Modeling tumor size and survival in patients with metastatic gastric cancer

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Introduction & Objectives
Introduction

• Rising importance of applying pharmacometrics in major disease areas such as cancer, Alzheimer and Parkinson diseases.

• High incidence of gastric cancer in Asian region

• Importance of collaborative efforts of pharmacometricians and oncologists to enhance treatment outcome
Objectives

- To develop a prediction model for tumor size and survival time (PFS and PPS) in Korean advanced gastric cancer patients (PPS: Post Progression Survival)

- To develop an application to use in routine clinical care of cancer patients

- To suggest an example of hospital-based pharmacometrics by conducting a collaborative project with medical oncology at Severance Hospital, Yonsei University, Korea
Materials & Methods
Data

• Data taken from ToGA (Trastuzumab for Gastric Cancer) study
• Open-label, international, phase 3, randomized, multi-center study
• A pivotal study that proved the benefit of trastuzumab given in combination with cytotoxic drugs (XP/FP) in HER2-positive advanced gastric cancer patients. (Bang et al., 2010, Lancet)
Data

- **69 patients** who received 1<sup>st</sup> line chemotherapy (XP, FP, or T+FP) enrolled into ToGA clinical trial: training dataset.

- **86 patients** who received XP/FP, T+XP/FP, T+P+TS–1, or FOLFOX: test dataset.

- All patients diagnosed with advanced gastric cancer with at least one distant metastasis (Liver, lung, bone, peritoneum, distant lymph nodes...)
Data

DV vs Time

![Graph showing DV vs Time]
Exploratory Analysis

- **Early shrinkage rate (Ksh)**: Percent reduction in tumor size at first reassessment divided by the visit interval.

- **Depth of response (DoR)**: The maximal tumor shrinkage observed in a patient.

- **Progression free survival (PFR)**: Survival time until progression of disease (PD) occurs.
Exploratory Analysis

Typical Tumor Response Curve

- Depth of Response
- Rate of Regrowth
- Early Tumor Shrinkage
- Length of SD

Time [months]

Size [mm]
Ksh vs Baseline

Early Shrinkage Rate vs. Baseline Tumor Size

Complete Responders

Non-responders
Depth of Response vs. Early Shrinkage Rate

- Depth of Response [DoR]
- Early Shrinkage Rate [Ksh]
PFS vs DoR

![Graph showing the relationship between PFS and Depth of Response (DoR)]
Key factors in Tumor size model

• Density dependent growth
• Drug resistance development
• Tumor heterogeneity
• Replicator equation
• Rate of selection
Density dependent growth

• Percentage(%) tumor growth rate decreases with larger tumor size.

• This is often due to competition for nutrients and blood supply.

• Such phenomenon is denoted as density dependence, and is often described using logistic or Gompertz growth models.
Norton Simon Hypothesis

“Therapy results in a rate of regression in tumor volume that is proportional to the rate of growth that would be expected for an unperturbed tumor of that size.”

Therefore, larger tumor grows slowly (density dependence) but also regresses slowly (Norton–Simon hypothesis) in response to chemotherapy.
Drug Resistance Development

- Drug resistance is the major reason for therapy failure in cancer patients.

- **Three major reasons** (Yang Kuang, John D. Nagy and Steffen E. Eikenberry, 2016)
  1. Growth fraction decreases as tumor advances.
  2. Drug penetrance into the tumor microenvironment declines as tumor gets larger.
  3. Heritable resistance by random genetic mutations followed by natural selection (**MOST IMPORTANT**).
Primary or Secondary?

Do resistant clones exist before treatment (primary resistance) or do they arise during treatment? (secondary resistance)
Luria and Delbruck (Nobel laureates in 1969) devised an experiment called a ‘fluctuation test’ to test which of the two hypotheses was correct.
Drug Resistance Development

(A) If mutations are induced by the media (phage), roughly the same number of mutants are expected to appear on each place.

(B) If mutations arise spontaneously during cell divisions prior to plating, each plate will have a highly variable number of mutants.

RESULT:
The number of resistant colonies on each plate varied drastically, supporting (B).
Growth rate constants of tumor sample #1 and #2 are not necessarily the same

→ Tumor heterogeneity

In evolutionary terms, growth rate constant is the **fitness** of the tumor.
Replicator Equation

- $k$: growth rate constant of a random sample

- $k_g$: population mean growth rate constant

- Denoting $f(k)$ as the fraction of tumor cells with a growth rate constant $k$:

$$\frac{df(k)}{dt} = (k - k_g)f(k) \quad (0 \leq f(k) \leq 1)$$

(Replicator Equation)
Replicator Equation

• If you are fitter than average, your genes will increase in proportion over successive generations.

