Tumor Regression Grading of Gastrointestinal Carcinomas Following Neoadjuvant Treatment

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107TH ANNUAL MEETING
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Case

- Male, 65 years
- History of reflux; dysphagia
- Endoscopy: tumor within Barrett's mucosa in the distal esophagus
- Histology: adenocarcinoma
- Endo- Ultrasound: uT2, uN1
- Staging: no distant metastases
- Multidisciplinary tumorboard:

  neoadjuvant RCTX followed by surgery

Endoscopic images courtesey of Prof. R. Wiest

Multimodal Therapy for Locally Advanced Gastrointestinal Carcinomas

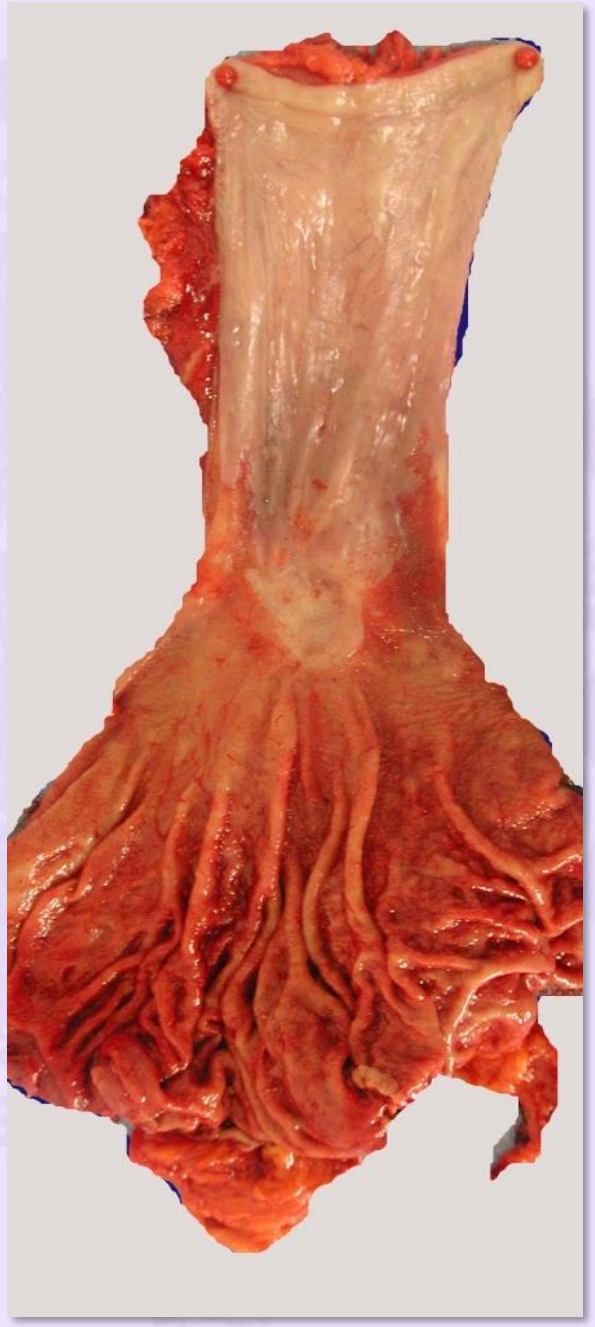
- **Esophageal, Gastric and Rectal Cancer**
- pre/perioperative (R)CTX + Surgery
- Downstaging
- Higher rates of complete resecion
- Higher distance to resection margins
- Lower rates of systemic and intraoperative tumor cell dissemination (micrometastases, isolated tumor cells)
- «in-vivo» testing of sensitivity to TX
- However, divergent response behavior of tumors

Pathology Findings after RCTX

- Transmural fibrosis
- Residual tumor islands throughout the muscular wall
- reaching the subserosal/adventitial tissue

- ypT3 N0 (0/23) L0, V0, R0

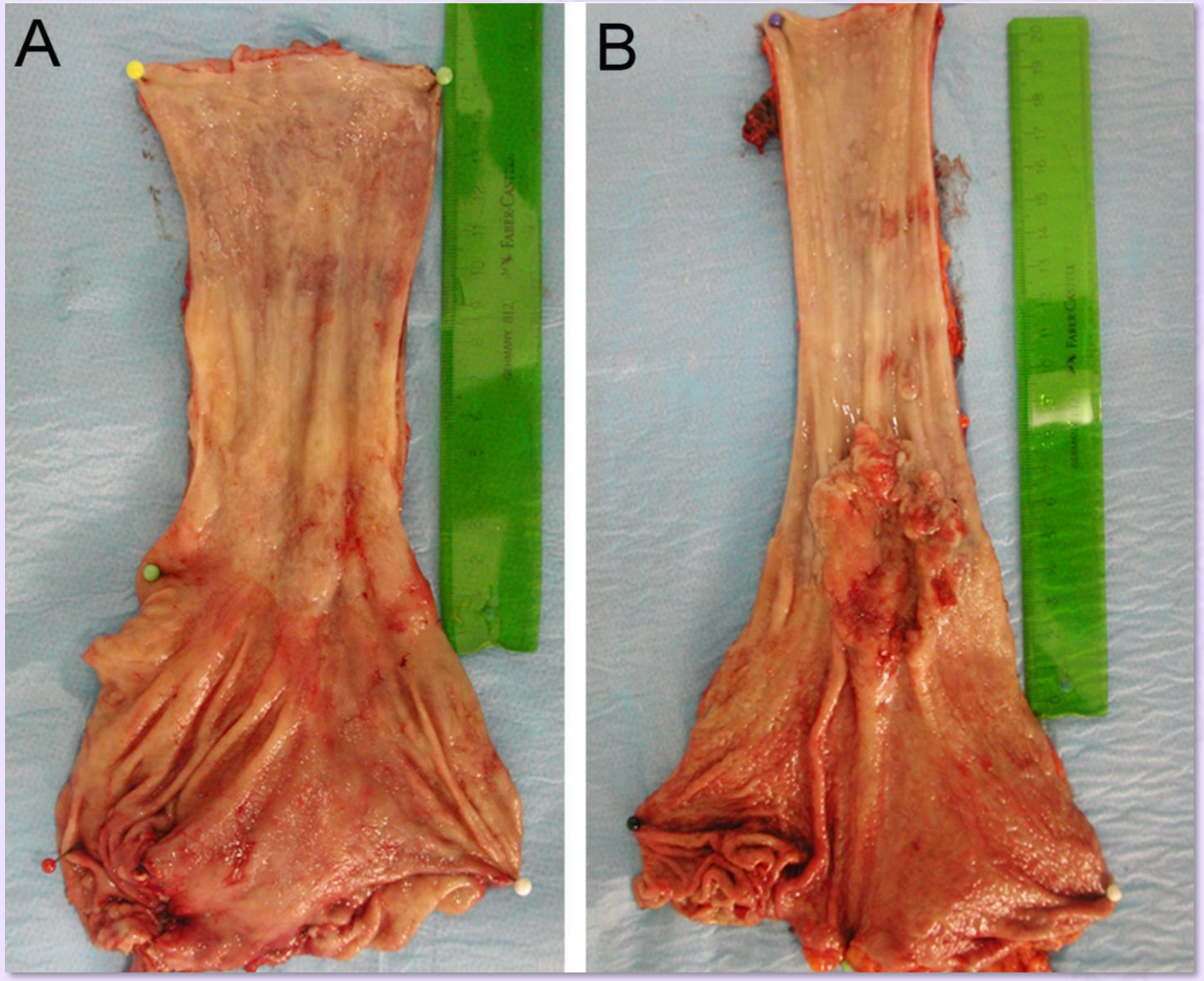
- How to report the regressive changes?
- Do they have any significance?



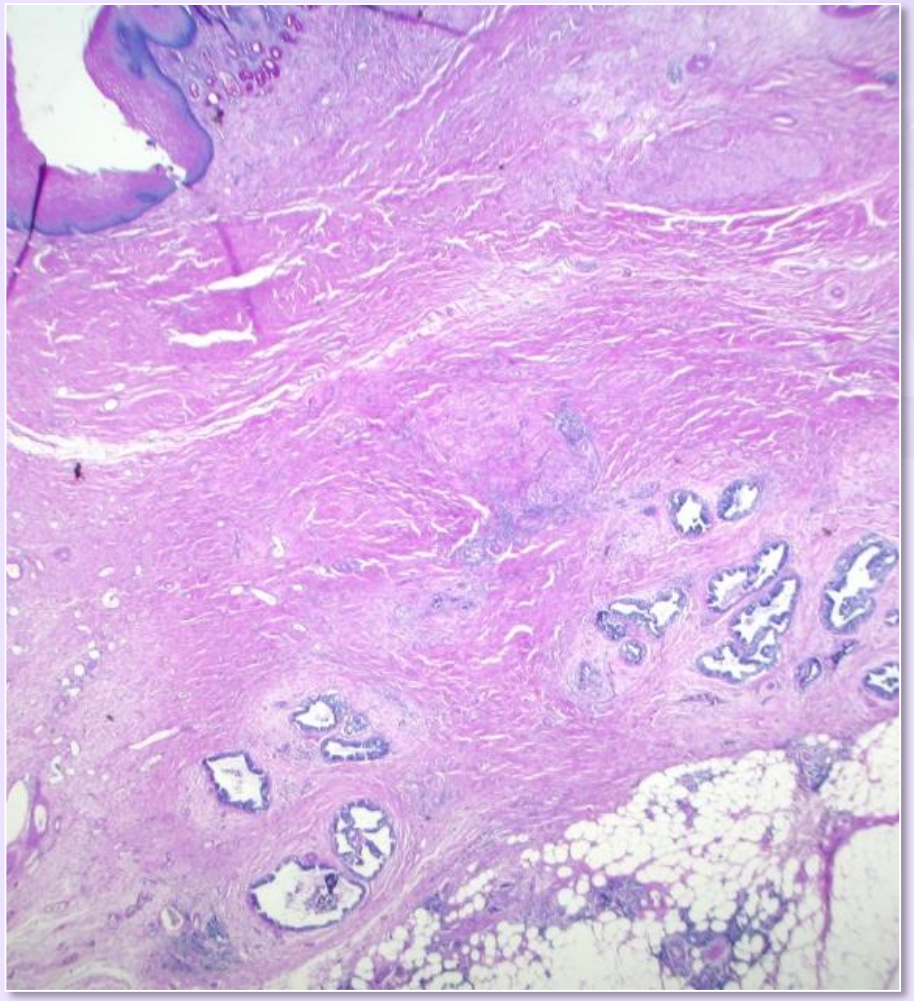
Outline

- Histopathology of tumor regression
- Work up of resection specimens
- Concepts of tumor regression grading
- Examples
- Critical issues
  - Interobserver variability
  - Prognostic value
- Lymph node metastases
- Future directions

