Quantitative Analysis of Immune Infiltrates in Primary Tumors and Liver Metastases of Colorectal Cancer

„from research to clinical application“

Niels Halama, MD

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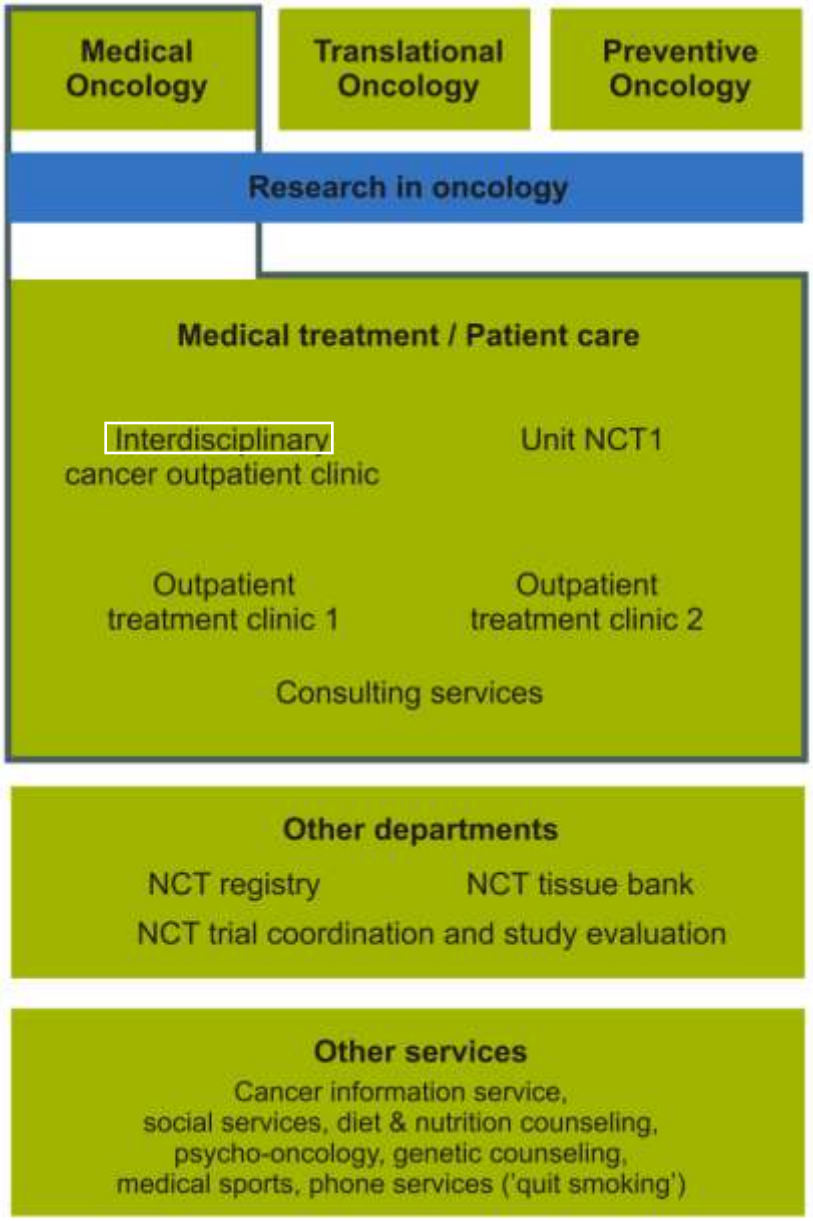
Focus

NCT: Key features



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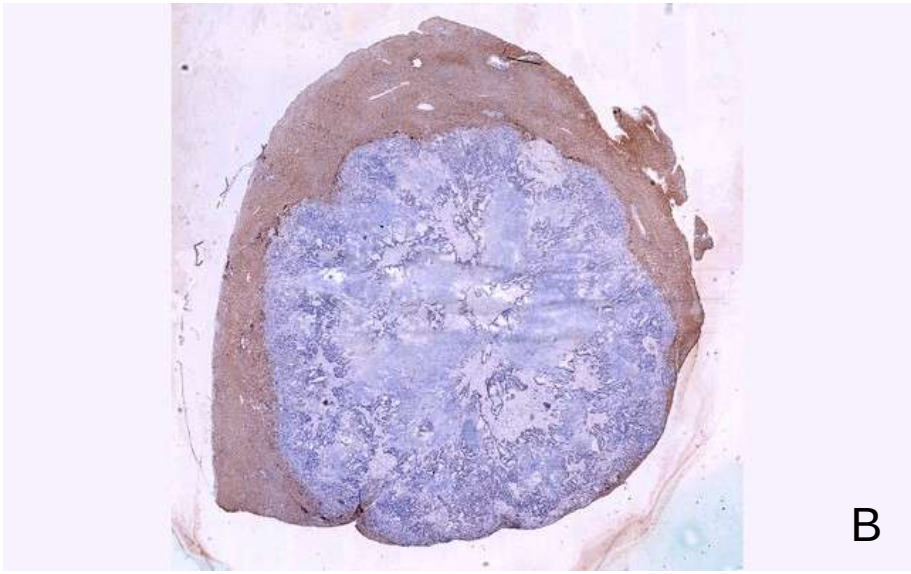
Immune infiltrates and response to chemotherapy?



Previous Work

Intraepithelial CD8$^+$ T-cell-count becomes a prognostic factor after a longer follow-up period in human colorectal carcinoma: possible association with suppression of micrometastasis

T Chiba[1,2], H Ohtani[*,2,3], T Mizoi[4], Y Naito[2], E Sato[2], H Nagura[2], A Ohuchi[5], K Ohuchi[6], K Shiiba[4], Y Kurokawa[1] and S Satomi[1]

[1]Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan; [3]Department of Pathology, Mito Medical Center, Ibaraki, Japan; [4]Division of Biological Regulation and Oncology, Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan; [5]Department of Surgery, Tohoku Rosai Hospital, Sendai, Japan; [6]Department of Surgery, Miyagi Cancer Center, Natori, Japan

British Journal of Cancer (2004) 91, 1711 – 1717

Prognostic Role of CD8+ Tumor-Infiltrating Lymphocytes in Stage III Colorectal Cancer With and Without Microsatellite Instability

FRIEDRICH PRALL, MD, THOMAS DÜHRKOP, VOLKER WEIRICH, MD, CHRISTIANE OSTWALD, PHD, PETER LENZ, MD, HORST NIZZE, MD, AND MALTE BARTEN, MD

HUMAN PATHOLOGY Volume 35, No. 7 (July 2004)

