THIRD ANNUAL
ISSPP Congress 2022
International Society for the Study of Pleura and Peritoneum

PERITONEAL ASSESSMENT

Pathology: PRGS and Its Value for Response Assessment and Prognosis

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1

Disclosures

- No relevant disclosures.

2

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Commonalities and differences among individuals in this population.
- Factors that determine the type and level of care that this patient population receives.

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3

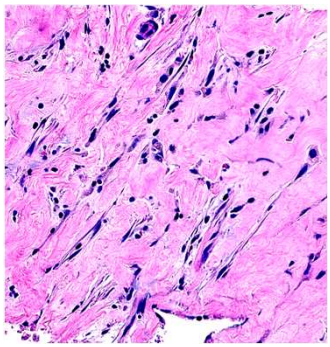
Peritoneal Regression Grading Score (PRGS)

- Scoring system for assessment of histological response after treatment of peritoneal metastasis (PM)
- Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)
- Can be assessed using peritoneal quadrant biopsies taken prior to each PIPAC treatment

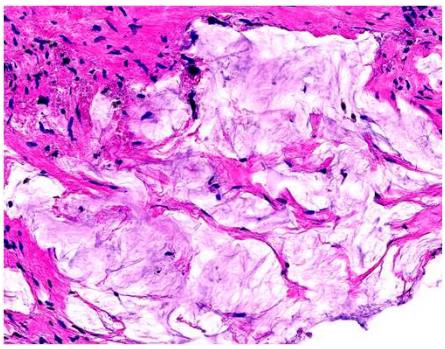
Source: Martin Graversen

4

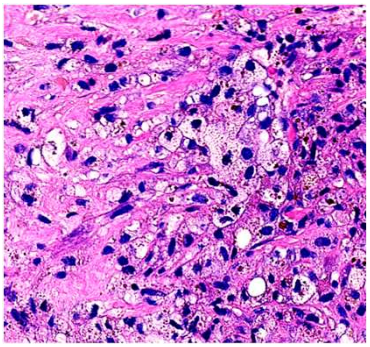
Histological Tumor Response – General Features



Regressive fibrosis



Acellular mucin lakes

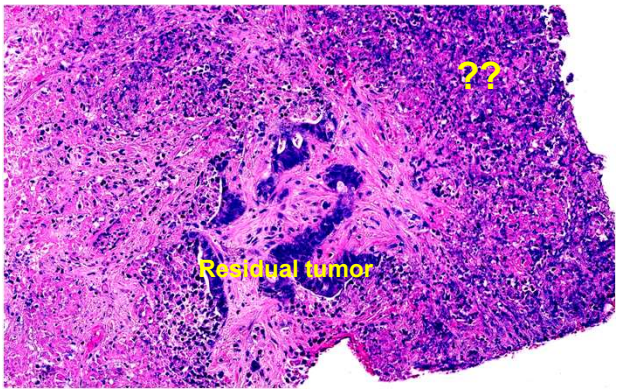


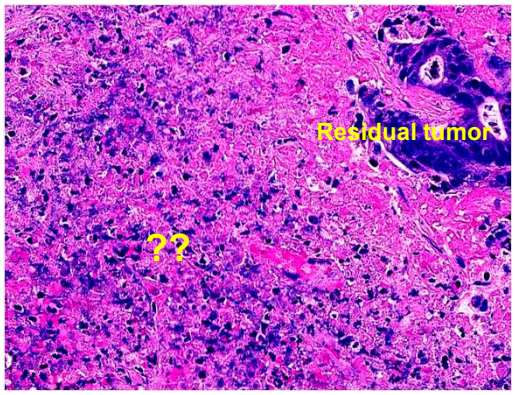
Foamy histiocytes
Inflammation

Source: Detlefsen S

5

Feature of Response?

