PCa Mortality vs Treatments

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In a recent NEJM paper the authors argue that there is no material difference between a prostatectomy and just "observation" on all classes of PCa. We lay out what is in our opinion a multiple set of deficiencies in their putative analysis.

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1 INTRODUCTION

In the recent paper by Wilt et al the authors state:

After nearly 20 years of follow-up among men with localized prostate cancer, surgery was not associated with significantly lower all-cause or prostate-cancer mortality than observation. Surgery was associated with a higher frequency of adverse events than observation but a lower frequency of treatment for disease progression, mostly for asymptomatic, local, or biochemical progression.

Put aside the adverse events since it is well known that any surgery has such a risk. We would focus on survival alone. The authors continue:

In conclusion, radical prostatectomy was not associated with significantly lower all-cause or prostate-cancer mortality than observation through 20 years of follow-up among men with localized prostate cancer that was diagnosed during the early era of PSA testing. Absolute differences remained below 6 percentage points. Death from prostate cancer was very uncommon among men with low-risk disease who were assigned to observation. Surgery may be associated with decreased mortality among men with intermediate risk prostate cancer, depending on the pathological classification. Surgery resulted in substantially greater long-term urinary incontinence and erectile and sexual dysfunction than observation and was associated with a significantly lower risk of disease progression and additional treatments, most for local or asymptomatic biochemical progression.

The problem with this analysis is as follows:

1. It is clinically well known that a small percentage of all PCa is of a highly aggressive form.

2. The highly aggressive form almost always results in death.

3. The highly aggressive form occurs early in the onset of the disease and metastasis is almost immediate.

4. The specific genetic makeup of this highly aggressive form is currently undetermined. Moreover there may be a pleiomorphic genetic presentation.

5. However, whenever it is suspected, such as presented in the above paper, the detailed genetic makeup of the cancer cells should and must be determined. It was not apparently done here. Not all PCa is the same.

Thus we examine the data from the perspective of the putative existence of a highly aggressive form.

The Press does take this report to arguable extremes as is usually the case. Science Daily states[1]:

[1] https://www.sciencedaily.com/releases/2017/07/170712201146.htm

Prostate cancer surgery offers negligible benefits to many men with early-stage disease, a major 20-year study demonstrates. In such men, who account for most cases of newly diagnosed prostate cancer, surgery did not prolong life and often caused serious complications such as infection, urinary incontinence and erectile dysfunction…In men with early prostate cancer, the study compared surgery with observation. With the latter, men only were treated if they developed bothersome symptoms, such as urinary difficulty or bone pain. Such symptoms may indicate progression of the cancer.

Many men in the observation group received no treatment at all because early-stage prostate cancer often grows slowly and rarely causes symptoms. To evaluate any potential benefits of surgery, the researchers randomly assigned 731 men in the U.S. with localized prostate cancer to receive either surgery or observation at one of 44 Department of Veteran Affairs Health Care Centers or eight academic medical centers, including Washington University. The average age of men in the study was 67 at the time of enrollment. Of the men who had prostate cancer surgery, 223 (61 percent) died of other causes after up to 20 years of follow-up, compared with 245 men (66 percent) in the observation group -- a difference that is not statistically different. Further, 27 (7 percent) men in the surgery group died of prostate cancer, compared with 42 men (11 percent) in the observation group, but that difference also is not statistically significant.

However, the data show that surgery may have a mortality benefit in some men, particularly those with a long life expectancy and intermediate-risk prostate cancer. (Such men generally have PSA scores of 10-20 ng/ml and a Gleason score of seven. The latter score signifies tumor aggressiveness.)

One of the major concerns here is that there is a limited amount of data on each patient. Since the progression of PCa can be dramatically different depending upon a plurality of factors at presentation, it is essential that such details be incorporated in such an analysis. Moreover, if such an incorporation were included then the size of the sample is easily an order of magnitude larger than what was done here.

Herein we examine some of the elements of this paper and consider critiques which require some attention. All too often papers like this end up as significant elements of policy and limiting care to men who require it. The definitive conclusions are in my opinion at best speculative.

2 DEFINITIONS

Let us begin with several definitions used and referred to in the paper. Namely the definitions of risk. The Table below is from Rodrigues et al and presents a list of Low, Intermediate and High risk criteria.

