Oncology Simulation Model: A Comprehensive and Innovative Approach to Estimate and Project Prevalence and Survival in Oncology

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Objective: We demonstrate a new model framework as an innovative approach to more accurately estimate and project prevalence and survival outcomes in oncology.

Methods: We developed an oncology simulation model (OSM) framework that offers a customizable, dynamic simulation model to generate population-level, country-specific estimates of prevalence, incidence of patients progressing from earlier stages (progression-based incidence), and survival in oncology. The framework, a continuous dynamic Markov cohort model, was implemented in Microsoft Excel. The simulation runs continuously through a prespecified calendar time range. Time-varying incidence, treatment patterns, treatment rates, and treatment pathways are specified by year to account for guideline-directed changes in standard of care and real-world trends, as well as newly approved clinical treatments. Patient cohorts transition between defined health states, with transitions informed by progression-free survival and overall survival as reported in published literature.

Results: Model outputs include point prevalence and period prevalence, with options for highly granular prevalence predictions by disease stage, treatment pathway, or time of diagnosis. As a use case, we leveraged the OSM framework to estimate the prevalence of bladder cancer in the United States.

Conclusion: The OSM is a robust model that builds upon existing modeling practices to offer an innovative, transparent approach in estimating prevalence, progression-based incidence, and survival for oncologic conditions. The OSM combines and extends the capabilities of other common health-economic modeling approaches to provide a detailed and comprehensive modeling framework to estimate prevalence in oncology using simulation modeling and to assess the impacts of new treatments on prevalence over time.

Keywords: epidemiology, Markov, modeling, oncology, OSM, prevalence

Introduction

Improvements in treatment and survival mean that many types of cancers that once had limited life expectancy can now be viewed as chronic diseases. A striking example is the introduction of tyrosine kinase inhibitors for chronic myelogenous leukemia, which meant a revolutionary shift from median survival of 3–4 years to up to 25 years.1 The introduction of targeted therapies, immunotherapies, and a greater understanding of cancer pathophysiology has led to a steady increase in 5-year cancer survival and overall survival in all major cancer types.2

Because of the rapidly changing treatment landscape and improvement in survival, reliance on incidence alone as a proxy for the number of patients living with a specific cancer type is becoming increasingly inaccurate for oncologic conditions. Large-scale registries in oncology such as the Surveillance, Epidemiology, and End Results (SEER) Program and GLOBOCAN provide detailed information on the incidence of newly diagnosed cancers by stage and mortality, but not prevalence or numbers of patients progressing from earlier stages (progression-based incidence). Additionally, data
on specific subpopulations (metastatic, biomarker groups, etc) are limited. More accurate measures of prevalence and progression are critical to understanding unmet need and public health strategies.

In general, incidence is defined as the number of new cases that develop over a period of time. Prevalence is defined as the total number of cases that exist at a specific point in time (new and existing). The prevalence of acute conditions is commonly estimated by incidence, a relatively good estimation when duration of disease is short (Figure 1). Prevalence of chronic conditions is commonly estimated with analysis of administrative claims data, registries, or public health surveys. These methods, specifically administrative claims data, fail to account for people who are undiagnosed or untreated, thus can significantly underestimate true population-level prevalence. Additionally, owing to a lag in data availability and changes in disease incidence, survival, screening rates, detection rates, and available treatments, the results of claims or registry analyses reflect historic rather than current or future prevalence.

Cancer can be thought of as a pseudo-chronic disease in that many patients live with cancer for an extended period of time. With the evolution of many cancers into a pseudo-chronic disease and a rapidly changing treatment landscape, modeling methods have been developed to overcome these limitations and better address the need of population-level prevalence estimation in oncology (Figure 1). It is important to estimate prevalence because these types of estimates are used by health policy decision makers (e.g., payers) to estimate the size of populations who may receive newly approved therapies and require reimbursement. It is also important to estimate the impact of new therapies on overall survival at the population level to help decision makers determine where new therapies fit within treatment paradigms. Together, these estimates can inform aspects such as resource planning, clinical trial feasibility, and (by highlighting likely treatment pathways) clinical practice. Understanding prevalence and progression among an entire population can inform strategic decisions for battling cancer going forward.

