Modeling survival to fully capture value

Scott Ramsey, MD, PhD
Fred Hutchinson Cancer Research Center
Seattle, Washington, USA

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Heterogeneity of patient populations: a problem for survival modeling

Heterogeneous study populations comprise

Cured patients  Uncured patients

- Some patients will be “cured” (e.g., durable remissions, return to normality)
- Compared with uncured patients, cured patients will have
  - Longer survival, similar to a disease-free person
  - Greater healthcare costs (due to additional long-term follow-up/surveillance)
- **Standard approach for survival modeling**: assess the mean for all patients in each treatment arm
- **Issue**: grouping cured and uncured patients together and reporting one mean value = potential bias

Issues with the standard approach to survival modeling

- Mean OS for **cured** patients is much greater than mean OS for **uncured** patients
  - Mean OS for cured patients may exceed the observation period of the study
- **Grouping** cured and uncured patients together and reporting one mean value for OS does **not account for heterogeneity** in the population and results in
  - **Incomplete assessment** of a therapy that cures a proportion of patients
  - **Biased assessments** of OS

OS, overall survival
Estimating mean overall survival with survival plateau

Survival curves plateau
- Mean OS cannot be estimated from an empirical curve

Standard approach and previous work
- Use parametric models to generate tail curve

Mixture cure models: basic approach

- General idea: explicitly model the mixture of “cured” and uncured patients
- Use regression models to
  - Estimate the probability that a patient is cured
  - Predict the survival of patients who are not cured

Population survival = \( p_{cured} \times \text{survival}_{cured} + (1-p_{cured}) \times \text{survival}_{uncured} \)

2. Kuk AYC, Chen CH. Biometrika. 1992;79:531–541;
Example: applying the mixture cure model to the ZUMA-1 trial of CAR T-cell therapy for patients with relapsed or refractory large B-cell lymphoma

- **ZUMA-1 trial**
  - Phase 2, single-arm, registration study (N = 111) of axi-cel in patients with relapsed or refractory large B-cell lymphoma
  - 54% of the patients achieved a complete response to therapy
  - At 18 months, the Kaplan-Meier estimated rate of OS was 52%
  - Median follow-up was 15.4 months
  - Responses were ongoing in 42% of the patients, including 40% with a complete response

Methods for fitting Kaplan-Meier curves

- Weibull and lognormal distributions without a cure proportion
- Mixture cure: weighted average of cured and noncured
  \[ S(t,x) = S_B(t,x)p(x) + (1 - p(x))S_E(t,x) \]
- Estimation of \( \int_0^\infty S_B(t)dt \) and \( \int_0^\infty S_B(t)S_E(t)dt \), respectively
- Percentile-based bootstrap 95% CIs calculated using 1000 bootstrap replicates
Lognormal, Weibull, and mixture cure models applied to the ZUMA-1 trial data vs a Kaplan-Meier curve

OS modeling in the SCHOLAR-1\textsuperscript{1} cohort

- We assumed age-matched US general population mortality rates for patients alive at the conclusion of SCHOLAR-1 follow-up (10 years)
Mean OS estimates for ZUMA-1

<table>
<thead>
<tr>
<th>Summary statistic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lognormal analysis (without cure modeling)</td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI) OS, years</td>
<td>4.6 (2.3–10.3)</td>
</tr>
<tr>
<td>Weibull analysis (without cure modeling)</td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI) OS, years</td>
<td>2.0 (1.5–3.0)</td>
</tr>
<tr>
<td>Mixture cure model analysis</td>
<td></td>
</tr>
<tr>
<td>Cure fraction (95% CI), %</td>
<td>50.2% (36.3–64.1)</td>
</tr>
<tr>
<td>Mean (95% CI) OS among cured patients, years</td>
<td>28.1 (26.0–30.1)</td>
</tr>
<tr>
<td>Mean (95% CI) OS among noncured patients, months</td>
<td>8.2 (7.1–9.9)</td>
</tr>
</tbody>
</table>

CI, confidence interval; OS, overall survival

When to consider using mixture cure models vs standard models

- All survival curves have some degree of a tail
- Based on simulations, there needs to be
  - **The possibility of cure**: compared with standard models, mixture cure modeling is less efficient and can overestimate survival when there is no cure
  - **Sufficient follow-up**: Mixture cure modeling is likely to underestimate survival when the true-cure fraction is > 5% and follow-up is < 50% of the time at which 95% of events would have been observed
    - The smaller the true-cure fraction, the longer the necessary follow-up

Bansal A, Basu A. Unpublished data
When to consider using mixture cure models in general

• Biological rationale
  – Is long-term remission (ie, “cure”) plausible?
• Shape of the Kaplan-Meier curve
  – What is the proportion of survivors at the end of the follow-up period?
• Duration of follow-up
  – Shorter follow-up = more uncertainty
  – Rules of thumb?
• Number of patients in each cohort

Conclusions

• Mixture modeling offers advantages over traditional survival modeling for extrapolation, when treatments produce a clear fraction of patients with long-term remission (ie, “cure”)
  – Typically, mean survival estimates with mixture cure modeling are substantially greater than those achieved using standard parametric approaches
• The benefits of mixture cure modeling lessen and errors increase as the “cure fraction” decreases
• To avoid errors in estimation, it is critical to consider the biological rationale, shape of the Kaplan-Meier curve, and duration of follow-up before using mixture cure modeling
THANK YOU