Morphological changes after Treatment - Macroscopy



Morphological changes after Treatment - Histology



time

tissue level

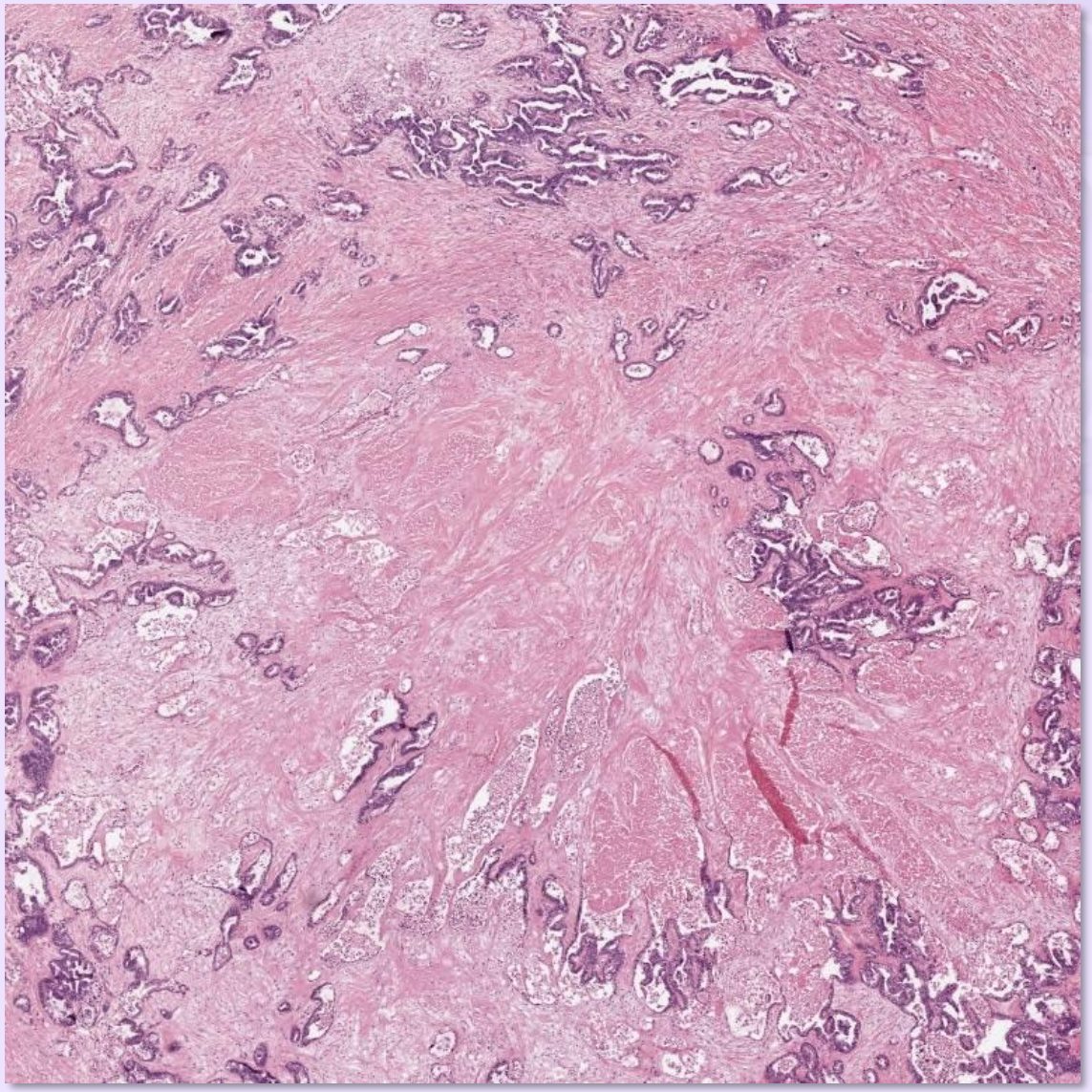
Necrosis

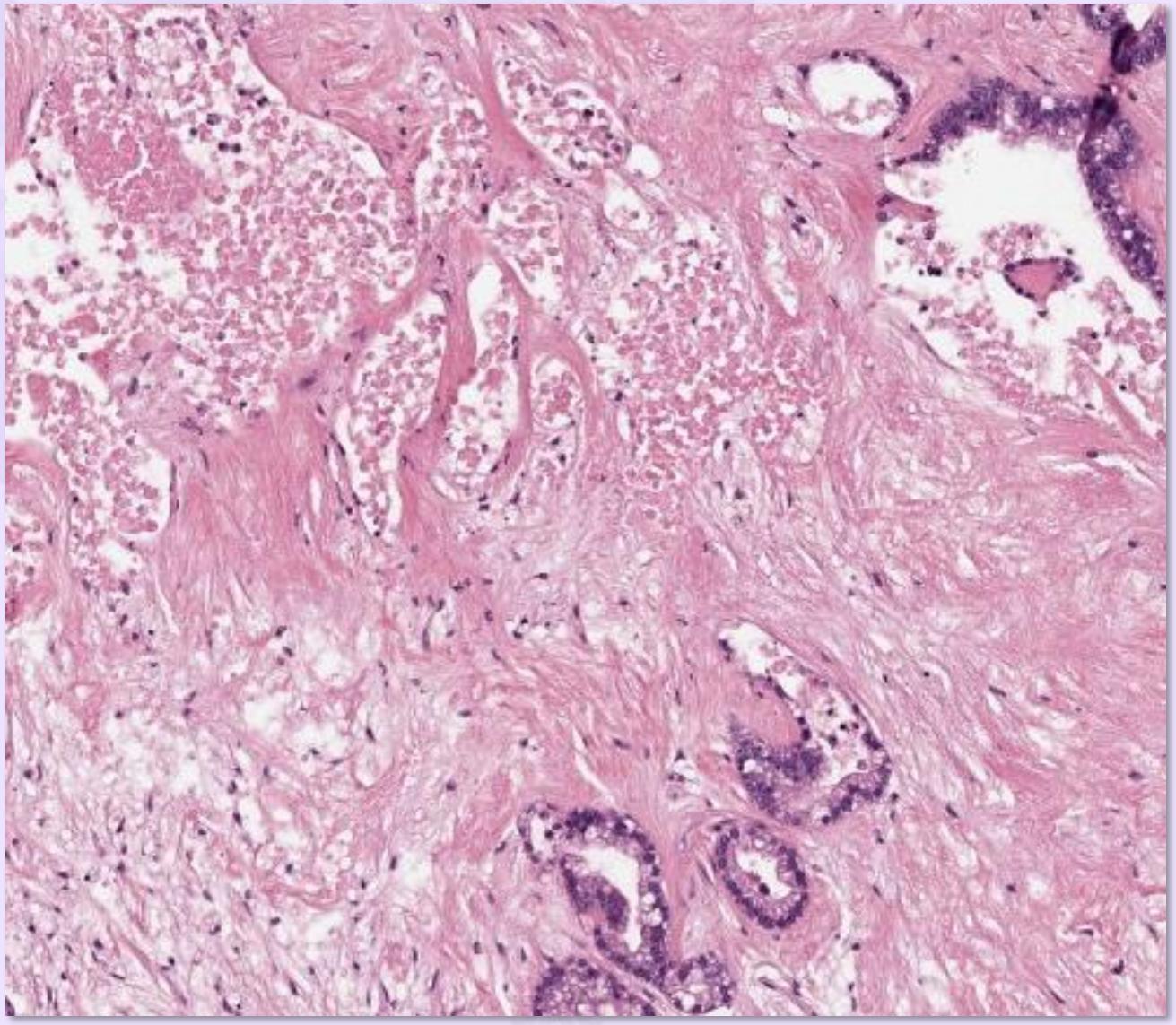
Inflammation

- Granulation tissue
- Resorbtion
- (histiocytic reaction, cholesterol deposits, foreign body reaction..)
- Calcification
- Acellular mucin

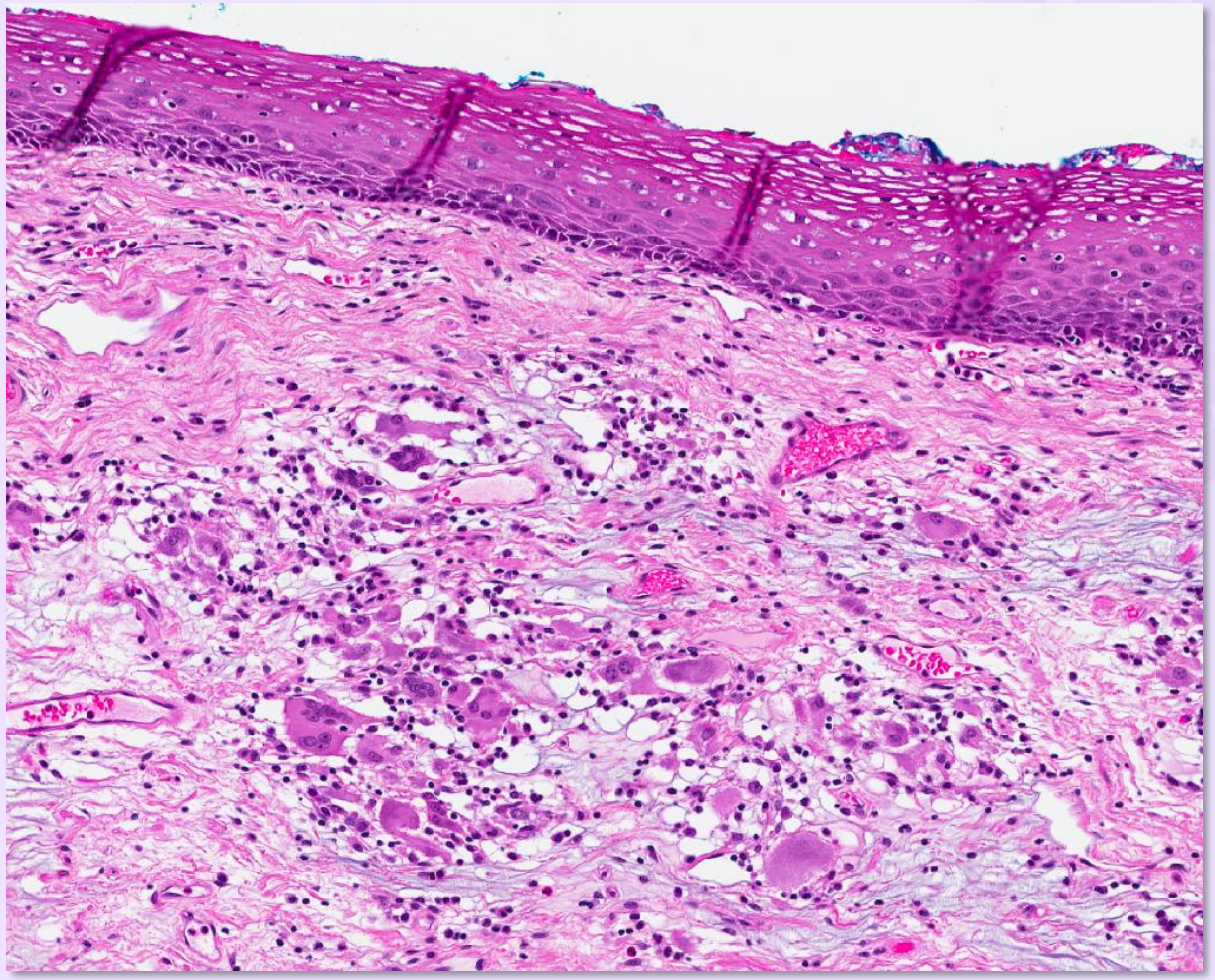
Scarring, fibrosis

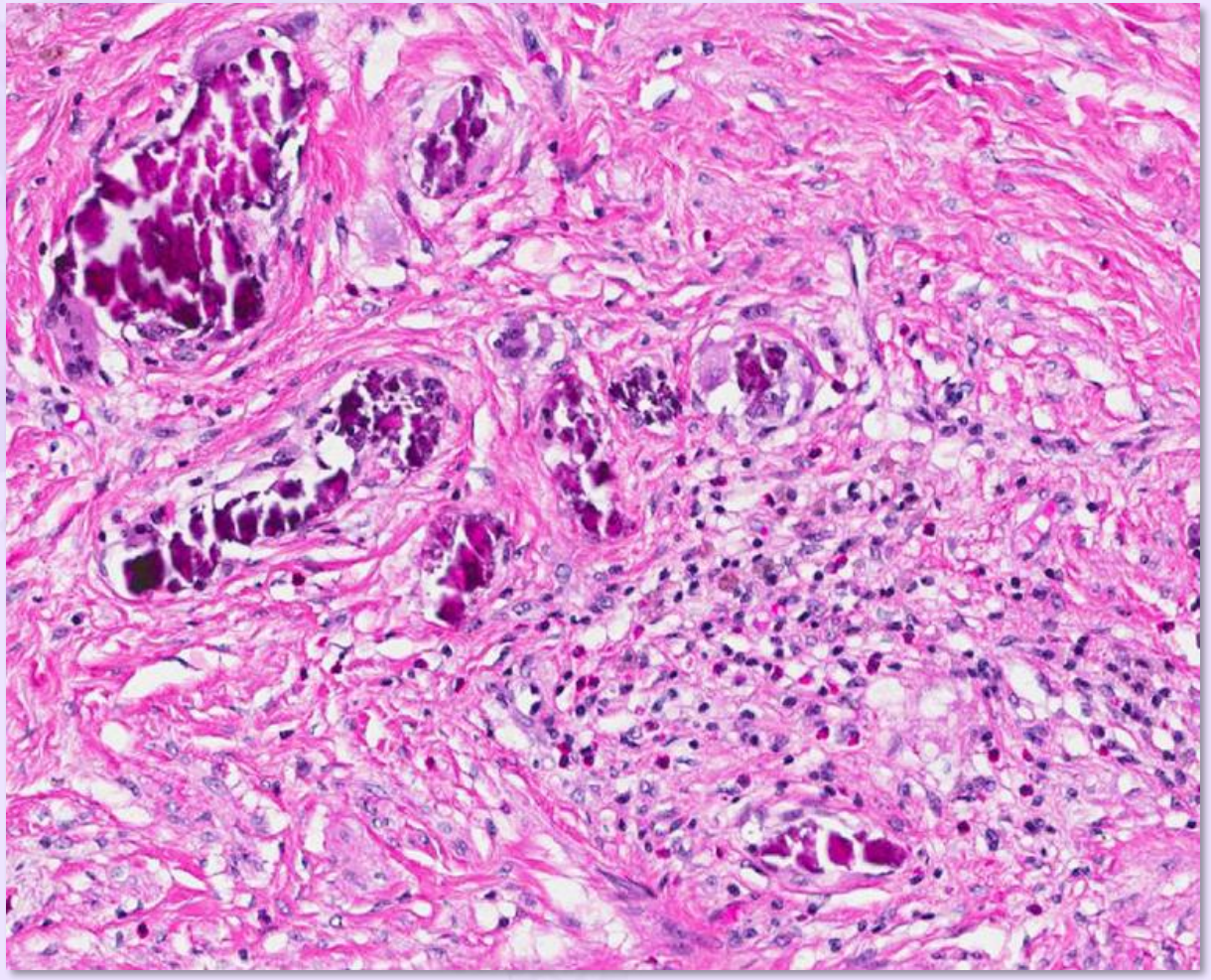
Necrosis and Fibrosis



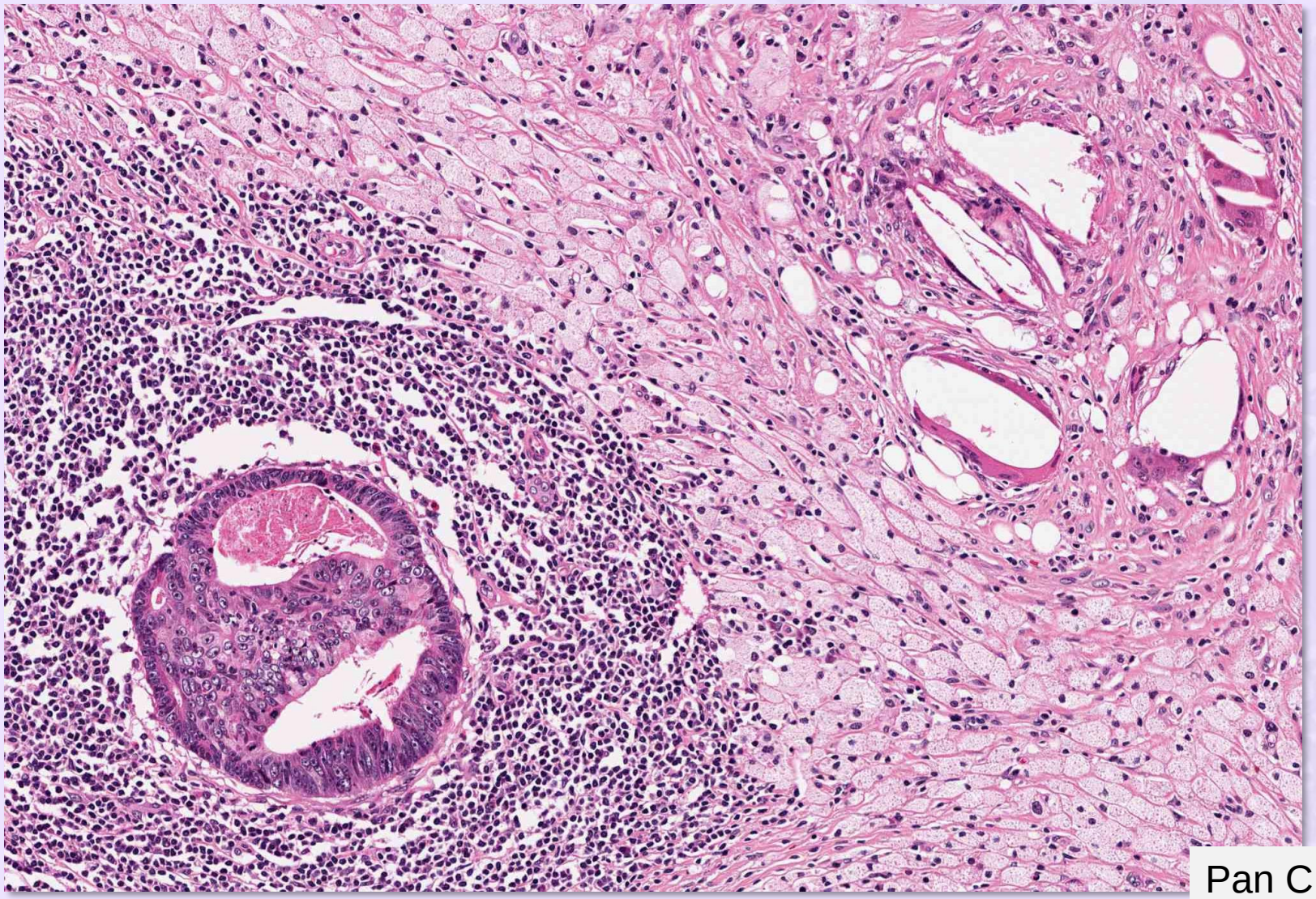


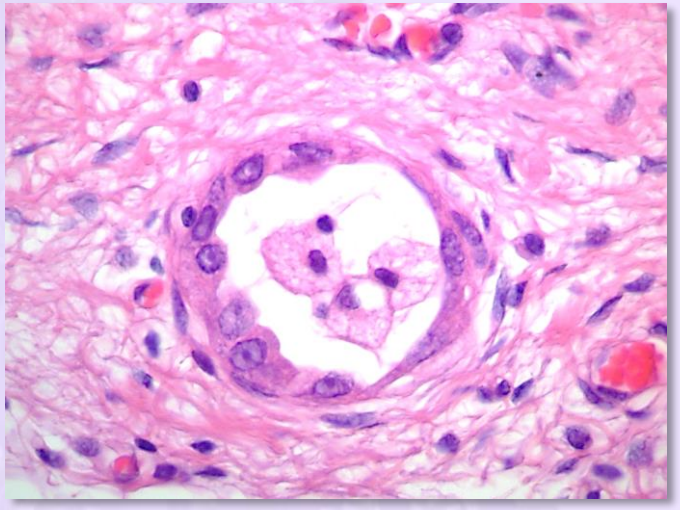
Resorbtion, foreign body reaction, hemorrhage, calcification