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

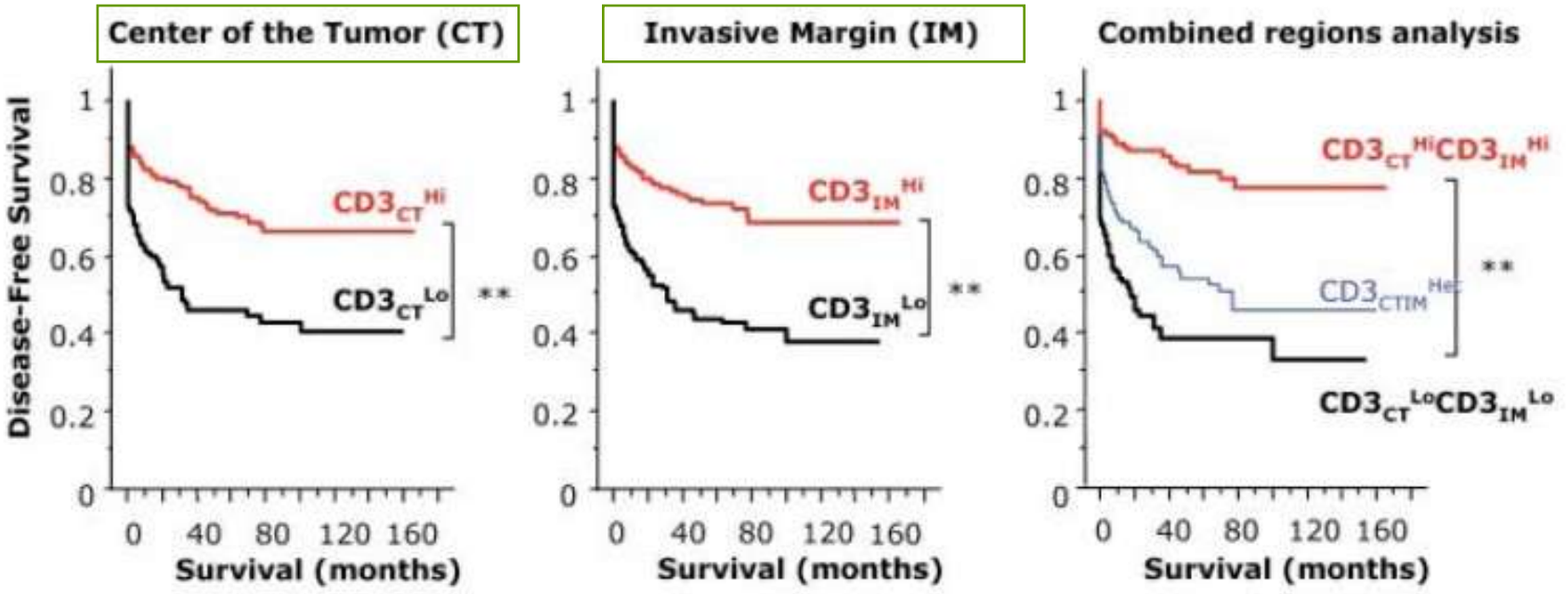
Jérôme Galon,[1*†] Anne Costes,[1] Fatima Sanchez-Cabo,[2] Amos Kirilovsky,[1] Bernhard Mlecnik,[2] Christine Lagorce-Pagès,[3] Marie Tosolini,[1] Matthieu Camus,[1] Anne Berger,[4] Philippe Wind,[4] Franck Zinzindohoué,[5] Patrick Bruneval,[6] Paul-Henri Cugnenc,[5] Zlatko Trajanoski,[2] Wolf-Herman Fridman,[1,7] Franck Pagès[1,7†]

The role of the adaptive immune response in controlling the growth and recurrence of human tumors has been controversial. We characterized the tumor-infiltrating immune cells in large cohorts of human colorectal cancers by gene expression profiling and in situ immunohistochemical staining. Collectively, the immunological data (the type, density, and location of immune cells within the tumor samples) were found to be a better predictor of patient survival than the histopathological methods currently used to stage colorectal cancer. The results were validated in two additional patient populations. These data support the hypothesis that the adaptive immune response influences the behavior of human tumors. In situ analysis of tumor-infiltrating immune cells may therefore be a valuable prognostic tool in the treatment of colorectal cancer and possibly other malignancies.

Science 2006

Immunohistochemistry in colorectal primary tumors

IHC: CD3, CD8, Granzyme B and CD45RO



Galon, Pages, Fridman et al. in Science 2006

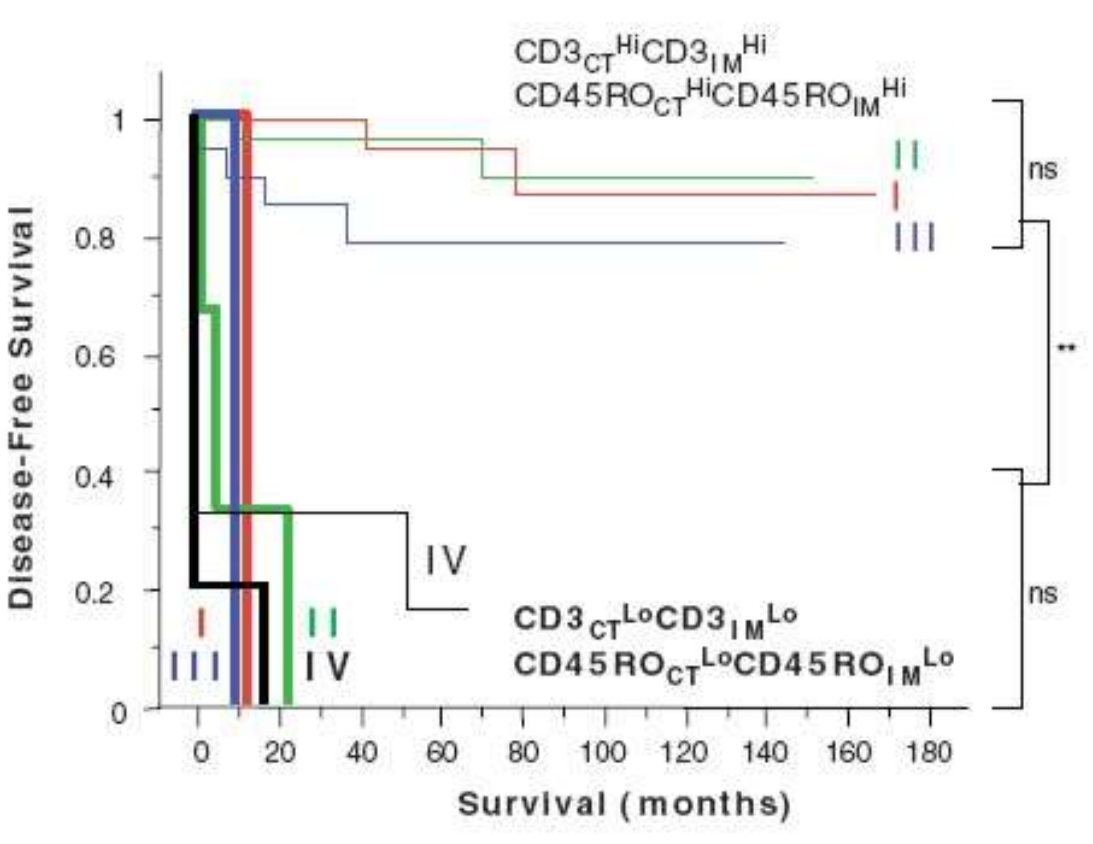
Local immune response versus UICC-TNM stage

