3.38: Oncology During COVID-19 & RCTs from Low- vs High-Income Countries with Dr. Christopher Booth

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We Discuss:

- Conversation with Dr. Christopher Booth [1:08]
- Oncology in the time of COVID [2:09]
- Research Parachutism [19:12]
- Policy recommendations [32:14]
- Meaningful living [37:51]

Plenary Session 3.38 Show Notes

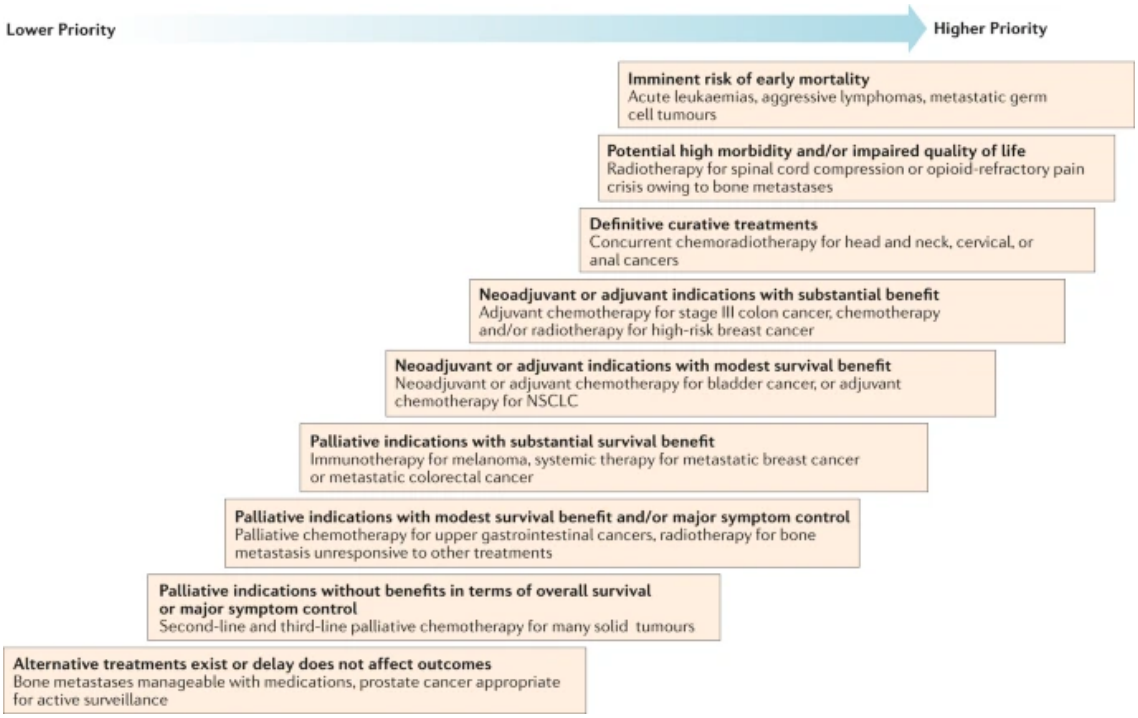
Overview

Conversation with Dr. Christopher Booth [1:08]

- **Introduction**
  - Dr. Booth is a Medical Oncologist, researcher, and Professor of Oncology at Queen's University
    - He earned his M.D. at Queen's University

        - He completed his postgraduate training in internal medicine and oncology at the University of Toronto

- **Oncology in the time of COVID [2:09]**
    - Publishing cancer research has become more difficult during this time but COVID research has taught us important lessons with the importance of the treatments we propose
        - Hopefully these lessons can be held accountable by society to make sure that we do high impact work
            - Dr. Prasad hopes that the oncologic community takes away some lessons in practice of high-value care from this time
    - Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic



Hanna et al.

