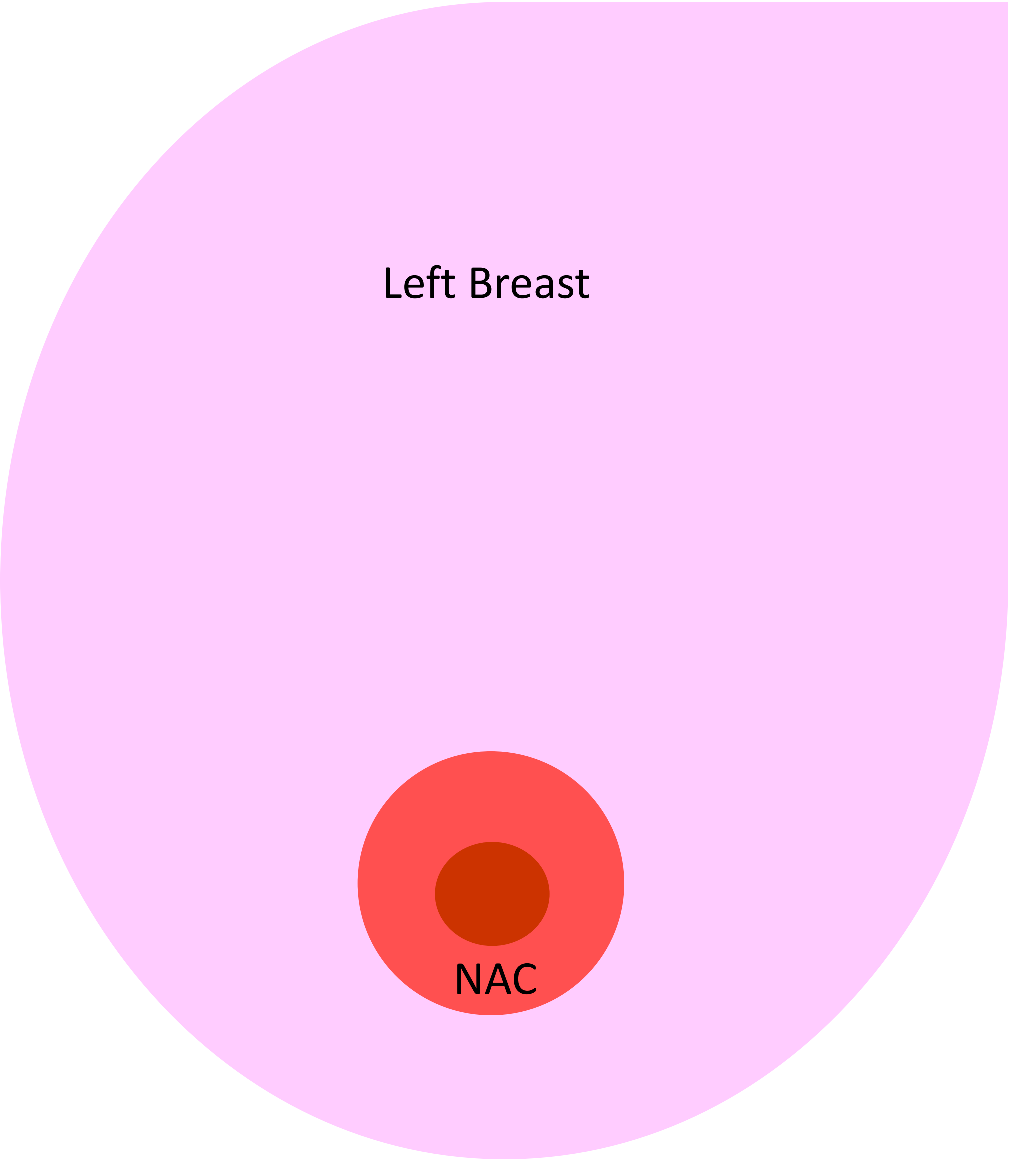
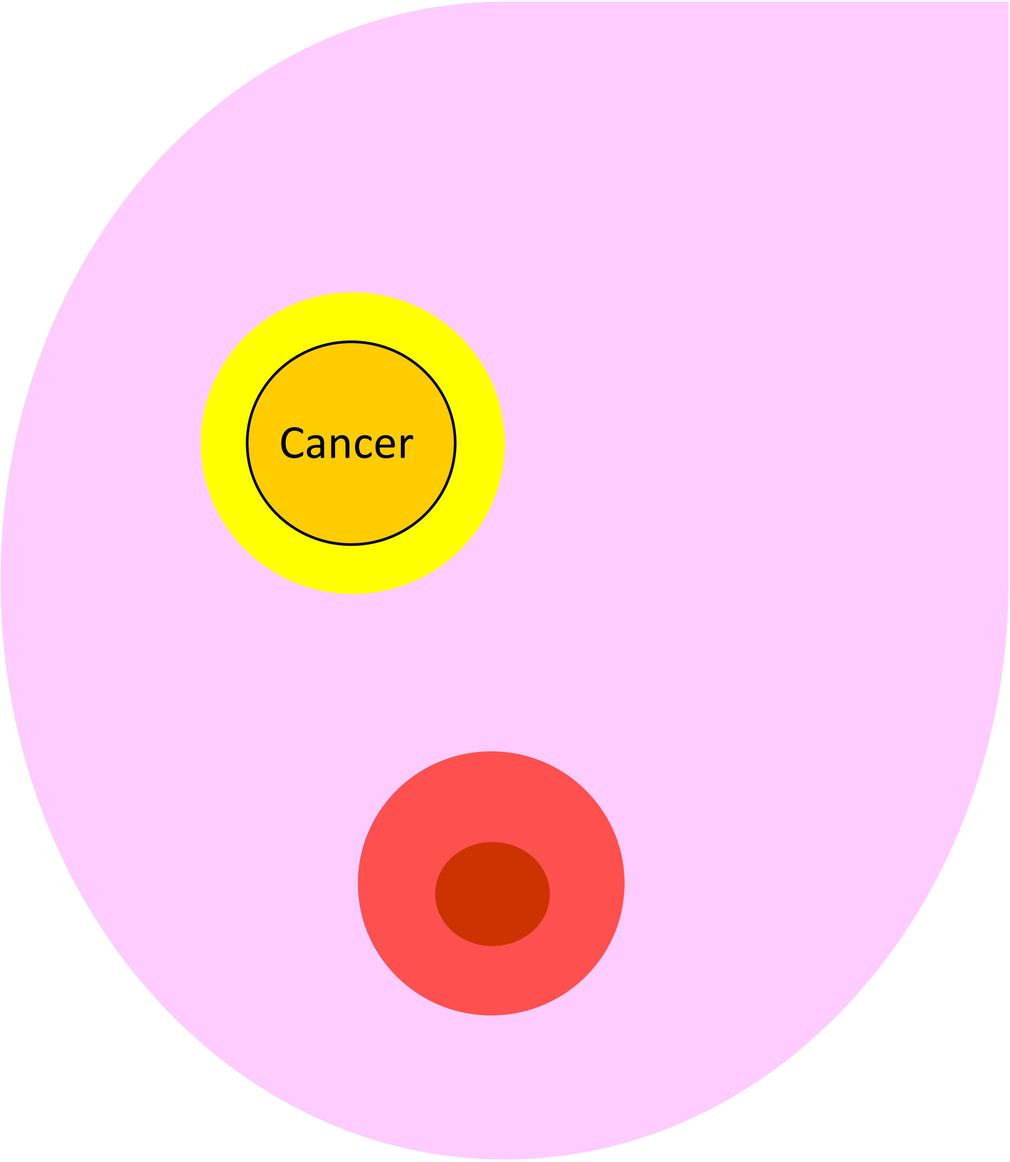
A Model of BCS and the Odds Ratio of Negative vs. Positive Margins (Part 1)

7 July 2018

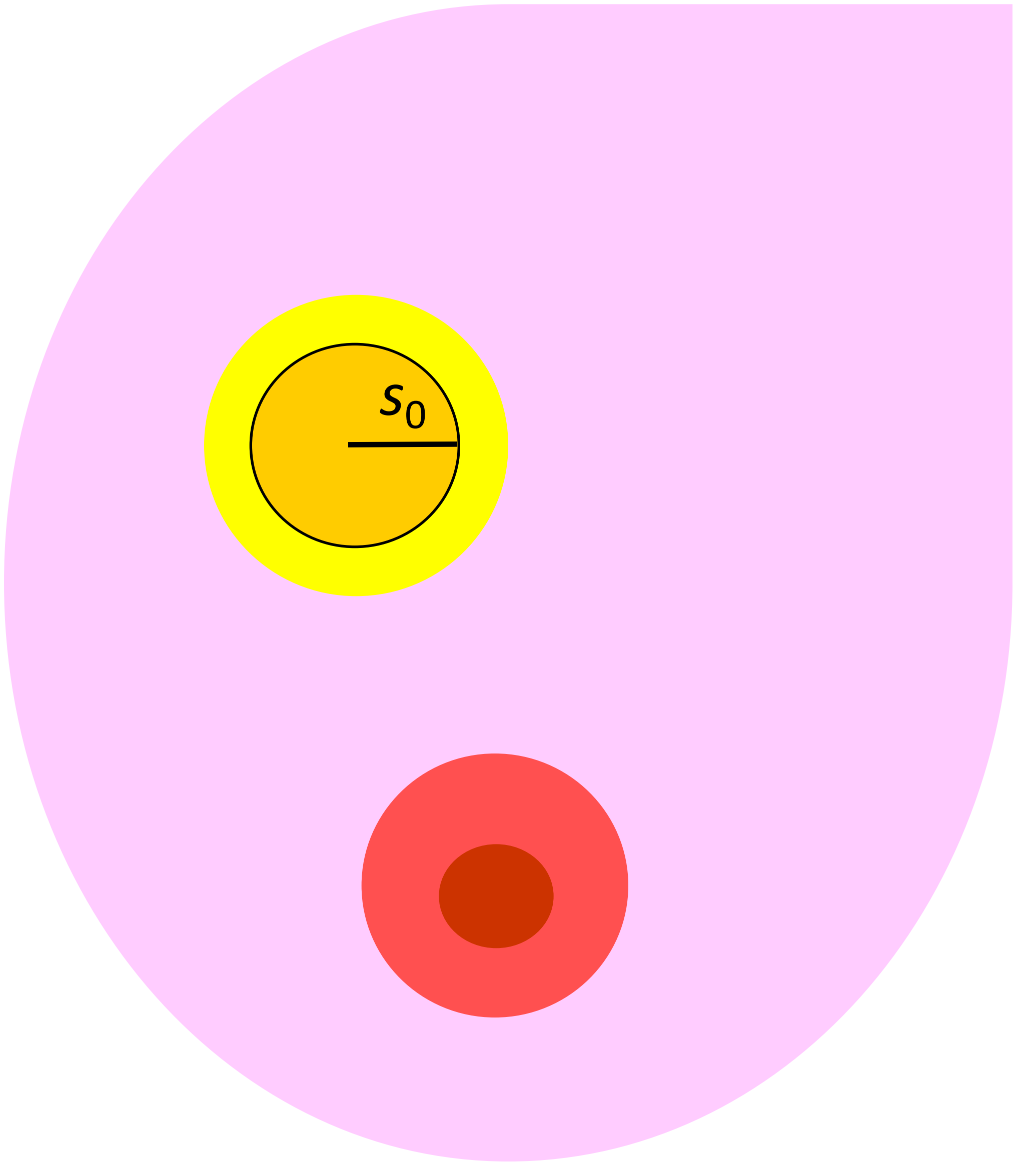
Model Assumptions

- The tumor/cancer is **spherical** (& unicentric)
- The **detected tumor** is **not all** existing tumor
- Excision is a spherically symmetric "coring out" of the tumor/cancer area
- The locoregional recurrence **hazard is proportional to** the **residual tumor**, and **time since surgery**
- **FU time** is the same for all patients
- **Independent censorship**
- The **surgeon's ability to excise cancer** is expressed as a simple probability distribution function
- Mathematical functions representing these assumptions should be as simple as possible

