A Model of BCS and the Odds Ratio of Negative vs. Positive Margins: Appendix

10-17 July 2018

Some More Topics

- The "meaning" of υ
- Relative effect of hazards
- Sensitivity analysis with gamma density
- Sensitivity analysis with z_0
- Different FU times
- Undetected cancer & background risk
- Effects of "covariates"

The Meaning of υ

- For the simple case where $\nu_0(t) = \eta_0 t$
- We defined $\nu_0 = \upsilon\lambda R(s_0)t_0^2/2$
- Thus, $\eta_0 = \upsilon\lambda R(s_0)t_0/2$
- So strictly, η_0 is a fraction $\upsilon/2$ of the residual tumor hazard at time t_0
- Though what we really meant was, the background *cumulative* hazard ν_0 is a fraction υ of the residual tumor *cumulative* hazard at time t_0

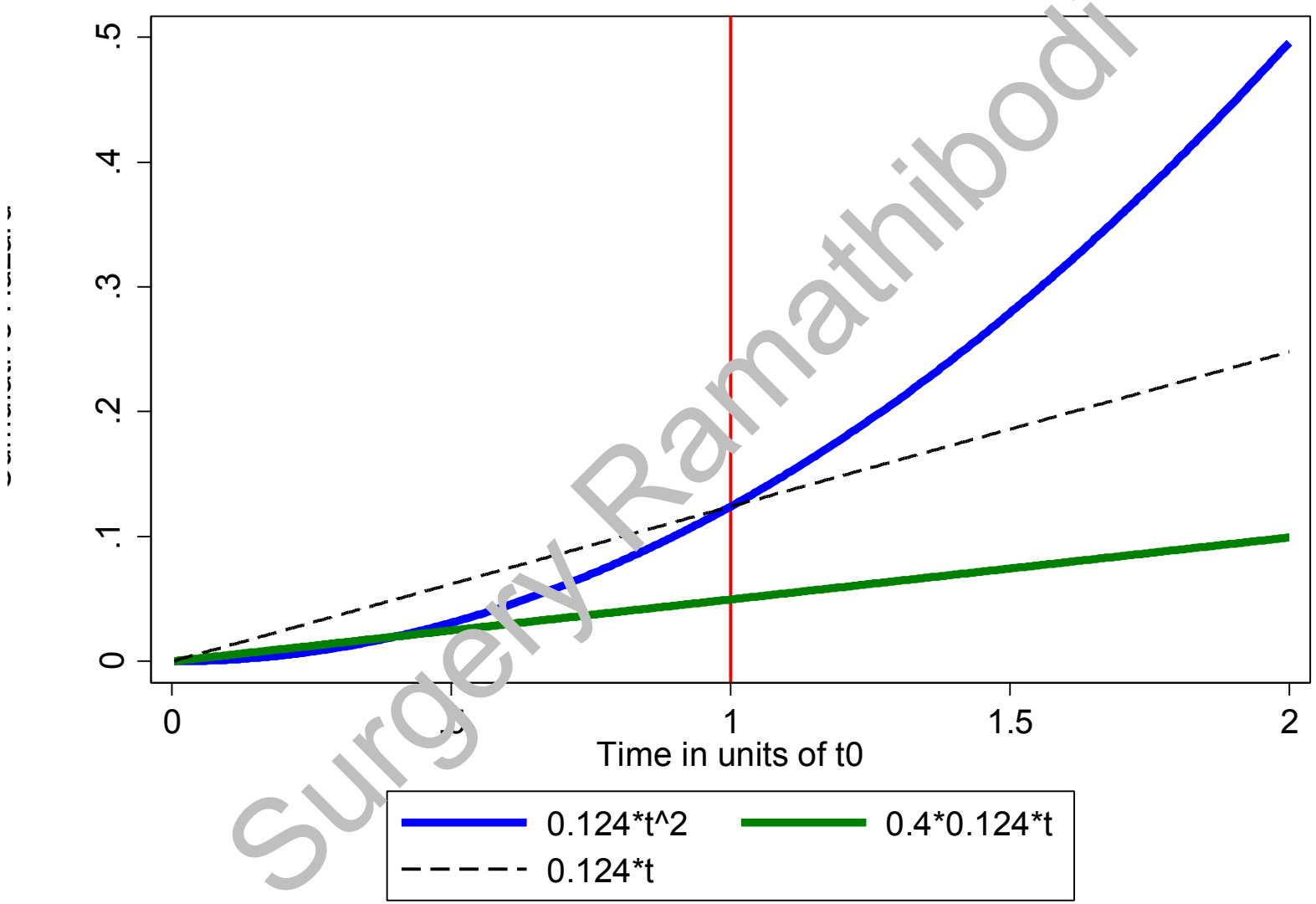
The Meaning of υ

- The *cumulative* hazard of recurrence $H(t)$, with background risk, is, in terms of ϕ

