# A Model of BCS and the Odds Ratio of Negative vs. Positive Margins (Part 2)

8-22 July 2018

# Part 2

- In the previous Part 1 we used definitions of OR's according to Houssami (2014)
- In Part 2, we will use definitions according to Wang (2012) and Marinovich (2016 – some parts)
- And will calculate OR's contrasting negative with *negative* margins as well



Houssami, et al. Ann Surg Oncol 2014;21:717-30
Wang, et al. J Natl Cancer Inst 2012;104:507-16
Marinovich, et al. Ann Surg Oncol 2016;23:3811-21

# Multiple Margins Comparison

- A comparison of various margins which are free from tumor can be done using a **common control**: e.g. a “positive” margin with a common upper limit, or even a “negative” margin control
- This will, to some extent, overcome certain problems with the use of OR’s as defined in the 1st part

# Multiple Margins Comparison

- We contrast, in terms of OR, various free or "negative" margins
$$s > s_0, s \geq s_1, s \geq s_2, .., s \geq s_i, etc.$$
- With "positive" margin(s)
$$s \leq s_0 \text{ or } s < s_1$$
- Where the $i > 0$ refers to free margins in mm
- And $i = 0$ is "ink on tumor"
- We calculate the Recurrence Probabilities associated with these margins, as before, and the corresponding OR's, for each one of the 2 positive controls, **then compare the OR's across the values of negative margins, for each positive control**
- This is (somewhat) according to Wang & Marinovich, who use both **open-ended** and **closed-ended** definitions of margins

# Recurrence Probability

Recurrence probabilities for various negative margin cut-offs $i$, and for positive margins with upper bound $k$, are:

- $\Pr(\geq s_i) = \left[\int_{s_i}^{\infty}\left(1-\exp\left(-\frac{\phi}{\epsilon}e^{-\epsilon(r-s_0)}r^2\right)\right)g(r)dr\right]/g(s_i,\infty)$
- $\Pr(< s_k) = \left[\int_{s_0}^{s_k}\left(1-\exp\left(-\frac{\phi}{\epsilon}e^{-\epsilon(r-s_0)}r^2\right)\right)g(r)dr + \int_{0}^{s_0}\left\{1-\exp\left(-\phi\left(\frac{s_0^3-r^3}{3}+\frac{s_0^2}{\epsilon}\right)\right)\right\}g(r)dr\right]/g(0,s_k)$

As was previously shown

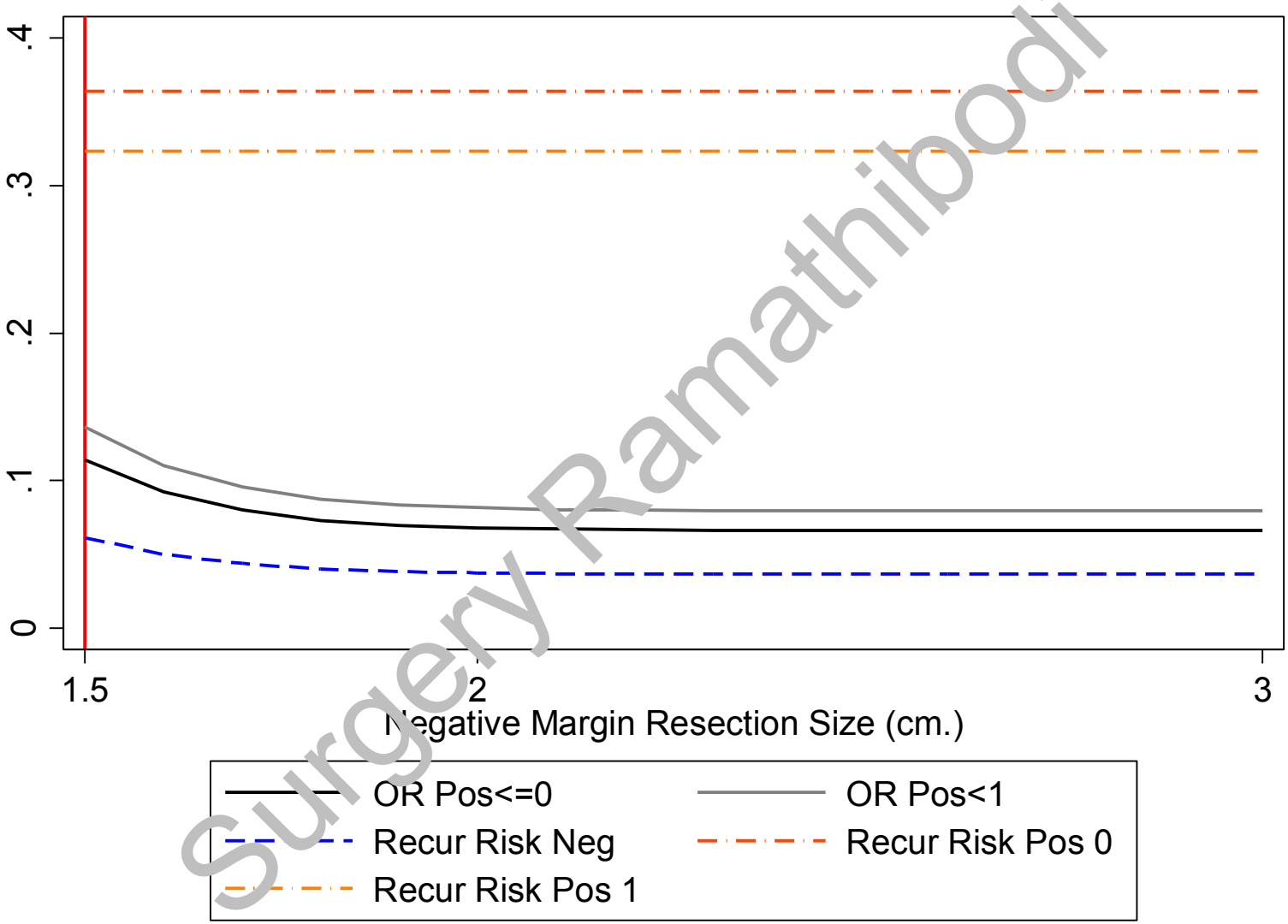
# Recurrence Probability

And recurrence probabilities **with background cancer risk**:

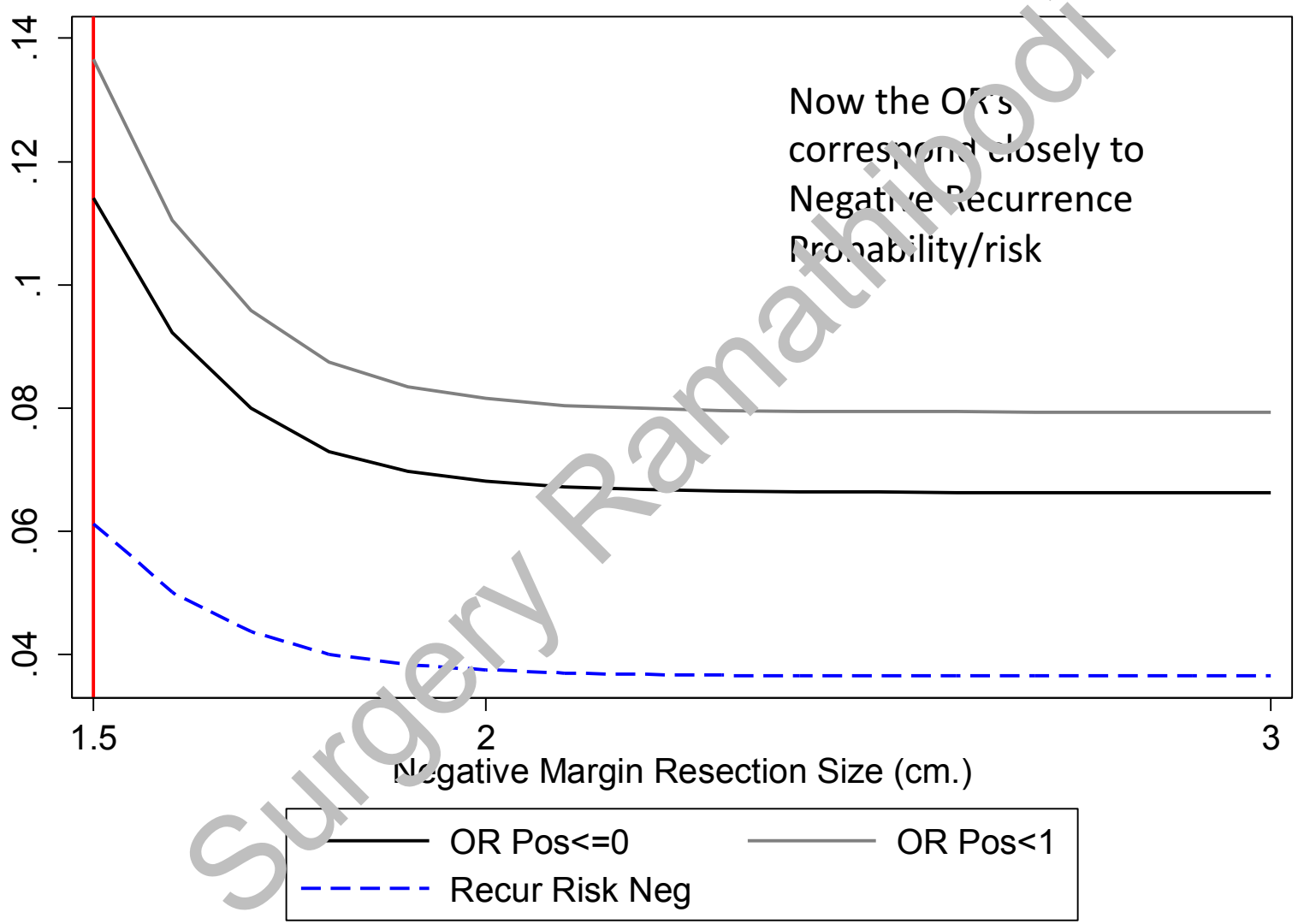
- $\Pr(\geq s_i) = \left[\int_{s_i}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r)dr\right] / g(s_i, \infty)$
- $\Pr(< s_k) = \left[\int_{s_0}^{s_k} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r)dr + \int_0^{s_0} \left\{1 - \exp\left(-\phi\left(\frac{s_0^3 - r^3}{3} + \frac{s_0^2}{\epsilon}\right) - \nu_0\right)\right\} g(r)dr\right] / g(0, s_k)$

