Azienda Ospedaliero Universitaria Careggi

VEQ ANATOMIA PATOLOGICA CICLO 2025: PRESENTAZIONE E COMMENTO DEI RISULTATI DEI PARTECIPANTI

Firenze 05 Febbraio 2026
AOU Careggi NIC 3, Aula Magna

Valutazione del Tumor Regression Grade nell'adenocarcinoma del retto

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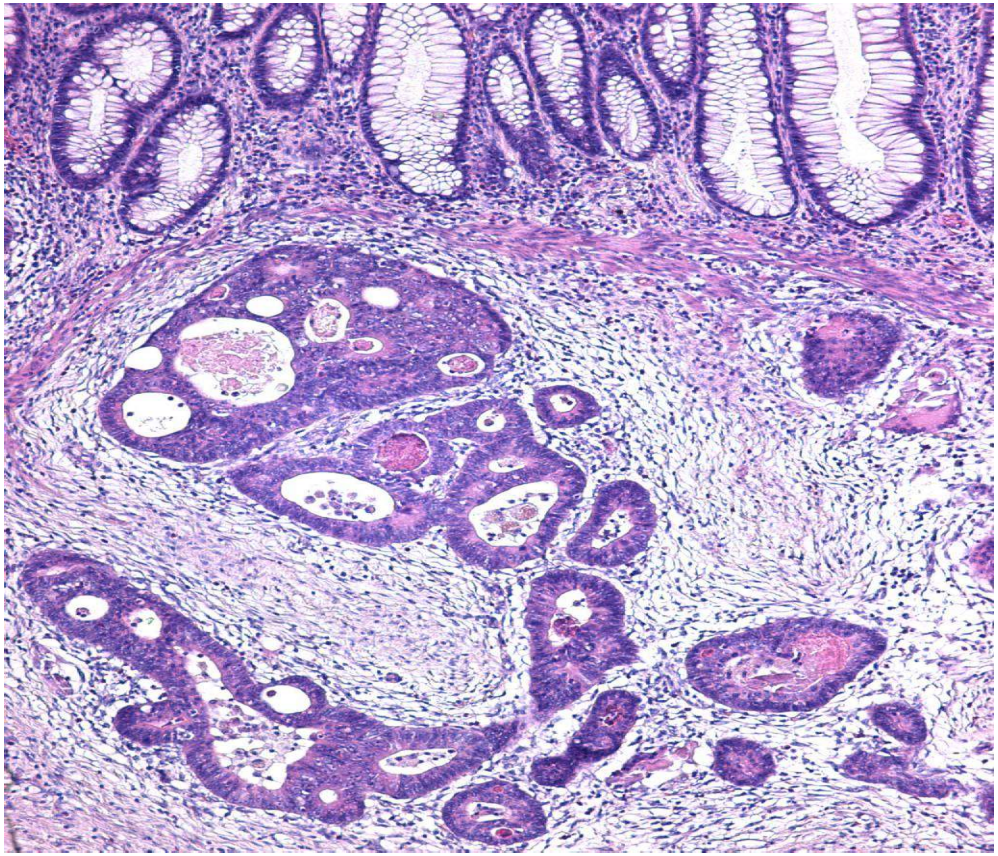
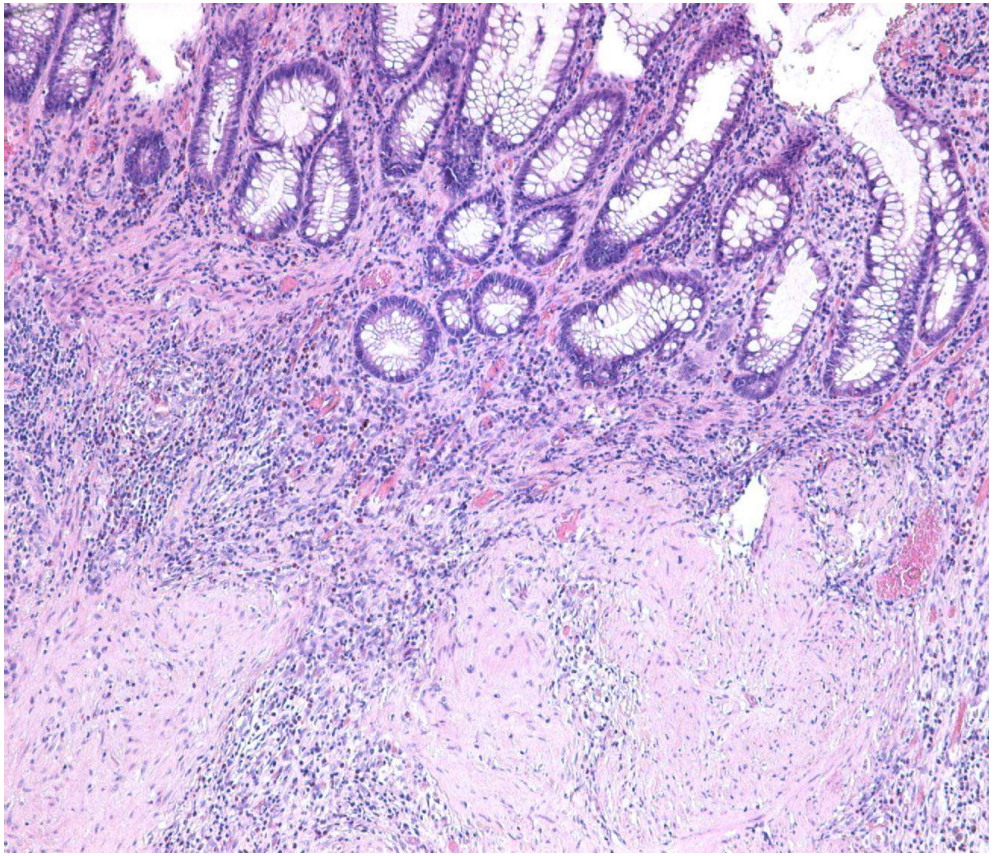
Università degli Studi di Firenze

Tumor regression grade in rectal cancer after preoperative chemoradiotherapy



Partial regression



Complete regression

What Is the Role for the Circumferential Margin in the Modern Treatment of Rectal Cancer?

Iris D. Nagtegaal and Phil Quirke

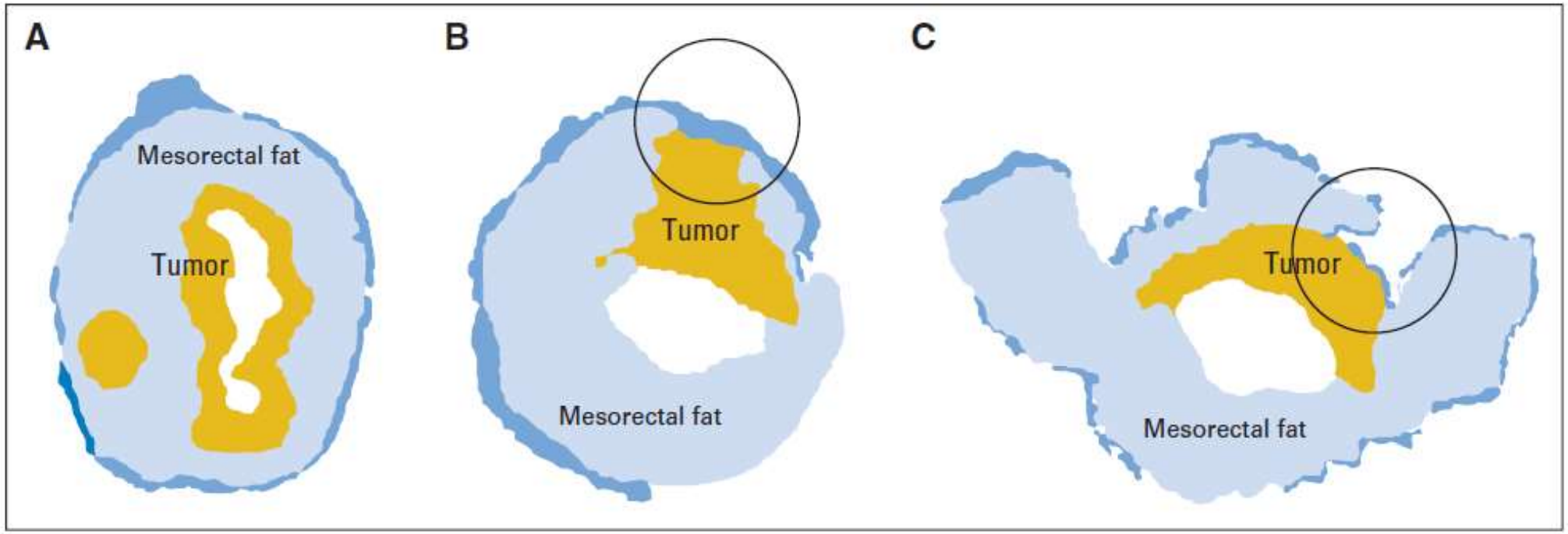


Fig 1. Schematic representation of the circumferential resection margin (CRM); the margin is marked with black ink. (A) Negative CRM. (B) Locally advanced tumor growth, directly into the circumferential margin. (C) Small tumor growing into the circumferential margin as a result of incomplete removal of the surrounding mesorectum. The plane of resection is onto the muscularis propria.

J Clin Oncol 26:303-312. © 2008 by American Society of Clinical Oncology

Macroscopic Evaluation of Rectal Cancer Resection Specimen: Clinical Significance of the Pathologist in Quality Control

By Iris D. Nagtegaal, Cornelis J.H. van de Velde, Erik van der Worp, Ellen Kapiteijn, Phil Quirke, and J. Han J.M. van Krieken and the Pathology Review Committee for the Cooperative Clinical Investigators of the Dutch Colorectal Cancer Group

Purpose: **Quality assessment and assurance are important issues in modern health care. For the evaluation of surgical procedures, there are indirect parameters such as complication, recurrence, and survival rates. These parameters are of limited value for the individual surgeon, and there is an obvious need for direct parameters. We have evaluated criteria by which pathologists can judge the quality or completeness of the resection specimen in a randomized trial for rectal cancer.**

Patients and Methods: **The pathology reports of all patients entered onto a Dutch multicenter randomized trial were reviewed. All participating pathologists had been instructed by workshops and videos in order to obtain standardized pathology work-up. A three-tiered classification was applied to assess completeness of the total mesorectal excision (TME). Prognostic value of this classification was tested using log-rank analysis of Kaplan-Meier survival curves using the data of all patients who did not receive any adjuvant treatment.**

Results: **Included were 180 patients. In 24% (n = 43), the mesorectum was incomplete. Patients in this group had an increased risk for local and distant recurrence, 36.1% *v* 20.3% recurrence in the group with a complete mesorectum (*P* = .02). Follow-up is too short to observe an effect on survival rates.**

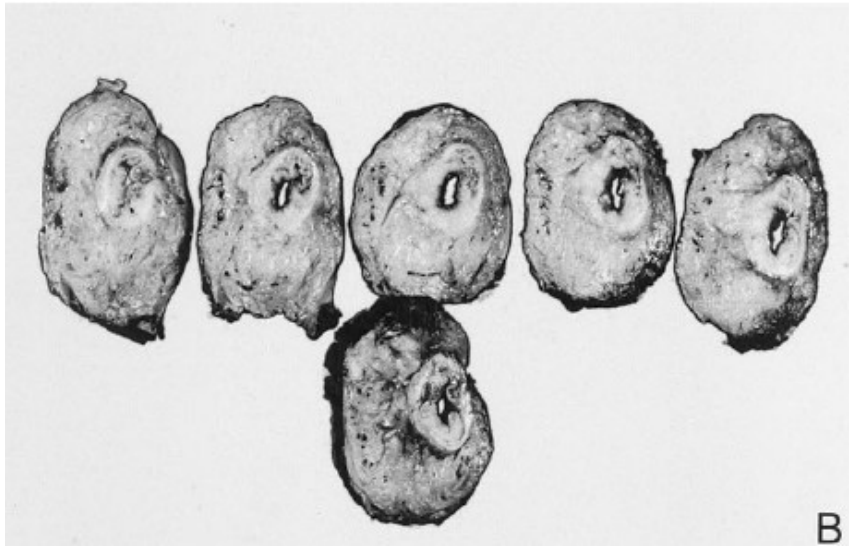
Conclusion: **A patient's prognosis is predicted by applying a classification of macroscopic completeness on a rectal resection specimen. We conclude that pathologists are able to judge the quality of TME for rectal cancer. With this direct interdisciplinary assessment instrument, we establish a new role of the pathologist in quality control.**

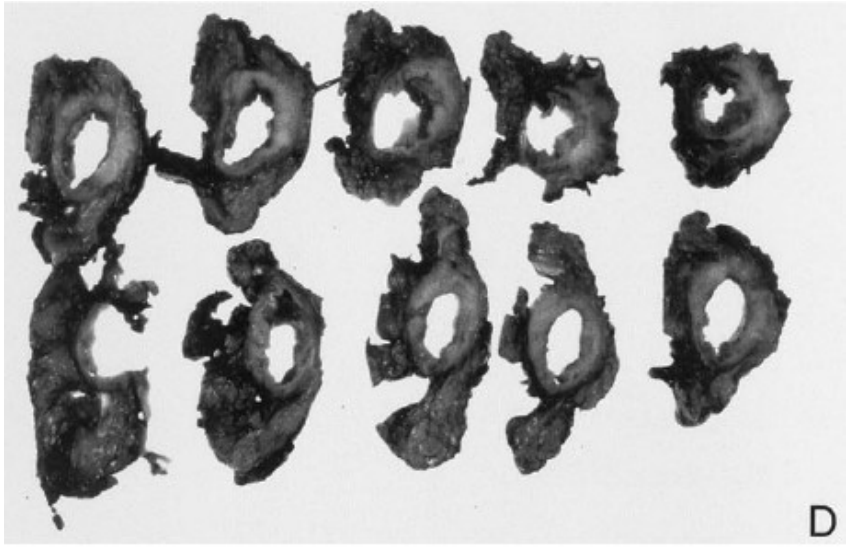
J Clin Oncol 20:1729-1734.

