Survival : Basic Concepts

Dr. Rajesh Dikshit
Professor-Epidemiology
Tata Memorial Hospital, Mumbai

ORGANIZATION OF THE LECTURE

Sources of data and incidence

Survival analysis

Follow up
Censoring and its types
Conventional methods
Period survival

Types of Cancer Registries

- Population-based Cancer Registry
- Hospital-based Cancer Registry
- Pathology Based Cancer Registry
- Special Purpose Cancer Registry

Charactestic	HBCR	PBCR
Primary Concern	Cancer patients in a hospital	Cancer in the community
Assessment of dimensions of the cancer problem	Number of diagnoses per year, relative frequencies of cancer by site in the hospital	Cancer Incidence, mortality and prevalence, trends in cancer incidence
Contribution to		
a) **Patient care**	Active follow-up and describes the length and quality of survival in relation to stage, site and treatment	Indirect follow-up, evaluates overall survival by site
b) Research - Treatment	Participates in clinical research to evaluate therapy	Provides background for clinical research
Prevention	Assists in case control studies; identifies groups with high and low frequencies	Assist in case control and prospective studies; Identifies low and high incidence groups
c**) Health services**	Helps assess the quality of care and cancer services in a hospital	Helps assess the effectiveness of preventive measures and community care

HBCR

Contributes in developing Clinical Trials

Provide evidence for one treatment protocol over other

Evaluate effectiveness of Evidence based treatment protocol in hospital.

Survival in Hospital.

PBCR

Evaluate effectiveness of protocol in community

Survival in Community

e

Estimates of survival from clinical trials : Strengths and limitations

Strengths :

Randomize design
Compare survival from two or more different protocol
Survival estimated using KM and/or Cox proportional hazard models.
Provide level 1 evidence for superiority of treatment

Limitations :

Selection bias
Generalization of superior treatment can not be proven.

Estimates of survival in hospital setting (HBCR) : Strengths and limitations

Strengths :

Provide evidence for effectiveness of treatment protocol proven by CT in hospital setting.

Estimate survival for particular site controlling for stage and co-morbid condition.

Survival estimated using KM and/or Cox proportional hazard model.

Limitations :

Generalization of superior treatment can not be proven.
Survivor in community can not be estimated.

Estimates of survival in community (PBCR) : Strengths and limitations

Strengths :

Estimate survival for cancer sites in community.
Provide evidence on availability of health care infrastructure and expertise in community.
Survival estimated using relative survival method.

Limitations :

Details of treatment, stage not available (?)

Method	Aim	Outcome	Contribution in Cancer Control
Clinical Trial	To evaluate the effect of intervention on patient survival	Provide evidence , which treatment is better	Provide insights into treatment to be provided.
Hospital Based Survival	To describe patient survival in defined population. To describe effect of stage and co-morbid condition on survival	Provide effectiveness of treatment protocol under expert supervision. Provide estimation of maximum possible survival for different stages and different co-morbid conditions	Provide insights for creation of health care facilities given cancer burden and considering survival benefits.
Population Based Survival	To describe patient survival in general population	Provide evidence for survival in communities	Provide insight into effectiveness/availability of health care infrastructure.

NEED FOR SURVIVAL ANALYSIS

Follow up studies

- Varying individual lengths of follow up time is encountered
  - Patients enter and leave study at varying points of time
- Identical person time at risk – say 100 py
  - 50 persons followed for 2 years
  - 100 persons followed for 1 year
- Rates calculated based on person time at risk
- Underlying assumption is that the rate of outcome event remains constant over time
- If not, survival analysis is the best approach

Requirement to conduct Survival studies

- An adequate and complete follow up is a pre-requisite for survival analysis
- Lengthy periods of time may be required for an outcome to occur
- Follow up is complete if the outcome is known by the end of follow up
- If not known, then the follow up is deemed to be incomplete

OTHER REQUISITES

- A clear “case definition”
- A clear and well defined starting point referred to as index date (eg. Date of dx, date of start/end of therapy, etc.)
- A clear and well defined outcome (eg. death, recurrence, occurrence of particular complication, etc.) – Each case can have one and only one end point
- Imposing a closing date of follow up for uniformity and summarizing survival data

OTHER REQUISITES

- A clear “case definition”
- A clear and well defined starting point referred to as index date (eg. Date of dx, date of start/end of therapy, etc.)
- A clear and well defined outcome (eg. death, recurrence, occurrence of particular complication, etc.) – Each case can have one and only one end point
- Imposing a closing date of follow up for uniformity and summarizing survival data