There exist multiple, commonly used estimation methods in public health and health data institutions globally, each subject to different limitations. An incidence-only approach is often used in oncology budget-impact models. Other models of chronic disease rely exclusively on prevalence and assume population size is relatively stable. However, in a disease state, such as cancer, where screening, diagnosis, and survival are constantly changing due to better technology, management, and treatments, the applicability of this approach is limited. Simulation models have been developed to estimate the population-level gain in survival resulting from new treatments over long periods of time. These models capture time-varying treatment patterns, but only for a single cancer stage and/or line of therapy, not for the entire patient journey from diagnosis to death.

Several types of age-period-cohort (APC) models have been developed to estimate and project cancer incidence and prevalence at a regional or national level. The Mortality and Incidence Analysis MODel (MIAMOD) estimates incidence

![Methodology](https://doi.org/10.2147/CLEP.S377093)

**Figure 1** Methods of estimating population size.

**Abbreviations:** MIAMOD, Mortality and Incidence Analysis MODel; OSM, oncology simulation model; PIAMOD, Prevalence and Incidence Analysis MODel.
and prevalence using mortality and survival data, and has been used to estimate and project breast cancer prevalence at regional levels. The Prevalence and Incidence Analysis MODel (PIAMOD) estimates prevalence by fitting a parametric incidence model to incidence data and combining with survival, and has been used to estimate the prevalence of colorectal cancer by phases of care, and the prevalence of pediatric cancers. Despite implementation of MIAMOD/PIAMOD, these types of APC models tend to be opaque, difficult to validate, do not account for multi-stage diseases, and/or do not utilize detailed treatment patterns or account for time-varying treatment patterns directly.

Here, we describe the oncology simulation model (OSM), an extension of established methods from economic modeling that includes incidence, dynamic treatment patterns, and survival. The OSM aims to overcome existing modeling limitations by providing a detailed and comprehensive framework. As a use case, here we illustrate our application of the OSM framework to estimate the prevalence of bladder cancer (BC) in the US. While there are published cost-effectiveness models for individual treatments in BC, there is a clear gap in the literature around BC prevalence, which, in addition to BC’s multiple disease stages and dynamic treatment landscape, make it a good choice for the OSM framework.

Methods
The OSM framework (outlined in Figure 2A) offers a customizable, dynamic simulation model to generate population-level estimates of prevalence, and progression-based incidence into a specific stage or line of therapy. Simulation begins at a specified calendar date and cycles forward in time until a specified time horizon. During each model simulation time-cycle, a newly incident cohort enters the model. To estimate the prevalent population and survival over time, the model simulates the entire disease landscape from early to late stage across multiple decades, accounting for continuous incidence of new diagnosis at each stage as well as progression from earlier to later stages. Time-varying inputs based on published real-world trends—such as incidence, stage at diagnosis, demographics, and treatment patterns—are specified by calendar time (typically calendar year but can be as granular as per model cycle) to account for real-world trends. The OSM framework is designed to be applicable to a wide range of oncological diseases since it relies on common measures of effectiveness, namely progression-free survival (PFS) and overall survival (OS). In addition, the OSM takes into consideration time-varying aspects of disease epidemiology, including disease incidence, treatment pathways, cure rates, and treatment patterns, all of which can change in a dynamic disease landscape. A comparison of the OSM with common health-economic models, which leverage similar methods, is shown in Table 1.

Figure 2 (A) Multi-stage model structure and (B) Markov structure within individual treatments.
Overall Framework

Patients enter and progress through the model for a defined unit of time (e.g., weekly, monthly, or yearly model cycles). The OSM framework supports a variable model-cycle length to ensure that the cycle length mirrors the time frame of the data available or the time frame of clinically relevant decision points. Patients enter the model based on annual incidence, converted to a per model-cycle incidence. Incident patients are distributed into disease stages based on the published distribution stage at diagnosis. Within each stage, patients can be treated or untreated. Treatment rates and country-specific available treatments are driven by regional regulatory approvals, reimbursement decisions, treatment guidelines, and real-world treatment patterns.

