RxRSI Derivation

Relation to LQ Model

GARD and RxRSI are centered around the derived α_g, which is absolutely defined with $n = 1$ and $d = 2$. As of this curent work, GARD and RxRSI do not capture changes in β, and therefore set it as a constant, and equal to the mean for a given disease site pulled from the literature. This is the crux of the analysis: this parameter is derived from the genomics and the LQ-model (as a surrogate for SF2), and then is subsequently used to determine overall effect of repeated doses.

Specifically, we define α_g as:

$$\alpha_g = \frac{\ln \mathrm{RSI}}{-nd} - \beta d, \tag{1}$$

which simplifies to

$$\alpha_g = \frac{\ln \mathrm{RSI}}{-(1)2\mathrm{Gy}} - \beta\, 2\mathrm{Gy}. \tag{2}$$

Code Excerpt:

Here we show a snippet of the code where we calculate α_g for each patient and plot the distribution as a function of RSI. the rich heterogeneity of RSI is preserved, but transformed (Figure 1). The data points represent patients used in the analysis, and this is an excerpt from the code we used for the paper, demonstrating that the original computation, and therefore results, match the clarified exposition.

```
n_e = 1
d_e = 2
beta = 0.05
df <- mutate(df, alpha_g = log(RSI)/(-n_e*d_e) - beta*d_e)
```

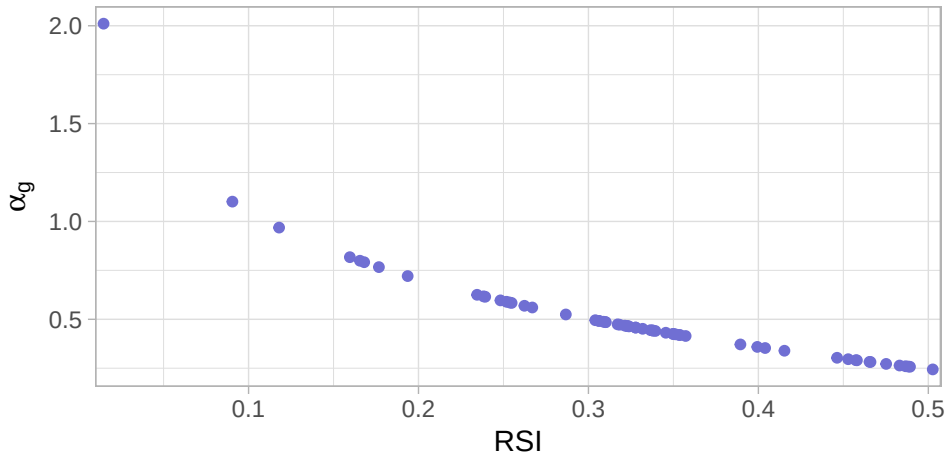

Figure 1: Relationship between α_g and RSI for the studied cohort.

Defining GARD_{2Gy}

We define here a new term "GARD_{2Gy}". This is defined as the *effect* of a 2Gy dose of radiation in terms of GARD.

$$\text{GARD}_{2Gy} = nd(\alpha_g + \beta d), \tag{3}$$

$$\text{GARD}_{2Gy} = (1) \cdot 2\text{Gy}(\alpha_g + \beta \cdot 2\text{Gy}), \tag{4}$$

$$\text{GARD}_{2Gy} = 2\text{Gy}\left[\frac{-\ln \text{RSI}}{2\text{Gy}} - \beta\, 2\text{Gy} + \beta\, 2\text{Gy}\right] = -\ln \text{RSI}. \tag{5}$$

For a clinical gard (i.e. the GARD a patient experiences upon repeated doses of radiation, which we will from here on denote GARD_c), one would have to scale this by the number of fractions given, so (assuming 2Gy fractions) this would yield

$$\text{GARD}_c = \frac{n_c}{n_e}(-\ln \text{RSI}), \tag{6}$$

where n_i where $i \in \{c, e\}$ is the number of doses given in the clinical scenario, and the experimental ($n_e = 1$) conditions.

