Allowing for exposure-estimation errors: Things learned at the Radiation Effects Research Foundation

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In 1986, RERF had a new dosimetry system and I decided it was time to do something major on the dose-estimation errors front.

Seymour Jablon had made a presentation to a NAS committee, saying that due to such errors, RERF risk estimates might underestimate true risk by a “factor of 2 or so”.

During 1986-90 Stram, Vaeth and I developed the basic RERF method to deal with dose-estimation errors. This was the dark ages for the topic, and our project on this was a saga.

Much of our thinking pertained to using the information provided by survival, not reflected in the dosimetry system.

Thought “adjusting doses” for this would be a hard sell, but it was not.

Saw need to think of $E(\text{true dose} \mid \text{estimated dose, survival})$ but what is this supposed to mean?

I was reluctant to consider “Mr. Watanabe’s dose” as a random variable --- not exactly necessary, though.

Generally, “survival” should be replaced by “selected for study cohort”.

TABLE I
Artificial Example Indicating Basic Concepts

True dose x (Gy)	Estimated dose z (Gy) 1	2	3	4	5	6	Number of survivors
—	—						—
—	—	—					—
2	250	500	250				1000
3		75	150	75			300
4			33	66	33		132
5				15	30	15	60
—					—	—	—
Avg($x \mid z$)	—	—	2.50	3.62	—	—	

In 1984 Gilbert carried out various calculations related to this "cohort" mode of thought regarding $E(true|estimated)$

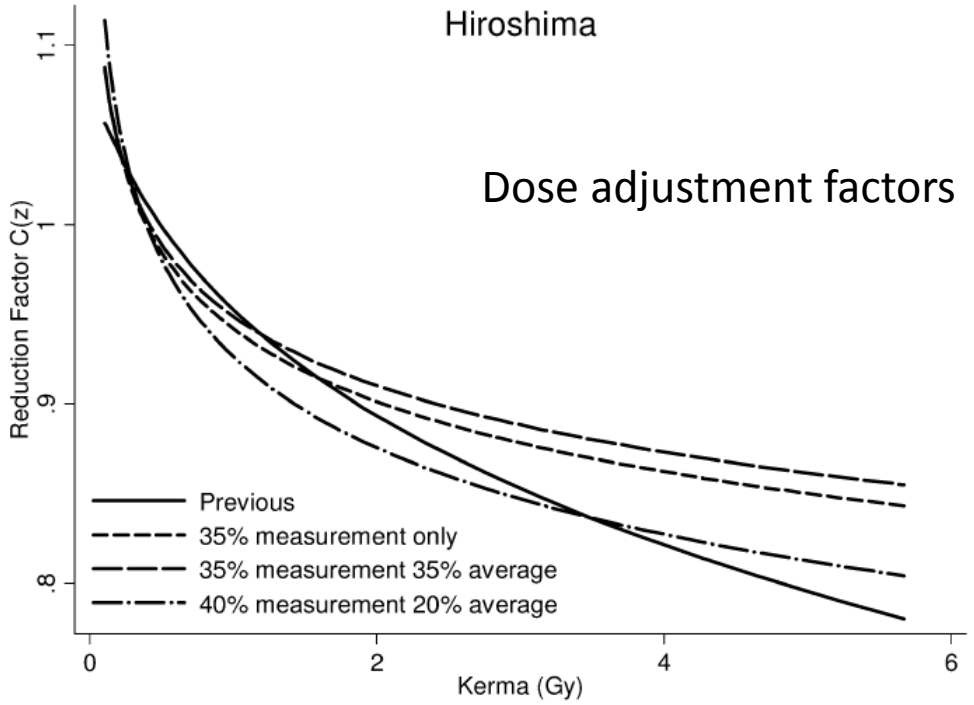
On completing in 1990 the line of work described below, we realized that her work was closer to what we were doing than we had thought.

At any rate, by 1990 we had a distinctly different approach than hers, in many respects, that I will report on now.

Our work, and Gilbert's, was based on assuming a lognormal distribution of dose-estimation errors, with a range of specified values of percent error relative to true dose.