Table 1. Organizational pre-treatment prostate cancer risk stratification systems

Institution/ organization	***Low risk***	***Intermediate risk***	***High risk***
Harvard (D'Amico) AUA EAU	T1-T2a and GS <6 and PSA <10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	>T2c or PSA >20 or GS 8-10
GUROC NICE	T1-T2a and GS <6 and PSA <10	T1-T2 and/or Gleason ٤7 and/or PSA ٤20 not low-risk	>T3a or PSA >20 or GS 8-10
CAPSURE	T1-T2a and GS <6 and PSA <10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	T3-4 or PSA >20 or GS 8-10
NCCN	T1-T2a and GS 2-6 and PSA <10 not very low-risk AND very-low risk category: T1c and GS <6 and PSA <10 and Fewer than 3 biopsy cores positive and 50% cancer in each core	T2b or T2c and/or GS =7 and/or PSA >10-20 not low-risk	T3a or PSA >20 or GS 8-10 not very high risk AND very high-risk category: T3b-4
ESMO	T1-T2a and GS <6 and PSA <10	Not high risk and not low risk (the remainder)	T3-4 or PSA >20 or GS 8-10

The D'Amico specific criteria are summarized below.

Institution/ organization	***Low risk***	***Intermediate risk***	***High risk***
D'Amico	T1-T2a and GS <6 and PSA <10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	>T2c or PSA >20 or GS 8-10

Note that for the low case we have Gleason score of less than 6 which is quite low and no Mets and a PSA less than 10. Most urologists are aware that even here there may be a small number, say 5%, who despite this favorable set of measurements go on to an aggressive cancer.

Let us also briefly summarize the issue of Staging[2]. This we do below:

Primary tumor (T)

- TX: Main tumor cannot be measured.
- T0: Main tumor cannot be found.
- T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.

Regional lymph nodes (N)

- NX: Cancer in nearby lymph nodes cannot be measured.
- N0: There is no cancer in nearby lymph nodes.
- N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer.

Distant metastasis (M)

- MX: Metastasis cannot be measured.
- M0: Cancer has not spread to other parts of the body.
- M1: Cancer has spread to other parts of the body.

We summarize these in the following Table. Note that for th prostate HG PIN is considered CIS. This is despite the fact that some HG PIN resolve uneventfully to a benign state. This has been noted in other cancers as well such as breast and melanoma.

Stage	**What it means**
Stage 0	Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer, but it may become cancer.
Stage I, Stage II, and Stage III	Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissues.
Stage IV	The cancer has spread to distant parts of the body.

[2] https://www.cancer.gov/about-cancer/diagnosis-staging/staging

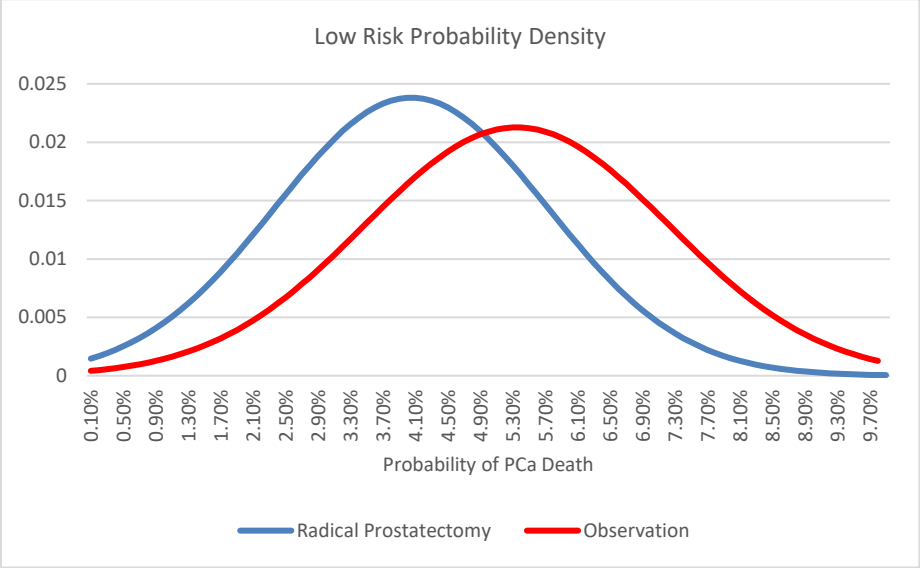
3 RESULTS

Let us begin by examining the Wilt et al data. Our focus is on Table 2. Cumulative Incidence of Death from Prostate Cancer through 19.5 Years. The data for that Table can be summarized as below:

