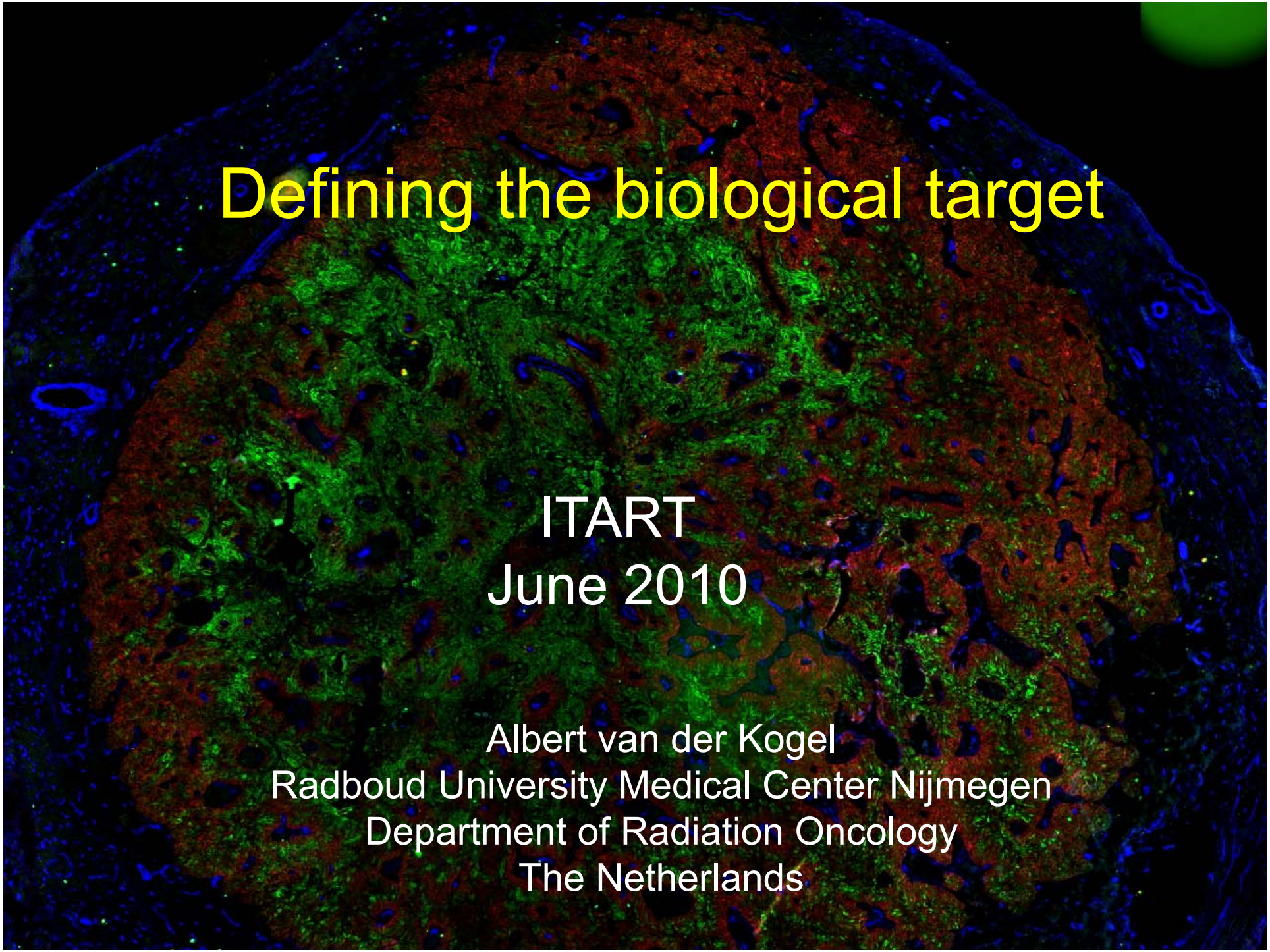
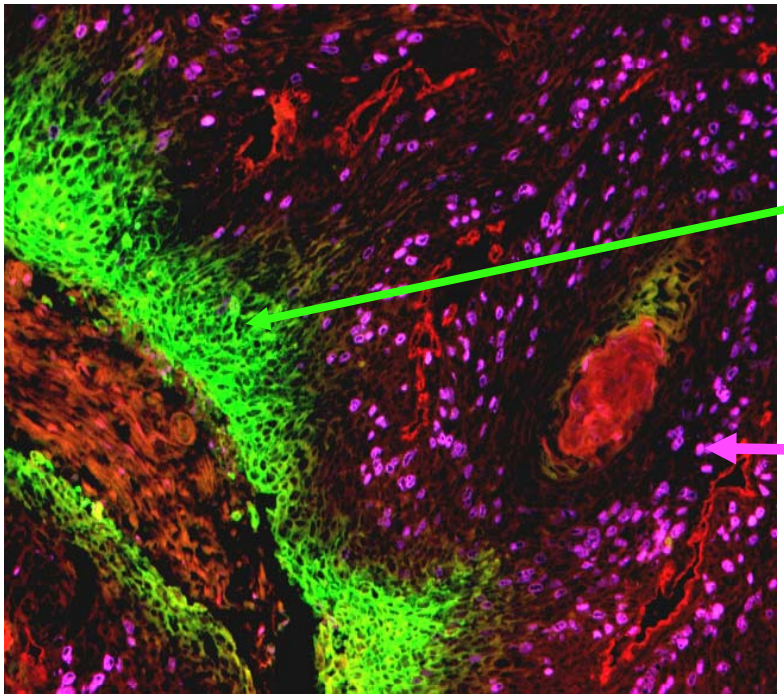


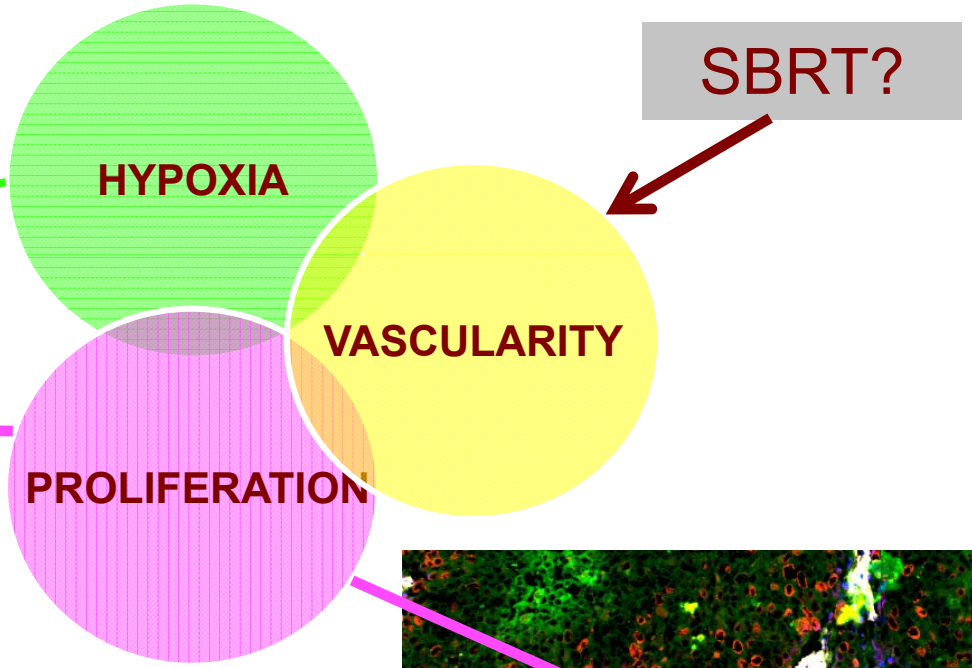
Defining the biological target

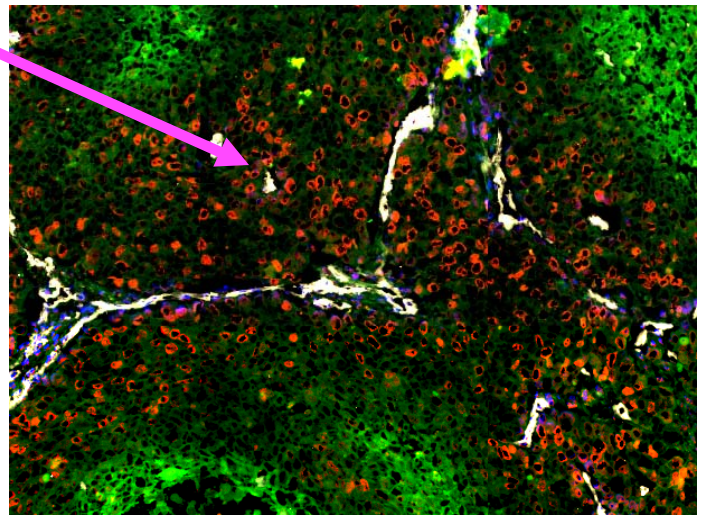
ITART
June 2010

Albert van der Kogel
Radboud University Medical Center Nijmegen
Department of Radiation Oncology
The Netherlands

