Dynamics of spatial metastatic systems during adaptive therapy

Jill Gallaher
Moffitt Cancer Center
CATMO 2020
To kill or control?

... BUT adaptive therapy can also be about characterization of the disease state
simple, right?
Primary

Metastatic Seeding Timing affects sizes of metastases

Metastases

Treatment
Heterogeneity within Primary Tumor gives rise to heterogeneity in Metastases.
Primary

Heterogeneity within Metastases

Metastases

Treatment
There could be seeding from mets to mets
Metastases are not binary.

“One of the reasons metastasis is so difficult to define is that the same word describes the process and the outcome.”

Do we need to redefine a cancer metastasis and staging definitions?

-Danny R. Welch, Ph.D.

Breast Dis, 2008; 26: 3–12.

“To me, cancer is a verb, not a noun. ‘You’re cancering.’ It’s not something the body gets, it’s something the body does.”

-David Agus

Pre-Tx

Post-Tx

Different distributions of mets

Change in mets over time
What affects adaptive therapy cycle dynamics?
### Parameter Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b)</td>
<td>total cell burden</td>
<td>20,000-150,000</td>
<td>cells</td>
</tr>
<tr>
<td>(m)</td>
<td>metastases count</td>
<td>1-10</td>
<td>mets</td>
</tr>
<tr>
<td>(s)</td>
<td>sensitivity</td>
<td>60-100</td>
<td>%</td>
</tr>
<tr>
<td>(d)</td>
<td>cell turnover</td>
<td>0-0.06</td>
<td>day(^{-1})</td>
</tr>
<tr>
<td>(\sigma_{S1})</td>
<td>Intertumor heterogeneity</td>
<td>0</td>
<td>%</td>
</tr>
<tr>
<td>(\sigma_{S2})</td>
<td>Intratumor heterogeneity</td>
<td>0</td>
<td>%</td>
</tr>
</tbody>
</table>

### Model: Cell Cycle Dependent Drug

- **proliferation**
- **resistance**

### Graphs

- PSA vs. time (weeks)
- Normalized PSA vs. time after treatment (weeks)
- Normalized burden vs. time (weeks)
- Regrowth time (weeks) vs. response time (weeks)

### AT Trial Data

- Normalized burden
- Treatment ON vs. Treatment OFF
Cell cycle independent drug shifts toward quicker response times and longer regrowth times
How does burden and number of metastases affect adaptive therapy cycling?

Longer cycles for few mets with high burden
Shorter cycles for many mets with low burden

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>20,000-150,000</td>
</tr>
<tr>
<td>m</td>
<td>1-10</td>
</tr>
<tr>
<td>s</td>
<td>100</td>
</tr>
<tr>
<td>d</td>
<td>0</td>
</tr>
<tr>
<td>$\sigma_{S1}$</td>
<td>0</td>
</tr>
<tr>
<td>$\sigma_{S2}$</td>
<td>0</td>
</tr>
</tbody>
</table>
Some correlation with
1. Shorter cycles: small burden and many mets
2. Longer cycles: higher burden and few mets
Shorter cycles: younger and smaller
Longer cycles: older and larger
How does *sensitivity* and *cell turnover* affect adaptive therapy cycling?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>50,000</td>
</tr>
<tr>
<td>m</td>
<td>1</td>
</tr>
<tr>
<td>s</td>
<td>60-100</td>
</tr>
<tr>
<td>d</td>
<td>0-0.06</td>
</tr>
<tr>
<td>$\sigma_{S1}$</td>
<td>0</td>
</tr>
<tr>
<td>$\sigma_{S2}$</td>
<td>0</td>
</tr>
</tbody>
</table>
More sensitive: quicker response/regrowth times
More turnover: quicker response times, longer regrowth times
How does seeding/heterogeneity affect observed burden?

- Simultaneous
- Sequential

Systemic Treatment

Detect/Remove Primary

Time
Metastases below the threshold of visibility

**Simultaneous Seeding**
- Number of cells: 0
- Number of mets: 100
- % Visibility: 0%

**Sequential Seeding**
- Number of cells: 10k threshold
- Number of mets: 0
- % Visibility: 100%

**Simultaneous Seeding, Heterogeneous**
- Number of cells: 10k threshold
- Number of mets: 0
- % Visibility: 100%

**Proliferation** → **Resistance**
Many mets with low burden could go undetected

- simultaneous seeding
- sequential seeding

- homogeneous
- heterogeneous

0 % visibility
100 % visibility

number of cells
number of visible mets

initial PSA
initial metastases

Many mets with low burden could go undetected.
How does heterogeneity affect longer term adaptive therapy dynamics?
CT better with intertumor heterogeneity

- Proportionality between CT and resistance
- Proliferation vs. resistance

Graphs showing the normalized burden over time for Treatment ON and Treatment OFF.
AT better with intratumor heterogeneity

proliferation

resistance

Treatment ON

Treatment OFF

normalized burden
time (w)

normalized burden
time (w)
Conclusions

1. A cell cycle independent drug leads to shorter response times than regrowth times.

2. Cycles are semi-correlated with burden and number of mets, but there are clear trends associated with tumor size, age, sensitivity, and cell turnover.

3. Micrometastases smaller than the imaging threshold can go undetected but still contribute to tumor burden.

4. CT works better with intertumor heterogeneity and AT works better with intratumor heterogeneity.

5. Characterizing metastases as only a binary state is inadequate.
Acknowledgements

Sandy Anderson
Maxi Strobl
Jeff West
Mark Robertson-Tessi

Bob Gatenby
Jingsong Zhang

Center of Excellence
Evolutionary Therapy