Model-based evaluation of spontaneous tumor regression in pilocytic astrocytoma

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ZiF Workshop
Multiscale Modeling of Tumor Evolution: Data, Validation and Uncertainty

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Pilocytic astrocytoma: characteristics & subtypes

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Pilocytic astrocytoma (PA)
Pilocytic astrocytoma is the most common brain tumor in pediatric patients.
Characteristics

■ classified as WHO grade I
■ epidemiology
  □ 75 % occurring in the first two decades of life
  □ highest age incidence: 5 - 15 years
■ location
  □ frequently: cerebellum (60 %)
  □ also: cerebellar hemisphere, optic chiasm, hypothalamus, brainstem, spinal cord
Characteristics

- tumors
  - grow as solid masses
  - well-circumscribed tumors
  - non-invasive

- subtypes
  - determined on molecular level
  - differ in their aggressiveness
Subtypes

PA I

- indolent behavior
- slowly growing
- considered as benign
- genetic level
  - activation of MAPK pathway sufficient
  - BRAF, KRAS, NF1
  - single-pathway disease

- MAPK activation
  - initially promotes cell proliferation
  - but also induces senescence by increased activity of TSG (e.g. CDKN2A)
  - oncogene-induced senescence
Subtypes

Narita, M. et al. 2011

PA II

- aggressive behavior
- malignant transformation
- senescence is overcome by additional *genetic alterations*, e.g. *CDKN2A*
- enables fast tumor growth

*Narita, M. et al. 2011*
Therapy

goร.” total resection

- treatment of choice
- favorable prognosis: 90% cured without additional therapy
- problem: location determines extent of resection
  - cerebellum, superficial cerebrum
  - optic pathway, brain stem tumors
Therapy

**gross total resection**

- treatment of choice
- *favorable prognosis:* 90 % cured without additional therapy
- *problem:* location determines extent of resection
  - cerebellum, superficial cerebrum
  - optic pathway, brain stem tumors

⇒ Only partial resection possible in many cases
Therapy

partial resection

- lower survival rates than patients with total resection
- prognosis is highly unpredictable
  - tumor regrowth or progression to PA-II
  - tumor growth arrest
  - tumor regression
- controversy about further therapy
  - wait and see approach?
  - radiation therapy?
  - extent of follow-up observation?
Question & strategy

How should clinicians treat a partially resected PA-I tumor?

Aim
Development of a mathematical model to predict the chance of spontaneous regression of residual PA-I tumors
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Assumptions

- 3 cell types: wild-type, PA-I, PA-II
- parameters
  - mutation from wild-type to PA-I cell with rate $u$
  - mutation from PA-I to PA-II cell with rate $v$
  - critical tumor size $N \ (9cm^3)$
- dynamics
  - neutral competition between wild-type and PA-I cells
  - mutations
- large fitness advantage of PA-II cells
- no spatial aspects
A. state space in the TGP model

B. one step dynamics in the TGP model

Mathematical model

- **TGP process** $X_t$
- state space $S = \{0, 1, 2, \ldots, N, E\}$
  - $0 \equiv$ all cells wild-type
  - $k \equiv$ $k$ type-I cells, no type-II cell, $1 \leq k \leq N$
  - $E \equiv$ at least one type-II cell
- two absorbing states $N$ and $E$ representing *PA I* and *PA II*
Mathematical model

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- two absorbing states $N$ and $E$ representing \textit{PA I} and \textit{PA II}

- tumor regression function

\[ \beta(\varrho) := \mathbb{P}(X_t = 0 \text{ for some } t | X_0 = N\varrho), \varrho \in [0, 1]. \]
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Model analysis: strategy

Aim: Derive PA tumor regression function describing the probability for spontaneous tumor regression in dependency of the residual tumor size.

1. Choose suitable parameter regime
2. Derive general tumor regression function in the model
3. Calculate relative frequencies of PA-I and PA-II-tumors in the model
4. Model calibration with epidemiological data
Model analysis 1: Parameter regime

\( Nu \ll 1 \)

- each mutant lineage can be investigated independently
- *biological implication*: tumor develops from a single mutated cell
Model analysis 1: Parameter regime

$Nu \ll 1$

- each mutant lineage can be investigated independently
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Risk coefficient $\gamma := (N\sqrt{v})^2 > 0$

- positive probability of absorption in both states $N$ and $E$
- *biological implication*: $PA \ I$ and $PA \ II$ are possible outcomes of the model
- $\gamma$ determines the *absorption probability* and therefore the fractions of $PA \ I$ and $PA \ II$ in the model
Model analysis 2: Tumor regression function

- Tumor regression function can be approximated by a diffusion approximation

\[ \beta_{\gamma}(\varrho) = \sqrt{1 - \varrho} \frac{I_1(2\sqrt{\gamma(1-\varrho)})}{I_1(2\sqrt{\gamma})} \]

(I\(\alpha\) denotes the modified Bessel function of the first kind)

- **Aim**: estimate \(\gamma\)
- **Idea**: \(\gamma\) influences fraction of both tumor types in the model
Model analysis 3: Fractions of PA subtypes in the model correspond to absorption probabilities

Derivation sketch for

- assume occurrence of single *successful* mutant and set $u = 0$
- **First step analysis**

$$\alpha^N(i) = \sum_{j=0}^{N} p(i, j)\alpha^N(j) \iff P\alpha^N = \alpha^N \iff (P - E)\alpha^N = 0$$

- **Linear system of equations**

$$P'\alpha^N = b$$

- **Cramer’s rule**

$$\alpha^N(1) = \frac{\det P'_{1}}{\det P'}$$

- **Limit $N \to \infty$**

$$\alpha(\gamma) := \lim_{N \to \infty} \alpha^N(1)$$
Model analysis 3: Fraction of PA subtypes

PA-I: $\alpha(\gamma) = \frac{1}{I_0(2\sqrt{\gamma})}$,  
PA-II: $1 - \alpha(\gamma)$.
Model analysis 4: Model calibration

For $\gamma = 0.152$ the relative frequency of diagnosed PA-I tumors corresponds to the frequency in the model.
Model prognosis

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<th>res. tumor size (cm³)</th>
<th>prob. (%)</th>
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<td>8</td>
<td>10.39</td>
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Clinical implications

- quantitative estimation of the chance of spontaneous tumor regression of residual PA-I tumors
- residual tumor size is an important prognostic factor
Clinical implications

- quantitative estimation of the chance of spontaneous tumor regression of residual PA-I tumors
- residual tumor size is an important prognostic factor
- qualitative difference to other brain tumors (glioblastoma): In PA
  - always resection
  - maximal resection
Discussion

- model based on population dynamics of tumor and wild-type cells
- only one parameter: risk parameter $\gamma$
- results robust to changes of $\gamma$
- limited long-term follow-up data
  - long-time observation and regression behavior of partially resected cases of PA
THANKS