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WHY PIPAC?

Assessing Histologic Response

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Disclosures

- I do not have any relevant financial relationships with any ineligible companies.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Outline

- What is Tumor Regression?
- What are some examples of Tumor Regression Grading?
- What does tumor regression look like histologically?
- What is PRGS, and how do we use it?
- What are upcoming questions or additional ways to evaluate tumor regression?

What is Tumor Regression?

- Neoadjuvant chemotherapy and/or radiotherapy, followed by surgery
- Standard of care in advanced gastrointestinal, hepatobiliary, and gynecologic cancers
- Assessed in primary tumor or metastatic (omental) tumor
    - Estimation of residual tumor in relation to initial tumor size
    - Estimation of regressive changes or tumor bed (milieu)

What Useful About Tumor Regression?

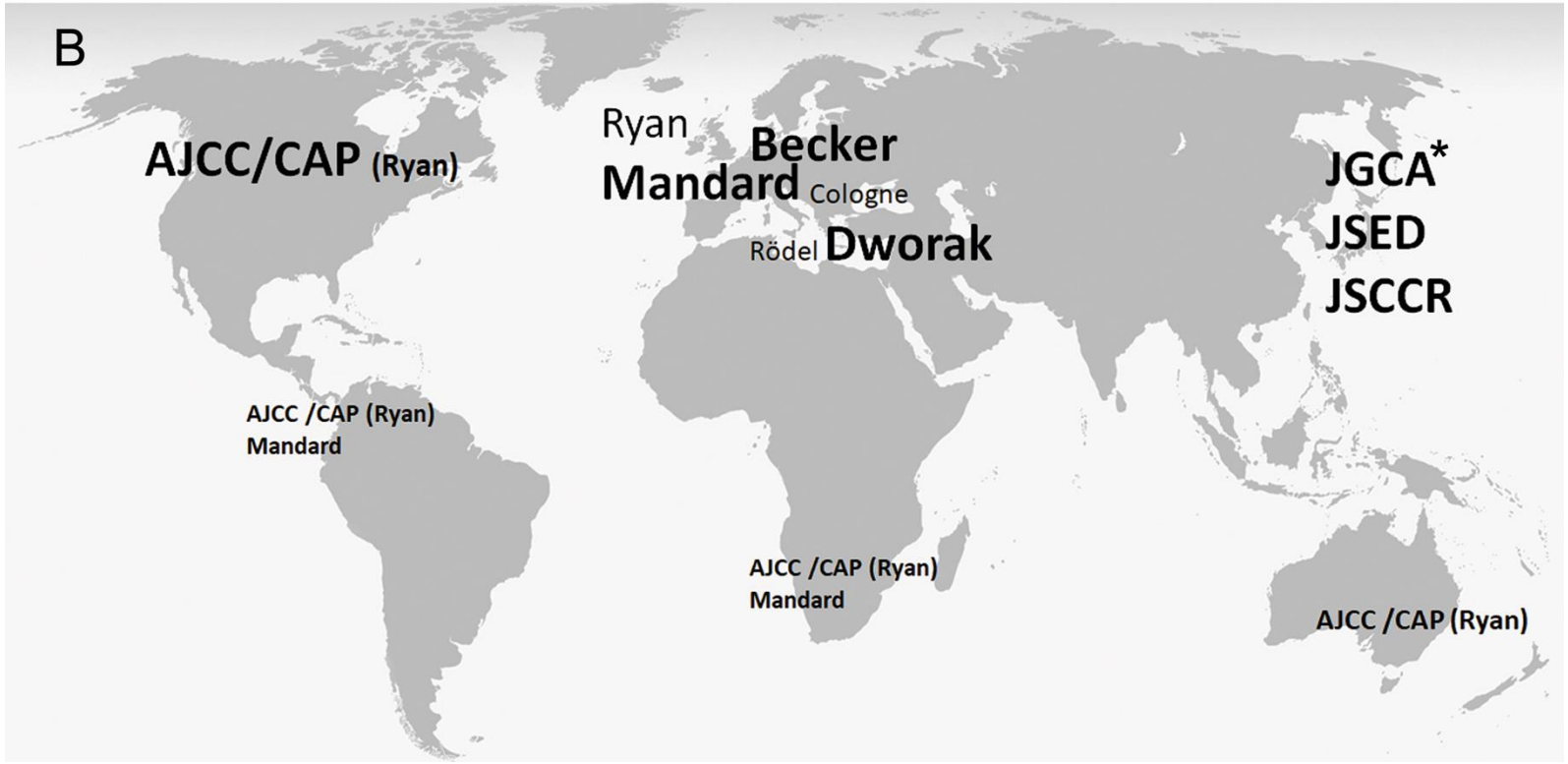
- Generally good interobserver reproducibility (Ryan)
  - Prognostic impact on either end (complete response vs. non-response)
  - Surrogate parameter for therapy response
  - Used as end points for some clinical trials
- IDEALLY:
  - Easily performed as part of routine pathologic diagnosis
  - Reproducible
  - Documents amount of viable tumor and amount of regressive features
- CAVEAT: No consensus or official system

