4.47: Malignant Book Club w/ Dr. Olivier Part 2 of 9

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

Plenary Session 4.47 Show Notes

Overview

- **The book**
  - **Malignant: How Bad Policy and Bad Evidence Harm People with Cancer**
- **Introduction [0:00]**
  - Dr. Olivier is a practicing oncologist at the **Hôpitaux Universitaires de Genève**
    - He is a visiting scholar at University of California San Francisco
      - His research interests span medicine, oncology, and public health policy

    - He is a member of the **VK Prasad Laboratory**
        - This lab focuses on drug policy, medical evidence, study design, and governmental regulation
- **The process of writing [1:00]**
    - VP had a rough framework of the book in his head and did the most of the work on lengthy flights to Europe
        - His main goals were to cover topics related to surrogate endpoints, cost of drugs, post protocol therapy, crossover, and financial conflicts of interest

> **Ernest Hemingway**
> Quote: “My working habits are simple: long periods of thinking, short periods of writing.”

- **Chapter 2 [3:28]**
    - **Surrogate Endpoints in Cancer:** What Are They and Where Are They Used?
        - Surrogate endpoints are an endpoint that the patient didn't know was important until the doctor said it was
            - A surrogate endpoint is anything that can be measured, quantified, and it has something to do with the condition or disease
                - It's often utilized as a proxy for what patients care about.
                    - And, of course, patients worry about just two things: living longer and living better

> “I think there's to some degree, you have to have some surrogates” - VP

    - Examples in other populations: Hemoglobin A1C

> ⚕️ *“For people who suffer from diabetes, the hemoglobin A1c blood test is another example of a surrogate end-point. It roughly correlates with the endpoints patients want to avoid, such as kidney failure, nerve damage, and blindness”* - Vinay Prasad

- Surrogates in oncology:
    1. Measures of tumor shrinkage (i.e., Response Rate)
        a. Tumor response means that, in a single patient, the burden of cancer has regressed beyond an arbitrary threshold.
            i. We would say the patient had a partial response if the lesions shrank by 30% in size (the arbitrary threshold)

> *“It is worth taking a look back in history to better understand where these arbitrary cutoffs come from. Why 30% shrinkage and not 40% or 80%? In the 1970s, Moertel and Hanley invited 16 experienced oncologists to measure spheres of varying sizes through pieces of foam rubber. This exercise was meant to simulate clinical practice at the time. In an era before routine CT scans, doctors had to use tools, such as calipers, to measure tumors by hand, feeling through the soft tissue, that is, the foam rubber. Moertel and Hanley asked a simple question: can you tell me which spheres are bigger and which are smaller? Of course, measuring spheres through foam rubber is not a perfect science, and two doctors could only reliably tell them apart when they were 50% smaller. From these humble beginnings, the use of arbitrary cut-points to document “response” began. In 1981, the World Health Organization established a 50% reduction in tumor area as its re- sponse cutoff. In 2000, a simplified, one-dimensional cutoff of 30% (rather than the WHO’s two-dimensional measurement) was created by RECIST (Response Evaluation Criteria in Solid Tumours) and became the current standard. The take-home point here is that cutoffs that were selected for operational reasons have become codified as an oncology standard because they can be told apart with simple tools, not because they predict clinical benefit for people with cancer.”* - Vinay Prasad

2. Measures of tumor growth

- What is a *composite* endpoint?
  - It is the period until one of numerous events occurs, whichever occurs first.
- Progression free survival

> *“Progression-free survival is perhaps the most common endpoint in recent cancer trials. PFS is a composite endpoint, meaning it is the time*
> *until one of several things happen. The first thing that could happen is the patient dies. This is the survival portion of the endpoint. The second thing that could happen is a patient develops a new tumor on his or her scans. The third thing that could happen is that the tumors the patient already had grown more than 20% from their smallest size. Progression-free survival is the time to one of these three events, whatever comes first, and progression means either new lesions on the scan*
> *or the growth of tumors more than 20%.”*
> - Vinay Prasad

- Disease free survival

> *“The other surrogate endpoint to understand is disease-free survival (DFS). This endpoint is also a composite, time-to-event endpoint. It is the time until either death or the recurrence of cancer. It is typically used in settings where a cancer has been fully removed and we know that only a fraction of patients will have recurrence, but we just don’t know which ones. Let me give you one specific example: breast cancer. In breast cancer, DFS is a big composite endpoint, comprising several events: time to a new primary breast cancer, a new case of DCIS (ductal carcinoma in situ—a precancerous lesion), a local recurrence of breast cancer, a distant recurrence of breast cancer, or death. Not all these things are equally ominous. Death is the worst, distant recurrence the second worst, and a new case of DCIS is arguably a lesser evil.”* - Vinay Prasad

- Why is it important to know about surrogates nowadays?

