Effect of Sample Size and Data Maturity on Parametric Survival Modeling Projections in Advanced Cancer

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INTRODUCTION AND OBJECTIVE

- Overall survival (OS) has become the primary outcome of choice for most oncology clinical trials. However, due to the cost of data collection and the need for new treatments to come to market as soon as possible, OS is often right censored (i.e., not all patients have died at the end of the trial).
- Parametric survival modeling (PSM) is often used in cost-effectiveness analyses of oncology treatments to aid in lifetime projections by extrapolating survival based on observed and censored events.
- We sought to better understand the effect of sample sizes and data maturity (follow-up time) on PSM projections to aid in the design of clinical trials and the interpretation of cost-effectiveness models.
- For this illustrative analysis, we modeled OS for patients with advanced colorectal cancer treated with first-line chemotherapy and/or a biologic.

DATA SOURCE AND PATIENT SELECTION

- Data for the analysis were obtained from the Surveillance Epidemiology and End Results (SEER)–Medicare linked database. The SEER population-based cancer registries are nationally representative and collect information on nearly all (98%) newly diagnosed cancer cases, including colorectal cancer, among individuals residing in 20 SEER registry areas in the United States.
- For this analysis, incident cancer cases (aged ≥65 years) recorded in SEER data from 2004 to 2009 were linked with Medicare claims data from 2003 to 2010.
- Patients with an incident diagnosis of metastatic colorectal cancer during 2004-2009 were identified using site codes from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The American Joint Committee on Cancer (AJCC) staging system was used to define metastatic (i.e., stage IV) cancer.
- To reflect patients who might be selected for current clinical trials, patients receiving chemotherapy and/or biologic therapy after the incident metastatic diagnosis were identified using the ICD-9 diagnosis and procedure codes and the Healthcare Common Procedural Coding System (HCPCS) codes.
- Patients were excluded if they died in the month of diagnosis (hence, did not have any data available for study follow-up) or had invalid data on the month of diagnosis.

ANALYSIS METHODS

- All programming was done in SAS statistical software (version 9.3. Cary, NC: SAS Institute, Inc.; 2011).
- Survival was estimated using Kaplan-Meier (K-M) and PSM methods using PROC LIFETEST (K-M analysis) and PROC LIFEREG (PSM analyses).
- From the full cohort of patients with metastatic colorectal cancer (n = 7,810), we randomly drew patients to match typical sample sizes from phase 2 and 3 clinical trials (n = 50, 100, 200, and 400) using PROC SURVEYSELECT with a specified seed of 1,234,567.
- Additionally, arbitrary data cutoffs were created to approximate clinical trial follow-up times (t = 3, 6, 9, 12, 24, and 36 months). Patients without event (no death) at each time point were censored.
- Using PSM methods, mean survival from the full cohort was compared with survival from the combinations of sample sizes and follow-up times.
- Parametric distributions tested were the exponential, Weibull, log-logistic, and log-normal.

Table 1. Goodness-of-Fit of Parametric Models

Distribution	AIC
Exponential	23,970.43
Weibull	23,956.00
Log-logistic	24,071.70
Log-normal	24,229.06

AIC = Akaike information criterion.

