# Statistical Evaluations in Oncology Trials

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PhUSE Single Day Events, Shanghai
Nov 3rd, 2017

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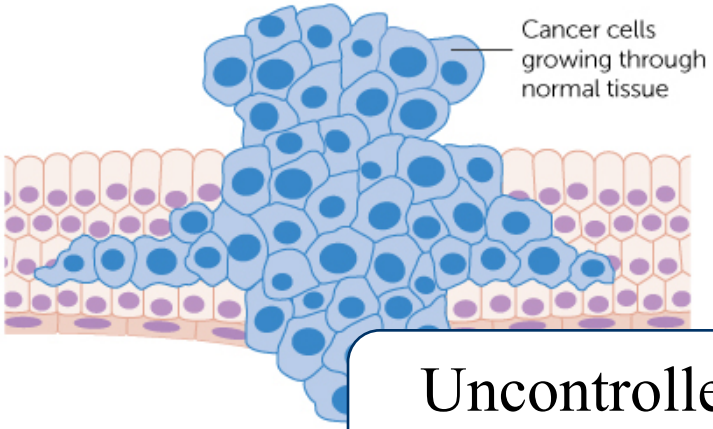
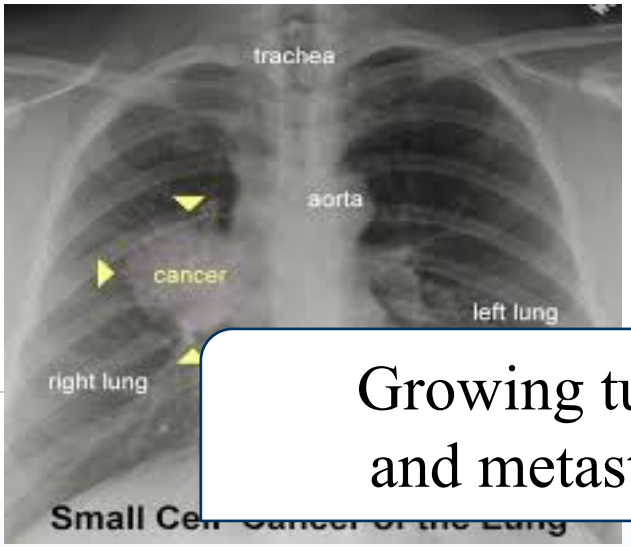
# What is cancer?




Uncontrolled cell growth




Growing tumor and metastasis

Painful disease

People die

# What do we evaluate in oncology trials?

| | |
|---|---|
| Efficacy | How long can patients live? |
| | How fast do tumors grow? |
| | Do tumors shrink? |
| | How long can a drug keeps tumors away from growing? |
| | Do tumors disappear? |
| | When do tumors reappear? |
| | When do cancer symptoms worsen? |
| | Do patients feel less painful? |
| | Do patients live better? |
| | Any biomarker tells who benefits more from the drug? |
| Safety | AE, SAE, related? |
| | When does an AE appear? |
| | Can AEs be prevented or treated? |

# Endpoints in oncology trials

## Overall survival

Time from randomization to death

- Most reliable
- No bias
- Long follow-up
- Affected by subsequent therapies

# Endpoints in oncology trials

- Endpoints based on tumor assessments (RECIST1.1, iRECIST)

## Disease Free Survival (DFS)

Time from randomization to recurrence of tumor or death

- Adjuvant therapy
- Tumors disappear after surgery or radiotherapy

## Objective Response Rate (ORR)

The proportion of patients with tumor size reduction of a predefined amount and for a minimum time period

- Can be evaluated in single-arm trials
- Quick to observe
- Not direct measure of benefit
- Only a subset of patients who benefit

# Endpoints in oncology trials

- Endpoints based on tumor assessments (RECIST1.1, iRECIST)

