Toxicity Management: Supportive Care Options for Children with Leukemia

Lillian Sung, MD, PhD

Speaker bio

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Dr. Lillian Sung is a Full Professor and Senior Scientist at The Hospital for Sick Children, Toronto, Ontario, Canada. She is certified in the specialties of pediatrics, infectious diseases, hematology and clinical investigation. She completed a PhD in Clinical Epidemiology from the University of Toronto in 2004. She has a clinical research program focused on supportive care for children with cancer. Her methodological focus is on randomized and observational trials, meta-analysis, and patient-reported outcomes. She is the principal investigator on multiple operating grants from the National Institutes of Health (NIH), Canadian Cancer Society Research Institute and the Canadian Institutes of Health Research.

Dr. Sung is the Chair of Cancer Control and Supportive Care in the Children's Oncology Group (COG). COG is the largest pediatric cancer clinical trials consortium and includes over 200 member institutions. She is the co-PI on the NCI Community Oncology Research Program (NCORP) Research Base grant which supports the Cancer Control and Supportive Care program within COG. Dr. Sung is also the co-PI on an NIH R25 grant to support the Clinical Research Training Institute, sponsored by the American Society of Hematology.

Toxicities of Leukemia Therapy

Treatment-Related Mortality and Acute Leukemia

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POGO Conference
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Healthier Children. A Better World.

SickKids
THE HOSPITAL FOR SICK CHILDREN

Outline

- Introduction and Challenges to Defining TRM
- Creation of TRM Definitions
- Population-based Epidemiology of TRM
- Conclusions

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Importance of TRM

- Devastating outcome of cancer diagnosis
- TRM versus disease-related death fundamental to identifying best strategy to improve survival in pediatric cancer
  - If TRM main cause of death – enhanced supportive care, possible reduction therapy
  - If disease main cause of death – treatment intensification or novel approaches

Areas of Inconsistency

- How TRM defined
  - Specific definition
    - ? Exclude based upon timing
    - ? Exclude based upon cause of death
  - Inclusion post relapse or HSCT

- Cause of death
  - For example, death due to infection or bleeding

Expectation on AAML1031

Date of Death:*	MM/DD/CCYY
Primary Cause of Death:*	[] – Due to this disease [] – Due to protocol treatment [] – Unknown [] – Due to other cause, specify
Contributing cause(s) of death:* • Check all that apply.	[] – Due to this disease [] – Due to protocol treatment [] – Due to other cause, specify [] – None
If "due to other cause, specify" is selected in either of the above questions, describe the cause of death not listed among the choices. If not, please leave this question blank. **Describe cause of death:**	TEXT

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2011 118: 5080-5083
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Lack of clarity in the definition of treatment-related mortality: pediatric acute leukemia and adult acute promyelocytic leukemia as examples

Marie-Chantal Ethier, Esther Blanco, Thomas Lehrnbecher and Lillian Sung

t al. BMC Cancer 2014, **14**:612
http://www.biomedcentral.com/1471-2407/14/612

RESEARCH ARTICLE Open Access

Lack of treatment-related mortality definitions in clinical trials of children, adolescents and young adults with lymphomas, solid tumors and brain tumors: a systematic review

Thai Hoa Tran[1], Michelle Lee[2], Sarah Alexander[1], Paul Gibson[3], Ute Bartels[1], Donna L Johnston[4], Carol Portwine[5], Marianna Silva[6], Jason D Pole[7] and Lillian Sung[1*]

