A Netowrk Meta Analysis of Treatments for Advanced Pancreatic Cancer Using Parametric and Non-Parametric Survival Models

Matthew Knowles

School of Health and Related Research,
University of Sheffield,
United Kingdom

Supervisor: Dr. Kate Ren

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Abstract

Five treatments for advanced pancreatic cancer were compared against the standard of care treatment in two network meta analyses. The first network meta analysis used parametric survival models, and the second used fractional polynomials. The parametric model results showed only one treatment gave improvements on the standard of care, but little to no improvements were found in overall survival.

Acknowledgements

For my late grandfather, Norman Fredrick Taylor (July 1943 - April 2015).

CONTENTS

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INTRODUCTION

1.1 Pancreatic Cancer

Pancreatic cancer is the 10th most common cancer in the UK, accounting for 3% of all new cases [Cancer Research UK, 2024]. Pancreatic cancer has a particularly poor prognosis. In 2016-2018, there were 9,558 deaths from 10,452 cases. Pancreatic cancer is hard to detect at early stages, meaning most people who present with symptoms already have advanced-stage pancreatic cancer. Often, patients only notice symptoms when the tumour has spread to surrounding tissues, or metastises to other organs [Kelsen et al., 1997]. The liver is the most common site of pancreatic cancer metastases [Deeb et al., 2015]. Common symptoms of pancreatic cancer include indigestion, stomach or back pain, loss of appeteite and jauncdice [Pancreatic Cancer UK, 2022].

Risk factors of pancreatic cancer include smoking, diabetes, obesity, and high-fat diets. Smoking is the dominant cause, with around 20% of cases being caused by cigarette smoking. In addition, cancers from smokers contain more genetic mutations when compared to cancers from non-smokers [Blackford et al., 2009].

1.2 Treatment Landscape

Gemcitabine (GEM) ($C_9H_{11}F_2N_3O_4$) is a standard first-line treatment for pancreatic cancer administered intrveneously [for Health and Excellence, 2018]. GEM is also used to treat other types of cancer, including breast cancer, bladder cancer and non-small-cell lung cancer [Wong et al., 2009]. GEM can be administered alone or in combination with another medication.

This dissertation considered five treatments that were given in combination with GEM: Cisplatin (CIS) ($PtCl_2(NH_3)_2$), Capecitabine (CAP) ($C_{15}H_{22}FN_3O_6$), Axitinib (AXI) ($C_{22}H_{18}N_4OS$), Pemetrexed (PEM) ($C_{20}H_{21}N_5O_6$), and Irinotecan (IRI) ($C_{33}H_{38}N_4O_6$).

SURVIVAL ANALYSIS BAKGROUND

2.1 Background and Survival Functions

Given a homogeneous population of individuals, the time of death for each individual is drawn from a continuous random variable $T > 0$ with probability density function $f(t)$ and distribution function $F(t) = \int_0^t f(\tau)d\tau$. Survival analysis is concerned with estimating the distribution T from Time-To-Event (TTE) data. There are two functions central to survival analysis, the *survival function* and *hazard function*.

> **Definition 2.1.1: Survival Function**
>
> The **Survival Function** $S(t)$, gives the probability of an individual surviving longer than time t.
> $$S(t) = P(T \geq t) = 1 - F(t) = \int_t^\infty f(\tau)d\tau$$

> **Definition 2.1.2: Hazard Function**
>
> The **Hazard Function** gives the risk of death at time t, given that the individual has survived up to time t.
>
> $$h(t) = -\frac{d}{dt}\log S(t)$$

2.2 Regression Models for Survival

The survival time of patients may be dependent on several explanatory variables such as age, sex, the presence of a genetic mutation, etc. We wish to incorperate these variables into our survival functions.

2.2.1 Accelerated Failure Time (AFT) Models

Let x be a vector of explanatory variables for each individual in a trial. The survival function can be extended to include this,

$$S(t, \mathbf{x}) = \mathbf{S_0}(\mathbf{t}\,(\mathbf{x})).$$

Here, $S_0(t) = S(t, \mathbf{x} = \mathbf{0})$, i.e the survival function at baseline. We define the density and hazard functions accordingly,

$$f(t, \mathbf{x}) = f_0(t\Psi(\mathbf{x})) \, (\mathbf{x})$$
$$h(t, \mathbf{x}) = h_0(t\Psi(\mathbf{x})) \, (\mathbf{x}).$$

This is equivalent to defining a random variable T such that

$$T = T_0/\Psi(\mathbf{x}).$$

Here, T_0 has survivor function S_0. It is required that $\Psi(\mathbf{x}) \geq \mathbf{0}$ and $\Psi(\mathbf{0}) = \mathbf{1}$ [[NOTE TO MATT: WHY?]], leading to the natural choice

$$\Psi(\mathbf{x}) = \exp(-\beta'\mathbf{x}).$$

We can then write

$$T = T_0/\Psi(\mathbf{x})$$
$$\implies E(T) = E(T_0)/E(e^{-\beta'x})$$
$$= E(T_0)/e^{-\beta'x}$$
$$= E(T_0)e^{\beta'x}$$

In practice, we assume a distribution for T, and estimate parameters using maximum likelihood estimation.

2.2.2 Proportional Hazards (PH) Models

Let h_0 represent the hazard function for an individual at baseline. In addition, let $\mathbf{x}$ be a vector of explanatory variables. The proportional hazards model, also known as the Cox model [Cox, 1972] is then given by

$$h(t, \mathbf{x}) = \mathbf{e}^{\beta'\mathbf{x}}\mathbf{h_0(t)} \tag{2.1}$$

Consider the following defintion.

> **Definition 2.2.1: Semi Parametric Model**
>
> A statistical model is a parameterised family of distributions $\{P_\theta : \theta \in \Theta\}$. For a parametric model, $\Theta \subseteq \mathbb{R}^k$ for $k \in \mathbb{N}$. Similarly, for a non-parametric model, $\Theta \subseteq V$, where V is some (possibly infinite) dimensional space V. A **Semi-parametric** model is a statistical model with both parametric and non-parametrc components. For a semi-parametric model we have $\Theta \subseteq \mathbb{R}^k \times V$.

The Cox model is semi-parametric then β is of finite dimension and $h_0(t)$ is infinite-dimensional and does not need to be specified.

2.3 Parametric Models for Survival Analysis

This section discusses the parametric models commonly used in Survival Analysis. In particular, the seven parametric models recommended by the National Institute for Health and Care Excellence (NICE) in Technical Support Document (TSD) 14 [Latimer, 2011]. All parametric model fitting for this project was performed in R using the `flexsurv` package [Jackson, 2016]. The first section outlines how the `flexsurv` package works.

2.4 Model Setup

The general model of a `flexsurv` survival model takes the form

$$f(t|\mu(\mathbf{z}), \alpha(\mathbf{z})). \tag{2.2}$$

Equation 2.2 gives the probability density for death at time $t \geq 0$. The *mean* or *location* of the distribution is given by $\mu = \alpha_0$. The remaining parameters, $\alpha^\mathbf{1} = (\alpha_\mathbf{1}, \ldots, \alpha_\mathbf{R})$ are called *ancillary* parameters.

Chapter 2 discussed AFT and PH models. Under the `flexsurv` framework, if the hazard function, $h(t) = \frac{f(t)}{S(t)}$, can be factorised as

$$h(t|\alpha, \mu(\mathbf{z})) = \mu(\mathbf{z})\mathbf{h_0}(\mathbf{t}|\alpha).$$

Then we have a PH model. On the other hand, an AFT model would be written as

$$S(t|\mu(\mathbf{z}), \alpha) = \mathbf{S_0}(\mu(\mathbf{z})\mathbf{t}/\alpha).$$

All parameters may depend on $\mathbf{z}$, a vector of covariates. This is done through the link-transformed linear models

$$g_0(\mu(\mathbf{z})) = \gamma_0 + \beta_\mathbf{0}^\mathbf{T}\mathbf{z}$$
$$g_r(\alpha_r(\mathbf{z})) = \gamma_r + \beta_\gamma^\mathbf{T}\mathbf{z} \tag{2.3}$$

g is usally chosen to be $log()$ if the parameter is positive, or the identity function if the parameter is unrestricted.

`Flexsurv` contains several built-in models. Appendix B.1 presents these models.

2.5 Fitting Models

Let t_i, $i \in \{1, \ldots, n\}$, be a sample of times from n individuals. Define c_i such that

$$c_i = \begin{cases} 1 & \text{if } t_i \text{ is an observed death time} \\ 0 & \text{if } t_i \text{ is censored} \end{cases}.$$

Introduce s_i, which are delayed-entry times. This means for an individual i who is delayed-entry, the survival time is only observed conditionally on individual i having survived up to time s_i. $s_i = 0$ when there is no delayed-entry.

2.5.1 Right Censoring

In the case of right-censoring and nothing else, the likelihood for the parameters $\theta = \{\gamma, \beta\}$ required in Equation 2.3 is given by

$$l(\theta|\mathbf{t}, \mathbf{c}, \mathbf{s}) = \frac{\prod_{i:c_i=1}\mathbf{f_i}(\mathbf{t_i})\prod_{i:c_i=0}\mathbf{S_i}(\mathbf{t_i})}{\prod_\mathbf{i}\mathbf{S_i}(\mathbf{s_i})} \tag{2.4}$$

2.5.2 Interval Censoring

In the case of interval-censoring, where the survival time is censored on $(t_i^{\min}, t_i^{\max})$, the likelihood for $\theta = \{\gamma, \beta\}$ is

$$l(\theta|\mathbf{t}^{\min}, \mathbf{t}^{\max}, \mathbf{c}, \mathbf{s}) = \frac{\prod_{i:c_i=1} f_i(t_i) \prod_{i:c_i=0} \left(S_i(t_i^{\min}) - S_i(t_i^{\max})\right)}{\prod_i S_i(s_i)} \tag{2.5}$$

Maximum Likelihood Estimation is performed in `R` using the analytic derivatives of Equation 2.4 and/or Equation 2.5.

MATHEMATICAL BACKGROUND OF FRACTIONAL POLYNOMIALS

The seminal paper on fractional polynomials is [Royston and Altman, 1994]. This chapters introduces the mathematical background of Fractional Polynmials.

3.1 Setup and Definitions

For a single covariate $x > 0$, an initial definition of a fractional polynomial may take the form

$$\phi_m(x, \zeta, \mathbf{p}) = \zeta_0 + \sum_{j=1}^{m} \mathbf{x}^{(\mathbf{p_j})}$$

Where $m \in \mathbb{N}$, $\mathbf{p} = (\mathbf{p_1}, \mathbf{p_2}, \ldots, \mathbf{p_m}) \in \mathbb{R}^{\mathbf{m}}$ with $p_1 < p_2 < \cdots < p_m$ and $\zeta = (\zeta_0, \zeta_1, \zeta_2, \ldots, \zeta_m) \in \mathbb{R}^{\mathbf{m+1}}$. Note that the $x^{(p_j)}$ term is the *Box-Tidwell Transformation*

Definition 3.1.1: Box-Tidwell Transformation

The **Box-Tidwell Transformation** for a variable x and power p is given by

$$x^{(p)} = \begin{cases} x^p & \text{if } p \neq 0 \\ \log(x) & \text{if } p = 0 \end{cases}$$

Recall, a conventional (real-valued) polynomial of degree m in a variable x is given by

$$f(x) = \sum_{j=0}^{m} a_j x^j = a_0 + a_1 x + a_2 x^2 + \cdots + a_m x^m.$$

Then it follows that $f(x) = \phi_m(x, \zeta, \mathbf{p})$ with $\zeta = (\mathbf{a_o} = \mathbf{0}, \mathbf{a_1}, \mathbf{a_2}, \ldots, \mathbf{a_m})$ and $\mathbf{p} = (\mathbf{1}, \mathbf{2}, \mathbf{3}, \ldots \mathbf{m})$. However, the current definition does not account for the situation where two concurrent powers are equal. Before giving the general form of a fractional polynomial, the following function that extends the Box-Tidwell transform must be considered.

Let $j = 1, 2, \ldots, m$. Then

$$H_j(x) = \begin{cases} x^{(p_j)} & \text{if } p_j \neq p_{j-1} \\ H_{j-1}(x) \log(x) & \text{if } p_j = p_{j-1} \end{cases}.$$

By default, $H_0(x) = 1 \ \forall \ X$.

Definition 3.1.2: Fractional Polynomial

For arbitrary powers $p_1 \leq p_2 \leq \cdots \leq p_m$ and $p_0 = 0$ a **Fractional Polynomial** is of the form

$$\phi_m(x, \zeta, \mathbf{p}) = \sum_{\mathbf{j=0}}^{\mathbf{m}} \zeta_{\mathbf{j}} \mathbf{H_j(x)}$$

The following example is chosen given the context of survival analysis.

Example 3.1.1: $m = 2$ **Fractional Polynomial**

Consider the set of powers $\mathbf{p} = (\mathbf{-2, -1})$ and let $\zeta = \mathbf{1}$. Then we have

$$\phi(x) = \sum_{j=0}^{2} H_j(x)$$
$$= H_0(x) + H_1(x) + H_2(x)$$
$$= 1 + \frac{1}{x^2} + \frac{1}{x}$$

A sketch of this polynomial can be seen below.
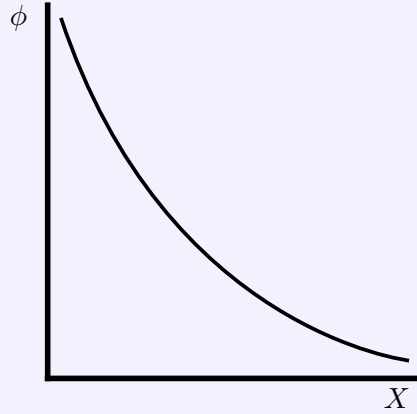
3.2 Fitting Fractional Polynomials to Data

The set of powers $\mathbf{p}$ for fitting fractional polynomials must be considered. The paper by [Royston and Altman, 1994] presents the set $\{-2, -1, -0.5, 0, 0.5, 1, 2, \ldots, \max(3, m)\}$. However, some of these models will not be acceptable in a survival analysis context. This is because of the conditions on any survival function $S(t)$. Firstly $S(0) = 1$, so if a $S(0)$ is undefined, it is not a valid survival function. Further, a survival must be monotonically decreasing.

Definition 3.2.1: Monotonically Decreasing

Let $f(x) : \mathbb{R}^+ \to \mathbb{R}$ be a differentiable function. f is **monotonically decreasing** over $\mathbb{R}^+$ if for any $x, y \in \mathbb{R}^+$ with $x < y$, $f(x) \geq f(y)$. Equivalently, $f'(x) \leq 0 \forall x \in \mathbb{R}^+$

Example 3.2.1: Invalid Survival Fractional Polynomial

Let $m = 2$, $\mathbf{p} = (-\mathbf{2}, \mathbf{1})$ and $\zeta = \mathbf{1}$. Then we have

$$\phi(x) = \sum_{j=0}^{2} H_j(x)$$
$$= H_0(x) + H_1(x) + H_2(x)$$
$$= 1 + \frac{1}{x^2} + x$$

This is clearly undefined at $x = 0$, But consider the first and second derivatives of this function.

$$\frac{d\phi}{dx} = 1 - 2x^{-3}$$
$$\frac{d^2\phi}{dx^2} = 6x^{-4}$$

There is a local minimum at $x = 2^{1/3}$, which is an inflection point in this case, meaning the curve starts increasing again after this point, which is not allowed in survival analysis, but also, the only real root is at $x = -1.4656$, which means for $x > 0$, there is no point at which the function reaches 0, and hense cannot be used to model survival, as not everyone would be able to die.

It would be possible to include 0 by setting the first ζ term to a sufficiently negative value to translate the curve down, but this does not escape the undefined at $X = 0$ issue.

In order to get around this issue, a survival function that uses a fractional polynomial must be written piecewise.

Definition 3.2.2: Fractional Polynomial Survival Function

Let $t \in \mathbb{R}^+$. For arbitrary powers $p_1 \leq p_2 \leq \ldots \leq p_m$ and p_0, a **Fractional Polynomical Survival Function** takes the form

$$S(t) = \begin{cases} 1 & \text{if } t = 0 \\ \phi_m(t, \zeta, \mathbf{p}) = \sum_{\mathbf{j=0}}^{\mathbf{m}} \zeta_\mathbf{j} \mathbf{H_j(t)} & \text{otherwise} \end{cases}$$

3.3   Fractional Polynomials for Flexsurv

NETWORK META ANALYSIS

4.1 Building a Network of Evidence

Consider a set of N two-arm clinical trials. In each trial $i \in 1, \ldots, N$, the patients are randomised to recieve a treatment A_i, or a placebo P_i. This can be represented as N graphs with two nodes, A_i and P_i, connected by an edge representing the trial comparing A_i and P_i. It is useful at this stage to recall the formal definition of an (undirected) graph.

