

A Network Meta-Analysis of Treatments for Locally Advanced/Metastatic Pancreatic Cancer

Matthew Knowles

University of Sheffield

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Background

Pancreatic Cancer

- Pancreatic cancer is the 10th most common cancer in the UK, accounting for roughly 3% of all new cases.
- The disease is associated with a particular poor prognosis, primarily due to late diagnoses.
- Most cases are pancreatic duct adenocarcinomas (PDAC), which form in the exocrine component of the pancreas. This part of the organ is responsible for producing digestive enzymes, and carrying the enzymes away from the pancreas.

Treatment Landscape

- Gemcitabine (GEM) is a standard, not-particularly toxic treatment for pancreatic cancer.
- GEM in combination with capecitabine (GEM-CAP) or GEM in combination with nab-Paclitaxel (GEM-NAB) have been shown to be better than GEM alone.
- FOLFIRINOX (FOL) has been shown to be significantly better than GEM, but is only given to patients who can tolerate it, which is not many.
- In current NICE guidance, there is uncertainty around the comparison between GEM-CAP and GEM-NAB.
- Several NMAs have been conducted on pancreatic cancer trials, but none using the Multilevel Network Meta-Regression (ML-NMR) framework.

Project outline

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- 2 Fit parametric survival models, and select a few best-fitting model candidates.
- 3 Use those models as likelihoods in the ML-NMR.
- 4 Conduct NMA, assess best treatments.

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- 2 Provide clarity on the comparison between GEM-NAB and GEM-CAP.
- 3 Corroborate findings of previous NMAs.

Methodology

Survival Analysis

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- Therefore, the standard parametric models (excluding the exponential model) were fit to the data from each study.
- Model fitting was conducted using the R package “flexsurv”.
- Based on the Akaike’s Information Criterion (AIC) scores, the log-logistic, log-normal, and Weibull models were selected.

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- The ML-NMR method lends itself really well to survival outcomes.

General ML-NMR Model

Definition: ML-NMR for general likelihoods

Individual:

$$L_{ijk|x}^{\text{Con}}(\xi; y_{ijk}, x_{ijk}) = \pi_{\text{Ind}}(y_{ijk} | \theta_{ijk}) \quad (1)$$

$$g(\theta_{ijk}) = \eta_{jk}(x_{ijk}) = \mu_j + x_{ijk}^T (\beta_1 + \beta_{2,k}) + \gamma_k \quad (2)$$

Aggregate:

$$L_{ijk}^{\text{Mar}}(\xi; y_{ijk}) = \int_{\mathfrak{X}} L_{ijk|x}^{\text{Con}}(\xi; y_{ijk}, x) f_{jk}(x) dx \quad (3)$$

$$L_{j\hat{k}}^{\text{Mar}} \propto \prod_{i=1}^{N_{jk}} L_{ijk}^{\text{Mar}}(\xi; y_{ijk}) \quad (4)$$

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- **The form of the survival and hazard function depends on the survival model chosen.**

