Predicting cancer's next move after local/regional recurrence (LR) for health economic evaluations: A pan-tumor case study

Pharmaco Evidence
Science-led HEOR & Tech-driven AI

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BACKGROUND

- State-transition models (STMs) are central to health economic evaluations of oncology treatments. When patients experience cancer recurrence, clinicians distinguish locoregional recurrence (LR) disease confined near the primary tumor or regional lymph nodes from distant recurrence (DR), involving metastatic spread. These two recurrence subtypes carry markedly different prognoses, and treatment pathways yet are frequently collapsed into a single post-progression state in cost-effectiveness models
- Parameterization of multi-state Markov models is often challenged by limited trial follow-up, sparse post-LR progression events, and protocol-driven analyses that may not distinguish LR→DR progression from post-LR mortality
- Population-level cancer registries such as SEER (Surveillance, Epidemiology, and End Results) report stage-stratified relative survival data for large patient cohorts. These aggregate level data capture the difference in prognostic patterns of LR and DR populations and provide a structured, publicly available source to inform STM parameterization externally, an approach that has been infrequently used in published health economic models
- Estimated progression rates following LR may inform statistical analysis planning and long-term OS projections for early-stage cancer trials and provide patients clearer prognostic expectations and insights on the time to explore their future treatment options and inform authorities on how early reductions in LR may translate into fewer distant recurrences
- DR often marks a critical turning point in cancer progression, associated with higher mortality, increased treatment costs, frequent hospitalizations, and reduced quality of life. Estimated transitions from the LR state in this study can be combined with recurrence- or disease-free survival endpoints to estimate distant metastasis-free survival, a key secondary endpoint in early-stage cancer trials providing meaningful insights into a drug's long-term efficacy

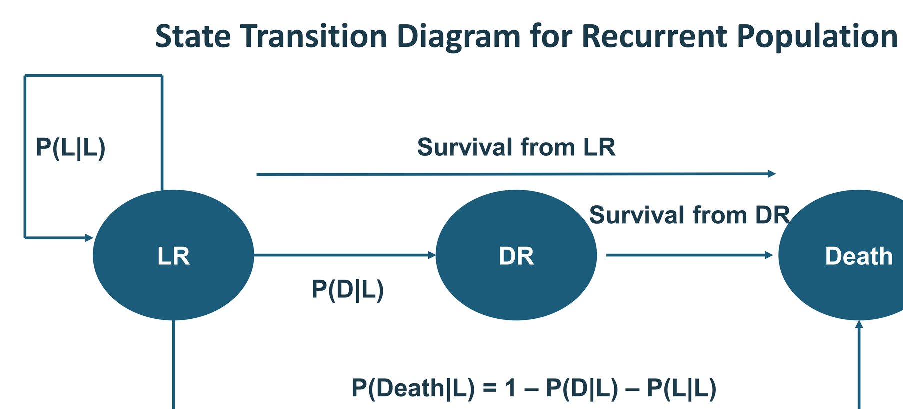
OBJECTIVES

- To address the limited availability of published data on post-LR progression rates through a cross-tumor case study using publicly available SEER data[1]
- To investigate the sensitivity of the transition estimates to the key parameters and structural assumptions of the proposed model.
- To compare the severity of progression following LR across multiple tumor types and characterize the relative disease burden associated with each

METHODS

- Post-recurrence relative survival data were sourced from SEER-17 registry[1] across 10 cancers: bladder, breast, colon & rectum, esophageal, kidney, liver, lung, ovarian, pancreatic, and stomach

State Transition Diagram for Recurrent Population



*The proposed approach does not actively estimate the value of monthly probability of death from LR state prior to experiencing DR. This quantity can be trivially estimated through the elicited values of P(D|L) and P(L|L).