> **Definition 4.1.1: Graph**
>
> A **Graph** is an ordered triple $G = (V, E, \varphi)$. Where V is a set of nodes, E is a set of edges, and $\varphi : E \to \{\{x, y\} | x, y \in V \text{ such that } x \neq y\}$ is an **incidence function** mapping every edge to a pair of verticesa.

We can construct N graphs under the formal definition. Namely, for trial T_i, we have $G_i = (V_i, E_i, \varphi_i)$ where $V_i = \{A_i, P_i\}$, $E_i = \{T_i\}$ and $\varphi_i : E_i \to \{\{x, y\} | x, y \in V_i \text{ such that } x \neq y\}$. For construction of the grpahs, we can drop the subscript on P_i, and take the placebo as a reference treatment. This is done under the assumption that the effect of placebo is constant across all trials. This is a strong assumption, and implications of this are discussed later. Under this assumption however, each V_i now contains a common element, P.

Let

$$V_{trts} = \bigcup_{i=1}^{N} V_i$$

$$E_{trials} = \bigcup_{i=1}^{N} E_i.$$

The incidence function becomes

$$\varphi : E_{trials} \to \{\{x, y\} | x, y \in V_{trts} \text{ such that } x = P\}.$$

Then the ordered triple $G = (V_{trts}, E_{trials}, \varphi)$ is the network of evidence given by these two arm trials that forms the basis of a network meta analysis. This process expands to trials that compare more than two treatments by weighting the edges by the number of trials making that particular comparison.

4.2 The Foundational Bayesian-NMA Model

The development of the core NMA model in this section follows that of [Dias et al., 2018].
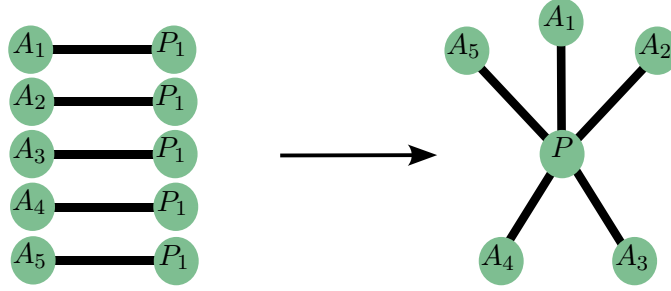
Figure 4.1: Visualisation of combining trials into a network of evidence

In this dissertation, trials with only two treatment arms were considered, we therefore develop the NMA model in this context. We also consider only random effects models, as it relies on less assumptions about the underlying population in the trials. The literature review performed for this dissertation was not particularly systematic, and therefore random effects models are more appropriate. Consider N two-arm trials. In a random effeects model, each study $i \in M$ provides an estimate of the study-specific treatment effects $\delta_i, 12$ between treatment 1 and 2 in study i. The $\delta_{i,12}$ are subject to the *exchangeability assumption*, which means the trial-specific treatment effects for each $i \in M$ come from a commond distribution, known as the *random effects distribution*. A common choice for this distribution is the normal distribution, such that

$$\delta_{i,12} \sim N(d_{12}, \sigma_{12}^2) \tag{4.1}$$

The d_{12} term in Equation 4.1 is the pooled effect of t reatment 2 compared with 1. This is the primary parameter of interest in an NMA. It follows that by setting σ_{12}^2 in Equation 4.1 gives the fixed effects model. Under a Bayesian framework, priors are required for the parameters that will be estimated. Since the data obtained from a study or trial should give the most weight to the estimated treatment effects, non-informative priors are used. The pooled treatment effect is assumedto be able to take any value in $\mathbb{R}$, so we may use $d_{12} \sim N(0, 100)$ as a non-informative prior. For the σ_{12}^2 term in Equation 4.1 has the constraint $\sigma_{12} > 0$, so a uniform distribution with a lower bound at 0 is an appropriate prior.

Consider Figure 4.1. The above model is equivalent to making five comparisons. One for each A_n with the reference P $(n = 1, \ldots, 5)$. But suppose a comparison of A_2 with A_3 was to be made. In the general framework, we want to compare treatments 1 and 3 from the evidence in the N trials. Assume that the $\delta_{i,13} N(d_{13}, \sigma_{13}^2)$ are exchangable. By transitivity, we obtain $\delta_{i,23} = \delta_{i,13} - \delta_{i,12} \sim N(d_{23}, \sigma_{23}^2) \implies d_{23} = d_{13} - d_{12}$ [Lu and Ades, 2009]. Further to this result, we have $\sigma_{23}^2 = \sigma_{12}^2 + sigma_{13}^2 - 2\rho_{23}\sigma_{12}\sigma_{13}$, where ρ_{23} is the correlation between the relative effects of treatment 3 compared to treatment 1 and of treatment 2 compared to treatment 1. If the patient populations are similar in the trials being considered, it is reasonable to assume that $\sigma_{12}^2 = \sigma_{13}^2 = \ldots = \sigma^2$.

> **Remark 4.2.1: Notation**
>
> As not all studies compare the same treatments, some notation must be introduced to distinguish between arm k of trial i and the treatment compared in that arm. The trial-specific treatment effects of the treatment in arm k, relative to the treatment in arm 1 of trial i are $\delta_{ik} \sim N(d_{t_{i1}}, t_{ik}, \sigma^2)$.

Under this notiaton, a trial comparing treatment 1 and 2 we have $d_{12} = d_{t_{i1}, t_{ik}}$ and for a trial comparing treatment 2 and treatment 3, $d_{23} = d_{t_{i1}, t_{ik}}$. In an NMA, only the d_1k are estimated, and are given the non-infomrative priort $d_{1k} \sim N(0, 100^2)$.

4.3 Generalized Linear Models in NMAs

A meta-analysis model can be written in the form of a Generalised Linear Model as follows,

$$
\begin{aligned}
g(\gamma) &= \theta_{ik} \\
&= \mu_i + \delta_{ik}.
\end{aligned} \tag{4.2}
$$

In the above, g is an appropriately chosen link function, θ_{ik} represents a continuous measure of the treatment effect in arm k of trial i. Further, μ_i and δ_{ik} are the trial-specific effects of the treatment in arm 1 of trial i and the the trial-specific treatment effects of the treatment in arm k relative to the treatment of arm k in trial i. A more concrete definition of δ_{ik} is

$$
\delta_{ik} \sim \begin{cases} 0 & \text{if } k = 1 \\ N(d_{1,t_{ik}} - d_{1,t_{i1}}, \sigma^2) & \text{if } k > 1 \end{cases}.
$$

Where d_{12} is the relative effect of treatment 2 compared with treatment 1 over some scale. Equation 4.2 is the *random effects* model. The *fixed effect* model is given by the similar result

$$
\begin{aligned}
g(\gamma) &= \theta_{ik} \tag{4.3} \\
&= \mu_i + d_{1,t_{ik}} - d_{1,t_{i1}} \tag{4.4}
\end{aligned}
$$

The remained of this subsection contains information about models relevant to survival outcomes.

4.3.1 Poisson Likelihood with Log Links

Let r_{ik} be the number of events ocurring during the trial followup period.

4.4 Network Meta-Analysis of Survival Data

4.4.1 Parametric Survival Curves: Single Treatment Effect

We assume a parametric survival model across the studies in the network, and obtain an acceleration factor or constant hazard ratio to incorperate in an NMA.

> **Example 4.4.1: Weibull NMA**
>
> ssume the survival times in study i follow a Weibull model, and that the treatment effect acts only on the scale parameter of this model. Define the treatment-specific hazard function $h_{ik}(u) = \lambda_{ik}\varphi_i u^{\varphi_i - 1}$ and implenent the NMA assuming the treatment effects on $\alpha_{0,ik} = \log(\lambda_{ik}\varphi_i)$, which gives the model
>
> $$
> \begin{aligned}
> \log(h_{ik}(u)) &= \alpha_{0,ik} + \alpha_{1,i}\log(u) \tag{4.5} \\
> \alpha_{0,ik} &= \mu_0, i + \delta_{0,ik} \tag{4.6} \\
> \delta_{0,ik} &= N(d_{0,1t_{ik}} - d_{0,1t_{i1}}, \sigma^2) \tag{4.7}
> \end{aligned}
> $$
>
> . In the above, $\alpha_{1,i} = (\varphi_i - 1)$. The α terms describe the hazard over time, and the pooled results are log-HRs.

SURVIVAL ANALYSIS OF PANCREATIC CANCER TRIALS

5.1 Trial Data

Figure 5.1 and Figure 5.2 present the OS KM curves for GEM and the comparators, respectively. In addition, Table 5.1 presents the median OS estimates by study for GEM and the comparator treatment. In all studies except Oettle, GEM had a higher median OS. Note that more information about each included trial is given in Section A.

	Treatment = GEM			Treatment = Comparator		
	Median Survival	L95% CI	U95%CI	Median Survival	L95% CI	U95%CI
Colucci	8.5157	7.412	10.2119	7.2514	6.3844	8.7499
Cunningham	6.0892	5.4991	7.34	7.1984	6.3016	7.9773
Kindler	9.9477	7.2714	11.1849	9.0388	7.0821	10.3769
Oettle	6.1769	5.5159	7.2945	6.4053	5.4246	6.9519
Rocha Lima	6.7424	5.6812	7.9758	6.3989	4.8554	7.6321

Table 5.1: Median OS data (in months) from each of the studies, along with lower and upper 95% confidence intervals

5.2 Parametric Models

For each study, the standard seven parametric models were fit to each treatment arm, up to a maximum time of five years. Figure 5.3 to Figure 5.7 present the fitted models for each study. The median estimates given for each treatment arm of the studies are presenteed in Table C.5 Table C.5.

Survival Probability vs **Time**

Legend: Colucci, Cunningham, Kindler, Oettle, RochaLima

Number at risk:

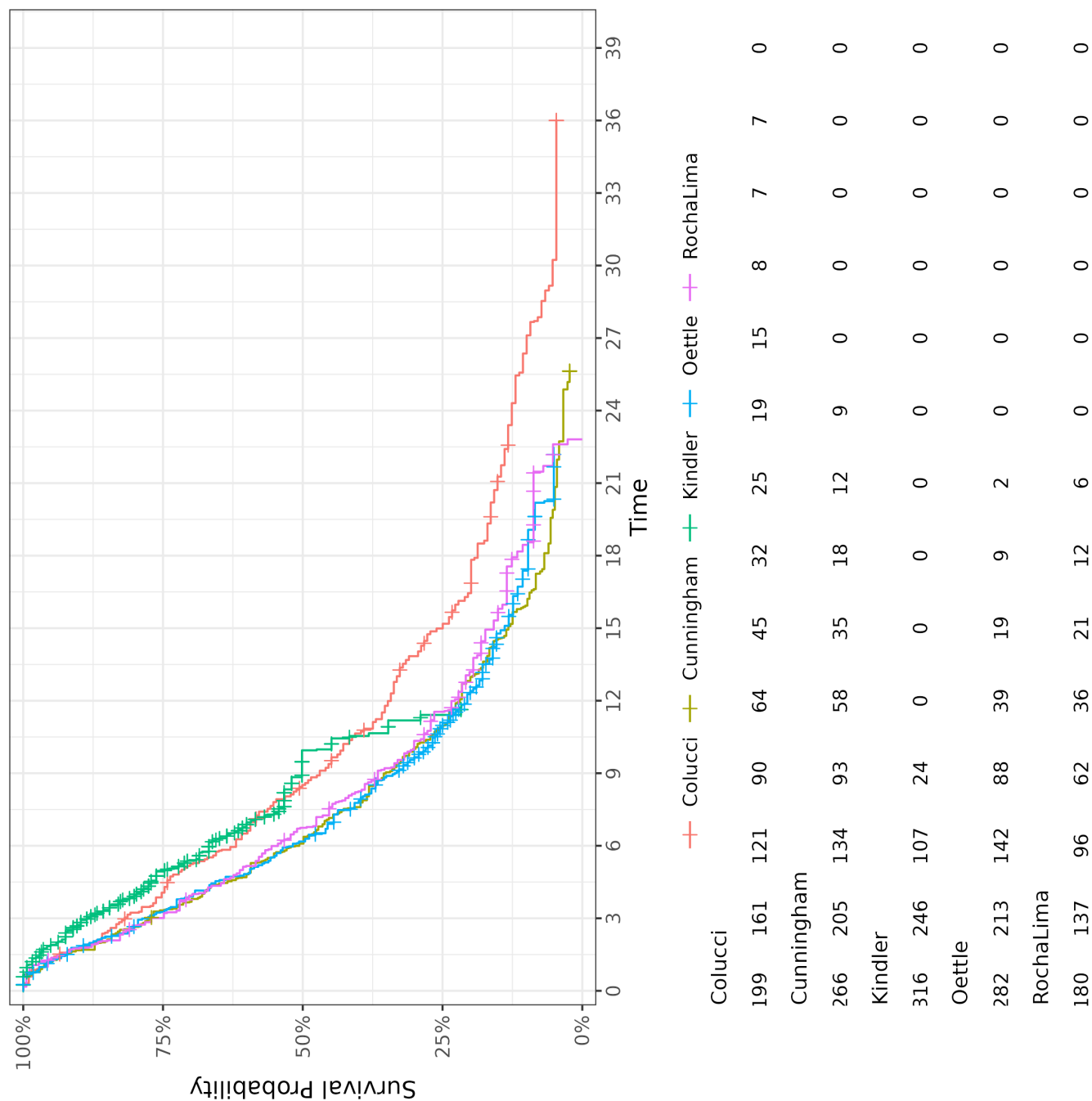| Group	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Colucci	199	161	121	90	64	45	32	25	19	15	8	7	0	0
Cunningham	266	205	134	93	58	35	18	12	9	0	0	0	0	0
Kindler	316	246	107	24	0	0	0	0	0	0	0	0	0	0
Oettle	282	213	142	88	39	19	9	2	0	0	0	0	0	0
RochaLima	180	137	96	62	36	21	12	6	0	0	0	0	0	0

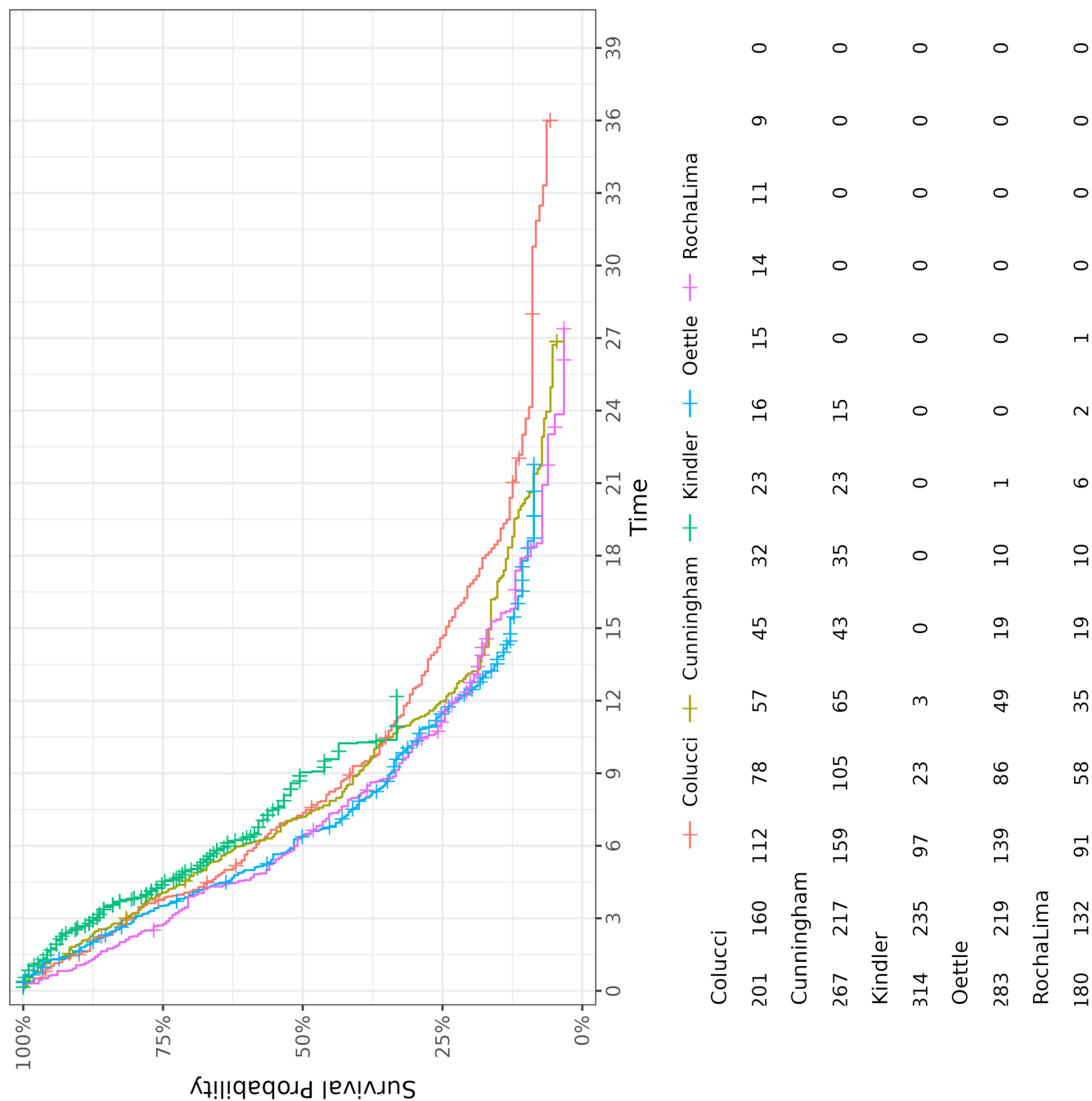Figure 5.1: OS Kaplan-Meier data for Gemcitabine

