Unveiling tumor heterogeneity through molecular imaging

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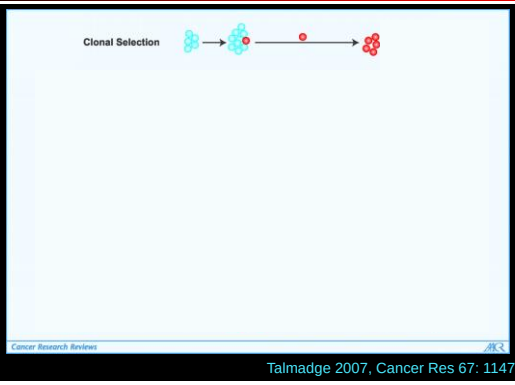
Tumors are heterogeneous



Talmadge 2007, Cancer Res 67: 11471-75

…and they are heterogeneous a lot!

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

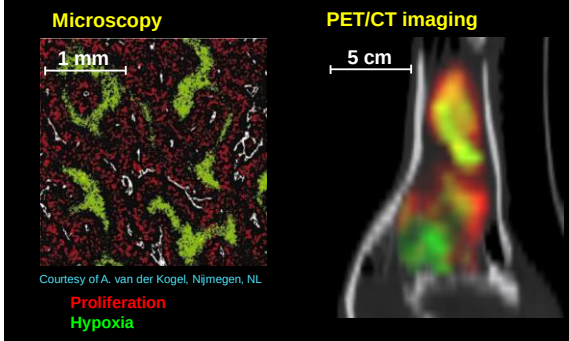
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D.,

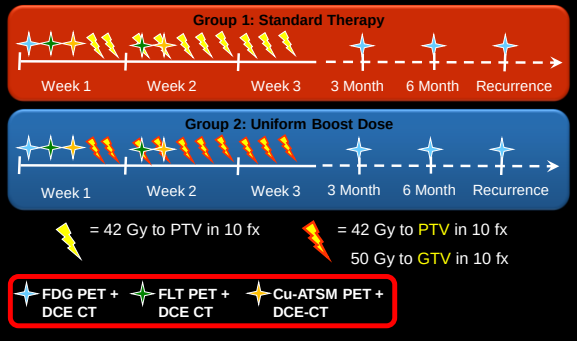
…branched evolutionary tumor growth, with **63 to 69%** of all somatic mutations not detectable across every tumor region…

Gerlinger et al 2012, N Engl J Med 366: 883.

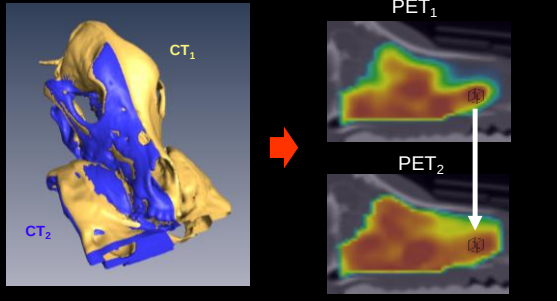
How to assess tumor heterogeneity?



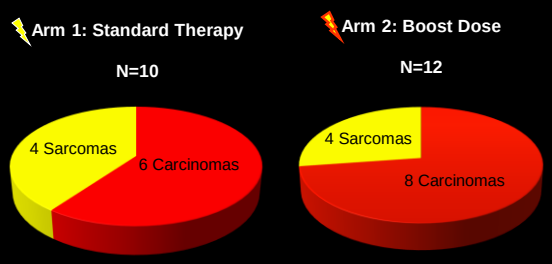
Canine dose painting clinical trial



Sub-mm registration – HD biology!

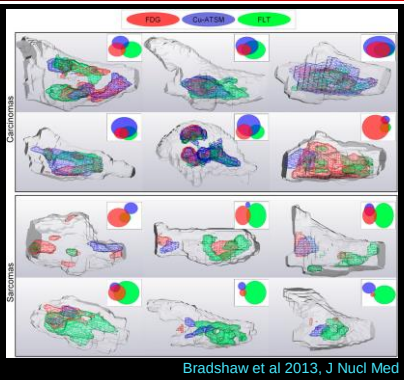


Subjects by treatment arm



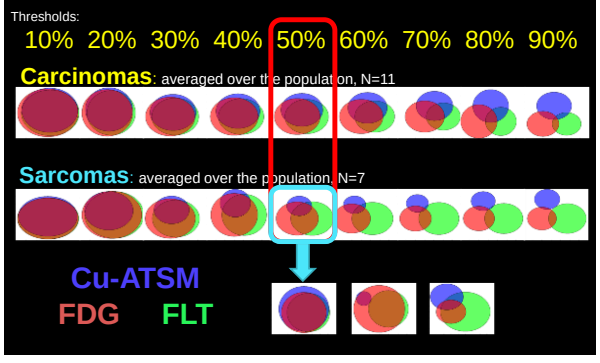
HOW HETEROGENEOUS ARE THE TUMORS?