Macroscopic Judgment of the Resection Specimen

The quality of the mesorectum was determined using pathology reports and scored using three grades:

- Complete: intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing (Fig 1A and 1B).
- Nearly complete: moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, with the exception of the insertion of the levator muscles.
- Incomplete: little bulk to mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin .





Pathologic Processing of the Total Mesorectal Excision

Molly Campa-Thompson, MD[1] Robert Weir, PA (ASCP)[1] Natalie Calcetera, MD[2]
Philip Quirke, BM, PhD, FRCPath[3] Susanne Carmack, MD[1]

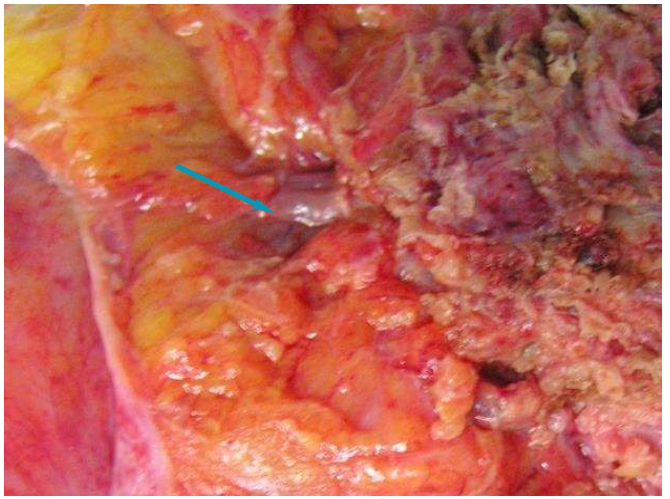
Clin Colon Rectal Surg 2015;28:43–52.

Tuscany Tumor Institute (ITT) guidelines for rectal cancer 2012

- Macroscopic evaluation of the quality of the mesorectum according to the Quirke's grading system

Complete (grade 3)

Nearly complete (grade 2)



Incomplete (grade 1)

- Complete: intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm.
- Nearly complete: moderate bulk to the mesorectum, but irregularity of the mesorectal surface.
- Incomplete: little bulk to mesorectum with defects down onto muscularis propria

J Clin Oncol 20:1729-1734. © 2002

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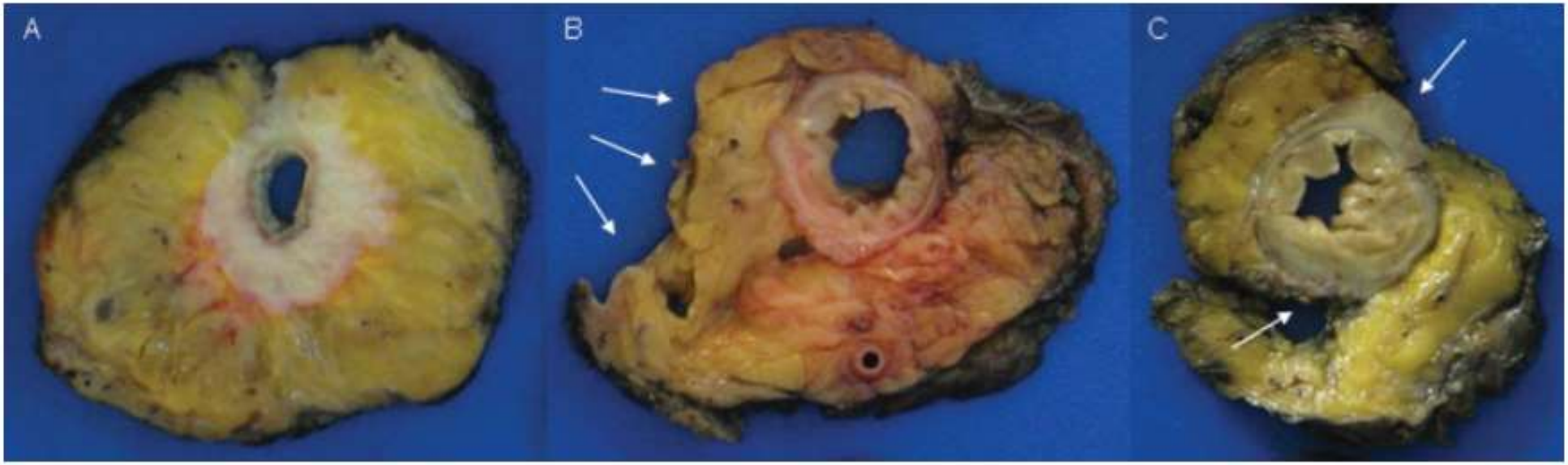
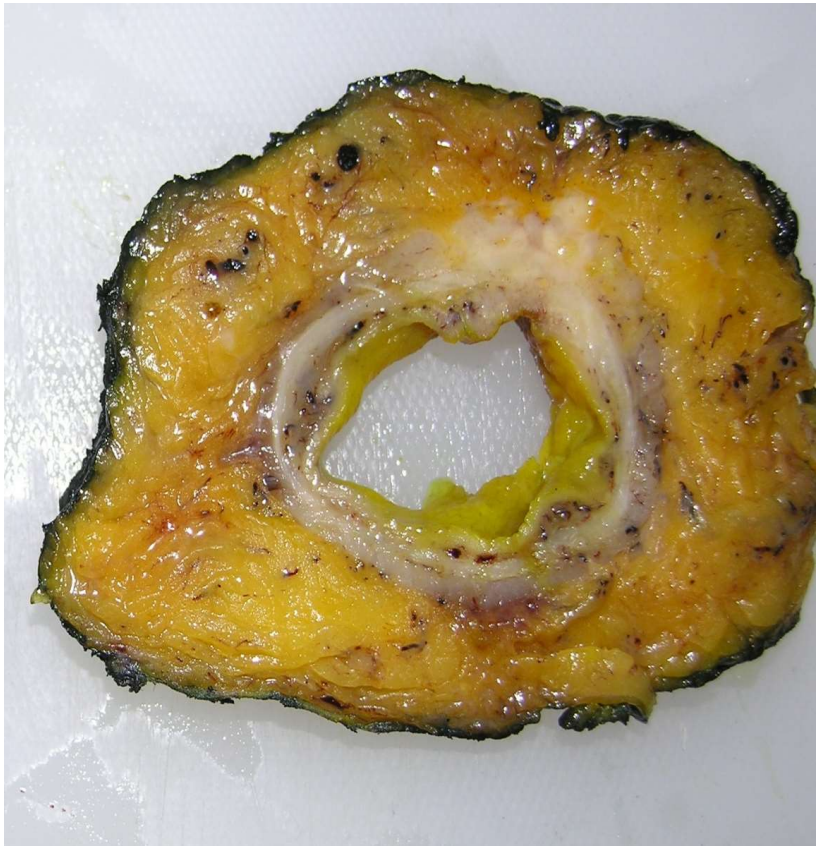
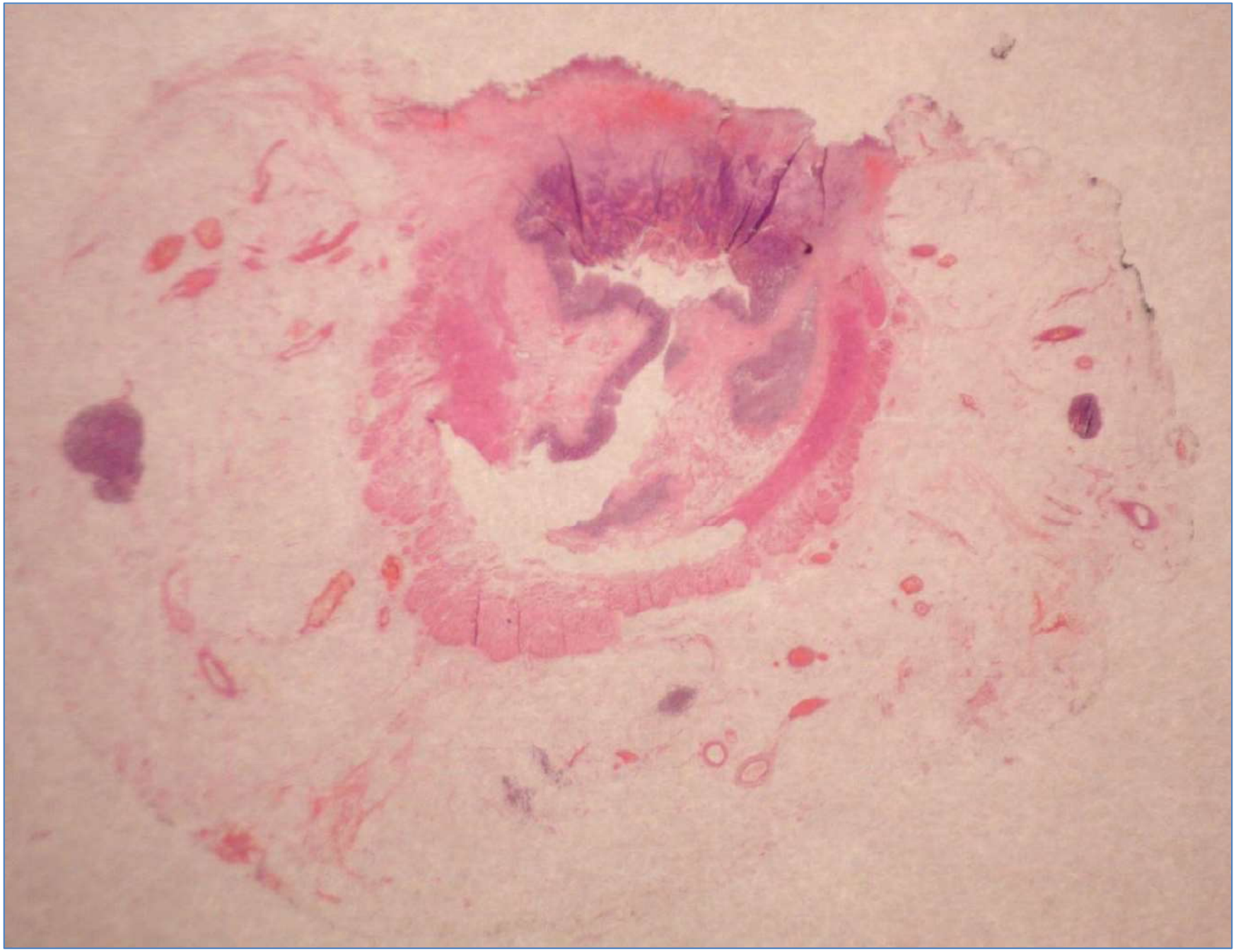


Fig. 2 Mesorectal grading—transverse sections (A) mesorectal plane; (B) intramesorectal plane with arrows denoting mesorectal defects; and (C) muscularis propria plane with arrows denoting the exposed muscularis propria.

