

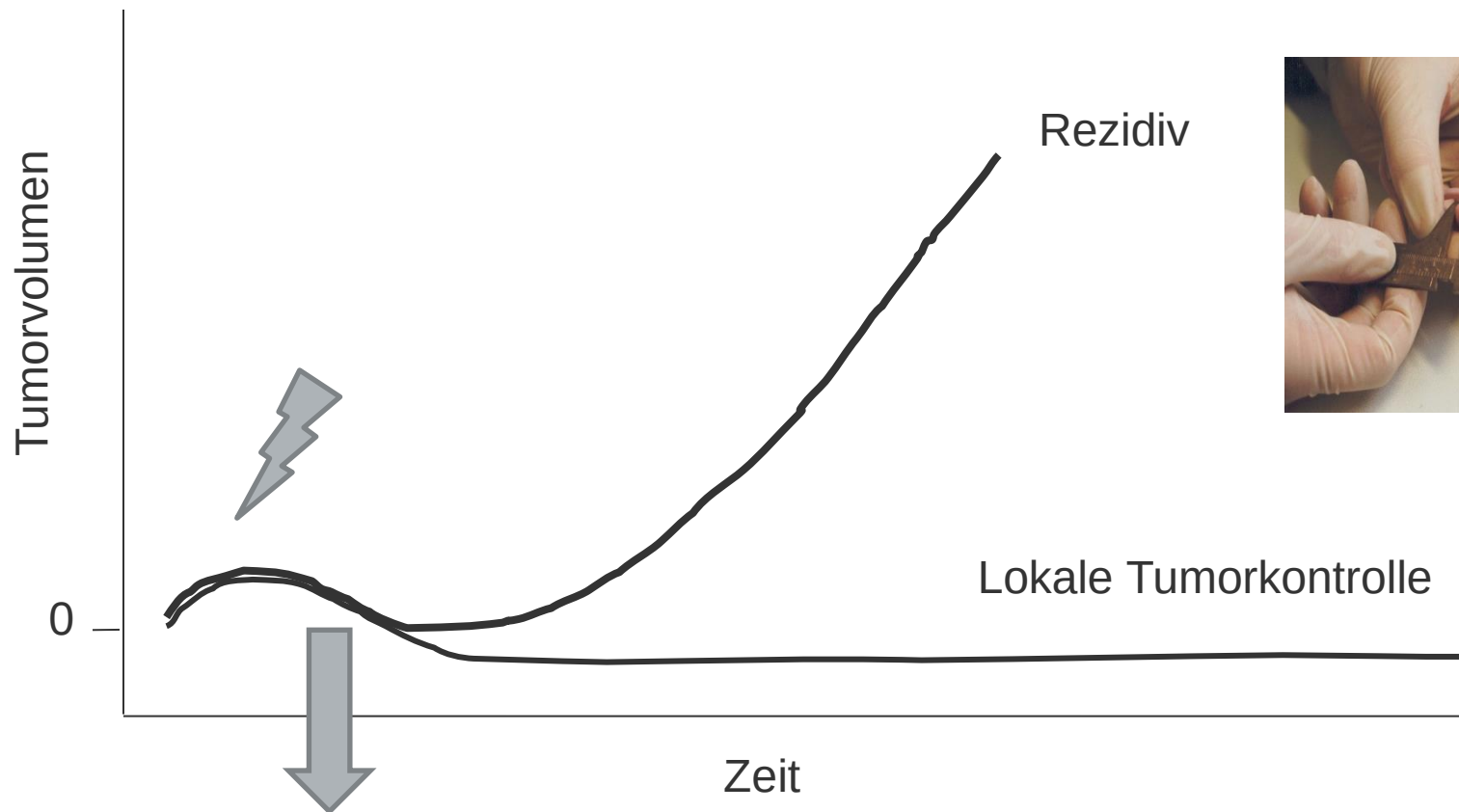


Grundlagen der Tumorstrahlenbiologie



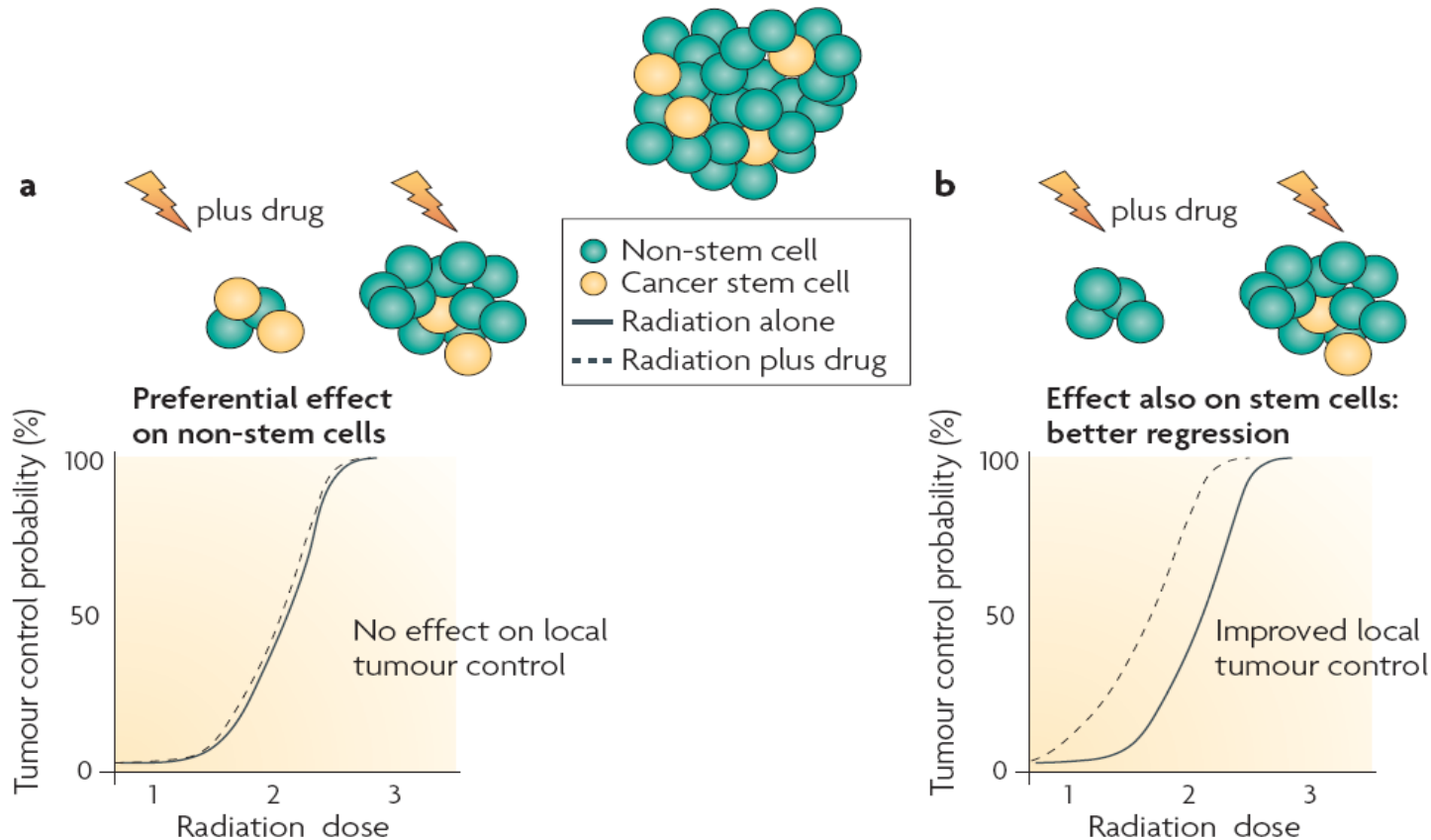
Effekt der Strahlendosis auf die lokale Tumorkontrolle

Strahlenantwort des Tumors



Tumorexzision und ex vivo Bestimmung der Anzahl klonogener Tumorzellen

Relevance of functional heterogeneity of cancer cells for outcome after radiotherapy



Strahlenempfindlichkeit von Tumoren



	Beispiel	Dosis (Gy)	Tumorkontrolle (%)
Sensitiv	Seminom, Lymphom	≤ 45	≥ 90
Intermediär	Plattenepithel-Ca, Adeno-Ca	50 60 70	≥ 90 (subklinisch) ~ 85 (Ø 1 cm) ~ 70 (Ø 3 cm) ~ 30 (Ø 5 cm)
Resistent	Glioblastom	≥ 60	nie

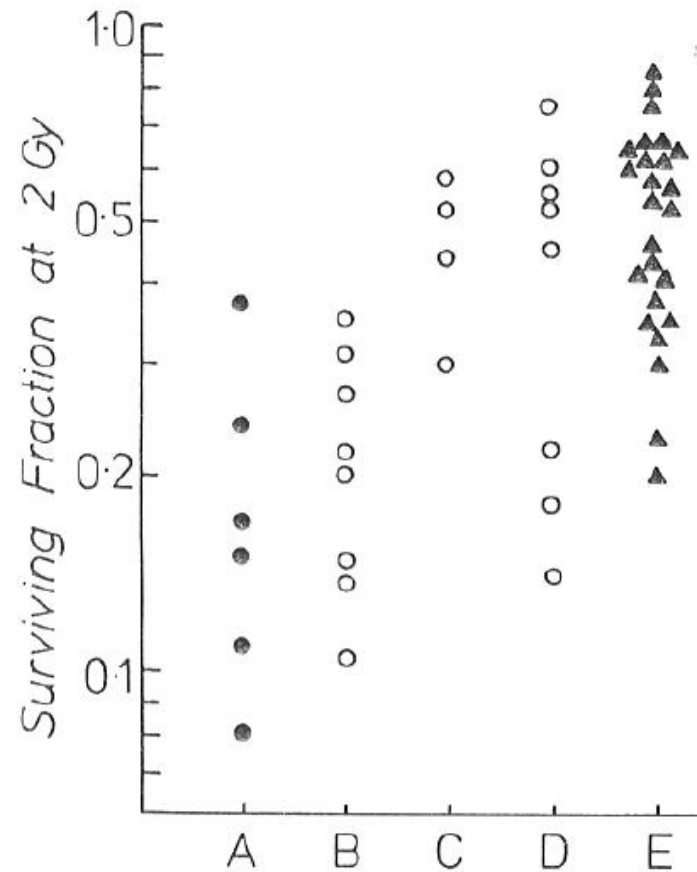
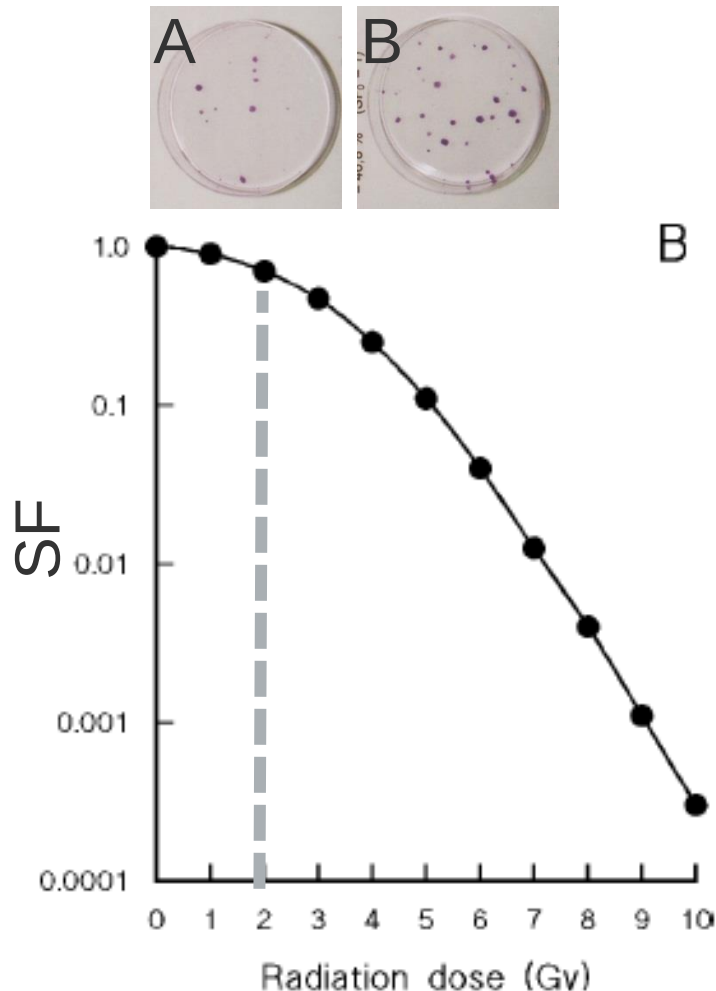


Strahlenbiologische Einflussfaktoren auf die lokale Tumorkontrolle nach fraktionierter Strahlentherapie