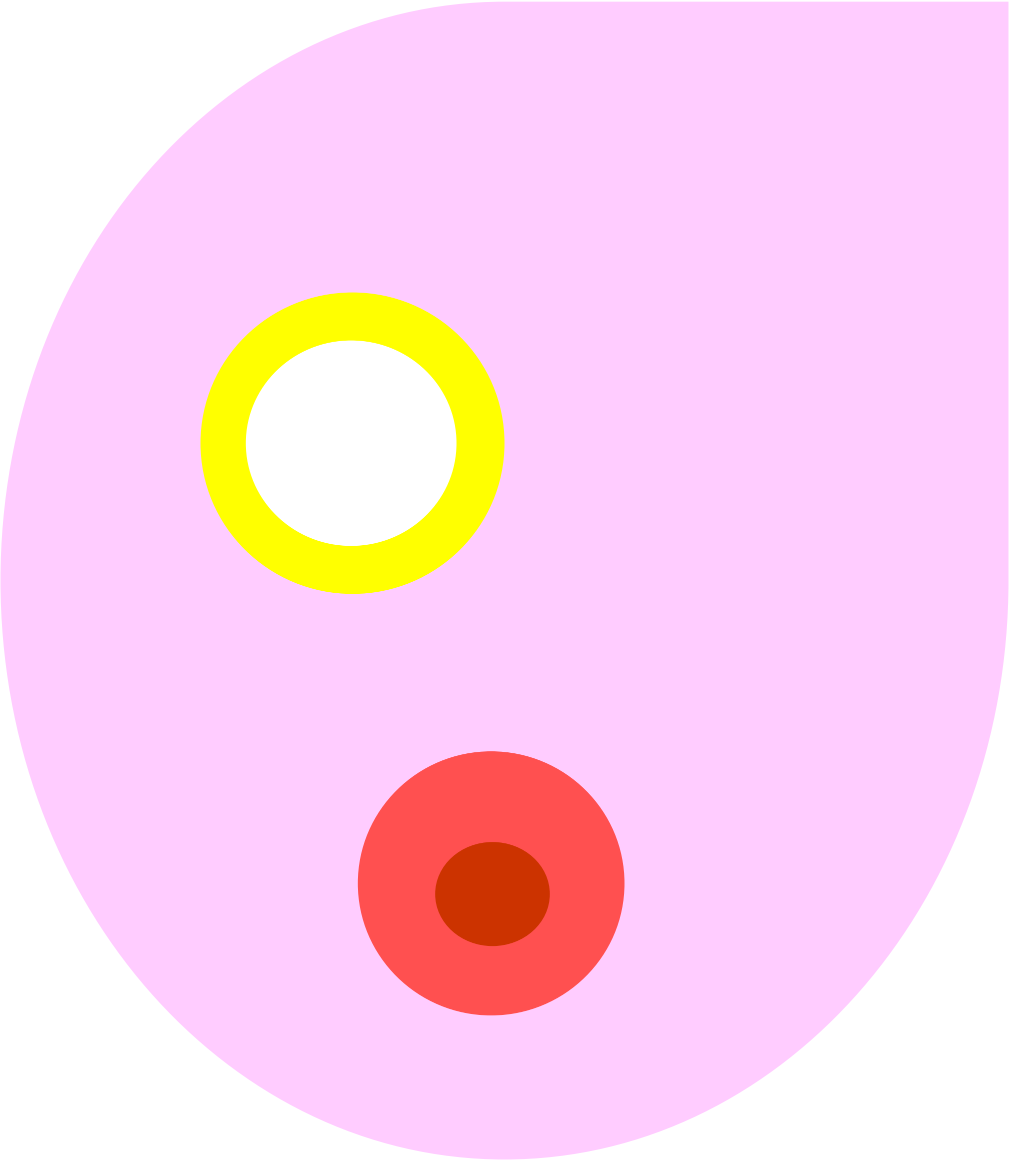

Left Breast
NAC



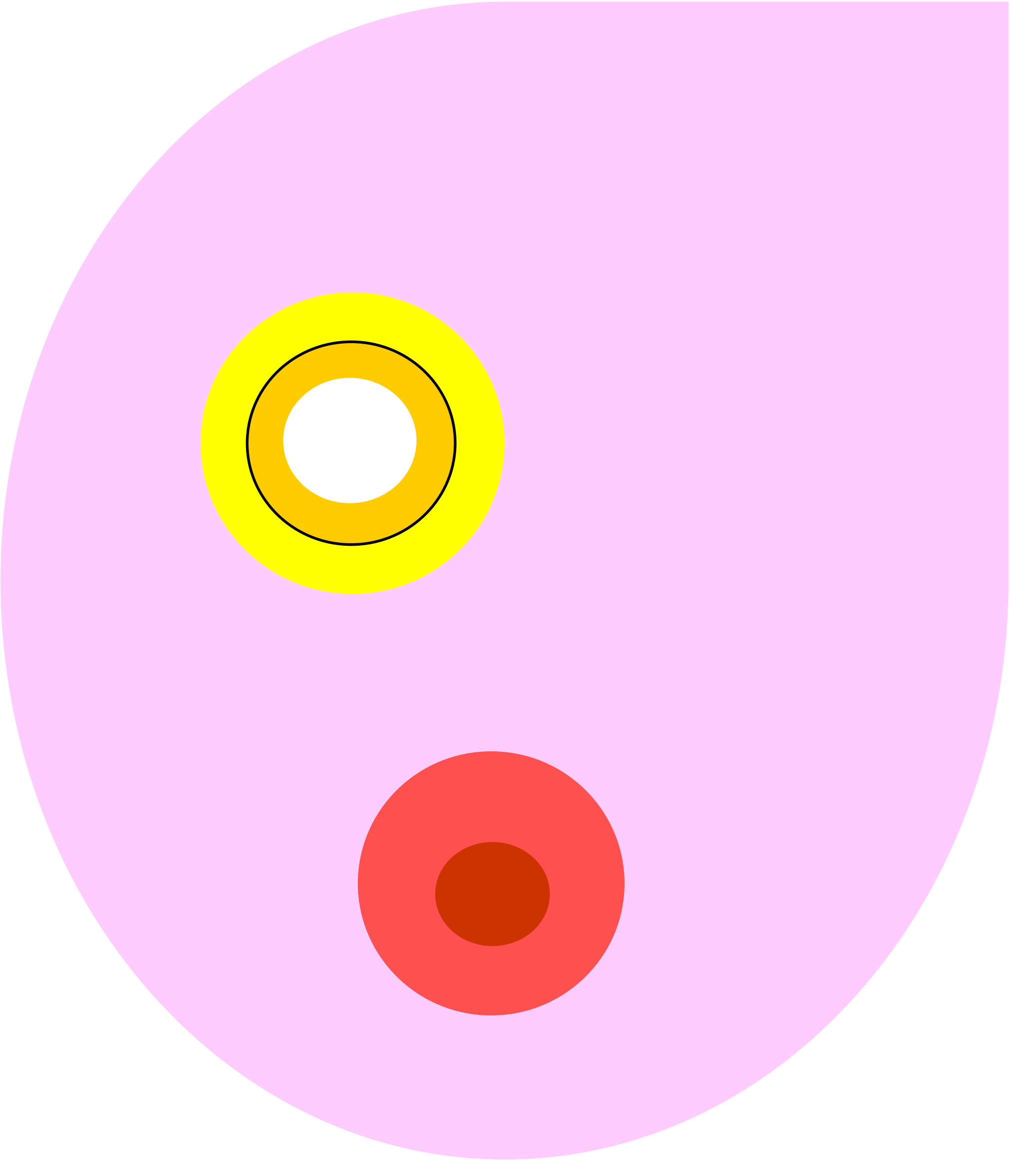
Detected cancer (orange) and peripheral undetected cancer (yellow)



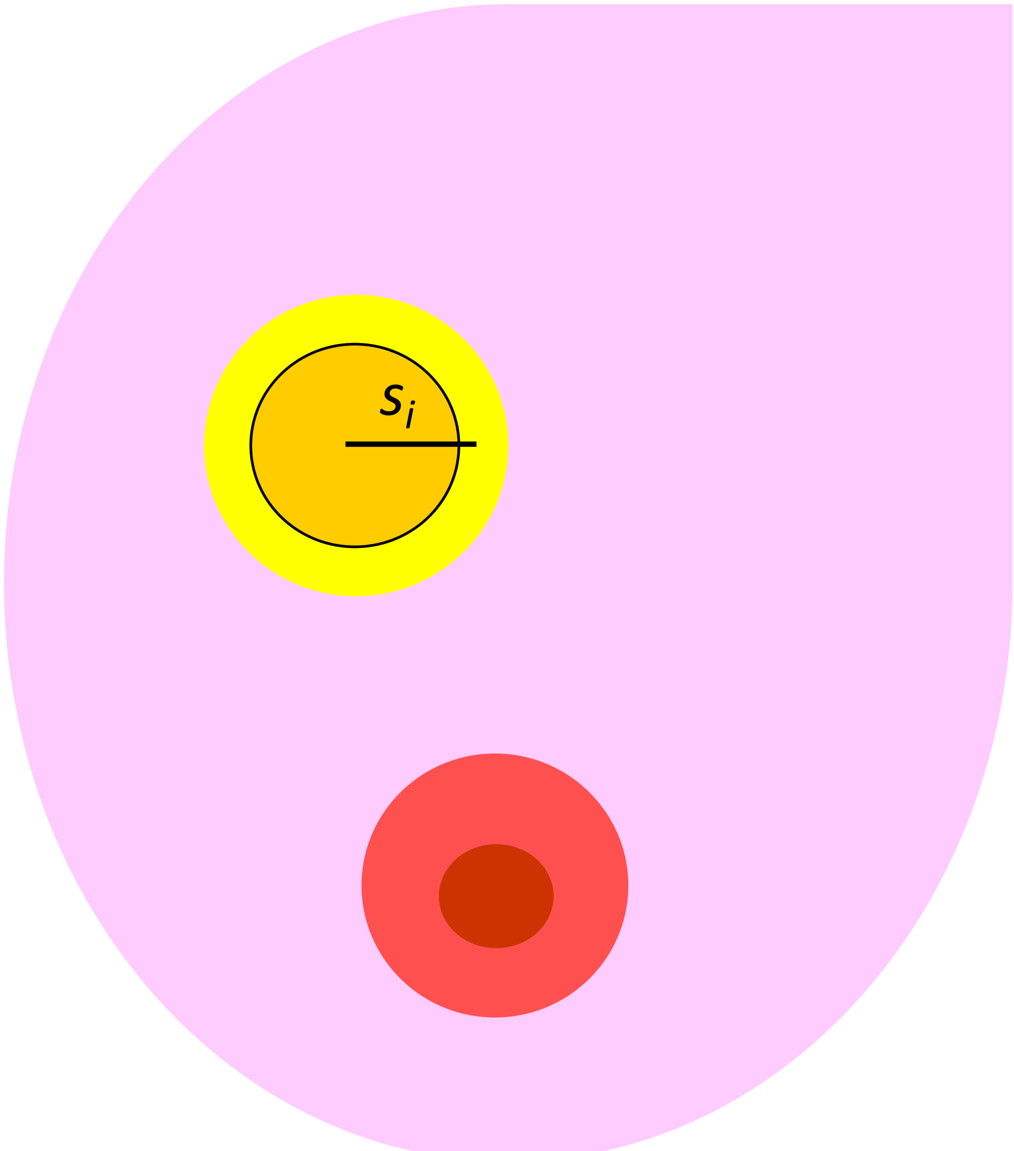
s_0 is the detected tumor size



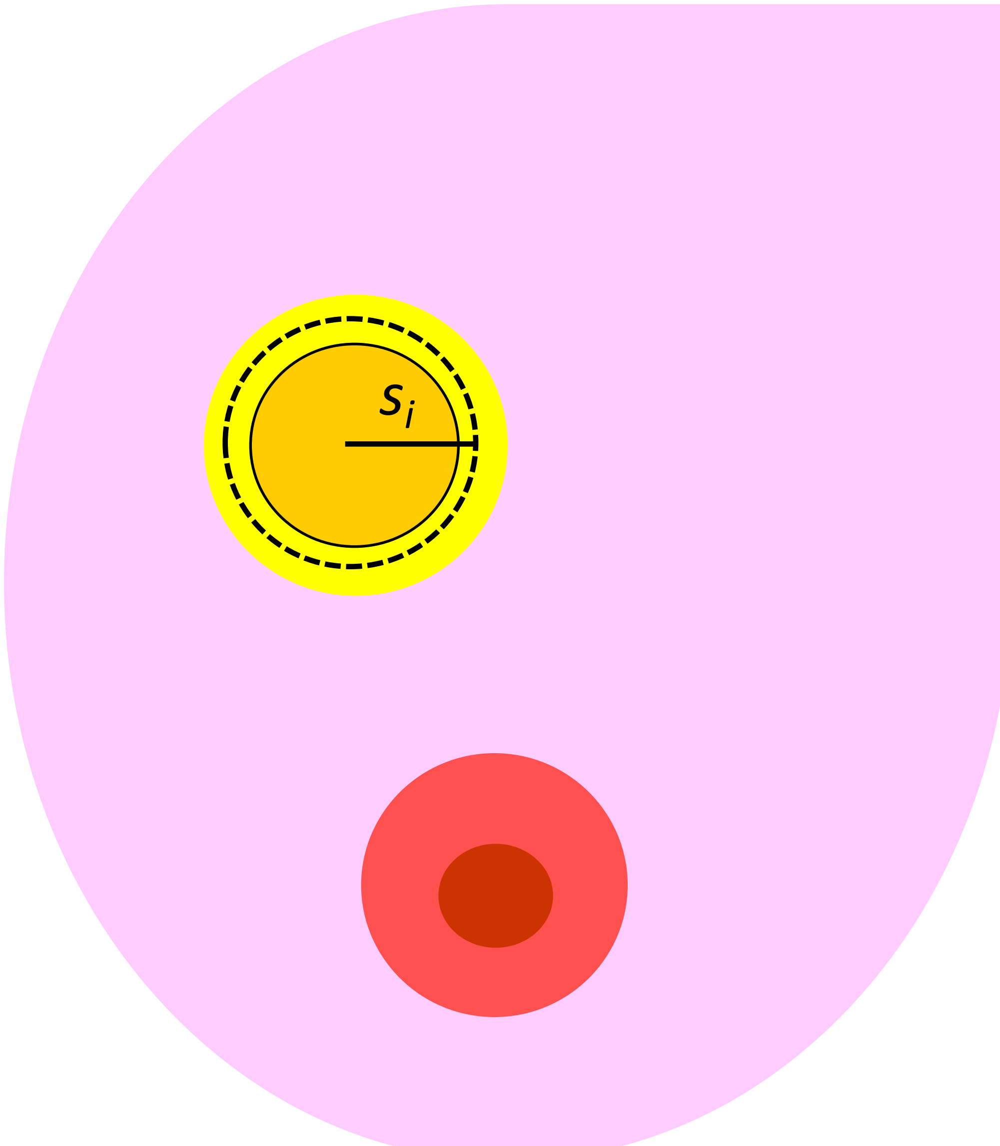
Ink on
tumor, or
just-ink-free,
resection