Our 1990 method for computing $E(\text{true}|\text{estim})$ was cumbersome.

In 1994 Kellerer and I resolved that problem, also allowing for 2 types of dose-estimation errors: measurement (classical) and averaging (Berkson).



In 2011 we developed a (computer) “laboratory” for evaluating effectiveness of the methods, and other needs.

Write *x* for true dose and *z* for estimated dose. A key issue is that even when $E(z \mid x) = x$ it is seldom true that $E(x \mid z) = z$. Rectifying this is referred to as *calibration* . Not achieved by the popular Monte Carlo methods -- must still be dealt with.

Since $pr(x \mid z) \propto pr(x)\ pr(z \mid x)$ assessing both factors is important. Often adequate to take $pr(z \mid x)$ as lognormal, but $pr(x)$ deserves more attention. Important in this to set aside any unexposed comparison group.

Major distinction between *measurement* (classical) errors and *averaging* (Berkson) errors. Difficult to define precisely, but we can say intuitively that for measurement errors "*z* is distributed around *x*" and for averaging errors "*x* is distributed around *z*". The latter mainly occurs when *z* is the average dose for some group.

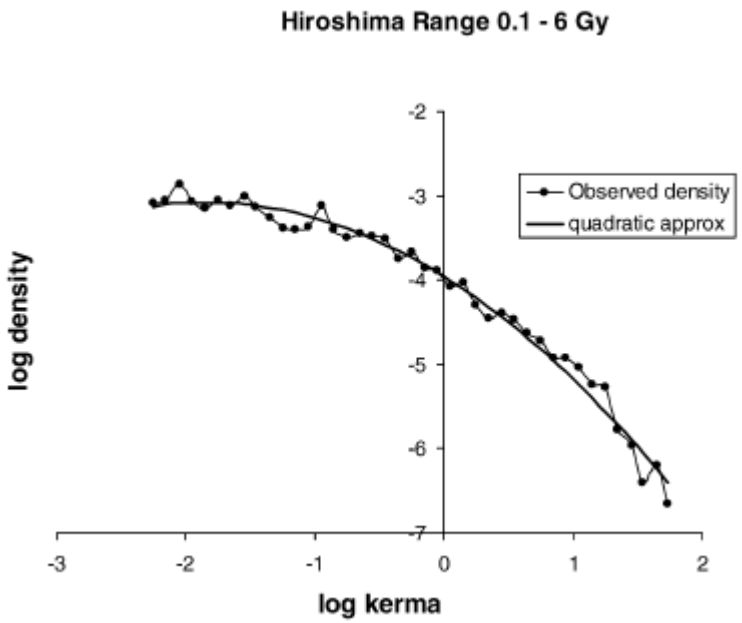
Write σ_M and σ_A for the SDs of these on a log scale, so that they can be interpreted as *coefficients of variation (CV)*. One can define a model with $z = x + e_M + e_A$, allowing for both types of error.

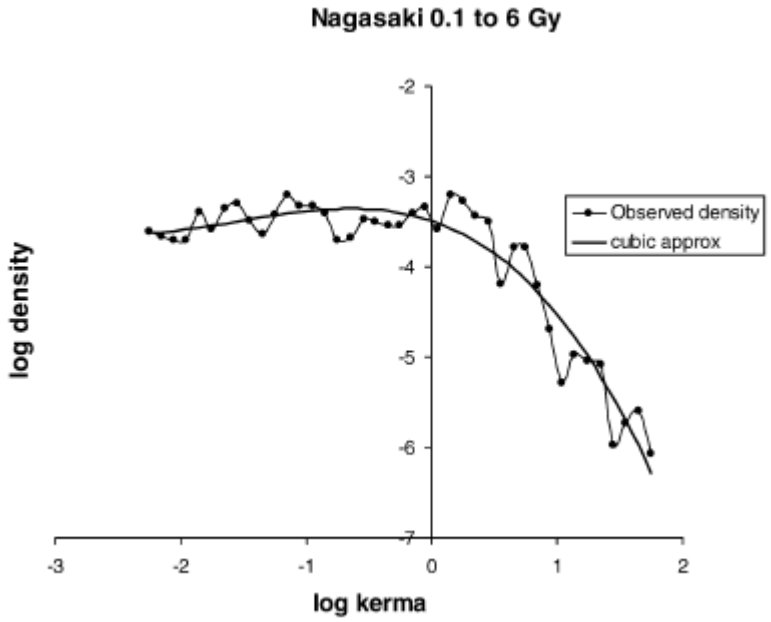
When both *x* and errors are lognormal, then

