A Landscape Assessment of the Statistical and Economic Modeling of Cure in Oncology

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Background and Objectives

- Economic modeling of cure is increasingly common in literature and health technology assessment (HTA) as an growing number of oncology treatments are emerging with curative potential. However, there is a lack of consistency in modeling approaches and assumptions. Innovative cure modeling methods are being used more frequently, including mixture cure modeling (MCM) and non-mixture cure modeling (NMCM), along with simplified cure assumptions implemented within health economic models. In the absence of long-term clinical trial follow-up at launch, robust clinical evidence and transparent, well-justified modeling methods are required
- The objectives of this study are to:
  - Understand the landscape of cure in oncology, including definitions of cure from various perspectives, previous methods of economic/statistical modeling, strengths and limitations, and HTA agency acceptability
  - Describe existing statistical and economic methods of estimating cure, including data requirements and validation needed to justify methods implemented in cost-effectiveness analysis and areas for possible future acceptance in HTA

Methods

- A targeted literature review was conducted to understand the statistical and economic modeling of cure landscape including:
  - Definitions of cure by stakeholder (clinician, patient, health economist, statistician)
  - Cure-related endpoints and outcomes
  - Visual inspection of survival and hazards over time
  - Statistical tests
  - Statistical cure frameworks
  - Explicit vs implicit cure modeling methods
- A structured targeted literature review using web scraping methods was conducted to understand HTA agency acceptance of cure modeling methods using the UK National Institute of Health Care and Excellence (NICE) as a case example, focusing on recent technology appraisals (TAs) (May 2020 to May 2025)[1]
  - TAs were reviewed for the inclusion of economic modeling of cure using Adobe Acrobat's search function for any mention of the term "cure." Search results were exported to a comma-separated values (CSV) file to identify and exclude NICE TAs that did not mention cure. Primary screening was based on non-terminated appraisals, the inclusion of cure modeling, and oncology indications. Secondary screening was based on implicit or explicit economic modeling of cure
  - Included studies were extracted to capture information including trial information, therapy area, type of intervention, model structure, cure modeling approach, cure timepoint/cure fraction, survival modeling framework, evidence used to support the existence of cure, acceptance/critique by the Evidence Assessment Group (EAG), and the reimbursement decision

Results

Definitions of cure by stakeholder

- The definition of cure varies depending on the stakeholder, therapeutic area, and setting. A commonly cited definition of cure comes from the Siracusa charter, which highlights both clinical and statistical perspectives: *The word "cured" refers to complete clinical remission of a cancer, regardless of the presence or absence of late sequelae of treatments. To correctly apply the word "cured," the time from the cancer diagnosis must be such that the patient's risk of death does not, because of cancer, exceed that of a sex- and age-matched general population. In other words, a cancer patient can be defined as "cured" only when his or her life expectancy is the same as that of a sex- and age-matched general population*[2]
- While "cured" patients may not experience the same sex- and age-matched survival as the general population, the word "cure" can allow for tailored survivorship care based on disease and patient characteristics. However, patients would be expected to die of causes other than their cancer[3,4]
- Clinicians and patients typically approach cure from the individual level, while health economists and statisticians usually view cure from the population level, comparing survival of a cancer cohort with general population mortality over time.[2,5-9] **Table 1** includes definitions, alternate terminology, outcomes, strengths, and limitations for each perspective of cure. HTA represents the intersection of these perspectives when evaluating the clinical, economic, and patient-related evidence
- Influential factors for cure include improvements in early cancer detection, cancer type/stage/other clinical factors, age at diagnosis, and the use of surgery with curative intent/innovative treatments[8,10-14]

Cure frameworks

- Three common frameworks include relative survival, disease-specific survival, and all-cause survival
- Relative survival models the excess hazards as the difference between all-cause hazards in the population with disease and general population hazards and has been recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21 and published literature[15,16]
- The disease-specific framework requires information on cause of death, which is often difficult to obtain, while the all-cause framework models survival directly, which can present challenges if background mortality in the population with disease differs from that in the general population[16]

