Understanding and identifying immortal-time bias in surgical health services research: An example using surgical resection of stage IV breast cancer

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ABSTRACT

Surgical health services researchers are increasingly utilizing observational data to assess associations between treatments and outcomes, especially since some procedures are unable to be evaluated through randomized controlled trials. However, the results of many of these studies may be affected by the presence of immortal-time bias, which exists when treatment does not occur on Day 0 of the study. This bias can result in researchers overestimating a treatment benefit, or even observe a treatment benefit when none exists. In this paper, we describe what immortal-time bias is, the challenges it presents, and how to recognize and address it using the real-world example of surgical resection of the primary tumor for stage IV breast cancer throughout. In our example, we guide researchers and illustrate how the early studies, which did not account for immortal-time bias, suggested a protective benefit of surgery, and how these results were supplanted by more recent studies through identifying and addressing immortal-time bias in their design and analyses.

1. Introduction

Health services research focused on the outcomes of surgery often encounters the challenge of immortal-time bias. Immortal-time is the person-time during a follow-up period when the event of interest (e.g. death) cannot occur as a function of how the exposure (or treatment) is defined. The bias arises from misattribution of this person-time to the treatment group. Understanding immortal person-time is particularly important for surgical health services research, since some procedures may not be as easy to evaluate through randomized controlled trials [1]. In this paper we describe the pitfalls and options for addressing immortal time bias in surgical research using the example of surgery in the treatment of advanced breast cancer.

The National Comprehensive Cancer Network guidelines state that surgical resection of the primary tumor is not the standard of care for patients diagnosed with stage IV breast cancer and should be limited to palliation [2]. This guideline is largely based on two decades of results from observational studies [3]. Initially, multiple retrospective observational studies (i.e. studies where both exposures and outcomes occur prior to the initiation of the study) suggested improved survival after surgery [4–6]. However, later prospective studies (i.e. eligible patients are enrolled and followed in real time, can be randomized controlled trials [RCTs] or observational) did not find the same protective benefit of surgical resection [7–10]. Most recently, the results of the ECOG 2108 trial reported no surgical benefit and is positioned as the new gold standard [10].

The drastic differences in reported benefits of surgery between the two study designs raise the question of what biases influenced the results from the retrospective studies, and how can we identify and avoid them moving forward. The inability to control for important confounders was recognized as a potential source of bias in earlier studies, but immortal-time bias was a less recognized problem, whose magnitude and impact is

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unknown [11–13]. Where selection and confounding bias relate more to the imbalance of pre-treatment characteristics, immortal-time bias relates to the time-dependent nature of treatment along a study's time-scale. All of which can act together to bias estimates of the treatment-outcome association. Therefore, the purpose of this manuscript is to highlight an era of surgical outcomes literature where researchers overcame issues with immortal-time bias relating to how treatment was defined and analyzed to address an evolving research question.

Our goal is to provide surgical health services researchers with the background knowledge and understanding of what immortal-time bias is, how to recognize it, and how to address it, using a real-world example in breast cancer surgery. The manuscript proceeds in four sections focusing on the early observational retrospective cohort studies, immortal-time bias and later prospective studies, approaches to address immortal-time, and a discussion.

2. Controversy in breast resection outcomes and an introduction to immortal time

Early studies in primary breast tumor resection and survival between 2000 and 2010 were partially motivated by conventional wisdom of the time that once metastases have occurred, aggressive local therapy such as surgery would not provide a survival advantage and should not be pursued [4]. On the other hand, it was hypothesized that the removal of the primary tumor could inhibit metastatic spread [5,14]. This latter idea was further supported by results from a 2001 clinical trial in stage IV renal cell carcinoma which found that patients randomized to the interleukin plus nephrectomy arm had prolonged survival compared to those receiving interleukin therapy alone [15].

The lack of published data on primary tumor resection and outcomes in stage IV breast cancer patients led to a number of observational studies evaluating the association between surgery and survival [4]. These studies largely found that surgery was associated with improved survival; a meta-analysis of studies between 2002 and 2012 reported that surgical patients were 30% less likely to die than patients who did not undergo surgery (HR 0.69; 95% CI 0.63, 0.77) [16]. These studies were a rational starting point given the lack of evidence, but correctly came under scrutiny for using an "ever vs. never" approach (i.e. comparing surgery at any point in time to never receiving surgery).

"Ever vs. never" classification of treatment is problematic for several reasons, including confounding by indication and immortal-time. In other words, patients with poor prognosis are less likely to receive treatment, and the misattribution of time accrued before treatment can artificially increase the amount of person-time among the treated [17]. Results from studies classifying treatment as "ever vs. never" are also difficult to translate to interventions, policies, or guideline recommendations because of a lack of clarity on when to implement a treatment and when to evaluate adherence to the recommendation. Condition severity also plays a critical role in clinical decision making; patients undergoing surgery within one month of a cancer diagnosis likely differ from patients undergoing surgery 18 months after diagnosis, however, in an "ever vs. never" scenario they are treated equally as "ever" surgery. More importantly, both of these groups likely differ from patients who do not undergo surgery because of ineligibility (e.g., patients with short life expectancy, poor prognosis, or at high predicted probability of surgery-related complications). Uncontrolled confounding by indication attributed to unknown disease severity and surgical eligibility, has been frequently recognized as a challenge with the prior work in stage IV breast cancer. However, another bias relating to the timing of surgery, immortal time bias, was common to many of these studies, largely unaddressed, and less frequently acknowledged at the time.