Systematic Reviews

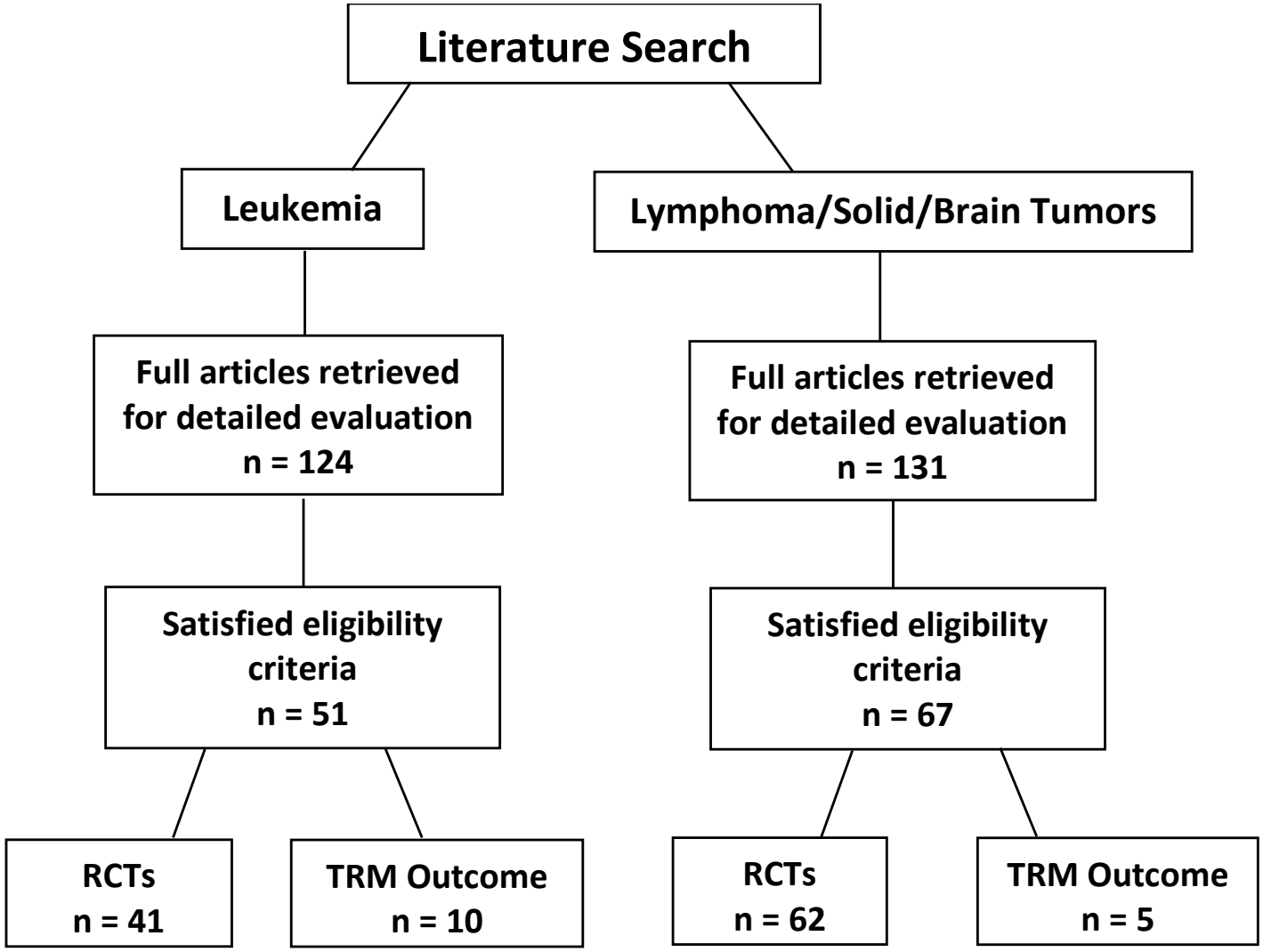
Aim: To describe how TRM has been defined in randomized therapeutic studies or any study design in which TRM was an outcome

Systematic Review Methods

- Two focused on TRM:
  - Pediatric acute leukemia
  - Pediatric lymphoma, solid tumors and brain tumors

- Eligibility Criteria:
  - Pediatric studies
  - RCTs evaluating anti-cancer treatment OR
    Any study type focused on TRM
  - Studies published ≥ 1990

Flow of Study Identification/Selection



Key Findings

- Two concepts - TRM and early deaths

- TRM defined in:
  - 9/51 (18%) leukemia
  - 0/72 (0%) lymphoma, solid or brain tumor

- Early death defined in:
  - 8/51 (16%) leukemia
  - 1/72 (1%) lymphoma, solid or brain tumor