- There will be only 2 positive controls, for which $k = 0,1$

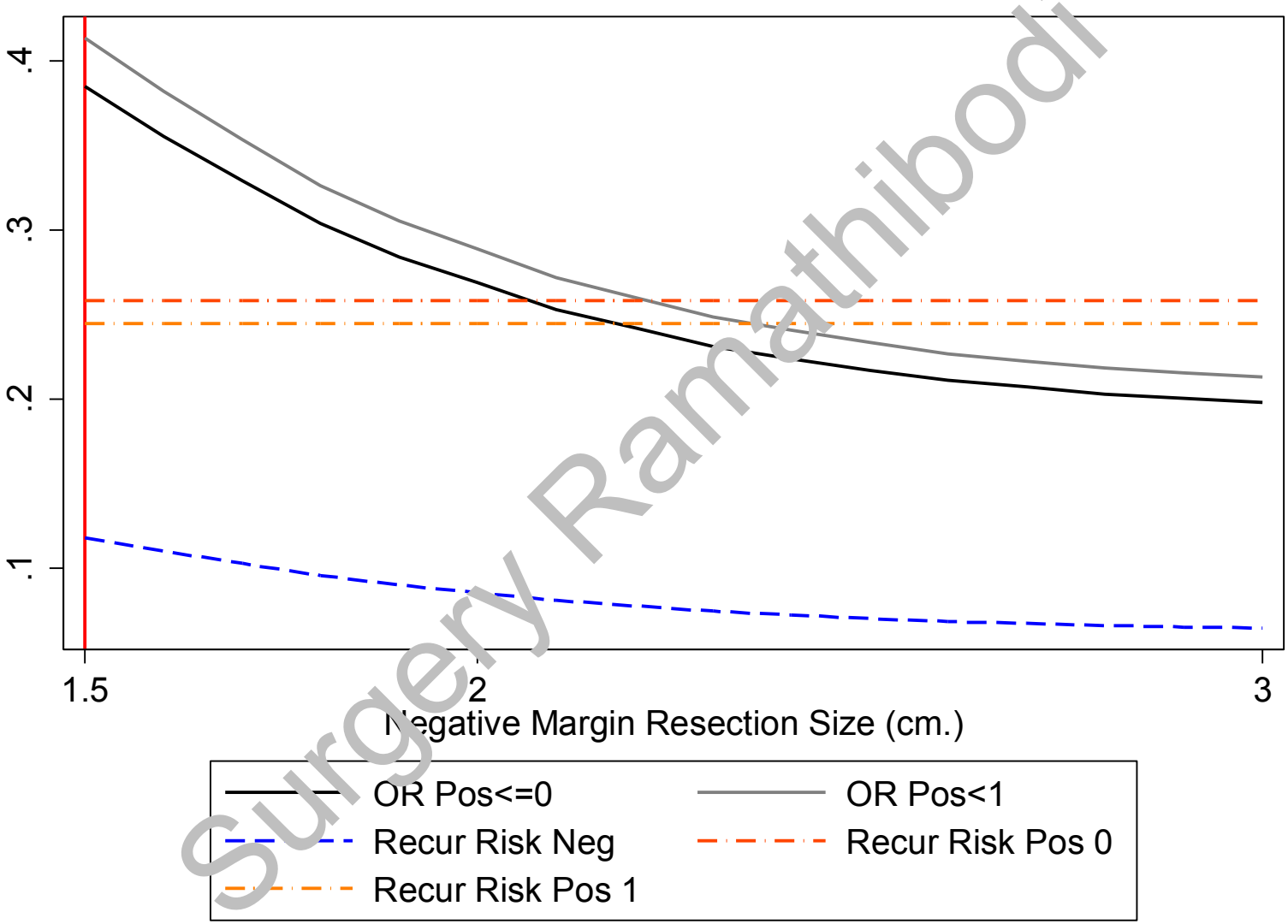
3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.1



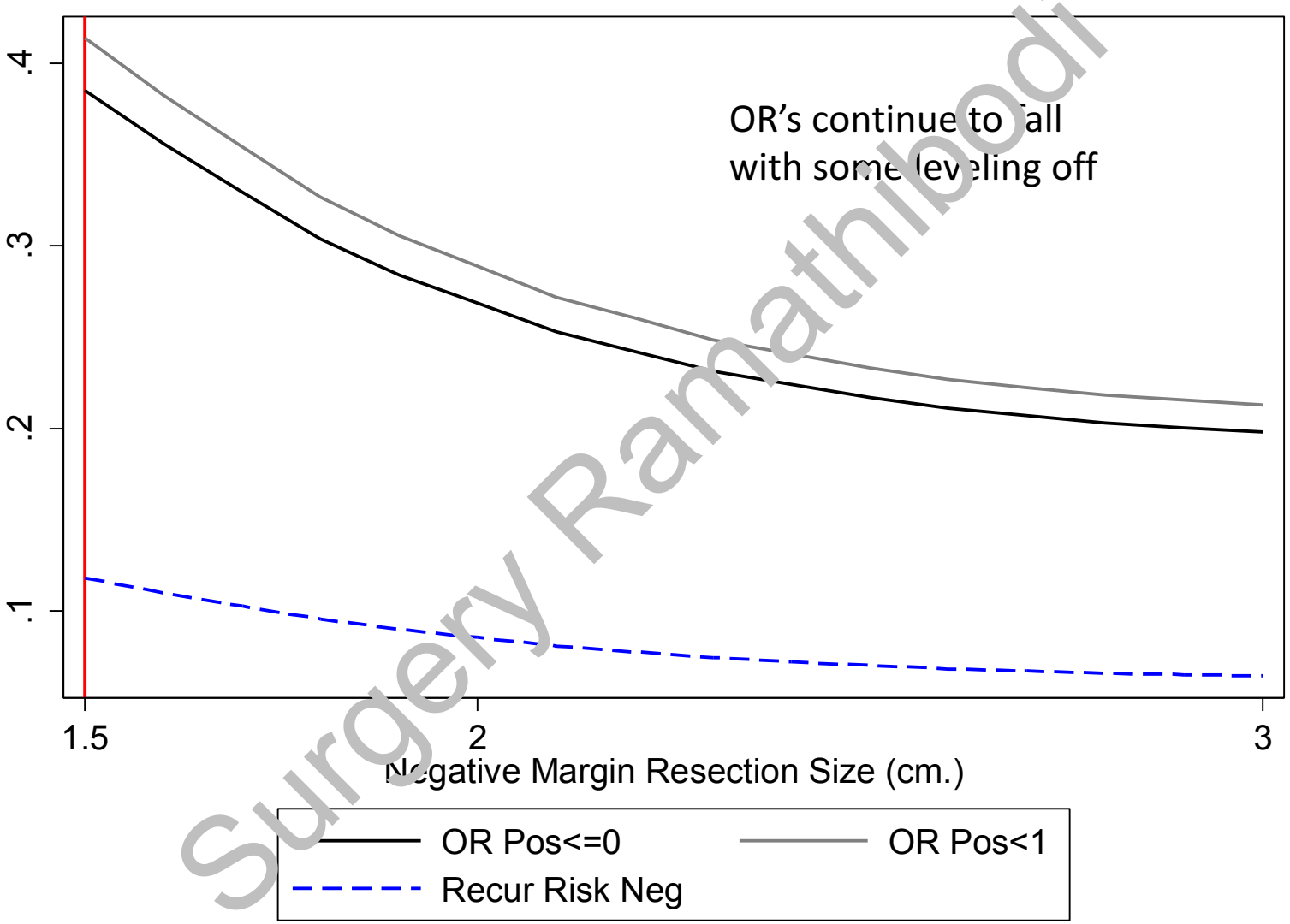
3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.1