Examples of Tumor Regression Grades (TRG)

System	Mandard	Ryan (CAP, AJCC)	Becker	Dworak	Bohm
No tumor cells (complete response)	1	0	1a	4	3
Single cells (near complete response)	2	1	1b	3	3
Residual cells with evident regression (partial response)	3	2	2	2	2
Minimal regression	4		3	1	1
Extensive residual cancer with no evident regression (poor/no response)	5	3		0	1
Organ System	Esophagus, GEJ	Esophagus, gastric, rectal	GEJ	Esophagus, rectal	Tubo-ovarian (omentum)

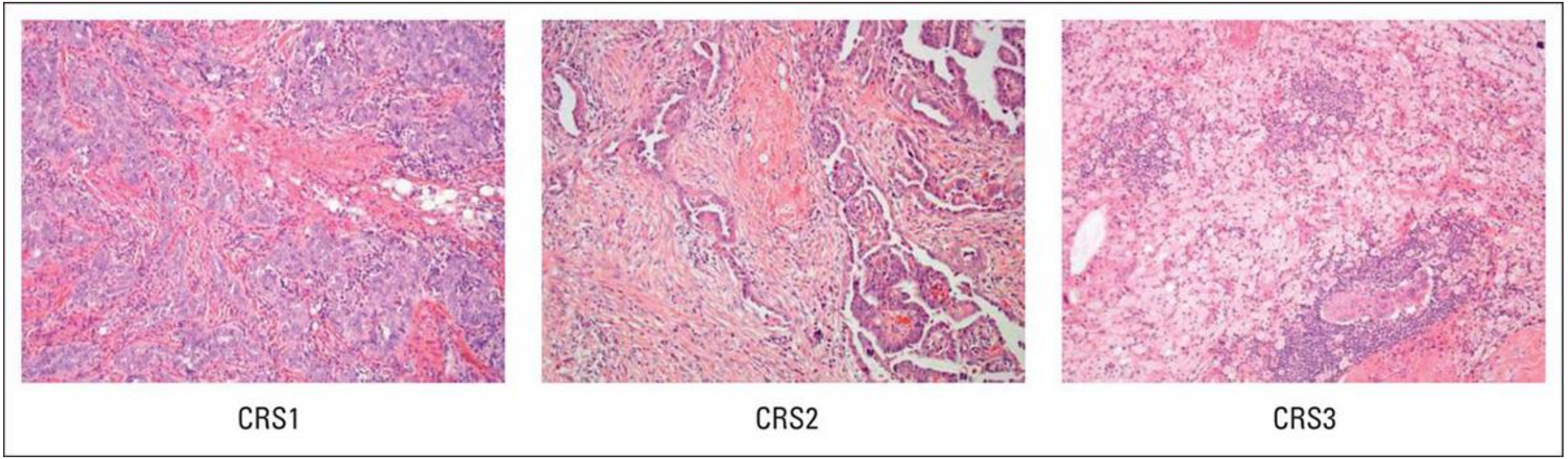
Examples of Tumor Regression Grades (TRG)

- Geographic difference
- Organ system difference



Westerhoff M, Osecky M, Langer R. Varying practices in tumor regression grading of gastrointestinal carcinomas after neoadjuvant therapy: results of an international survey. Mod Pathol. 2020 Apr;33(4):676-689. PMID: 31673084.