        - Dr. Booth worries that there will be economic pressure from the consequences of COVID in the future, but hopes that it will force healthcare systems to take value-based care seriously

        - Dr. Prasad counters that he worries that the loss of profit in 2020 will cause providers to ramp up marginal testing downstream interventions and low value surgeries

- **Global Oncology [9:17]**
    - An Analysis of Contemporary Oncology Randomized Clinical Trials From Low/Middle-Income vs High-Income Countries
        - Published in JAMA Oncology
    - Background
        - The mainstream cancer research ecosystem appears to have lost touch with with reality (i.e., what matters to patients in high income countries, but also what happens in the rest of the world outside Western Europe and North America)
            - Is there a way that we could undertake a study to explore the extent to which randomized control trials are being done globally?
                - The team overviewed all cancer randomized trials published over three years for anti-cancer therapy
                    - From 2275 publications, they found 694 RCTs
        - They asked a number of questions:
            - How did how does the design of trials differ across settings? What can we learn broadly from the global RCT ecosystem? How do the results vary between different economic settings? What is the output? Where do these things go? How are they published? And how are they implemented into practice?
    - Results
        - There were a number of surprising results from this analysis:
            1. The RCT landscape is dominated by investigators in HICs and the diseases studied do not match the global burden of cancer
                - Gastroesophageal, liver, pancreas, and cervical cancers are substantially under-represented in RCTs.
            2. Most RCTs are funded by the HIC-based pharmaceutical industry and focused disproportion-ally on systemic therapies in the palliative setting

3. RCTs testing new approaches in surgery and radiotherapy account for only 13% of all RCTs.
4. Use of putative surrogate endpoints is pervasive
5. Only one-third of positive trials identify a new treatment that is associated with substantial clinical benefit.
6. Compared with RCTs from HICs, RCTs from LMICs are more likely to be positive and identify a larger magnitude of benefit
7. We have identified a very substantial publication bias; despite being more likely to be positive and having a larger magnitude of benefit, RCTs from LMICs are published in journals with far lower IFs than trials from HICs

- Moving forward
  - Dr. Booth acknowledges that chemotherapy plays a very important role in increasing long term survival, palliative care, and cure rates
    - But at the end of the day, what provides cure for patients is radiotherapy and surgery
      - These interventions have been *neglected* when it comes to the global research ecosystem

Table 1. Characteristics of Oncology Phase 3 RCTs Published, 2014-2017

Characteristic	RCTs, No. (%)		
		Country of first author	
	All (n = 694)	HIC (n = 636)	LMIC (n = 58)
Disease site			
Breast	121 (17)	115 (18)	6 (10)
Lung	104 (15)	84 (13)	20 (35)
Colorectal	58 (8)	55 (9)	3 (5)
Head and neck	34 (5)	24 (4)	10 (17)
Gastroesophageal	38 (6)	33 (5)	5 (9)
Leukemia and lymphoma	90 (13)	87(14)	3 (5)
Other[a]	249 (36)	238 (37)	11(19)
Treatment intent, No./total No. (%)			
Palliative	448/692 (65)	411/634 (65)	37 (64)
Curative	68/692 (10)	61/634 (10)	7 (12)
Neoadjuvant or adjuvant	176/692 (25)	162/634 (26)	14 (24)
Experimental group			
Systemic	601 (87)	556 (87)	45 (78)
Radiation	38 (6)	34 (5)	4 (7)
Surgery	16 (2)	15 (2)	1 (2)
Other[b]	39 (6)	31 (5)	8 (14)
Study design			
Superiority	610 (88)	559 (88)	51 (88)
Noninferiority or equivalence	84 (12)	77 (12)	7 (12)
Primary end point			
OS	215 (31)	198 (31)	17 (29)
DFS, EFS, or RFS	149 (22)	142 (22)	7 (12)
PFS or TTF	232 (33)	213 (34)	19 (33)
Other[c]	98 (14)	83 (13)	15 (26)
Industry funding			
Yes	488 (70)	464 (73)	24 (41)
No	173 (25)	149 (23)	24 (41)
Unstated	33 (5)	23 (4)	10 (17)