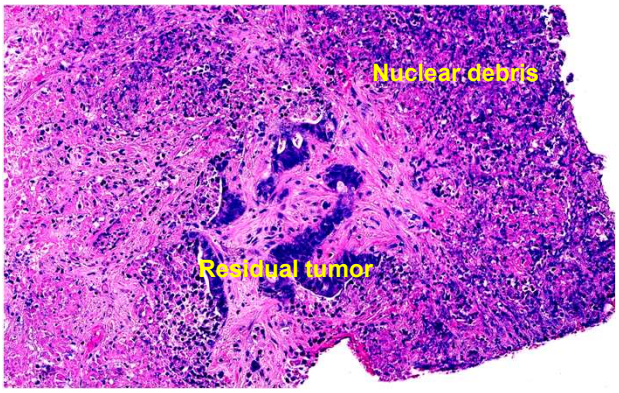


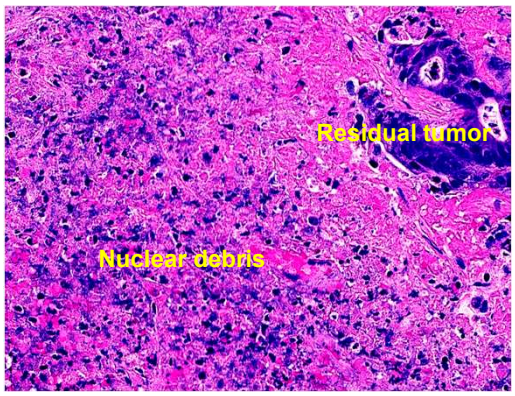


Source: Detlefsen S

6

Feature of Response?



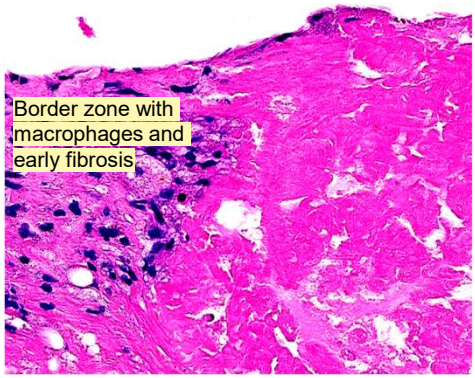


Source: Detlefsen S

7

Histological Tumor Response – General Features

„Infarct-like“ necrosis

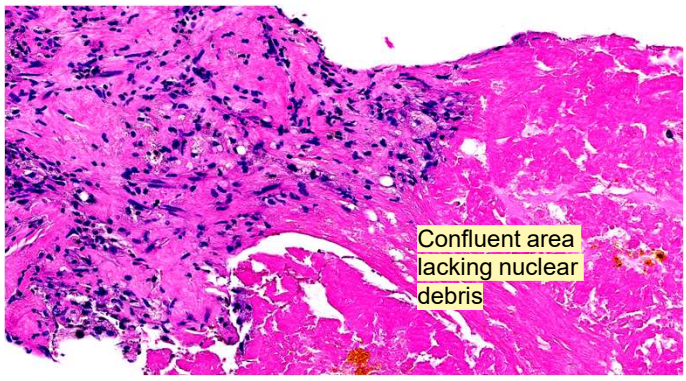


„Infarct-like“ necrosis

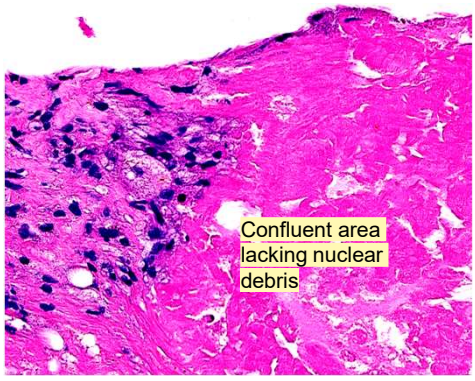
Source: Detlefsen S
Chang et al. 2012; Am J Surg Pathol 36:570–576

8

Histological Tumor Response – General Features



„Infarct-like“ necrosis



„Infarct-like“ necrosis

Source: Detlefsen S
Chang et al. 2012; Am J Surg Pathol 36:570–576

9

Tumor Regression Grade (TRG) – Neoadjuvantly Treated (NAT) GI Malignancies incl. Colorectal Liver Metastasis (CRLM) (Surgical Specimens)

TRG5 – no response
TRG4 – minor response (R << Tu)
TRG3 – major response (R >> Tu)