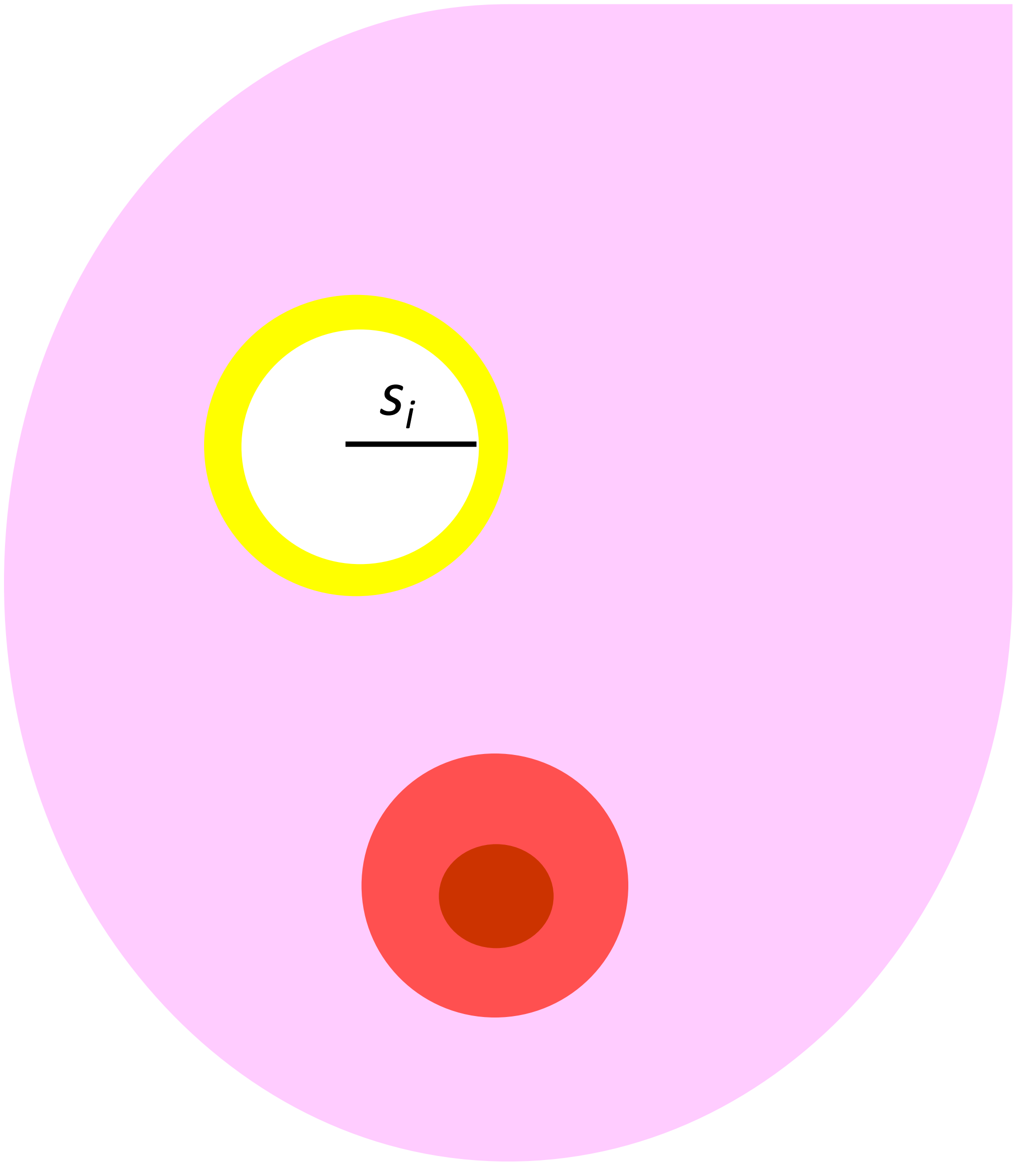
Positive
margin
resection



s_i is the resection size with margin i



s_i



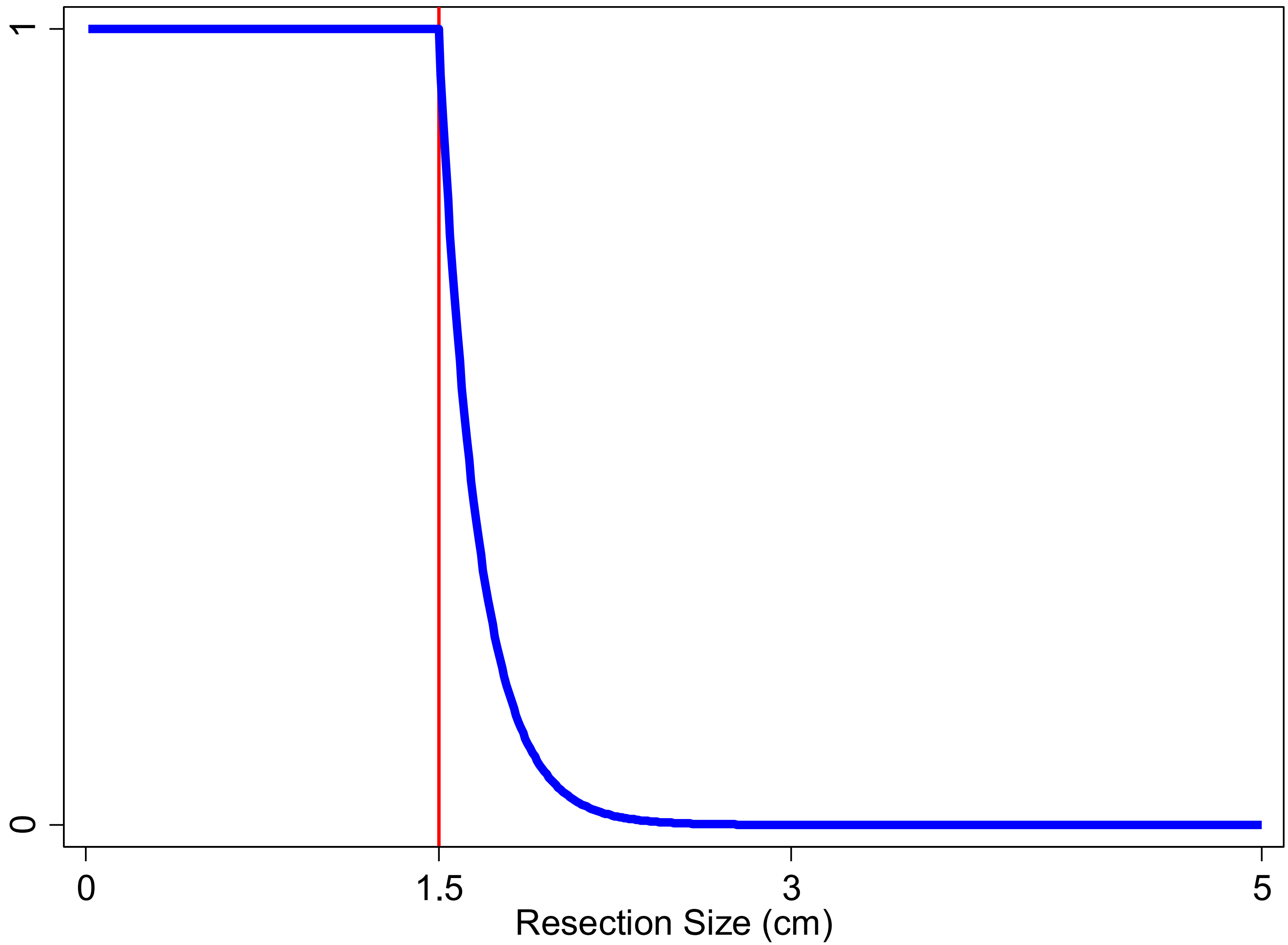
Negative margin resection

The Tumor

Comprises of two portions:

- The **central portion**, or **detected/detectable cancer**, with a uniform tumor density
- The **peripheral undetected portion** surrounding the detectable cancer, with density falling off with distance in an approximately exponential fashion
- Embedded in a breast of “infinite” size

Tumor Density of a 3-cm spherical cancer, beginning from the center of the tumor



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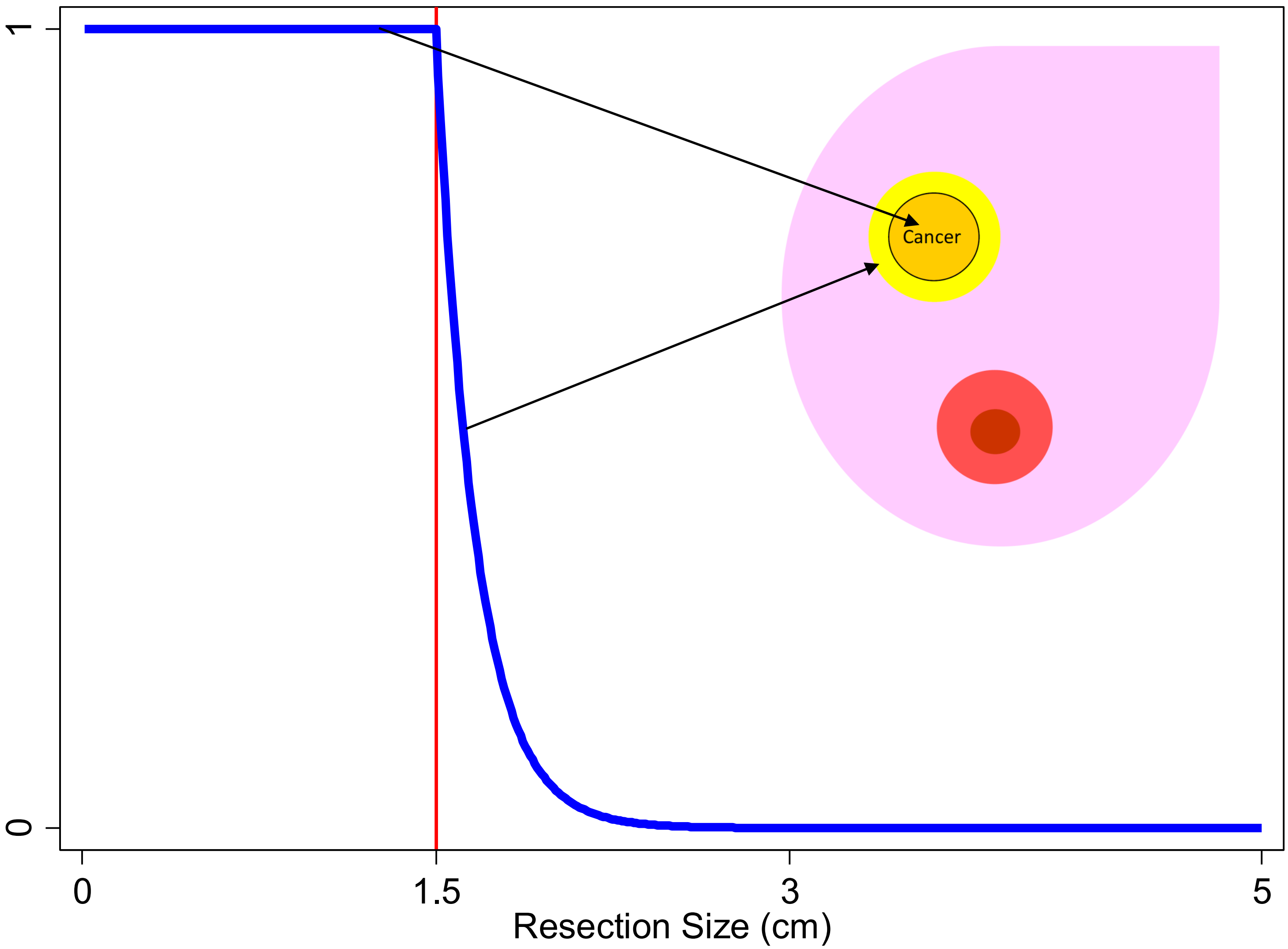


The Tumor: Model Details

- Detectable tumor size (radius) $\equiv s_0$
- Density of the detected tumor $\equiv \rho(s) = \rho_0$ if $s \leq s_0$
- Density of the undetected tumor $\rho(s) \cong \rho_0 e^{-\epsilon(s-s_0)}$ ("exponential") if $s > s_0$
- Where s is the distance from the tumor center and ϵ and ρ_0 are constants

Tumor Burden

Amount of tumor at any distance s from the tumor center:

$$T(s) = \int_0^s \rho(r) 4\pi r^2 dr$$

- $T(s) = 4\pi\rho_0 s^3/3$ if $s \leq s_0$
- $T(s) = 4\pi\rho_0 \left(\frac{s_0^3}{3} + \frac{s_0^2}{\epsilon} - e^{-\epsilon(s-s_0)}\frac{s^2}{\epsilon}\right)$ if $s > s_0$
- **Total amount** of tumor is $\omega = 4\pi\rho_0 \left(\frac{s_0^3}{3} + \frac{s_0^2}{\epsilon}\right)$
  - Note that the function $\rho(s)$ for $s > s_0$ is *not* exponential if the above expression is strictly true – but is exponential if above is approximately true, for $\epsilon \gg s_0$

