Cure Models

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OUTLINE

- The concept of cure in the relative survival framework
- Modelling the cure of cancer
  - Mixture models
  - Non mixture models
- Direct/Indirect use of cure models
- Eurocare-4 application
- Advantages and drawbacks of cure models
- Software availability
- Open questions
THE CONCEPT OF CURE IN THE RELATIVE SURVIVAL FRAMEWORK

• Attainment and maintenance of an interval specific relative survival of 1 (corresponding to a flattening of the cumulative relative survival curve) indicates that there is no excess mortality due to cancer and the patients are assumed to be ‘statistically cured’

• It is a definition from a population perspective, it does not provide any information on individuals, therefore it does not necessarily imply that all patients are medically cured (no longer display of disease symptoms)
For many cancers, the pattern of excess mortality shows high excess mortality soon after diagnosis and statistical cure reached after approximately 6–8 years (as is the case for stomach, colon … cancers)

Data Source: SEER 9 data, cohort 1981-88, 20 years of follow-up
A notable exception is female breast cancer where excess mortality remains at a relatively constant level for many years following diagnosis.
When the assumption of cure for a proportion of patients is reasonable, it may be appropriate to fit models that explicitly allow the estimation of a cure fraction.

There are two main types of cure fraction models based on the same two assumptions:

1. a proportion of cancer patients is cured
2. survival time of uncured patients can be described by a chosen parametric distribution
– **Mixture cure fraction models**\(^1\)

\[
S(t) = C + (1-C) S_u(t)
\]

HP: two groups exist: those who are ‘cured’ of their disease, and thus have a similar mortality rate to that expected in the general population, and those who are ‘uncured’, or ‘bound to die’, of their cancer

– **Non mixture cure fraction** (or **promotion time cure, or bounded cumulative hazard**) **models**\(^2\)

\[
S(t) = C^{Fz(t)}
\]

Originally developed in the modelling of tumour\(^3\) recurrences, the motivation behind non-mixture cure fraction models is that “after treatment,” it is assumed that an individual is left with \(N_i\) “metastatic-competent” cancer cells, i.e. a tumor cell that has the potential of metastasizing.

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\(^1\) Verdecchia 1998, De Angelis 1999, Yu 2004  
\(^2\) Lambert 2007, Andersson 2011  
\(^3\) Tsodikov et al., 2003
A key point for the model specification is the choice of the survival distribution for uncured patients:

- Mixture cure models use standard parametric survival curve functions (Weibull, exponential are the most frequently used, but also lognormal, log-logistic, Gompertz)

- flexible parametric survival model is as special case of non-mixture cure models where restricted cubic splines are used to estimate the cumulative excess hazard

Structure of input data: aggregated versus individual data
THE USE OF CURE MODELS

1. **Direct use** ➔ for description and interpretation of survival trends and geographical patterns, addressed to:
   - Clinicians (to improve understanding and communication with patients community)
   - Policy makers (to better allocate health care resources)

2. **Indirect use** ➔ to provide information needed for other analyses:
   - Survival models used in MIAMOD/PIAMOD method
   - Survival models used in COMPLETENESS INDEX method
   - For estimating the CURE PREVALENCE
Cure model parameters plan: framework for results interpretation

- Diagnostic anticipation
- Increasing survival
- Improvement of cure
- Selective improvement

Proportion of cured

Time to death
THE EUROCARE EXPERIENCE: CURE PROPORTION IN EUROPEAN COUNTRIES

• Aim: description and interpretation of cancer survival in 18 European countries, for major cancer sites, over the period 1988-1999
• Input data: stratified by age class and period of diagnosis (source: EUROCASE-4 study data base), six-months follow-up intervals
• Analysis: lung, stomach, colon-rectum, breast, prostate, all cancer combined
• Mixture cure survival models, with Weibull distribution for uncured patients,
Geographical patterns: lung and colon-rectum cancer

Time to death

Proportion of cured

A = AUSTRIA
FIN = FINLAND
S = SWEDEN
CZ = CZECH REP.
I = ITALY
SCO = SCOTLAND
D = GERMANY
ICE = ICELAND
N = NORWAY
PL = POLAND
DK = DENMARK
SLO = SLOVENIA
E = SPAIN
NL = NETHERLAND
UK = ENGLAND
F = FRANCE
WAL = WALES

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Age (all cancers in women) and period trends (colon and rectum, men and women combined)

Proportion of cured
X.Q. Yu (Cancer Epidemiology, 2013) compares different modelling approaches using three different examples (breast female, ovary, colon) in order to give some practical advise to model users.
CRITICISMS OF USING CURE MODELS

A crucial issue with the cure models is the identifiability of the cure fraction and parameters of latency distribution and the length of follow-up time.

- First scenario (breast cancer any age group) → **cure assumption is not reasonable** … just producing an estimate does not mean the approach is sensible.

- Second and third scenarios → **cure is reasonable**
  
  → (colon, ovary, two younger age groups <60, 60-74) uncured survival distribution is appropriate, all models fit and produce similar estimates.

  → (colon, ovary, 75+) **distributional assumption is not appropriate**, results widely vary according to the uncured survival distribution and the structure of input data, … the use of grouped data with annual fup intervals, averages out the high excess mortality in the first few months since diagnosis.
SOME ADVICE FOR USERS

- test the reasonability of cure assumption → visual examination of relative survival life tables estimates by key prognostic factors to determine whether or not survival curves tend to level off after a certain period of follow-up

- test the uncured survival distribution → compare results from models with different survival distributions (Weibull vs flexible) and/or using different data input (aggregated versus individual, yearly versus monthly follow-up intervals)

- Input data prerequisites → large samples, long follow-up, individual versus grouped data
Software availability

• Stata commands (http://www.stata-journal.com/): Lambert Stata J 2007: `strsmix`, `strsnmix` allow to estimate the cure fraction in population-based cancer studies; Lambert- Andersson Stata J 2012: have updated the `stpm2` command for flexible parametric models to enable cure modeling.

• SAS routine, mixture-grouped data (available on request http://www.eurocare.it/MiamodPiamod/tabid/60/Default.aspx#software)

• CANSURV is a statistical software to analyze population-based survival data. For grouped survival data, it can fit both the standard survival models and the mixture cure survival models (http://surveillance.cancer.gov/cansurv/)
OPEN QUESTIONS

• Is the assumption of cure reasonable for all cancers/age groups? How much levelling is sufficient to allow the application of cure models?

• How do we choose the appropriate models features (survival distribution weibull/flexible, grouped/individual data)?

• Is there any caution we should take according to the specific purpose of our estimate (either description/interpretation or information for other analyses)?