UICC-TNM stadium as reference

$CD3_{CT}CD3_{IM}$ evaluation

plus

$CD45RO_{CT}CD45RO_{IM}$ evaluation

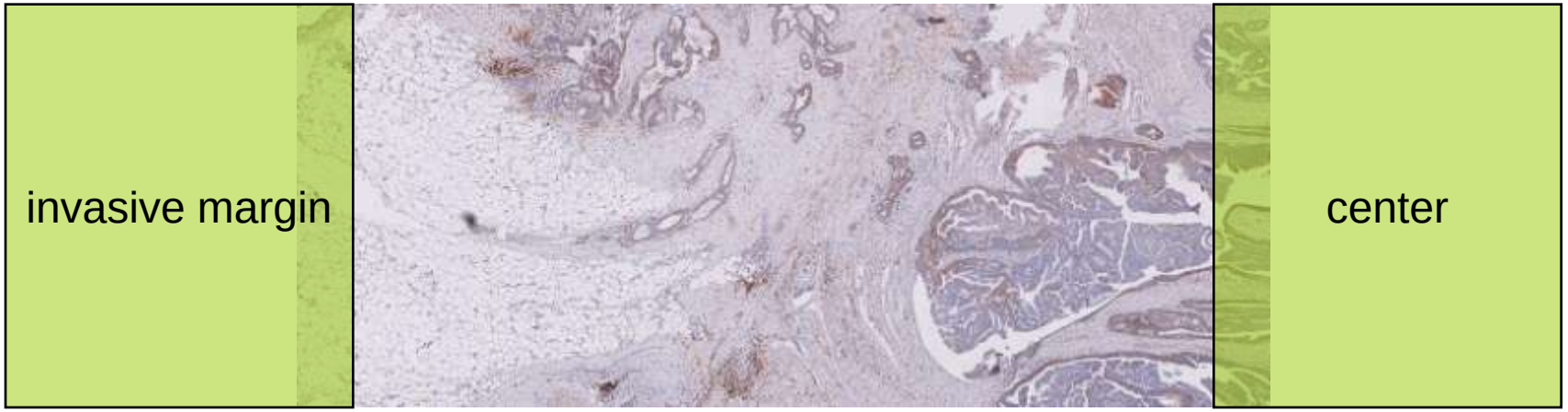


Galon et al. in Science 2006

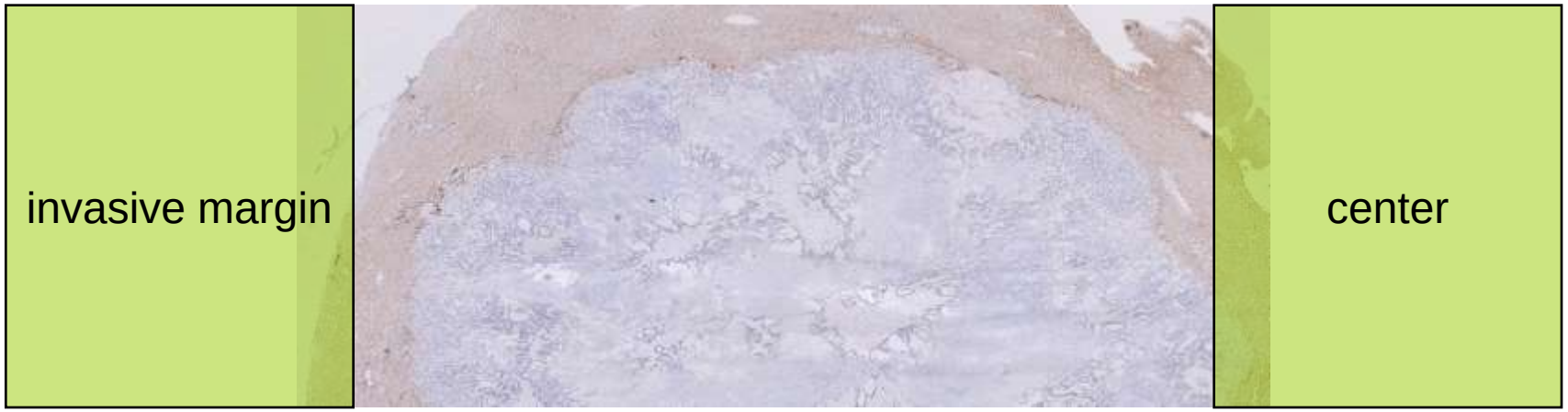
Better local immune response = better chemotherapy response?

Sample analysis I: *localization*

(colorectal cancer)



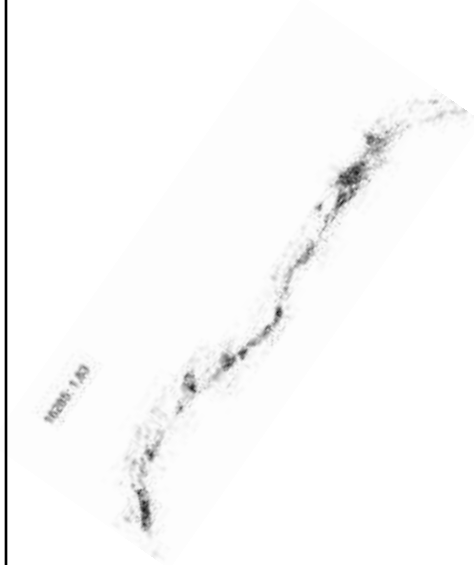
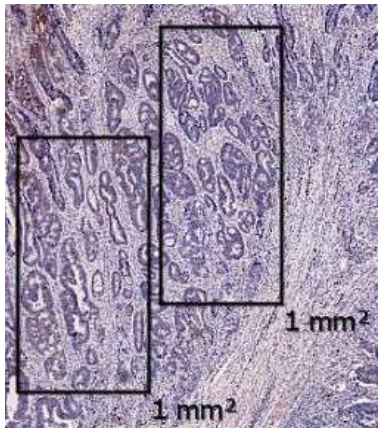
Primary colorectal tumor



