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!

How to assess tumor heterogeneity?

- Microscopy
- PET/CT imaging

Canine dose painting clinical trial

Group 1: Standard Therapy
- Week 1
- Week 2
- Week 3
- 3 Month
- 6 Month
- Recurrence

Group 2: Uniform Boost Dose
- Week 1
- Week 2
- Week 3
- 3 Month
- 6 Month
- Recurrence

- 42 Gy to PTV in 10 fx
- 50 Gy to GTV in 10 fx

FDG PET + DCE CT
- FLT PET + DCE CT
- Co-ATSM PET + DCE-CT

Sub-mm registration – HD biology!
Subjects by treatment arm

Arm 1: Standard Therapy
- N=10
- 4 Sarcomas
- 6 Carcinomas

Arm 2: Boost Dose
- N=12
- 4 Sarcomas
- 8 Carcinomas

HOW HETEROGENEOUS ARE THE TUMORS?

Spatial heterogeneity

Bradshaw et al 2013, J Nucl Med 54(11),1931
Histology-dependent heterogeneity

Thresholds:
10% 20% 30% 40% 50% 60% 70% 80% 90%

Carcinomas: averaged over the population, N=11

Sarcomas: averaged over the population, N=7

Cu-ATSM
FDG
FLT

Structural heterogeneity?

Sarcoma Example
R = 0.19

Carcinoma Example
R = 0.94

R = 0.19
R = 0.94

FDG, FLT, Cu-ATSM

0.66
0.80

0.68
0.82

0.39
0.82

p=0.02
p=0.04
p=0.0001

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

Heterogeneity in humans

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
Pre-treatment
P_CuATSM=0.88

Mid-treatment

FLT
Pre-treatment
PFLT=0.22

Mid-treatment
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ρ = 0.77

ρ = 0.88
Cu-ATSM and FLT stability

Extremely high correlations!


FLT Scatter Plots


Cu-ATSM Scatter Plots

Stability in humans

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

• $\beta$ and $R^2$ for each tracer, for each patient
Voxel regression modeling

- $\beta$ and $R^2$ for each tracer, for each patient
- Multivariable voxel regression

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

Where $Y_i$ is the $i^{th}$ voxel's post-treatment FDG SUV
$FDG_i$ is the $i^{th}$ voxel's FDG SUV
$\beta_{FDG}$ is FDG regression coefficient

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

Results – univariable regression

$\beta$ 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

Median $R^2 < 0.20$ for all variables

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

Results – univariable regression

$R^2 = 0.61$

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

Results – multivariable regression

Median $R^2 = 0.30$

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

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