Specific TRM Definitions

	n
Leukemia	
Death from causes other than progressive disease where failures at the end of two courses, relapses and deaths from progressive disease were competing events.	3
Induction death or death in first complete remission. Excluded deaths prior to start treatment and following SCT.	3
Death after day 42 in those in complete remission and those between day 42 and 150 who did not respond to treatment. *Excluded relapse patients.*	2
Death unrelated to refractory or progressive disease occurring before day 42 or any death after day 42. *Excluded relapse patients.*	1
Lymphoma/Solid Tumor/Brain Tumor	
	0

Specific Early Death Definitions

	n
Leukemia	
≤ 42 days of treatment start	4
Within 60 days of diagnosis	1
< 14 days from start of therapy	1
Before 8 days	1
Before response to therapy could be established	1
Lymphoma/Solid Tumor/Brain Tumor	
Within 42 days of treatment start	1

Summary

- TRM only defined in acute leukemia, not solid tumors or brain tumors
- Two concepts: TRM and early deaths
- Tremendous variability across studies
- Can use identified definitions to dissect elements contributing to TRM delineation

Elements Used to Define TRM Identified in Systematic Review

- Relapse
- Progressive disease at death
- Remission at death
- HSCT
- Induction failure
- Date end of induction
- Day of therapy

Classification of treatment-related mortality in children with cancer: a systematic assessment

Sarah Alexander, Jason D Pole, Paul Gibson, Michelle Lee, Tanya Hesser, Susan N Chi, Christopher C Dvorak, Brian Fisher, Henrik Hasle, Jukka Kanerva, Anja Möricke, Bob Phillips, Elizabeth Raetz, Carlos Rodriguez-Galindo, Sujith Samarasinghe, Kjeld Schmiegelow, Wim Tissing, Thomas Lehrnbecher, Lillian Sung, on behalf of the International Pediatric Oncology Mortality Classification Group

Focus Group

Aim: To agree upon a definition of TRM and development of a system for cause of death attribution

Alexander Lancet Oncology 2016

Underlying Assumptions

- Intent broad purpose, applicable to populations and trials
- No perfect system and clinicians will disagree
  - Goal to create reproducible system
- Ideal definition:
  - Easy to abstract, reliable, minimizes subjectivity
  - Does not rely upon physician actions (variable)
  - Can be applied across different co-operative groups
  - Can be applied across different diseases
  - Adaptable e.g. relapse or HSCT

Consensus Decisions in Defining TRM

- Not use deaths in induction
  - Variable between diseases, groups
- Not use deaths within a set number of days
  - Not helpful for identifying cause of death
  - Dependent on specific protocols
- Allow deaths before starting cancer treatment
  - Receipt of cancer treatment provider-driven
  - May benefit from enhanced supportive care

Elements Used to Define TRM Identified in Systematic Review

- Relapse
- Progressive disease at death
- Remission at death
- HSCT
- Induction failure
- Date end of induction
- Day of therapy

Consensus Definition

Death defined as TRM:

- **Diagnosed with cancer**
- **Absence of progressive disease at death**

- Could include or exclude relapse or HSCT
- No requirement to have received cancer treatment
- No element of time
- Defined “treatment” broadly

Cause-of-Death Attribution

- Patients commonly have multiple events contributing to death e.g. leukemia, infection, metabolic disturbance, etc.
  - System must allow multiple main causes
- In general, no guidance provided to data abstractors or clinicians
- Reliability poor

Cause-of-Death – ICD10 Philosophy

- “all those diseases, morbid conditions or injuries which either resulted in or contributed to death and the circumstances …which produced any such injuries”

- Purpose ensure all relevant information recorded and ensure recorder not selective about which condition listed

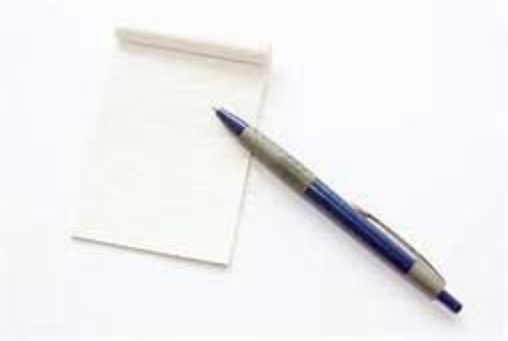
- Should not include symptoms and modes of dying, such as heart failure or respiratory failure