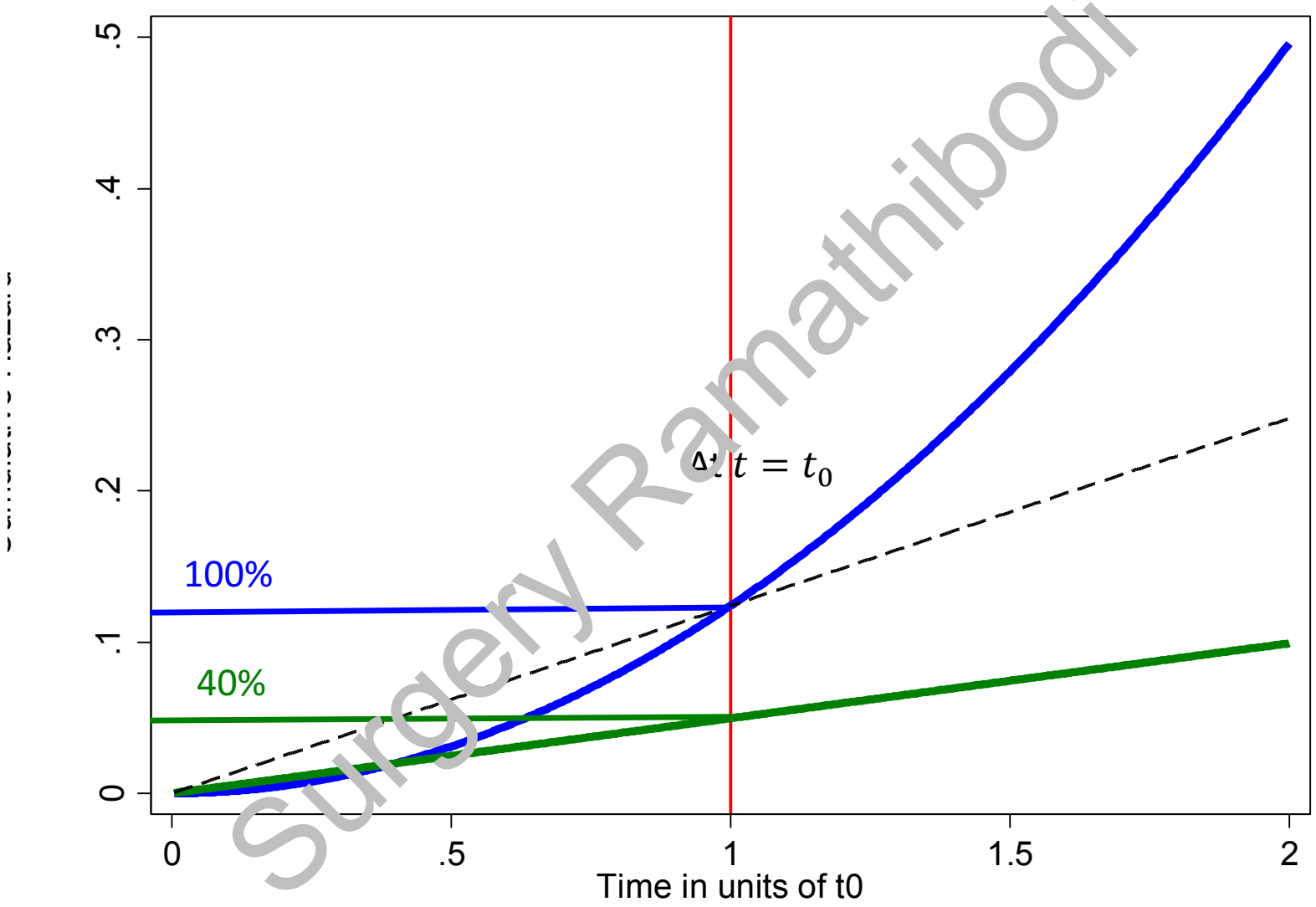
$$H(t) = \frac{s_0^2\phi}{\epsilon}\left(\frac{t}{t_0}\right)^{\epsilon} + \upsilon\frac{s_0^2\phi}{\epsilon}\left(\frac{t}{t_0}\right)$$

- Let's plot a graph contrasting the first & second terms (blue & green, resp.) for $\upsilon = 0.4$

3-cm tumor; 0.8 dis free; 20% undetected CA; $\upsilon = 0.4$



This is the “meaning” of υ



Relative Effect of 2 Hazards

- The relative effect of the 2 hazards – residual cancer at the primary site and background risk – **on probability of recurrence**
- **This is not easy to address directly**
- But let's assume that there are 2 groups of patients, one with only the residual cancer component and the other with only the background risk component as the driver of recurrence
- Then we can calculate a form of "relative effect"

Relative Effect

- At time t_0 we can compare these effects in terms of the Recurrence Probability Ratio ξ (*r*=residual tumor; *b*=background)

$$\xi \equiv \frac{F_{t_{0b}}}{F_{t_{0r}}} = \frac{1 - e^{-\upsilon s_0^2 \phi/\epsilon}}{1 - e^{-s_0^2 \phi/\epsilon}}$$

- Assuming small values of the exponent, and using Taylor's expansion, keeping the first 2 terms, we get

$$\xi = \upsilon \frac{\left(1 - \upsilon s_0^2 \phi/2\epsilon\right)}{\left(1 - s_0^2 \phi/2\epsilon\right)}$$

Relative Effect

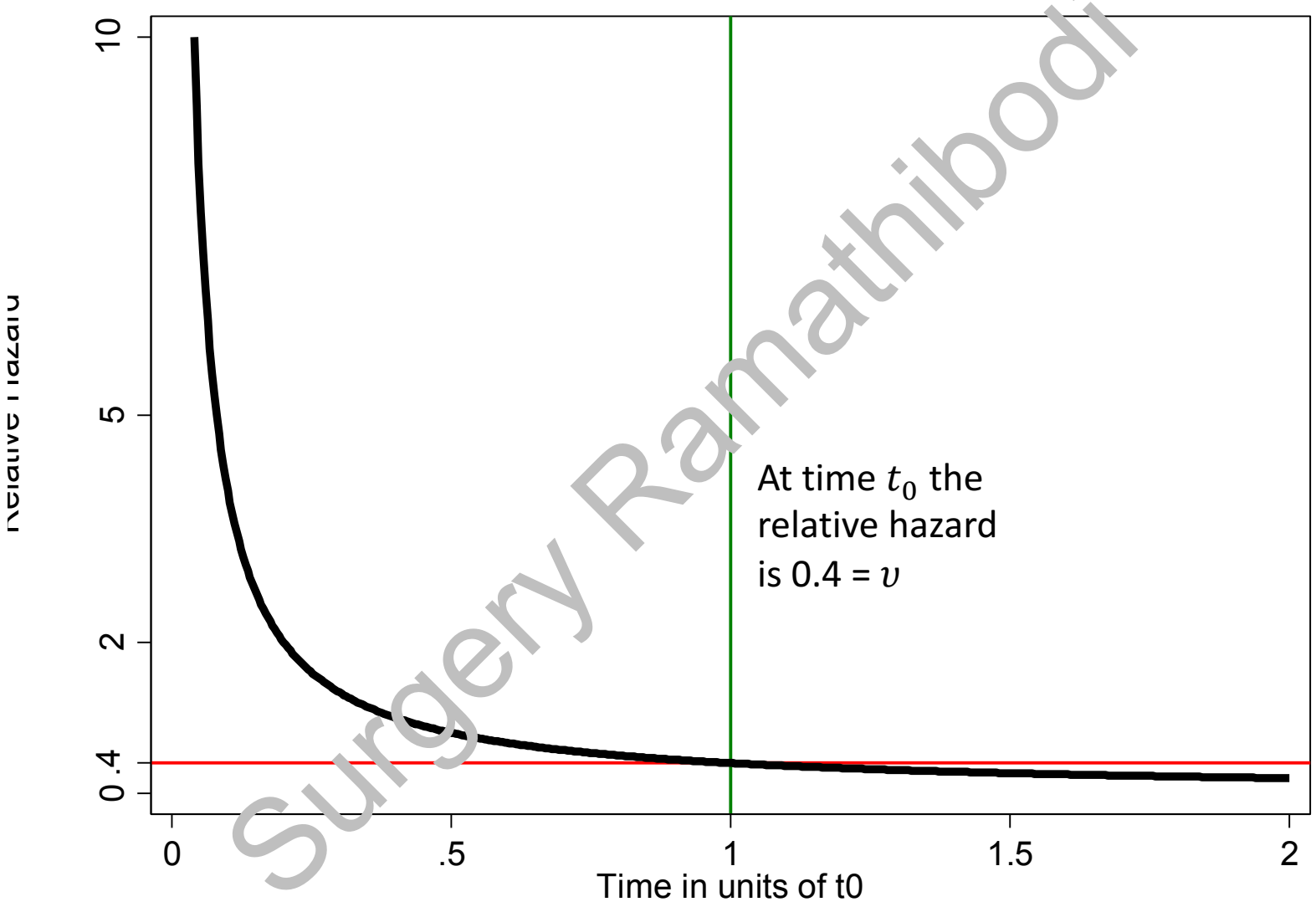
- Thus the cancer recurrence "effect" of the background risk relative to the residual primary tumor is slightly more than υ
- For example, if $\upsilon = 0.4$, and $\frac{s_0^2\phi}{\epsilon} = 0.124$ then $\xi = 0.415$
- *Loosely speaking*, the background risk "contributes" to recurrence at 41.5% of the residual cancer (importantly **this is not** 41.5% of the total Recurrence Probability) at time t_0