Figure 1. Overall Survival K-M Plot and Weibull Parametric Curve

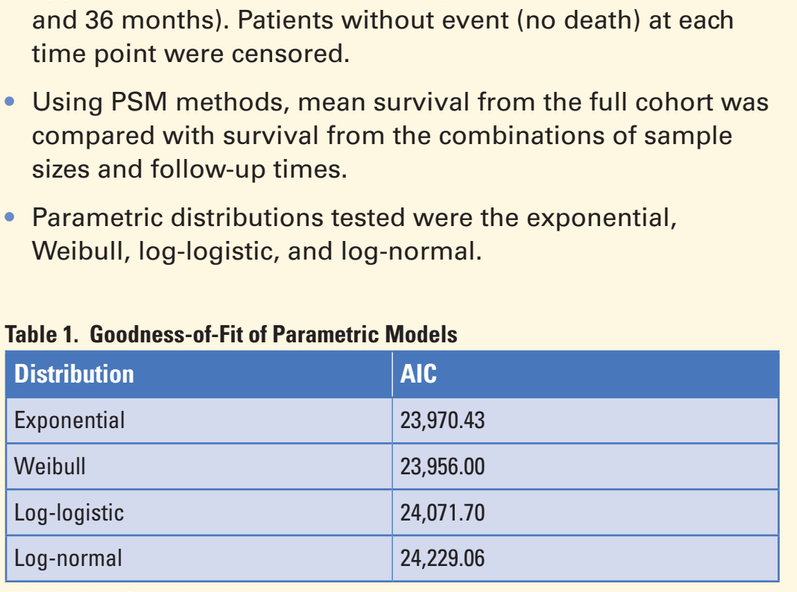

Table 2. Events and Censored Events

Analysis Time	Observed Events	Censored Events	Censoring %	Analysis Time	Observed Events	Censored Events	Censoring %
Full cohort	6,221	1,589	20.3%	Full cohort	6,221	1,589	20.3%
n = 50				n = 200			
3 months	13	37	74.0%	3 months	33	167	83.5%
6 months	20	30	60.0%	6 months	54	146	73.0%
9 months	23	27	54.0%	9 months	70	130	65.0%
12 months	27	23	46.0%	12 months	88	112	56.0%
24 months	35	15	30.0%	24 months	125	75	37.5%
36 months	41	9	18.0%	36 months	146	54	27.0%
n = 100				n = 400			
3 months	18	82	82.0%	3 months	64	336	84.0%
6 months	29	71	71.0%	6 months	102	298	74.5%
9 months	38	62	62.0%	9 months	138	262	65.5%
12 months	45	55	55.0%	12 months	172	228	57.0%
24 months	59	41	41.0%	24 months	252	148	37.0%
36 months	72	28	28.0%	36 months	287	113	28.3%