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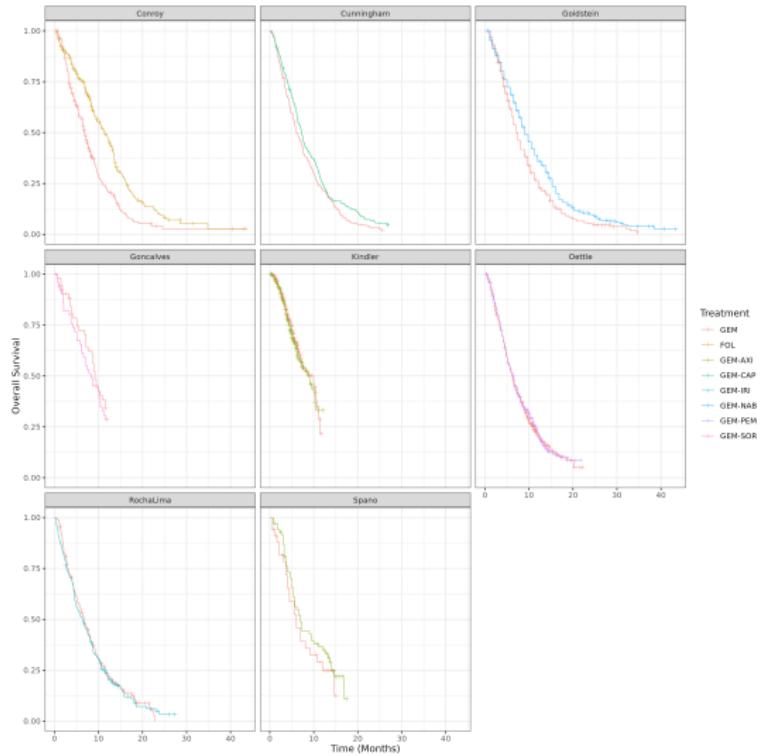
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$$\begin{aligned} L_{ijk}^{\text{Mar}}(\xi; t_{ijk}, c_{ijk}) &= \int_{\mathfrak{X}} L_{ijk|x}^{\text{Con}}(\xi; t_{ijk}, c_{ijk}, x) f_{jk}(x) dx \\ &= \int_{\mathfrak{X}} S_{jk}(t_{ijk}|x_{ijk}) h_{jk}(t_{ijk}|x_{ijk})^{c_{ijk}} f_{jk}(x) dx \end{aligned}$$

Trials

KM Curves



KM Considerations

- The Goncalves and Kindler studies had comparatively immature data. They were included in the main NMA, but a sensitivity analysis was conducted where they were excluded.

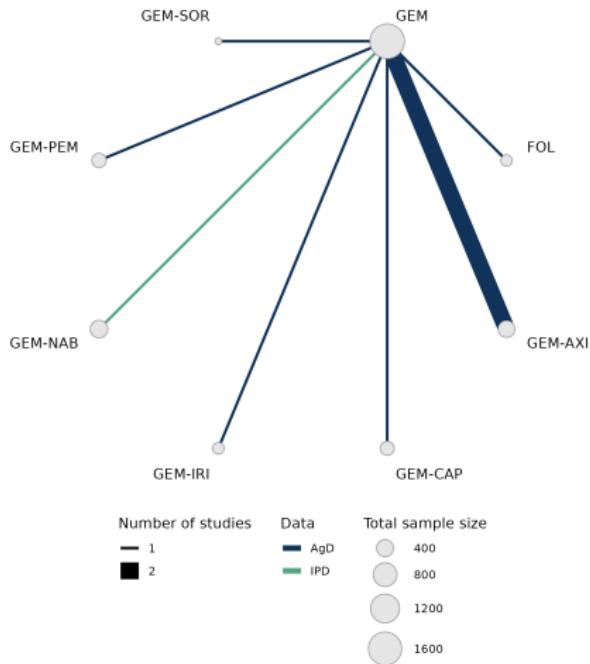
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- In the Kindler, Oettle, and Rocha Lima studies, the GEM and comparator arm were very similar.
- Conroy and Goldstein have data on FOL and GEM-NAB respectively. The apparent improvement in OS that was observed in the literature review is visible from these studies.