TRM Attribution Approach

- Eliminate primary versus secondary/contributing
- List all important events proximal to death
  - 2 weeks

- Certainty of attribution
  - Definite/Probable vs Possible

Creation



- Began with ICD10 categories
- Initial draft used CTCAE v4.0.
  - If grade 4/5 - definite/probable
  - If grade 3 - possible
  - If < grade 3, do not include
- Refined draft in series of working group calls

Cause of Death Attribution *14 days prior to death			
	Probable	**Possible**	**Not Present**
Infections	❑ Clinically or radiographically documented infection with associated microbiologically documented organism *Infection name:*_____ *Infection site:*_____	❑ Clinically or radiographically documented infection **without** associated microbiologically documented organism	❑
Hemorrhage	❑ Acute symptomatic intracranial hemorrhage demonstrated by imaging or pathology ❑ Acute symptomatic pulmonary hemorrhage demonstrated by imaging or pathology ❑ Acute symptomatic bleeding resulting in hypotension or urgent transfusion or fluid bolus	❑ Acute symptomatic pulmonary hemorrhage **without** demonstration by imaging or pathology	❑
Thrombosis	❑ Acute symptomatic intracranial thrombosis or embolism demonstrated by imaging or pathology ❑ Acute symptomatic pulmonary thrombosis or embolism demonstrated by imaging or pathology ❑ Acute symptomatic hepatic thrombosis or embolism demonstrated by imaging or pathology	❑ Acute symptomatic pulmonary thrombosis or embolism **without** demonstration by imaging or pathology	❑
Cardiac System **exclude terminal event*	❑ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia demonstrated by electrocardiogram ❑ Acute symptomatic cardiac dysfunction defined by echocardiogram or cardiac imaging or pathology	❑ Acute symptomatic arrhythmia excluding sinus tachycardia/bradycardia **without** demonstration by electrocardiogram	❑
Immune Mediated	❑ Acute, allergic reaction or anaphylaxis with symptomatic bronchospasm or edema/angioedema or hypotension ❑ Worsening symptomatic graft versus host disease ❑ Acute symptomatic hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome or cytokine-release syndrome	❑ Stable graft versus host disease	❑
Metabolic	❑ Clinically diagnosed tumor lysis syndrome with cardiac arrhythmia or seizure or creatinine > 3x ULN		❑
Nervous System	❑ Acute symptomatic central nervous system necrosis demonstrated by imaging or pathology ❑ Acute symptomatic encephalopathy demonstrated by imaging or electroencephalography ❑ Acute symptomatic hemorrhage or stroke demonstrated by imaging or pathology ❑ Acute symptomatic hydrocephalus or raised intracranial pressure demonstrated by imaging or pathology or measurement of intracranial pressure ❑ Seizure lasting at least 30 minutes within 48 hours of death	❑ Acute symptomatic central nervous system necrosis **without** demonstration by imaging or pathology ❑ Acute symptomatic encephalopathy **without** demonstration by imaging or electroencephalography ❑ Acute symptomatic hemorrhage or stroke **without** demonstration by imaging or pathology ❑ Acute symptomatic raised intracranial pressure **without** demonstration by imaging or pathology or measurement of intracranial pressure ❑ Seizure lasting 5 - <30 minutes within 48 hours of death	❑
Respiratory System	❑ Acute symptomatic respiratory distress leading to ventilator support such as intubation, or other mechanisms of pressure support including BIPAP and CPAP	❑ Acute symptomatic respiratory distress **without** ventilator support **Note: Exclude terminal event*	❑
GI System	❑ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation demonstrated by imaging or pathology ❑ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin > 10x ULN or high ammonium > 2.5x ULN or INR > 2.5x ULN ❑ Acute clinically diagnosed pancreatitis with hemorrhage or peritonitis or necrosis or hemodynamic instability (evidenced by hypotension or urgent transfusion or fluid bolus or vasopressors)	❑ Acute symptomatic bowel pathology resulting in necrosis or obstruction or perforation **without** demonstration by imaging or pathology ❑ Acute clinically diagnosed hepatic dysfunction associated with increased conjugated bilirubin >1.5 to ≤10x ULN or INR >1.5 to ≤2.5x ULN or ammonium >1.5 to ≤2.5x ULN	❑
Renal System	❑ Acute kidney injury with dialysis/renal replacement therapy planned or received		❑
External Causes	❑ Unintentional injury (e.g. accident) ❑ Suicide ❑ Homicide		❑