$$\log E(x \mid z) = w \log E(x) + (1-w) \log z$$

with *w* depending on $\sigma_M / SD(\log x)$. A factor of $\exp(\sigma_M^2 / 2)$ hinges on whether *z* is unbiased on the dose scale or the log dose scale!

For general $pr(x)$ our initial methods were cumbersome --- in 2004 Kellerer and I developed a much better method for this.





The calibration factor at dose *z* depends on the first two log-log derivatives at *z* of the *pr(x)* density. When the fitted smooth is quadratic, as for Hiroshima, the distribution is lognormal --- it is not so in Nagasaki. These calculations use only those with positive doses.

The derivatives enter due to the local dependence on *pr(x)* of

$$E(x \mid z) = \int x \, pr(x) \, pr(z \mid x) \, dx$$

Our aim is factor $C(z)$ such that $E(x \mid z) = C(z)\, z$. Formula is

$$\log[C(z)] = \frac{1 + 2d_1(z)}{1 - \sigma_M^2 d_2(z)} \frac{\sigma_M^2}{2},$$

Here $d_1(z)$ and $d_2(z)$ are the derivatives regarding the distribution of *true* doses. The (only) role of σ_A is adjusting the derivatives of the distribution of *estimated* doses, to approximate those needed, a step referred to as *deconvolution*.

$$d_1(z) = \hat{d}_1(z)/[1 + (\sigma_M^2 - \sigma_A^2)\hat{d}_2(z)]$$

$$d_2(z) = \hat{d}_2(z)/[1 + (\sigma_M^2 - \sigma_A^2)\hat{d}_2(z)].$$

This provides a programmable means of approximating $E(x \mid z)$ as a function of σ_M and σ_A , allowing for both measurement and averaging errors --- a process not possible in the 1990 development of the methodology.

These developments have enabled us to carry out simulations of the performance of the methods.

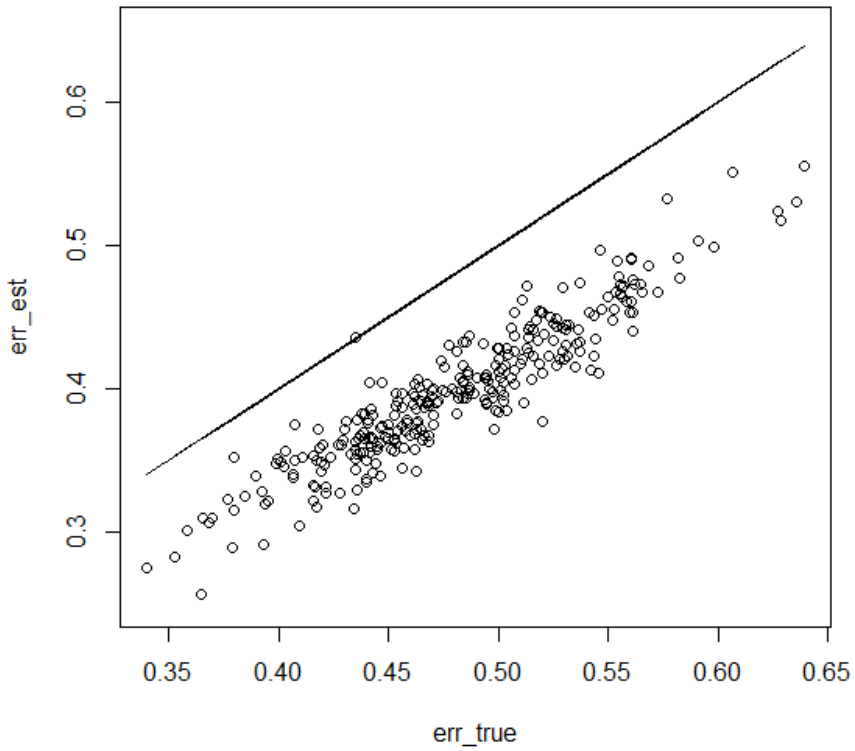
Take the actual (adjusted) dose estimates as true values. Generate cases using these. Generate dose estimates, adding to the true doses both measurement and averaging errors. Next, compute the calibrated estimates.