Network of Evidence



Results

Model Selection Statistics

Likelihood	Type	DIC	LOOIC
Log-logistic	FE	16974.3668	16972.9184
Log-logistic	RE	16972.2638	16972.8786
Log-normal	FE	107813403.9532	48652.0393
Log-normal	RE	16977.7101	16973.7934
Weibull	FE	16989.2670	16992.9722
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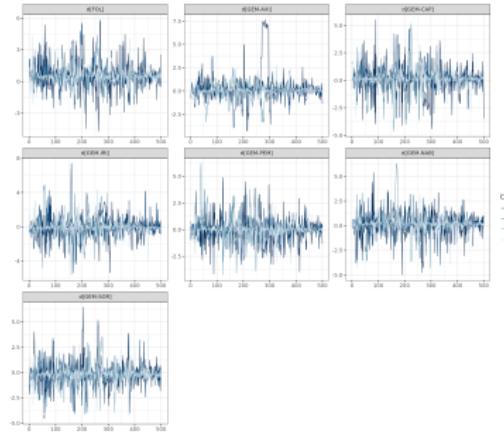
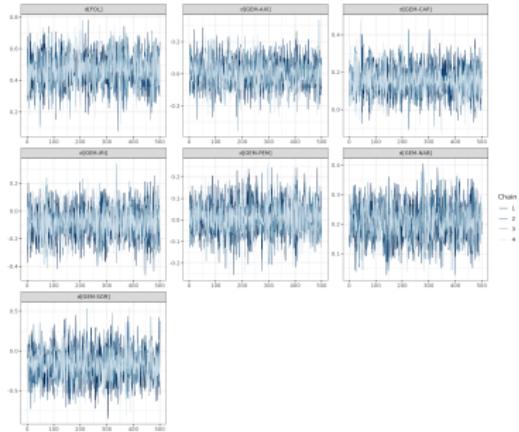
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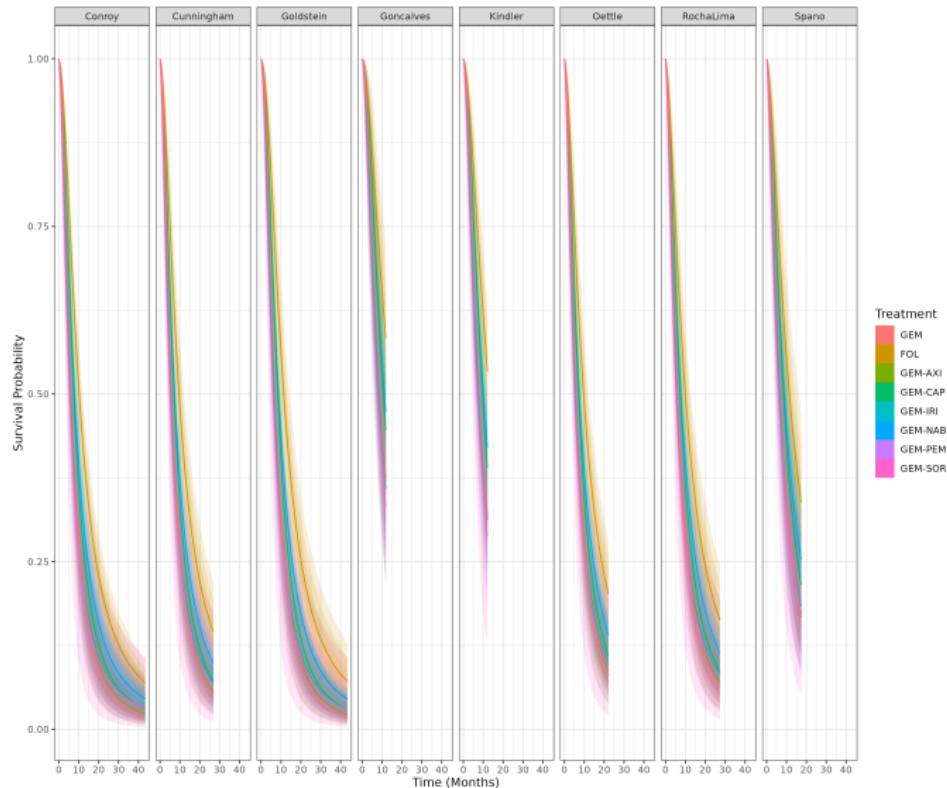
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- The model fit was assessed using trace plots.