## Time To Progression (TTP)

Time from randomization to objective disease progression

- Usually in situations where most deaths are unrelated to cancer

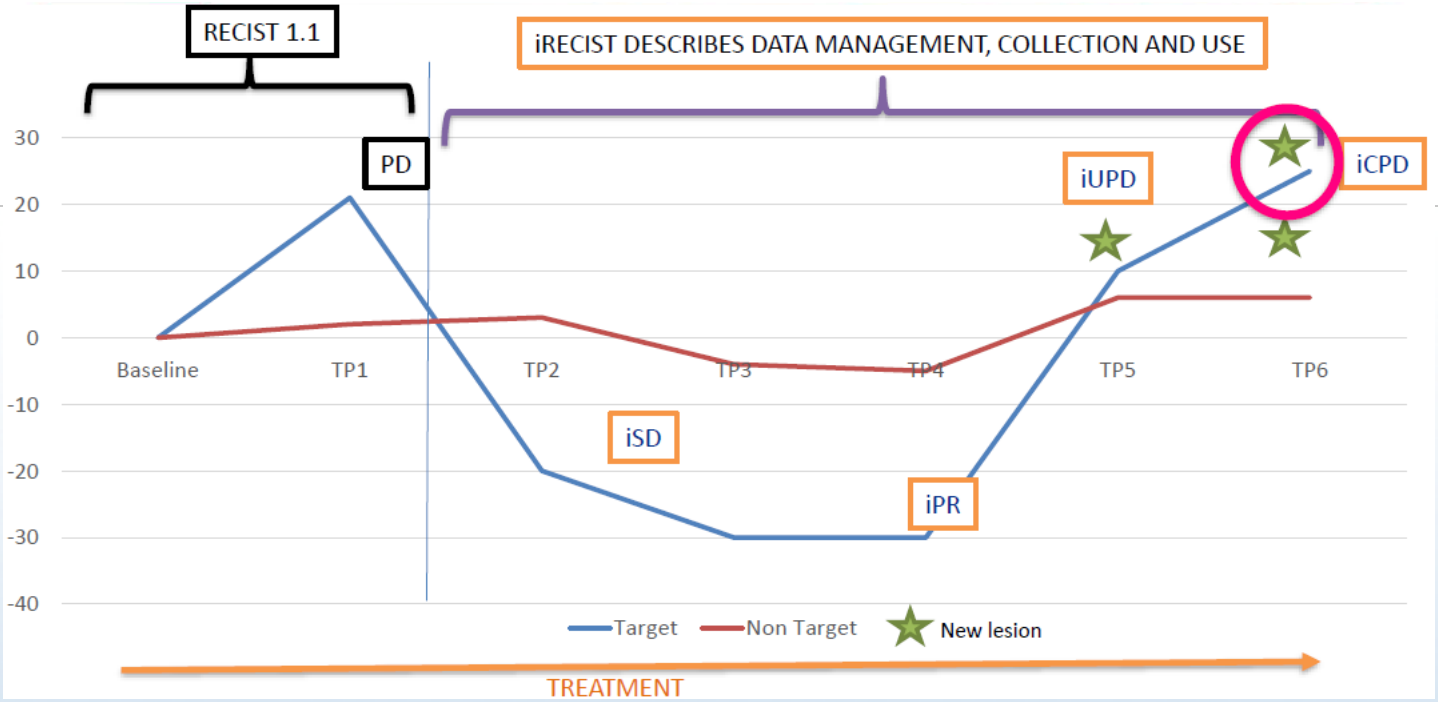
## Progression Free Survival (PFS)

Time from randomization to objective disease progression or death

- A better correlate to death
- Preferred to TTP
- Quicker to get than OS

# Endpoints in oncology trials

- Endpoints based on tumor assessments (RECIST1.1, iRECIST)




Time to iCPD (confirmed PD)

# Endpoints in oncology trials

- Endpoints involving symptomatic assessments

Time To Symptomatic Progression (TTSP)

Patient Reported Outcome (PRO)
- Quality of life questionnaires

# Types of efficacy endpoints

- Categorical
  - Objective response (yes/no)
  - Stable disease (yes/no)
- Continuous
  - Change of tumor size from baseline
  - Time to objective response
- Time-to-event
  - Overall survival (OS)
  - Progression free survival (PFS)
  - Time to disease progression (TTP)
  - Duration of objective response (DOR)