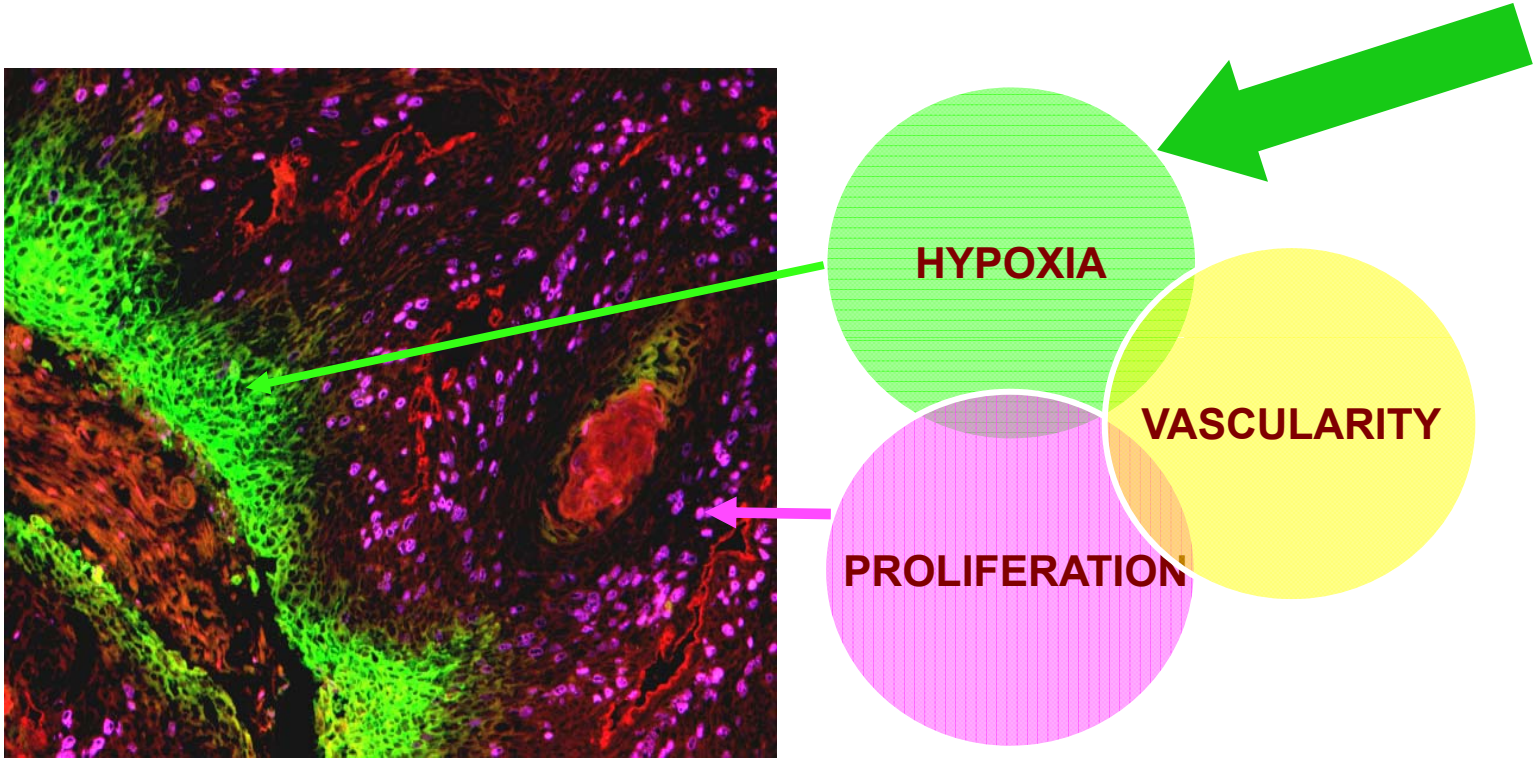
The primary biological targets for RT: hypoxia & proliferation





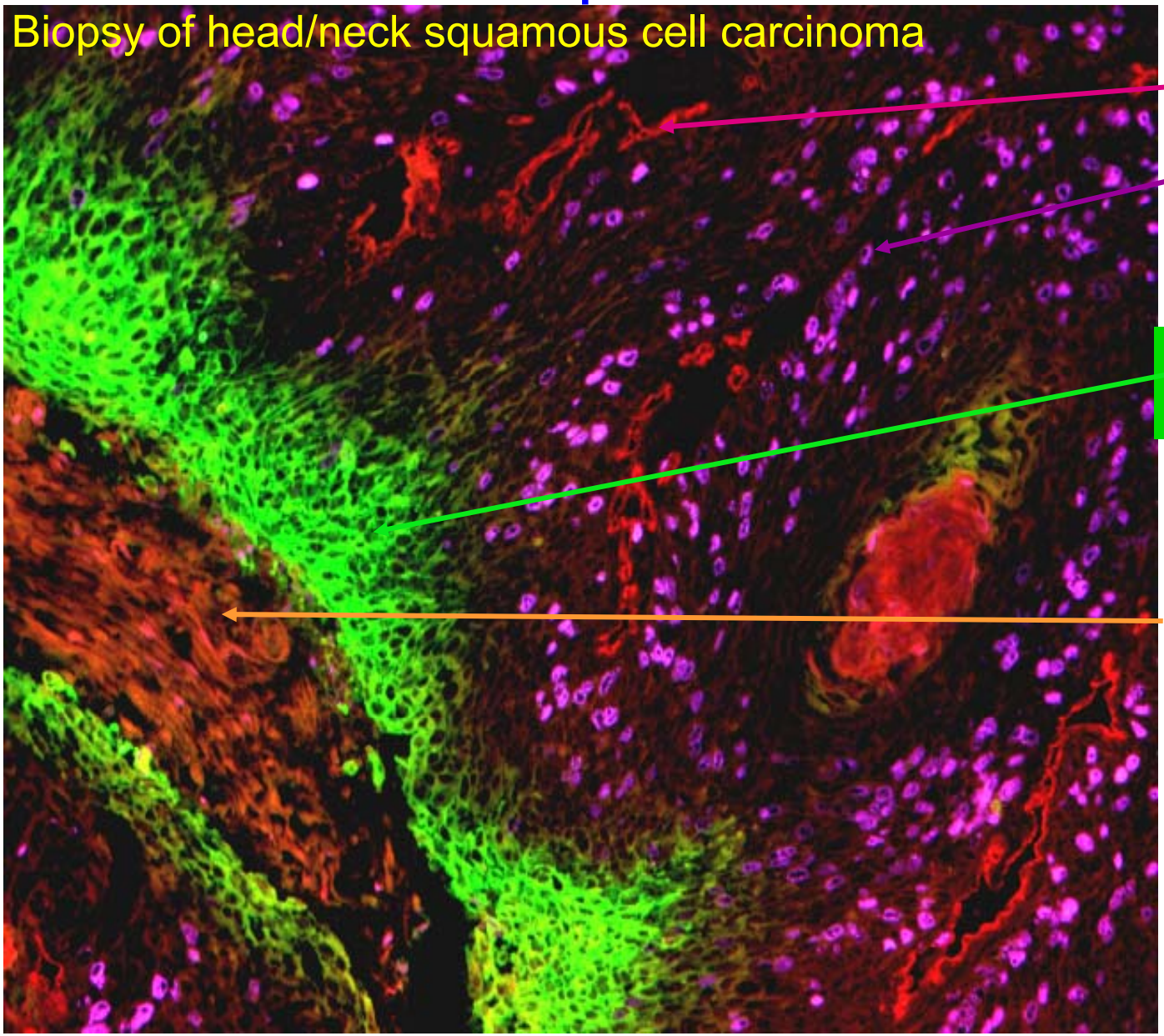


A classic resistance mechanism in radiotherapy: hypoxia

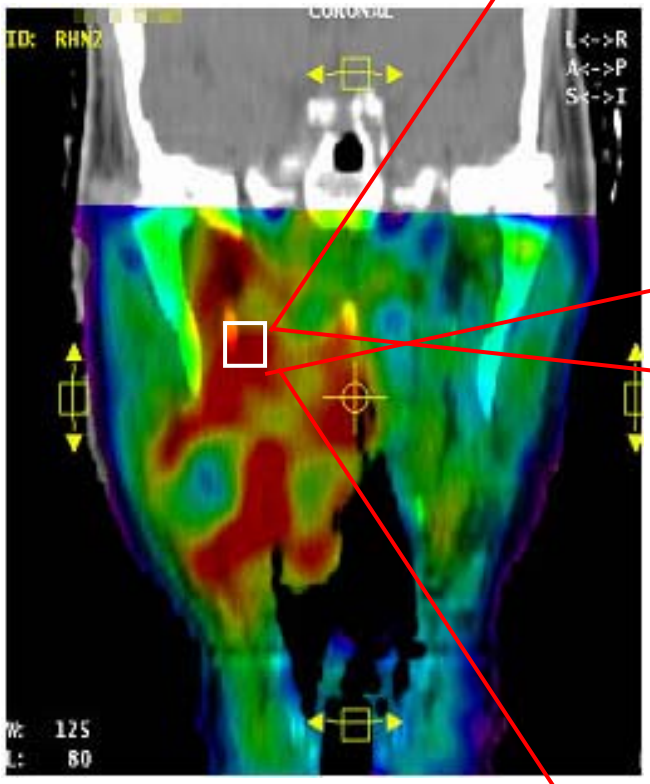


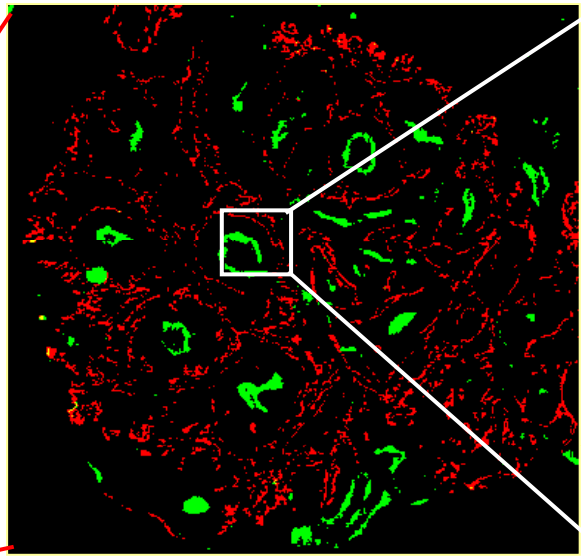
Hypoxia is not a static condition, and generally changes in response to irradiation and many chemotherapeutic and biological agents