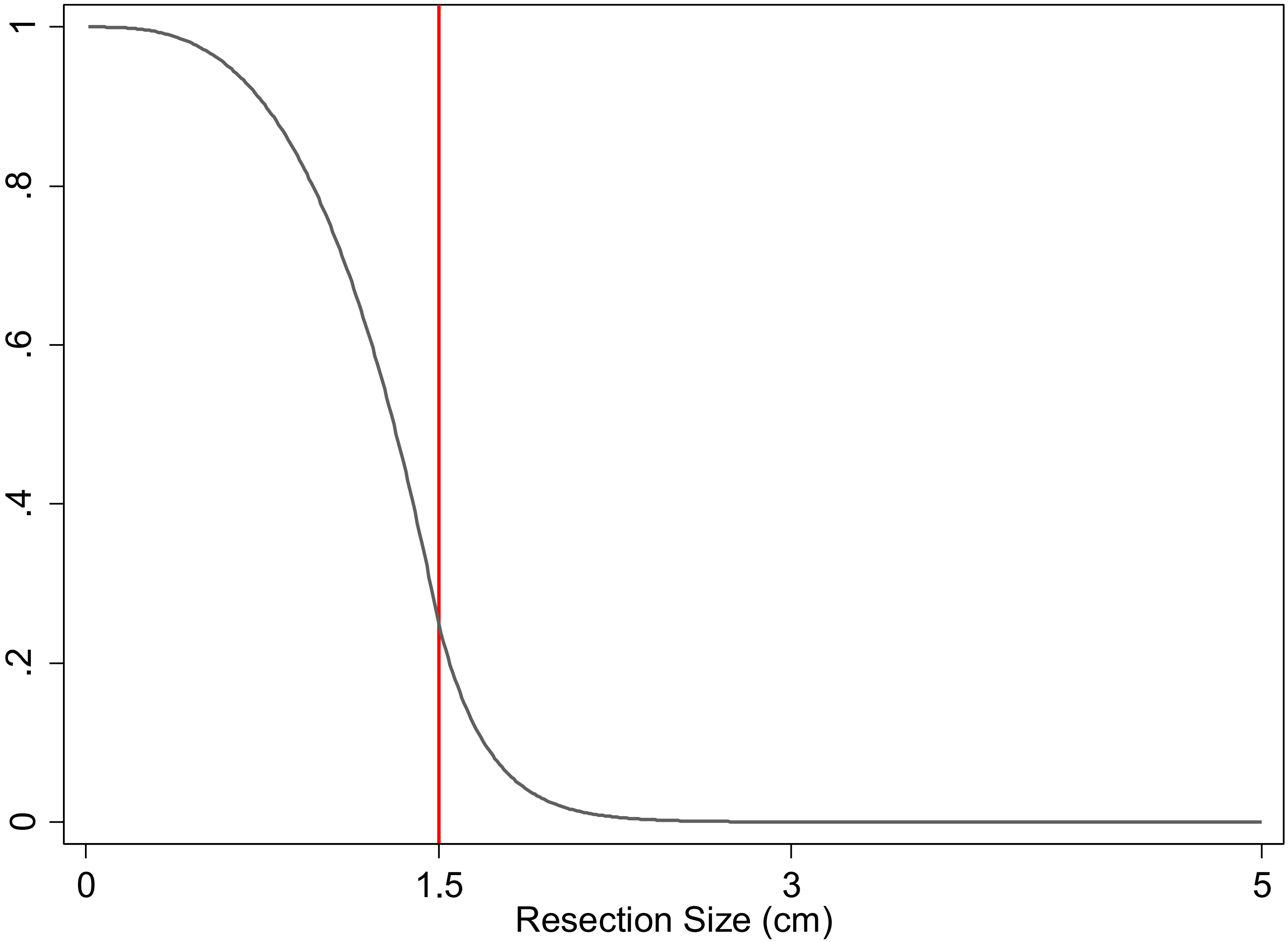
Residual Cancer

If the cancer is resected at any "core-out" distance s ("**resection size/distance**"), then the remaining, or residual, tumor would be

$$\omega - T(s) = R(s)$$

- $R(s) = 4\pi\rho_0\left(\frac{s_0^3 - s^3}{3} + \frac{s_0^2}{\epsilon}\right)$ if $s \le s_0$
- $R(s) = 4\pi\rho_0 e^{-\epsilon(s-s_0)} s^2/\epsilon$ if $s > s_0$

Proportion of Residual Tumor at various resection sizes:
assuming 25% residual cancer after *exact* resection of detected tumor



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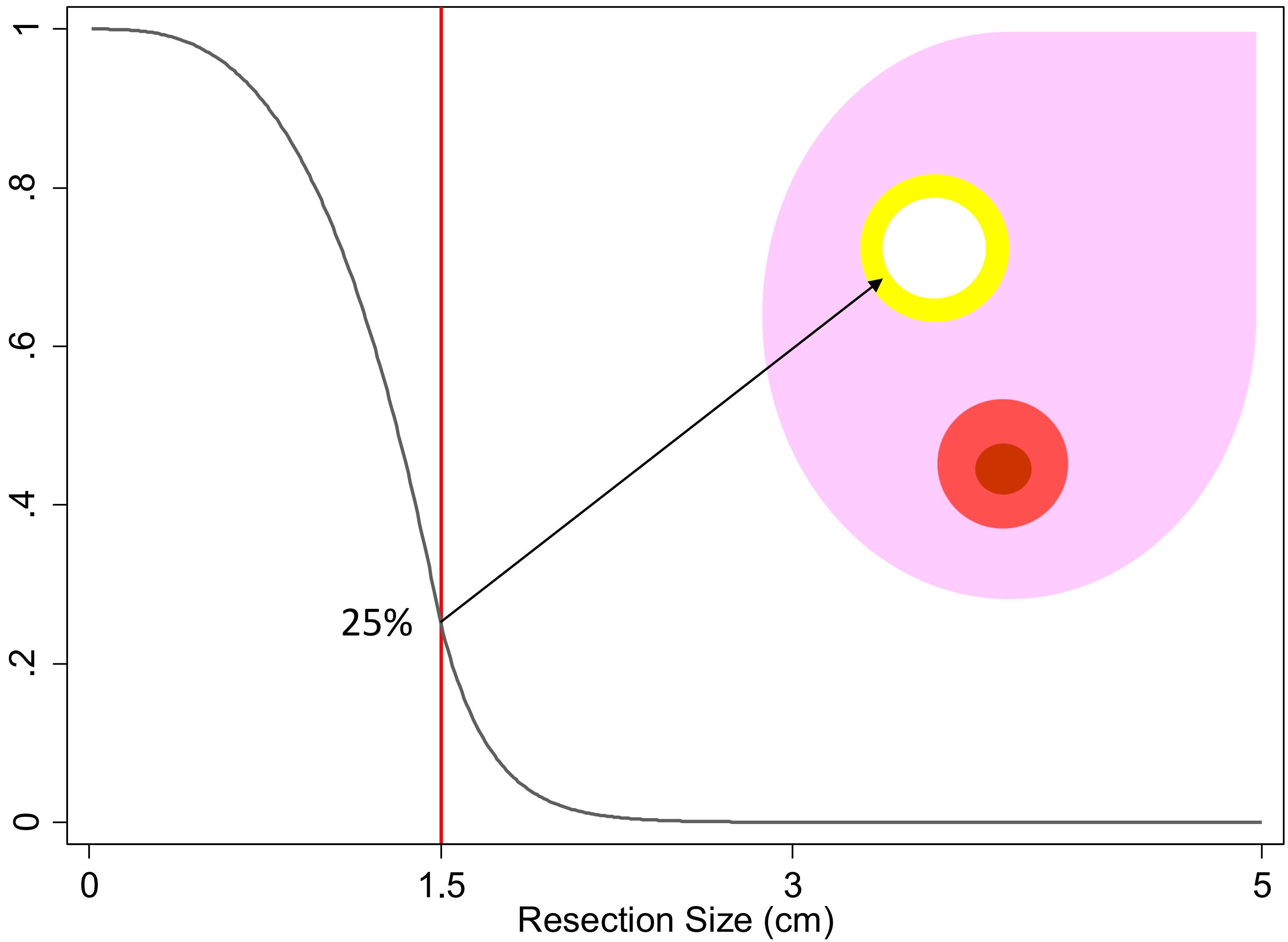


Recurrence Hazard

The **hazard** (as in “Survival Analysis”) of disease recurrence at time t after surgery, is formulated as

$h(t) = \lambda R(s) t$ with λ a proportionality constant (may we ignore deaths here?)

- The **recurrence-free probability** is
$$S_t = S(t) = e^{-\lambda R(s) t^2/2}$$
- And hence the **recurrence probability** at time t is
$$F(t) = 1 - e^{-\lambda R(s) t^2/2}$$

Comparing Margins: Odds Ratio

- Imagine a study comparing the recurrence of cancer between patients undergoing resection at or above a certain margin, say 1 mm, and those resected below that margin (including “positive” margins as well)
- We might use the **odds ratio (OR)** as the outcome measure: thus we define

$$OR = \frac{\Pr(\geq s_i)/(1-\Pr(\geq s_i))}{\Pr(<s_i)/(1-\Pr(<s_i))}$$

- where s_i is the resection distance associated with margin i, say 1 mm

Recurrence Probability

- $\Pr(\geq s_i)$ is short hand for $\Pr(Recur = 1|s \geq s_i)$
- "The probability of recurrence *given* resection size at or larger than the size associated with a margin i"
- A similar meaning for $\Pr(< s_i)$: the probability of recurrence given resection size less than the size associated with margin i
- **The objective of the present calculations is the presentation of these OR's for various margins and scenarios**

Recurrence OR: Clinical Studies

- Before going further, it might be helpful to reread some systematic reviews and guidelines which use these Odds Ratios, and how in clinical studies these OR's are defined
- This will motivate our mathematical models

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

Moran, et al. Ann Surg Oncol 2014;21:704-16

Recurrence Probability: Details

- The probability of recurrence at any time t, say 10 years after surgery, with a resection size s is
$$F(t) = 1 - e^{-\lambda R(s) t^2/2}$$
- But if the resection size is not fixed, and each s has a *probability distribution* (density) $g(s)$, then the probability of recurrence given $s \geq s_i$ will be

$$\Pr(\geq s_i) = \frac{\int_{s_i}^{\infty} \left(1 - e^{-\lambda R(r) t^2/2}\right) g(r) dr}{\int_{s_i}^{\infty} g(r) dr}$$

Recurrence Probability: Interpretation

But what does this probability mean? Two interpretations:

- For *one patient* – this is the probability of recurrence at t **if the resection size is known only to be** $\boldsymbol{s \geq s_i}$
- For a *infinite sample of patients* – this is the **weighted average of recurrence probabilities** of all patients with resection sizes $s \geq s_i$
- The “weight” $g(s)$ also tells how the surgeon does his surgery! (see later)

Recurrence Probability: Connection

- What’s the connection with clinical studies?
- The weighted average interpretation is *approximately* a **proportion:** number of patients with resection sizes $s \geq s_i$ who had recurrence, divided by total number of patients with those resection sizes (at some given time)
- These proportions or “recurrence rates” are routinely obtained in clinical studies, and used in the calculation of OR’s

The Resection Size Probability

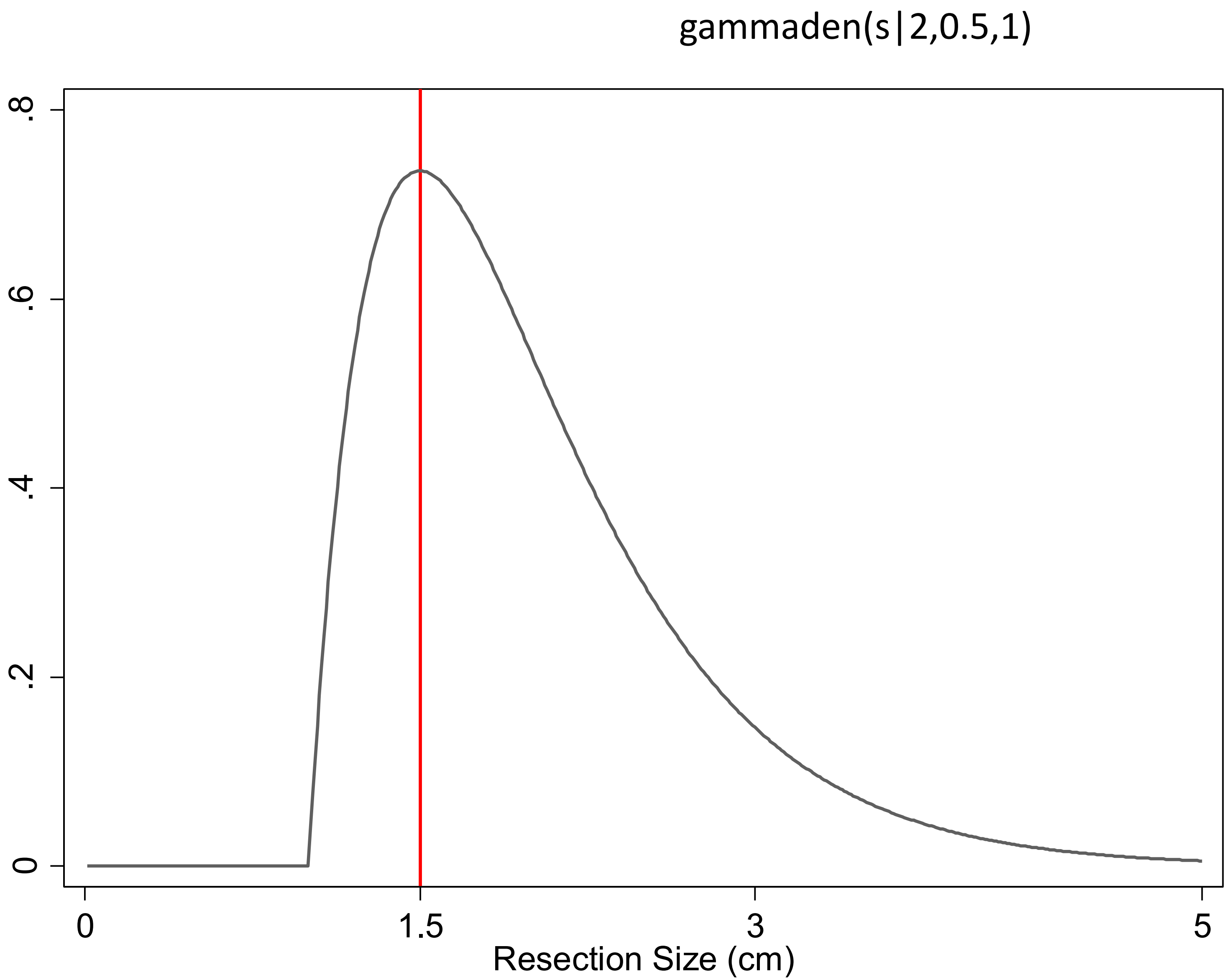
- What is the **resection size probability distribution** (density) $g(s)$?
- This is something that no clinical studies discuss or examine explicitly
- It tells us how likely, for a given tumor size s_0, the resection will be of any size s, i.e., whether the resection will likely have a large margin, or small margin or likely to have a positive margin, etc.