What does tumor regression look like histologically?



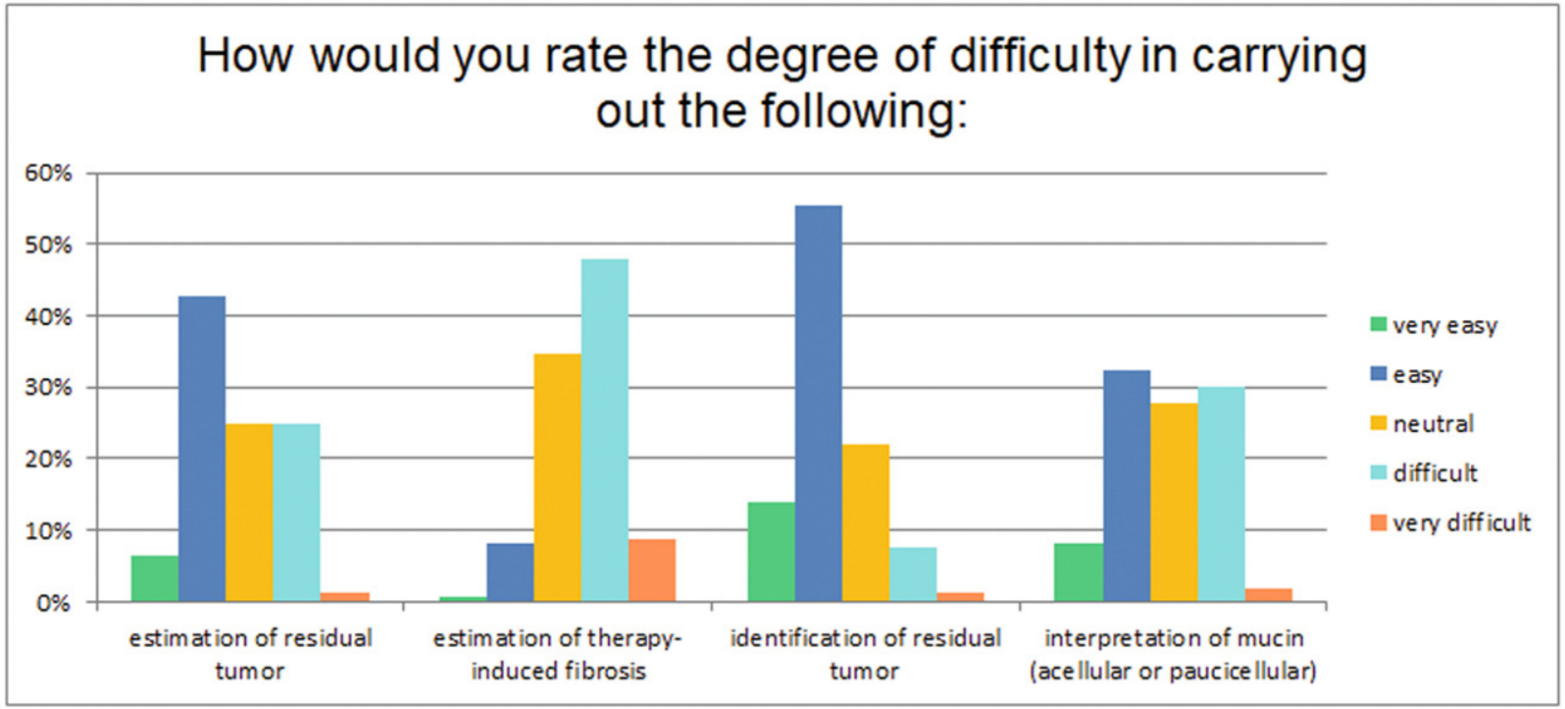
Examples of histopathologic features corresponding to chemotherapy response score (CRS) 1 to 3.