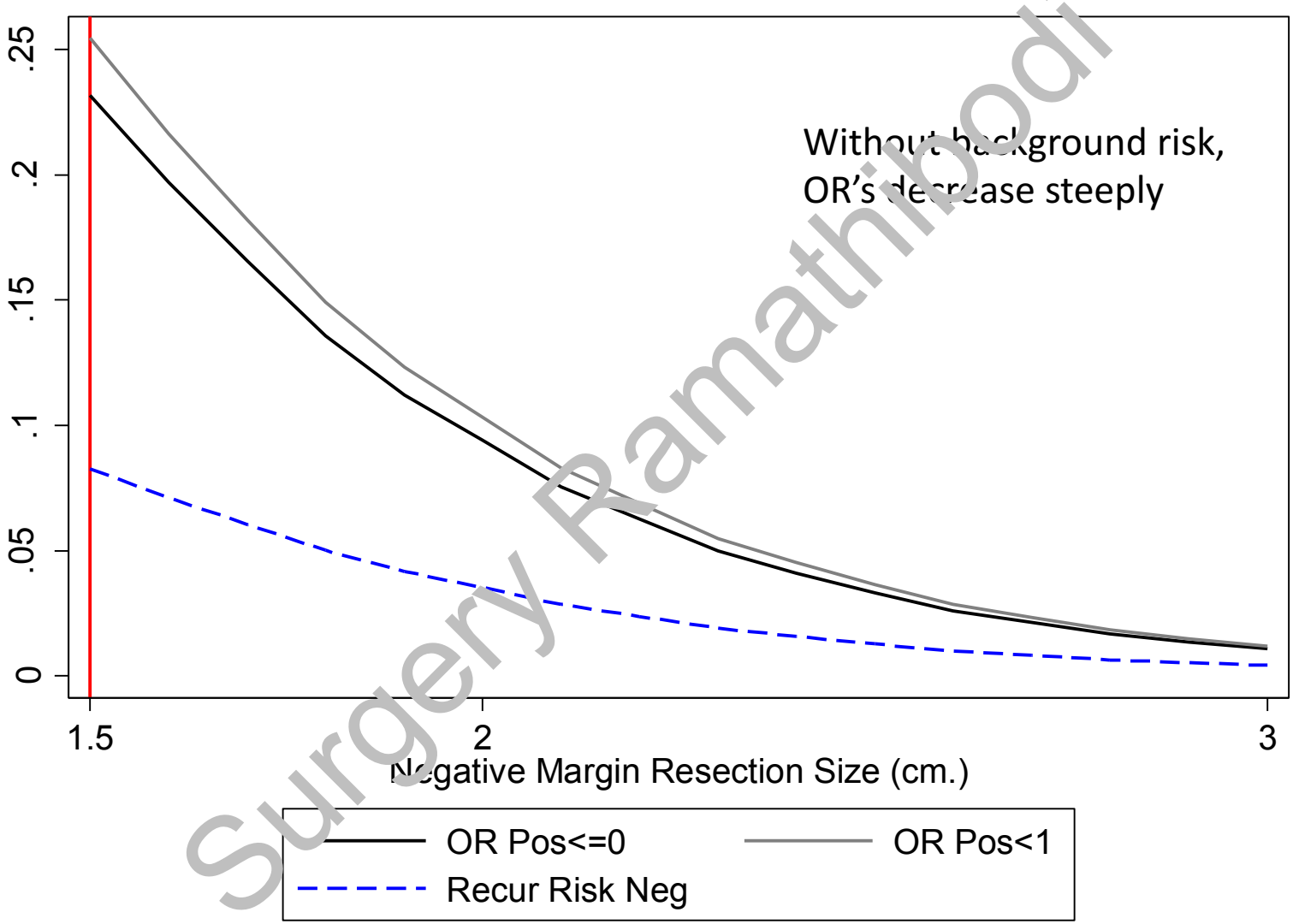
3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 40% undetected CA; v = 0.2



3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 40% undetected CA; v = 0.2



3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 40% undetected CA; v = 0

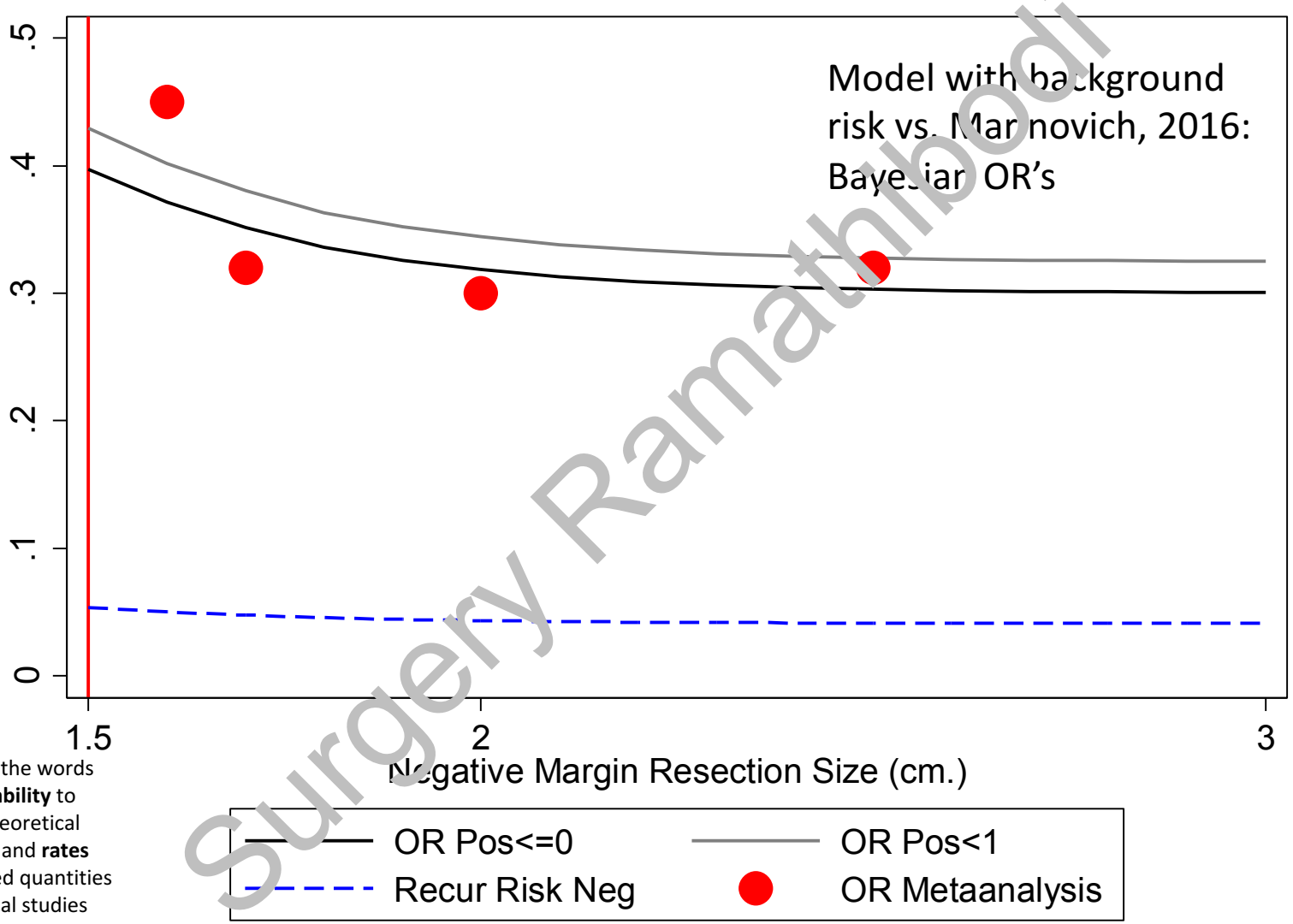


# Model “Fitting”

Similar to what we did for the Houssami data, for the Marinovich data:

- We used DerSimonian & Laird random effects model to estimate frequentist OR’s & Recurrence Rates and used these as data for “fitting” models with variable cutoffs
- But we also have Bayesian estimates; these were used for fitting models with common controls