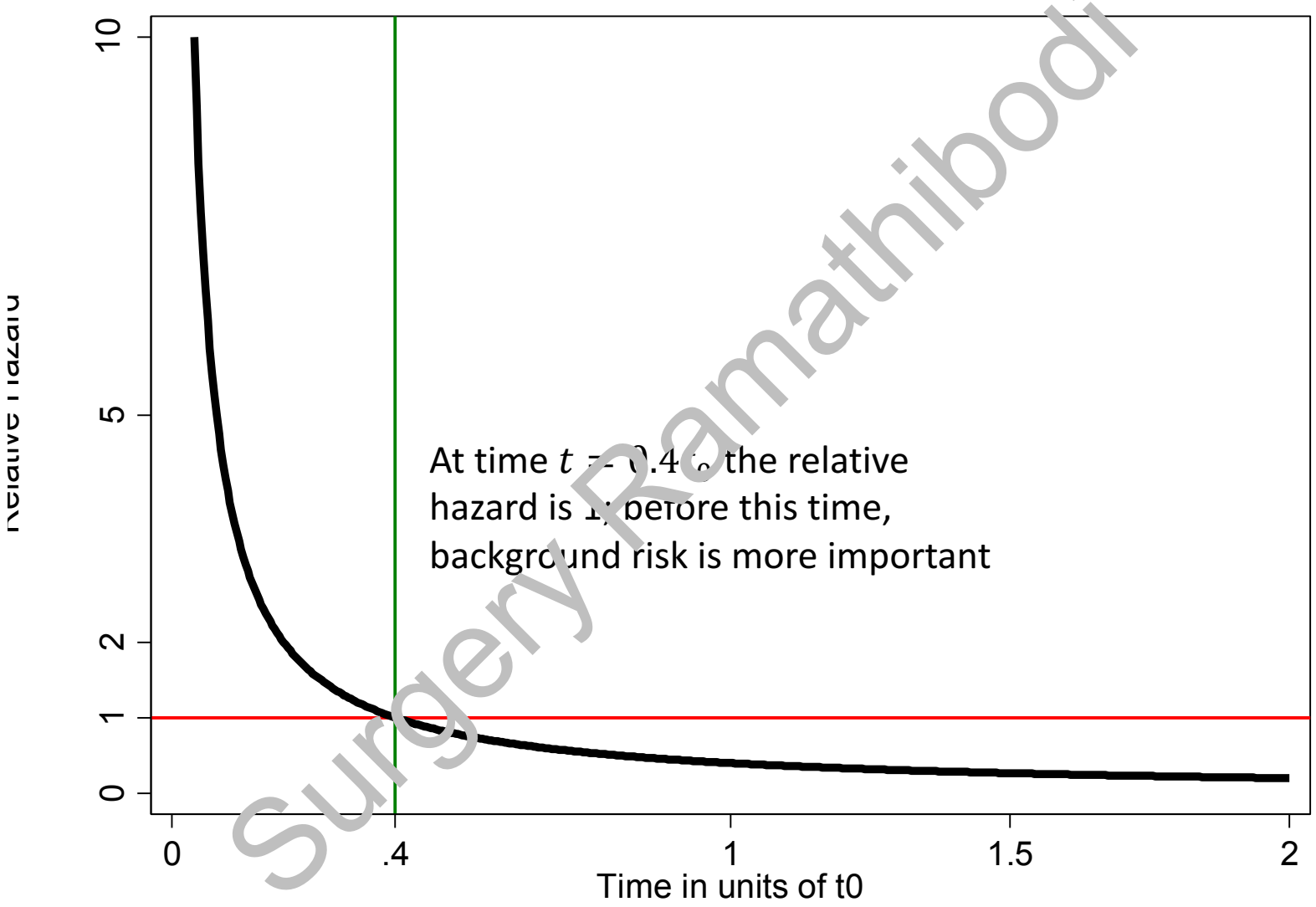
Relative Effect: Hazards

- On the other hand, looking at the relative effect of the 2 cumulative hazards in themselves is easy
- From the previous expression, the ratio of the cumulative hazards is, in any given patient or a group of similar patients (*R*elative *H*azard):

$$RH(t) \equiv \frac{\upsilon t_0}{t}$$

- This is the ratio of the background hazard to the residual cancer hazard
- Graphically, if $\upsilon = 0.4$, and in units of t_0:





Relative Hazard

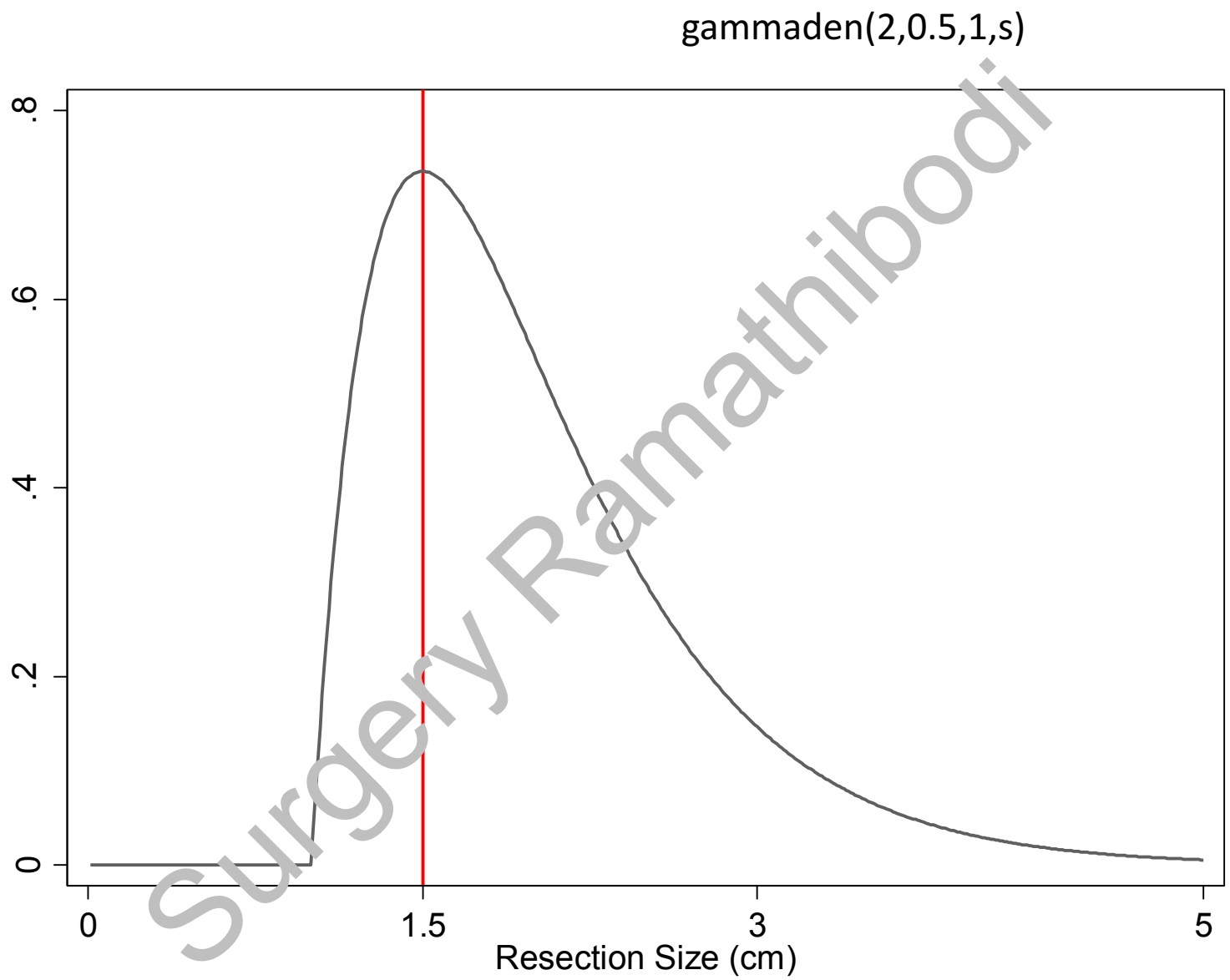
- Thus the effect of background hazard relative to the residual cancer hazard diminish with time
- But the relative effect is very large at times just after surgery
- Recurrence right after surgery is usually due to unrecognized multicentric or multifocal disease, unless there is a large amount of residual cancer at the primary tumor site

