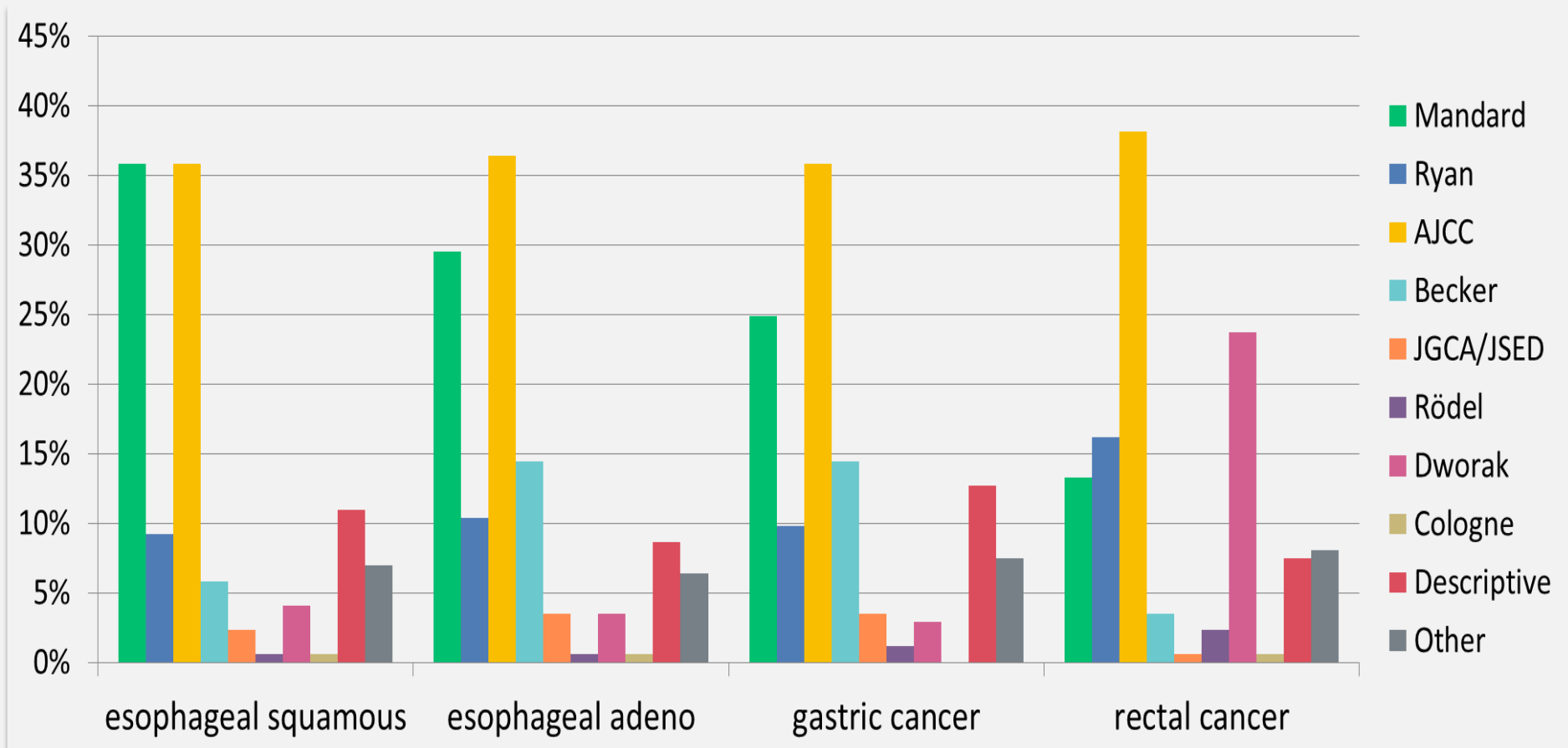
	AJCC		Rodel modification of Dworak	
No regression	5	4	1	No regression
Dominant tumor mass with obvious fibrosis	4	3	2	< 25% regression
Tumor cells easy to find	3	2	3	25% - 50% regression
Tumor cells difficult to find	2	1	4	> 50% regression
No residual tumor cells	1	0	5	Complete regression

Mandard

DIFFERENT STAGE GROUPING



Varying practices in tumor regression grading of gastrointestinal carcinomas after neoadjuvant therapy - results of a world wide survey



Courtesy of Rupert Langer

INTEROBSERVER VARIABILITY IS HIGH

Human Pathology (2012) 43, 1917–1923



Original contribution

International study group on rectal cancer regression grading: interobserver variability with commonly used regression grading systems

Runjan Chetty MB BCh, FRCPath, DPhil^{a,*}, Pelvender Gill MB ChB^a, Dhirendra Govender MB ChB, FRCPath, PhD^b, Adrian Bateman FRCPath^c, Hee Jin Chang MD^d, Vikram Deshpande MD^e, David Driman MD^f, Marisa Gomez MD^g, Godman Greywoode FRCPath^a, Eleanor Jaynes FRCPath^c, C. Soon Lee FRCPA, PhD^h, Michael Locketz FRCPath^b, Corwyn Rowsell FRCPCⁱ, Anne Rullier MD^j, Stefano Serra MD^k, Neil Shepherd FRCPath^l, Eva Szentgyorgyi FRCPC^k, Rajkumar Vajpeyi FRCPC^k, Lai Mun Wang FRCPath^a, Andrew Bateman MD^m

Human
PATHOLOGY
www.elsevier.com/locate/humpath

A Distribution of Kappa Statistic. Each Observer And The Study Standard Using The Mandard Scoring System

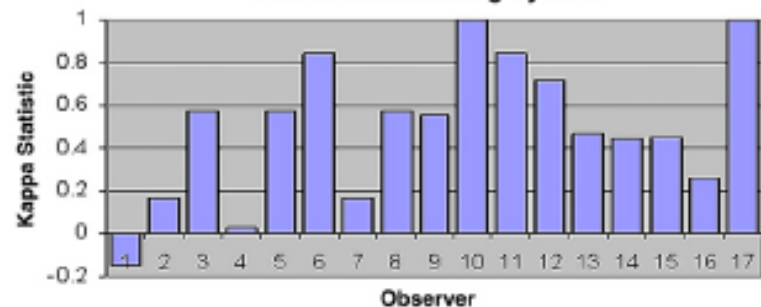


Table 4 Overall agreement statistics between 17 observers

Statistic	Mandard	Dworak	m-RCRG
κ	0.28	0.35	0.38
KCC	0.80	0.82	0.62
KCC <i>P</i> value	<.001	<.001	<.001
Overall % agreement between all observers	0%	0%	10% (1 case)

UP TO 32% REGRESSION WITHOUT RADIOTHERAPY

Table 4 Tumour regression grading (TRG) in different treatment groups

Tumour regression grade ^a	5	4	3	2	1
Preoperative radiotherapy [number of patients (%)]					
No radiotherapy (n=40)	27 (68)	12 (30)	0	1 (2) ^b	0
25 Gy (n=42)	12 (29)	21 (50)	8 (19)	1 (2)	0
50 Gy (n=44)	4 (9)	8 (18)	15 (34)	14 (32)	3 (7)

^aTRG 1, 2 and 3 correspond to a regression exceeding 50% of the tumour mass

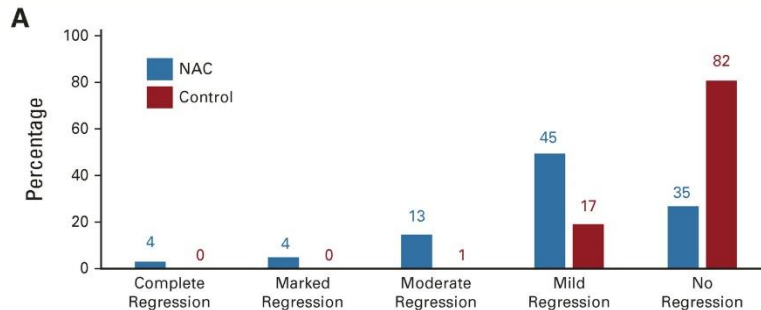
^bThis patient had a small polypoid lesion, which was originally removed endoscopically with snare and electrocoagulation. Only a 7-mm lesion was seen in the resected specimen

Int J Colorectal Dis (2005) 20: 440–445
DOI 10.1007/s00384-004-0733-y

ORIGINAL ARTICLE

J. Vironen
M. Juhola
M. Kairaluoma
I. Jantunen
I. Kellokumpu

Tumour regression grading in the evaluation of tumour response after different preoperative radiotherapy treatments for rectal carcinoma



FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer.