• If you are less fit than average, your genes will decrease in proportion and eventually become extinct.
Rate of Selection

• Often, what we are interested is the rate of change of the population mean over time \( (= \frac{dk_g}{dt} ) \)

• It can be derived mathematically that:

\[
\frac{dk_g}{dt} = \int (k - k_g)^2 f(k) \, dk = \text{Var}(k)
\]

• Rate of selection is simply equal to the population fitness variance!

• \( \text{Var}(k) \) will be denoted using the symbol \( \sigma^2 \)
In fact, this result has been long known in the field of population genetics.

It was formulated by Ronald A. Fisher, and is often called “Fisher’s fundamental theorem”
Assuming that fitness (i.e. growth rate constant) is initially normally distributed, it can be mathematically derived that rate of progression is linear in time.
Summary of tumor size model

• **Cancer growth:** Logistic, Gompertz, and etc → **Density dependence**
  - Responsible for growth saturation

• **Cancer progression:** Change of $k_g$ over time (e.g., Tumors with higher histologic grade tend to grow faster) → **Time dependence**
  - Responsible for resistance development

• Rate of change of $k_g$ is equal to the variance of tumor growth rate constant; $dk_g/dt = \text{var}(k)$
Summary of tumor size model

• We can apply linear disease progression model to \( k_g \) if its initial distribution is assumed to be normal;

\[
k_g = k_g (0) + \sigma^2 \cdot t
\]

• Generally, the more diverse the cancer cell population and/or the microenvironment, the higher would be the variance of \( k \).

• Tumor heterogeneity is the key to understanding cancer progression and resistance development
Tumor Heterogeneity and Drug Resistance

By Daniel L. Dexter and John T. Leith

Drug resistance has long been identified as a major reason for therapy failure in cancer patients. Concurrently, work from many laboratories in the past 10 years has established tumor heterogeneity as a phenomenon of critical importance in the natural history of individual neoplasms. The two most sinister aspects of intraneoplastic diversity in human solid tumors are the genesis of clones with metastatic potential, and the existence of drug-resistant variants in primary cancers and their metastases. Thus, recent investigations on drug resistance and on tumor heterogeneity have converged to focus attention on the clonal organization of primary tumors and their metastases as the underlying basis for anticancer drug resistance. This review examines the degree of heterogeneity observed within tumors and the relationship of this diversity to resistance that might be anticipated for any given agent. A question critical to our discussion is “How many subpopulations are there?” The impact of multiple tumor clones on therapy is next discussed in relationship to normal tissue tolerance, the barrier clinicians face regardless of the specific agent used in treatment. Finally, laboratory and clinical approaches are presented for addressing a drug resistance problem that is seemingly overwhelming because of its complex biological roots.

Emerging understanding of multiscale tumor heterogeneity

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Diagnostic Imaging and Biomedical Technologies, GE Global Research, Niskayuna, NY, USA

Cancer is a multifaceted disease characterized by heterogeneous genetic alterations and cellular metabolism, at the organ, tissue, and cellular level. Key features of cancer heterogeneity are summarized by 10 acquired capabilities, which govern malignant transformation and progression of invasive tumors. The relative contribution of these hallmark features to the disease process varies between cancers. At the DNA and cellular level, germ-line and somatic gene mutations are found across all cancer types, causing abnormal protein production, cell behavior, and growth. The tumor microenvironment and its individual components (immune cells, fibroblasts, collagen, and blood vessels) can also facilitate or restrict tumor growth and metastasis. Oncology research is currently in the midst of a tremendous surge of comprehension of these disease mechanisms. This will lead not only to novel drug targets but also to new challenges in drug discovery. Integrated, multi-omic, multiplexed technologies are essential tools in the quest to understand all of the various cellular changes involved in tumorigenesis. This review examines features of cancer heterogeneity and discusses how multiplexed technologies can facilitate a more comprehensive understanding of these features.

Keywords: cancer, heterogeneity, tumor microenvironment, multiplexing, tumor mechanisms, multi-omic analysis, next-generation sequencing
Microenvironmental Heterogeneity Parallels Breast Cancer Progression: A Histology–Genomic Integration Analysis

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Survival Time Model

- **PFS**: Time to PD (Progression of disease)
  - *Target lesion PD*: >20% increase relative to best response
  - *Non-target lesion PD*

- **PPS**: Time to death after PD

- **OS** = PFS + PPS

- Time to dropout (censored time)
Time to non-target lesion PD

- Some patients were diagnosed with PD due to appearance of new metastatic lesion or substantial clinical deterioration.

- Such events are independent of target lesion dynamics.