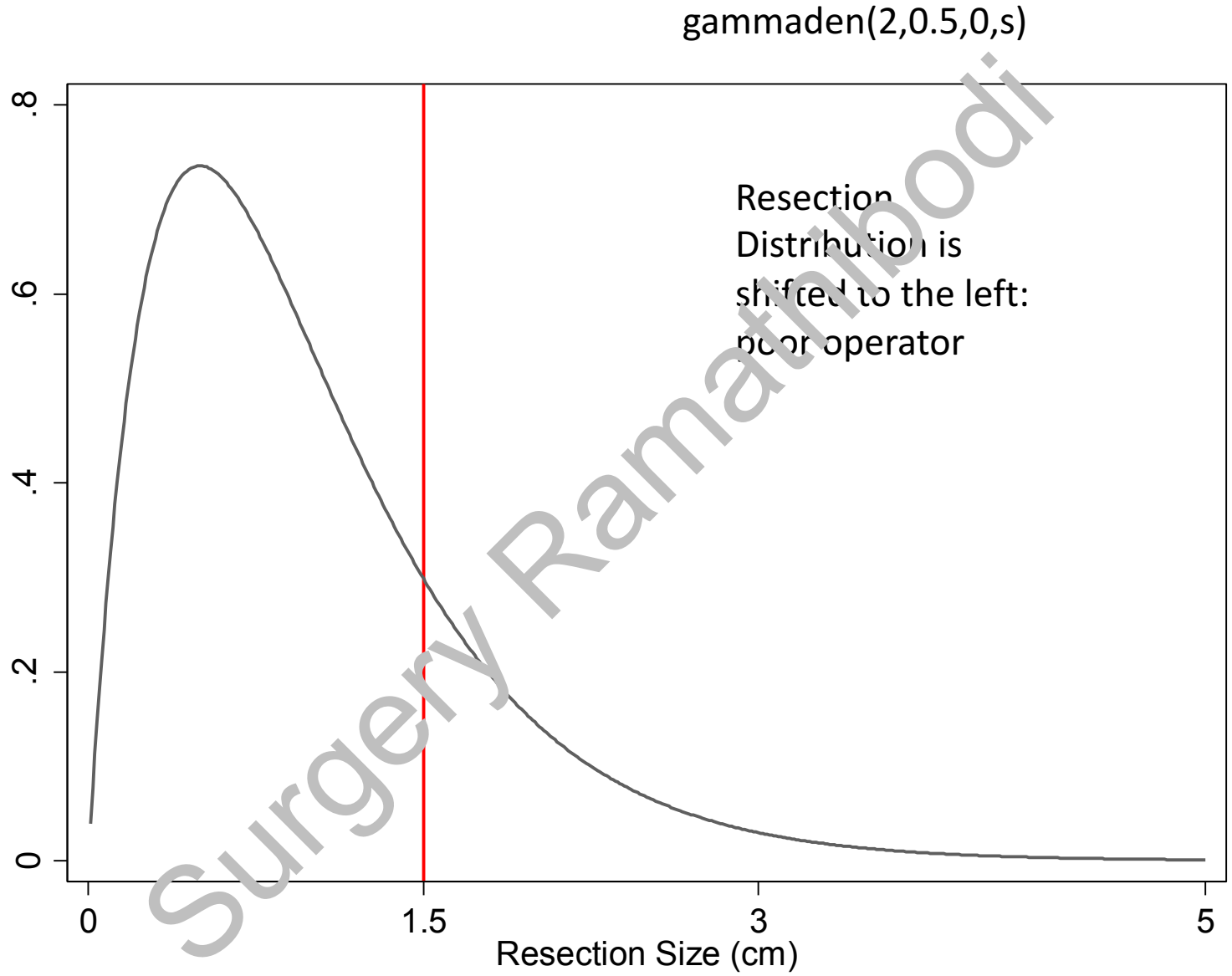
Sensitivity Analysis: gammaden

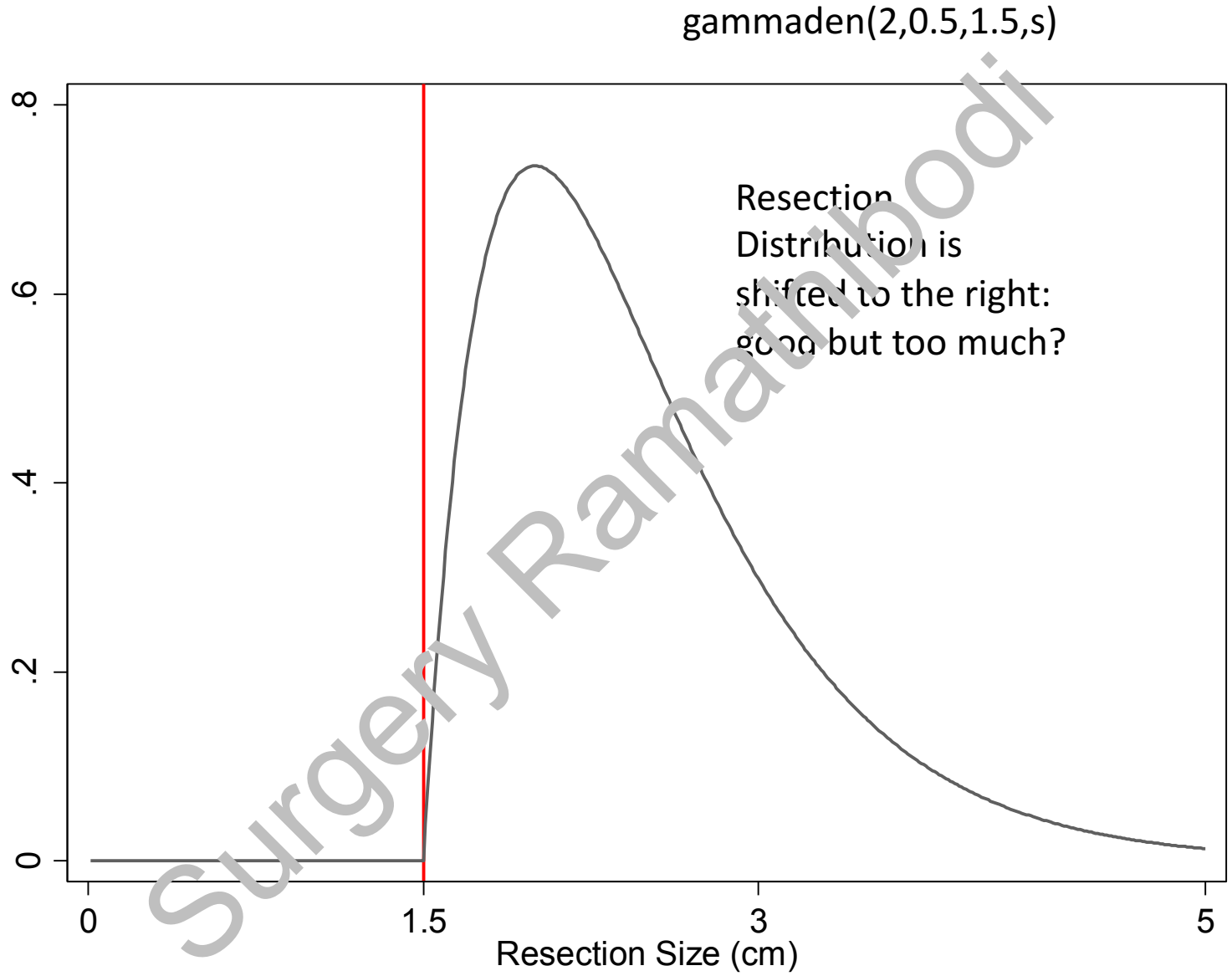
For a 3-cm tumor; recurrence-free prob of 0.8; 30% undetected cancer; and $v = 0.4$ (Marinovich, 2016)