Liver metastasis of colorectal cancer

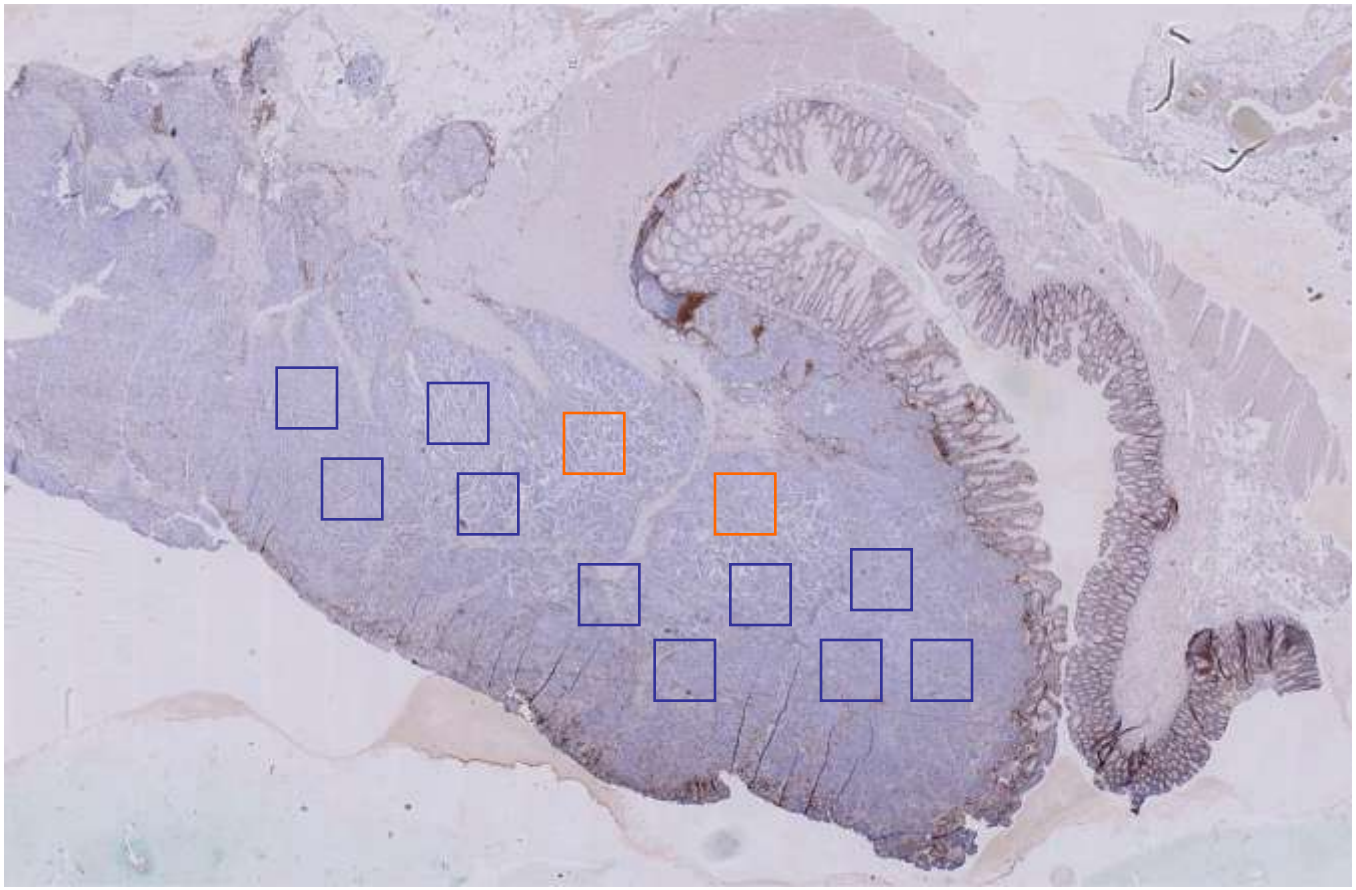
Sample analysis II: *numbers*

(colorectal cancer)

Step I: Manual cell counts	Step II: Relative cell counts	Step III: automated large scale cell counting
		

Sample analysis III: *sampling size*

(colorectal cancer)

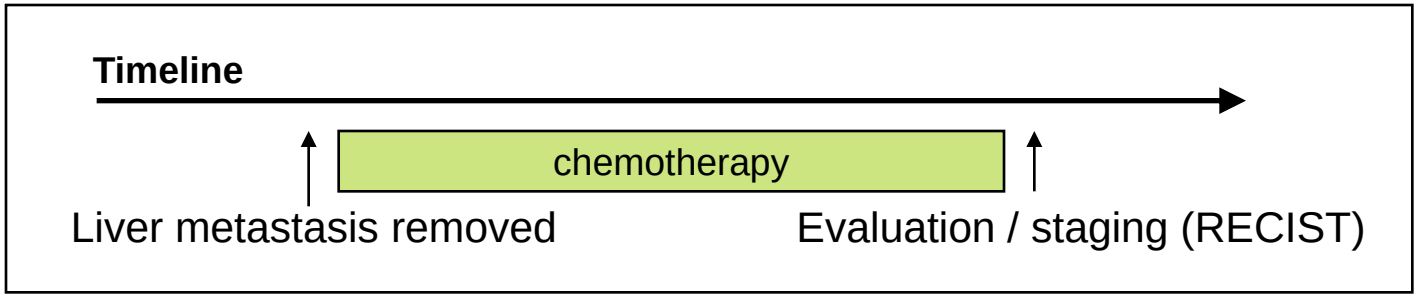


Tissue microarray analyses (TMA): 2 cores (each ~1 mm²)