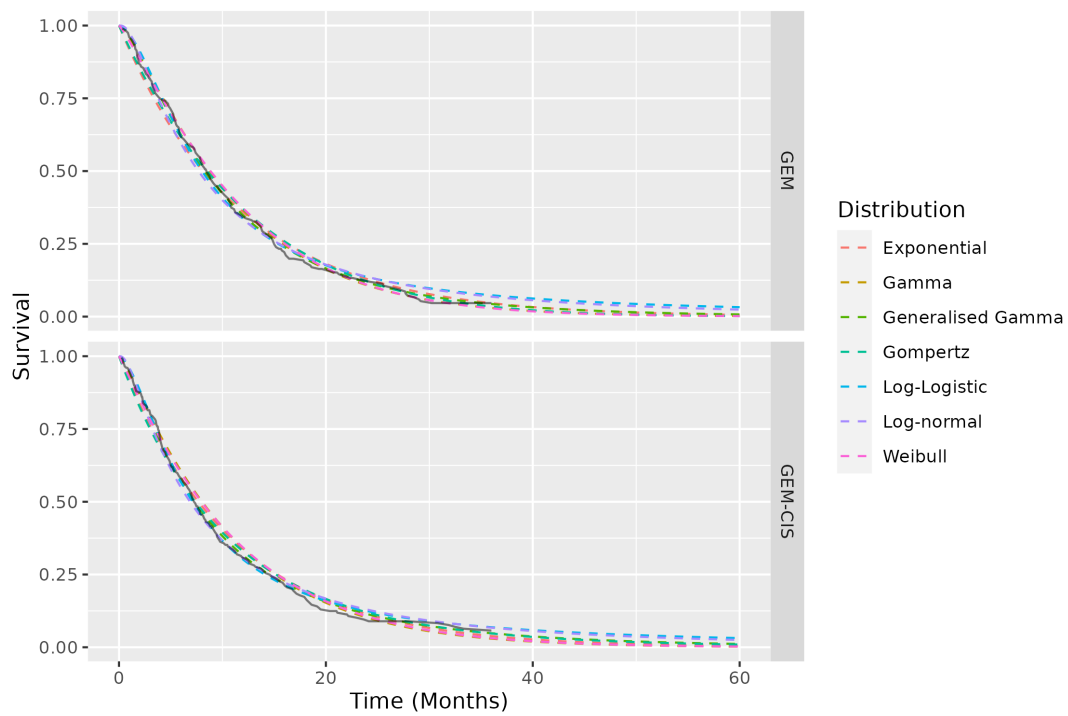Figure 5.2: OS Kaplan-Meier data for comparators
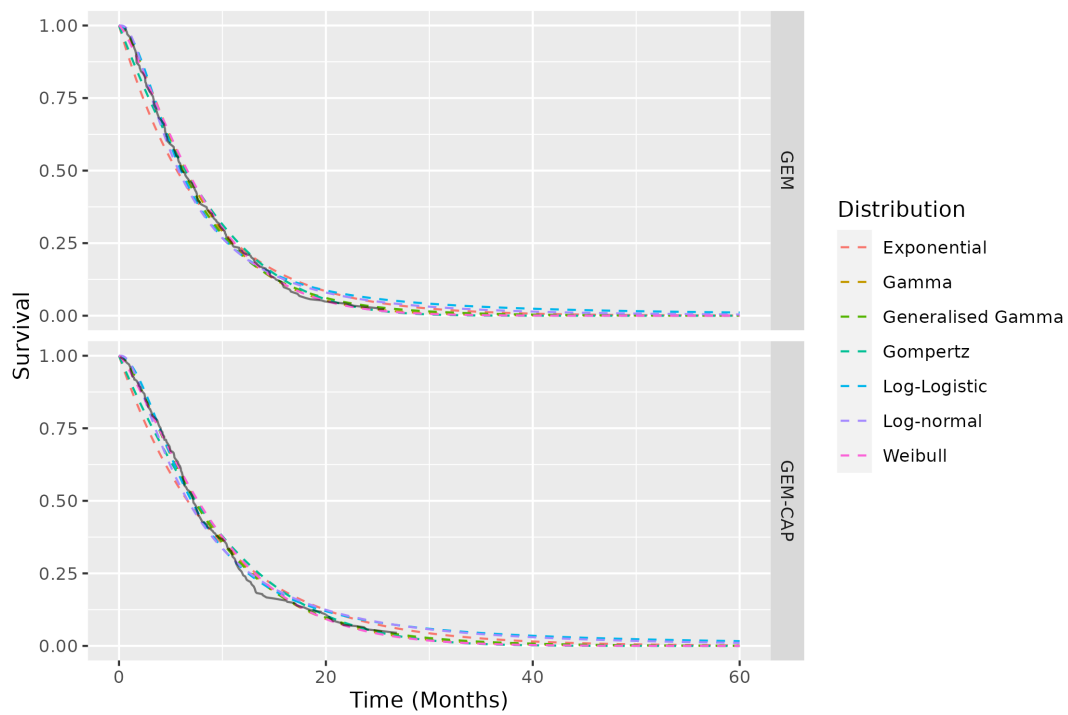
Figure 5.3: Colucci 2010 Models

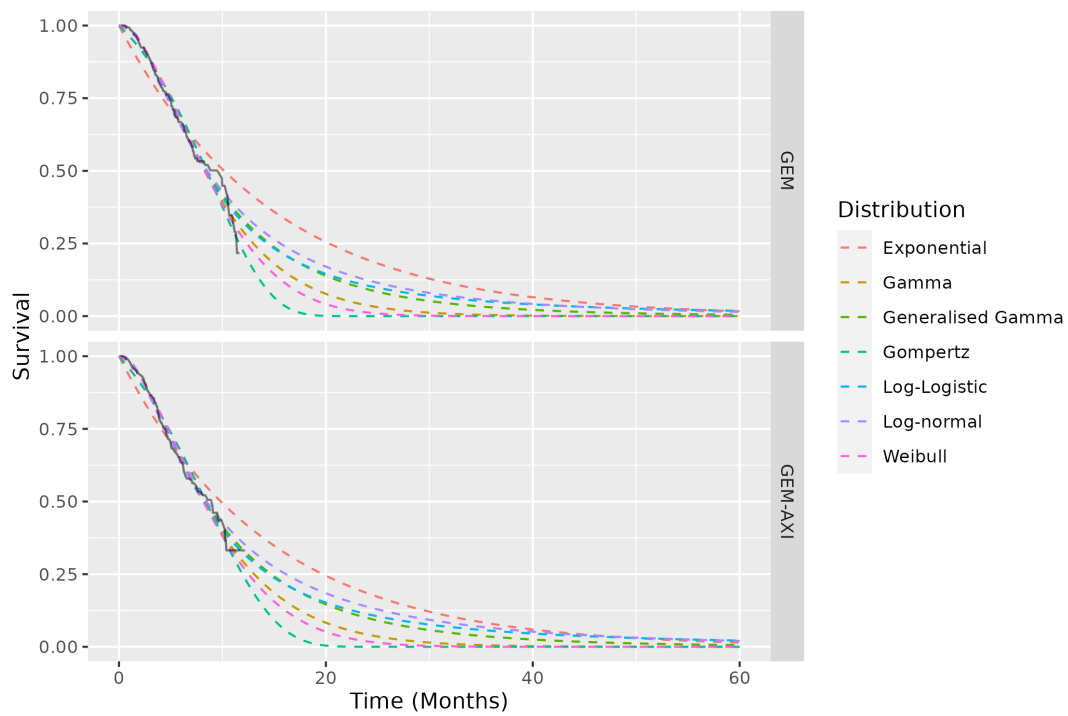Figure 5.4: Cunningham 2009 Models

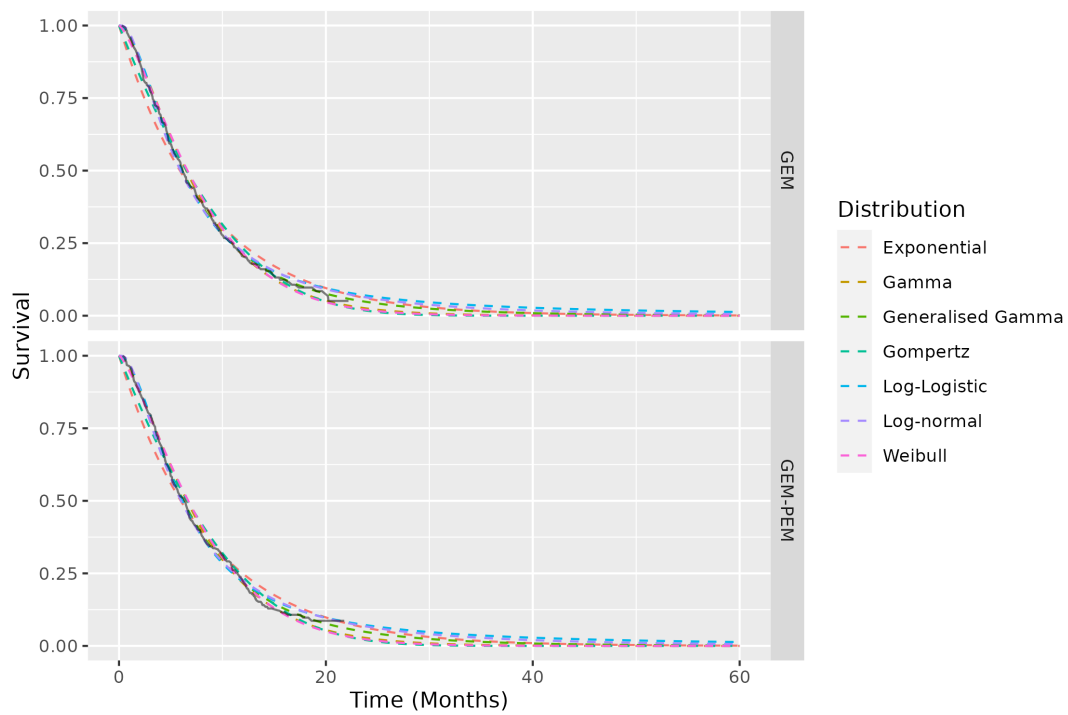Figure 5.5: Kindler 2011 Models

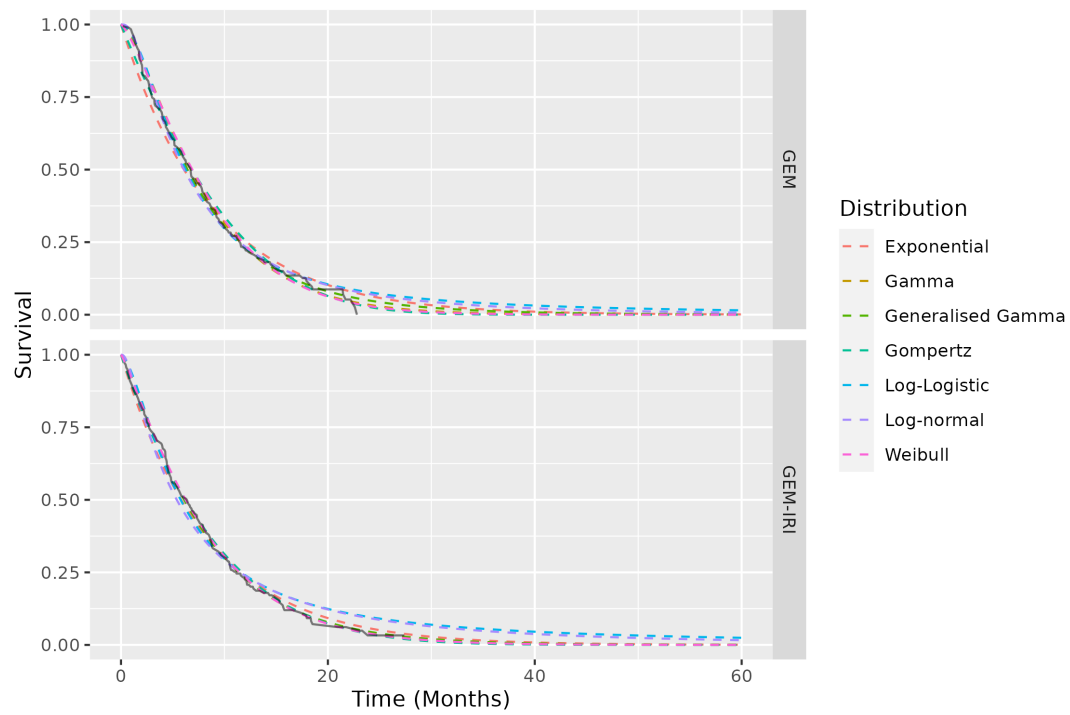
Figure 5.6: Oettle 2006 Models

Figure 5.7: Rocha Lima 2004 Models

NMA OF PANCREATIC CANCER TRIALS

6.1 Data

The NMA is performed on median survival estimates given by the best fitting survival model to each treatment arm in each study. We use the medians given by the survival estimates as opposed to the trial data to account for heterogeneity between the trials. An NMA based on hazard ratios was considered, but deemed inappropriate due to the log-cumulative hazard plots of each trial, as presented in Section C, crossing in every trial, suggesting violation of the PHA.

The `multinma` package requires a standard error for each median value, which we do not have by default. We calculate it from the 95% confidence interval by

$$SE = \frac{(U_{95} - L_{95})}{2 * qnorm(0.975) * \sqrt{n}}.$$

Where n is the number of patients in the trial, and $qnorm(0.975) \approx 1.96$ is the Z-value for a 95% confidence interval for a $N(0,1)$ distribution. L_{95} and U_{95} give the values of the upper and lwoer 95% CI values for a given model. Figure 6.1 presents the network of evidence used in the NMA.

6.2 Parametric Models

Table 6.1 presents the input data used for the parametric NMA.