- Kim C, **Prasad V.** Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US Food and Drug Administration approvals. *JAMA Intern Med*
- Kim C, Prasad V. Strength of Validation for Surrogate End Points Used in the US Food and Drug Administration's Approval of Oncology Drugs. *Mayo Clinic Proceedings.*

> "Two-thirds of our drugs are basing their use on these endpoints, they have huge importance. We are been seduced by them. We're in love with them. Every day I go people talk about them. And the problem is in the minds of many oncologists, they have confused that the surrogate is not a stand in for what they care about that's imperfect. They believe it is the endpoint in and of itself, that's valuable" - VP

- Surrogates can mislead

> ⚕ *"It is important to recognize that surrogates may fail to predict the end- points patients care about. It is instructive to review the times these surrogates have failed to do so. In 2008, bevacizumab (Avastin) received accelerated approval (more to come on this) from the FDA for metastatic breast cancer based on one clinical trial, where its addition to chemotherapy dramatically improved PFS. However, just three years later, three randomized trials failed to show that bevacizumab improved survival in the same malignancy. Moreover, the benefit in PFS was smaller in these other studies than in the initial study. Because bevacizumab has harmful side effects and didn't improve survival, the FDA revoked its marketing authorization."* - Vinay Prasad

- Validating surrogates

        - There are several prognostic factors in cancer; if you have a certain biomarker that acts as a prognosis marker, you're more likely to fare well
            - These prognostic markers not only tell you what could happen to you in the future, but they also tell you which therapies may especially help you.
                - But a surrogate is a different endpoint
                    - A surrogate is a marker that captures the variability in the endpoint you care about by variability in a separate endpoint
                        - In other words, it says that drugs that increase PFS, on average, do they increase OS?
                            - **Prasad V**, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. *JAMA Intern Med.*

- **Chapter 3 [34:00]**
    - **The Use and Misuse of Surrogate Endpoints for Drug Approvals**

Yet, a recent trial called BOLERO-2 raises suspicions. In this study, patients were randomized to an antihormonal drug with or without everolimus, a drug mentioned earlier in this chapter. Everolimus is one of the toxic, marginally beneficial, costly new cancer drugs we have discussed before, and was profiled in the Milwaukee Journal Sentinel. In this trial, many patients were censored very early on in the study, and it appears (from visual inspection) that this happened at a higher percentage in the everolimus arm. In 2014, I spent a year at Johns Hopkins University. At that time, I met Usama Bilal, an epidemiologist. Usama wrote a computer program to reconstruct the progression-free survival in the BOLERO-2 trial, assuming patients who were censored were more or less likely to have progression than those who remained behind. In other words, Usama made six curves for this trial, seen in figure 3.1. Patients getting everolimus are in light gray, and those getting placebo are in dark gray. The thick solid lines are the reported results and the dotted lines and the thin solid lines are the results assuming patients who were censored all lived, or all died." - Vinay Prasad

