Long-term survival rate of stage I-III small cell lung cancer patients in the SEER database - application of the lognormal model

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Introduction: PCI studies

- Many published studies for small cell lung cancer have short follow-up.
- Although published meta-analyses favor the use of prophylactic cranial irradiation (PCI) in complete responders, the degree of long-term benefit is not well established.
- Some studies show convergence of survival curves with long-term follow-up of patients who received (PCI+) and did not receive PCI (PCI-), while others do not.
Introduction: basis for study methodology

• We studied long-term survival of small cell lung cancer patients in the Surveillance, Epidemiology and End Results (SEER) database, which is a population database and covers 26% of the United States population.

• A parametric statistical model, Boag's lognormal model, was retrospectively validated, using the SEER data and the actuarial Kaplan-Meier method of calculation.
Introduction: What is meant by a “log-normal” distribution

- We are all familiar with the bell-shaped normal distribution for a large sample or population.

- Survival times of a large sample of cancer patients tend to have a high initial mortality and then gradually fall to a low mortality.
Survival time of a large sample or population
The logarithm of survival time is found to follow a normal distribution.
Introduction: What is the use of log-normal distributions?

• Log-normal prediction modelling for long-term cancer survival rates using short-term follow-up data.
• Available for usage for some 50 years.
• A new standard for the 21st century?
Four groups of patients in Boag’s lognormal model

If not lost to follow up,
- Gp 1 patients died from the specific cancer
- Gp 2 patients died from intercurrent disease
- Gp 3 patients were alive and free of clinical evidence of disease
- Gp 4 patients were alive with persistent or recurrent disease.
Survival prediction: *Phase I*

- Goodness of fit of survival time distribution of the uncured group to a log-normal distribution by minimum chi-square method
- Breast (Boag 1949)
- Subsites in Head and Neck (Mould 1976)
- Breast (Rutqvist 1984, 1985)
- 23 cancer sites of UK data (Berg 1965)
- 40 cancer sites of SEER data (Tai 2002)
Survival prediction: **Phase 2**

- Uses short-term follow-up data (e.g. 2-6 years) to predict long-term survival of 10-20 years by maximum likelihood method.
- Validation by comparing with cancer-specific survival rates of Kaplan-Meier calculations: e.g.,
  - Cervix (Mould & Boag 1975)
  - Lung, breast, ovary, larynx, prostate, bladder, cervix, thyroid (Tai 2002)
  - Small cell lung cancer (Tai 2003)
  - Breast (Tai 2003)
Cancer sites with survival times demonstrated to follow lognormal distribution in the literature (*phase 2 validation also performed, i.e. concordance between Kaplan-Meier method and lognormal model.)

- Head and neck cancer: Berg, Mould
- Mouth and throat cancer: Boag
- Thyroid: Tai*
- Larynx, tongue: Mould & Tai*
- Non small cell lung cancer: Berg
- Small cell lung cancer: Tai*
- Intraocular melanoma: Gamel
- Cutaneous melanoma: Gamel
- Breast cancer: Boag, Berg, Rutqvist, Gamel, Haybittle, Royston, Tai*
- Bone sarcomas: Berg
- Cancer of uterine cervix: Mould & Boag*, Berg
- Ovarian cancer: Berg, Tai*, Royston
- Hypernephroma: Berg
- Bladder cancer: Berg
- Prostate cancer: Mould & Tai*
- Gastric cancer: Berg, Maetani
- Lymphoma: Berg
- Chronic leukemia: Tivey
- Brain tumours: Berg
Methods

• From 1988-1991, there were 1060 incident cases of stages I-III small cell lung cancer in the 9 registry areas that comprise the SEER database, of whom 132 received (PCI+) and 928 did not receive PCI (PCI-).

• Two 2-year periods of diagnosis (1988-1989 and 1990-1991) were combined and then patients were followed-up as a cohort for an additional two years.
Results

- The survival time of uncured patients who received (PCI+) and did not receive PCI (PCI-) followed two different lognormal distributions.
Results

• For PCI+ and PCI- patients respectively, the five-year cancer-specific survival rates, calculated using the Kaplan-Meier method and actual follow-up data to the year 2000, were 18±3% and 12±1%. The corresponding predictions, using the lognormal model were 15% and 11% respectively.
Results

- The 10-year cancer-specific survival rates were 10±3% and 9±1%, when calculated by the Kaplan-Meier method, and 12% and 10% as predicted by the lognormal model.

- The available follow-up was not long enough to provide 15-year cancer-specific survival rates by the Kaplan-Meier method, but the lognormal model predicted them to be 12% and 10% respectively.
Results

• The PCI+ and PCI- cancer-specific survival curves almost converged in long-term follow-up.

• The difference in the two survival curves, as calculated by the logrank test (which takes into account the whole duration of follow-up), was highly statistically significant (p<0.001).

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Discussion

• This log-normal survival prediction method works for all sites as long as not a lot of patients are lost to follow-up.

• Potentially can obtain results faster

• Speed up development of future trials

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Small cell lung Ca example for survival prediction in another dataset

- Saskatchewan Cancer Registry data
- Estimated 10-year Cause-Specific Survival Rate (CSSR) = 13% by log-normal model.
- Kaplan-Meier Method = 15 ± 3%.

(Tai et al, IJROBP 2003;56:626-33)
Cause-specific survival for 122 patients with small cell lung cancer, estimated by the log-normal model versus actuarial survival calculated by Kaplan-Meier method.

(Tai et al, IJROBP 2003)
Conclusions

• The survival benefit with PCI is more apparent in the short-term, and diminishes with longer-term follow-up in the SEER database.

• The lognormal model has the potential to predict the results of on-going prospective PCI trials earlier than would be possible with the use of the Kaplan-Meier method.

• This may become a useful tool in outcome research.