Table 1. Cure perspectives by stakeholder

	Individual-Level		Population-Level	
	Clinician	**Patient**	**Health economist**	**Statistician**
Definition	Persistent clinical remission of a tumor (ie, very low risk of further tumor recurrence or death), regardless of the presence or absence of late or long-term sequelae of treatments[2,4]	Return to personal and professional life after cancer, reduced risk of work and insurance discrimination, improvements in quality of life[5,6]	Mortality equivalent to the general population and extrapolated over time. Models capture long-term surveillance costs and population-level utilities associated with cured patients[7,8]	When the all-cause hazard function for mortality for the modeled patient group converges with the general population hazard function: this indicates that the disease-specific hazard has fallen to zero[9]
Alternate terminology	Cancer survivor,[6] long-term survivor,[5] achieving long-term remission,[25] achieving long-term response,[25] achieving long-term disease-free interval,[25] functional cure[5]	Cancer survivor,[6] psychological cure[6]	Long-term survival[7,17]	Statistical cure[6]
Outcomes	No evidence of disease at X years, progression-free at X years[25]	Being told by a clinician that they are "cured," facilitating a return to personal and professional life[5,6,25]	Life-years, quality-adjusted life-years, cost per cured patient, costs and outcomes for cured vs not cured patients, number needed to treat[8,26]	Cure fraction (π): Proportion of patients experiencing the same mortality rates as their peers in the general population Time-to-cure (τ): The number of years needed for cancer patients to reach a similar life expectancy to their peers[4,27]
Strengths	Clear brightline on when a patient can be considered cured, focus on patients being disease-free	Helps patients receive appropriate care, such as lifestyle modifications (like addressing comorbidities) or secondary cancer prevention[27]	Benefits to the cured population are captured to highlight the unique outcomes of an intervention vs comparators	Provides information on the likelihood and time to cure to inform discussions between clinicians and patients as well as population-level modeling
Limitations	Potentially difficult to estimate for a patient, as clinical markers such as the absence of residual disease or detectable cells are not necessarily predictive of cure[5]	Uncertainty of cure until the cure point; clinicians may be more conservative as to when they believe a patient is cured[25]	Given limited follow-up of clinical trials, especially at launch, there is substantial uncertainty in survival projections and curative potential; use of general population mortality	Given limited follow-up of clinical trials, especially at launch, there is substantial uncertainty in survival projections and curative potential; use of general population mortality

Cure-related endpoints and outcomes

- Three relevant endpoints to quantify cure are recurrence-free survival (RFS) (% of all patients who are recurrence-free and alive), recurrence (% of all surviving patients who experience a recurrence, treating death as a censoring event), and overall survival (OS) (% of all patients who are alive regardless of recurrence status)[16,17,18]
  - RFS is useful in early-stage cancers as it explicitly accounts for recurrence, has an earlier read-out compared with OS, and reduces potential confounding effects from subsequent treatments. However, it is more difficult to benchmark to the general population and only addresses the initial recurrence[17]
  - Recurrence is similar to RFS but treats death as a censoring event. RFS includes non-cancer deaths. Definitions of RFS may sometimes include secondary primary tumors as events in the absence of prior recurrence. Neither of these events are equivalent to recurrence[18]
  - OS is clearly defined and easily modeled vs the general population but fails to capture the inherent benefits of being recurrence-free (including utilities and costs), includes non-cancer deaths, and requires longer follow-up for cure to become evident[16,17]
- Cure-related survival outcomes include relative survival, cause-specific survival, conditional survival, conditional relative survival (CRS), and competing risk-adjusted incidence (**Table 2**). Each metric provides insights into potential cure fraction and cure timepoints
- Cancer survivors may be at higher risk of death compared to an age- and gender-matched general population, including factors such as comorbidities, lifestyle factors, or side effects of treatment. The result would be a standardized mortality ratio (SMR) greater than 1, as SMR compares the observed number of deaths in the patient population with the expected number of deaths from the general population. This can be applied to background mortality to ensure that cure models are fitted appropriately[16,19]