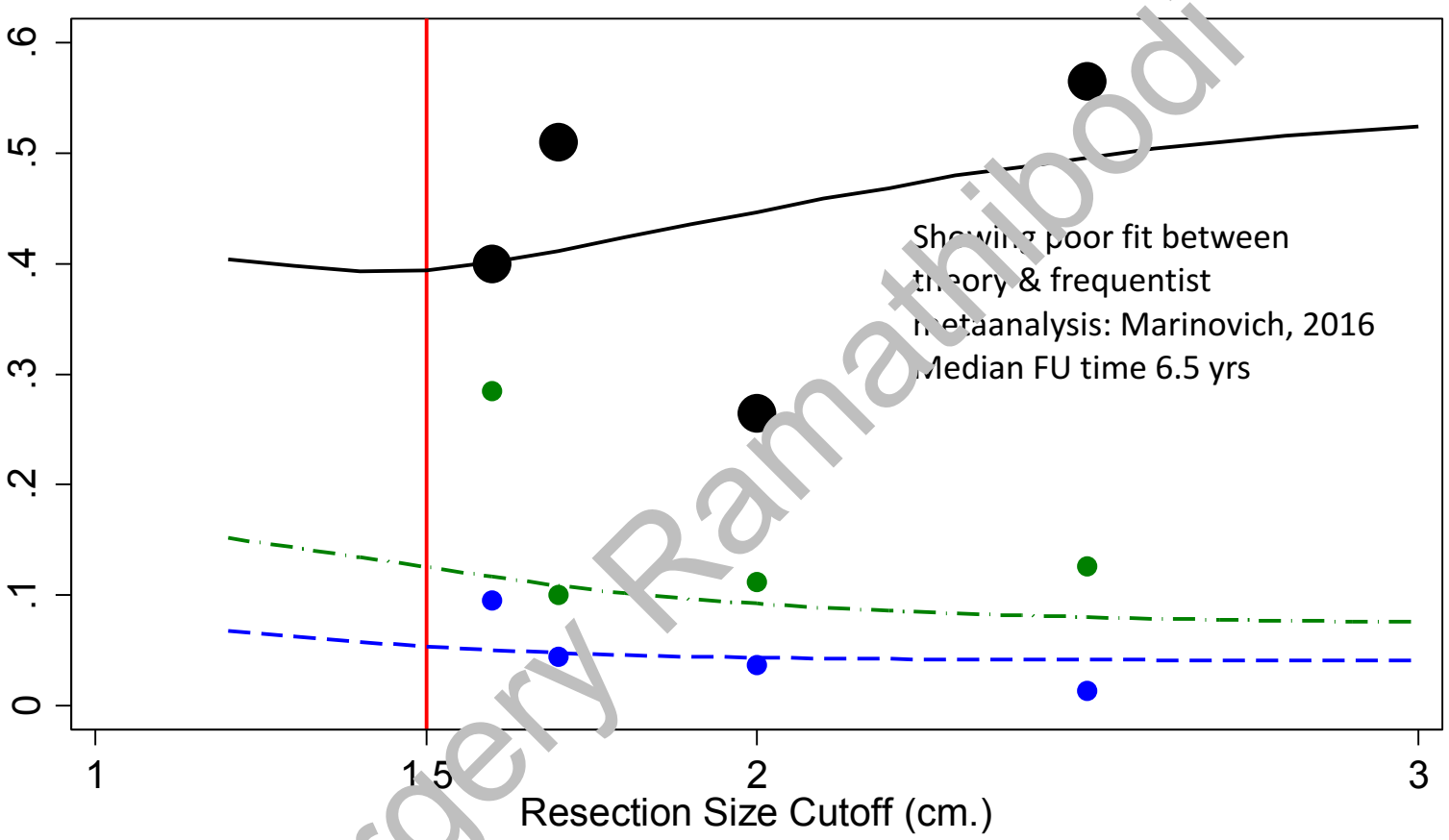
3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4





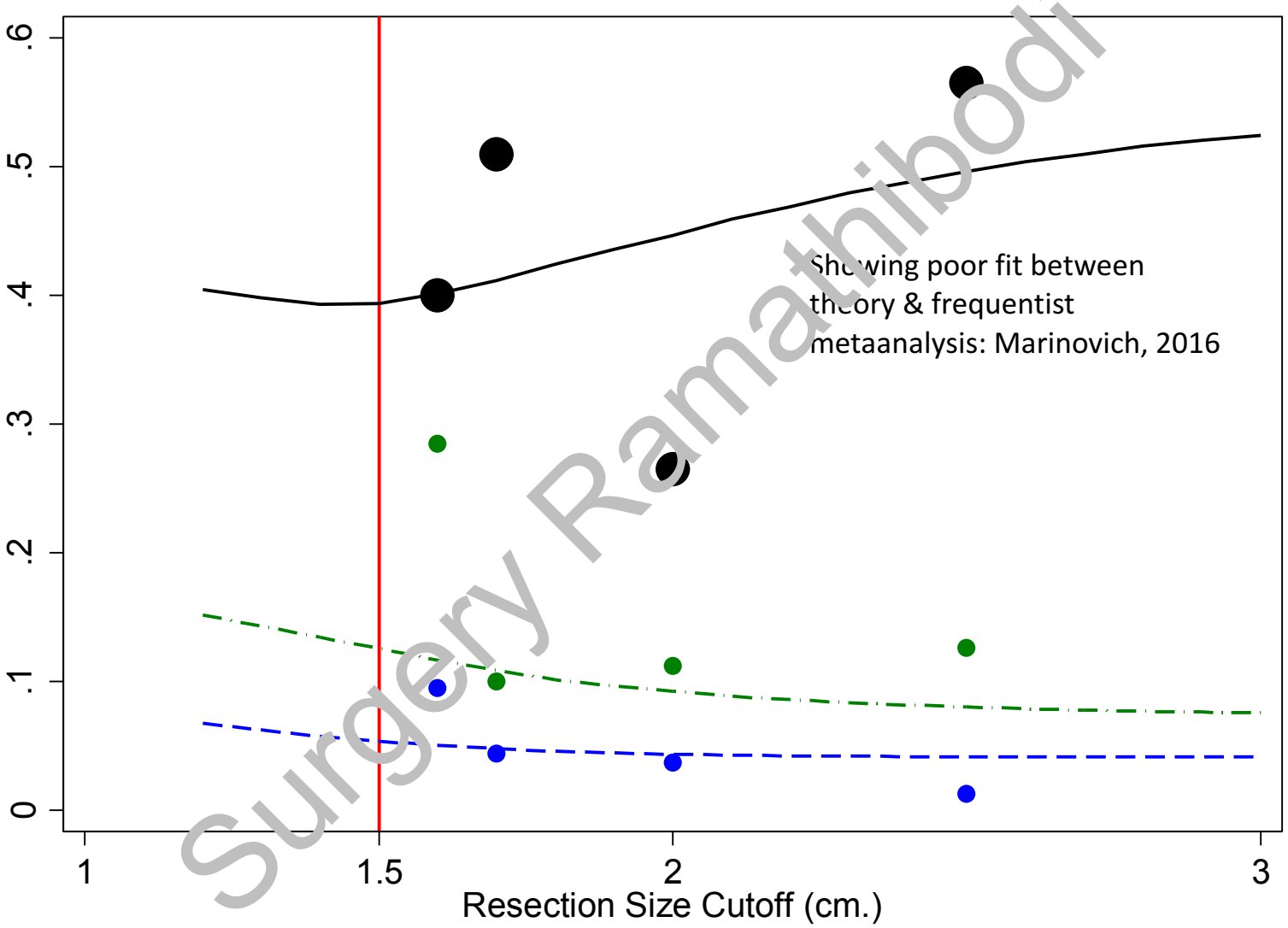

Note: Use the words **risk/probability** to refer to theoretical quantities and **rates** to observed quantities from clinical studies

3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4

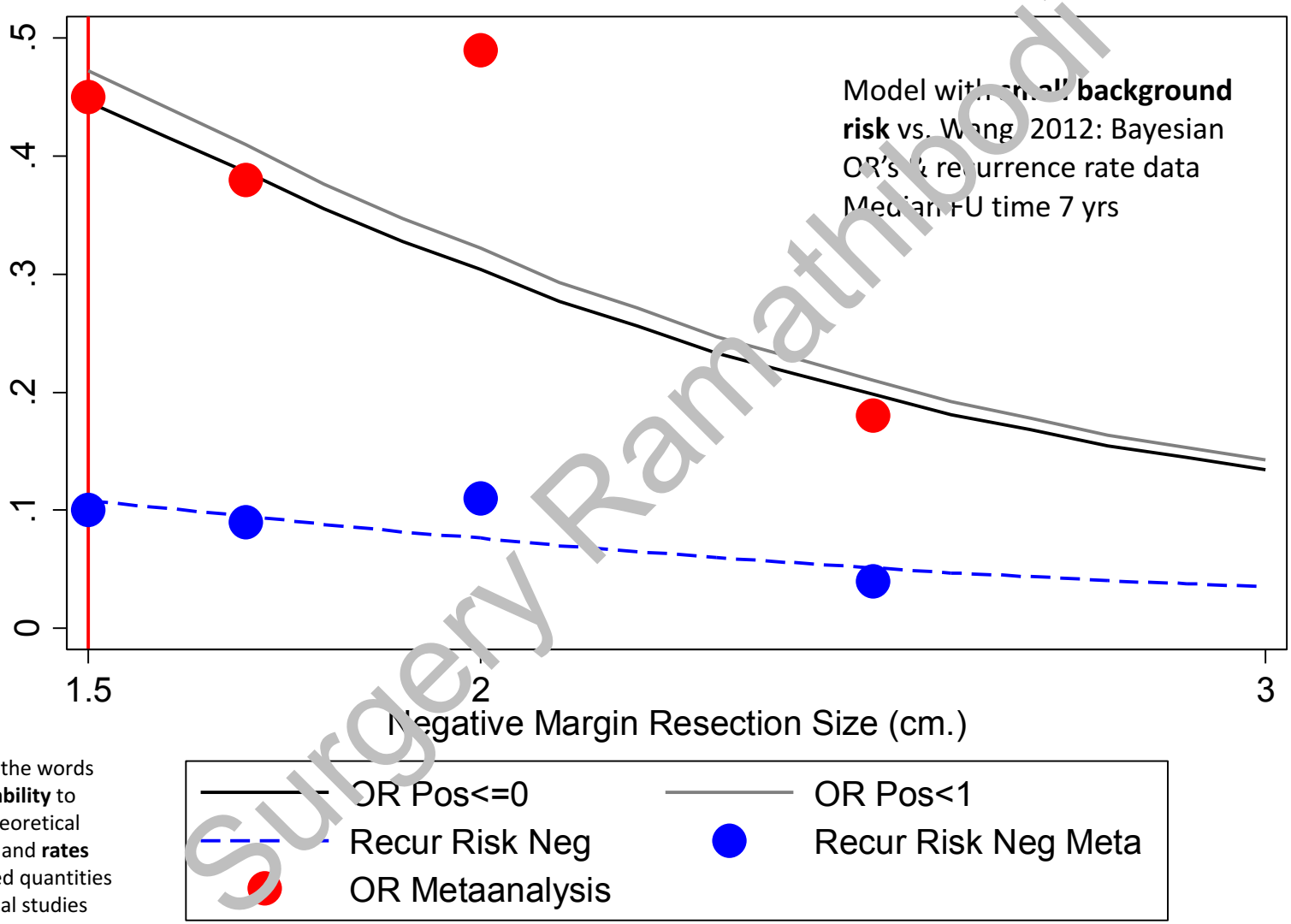



Note: Use the words **risk/probability** to refer to theoretical quantities and **rates** to observed quantities from clinical studies