SURVIVAL ANALYSIS

Subject Calendar Time

y_0----------y_1----------y_2----------y_3----------y_4

[----Period of registration----]

[----------Period of Follow up----------]

A i----------death

B i----------lost to follow-up

C i----------widthdrawn

Subject Follow-up Time

t_0----------t_1----------t_2----------t_3----------t_4

[----------Duration of Follow up----------]

A i----------1

B i----------0

C i----------0

Censoring is unique; Complete & incomplete f/u

METHODS OF FOLLOW UP

Passive Follow-up

- When the data on follow up especially mortality is received by law or an understanding from the vital statistics division
- If no information on death is received, the patients are presumed to be ‘alive’ until that point
- Main requirement is good HIS especially mortality statistics and unique data linkage possibilities

Active Follow-up

- House visits
- Postal / telephone enquiries
- Matching with death certificates from the region
- Repeated scrutiny of records
- Matching with health registers in the local area

FOLLOW UP IN INDIA IS PREDOMINANTLY ACTIVE

CENSORING

- A unique feature in survival analysis
- Arises from the fact that it is impractical to follow all the patients until the occurrence of the outcome
- Exact lifetimes are known for a portion of the patients and is known to exceed certain values in the remainder
- Hence, the information of follow up available for ‘censored’ cases is partial

Right censoring

This occurs when we know that the outcome has not occurred until certain time and we are unable to follow the patients further

CENSORING

Random or non-informative censoring

- When censoring is solely ‘technical’ (i.e.) due to termination of study at the closing date
- Wilful withdrawl or loss to follow up unrelated to the outcome being studied, say death

Non-random or informative censoring

- When censoring is NOT ‘technical’ (i.e.) due to patients not traceable up to the closing date
- Drop-outs or loss to follow up that is ‘related’ to the outcome being studied, say death

In most developing countries, censoring is not always technical and informative censoring is anticipated

LOSS TO FOLLOW-UP (LFU)

- Commonly encountered in data from developing countries
- Directly dependant on individual efforts of follow-up
- Published data reveals a wide range: from < 1% to > 30%
- Little attention paid to LFU in the statistical methodology so far

SURVIVAL ANALYSIS : METHODS

- Actuarial method
- Kaplan-Meier.
- Relative Survival
- Period analysis
- Cox proportion Hazard models

ACTUARIAL METHOD

- Estimation of survival probability is done for “grouped intervals” of follow up time
- Handles censoring assuming it as “random”
- The method involves construction of life tables which permit calculation of cumulative probability of survival at time t_{i+1} from the conditional probabilities of survival during consecutive intervals of follow up time up to and including t_{i+1}
- Subjects who are alive and at risk of death during t_i to t_{i+1} but who are censored at some point of time during the interval, are assumed to have been followed up for, on an average, half the interval

LAYOUT OF LIFE TABLE, ACTUARIAL METHOD

Time Interval	Alive at beginning	Censored	Dead	Actuarial persons at risk	Prob. of Death	Survival Prob.	Cum. Surv. Prob.
$t_i - t_{i+1}$	n_i	w_i	d_i	(N_i) $n_i - (w_i / 2)$	(q_i) d_i / N_i	(p_i) $1 - q_i$	(P_i) Πp_j

Source: Black and Swaminathan (1998)

KAPLAN-MEIER ESTIMATE

- Estimation of survivor function is done for “exact” follow up times” of outcome or censoring
- Survival probabilities are calculated on ordered exact times at every time of occurrence of the outcome without aggregating the time intervals
- Handles censoring assuming it as “random” (i.e.) censoring is independent of the outcome
- The method involves a life table approach which permits calculation of cumulative probability of survival at time t_{i+1} from the conditional probabilities of survival during consecutive follow up times up to and including t_{i+1}

Relative Survival

Ratio of observed survival to expected survival

Expected survival estimated using life tables for the region

It Is the measure of interest for Population Based Survival studies.

Relative survival is the survival analog of excess mortality.

The cumulative relative survival ratio can be interpreted as the proportion of patients alive after *i years of follow-up in the hypothetical situation where the* cancer in question is the only possible cause of death.

TAKE HOME MESSAGES

- Complete follow up is the key to survival analysis despite analytical adjustments for LFU
- Active follow up should be integrated into ANY survival study involving cancer patients
- Recognition of informative censoring will be helpful to quantify the bias in estimation
- Kaplan-Meier method is preferred when exact times are available and the sample is small; Actuarial method also gives similar results at 5-years or more from diagnosis
- Period approach of survival gives up-to-date survival estimates and closely predict the survival of cases diagnosed in that period