A New Approach in Network Meta-Analysis Using Blended Survival Curves to Extrapolate Long-term Survival from Immature Data

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INTRODUCTION

In the absence of head-to-head trials, synthesis of clinical effectiveness plays an essential role in health economic evaluations. While traditional methods of network meta-analysis (NMA) assume constant treatment effect over whole time horizon, guidance from various health authorities have indicated implausibility of the assumption and suggested incorporation of external data further. This study develops a new extrapolation technique called blended survival curves into the NMA setting to leverage real-world evidence for reliable extrapolation.

METHODOLOGY

The main idea of blended survival curves is to mix a flexible model to fit the observed data $\boldsymbol{S_{obs}}$ in the best way and a parametric model encoding external assumptions on the expected behaviour of underlying long-term survival $\boldsymbol{S_{ext}}$.

The "blended" survival curve is described as

$$S_{ble}(t|\boldsymbol{\theta}) = S_{obs}(t|\boldsymbol{\theta}_{obs})^{1-\pi(t;\alpha,\beta,a,b)} \times S_{ext}(t|\boldsymbol{\theta}_{ext})^{\pi(t;\alpha,\beta,a,b)}$$

- where: $\pi(t;\alpha,\beta,a,b) = \Pr\left(\mathrm{T} \le \frac{t-a}{b-a}\middle|\alpha,\beta\right) = F_{Beta}(\frac{t-a}{b-a}|\alpha,\beta)$

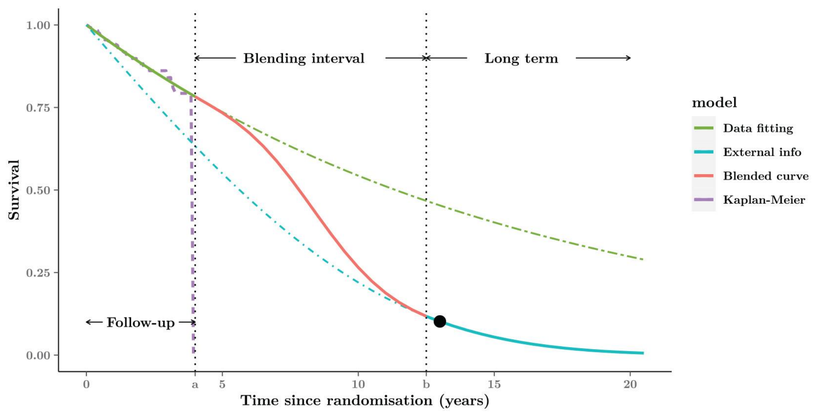


Figure 1: Graphical representation of the blended curve method

The blending hazard function is obtained as

$$h_{ble}(t) = \big(1-\pi(t)\big) \times h_{obs}(t) + \pi(t) \times h_{ext}(t)$$
$$+ \frac{f_{Beta}(\frac{t-a}{b-a})}{b-a} \times (H_{ext}(t) - H_{obs}(t))$$

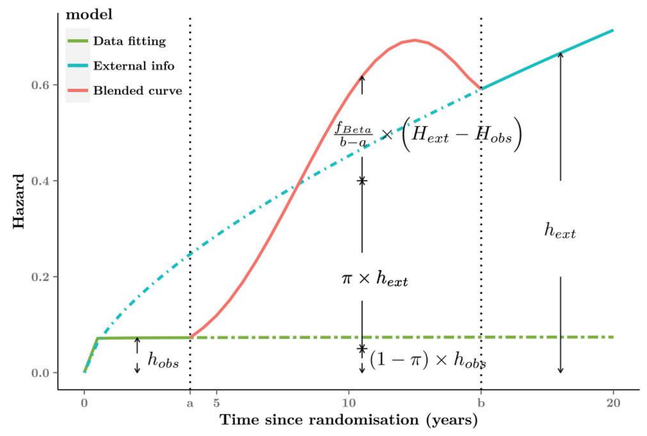


Figure 2: Graphical representation of the blended hazard

In the NMA of blended survival curves, it involves two separate processes: 1) standard model fitted to the network of short-term data; 2) external curves encoding long-term assumptions. Finally, we blend them together.