The Resection Size Probability

Modeled here as a Gamma density:

- $g(s) \equiv ga(s|a, b, c) = \frac{b^{-a}}{\Gamma(a)}(s - c)^{a-1}e^{-(s-c)/b}$
- Where $\Gamma(a)$ is the Gamma Function and a, b, c are shape, scale & location parameters resp.
- Denote

$$g(s_1, s_2) = \int_{s_1}^{s_2} g(r)dr$$


gammaden(s|2,0.5,1)
.8
.6
.4
.2
0
0
1.5
3
5
Resection Size (cm)

Recurrence Probability: Final 1

Recurrence probability for various margin cut-offs i

For $\boldsymbol{s_i \geq s_0}$

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

- With $\phi \equiv 2\pi\rho_0\lambda t_0^2$ for some fixed $t = t_0$

Recurrence Probability: Final 2

For $s_i < s_0$

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

- We numerically integrate these quantities using Stata v. 14.2
- Knowing both $\Pr(s \geq s_i)$ & $\Pr(s < s_i)$ for any i we can calculate OR's for any i

Notes on Parameters

- If we set the baseline recurrence-free probability for fixed $t = t_0$ and $s = s_0$, i.e. the detectable tumor size, at e.g. 0.9 (perhaps at 10 years), then

$$-\log(0.9) = -\log(S_{t_0}) = 2\pi\rho_0\lambda s_0^2 t_0^2/\epsilon$$

- And thus

$$\phi = -\epsilon\log(S_{t_0})/s_0^2$$

Notes on Parameters

- If we set the peripheral component of the tumor to be a proportion z_0 of the *whole tumor* (both detectable and undetectable):

$$\frac{\frac{s_0^2}{\epsilon}}{\left(\frac{s_0^3}{3}+\frac{s_0^2}{\epsilon}\right)} = z_0$$

- Then $\epsilon = \frac{3}{s_0}\left(\frac{1}{z_0} - 1\right)$; and $\phi = -\frac{3}{s_0^3}\left(\frac{1}{z_0} - 1\right)\log(S_{t_0})$

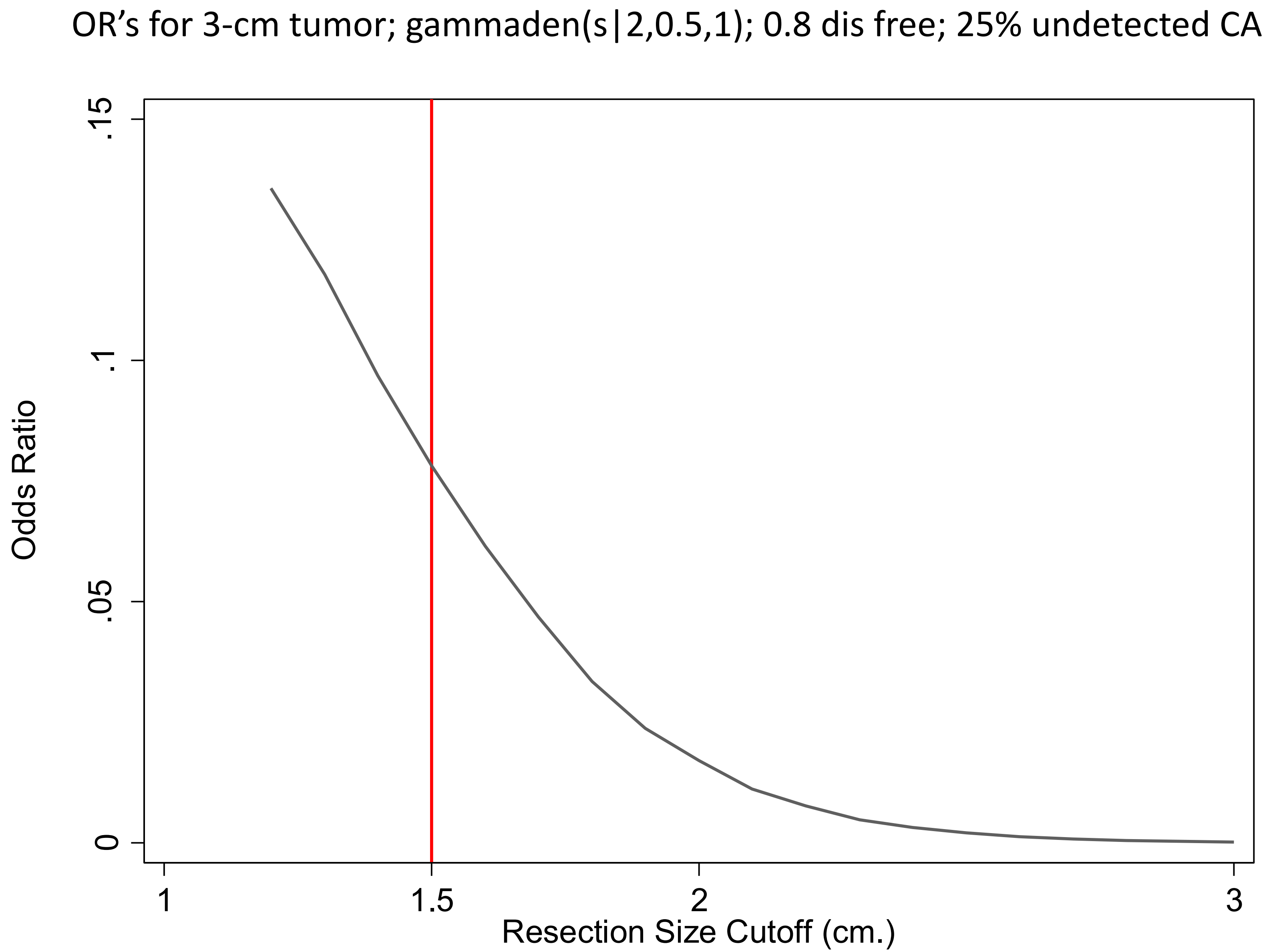
- And we only need to **plug in 3 numbers**: s_0, z_0, S_{t_0} to determine ϕ, ϵ

Some Scenarios 1

- A breast cancer patient with a *detected* 3-cm tumor
- The radius of the tumor is thus 1.5 cm
- What is the **OR of locoregional recurrence** at 10 years for margins > 0 (“no ink on tumor”), 1 ,2, 3, 4 mm etc. from the detected tumor edge? We can look at positive margins -1, -2, -3 mm, etc., as well, which is possible only in theory
- Given that the standard 10-yr recurrence is 20% (0.2), or a recurrence-free probability of 0.8
- And the undetected cancer is 25% (0.25) of total

Some Scenarios 1

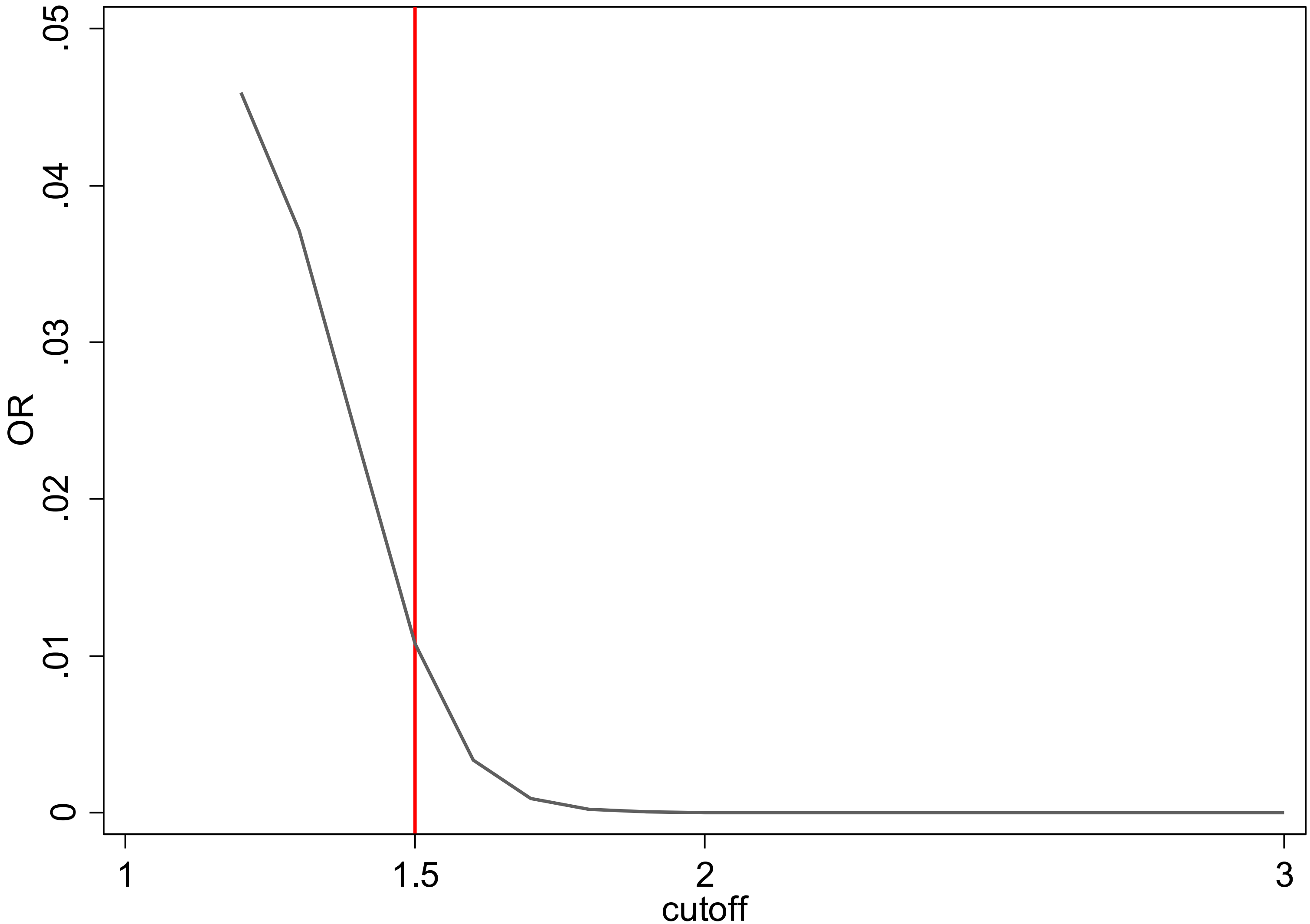
- Given the surgeon's operative ability as gamma density $ga(s|2,0.5,1)$
- Plug in $S_{t_0} = 0.8, z_0 = 0.25, s_0 = 1.5$
- Calculate $\Pr(\geq s_i)$'s etc. using a user-written numerical integration program in Stata v. 14.2
- And thus calculate the OR's


OR's for 3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 25% undetected CA
Odds Ratio
0
.05
.1
.15
1
1.5
2
3
Resection Size Cutoff (cm.)

Comments

- Here, the OR is a strictly decreasing function of resection size
- All OR's are (much) less than 1 (their precise values are model-dependent)
- There is no "leveling off" at the point of *detectable tumor size* – the OR continues to decrease
- This may result from assumptions concerning undetectable tumors
- There is steeper fall, and some leveling, if less undetectable cancer is assumed

OR’s for 3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; **10% undetected CA**



Some Limitations

- Distribution of residual cancer is not realistic (we model “effective residual cancer”: those able to clinically recur)
- Recurrence hazard is not realistic; has no covariates
- Resection is not spherical!
- Other treatments not directly taken into account
- Multicentric cancers?
- etc.

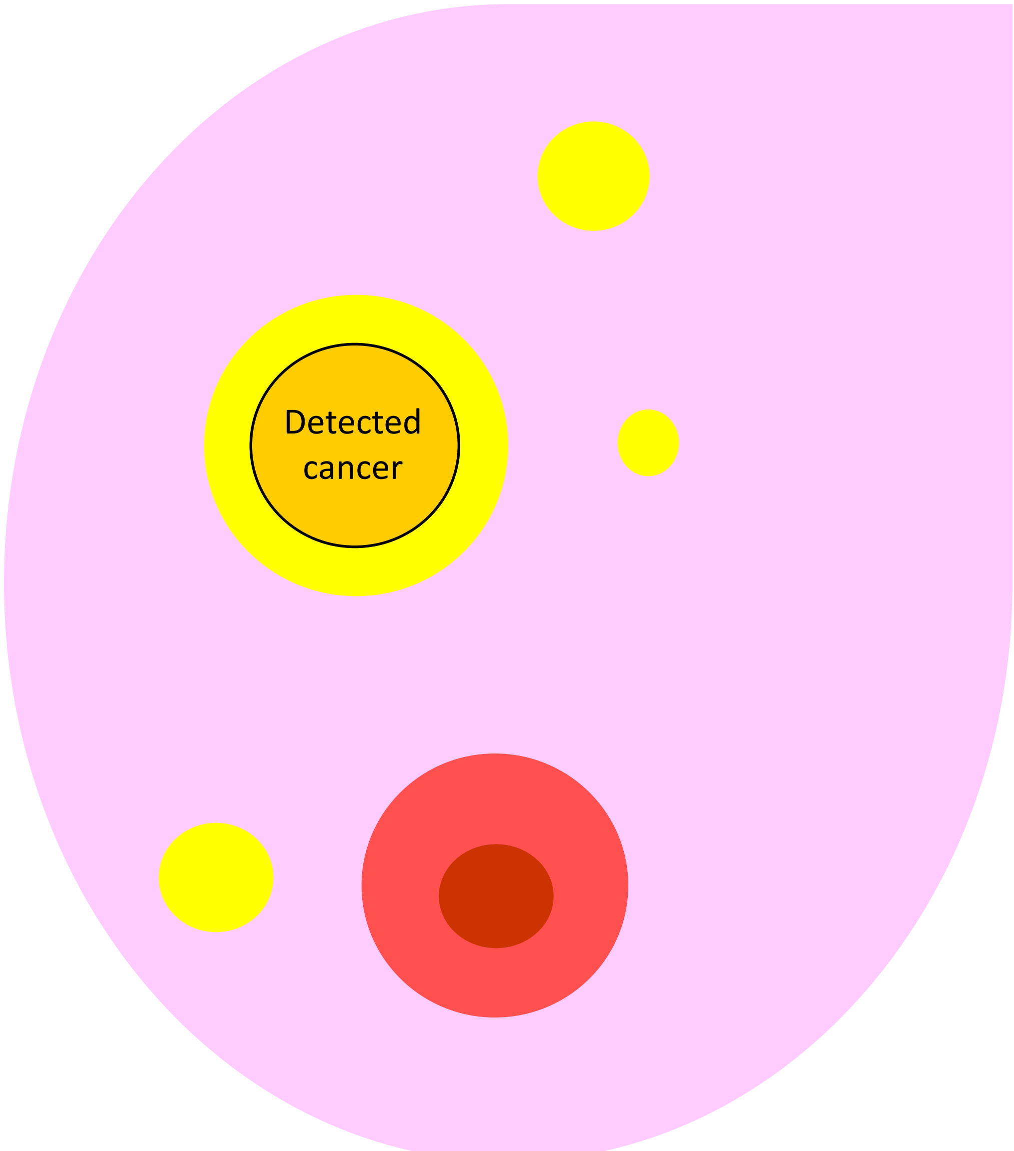
A More Realistic Model

Let's add a constant **background risk** of in-breast recurrence, unrelated to "residual tumor", to the hazard:

$$h(t) = \lambda R(s)t + \eta_0$$

- Thus the recurrence-free probability will be

$$S(t) = e^{-\frac{\lambda R(s)t^2}{2} - \eta_0 t}$$



The **background risk** may be **interpreted as** undetected cancer **at other centers/foci** or other **underlying risks** that *does not depend on the detected tumor*