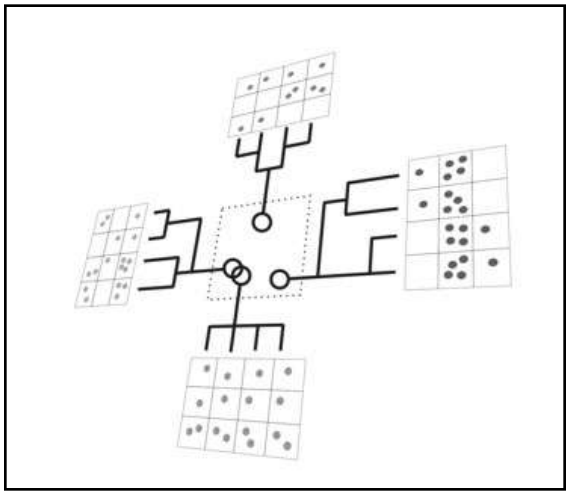
Virtual microscopy: 10 to 12 mm²

Results: *metastases, invasive margin*

Patients‘ characteristics / Data acquisition

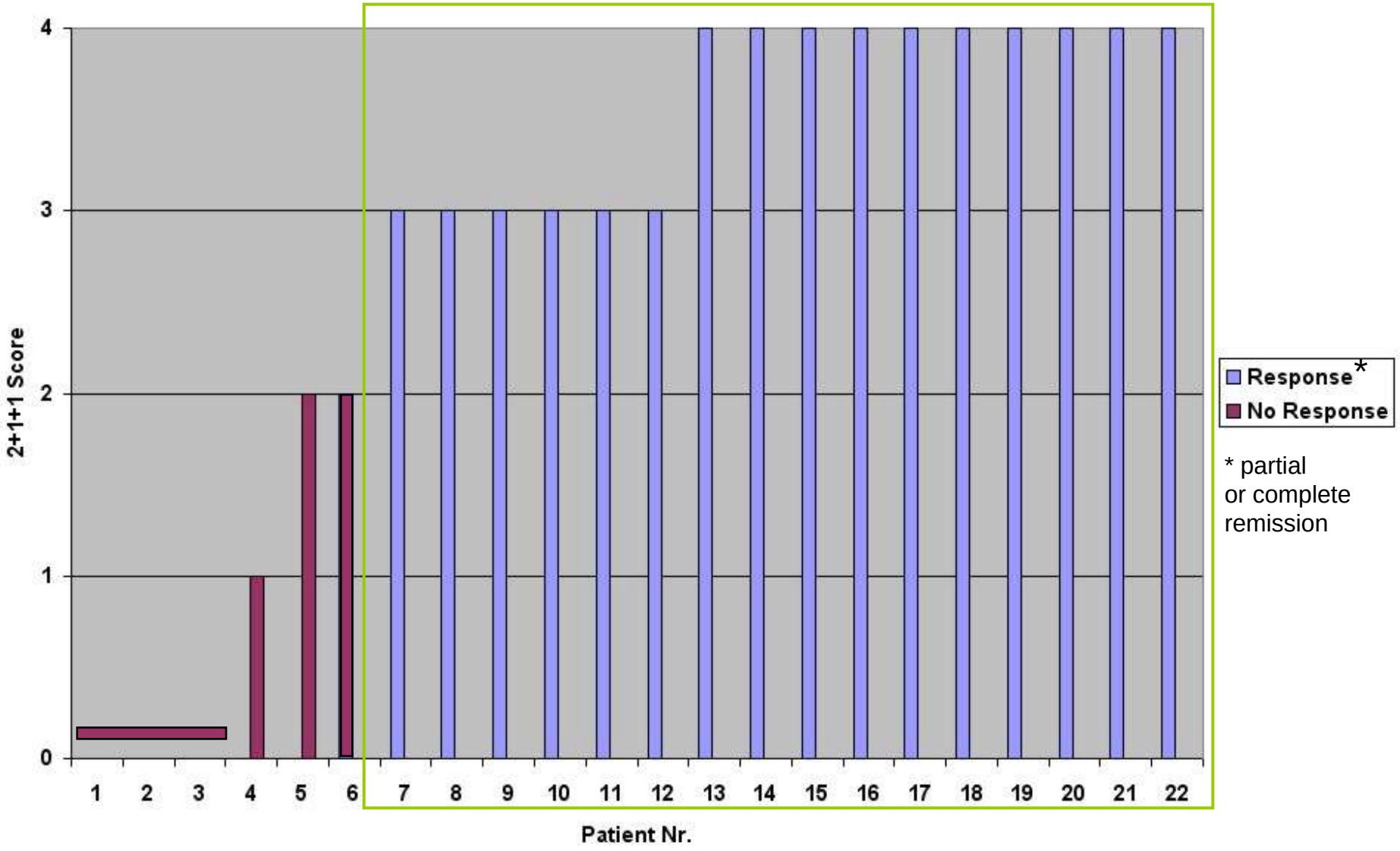


Clustering

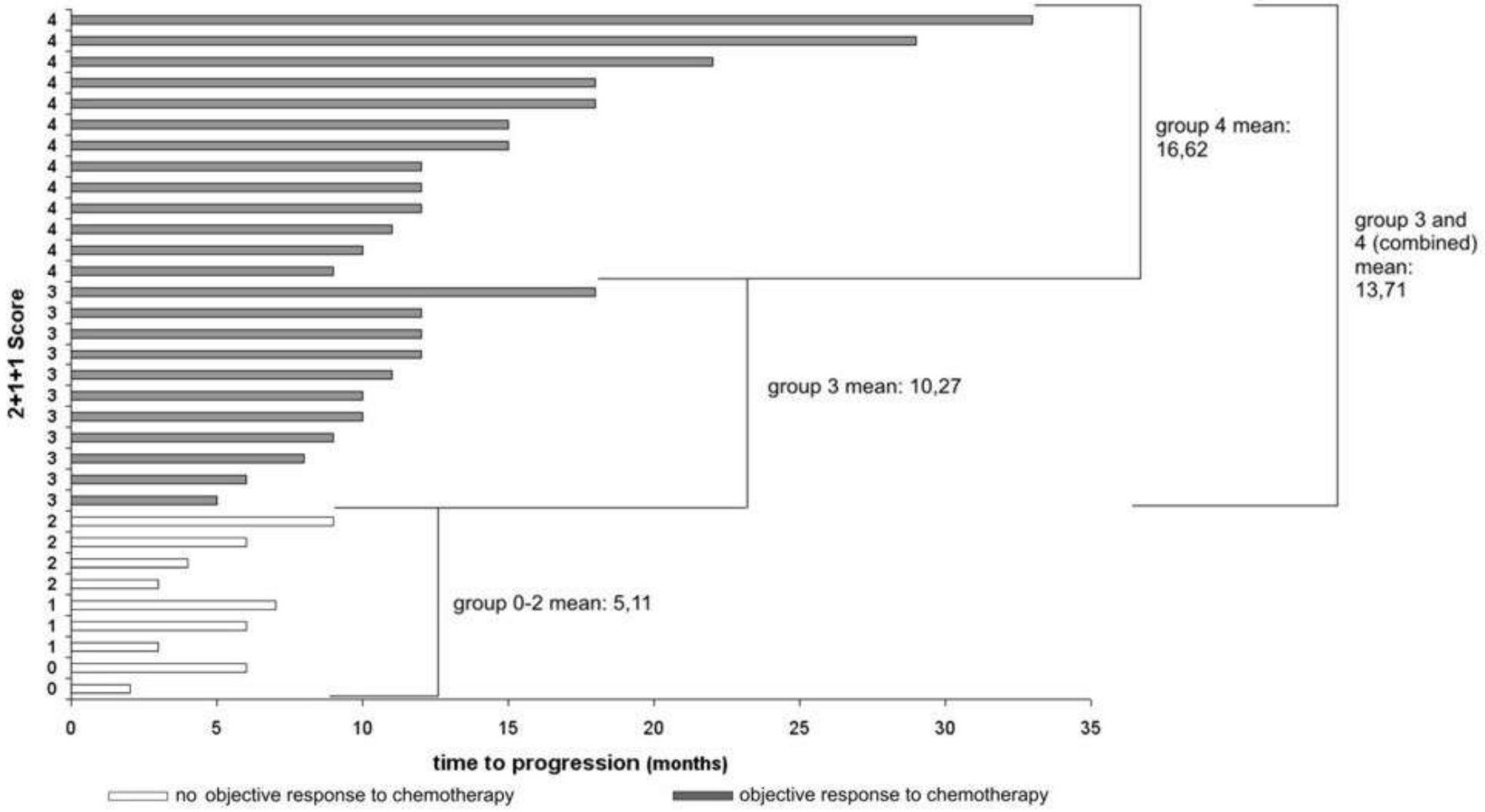


Generation of a score system (‚2+1+1‘)

Results: *metastases, invasive margin*



Results: *metastases, invasive margin*



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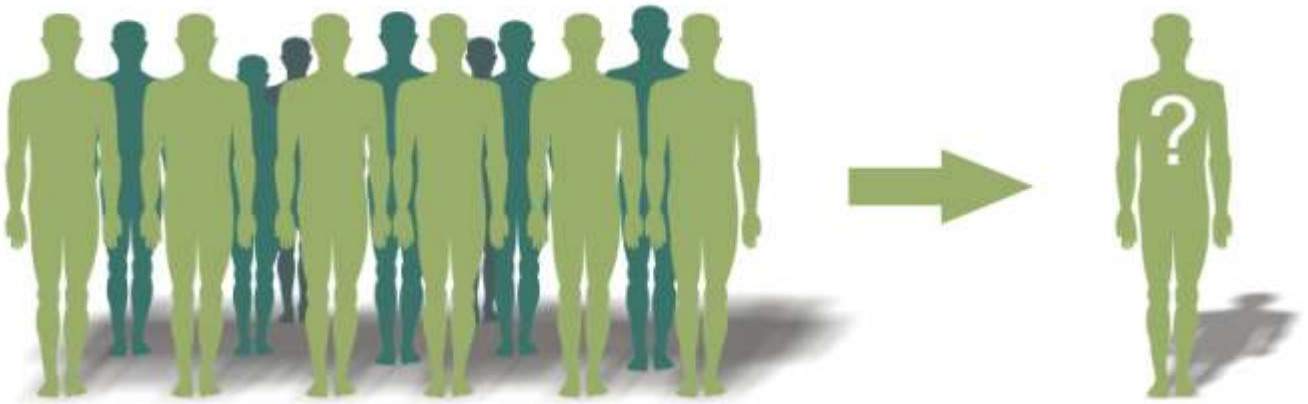
Results: *primary tumors*