Step 1: Parametric Modelling of Relative Survival & Model Blending (AIC/BIC)

Step 2: Adjusting Modeled Relative Survival with General Population Survival

Step 3: Estimating Long-Term Area Differential between Modeled Unconditional Survival from LR and DR; Solve for P(L|L)

Step 4: Quadratic Optimization Model to Derive P(D|L)

Sensitivity Analyses: Model Blending with AIC vs BIC Time Horizon: Lifetime / 20y / 5y

- Monthly transition probabilities from the LR state were estimated using a combination of survival analysis and constrained quadratic optimization, as previously developed and demonstrated in melanoma by Pandey et al. (2026)
- Relative survival data from SEER[1] were available only as annual estimates over a five-year horizon. Seven standard parametric[2] models (SPMs) recommended by NICE Technical Support Document 21 were fitted separately to the available relative survival data for LR and DR
- To reduce uncertainty associated with model selection in long-term projections, top three models, selected using Akaike Information Criterion (AIC) in the base case or Bayesian Information Criterion (BIC) in the sensitivity analysis, were then combined using information-criterion weights to produce final relative survival estimates over time for both groups
- Age- and sex-adjusted general population survival, derived from publicly available US CDC life tables[3], was used to adjust extrapolated relative survival curves
- For simplicity, transitions from the LR state were assumed to be constant over time and for internal consistency, same statistical fit criterion was used for blending of SPMs across both states
- The probability of remaining in the LR state was derived from the difference in area under the extrapolated unconditional survival curves for the LR and DR states. This approach was valid given the irreversible nature of progression from the LR state
- The transition probability from LR to DR, P(D|L), was estimated by solving a quadratic optimization model minimizing the discrepancy between two independent estimates of unconditional LR survival (i) a convolution-based estimate obtained by combining state-transition probabilities with the modeled unconditional DR survival (ii) an estimate derived directly from blended parametric models fitted to LR relative survival data
- Individual and combined effects of varying model blending criteria and time horizon on the results were investigated by sensitivity analyses

RESULTS

- Under the same model blending criteria, the lifetime-horizon analyses indicated that both the functional forms of the top three SPMs and their associated weights were broadly consistent across all cancer types, with only minor variation
- When blending was based on BIC, the weights assigned to the top three SPMs were more evenly distributed. In contrast, under AIC, the best-fitting SPMs dominated the weighting, receiving substantially higher weights than the second- and third-ranked models, resulting in a more imbalanced distribution
- Cancer rankings for progression from LR to DR were sensitive to both model blending criteria and the time horizon for extrapolations. Relative to lifetime-horizon analyses, restricting extrapolations to a 5-year horizon led to systematically shorter mean sojourn times in the LR state and higher LR-to-DR transition rates across cancers
- In the base case, pancreatic and liver cancers exhibited the shortest mean sojourn times in local recurrence and the most aggressive progressions from LR to DR, whereas breast and kidney cancers showed the longest sojourn times and the slowest progressions from LR to DR, reflecting a markedly more indolent post-recurrence trajectory
- Regardless of the model blending criteria, the lifetime-horizon analyses consistently showed that breast, ovarian, kidney, and colorectal cancers had the most prolonged post-recurrence trajectories, characterized by the highest probabilities of remaining in the LR state and the lowest LR-to-DR transition probabilities.
- The LR-to-DR transition probability exhibited the greatest sensitivity to the extrapolation time horizon for breast and ovarian cancers, consistently under both model blending criteria