Health States

Within each treatment, cohorts move between mutually exclusive, well-known health states of cured, progression-free, progressed disease (PD), or death (Figure 2B). Health-state transitions are informed by published data on progression-free survival (PFS) and overall survival (OS).

The PD health state is defined as a state in which a patient lives with a worsening disease and is assumed to receive no further treatment. Patients enter this state either at initial diagnosis (choosing to receive no treatment) or after a non-death progression event with no subsequent treatment. Patients who do not receive treatment by choice or due to a lack of treatment options remain in the PD state of their current stage. The PD state is considered non-curative, and patients remain in this state until death. Probability of being in this state is based on the difference between the overall survival

| Table 1 | Comparison of the OSM with Common Approaches to Health-Economic Modeling |
|-----------------|-----------------|-----------------|
| **Scope**       | Budget-Impact Model | Cost-Effectiveness Model | Oncology Simulation Model (OSM) |
| Treatments      | Single line of therapy | Single line of therapy | Full disease landscape |
| Time            | Time-varying market share and static annual incidence | No impact of time | Time-varying efficacy |
| Historical      | Prevalence not typically included; incidence-only perspective | Single patient treatment trajectory | Aggregated cohort trajectories including historical treatment pathways |
| Outputs         | Population estimates for single therapy based on annual incidence alone | Efficacy of treatments for single patient | Prevalence of all lines of therapy and population treatment pathway composition |
| Benefits        | Incidence data are typically readily available | Detailed treatment trajectory of a single patient | Full disease landscape prevalence |
|                 | Easy to interpret and follow calculations | Methods well understood | Predicted disease prevalence and impact of new treatment |
|                 | Fairly quick model-development time | Treatment efficacy can usually be informed from literature | Detailed population-level output representing a multitude of patient journeys and treatment pathways |
| Challenges      | Lacks precision to estimate prevalence | Calculations can be difficult to follow “memoryless” (Markov assumption) | Calculations can be difficult to follow |
|                 | Limited to single line of therapy | Difficult to track treatment pathways and sequencing | Difficulty finding data for efficacy and treatment % for the full disease landscape |
|                 | Difficult to capture dynamic effects in a changing treatment environment | Difficulty finding data for more complex models | Model-development time based on complexity or data availability |

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(OS) and progression-free survival (PFS) curve (PD = OS – PFS), subtracting those patients who go on to subsequent treatment.

The progression-free health state is defined as a state in which a patient lives with the disease but does not get worse. Patients enter this health state upon start of treatment, either after initial diagnosis or progression from a previous treatment. Transitions out of this state are driven by a progression event, defined as disease worsening or death from any cause. The cured health state is defined as a state in which a patient is considered cured and no longer at risk of progression. Cured is defined as a number of years progression-free, at which point a patient moves from the progression-free state to the cured state. The specific number of years progression-free that constitutes cured varies depending on the disease modeled but is typically 5 years. Cured patients are no longer considered a part of the prevalent disease population and are assumed to have an underlying mortality equivalent to the general population based on the census for the specific region of interest. Lastly, patients can enter the death state from any other health state. All-cause mortality is driven by OS curves, considering underlying age- and gender-specific mortality as a lower bound.

The progression rate associated with each treatment is defined by summary survival metrics (such as median PFS) or detailed Kaplan–Meier PFS curves derived from the most contemporary data available. Treatment-specific survival data are based on published meta-analyses when multiple studies are available. If meta-analysis is not available, clinical trials cited by established medical guidelines are used.