Table 2. Cure-related survival outcomes

	Relative Survival[28,29]	Cause-Specific Survival[26,30,31]	Conditional Survival[32,33]	Conditional Relative Survival (CRS)[34,35,36]	Competing Risk-Adjusted (Cumulative) Incidence[18]
Definition	The ratio at time *t* of the observed survival vs the expected survival in a comparable group from the general population	The probability of surviving to time *t* without dying from the disease of interest, treating deaths from other causes as censored (ie, not counted as events)	The probability of surviving an additional X years, given they have lived to Y years Cancer-specific: For patients who are alive at X years, Y% of patients will not die due to their cancer at X+Z years All-cause: For patients who are alive at X years, Y% of patients will live to X+Z years	The probability of surviving a given number of years relative to a comparator population, having already survived a specified length of time	Recurrence (incidence, cumulative incidence), treating death without recurrence (and potentially second primary cancers without recurrence) as a censoring event An example in colon cancer defined a recurrence probability of <0.5% as negligible risk of recurrence
Assumptions	Assumes that cancer deaths are a negligible proportion of all deaths and that cancer and non-cancer deaths are independent	Assumes correct classification of deaths (cause-specific vs not)	Conditional survival can be framed as all-cause and/or cancer-specific survival based on the cause of death	Excess mortality thresholds can be classified as substantial (CRS <90%), little (CRS between 90% and 95%), and minimal (CRS >95%)	Requires detailed information on deaths/second primary cancers without recurrence
Advantages	• Does not rely on information regarding cause of death as it may not be available or reliable • Estimates how much mortality is attributable to the disease without needing cause of death information	• Can provide useful information to clinicians and patients to reflect a cancer prognosis, which is not impacted by other changes in mortality	• Can provide useful information to clinicians and patients • Easy to communicate and understand	• When plotted over time, can highlight excess mortality remaining among patients with cancer after a specific point in time post-diagnosis • Can provide a more pragmatic estimation of long-term survival	• Can also explore conditional cumulative incidence to explore the potential for cure starting at different points in time
Limitations	• Assumes that population life tables represent the same causes of mortality in a cohort of cancer patients vs a cohort of non-cancer patients • OS outcomes often require longer follow-up compared to recurrence or progression-based outcomes, delaying detection of cure and producing lower cure rates	• Cause of death may be unavailable or unreliable, which could lead to misclassification • Patients at older ages may be more likely to be misclassified, as physicians may be more prone to assigning death to cancer vs other causes • OS outcomes often require longer follow-up compared to recurrence or progression-based outcomes, delaying detection of cure and producing lower cure rates	• Long-term follow-up data is needed, which may be limited from RWE or clinical trials • Cause of death may be unavailable or unreliable, which could lead to misclassification when using a cancer-specific survival framework • OS outcomes often require longer follow-up compared to recurrence or progression-based outcomes, delaying detection of cure and producing lower cure rates	• Requires the application of a CRS threshold to determine excess mortality • OS outcomes often require longer follow-up compared to recurrence or progression-based outcomes, delaying detection of cure and producing lower cure rates	• Long-term follow-up data is needed, which may be limited from RWE or clinical trials

Visual inspection of survival and hazards over time

- Survival curves for RFS and OS and curves of cumulative incidence of recurrence with death as a competing risk can be visually inspected to see if a nearing of a plateau becomes apparent, which could indicate the presence of a cure. However, there are a multitude of factors that impact the shape of the Kaplan-Meier {KM) curve, including a decreasing rate of the event of interest, censoring, background mortality of the patient population, and sufficiency of follow-up. Additional exploration may be needed, including disease-specific knowledge on plausibility of cure and mechanism of action, review of disease-specific survival, evaluating hazards over time, and time of convergence to general population mortality[17,20,21]

Statistical tests

- Statistical tests can be conducted to understand sufficiency of follow-up and the presence of cure based on relative survival to a general population using a minimum version of a one-sample log-rank test[22,23]

Economic modeling of cure

- Economic models have included explicit cure modeling (use of statistical models to directly model clinical outcomes) and implicit cure modeling (use of simple assumptions applied to survival curves in an economic model to transparently and flexibly explore cure)[16,24] (**Table 3**)

Table 3. Explicit vs implicit cure modeling in economic models

	Explicit[16,24]	Implicit[24]
Definition	Use of statistical cure models to directly model clinical outcomes	Use of simple cure assumptions applied to survival curves to transparently and flexibly explore cure
Methods	**MCM:** Assumes the trial population is a mixture of two latent groups, a "cured" fraction with survival anchored to general population mortality and an "uncured" fraction whose survival follows a parametric distribution, estimating both the cure proportion and the survival of the uncured **NMCM:** Models the trial population as a cohort and the point at which modeled hazards converge to the general population is identified as the cure timepoint. When using flexible parametric models, the cure timepoint can be specified within the statistical model if desired. The cure fraction is the proportion of patients remaining event-free at the cure timepoint. Other approaches include Bayesian hierarchical MCM (BHMCM) (incorporating external information and borrowing from more mature endpoints with flexibility to model multilevel structure), semi-parametric MCM, and multilevel cure models with random effects[37-40]	Unlike the explicit approach, this method allows users to directly modify survival extrapolations in the economic model by specifying (1) cure timepoint, (2) cure time window, and (3) risk reduction. The cure fraction is the proportion of patients remaining event-free at the user specified cure timepoint.
Advantages	Uses the clinical trial directly to inform long-term survival, cure fraction, and cure timepoints	• Flexible application of cure timepoint based on data and/or clinical opinion • Cure assumptions can be explored and varied in scenario analyses • Can use standard and/or flexible parametric fittings • MCM and NMCM can inform inputs and validation
Limitations	• Data may not be mature enough to detect a reliable cure proportion • NMCM requires the placement of a boundary knot informed by external data	• Does not directly utilize clinical trial insights of intervention of interest • Relies on a combination of data sources to inform key model parameters like cure point, cure time window, and cure fraction validation
SMR[16]	Both approaches can apply a SMR to adjust survival in cancer survivors, which may differ from general population survival	