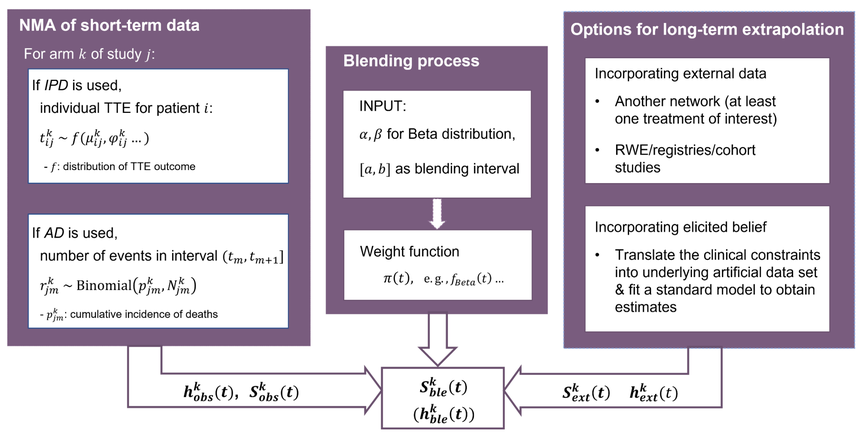
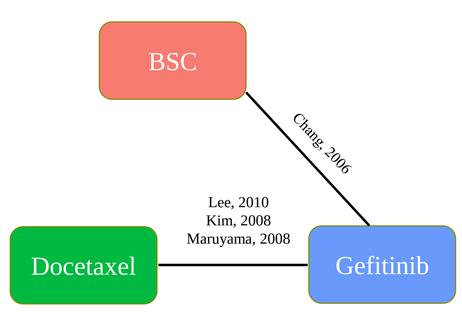


Figure 3: Framework of NMA modelling structure

ILLUSTRATIVE EXAMPLE

Four non-small cell lung cancer (NSCLC) trials were used comparing gefitinib with best-supportive care (BSC) (1 study) and gefitinib with docetaxel (3 studies).



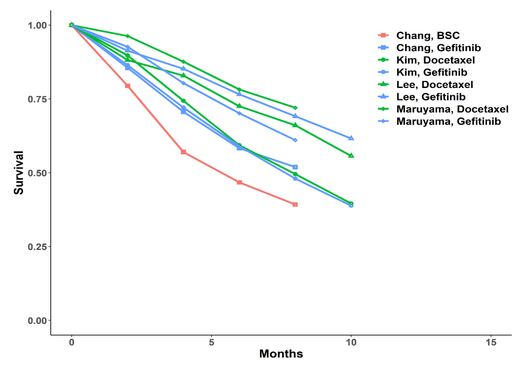
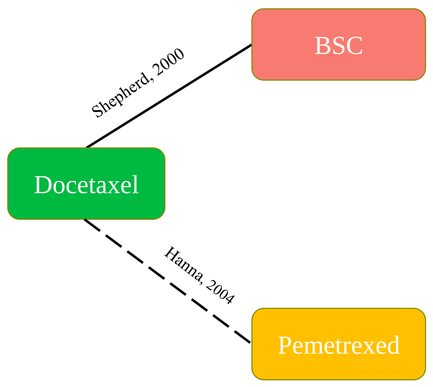


Figure 4 Reconstructed Kaplan-Meier curves in the example network of overall survival

Incorporating external information

- *External data:* Other trials were identified using BSC (1 study) and docetaxel (2 studies) with relatively longer follow-up until 20 months.



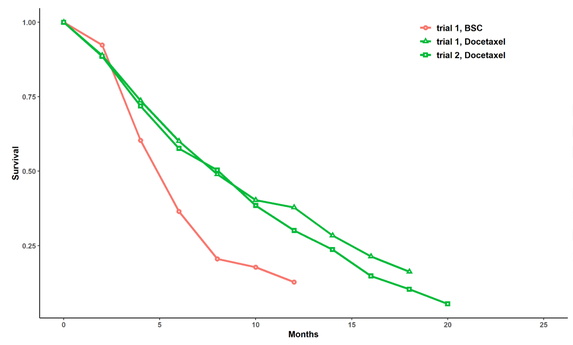
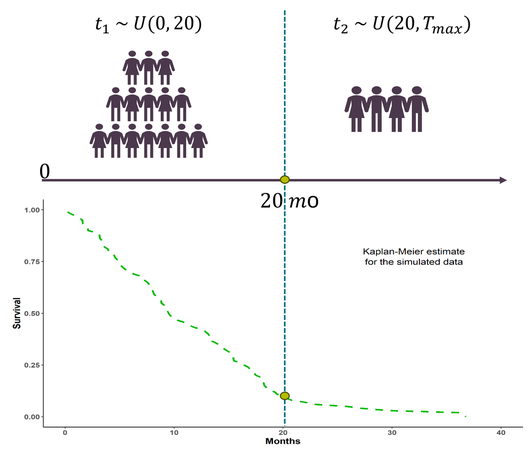


Figure 5 Reconstructed Kaplan-Meier curves of long-term data from other trials for BSC and docetaxel

- *Expert judgement*: clinical opinion is assumed for arm gefitinib, that 10% of the cohort would be alive beyond 20 months.