Immunohistochemical imaging of hypoxia and proliferation

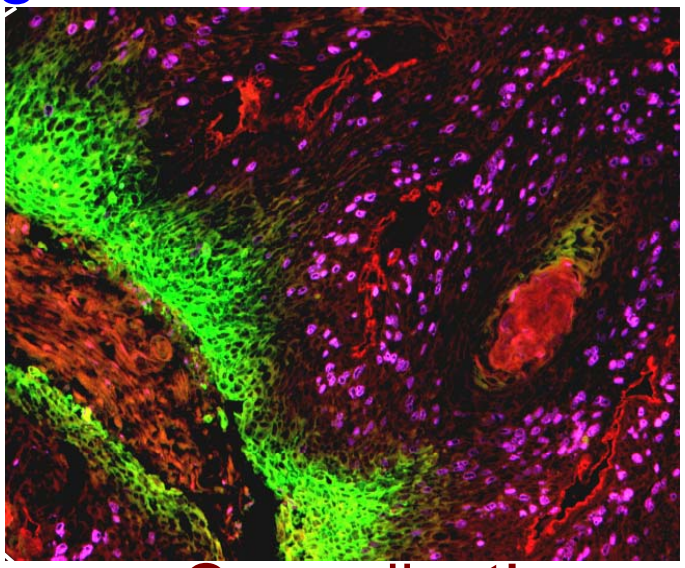


Hypoxia imaging - from PET hypoxic voxel to microregional distribution

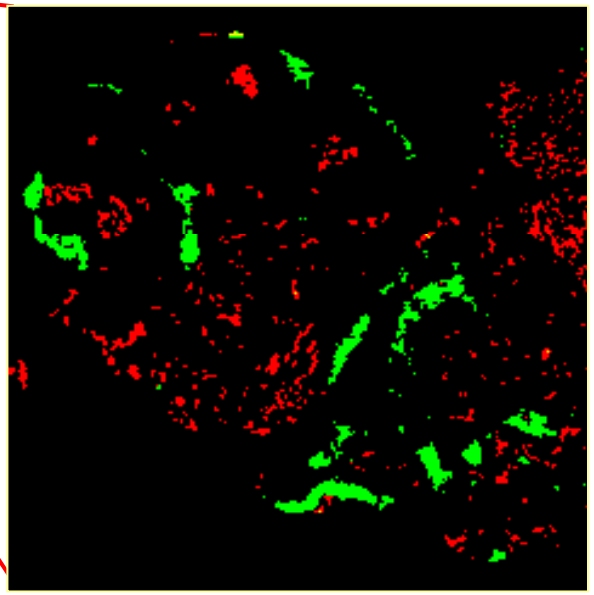




biopsy

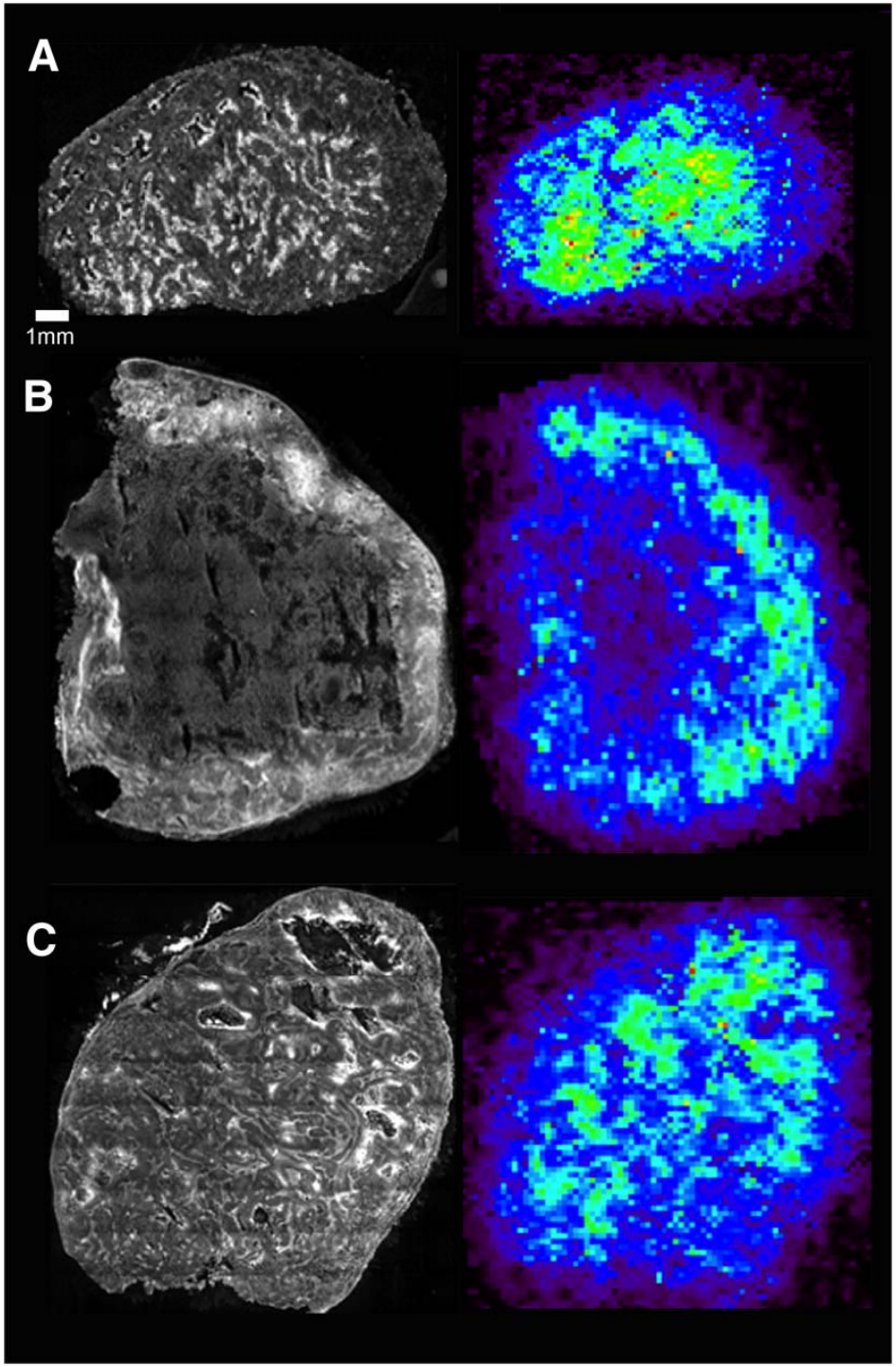


pO_2 gradient!



Hypoxia is not binary, and identical hypoxic voxels may represent different biological characteristics

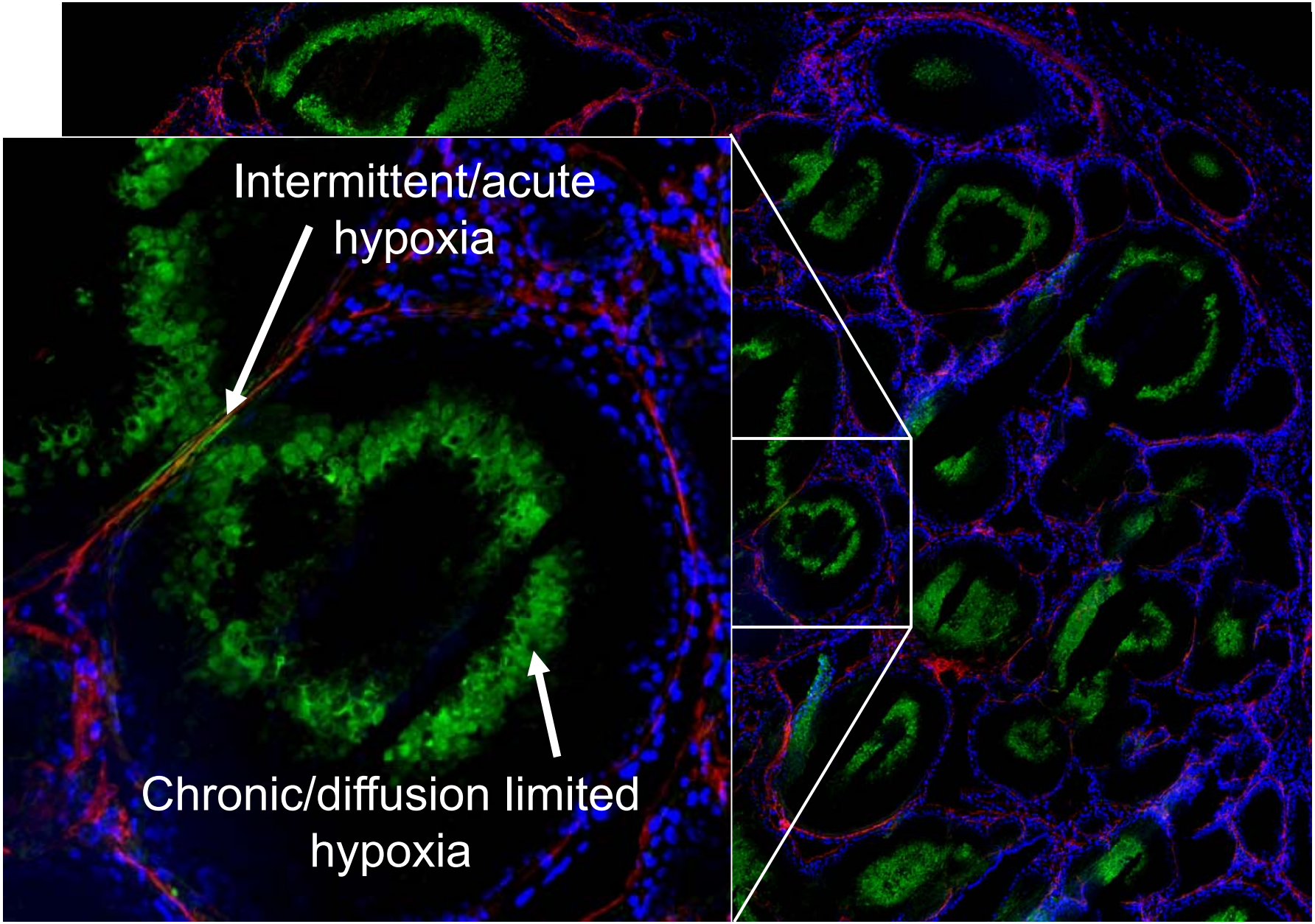
^{18}F-misonidazole autoradiography vs. pimonidazole IHC: correlation related to tumor structure



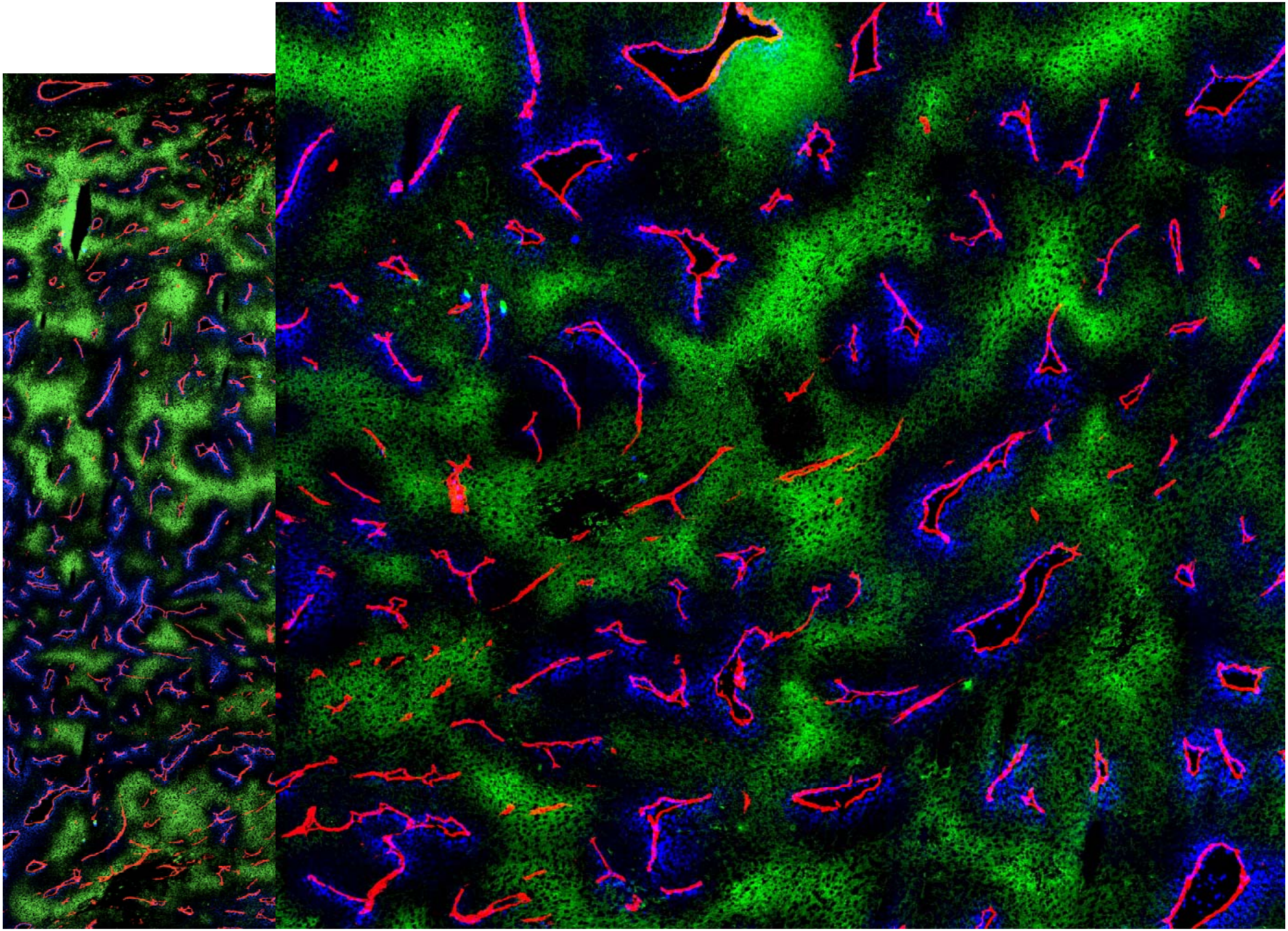
Gray-value images after immunohistochemical staining of pimonidazole (left) and ^{18}F-FMISO autoradiography (right) of SCCNij3 (A), SCCNij153 (B), and SCCNij86 (C) xenografted human squamous cell carcinomas of head and neck.
Pimonidazole and ^{18}F-FMISO correlate for SCCNij3 and SCNij153 but not for SCCNij86.