Code Excerpt:

Here GARD_c is calculated computationally as a function of treatment dose and individual α_g.

```
df <- mutate(df, GARD_c = n_c*d*(alpha_g + beta*d))
```

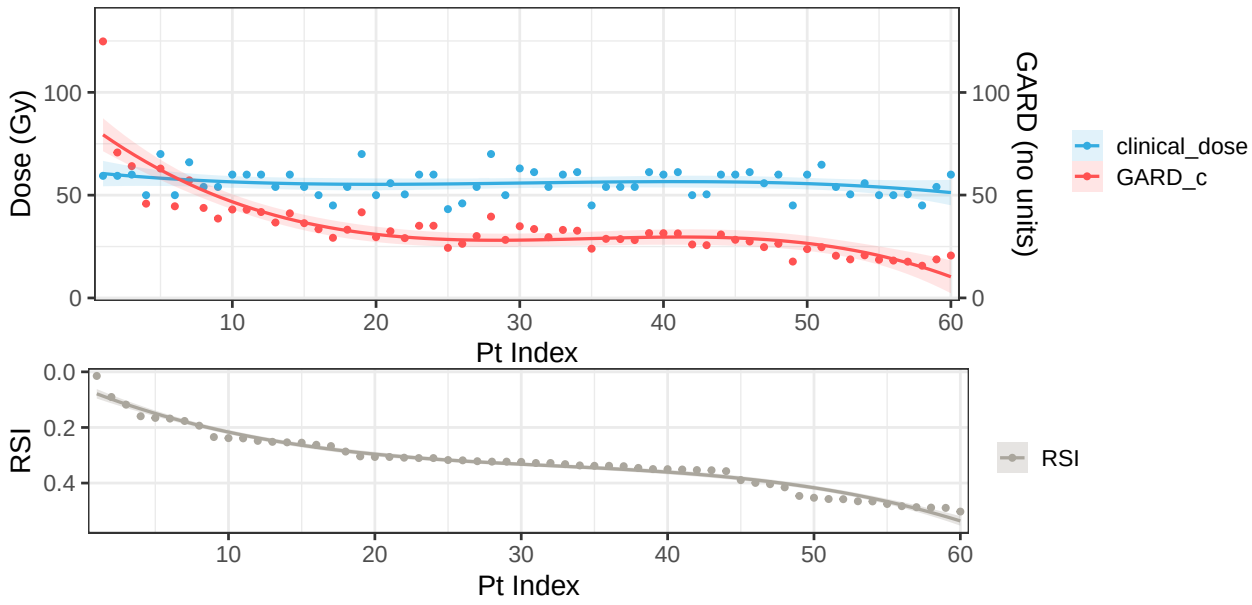

Figure 2: (Top) GARD_c vs. clinical dose for each patient, with associated RSI aligned (bottom). Each point along the x-axis represents an individual patient. RSI for each patient (matched vertically between the plots) is plotted underneath in order to demonstrate the relationship between between the two parameters.

In our previous paper (Scott et al. Lancet Oncology, 2016), we hoped to capture the spirit of GARD, a unitless parameter, which is *similar* to BED, but not mathematically equivalent, in order to appeal to the understanding of clinicians. The mathematical definition of GARD takes the same form we use here, which is the same form as *biological Effect*: $E = nd(\alpha + \beta d)$, and subsequently GARD $= n_c d(\alpha_g + \beta d)$.

$$\alpha_g = \frac{-\ln RSI}{n_e d} + \beta d \quad \text{and,} \tag{7}$$

$$\text{GARD}_c = n_c d(\alpha_g + \beta d). \tag{8}$$

Derivation of RxRSI

Once GARD_c is derived for every individual patient in the cohort (i.e. using each individually derived α_g and the actual dose of radiation received: $n_c d$), a distribution can be visualized.

Code Excerpt:

The left plot below shows the Kaplan-Meier plot of the 60 patient cohort. The right side shows the kernel density estimate of the calculated GARD_c. These are the same values shown in Figure 2 (top).

```
km <- survfit(Surv(time,event) ~ 1, data = df)
```