Validation of TRM Designation System

Aim: To validate the TRM algorithm in a random sample of 30 deaths occurring between Jan 1, 2003 and Dec 31, 2012 at SickKids

- Two CRAs independently reviewed cases and classified TRM (yes vs no) and cause-of-death
- Two pediatric oncologists performed same evaluation
- Hypothesized k ≥ 0.60 between CRA and physician TRM classification
- Qualitatively evaluated cause-of-death attribution

TRM Classification Reliability and Validity

Clinician Reliability

Kappa 0.84 (95% CI 0.63 to 1.00)

CRA Reliability

Kappa 0.83 (95% CI 0.60 to 1.00)

Criterion Validity

Kappa 0.92 (95% CI 0.78 to 1.00)

Summary of TRM

- 9/30 (30%) TRM

- Number of definite/probable attributions
  – median 2 (range 2 to 5)

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Application of System in Population-based Analysis

Aim: To describe the proportion of deaths due to TRM and to identify risk factors and probable causes of TRM in a population-based cohort for children who died Jan 1, 2003 and Dec 31, 2012

Provincial Review of Deaths

- POGO – all 5 tertiary care pediatric cancer centers in Ontario

- Almost complete capture up to 14 years of age

- All HSCT procedures - SickKids

*https://ec.gc.ca/cas-aqhi/55517B0A-DA24-455F-93DD-0FF5314C9A00/AQ_prov_ON_400.jpg

Designation Procedure

- 6 CRAs trained and evaluated with 10 randomly chosen cases with correct response determine by 2 pediatric oncologists
- Required 9/10 correct TRM designations before could review independently
- CRAs travelled to each site
- TRM designation did not censor at relapse or HSCT

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Overall Conclusions and Next Step

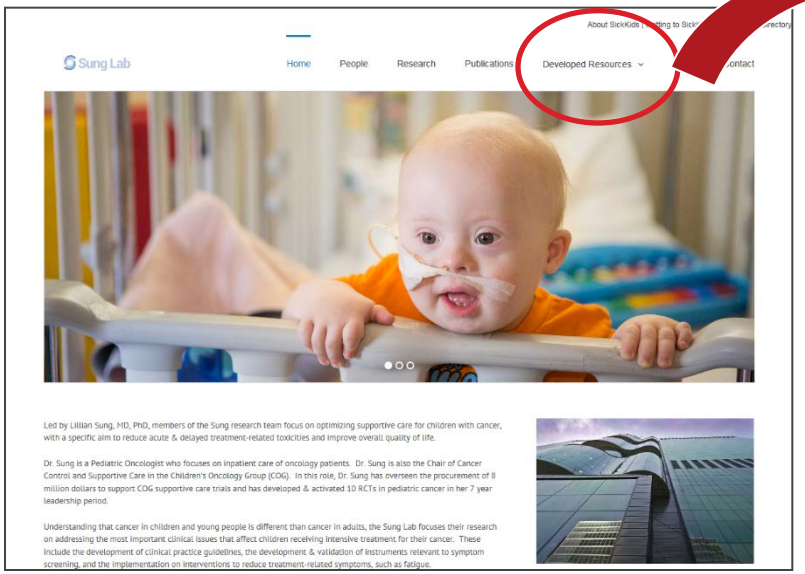
- Created new TRM definition – reliable, feasible and flexible

- In Ontario, TRM - 26% pediatric cancer deaths

- Next steps – describe TRM rate:
  - Among newly diagnosed cancer in Ontario
  - Disseminate new system

TRM Training

http://lab-stg.research.sickkids.ca/sung/http://lab-stg.research.sickkids.ca/sung/



Acknowledgements

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TRM Working Group Members

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Carlos Rodriguez-Galindo MD – US