Distribution	Treatment	Median	L95	U95	Study	n	SE
Gompertz	GEM	8.5075	7.0869	9.9992	Colucci	400	14.859
Generalised Gamma	GEM-CIS	7.3009	6.2111	8.5350	Colucci	400	11.857
Log-Logistic	GEM	5.9954	5.4301	6.6452	Cunningham	533	7.1564
Generalised Gamma	GEM-CAP	7.2947	6.5520	8.1846	Cunningham	533	9.6151
Exponential	GEM	10.154	8.5389	12.230	Kindler	632	23.675
Exponential	GEM-AXI	9.8440	8.0901	11.928	Kindler	632	24.613
Generalised Gamma	GEM	6.1225	5.4602	6.9002	Oettle	565	8.7319
Gamma	GEM-PEM	6.5691	5.9814	7.2575	Oettle	565	7.7381
Gamma	GEM	6.7650	5.9708	7.6333	Rocha Lima	360	8.0471
Weibull	GEM-IRI	6.2512	5.3539	7.3042	Rocha Lima	360	9.4399

Table 6.1: Input data for the parametric NMA

Figure 6.2 presntes the forest plots of the NMA conducted on median survival estimates. Both fixed and random effects models were fit. There was little difference between the two models, as shown by the selection statistics in Table 6.2. Note that the forest plots in Figure 6.2
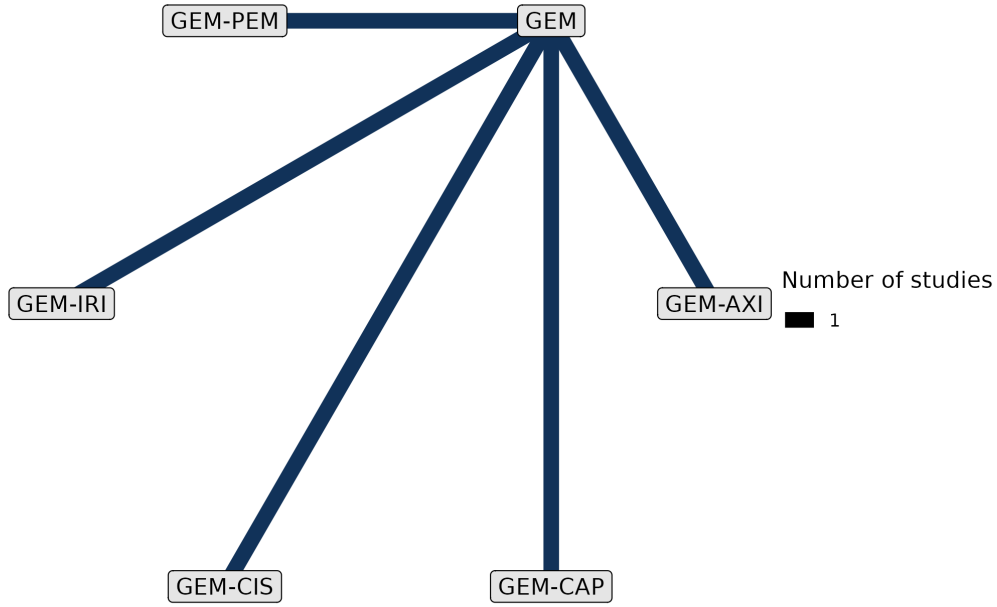
Figure 6.1: Network of evidence

have been zoomed in to show the differences more clearly, the full figures are presented in Section D, along with further model diagnostic plots. The models were fit with uninformative priors of $N(0, 100^2)$, $N(0, 10^2)$, and $hN(0, 5^2)$ for the intercept, treatment and heterogeneity respectively. Here hN is the half-normal distribution. The trace plots, as presented in Section D suggested good convergence for both models.

Model	pD	DIC
Fixed Effects	6.5	13.1
Random Effects	6.6	13.3

Table 6.2: Model selection statistics for the parametric NMA models
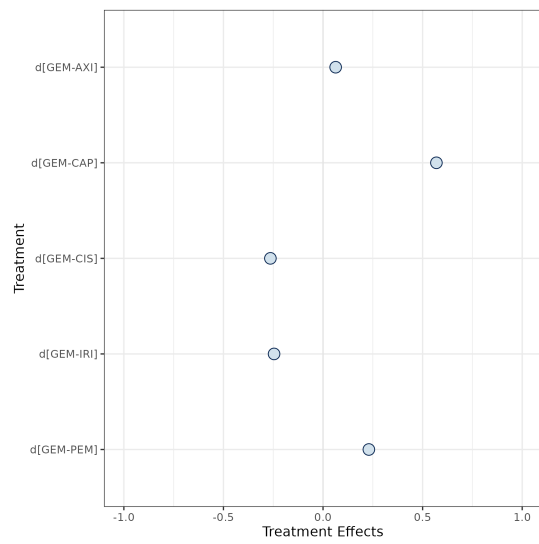
(a) Fixed Effects forest plot for parametric models
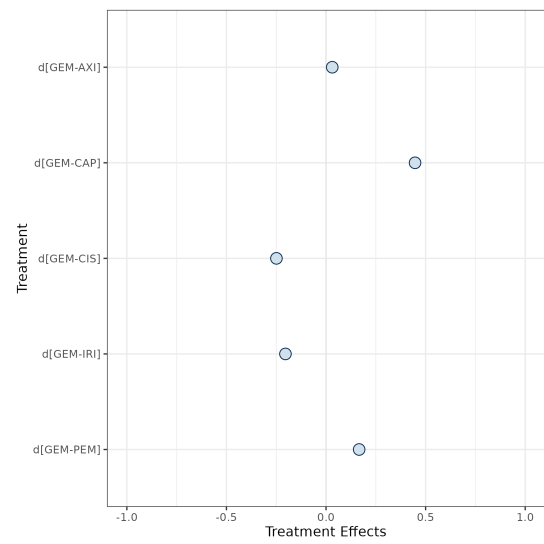
(b) Random Effects forest plot for parametric models

Figure 6.2: Forest plots for the fixed and random effects models of survival

CONCLUSIONS AND RECOMMENDATIONS

The conclusions of the five studies included in the NMA are given below (with drug names abbreviated).

- Colucci: "GEM-CIS failed to demonstrate any improvements as a first-line treatment of advanced pancreatic cancer"

- Cunningham: "GEM-CAP should be considered as one of the standard first-line options in locally advanced and metastatic pancreatic cancer"

- Kindler: "GEM-AXI does not improve overall survival in advanced pancreatic cancer"

- Oettle: "GEM-PEM therapy did not improve OS"

- Rocha Lima: "IRI-GEM safely improved the tumour response rate compared with GEM but did not alter overall survival"

7.1 Parametric NMA

Based on guidance from NICE TSD 2 [Dias et al., 2011], the fixed effects model was selected as the best fitting model due to having a lower DIC score. However it should be noted that the differences between the models were very small, with only 0.2 seperating the DIC scores. **The model showed no significant change in overall survival for any of the 5 comparators to GEM in the treatment of pancreatic cancer**. GEM-AXI, GEM-CAP, and GEM-PEM had positive treatment effects, although GEM-AXI and GEM-PEM were close to 0. GEM-CIS and GEM-IRI had slightly negative treatment effects, but were both close to 0.

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Appendices

INCLUDED TRIALS

This appendix presents the trial data for each trial included in this study. It should be noted that due to having to digitise the survival data, as opposed to having IPD, there may be some slight discrepencies between the numbers presented here, and in the original publications. Table A.1 presents the hazard ratios

Study	Comparator	HR	L95	U95	Time (Months)
Colucci	GEM+CIS	1.0746	0.8729	1.3227	36
Cunningham	GEM+CAP	0.8249	0.6928	0.9820	27
Kindler	GEM+AXI	1.0606	0.8132	1.3835	13
Oettle	GEM+PEM	0.9826	0.8186	1.1796	24
RochaLima	GEM+IRI	1.0365	0.8305	1.2936	30

Table A.1: Hazard ratios for each study

A.1   Colucci, 2010

The Colucci et. al study [Colucci et al., 2010] compared Gemcitabine plus Cistplatin (GEM+CIS) with Gemcitabine (GEM) in a total of 400 patients.
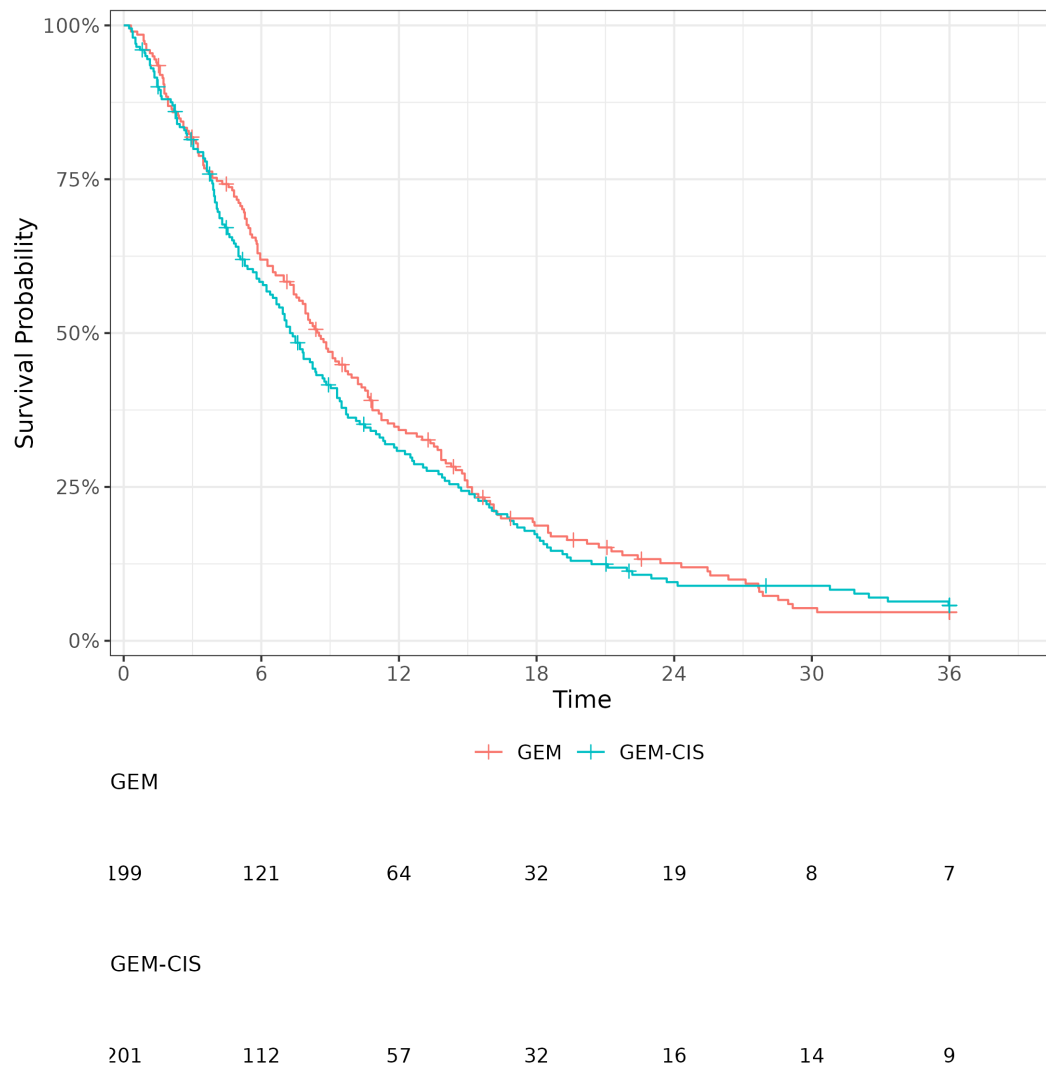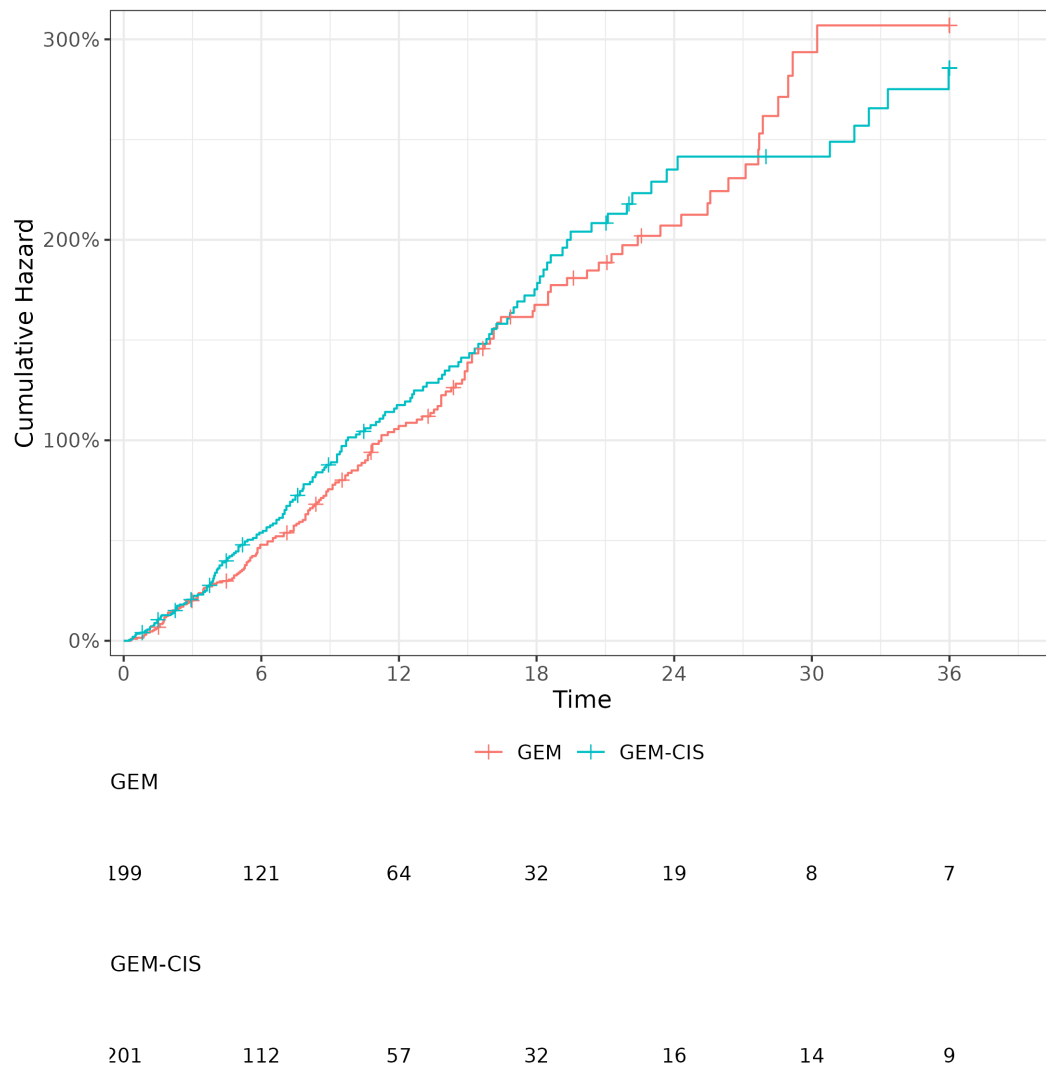
Figure A.1: Colucci 2010 KM Curve

Figure A.2: Colucci 2010 Cumulative Hazard

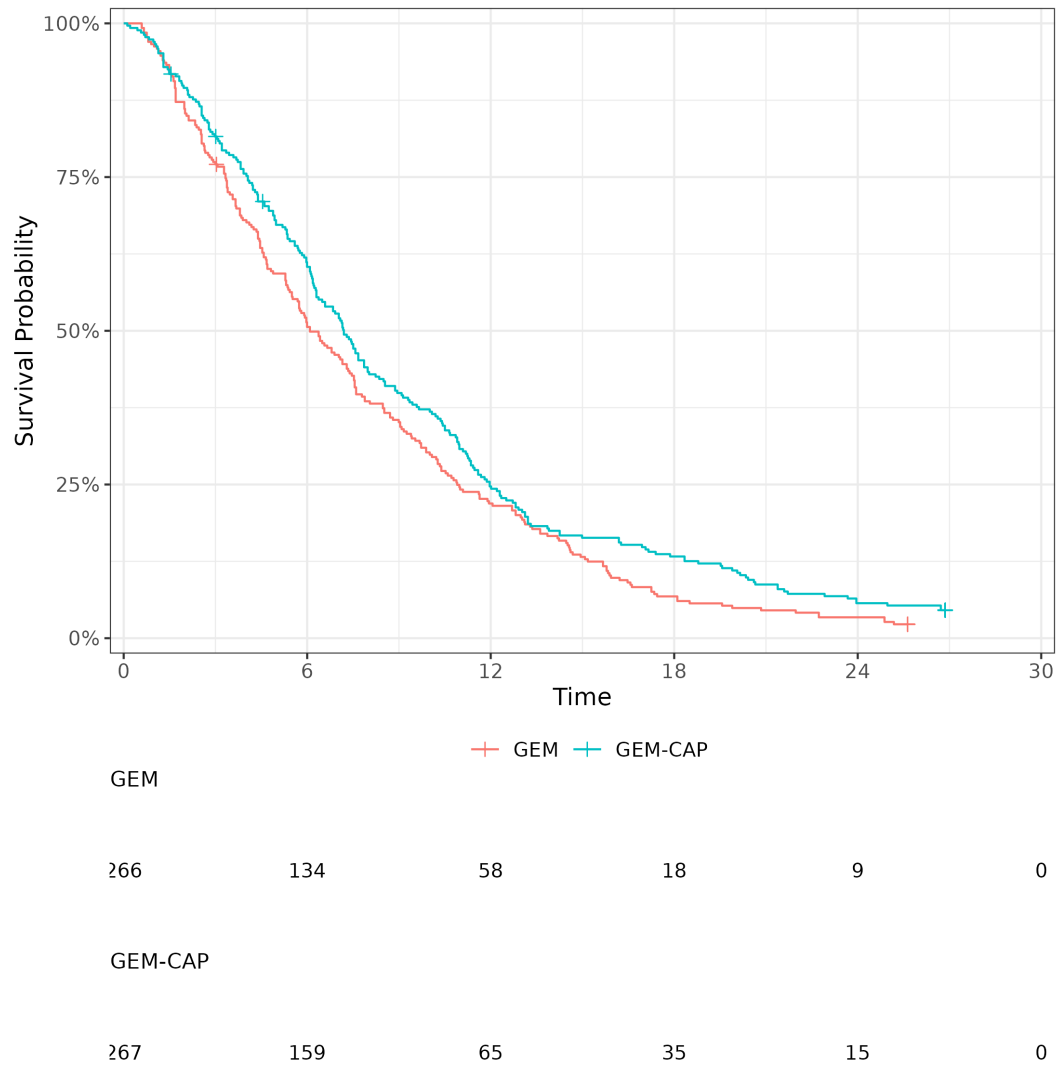|					
GEM					
266	134	58	18	9	0
GEM-CAP					
267	159	65	35	15	0

Figure A.3: Cunningham 2009 KM Curve

A.2 Cunningham, 2009

The Cunningham et. al study [Cunningham et al., 2009] compared Gemcitabine plus Capecitabine (GEM+CAP) with Gemcitabine (GEM) in a total of 533 patients.