1. Radiation sensitivity
2. Repopulation
3. Recovery
4. Reoxygenation
5. Redistribution

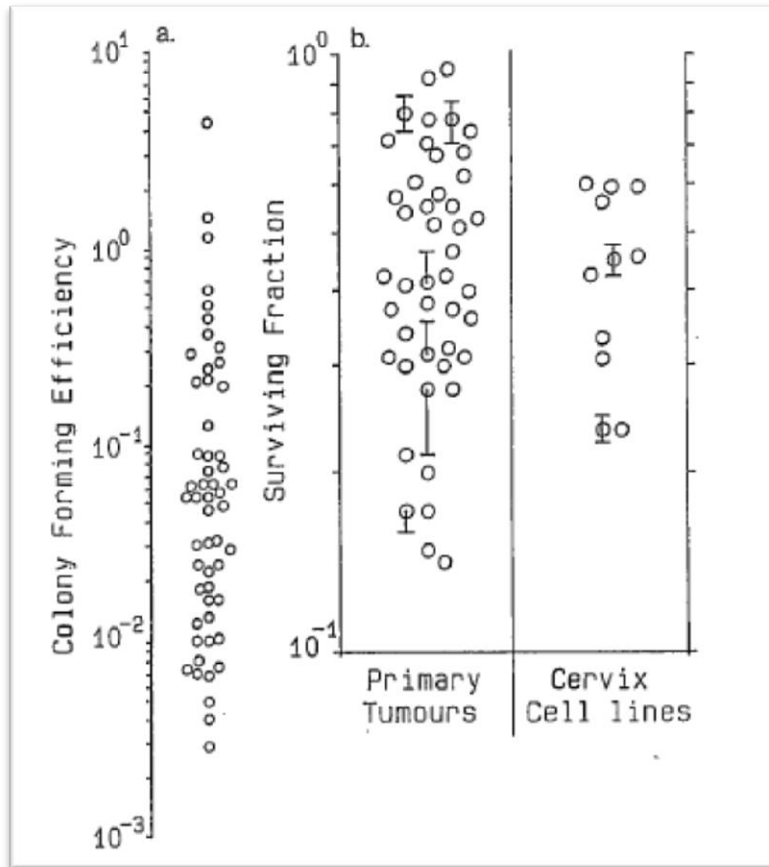
Tumorvolumen (Anzahl rezidivfähiger Tumorzellen)

Intrinsische (zelluläre) Strahlenempfindlichkeit von Tumorzellen

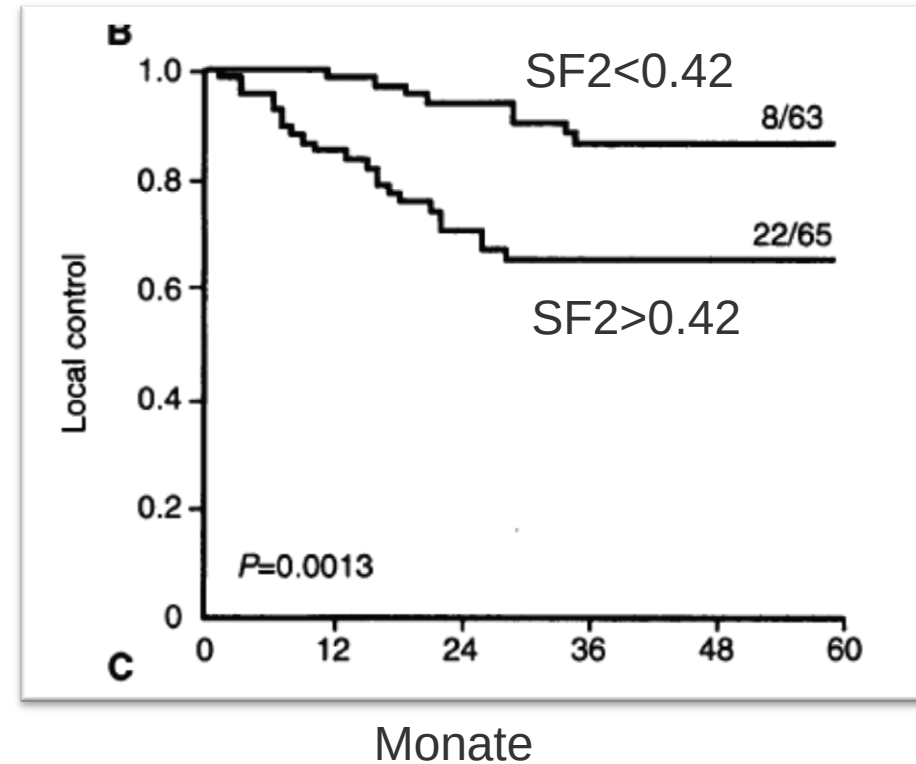


A: Lymphome,
Myelome,
Neuroblastome
B: kleinzelliges Ca,
Medulloblastom
C: Mamma,
Urothel, Cervix
D: Pankreas,
colorektal,
Plattenepithel
Lunge
E: GBM, Melanom,
RCC, Osteosarkom

Intrinsische (zelluläre) Strahlenempfindlichkeit von Tumorzellen



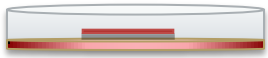
West CM et al., IJRB 1989; 56: 751-765



West CM et al., Br J Cancer 1997; 76:1184-1190

γ H2AX assay in *ex vivo* irradiated tumour specimens

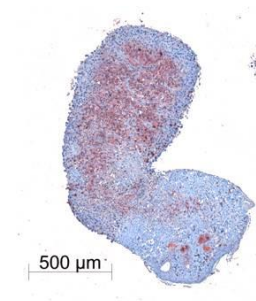
Taking of biopsy/
specimen



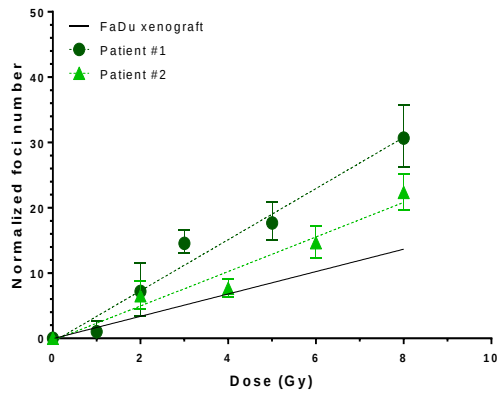
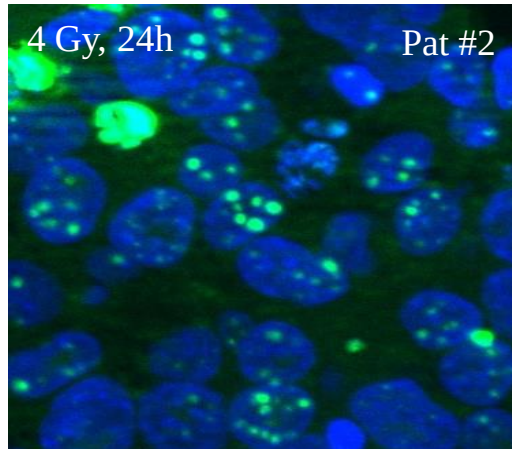
Ex vivo Irradiation of
biopsies/ specimens



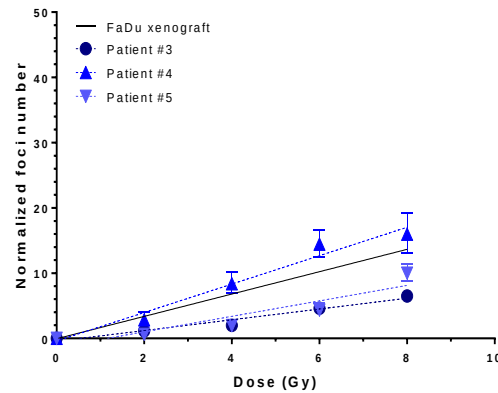
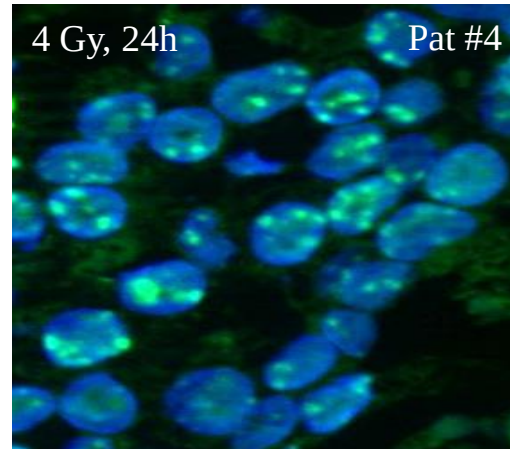
Formalin fixation/
paraffin embedment



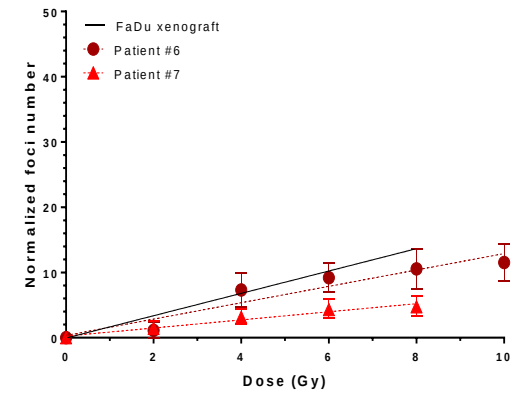
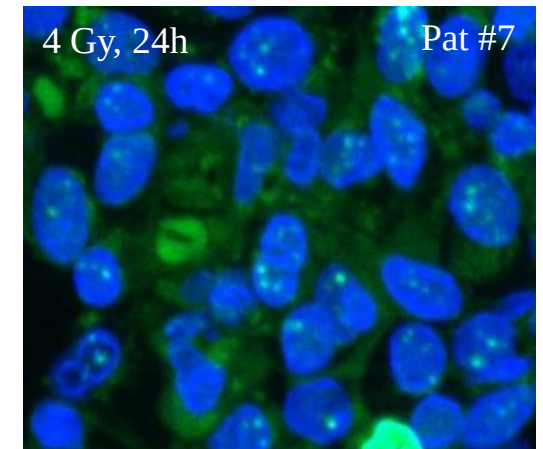
Seminoma