TRG2 – near-total response („next to nothing“)
TRG1 – complete response

Rubbia-Brandt et al. 2007; Annals of Oncology 18: 299–304

10

Tumor Regression Grade (TRG) in CRLM

TRG 1&2

TRG 3

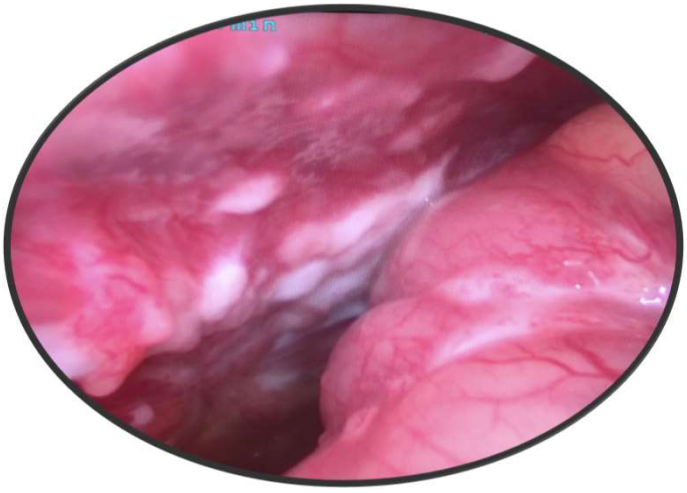
TRG 4&5

106 pts. with CRLM treated with NAT

Rubbia-Brandt et al. 2007; Annals of Oncology 18: 299–304

11

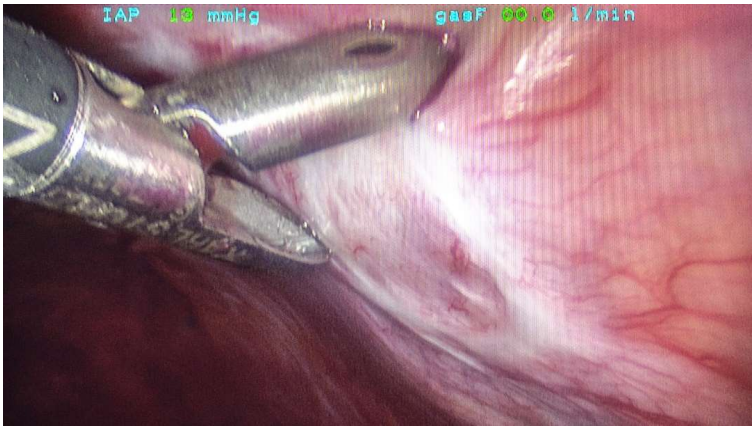
How to Assess Response to Therapy in Peritoneal Metastasis (PM)?



Source: Martin Graversen

12

Laparoscopic biopsy of Peritoneal Metastasis (PM)



Source: Martin Graversen

13

Peritoneal Regression Grading Score (PRGS)

Wiebke Solass, Christine Sempoux, Sönke Detlefsen, Norman J. Carr and Frédéric Bibeau*

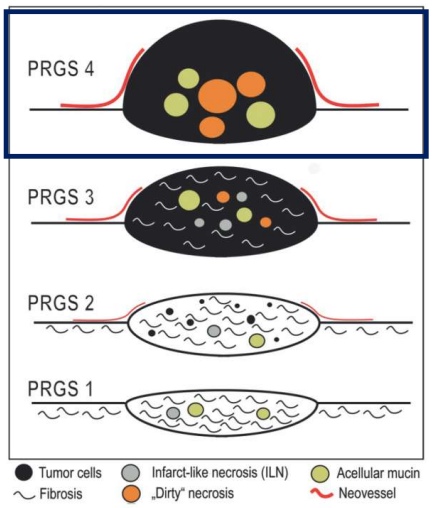
Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS)

- Biopsies much smaller than surgical resection specimens
- Should be applicable to a wide range of different types of primary tumours
- 4 grades, 4 peritoneal punch biopsies (one from each quadrant)
- Diameter at least 3 mm (better 5 mm or more)
- Each quadrant biopsy scored – maximum and mean PRGS reported

Pleura and Peritoneum 2016;1(2):99 - 107

14

Peritoneal Regression Grading Score (PRGS)



PRGS-4 – no response (only Tu)

PRGS-3 – minor response (R << Tu)

PRGS-2 – major response (R >> Tu)