JCO 2023; 41(8)

BUT THERE IS A CLEAR DIFFERENCE

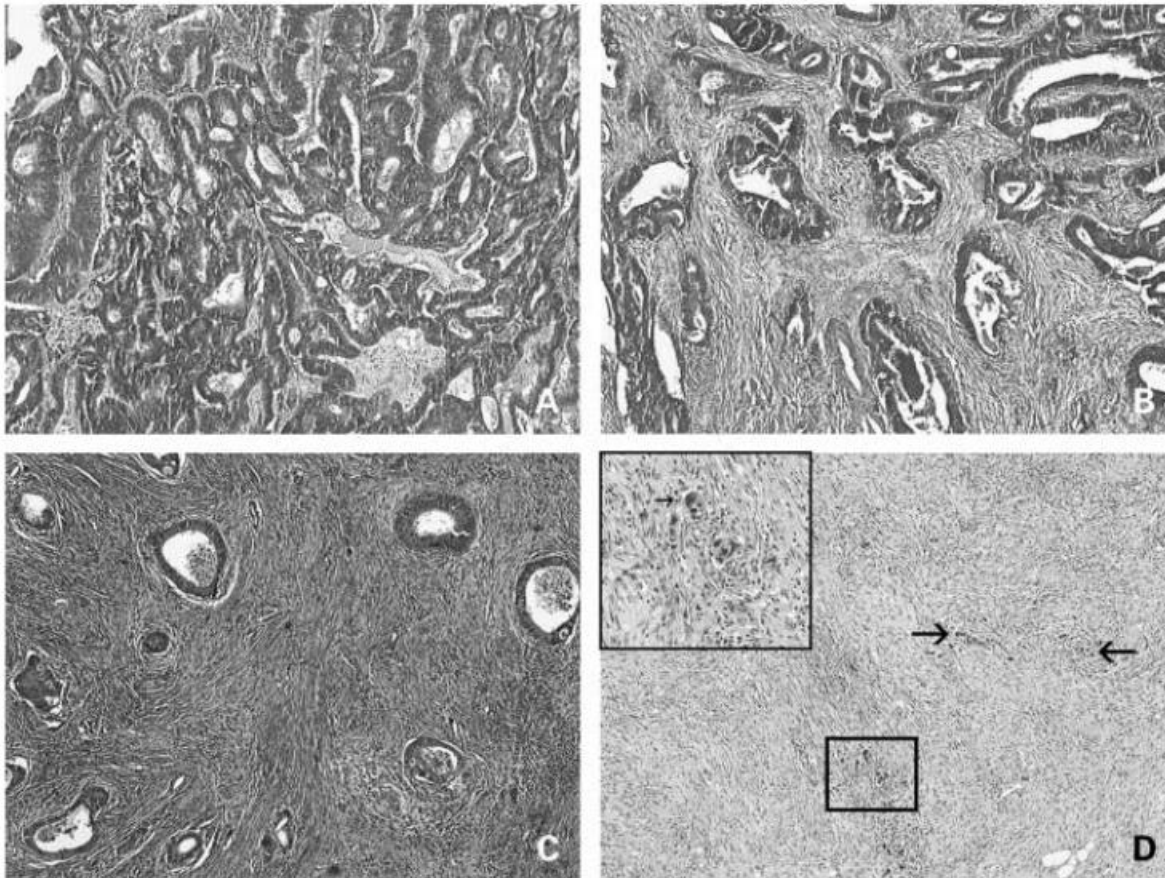
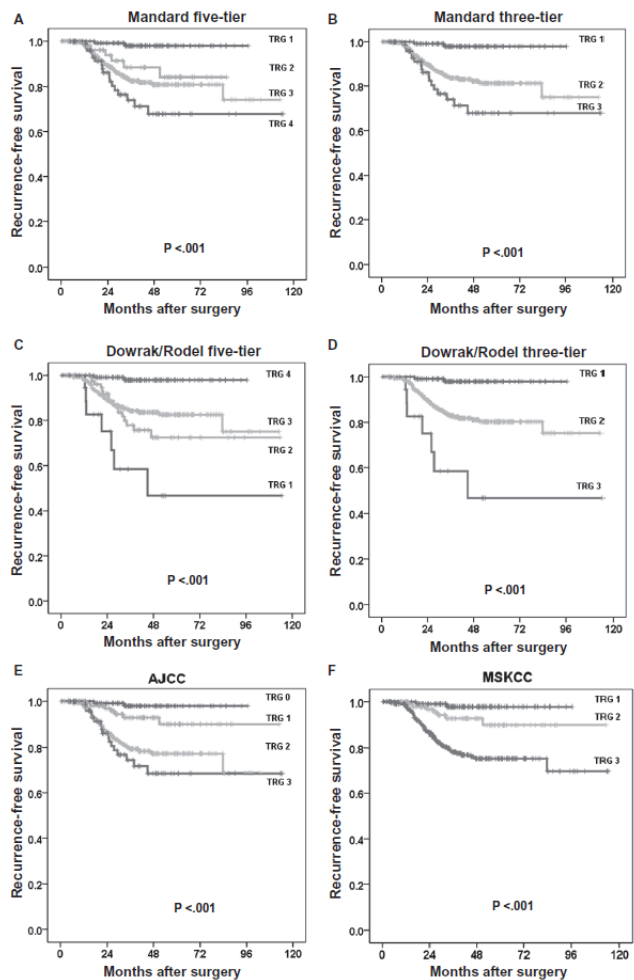


Fig. 1. Representative slides stained with H&E of different degrees of tumor regression observed after radio(chemo)therapy in patients with LARC. *A*, no sign of regressive changes, the fibrosis present is probably intrinsic to tumor development. Original magnification, $\times 50$. *B*, marked fibrosis but large masses of vital tumor can still be observed. Original magnification, $\times 50$. *C*, predominately fibrotic changes with smaller tumor masses. Original magnification, $\times 50$. *D*, extensive tumor regression with few small clusters of tumor cells (*arrow*) scattered through the fibrotic area. Original magnification, $\times 50$. The boxed area in *D* is depicted with a higher magnification as an insertion in this panel. Three small clusters of tumor cells can be appreciated. Original magnification, $\times 400$.

AND A CORRELATION WITH OUTCOME



DOI:10.1093/nci/dju248
First published online September 23, 2014

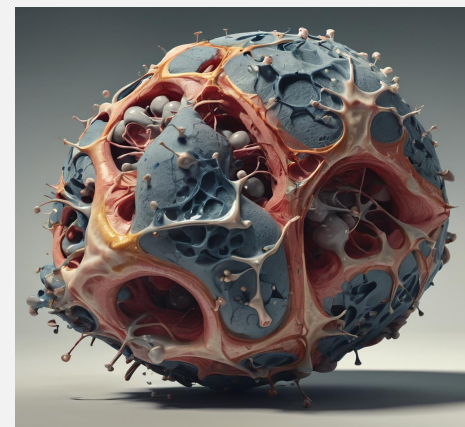
©The Author 2014. Published by Oxford University Press. All rights reserved.
For Permissions, please e-mail: journals.permissions@oup.com.

ARTICLE

Comparison of Tumor Regression Grade Systems for Locally Advanced Rectal Cancer After Multimodality Treatment

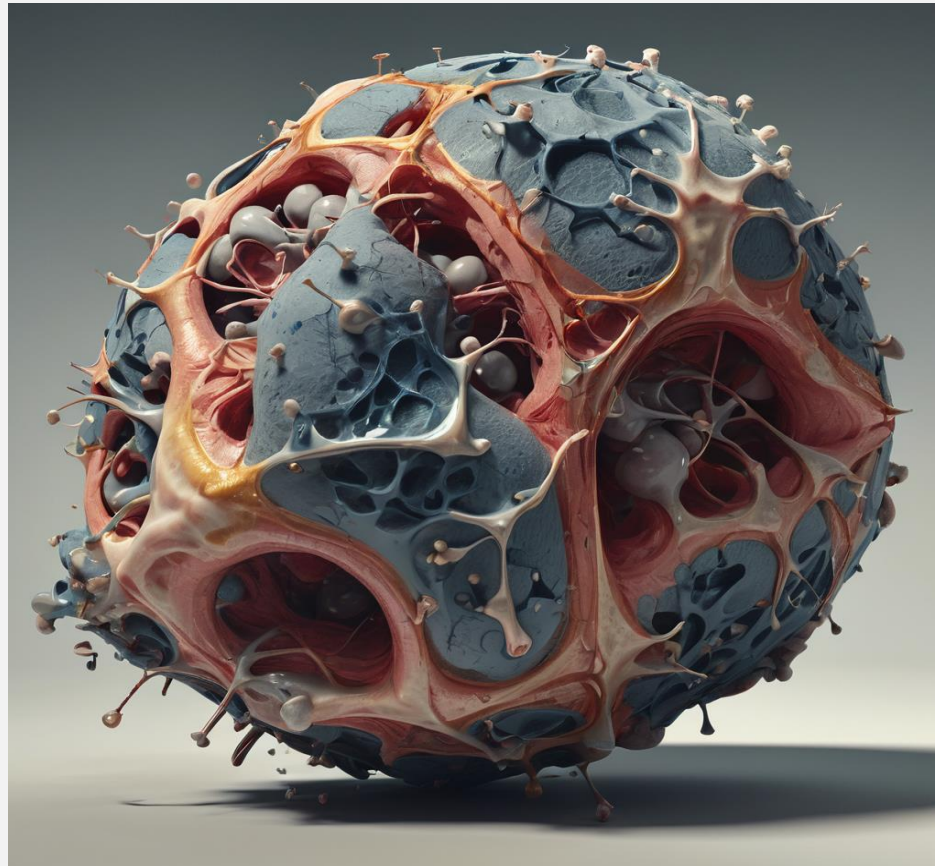
Atthaphorn Trakarnsanga, Mithat Gönen, Jinru Shia, Garrett M. Nash, Larissa K. Temple, José G. Guillem, Philip B. Paty, Karyn A. Goodman, Abraham Wu, Marc Gollub, Neil Segal, Leonard Saltz, Julio Garcia-Aguilar, Martin R. Weiser

There are limitations to this study, which was performed at a tertiary cancer center. Highly trained pathologists specializing in gastrointestinal malignancy graded the tumor response. In a different setting, with less experienced/specialized pathologists, it would be necessary to assess interobserver variability before incorporating a grading system.