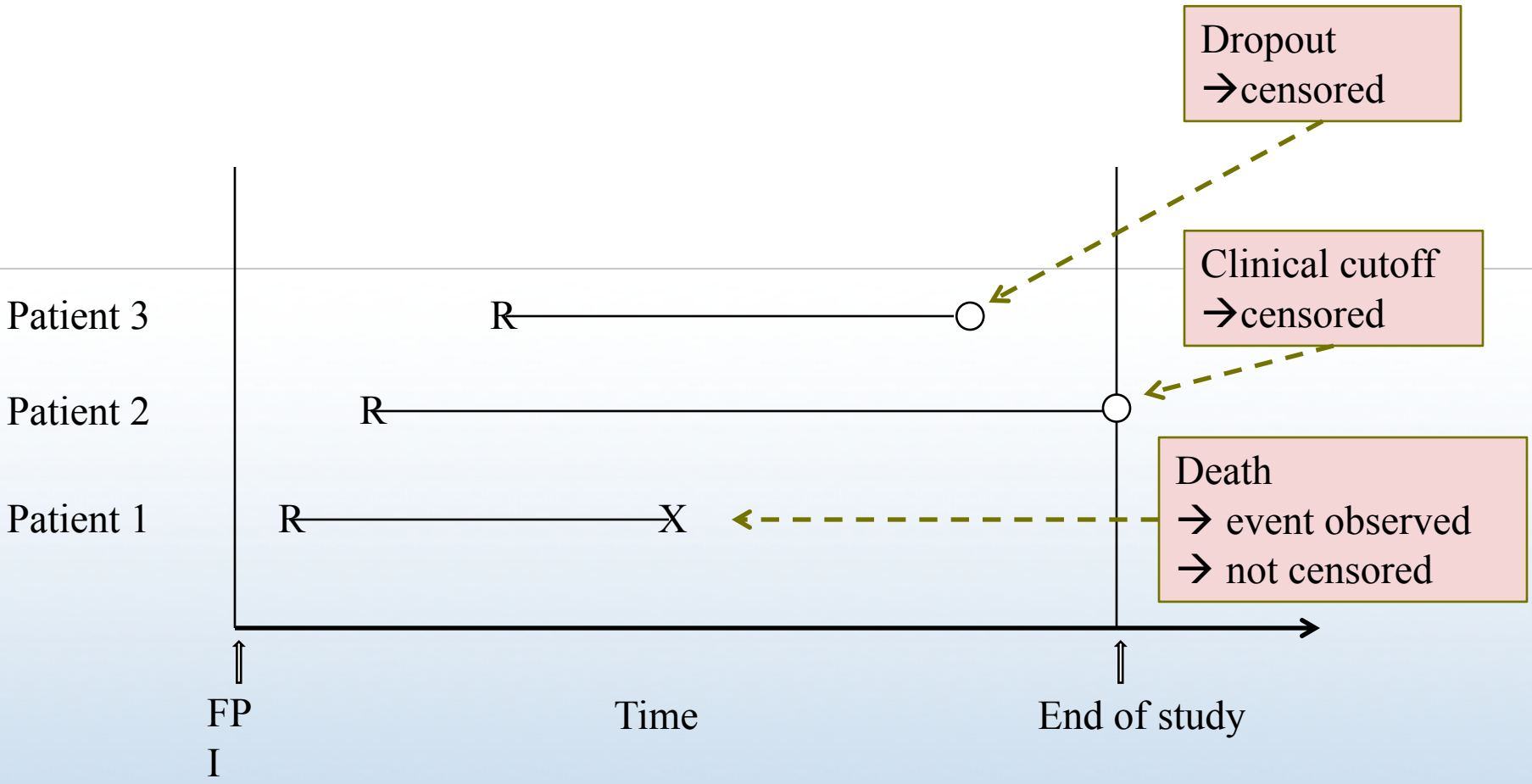
# Time-to-event Endpoints

Two components of time-to-event data:

- **Time** from _____ to ___(event)_____ s .
  - Time from ____randomization___ to __death_____.
  - Time from ____randomization___ to __disease progression or death.

- **Censoring**
  - The event itself is not observed. We only know the event occurs after a time point.
  - E.g., drop out before progressive disease, in follow-up without PD/death at the time of clinical cutoff.