Problem: heterogeneity of the tumor (center)

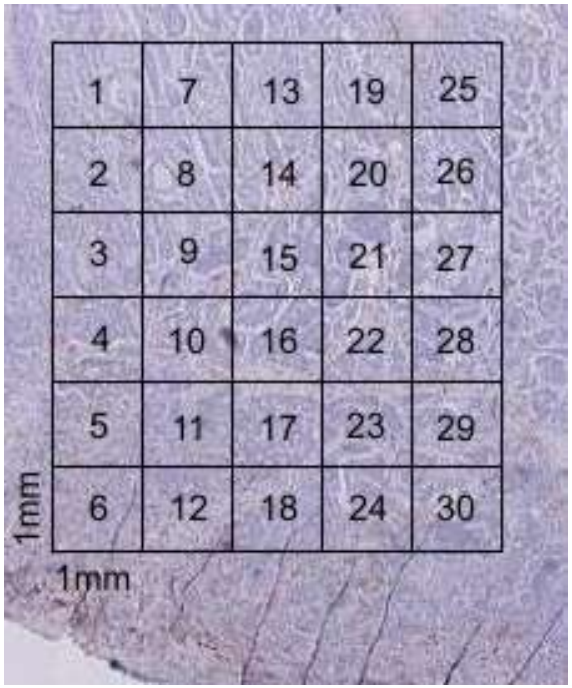
From many to just one…



TMA-Analyses

Individual patient

Heterogeneity of immune infiltrate density (I)

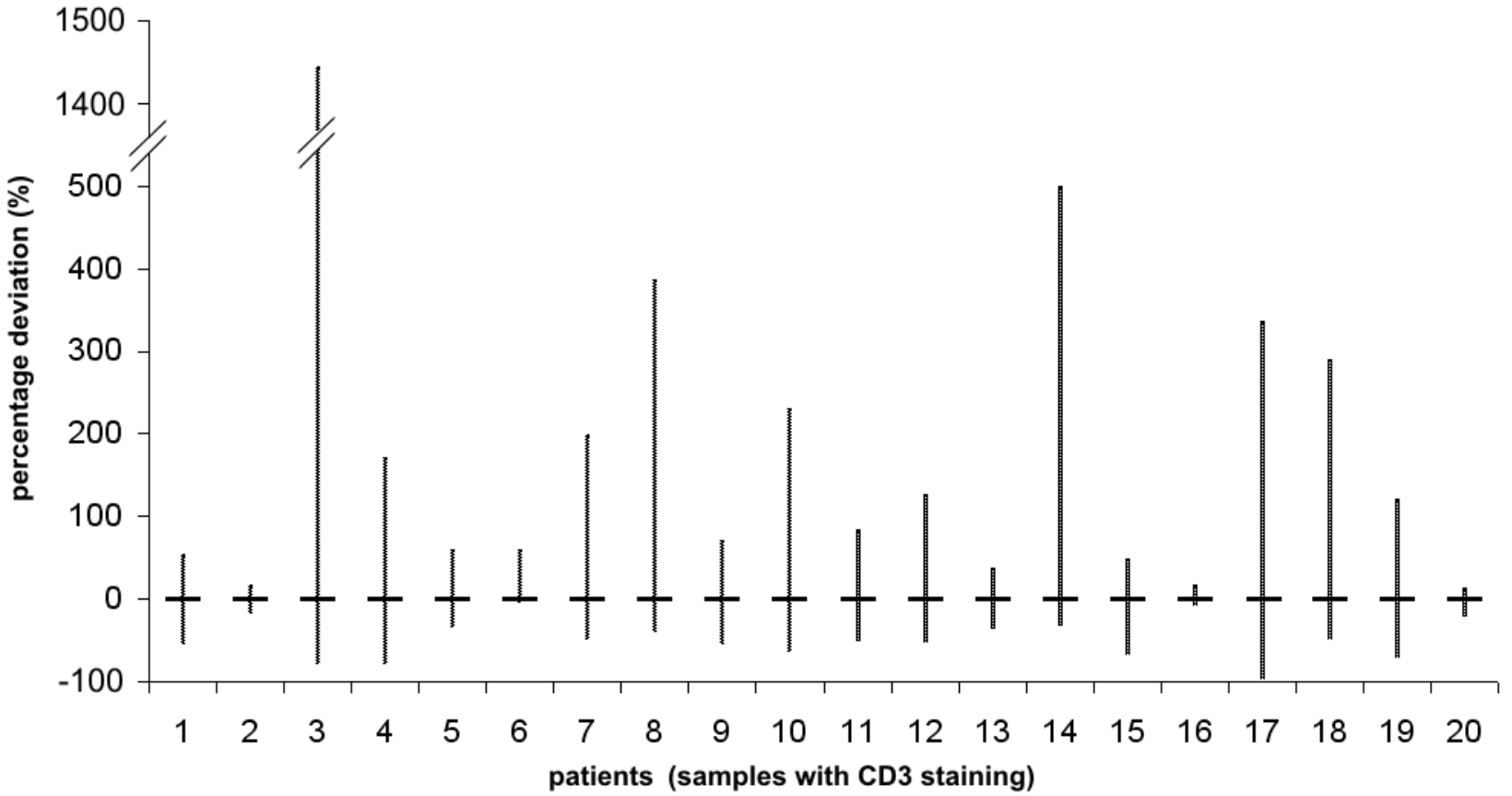


Measurements:

Median number of
positively stained cells (across all fields)