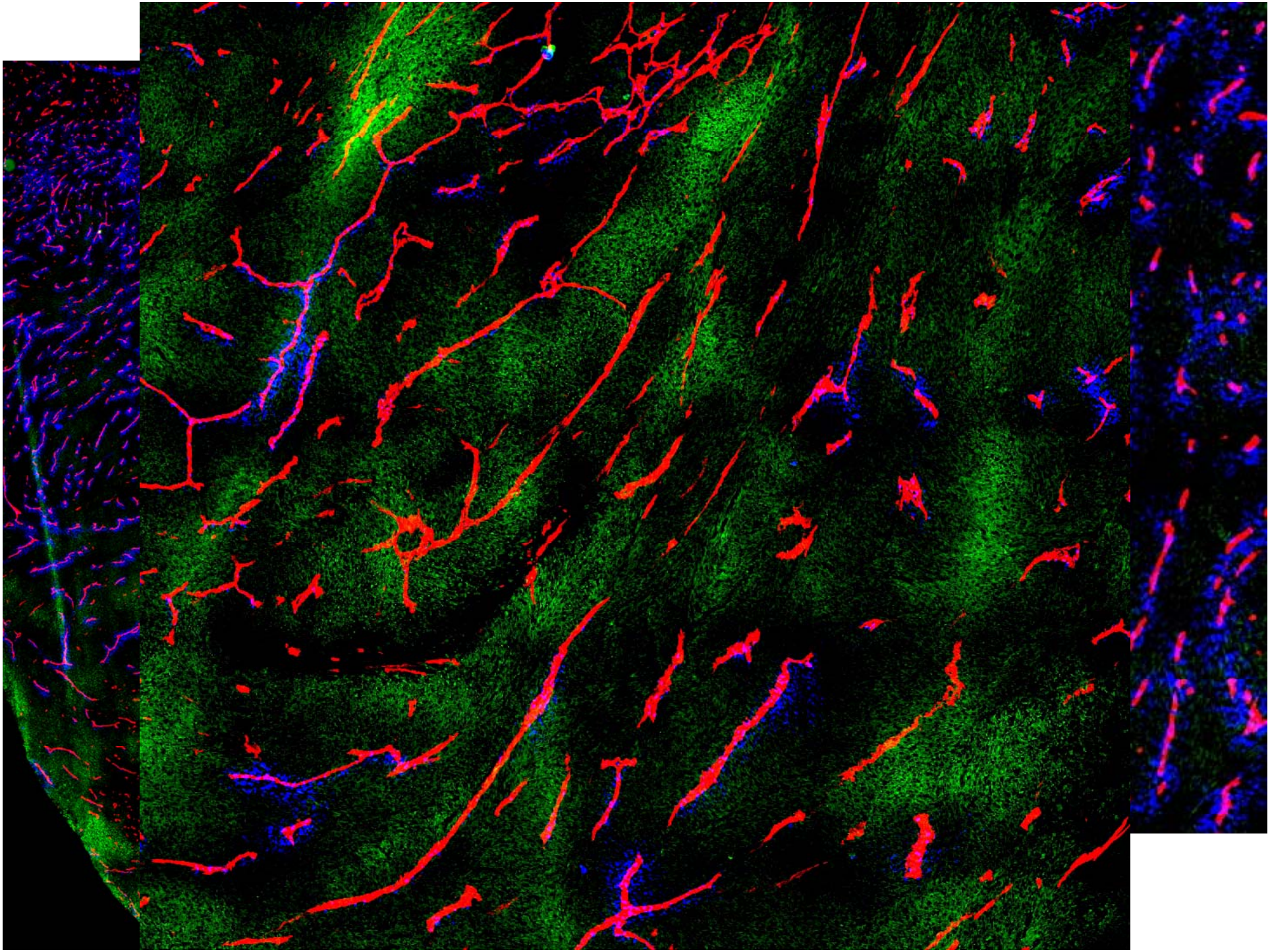
Troost et al, Eur J Nucl Med 2008

Different types of hypoxia in same tumor

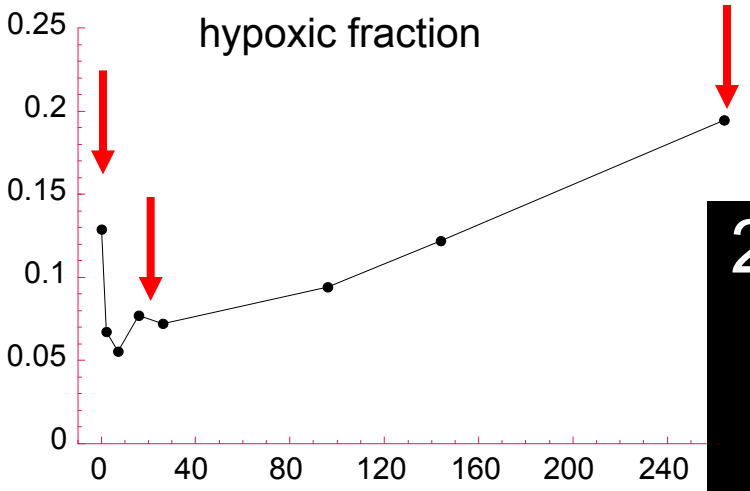


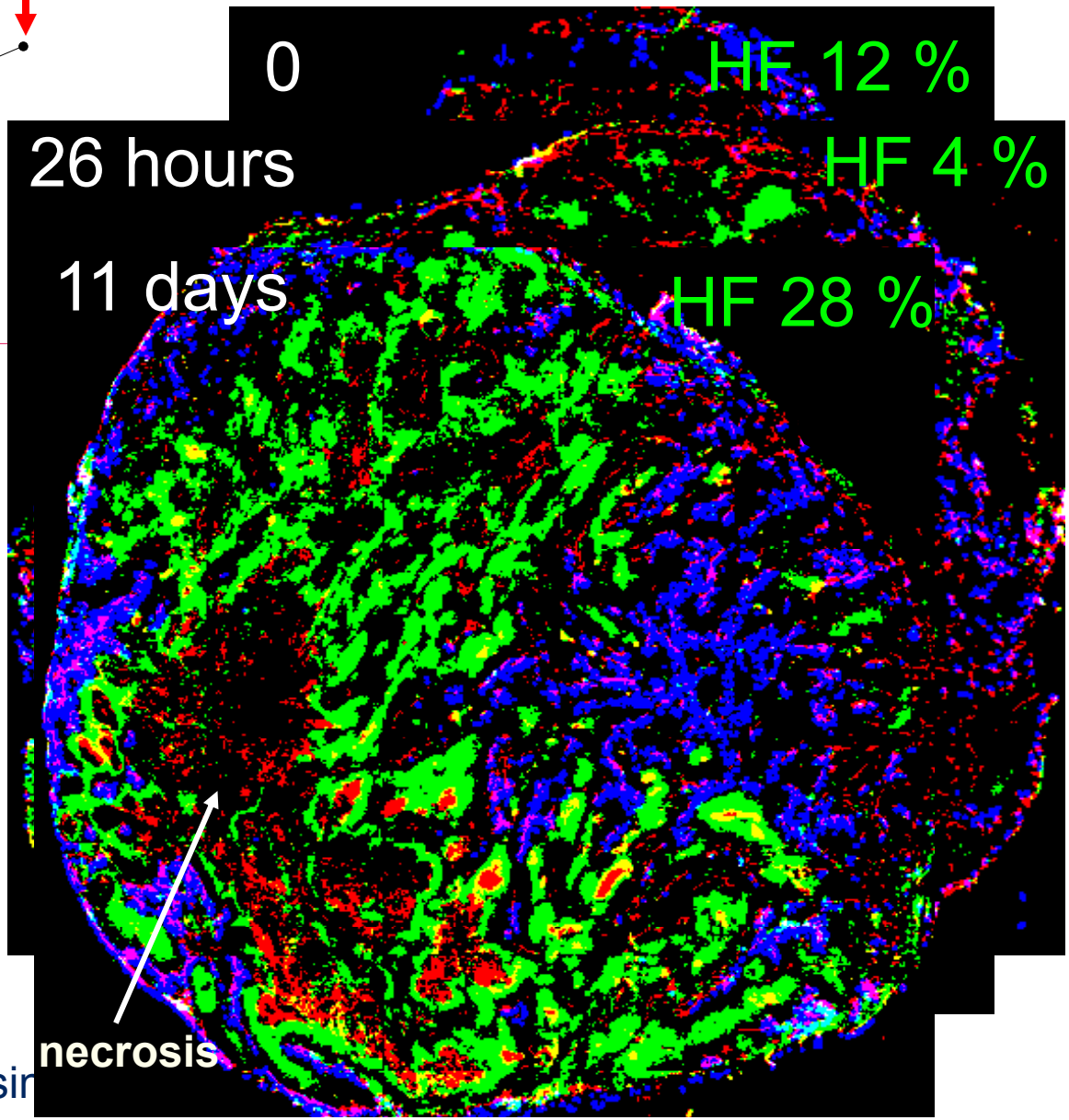
heterogeneity in hypoxia (R1 tumor)