# Time-to-event Endpoints

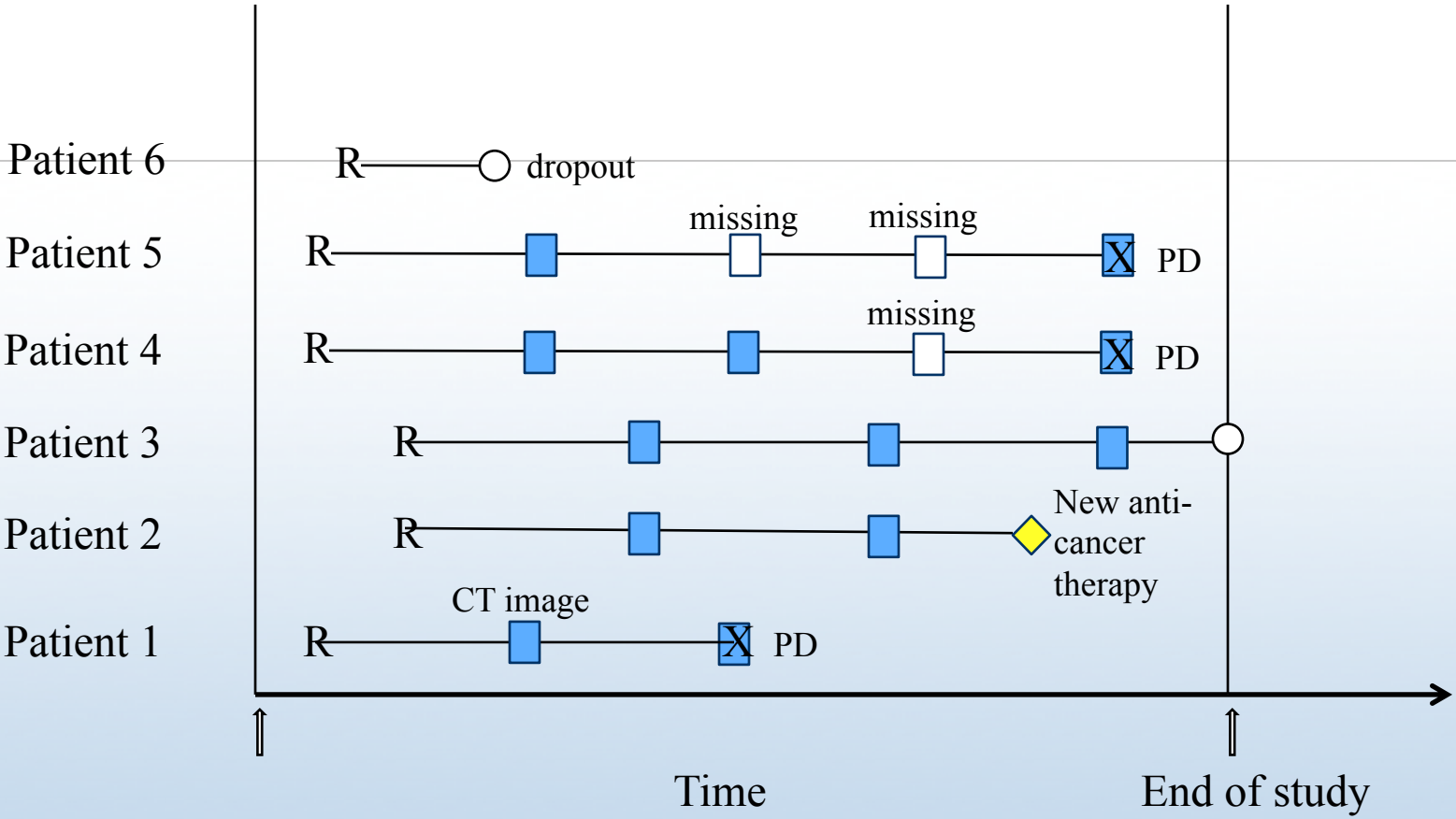


# Censoring rules can be complicated
# Example - PFS

Event or censored?

Event time? Censored where?

FDA Guidance for Industry
Clinical Trial Endpoints for the
Approval of Cancer Drugs and
Biologics



# Censoring Rules for PFS - one possible example

| Situation | Date of event or censoring | Outcome |
|---|---|---|
| **Without post-baseline radiological assessments** | | |
| **1. Alive** | Date of randomisation | Censored |
| **2a. Death prior to the second scheduled image** | Date of death | Event |
| **2b. Death beyond the second scheduled image** | Date of randomisation | Censored |
| **With post-baseline radiological assessments BUT no other anti-cancer therapy** | | |
| **3. Alive and no progression** | Date of last radiological assessment of measured lesions | Censored |
| **4a. Death but no progression, zero or one missed image prior to death** | Date of death | Event |
| **4b. Death but no progression, two or more missed images prior to death** | Date of last radiological assessment of measured lesions | Censored |
| **5a. Progression, zero or one missed image prior to progression** | Date of radiological assessment of progression | Event |
| **5b. Progression, two or more missed images prior to progression** | Date of last radiological assessment of measured lesions prior to progression | Censored |
| **With post-baseline radiological assessments AND other anti-cancer therapy** | | |
| **6. New anti-cancer therapy started before progression (or death)** | Date of last radiological assessment before other new anti-cancer therapy | Censored |
| **7a. Progression before new anti-cancer therapy, zero or one missed image prior to progression** | Date of radiological assessment of progression | Event |
| **7b. Progression before new anti-cancer therapy, two or more missed image prior to progression** | Date of last radiological assessment of measured lesions prior to progression | Censored |