PRGS-1 – complete response (only R)

Solass, Sempoux, Detlefsen et al; Pleura and Peritoneum 2016;1(2):99 - 107

15

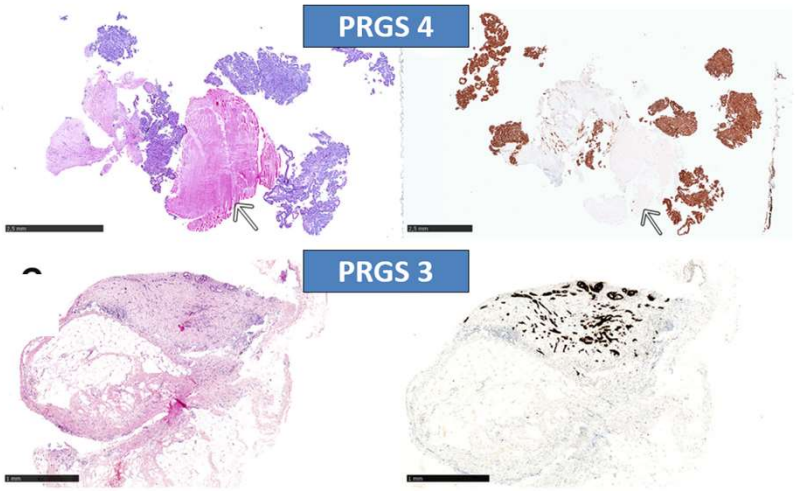
Peritoneal Regression Grading Score (PRGS)

Grade	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	Few tumor cells (isolated or small clusters)	Fibrosis, and or acellular mucin pools, and or infarct-like necrosis predominant over tumor cells
PRGS 3 – minor response	Predominant tumor cells	Tumor cells predominant over fibrosis, and or acellular mucin pools, and or infarct-like necrosis
PRGS 4 – no response	Visible tumor cells	No regressive changes

Solass, Sempoux, Detlefsen et al; Pleura and Peritoneum 2016;1(2):99 - 107

16

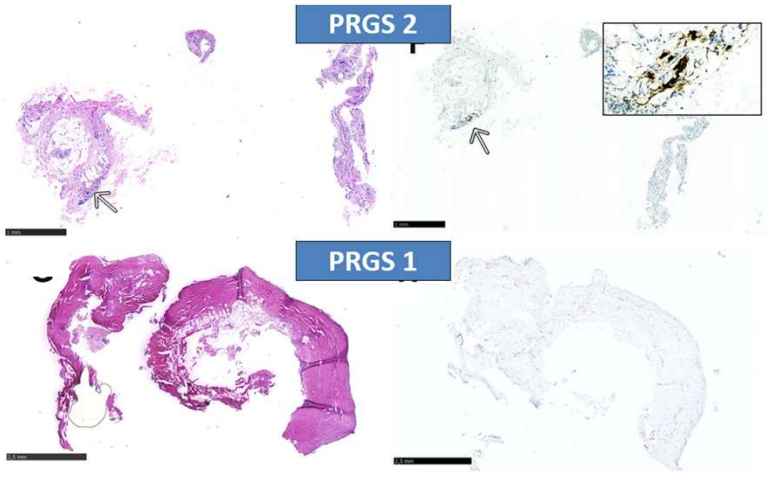
Peritoneal Regression Grading Score (PRGS)



Detlefsen et al. 2022; Human Pathology 120 :77-87

17

Peritoneal Regression Grading Score (PRGS)