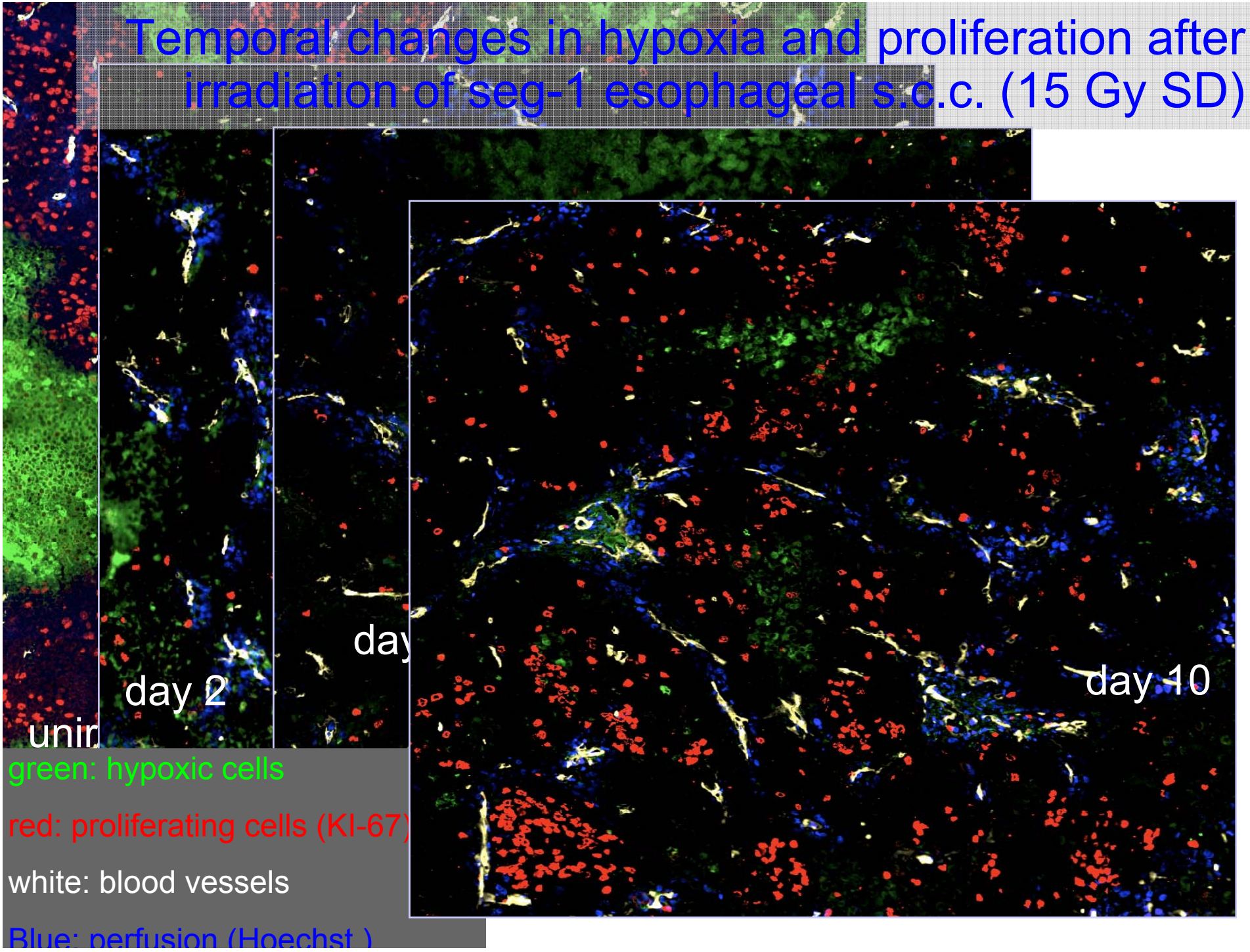
Effect of irradiation on hypoxia



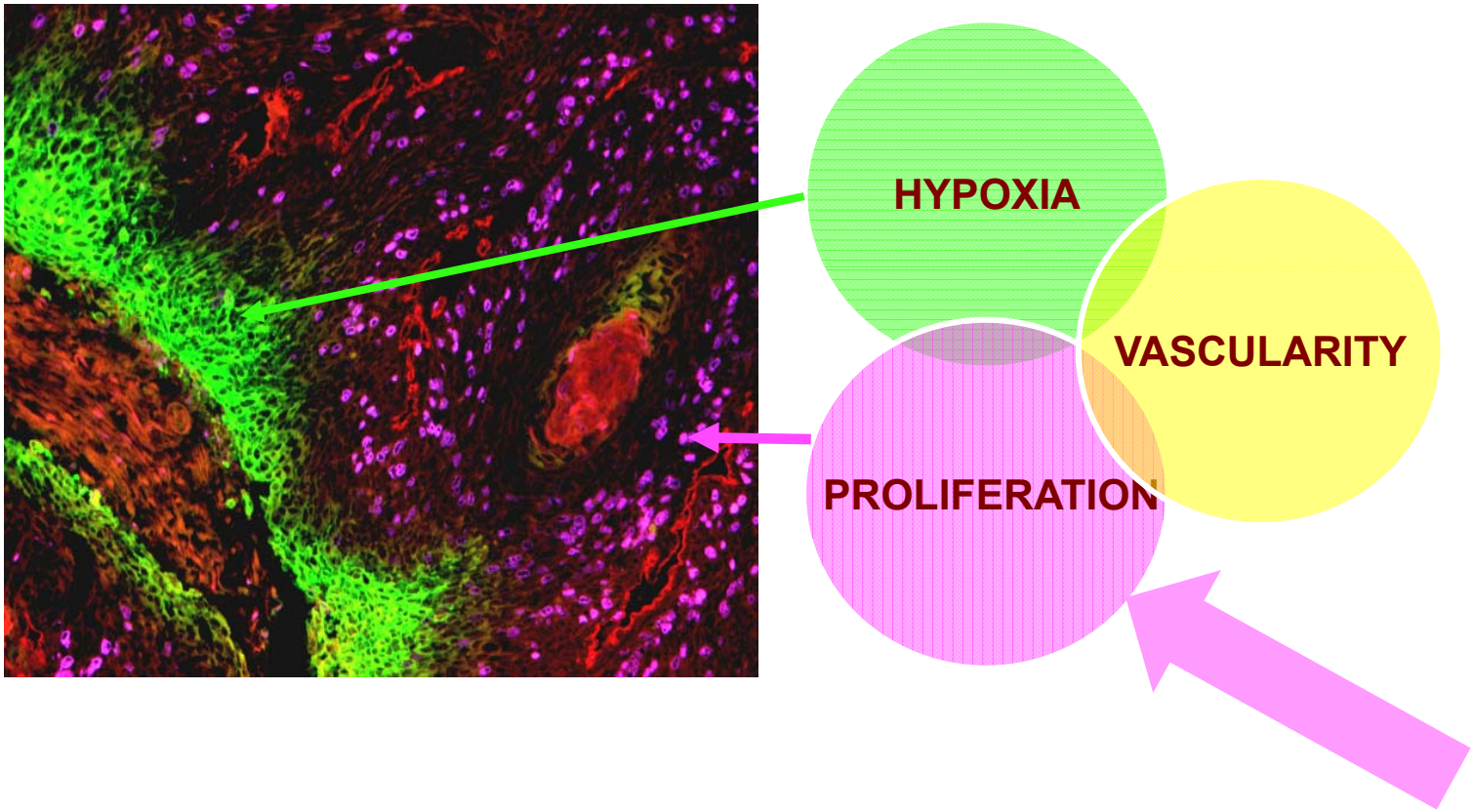


Bussi

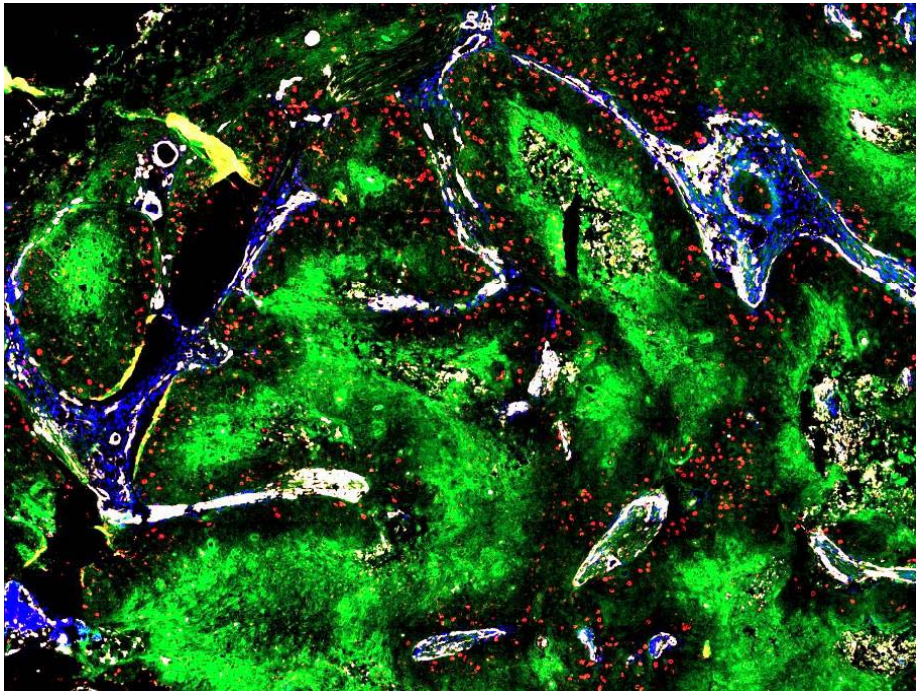
Temporal changes in hypoxia and proliferation after irradiation of seg-1 esophageal s.c.c. (15 Gy SD)