Table 2. Results of Oncology Phase 3 RCTs Published, 2014-2017

Characteristic	RCTs, No./total No. (%)			P value
		Country of first author		
	All (n = 694)	HIC (n = 636)	LMIC (n = 58)	
Total sample size, median (IQR)	443 (246-718)	474 (262-743)	219 (137-363)	<.001
Primary end point met, No. (%)				
Yes	325 (47)	286 (45)	39 (67)	.001
No	369 (53)	350 (55)	19 (33)	
P < .05 for primary end point[a]				
Yes	262/607 (43)	229/557 (41)	33 (66)	<.001
No	345/607 (57)	328/557 (59)	17 (34)	
HR for all superiority RCTs, median (IQR)[a]	0.82 (0.65-0.96)	0.84 (0.67-0.97)	0.62 (0.54-0.76)	<.001
HR for positive superiority RCTs, median (IQR)[b]	0.63 (0.51-0.74)	0.65 (0.52-0.75)	0.59 (0.43-0.66)	.02
ESMO-MCBS grade[c]				
No.	166	145	21	.13
Substantial benefit (A, B, 4, 5)	55/166 (33)	45/145 (31)	10/21 (48)	
Not substantial benefit (C, 1, 2, 3)	111/166 (67)	100/145 (69)	11/21 (52)	

Wells et al.

- **Research Parachutism [19:12]**

> *"The marked difference in rates of industry funding may also reflect a reluctance of industry to sponsor studies in countries with less established research infrastructure. A related theme is the practice of investigators from HICs leading a drug registration trial that predominantly enrolls patients in LMICs where the treatment would have no chance of being available after the clinical trial; this in itself represents a distinct form of research parachutism." - Wells et al.*

  - The idea of conducting a clinical trial, in a country in which you are not planning to really offer that treatment if it's successful is problematic for two reasons:
    1. If the trial is being delivered in a context where standard of care does not match the standard of care in the environment in which you wish to roll out that treatment, then the patients who are being offered this treatment in the HIC are suffering because they're being offered treatments based on data that does not actually apply to them

2. It's totally inappropriate to be doing clinical trials in countries that have limited resources and offering these expensive, toxic, unproven therapies with no hope that the patients in those systems will ever have access to them

> "It is the traditional colonial model of global health: Going in, taking data, and leaving" - Dr. Booth

- Publication bias
  - Despite being more likely to be positive and having a larger magnitude of benefit, RCTs from LMICs are published in journals with far lower IFs than trials from HICs
    - 21 for HICs vs. 7 for LMICs
      - A positive trial for HICs is 25 vs. 9 for LMICs
      - A negative trial for HICs is 18 vs. 5 for LMICs
- Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial
  - Published in The Lancet Oncology
- Evolution of the randomized controlled trial in oncology over three decades
  - Published in the JCO

- **Policy recommendations [32:14]**

1. There is an urgent need to correct the global research funding paradox
   - Philanthropic and government funding agencies should uphold their moral and scientific duty to support re-search in LMICs.
2. Initiatives to build research infrastructure and human capacity in low-resource settings must be promoted and supported, with a particular emphasis on creating networks of countries with similar context-specific needs
3. The pressing clinical volumes in LMICs need to be recognized and supported with additional health care professionals to allow clinical investigators to develop their own independent research programs
   - This should be an integral component of health systems strengthening

4. Our finding of a publication bias against RCTs from LMICs cannot be ignored. Oncology journals need to recognize their role in promoting and disseminating high-quality research regardless of the country of origin
    - Increasing LMIC representation on editorial boards is one important first step in this regard.
        - Global oncology-specific journals also play an important role but do not absolve other journals from the responsibility to ensure that high-quality work is published
5. Sustained effort is needed to increase RCTs that address new surgical and radiotherapy techniques
6. We make an urgent plea to oncologists and investigators worldwide to recognize the importance and synergies that can emerge from global research efforts that are truly collaborative in spirit, bidirectional, and mutually beneficial - Wells et al.

- **Meaningful living [37:51]**
    - How to make the most of your time–The CV Method:
        - Take your CV and 3 highlighters:
            - Green
                - Impactful–this research would have not been done if it wasn't for YOU
            - Yellow
                - Supportive–It helped the field and showed important relationships
            - Red
                - Not impactful–methodologically sound but the research did not resonate with anyone
    - <u>On the determinants of academic success as a clinician-scientist</u>
        - By David Sackett

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Written By: Kerrington L. Powell B.S.