Assessing Model Fit

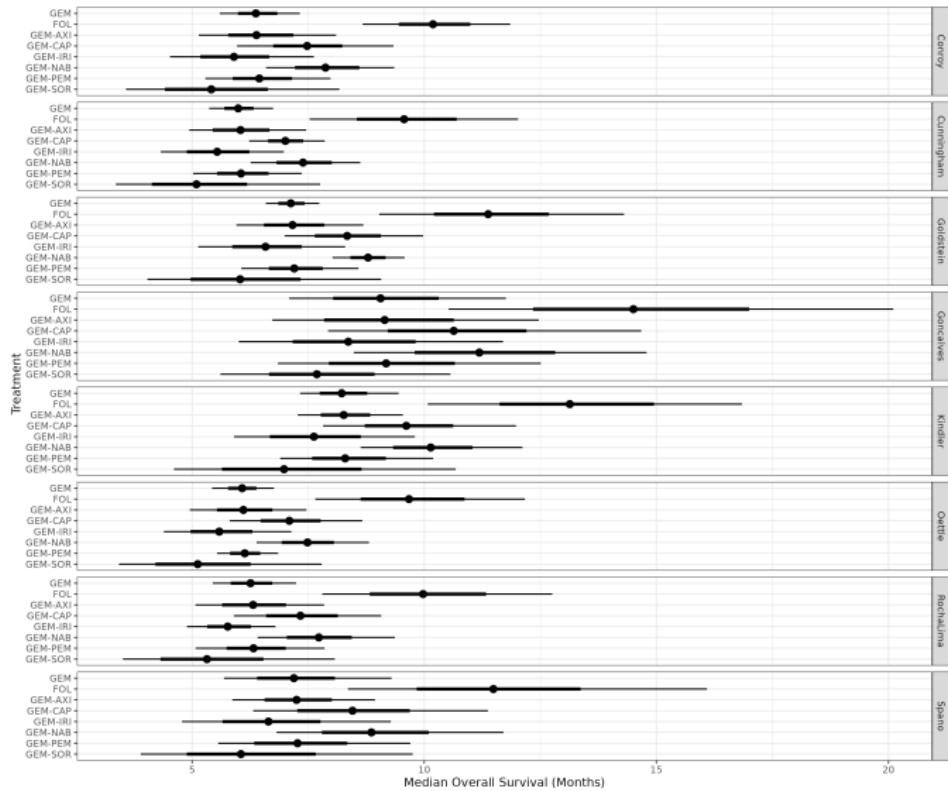


The left figure is the FE model, and the right figure is the RE model. Clearly, the FE model had better convergence