Assessment and processing of the resection specimen

- Evaluation of the fresh specimen
- Grading of the mesorectum
- Orientation and inking of the non-peritonealized surface
- Opening and fixation (48-72 hours before sectioning)
- Sectioning and sampling (transverse sections at 5 mm intervals)
- Tranverse slices are examined to note:
  - -the extent of tumor and the closest distance of the tumor to the circumferential resection margin (CRM)
  - -positive lymph nodes or tumor deposits and their relationship to the CRM
  - - areas suspicious for extramural vascular invasion
- Significative sections are embedded in paraffin mega blocks
- Histological examination of the whole mount sections





Whole mount section

Lymph Node Retrieval in Rectal Cancer is Dependent on Many Factors—the Role of the Tumor, the Patient, the Surgeon, the Radiotherapist, and the Pathologist

Leonie J. M. Mekenkamp, MD, Johan H. J. M. van Krieken, MD, PhD,**
Corrie A. M. Marijnen, MD, PhD,† Cornelis J. H. van de Velde, MD, PhD,‡ and
Iris D. Nagtegaal, MD, PhD, for the Pathology Review Committee and the Co-operative Clinical Investigators*

A total of 1227 patients were selected from a multicenter prospective randomized trial investigating the value of neoadjuvant radiotherapy. The median number of examined lymph nodes in all patients was 7.0. The number of retrieved lymph nodes in patients with node metastasis was significantly higher than in node negative patients. After neoadjuvant radiotherapy fewer lymph nodes were retrieved (6.9 vs. 8.5; $P < 0.0001$). Variations in lymph node yield between pathology laboratories and individual pathologists were striking.

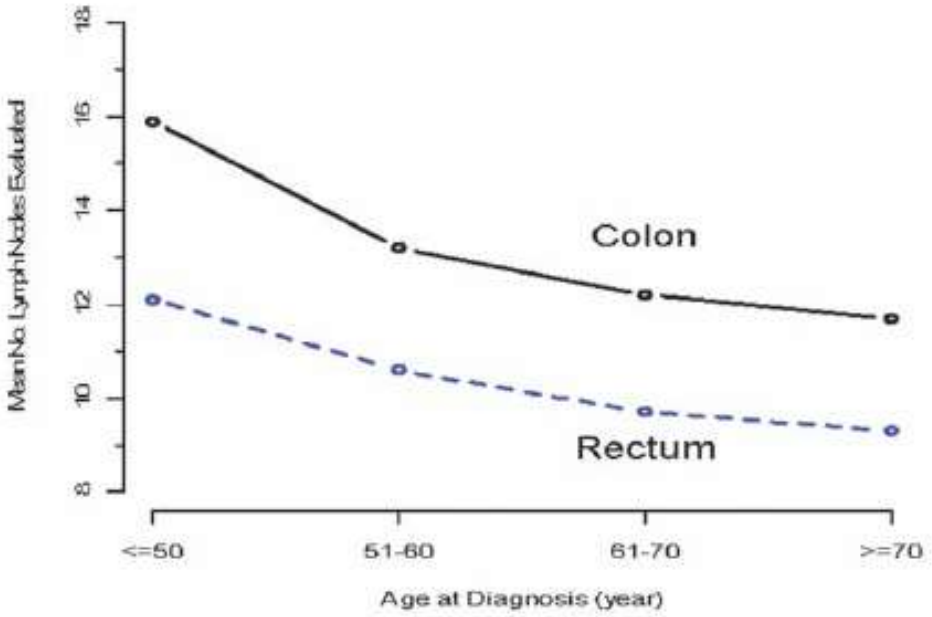
The following patient and tumor characteristics are associated with a significant lower lymph node retrieval: age over 60 years, overweight, small size, and low invasion depth of the tumor, poor differentiation grade, and absence of a lymphoid reaction. Node negative patients in whom seven or less lymph nodes were examined had a lower recurrence free interval than patients in whom at least 8 lymph nodes were examined (17.0% vs. 10.7%, $P = 0.016$). We conclude that in pathology laboratories a median of at least 8 lymph nodes need to be examined in rectal cancer specimens, but that higher numbers are desirable and achievable in most cases, even after preoperative radiotherapy.

Am J Surg Pathol 2009;33:1547–1553

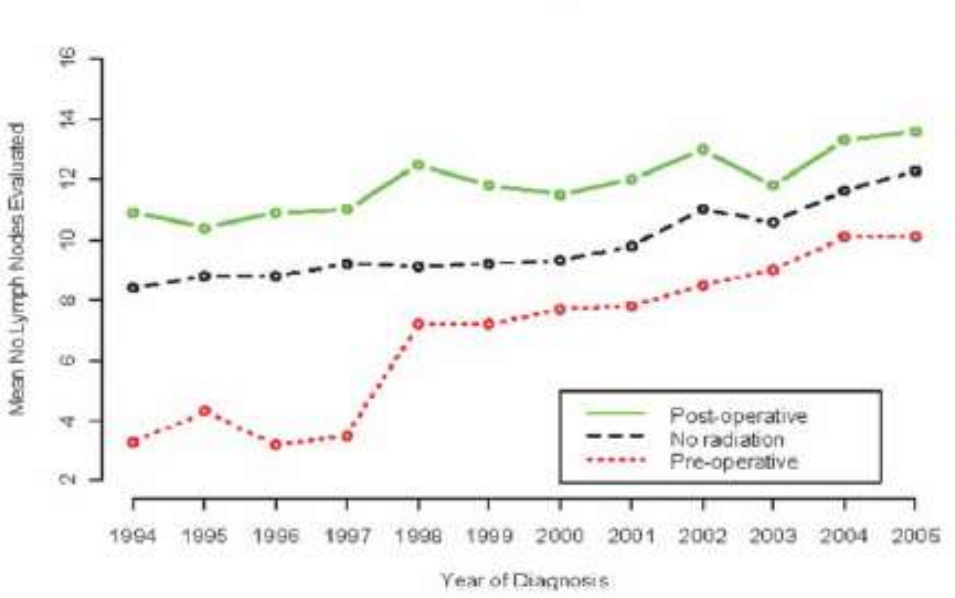
Clinical and Pathologic Factors That Predict Lymph Node Yield From Surgical Specimens in Colorectal Cancer

A Population-Based Study

Joanne F. Chou, MPH[1]; David Row, MD[2]; Mithat Gonen, PhD[1]; Yi-Hai Liu, MS[1]; Deborah Schrag, MD[1,3]; and Martin R. Weiser, MD[2]



Age was a consistently important determinant of LN yield. The mean number of LNs harvested from colon and rectal cancer patients ≥70 years of age was 11.7 and 9.3, respectively; and, for every 10-year incremental increase in age, there was an average reduction of 9% in LN harvest in both cohorts (Table 3). This phenomenon



It is noteworthy that we observed a 25% average reduction in LN harvest when comparing the preoperative radiation and no radiation treatment groups ($P < .01$)

*153,483 cases; only 49.2% met the reccomended LN yield

Cancer June 1, 2010

The Effects of Preoperative Chemoradiotherapy on Lymph Node Sampling in Rectal Cancer

Eric D. Miller, Ph.D.[1] • Bruce W. Robb, M.D.[2] • Oscar W. Cummings, M.D.[3]
Peter A. S. Johnstone, M.D.[1]

TABLE 1. Summary of literature data reporting lymph node yield with and without preoperative chemoradiotherapy

					CRT before surgery			*No CRT before surgery*				
Reference	*Study type*	*RT dose, Gy*	*CT*	*OTT*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	p	*Decrease, %*
de la Fuente et al[11]	RR	50.4	5-FU	NR	188	14.6	8.2	88	17.2	10.3	<0.029	15
Doll et al[15]	RR	45	5-FU	9–10 wk	102	12.9	5.1	114	21.4	10.8	<0.0001	40
Ha et al[10]	RR	50.4	1 of 4 regimens	9.5–13.5 wk	399	14.4	7.1	216	21.6	10.2	<0.001	33
Klos et al[16]	RR	45–50.4	5-FU	10–14 wk	221	13	7	164	14	7	NR	7
Latkauskas et al[17]	RR/PDB	25 or 50	5-FU with 50 RT	7 or 11 wk	38	6.3	2.9	138	13.5	7.2	<.001	53
Morcos et al[6]	RR	45	5-FU	11–16 wk	59	15.8	8.2	57	19.2	8.3	0.004	18
Wichmann et al[12]	PDB	45	5-FU	9–11 wk	42	13.6	5.8	184	19.1	10.9	<0.05	29

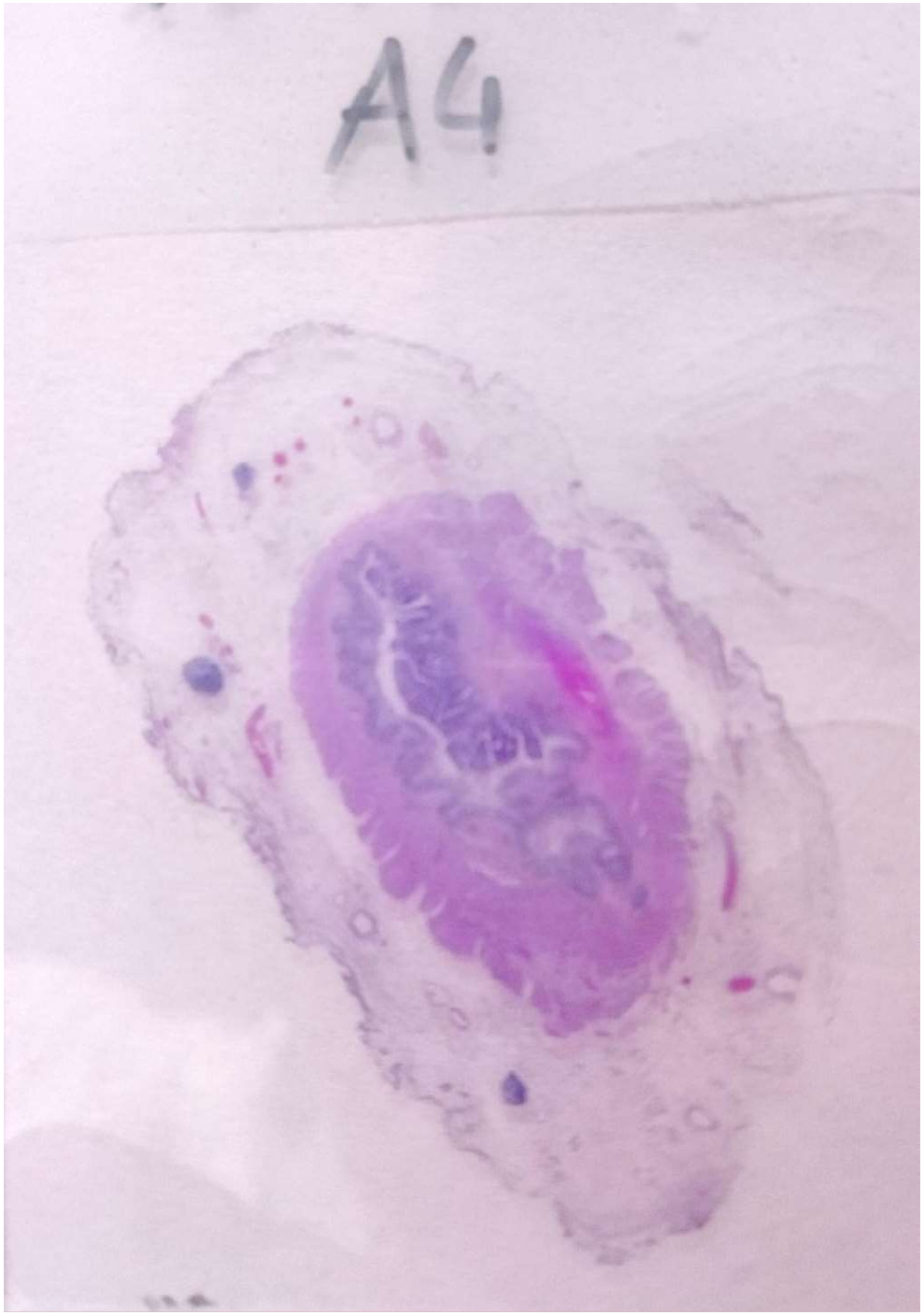
CRT = chemoradiotherapy; NR = not reported; OTT = overall treatment time, which is equal to the duration of radiation plus the time to surgical resection; PDB = prospective database; RR = retrospective review; 5-FU = 5-fluorouracil; RT = radiotherapy.