THE SITUATION IS MORE COMPLEX

- a biological explanation -



WHAT ACTUALLY HAPPENS:

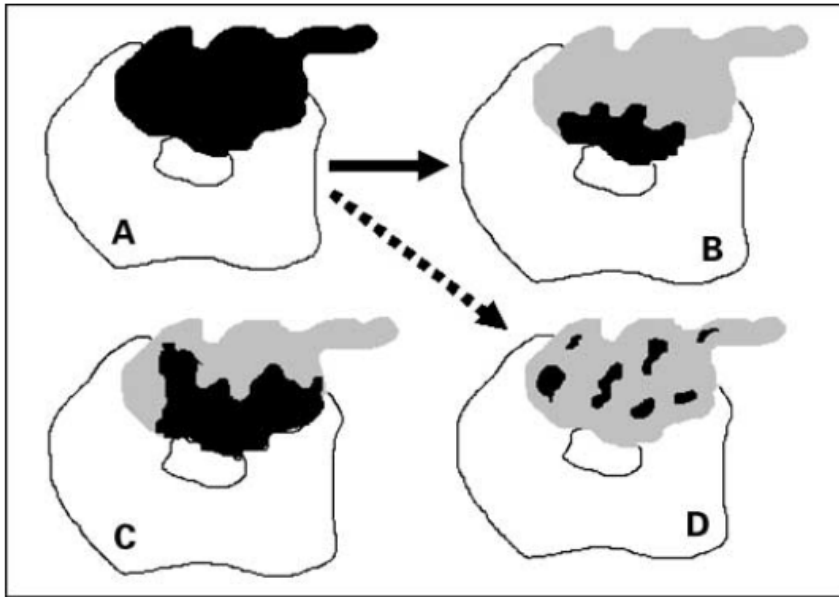


Fig. 3. Schematic representation of the relation between the degrees of tumor regression and CRM involvement. Black, areas with vital tumor cells; gray, fibrotic areas. *A*, pretreatment situation: the tumor is locally advanced (cT4) and the CRM is threatened. The contours of this pretreatment stage are also depicted in *B*, *C*, and *D*. *B* and *D*, after neoadjuvant long-course radiotherapy or radiochemotherapy, two different scenarios about tumor regression are sketched. *B*, "tumor shrinkage" scenario in which the infiltration depth is less extensive than in the pretreatment situation. *D*, "tumor fragmentation" scenario that implies scattered tumor cells throughout the whole fibrotic area, reaching the initial infiltration depth. However, if the CRM is still positive after tumor shrinkage (*C*), patient's outcome will still be poor irrespective of the degree of tumor regression.

Circumferential Margin Involvement Is the Crucial Prognostic Factor after Multimodality Treatment in Patients with Locally Advanced Rectal Carcinoma

Marleen J.E.M. Gossens,^{1,4} René A. Klaassen,⁵ Ivonne Tan-Go,³ Harm J.T. Rutten,¹ Hendrik Martijn,² Adriaan J.C. van den Brule,³ Gard A.P. Nieuwenhuijzen,¹ J. Han J.M. van Krieken,⁴ and Iris D. Nagtegaal⁴

Clin Cancer Res 2007; 15 (22): 6617-6623

ADDITIONAL EVIDENCE

Background: The main tenets of local excision of rectal cancer following neoadjuvant chemoradiation (CRT) are that the mucosal scar represents the main focus of residual disease and a solid conglomerate around this rather than being scattered (fragmented) through the bowel wall.

Methods: Retrospective review of a prospective cohort of patients with residual rectal ypT1-2N0 adenocarcinoma with small residual tumors (≤ 3 cm) following CRT who underwent transanal endoscopic microsurgery (TEM) with 1-cm margins around the residual mucosal abnormality was performed. Distribution and morphology (solid vs. fragmented) of tumor spread were studied and correlated to postoperative oncological outcomes.

Results: Thirty patients were included. Twenty percent ($n = 6$) were ypT1, 60% ($n = 18$) were ypT2, and 20% ($n = 6$) were ypT3 tumors. Fragmentation was present in 37%. The mean distance between foci of residual scattered tumor was 3.6 ± 2.0 mm. Lateral spread under normal mucosa was present in 19 specimens (53%; mean extension 4.8 ± 2.4 mm). With a median follow up of 32 months, none of these findings impacted upon development of recurrence.

Conclusions: Both occult lateral spread and fragmented tumor patterns are common findings after CRT. Despite the potential of occult spread to mislead surgeon choice of resection margin, its presence did not influence oncological outcome in this series.

Journal of Surgical Oncology 2014;109:853-858

Fragmented Pattern of Tumor Regression and Lateral Intramural Spread May Influence Margin Appropriateness After TEM for Rectal Cancer Following Neoadjuvant CRT

RODRIGO O. PEREZ, MD, PhD,^{1,2,3} ANGELITA HABR-GAMA, MD, PhD,^{1,4*} FRASER M. SMITH, MD,^{1,5}
LAUREN KOSINSKI, MD,^{1,6} CUILHERME P. SÃO JULIÃO, MD,¹ ESTEBAN GRZONA, MD,^{1,7}
VIVIANE RAWET, MD,¹ MARIA REGINA VIANNA, MD,⁸ IGOR PROSCURSHIM, MD,¹
PATRICIO BERNARDO LYNN,¹ AND JOAQUIM GAMA-RODRIGUES¹⁻⁴

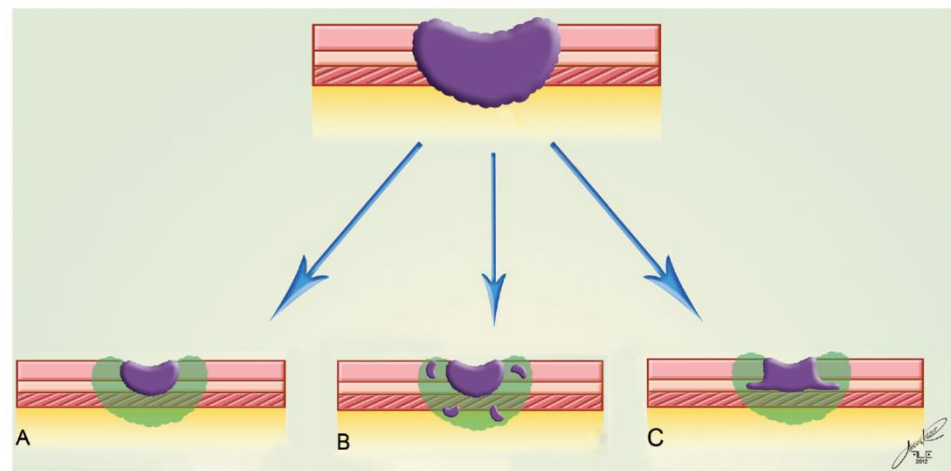


Fig. 1. Illustration of tumor regression after neoadjuvant CRT showing (A) a single block of residual cancer; (B) the presence of scattered foci of tumor cells (fragmented pattern), or (C) presence of lateral (intramural) spread of cancer cells (≥ 1 mm) beyond the limits of the cancer on the mucosal layer.

AND MORE....