Recurrence Probability, Modified

The recurrence probability will be modified thus:

For $\boldsymbol{s_i \geq s_0}$

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

- Where $\nu_0 \equiv \eta_0 t_0$ (note: actually, any ν_0 with no s dependence will do)
- And similarly for $s_i < s_0$

More on Parameters

- With a new parameter ν_0 for fixed t_0
- We must plug in more values
- In the this model, we still have $\epsilon = \frac{3}{s_0}\left(\frac{1}{z_0} - 1\right)$
- But now ϕ will be different

More on Parameters

- Let's assume that the background hazard is **a fraction** υ of that of the residual tumor at a fixed t_0, e.g. when the recurrence-free probability is 0.9 = S_{t_0}, with resection at s_0 as before, thus

$$-\log(S_{t_0}) = \frac{\lambda R(s_0) t_0^2}{2} + \nu_0$$

- **So let** $\nu_0 = \upsilon \lambda R(s_0) t_0^2 / 2$
- And as before set $\phi \equiv 2\pi\rho_0\lambda t_0^2$

More on Parameters

We find

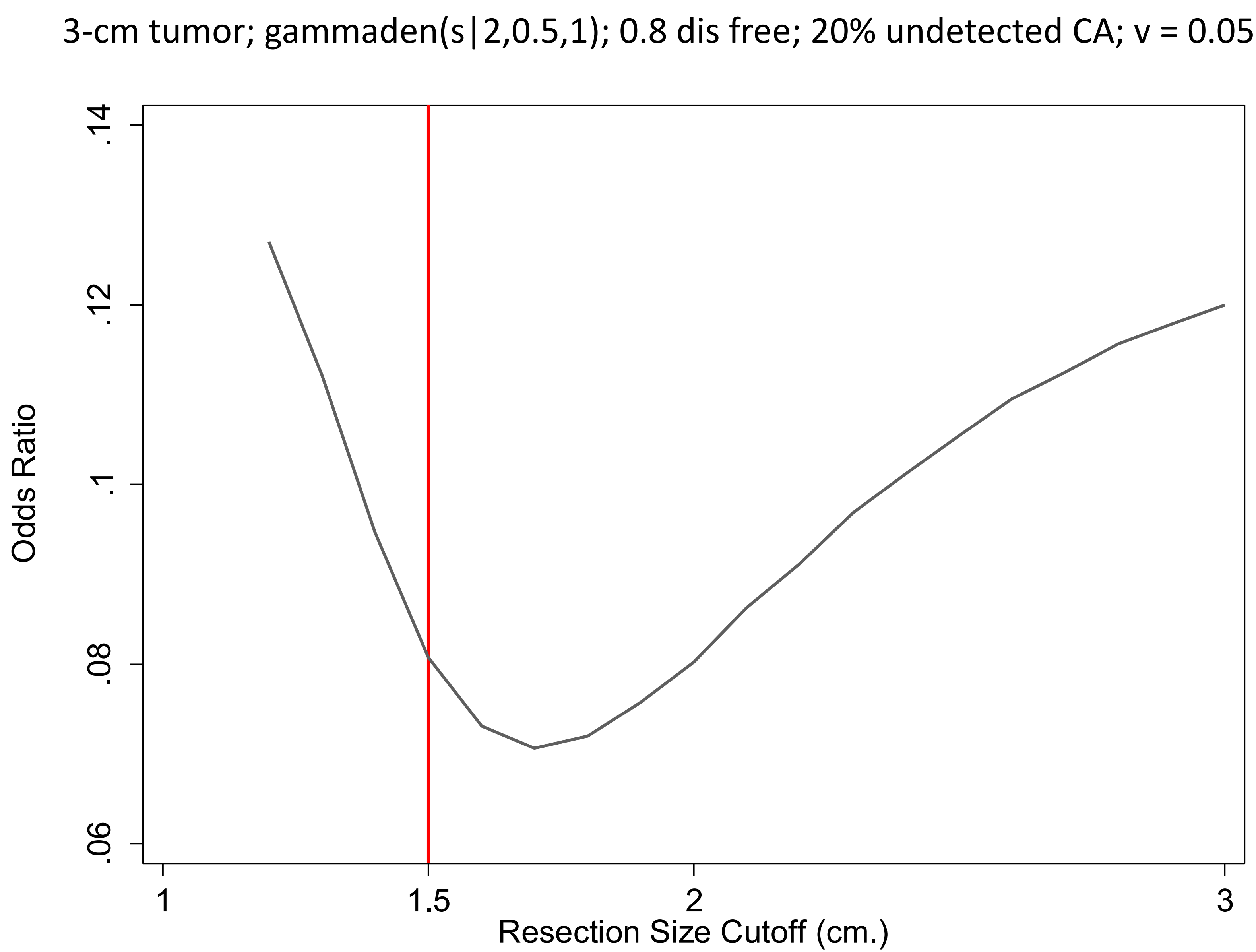
$$\phi = \frac{-3\log(S_{t_0})}{s_0^3(1+2\upsilon)}\left(\frac{1}{z_0} - 1\right)$$

$$\nu_0 = \frac{-2\upsilon\log(S_{t_0})}{(1+2\upsilon)}$$

- So we must now plug in **4 numbers**: $s_0, z_0, S_{t_0}, \upsilon$ to determine ϕ, ϵ, ν_0

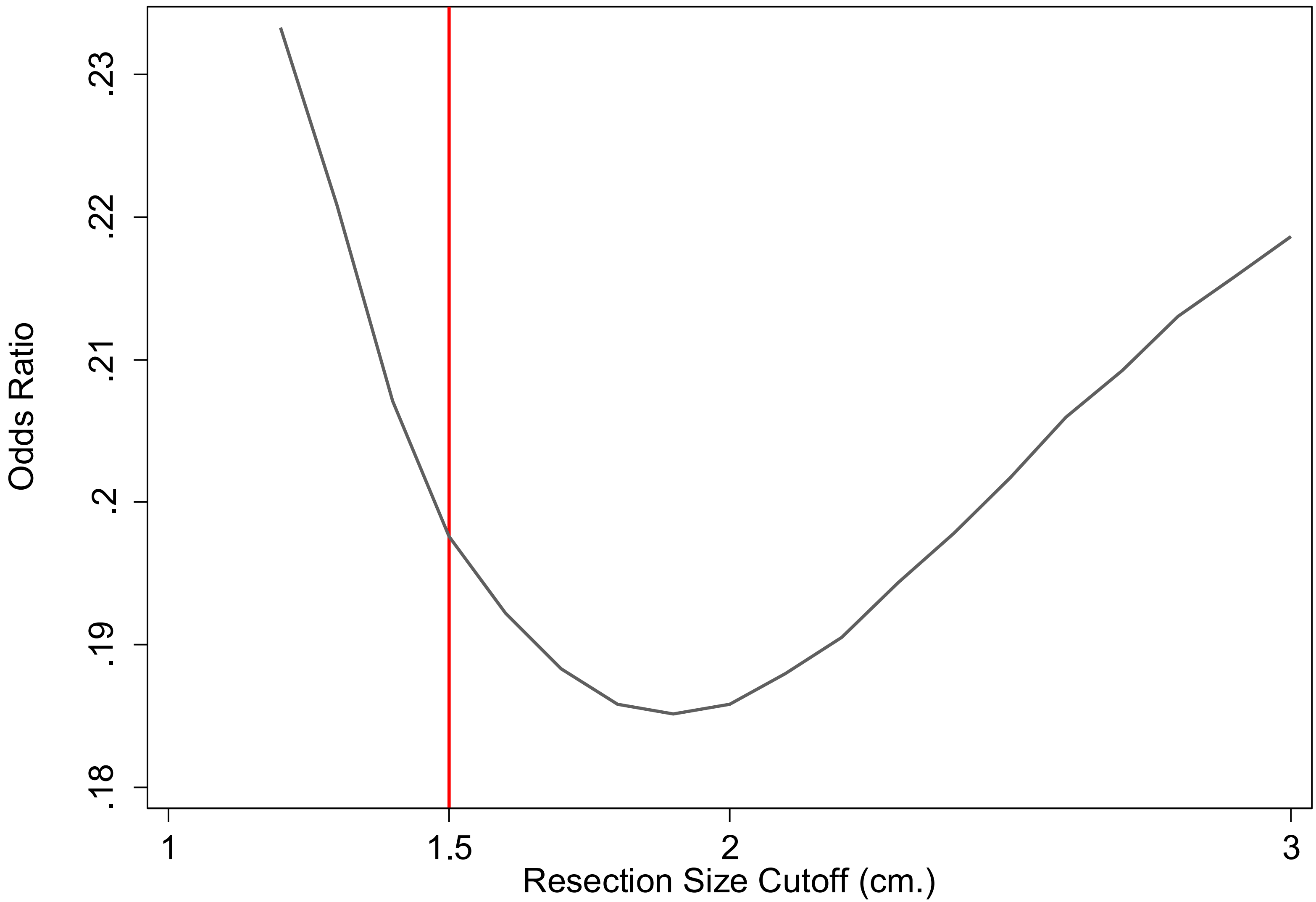
Some Scenarios 2

- Let's look at how OR's are affected as we increase the fraction υ due to background hazard/risk
- That is, as the importance of undetected multicentric/focal cancer and other underlying risks increases
- And also as the amount of other undetected cancers increases



3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.05
Odds Ratio
.06
.08
.1
.12
.14
1
1.5
2
3
Resection Size Cutoff (cm.)

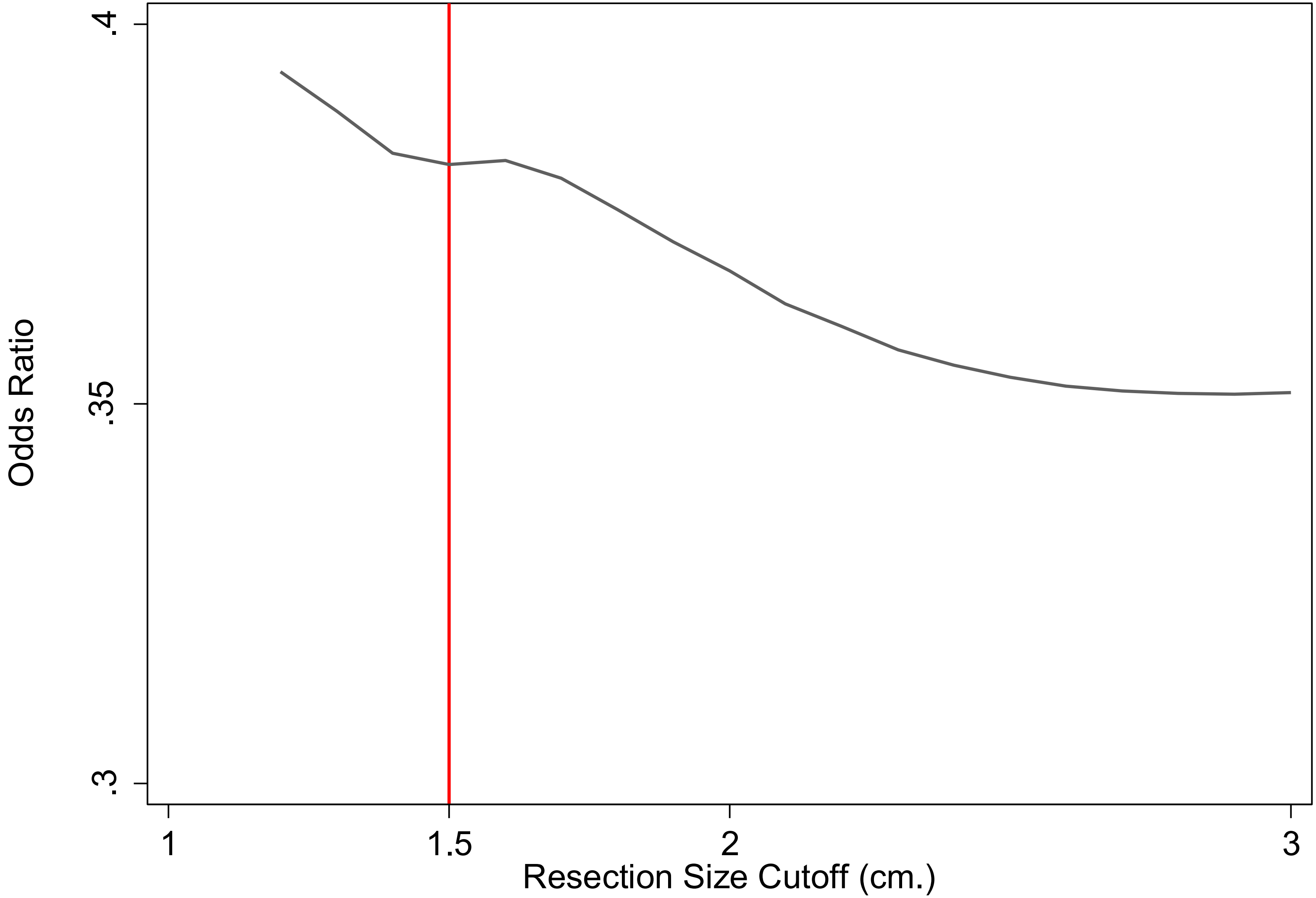
3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 30% undetected CA; v = 0.1