Then we can compute cancer risk estimates using true doses, estimated doses, and calibrated estimated doses.

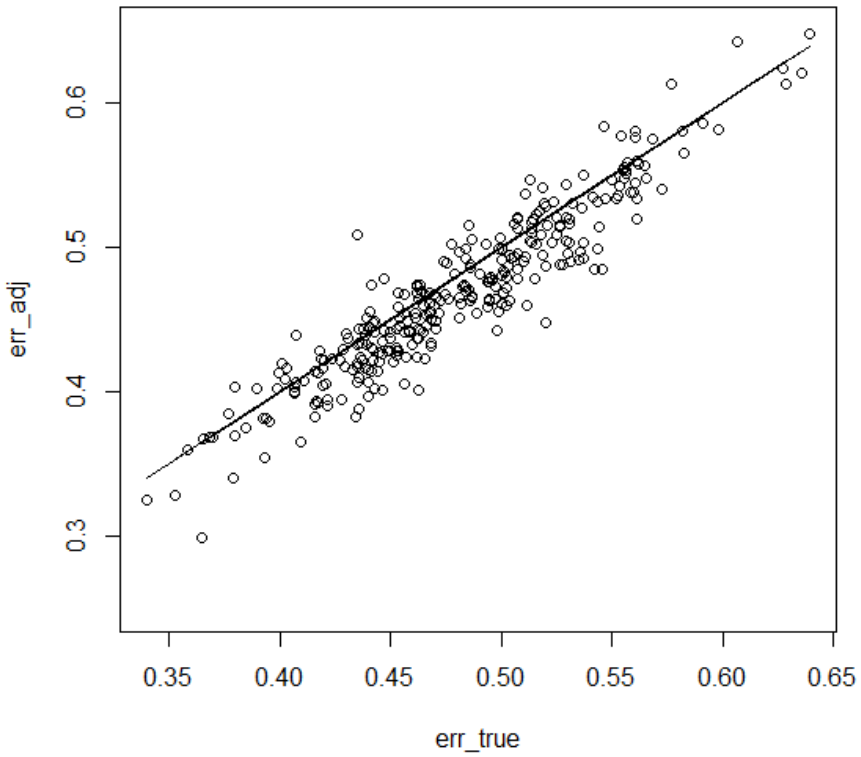
To avoid simulating deaths to other causes, we keep the CoxReg risk sets as fixed. Some trickery is needed to usefully generate averaging errors.

Cancer risk estimates for 40% measurement and 20% averaging (Berkson) errors, where the assumed and true error levels are the same