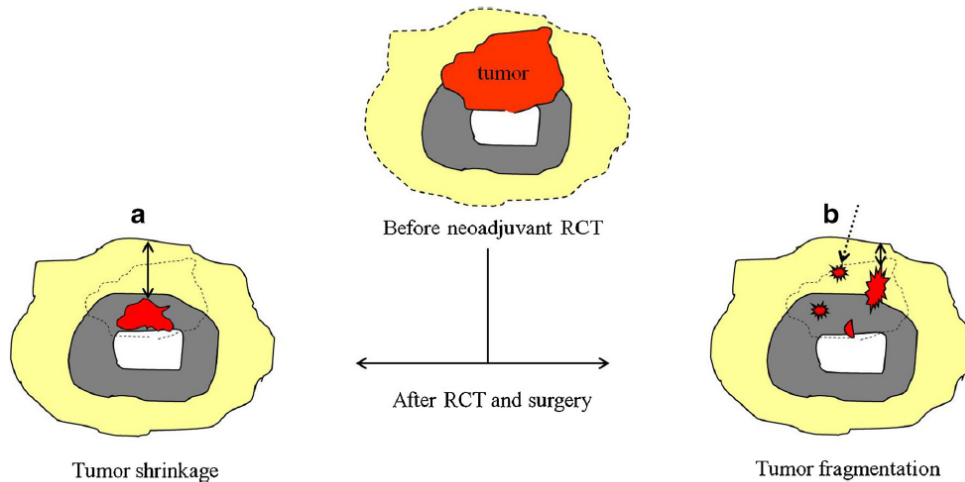


Fig. 2 Two possible forms of response to preoperative RCT. Preoperative RCT can result in either shrinkage or fragmentation of the primary tumor. Tumor shrinkage (a) reflects good response to RCT and is associated with favorable prognosis since it is associated with larger CRM (*long, two-headed*

arrow). If response to RCT takes the form of tumor fragmentation (b), the patient may have unfavorable prognosis, not only because tumor fragmentation can generate mesorectal tumor deposits (*dotted arrow*) but also because the CRM might still be at risk (*short, two-headed arrow*)

- In case of shrinkage: less LNM
- Presence of “TD” is associated with poor prognosis
- Dworak is not predictive

Virchows Arch (2015) 466:517–523
DOI 10.1007/s00428-015-1723-x

ORIGINAL ARTICLE

Prognostic value of tumor shrinkage versus fragmentation following radiochemotherapy and surgery for rectal cancer

Monirath Hav · Louis Libbrecht · Karen Geboes ·
Liesbeth Ferdinande · Tom Boterberg · Wim Ceelen ·
Piet Pattyn · Claude Cuvelier

TUMOR FRAGMENTATION AS RESPONSE MECHANISM

1. Downstaging and tumor regression are different
2. Remaining tumor cells are present in the deeper layers of the bowel
3. Posttreatment biopsies do not present an adequate picture
4. Patients with a near complete pCR can have a poor prognosis
5. Tumor deposits after neoadjuvant therapy are something else....

DOWNSTAGING VERSUS TUMOR REGRESSION

What Is the Ideal Tumor Regression Grading System in Rectal Cancer Patients after Preoperative Chemoradiotherapy?

Results

All four TRG systems were significantly predictive of both RFS and OS ($p < 0.001$ each), however none was a better predictor of prognosis than ypStage. Among the four TRGs, the mDworak TRG system was a better predictor of RFS and OS than the AJCC, Dworak, and Ryan TRG systems, and both the chi-square and C statistics were higher for the former, although the differences were not statistically significant. The combination of ypStage and the modified Dworak TRG better predicted RFS and OS than ypStage alone.

Table 4. Multivariate analysis of factors influencing RFS and OS

Factor	RFS		OS	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
ypStage				
0 & I	1.000	< 0.001	1.000	< 0.001
II	2.057 (1.253-3.379)		2.668 (1.449-4.913)	
III	4.514 (2.888-7.055)		4.747 (2.686-8.389)	
Perineural invasion				
Absent	1.000	< 0.001	1.000	< 0.001
Present	2.440 (1.802-3.304)		2.161 (1.504-3.105)	
Circumferential resection margin				
Negative	1.000	0.010	1.000	< 0.001
Positive	1.656 (1.128-2.430)		2.942 (1.979-4.375)	

RFS, recurrence-free survival; OS, overall survival; CI, confidence interval.

Soo Hee Kim, MD^{1a}
Hee Jin Chang, MD, PhD^{1,2}
Dae Yong Kim, MD, PhD²
Ji Won Park, MD, PhD³
Ji Yeon Baek, MD, PhD²
Sun Young Kim, MD, PhD²
Sung Chan Park, MD, MS²
Jae Hwan Oh, MD, PhD²
Ami Yu, PhD⁴
Byung-Ho Nam, PhD⁴

DOWNSTAGING HAS MORE PROGNOSTIC IMPACT

Impact of Tumor Response on Survival After Radiochemotherapy in Locally Advanced Rectal Carcinoma

Anne Rullier, PhD, Christophe Laurent, PhD,† Maylis Capdepon, CRA,‡
Véronique Vendrely, MD,‡ Paulette Bioulac-Sage, MD,* and Eric Rullier, MD†*

TABLE 3. Multivariate Analysis

	Odds Ratio	95% Confidence Interval	P
Five-year disease-free survival			
Circumferential margin ≤ 1 mm	3.15	1.87-5.29	< 0.001
No downstaging	2.23	1.18-4.22	0.013
No preoperative chemotherapy	2.04	1.33-3.13	0.001
ypN1-2	1.87	1.17-3.00	0.009
Vascular invasion	1.61	1.05-2.49	0.031
Age > 65 y	1.53	1.01-2.31	0.046
Five-year overall survival			
Circumferential margin ≤ 1 mm	3.62	1.95-6.75	< 0.001
No downstaging	2.56	1.15-5.67	0.021
Male	2.17	1.24-3.83	0.007
Age > 65 y	1.92	1.18-3.14	0.009
ypN1-2	1.86	1.09-3.16	0.023
Vascular invasion	1.75	1.05-2.93	0.033

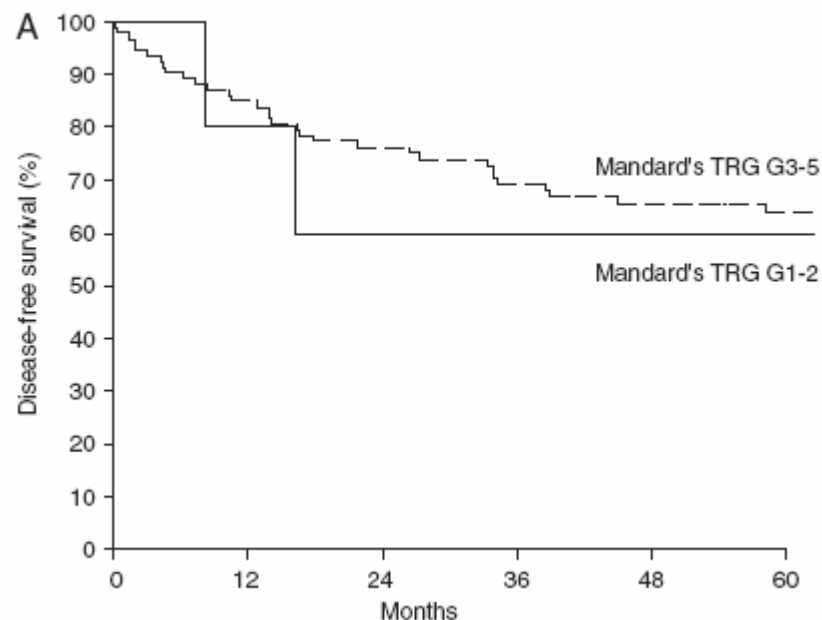
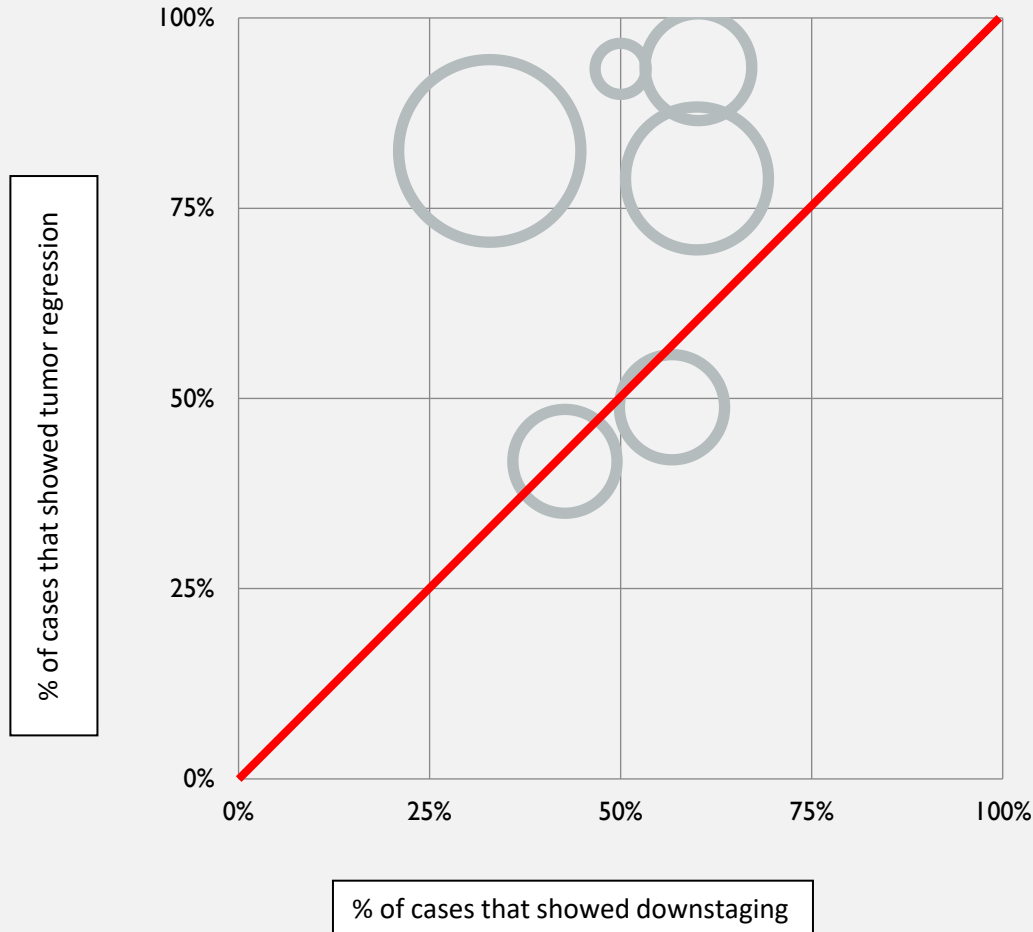


Figure 5. Correlation between downstaging and tumour regression grading. The size of the bubble indicates the size of the cohort. In total 933 patients from 6 studies are included⁵⁷⁻⁶².