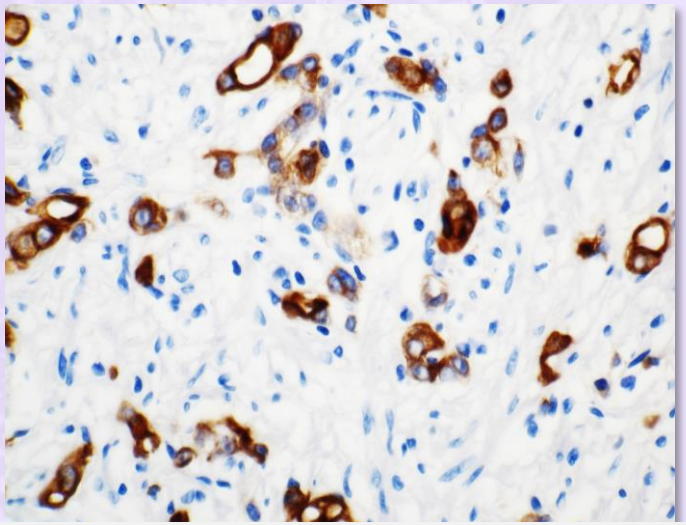




Foamy histiocytes, cholesterol clefts

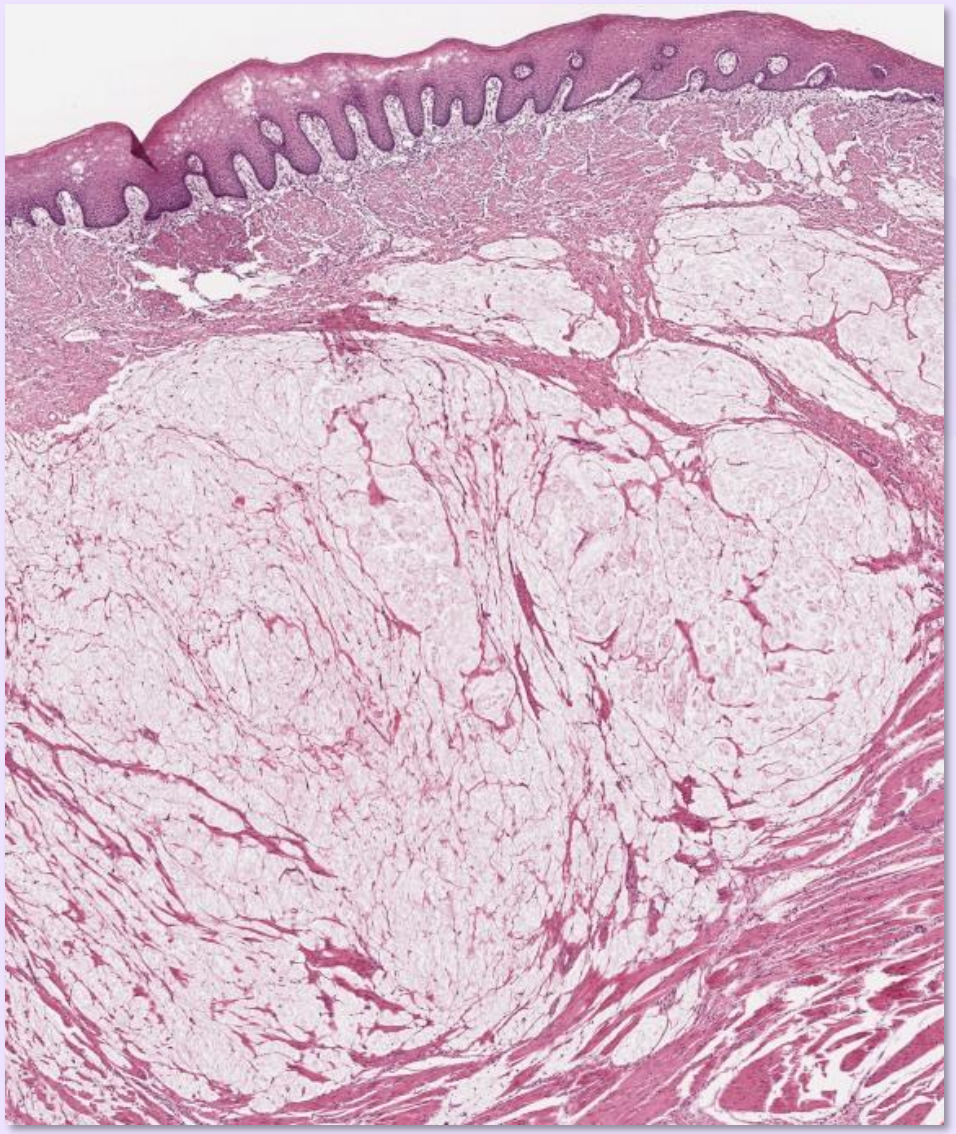


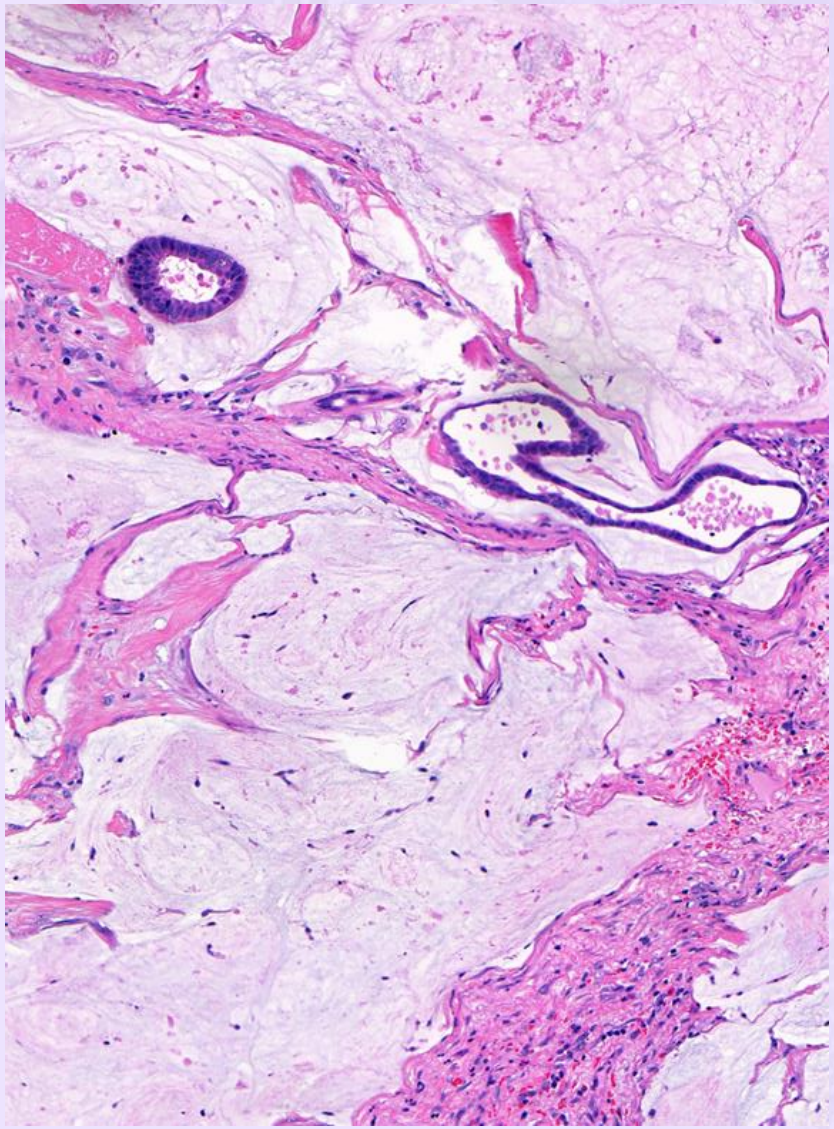


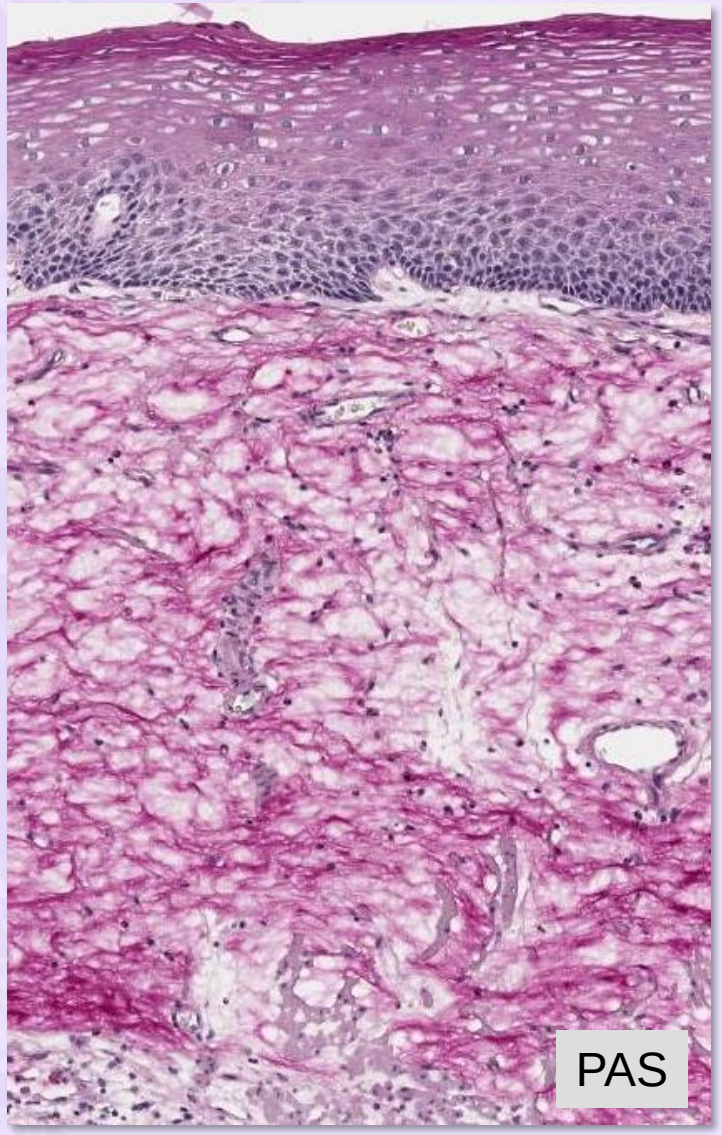


Pan CK for highlighting carcinoma cells

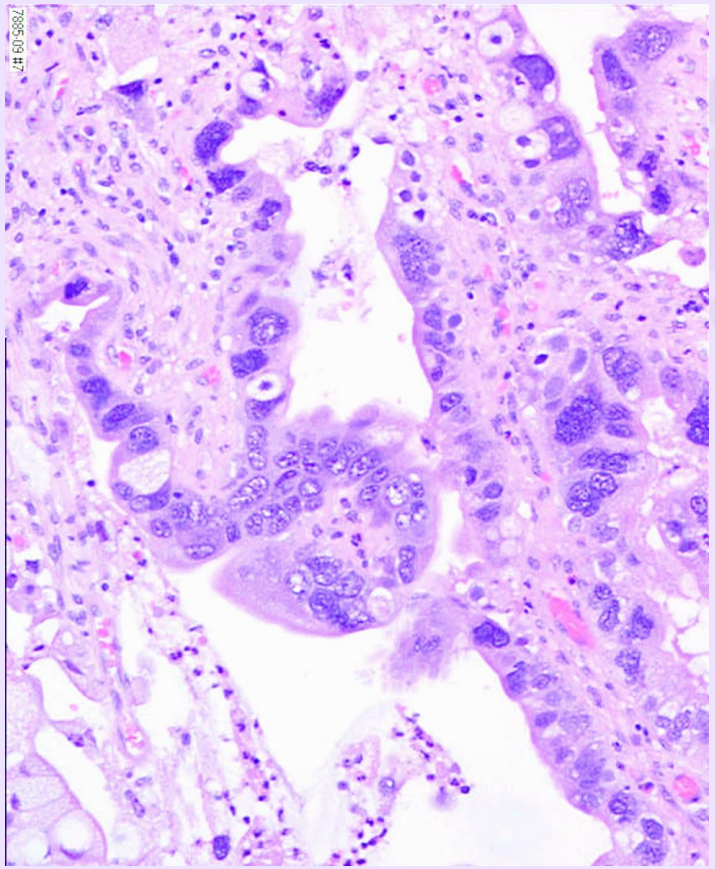
Pauci or acellular mucin (Adenocarcinomas)