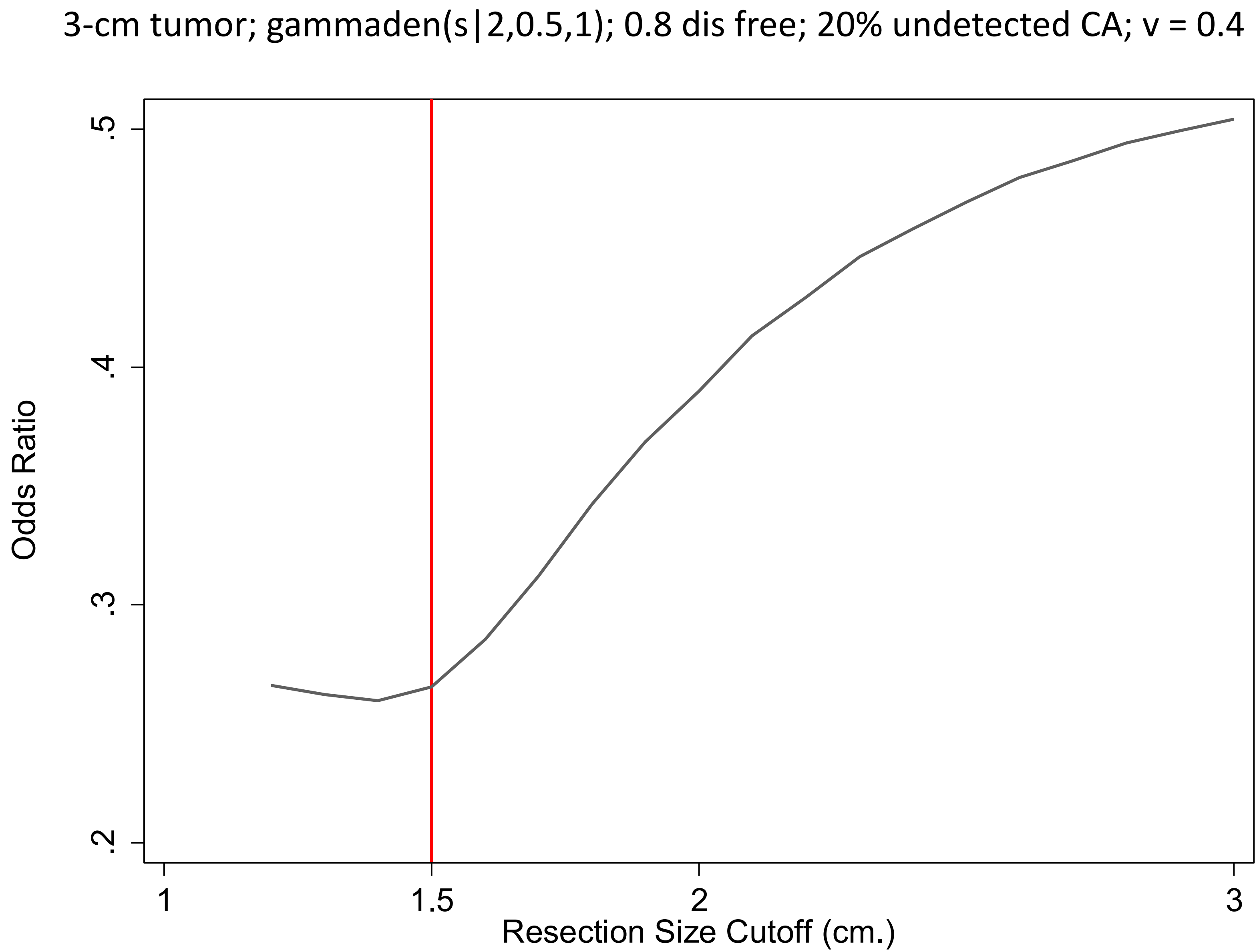


Comments

- There is now a “nadir” in OR values, for certain scenarios!
- At margins > no ink on tumor! (e.g. resection size > detected tumor size)

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; 20% undetected CA; v = 0.4
Odds Ratio
.2
.3
.4
.5
1
1.5
2
3
Resection Size Cutoff (cm.)

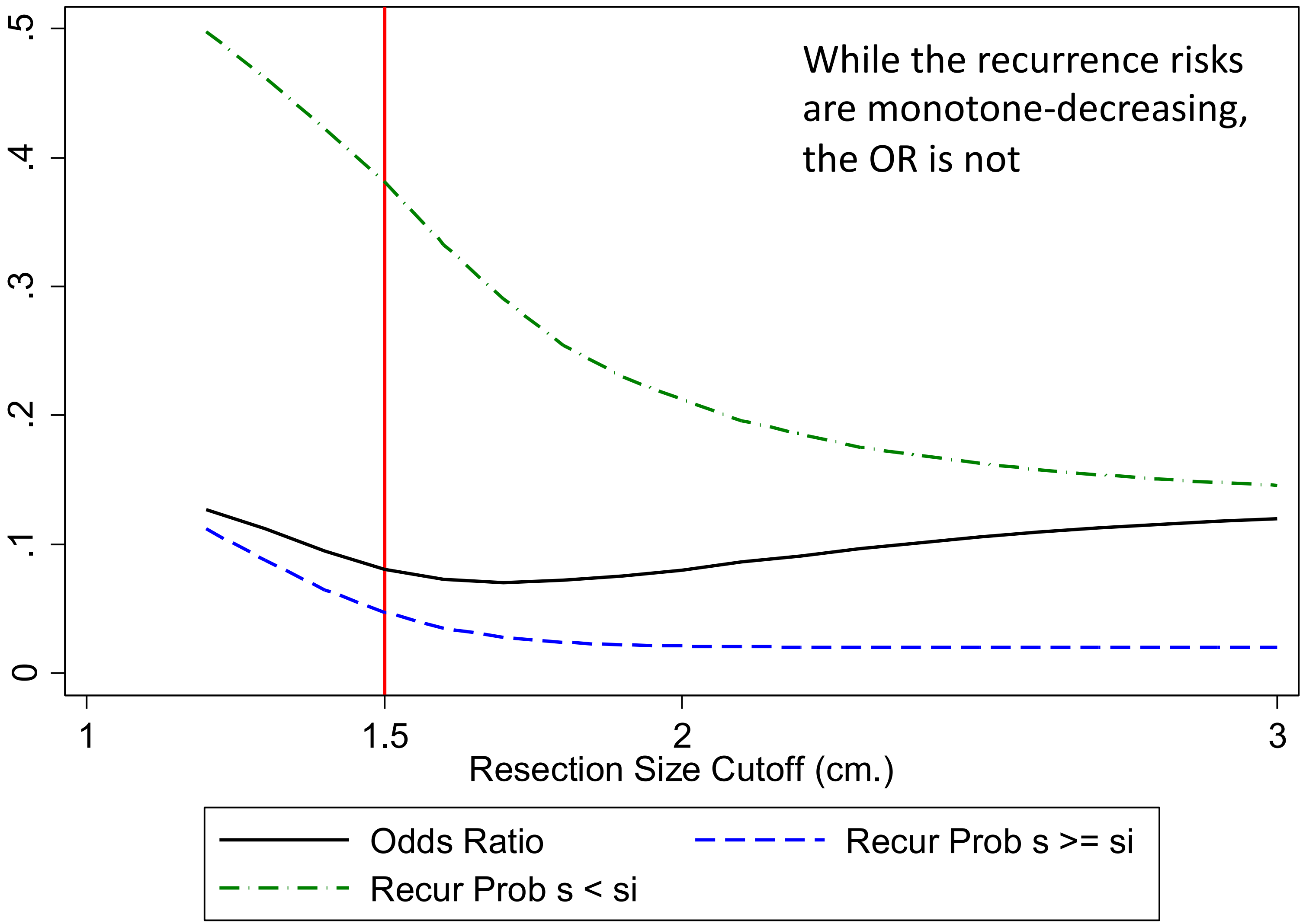
Comments

- As undetected breast cancers become proportionately larger and/or background risk becomes more important the OR's become more bizarre
- There is leveling effect if a large amount of undetected cancer exists at the primary site
- There is a large increase in OR with resection size if background risk is large

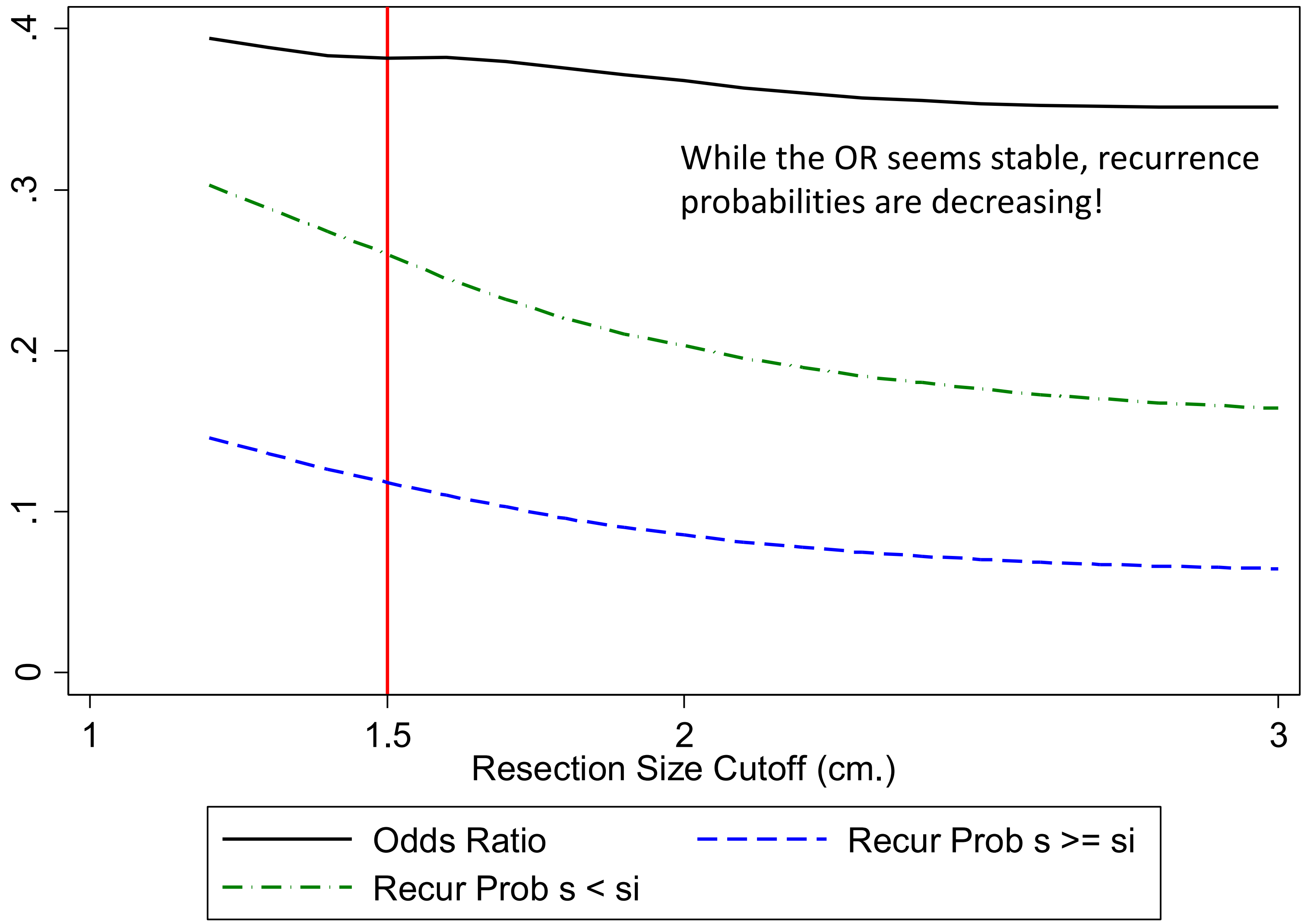
Don’t be Fooled By OR’s

- What are we trying to measure, exactly?
- Are we looking for a **cutoff margin with the lowest recurrence probability/risk**?
- So that we can use that margin when doing BCS?
- Then the OR’s (or any *relative risk* measure) that we calculated will not really help
- **The lowest possible OR does not theoretically imply the lowest possible recurrence risk!** (Unless there is no background risk, or a *common control* is used, see later)
- See some examples for yourself

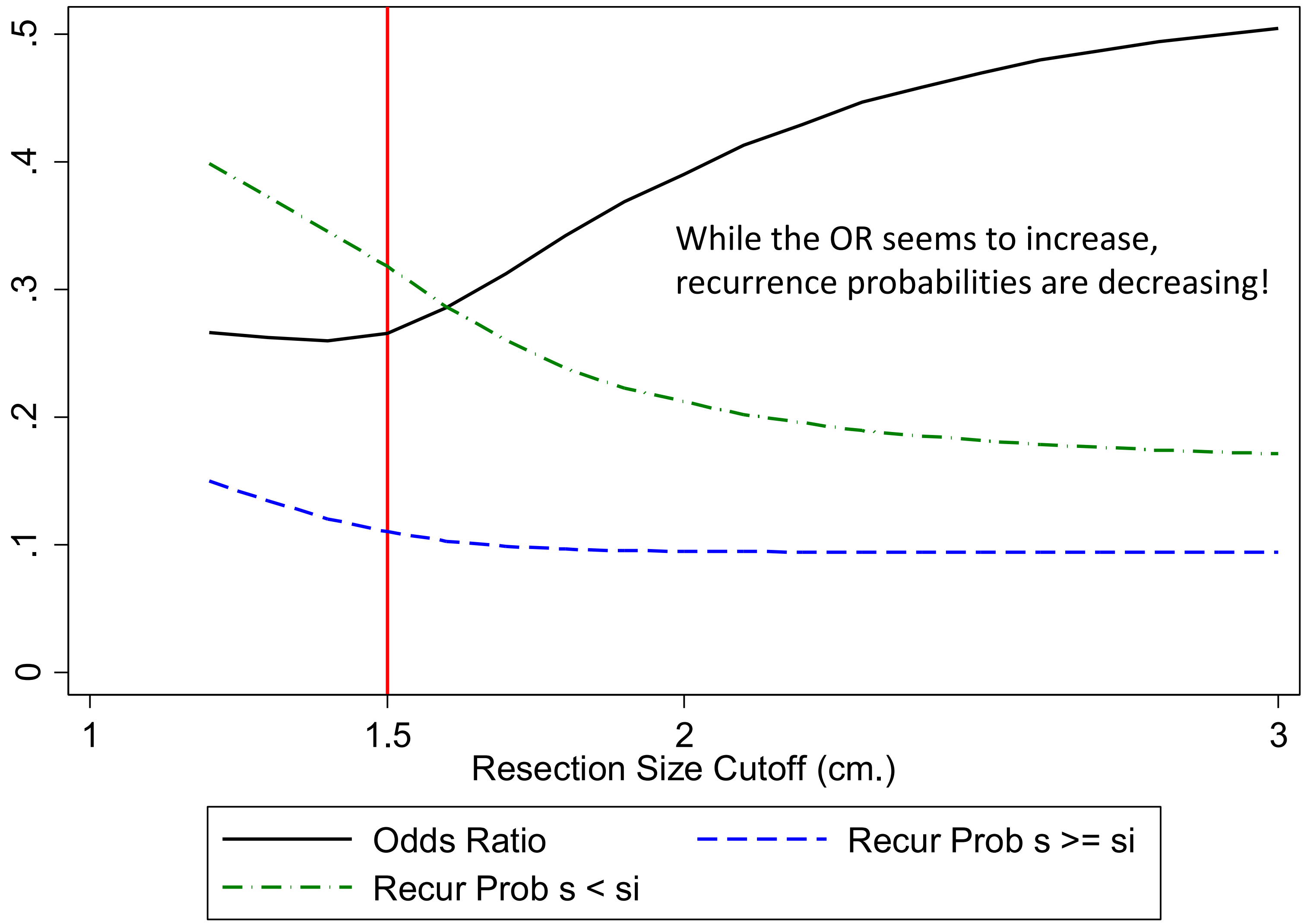
3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.05