**Incidence and Treatment**

For each model cycle, new cohorts enter the model based on age- and gender-specific annual incidence rates. These incidence rates can be time-varying by calendar time. Overall incidence is divided into stages (eg, early, advanced, late) by applying a distribution of stage at diagnosis derived from published literature. Incidence and stage at diagnosis can be varied with time to capture changes over time such as uptake or improvement of screening, which leads to increased and/or earlier detection.

Patients can receive treatment upon new diagnosis and upon progression. The proportions of patients treated and untreated are applied for each stage and line of therapy, which can also be time-varying. Treatment patterns are defined as the proportion of patients in a specific disease stage or line of therapy treated with specific treatments. Treatment patterns can be specified by calendar month/year to account for the introduction of novel therapies over time and changes in guideline-directed standard of care. Treatment rates and treatment patterns in each disease stage and line of therapy are informed by published literature. Expert clinician opinion—which is applicable when published literature is out of date, unavailable, or if utilization of the most contemporary treatment patterns is needed—is disclosed when used. Treatment options available to patients can be configured to be dependent on previous treatments received, allowing for modeling of treatment pathways that require progression on specific treatments before patients are eligible for novel and emerging therapies.

**Framework Dynamics**

All patients who initiate treatment begin in the progression-free state. Cohorts transition to the PD, cured, or death states in each model cycle. Model-cycle transition probabilities are dependent on time from start of treatment, informed by the PFS and OS curves for each treatment, and can be assumed to have constant hazard (exponential curve), as survival is most readily available as median PFS or OS from trials or meta-analyses. The model allows for more detailed transition probabilities to be defined through survival-curve fitting or direct data look-up to match PFS and OS curves. The survival hazard function for each specific treatment is assumed to be independent of calendar year. Nevertheless, changes in the PFS and OS of specific treatments over time, such as introduction of supportive therapies that improve adherence and—indirectly—survival, can also be accounted for.

Key considerations in simulation modeling are initial conditions and model run-in. At any point in time, the point prevalence is a compilation of cohorts that were diagnosed at various times in the past and at various stages of disease. This is especially important when a model is considering the impacts of patients with early- or late-stage disease. The OSM operates from a “cold-start” concept, with no prevalent patients at time zero. However, once a time frame has been run for long enough, the estimated prevalence achieves equilibrium, which is assumed to approximate real-world
prevalence since it reasonably incorporates all historical cohorts. To achieve sufficient accuracy, the model start year must be far enough in the past to allow for sufficient run-in time to get a reasonable answer in the present. The necessary run-in time and historical start year depend on the level of precision desired. In general, the simulation will approximate real-world prevalence after 5 years multiplied by the number of stages of disease modeled. Often, a desired output of the OSM is to determine the impact on prevalence due to a shift in the treatment landscape. It is recommended that the simulation achieve equilibrium before applying significant treatment variations to capture impacts that can be reasonably attributed to the treatment landscape.

Bladder Cancer as a Case Study Application

To test the practical application of the OSM, this framework was used to estimate the prevalence of BC in the US. Urothelial carcinoma (UC; also known as transitional cell carcinoma) is the most common form of BC.\(^{10}\) UC originates in the urothelial cells that line the inside of the bladder (more than 90% of US), and in other portions of the urinary tract, including the renal pelvis (8%), ureter, and urethra (2% overall).\(^{17}\) A small proportion of UC cases originating outside of the bladder are included in this study; however, for simplicity, we use the term BC to refer to all included cases in our reporting. Significant data gaps exist in the understanding of country-specific epidemiology of BC and locally advanced or metastatic urothelial carcinoma (la/mUC), including rate of progression from early-stage disease to la/mUC, country-specific treatment rates, treatment patterns, cisplatin eligibility, and impact of recently approved and emerging therapies.\(^{15}\) In addition to these data gaps, aspects of BC progression and treatment which make it an ideal use case for the model include the multiple stages of disease and the dynamic, continuously evolving treatment landscape, permitting evaluation of the flexibility of the framework. The OSM has been used previously to estimate disease prevalence of patients undergoing treatment in Canada for this indication\(^{18}\) and has also been used to estimate disease prevalence in breast cancer,\(^{19}\) and PFS and OS in classical Hodgkin Lymphoma,\(^{20}\) and peripheral T-Cell Lymphoma.\(^{21}\) The framework was implemented in Microsoft Excel for transparency and consistency with contemporary best practices for modeling, although it can be implemented in any computational platform of choice (Excel, R, Python, C, etc). To populate the model, we conducted a targeted literature review to derive model inputs including BC incidence, treatment patterns over time, guideline-directed standard of care, and survival. The literature review focused on studies published in peer-reviewed journals, up through December 2020. Model inputs were further informed by expert opinion where published data were unavailable or model inputs were future-looking.