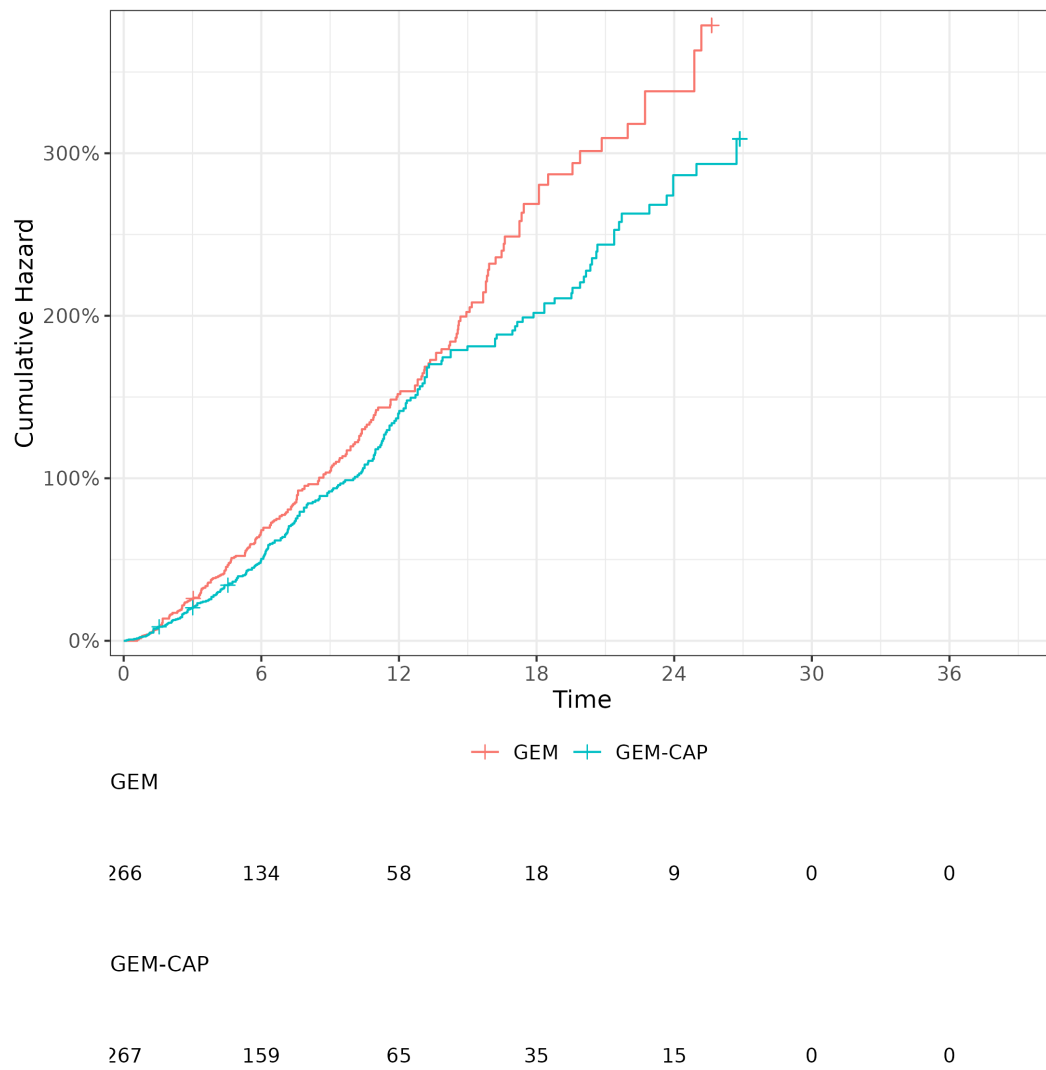|						
GEM						
266	134	58	18	9	0	0
GEM-CAP						
267	159	65	35	15	0	0

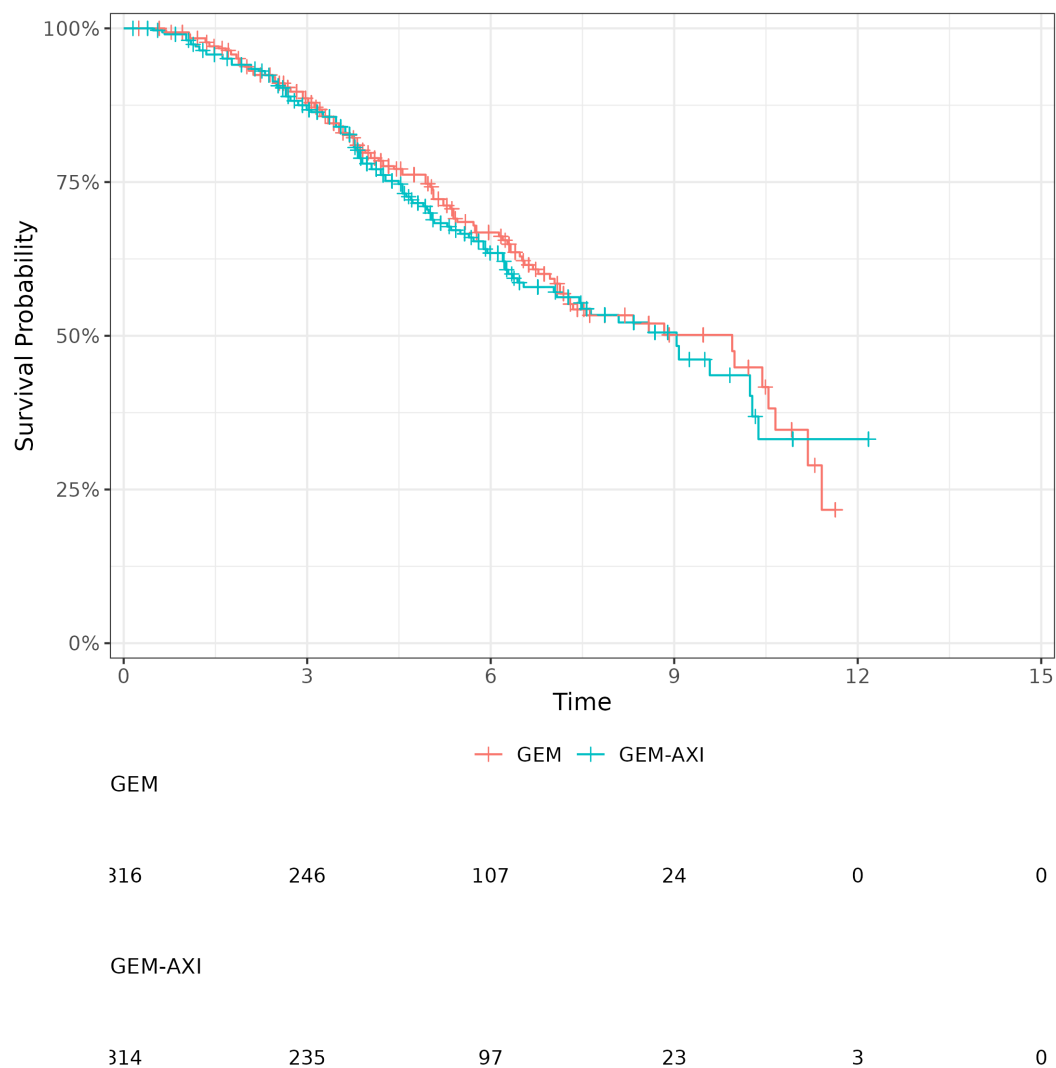Figure A.4: Cunningham 2009 Cumulative Hazard

Figure A.5: Kinder 2011 KM Curve

A.3   Kindler, 2011

The Cunningham et. al study [Kindler et al., 2011] compared Gemcitabine plus Axitinib (GEM+AXI) with Gemcitabine (GEM) in a total of 632 patients.

Figure A.6: Kinder 2011 Cumulative Hazard

GEM				
282	142	39	9	0
GEM-PEM				
283	139	49	10	0
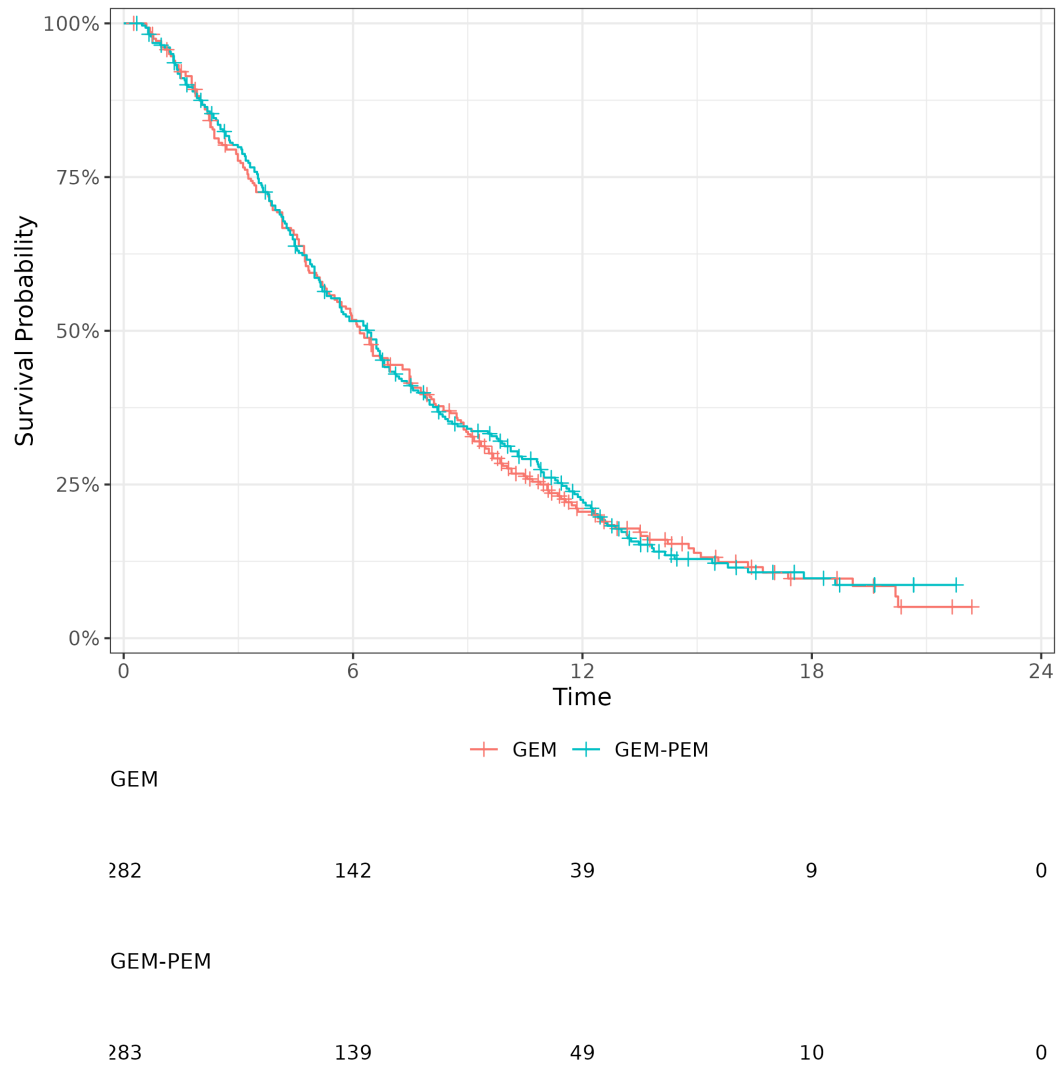
Figure A.7: Oettle 2005 KM Curve

A.4 Oettle, 2005

The Cunningham et. al study [Oettle et al., 2005] compared Gemcitabine plus Pemetrexed (GEM+PEM) with Gemcitabine (GEM) in a total of 565 patients.