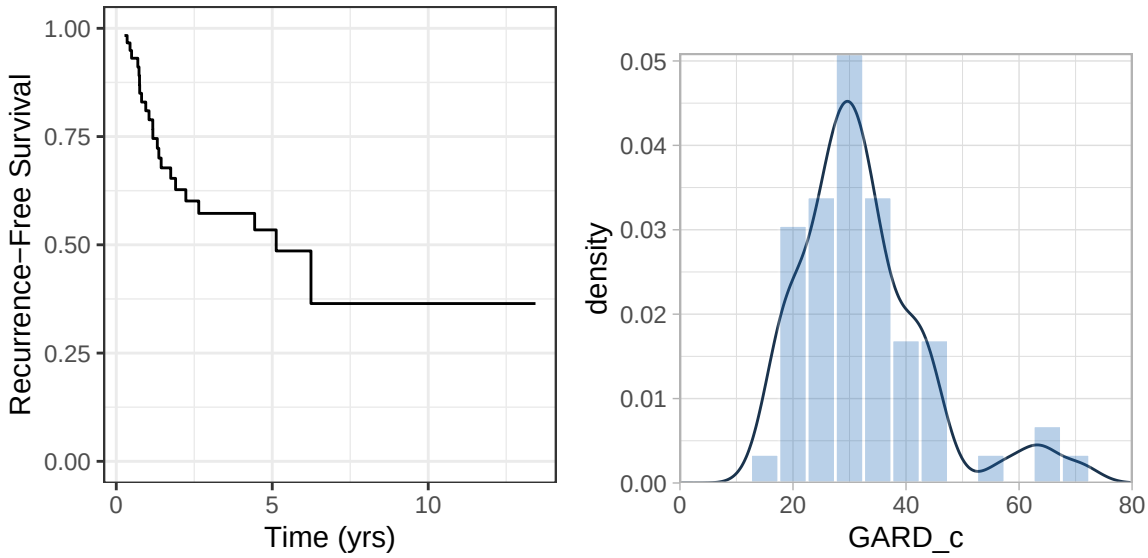

Figure 3: All patients survival and calculated GARD_c. A Kaplan-Meier plot (left) for all patients in the clinical cohort and (right) a histogram and associated KDE for the calculated GARD for all patients.

This distribution was then used to find an optimal GARD threshold (GARD_T), which minimizes the $p-$value of the Kaplan-Meier statistic using the clinical outcomes.

Code Excerpt:

Cox proportional hazard models are shown below in order to briefly illustrate the relationship between GARD_c and outcomes, first as a linear variate (Table 1) and then with the derived threshold value (Table 2).

```
fit <- cph(Surv(time,event) ~ GARD_c, data = df,x = T, y= T )
```

Table 1: Summary of Cox regression for linear GARD_c

coef	exp(coef)	se	z	chi-sq	p
-0.04	0.96	0.02	-1.82	3.31	0.07

```
fit <- cph(Surv(time,event) ~ GARD_c<33, data = df,x = T, y= T )
```

Table 2: Summary of Cox regression for $\text{GARD}_c = 33$

coef	exp(coef)	se	z	chi-sq	p
1.23	3.44	0.51	2.41	5.80	0.02

The Kaplan-Meier curves demonstrate the above described stratification with GARD_T as applied to this patient cohort.

```
km <- survfit(Surv(time,event) ~ GARD_c<33, data = df)
```

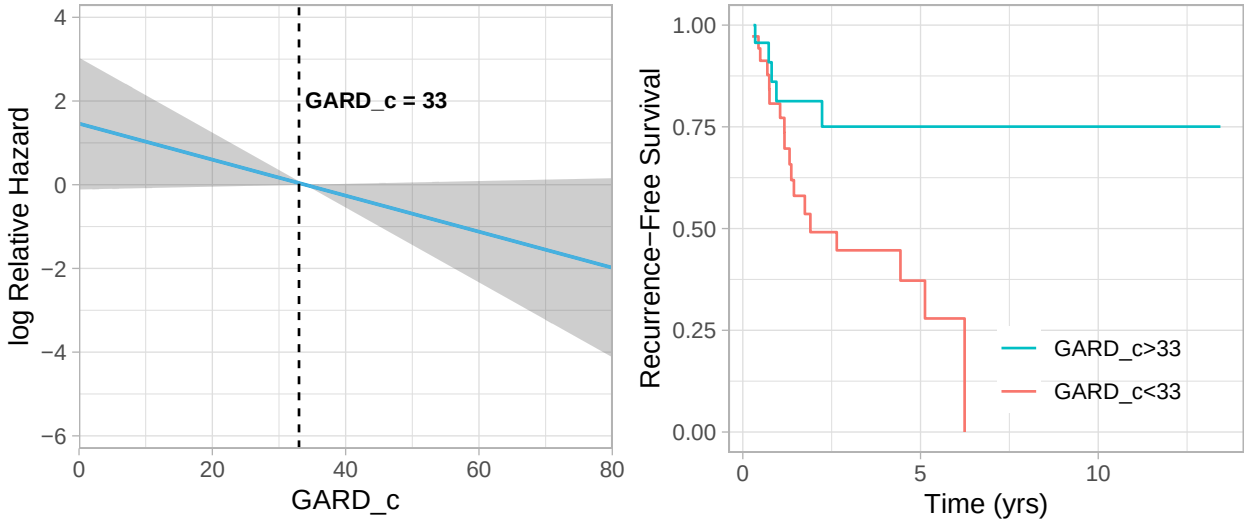

Figure 4: Kaplan-Meier curve stratified by GARD_T.