Bladder cancer was modeled with five different stages/lines of therapy: non-muscle-invasive BC (NMIBC), muscle-invasive BC (MIBC), first-line (1L) la/mUC, second-line (2L) la/mUC, and third- or later-line (3L+) la/mUC (Figure 3). These stages and various subgroups were chosen as an appropriate level of detail given the available data and initial research questions. The OSM framework allows for simpler or more detailed refinement as future research questions arise. Based on published literature, BC has an annual incidence of 25.2 per 100,000 of the population, with distribution of stage at diagnosis of 68% NMIBC, 20% MIBC, and 12% la/mUC (specific to BC).\(^{12,22,23}\) Treatment rates among eligible patients by each stage or line of therapy were assumed to be 100% in NMIBC (predominately owing to transurethral resection of the bladder tumor [TURBT] as both a diagnostic and treatment procedure), 75% in MIBC, 74% in 1L la/mUC, 34% in 2L la/mUC who have progressed on 1L, and 35% in 3L la/mUC who have progressed on 2L.\(^{24,25}\) The proportions treated in each line of therapy apply to both patients who progress to la/mUC and are la/mUC at diagnosis. Tables of specific treatments, survival, and sources are included in Tables S1–S13.

Results

OSM outputs are shown as a patient flow with prevalence estimates for different stages of the disease, resulting in estimated treated prevalence and annual patient flow for BC in the US during 2022 (Figure 4). A sample two-way sensitivity analysis is shown in Figure 5, illustrated as a contour plot. The two-way sensitivity analysis is critical to exploring which inputs are highly impactful, especially when a number of inputs have a wide range of potential values. The horizontal and vertical axes of the plot represent two input parameters of interest, usually those parameters with high uncertainty. To generate the contour plot, the simulation is run multiple times, each time taking a unique combination of input values for the two parameters and recording the output of interest. Output values are bucketed together into regions to provide a set of colored bands. The contour plot provides a unique ability to allow a high-level estimate of the output
when given any two values of the input parameters. This estimate can be obtained by finding the intersection of the horizontal and vertical values in the contour plot and identifying the colored band it falls within. In our use case, the horizontal axis represents the 1L la/mUC treatment rate, and the vertical axis represents the 2L la/mUC treatment rate. The colored bands represent the output range from runs of the OSM. In our illustrative example, our estimate of 33,002 patients for the 1-year la/mUC–treated prevalence reflects our base-case assumption of 74% 1L la/mUC treatment rate and 34% 2L la/mUC treatment rate.

Due to the dynamic nature of the treatment landscape and the data lag in published manuscripts, the BC treatment patterns used in the base case may require updating. Additional BC treatment patterns data have been published recently, which are similar to the current OSM inputs. The differences in these treatment patterns can be explored in the sensitivity analyses conducted for the BC case study.

**Discussion**

The OSM framework is a customizable, dynamic simulation approach to generating population-level estimates of prevalence, progression-based incidence, and survival in oncology. Because the framework is flexible, extensible, and facilitates granular calculations, it enables detailed prevalence estimates when needed, or simpler estimates when not. A key design feature is to let the availability of data and the desired precision of the results drive the model structure since the number of stages and treatments are easily scaled. To estimate the prevalent population and survival over time, the model simulates the entire disease landscape from early stage to late stage over time, accounting for continuous incidence of the disease at each stage as well as progression to later stages. Additionally, highly granular prevalence predictions can be generated, stratifying or focusing results by stage, month/year of diagnosis, treatment history/trajectory, time spent on a specific treatment, or time between progression events. The OSM framework is particularly suited to oncology because
Figure 4 US 2022 la/mUC patient flow and annual treated prevalence.