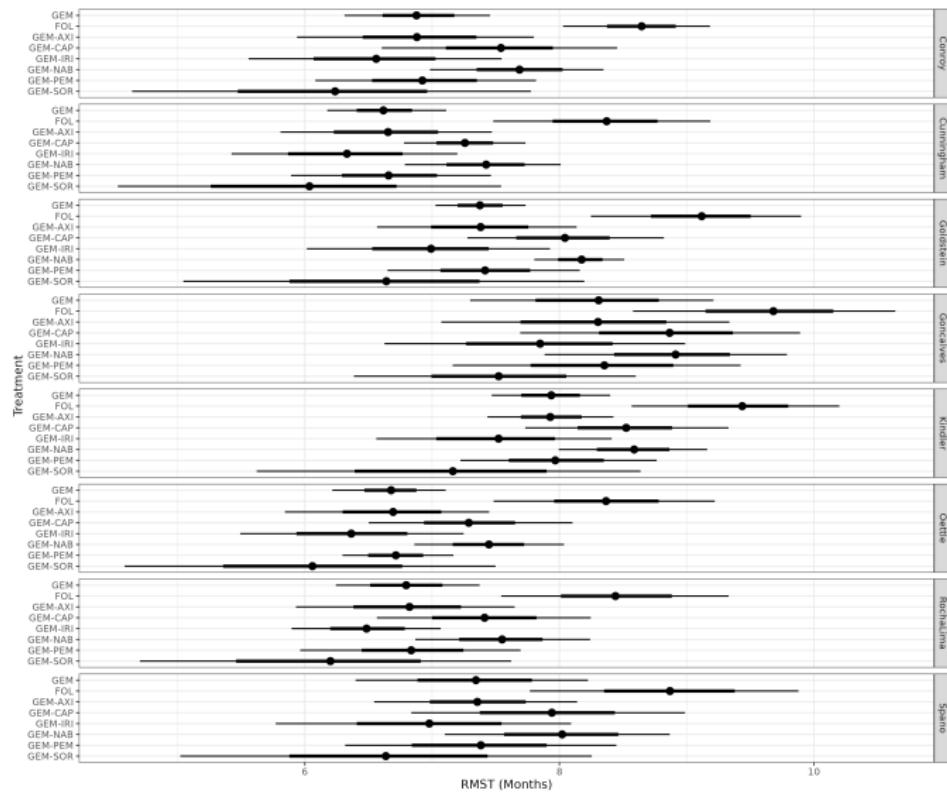
Predicted KM Curves



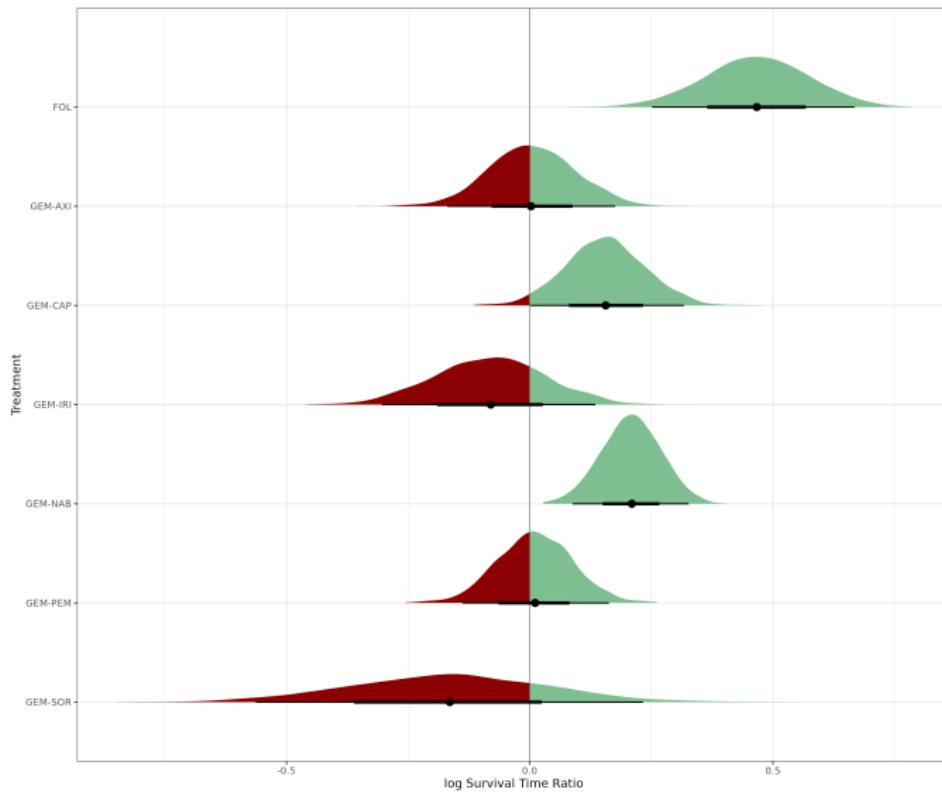
Predicted Median OS



Predicted Restricted Mean Survival Time



Relative effectiveness compared to GEM



Conclusions and Future Work

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- GEM-NAB provides slightly better OS than GEM-CAP, but not significantly better. (Aim 2)
- GEM-SOR and GEM-IRI provided worse OS than GEM.

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- The ISPOR good practice guidelines for NMAs were considered to ensure validity of the NMA. These were addressed in an appendix of the dissertation itself.
- Future work will include more studies. It would be nice to implement some form of parallel-processing, to make the computing process more efficient.

Thank you