Tumor	Baseline Age	BASE CASE- MBC: AIC, HORIZON:LIFETIME		SA1 - MBC: BIC, HORIZON:LIFETIME		SA2 - MBC: BIC, HORIZON:20 YEARS		SA3 – MBC: BIC, HORIZON:5 YEARS		SA4 - MBC: AIC, HORIZON:20 YEARS		SA5 – MBC: AIC, HORIZON:5 YEARS	
		P(L|L)	P(D|L)	P(L|L)	P(D|L)	P(L|L)	P(D|L)	P(L|L)	P(D|L)	P(L|L)	P(D|L)	P(L|L)	P(D|L)
Bladder	65	0.9910	0.0089	0.9916	0.0083	0.991	0.0090	0.9524	0.0476	0.9903	0.0096	0.9524	0.0475
Breast	61	0.9952	0.0047	0.9951	0.0048	0.994	0.0059	0.9392	0.0608	0.9940	0.006	0.9412	0.0588
Colon & Rectum	61	0.9938	0.0062	0.9936	0.0063	0.9931	0.0068	0.9571	0.0429	0.9932	0.0067	0.9576	0.0423
Esophageal	63	0.9802	0.0197	0.9846	0.0153	0.9826	0.0174	0.9411	0.0588	0.9791	0.0208	0.9420	0.0579
Kidney	61	0.9942	0.0057	0.9941	0.0059	0.9933	0.0067	0.9491	0.0509	0.9933	0.0066	0.9495	0.0504
Liver	63	0.9770	0.0229	0.9771	0.0229	0.976	0.0240	0.9432	0.0567	0.9760	0.0239	0.9413	0.0586
Lung	65	0.9846	0.0153	0.9846	0.0153	0.9834	0.0166	0.9373	0.0627	0.9834	0.0166	0.9368	0.0632
Ovarian	59	0.9929	0.0071	0.9928	0.0072	0.9908	0.0092	0.9266	0.0734	0.9907	0.0092	0.9293	0.0707
Pancreatic	63	0.9690	0.0309	0.9772	0.0228	0.9743	0.0256	0.9267	0.0732	0.9679	0.0321	0.9277	0.0723
Stomach	63	0.9899	0.0100	0.9910	0.0089	0.9900	0.0099	0.9568	0.0432	0.9890	0.0109	0.9569	0.0430

P(L|L): Monthly probability of remaining in the LR state, P(D|L): Monthly probability of moving from LR state to DR state, SA: Sensitivity Analysis, MBC: Model blending criteria, Age: Baseline Age in LR