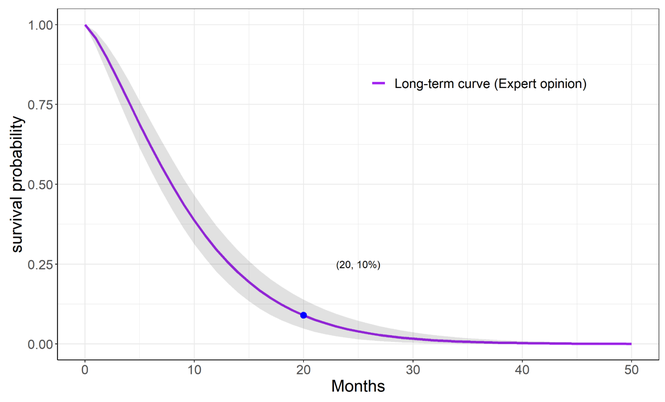


Figure 6 External survival curve based on subjective judgement; fitting results of the Gompertz model to the synthetic dataset

RESULTS

For each treatment, the short-term and long-term estimates are blended over the time interval between the 8 mo and 30 mo ($a = 8, b = 30$) based on the weight function with $\alpha = \beta = 3$.

Estimate		Mean	Median	95% Confidence Interval
Driven by short-term data	BSC	10.185	7.693	[6.880, 15.038]
(model: Weibull)	Docetaxel	13.385	11.398	[11.524, 15.589]
	Gefitinib	15.375	11.265	[11.347, 13.236]
Using external information	BSC	6.085	5.175	[5.089, 8.130]
(long-term data: piecewise model;	Docetaxel	9.768	8.014	[8.701, 11.542]
and expert opinion)	Gefitinib	9.549	7.935	[8.0160, 11.306]
Blended curve	BSC	8.516	7.575	[6.550, 11.339]
(Weight: blending interval [8, 40];	Docetaxel	11.741	10.969	[10.540, 13.591]
$\alpha = \beta = 3$)	Gefitinib	11.766	10.632	[10.613, 13.016]

Table 1 mean survival time at 50 months for blended results and two separate components: observed and external estimates.

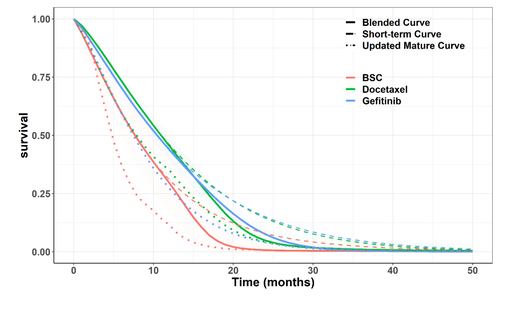


Figure 7 Blended survival curves for BSC, docetaxel and gefitinib

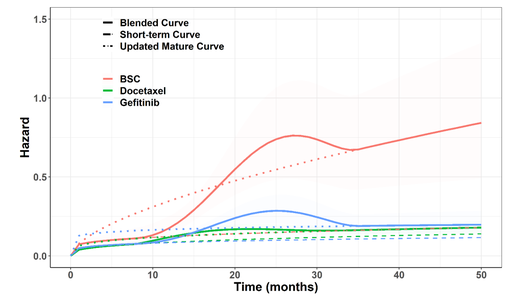


Figure 8 Blended hazard curves for BSC, docetaxel and gefitinib

CONCLUSION

Long-term extrapolation entirely driven by the less mature data is highly implausible and various assumptions can have a huge impact on the survival estimate. The blending approach in NMA allows for taking advantage of external data to guide extrapolation.

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https://github.com/StatisticsHealthEconomics/blendR

https://journals.sagepub.com/doi/full/10.1177/0272989X221134545