How to measure tumour response in rectal cancer? An explanation of discrepancies and suggestions for improvement

Iris D. Nagtegaal^{a,*}, Rob Glynn-Jones^b

TUMOR FRAGMENTATION AS RESPONSE MECHANISM

1. Downstaging and tumor regression are different
2. Remaining tumor cells are present in the deeper layers of the bowel
3. Posttreatment biopsies do not present an adequate picture
4. Patients with a near complete pCR can have a poor prognosis
5. Tumor deposits after neoadjuvant therapy are something else....

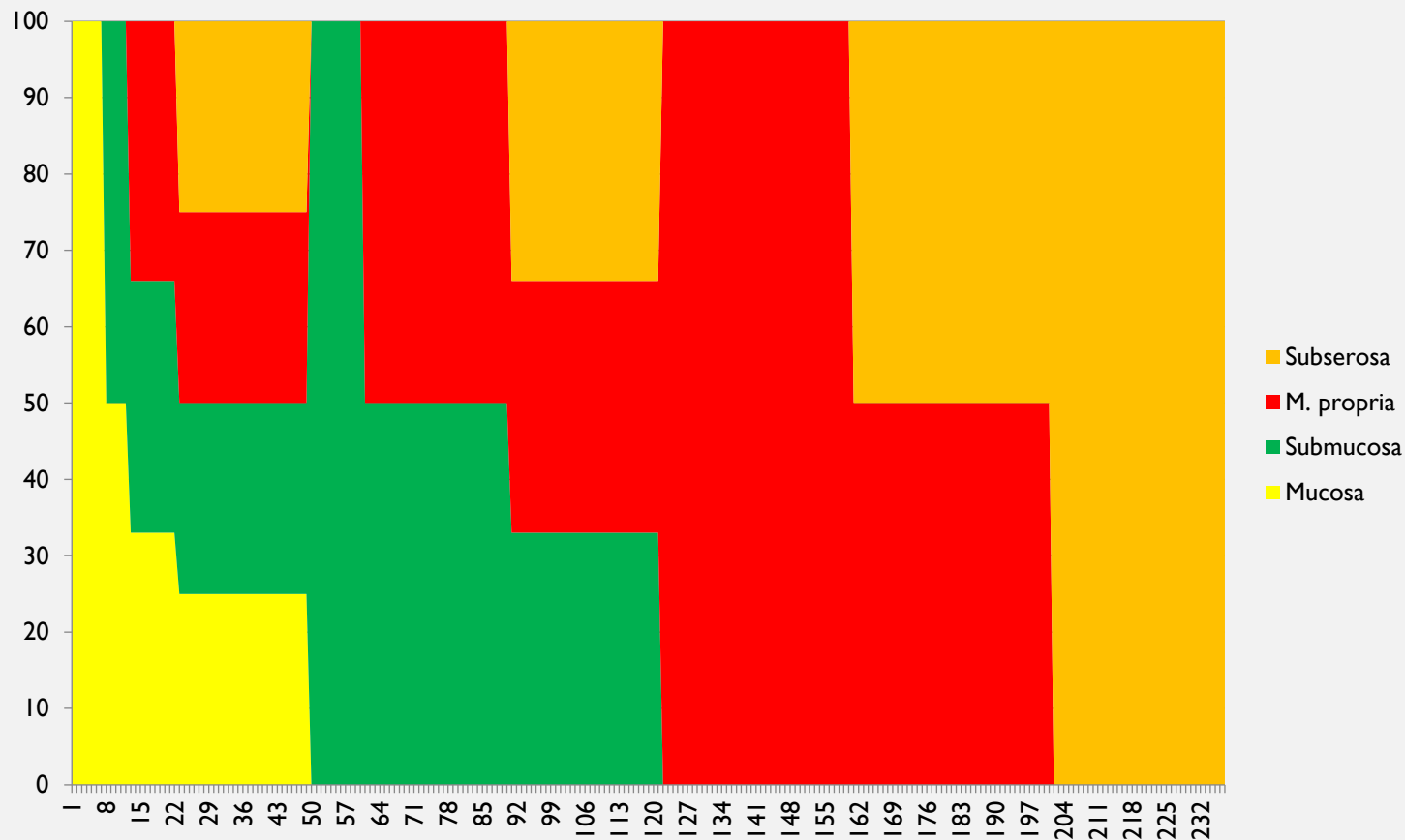


Figure 2. The distribution of residual tumour cells within the rectal wall, including 7 patients with ypTis (patient 1-7), 16 patients with ypT1, 79 patients with ypT2, 127 patients with ypT3 and 8 patients with ypT4 rectal cancer. Along the x-axis the individual patients are depicted. Submucosal tumour was absent in 116 patients with ypT2-4 cancer (patient number 121-237, 54%). Adapted and combined data from Duldulao et al³¹ and Xiao et al³².

TUMOR FRAGMENTATION AS RESPONSE MECHANISM

1. Downstaging and tumor regression are different
2. Remaining tumor cells are present in the deeper layers of the bowel
3. Posttreatment biopsies do not present an adequate picture
4. Patients with a near complete pCR can have a poor prognosis
5. Tumor deposits after neoadjuvant therapy are something else....

VALUE OF POST-TREATMENT BIOPSIES

Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: can they rule out persisting cancer?

R. O. Perez*†, A. Habr-Gama†, G. V. Pereira‡, P. B. Lynn†, P. A. Alves*†, I. Proscurshim*†, V. Rawet§ and J. Gama-Rodrigues†

Table 4 The result of biopsy compared with findings on histopathological examination of the resected specimen.

Biopsy finding	Incomplete histopathological response	Complete histopathological response	Total
Positive	25	0	25
Negative	11	3	14
Total	36	3	39

Sensitivity = 69%; specificity = 100%; positive predictive value = 100%; negative predictive value = 21%; accuracy = 71%.

In conclusion, our study demonstrates that in patients showing downsizing of rectal cancer but with still clinically detectable residual disease following neoadjuvant CRT, post-CRT biopsies performed at least 8 weeks after CRT are of limited clinical value in ruling out residual cancer. Negative biopsies are rarely associated with complete tumour regression and should not prevent surgery for treatment or diagnostic purposes. In addition false-negative biopsies are not associated with earlier disease staging or with an improved response to CRT.

VALUE OF POST-TREATMENT BIOPSIES

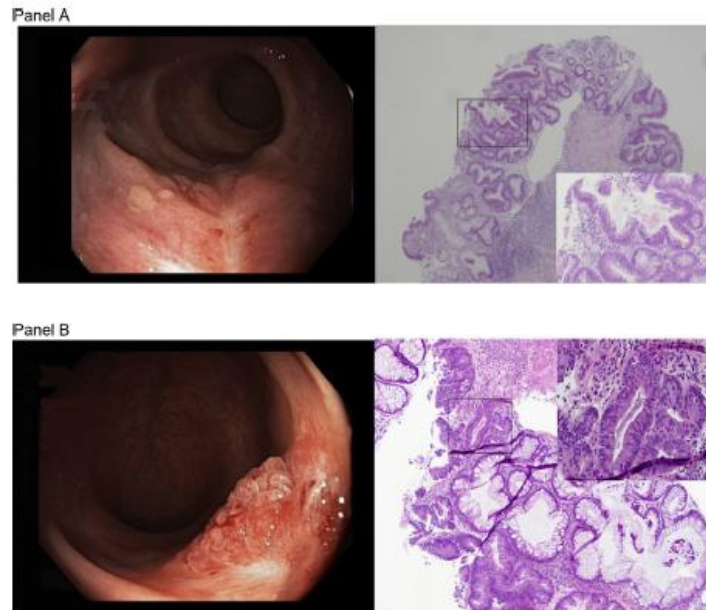


Figure 2. Endoscopic examination and corresponding pathological examination. Panel A: Patient No 4 in Table 2. At endoscopy a 2.5 cm lesion was seen after radiotherapy. Tubular adenoma with low-grade dysplasia was diagnosed in an endoscopic mucosal resection specimen. Panel B: Patient No 3 in Table 2. At endoscopy a 1 cm sessile polyp was seen at the scar edge. High-grade dysplasia (4.3 according to the revised Vienna classification – suspicious for invasive carcinoma) was diagnosed in a biopsy. Cancer (ypT2) was diagnosed in a local excision specimen (not shown).