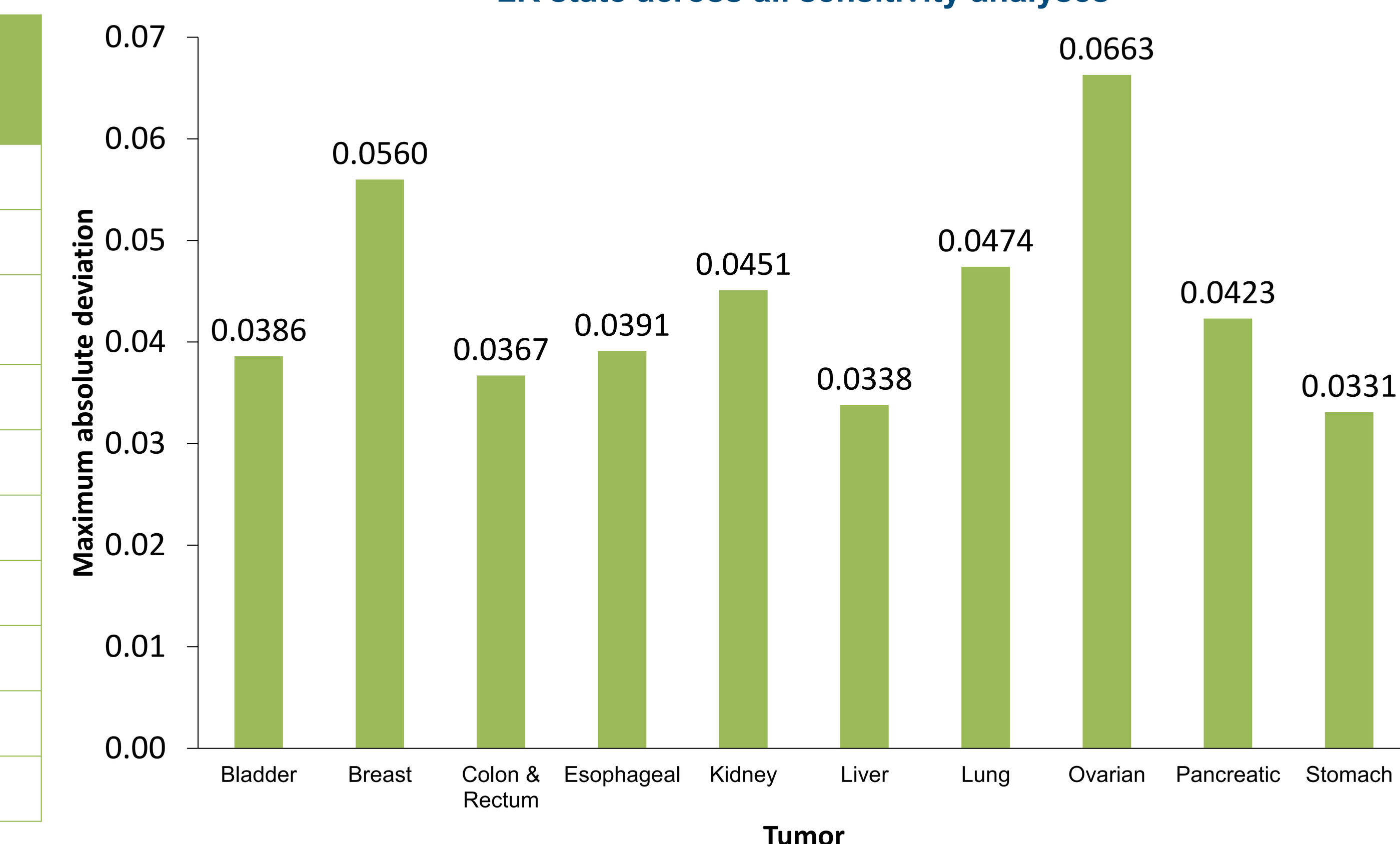
Tumor	Model Blending Weights — Top 3 SPMs, BIC (Lifetime Horizon)						Model Blending Weights — Top 3 SPMs, AIC (Lifetime Horizon)					
	LR (1st Fit)	LR (2nd Fit)	LR (3rd Fit)	DR (1st Fit)	DR (2nd Fit)	DR (3rd Fit)	LR (1st Fit)	LR (2nd Fit)	LR (3rd Fit)	DR (1st Fit)	DR (2nd Fit)	DR (3rd Fit)
Bladder	LN (34%)	GMP (33%)	LL (33%)	LN (34%)	LL (34%)	GAM (33%)	EXP (57%)	LN (21%)	GMP (21%)	EXP (57%)	LN (22%)	LL (22%)
Breast	LN (33%)	LL (33%)	GAM (33%)	LN (34%)	LL (33%)	GAM (33%)	EXP (58%)	LN (21%)	LL (21%)	EXP (57%)	LN (22%)	LL (22%)
Colon & Rectum	LN (33%)	LL (33%)	GAM (33%)	LN (34%)	LL (33%)	GAM (33%)	EXP (57%)	LN (21%)	LL (21%)	EXP (56%)	LN (22%)	LL (22%)
Esophageal	LN (34%)	LL (33%)	GMP (33%)	LN (34%)	LL (34%)	GAM (32%)	EXP (57%)	LN (22%)	LL (21%)	EXP (56%)	LN (22%)	LL (22%)
Kidney	LN (33%)	LL (33%)	GAM (33%)	LN (34%)	LL (33%)	GAM (33%)	EXP (58%)	LN (21%)	LL (21%)	EXP (57%)	LN (22%)	LL (21%)
Liver	LN (34%)	LL (33%)	GAM (33%)	LN (34%)	LL (34%)	GAM (33%)	EXP (57%)	LN (22%)	LL (21%)	EXP (56%)	LN (22%)	LL (22%)
Lung	LN (34%)	LL (33%)	GAM (33%)	LN (34%)	LL (33%)	GAM (33%)	EXP (57%)	LN (22%)	LL (21%)	EXP (57%)	LN (22%)	LL (22%)
Ovarian	LN (33%)	LL (33%)	GAM (33%)	LN (34%)	LL (33%)	GAM (33%)	EXP (57%)	LN (21%)	LL (21%)	EXP (56%)	LN (22%)	LL (22%)
Pancreatic	LN (34%)	LL (33%)	GMP (33%)	LL (34%)	LN (34%)	GAM (33%)	EXP (56%)	LN (22%)	LL (22%)	EXP (56%)	LL (22%)	LN (22%)
Stomach	LN (34%)	GMP (33%)	LL (33%)	LN (34%)	LL (34%)	GAM (32%)	EXP (57%)	LN (22%)	GMP (21%)	EXP (56%)	LN (22%)	LL (22%)