Spatial heterogeneity

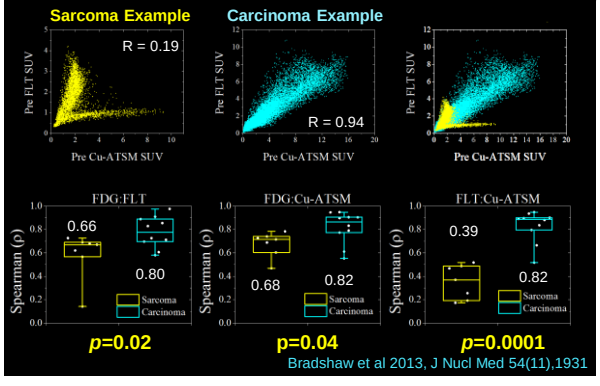


Bradshaw et al 2013, J Nucl Med 54(11),1931

Histology-dependent heterogeneity

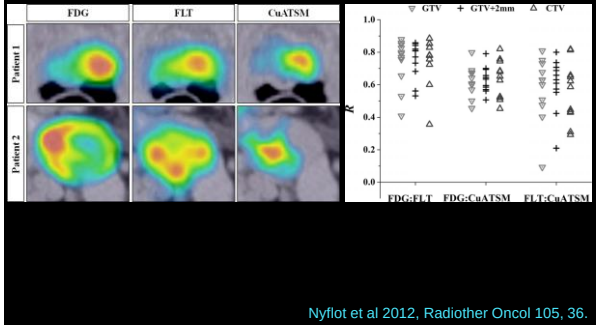


Structural heterogeneity?



Bradshaw et al 2013, J Nucl Med 54(11),1931

Heterogeneity in humans



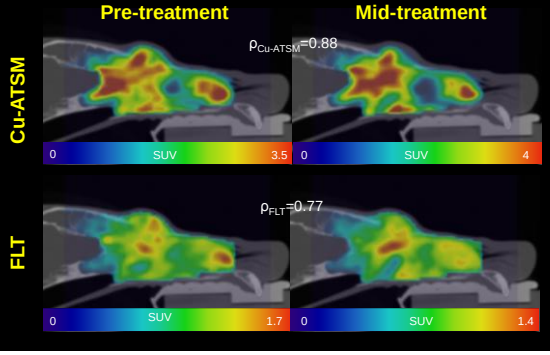
Nyflot et al 2012, Radiother Oncol 105, 36.

How heterogeneous are tumors?

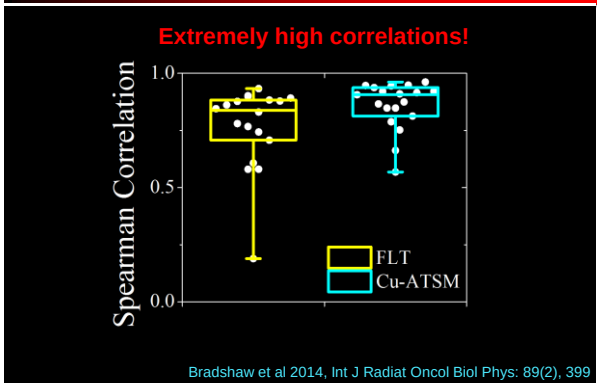
- Tumors appear to have **"structural heterogeneity"**
- The level of heterogeneity **persists across the phenotypes**
  - High correlation between proliferation, hypoxia, metabolism
  - Histology-dependent heterogeneity
- Tumor heterogeneity **similar across species**

IS HETEROGENEITY STABLE?