- 2/7 of benign lesions (clinically and on initial biopsy) turned out to be cancer

Watch and wait policy after preoperative radiotherapy for rectal cancer; management of residual lesions that appear clinically benign

M. Rupinski ^{a,b}, M. Szczepkowski ^{c,d}, M. Malinowska ^c, A. Mroz ^{a,b},
L. Pietrzak ^f, L. Wyrwicz ^b, A. Rutkowski ^b, K. Bujko ^{f,*}

Author	n	negative biopsies		specificity	sensitivity	PPV	NPV	accuracy
		n	pCR					
Perez ⁶⁸	39	14	3	100.0%	69.4%	21.4%	100.0%	71.8%
Xiao ³²	79	66	16	94.1%	19.4%	24.2%	92.0%	35.9%
Kuo ¹¹	166	117	25	100.0%	34.7%	21.4%	100.0%	44.3%
Lopez-Lopez ¹⁴	67	35	18	100.0%	65.3%	51.4%	100.0%	74.6%
Total	351	232	62	98.4%	41.0%	26.7%	99.0%	51.3%

Table 1. Relevance of postoperative biopsies for detection of complete pathological response (pCR). PPV: positive predictive value, NPV: negative predictive value

TUMOR FRAGMENTATION AS RESPONSE MECHANISM

1. Downstaging and tumor regression are different
2. Remaining tumor cells are present in the deeper layers of the bowel
3. Posttreatment biopsies do not present an adequate picture
4. Patients with a near complete pCR can have a poor prognosis
5. Tumor deposits after neoadjuvant therapy are something else....

THIS EXPLAINS THE NEAR-PCR PROGNOSIS

Is Pathologic Near-Total Regression an Appropriate Indicator of a Good Response to Preoperative Chemoradiotherapy Based on Oncologic Outcome of Disease?

Jee Yeon Kim, MD, In Ja Park, MD, PhD, Seung Mo Hong, MD, PhD, Jong Lyul Lee, MD, Yong Sik Yoon, MD, PhD, Chan Wook Kim, MD, Seok-Byung Lim, MD, PhD, Jung Bok Lee, PhD, Chang Sik Yu, MD, PhD, and Jin Cheon Kim, MD, PhD

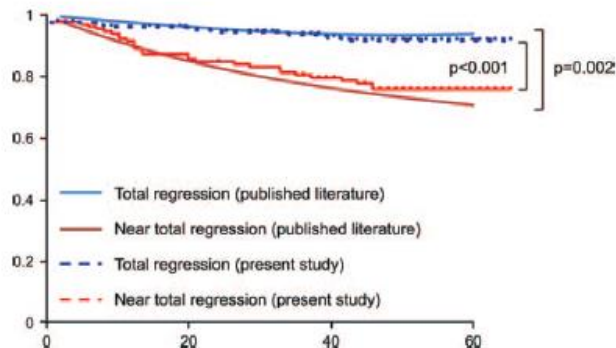
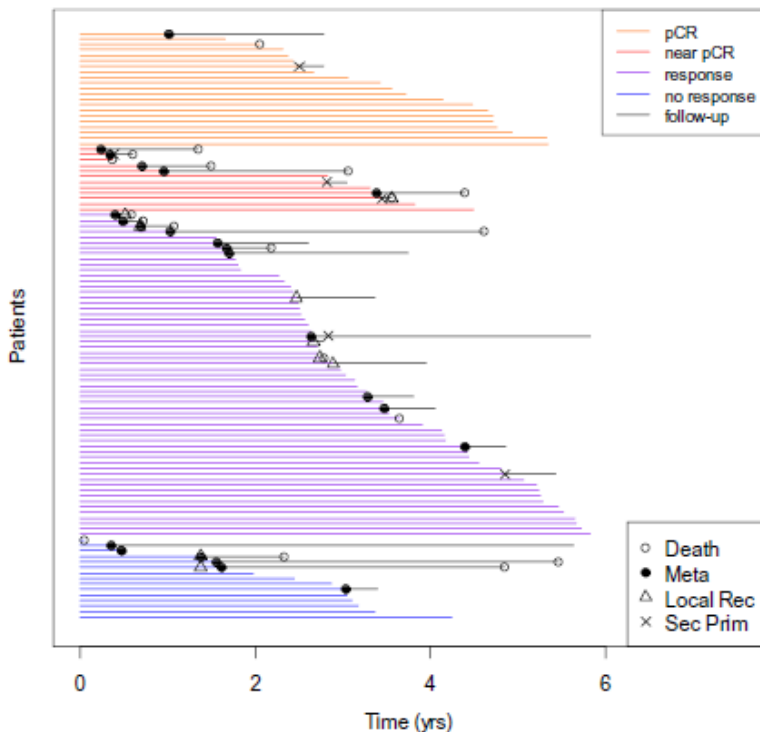


FIGURE 3. Comparison of the recurrence-free survival (RFS) in the present study with that of the published literature. Summary of the RFS rates in the published literature was assessed using generalized mixed linear model. Survival curves of each analysis showed similar difference between the total regression and the near-total regression groups.

In conclusion, NTR demonstrates significantly poorer oncologic outcomes than TR. Therefore, consideration of NTR as an indicator of good response together with TR may not be appropriate. Future prospective studies with a larger number of patients and a longer follow-up duration should provide further subdivision and risk stratification among patients who are treated with PCRT in rectal cancer.

THIS EXPLAINS THE NEAR-PCR PROGNOSIS

		n	3-year DMFI			3-year DFS			3-year OS		
			%	95% CI	p-Value	%	95%CI	p-Value	%	95% CI	p-Value
TRG	pCR	21	95	87-100	0.002	84	69-100	0.001	95	86-100	<0.001
	Near pCR	12	65	42-100	0.02	50	28-88	0.02	67	45-99	0.002
	Response	59	86	77-95		76	65-89		91	83-99	
	No response	15	64	44-95		60	40-91		79	61-100	



Chemoradiotherapy of rectal cancer

Tumour regression grading after chemoradiotherapy for locally advanced rectal cancer: A near pathologic complete response does not translate into good clinical outcome[☆]

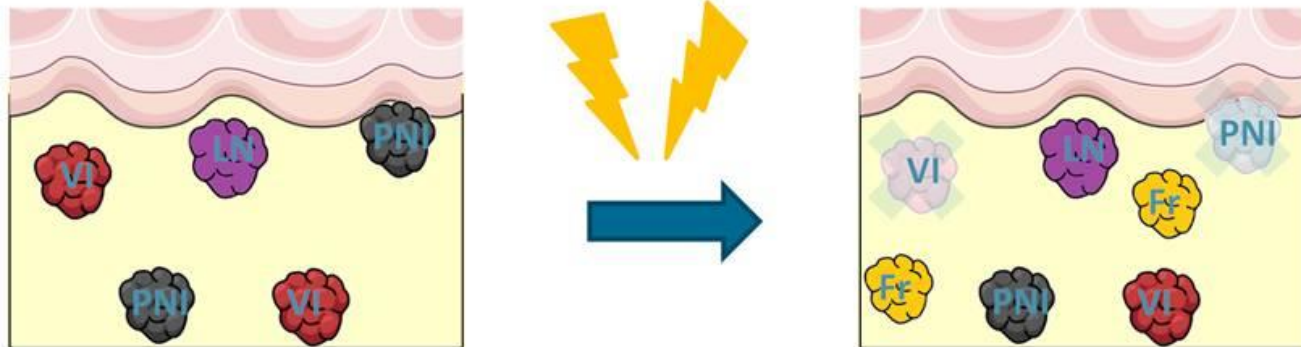
Hendrik A.M. Swellengrebel^a, Steven L. Bosch^b, Annemieke Cats^a, Andrew D. Vincent^c, Luc G.H. Dewit^d, Vic J. Verwaal^e, Iris D. Nagtegaal^b, Corrie A.M. Marijnen^{d,f,*}

TUMOR FRAGMENTATION AS RESPONSE MECHANISM

1. Downstaging and tumor regression are different
2. Remaining tumor cells are present in the deeper layers of the bowel
3. Posttreatment biopsies do not present an adequate picture
4. Patients with a near complete pCR can have a poor prognosis
5. Tumor deposits after neoadjuvant therapy are something else....

TUMOR DEPOSITS AFTER NEOADJUVANT THERAPY

factor	No therapy	Neoadjuvant setting
Lymph node	RR 4.2 (95% CI 3.2-5.4)	RR 1.7 (95% CI 1.1-2.6)



-2.2) -10.8)
 The biological background is different!

HOW DO WE DO THIS?