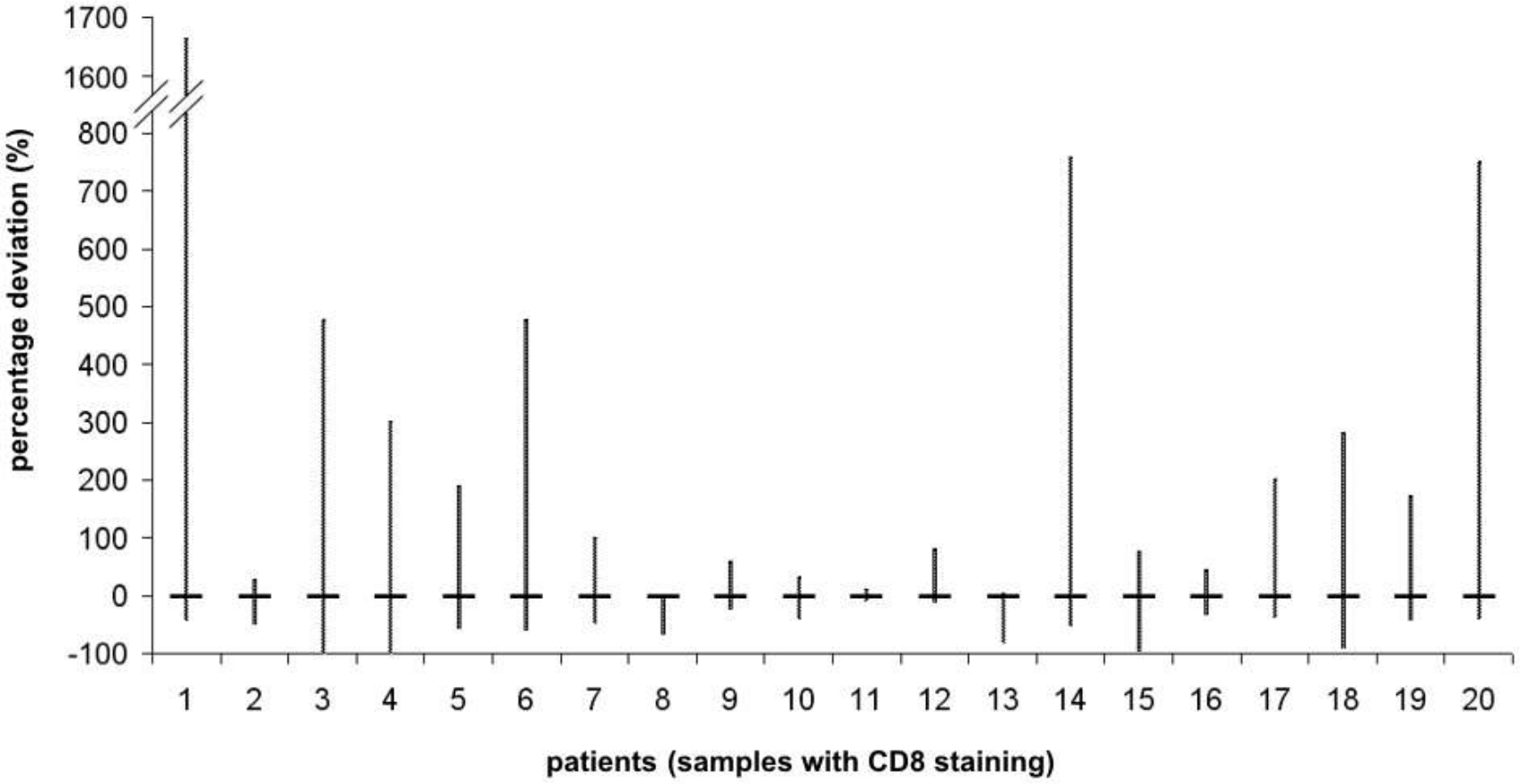
Single field evaluation

Heterogeneity of immune infiltrate density (II)



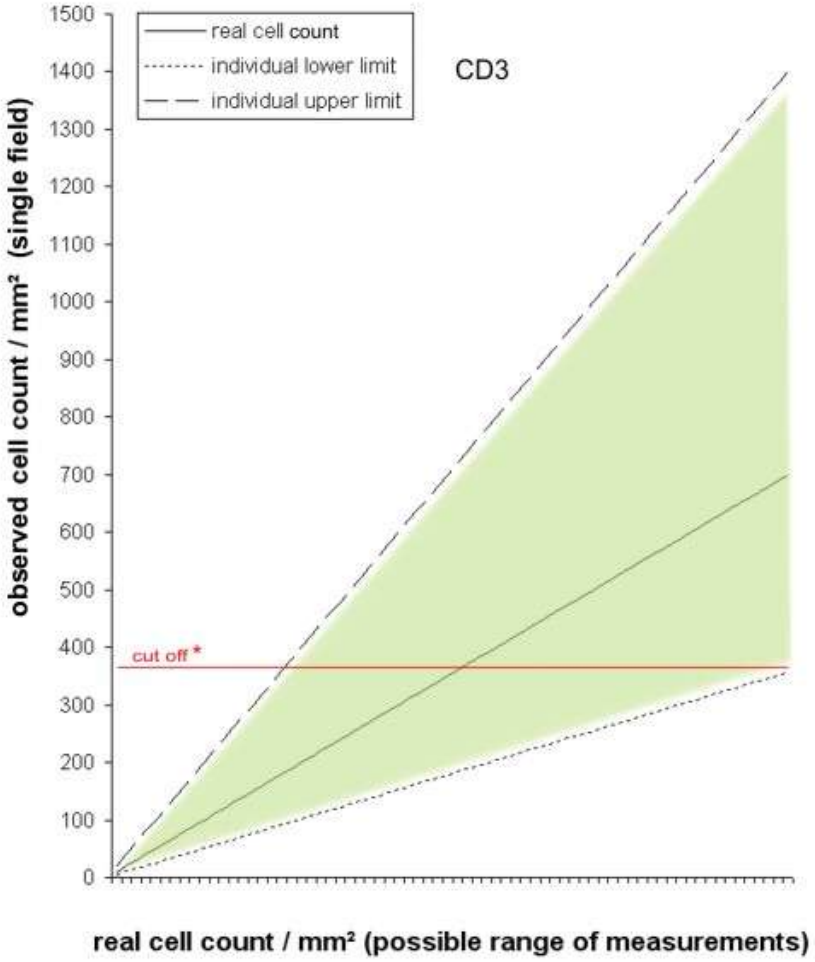
Lower and upper (maximum) deviation in cell counts / mm² as observed in samples from 20 different patients presented in percentage deviation from median (horizontal bars, negative percentage represents lower deviation, positive percentage represents upper deviation, bar length indicates maximum deviation) for CD3 staining.

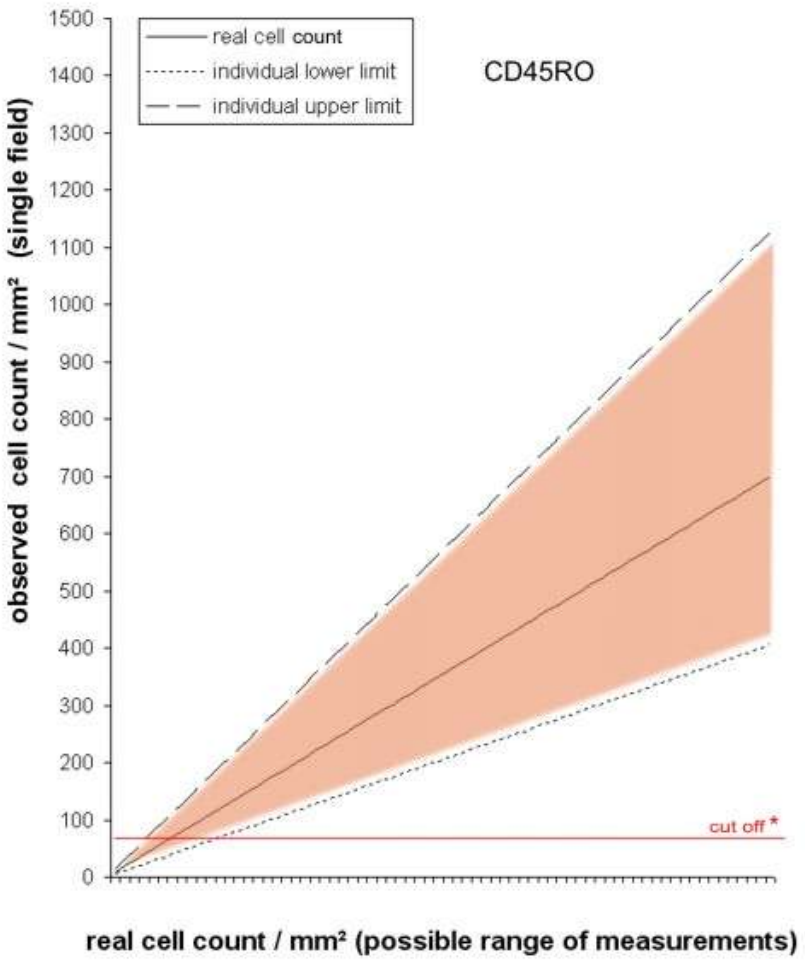
Heterogeneity of immune infiltrate density (III)