Detlefsen et al. 2022; Human Pathology 120 :77-87

18

PRGS Validation Studies

Histopathology

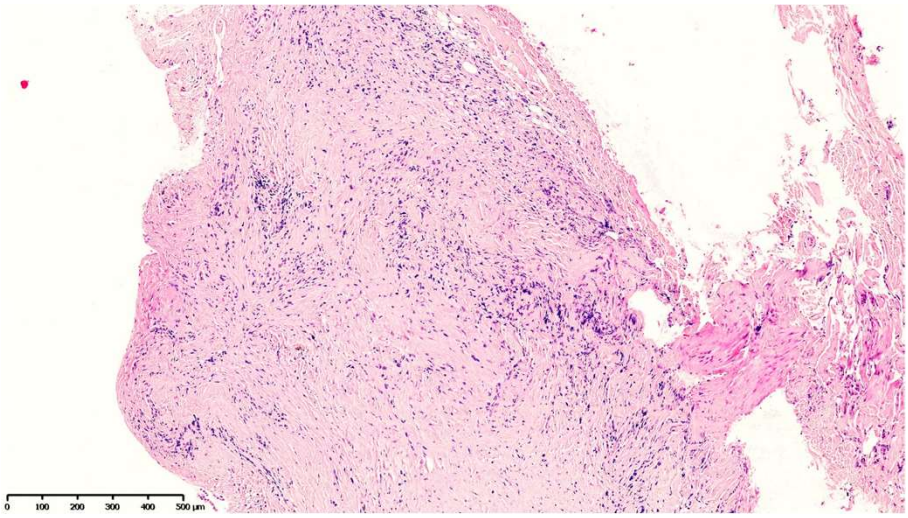
Histopathology 2019, 74, 1014–1024. DOI: 10.1111/his.13829

Reproducibility of the peritoneal regression grading score for assessment of response to therapy in peritoneal metastasis

Wiebke Solass,[1] Christine Sempoux,[2] Norman J Carr,[3] Frederic Bibeau,[4] Daniel Neureiter,[5] Tarkan Jäger,[6] Tina Di Caterino,[7] Christophe Brunel,[2] Eckhard Klieser,[5] Claus W Fristrup,[8,9] Michael B Mortensen[8,9,10] & Sönke Detlefsen[7,8,10]

✓ Reproducibility of PRGS when using H&E moderate-good

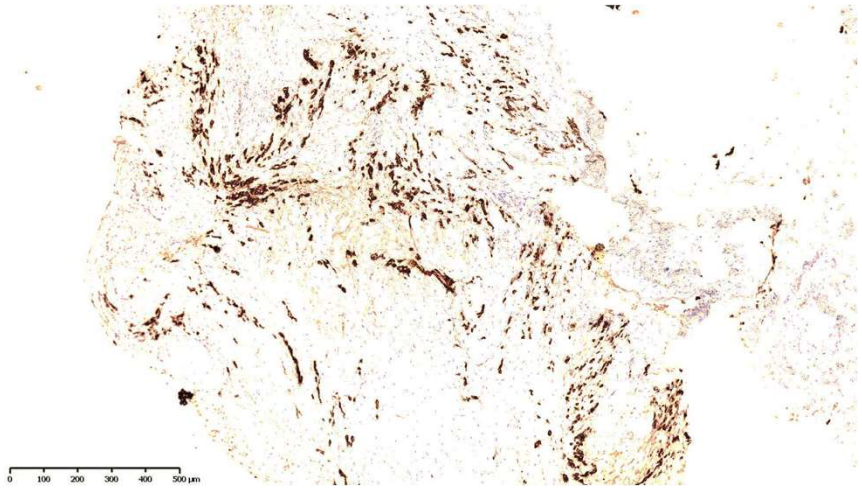
PRGS 1 = No Residual Tumor???



Hematoxylin & Eosin (H&E)

Source: Detlefsen S

PRGS 4 – No Response



EP4 (Ep-CAM) immunohistochemistry

Source: Detlefsen S

21

PRGS Validation Studies

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Role of immunohistochemistry for interobserver agreement of Peritoneal Regression Grading Score in peritoneal metastasis☆

Sönke Detlefsen MD, PhD [a,b,c,*], Tobias Windedal MD [a,c], Frédéric Bibeau MD, PhD [d], Lærke Valsøe Bruhn MD [a], Norman Carr MB, BS, FRCPath [e], Martin Graversen MD, PhD [b,f], Katharina Markowski MD [g], Michael Bau Mortensen MD, PhD [b,c,f], Daniel Neureiter MD [g], Christine Sempoux MD, PhD [h], Wiebke Solass MD [i,j], Malene Theilmann Thinesen MD [a], Claus Fristrup MD, PhD [b,f]