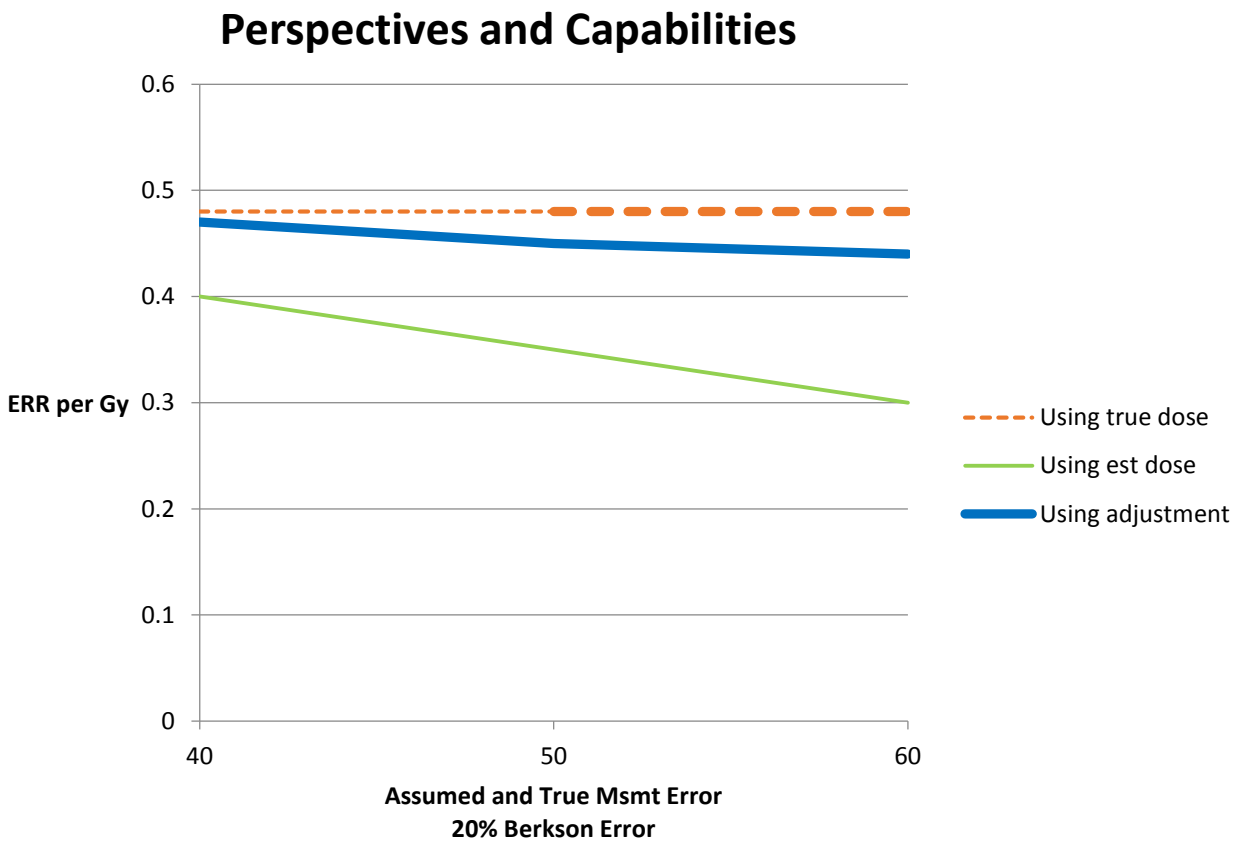
ERR using est dose



ERR using adj dose

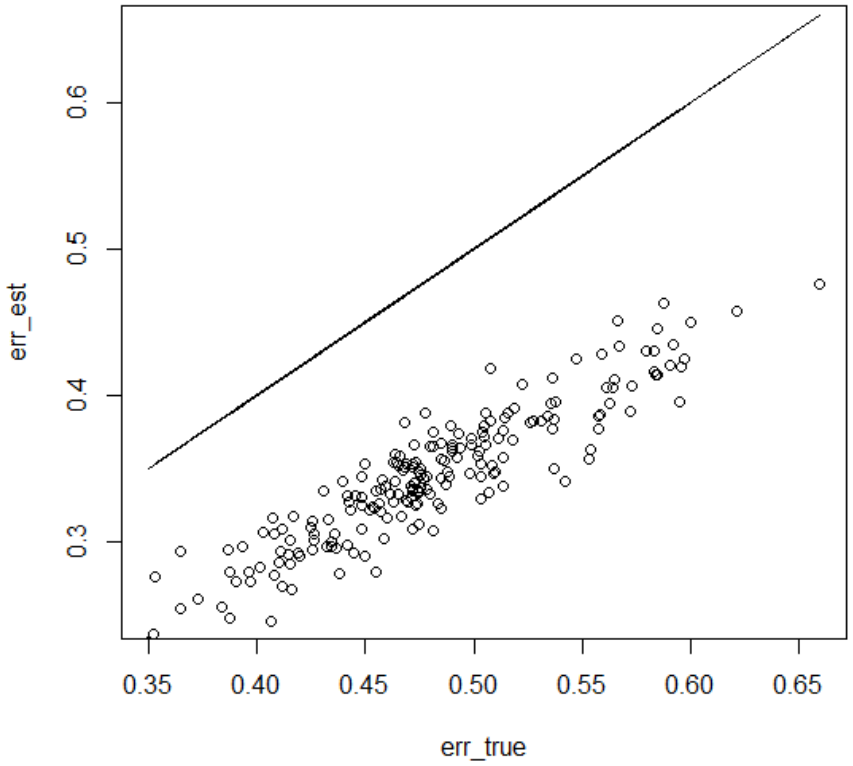


Same issue, presented differently and for a