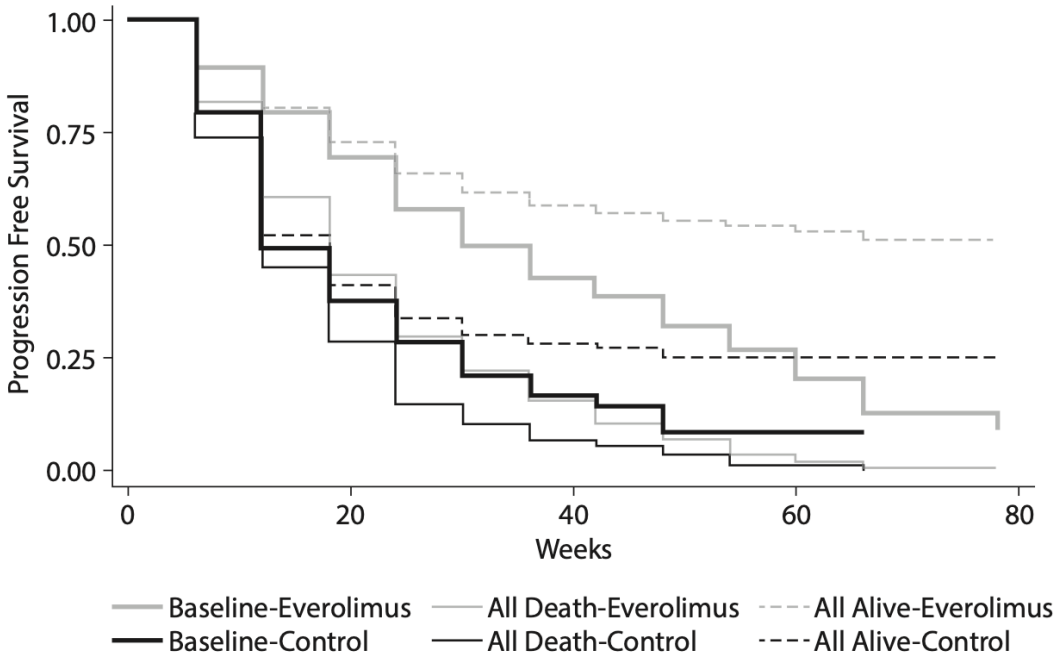

Figure 3.1. The role of censoring in BOLERO-2. Best-case and worst-case scenarios for censoring in the BOLERO-2 study. Thick, solid lines represent actual progression-free survival (PFS) curves reported from trial. Dotted curves represent PFS if every censored patient had no progression. Thin, solid curves represent PFS if all censored patients experienced progression.
Used with permission by Elsevier *European Journal of Cancer.*

- Push back

> *"An analogy may help. Imagine you are running a marathon. Normally, you drink Gatorade to keep you going without leg cramps. Now, someone sells you a special energy drink that can only be drunk once at mile marker 2. Imagine you run miles 3 and 4 slightly faster than you otherwise would, but you lose steam and run miles 18 and 19 slightly slower than you normally would have run them, even though you go back to using Gatorade for these miles. In the end, you finish at the same time. Would you conclude that the value of the drink was diluted by the subsequent miles or that the new drink adds nothing?"* - Vinay Prasad

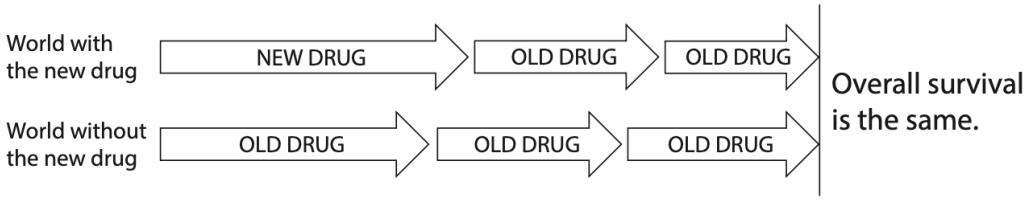

Figure 3.2. Visual of the "survival post-protocol" argument. The argument claims that the positive effects of new treatments (arrow) are diluted by older, subsequent treatments (arrows), making it difficult to judge a new drug's benefit. But, if how long you live is the same, then what value did the new medicine truly provide?

- **Closing thoughts [49:00]**
- **People mentioned:**
  - Adam Cifu
  - Tito Fojo
- **Other literature mentioned:**
  - Kemp R, **Prasad V.** Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Medicine*
  - Haslam A, Hey SP, Gill J, **Prasad V**A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. *European Journal of Cancer*
  - Chen EY, Joshi SK, Tran A, **Prasad V.** Estimation of Study Time Reduction Using Surrogate End Points Rather Than Overall Survival in Oncology Clinical Trials. *JAMA Interna; Medicine*
  - Chen E, Haslam A, **Prasad V.** FDA Acceptance of Surrogate Endpoints for Cancer Drug Approval: 1992-2019. *JAMA Internal Medicine*
  - Woloshin S, Schwartz LM, White B, et al. The fate of FDA postapproval studies.
    New Engl J Med. 2017
  - Powell K, Lythgoe M, **Prasad V.** The ODAC Votes of April 27-29: Implications for the Fate of Accelerated Approval. JAMA Oncology.

- **Prasad V**, Bilal U. The role of censoring on progression free survival: oncologist discretion advised. *Eur J Cancer.*
- Cancer lectures

Plenary Session is a podcast on medicine, oncology, & health policy.

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