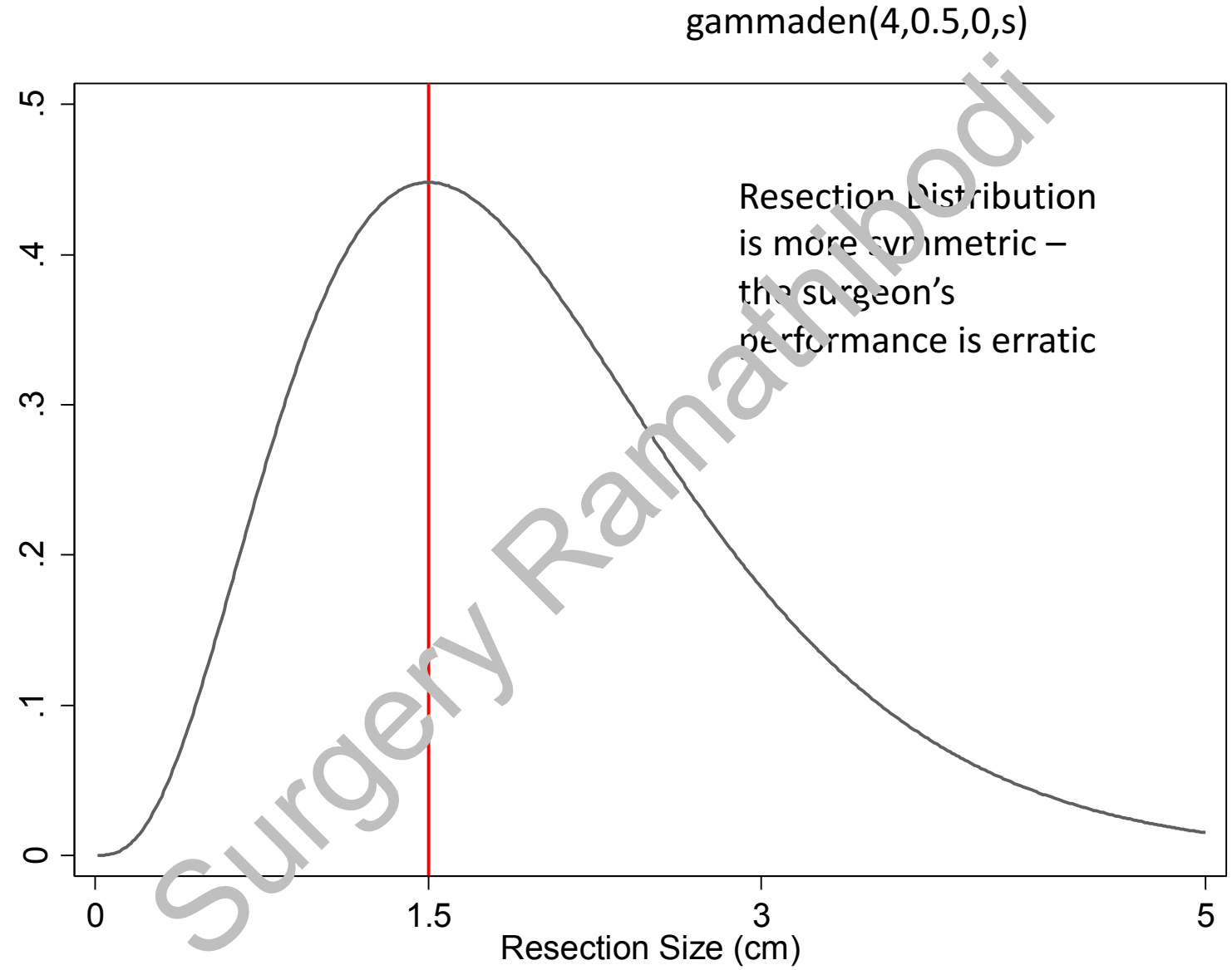
For a 3-cm tumor; recurrence-free prob of 0.94; 20% undetected cancer; and $v = 0.6$ (Houssami, 2014)

- Varying the gamma density:
- ga(2,0.5,1); ga(2,0.5,0); ga(2,0.5,1.5); ga(4,0.5,0)
- **Results** are all practically different, and except for ga(2,0.5,1), **do not really fit the data** (not shown)









Sensitivity Analysis: z_0

The model for Houssami (2014)

ga(2,0.5,1); S_{t_0} = 0.94; z_0 = 0.2; ω = 0.6

- Varied z_0 : 0.1, 0.05 did not fit data (OR's too low)

Different FU Times

- A source of unrealism in the model is the assumption that all studies have the same FU time; whereas in reality FU time varies among studies
- The occurrence of censoring, which is not mentioned in any study, is also ignored here
- We can incorporate different FU times in the model, but this increases its complexity, which we will not dwell into now
- We outline an approach to doing so

FU Time Distribution

- We must assume an appropriate FU time probability distribution/density
- Assume this to be another gamma distribution/density, with which we can exclude FU times that are implausible quite easily
- We illustrate the Recurrence Probability for $s \geq s_i$

Recurrence Probability

The recurrence probability is

$$\Pr(\geq s_i) = \left[\int_{s_i}^{\infty}\left\{\int_0^{\infty}\left(1-\exp\left[-\left(\frac{\lambda R(r)t^2}{2}+\nu_0(t)\right)\right]\right)g_t(t)dt\right\}g_s(r)dr\right]/g_s(s_i,\infty)$$

- Where the time-integration is over all times
- We can restrict the time interval but this may be unnecessary
- If the FU time probability density is already restrictive enough

Undetected Cancer

- Our definition of undetected periphery tumor is vague (the word undetectable is not really appropriate)
- Let us be more precise
- **It is a rim of cancer not seen radiologically or on gross examination**
- It is usually difficult to detect histologically, unless the rim is large (and the probability of detecting any "rim cancer" should increase with rim size)

Undetected Cancer

- If special staining techniques are used, perhaps these rim cancers can be readily seen
- But here we focus on H&E staining
- If any rim cancer is seen, it is obvious that the margin will be come narrower than initially estimated
- If such is the case, the patient will be grouped in the narrower margin category, not in one with larger margin as initially expected
- There is thus some sort of “stage migration” effect in real life, as oppose to “theoretical life”

Undetected Cancer

- {So the OR is real life is closer to 1 than in theory?}
- There is the question of whether such “rim cancer” truly exists, or commonly exists, and how to detect it
- Fortunately there are some studies addressing this or similar questions
- In terms of Cancer Detection Probability