# Statistical analysis for time-to-event endpoints

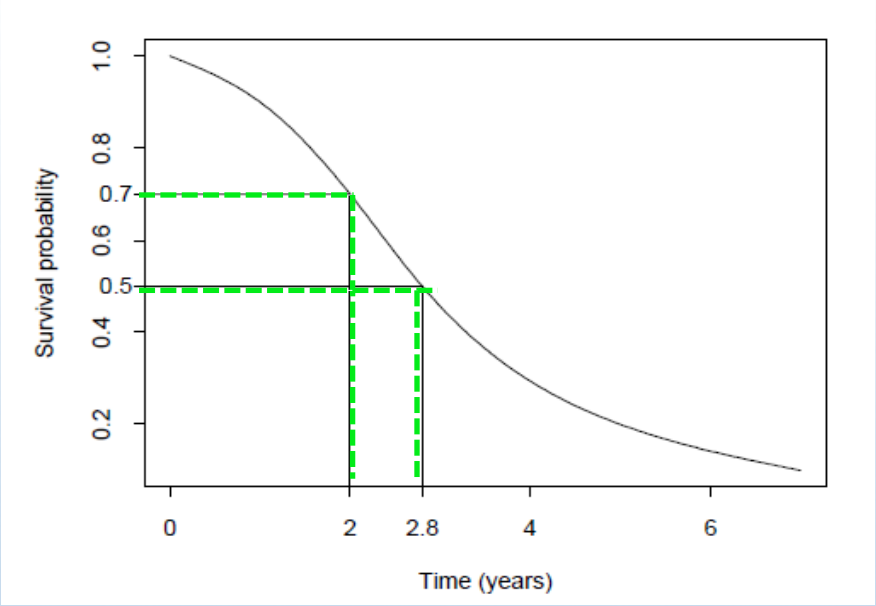
- Probability of surviving at time t = S(t)

  E.g., "5 year survival probability = 0.2" means

  "20% patients survived beyond 5 years".

- Question: how to estimate survival probability at all the time points?

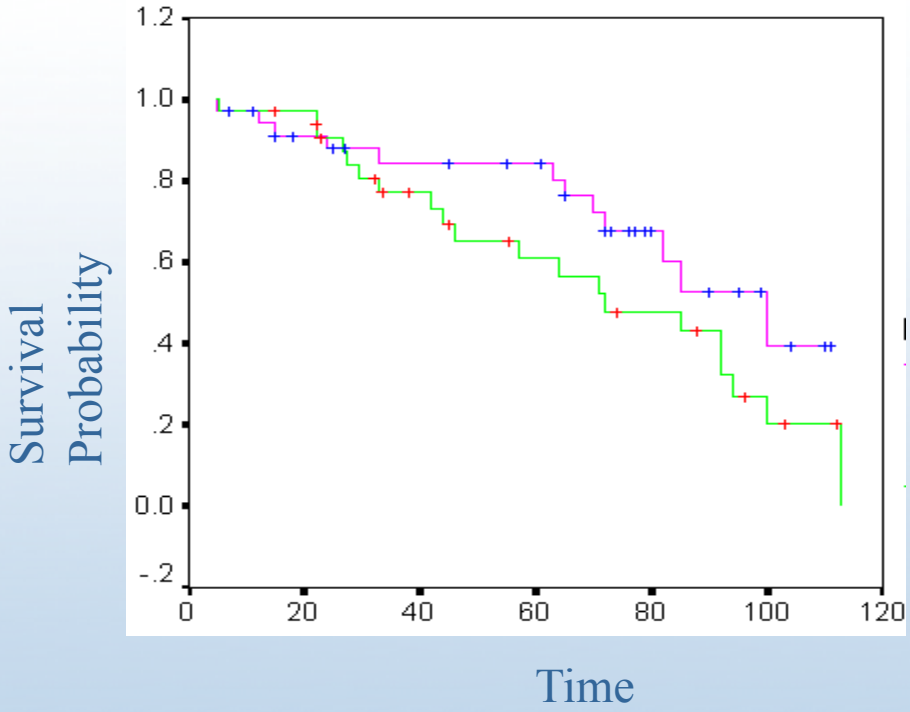
  estimate S(t) for all t. → a survival curve.



# Kaplan-Meier method

- Kaplan-Meier method is to estimate
  - survival curves;
  - survival probabilities, e.g. 2-year survival probability;
  - event rates, e.g. 2-year progression rate;
  - median survival time (the time when survival probability = 0.5, i.e. half died half alive).

- KM curves "drop" only at event time points, and stay flat at censored time points.




KM curves decrease from 1 to 0.

+ / + indicates a subject is censored at that time point.

# Log-rank test and Cox model

## Log-rank test

Test whether two survival curves differ,
i.e. whether a drug makes a difference

- Non-parametric

## Cox model

Under proportional hazard assumption,
Test whether a drug makes a difference
Tell how much is the difference

- Semi-parametric

# Thank you!

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