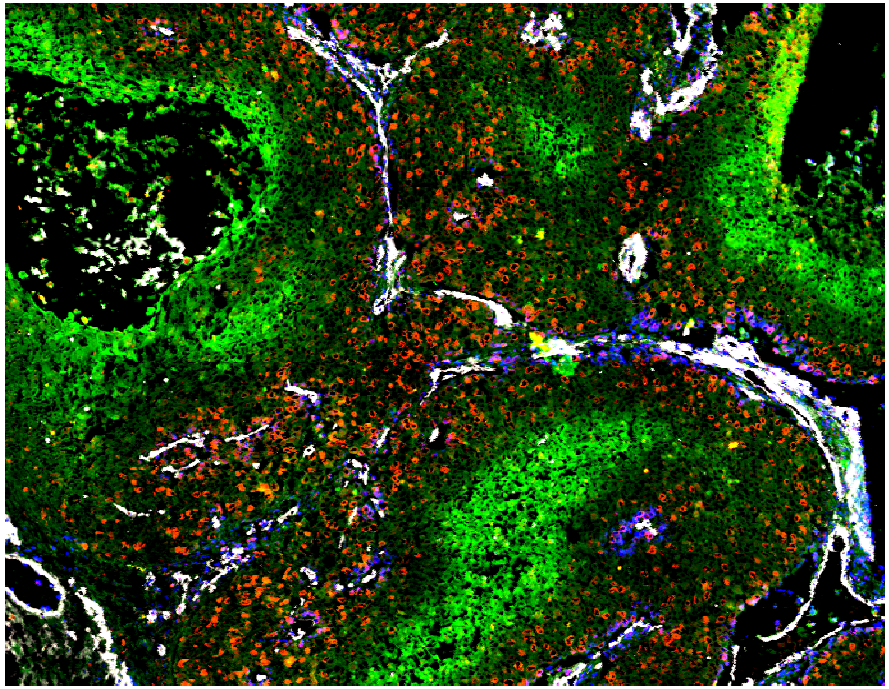


Overall treatment time-related loss of effect: proliferation



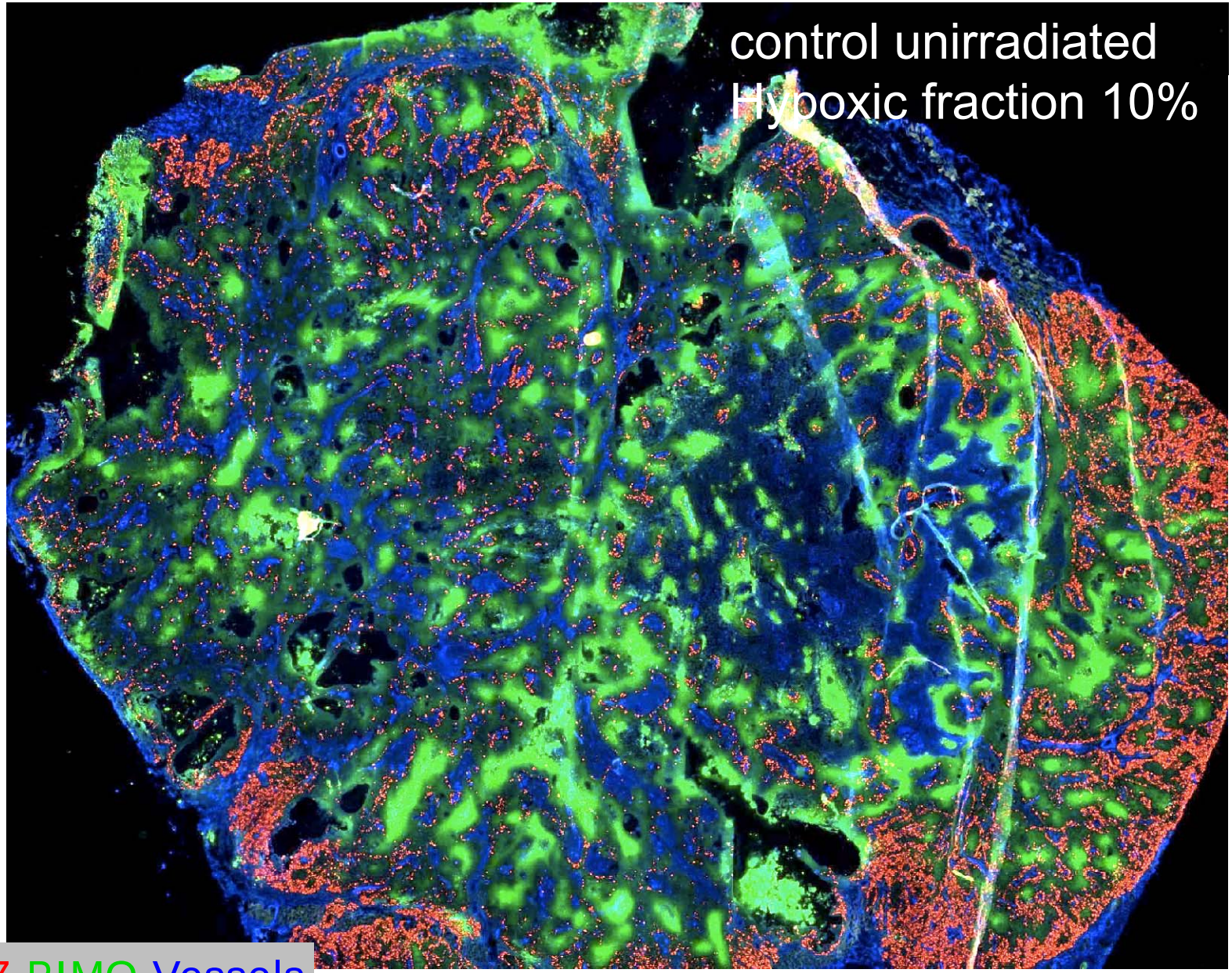
Larynx carcinoma xenografts showing different proliferation patterns





Hypoxia (pimonidazole)
Blood vessels (CD31 a.o.)
Perfused vessels (Hoechst dye)
Proliferating cells (BrdU)

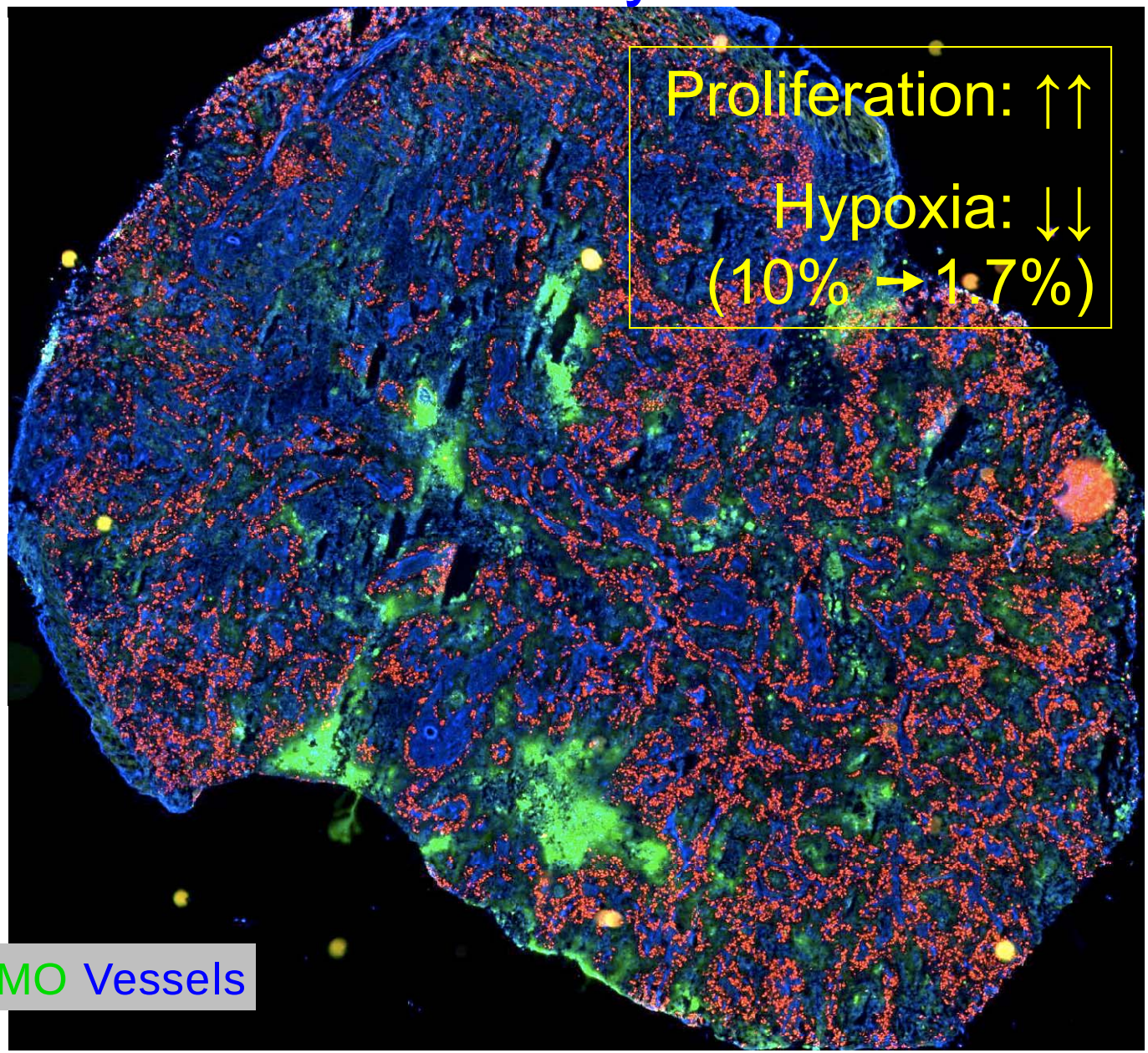
Proliferation & hypoxia in human s.c.c. xenograft