Figure A.8: Oettle 2005 Cumulative Hazard

Figure A.9: Rocha Lima 2004 KM Curve

A.5 Rocha Lima, 2004

The Cunningham et. al study [Rocha Lima et al., 2004] compared Gemcitabine plus Irinotecan (GEM+IRI) with Gemcitabine (GEM) in a total of 360 patients.
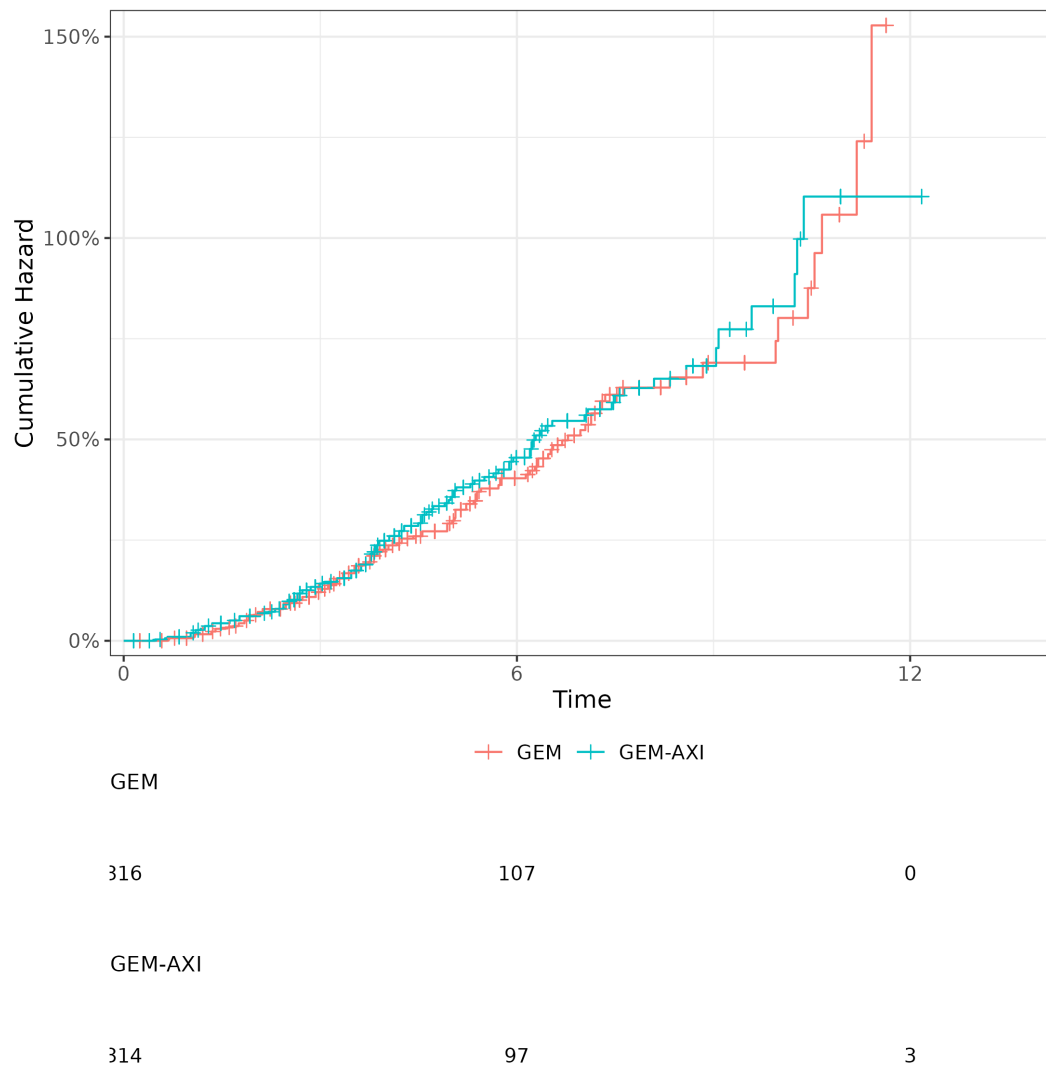
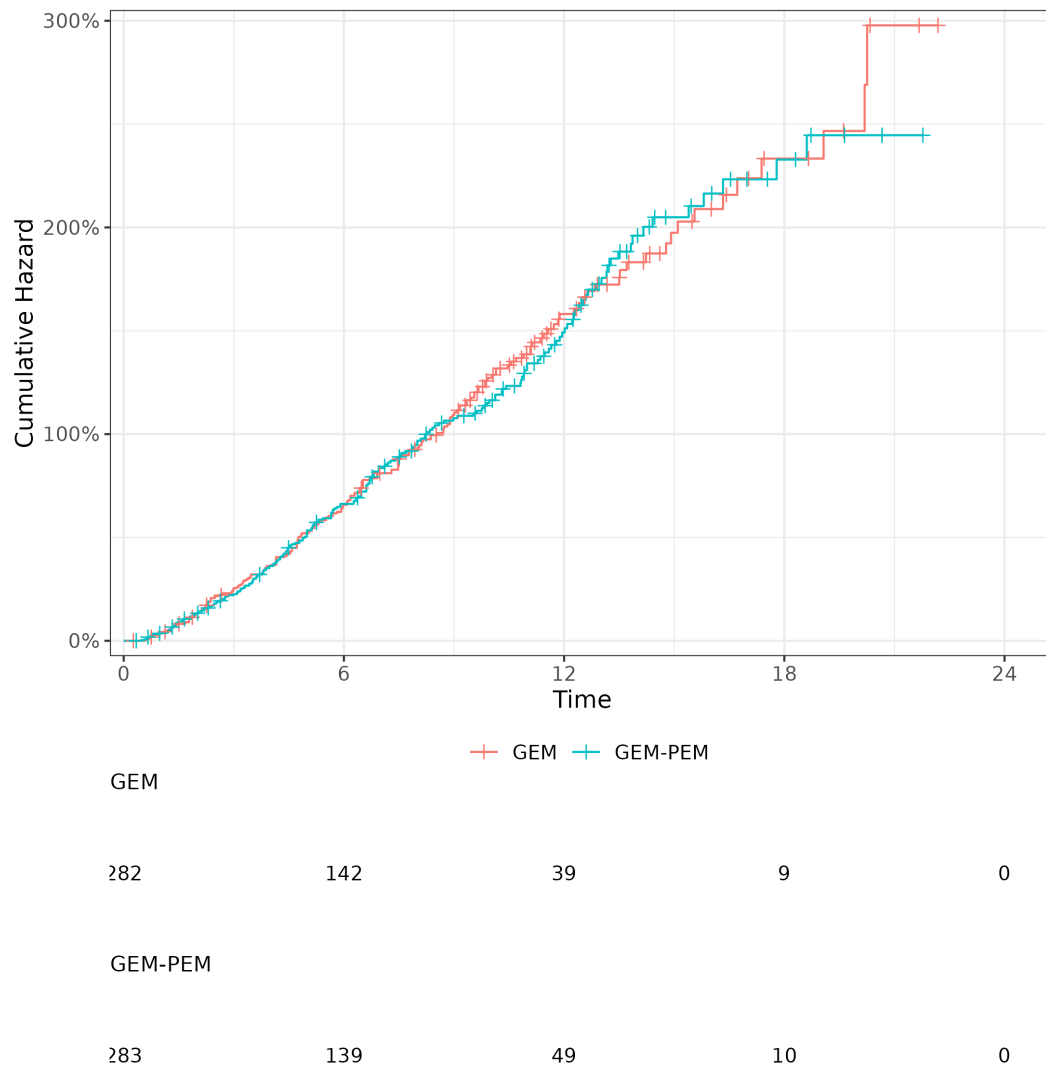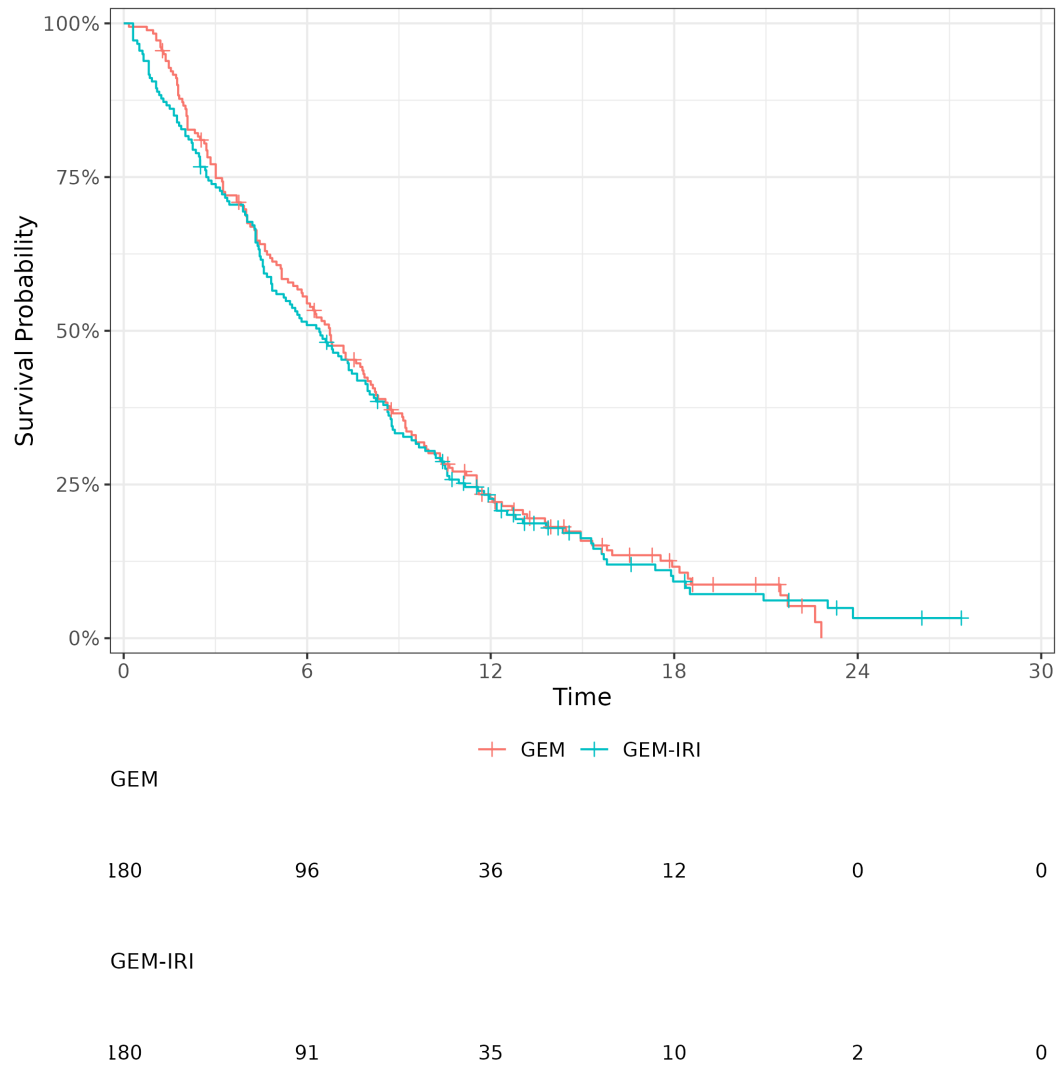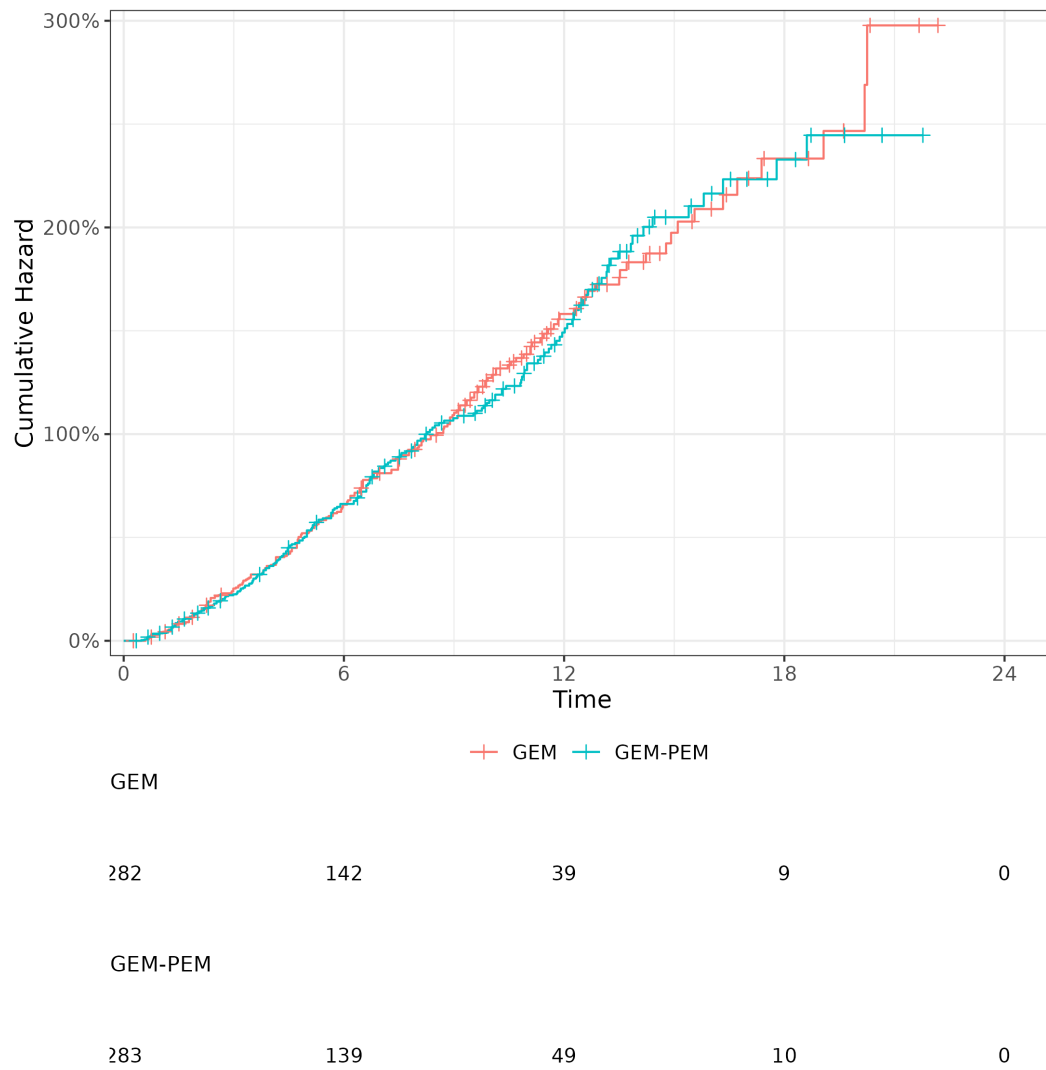Figure A.10: Rocha Lima 2004 Cumulative Hazard

SURVIVAL DISTRIBUTIONS REFERENCE

This appendix outlines the mathematical definitions of the parametric and non-parametric survival models used in this project. In addition, some information on model selection is given.

B.1 Parametric Survival Models

B.1.1 Exponential Model

The survival function for the exponential model is given by

$$S(t|\lambda) = \exp(-\lambda t)$$

for $\lambda > 0$.

B.1.2 Gamma

The survival function for the gamma model is give by

$$S(t|a, \mu) = 1 - \int_0^t \frac{x^{a-1} \exp(-x/\mu)}{\mu^a \Gamma(a)} dx$$

for $\mu > 0, a > 0$.

B.1.3 Generalised Gamma

The survival function for the generalised gamma model, by default, uses the Prentice parameterisation [REFERENCE]. The survival function is given by

$$S(t|\mu, \sigma, Q) = \begin{cases} S_G(\frac{\exp(Qw)}{Q^2}|\frac{1}{Q^2}, 1) & \text{if } Q > 0 \\ S_L(t|\mu, \sigma) & \text{if } Q = 0 \\ 1 - S_G(\frac{\exp(Qw)}{Q^2}|\frac{1}{Q^2}, 1) & \text{if } Q < 0 \end{cases}$$

Where S_G, S_L are the survival functions gor the gamma and log-normal distributions respectively. In addition, $w = \frac{\log(t) - \mu}{\sigma}$. Where $\sigma > 0$.

B.1.4 Gompertz

The survival function for the Gompertz model is given by

$$S(t|a, b) = \exp(-(b/a) \exp(at) - 1)$$

for $b > 0$.

> **Remark B.1.1: Gompertz special case**
>
> Strictly speaking, $a < 0$ is permitted, however, this causes the survival function to take the form $S(t|a,b) = \exp(b/a \exp(at) - 1)$. We therefore have, using the fact that $\lim_{t \to \infty} \exp(at) = 0$,
>
> $$S(t) = \exp(b/a \exp(at) - 1)$$
> $$\lim_{t \to \infty} S(t) = \lim_{t \to \infty} \exp(b/a \exp(at) - 1)$$
> $$\lim_{t \to \infty} S(t) = \exp(-1).$$
>
> Therefore, $S(t)$ tending to a non-zero probability as $t \to \infty$ is clinically inplausible.

B.1.5 Log-Logistic

The survival function for the log-logistic model is given by

$$S(t|a,b) = \frac{1}{1 + (t/b)^a}$$

for $a > 0, b > 0$.

B.1.6 Log-Normal

The survival function for the log-normal model is given by

$$S(t|\mu,\sigma) = 1 - \int_0^t \frac{1}{x\sigma\sqrt{2\pi}} \exp\left(-\frac{(\log x - \mu)^2}{2\sigma^2}\right) dx$$

for $\sigma > 0$.

B.1.7 Weibull

The AFT Weibull parameterisation is used in this project. The survival function for the AFT Weibull is given by

$$S(t|\mu,a) = \exp(-(t/\mu)^a)$$

B.2 Selection of Survival Models

Selecting the survival model for a given study is done for the GEM arm only, as this is the reference treatment. Akiakie's Information Criterion (AIC) [REFERENCE] is used.

> **Definition B.2.1: Akaikie's Information Criterion**
>
> For a given set of models, the **Akaike's Information Criterion (AIC)** score is given by
>
> $$AIC = 2k - 2\log(\hat{L}).$$
>
> Where k is the number of parameters in the model, and $\hat{L}$ be the maximised value of the likelihood function for the model.

When selecting models based on AIC score, the lowest scoring model is considered the best fitting model. The intrinsic value of the scores is irrelevant, only their values relative to one another. Models with an AIC score of ≤ 2 of the best fitting model are also considered well-fitting models.