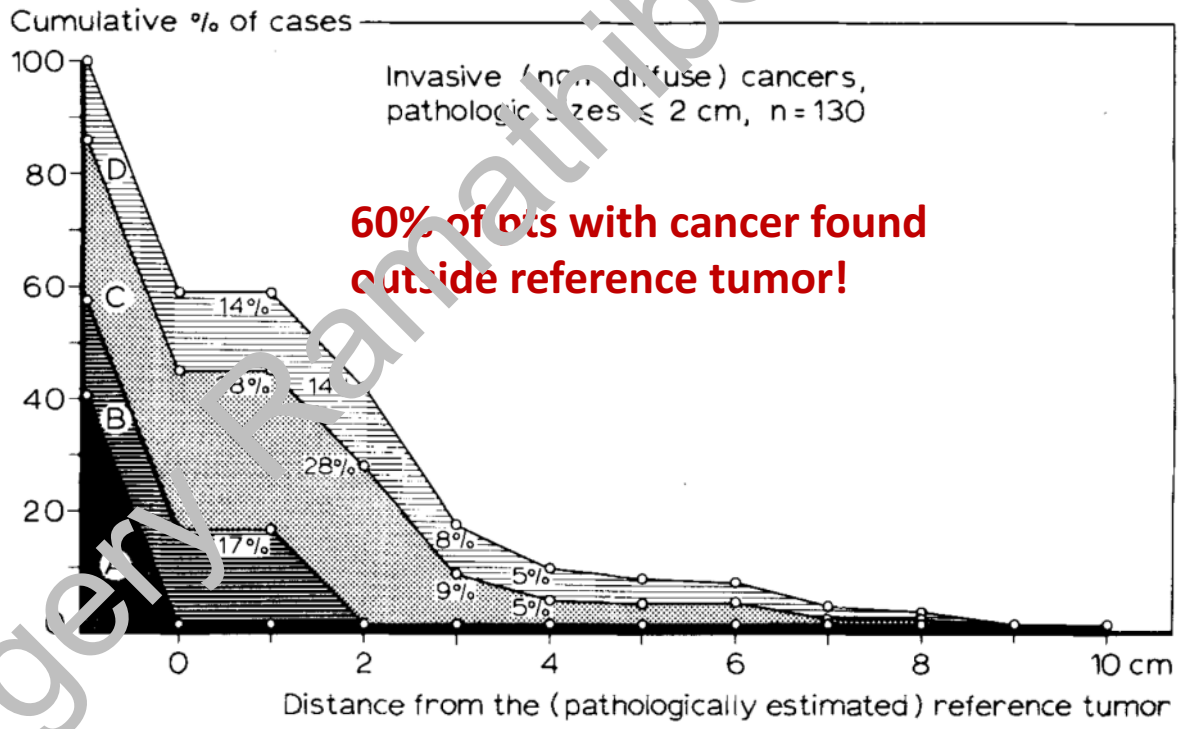
Cancer Detection Probability

- **Redefine *normalized* tumor density** as **conditional probability of cancer detection** at (given) any distance from tumor center?
- Thus, a normalized density of 1 refers to the certainty of detecting cancer (definite area of detected cancer) at a given distance in any direction
- A density of less than 1 refers, proportionately, to lower probability of detection
- This is to correspond to the data of Holland, 1985

Holland R. Cancer 1985;56:979-90

Holland Data

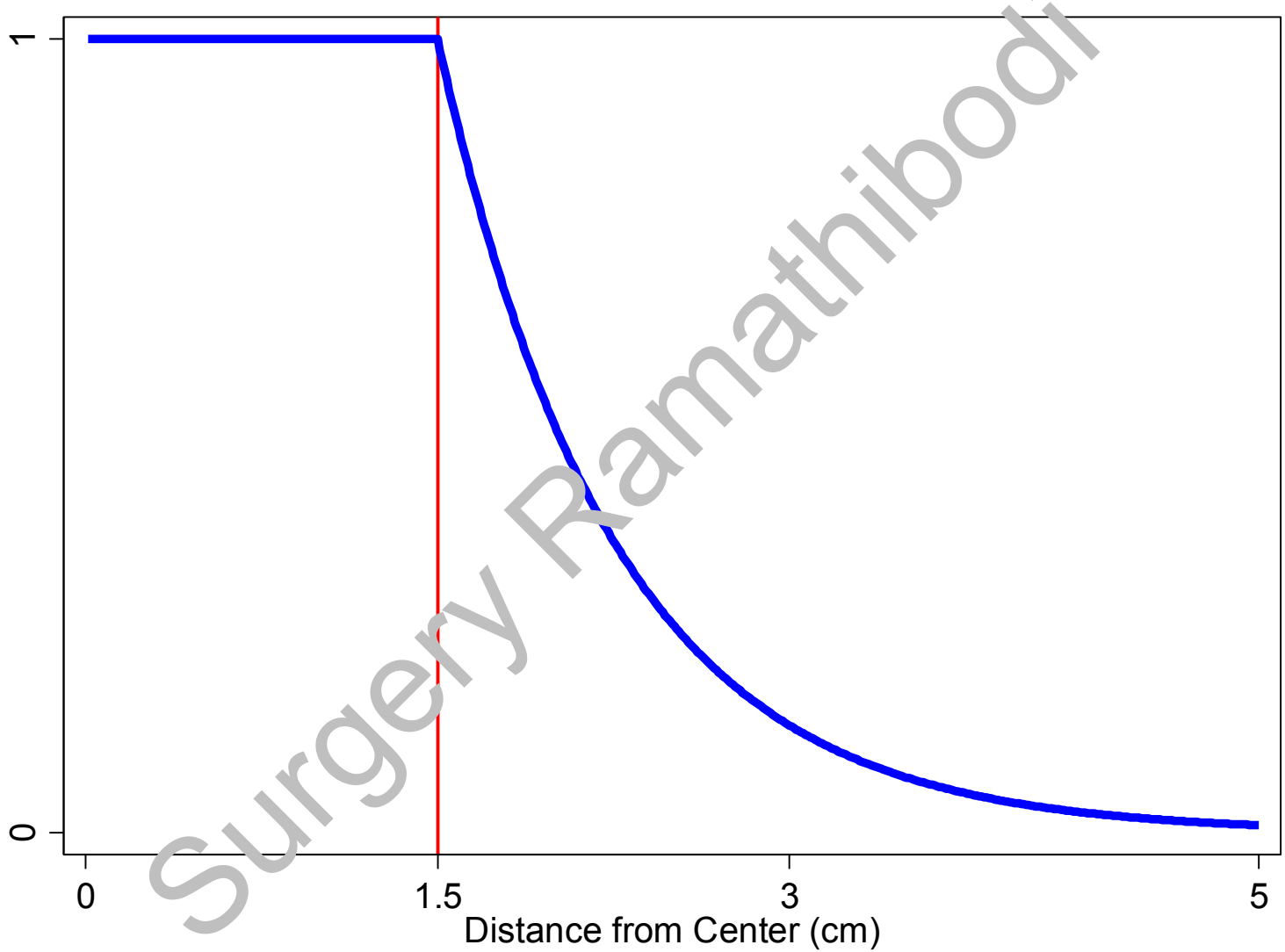
FIG. 2. Distribution of tumor foci at different distances from the reference tumor and proportions of cases with and without tumor foci around the reference tumor. The pathologic size served as reference size. For Figs. 2–7, the cases are divided into four groups—A: Cases without tumor foci outside of the reference tumor. B: Cases with tumor foci within 2 cm of the reference tumor. The exact distance of these foci and their invasive or noninvasive character was not further specified. C: Cases with noninvasive tumor foci at a distance greater than 2 cm from the reference tumor. D: Cases with invasive tumor foci, at a distance greater than 2 cm from the reference tumor. The values of percentages within the groups indicate the proportion of cases with tumor foci located at or beyond the point given on the abscissa (distance from reference tumor).