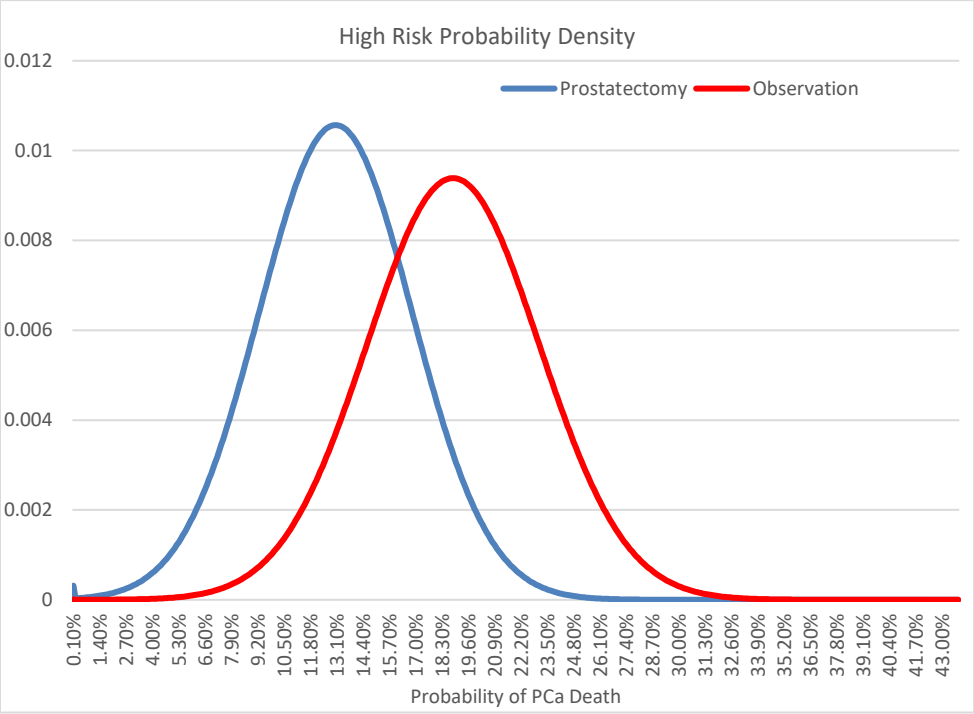
	Radical Prostatectomy			Observation		
	Low	Medium	High	Low	Medium	High
Total	148	129	77	148	120	80
Mean	4.100	8.500	13.000	5.400	15.800	18.800
Low	1.900	4.800	7.200	2.800	10.400	11.700
High	8.600	14.600	22.300	10.300	23.400	28.700
Sigma	1.675	2.450	3.775	1.875	3.250	4.250

We have added percent numbers to the data for clarity. They are percent mortality.

Let us examine a simple case. First for the Low Risk we have a mean death from PCa as 4.1%. In the Observation class the death was 5.4% The probability density for these are shown below:



There clearly is a greater risk in just Observation. Now consider the High risk case. This we show below:



Again there is a substantially high rate of death.

4 MODEL

Assume there are two distinct types of PCa. In each generic class there are these two genetic classes. We first limit to one class of patients, say the Low Risk Class. This can be readily generalized to include all. Our goal is to try to determine how large a sample we need to determine the two means from a sample containing a mix of the two. We further assume we do not know the genetic difference that makes one in a class.

4.1 A SIMPLE EXAMPLE

Thus consider the following simple thought experiment. Let us assume we have 100 cases of Low Risk PCa. Let us assume that 5% of these or 5 cases are of the highly aggressive form. Namely no matter what one does they will lead to death. Let us further assume that we can perform a prostatectomy or observe.