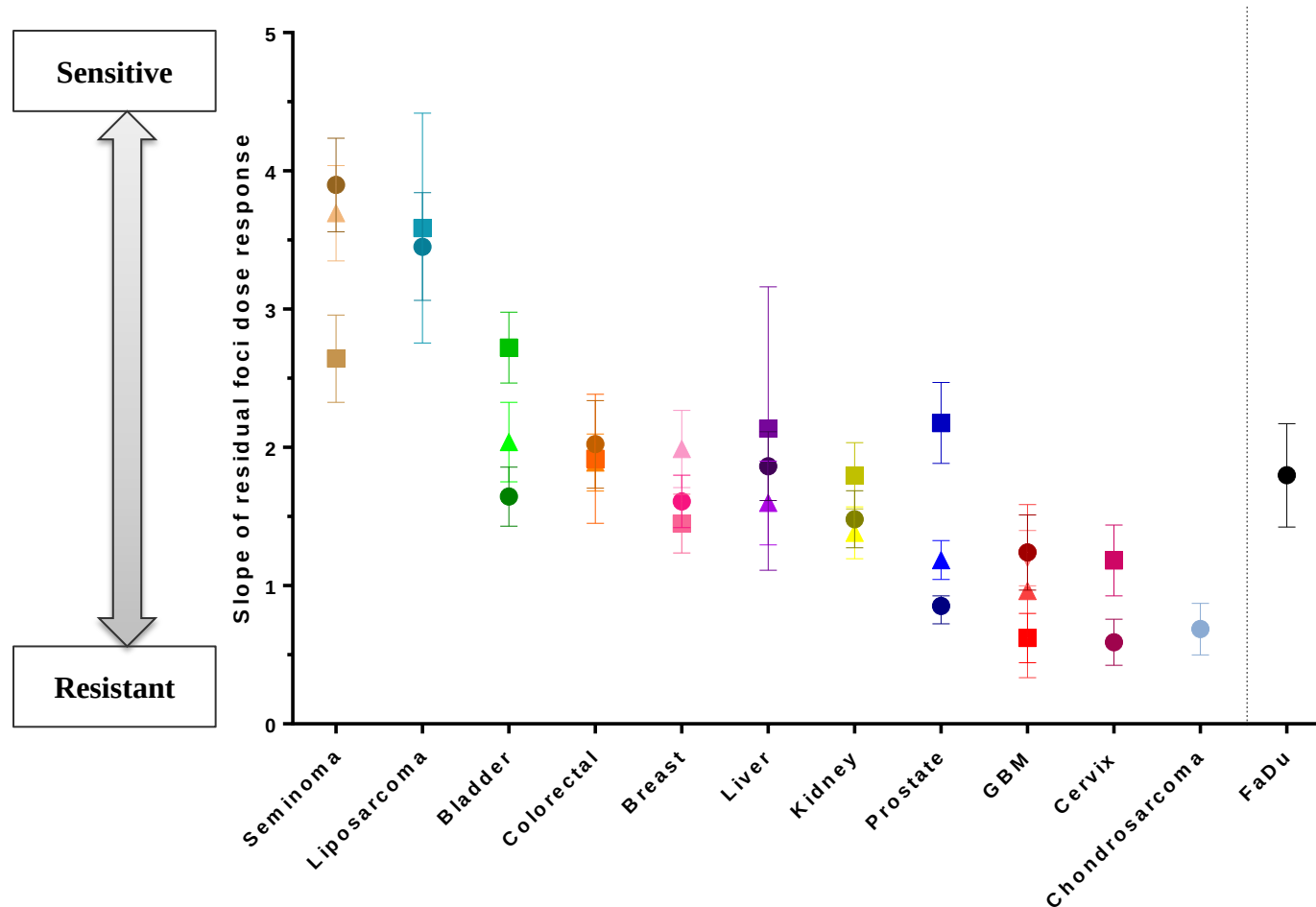
Prostate Adeno-Ca



GBM



Slope of residual γ H2AX foci dose response



Error bars: 95% C.I. of the slope estimation

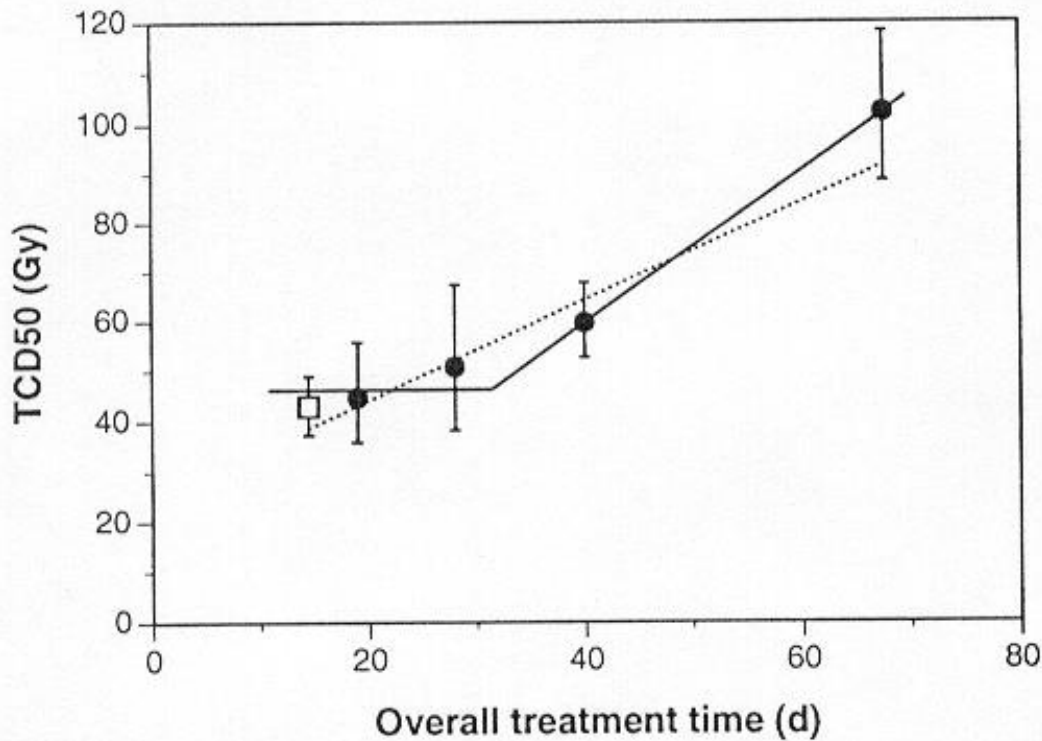


Intrinsische (zelluläre) Strahlenempfindlichkeit von Tumorzellen

- Korrelation mit lokaler Tumorkontrolle nach fraktionierter RT (prognostisch)
- bisherige Daten: als alleiniger Prognosefaktor geringe Aussagekraft
- Methodik für klinische Anwendung kritisch

Repopulierung

Gesamtbehandlungszeit: FaDu hSCC



Arm A: 30 fx/15 Tagen

|||||
|||||

Arm B: 30fx/3.5 Wochen

|||| |||| ||||
|||| |||| ||||

Arm C: 30fx/6 Wochen

|||| |||| |||| |||| |||| ||||

Arm C: 30fx/10 Wochen

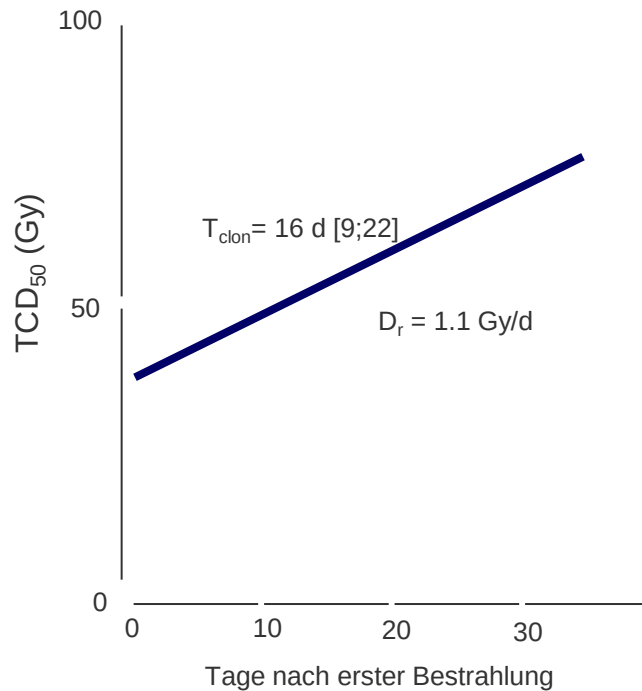
|||| |||| |||| |||| |||| |||| |||| |||| |||| ||||

$$D_P = 1.1 \text{ Gy/d}$$

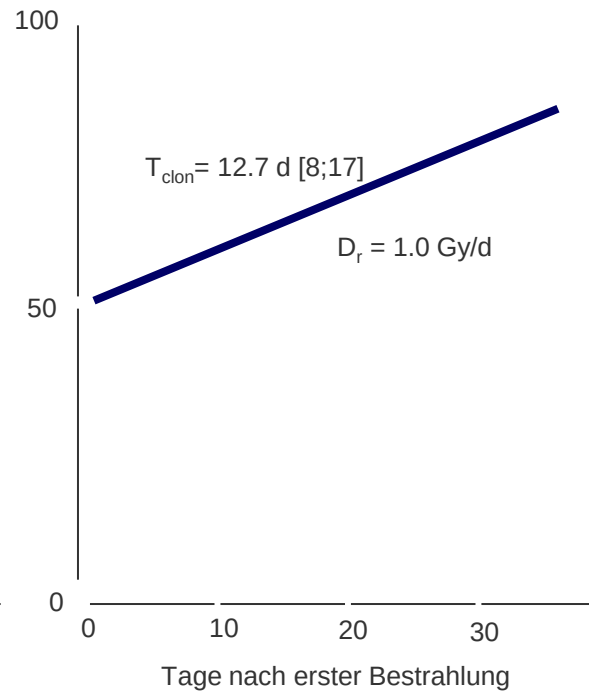
Repopulierung

intratumorale Heterogenität

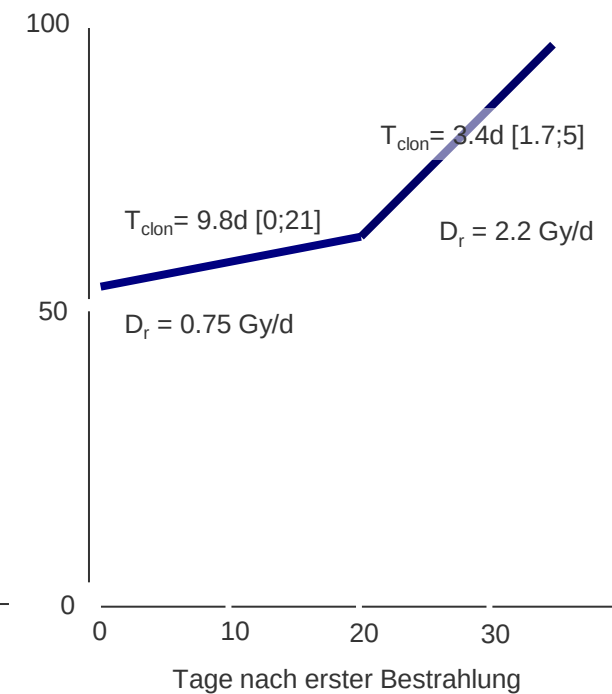
UTSCC-14



GL

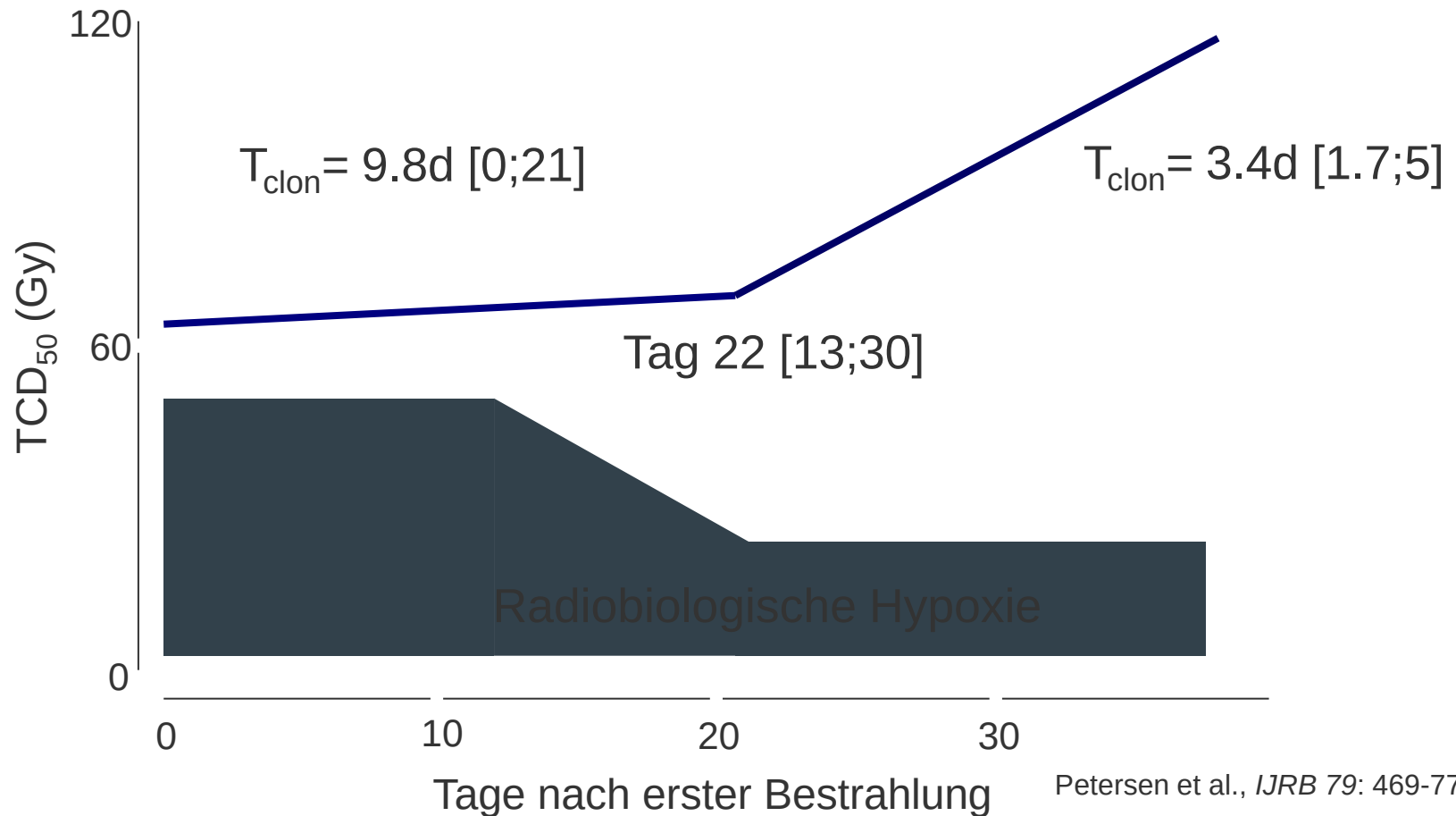


FaDu



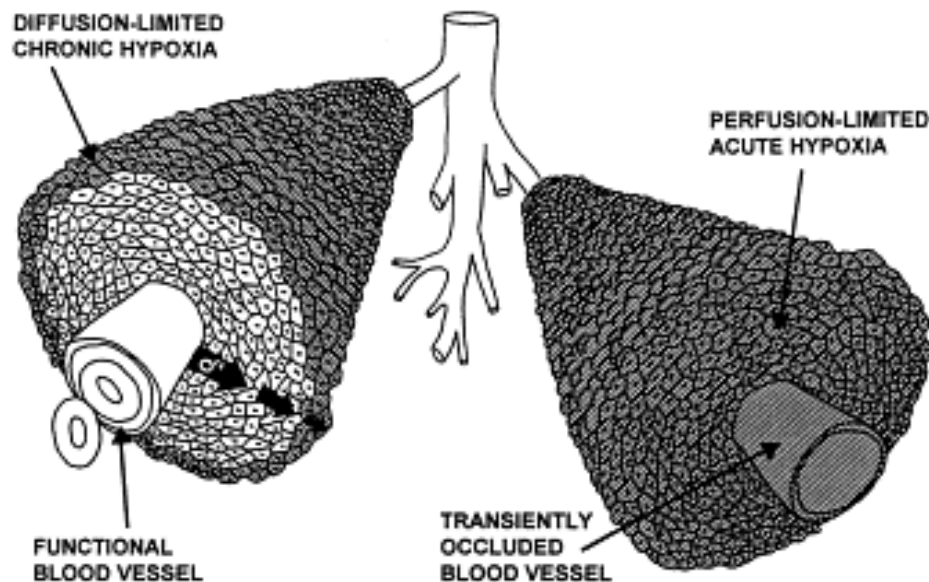
Repopulierung

Zusammenhang Repopulierung und Reoxygenierung (FaDu hSCC)



Repopulierung

Zusammenhang Repopulierung und Reoxygenierung



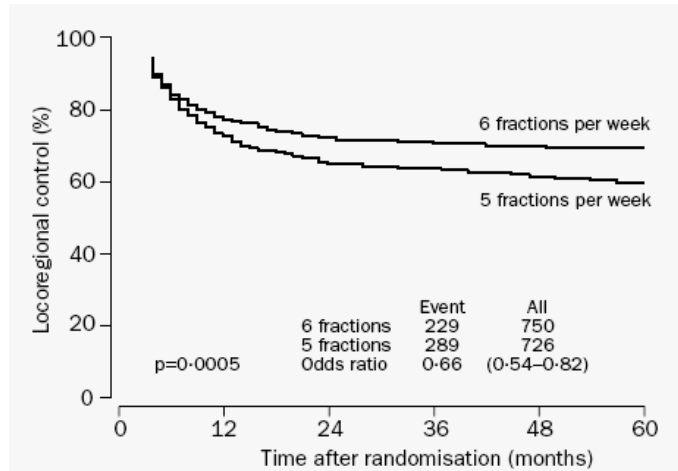
„The phantom of rapid proliferation unmasked“