Cu-ATSM and FLT stability

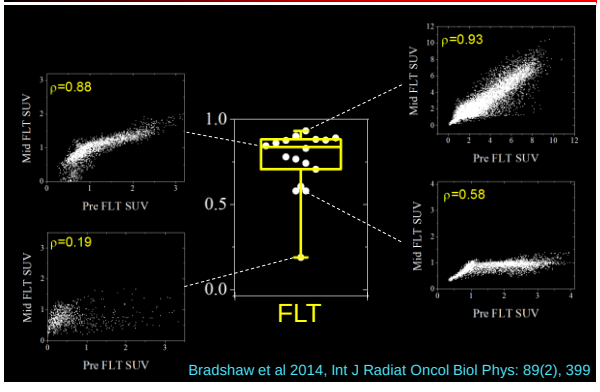


Cu-ATSM and FLT stability



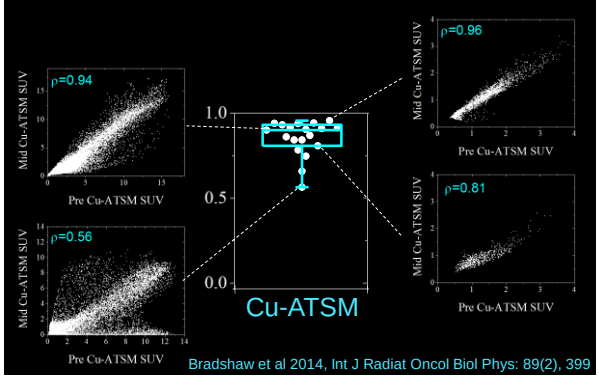
Bradshaw et al 2014, Int J Radiat Oncol Biol Phys: 89(2), 399

FLT Scatter Plots



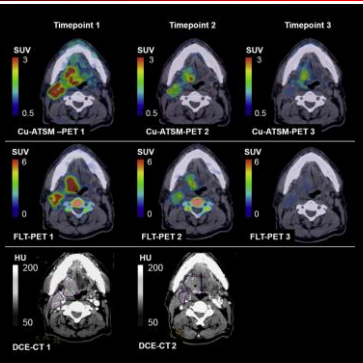
Bradshaw et al 2014, Int J Radiat Oncol Biol Phys: 89(2), 399

Cu-ATSM Scatter Plots



Bradshaw et al 2014, Int J Radiat Oncol Biol Phys: 89(2), 399

Stability in humans



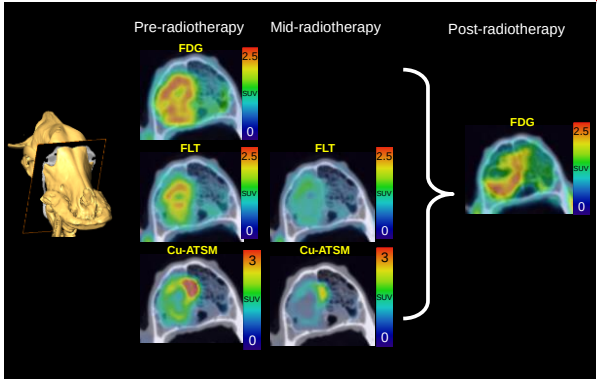
Nyflot et al 2015, Int J Radiat Oncol Biol Phys 91(5), 942

Is heterogeneity stable?

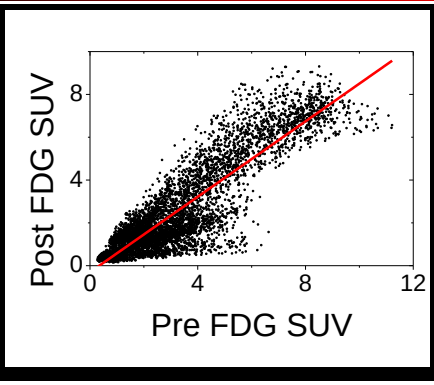
- Heterogeneity appears to be **relatively stable** through the course of radiotherapy
- Level of stability **varies across different phenotypes**
- Stability of heterogeneity **preserved across species**

CAN HETEROGENEITY PREDICT RESISTANCE?

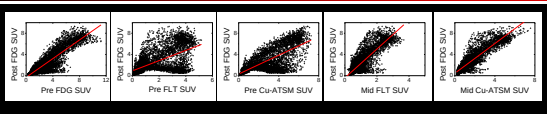
Does heterogeneity predict outcome?