Then if after some period, say 20 years, we find the following:

a. Prostatectomy yields 5 deaths.
b. Observation yields 8 deaths.

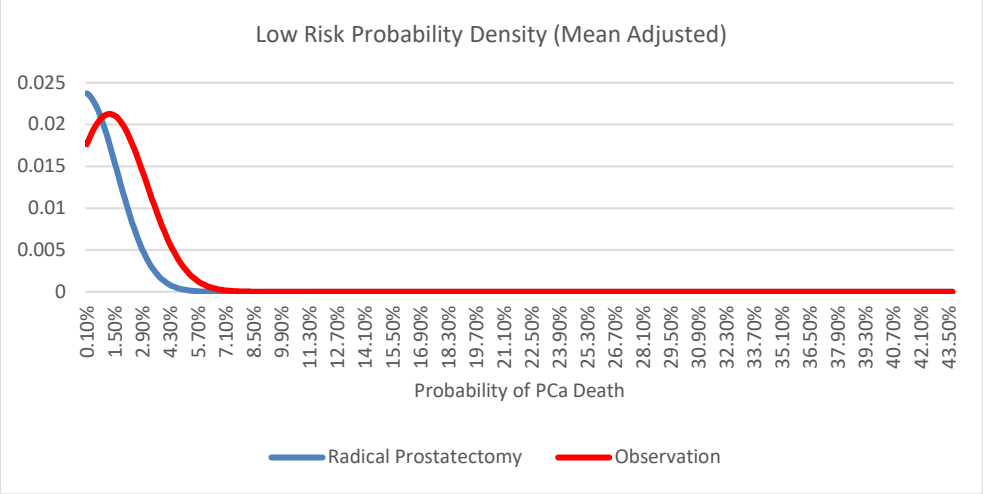
Then we could say that even if we were to remove the tumor, in the 5 cases after prostatectomy the patient would still die of the disease.

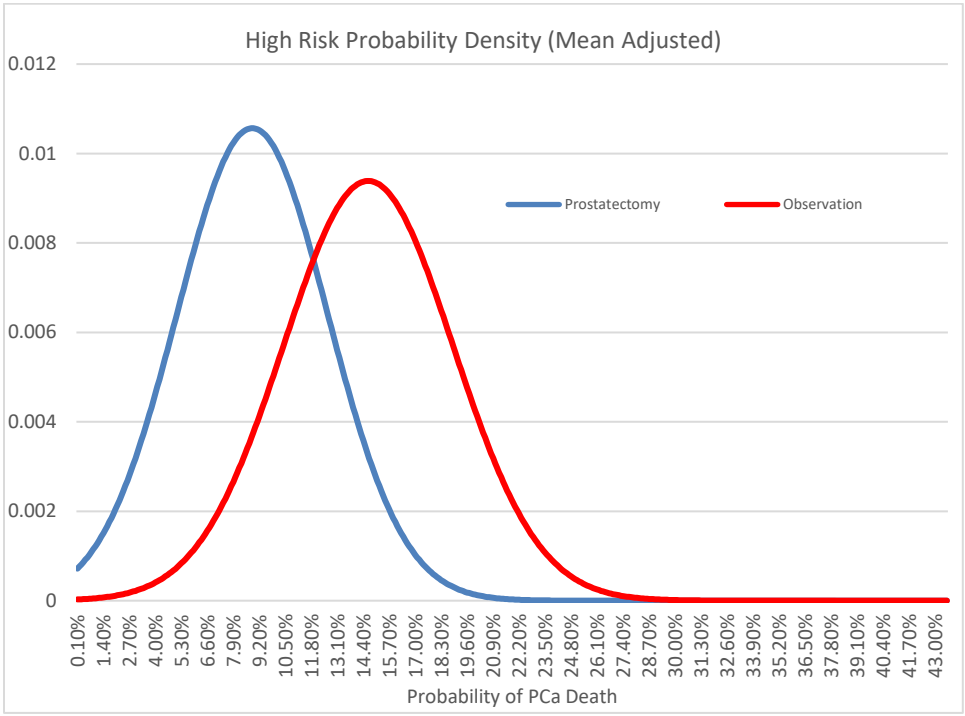
In contrast in observation, in a similar 100 cases, 5 also would die of the disease as well as an additional 3 because of non-treatment.