J. Fowler Radiother Oncol. 1991
Nov;22(3):156-8.

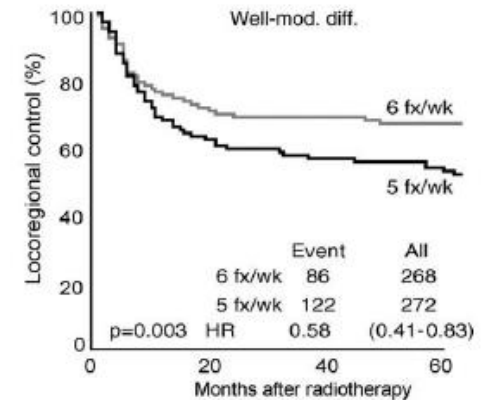
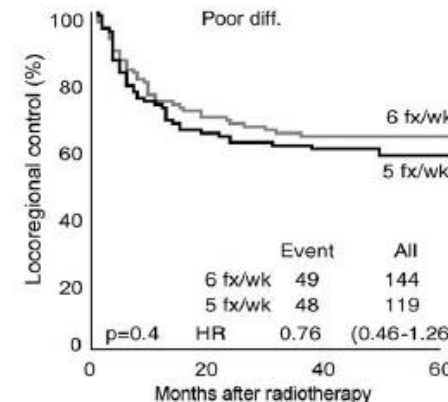
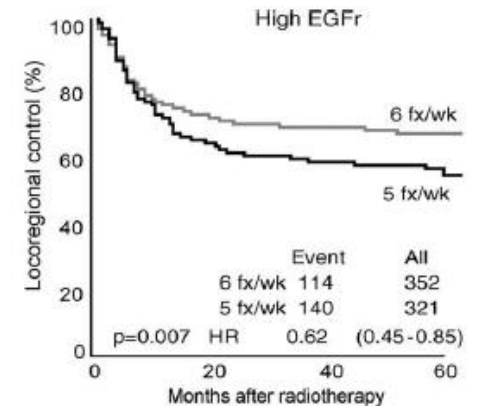
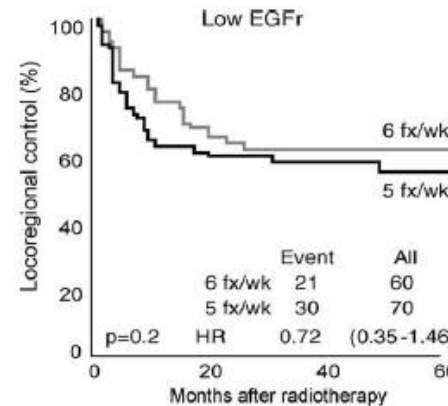
Akzelerierte Repopulierung ist ein passiver Effekt ausgelöst durch Veränderungen im Tumormikromilieu

Repopulierung

DAHANCA 6&7



Overgaard J et al., Lancet 2003; 362:933-940



Eriksen J et al., Radiother Oncol 2005; 74:93-100

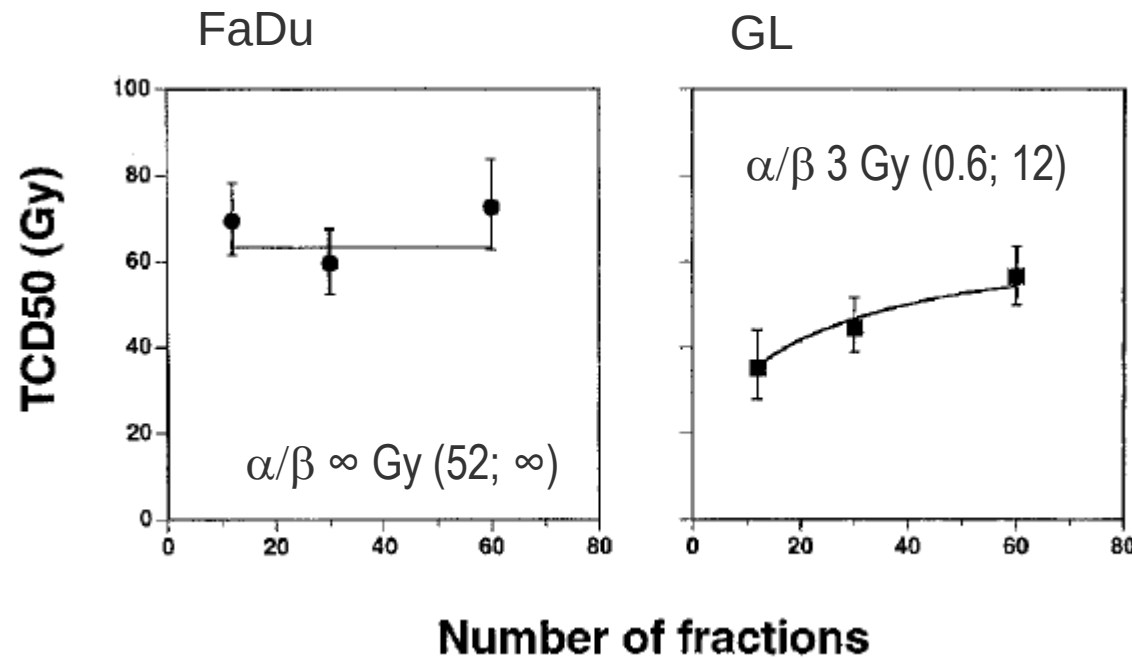
Repopulierung von Tumorzellen ist ein aktiver „regenerativer“ Prozess mit molekularer Regulation ähnlich korrespondierender Normalgewebe



Repopulierung

- strahlenbiologische Grundlage des Zeitfaktors der fraktionierten RT
- Repopulierungskapazität wichtiger Resistenzfaktor
- strahlenbiologische Mechanismen: Regulation durch regenerative Antwort versus durch Veränderung im Tumormikromilieu

Recovery (Erholung, Fraktionierungsempfindlichkeit)





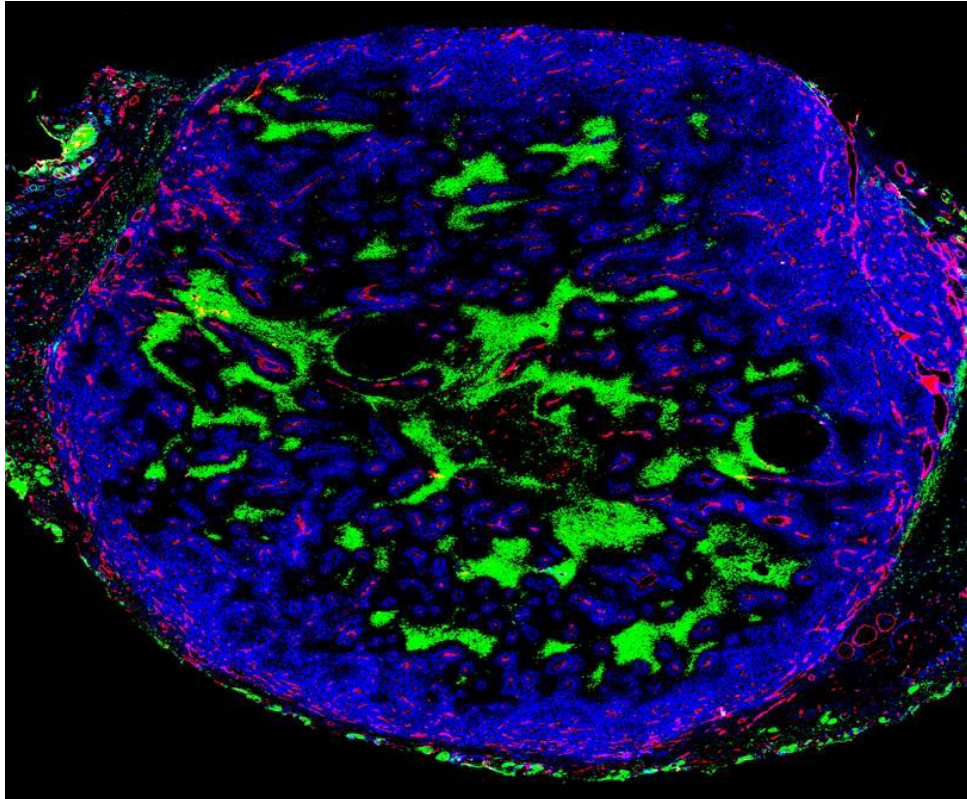
Recovery (Erholung, Fraktionierungsempfindlichkeit)

- Erholungskapazität von Tumoren variiert sehr stark und kann die lokale Tumorkontrolle nach fraktionierter RT beeinflussen
- bei fraktionierungsempfindlichen Tumoren (α/β -Wert niedrig) trägt die Erholungskapazität zur Resistenz bei (siehe Vortrag Hypofraktionierung)



Reoxygenierung

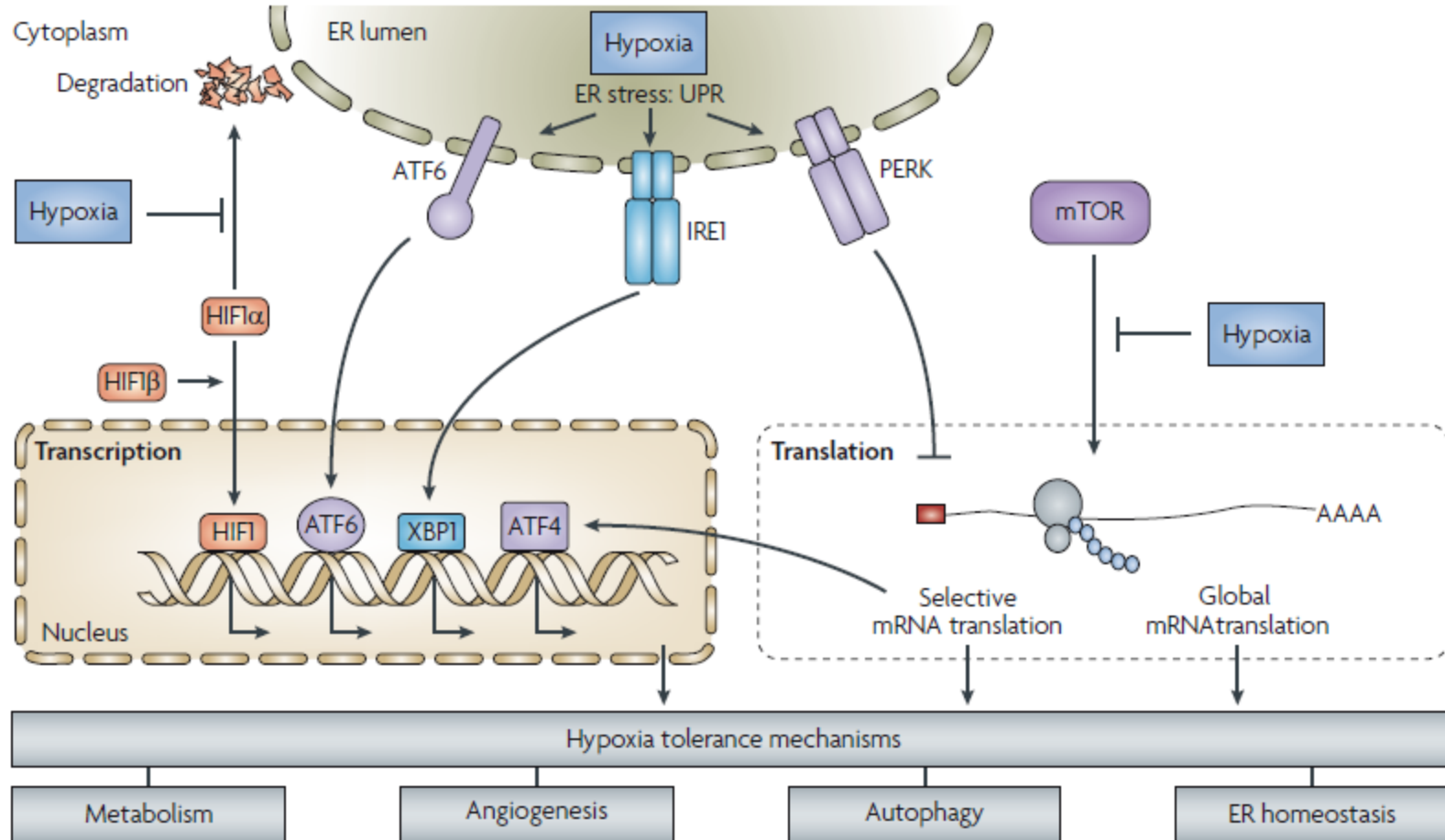
Tumorhypoxie



- maligne Zellen tolerieren schwere Gewebhypoxie
- Ursachen der Tumorhypoxie: pathologische Gefäße, O₂-Verbrauch, Anämie
- Formen: chronisch versus akut
- Molekulare Konsequenzen
- Mechanismen der hypoxie-bedingten Strahlenresistenz

