A biologically-based mathematical model for prediction of metastatic relapse

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BACKGROUND & OBJECTIVES

- Metastasis is the cause of 80% of deaths from solid tumors (Chaffer and Weinberg. Science 2011)
- ~20-30% of breast cancer patients will relapse with distant metastases (EBCTG, Lancet, 2005)
- For breast cancer, the current factors influencing decision for adjuvant therapy are: tumor size, nodal involvement, molecular factors (hormonal receptors and HER2 status), histological type and grade.

Objective: establish a biologically-based mathematical model for individualised prediction of metastasis

AN ELEMENTARY THEORY OF METASTATIC DYNAMICS:
GROWTH + DISSEMINATION

Growth rates of primary and secondary tumors $\gamma$ and $\mu$

$$\frac{dV_p(t)}{dt} = \gamma V_p(t)$$

Poisson process for the dissemination with rate $\delta(W) = \mu W$

Size distribution of the metastases $\rho(v)$

$$\frac{d\rho(v,t)}{dt} = \rho(v,0) - \delta(v)$$

Number of visible metastases

$$N(t) = \int_0^\infty \rho(v,t) dv$$

Total metastatic mass

$$M(t) = \int_0^\infty v \rho(v,t) dv$$

PRECLINICAL DATA AND POPULATION APPROACH

Data $\mathcal{M} = \mathcal{M}(\theta, \gamma) = \mathcal{M}(\bar{\theta} + \epsilon \mathcal{M}(\theta, \gamma))$, $\epsilon \sim \mathcal{N}(0,1)$

Individual parameter $\theta$

$$\theta = \theta_{base} + \epsilon \theta_{base}$$

Population fits (nonlinear mixed-effects)

CONCLUSION AND FUTURE DIRECTIONS

- A biologically-based mathematical model was able to describe preclinical and clinical data of metastatic development in breast, lung and kidney cancer
- Machine learning algorithms used here don’t account for censored data + limited to prediction of relapse event at a fixed horizon
- The biological model accounts for these and could give predictions of the metastatic state at diagnosis and future evolution in order to guide therapeutic intervention
- Predictive power is only modest so far but only the primary tumor size was considered here as a feature with only other source of inter-subject variability being the dissemination parameter $\mu$ - include more features and link parameter $\mu$ and others to clinical features and biomarkers in a biologically relevant way