CRS 1: tumor with lymphocytic inflammatory infiltrate; the latter should not be mistaken for chemotherapy regression changes.
CRS 2: both tumor and regressive changes are readily identified and uniformly distributed, although in any proportion.
CRS 3: irregularly distributed and scant tumor deposits amid extensive chemotherapy regressive changes.

From: Bohm: J Clin Oncol, Volume 33(22).August 1, 2015.2457-2463

What does tumor regression look like histologically?

- Residual tumor (easy to identify)
- Regressive changes (challenging to identify)
- Mucin (real vs artifact)



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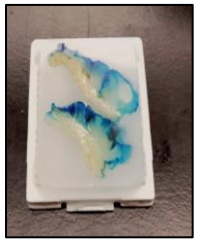
Standardized Sampling

- Peritoneal Carcinomatosis Index (PCI)
- At least 4 biopsies, parietal peritoneum
    - Some studies say at least 3 biopsies
    - At least 3 mm, ideally 5 mm
- Additional local peritonectomy
- Peritoneal cytology, if negative peritoneal histology is suspected

Solass W, Sempoux C, Detlefsen S, Carr NJ, Bibeau F. Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS). Pleura Peritoneum. 2016 Jun 1;1(2):99-107. PMID: 30911613.

Standardized Processing

- Formalin fixation
- H&E staining, recommend 3 step sections
- Immunohistochemical staining or molecular testing may be needed
    - Variably applied



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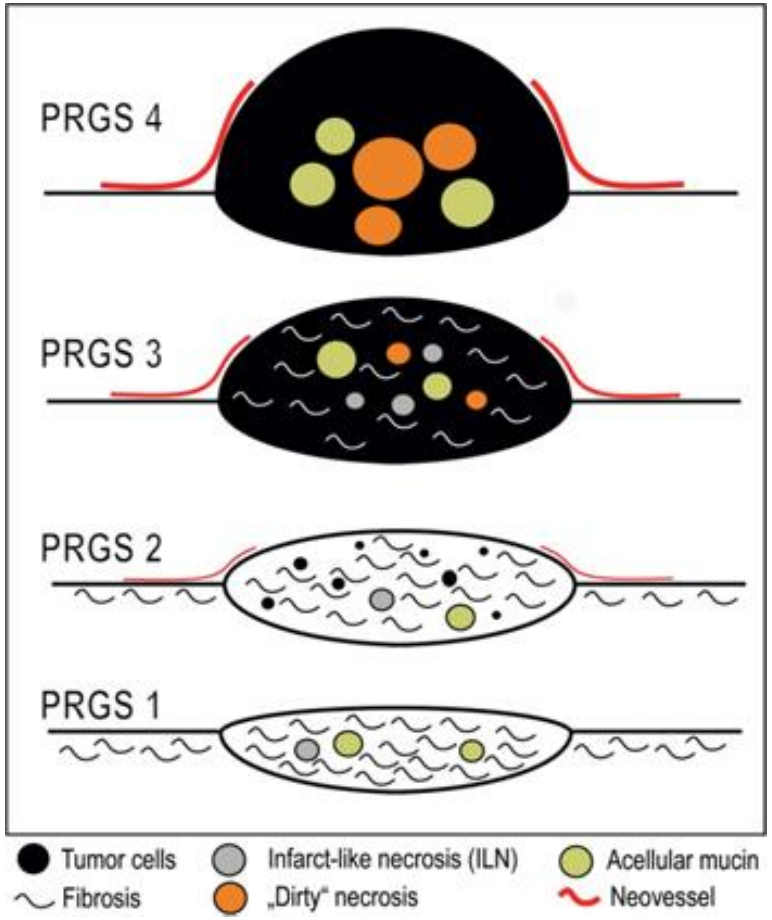
Standardized Reporting