ADDITIONAL SURVIVAL RESULTS

C.1 Parametric Models

C.1.1 OS Models Medians

Distribution	Treatment	Median	L95	U95
Observed	GEM	8.5157	7.412	10.2119
	GEM-CIS	7.2514	6.3844	8.7499
Exponential	GEM	8.1234	6.9493	9.4466
	GEM-CIS	7.6616	6.6008	8.9021
Gamma	GEM	8.7724	7.6247	10.003
	GEM-CIS	8.0314	6.9656	9.1877
Generalised Gamma	GEM	8.2727	7.1396	9.6683
	GEM-CIS	7.3009	6.2946	8.5681
Gompertz	GEM	8.5075	7.2161	9.8798
	GEM-CIS	7.3675	6.1209	8.7140
Log-logistic	GEM	8.0213	6.9556	9.2219
	GEM-CIS	7.1097	6.1058	8.2559
Log-normal	GEM	7.6805	6.6084	8.8155
	GEM-CIS	6.8680	5.9323	8.0454
Weibull	GEM	8.8475	7.7009	10.2251
	GEM-CIS	7.9688	6.7904	9.3044

Table C.1: Median OS given by parametric models in the Colucci study

Distribution	Treatment	Median	L95	U95
Observed	GEM	6.0892	5.4991	7.3400
	GEM-CAP	7.1984	6.3016	7.9773
Exponential	GEM	5.6085	4.9624	6.3901
	GEM-CAP	6.6375	5.8911	7.5465
Gamma	GEM	6.4666	5.8425	7.1250
	GEM-CAP	7.4944	6.7405	8.3269
Generalised Gamma	GEM	6.1874	5.5036	7.0080
	GEM-CAP	7.2947	6.4937	8.1853
Gompertz	GEM	6.4492	5.6250	7.2386
	GEM-CAP	7.3936	6.4646	8.3530
Log-logistic	GEM	5.9954	5.3559	6.6976
	GEM-CAP	7.0087	6.2950	7.7824
Log-normal	GEM	5.7668	5.1624	6.4003
	GEM-CAP	6.6665	5.9897	7.5201
Weibull	GEM	6.6091	5.9635	7.3700
	GEM-CAP	7.6326	6.8715	8.5703

Table C.2: Median OS given by parametric models in the Cunningham study

Distribution	Treatment	Median	L95	U95
Observed	GEM	9.9477	7.2714	11.185
	GEM-AXI	9.0388	7.0821	10.377
Exponential	GEM	10.1538	8.3617	12.2346
	GEM-AXI	9.8440	8.0866	11.9079
Gamma	GEM	8.2747	7.3351	9.3104
	GEM-AXI	8.1444	7.0687	9.2525
Generalised Gamma	GEM	8.4180	7.3651	10.0551
	GEM-AXI	8.3027	7.2284	9.8471
Gompertz	GEM	8.4702	7.6250	9.3354
	GEM-AXI	8.3951	7.5094	9.4282
Log-Logistic	GEM	8.3027	7.2623	9.5072
	GEM-AXI	8.1373	7.1005	9.3542
Log-normal	GEM	8.5320	7.3888	9.8280
	GEM-AXI	8.4620	7.2940	9.8507
Weibull	GEM	8.2853	7.3825	9.3263
	GEM-AXI	8.1662	7.2363	9.2119

Table C.3: Median OS given by parametric models in the Kindler study

Distribution	Treatment	Median	L95	U95
Obserced	GEM	6.1769	5.5159	7.2945
	GEM-PEM	6.4053	5.4246	6.9519
Exponential	GEM	5.8920	5.1904	6.6821
	GEM-PEM	5.9741	5.2446	6.7782
Gamma	GEM	6.4966	5.8781	7.1511
	GEM-PEM	6.5691	5.9370	7.2294
Generalised Gamma	GEM	6.1225	5.4698	6.8491
	GEM-PEM	6.2246	5.5628	7.0092
Gompertz	GEM	6.5459	5.7562	7.3281
	GEM-PEM	6.6121	5.7187	7.3890
Log-Logistic	GEM	6.0681	5.4335	6.7508
	GEM-PEM	6.1365	5.4998	6.9122
Log-normal	GEM	5.9424	5.3308	6.6071
	GEM-PEM	6.0029	5.3325	6.6544
Weibull	GEM	6.6223	5.9917	7.3652
	GEM-PEM	6.6945	6.0326	7.4350

Table C.4: Median OS given by parametric models in the Oettle study

Distribution	Treatment	Median	L95	U95
Observed	GEM	6.7424	5.6812	7.9758
	GEM-IRI	6.3989	4.8554	7.6321
Exponential	GEM	6.0863	5.2315	7.0918
	GEM-IRI	5.8213	5.0071	6.8319
Gamma	GEM	6.7650	5.9739	7.6337
	GEM-IRI	6.1703	5.3646	7.1195
Generalised Gamma	GEM	6.4347	5.5706	7.4502
	GEM-IRI	6.1123	5.1773	7.3023
Gompertz	GEM	6.8572	5.8092	7.9001
	GEM-IRI	6.2212	5.1709	7.3794
Log-Logistic	GEM	6.2578	5.4026	7.2107
	GEM-IRI	5.7680	4.9301	6.8834
Log-normal	GEM	6.0975	5.2549	7.0205
	GEM-IRI	5.3922	4.6066	6.4738
Weibull	GEM	6.8985	6.0681	7.9502
	GEM-IRI	6.2512	5.3474	7.2818

Table C.5: Median OS given by parametric models in the Rocha Lima study

ADDITIONAL NMA RESULTS

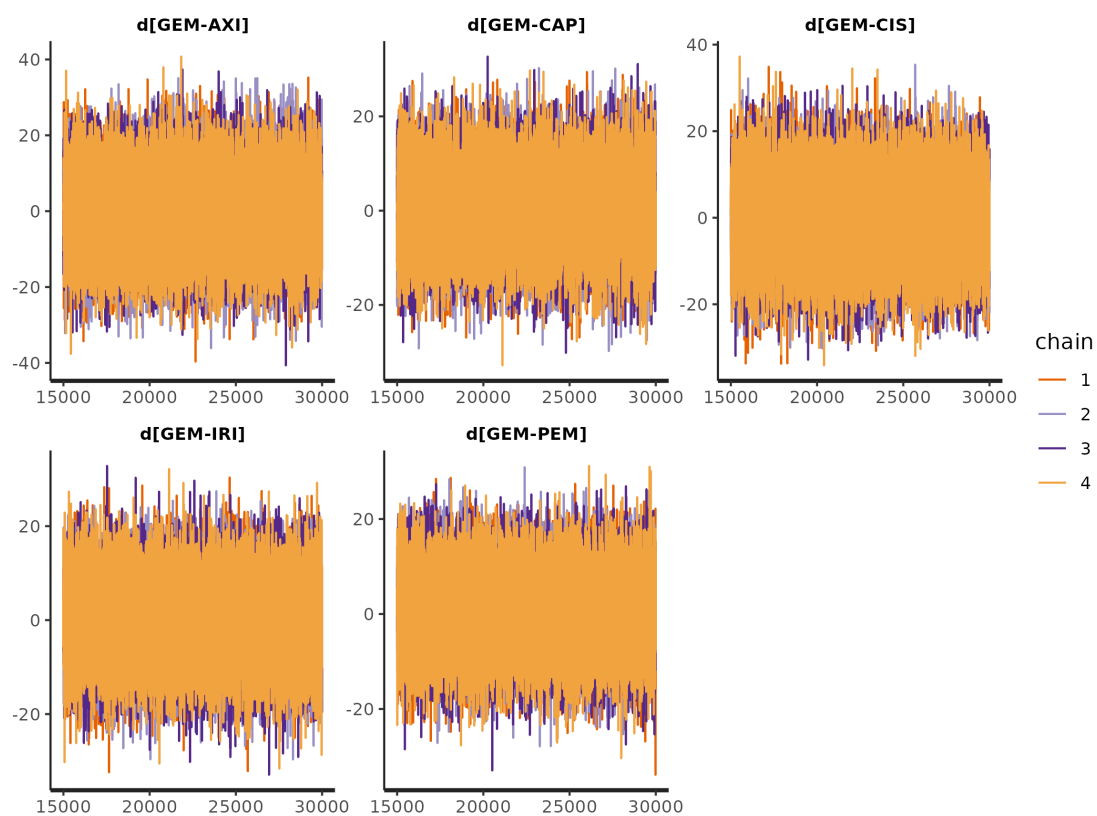## D.1 Parametric Models

D.1.1 Fixed Effects Model

Figure D.1: Trace plot of the fixed effect parametric NMA
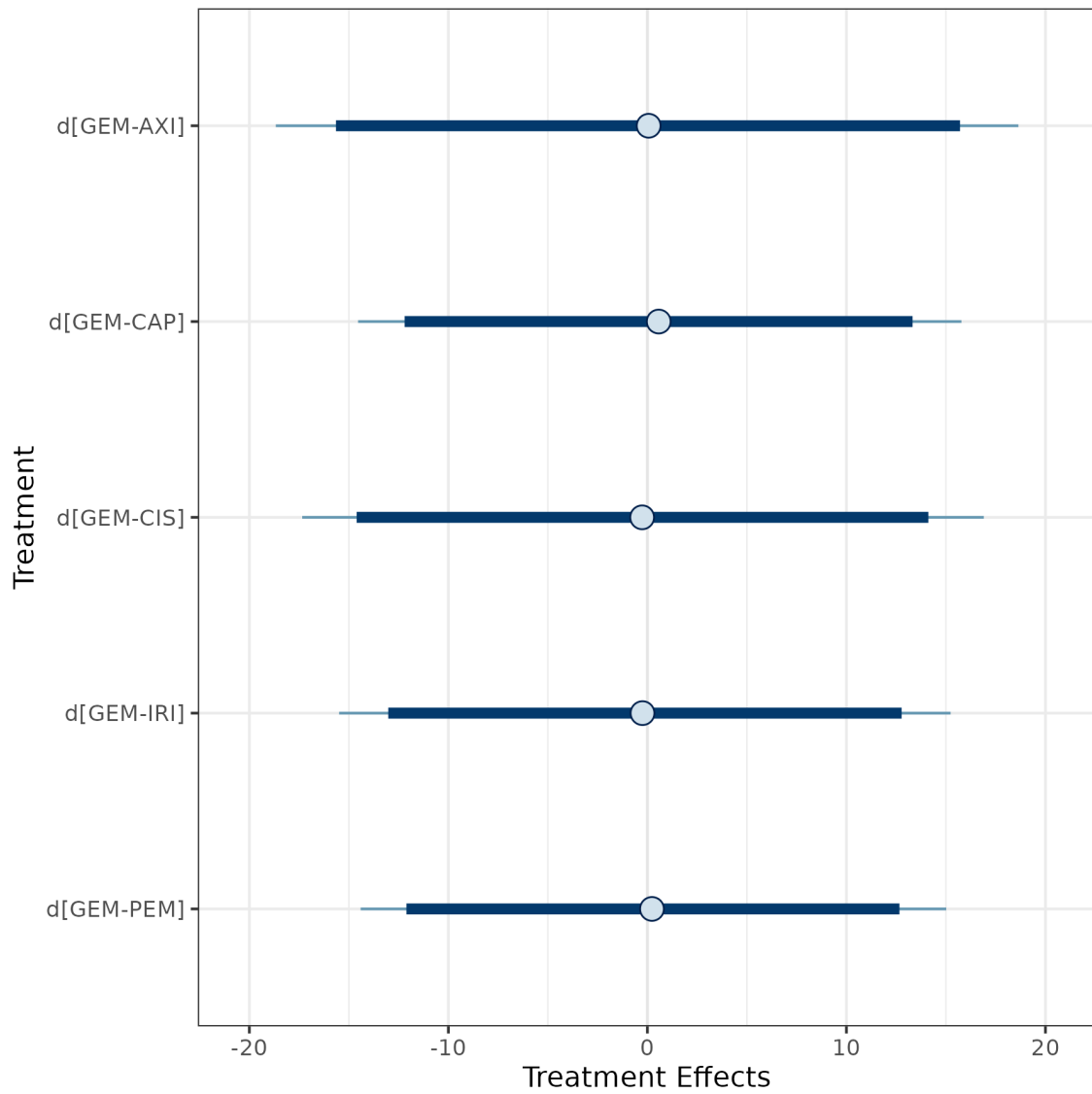
D.2 Random Effects Model

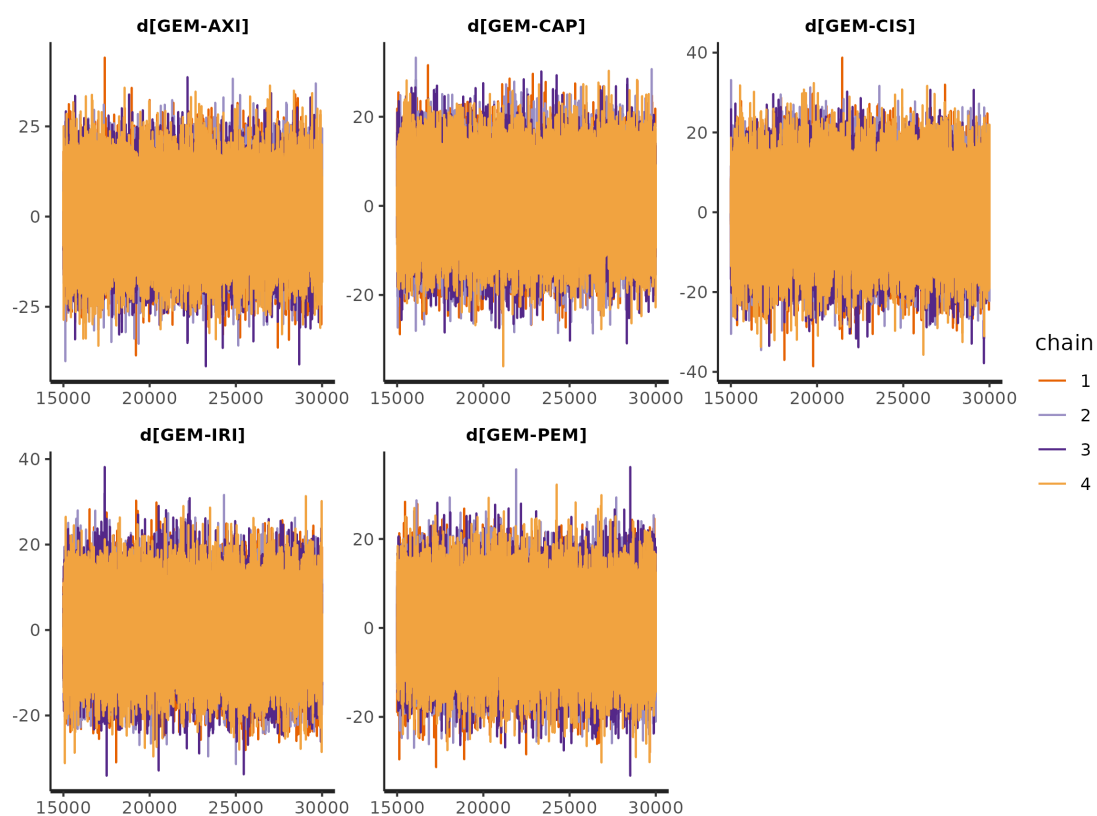Figure D.2: Full forest plot of the fixed effect parametric NMA
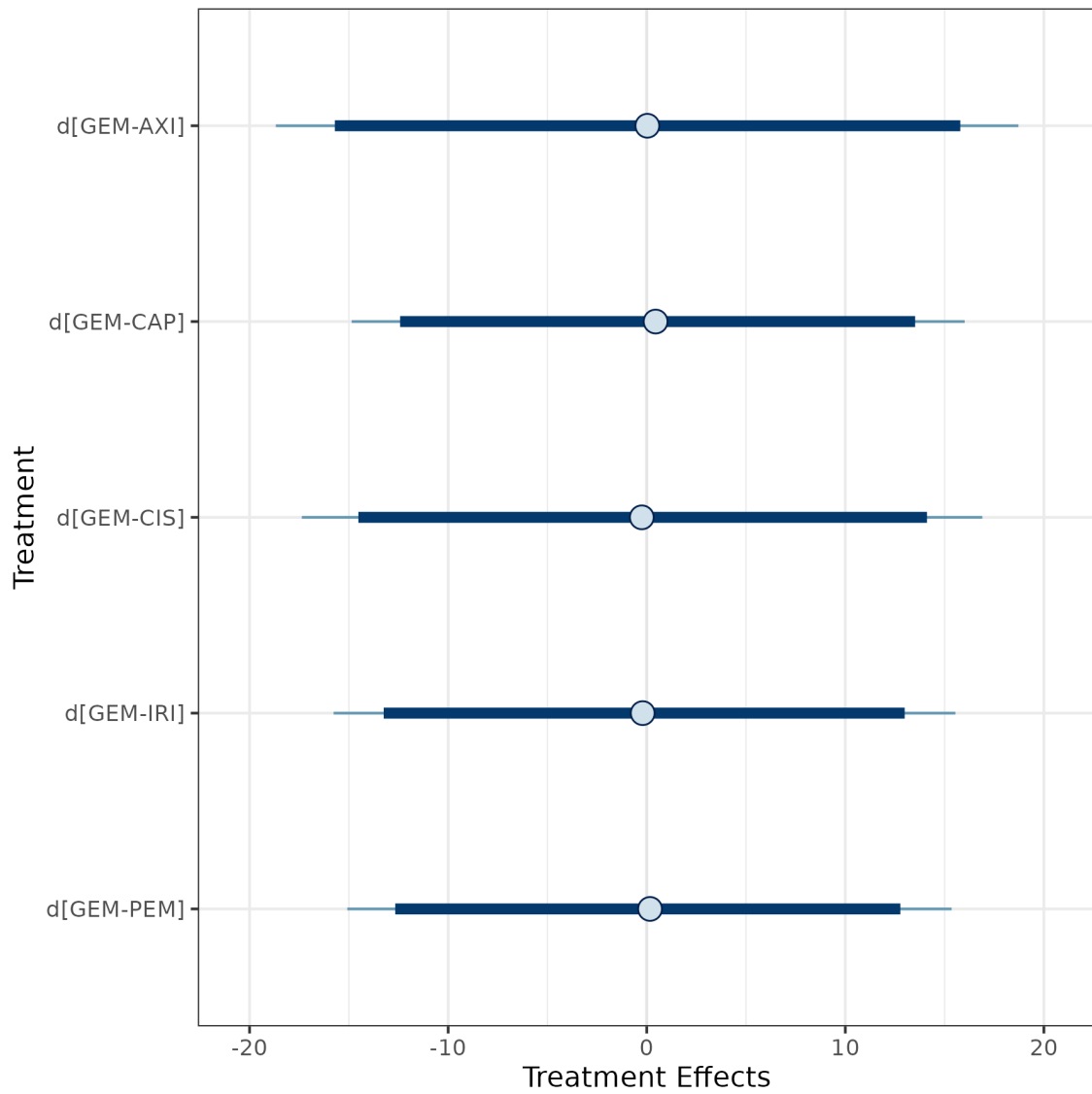
Figure D.3: Trace plot of the fixed effect parametric NMA

Figure D.4: Full forest plot of the random effects parametric NMA

THE PCNMA PACKAGE

To facilitiate the analysis conducted in this project, an `R` package was constructed. Performing the analysis in this way ensures easy reproducibility for further analysis in the future. The package is roughly split into two parts: survival code, and NMA code.