TABLE 2. Percentage of patients with lymph node yield of 12 or more

Reference	*CRT before surgery, %*	*No CRT before surgery, %*	p
Doll et al[15]	61	NR	NR
Ha et al[10]	60.2	85.6	NR
Latkauskas et al[17]	5	55	<0.05
Morcos et al[6]	64	88	0.003
Wichmann et al[12]	88	93	0.06

CRT = chemoradiotherapy; NR = not reported

Dis Colon Rectum 2012; 55: 1002–1007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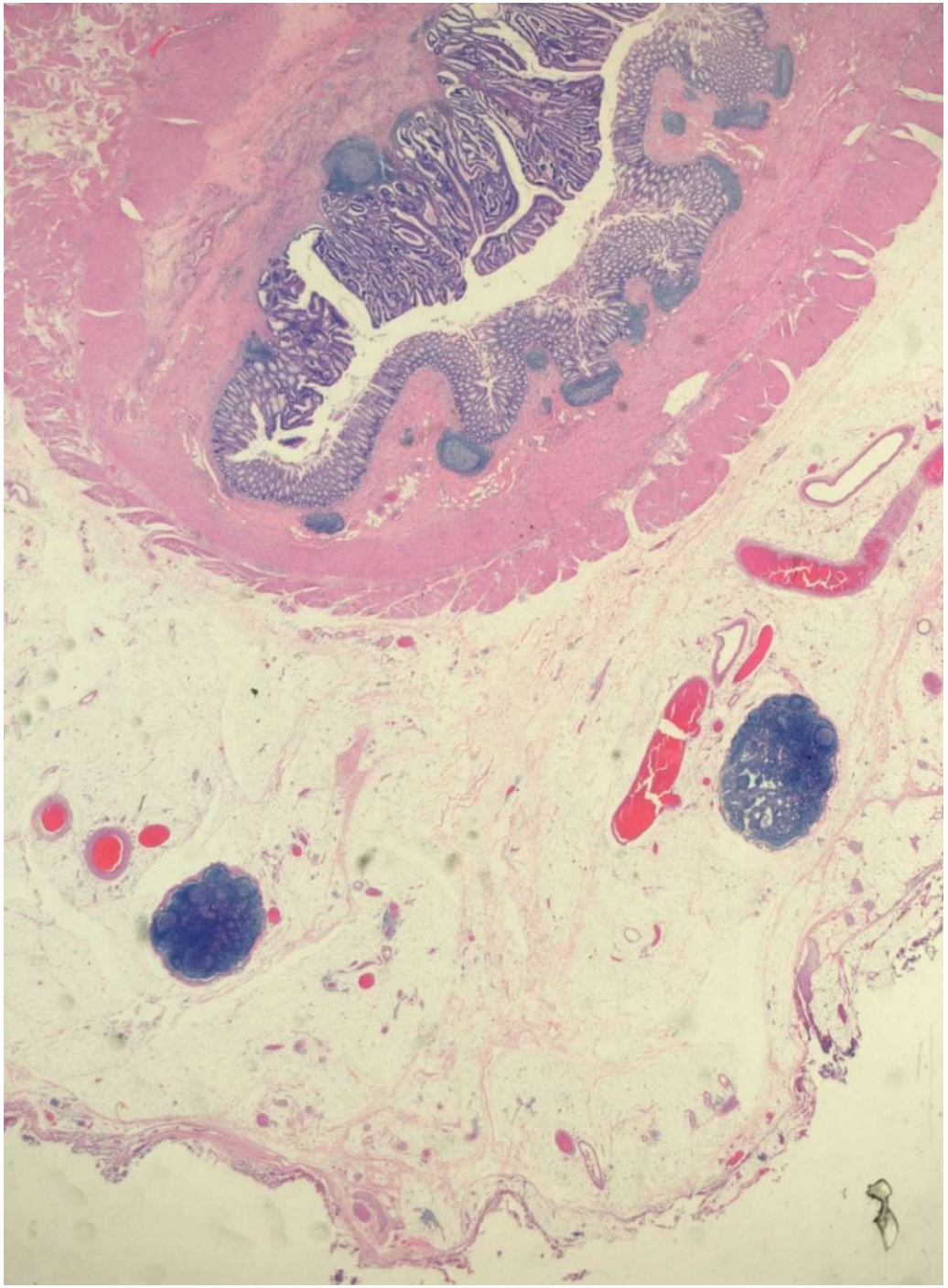
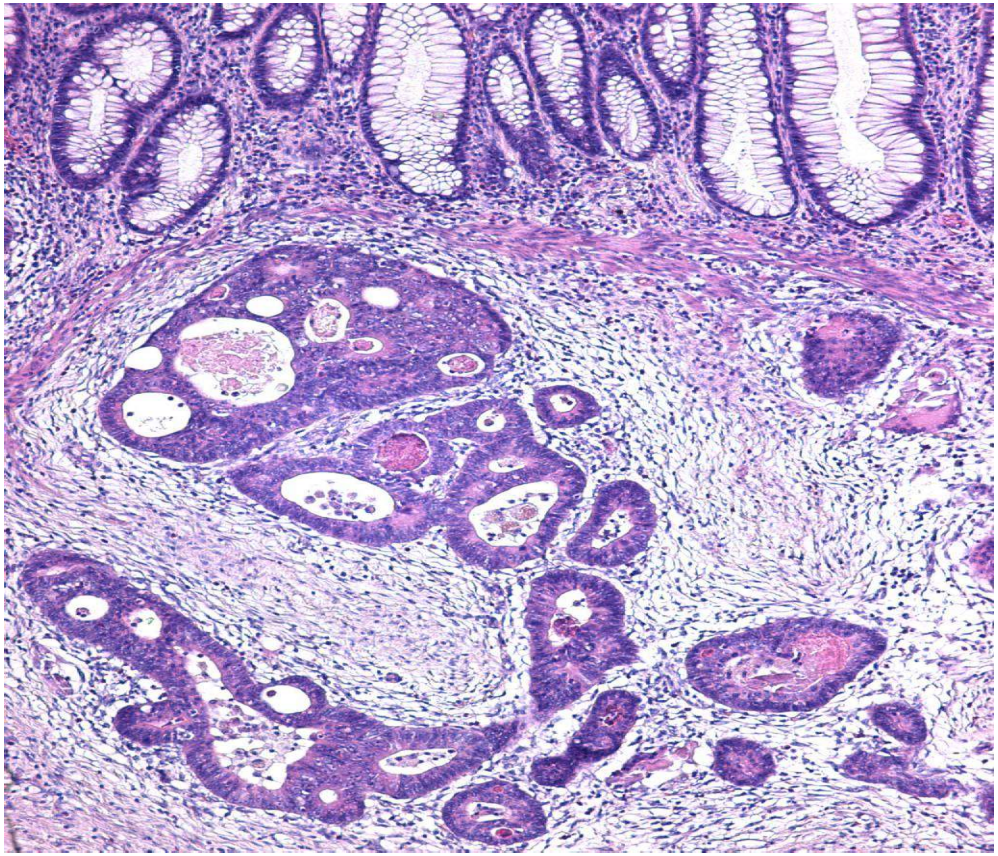
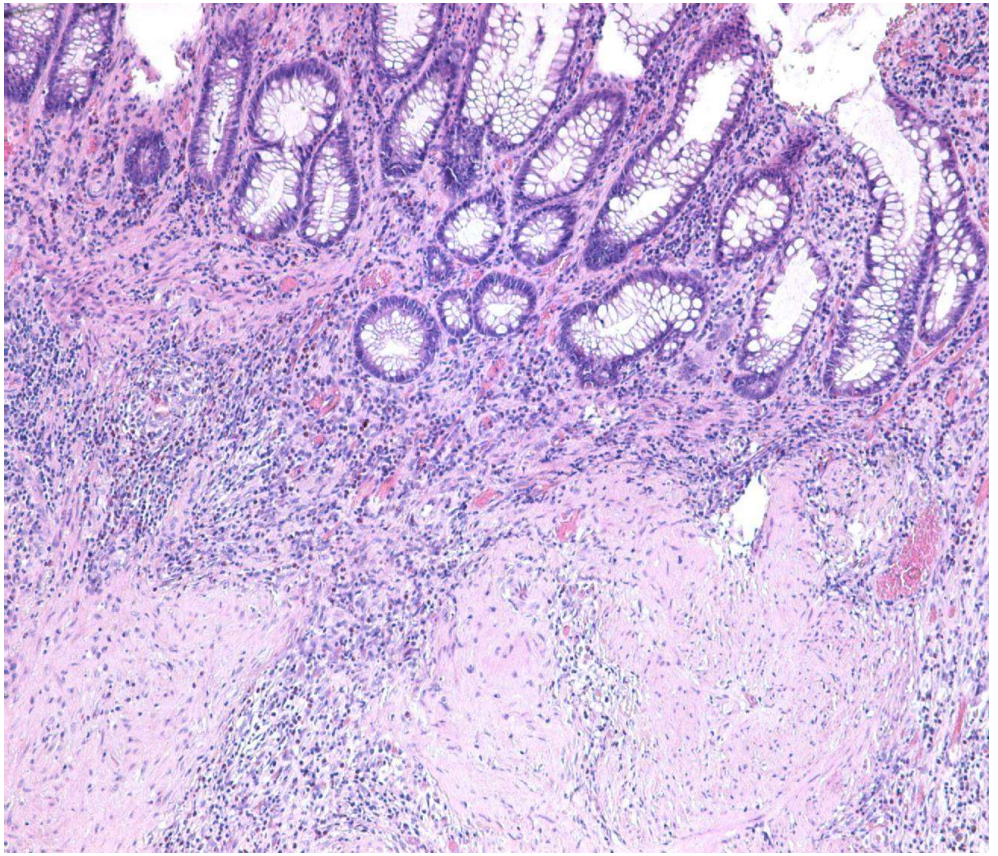


Tumor regression grade in rectal cancer after preoperative chemoradiotherapy



Partial regression



Complete regression

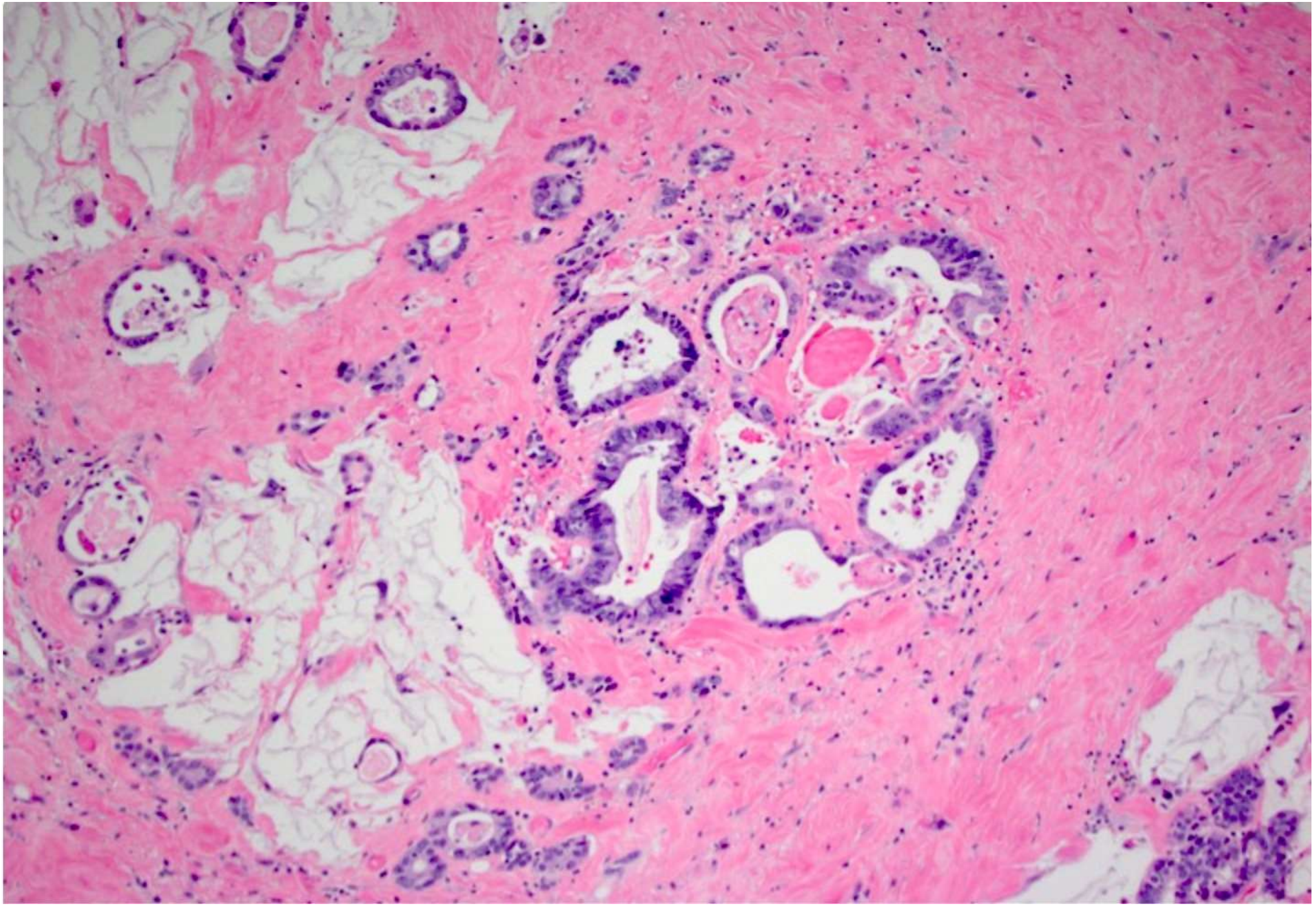
Comparison of Tumor Regression Grade Systems for Locally Advanced Rectal Cancer After Multimodality Treatment