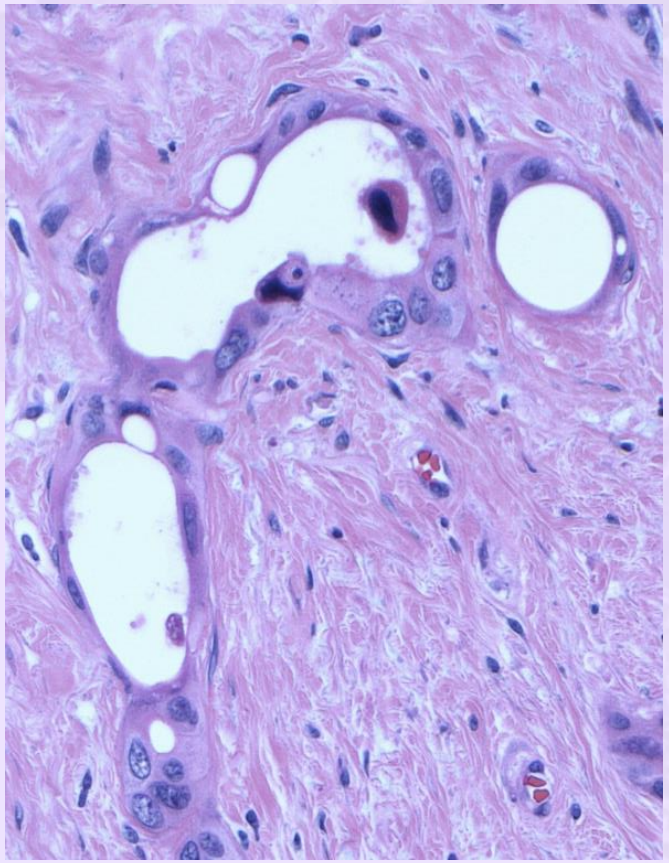






Morphological changes after Treatment - Histology

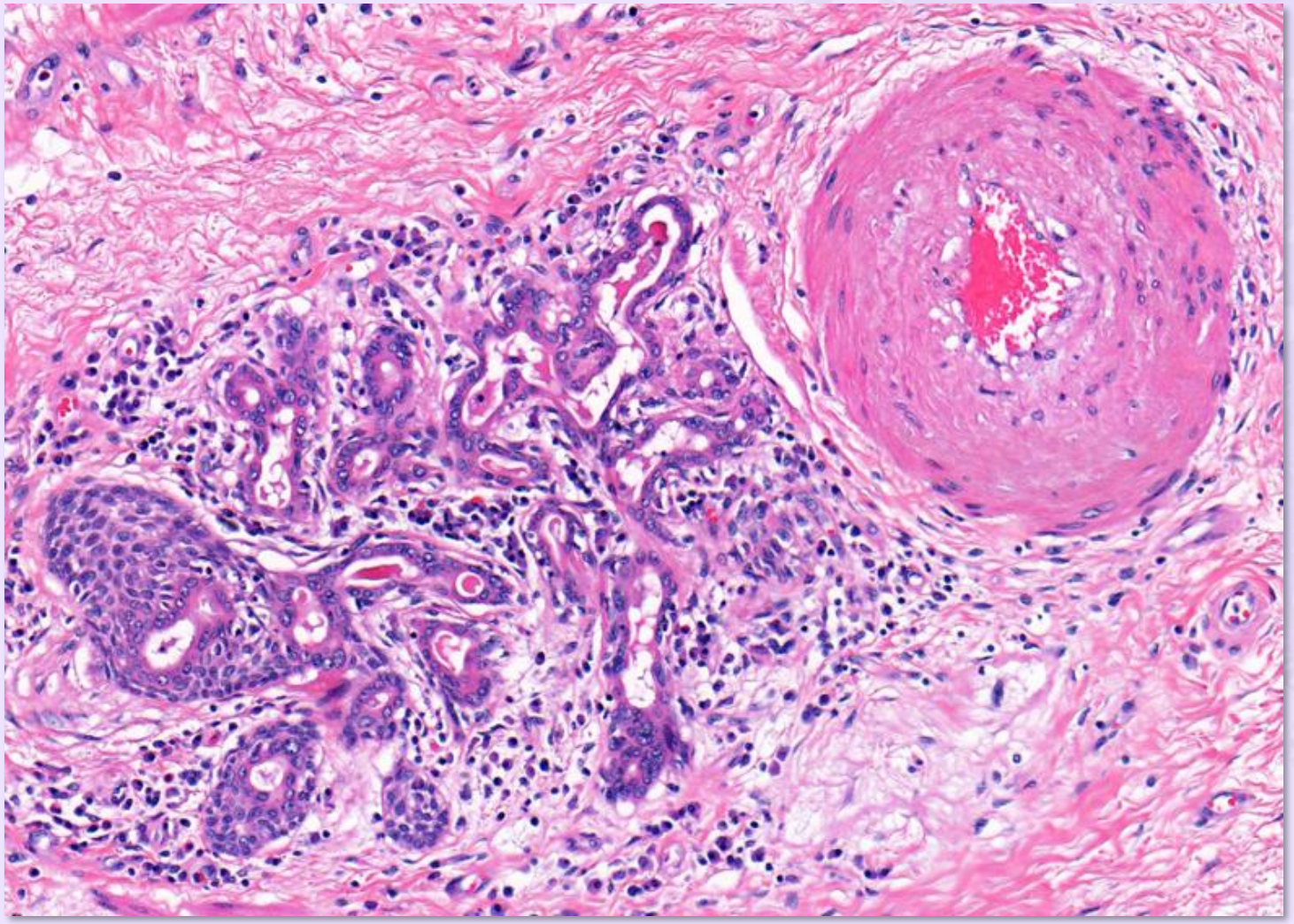


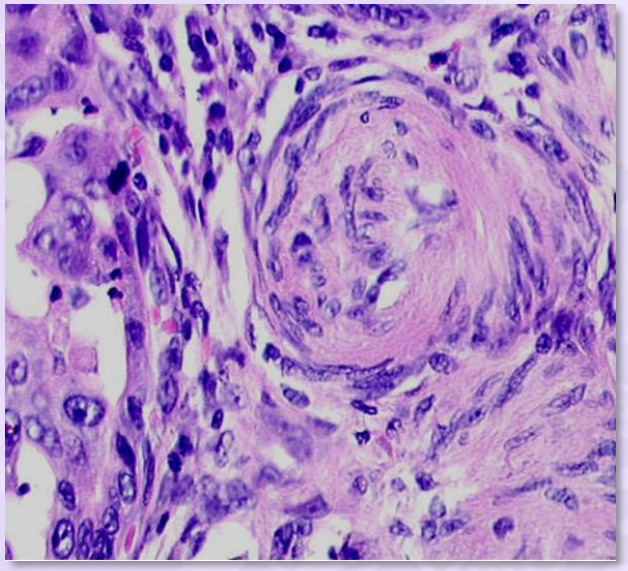


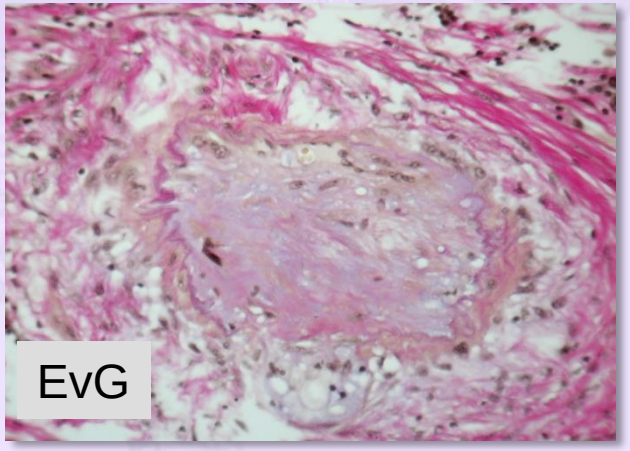
Cellular level

Increase of nuclear size
Cytoplasmic vacuolisation
Cytoplasmic eosinophily
Giant cells
Cytopathic atypia
Nuclear pyknosis
Karyorrhexis
Increase of nucleoli (size and number)
Apoptoses

Morphological Changes after Treatment non-neoplastic tissue – vessels and glands







Specific changes?

- Foamy histiocytes
- Acellular mucus
- Central fibrosis (but not fibrosis in general)
- Vascular changes
- Extramural vascular changes

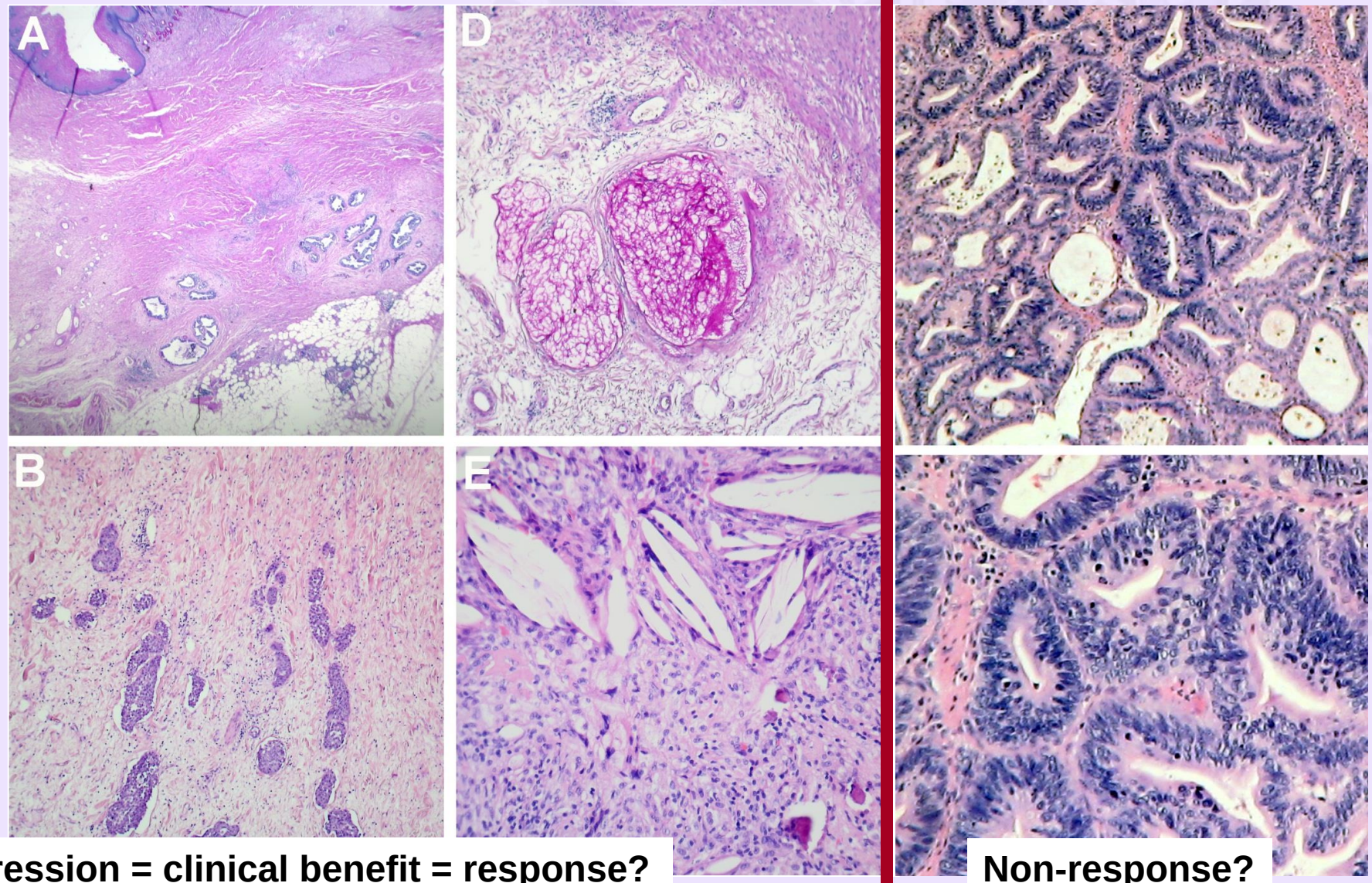
Becker et al., 2003 Specificity treatment-induced changes

Comparison of Histologic Findings in Gastric Carcinomas Treated by Surgery Alone (n = 36) and Gastric carcinoma after Preoperation Chemotherapy

Characteristic	Surgery alone (%)	After chemotherapy (%)
Primary tumor		
Ulcer	83.3	83.3
Mucosal edema	5.6	8.3
Inflammation	25	22.2
Foamy histiocytes	8.3	36.1
Cholesterol granulomata	8.3	8.3
Hemorrhage	38.9	19.4
Necrosis	38.9	33.3
Acellular mucus	2.8	16.7
Fibrosis	52.8	66.7
Central fibrosis	—	19.4
Vascular changes[a]	27.8	66.7
Extramural vascular changes[a]	—	27.8
Cytology		
Condensed, enlarged nuclei	61.1	72.2
Giant cells	44.4	36.1
Multinucleated cells	50	25
Nuclear inclusions	27.8	25
Apoptotic foci	63.9	33.3
Lymph node metastases		
Necrosis	22.2	27.8
Hemorrhage	22.2	5.6
Foamy histiocytes	2.8	14.9
Fibrosis	61.1	66.7
Nodular fibrosis, hyalinosis	—	19.4

[a] Intimal proliferation, inflammation, endanglitis obliterans, thrombotic occlusion with organization.

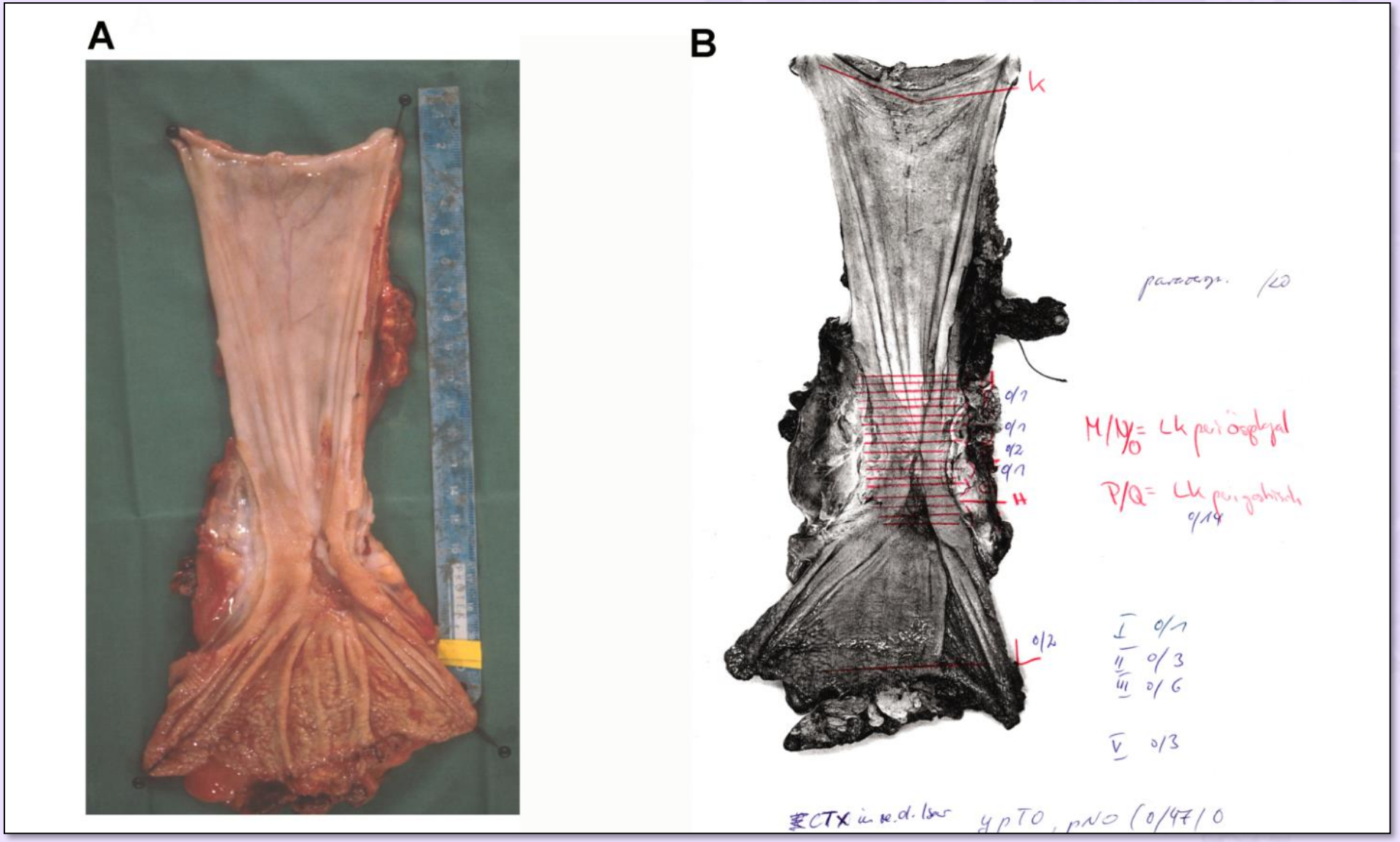
Clinical Significance of tumor regression?

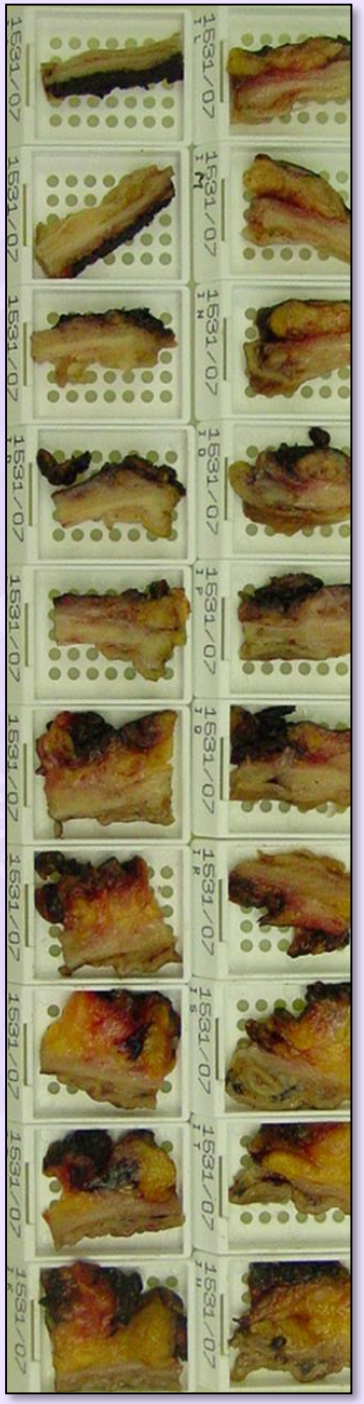


Regression = clinical benefit = response?