Grade	Peritoneal regression grading score (PRGS)	
	Tumor cells	**Regression features**
PRGS 1–complete response	No tumor cells	Abundant fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS 2–major response	Regressive changes predominant over tumor cells	Fibrosis and/or acellular mucin pools and/or infarct-like necrosis predominant over tumor cells
PRGS 3–minor response	Predominance of tumor cells	Tumor cells predominant over fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS 4–no response	Solid growth of tumor cells (visible at lowest magnification)	No regressive changes



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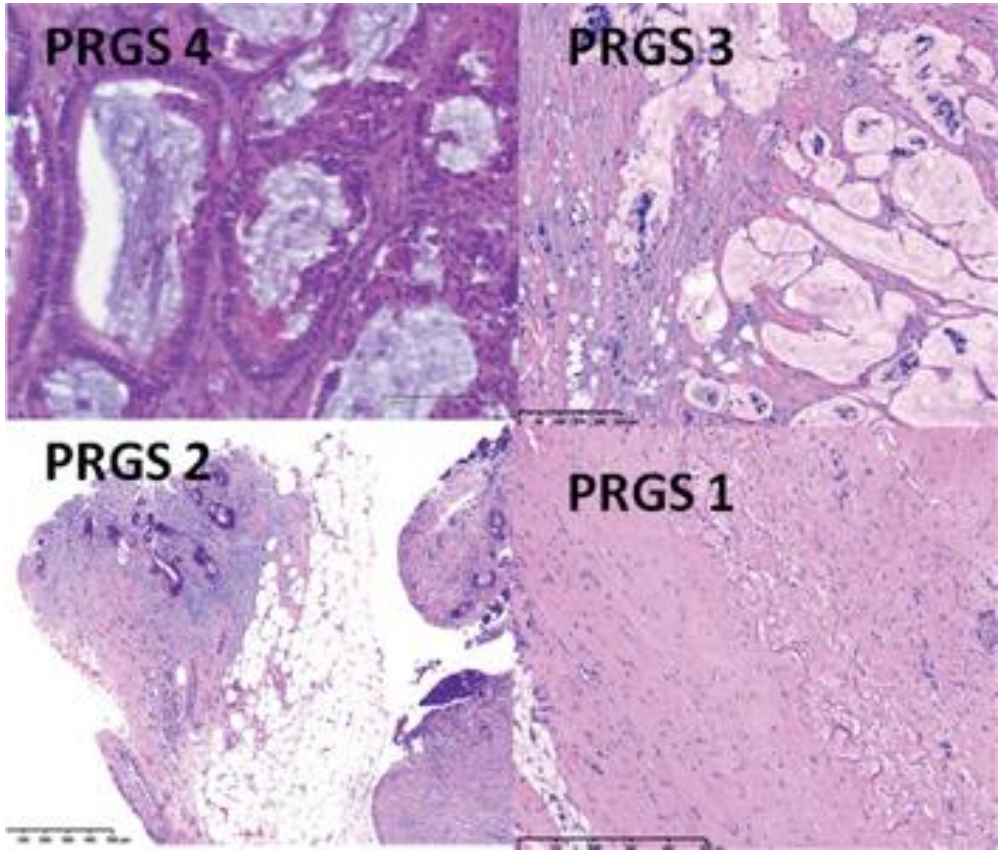
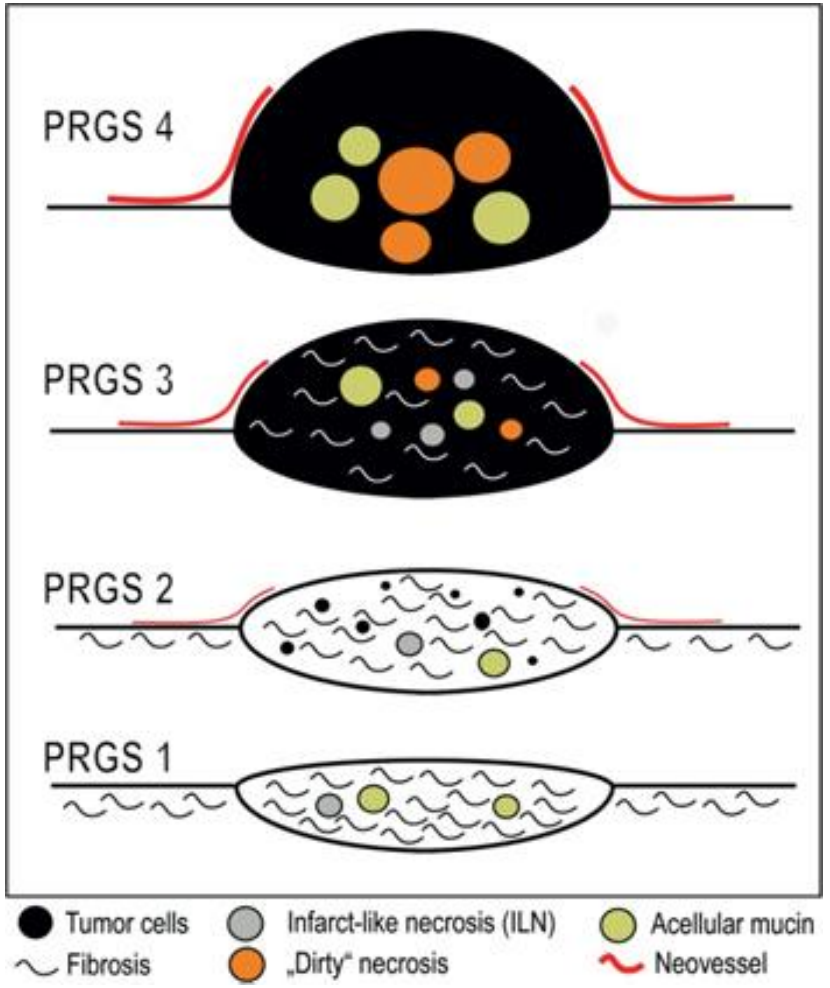
Standardized Reporting