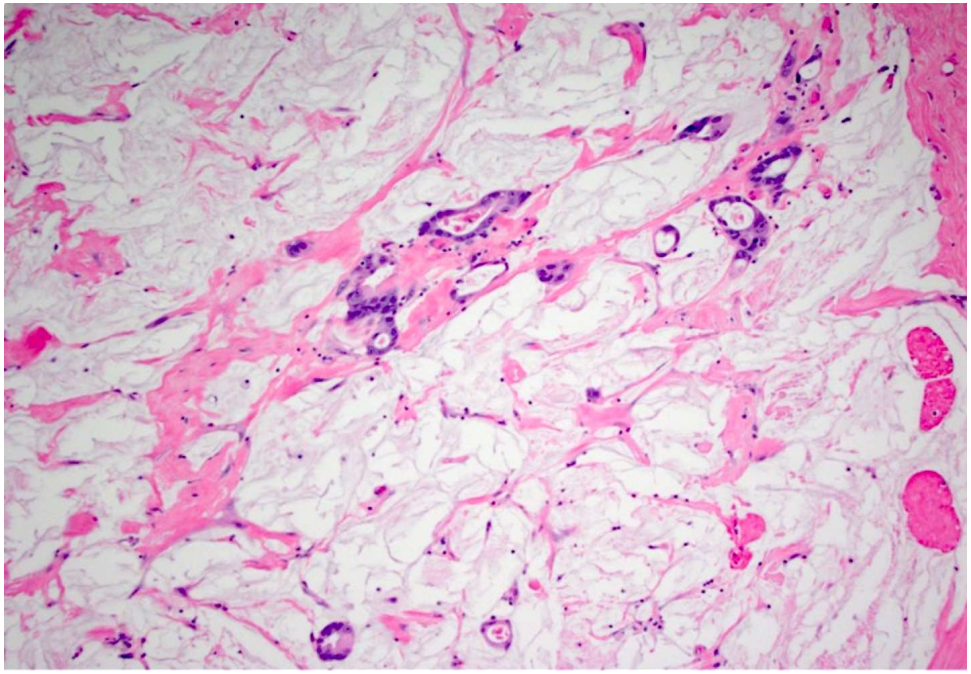
Atthaphorn Trakarnsanga, Mithat Gönen, Jinru Shia, Garrett M. Nash, Larissa K. Temple, José G. Guillem, Philip B. Paty, Karyn A. Goodman, Abraham Wu, Marc Gollub, Neil Segal, Leonard Saltz, Julio Garcia-Aguilar, Martin R. Weiser

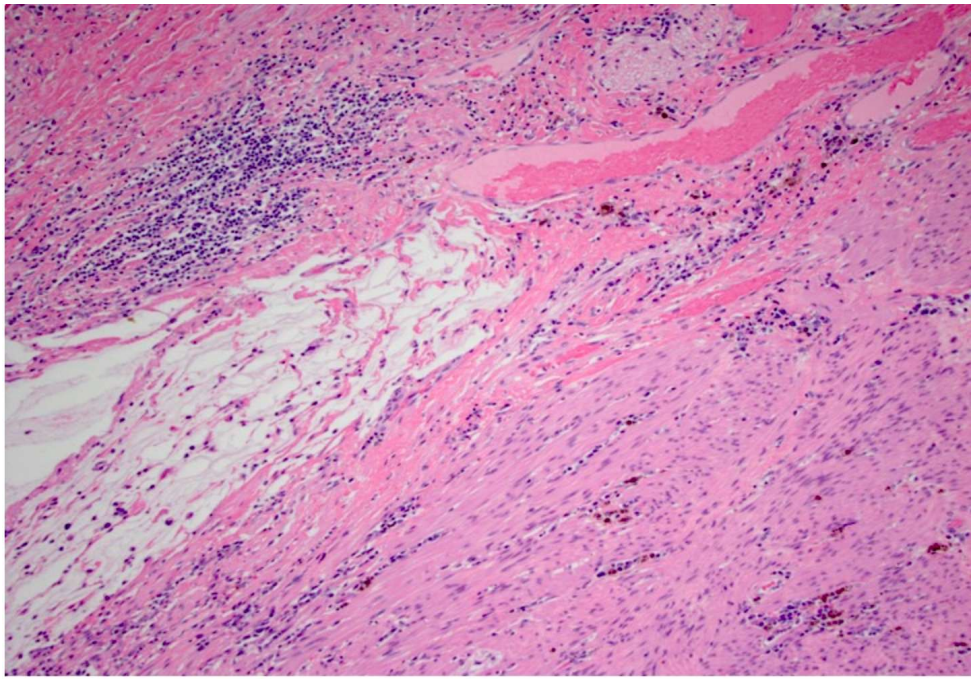
Tumor Regression Grade Systems

TRG was determined by specialized gastrointestinal pathologists who measured the proportion of tumor mass replaced by fibrosis. Percent response was defined based on the percent of the lesion composed of fibrous or fibro-inflammatory tissues (18). Patients were classified according to various TRG schemes, including the Mandard (five, three-tier), Dowrak/Rödel (five, three-tier), MSKCC, and AJCC systems. The definition of each TRG grading system is presented in Table 1.

Irrespective of the grading system, assessment of pathological response is based on: 1) residual tumor cells and 2) tissues replacing tumor cells in areas where the tumor has regressed. These "replacement" tissues may be fibrotic or inflammatory; they may consist of acellular mucin pools, or, occasionally, necrosis and calcifications.







Acellular mucin should not be interpreted as residual tumor
(Am J Surg Pathol 2011;35:127)

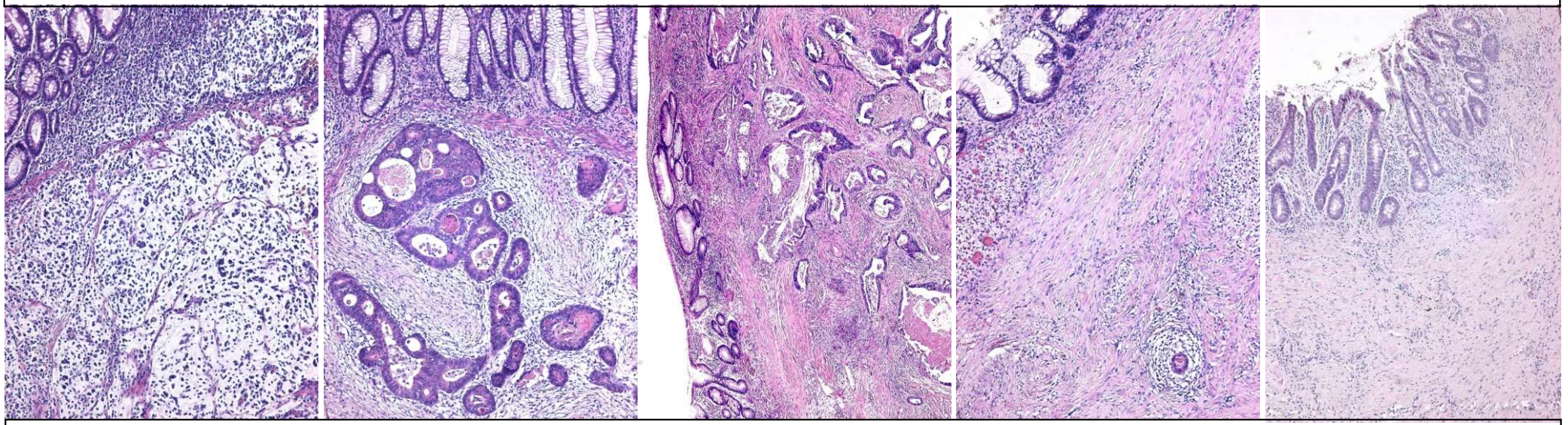
Deeper sections to search for rare residual tumor cells has little bearing on patient outcome (Histopathology 2011;59:650)

Only residual viable tumor cell are counted in this evaluation, frankly necrotic tumour should be not included in staging
Non viable cells are characterized by nuclear hyperchromasia, piknosis, nuclear fragmentation, and cytoplasmic eosinophilia (Odze 2023)

Tuscany Tumor Institute (ITT) guidelines for rectal cancer 2012

- Tumor regression grade (TRG)

Dworak system 1997



TRG	0	1	2	3	4

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

Review of a prospective database identified 563 patients with locally advanced rectal cancer (T3/4 and/or N1)

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)
TRG0	-	No residual tumor cells	No regression	-	-	-
TRG1	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
TRG2	Rare cancer cells	Residual cancer with desmoplastic response	Fibrosis 25%-50% of tumor mass	95%-99% Tumor response	Rare cancer cells or fibrosis outgrowing residual cancer	Fibrosis 25%-99% of tumor mass
TRG3	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
TRG4	Residual cancer outgrowing fibrosis	-	Complete regression	-		
TRG5	Absence of regressive change	-	-	-		

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

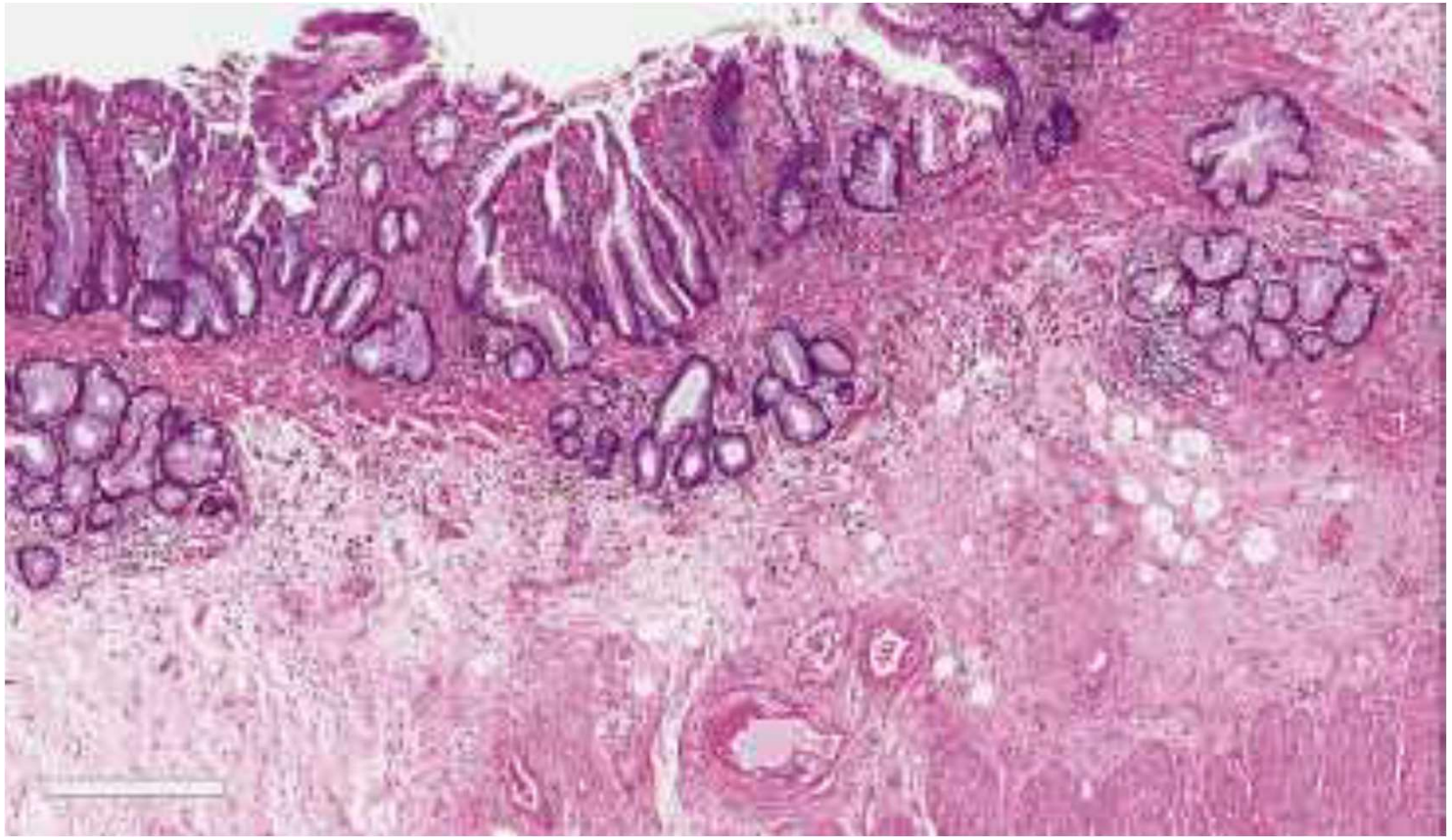
All TRG systems were predictive of recurrence. Concordance indices of the three-tier Mandard, three-tier Dowrak/Rödel, three-tier MSKCC, and four-tier AJCC systems were: 0.665, 0.653, 0.683, and 0.694, respectively (higher number = better prediction). The AJCC system more accurately predicted recurrence than the three-tier Mandard ($P = .002$) or Dowrak/Rödel ($P = .006$) and had a higher concordance index than MSKCC, although this did not reach statistical significance ($P = .068$).