Non-response?

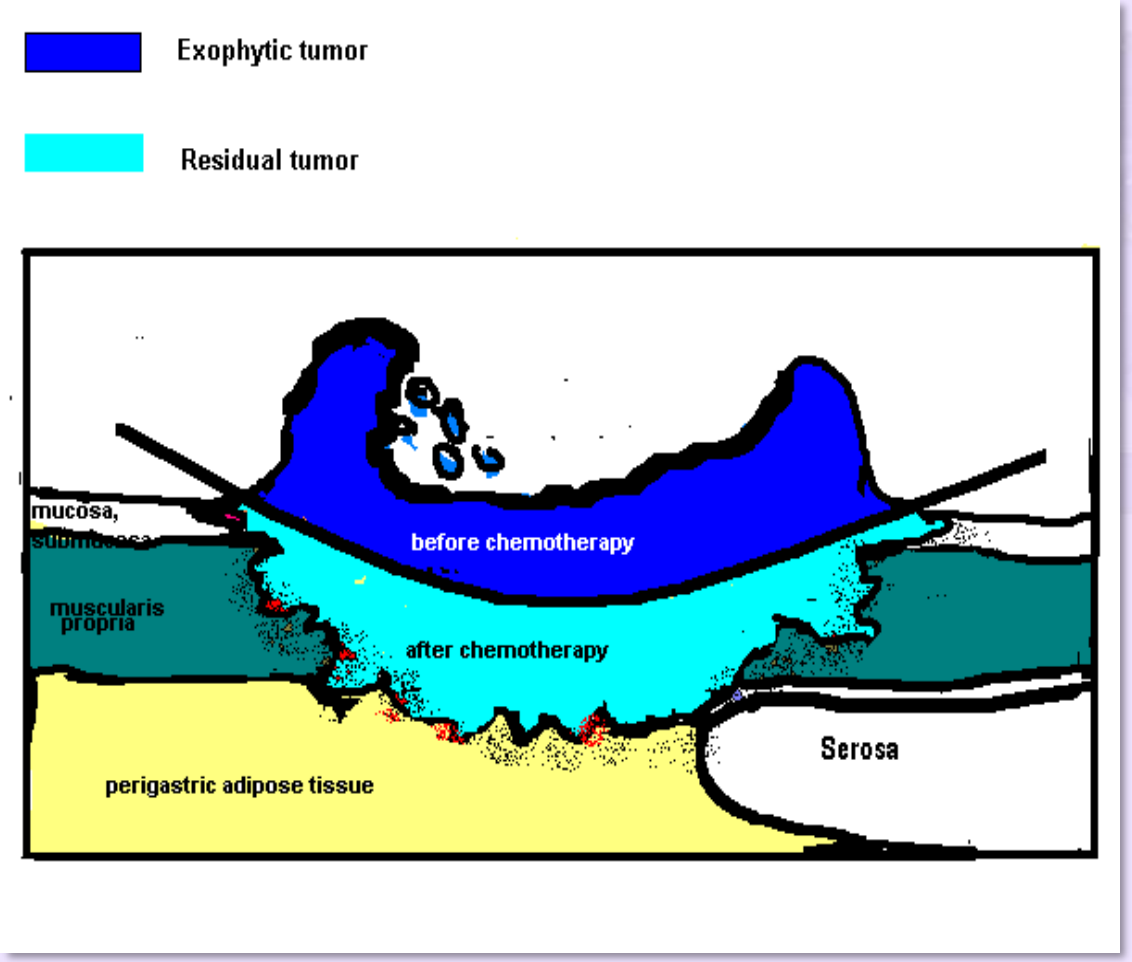
Grossing (e.g. Esophagus)

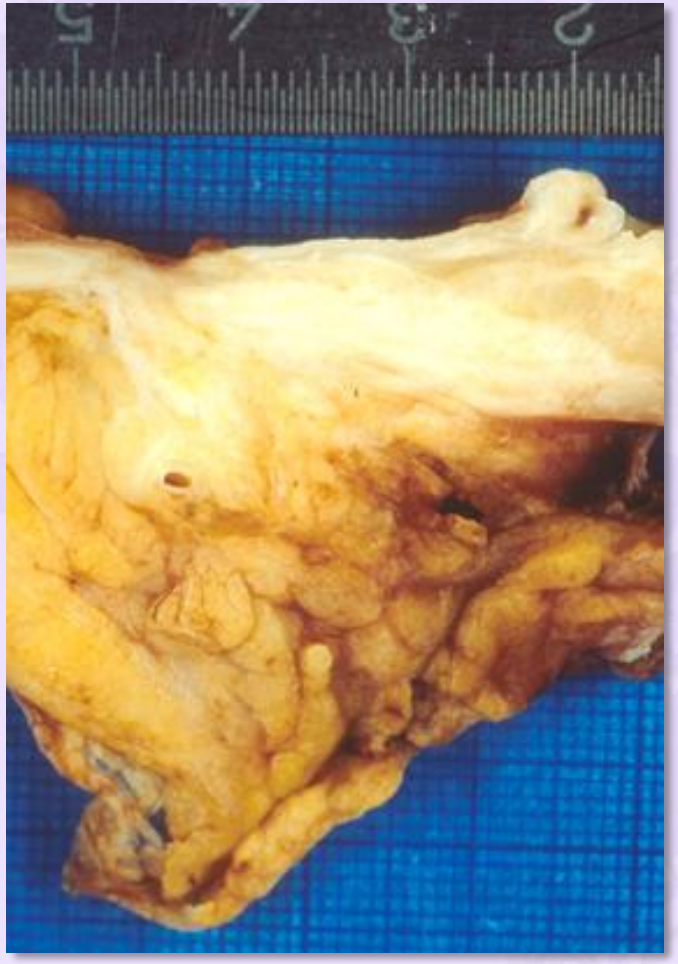


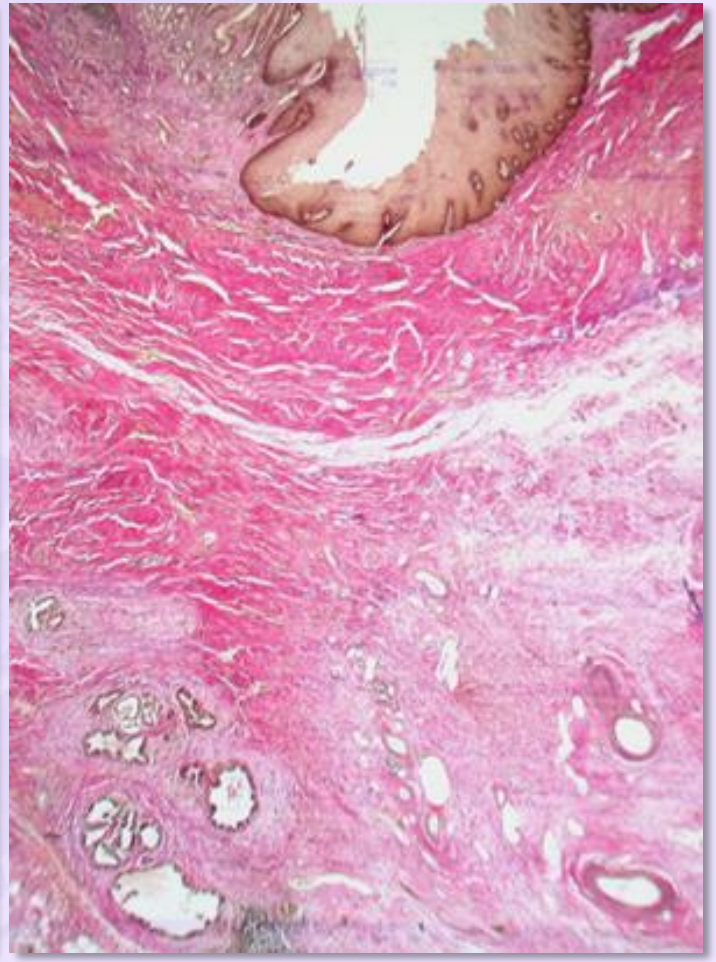


Becker et al., Cancer 2003; Langer et al, Mod Pathol 2009

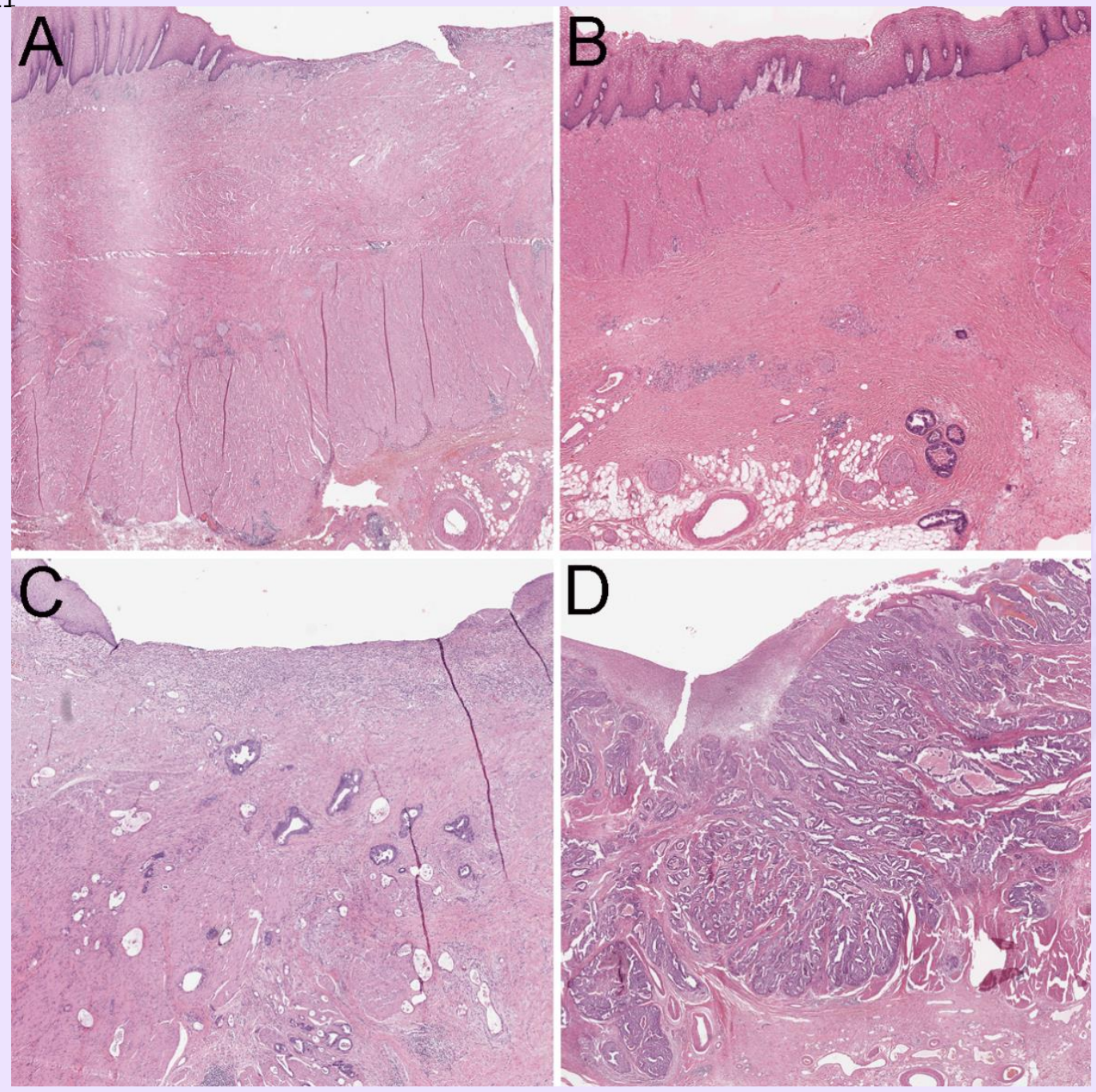
Centrifugal Pattern of Tumor Regression







Images courtesy Karen Becker



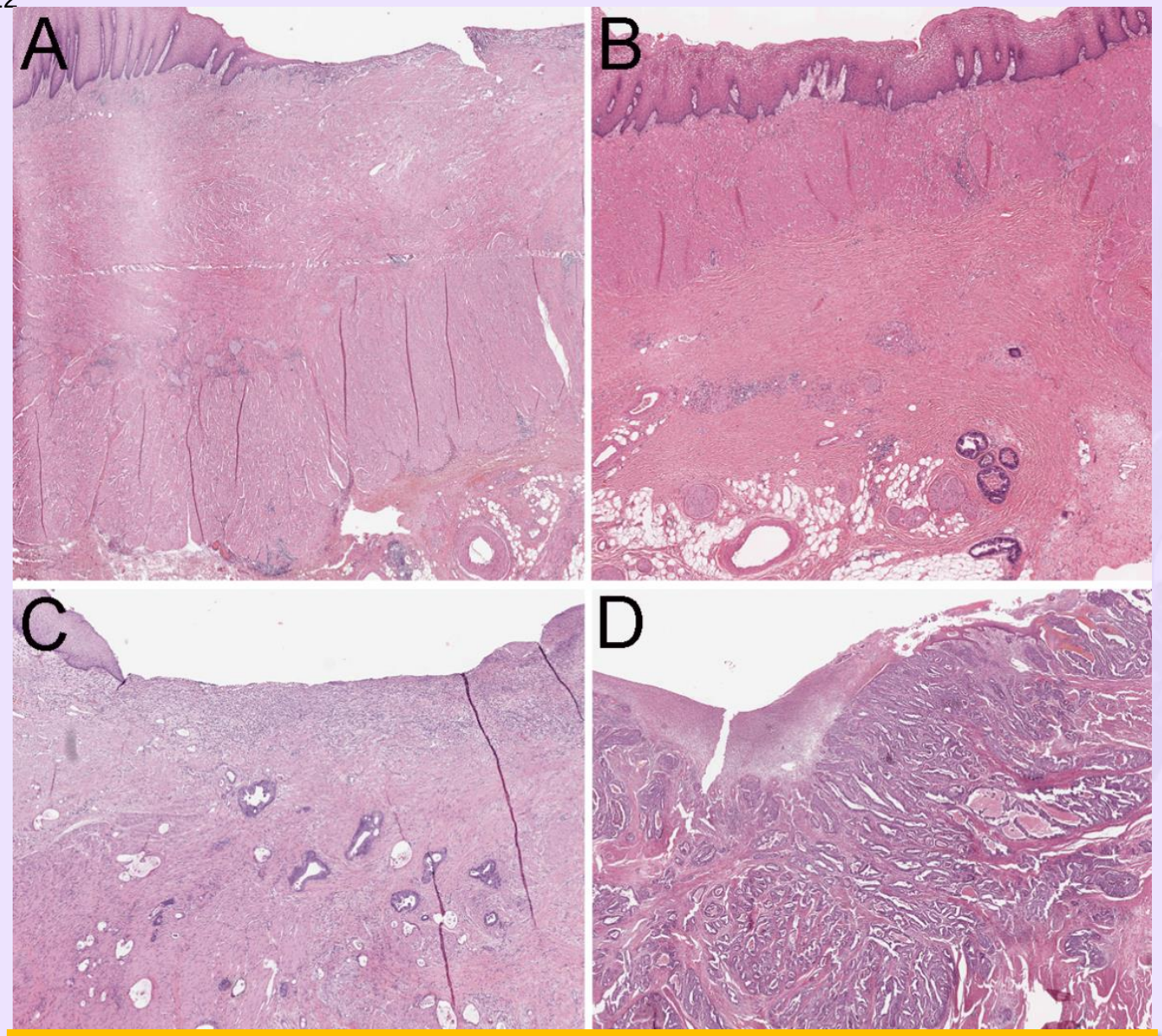
Histology and Grading of Tumor Regression