3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4



3-cm tumor; gammaden(s|2,0.5,1); **0.83** dis free; 50% undetected CA; **v = 0.05**




Note: Use the words **risk/probability** to refer to theoretical quantities and **rates** to observed quantities from clinical studies

# Comments

- What is remarkable is how simple models actually reflect reality to a certain extent
- However, the data is messy and flawed
- There are problems with margin definitions and variation in data collection and surgical practice
- And the models are certainly not very realistic
- So flawed logic corresponds to flawed reality!

# Comments

Some fundamental differences, according to models:

- Houssami & Marinovich "found" significant background risk (Undetected multicentric cancer? High-risk genetic mutations?) while Wang did not
- **Why? Must find out more from their study selection criteria**
- There is more residual cancer at the primary tumor area for DCIS after surgery, while there is more underlying or background cancer risk for IDC

# The OR of Real Interest

- The OR's of real interest, as was also noted in all metaanalyses, are ones contrasting the various cutoffs, or technically the comparison among Recurrence Probabilities of $s \geq s_0, s \geq s_1, s \geq s_2, s \geq s_3$ and so on
- For example in Houssami (2014), the contrast was between $s \geq s_1$ and the rest (0, 2, 5 mm), and in Marinovich (2016) it was 0-1 against 2, 3-5, 10 mm
- We will do theoretical calculations for these

# The OR of Real Interest

- In the metaanalyses, the OR's were obtained *indirectly* by way of statistical modeling: as estimated coefficient-parameter values of a covariate-adjusted GLMM or via "analogous" Bayesian models
- Here, we will calculate in our usual, direct way
- Then we will compare theoretical values with statistical estimates from metaanalyses

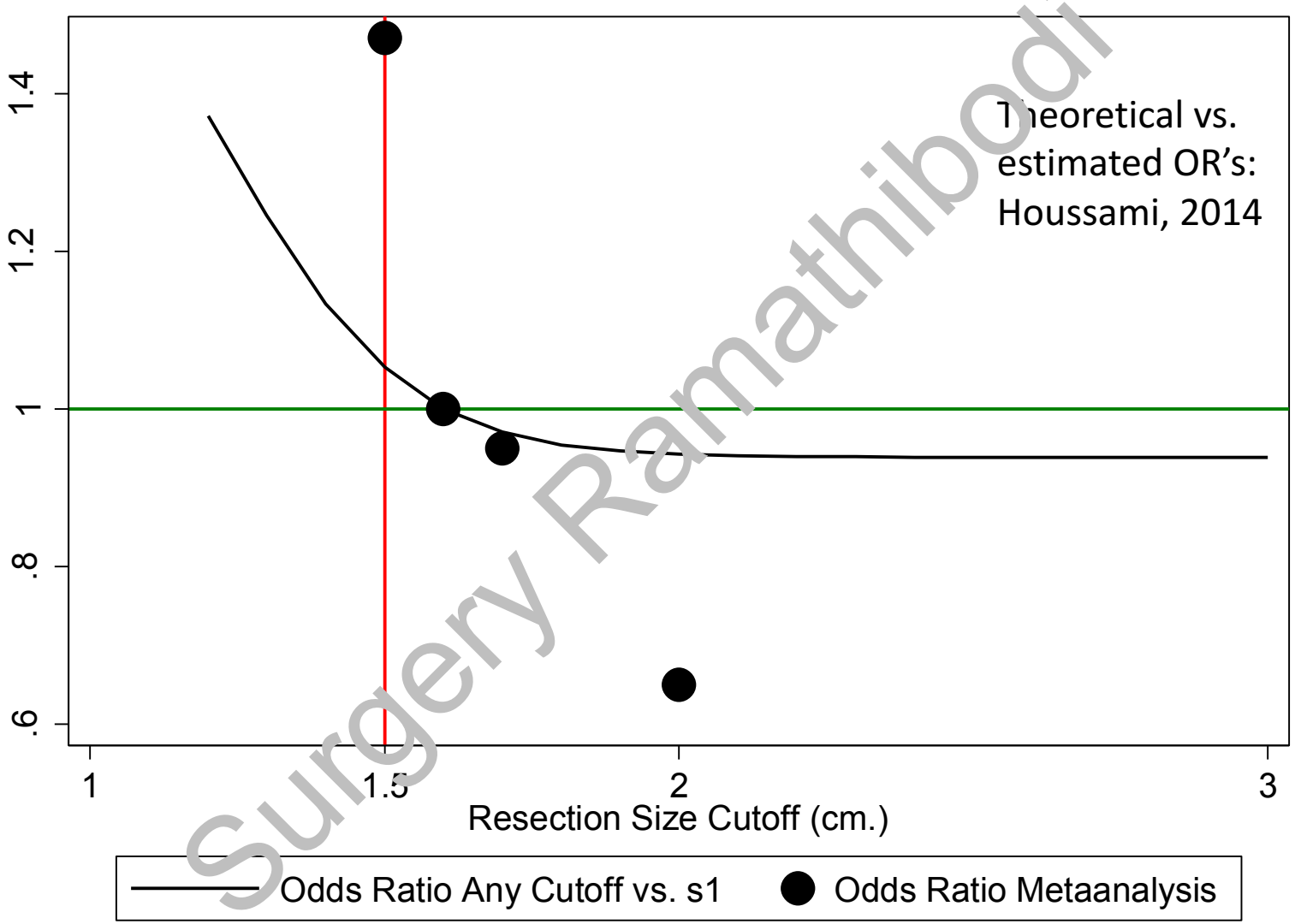
# Recurrence Probabilities

We contrast recurrence probabilities of cutoff 1 mm with all others (background risk assumed)

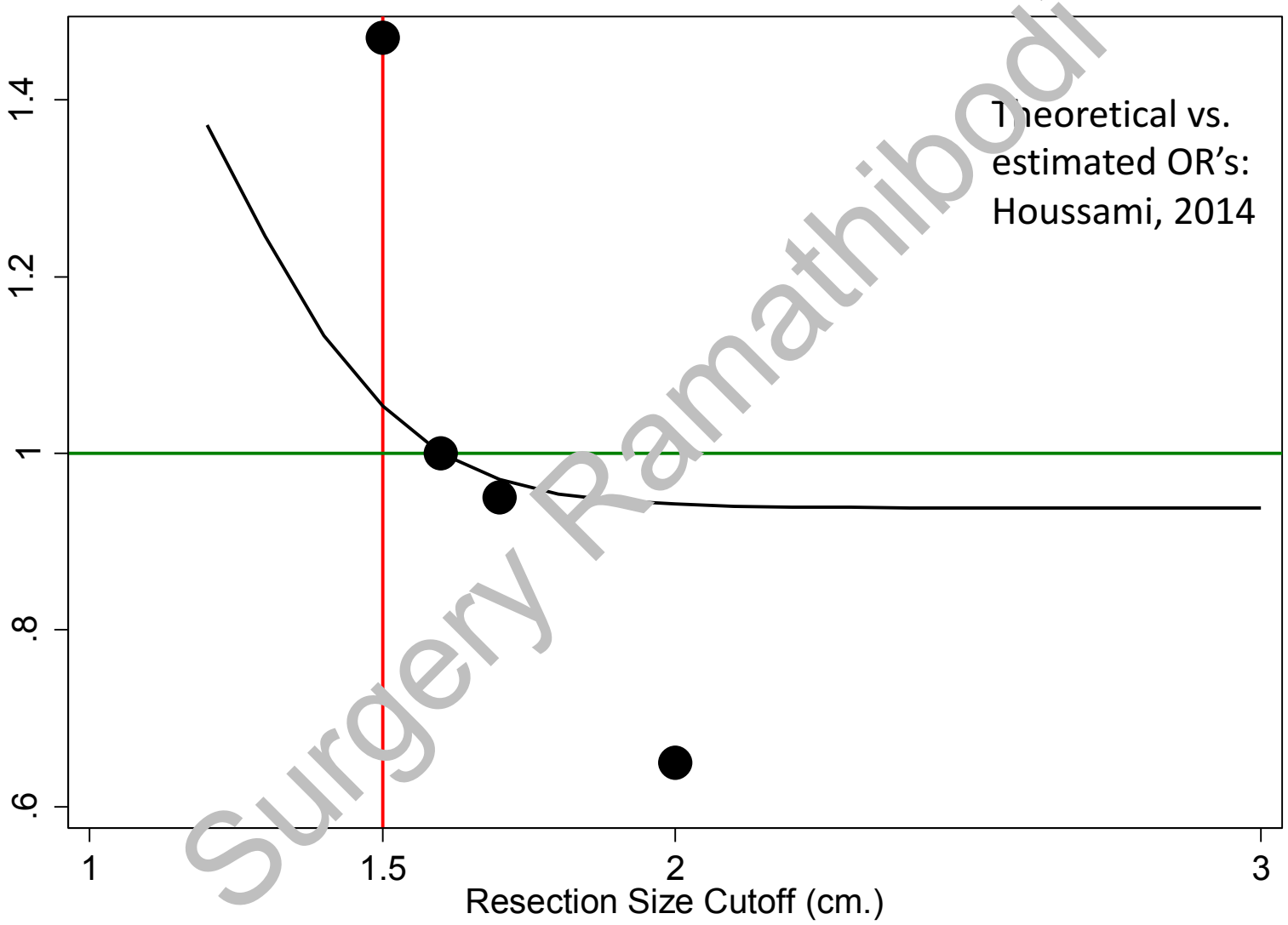
- $\Pr(\geq s_1) = \left[\int_{s_i}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r)dr\right] / g(s_1, \infty)$
- $\Pr(\geq s_k) = \left[\int_{s_k}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r)dr\right] / g(s_k, \infty)$