✓ Reproducibility of PRGS when using H&E moderate-good

✓ Reproducibility of PRGS when using IHC good-almost perfect

Human Pathology 2022; 120 :77-87

22

Prognostic Value of PRGS

- iPRGS+ Increase in highest or mean PRGS from PIPAC 1 to PIPAC 3
- iPRGS- No increase or even decrease of PRGS from PIPAC 1 to PIPAC3

p = 0.295 p = 0.064

Increase in highest or mean PRGS from PIPAC 1 to PIPAC 3 had no significant prognostic value

Benzerdjeb et al 2020; Histopathology 77:548 - 559

23

Prognostic Value of PRGS

Maximum PRGS

p = 0.005

- PC Peritoneal cytology
- CPI Combined positive index = iPRGS+ and/or PC positive at PIPAC3

Increase in maximum PRGS and/or positive peritoneal cytology at PIPAC3 had negative prognostic value. Cytology alone had no significance for survival.

Benzerdjeb et al 2020; Histopathology 77:548 - 559

24

Prognostic Value of PRGS. The PIPAC-OPC-2 Study

ENDPOINTS

Main:

- Evaluate if PIPAC can induce major/complete histologic response (PRGS 1+2) within a series of three PIPAC procedures.

Secondary (among others):

- To evaluate if PRGS holds prognostic value in PIPAC-treated PM
- …

Graversen, Detlefsen, ….Mortensen; submitted

25

Prognostic Value of PRGS. The PIPAC-OPC-2 Study

	Total
Number of patients	110
Age, median year (range)	63 (34-80)
Sex, male (%)	44 (40%)
Primary tumor origin	
Stomach	26 (23%)
Colorectal	25 (23%)
Pancreas	21 (19%)
Ovarian	14 (13%)
Appendix	10 (9%)
Bile duct	4 (4%)
Esophagus	3 (3%)
MPM	2 (2%)
Small bowel	2 (2%)
Breast	1 (1%)
Unknown primary	1 (1%)
MUP	1 (1%)
Resection of primary (%)	54 (49%)
Extrap. mets at inclusion (%)	18 (16%)

~ 80%

Graversen, Detlefsen, ….Mortensen; submitted

26

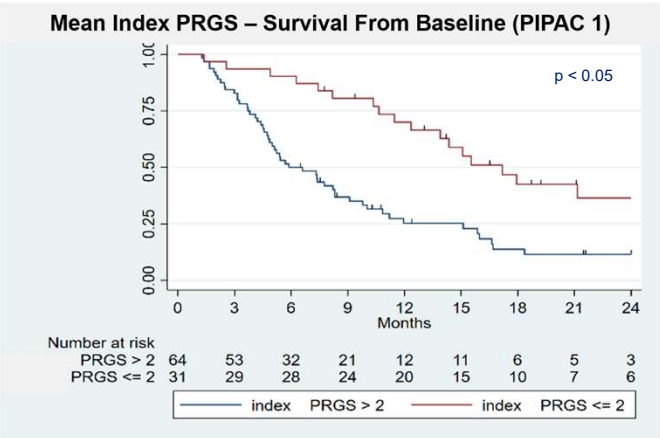
PIPAC-OPC-2 Study

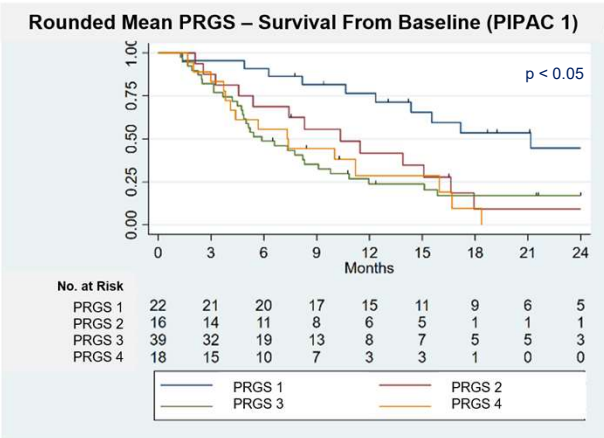
	PIPAC 1 (n = 110)	PIPAC 2 (n = 81)	PIPAC 3 (n = 62)
	PRGS mean		
PRGS mean (SD)	2.50 (0.97)	1.92 (0.82)	1.79 (0.88)
Response, n (%)		52 (64%)	36 (58%)
Major/complete response, n (%)			38 (61%)
	PRGS max		
PRGS max (SD)	2.98 (1.14)	2.31 (1.07)	2.14 (1.16)
Histological response, n (%)		43 (53%)	29 (47%)
Major/complete response, n (%)			35 (56%)