The question then is; can we use the data to examine such a hypothesis? Secondly; how does the inclusion of such a hypothesis change the results from the NEJM paper?

Thus let us consider the data as follows. Assume that in the Low Risk Prostatectomy case we have a percent death caused by PCa as given but assume that is due to a genetic only risk of highly aggressive tumors. Then remove that from the samples and consider what remains. The data we show below.

	Radical Prostatectomy			**Observation**		
	Low	Medium	High	Low	Medium	High
Total	148	129	77	148	120	80
Initial Data	4.100	8.500	13.000	5.400	15.800	18.800
Mean	0.000	4.400	8.900	1.300	11.700	14.700
Low	1.900	4.800	7.200	2.800	10.400	11.700
High	8.600	14.600	22.300	10.300	23.400	28.700
Sigma	1.675	2.450	3.775	1.875	3.250	4.250





The conclusions from the above seem to be:

1. If you do not have a genetically aggressive form, then the risk of dying from a Low Grade PCa is about 2.5%

2. If, however, you have a High Grade form at presentation, and not an aggressive form, then you have a 7% chance of dying from PCa versus an 18% chance with Observation alone.

3. The question is; are you willing to forego a 2.5:1 risk while avoiding surgical issues?

4.2 ROBUST MODEL

We can also present this analysis in a more robust manner. Let us define:

Class 0=class of all PCa which have a benign type of progression

Class 1 = class of all PCa which have an aggressive type of progression

Then:

$$p_0 = P\left[s_k \in C_0\right]$$
and
$$p_1 = P\left[s_k \in C_1\right]$$
where
$$s_k = sample\_k$$

Now further assume that the mortality in the aggressive type is high and that in the progression type is low.

The problem can now be defined as follows. Assume a collection of N samples in some meta class, such as Low. Assume we have both Type 1 and Type 0. Assume further than the probability of a Type 0 is substantially higher than a Type 1, namely an aggressive type. Then we can write the probability of disease caused death as:

$$P_{death\_disease} = p_0 P_{0,death} + p_1 P_{1,death}$$

Now we have a mixed sample and we have no knowledge of the p or P values. We can estimate the combine number but are unable to determine the separate elements. The question than is; is there a technique to determine the two classes?

In a classic statistical model we are often asked to determine the sample mean and then to say how close the sample mean is to the ensemble mean. Thus we often see a range in which the ensemble mean would occur with some probability. For example the ensemble mean would be in the range of:

$[x_{\min}, x_{\max}]$

where

$$x_{sample} = \text{sample mean} = \frac{1}{N}\sum_{i=1}^{N} x_i$$

and

$$x_{\min} = x_{sample} - 2\sigma$$

$$x_{\max} = x_{sample} + 2\sigma$$

and

$$\sigma^2 = \frac{1}{N}\sum_{i=1}^{N}(x_i - x_{sample})^2$$

which would give a 95% probability interval.

But within the data we have the majority at one ensemble mean and a smaller subset at a larger mean. The question then is; how to identify, separate, and evaluate. That does not seem possible with the existing information.

5 OBSERVATIONS

The data presented in the paper raises more questions than can be answered. For example:

5.1 MORTALITY IS LOWER

If we examine the data as presented and look at Prostatectomy vs Observation, for each of the three risk categories there is a clear advantage in lowered mortality in a prostatectomy. The authors further state:

Reducing overtreatment is needed. Men with low-risk and PSA based screening–detected disease can safely avoid harms and costs of early radical intervention or of biopsy-guided active surveillance with delayed radical treatment. Observation, PSA-based monitoring, and active surveillance with delayed radical intervention remain infrequently used, even among older men, despite a frequency of metastatic progression of less than 3%, prostate cancer mortality of 1% or less, and cost-effectiveness that is superior to that with early radical intervention. PSA-based monitoring and biopsy based active-surveillance programs should reduce the frequency of surveillance biopsy and increase biopsy and PSA thresholds that trigger radical interventions.

We now comment on this conclusion.