- Where k is 0 or 2, 3, 5, 10 mm, etc.

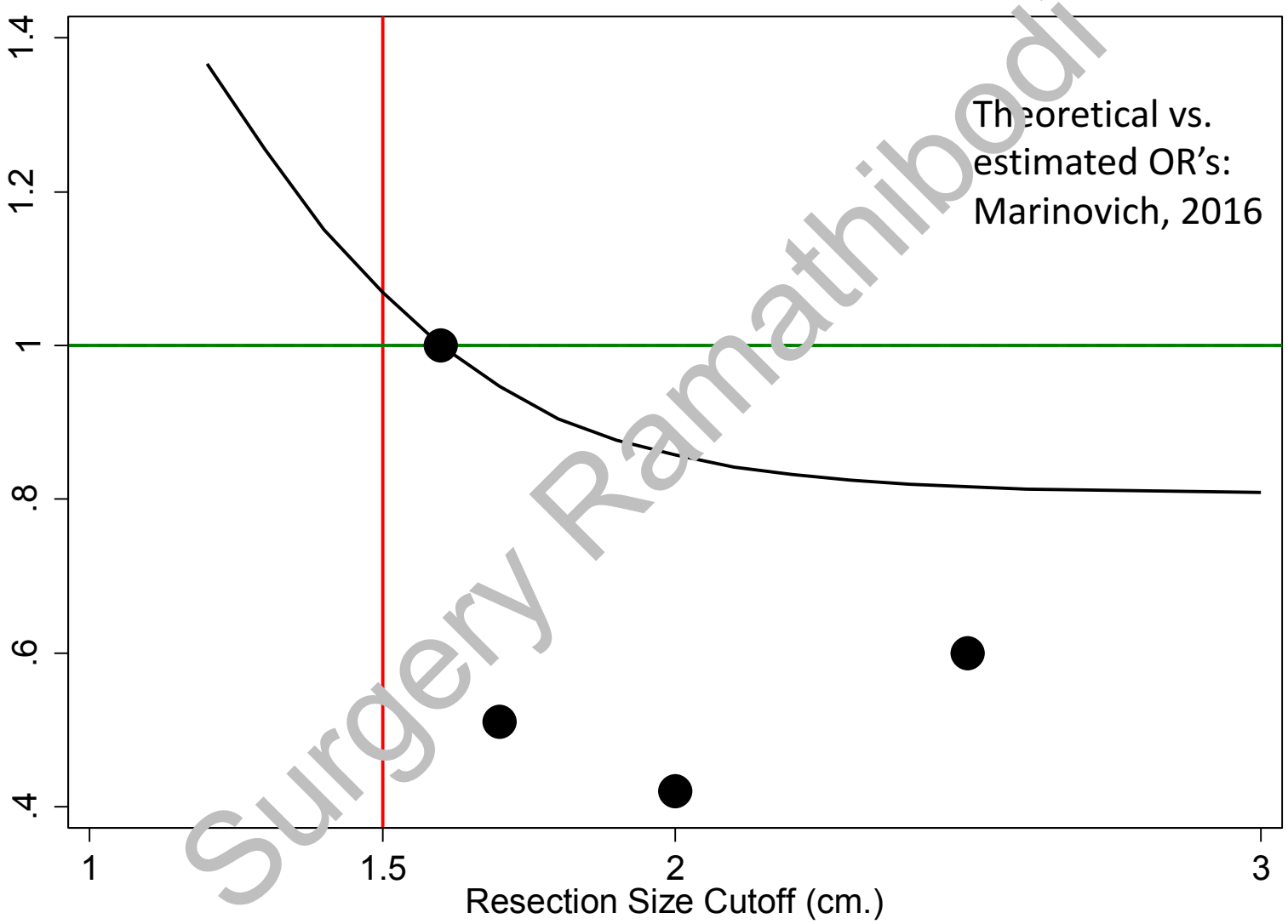
3-cm tumor; gammaden(s|2,0.5,1); **0.94** dis free; 20% undetected CA; **v = 0.6**



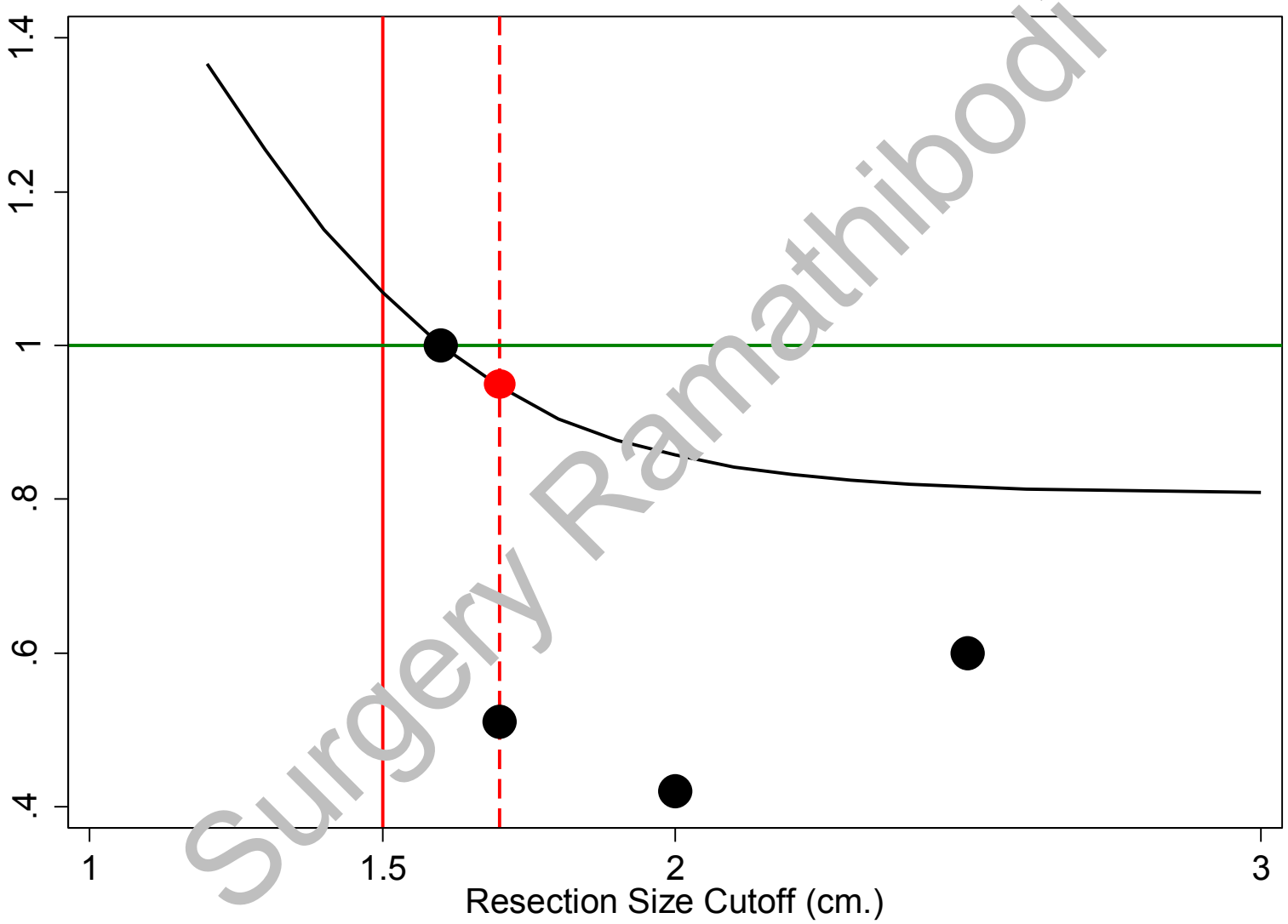
3-cm tumor; gammaden(s|2,0.5,1); **0.94** dis free; 20% undetected CA; **v = 0.6**