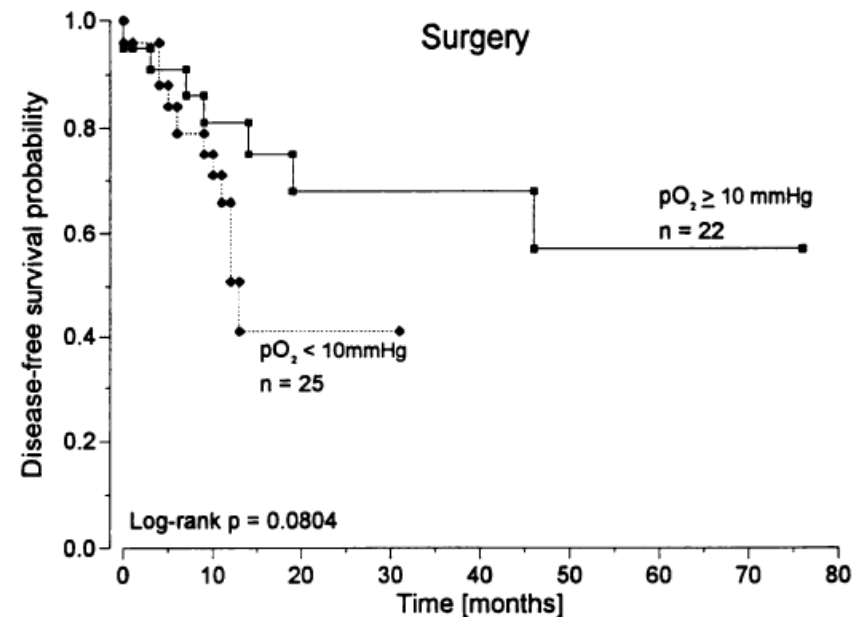
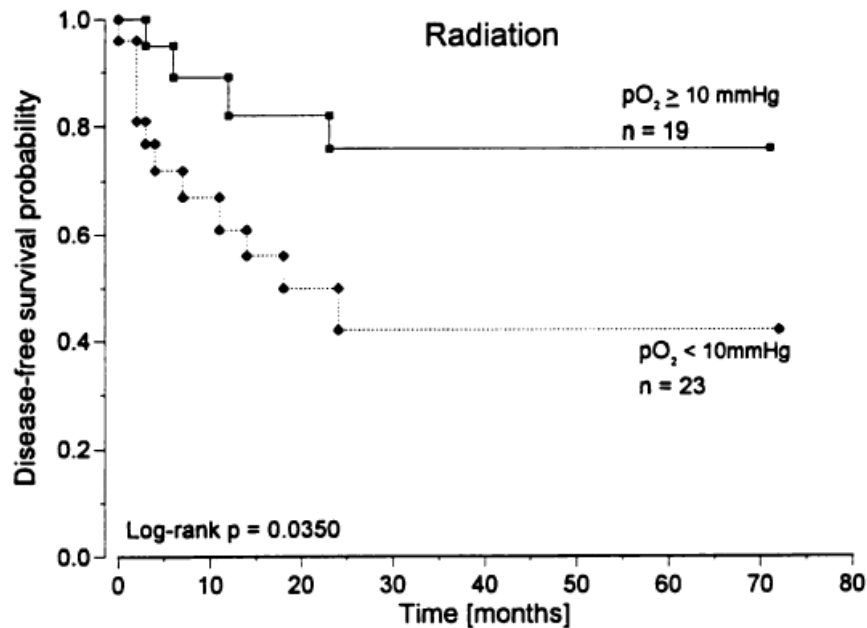
Molekulare Mechanismen der Hypoxietoleranz

Wouters and Koritzinsky, *Nature Reviews Cancer*, 2008

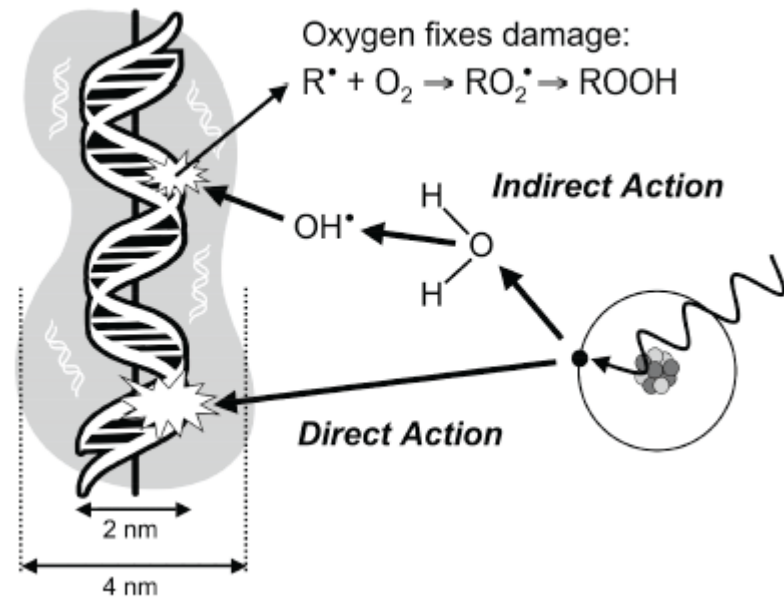
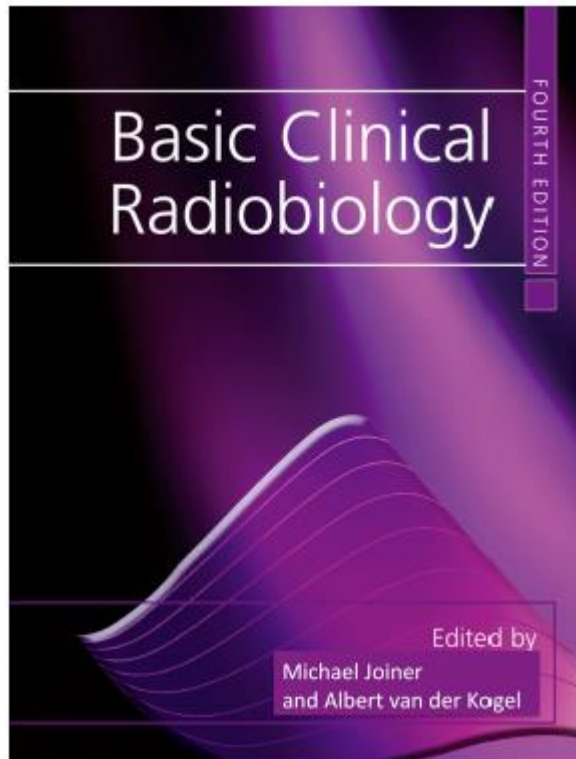


Hypoxie führt zu Therapieresistenz

Cervix-Karzinome

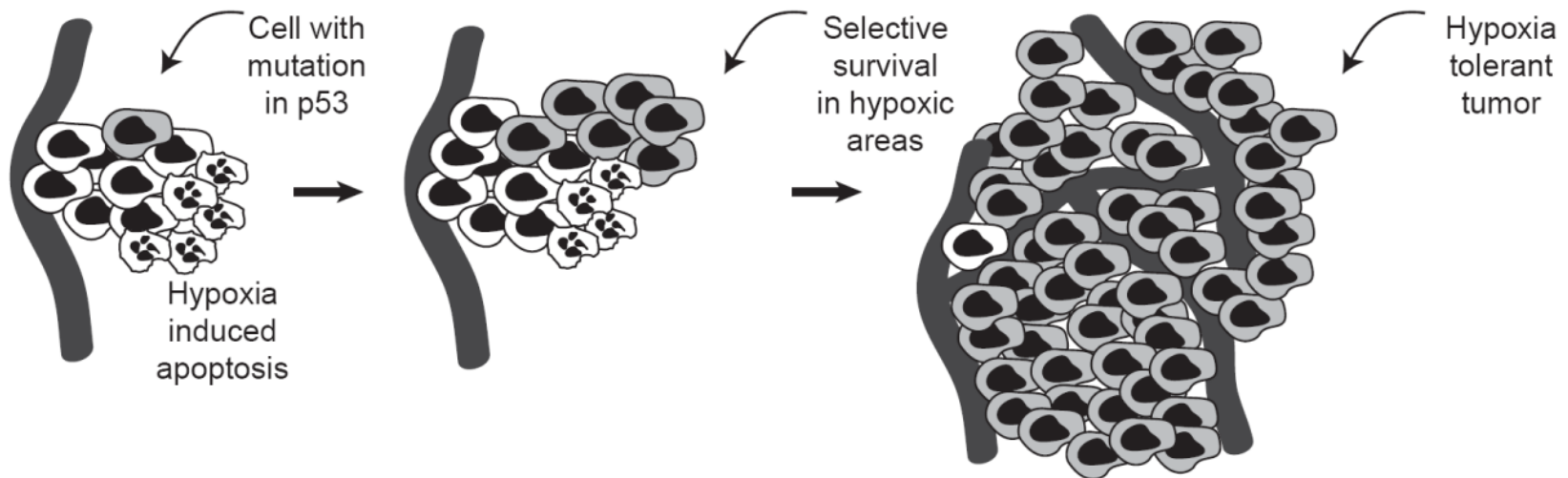


Hypoxie und Strahlenresistenz: Sauerstoff-Fixationshypothese



Basic clinical radiobiology, 2009, 15: figure 15.3, page 208

Hypoxie und Therapieresistenz: *klonale Selektion von mutierten Tumorzellen*



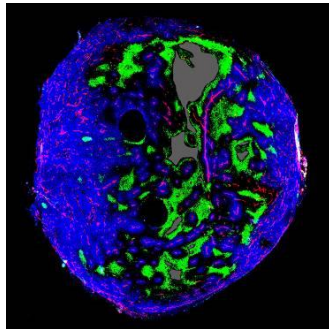


Konzepte der hypoxie-bedingten Strahlenresistenz

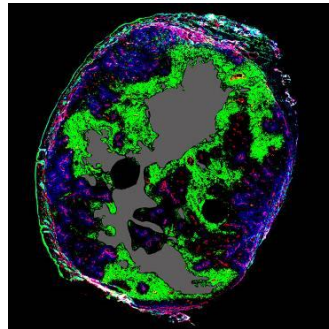
- Hypoxie führt zu Therapieresistenz von Tumoren
- radiochemischer Sauerstoffeffekt: Sauerstoff-Fixationshypothese
- Therapieresistenz durch Hypoxietoleranz: hypoxia signaling, clonale Selektion, genetische Instabilität, Aktivierung von Immuneffekten

Hypoxie, Perfusion, Gefäßdichte

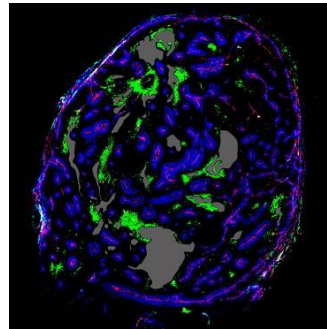
FaDu



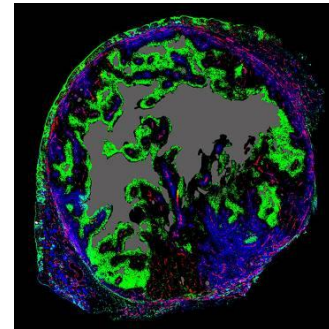
UT-SCC-15



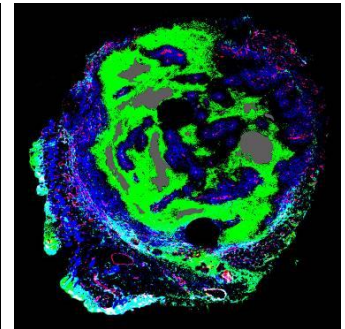
UT-SCC-14



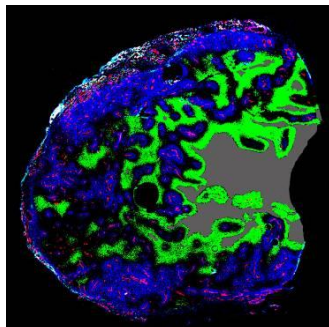
XF354



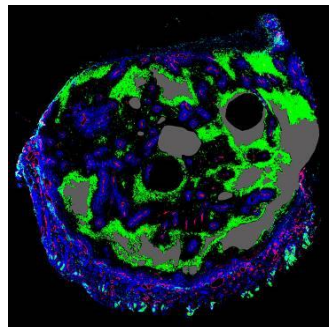
UT-SCC-5



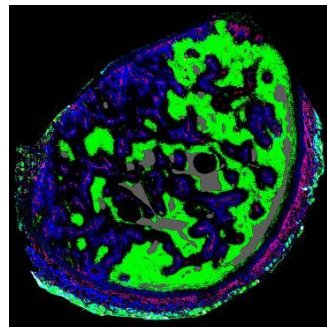
SAS



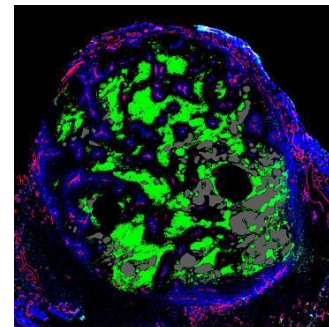
UT-SCC-45



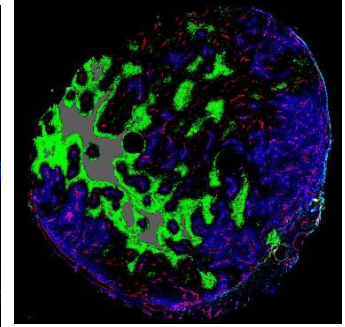
CAL33



HSC4

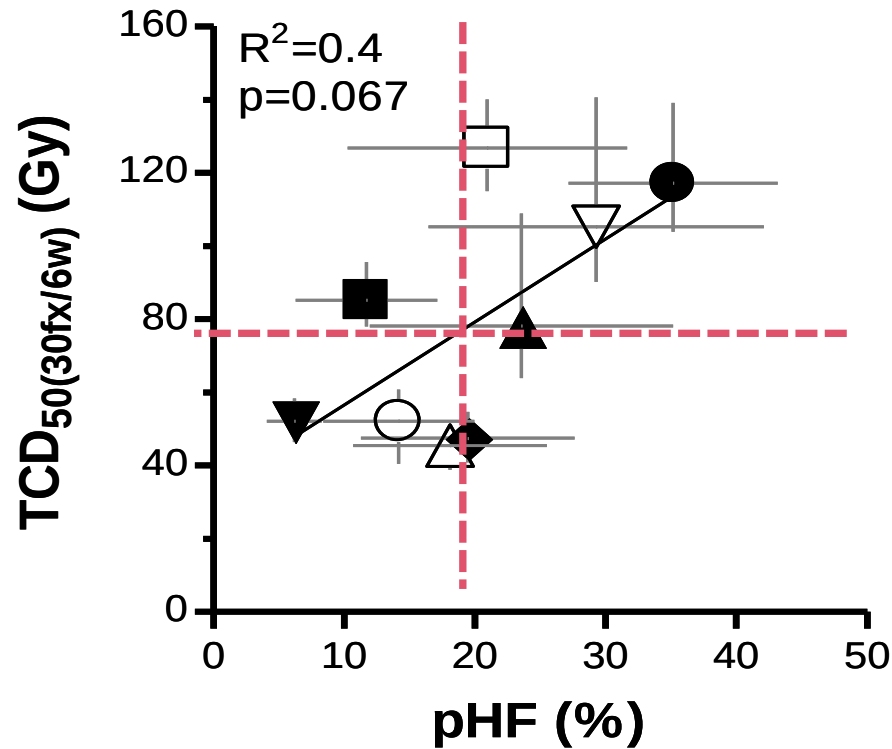


UT-SCC-8



Hypoxie (Pimonidazol) Gefäße (CD31) Perfusion (Hoechst)