Voxel regression modeling

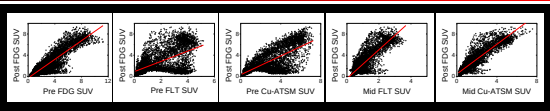


Voxel regression modeling



- β and R^2 for each tracer, for each patient

Voxel regression modeling



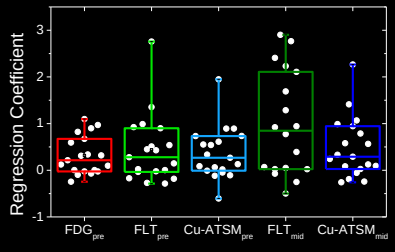
- β and R^2 for each tracer, for each patient
- Multivariable voxel regression

$$Y_i = \beta_0 + \beta_{FDG} FDG_i + \beta_{FLT} FLT_i + \cdots$$

Where Y_i is the i[th] voxel's post-treatment FDG SUV
FDG_i is the i[th] voxel's FDG SUV
β_{FDG} is FDG regression coefficient
…

Bowen et al 2012, Radiother Oncol 105(1): 41

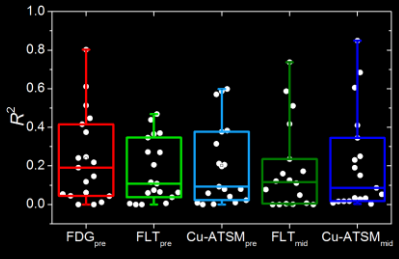
Results – univariable regression



β values were significantly positive for all variables ($P < 0.05$)

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

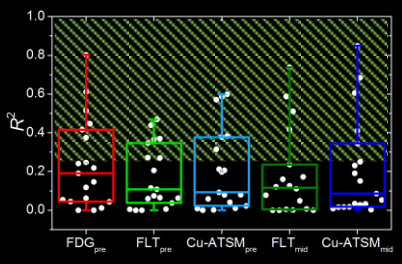
Results – univariable regression



Median $R^2 < 0.20$ for all variables

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

Results – univariable regression

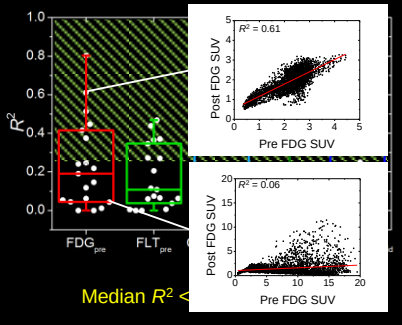


$r > 0.5$

Median $R^2 < 0.20$ for all variables

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

Results – univariable regression

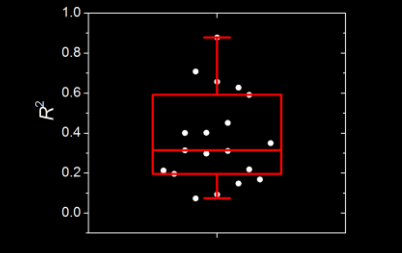


$r > 0.5$

Median $R^2 <$

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

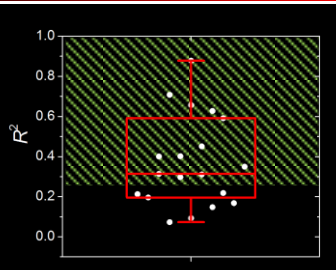
Results – multivariable regression



Median $R^2 \approx 0.30$

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

Results – multivariable regression



$r > 0.5$

Median $R^2 \approx 0.30$

Bradshaw et al 2015, Phys Med Biol 60, 5211-24

Can heterogeneity predict resistance?

- Heterogeneity appears **correlated to resistance**
- However, correlation between heterogeneity and resistance varies between **different tumors!**
- **Hypothesis: Primary tumors** should not be seen as single tumors, but rather composites of **multiple tumors** with distinctive (radio)biological characteristics

Conclusions

- Tumor heterogeneity is **real!**
  - Why do we keep delivering uniform dose?
- Tumor heterogeneity appears **"structural"**
  - Multiple phenotypes have a similar level of heterogeneity, which is histology dependent
- Tumor heterogeneity appears **stable**
  - Multiple phenotypes are spatially stable, but stability slightly varies across phenotypes
- Tumor heterogeneity appears to be related to **resistance**
  - However, not for all tumors, and not for all parts of tumors
- **Hypothesis: Primary tumors** are composites of **multiple tumors**