wider range of Msmt errors

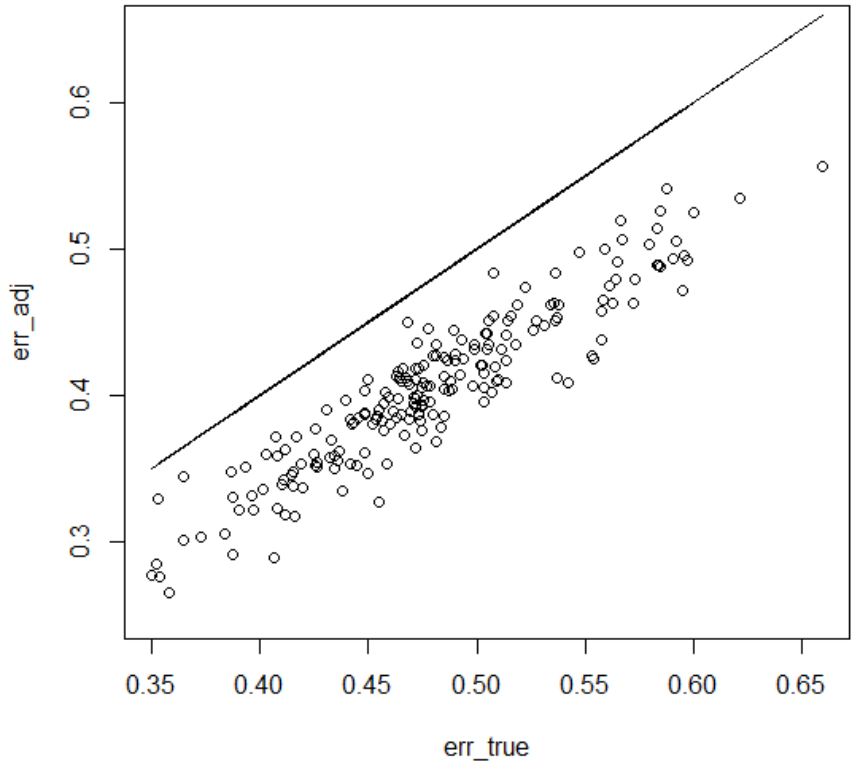


This is for assumed 40% msmt and 20% averaging, when the true values are 50% msmt and 00% averaging