NICE technology appraisals review

- A total of 432 NICE TA records were searched, with 320 excluded after initial screening (exclusions included terminated appraisals [97], no mention of cure [188], and cure included, but not in oncology [35]). Of the 112 considered for inclusion, 65 did not include implicit or explicit economic modeling of cure
- As a result, 47 oncology TAs were identified with cure modeling methods included in the submission, 55% of which were in hematological cancer. There has been a notable increase in the use of cure models in NICE oncology appraisals over the past five years, with 6 in 2021 (first full year of study selection window), 10 in 2024, and 8 in 2025 (up through May 2025)
- Among cure model approaches:
  - **Implicit cure models** are the most common (68%), driven by their relative ease of implementation and lower data requirements
  - **MCMs** are the second most frequently used (19%), predominantly in hematological cancers, with application in solid tumors increasingly emerging
  - **NMCMs** have been rarely employed, with only one known submission in hematological cancer
- Approximately 91% of submissions fit survival outcomes in an all-cause survival framework, while the remaining 9% fit survival outcomes in a relative survival framework. Alternate frameworks were used to estimate SMR and/or validate survival extrapolation, including relative survival (19%), conditional survival (4%), conditional relative survival (6%), and disease-specific survival (9%)
- Critical evidence supporting cure assumptions is noted in order of impact in **Table 4**, highlighting the importance of clinical plausibility and validation for HTA acceptance
- Despite limited direct evidence and inherent model uncertainties – such as the timing of cure, cure fraction, and residual risk of recurrence or death among "functionally cured" patients – implicit cure models have generally been accepted in submissions where clinical plausibility of cure is sufficiently demonstrated
- EAGs have occasionally challenged the use of MCMs in base case analyses, recommending alternative approaches such as standard parametric or other flexible survival models

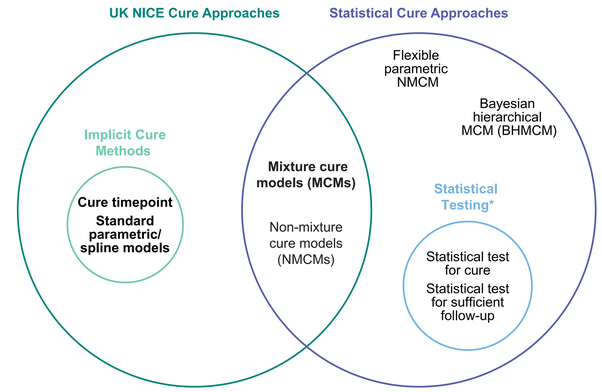
Table 4. NICE EAG acceptance of evidence supporting cure

Evidence Type and Possible Tactics	NICE EAG Acceptance	Mitigation Measure If Unavailable
Clinical plausibility of cure: Disease characteristics, treatment intent **Clinical validation of cure assumptions:** Endpoint defining cure, timepoint, risk of recurrence/death for "functionally cured" patients	Clinical cornerstone for cure, but the credibility of the manufacturer submission and supporting advisory board evidence was sometimes questioned by EAG due to lack of details and transparency	EAG might consult clinical expert regarding cure assumptions independently Scenario analyses to remove cure assumptions or test alternative cure timepoints and risk of recurrence/death
Pivotal trial data with sufficient follow-up*: Identify a survival curve approaching a plateau and reduction in hazards over time	Benchmark data to demonstrate cure, but majority of appraisals didn't have it	Company provides analyses based on more mature trial data
Precedent NICE appraisals: Establishing cure assumptions for treatment with similar mechanism of action in a similar population	Accepted by EAG to ensure consistency unless the previous NICE appraisal was not deemed similar enough Often supplemented with external trial data and real-world evidence to support cure assumptions	Company conducts targeted literature search to identify data relevant to the treatment and population of interest
External trial data and real-world evidence: Establishing cure with sufficient follow-up for a similar treatment in a similar population	Contemporaneous data, duration of follow-up, similarity between treatments, and generalizability of population are the main areas of examination by EAG If data quality reasonable and supplemented with other types of evidence, often accepted by EAG	Company strengthens the other types of evidence

Ranked by impact

*If data with sufficient follow-up were available, this would have the greatest impact; however, most appraisals include relatively short follow-up, reducing the ability to identify cure at time of submission.

Figure 1. UK NICE acceptability of cure modeling methods



Most used by UK NICE. *Statistical tests would aid in justifying the application and selection of cure modeling approaches described within the figure.

Conclusions

- As economic modeling of cure becomes more relevant and accepted in oncology HTA, the inherent uncertainty and limited trial follow-up of interventions with a propensity for cure can be mitigated through robust methods and evidence
- UK NICE prefers more conservative and established methods, including a subset of statistical models or implicit cure methods used to capture cure in economic models. While there is methodological innovation in the cure modeling space, these methods have not yet been used or accepted by UK NICE. Exclusion of these methods risks insufficiently capturing the curative potential of recent innovations, along with the clinical and economic value (**Figure 1**)

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