A complete

B subtotal

C partial

D no regression



Histology and Grading of Tumor Regression

A complete

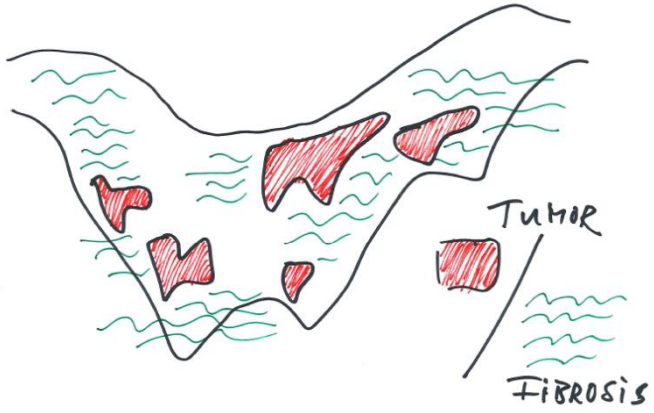
B subtotal

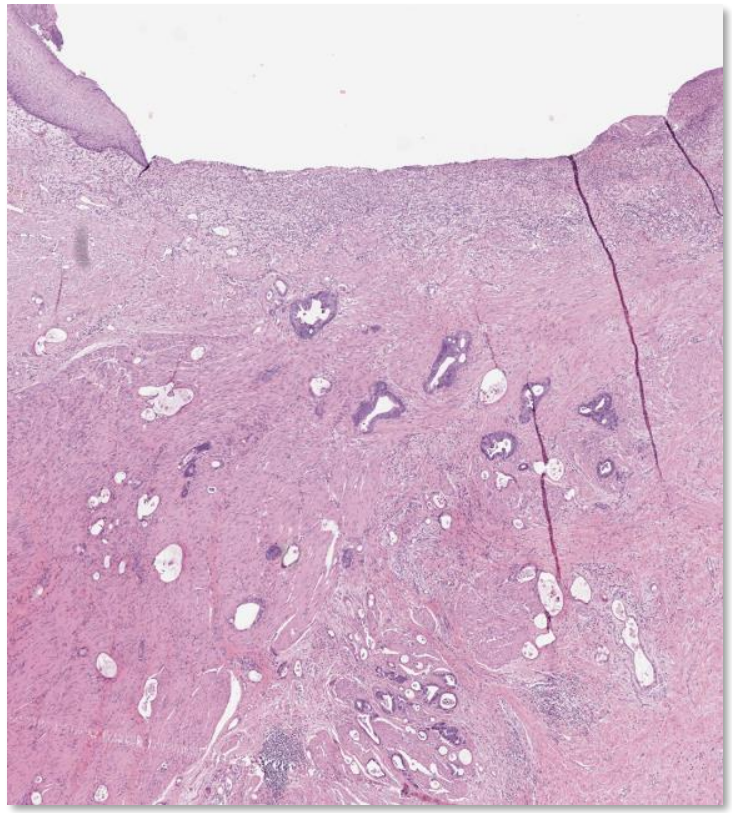
C partial

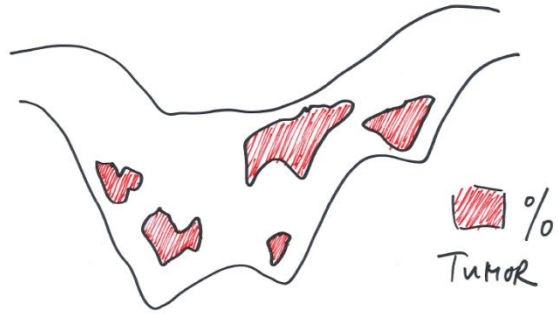
D no regression

Basing on which parameter?

Parameters for the Determination of Tumor Regression







Residual tumor vs. Fibrosis

Residual tumor in % or descriptive

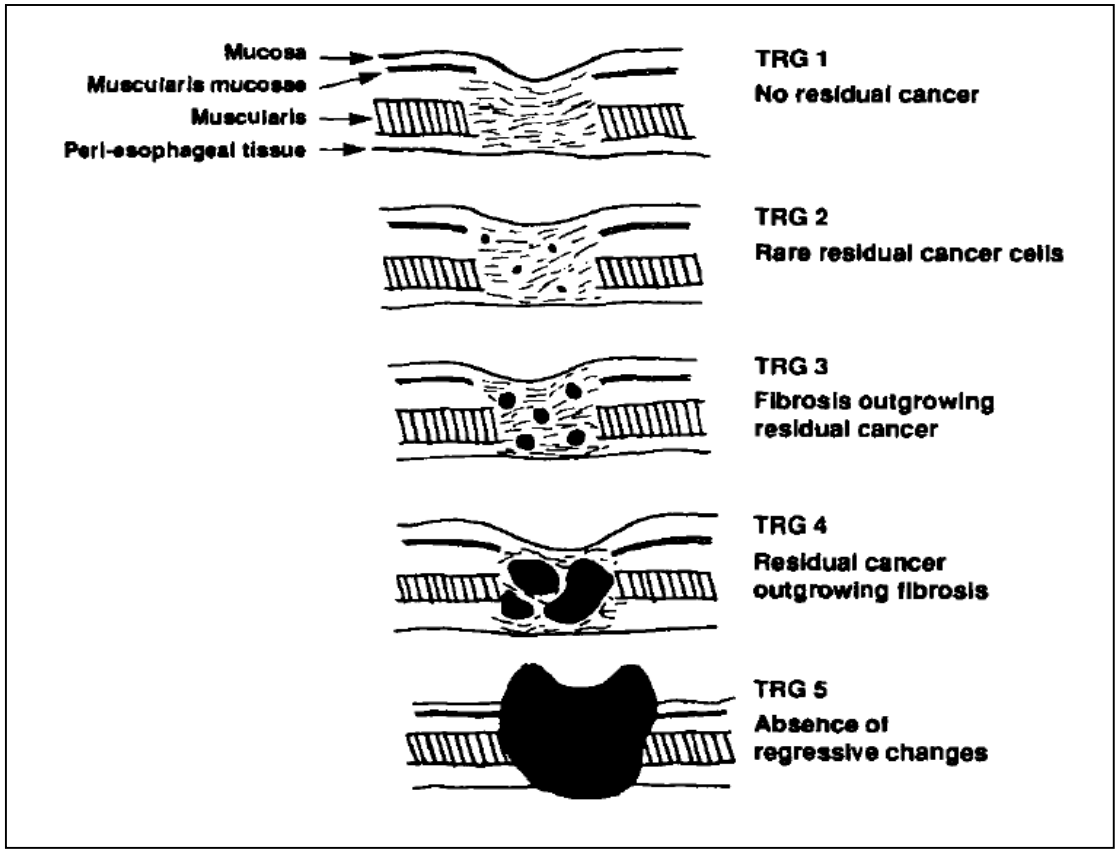
Mandard Classification

SCC Esophagus after RCTX
residual tumor/fibrosis

Pathologic Assessment of Tumor Regression after Preoperative Chemoradiotherapy of Esophageal Carcinoma

Clinicopathologic Correlations

Anne-Marie Mandard, M.D., Frédéric Dalibard, M.D.,†*
Jean-Claude Mandard, M.D.,† Jacques Marnay, M.A., Michel Henry-Amar, M.D.,‡*
Jean-François Petiot, Ph.D.,§ Alain Roussel, M.D.,‖ Jacques-Henry Jacob, M.D.,¶
*Philippe Segol, M.D.,# Guy Samama, M.D.,# Jean-Marie Ollivier, M.D.,***
Sylvie Bonvalot, M.D.,# and Marc Gignoux, M.D.#



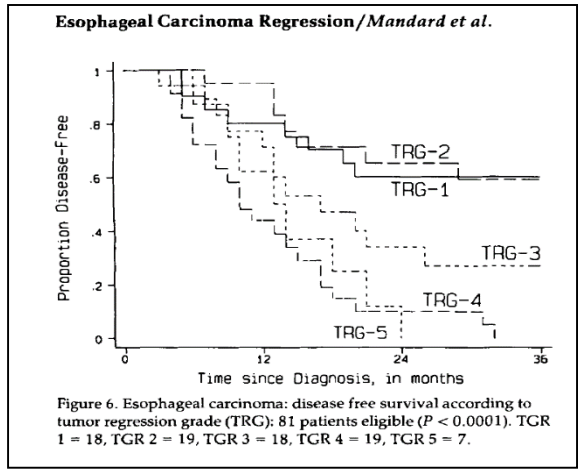
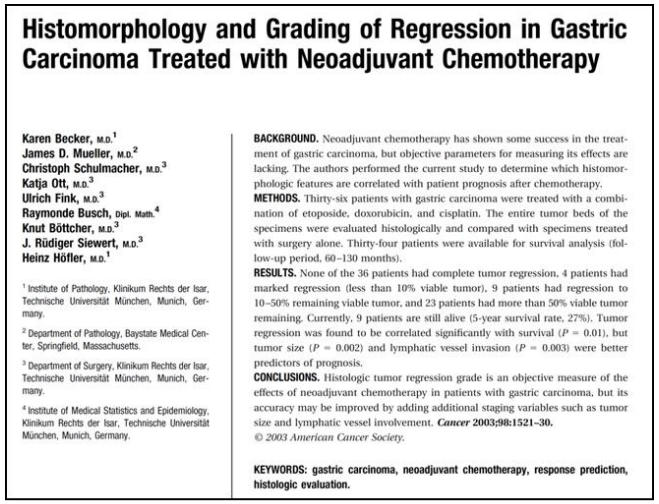


Figure 6. Esophageal carcinoma: disease free survival according to tumor regression grade (TRG): 81 patients eligible ($P < 0.0001$). TGR 1 = 18, TGR 2 = 19, TGR 3 = 18, TGR 4 = 19, TGR 5 = 7.

We have described the gross and histologic features of tumor regression seen after preoperative chemoradiotherapy in 93 cases of esophageal carcinoma. This regression was assessed by comparing the proportion of residual carcinoma to scarring, and our results were found to correlate with patients' survival. The preliminary assessment was performed using a tumor regression grading of five grades. Multivariate analysis showed two groups of tumor regression grade that were prognostically relevant: Grades 1, 2, and 3 versus Grades 4 and 5.



Histomorphology and Grading of Regression in Gastric Carcinoma Treated with Neoadjuvant Chemotherapy

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Christoph Schulmacher, M.D.[3]
Katja Ott, M.D.[3]
Ulrich Fink, M.D.[3]
Raymonde Busch, Dipl. Math.[4]
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[4] Institute of Medical Statistics and Epidemiology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany.

BACKGROUND. Neoadjuvant chemotherapy has shown some success in the treatment of gastric carcinoma, but objective parameters for measuring its effects are lacking. The authors performed the current study to determine which histomorphologic features are correlated with patient prognosis after chemotherapy.

METHODS. Thirty-six patients with gastric carcinoma were treated with a combination of etoposide, doxorubicin, and cisplatin. The entire tumor beds of the specimens were evaluated histologically and compared with specimens treated with surgery alone. Thirty-four patients were available for survival analysis (follow-up period, 60–130 months).

RESULTS. None of the 36 patients had complete tumor regression, 4 patients had marked regression (less than 10% viable tumor), 9 patients had regression to 10–50% remaining viable tumor, and 23 patients had more than 50% viable tumor remaining. Currently, 9 patients are still alive (5-year survival rate, 27%). Tumor regression was found to be correlated significantly with survival ($P = 0.01$), but tumor size ($P = 0.002$) and lymphatic vessel invasion ($P = 0.003$) were better predictors of prognosis.

CONCLUSIONS. Histologic tumor regression grade is an objective measure of the effects of neoadjuvant chemotherapy in patients with gastric carcinoma, but its accuracy may be improved by adding additional staging variables such as tumor size and lymphatic vessel involvement. ***Cancer* 2003;98:1521–30.**

KEYWORDS: gastric carcinoma, neoadjuvant chemotherapy, response prediction, histologic evaluation.

Becker Classification

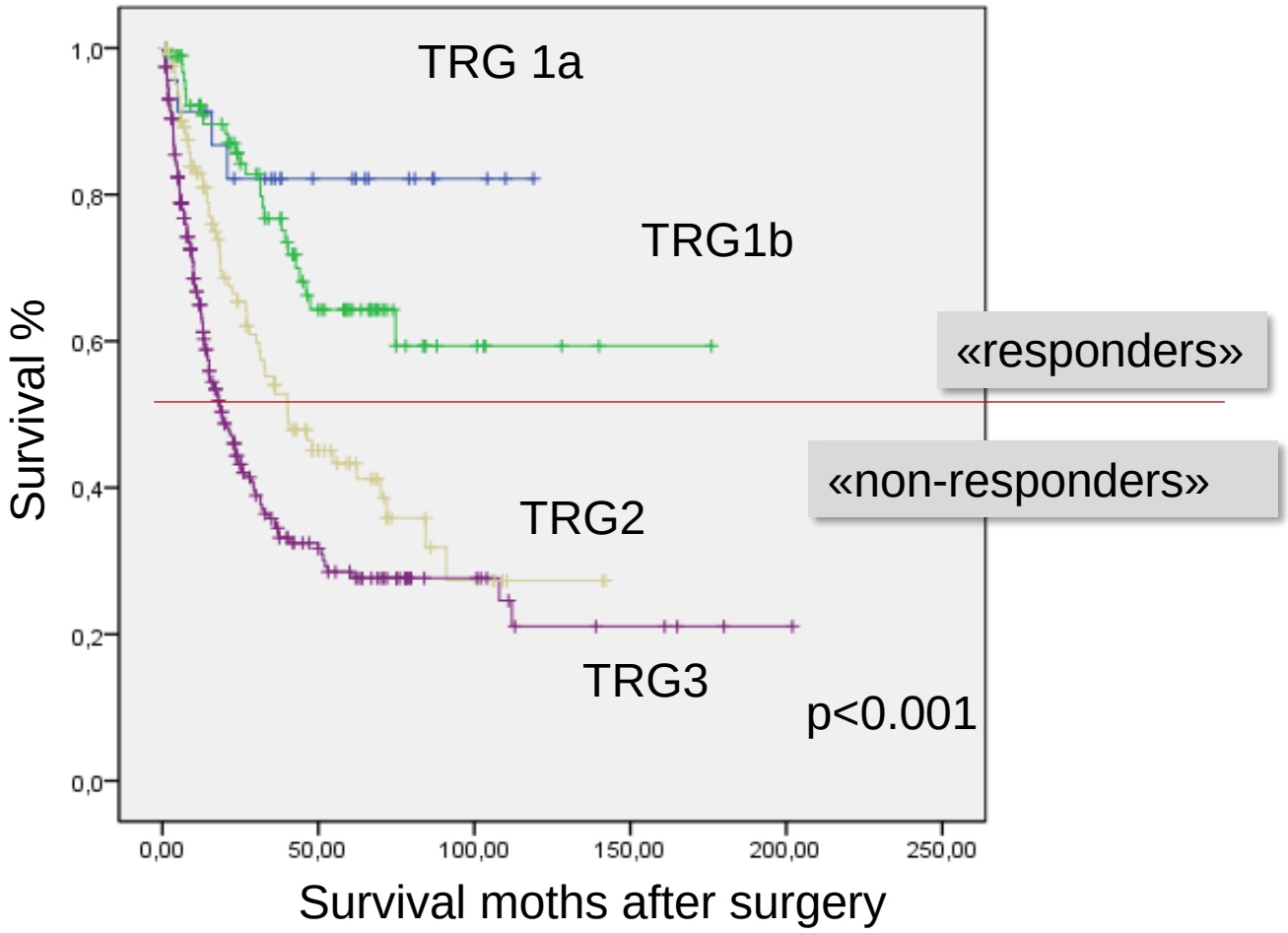
Gastric Adenocarcinoma after nCTX
residual tumor/tumorbed %