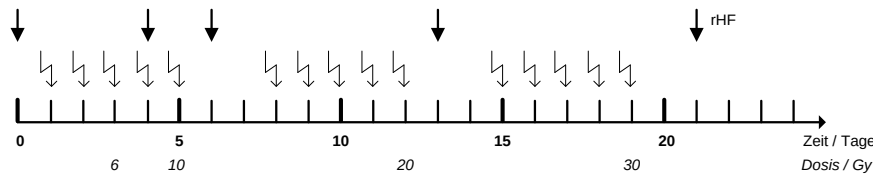
Hypoxie und Tumorkontrolle nach fraktionierter Bestrahlung



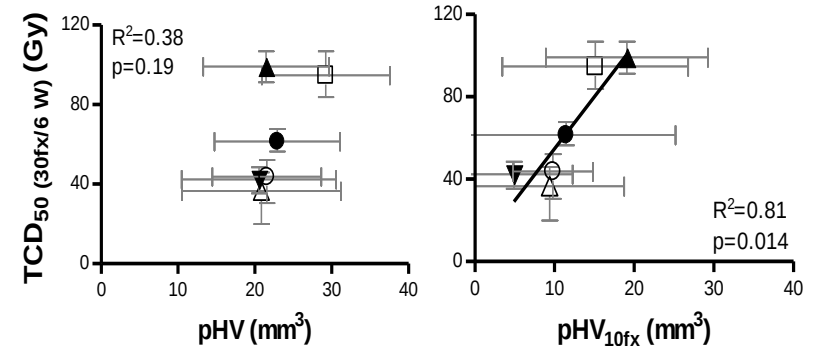
Hypoxie und Tumormikromilieu während fraktionierter Bestrahlung

vor Therapie

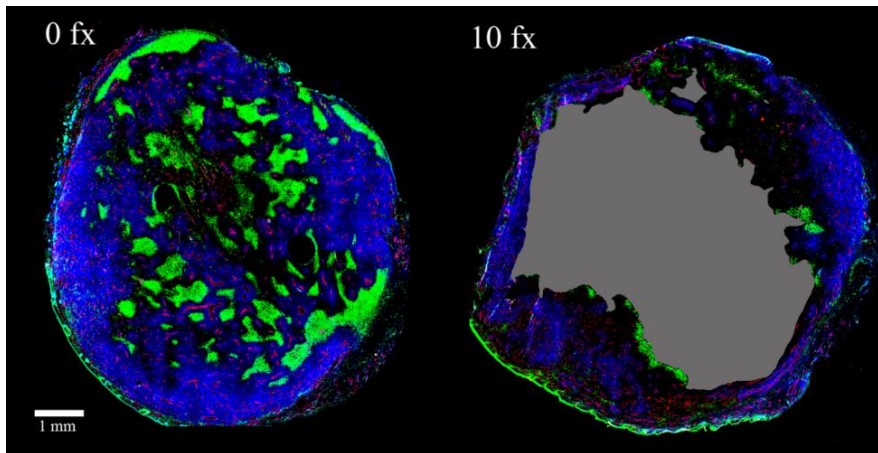
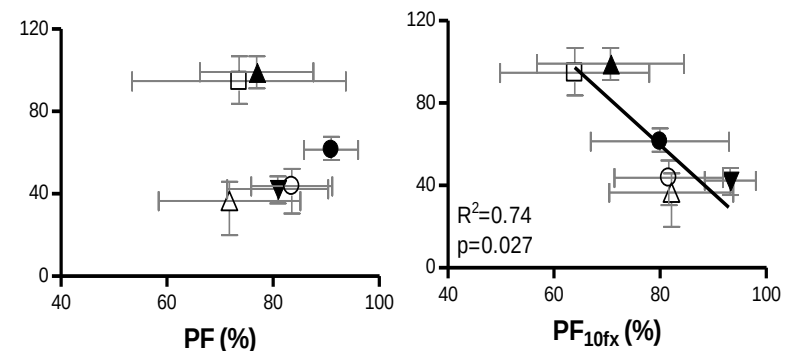
nach 10fx



Hypoxie



Perfusion



Yaromina et al., *IJROBP*, 2011

Hypoxie und Tumormikromilieu während fraktionierter Bestrahlung

F-Misonidazole PET/CT

- stage III/IV inoperable HNSCC (explorative cohort, n=25, mean follow-up all 12 months, mean follow-up survivors 32 months; validation cohort recruiting, planned n=25)
- Radiochemotherapy:

RT: PTV1 (GTV) 72 Gy/6 W, PTV 2 (elektiv) 59.4 Gy/ 5 W

Chemo: A) 5-FU [600mg/m² d 1-5] plus CDDP [30mg/m²] d1, 8, 15, 22, 28, 35

B) 5-FU [600mg/m² d 1-5] plus MMC [10mg/m²] d 5, 35



Woche	Vor RTx	1	2	3	4	5	6
Dx	o						
CTx		x	x	x	x	x	x
		oder: ↑				↑	
RTx							Boost
PET-CT	☐ ●	●	●			☐ ●	

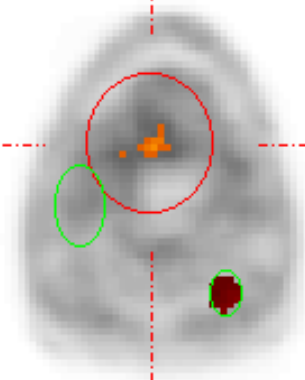
Dx: Histo Sono Abdomen CTx: x Cis; ↑ MMC RTx: D/fx 2.0 Gy (|),
Rö.-Thorax CT/MRT Kopf/Hals - 5-FU bzw. 1.4 Gy (|)

PET-CT ☐ 18-FDG + diagn. CT Ganzkörper
● F-MISO + LD CT K

Hypoxie und Tumormikromilieu während fraktionierter Bestrahlung

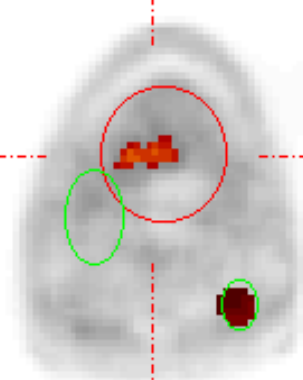
[^{18}F]-Misonidazole PET, hypoxic volume tumour/background 1.4:1

baseline



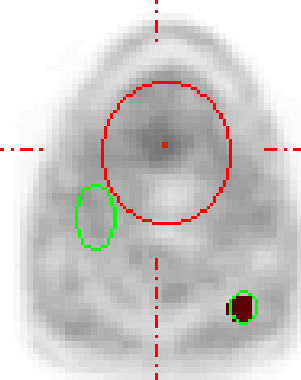
HV=2.8 cm³
SUV_{max} 1.95

8 Gy



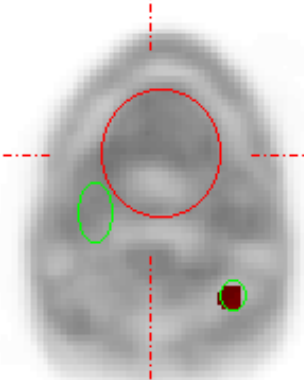
HV=3.5 cm³
SUV_{max} 2.18

20 Gy



HV=0.1 cm³
SUV_{max} 1.79

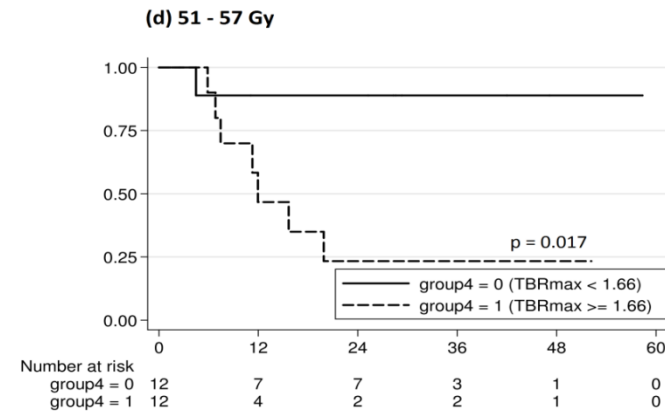
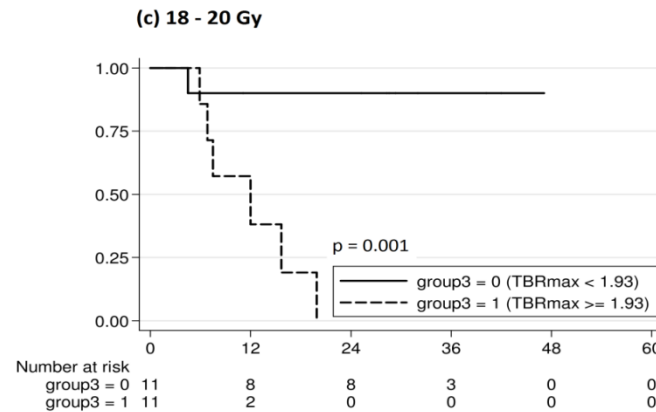
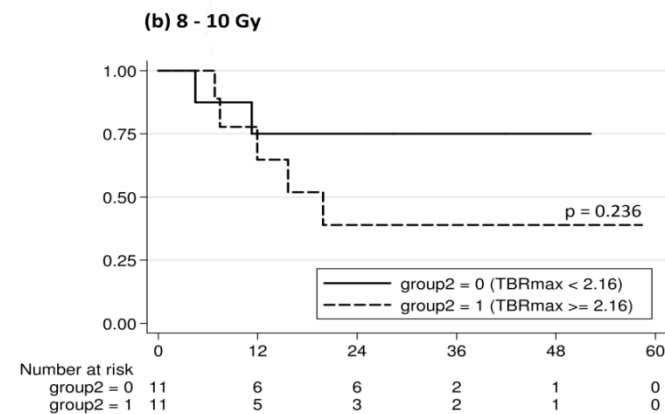
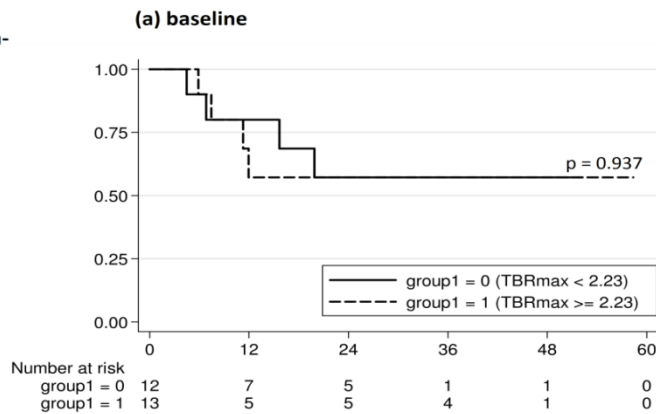
57 Gy



HV=0 cm³

Hypoxie und Tumormikromilieu während fraktionierter Bestrahlung

Local-
progression-
free
survival



Analysis time (months)

Zips D, ..., Baumann M, Radiother Oncol, 2012

HDP in HNC Study Design (Randomized Phase 2)