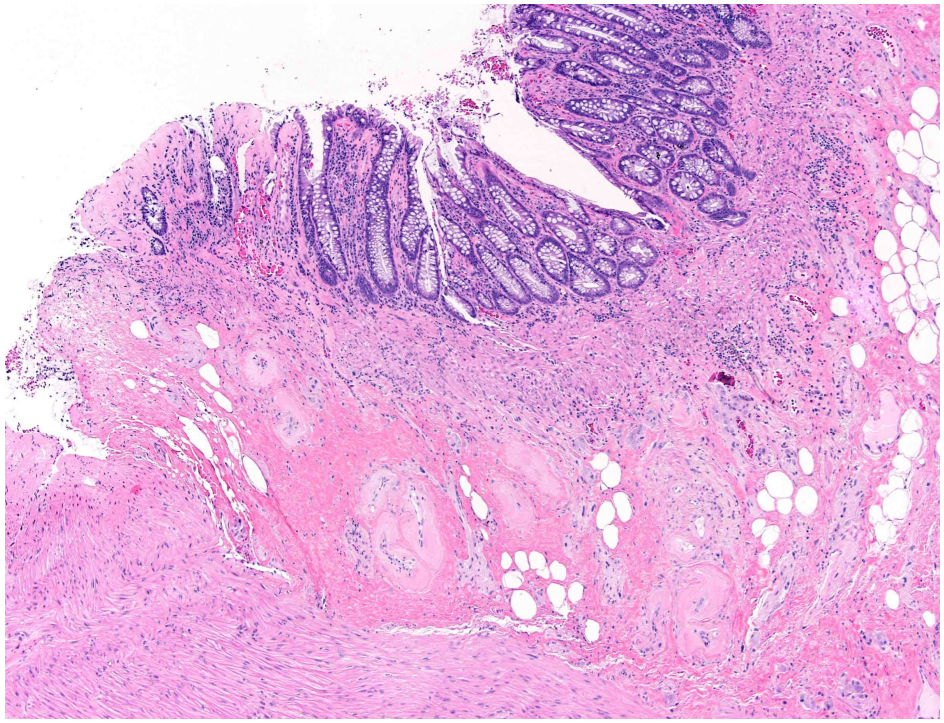
Table 6.03 Overview of the most commonly used systems for assessing tumour regression grade (TRG) {2036,1786}

Grade	Mandard	AJCC 2010	Rödel	MSKCC
TRG 0	–	No residual tumour cells	No regression	–
TRG 1	Absence of residual cancer, with fibrosis extending through the various layers of the oesophageal wall (complete regression)	Single cells or small groups	Fibrosis < 25% of tumour mass	100% response
TRG 2	Rare residual cancer cells scattered through the fibrosis	Residual cancer with desmoplastic response	Fibrosis 25–50% of tumour mass	86–99% response
TRG 3	An increase in the number of residual cancer cells, but fibrosis still predominates	Minimal evidence of tumour response	Fibrosis > 50% of tumour mass	< 86% response
TRG 4	Residual cancer outgrowing fibrosis	–	Complete regression	–
TRG 5	Absence of regressive changes	–	–	–

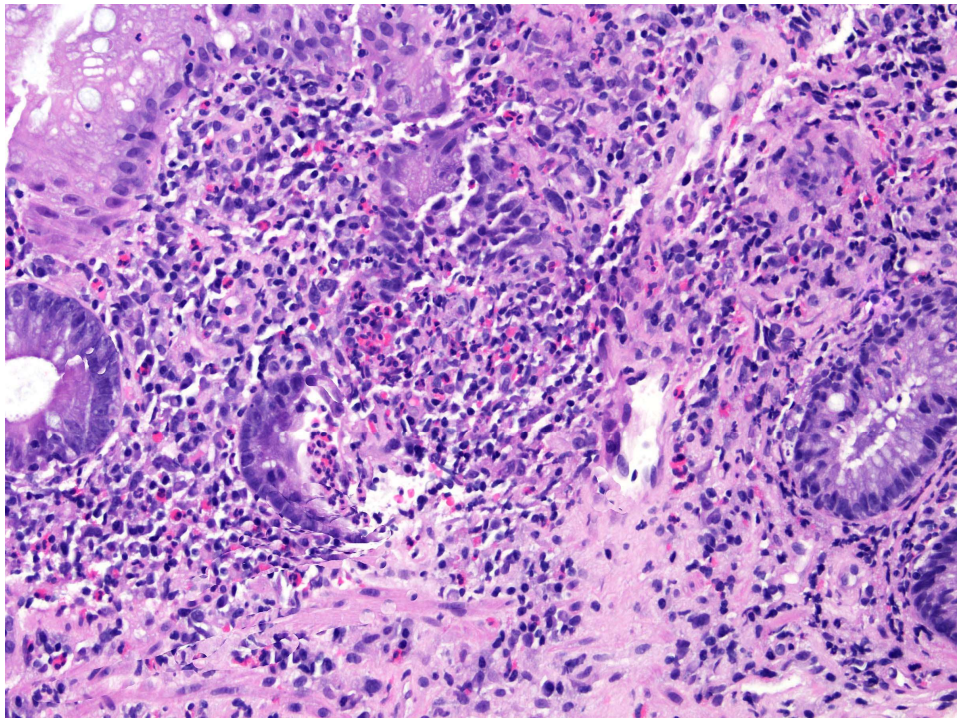
AJCC, American Joint Committee on Cancer; MSKCC, Memorial Sloan Kettering Cancer Center.