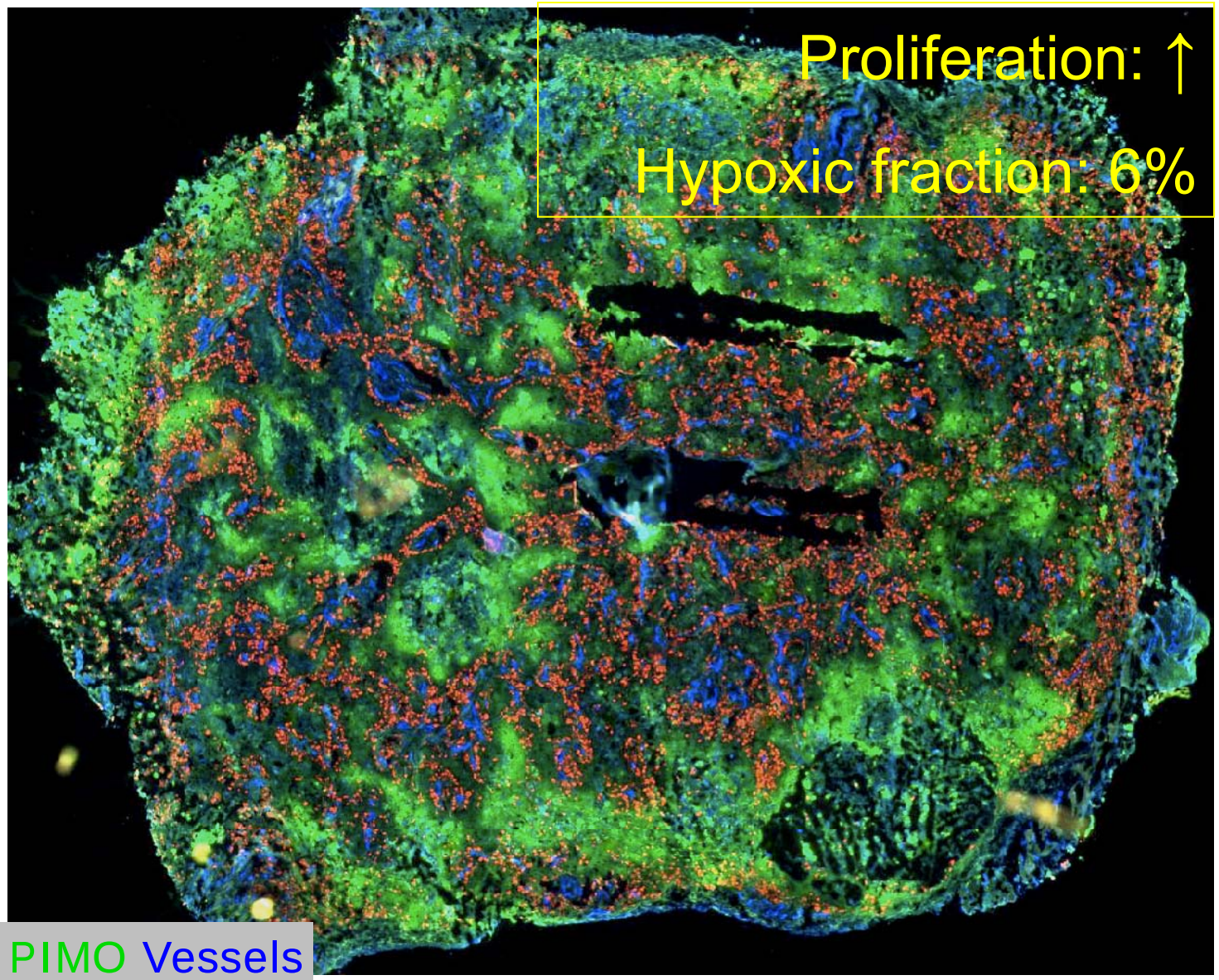
Ki67 PIMO Vessels

T Kruser et al, Clin Canc Res 2010

Proliferation & hypoxia in human s.c.c. xenograft after 8 X 3 Gy/4 weeks

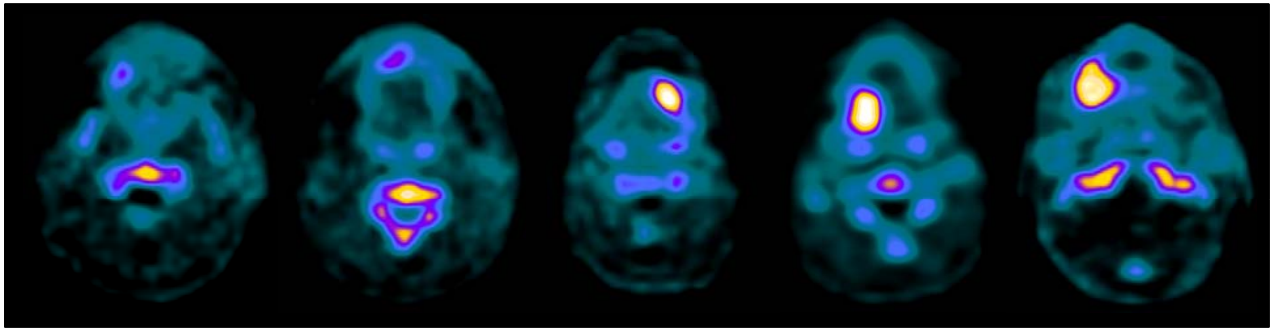


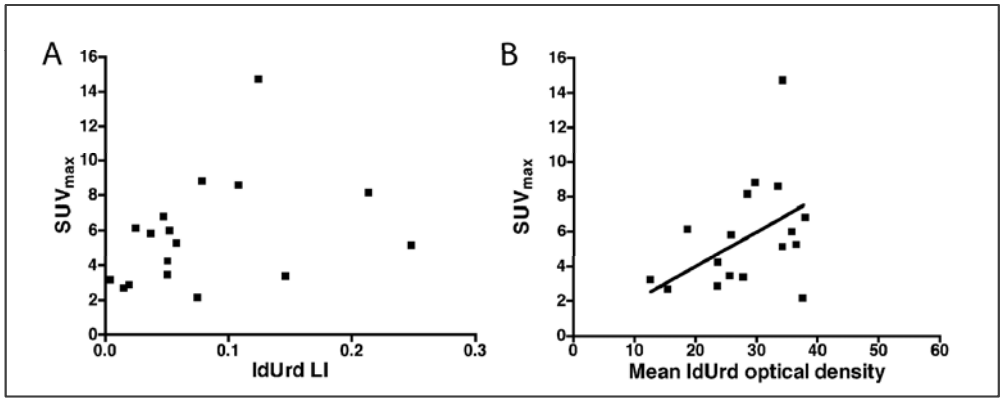
Proliferation & hypoxia
after 8 X 3 Gy/4 weeks + VEGFR2 inhibitor



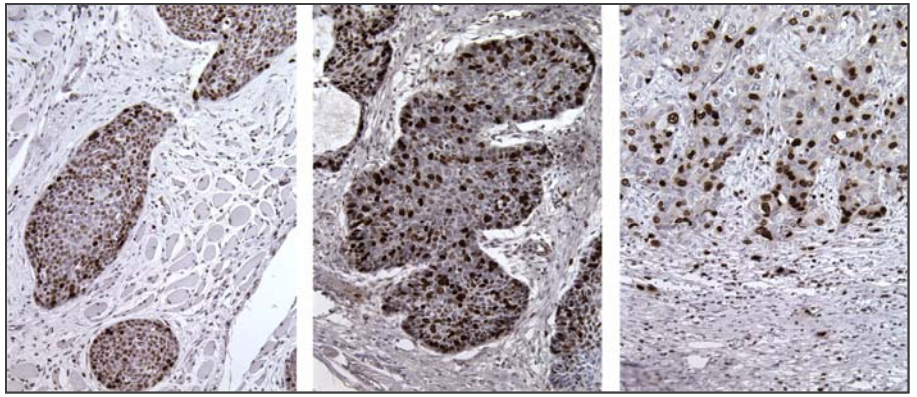
T Kruser et al, Clin Canc Res 2010

FLT-PET: weak correlation with immunohistochemical IdUrd labeling

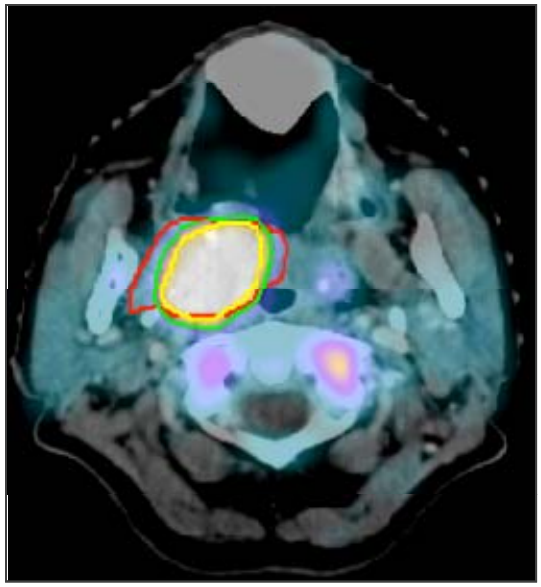




p<0.0001

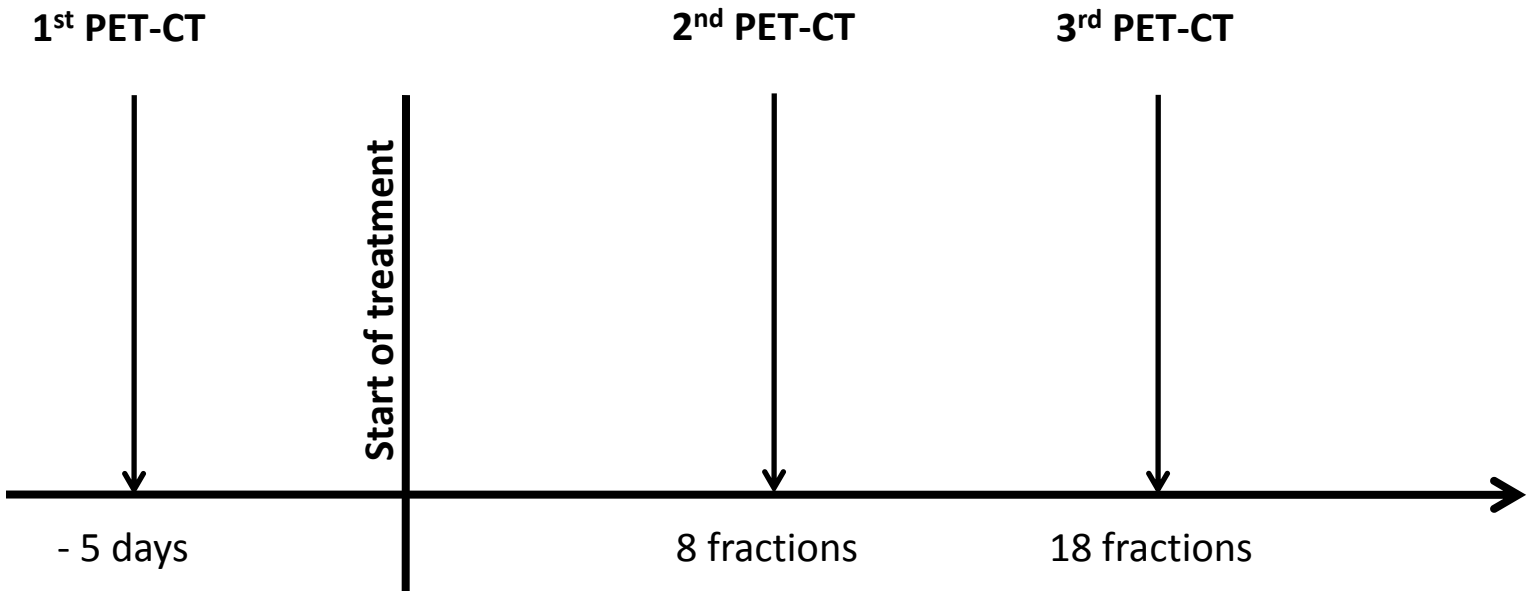


Multiple FLT-PET in oropharyngeal tumors



10 patients with oropharyngeal tumours undergoing (chemo)radiation

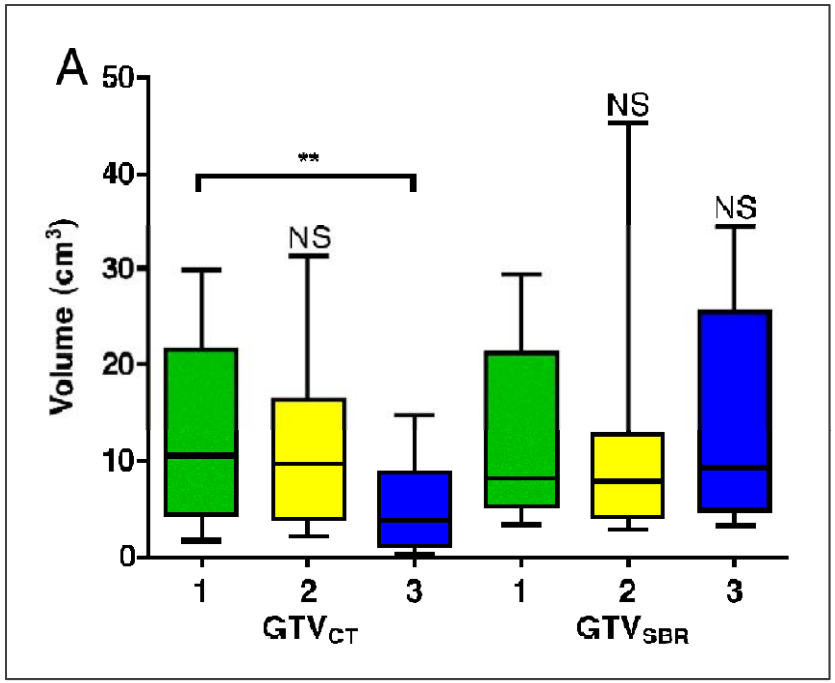
3 FLT-PET-CT scans with i.v. contrast agent