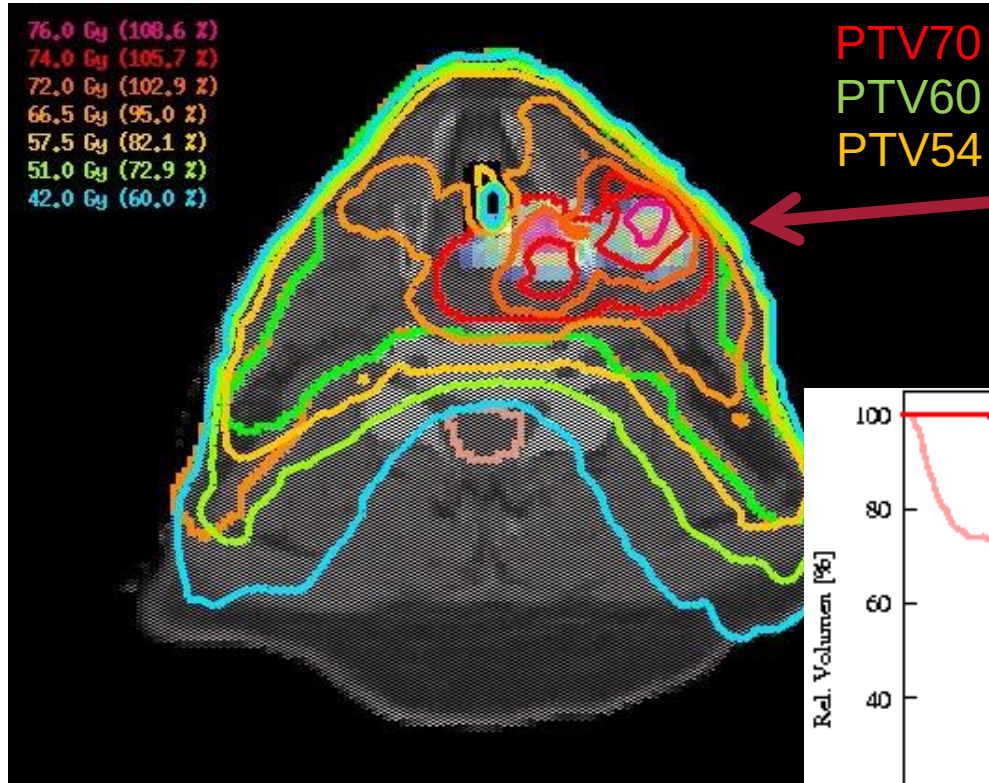
Imaging

- Planning-CT + FDG PET/CT
- Dynamic FMISO PET/CT with RT-positioning
- Second dyn. FMISO PET/CT after approx. 2 weeks

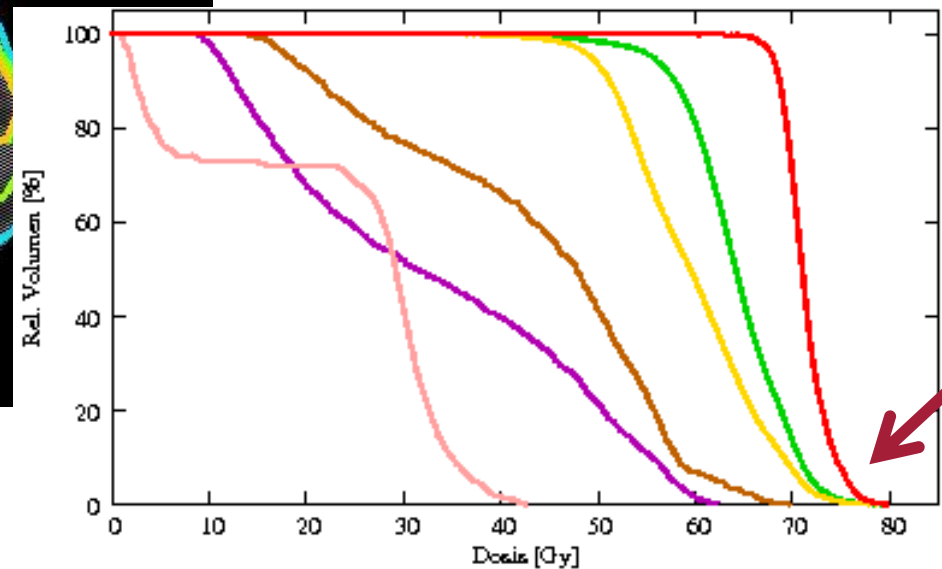
Treatment

- Randomization of hypoxic patients into 2 arms:
 - **Arm 1:**
Standard IMRT with 70 Gy
 - **Arm 2:**
Homogeneous dose escalation of 10% in hypoxic tumour areas discriminated on basis of the dynamic FMISO PET data ($\ln M > 1$).

Example Patient 3



Dose Painting to hypoxic subvolume

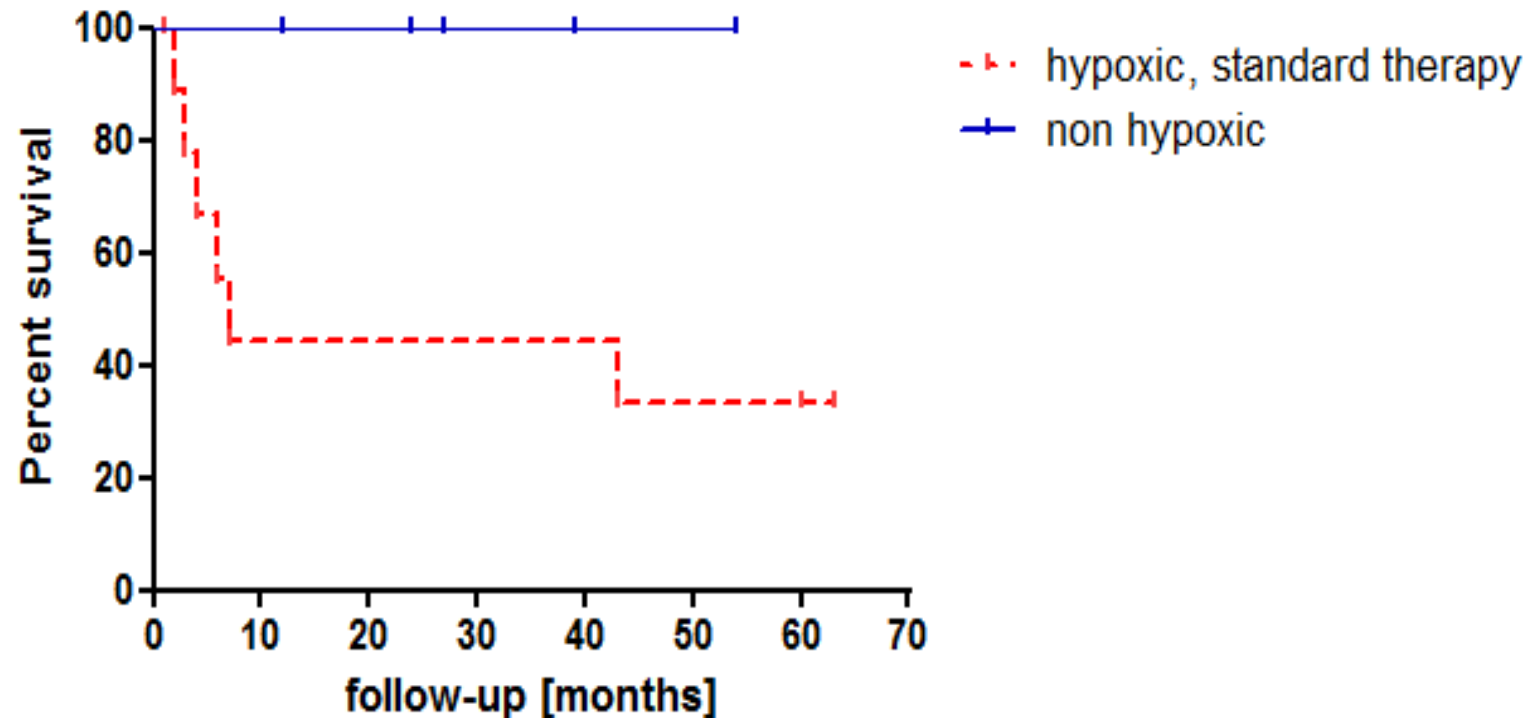


Patient 3: IMRT - Plan 70/77 Gy



HDP in HNC (Randomized Phase 2)

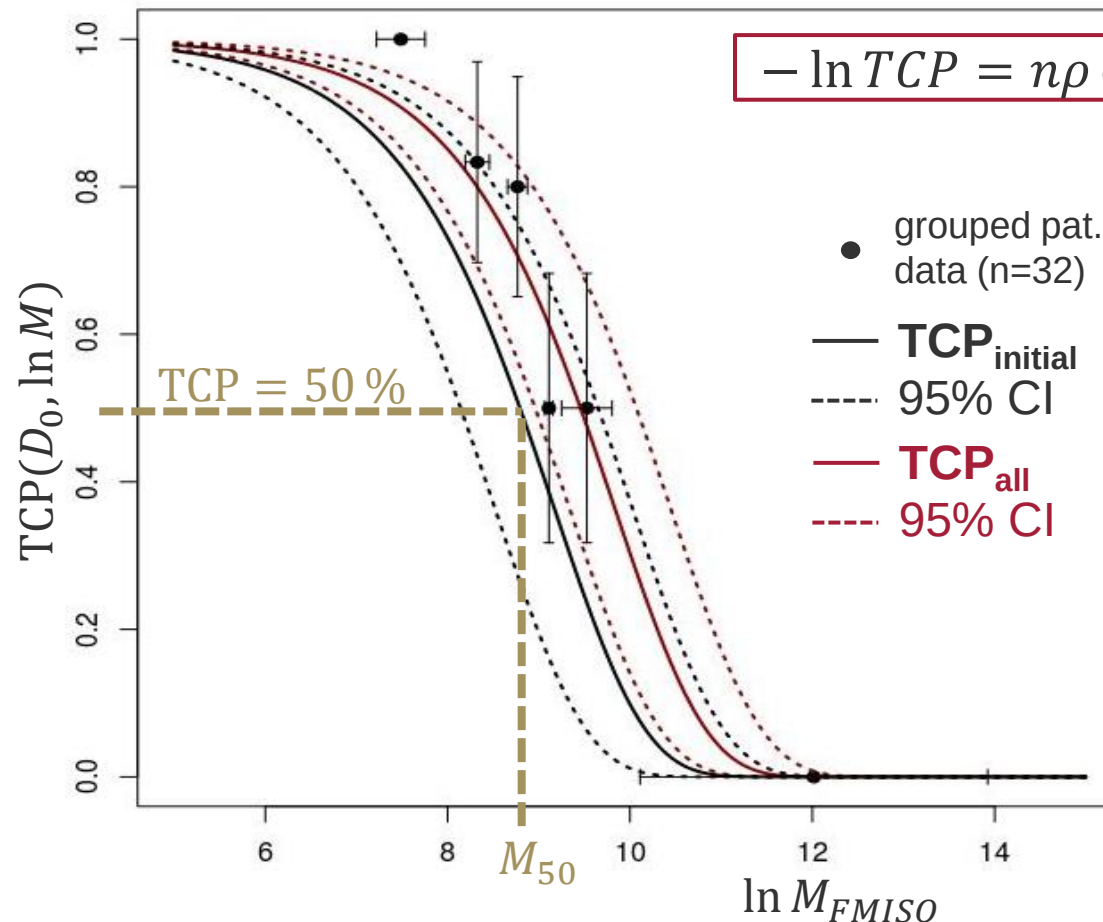
Planned interim analysis (n=25)



Welz S, Thorwarth D et al., ESTRO33

Validation of the hypoxia TCP model in HNC

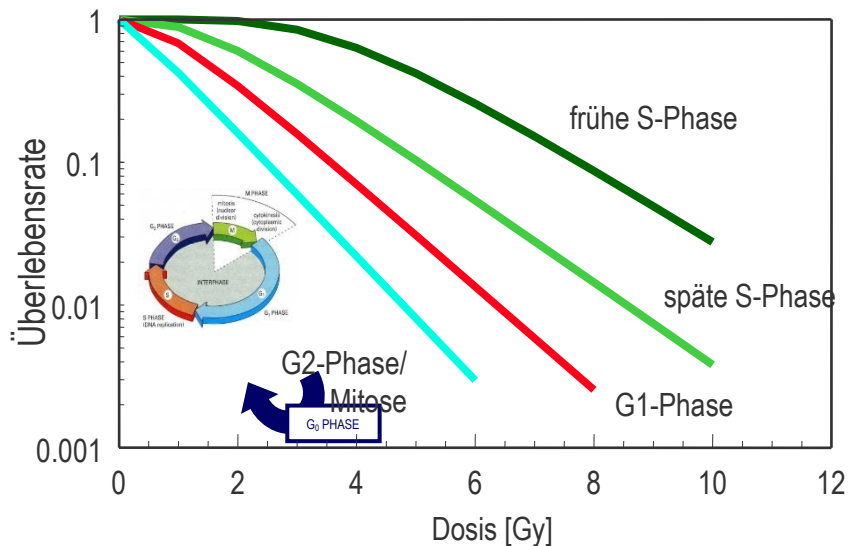
Thorwarth D et al., ESTRO33



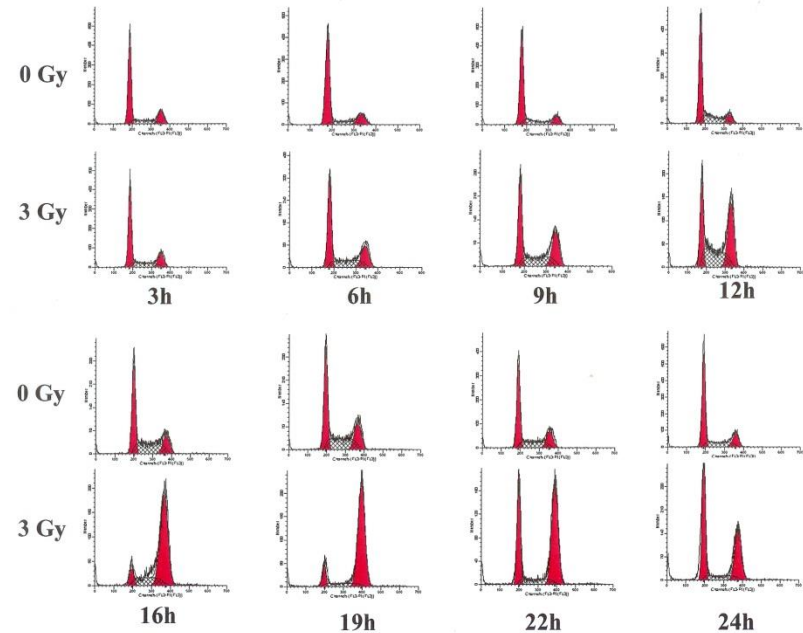
- **Validation of hypoxia TCP model** by data of the HPD trial
- Test for difference of models:

$p = n.s.$

Redistribution



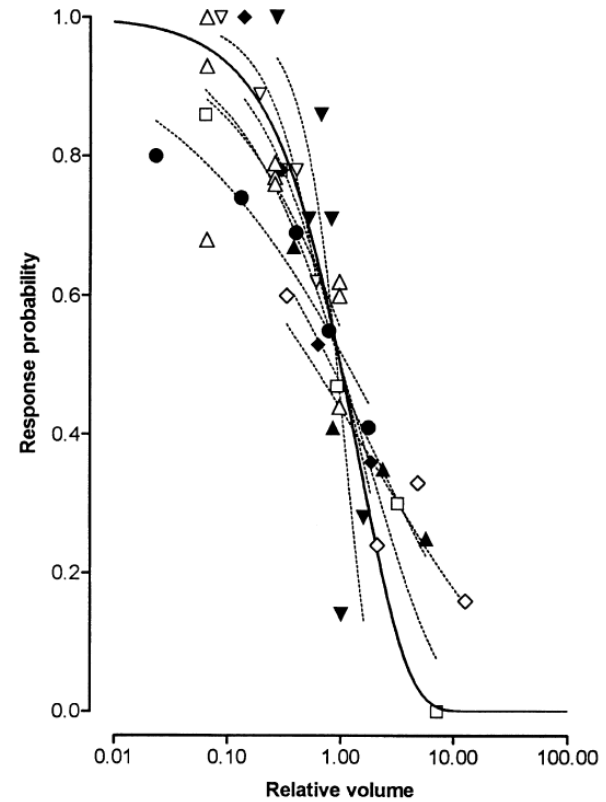
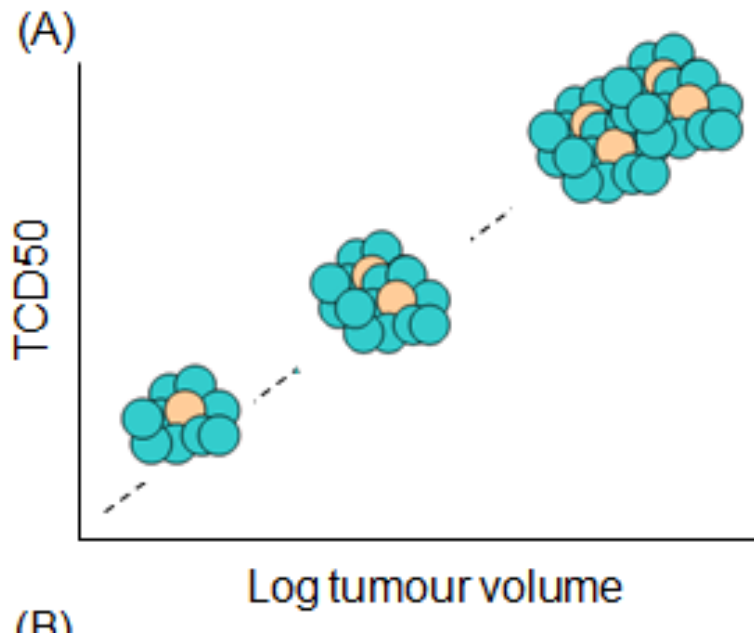
HeLa



Chaudhry *Cancer Cell International* 2007 7:15

- In asynchronen Zellpopulationen Abtötung $G2/M > G1 > S$
- Zellzyklusverzögerung (ca. 2h/Gy)
- Rückverteilung (Redistribution) zwischen den Fraktionen
- Bedeutung für Tumorstrahlenempfindlichkeit unklar

Tumorvolumen



Dubben et al., *Radiother. Oncol* 47: 167, 1998



Tumorvolumen

- Wichtiger Einflussfaktor auf lokale Tumorkontrolle nach fraktionierter Bestrahlung
- Anzahl rezidivfähiger Tumorzellen, Hypoxie



Strahlenbiologische Einflussfaktoren auf die lokale Tumorkontrolle nach fraktionierter Strahlentherapie

1. Radiation sensitivity
2. Repopulation
3. Recovery
4. Reoxygenation
5. Redistribution

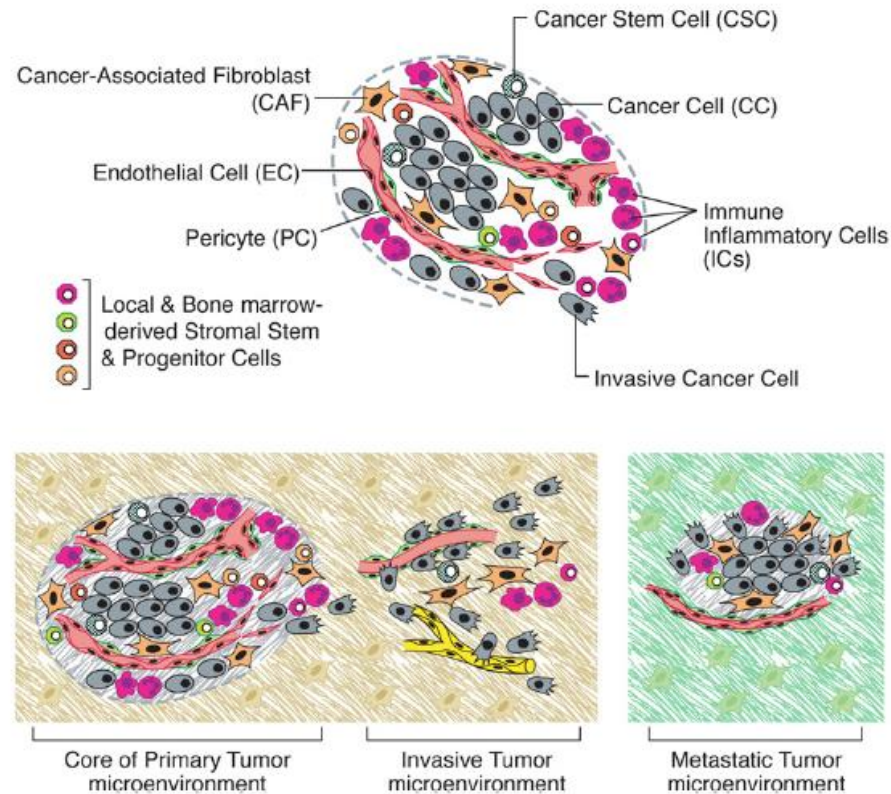
Tumorzellen (Anzahl rezidivfähiger Tumorzellen)



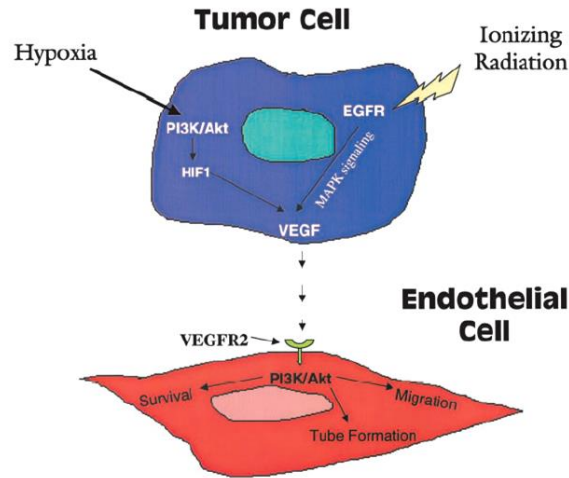
Potential radiobiological mechanisms underlying treatment resistance of CSC-marker positive cells

- quiescent, slowly proliferating
- activated developmental pathways (shh, wnt, notch, EMT)
- reside in a protective niche (interaction with microenvironment)
- lower ROS-levels, lower levels of DNA damage induction
- more efficient DNA damage response and repair
- radiation-induced reprogramming of non-CSC progenitors into CSC

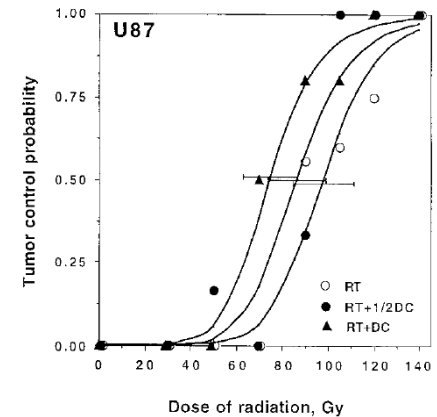
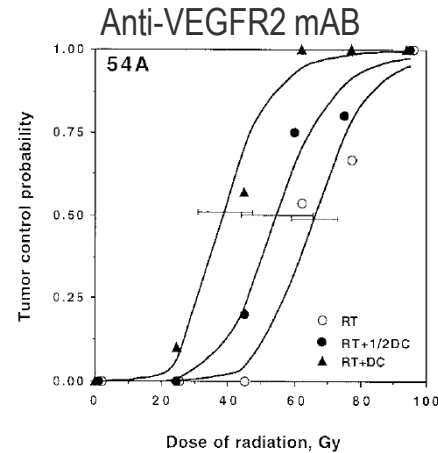
Einfluss von Immunzellen und Tumorstroma auf die Tumorstrahlenempfindlichkeit



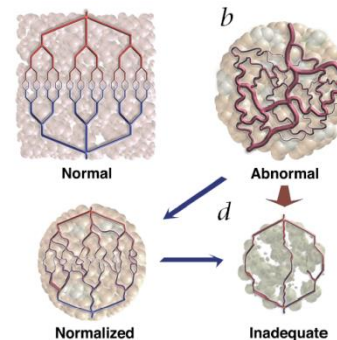
Tumorgefäße und Tumorstrahlenempfindlichkeit



Wachsberger et al. *Clin Cancer Res* 2003



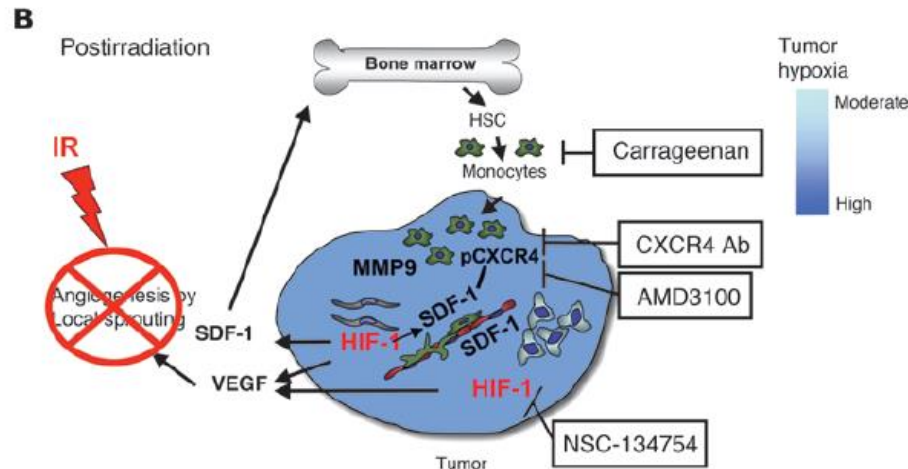
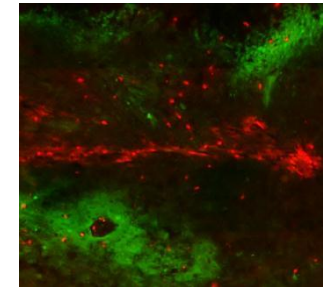
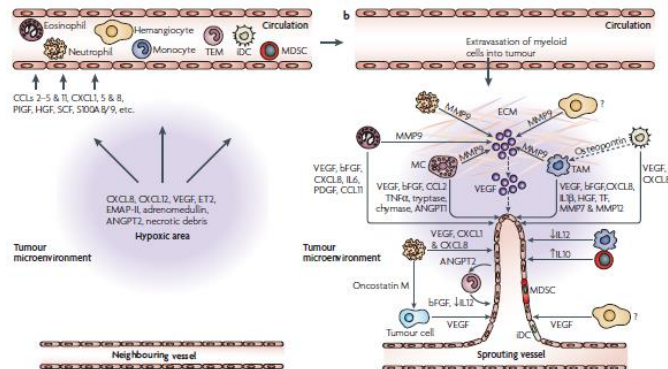
Kozin SV et al., *Cancer Res* 61, 39-44, 2001



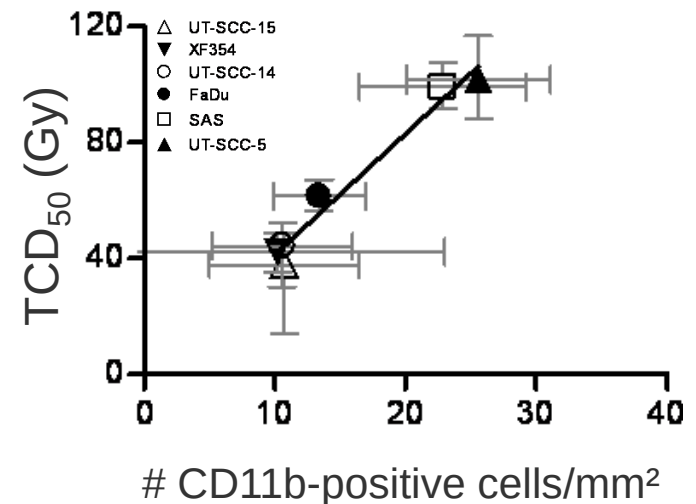
Jain R, *Nature*, 2001

Tumorgefäße und Tumorstrahlenempfindlichkeit

Vaskulogenese in bestrahlten Tumoren und infiltrierende Immunzellen



Kioi et al., JCI 120:694-705, 2010



Zaleska et al. Radiother. Oncol. 2011