- Survival model of non-target lesion PD was constructed.
Model for PFS

- Algorithm:

  If \( \min(PFS1, PFS2) < \text{CENSTIME} \):
    
    \[
    PFS = \min(PFS1, PFS2) \\
    PD = 1 \quad \#\text{PD event}
    \]
  
  Else:
    
    \[
    PFS = \text{CENSTIME} \\
    PD = 0 \quad \#\text{Censored}
    \]

* \(PFS1\): Predicted PFS for target lesion PD
* \(PFS2\): Predicted PFS for non-target lesion PD
* \(\text{CENSTIME}\): Censored time
Model for PPS

• Algorithm

If PPS > CENSTIME:

    PPS = CENSTIME

    CEN = 0  # Censored

Else:

    CEN = 1  # Patient died

Return (PPS, CEN)
• Fr: Fraction of tumor cells sensitive to drug
• \( k_g \): Linearly increases with time due to clonal evolution
Model Equations

\[ \frac{dS}{dt} = (k_g - k_{\text{eff}} \cdot \log(1 + \text{drug exposure})) \cdot S \cdot \left(1 - \frac{T}{T_{\text{max}}}\right) \]

\[ \frac{dR}{dt} = k_g \cdot R \cdot \left(1 - \frac{T}{T_{\text{max}}}\right) \]

\[ T = S + R \]

\[ k_g(t) = k_g(0) + \sigma^2 \cdot t \]

\[ k_g(0) = \text{Intercept} + \text{Slope} \cdot \log(T_{\text{baseline}}) \]

- drug exposure: K–PD model
- S: Sensitive cell, R: resistant cell
- \( \sigma^2 \): variance of growth rate constant; \( \sigma^2 = \text{var}(k) \)
- Initially, \( x(\%) \) is sensitive and \( 100 - x \) (\%) is resistant.
Resistant cells

- Resistant cells were further subdivided into subgroups based on drug resistance/sensitivity profiles.
  (i) Cells resistant to one of the drugs (3 subgroups)
  (ii) Cells resistant to two of the drugs (3 subgroups)
  (iii) Cells resistant to all three drugs (1 subgroup)

→ Total 7 subgroups for resistant cells
Results
Key covariates

- HER2 3+ status was found to be associated with higher uncertainty in fraction resistant to chemotherapy.
Key covariates

- Histologic grade was found to correlate positively with $\sigma^2$.

- Log tumor size was found to be proportional to $\sigma^2$.

\[ \sigma^2 = \text{function(histology, log tumor size)} \]

\[ K_g(t) = K_g(0) + \sigma^2 t \]

($K_g$: growth rate constant)
## Tumor size model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimate (%RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural Parameter</strong></td>
<td></td>
</tr>
<tr>
<td>Efficacy coefficient of XP</td>
<td>24.52 (19.74%)</td>
</tr>
<tr>
<td>Efficacy coefficient of Herceptin</td>
<td>1.85 (12.62%)</td>
</tr>
<tr>
<td>$\sigma$ (Histologic grade=1)</td>
<td>0 FIX (near zero estimate)</td>
</tr>
<tr>
<td>$\sigma$ (Histologic grade=2)</td>
<td>0.036 (24.18%)</td>
</tr>
<tr>
<td>$\sigma$ (Histologic grade=3)</td>
<td>0.05 (30.93%)</td>
</tr>
<tr>
<td>$\sigma$ (Histologic grade=4)</td>
<td>0.11 (45.42%)</td>
</tr>
<tr>
<td>Fraction of cells resistant to XP</td>
<td>0.89 (17.51%)</td>
</tr>
<tr>
<td>Fraction of cells resistant to Herceptin</td>
<td>0.64 (14.08%)</td>
</tr>
<tr>
<td>KDE (/month)</td>
<td>0.73 (11.17%)</td>
</tr>
<tr>
<td>Maximum tumor size (mm)</td>
<td>71.2*log(base) (0.026%)</td>
</tr>
<tr>
<td>Intercept of initial growth rate</td>
<td>-0.13 (14.94%)</td>
</tr>
<tr>
<td>Slope of initial growth rate</td>
<td>0.03 (21.74%)</td>
</tr>
</tbody>
</table>
# Tumor size model parameters

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<thead>
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<tr>
<td><strong>Variance Parameter</strong></td>
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<tr>
<td>IIV Intercept of initial growth rate (CV%)</td>
<td>72.9 (18.22%)</td>
</tr>
<tr>
<td>IIV $\sigma^2$ (CV%)</td>
<td>195.1 (16.28%)</td>
</tr>
<tr>
<td>IIV Fraction of cells resistant to XP (HER2 3+) (CV%)</td>
<td>161.8 (22.06%)</td>
</tr>
<tr>
<td>IIV Fraction of cells resistant to Herceptin (HER2 3+) (CV%)</td>
<td>233.1 (23.68%)</td>
</tr>
<tr>
<td>IIV Fraction of cells resistant to XP (HER2 0, 1+, 2+) (CV%)</td>
<td>58.85 (19.6%)</td>
</tr>
<tr>
<td>IIV Fraction of cells resistant to Herceptin (HER2 0, 1+, 2+) (CV%)</td>
<td>52.77 (45.74%)</td>
</tr>
<tr>
<td><strong>Residual Parameter</strong></td>
<td></td>
</tr>
<tr>
<td>Standard deviation of additive residual error</td>
<td>2.54 (13.73%)</td>
</tr>
</tbody>
</table>

