Estimating and modelling the cure fraction in population-based cancer survival analysis

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Specific aims of the research

1. Develop statistical methods for estimating and modelling the cure fraction in population-based cancer survival analysis.
2. Apply the methods to data from Sweden, Finland, England, and the USA with the joint aim of evaluating the new methodology as well as studying temporal trends in cancer patient survival.

Background: Relative Survival

Relative Survival = \( \frac{\text{Observed Survival}}{\text{Expected Survival}} \)

\( R(t) = \frac{S(t)}{S^*(t)} \)

- Expected survival obtained from national population life tables stratified by age, sex, year of diagnosis, other covariates.
- Estimate of mortality associated with a disease without requiring information on cause of death\( (1; 2; 3) \).
- On hazard scale

\[ \lambda(t) = h(t) - h^*(t) \]

Excess Mortality Rate = Observed Mortality Rate - Expected Mortality Rate
For many cancers the excess mortality (hazard) rate returns to the same level as that in the general population. When this occurs the relative survival curve is seen to reach a plateau. This is Population or Statistical Cure. Information of cure at the individual level not available. For the ‘uncured’ we can obtain a summary measure of survival.
Relative Survival for Cancer of the Colon in Finland

![Graph showing relative survival over time for different intervals.](image)

Relative Survival Models and Cure Models

**Relative Survival Models**

\[ S(t) = S^*(t)R(t) \]
\[ h(t) = h^*(t) + \lambda(t) \]

- When modelling cure we define an asymptote at the cure fraction, \( \pi \), for the relative survival function, \( R(t) \).

**Mixture Cure Model**

\[ S(t) = S^*(t)(\pi + (1 - \pi)S_u(t)) \]

Survival for the ‘Uncured’

- As well as the cure fraction, summaries of the ‘uncured’ (those ‘bound to die’) are potentially useful.
- For example, mean or median survival or some other percentile of the survival distribution.
- We need to choose parametric form for \( S(t) \).
- For many scenarios the Weibull distribution provides a good fit.
Interpreting changes over time

(a) General Improvement
(b) Selective Improvement
(c) Improved palliative care
(d) Inclusion of subjects with no excess risk

Survival of Uncured Cure Fraction

Adapted from Verdeccia (1998)
Interpreting changes over time

(a) General Improvement
(b) Selective Improvement
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Survival of Uncured
Cure Fraction

Adapted from Verdeccia (1998)

The cure proportion is not affected by lead time

Onset Detectability Symptoms Death

DETECTABLE PRECLINICAL PHASE

LEAD TIME SURVIVAL TIME

Early diagnosis Clinical diagnosis Postponed death

Time

Dickman et al. Cure models for cancer patient survival 10/21
Time Trends for Cancer of the Colon

Cure Fraction

Year of Diagnosis

Cure Fraction

Median Survival of Uncured

Year of Diagnosis

Time Trends for Cancer of the Colon

Quantifying Differences

Relative Odds of Cure (Age Group 70−79 / Age Group <50)

Years from Diagnosis

Odds Ratio
Quantifying Differences

Difference in Cure Fraction (Age Group <50 – Age Group 70–79)

Years from Diagnosis

Time Trends for Cancer of the Rectum

Cure Fraction

Year of Diagnosis

Median Survival of Uncured

Year of Diagnosis
Factors contributing to improvements

- Surgical and anaestesiological techniques have become more aggressive and sophisticated over time.
- The age of the patient at which surgeons are prepared to operate has increased over time, which may explain the reduced differences in the proportion cured between age groups.
- Better awareness among the public and doctors about the importance of early diagnosis for cure.
- Some of the trends over time are likely to be due to the "learning period" when gradually introducing new techniques within and between hospitals.

Greater improvements for rectal than colon cancer

- Rectal cancer surgery is much more demanding than colon cancer surgery, and the general improvements in anaesthesiology and postoperative care seen in the late 1960s/early 1970s were relatively much more important for rectal than colon cancer.
- The steep increase during the 1990s seen in all age groups likely reflects the marked decrease in the risk of a local failure after rectal cancer surgery seen after the introduction of total mesorectal excision (TME) and increased use of preoperative radiotherapy or postoperative radiochemotherapy.
- A local failure is a much less clinical problem in cancer of the colon than in cancer of the rectum.
- Metastatic disease has been the predominant cause of death among colon cancer patients.
- The natural course of local failure is longer than that of metastatic disease (which often involves the liver).

Time Trends for AML in Sweden
Challenges and current/future research

- How do the models behave when cure is not reached (e.g., female breast cancer).
- Preliminary evidence suggests the models perform best when mortality is neither high nor low.

Cure models may fit poorly when early mortality is high:
Cancer of the Colon: Weibull and Mixture of Weibulls

![Graph showing relative survival over years from diagnosis for Age Group 80+ with Ederer II, Weibull, and Mixture of Weibulls models.](image)

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