Defining GARD_T

At this point, GARD_T is a **set, static number: a target biological Effect to achieve through physical dosing**, it no longer has the α_g term in it. Therefore, when we define RxRSI, using GARD_T

$$\text{RxRSI} = \frac{\text{GARD}_T}{\alpha_g + \beta d}, \tag{9}$$

Note here that the units of RxRSI are now Gy. For each patient, we calculate what physical dose (nd), modulated by their biology (through α_g) is needed to reach this **target effect ($\text{GARD}_T = 33$)**.

$$\text{RxRSI} = \frac{33}{\alpha_g + \beta d}. \tag{10}$$

Code Excerpt:

```
GARD_T = 33
df <- mutate(df, RxRSI = GARD_T/(alpha_g + beta*d))
```

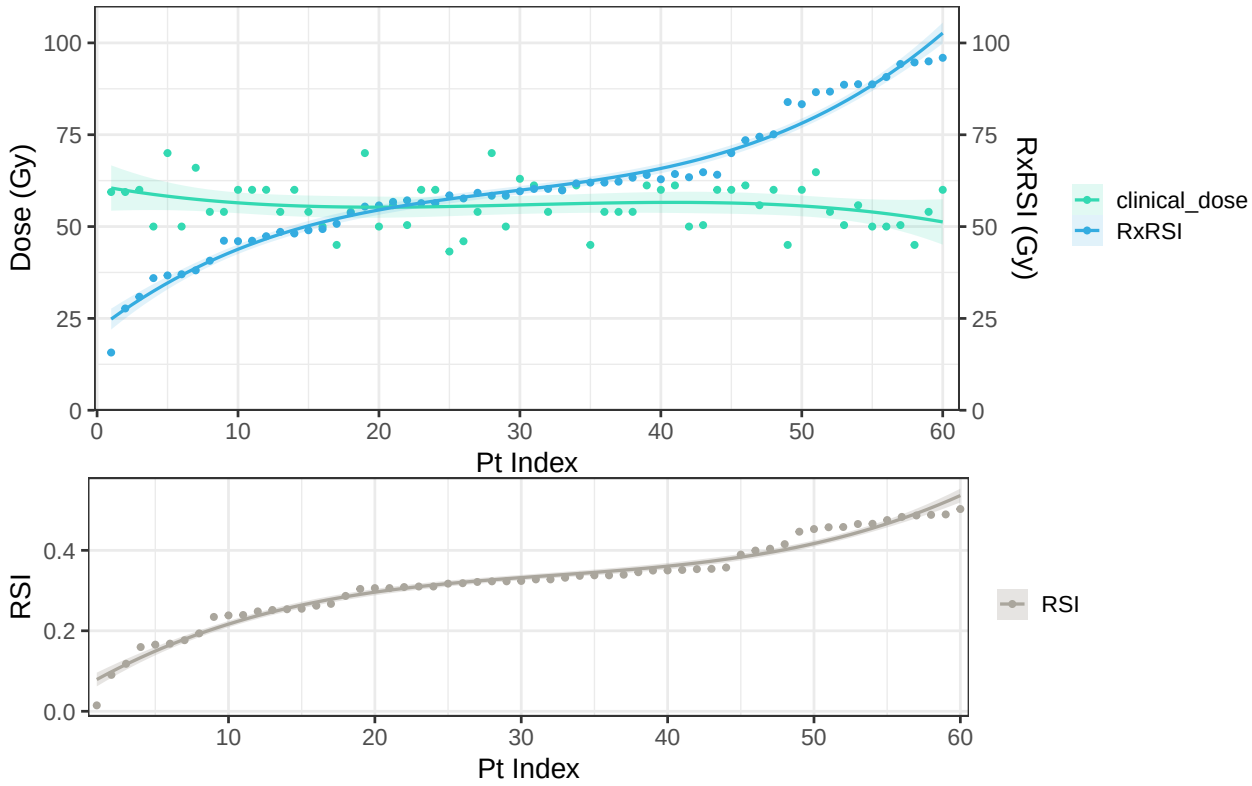

Figure 5: Clinical dose and RxRSI plotted for each patient. The axis for RxRSI shares the same scale and unit (Gy) as clinical dose.