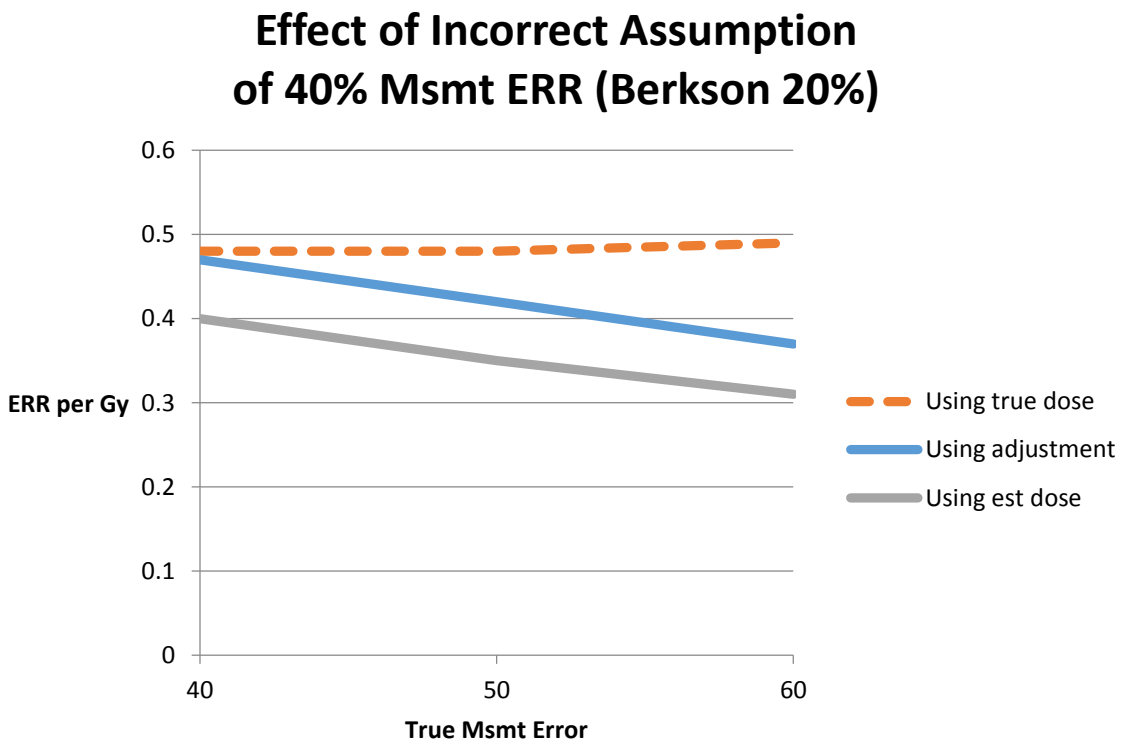
ERR using est dose



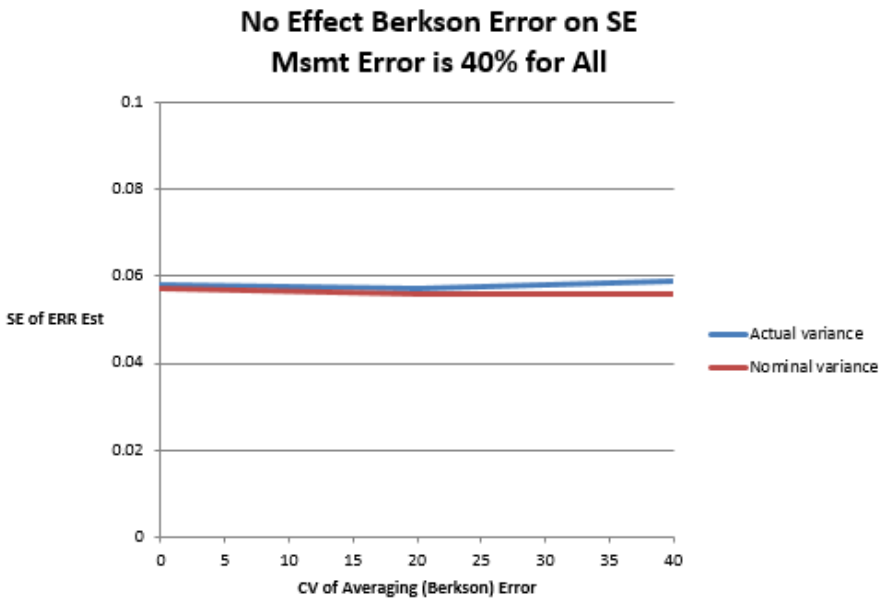
ERR using *adj* dose



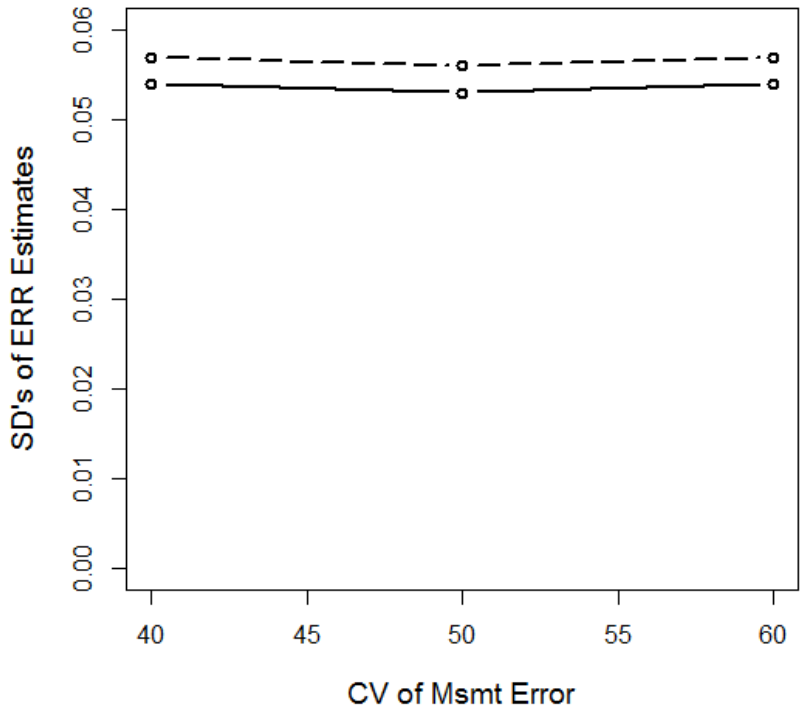
Same issue, presented differently and for a wider range of Msmt errors



For cancer risk estimation, Averaging Error has no effect on SEs (or bias). Only effect is in adjusting from distn of estimated doses to distn of true doses



Measurement errors, when correctly adjusted for, have negligible effect on precision of cancer risk estimates. This is because the variation in the "binary-like" cancer outcome dominates. The "only" cost of these random errors is that correct calibration assumptions are required to remove their effect.



The result on the last slide is important and “surprising”, though we have been arguing this theoretically since the beginning.

Theoretically, result expected not just for RERF setting but for all cancer studies.

Brings into question the value of Monte Carlo for assessment of uncertainties (in cancer risk estimation) due to dosimetry errors.

However, the cost of needing the information for the calibration is not negligible.

The effect on SEs, and other aspects, would be greater for endpoints that are not “binary-like”, e.g. binomial.

RERF will probably turn to 40% Msmt error and 20% Averaging error.

The 40% is a “uncertain”. Are reasons to think that 35% was optimistic --- the 20% Avging error is not consequential.

Attempts to directly estimate these things can be misguided, and assumptions/sensitivity analysis more useful

For Msmt error levels much greater than 50% unexpected things develop, as below.