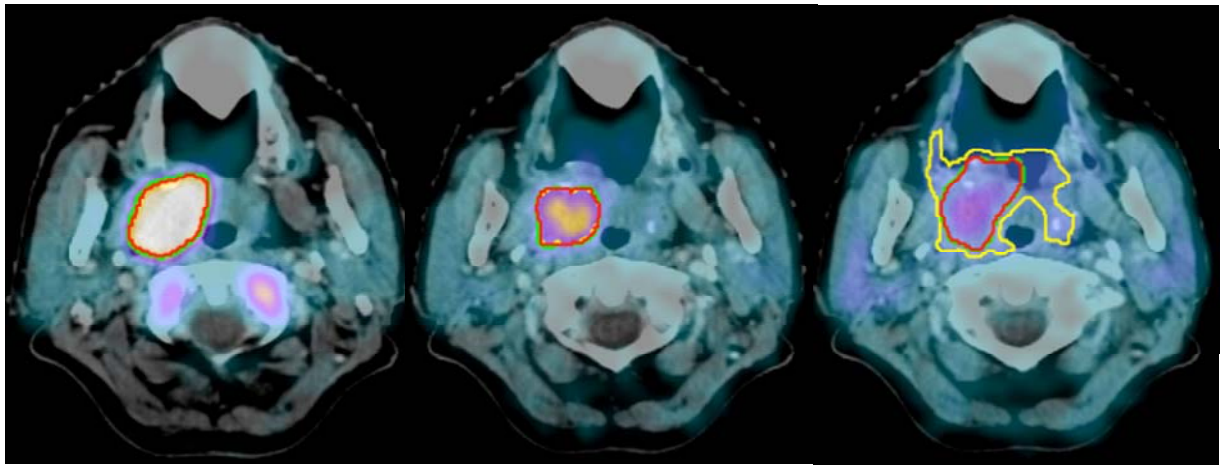


Troost et al, 2009 & 2010

CT vs FLT-PET : repeated measurements

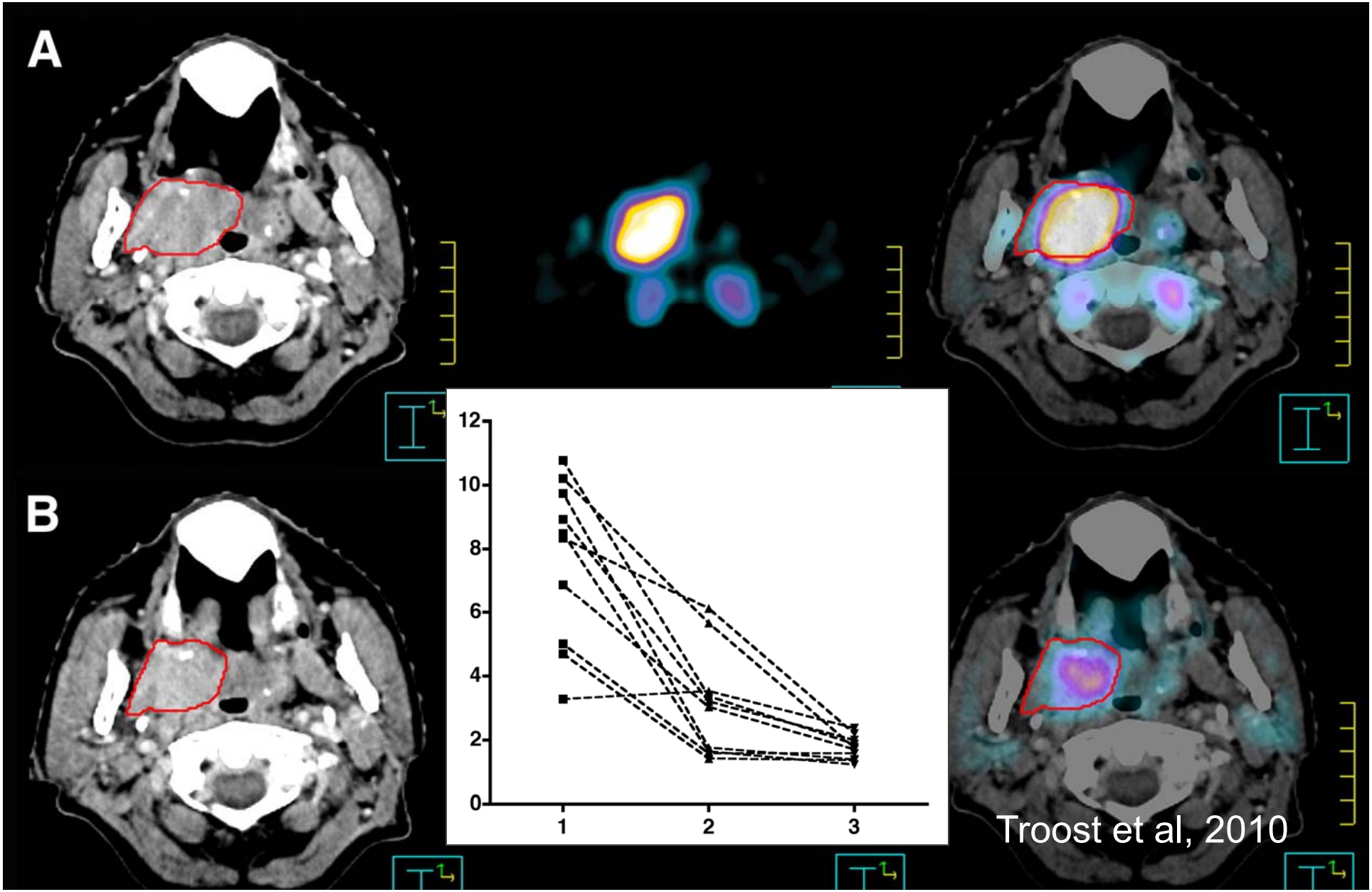
- The mean gross tumor volume on CT (GTV_{CT}) was 12.7 cm^3 prior to treatment, 11.1 cm^3 in the second and 5.0 cm^3 in the fourth week of treatment
- GTV_{CT} decreased significantly after 18 fractions ($p < 0.001$)
- $GTV_{FLT/PET}$ did not change significantly





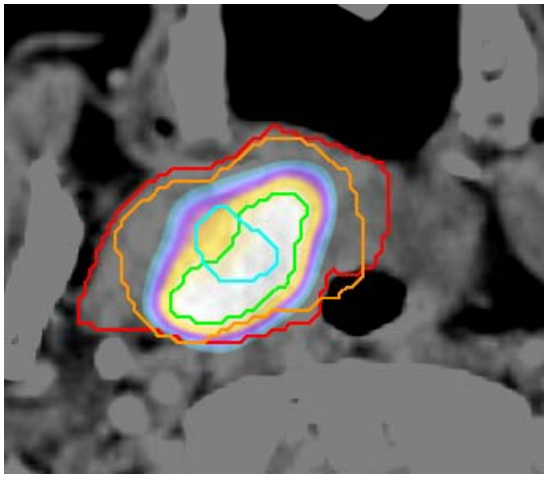
Troost et al, JNM 2010

Individual differences in reduction of FLT/PET signal

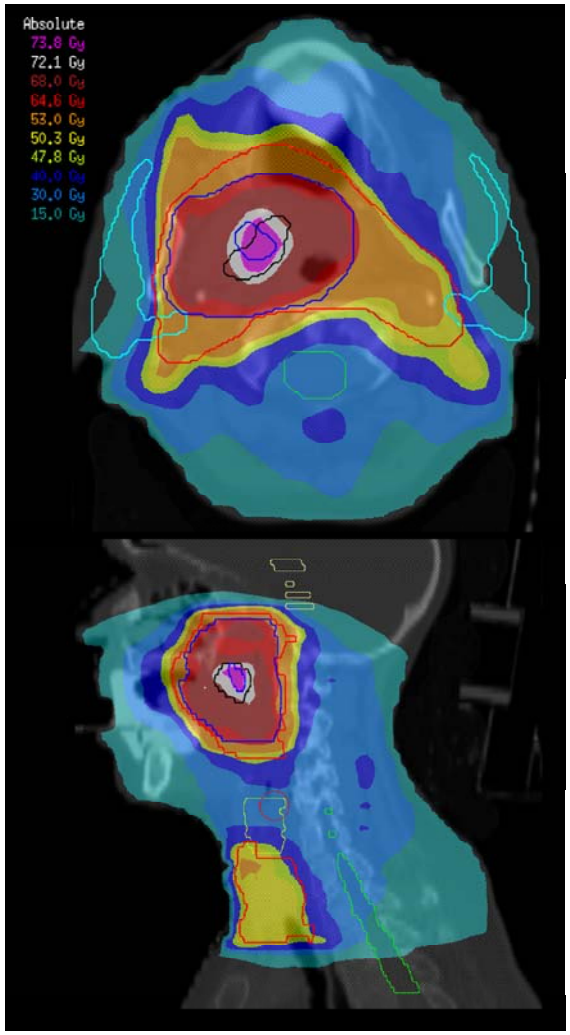


Boosting of highly proliferative subvolume

- Definition of subvolume using 80% of maximum SUV ($GTV_{80\%}$) in **first** and **second** FLT-PET scan



- Creation of radiation treatment plan using IMRT with simultaneous integrated boost



Troost et al, 2010

conclusions

- Both hypoxia and proliferation are highly dynamic and heterogenously distributed in tumors
- Hypoxia is not a binary event, and the most hypoxic cells that dominate a hypoxic voxel may be biologically the least relevant
- Clearly dose-painting or adaptive RT needs repeated imaging before and (early) during therapy
- Later into therapy, extensive cell death and vascular injury will mask the extent of clinically relevant hypoxia and proliferation

Acknowledgements

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