5.2 IT IS NOT AT ALL CLEAR THAT THE DATA MAKES ANY SENSE.

Let us examine total mortality, namely from any cause, over the 20 year period. This is summarized below:

	Prostatectomy		Observation	
	Events	Percent	Events	Percent
Low (Local)	82/148	55.4 (47.4 to 63.2)	83/148	56.1 (48.0 to 63.8)
Intermediate	77/129	59.7 (51.1 to 67.8)	89/120	74.2 (65.7 to 81.2)
High	55/77	71.4 (60.5 to 80.3)	59/80	73.8 (63.2 to 82.1)
Low (Central)	58/111	52.3 (43.0 to 61.3)	67/122	54.9 (46.1 to 63.5)
Intermediate	97/155	62.6 (54.7 to 69.8)	99/139	71.2 (63.2 to 78.1)
High	55/78	70.5 (59.6 to 79.5)	63/85	74.1 (63.9 to 82.2)

Note that almost 75% of the High Risk patients died of something in the 20 year period. Not knowing the age data and normal mortality data this is relatively meaningless. In contrast these deaths in the High Risk cohort due solely to PCa are between 19% and 26%. Thus the other causes of death are 3 to 4 times greater. One wonders what that means. The Table below is the PCa death only data.

	Prostatectomy		**Observation**	
	Events	Percent	Events	Percent
Low (Local)	6/148	4.1 (1.9 to 8.6)	8/148	5.4 (2.8 to 10.3)
Intermediate	11/129	8.5 (4.8 to 14.6)	19/120	15.8 (10.4 to 23.4)
High	10/77	13.0 (7.2 to 22.3)	15/80	18.8 (11.7 to 28.7)
Low (Central)	1/111	0.9 (0.2 to 4.9)	8/122	6.6 (3.4 to 12.4)
Intermediate	14/155	9.0 (5.5 to 14.6)	12/139	8.6 (5.0 to 14.5)
High	10/78	12.8 (7.1 to 22.0)	20/85	23.5 (15.8 to 33.6)

Here one wonders that those with High Grade at presentation have a disease cause mortality of such a small rate over this period. It is a large Gleason grade plus Mets! One knows that PCa Mets rapidly to the bone and from there one all too often sees IDC occurring which is fatal.

Moreover, if a patient presents with >T2c, or PSA >20, or GS 8-10, then one would expect a rather dire result from the PCa. Instead we see after 20 years a modest death rate. This data does not conform to certain realities.

There is clearly a complex underlying dynamic at play here and it clearly demands a deeper analysis.

5.3 HOW BIG IS BIG

The size of the samples is small, just over 100 patients. In view of the potential for an even smaller size of the subset of aggressive types which would be as small as 5%, then frankly a much larger sample is demanded.

5.4 WHAT IS THE GENETIC MAKEUP?

The results are totally devoid of any genetic makeup of the cancers. Not only is the nature of the spread missing but the genetic makeup is now considered as an essential element of any analysis.

What genetic flaws were in the cells of the patients who died of PCa and what in those who survived.

5.5 DYNAMICS OF SURVIVAL

There is a somewhat complicated analysis on survival or mortality. If as this study states, for example, only 20% of the patients died of PCa but 80% died of any cause, then depending when this occurred, the percent of PCa deaths could be misrepresented. Namely if the 80% occurred short term, then the size of the sample is reduced by that number and if the 20% died when the 80% were dead then the death rate would be much higher. The denominator would be lower. Without such dynamic data one is hard put to understand the results.

5.6 A BAYESIAN ANALYSIS

Any analysis of PCa must include a Bayesian analysis. Namely one must consider disease caused death subject to underlying facts. First important fact is that not all PCa is identical. There are genetically different classes and any analysis that disregards this fact is fundamentally flawed. Namely if we have several classes then we need to have mortality by class. This has been grossly neglected in this analysis and it thus provides results which are fatally flawed.

For example. If for each patient one had; family history, PSA velocity, previous biopsy history, and the like, then one could segment the results to ascertain some reasonable a priori risk factors. Secondly the same would be the case if the tumors were sequenced for a set of reasonably well know genetic markers. Third, the time to death, that is from diagnosis to death is essential. Fourth, the tumor status of those surviving, over time, is also essential.

Devoid of any of this data the results are in my opinion of questionable use.

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