**Note:** The estimated 1-year period prevalence in 2022 for each population is as follows: total la/mUC treated prevalence = 33,000; 1L la/mUC treated prevalence = 28,530; 2L la/mUC treated prevalence = 7,290; and 3L la/mUC treated prevalence = 2,070.

**Abbreviations:** 1L/2L/3L, first-/second-/third-line; EPP, estimated 1-year period prevalence; la/mUC, locally advanced or metastatic urothelial carcinoma; MIBC, muscle-invasive bladder cancer.
of the disease’s generally well-known incidence with medium-term duration (>1 year, <10 years), changing duration of disease (ie, survival) over time, and continuously changing treatment guidelines.

The OSM framework predicts prevalence through more detailed, time-varying, and multi-staged methods, compared with simpler, incidence-based population funnels. This method leverages well-established practices in budget-impact analysis and Markov methods typically used in cost-effectiveness analysis to simulate and predict population-level prevalence in oncology. In addition, the OSM framework extends cost-effectiveness analysis by considering continuous input of incidence and utilizing date-specific, real-world treatment patterns. One limitation of traditional Markov models is the concept of “memorylessness” (ie, given the present, the future does not depend on the past). In the OSM framework, cohorts within a specific state retain knowledge of when they entered the state, removing the “memoryless” limitation of traditional Markov modeling.

The OSM framework also extends the MIAMOD/PIAMOD utilization of time-varying incidence by executing a full simulation, which includes specific treatment patterns and survival curves that also vary over time. It solves existing shortcomings by adding needed detailed treatment patterns and stages in a transparent and reproducible form.

Validation of the OSM can be achieved by comparing outputs to known data points. The OSM framework simulates and predicts progression rates across multiple levels, which can be directly used for validation against published real-world progression rates and relative survival. In the BC case study, aggregate OSM results are similar to published real-world data, lending credence to detailed model results. The OSM predicts a 22% 5-year progression rate in NMIBC compared with a published 20% to 25% rate, and a 60% 5-year progression rate in MIBC compared with a published 52% to 61% rate. Similarly, we cross-referenced the OSM survival estimate in bladder cancer with published data from the Surveillance, Epidemiology, and End Results program (SEER), as shown in Figure S1. Based on SEER estimates, the 5-year relative overall survival (rOS) of US patients with BC with distant metastases was 6.4% in 2017. Using US specific model inputs from 2017, OSM estimated a similar 5-year rOS estimate of 6.0%. Future work seeks to validate the OSM against known prevalence in a closed, population-based registry system.

There are limitations to the OSM approach. In particular, this method can be data intensive. Treatment patterns and survival data for each treatment in each stage must be sourced and validated. While survival can be estimated from single published metrics such as median OS and PFS, fitting individual survival curves adds precision. Treatment patterns are particularly difficult to source, especially in late-stage cancer where there is often lack of a clear standard of care, significant heterogeneity in treatment patterns within and across different geographic regions, and fewer patients to
inform these analyses. While the model can account for heterogeneity between geographic regions since OSM inputs are largely based on data from published literature, there are limitations in drawing these data from published sources (ie, time delay in data, heterogeneity in data sources and methods across studies, or generalizability of reported data) which should be considered when interpreting output results from the OSM model. In addition, some inputs (ie, current treatment patterns and treatment rates) are either unavailable in published literature, or published data do not reflect contemporary data. In these cases, model inputs are based on expert opinion or loco-regional expertise. Country-specific prevalence estimates can be challenging owing to limited sources of geographic-specific treatment patterns, but where possible can inform other local analyses including cost-effectiveness and budget-impact analyses. Simplification of complex treatment landscapes is needed to fit OSM parameters. The number of treatments in each stage that is modeled must be weighed against the complexity of the model. Repeat treatments and other confounding treatment modalities within a stage are simplified to a stage-level progression and survival to keep complexity reasonable, at some expense to model accuracy. The important decision to make when implementing the OSM framework is the level of detail required to arrive at a reasonable prevalence estimate. The higher the uncertainty of inputs, the less the need for granular detail of a greater number of inputs, which would impart false precision. However, if prevalence estimates for very specific subgroups or treatment history-specific cohorts are desired, then the OSM framework is well suited to provide the necessary level of detail. Because the OSM structure is flexible and implements all inputs as time-varying parameters, its key feature is to allow the precision of the inputs guide the detail of the structure, not let the structure dictate what inputs must be found.