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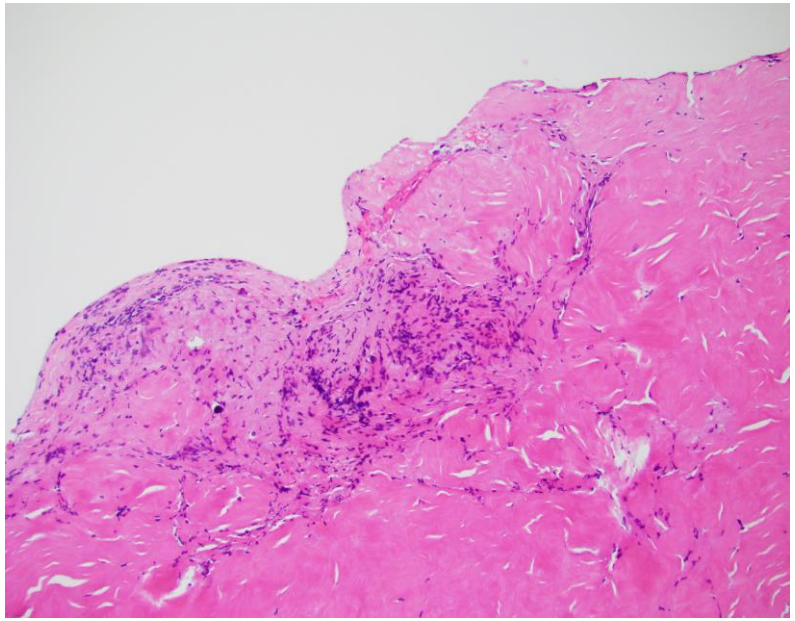
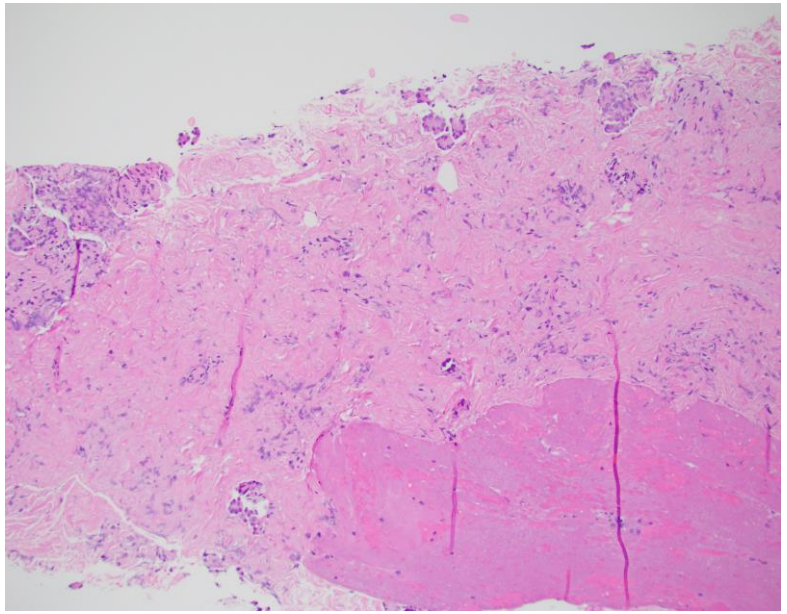
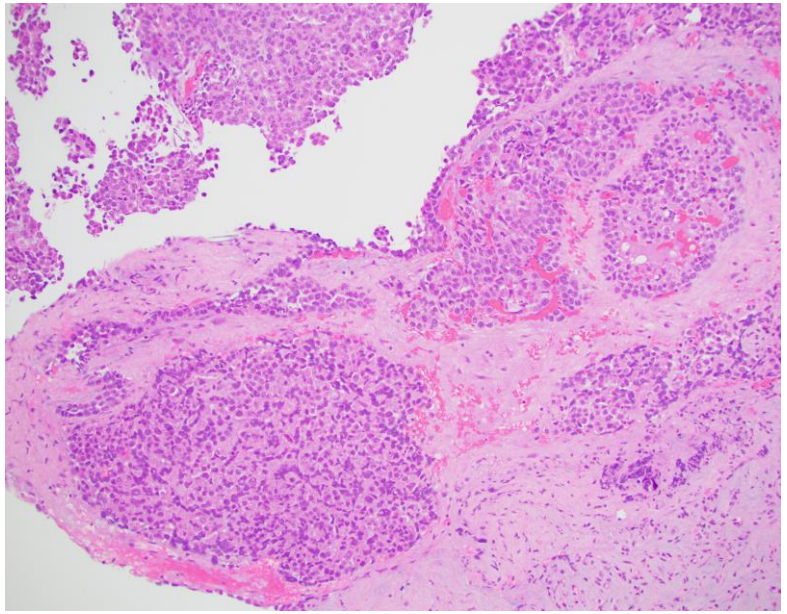
PRGS in tubo-ovarian serous carcinoma