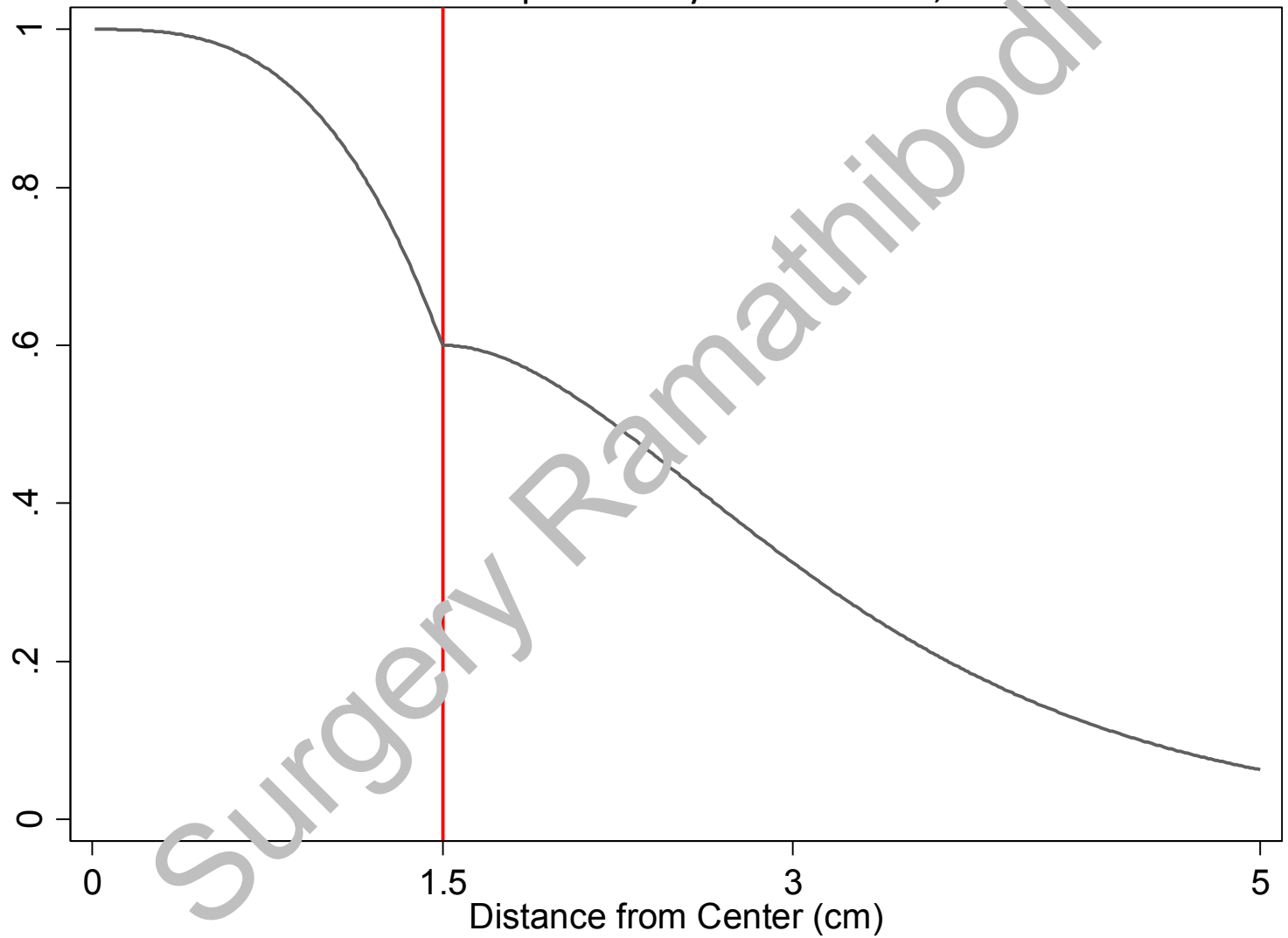
60% of pts with cancer found outside reference tumor!

Holland R. Cancer 1985;56:979-90

“Probability of Cancer Detection”, as a Function of Distance: 0.91 dis free; 60% Undetected Cancer



“Cumulative” Proportion of Residual Cancer, as a Function of Distance: 0.91 dis free; 60% Undetected Cancer: NOT cancer detection probability as in Holland, 1985



Cancer Detection Probability?

- $\Pr(c = 1|s) = 1 \; if \; s \leq s_0$
- $\Pr(c = 1|s) = e^{-\epsilon(s-s_0)} \; if \; s > s_0$ (or approx. so)
- Note that, here, $\Pr(c = 1|s_i) = \Pr(c = 1|s \geq s_i)$

"Expected cancer density" at any s

- $E(\rho|s) = \rho(s) \; if \; s \leq s_0$
- $E(\rho|s) = \rho(s)e^{-\epsilon(s-s_0)} \; if \; s > s_0$ (or approx. so)
- Tumor density $\rho(s)$ should depend on s : less dense outside of detected cancer

Background Risk

- What is background risk of breast cancer?
- Just any risk that does not depend on the primary tumor
- The risk can have a constant value or non-linear time dependence
- Thus, the risk could be due to existing multifocal cancers, genetic predisposition, existing high-risk breast lesions, and so on
- Interesting to mathematically model this

Effects of Covariates

- "Covariates" is a statistical term referring to other risk factors, in this case modifying the effects of residual tumor on the hazard of recurrence
- We can do this "statistically", e.g. using Cox proportional hazards regression modeling
- Or we directly model the effects using stochastic or deterministic approaches to mathematical cancer modeling
- Focus on: **tumor biology**, **adjuvant treatment**, **cancer detection ability** (?)

Effect of Closed vs. Open Margins

- We can model specific studies where some margin categories are closed (e.g. $s_j \leq s < s_i$) and some are open ($s \geq s_i$)
- And compare with previous results