Graversen, Detlefsen, ….Mortensen; submitted

27

Prognostic Value of PRGS

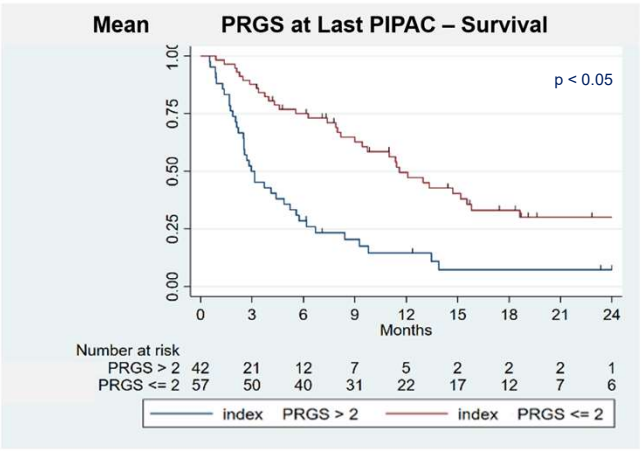


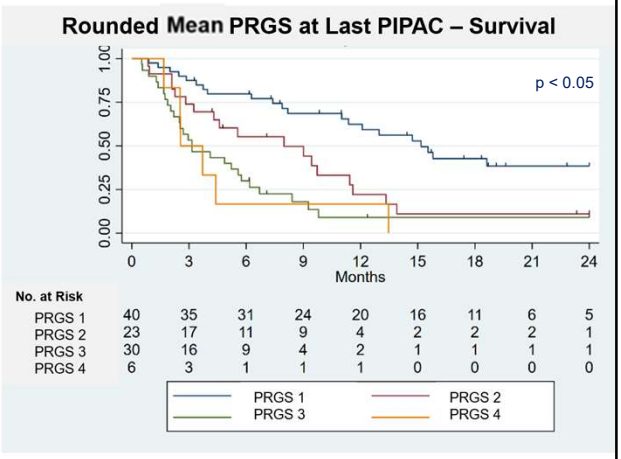


Graversen, Detlefsen, ….Mortensen; submitted

28

Prognostic Value of PRGS



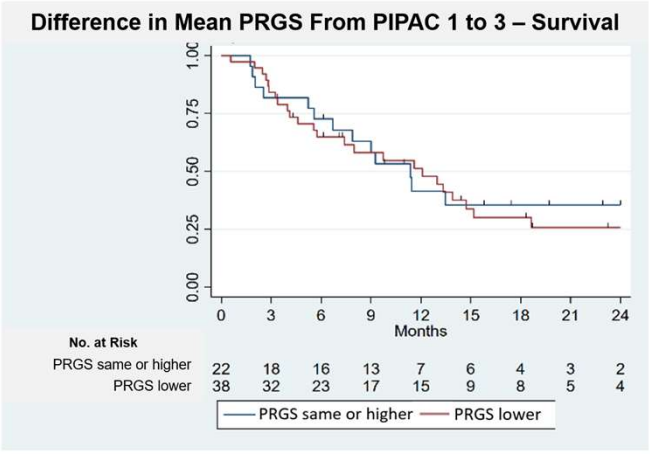


PRGS ≤ 2 at PIPAC 3 was also a significant prognostic variable in a multivariate analysis including sex, age and primary colorectal cancer ($p < 0.05$)

Graversen, Detlefsen, ….Mortensen; submitted

29

Prognostic Value of PRGS



Graversen, Detlefsen, ….Mortensen; submitted

30

Conclusion

- Histological response to PIPAC can be assessed using the PRGS
- 1-3 PIPAC treatments can induce a major histological response according to PRGS
- Immunohistochemistry can increase the reproducibility of the PRGS
- Data regarding the prognostic role of the PRGS are interesting
- Cytology in addition to the PRGS may contribute with additional information

31

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Many Thanks for Your Attention!

32