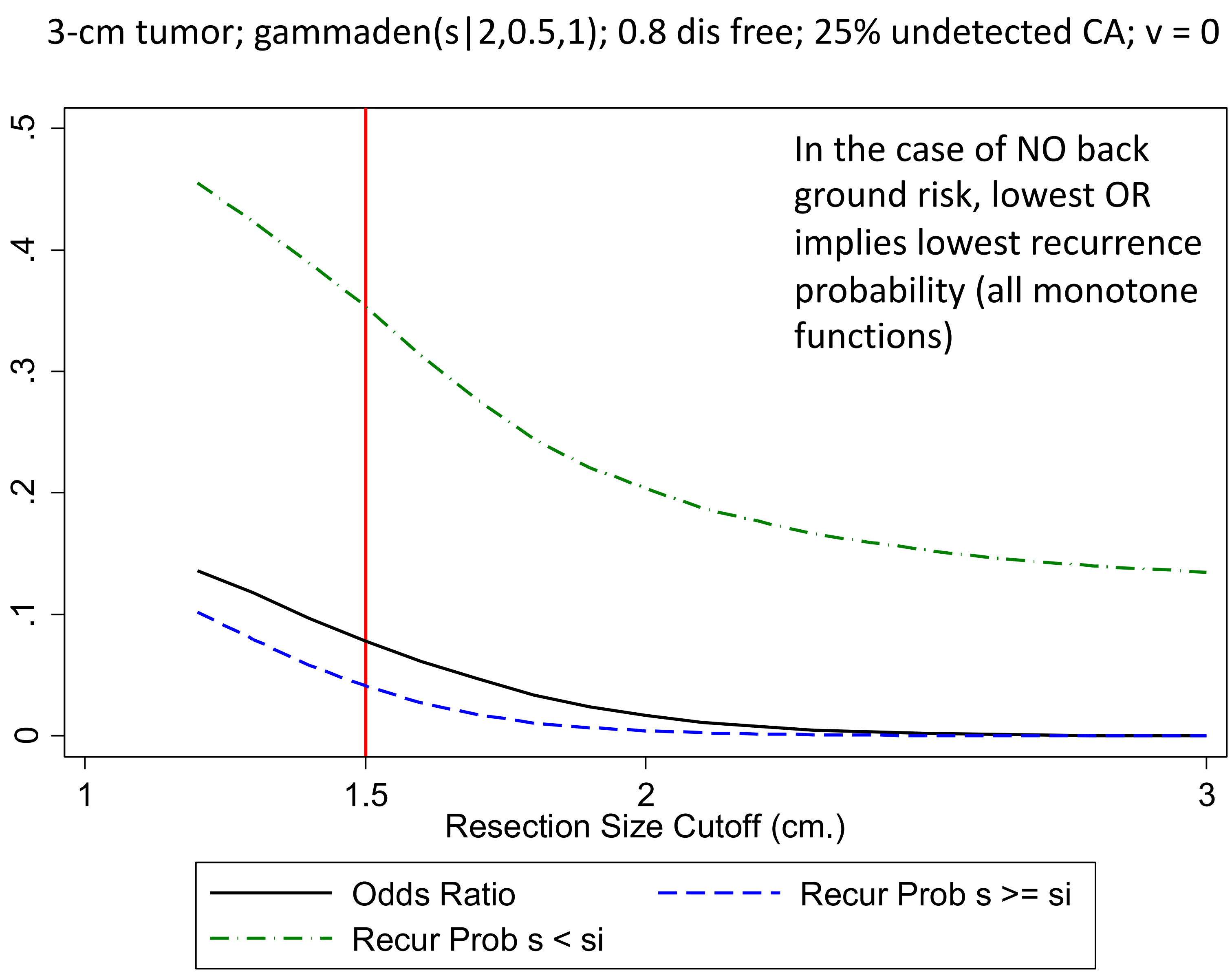


3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 40% undetected CA; v = 0.2

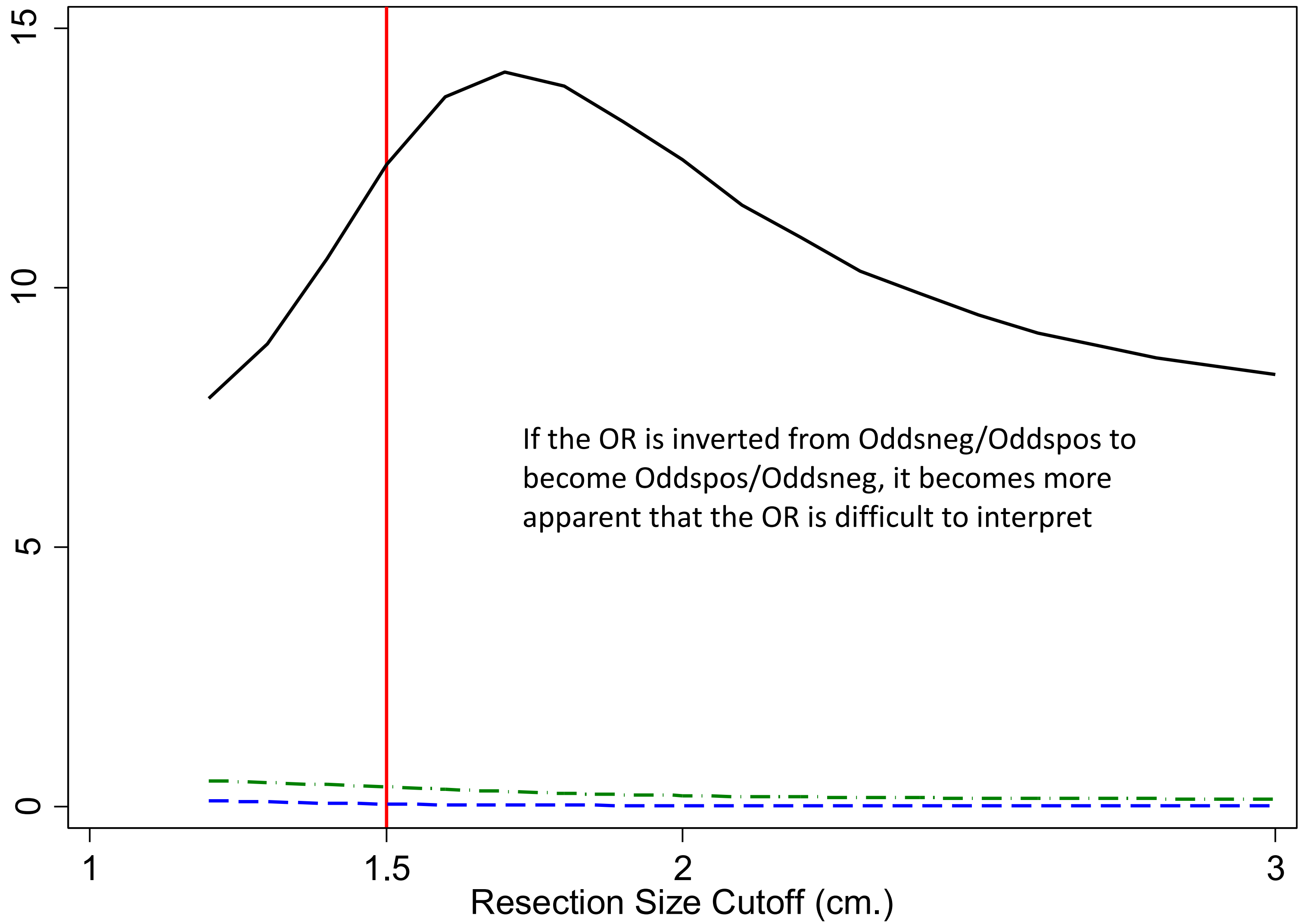


3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.4




3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 25% undetected CA; v = 0
In the case of NO back ground risk, lowest OR implies lowest recurrence probability (all monotone functions)
0
.1
.2
.3
.4
.5
1
1.5
2
3
Resection Size Cutoff (cm.)
Odds Ratio
Recur Prob s >= si
Recur Prob s < si

3-cm tumor; gammaden(s|2,0.5,1); 0.8 dis free; 20% undetected CA; v = 0.05

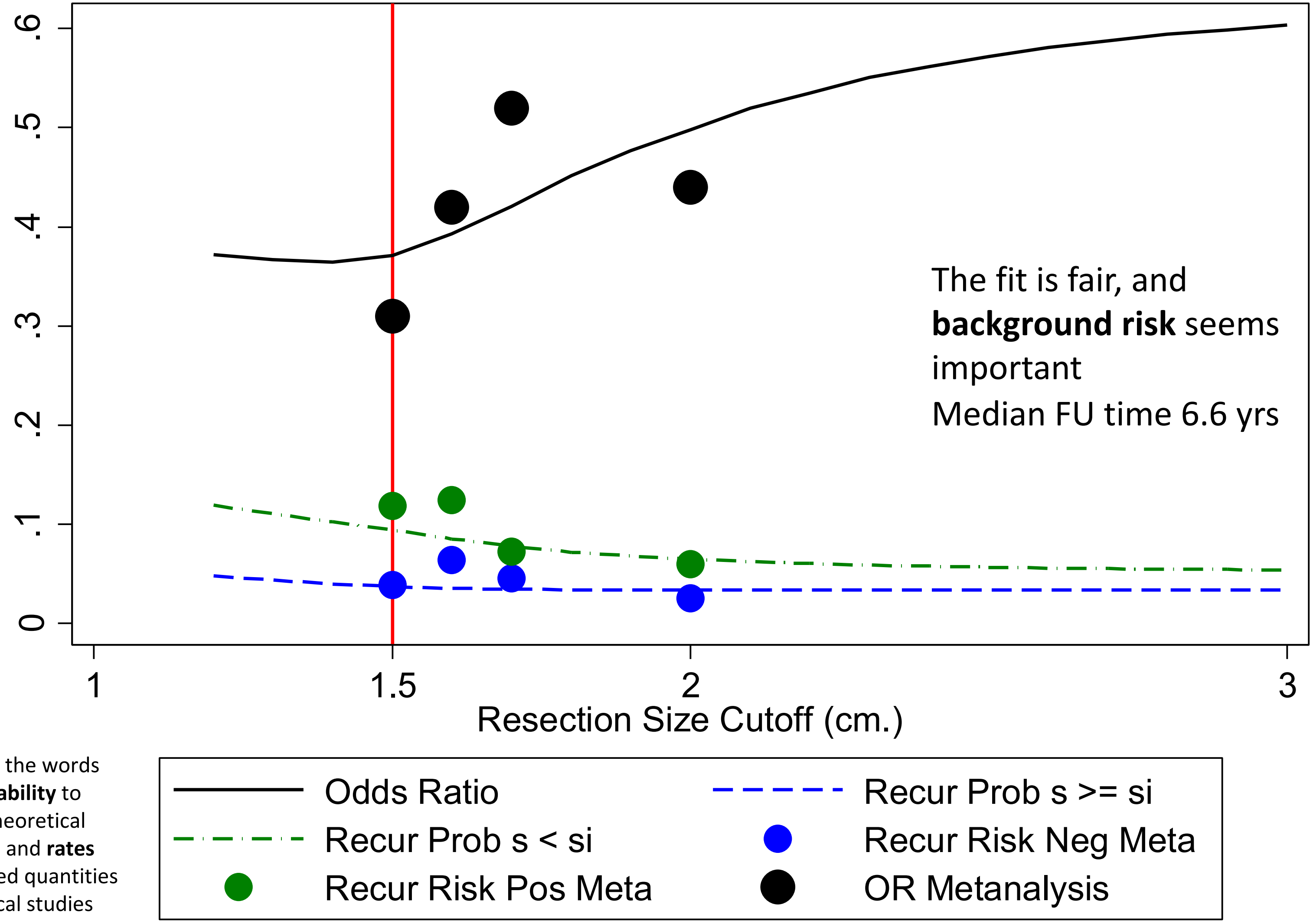


Model "Fitting"

- We attempt to "fit" a model, with appropriate parameters, to the Houssami (2014) data
- There are 4 negative margins: > 0 (no ink on tumor), 1, 2, and 5 mm
- Using the Houssami data, we estimated the **pooled OR** and **recurrence rate** for each margin using the DerSimonian & Laird random effects model
- The pooled OR's & rates are used as data for model "fitting"

Houssami, et al. Ann Surg Oncol 2014;21:717-30

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



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

OR Not Appropriate?

- The OR as defined here, is based on that of Houssami (2014)
- One problem is the lack of a **common control** in the OR calculations
- Thus, lower OR does not necessarily reflect lower recurrence probability/risk
- If the *positive margin* control were the same for all OR calculations, then lower OR will reflect lower recurrence probability/risk