What appears to be nearly linear response may when corrected show so much downward curvature that linear risk estimation becomes of limited interest.

In many other studies, the RERF method may be overly elaborate, and one may want to rely on the result of slide 6 regarding lognormal distributions of true dose.

Then, on the log scale, E(x | z) is a weighted average of *z* and *E(x)*, with weights depending on $\sigma_M / SD(\log x)$

With Averaging error, may be able to take *E(x)* as *E(z)* for this, but not var(*x*) = var(*z*) since Averaging error decreases the variance of dose estimates .

What has been learned at RERF is useful in that: (a) such precise risk estimation is possible, and (b) there is such continued interest in the cohort.

Was important to learn that the naïve bias is not really large, in view of other uncertainties.

Many useful side effects, e.g. becoming cognizant of “residual confounding”.

For example, we knew right away why those reporting acute effects had apparently higher radiation risk for cancer --- not that they were “more sensitive to radiation’ but …

References

Pierce, Stram and Vaeth. Allowing for random errors in radiation dose estimates … . *Radiation Research* **1990**, 275.

Pierce and Kellerer. Adjusting for covariate errors wih nonparametric assessment of the true covariate distribution. *Biometrika* **2004**, 863.

Pierce, Vaeth and Cologne. Allowance for random dose errors …: A revision . *Radiation Research **2008**, 118.*

These slides can be obtained at :

www.science.oregonstate.edu/~piercedo/