WHO 2019

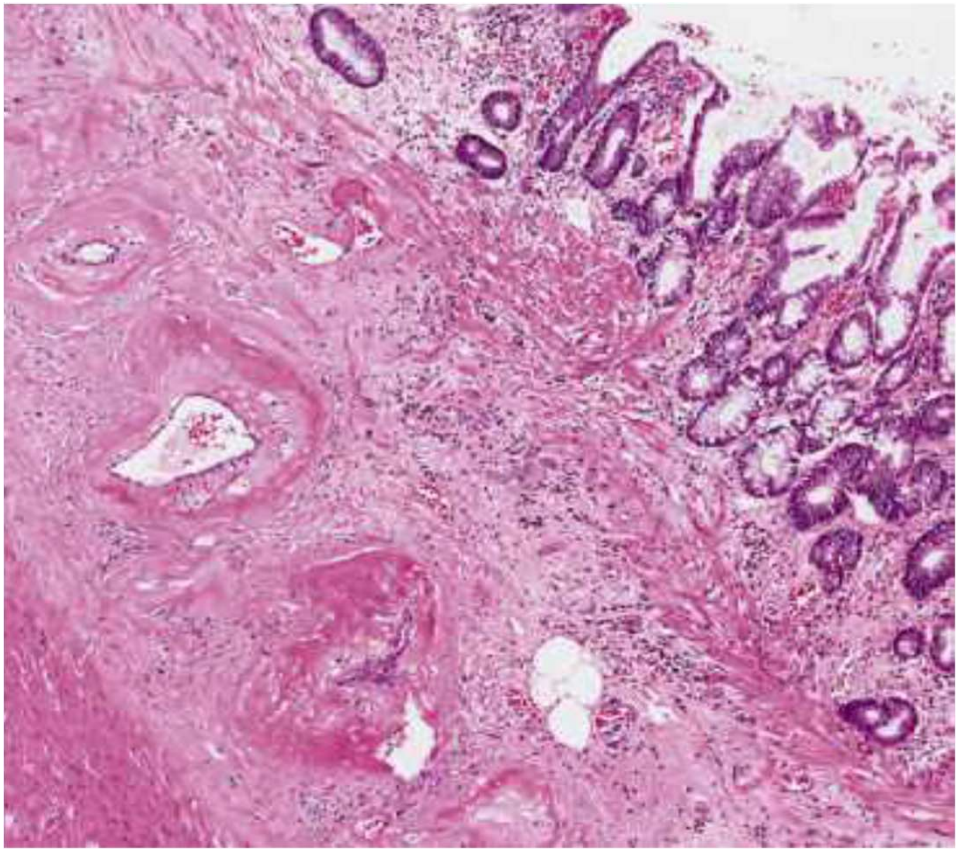


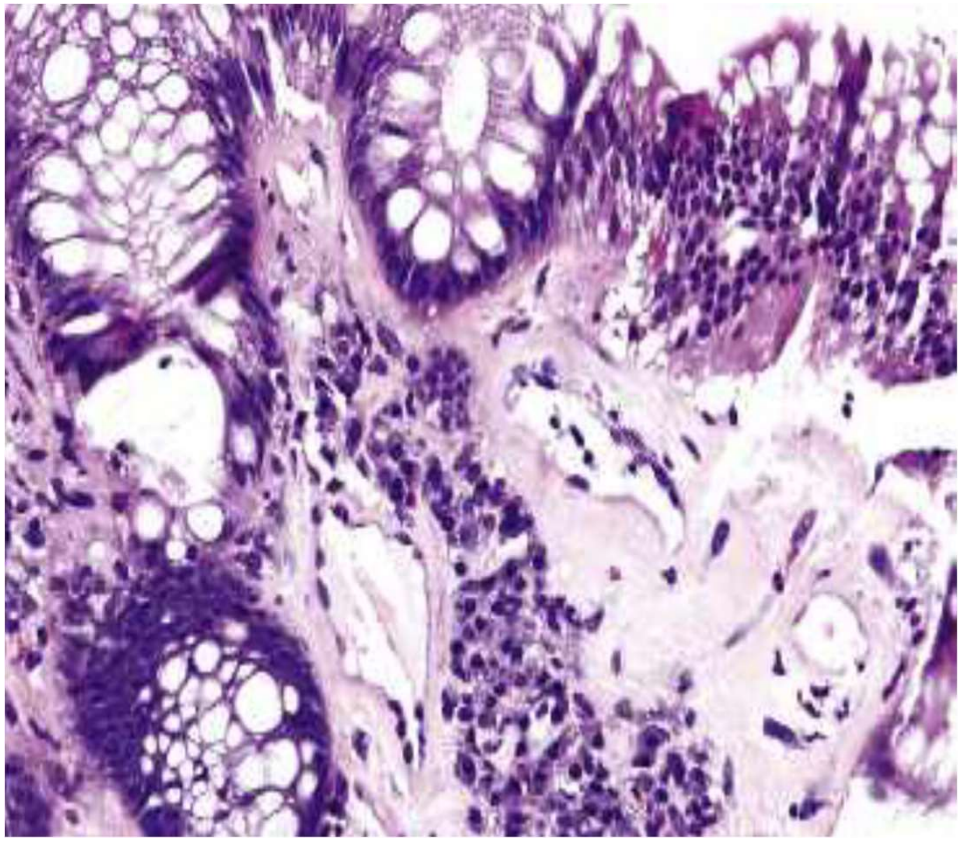


Fibrosi della lamina propria
vasi ectasici e ialinizzati

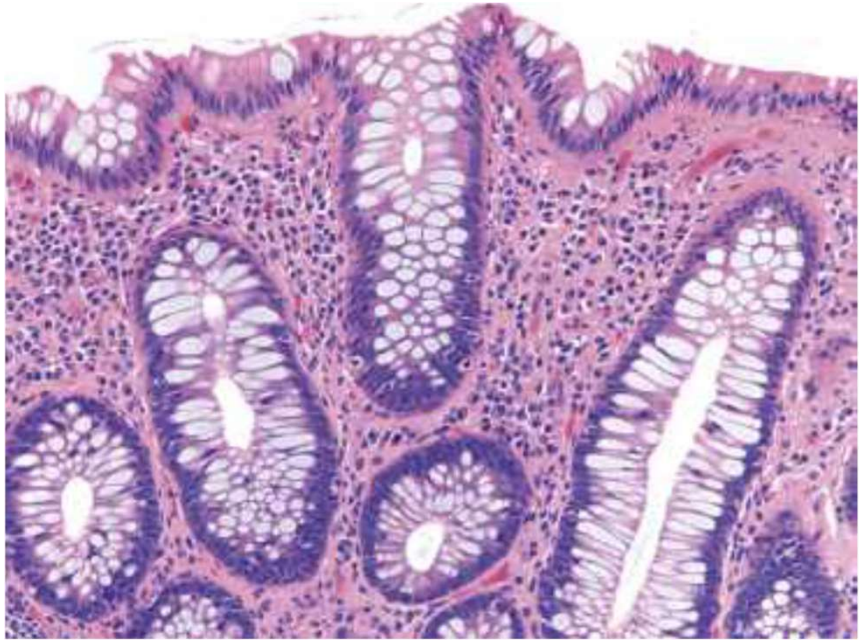


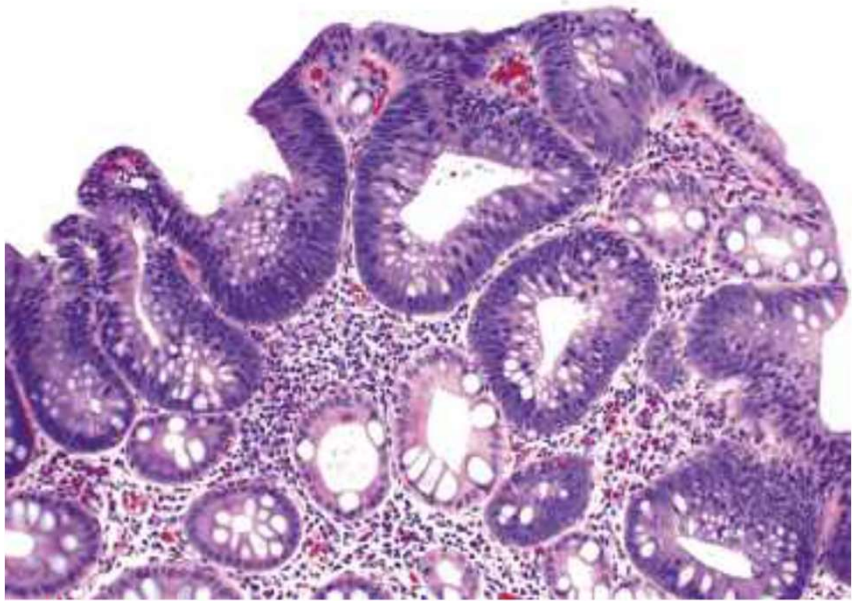
Cripte «rigenerative», flogosi, necrosi

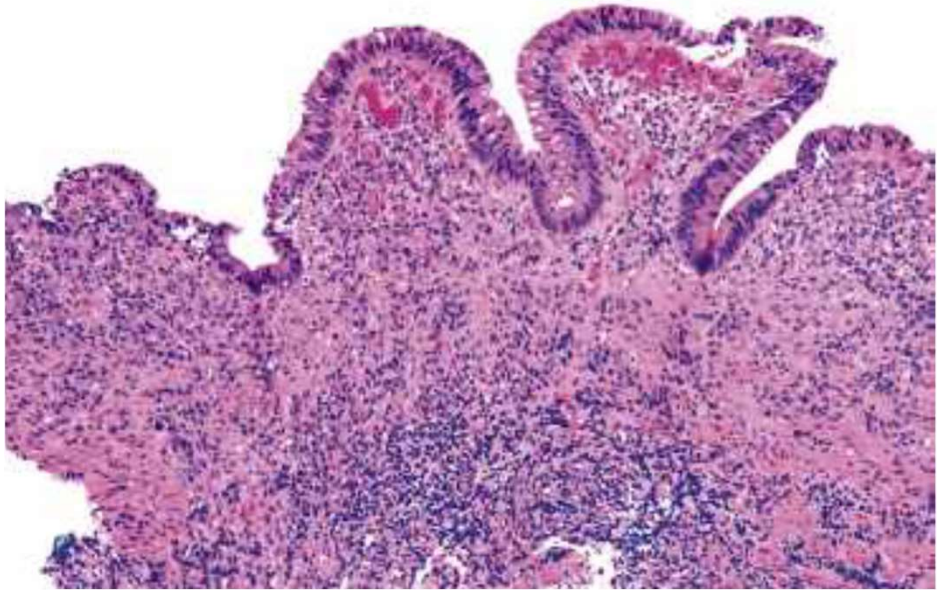




Dilated capillaries of the rectal mucosa have abnormally prominent endothelial cell nuclei and
are surrounded by a cuff of hyalinized lamina propria.
Markedly hyalinized submucosal arteries with obliteration of the lumen and foam cell change in the setting of radiation-induced vasculopathy.

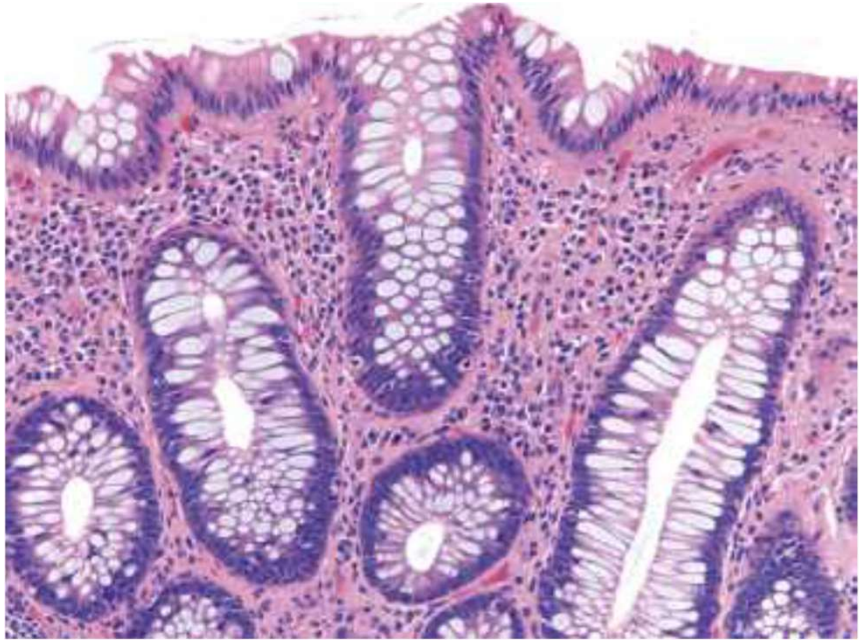




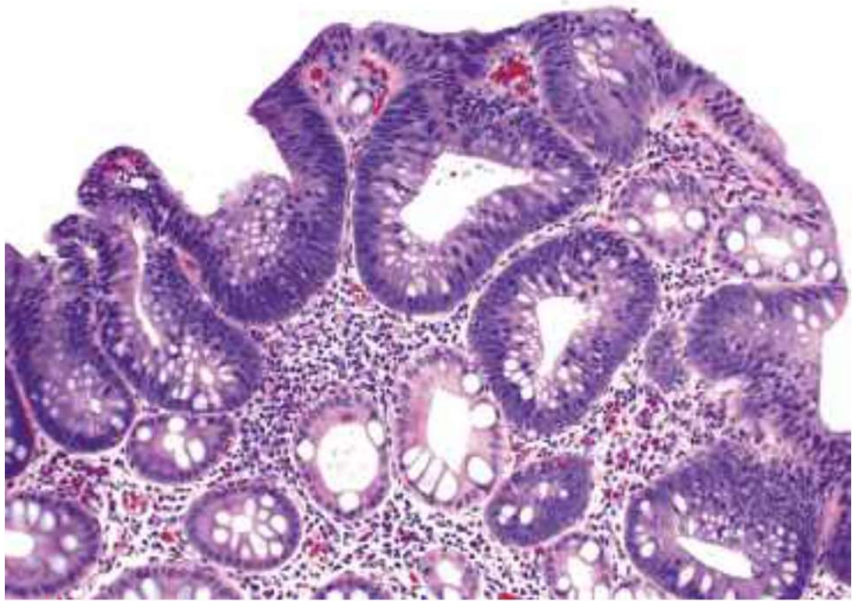


Features	Regenerative change	Dysplasia
Nuclear atypia	May be present	Always present
Vesicular chromatin	Usually absent	Present HGC)
>N/C	May be present	Always present
Increased mitoses	May be present	Usually present
Atypical mitotic figures	Usually absent	Present
Loss of surface maturation	Absent	Present
Epithelial “atypia” overlying inflamed stroma that lacks glands	Present	Usually absent
Intraepithelial neutrophils	Usually present	May be present
Complex glandular architecture	Absent	Present (HGD)