Tumor Regression Grade (TRG)	Description
1a	No residual tumor/tumor bed + chemotherapy effect*
1b	< 10% residual tumor/tumor bed + chemotherapy effect*
2	10-50% residual tumor/tumor bed + chemotherapy effect*
3	> 50% residual tumor/tumor bed + / - chemotherapy effect*

Comment:

- TRG according to Baldus/Schneider («Cologne-System»): same cut-offs, but inverse grading.
- Same as MD Anderson System (Chireac/Wu);
- also mentioned in Textbooks (e.g. WHO)

Becker Tumor Regression Grading and Survival
580 Gastroesophageal Adenocarcinomas after nCTX



Variable	HR	95,0% CI for HR		p-value
		min	*max*	
ypT Cat	1,211	,994	1,476	,057
ypN Cat	1,597	1,118	2,280	,010
LVI	1,328	1,019	1,731	,036
Grading	1,315	1,013	1,708	,040
R status	1,320	1,056	1,651	,015
TRG	1,377	1,129	1,679	**,002**

Becker et al. 2011, Langer et al 2009

Gastric Cancer
DOI 10.1007/s10120-014-0401-z

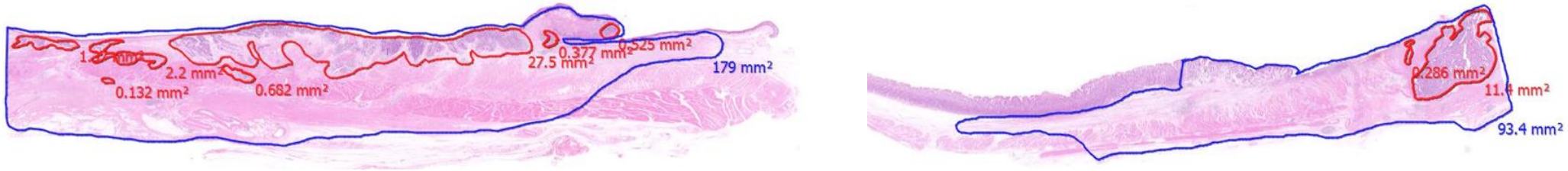
ORIGINAL ARTICLE

Determination of the optimal cutoff percentage of residual tumors to define the pathological response rate for gastric cancer treated with preoperative therapy (JCOG1004-A)

Kenichi Nakamura · Takeshi Kuwata · Tadakazu Shimoda · Junki Mizusawa · Hiroshi Katayama · Ryoji Kushima · Hirokazu Taniguchi · Takeshi Sano · Mitsuru Sasako · Haruhiko Fukuda

Japanese/Asian Classifications: cutoffs 33% - 66%

- Morphometric study using 0%, 1–10 %, 11–33 %, 34–50 %, 51–66 %, and 67–100 % residual tumors



- Conclusions: “the 10 % cutoff should be the global standard cutoff of % residual tumor to determine TRG in GC”

(may not apply for linitis pl./diffuse type GC)

Rectal Cancer: two more players

Ryan «original»

Table 1. Tumour regression grade

Five-point TRG	Description	Three-point TRG
1	No viable cancer cells	1
2	Single cells or small groups of cancer cells	
3	Residual cancer outgrown by fibrosis	2
4	Significant fibrosis outgrown by cancer	3
5	No fibrosis with extensive residual cancer	

Histopathology

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Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer

R Ryan, D Gibbons, J M P Hyland, D Treanor, A White, H E Mulcahy, D P O'Donoghue, M Moriarty, D Fennelly, K Sheahan

First published: 25 July 2005 Full publication history

Dworak

Table 1.
Dworak Regression Grading Classification for the Rectal Cancer Underwent Preoperative Therapy

Grade regression 4	No tumor cells, only fibrotic mass (total regression or response)
Grade regression 3	Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance
Grade regression 2	Dominantly fibrotic changes with few tumor cells or groups (easy to find)
Grade regression 1	Dominant tumor mass with obvious fibrosis and/or vasculopathy
Grade regression 0	No regression

CAP-Protocols

esophagus / rectum

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

Called **“modified Ryan”,** recommended for esophagus and rectum, which explicetely does not exclude the usage of other TRG systems (e.g. MD Anderson/Becker)

AJCC

- No residual tumor cells
- Single cell or small group of cells
- Residual cancer with desmoplastic response
- Minimal evidence of tumor response

gastric cancer

Description	TRG
No viable cancer cells (complete response)	0
cells or small groups er cells (Moderate response)	1
al cancer outgrown by fibrosis al response)	2
l or no tumor kill; ve residual cancer esponse)	3

Referring to **Ryan et al.** recommended for gastric cancer, which explicetly does not exclude the usage of other TRG systems (e.g. Memoriam Sloan Kettering Cancer Center)

ORIGINAL CONTRIBUTION

American Joint Committee on Cancer and College of American Pathologists Regression Grade: A New Prognostic Factor in Rectal Cancer

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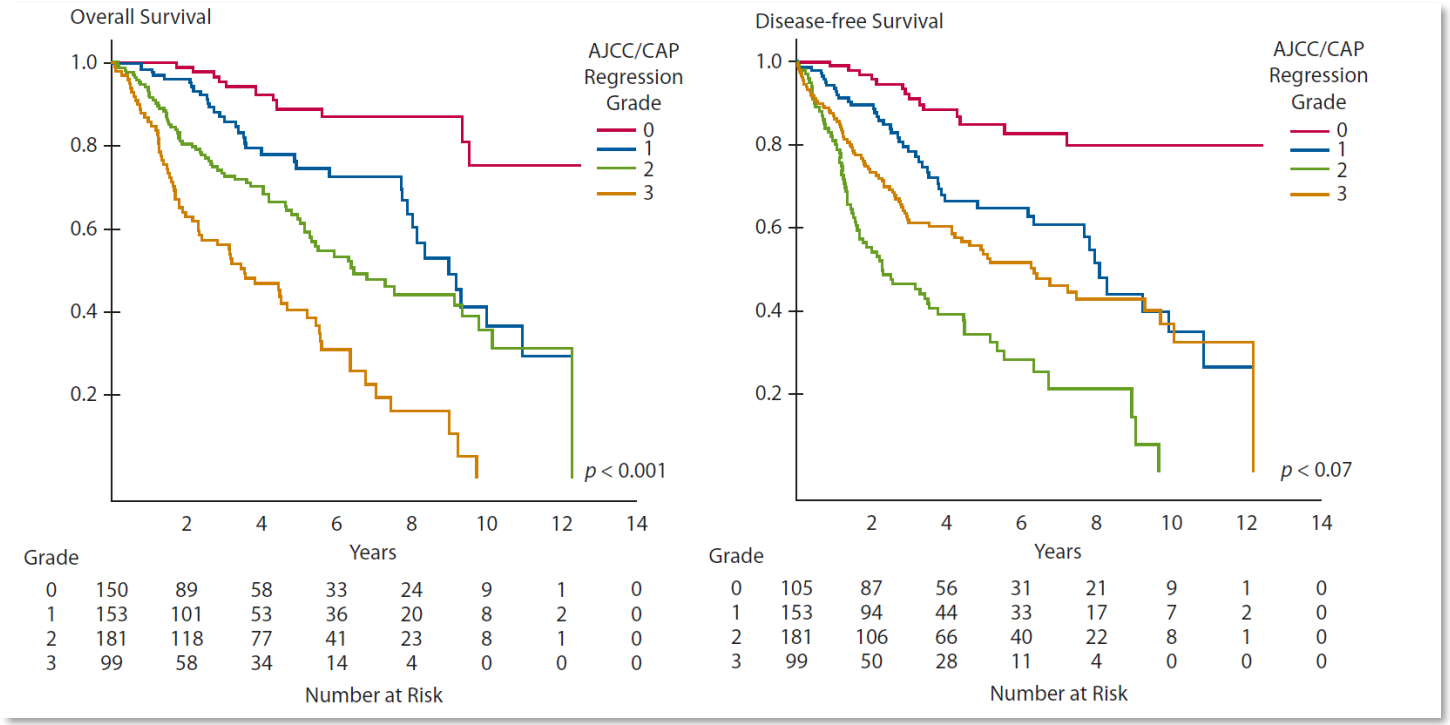
N=583

Grade 0 (complete response)	105 (19.5%)
Grade 1 (subtotal)	153 (28.4%)
Grade 2 (partial)	181 (33.6%)
Grade 3 (no response)	99 (18.4%)

“After adjusting for significant covariates, including pathologic stage, AJCC/CAP grade remained an independent predictor of overall survival ($p < 0.001$), disease-free survival ($p < 0.001$), and cumulative recurrence ($p < 0.001$) in Cox regression analyses».



TRG in Meta-Analyses and Clinical Trials

- ***Esophagus***

- Cunningham et al. 2017 (UK STO3); 1063pts. p<0.0001*
- Alderson et al. 2017 (UK OE05); 897pts; p=0.028; p<0.0001*
- Noble et al. 2017 (Multicenter Study), 1392 pts. p<0.001*

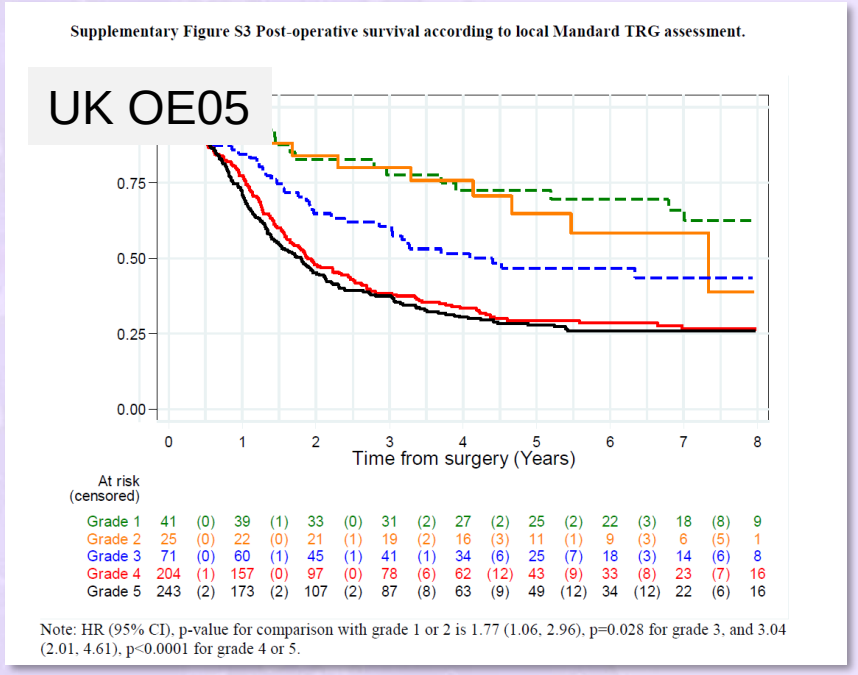
- ***Stomach***

- Smyth et al. (MAGIC); 330 pts. p=0.02*
- Al-Batran et al. (FLOT-AIO) 2016; 300pts. p<0.001**
- Tomassello et al. 2017 (Meta-A; 17 studies; 3145 pts.), p<0.0001
- Spoerl et al. (AIO, Multicenter); 461pts. p=0.031 (intestinal T)**

- ***Rectum***

- Fokas et al. 2017, (CAO/ARO/AIO), 1179 pts. p<0.001***
- Kim et al. 2017 (single center), 933 pts. p<0.001***,****

*Mandard ** Becker ***Dworak ****AJCC



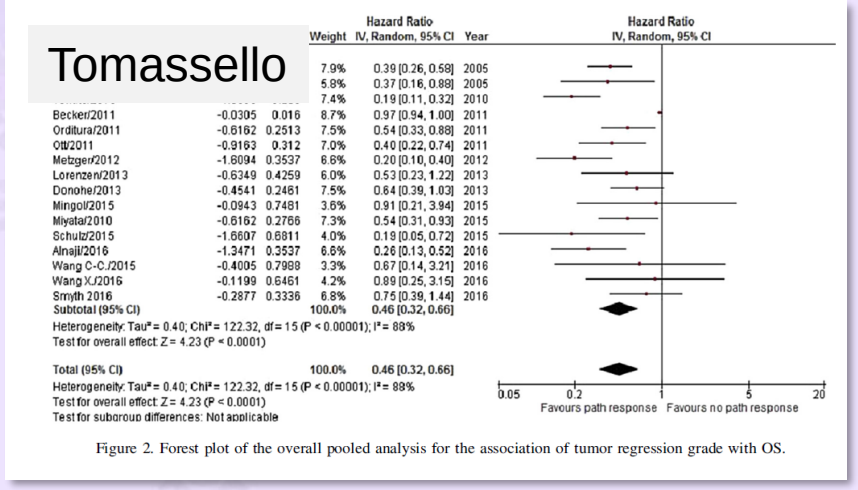


Figure 2. Forest plot of the overall pooled analysis for the association of tumor regression grade with OS.

Which TRG System should we use?

Which TRG System should we use?