LR: locoregional recurrence, DR: distant recurrence, SPM: Standard Parametric Model, LN: Log-normal, LL: Log logistic, GAM: Gamma, GMP: Gompertz, EXP: Exponential

Estimated Mean Sojourn Times in LR State (Months)

Tumor	Base Case (AIC, Lifetime)	SA1 (BIC, Lifetime)	SA2 (BIC, 20-yr)	SA3 (BIC, 5-yr)	SA4 (AIC, 20-yr)	SA5 (AIC, 5-yr)
Bladder	143.3	147.9	31.4	3.5	30.2	3.5
Breast	104.8	103.5	20.1	2.7	20.3	2.8
Colon & Rectum	119.3	116.4	19.2	3.5	19.7	3.6
Esophageal	215.7	217.3	55.8	3.7	50.8	3.2
Kidney	121.4	119.2	21.4	3.2	21.8	3.2
Liver	234.3	239.9	63.1	3.4	59.3	3.2
Lung	158.0	160.6	35.6	2.8	34.2	2.7
Ovarian	105.7	105.2	17.1	2.1	17.1	2.2
Pancreatic	268.2	267.5	85.7	4.3	80.1	3.3
Stomach	161.1	166.0	31.1	3.7	29.2	3.5

Maximum absolute deviation from base-case transition estimates from LR state across all sensitivity analyses



CONCLUSIONS

- This study helps bridge a key gap in the literature for a broad range of cancer—the limited availability of published estimates for post-recurrence transitions from the LR state—by effectively applying a combined survival-analytic and optimization framework.
- Transitions derived in this study reflect a mix of US standard-of-care treatments and remain valid provided treatment landscapes in LR and DR undergo only minimal changes.
- While treatments' mechanism of action may influence transitions from the LR state, in the absence of mature post-recurrence survival data from clinical trials, multi-state cost effectiveness models distinguishing LR and DR may use identical parameterization across comparators, and estimates from this study can serve as a valuable pan-tumor benchmark
- Transitions from the LR state estimated in this study can guide pharmacovigilance priorities for a range of cancers and patient monitoring during LR, as progression to DR may involve different safety exposures, concomitant medications, and adverse event risks

LIMITATIONS

- For simplicity, transitions from the LR state were assumed constant over time, implying exponentially distributed sojourn time. Incorporating differences in the second moments of the LR and DR survival distributions may enable derivation of gamma- or beta-distributed sojourn times in the LR state, thereby relaxing the stationarity assumption for the probability of remaining in the LR state.
- Limited follow-up and annually reported SEER relative survival data restricted the framework to SPMs, as survival plateaus and inflection points could not be identified. However, the proposed framework remains flexible to incorporate mixture cure or spline-based models with longer follow-up and more granular data to better capture complex survival trends.
- As SEER-17 covers only the U.S. treatment landscape and cases through 2021, derived transition probabilities may not be directly generalizable to other settings or treatment eras without recalibration. Moreover, due to lack of detailed comorbidity information in SEER-17, reported relative survival estimates may be imprecise in older populations.

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