Conclusions
Oncology is a dynamic disease area with new therapeutic options leading to changes in standard of care and improvements in treatment and survival. Consequently, existing epidemiology approaches that rely on incidence alone to estimate the number of patients living with a cancer type are increasingly inaccurate. The OSM framework provides a new method to generate detailed prevalence estimates across stages of oncologic disease. Population survival and progression-based incidence estimates can also be generated, filling a data gap when both de novo and progressed patient incidence in later stages need to be accounted for. We provide an overview of the implementation of the OSM in BC, producing plausible and clinically relevant estimates for prevalence by stage and line of therapy. Detailed prevalence, survival, and progression estimates can help inform clinical practice by highlighting treatment pathways clinicians are likely to encounter. Predicting prevalence and survival is important to understanding disease and treatment landscapes at a population level and can only achieve the level of detail necessary through comprehensive simulation of the entire treatment landscape.

The OSM was developed for oncology but is applicable to a wide range of diseases. Further refinement and advancement is encouraged, such as expansion of modeled health states, survival-curve analysis, and expansion to non-oncological diseases. Another potential expansion of the OSM includes incorporation of a tumor growth and detection model which would enable estimates of undiagnosed cases and measure benefits of cancer screening technologies in the population.

Abbreviations
1L/2L/3L, first-/second-/third-line; APC, age-period-cohort; BC, bladder cancer; BCG, bacillus Calmette-Guérin; CCRT, concurrent chemoradiation therapy; KOL, key opinion leader; la/mUC, locally advanced or metastatic urothelial carcinoma; MIAMOD, Mortality and Incidence Analysis MODel; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; OSM, oncology simulation model; PD, progressed disease; PFS, progression-free survival; PIAMOD, Prevalence and Incidence Analysis MODel; SEER, Surveillance, Epidemiology, and End Results; TURBT, transurethral resection of the bladder tumor; UC, urothelial cancer; US, United States.

Data Sharing Statement
This analysis is based on previously published data.
Ethics Approval and Informed Consent
This analysis is based on published data and ethical approval was not required.

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Author Contributions
All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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BB, JT, and LB are employees of Curta Inc., paid consultants to Seagen Inc. in connection with this study. HSW and ZH are employees and stockholders of Seagen Inc. HSW is also stockholder of Amgen Inc. and Teva Pharmaceuticals. CM is an employee and stockholder of Astellas, Inc. and also a stockholder of Merck and J&J. MDG has served as an advisory board member and consultant for Aileron Therapeutics, Astellas, AstraZeneca, Basileia, BioMotiv, BMS, Dendreon, Dracen, Dragonfly, EMD Serono, Genentech, GSK, Incyte, Inovio Pharmaceuticals, Janssen, Lilly, Merck, Novartis, Numab, Pfizer, Seagen Inc., and Urogen; has equity ownership in Rappta Therapeutics; holds patents/royalties for “Methods and compositions for treating cancer and related methods (20120322792)”; and has received research funding from AstraZeneca, BMS, Dendreon, Genentech, Janssen, Merck, and Novartis.

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