- Interobserver Variability

"Interobserver agreement was excellent for extent of residual carcinoma (κ=0.84) and was good for ypT stage (κ=0.71). Agreement was excellent for all categories of residual carcinoma: P0 (κ=0.87), P1 (κ=0.81), and P2 (κ=0.85)". *Wu et al. Am J Surg Path 2007: 3tiered system (% "modified Becker")*

"There was 94.3% concordance between pathologists as regards TRG/staging."
Fareed et al, Histopathology 2009: Mandard

- Prognostic significance

Large number of studies show prognostic value but use different TRG systems and different cut-offs for "response"

- One TRG for all GI carcinomas?

no constant application of TRGs in case studies and clinical trials

Human Pathology (2012) xx, xxx–xxx

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

Human PATHOLOGY
www.elsevier.com/locate/humpath

- 17 participants
- Mandard, Dworak, modified rectal cancer TRG (UK)
- 10 representative slides of rectal cancer after nRCTX

Table 3 Participant grading using the 3 grading systems

Case	Scoring systems												
	Mandard					Dworak					m-RCRG		
	1	2	3	4	5	0	1	2	3	4	1	2	3
1	0	1	5	9[a]	2	1	13[a]	2	1	0	0	6	11[a]
2	6	11[a]	0	0	0	0	0	0	12[a]	5	17[a]	0	0
3	0	2	13[a]	2	0	0	0	0	12[a]	5	2	14[a]	1
4	5	9[a]	3	0	0	0	0	3	9	5	12	5	0
5	6	10[a]	1	0	0	0	0	1	11	5	14	3	0
6	1	4	12[a]	0	0	0	0	13	4	0	6	10	1
7	0	1	0	10[a]	6	6	10[a]	1	0	0	1	1	15
8	5	12[a]	0	0	0	0	0	0	13[a]	4	13	3[a]	1
9	1	6	10[a]	0	0	0	0	13[a]	4	0	10	6[a]	1
10	6	11[a]	0	0	0	0	0	0	12[a]	5	13	4[a]	0

[a] Study standard grading for each case.

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 *P* value	<.001	<.001	<.001
Overall % agreement between all observers	0%	0%	10% (1 case)

In conclusion, 17 GI pathologists could not reach good concordance on regression grading using 3 systems, 2 of which are used widely in practice and also recommended in several publications on regression. This was attributed to lack of clarity or specificity in the criteria that make up existing systems and their subsequent interpretation.

Chetty et al. 2012, Wu et al., 2007, Trakarnsanga et al., 2014

- Disappointing results – very bad concordance
- unanimous agreement in only one case in one TRG system (case 2)
- Other studies, however, show a **good reproducibility of TRGs** when comparing one or more TRG systems of the same concept:
- in **esophageal carcinomas kappa values of 0.71** (MD Anderson/ Becker system) or **0.84** (simplified three-tiered MD Anderson/Becker system), or in **rectal cancers** concordance indices of **0.65** (Dworak system), **0.665** (simplified three-tiered Mandard system) and **0.69** (AJCC system)

Critical Issues of Tumor Regression Grading

Subjectivity
lack of accuracy

An issue with the Dworak system was interpretation of "difficult to find microscopically" and "easy to find," which are used to distinguish grade 3 from grade 2 regression. It is assumed that "difficult to find" means tumor cells found only after assiduous high-power search.

Insufficient clarity
Subjectivity

In the study herein, interpretation of the criteria within each grade of the 3 scoring systems was a source of discrepancy. *Mandard grade 2* is defined as the "presence of rare residual cancer cells" and *grade 3* as "an increase in the number of cancer cells, but predominantly fibrosis." There is insufficient clarity how to separate these 2 categories. Terms such as *rare* and *an increase in the number* are subjective,

Definition of fibrosis
- Therapy associated
- Higher importance of the amount of residual tumor?

We recommend that regression-associated fibrosis should defined as fibrosis that is intimately associated with 1 or more of the following histologic features: pools of mucin (with or without tumor cells), necrosis, foamy macrophages, cholesterol clefts, foreign body giant cells, or foci/islands of residual tumor embedded within areas of fibrosis.

Although regression change is important, the amount of residual tumor is probably more important because this influences outcome. All participants felt that both regression and residual tumor should be assessed.

Chetty et al. 2012

Comparison Fibrosis/Tumor relation vs. %:
Mandard vs. Becker

Am J Surg Pathol • Volume 38, Number 11, November 2014

ORIGINAL ARTICLE

Assessment of Tumor Regression of Esophageal Adenocarcinomas After Neoadjuvant Chemotherapy

Comparison of 2 Commonly Used Scoring Approaches

Eva Karamitopoulou, MD, Svenja Thies, MD,* Inti Zlobec, PhD,* Katja Ott, MD,† Marcus Feith, MD,‡ Julia Slotta-Huspenina, MD,§ Florian Lordick, MD,‖ Karen Becker, MD,§ and Rupert Langer, MD**

.. **interobserver agreement for the Becker system showed better weighted K values compared with the Mandard system** (0.78 vs. 0.62). **Evaluation of the whole embedded tumor site showed improved results** (Becker: 0.83; Mandard: 0.73) as compared with only 1 representative slide (Becker: 0.68; Mandard: 0.71)..

International Scholarly Research Network
ISRN Pathology
Volume 2012, Article ID 519351, 8 pages
doi:10.5402/2012/519351

Clinical Study

Assessment of Histopathological Response in Gastric and Gastro-Oesophageal Junction Adenocarcinoma following Neoadjuvant Chemotherapy: Which Scoring System to Use?

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..There was reasonable interobserver agreement for the grading systems: κ-scores = 0.44 (Mandard), 0.28 (Japanese), and 0.51 (Becker). **Only Mandard and Becker scores provided prognostic information**: 5-year overall survival rates of 100% for complete or near complete responders versus 35% for nonresponders for both…
.. the **Becker system was slightly more reproducible**..

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

Manuscript received September 25, 2013; revised March 27, 2014; accepted July 8, 2014.

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	-	-	-		

…TRG may provide a valuable tool for clinical decision making …The data from Trakarnsanga et al. provide guidance as to which of the TRG systems is most predictive for recurrence following preoperative RCX and surgery for rectal cancer. **Despite the caveats discussed above, the four-tier AJCC TRG system appears to be a good choice**. However, this classification system needs to be prospectively tested on multiple datasets to validate its reproducibility in the broader setting (Editorial by Bruce D Minsky and Claus Rodel)

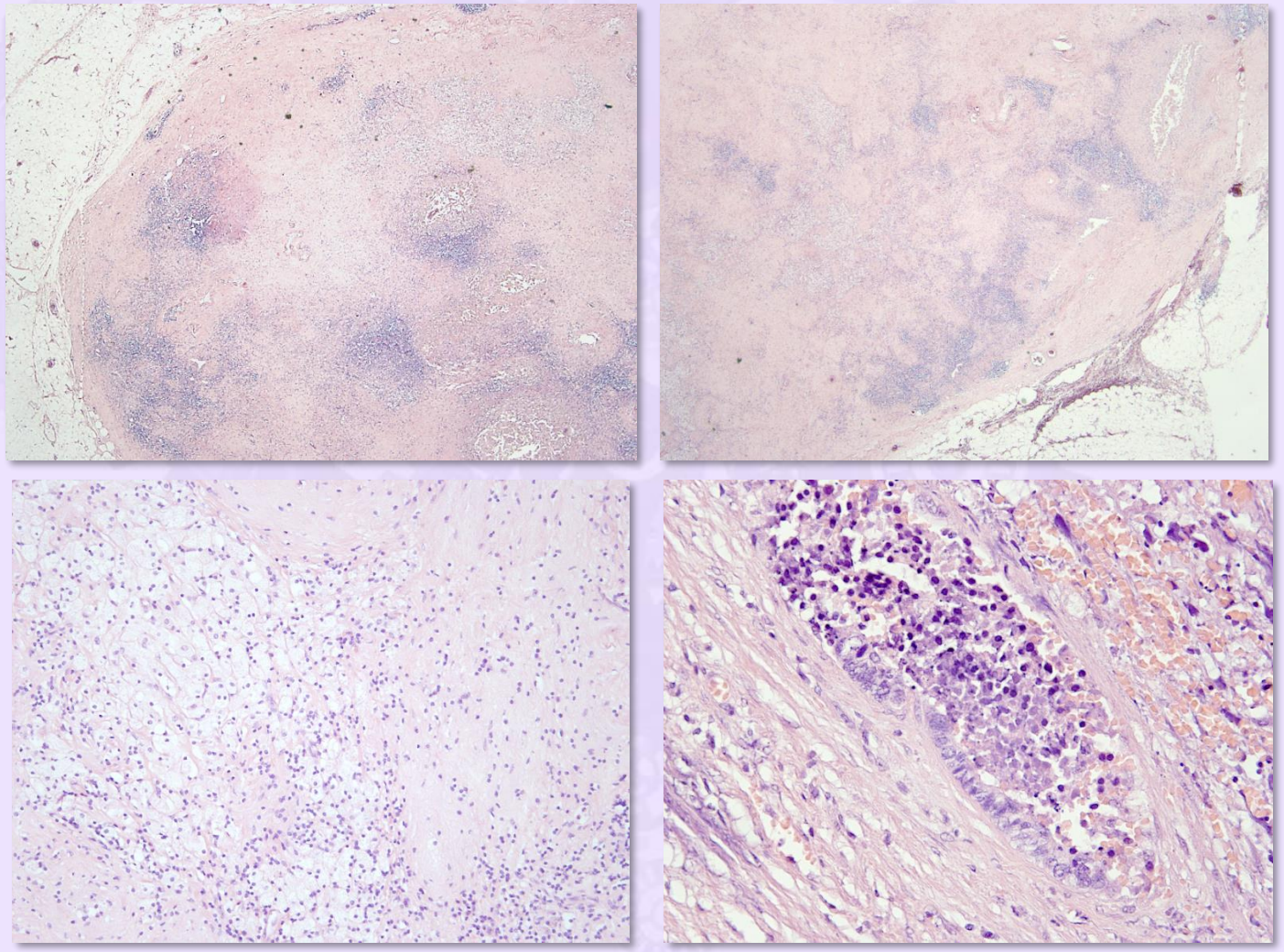
Tumor Regression in Lymph Nodes

ypN0

- Inflammation
- necrosis
- Fibrosis
- Hyalinosis
- Hemosiderin
- Histiocytes
- Cholesterol clefts
- Single (viable?) tumor cells

ypN1

CAVE: in some cases divergent regression behavior between primary tumor site and LN may be observed (i.e. ypT0, L1, N1)



Tumor Regression in Lymph Nodes

- Tumor regression in lymph nodes is a frequent finding
- **Presence of LN metastases strong(est) prognostic parameter**
- Nodular hyalinosis and fibrosis and foamy histiocytes indicative of tumor regression
- CAVE: fibrotic changes unrelated to tumor (e.g. mediastinum)
- CAVE: pretherapeutic staging may not be accurate
- Regression grading may be biased
- First reports about prognostic value in esophagus and rectum
- At present: no recommendation to perform regression grading on LN (but describe and comment; use UICC/AJCC TNM classification: ypN)

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the Journal of Cancer Surgery
EJSO 38 (2012) 319–325
www.ejso.com

Preoperative chemotherapy does not influence the number of evaluable lymph nodes in resected gastric cancer

J.L. Dikken [a,b], N.C.T. van Grieken [c], P. Krijnen [d], M. Gönen [e], L.H. Tang [f], A. Cats [g], M. Verheij [h], M.F. Brennan [a], C.J.H. van de Velde [b], D.G. Coit [a,*]

ORIGINAL ARTICLE

Postoperative Nodal Status and Diffuse-type Histology Are Independent Prognostic Factors in Resectable Advanced Gastric Carcinomas After Preoperative Chemotherapy

Young Wha Koh, MD, Young Soo Park,* Min-Hee Ryu,† Baek-Yeol Ryoo,† Hye Jin Park,* Jeong Hwan Yook,‡ Byung Sik Kim,‡ and Yoon-Koo Kang, MD, PhD†*

TABLE 2. Multivariate Analysis for Survival, Including UICC 2002 ypT-category (ypT0–4), ypN-category (ypN0–3), ypL-category (lymphatic vessel invasion, ypL0–1), tumor resection status (R0 vs. R1/2), Tumor regression grading (TRG 1 vs. 2/3), Tumor differentiation (G1–4) and Lauren´s Classification (intestinal vs. diffuse vs. mixed/unclassifiable)

Factor	EXP (B)	95% CI	*P*
UICC ypT classification	1.14	0.9–1.44	0.23
UICC ypN classification	1.65	1.37–2.0	<0.001
UICC ypL classification	0.92	0.64–1.3	0.61
Tumor regression grade	1.03	1.0–1.06	0.009
Tumor resection status	1.23	0.95–1.6	0.12
Tumor differentiation grade	1.22	0.93–1.58	0.14
Lauren´s classification	0.92	0.76–1.11	0.43

CI, confidential interval.

Becker et al, 2012

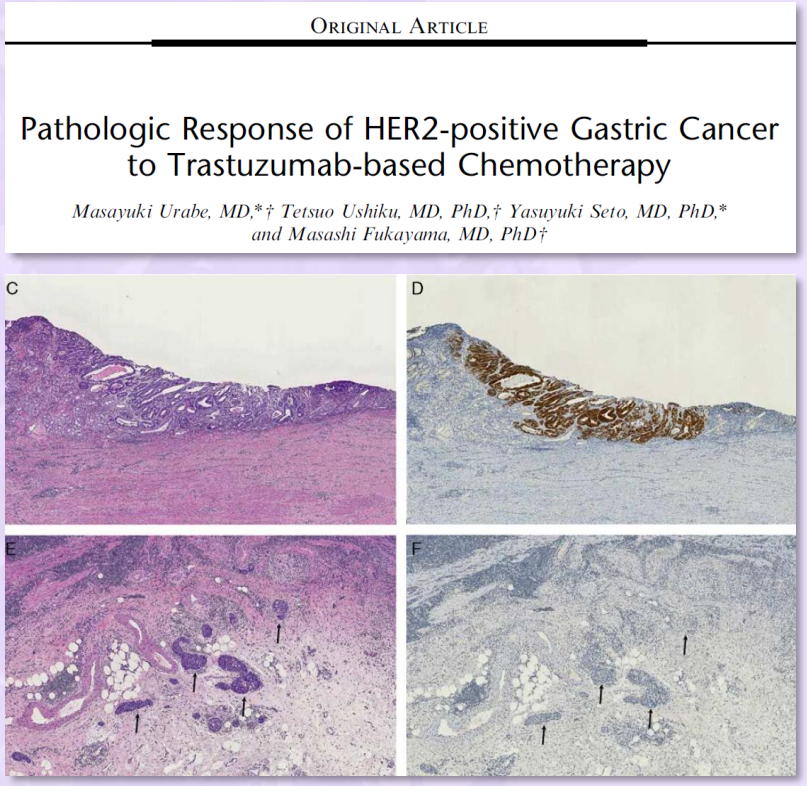
Regression Grading after Neoadjuvant Therapy – Challenges for the Future

- Existing data about «conventional» nRCTX/nCTX
- Modification of nTX (i.e. short courses)
- First data about novel approaches

  (incl. immunotherapy or targeted therapy)

-> *Data acqisition mandatory*

- Comparison with convential TX
- Determination of prognostic/biologic impact
- Similar to conventional TX: macroscopic work up and histopath reporting



ORIGINAL ARTICLE

Pathologic Response of HER2-positive Gastric Cancer to Trastuzumab-based Chemotherapy

Masayuki Urabe, MD,† Tetsuo Ushiku, MD, PhD,† Yasuyuki Seto, MD, PhD,* and Masashi Fukayama, MD, PhD†*

Tumor Regression Grading – Final (?) Points

- TRGs offer valuable morphologic and prognostic information.
- work up: complete embedding; consider step sections or proper slides before diagnosis of complete regression
- histology: use whole tumorbed, not «worst area» for reporting TRG
- Use (y) pTNM **and TRG** (at the moment no general recommendation; preferrably 4 tiered TRG: e.g. CAP/AJCC, Becker, etc), clearly indicate the reference and provide additional text (e.g. «TRG1b (Becker): <10% residual tumor/tumorbed»)
- Standardization necessary -> challenge for pathology community
- Announcement: upcoming international survey (Maria Westerhoff, RL) about the usage of TRG and related issues

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THANK YOU