Figure 2. Sample Size n = 50

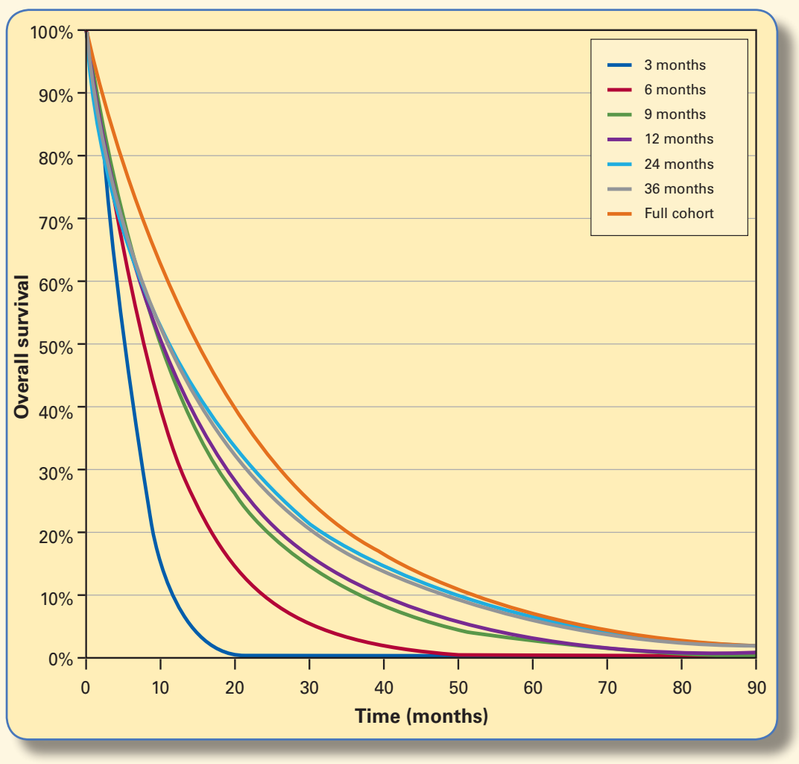

Figure 3. Sample Size n = 100

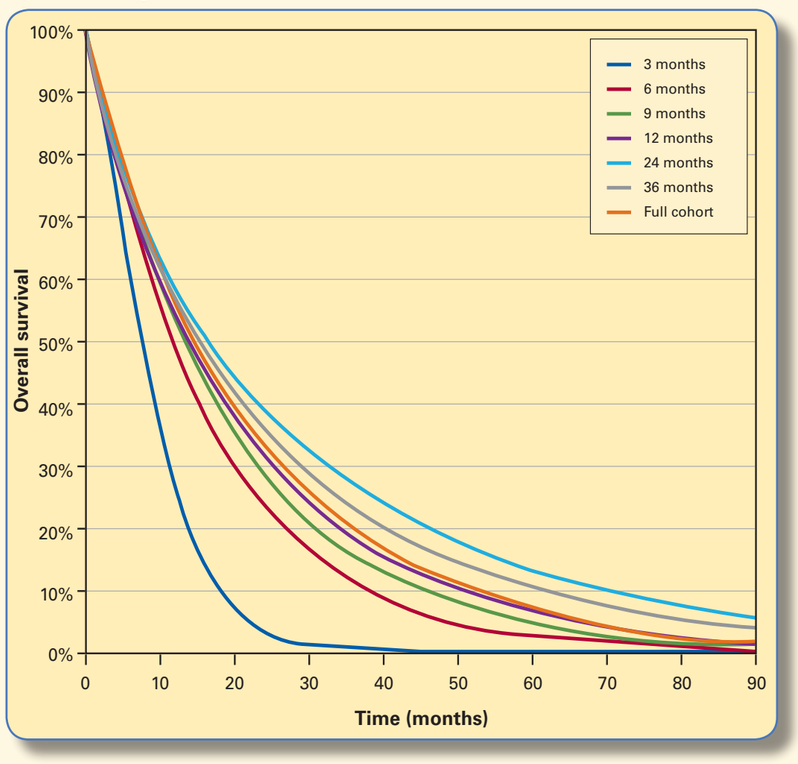

Figure 4. Sample Size n = 200

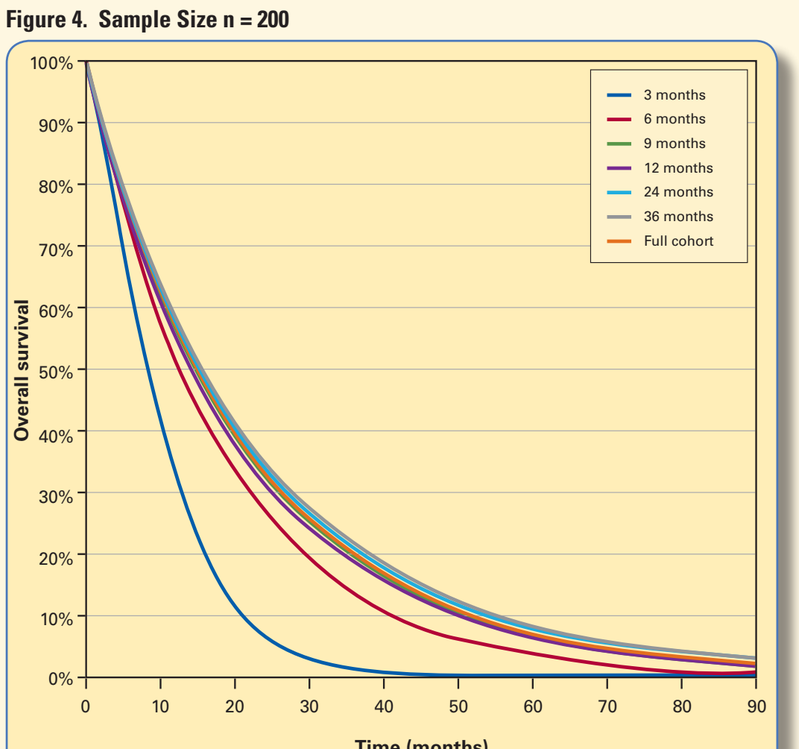

Figure 5. Sample Size n = 400

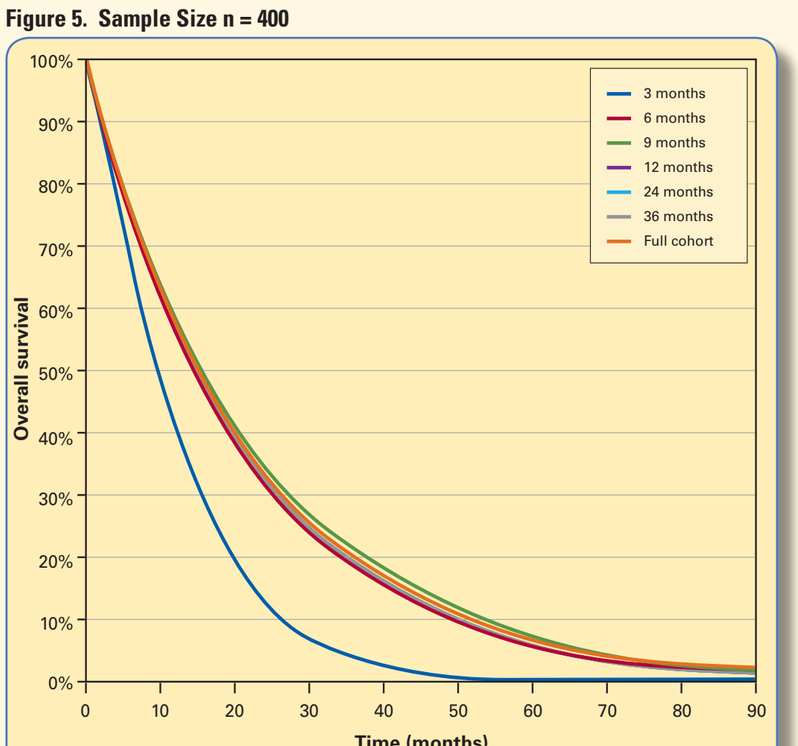

Table 3. Mean Survival Estimates

Sample Size	Follow-up Time (Months)					
	3	6	9	12	24	36
50	5.93	10.45	15.17	16.10	19.93	19.93
100	8.91	16.41	19.15	20.98	28.00	24.92
200	10.28	18.03	21.92	21.01	23.02	22.38
400	12.42	21.20	22.44	21.76	21.88	21.80

Table 4. Percentage Difference From Full Sample

Sample Size	Follow-up Time (Months)					
	3	6	9	12	24	36
50	–73%	–52%	–31%	–27%	–9%	–9%
100	–59%	–25%	–13%	–4%	28%	14%
200	–53%	–18%	0%	–4%	5%	2%
400	–43%	–3%	2%	–1%	0%	–1%

RESULTS

- Using the K-M method, 6% of patients were alive at the end of the follow-up period (6.5 years). Median OS was 1.21 years (95% confidence interval, 1.17-1.24 years).
- Based on graphical overlay of the fitted curves and the K-M plot (Figure 1) and on the Akaike information criterion (a statistical measure of goodness-of-fit where lower numbers represent better fit to the observed data) (Table 1), the Weibull distribution was deemed to be the best-fit distribution.
- A summary of observed and censored events for each analysis is shown in Table 2.
- Mean OS from the full cohort was estimated to be 21.9 months using the PSM method (best-fit Weibull curve) and 21.4 using the K-M method (area under the curve).
- Survival projections based on the sample sizes and data cutoffs selected are shown in Figures 1-4. The full cohort analysis Weibull OS curve is shown on each figure to demonstrate the effects of sample size and time and their ability to reflect true survival.
- OS estimates for the sample size and follow-up time combinations ranged from 5.9 to 28.0 months (Table 3).
- Minimum and maximum survival projections represented a 73% underestimation and 28% overestimation, respectively, of survival compared with the full cohort projection. All deviations from the full sample are summarized in Table 4 in the form of percent differences from the projected mean of the full sample.
- Despite low censoring rates with increased follow-up time (Table 2), small sample sizes were not able to accurately project OS when compared with the full sample.
- Overall, projection accuracy was improved when t ≥ 6 months and n ≥ 200.

CONCLUSIONS

- Both sample size and data maturity have a profound effect on survival projections.
- Care should be taken when interpreting projections in cost-effectiveness models, especially when sample size is low and follow-up time short.
- Where possible, PSM survival projections from clinical trial data should be compared with other sources and, if deviations exist, be supported by rational arguments. Otherwise, validity of projections should be questioned.
- In addition to power calculations for effect size of OS and progression-free survival hazard ratios, clinical trial design should account for these issues.
- Additional analyses in other cancer types may provide further guidance for optimum trial design.

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Presented at:

ISPOR 17th Annual European Congress
November 8-12, 2014
Amsterdam, The Netherlands