PRGS 1



PRGS 2



PRGS 3 or 4

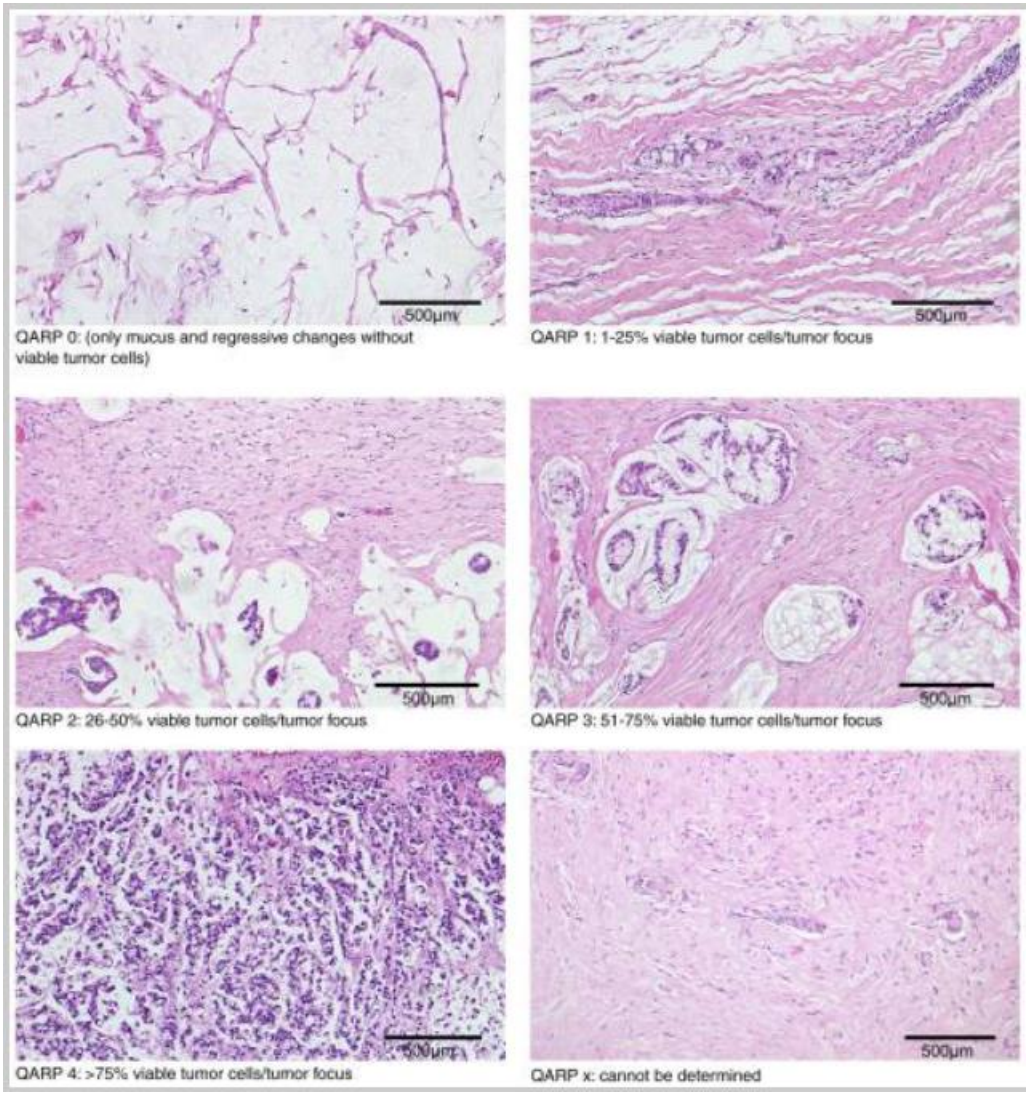
PRGS

- Moderate to good inter-observer agreement
- Good to excellent intra-observer agreement
- Utilizes routine histologic preparations and tools

Solass W, Sempoux C, Carr NJ, Bibeau F, Neureiter D, Jäger T, Di Caterino T, Brunel C, Klieser E, Fristrup CW, Mortensen MB, Detlefsen S. Reproducibility of the peritoneal regression grading score for assessment of response to therapy in peritoneal metastasis. Histopathology. 2019 Jun;74(7):1014-1024.

Future Directions

- Combine PRGS with peritoneal cytology for a Combined Progression Index (CPI)
- NGS to assess for minimal residual disease (MRD)
- QARP Grading System (0 to 4)
- mRNA of fibrotic regressive changes



Benzerdjeb N, et al. Prognostic impact of combined progression index based on peritoneal grading regression score and peritoneal cytology in peritoneal metastasis. Histopathology. 2020 Oct;77(4):548-559.

Detlefsen S, et al. RNA expression profiling of peritoneal metastasis from pancreatic cancer treated with Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). Pleura Peritoneum. 2024 Jun 3;9(2):79-91. PMID: 38948326.

Abbas M, et al. Modified scoring system for the quantitative assessment of histological regression in peritoneal carcinomatosis after pressurized intraperitoneal aerosol chemotherapy: A pilot study. Oncol Lett. 2024 May 9;28(1):308. PMID: 38784603.

Pathologic assessment is an ongoing effort

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