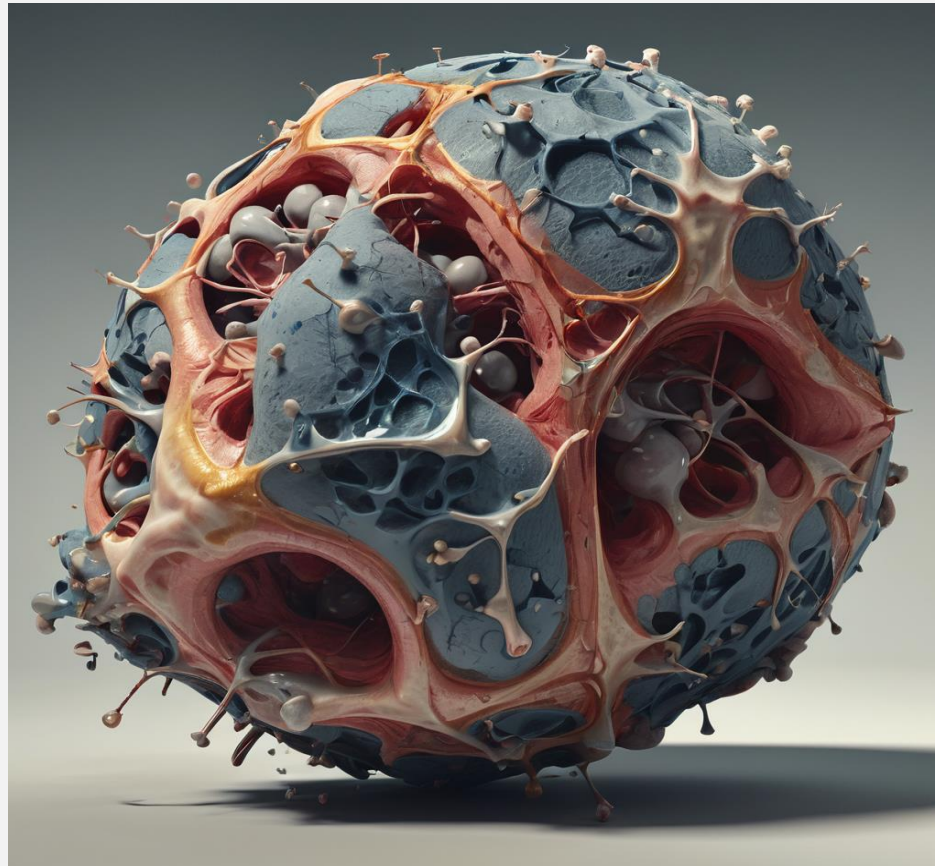
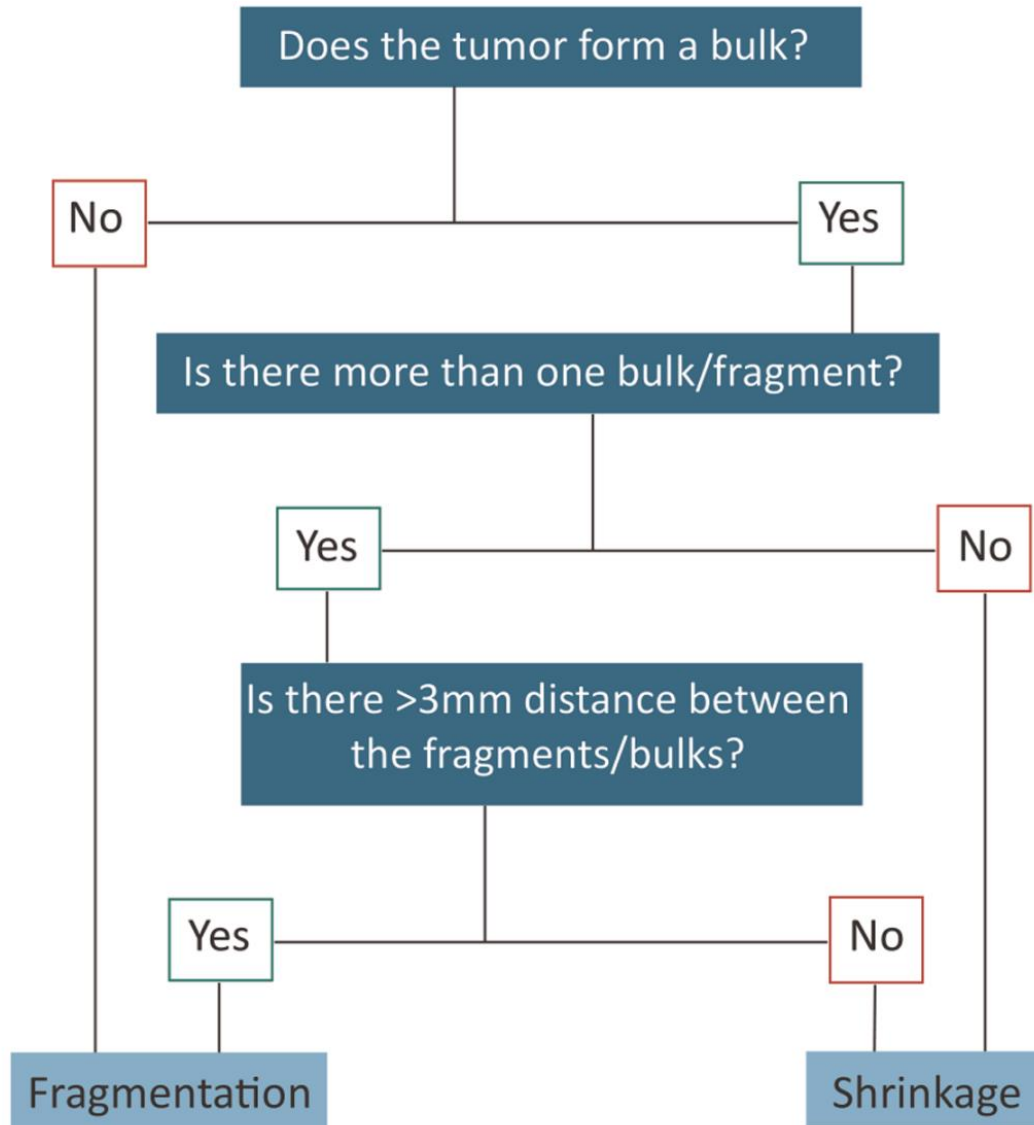
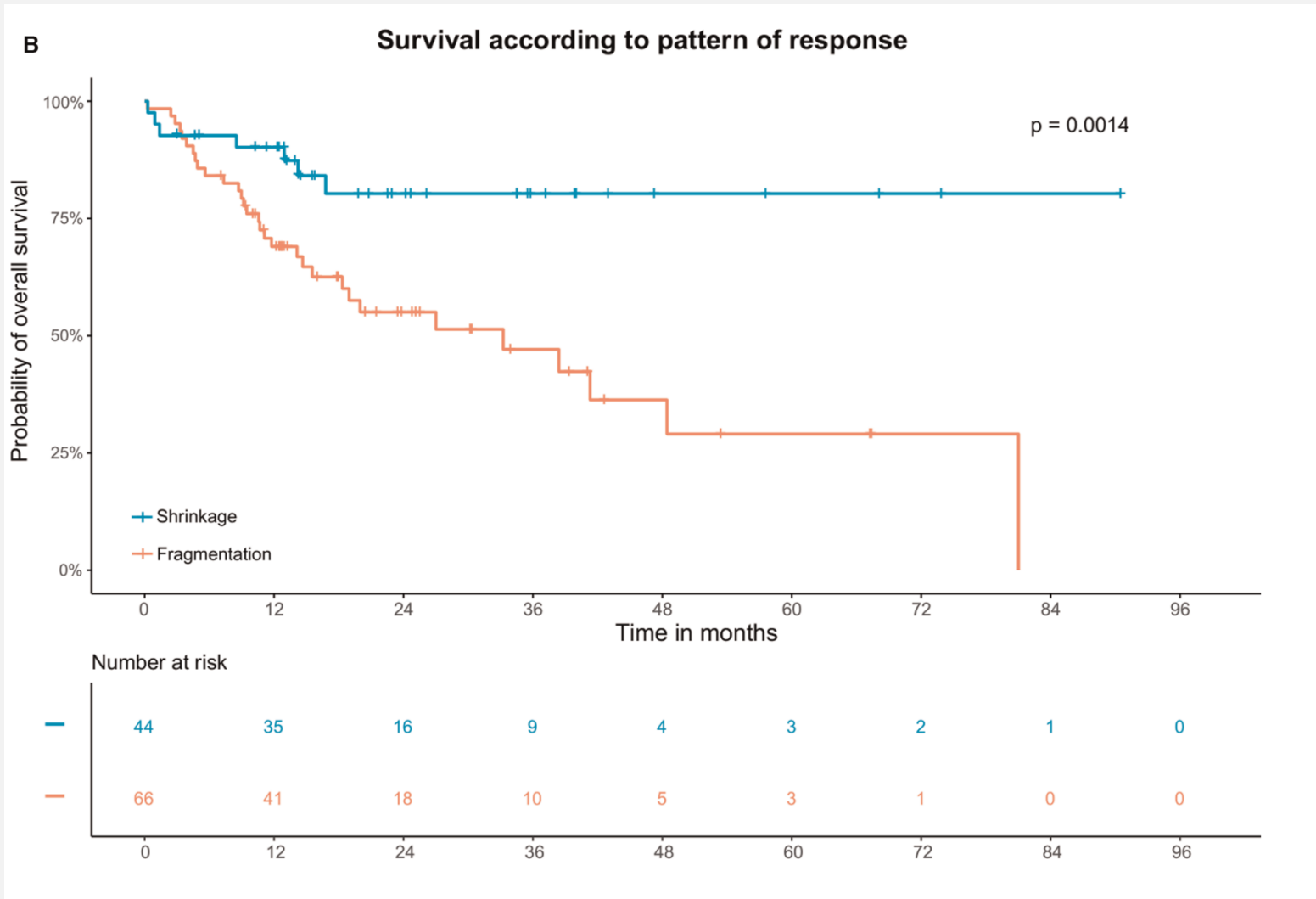