*Very large random IIV*
Goodness of fit

DV vs Time

IPRED vs Time
Survival model parameters: PFS

- PFS ~ Log-logistic hazard + previous gastrectomy history + ECOG score

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<td><strong>Structural Parameter</strong></td>
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<tr>
<td>Baseline hazard</td>
<td>0.099 (27.98%)</td>
</tr>
<tr>
<td>Shape parameter</td>
<td>2.07 (25.23%)</td>
</tr>
<tr>
<td>Previous Op ECOG</td>
<td>-1.89 (23.6%)</td>
</tr>
<tr>
<td>ECOG</td>
<td>0.87 (38.46%)</td>
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</table>
Survival model parameters: PPS

- Post-progression Survival = Overall survival – PFS
- PPS ~ Weibull hazard + PFS + histologic grade + tumor size at last assessment

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<td><strong>Structural Parameter</strong></td>
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<tr>
<td>Baseline hazard</td>
<td>0.17 (22.98%)</td>
</tr>
<tr>
<td>Shape parameter</td>
<td>0.78 (30.55%)</td>
</tr>
<tr>
<td>PFS (if histologic grade ≥ 3)</td>
<td>-0.62 (41.87%)</td>
</tr>
<tr>
<td>Last tumor size (if histologic grade ≥ 3)</td>
<td>0.35 (32.87%)</td>
</tr>
</tbody>
</table>
External validation: Tumor size

VPC (n=100) of the tumor size model generated using the test dataset.

The colored region represents the 95% prediction interval.

Blue: Median of 2.5% of predictions

Green: Median of 50% of predictions

Red: Median of 97.5% of predictions
External Validation: PFS (n=1,000)
External validation: PPS (n=1,000)
Application Development
Registering New Patient

New Patient Log

- Enter New Patient ID: 
- Enter Baseline Tumor Size (mm): 
- Enter HER2 receptor status: 
- Enter ECOG score (1 for greater or equal to 1): 
- Presence of Liver Metastasis (1: Yes, 0: No): 
- Histologic Grade:
  1: Well-differentiated
  2: Moderately-differentiated
  3: Poorly-differentiated
  4: Signet ring cell
- History of previous gastrectomy:
Tumor size simulation (1)
Tumor size simulation (2)
Survival simulation (1)
Survival simulation (2)
Bayesian Fitting

Patient ID: 1
Baseline tumor type: HER2 status
Histologic Grade
Previous surgery
Presence of Lymph node
ECOG score

Objective function value: 144.153505
ETA1: Median -1.16 (95% CI = [-1.99, 0.13])
ETA2: Median 2.21 (95% CI = [0.40, 3.45])
ETA3: Median 1.18 (95% CI = [0.14, 2.23])
ETA5: Median -3.05 (95% CI = [-4.53, -2.53])
Discussion
Main contributions

• From a modeling perspective, the main contributions of our work are:

(1) Knowledge-based model development with drug resistance fractions and tumor heterogeneity playing crucial roles in treatment response and tumor progression, respectively.

(2) Incorporation of non-target lesion PD and dropout

(3) External validation using an out-of-sample dataset.
Clinical implications

• From a clinical perspective, we have identified the following information to be predictive of PFS.

  (i) Depth of response
  (ii) ECOG score
  (iii) Histologic grade
  (iv) Previous gastrectomy status
  (v) HER2 receptor status

• High HER2 receptor density was found to lead to higher uncertainty in treatment response.
Clinical implications

• Once PD has occurred, longer PFS is generally a favorable predictor of longer PPS.

• However, if histologic grade is poor, such benefit disappears.

• In other words, in patients with poor histologic grade, outcome from 1\textsuperscript{st} line therapy does not predict response to 2\textsuperscript{nd} line and 3\textsuperscript{rd} line therapy.
Limitations

- Following are some of the shortcomings of our model.

1. Absence of concentration information → Use of a KPD model (Dose instead of concentration)

2. Large OMEGA estimates of important model parameters such as resistance probability or $\sigma^2$.

3. (1) and (2) might be related in the sense that unrecognized variability in drug exposure might have been transferred to variability in resistance probability.

4. No standard criteria for non-target lesion PD

5. Inter-individual and/or inter-study variation in reasons for dropout
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