Sujith Samarasinghe MD – UK

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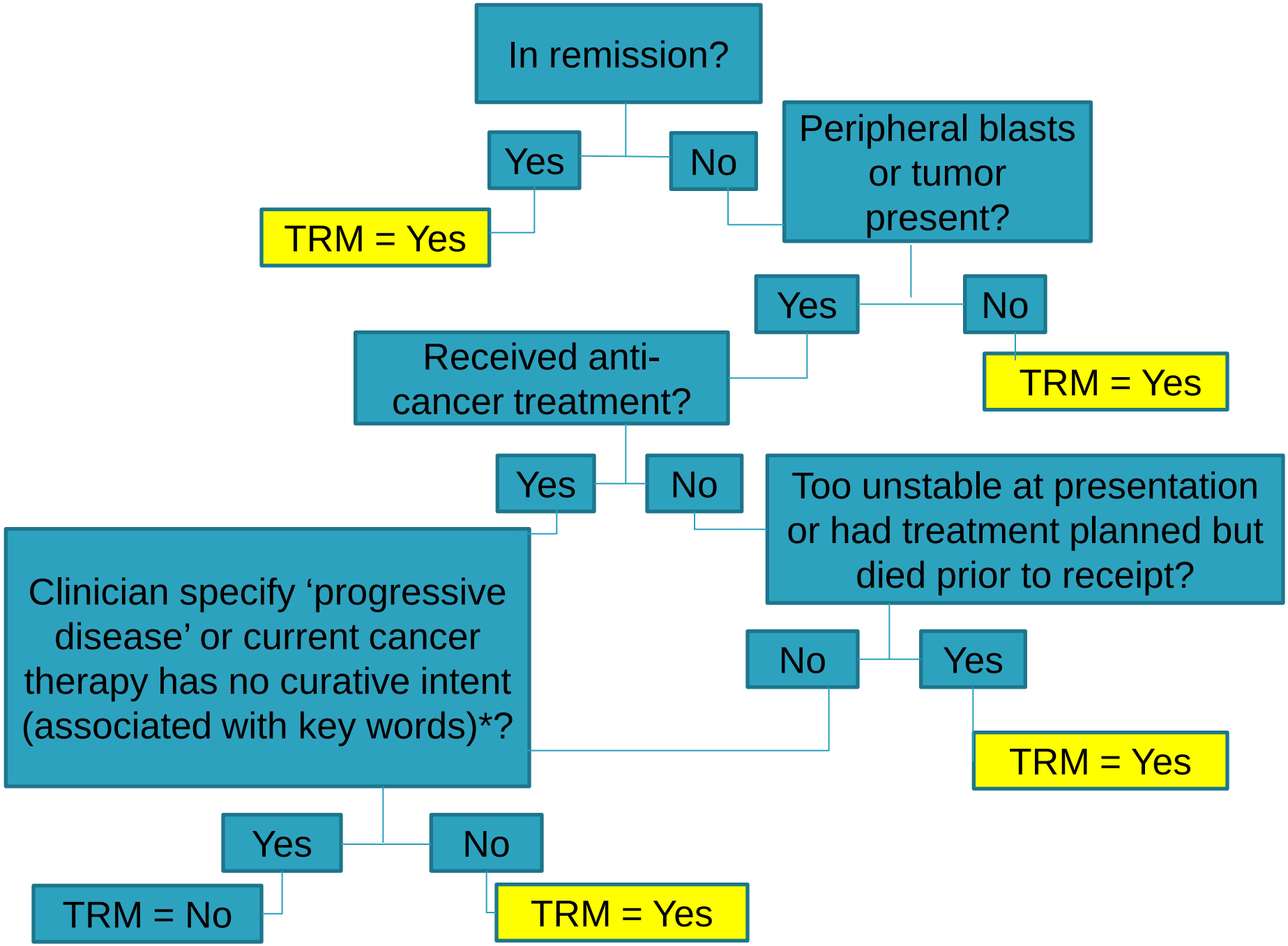
Wim Tissing MD - Netherlands


THANK YOU


In remission?
Yes
No
TRM = Yes
Peripheral blasts or tumor present?
Yes
No
TRM = Yes
Received anti-cancer treatment?
Yes
No
Too unstable at presentation or had treatment planned but died prior to receipt?
No
Yes
TRM = Yes
Clinician specify ‘progressive disease’ or current cancer therapy has no curative intent (associated with key words)*?
Yes
No
TRM = No
TRM = Yes