DIAGRAM FOR PATTERN OF RESPONSE ASSESSMENT





Shrinkage versus fragmentation response in neoadjuvantly treated oesophageal adenocarcinoma: significant prognostic relevance

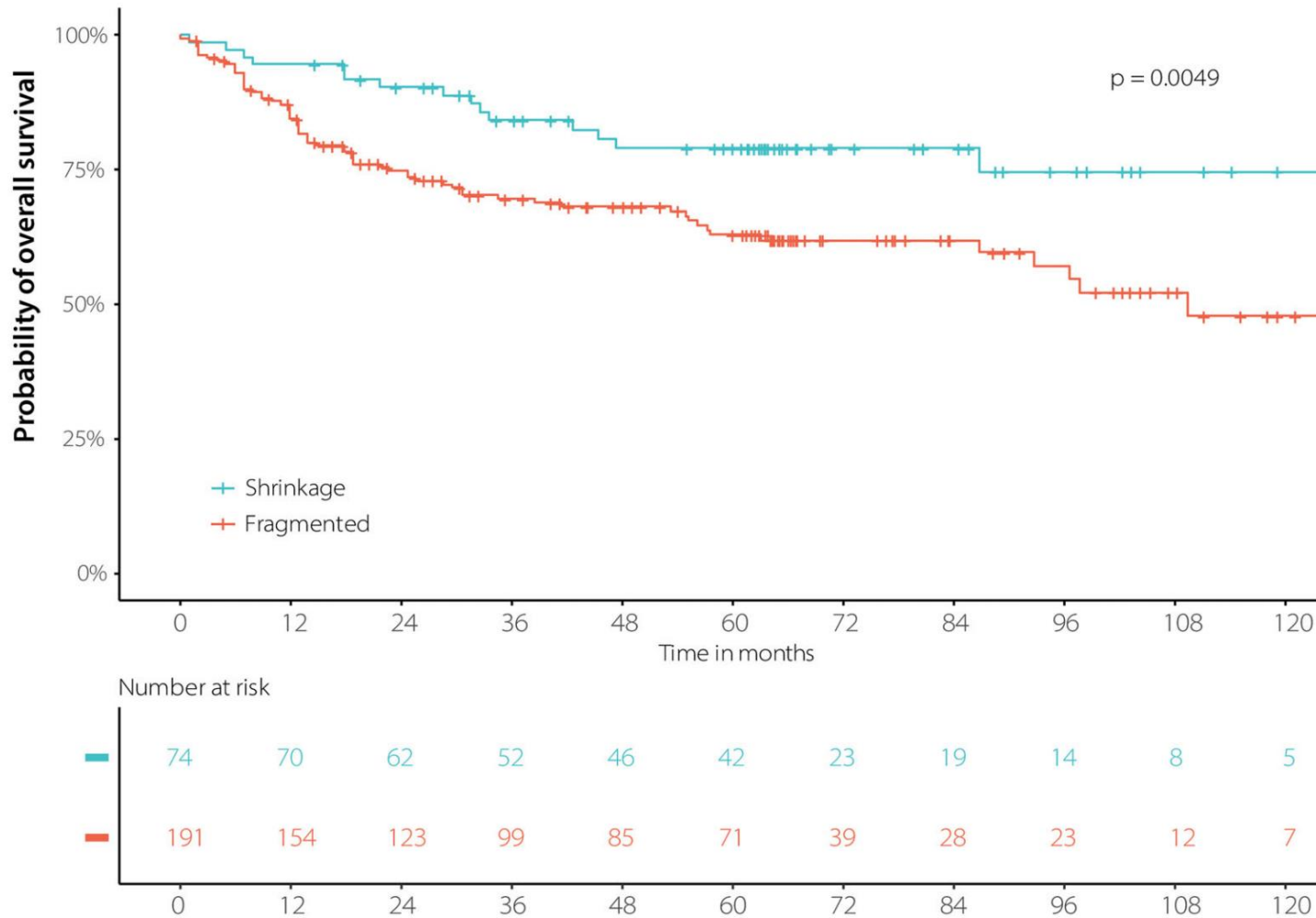
Cristina Graham Martinez,¹  Sonay Kus Öztürk,^{1,*} Ali Al-Kaabi,^{2,*} Maria J Valkema,^{3,*} John-Melle Bokhorst,¹ Camiel Rosman,⁴ Heidi Rütten,⁵ Carla A P Wauters,⁶ Michail Doukas,⁷ Joseph Jan-Baptist van Lanschot,³ Peter D Siersema,² Iris D Nagtegaal¹  & Rachel Sofia van der Post¹

Histopathology 2022, **80**, 982–994. DOI: 10.1111/his.14644

Table 2. Univariate and multivariate analysis of factors associated with overall survival in both cohorts (test + validation cohort)

Covariate	Number (%)	Univariate analysis		Multivariate analysis	
		HR	95% CI	HR	95% CI
Gender					
Male	191 (85%)	1.18	(0.67–2.06)		
Female	34 (15%)	(1.00)			
Age		1.02	(0.98–1.00)		
Medical centre					
Centre 1	81 (36%)	(1.00)			
Centre 2	29 (13%)	1.15	(0.59–2.24)		
Centre 3	115 (51%)	1.14	(0.72–1.82)		
Clinical stage	<i>n</i> = 223 ^a				
I	1 ^b (1%)	2.7 10 ⁻⁷	(0.00–Inf) ^b		
II	38 (17%)	0.64	(0.32–1.31)		
III	144 (64%)	0.97	(0.59–1.58)		
IV	40 (18%)	(1.00)			
Pathological stage				1.86	(1.32–2.62)
I	47 (21%)	0.14	(0.06–0.31)		
II	92 (41%)	0.20	(0.10–0.40)		
III	74 (33%)	0.39	(0.20–0.76)		
IV	12 (5%)	(1.00)			
Response pattern				1.76	(1.04–2.97)
Shrinkage	67 (30%)	(1.00)			
Fragmentation	158 (70%)	2.30	(1.41–3.76)		
Downstaging	<i>n</i> = 223 ^a			1.19	(0.70–2.05)
Yes	144 (65%)	0.50	(0.34–0.72)		
No	79 (35%)	(1.00)			
Mandard score					
2	48 (21%)	0.54	(0.24–1.21)		
3	147 (65%)	1.36	(0.72–2.55)		
4	30 (13%)	(1.00)			

(B) Disease-free survival according to main response patterns in all cohorts



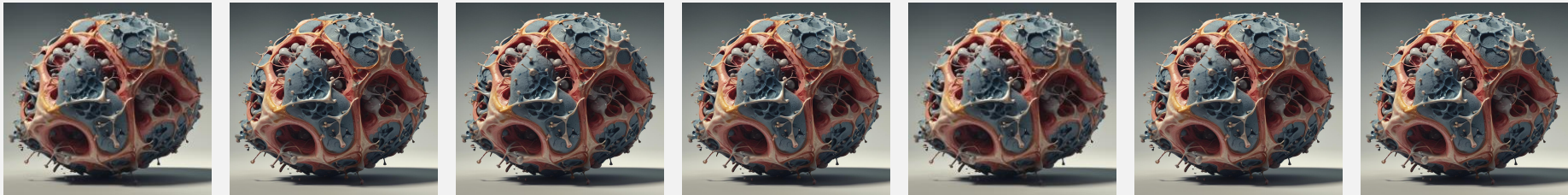
„B: Overall survival and disease-free survival curves according to two main response patterns in combined cohorts.

Relevance of shrinkage versus fragmented response patterns in rectal cancer

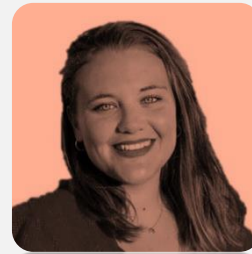
Sonay Kus Ozturk,¹ Cristina Graham Martinez,¹ Kieran Sheahan,² Desmond C Winter,³ Susan Aherne,² Éanna J Ryan,³ Cornelis JH van de Velde,⁴ Corrie AM Marijnen,⁵ Geke AP Hospers,⁶ Annet GH Roodvoets,⁴ Michail Doukas,⁷ David Mens,⁸ Cornelis Verhoef,⁸ Rachel S van der Post¹ & Iris D Nagtegaal¹

CONCLUSIONS

- Many problems with TRG: need for standardisation and consensus
 - Digital pathology
 - Comparisons with MRI
- More insights in biology of tumor response: shrinkage versus fragmented
- TRG on itself is not independent prognostic
- TD after neoadjuvant therapy are different



ACKNOWLEDGEMENTS





NEOADJUVANT THERAPY IN RECTAL CANCER

Tumor response: A complex issue