Lower and upper (maximum) deviation in cell counts / mm² as observed in samples from 20 different patients presented in percentage deviation from median (horizontal bars, negative percentage represents lower deviation, positive percentage represents upper deviation, bar length indicates maximum deviation) for CD8 staining.

Visualization of Heterogeneity





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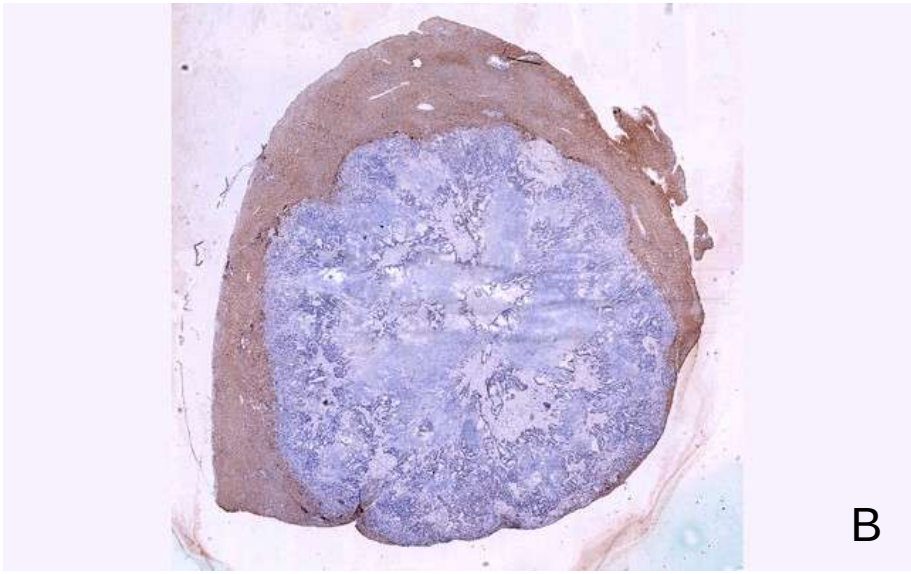
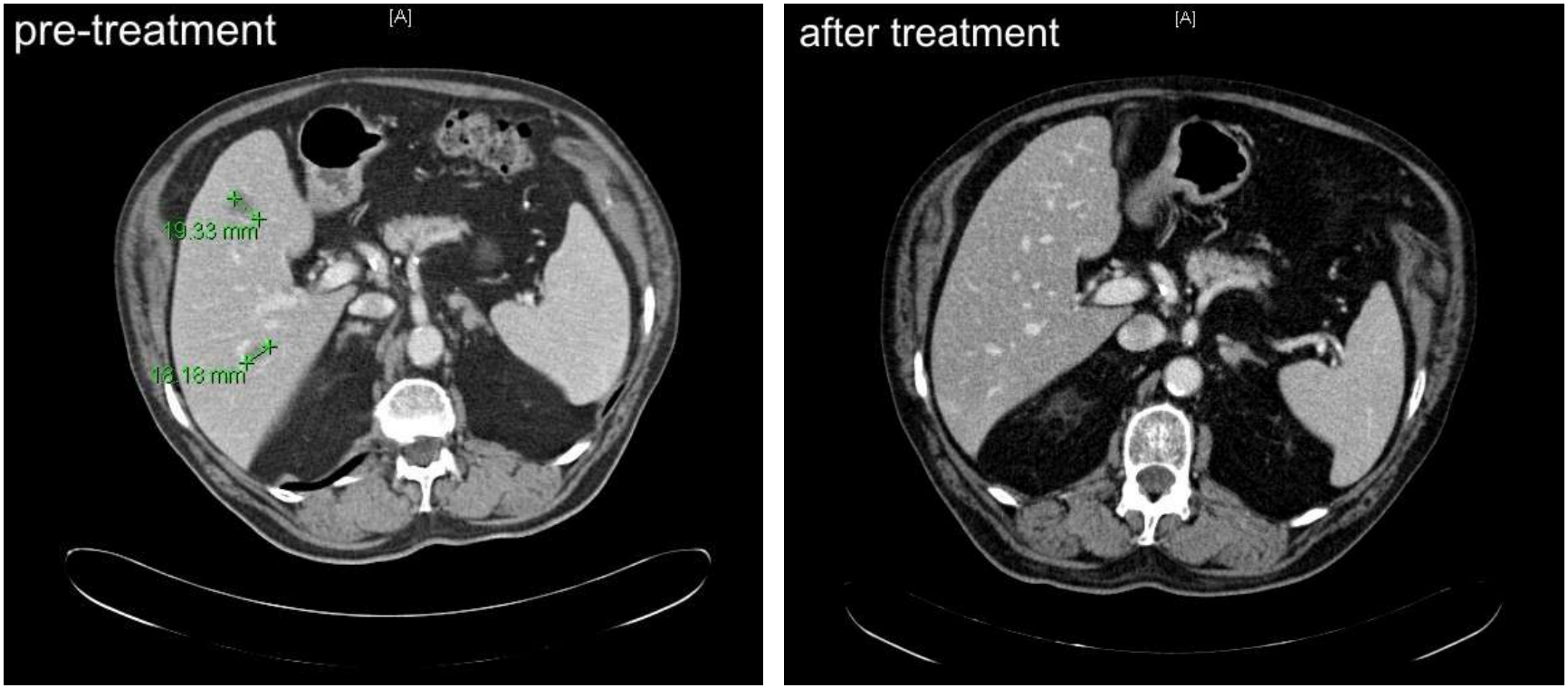
Immune infiltrates and response to chemotherapy?



Immune infiltrates and response to chemotherapy

Response to chemotherapy…a clinical example



CT scans, pre- and post-treatment, Irinotecan-based regimen, four cycles chemotherapy (8 weeks)

Patient A has had a complete remission of all liver metastases…

Acknowledgements / Contributors


Matthias Kloor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Can we use Virtual Microscopy to identify (immunologic) parameters in patient cohorts
AND
make predictions for individual patients?


YES WE CAN
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