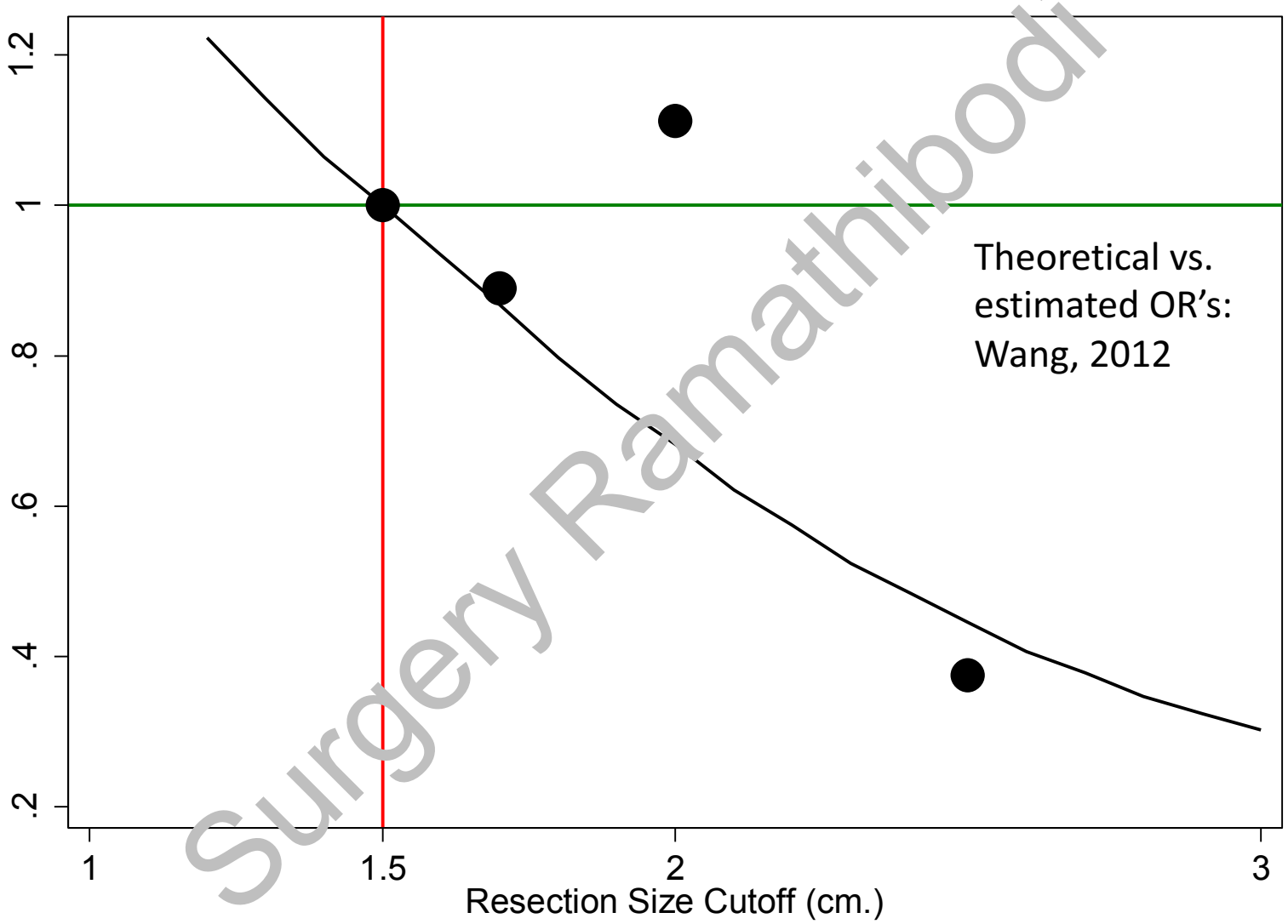
3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4



3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4



3-cm tumor; gammaden(s|2,0.5,1); **0.83** dis free; 50% undetected CA; **v = 0.05**



# Comments

- Theoretical OR's and those from metaanalyses do not correspond as well as may be expected
- Even though most theoretical values are included in the corresponding 95% CI's (close to the limits!)
- Although again there was only one "outlier" for the Wang data

# Comments

- **Houssami data & fitted** theoretical values suggest no great differences among > 0, 1, 2 mm margins, and also an early leveling of OR values
- **Marinovich fitted values** suggest similarly that > 0, 1, 2 mm margins are not so different as *the data seem to say*; but there is later leveling
- **Wang data & fitted** values suggest something else entirely: large differences among all cutoffs of interest and no leveling

# Comments

What does this all mean?

- For Houssami & Marinovich:
- Theoretically, with some input from metaanalyses, there seem to be no great differences in terms of local recurrence if margins are free (> no ink on tumor) whether for invasive or noninvasive cancers
- But for Wang:
- Theoretically, the wider the margin, the lower the risk of local recurrence, and substantially so

# Comparing Precise Margins

- As a theoretical exercise, we can compare recurrence probabilities between each *precise* margin, e.g. comparing 1 mm precisely with 2 mm precisely (not ≥ 1 mm with ≥ 2 mm)
- This is probably the **ideal comparison**
- But this can be difficult to do in reality, since it would require a **large number of patients** with very precisely defined margin of resection for each and every margin

# Comparing Precise Margins

- However, this is very easy to do theoretically
- We can then contrast how the OR's differ between different ways of defining margins: between precise and open ended definitions (as was done previously)

# Comparing Precise Margins

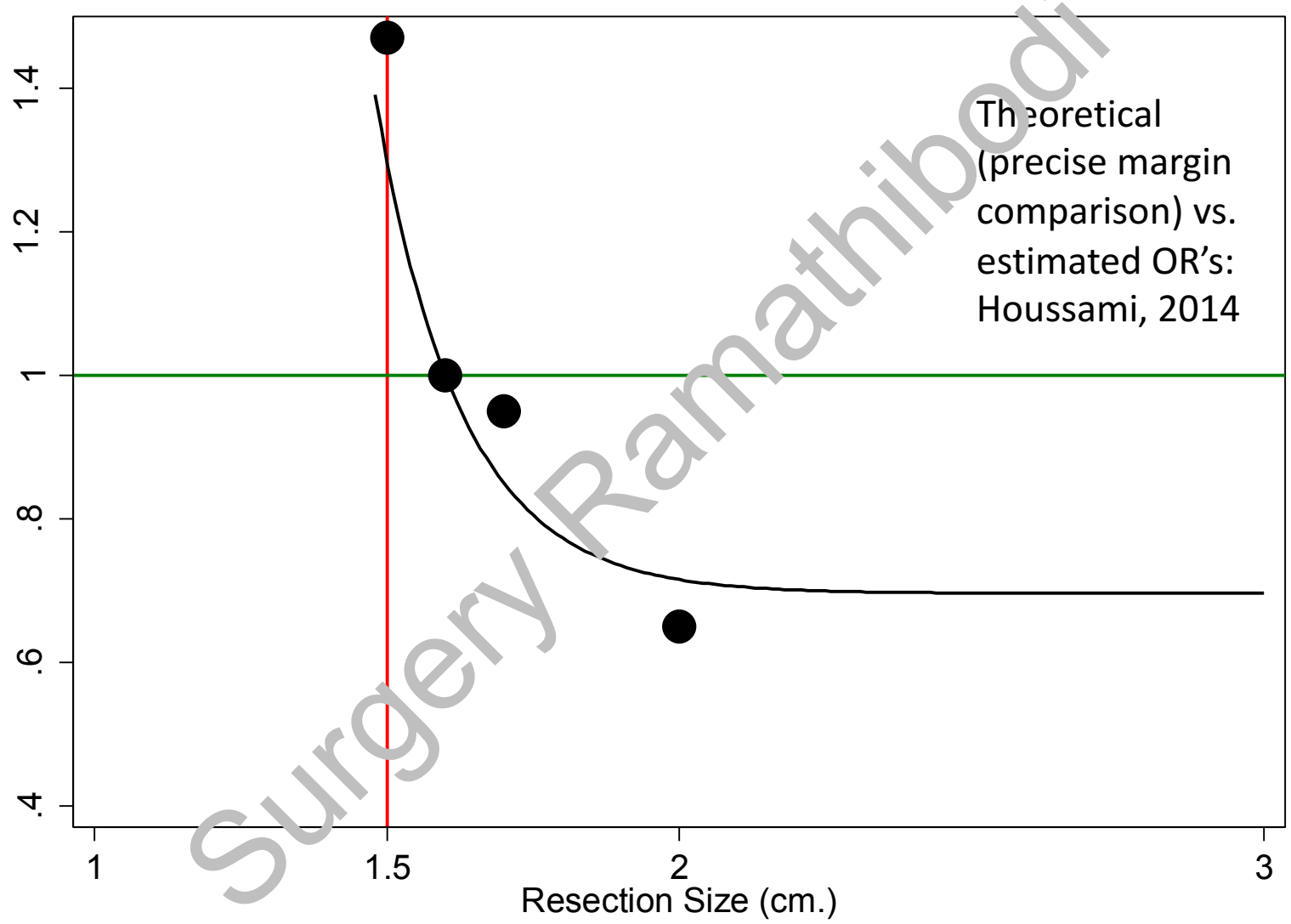
The Recurrence Probabilities are, for $s > s_0$,