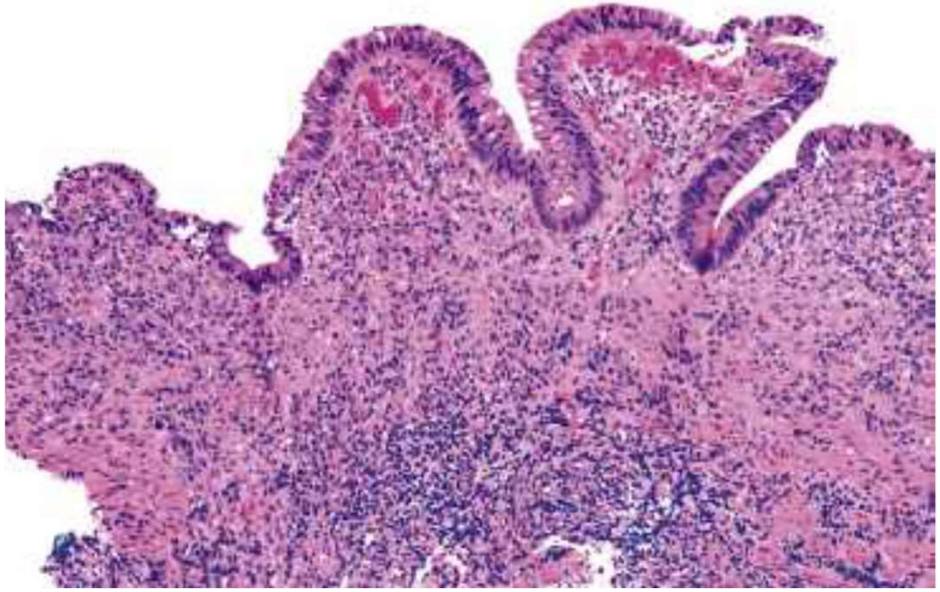
Modificata da Odze 2023



Negative



LGD

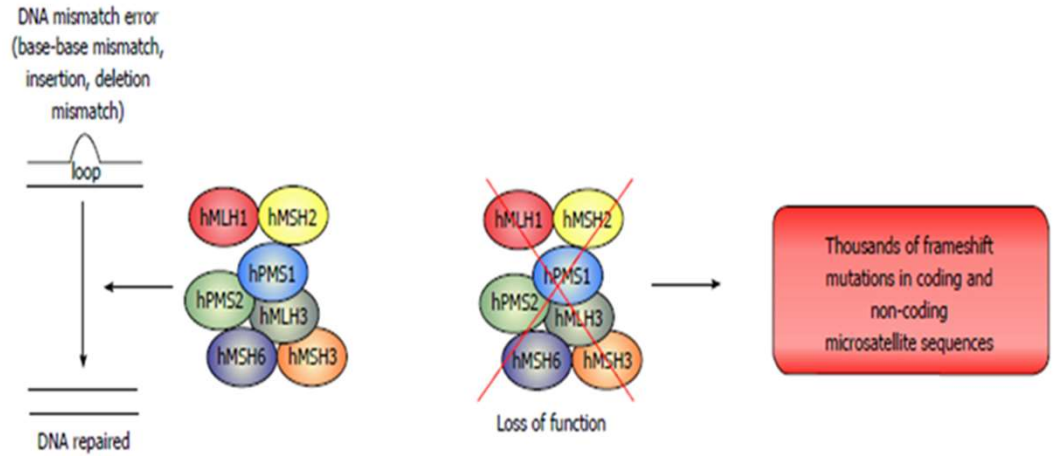


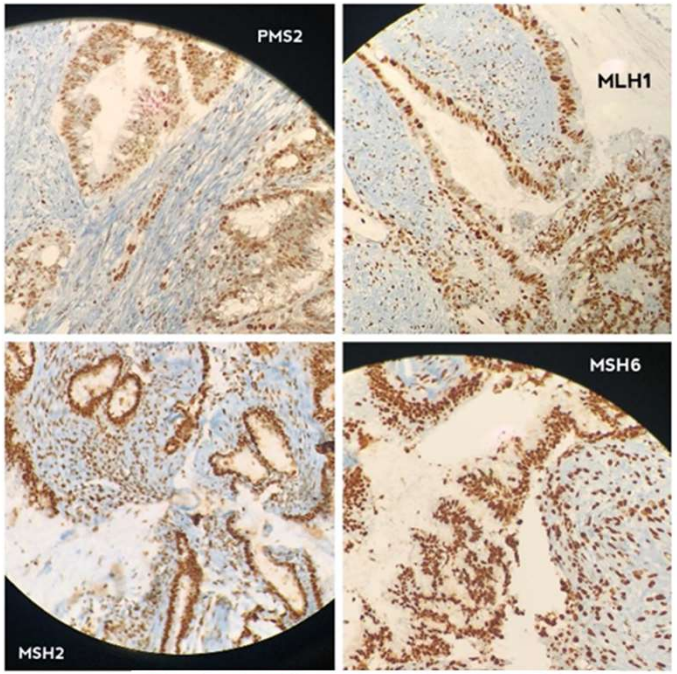
Indefinite

Box 6.02 Essential and desirable diagnostic criteria for colorectal cancer

- Histological subtype
- Differentiation grade: Low/high
- Invasion depth: According to TNM, specify if invasion in other organs (pT4) or tumour perforation
- Presence of (lympho)vascular invasion: Intramural vascular invasion, extramural vascular invasion, lymphatic invasion
- Perineural growth: Present/absent
- Resection margin status (proximal, distal, circumferential): Positive, negative, distance in cm
- Diameter of the tumour
- Site/localization of the tumour
- Quality of the resection specimen
- Number of investigated lymph nodes
- Number of positive lymph nodes
- Presence of treatment response: Yes/no; if yes, partial or complete response
- Microsatellite status / presence of DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2): Microsatellite-stable or -instable, staining for mismatch repair proteins present or absent
- Tumour budding status
- Immune response
- Presence or absence of relevant mutations

WHO 2019

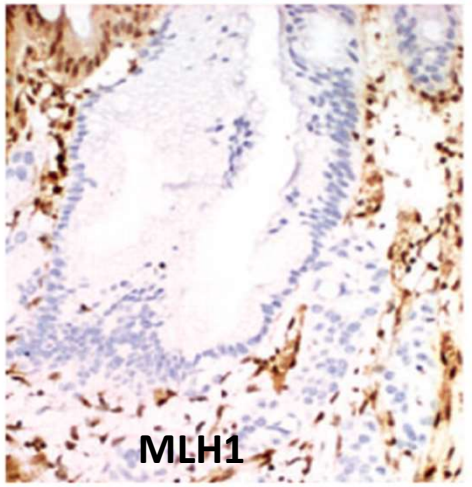


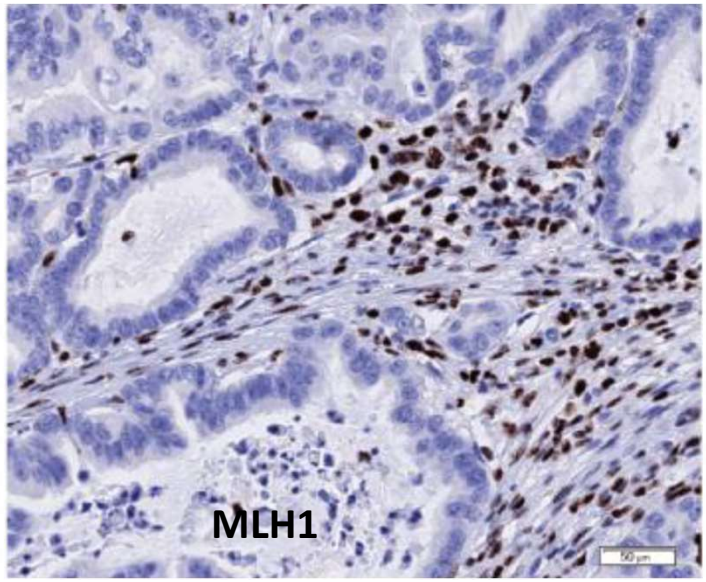


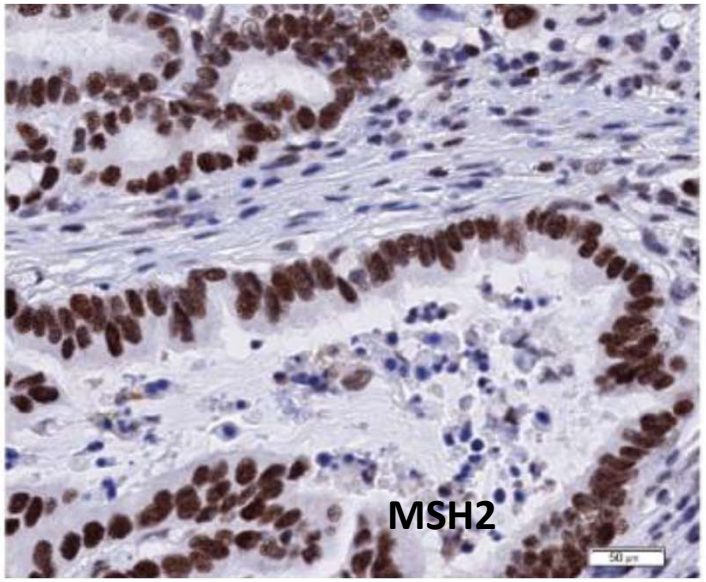
The first test of choice is IHC, using antibodies recognising the four MMR proteins: MLH1, MSH2, MSH6 and PMS2.

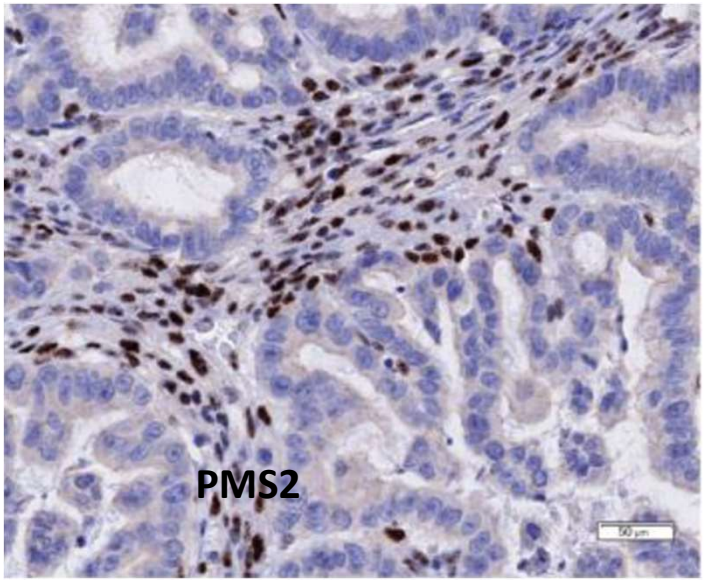
In case of doubt of IHC, confirmatory molecular analysis is mandatory.

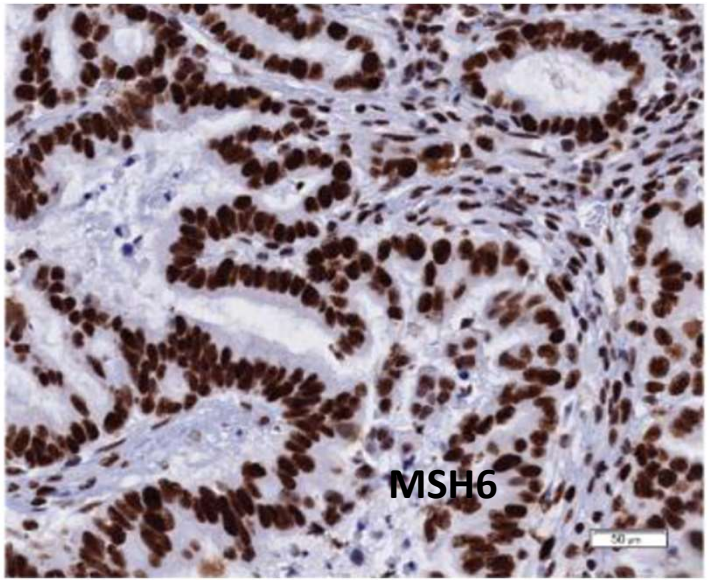
ESMO recommendations on microsatellite instability




MLH1


MSH2

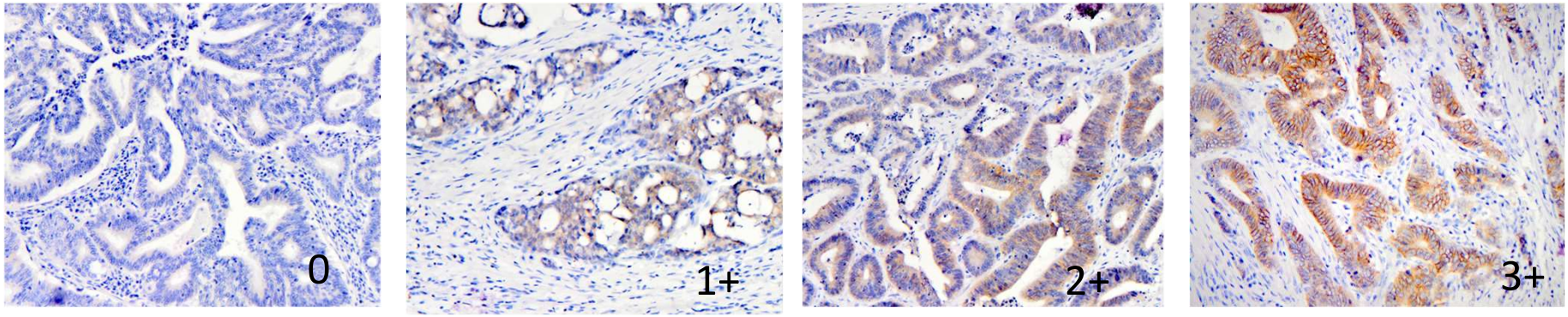

PMS2


MSH6

Loss of nuclear expression of MLH1 and PMS2: testing for methylation of the MLH1 promoter or mutation of BRAF is indicated (the presence of a BRAF V600E mutation or MLH1 methylation suggests that the tumor is sporadic and germline evaluation is probably not indicated; absence of both MLH1 methylation and of BRAF V600E mutation suggests the possibility of **Lynch syndrome**, sequencing or large deletion / duplication testing of germline MLH1 may be indicated.

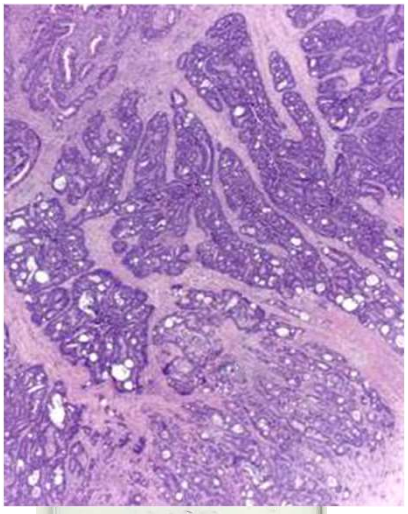
HER2 and colo-rectal cancer

IHC staining	IHC expected pattern	IHC classification	FISH test
No staining (0)	---	Negative	No
Faint staining (1+)	Segmental or granular	Negative	No
Moderate (2+) in < 50% cells	Any	Negative	No
Moderate (2+) in ≥ 50% of cells	Circumferential basolateral or lateral	Equivocal	Yes
Intense (3+) in ≤ 10% cells	Circumferential basolateral or lateral	Negative	No
Intense (3+) in > 10% cells	Circumferential basolateral or lateral	Positive	No



Selezione del tessuto

Selezione area significativa



1 sezione 4 µm EE

5 sezioni 20 µm non colorate

Eppendorf