E.1 Survival Functions

The central function in the package for survival analysis is the *fit_distribution* function. This function is a wrapper around the *flexsurvreg* function from `flexsurv`. It is designed to take a list object containing the names of distributions and the associated argument to pass that distribution to `flexsurv`. For example,

```
1   distributions <- list("Weibull" = "weibull")
```

The reason for defining the distributions in this way is because the default `Flexsurv` arguments are somewhat untitdy. For example, the exponential distribution is passed as just "exp". The beauty of the *fit_distribution* function is that several distributions can be passed with a tidier name, which *flexsurvreg* never sees. This purely aesthetic change can be seen by comparing Figure E.1, and Figure E.2.

Any default `flexsurv` distribution will work with *fit_distribution*, it just needs a suitable name in the list object . The *fit_distribution* function itself doesn't actually fit any distributions. There is a sub-function, *.fit_distribution* which takes a single distribution as an argument, and some data on which to fit that distribution. This function takes the "weibull" element of the above list and passes it to flexsurv. The *fit_distribution* function maps *.fit_distribution* across the list of distributions, using the `purrr::map` function [Wickham and Henry, 2023]. After some data cleaning, the object that is returned by *fit_distribution* is given the class "fitted_distribution".

Several S3 methods exist for objects of class "fitted_distribution", these are *plot.fitted_distribution*, *summary.fitted_distribution*, and *coef.fitted_distribution*. These functions allow for plotting fitted models, accessing information such as AIC scores, and accessing the model coefficients respectively.

Package 'PancSurv'

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Type Package

Title Parametric and Non-Parametric Survival Models in Pancreatic Cancer Trials

Version 0.1

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Author Matthew Knowles

Maintainer Matthew Knowles <mattknowles314@gmail.com>

Description This package contains the functions and data for my MSc Thesis, concerning the use of parametric and non-parametric models for survival in pancreatic cancer

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RoxygenNote 7.2.3

Encoding UTF-8

R topics documented:

.fit_distribution   *Fit a single survival distribution*

Description

This function is a wrapper on 'flexsurv::flexsurvreg', and fits a single distribution to the specified data.

Usage

```
.fit_distribution(distribution, data, strata = "Treatment")
```

Arguments

distribution	A single distribution
data	An IPD dataset
strata	Strata for the RHS of the 'survival::Surv' function

Value

A [flexsurv::flexsurvreg] object

---

boxTid   *Box-Tidwell Transformation*

Description

Box-Tidwell Transformation

Usage

```
boxTid(x, p)
```

Arguments

x	A real value
p	The p-value to raise x to

coef.fitted_distribution

Coefficients of fitted models

Description

Coefficients of fitted models

Usage

```
## S3 method for class 'fitted_distribution'
coef(fit, studies, ...)
```

Arguments

fit	A [PCNMA::fitted_distribution] object
...	for S3 consistency

fit_distribution   *Fit survival distributions to a dataset.*

Description

This function extends the 'PCNMA:::.fit_distribution' function, by fitting a given set of distributions to a TTE dataset.

Usage

```
fit_distribution(distributions, data, strata = "Treatment", maxT = 60)
```

Arguments

distributions	A list of distributions
data	An IPD dataset
strata	Stratification variables
maxT	maximum time to calculate fitted values at

Value

A dataframe with fitted values

`fit_model`   *Run an NMA*

Description

Run an NMA

Usage

```
fit_model(network, effects, iter, seed = 1, chains = 4)
```

Arguments

network	A [multinma::nma_data] object
L	Character string specifying a likelihood function
link	Character string specifying a link function (defaults to "log")
...	Other parameters to pass to [multinma::nma]

`gen_network`   *Generate a network of evidence*

Description

Generate a network of evidence

Usage

```
gen_network(net_data, ref)
```

Arguments

net_data	A dataset created by [PCNMA::gen_network_data]
ref	A character reference treatment

Value

A [mutlinma::nma_data] object

gen_network_data   *Generate network data*

Description

Generate network data

Usage

```
gen_network_data(data, ref)
```

Arguments

data	A date extraction dataset
ref	A character reference treatment

Value

A dataframe

H   *H-function for FPs*

Description

H-function for FPs

Usage

```
H(x, P, zeta, j)
```

Arguments

x	A real value
P	A vector of powers
zeta	A vector of zeta values
j	The index

---

hr   *Hazard Ratio*

Description

Hazard Ratio

Usage

```
hr(TTE, strata = "1")
```

Arguments

TTE   A TTE dataframe

strata   A strata variable

---

km_estimates   *Generate KM estimates*

Description

Generate Kaplan-Meier estimates from a TTE object. Uses 'ggsurvfit::survfit2' to generate KM estimates. Only requires strata to be specified.

Usage

```
km_estimates(TTE, strata = "1")
```

Arguments

TTE   A TTE dataframe

Value

A [PCNMA::km_obj] object

phi   *Fractional Polynomial Function*

Description

Fractional Polynomial Function

Usage

```
phi(x, m, P, zeta)
```

Arguments

x	A real valye
m	The degree of the polynomial
P	A vector of powers
zeta	A vector of zeta values

plot.fitted_distribution
Plot a fitted distributions object

Description

Creates a plot for a result of 'PCNMA::fit_distribution'.

Usage

```
## S3 method for class 'fitted_distribution'
plot(
  fit,
  CI = FALSE,
  km = FALSE,
  km_alpha = 0.5,
  linewidth = 1,
  facet_by = "Treatment",
  ...
)
```

Arguments

fit	A 'PCNMA::fitted_distribution' object
CI	Include a confidence interval?
km	Add the original KM curve?
...	For S3 consistency

---

plot.fitted_model   *Plots for an NMA model*

Description

Plots for an NMA model

Usage

```
## S3 method for class 'fitted_model'
plot(model, type = "trace", pars = parsForStan)
```

Arguments

model	A 'PancSurv::fitted_model' obj
type	Type of plot to produce

---

plot.km_obj   *Plot a KM curve*

Description

Plot a KM curve

Usage

```
## S3 method for class 'km_obj'
plot(
  fit,
  type = "survival",
  risk.table = TRUE,
  break.x.by = 5,
  xMax = 40,
  risktable.height = 0.3,
  ...
)
```

Arguments

fit	A 'PCNMA::km_obj' object
type	See 'ggsurvfit::ggsurvfit' for details.
risk.table	Add numbers at risk?
break.x.by	A numeric value for splitting x axis
xMax	The maximum time value to plot
risktable.height	
	The proportion of the figure to be taken up by the risk table
...	For S3 consistency

Value

A plotted km curve

---

plot_aic	*Plot AIC Bar plot*

Description

Plot AIC Bar plot

Usage

```
plot_aic(model)
```

Arguments

model   A [PCNMA::fitted_distribution] object

---

plot_network	*Plot a network of evidence*

Description

Plot a network of evidence

Usage

```
plot_network(network, ...)
```

Arguments

network   A network dataset

---

save_nma_summary   *Write model summary to xlsx*

Description

Write model summary to xlsx

Usage

```
save_nma_summary(nma, PARAMCD, effects, model_type)
```

Arguments

nma	A [mutinma::stan_data] object
PARAMCD	one of OS or PFS
model_type	one of parametric or fp
effect	type

---

summary.fitted_distribution
                      Summary of a set of fitted models

Description

Summary of a set of fitted models

Usage

```
## S3 method for class 'fitted_distribution'
summary(fit, AIC = FALSE, median = FALSE)
```

Arguments

fit	A 'PCNMA::fitted_distributions' object.
AIC	Returns the AIC scores for a set of models
median	Returns a table of median estimates for a set of models

summary.hr_obj	*Summarise a Hazard Ratio*

Description

Summarise a Hazard Ratio

Usage

```
## S3 method for class 'hr_obj'
summary(hr)
```

summary.km_obj	*Summarise KM data*

Description

Summarise KM data

Usage

```
## S3 method for class 'km_obj'
summary(fit, ...)
```

Arguments

fit   A 'PCNMA::km_obj' object
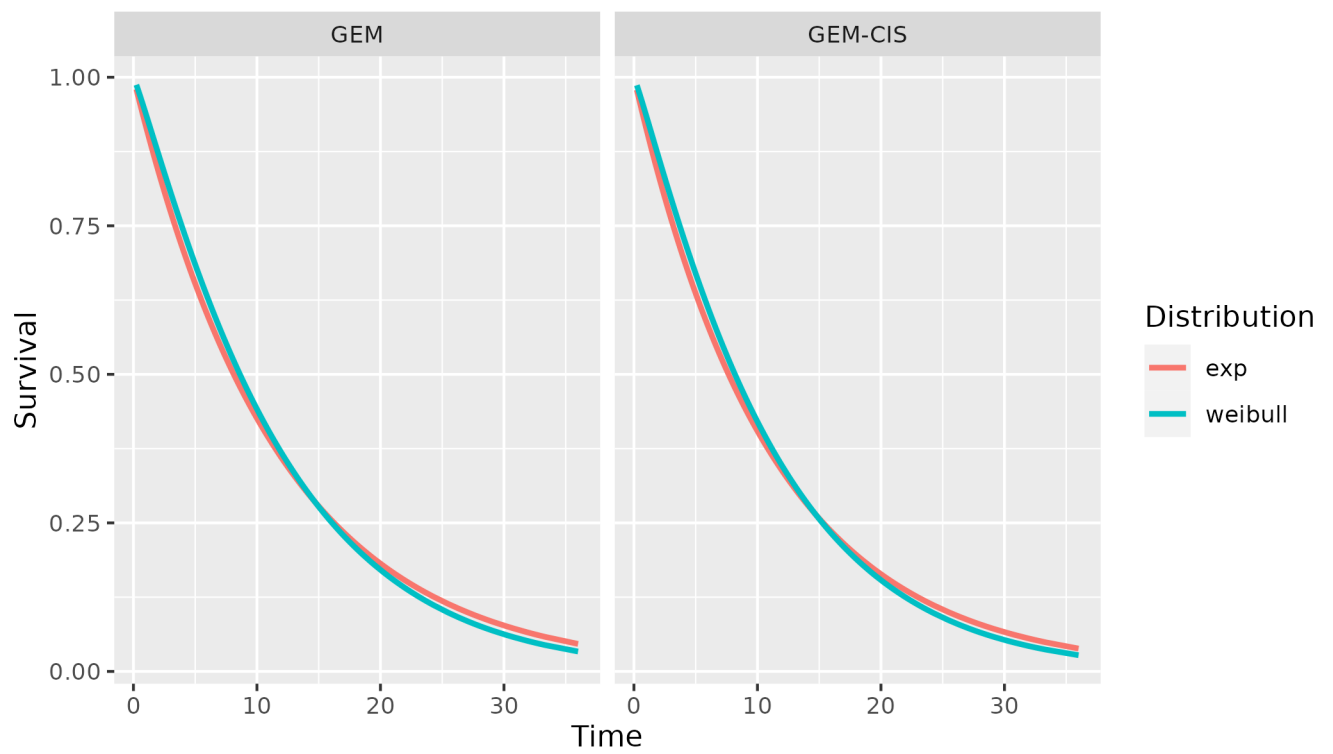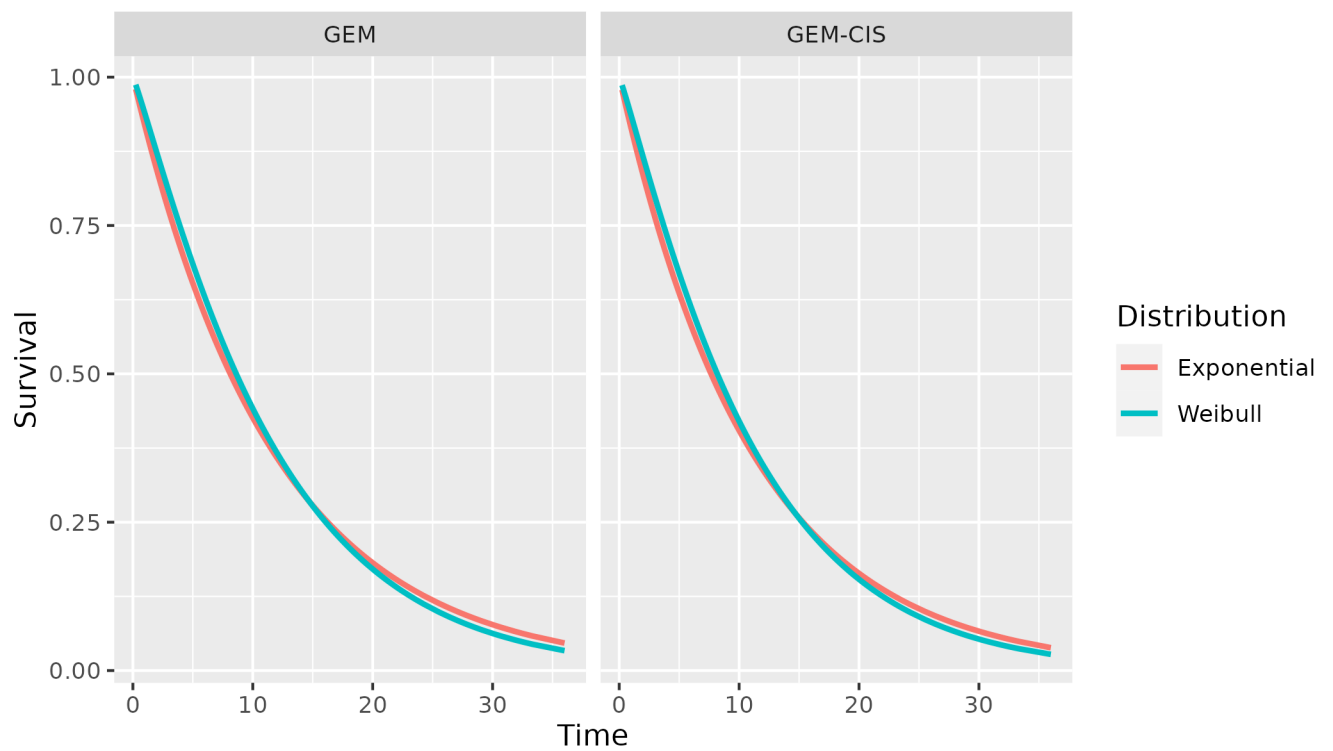
Value

A summary table of the KM data

Index

Figure E.1: Fitted Models as in Flexsurv

Figure E.2: Fitted Models with *fit_distribution*