- $\Pr(= s_1) = \left\{1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(s_1 - s_0)} s_1^2 - \nu_0\right)\right\}$
- $\Pr(= s_i) = \left\{1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(s_i - s_0)} s_i^2 - \nu_0\right)\right\}$

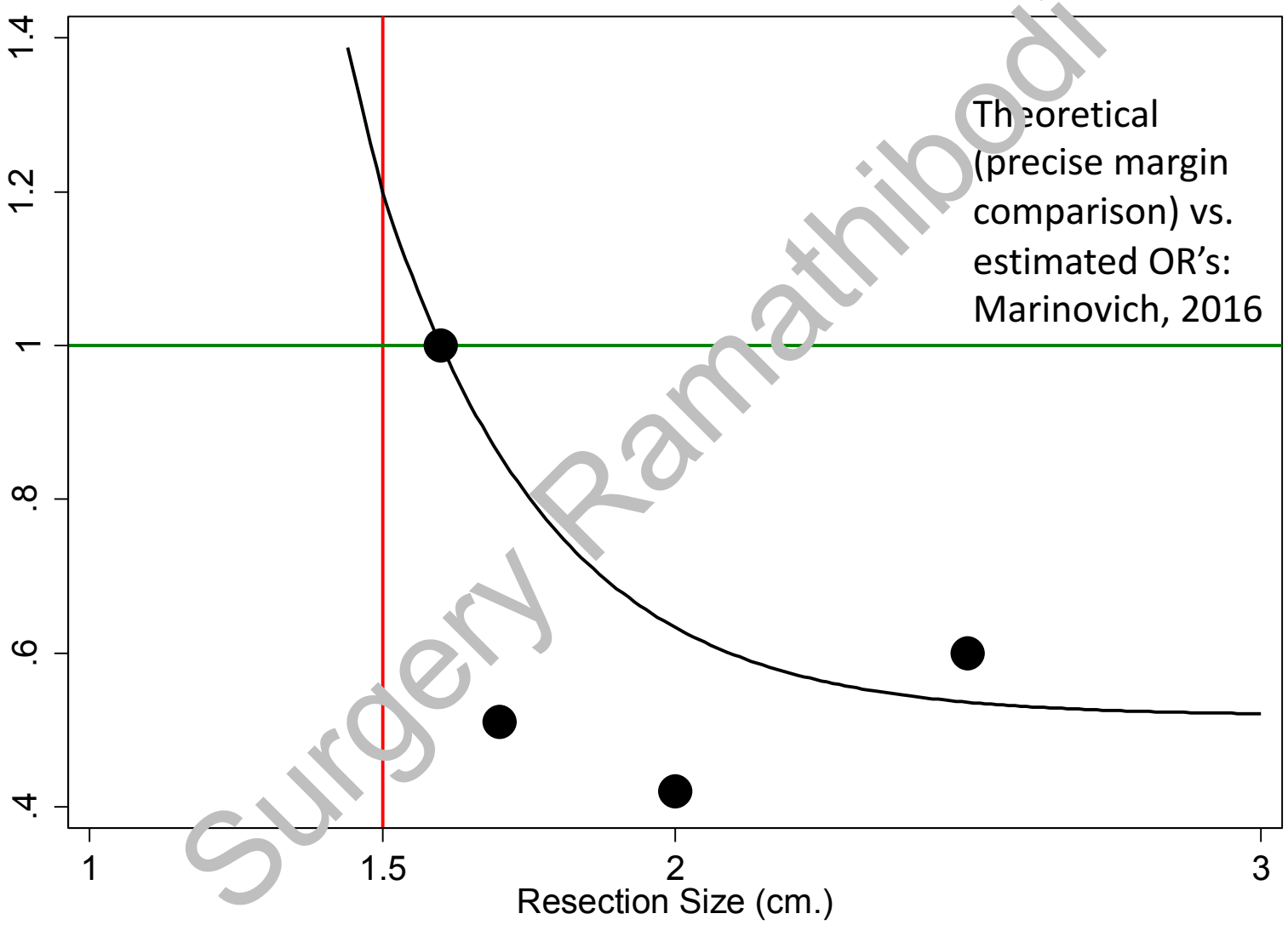
The Odds Ratio of margin $i$ compared with 1 is, asymptotically as $s_i \to \infty$,

$$OR = \frac{e^{-\frac{\phi}{\epsilon} e^{-\epsilon(s_1 - s_0)} s_1^2} (1 - e^{-\nu_0})}{1 - e^{-\frac{\phi}{\epsilon} e^{-\epsilon(s_1 - s_0)} s_1^2 - \nu_0}}$$

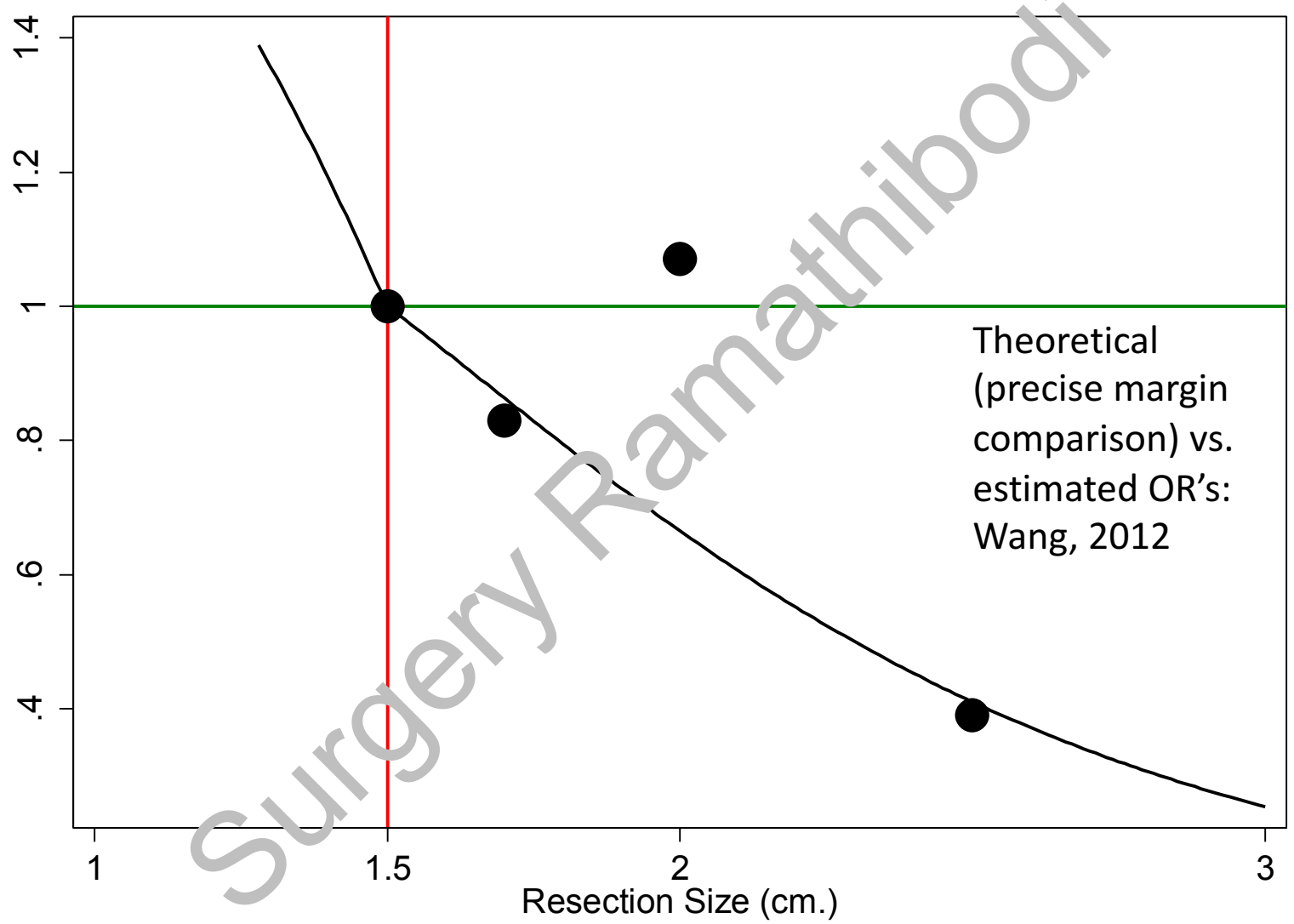
3-cm tumor; gammaden(s|2,0.5,1); **0.94** dis free; 20% undetected CA; **v = 0.6**



3-cm tumor; gammaden(s|2,0.5,1); **0.91** dis free; 30% undetected CA; v = 0.4



3-cm tumor; gammaden(s|2,0.5,1); **0.83** dis free; 50% undetected CA; **v = 0.05**



# Comments

- Precise margin comparisons fit the data much better than the open-ended margin comparisons
- I am not really sure why
- Models for Houssami & Marinovich have a similar pattern though the model for Marinovich has deeper fall in OR's and later leveling
- And there is considerable attenuation of the OR between 1mm & 2 mm margins
- Whatever we do, theory always fit Wang's data!

# Comments

- Back to the original question: can resections with positive margins be left alone (no further surgery) in some instances?
- Can patients with DCIS be left alone even if margins are just > 0 mm?
- Theoretically yes – if this is a **minimal addition** to what is already there in terms of undetectable/ undetected cancer and background risk