3. The impact of immortal-time bias

In a cohort study where treatment is defined as "ever vs. never", the immortal time occurs between the start of study follow-up (e.g. stage IV breast cancer diagnosis) but before treatment occurs (e.g. surgical resection) [18]. Immortal person-time overestimates time at risk for the outcome and underestimates events, which can lead to observed treatment benefits even when there are none. This issue becomes clearer when this study design is compared to a hypothetical RCT.

In an RCT, eligible patients would be randomized to undergo surgical resection or not at the start of follow-up (e.g. diagnosis) and then followed until death or the end of the study period. Importantly, in an intention-to-treat analysis, patients randomized to the surgical treatment arm would be included in the surgery group regardless of whether they actually receive treatment or die before their scheduled surgery (Fig. 1A). In the analysis of data that has already been collected (e.g. observational retrospective cohort studies), treatment can only be assigned after a patient *actually* receives treatment (Fig. 1B). This critical design difference (treatment assignment and start of follow-up are not aligned) is what introduces bias. In our example (Fig. 1), Patient 1 in the observational study 'cannot' die before they received surgery, otherwise they would not be classified as having received surgery, which is what happens to Patient 2. Essentially, we introduce bias because we are only able to define actual treatment, instead of planned treatment at time of diagnosis.

The "ever vs. never" treatment classification in an observational cohort study is particularly problematic because the interval from the start of follow-up to treatment receipt (e.g. date of diagnosis until date of surgery) and the amount of immortal-time is variable across each patient. Understanding the length of time between start of follow-up and treatment classification is critical for evaluating the magnitude and potential effect of immortal person-time in observational cohort studies using "ever vs. never" treatment classification. In the stage IV breast cancer surgery literature, median time to surgery was sporadically reported and ranged from 24 days to 8 months [19–23]. Meaning that surgery patients in these analyses contributed upward of 8 months of person-time in which they could not experience death, consequently artificially inflating their survival time.

As a response to the initial results and recognition of challenges to observational retrospective cohort studies, investigators designed several prospective cohort studies (observational and RCTs) to further evaluate the surgery-survival association (Table 1). These studies did not suffer from immortal person-time bias since planned treatment could be captured, and largely found no survival benefit after surgical resection, contradicting the earlier retrospective study findings. However, prospective studies are not the only way to obtain unbiased results when treatment is not planned/assigned (or known) at the start of follow-up. In this next section, we highlight methods that can be used to minimize the impact of immortal-person time in observational cohort studies.

4. Analytic approaches to mitigate immortal person-time in observational data

Findings from well designed and analyzed observational studies – both prospective and retrospective - can support decisions made by clinicians and policymakers [24]. Additionally, RCTs may be unethical, too expensive, or take too long to conduct. Conversely, studies with unrecognized biases may lead to poor decision-making. Therefore it is important to be able to recognize and address immortal-time bias in observational research. This notion is furthered given the high volume of surgical procedures performed each year, and the much lower frequency of patients enrolling in these clinical trials [25]. In this section we focus on providing guidance and conceptual understanding of the design and analytic options available to identify and address immortal-time bias in surgical health services research.

In the design of an observational study for surgical health services research, approaches that mitigate the impact of immortal-time should be included, and justifications for the choice should be explicit. The synchronization of eligibility, treatment assessment, and the start of

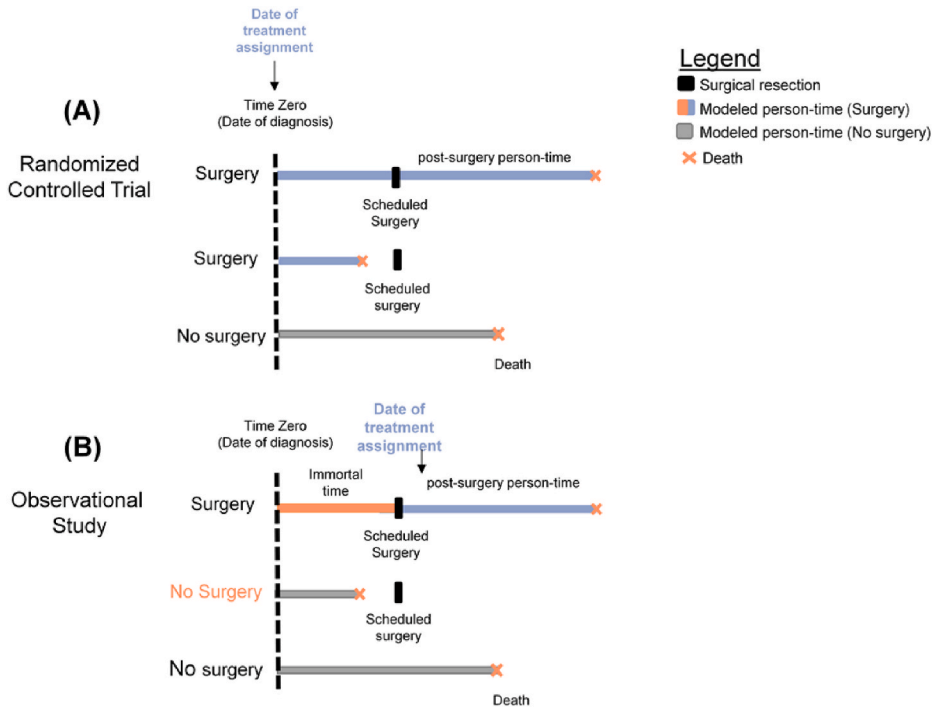

Fig. 1. Randomized controlled trial and observational data designation of surgery and non-surgery person-time.

Table 1
Prospective studies assessing the role of surgical resection of the primary tumor in stage IV breast cancer patients.

Authors	Trial	Clinicaltrials.gov identifier	Treatment Assignment	Comparison	Primary Findings
Badwe, 2015	Tata Memorial "Assessing Impact of Loco-regional Treatment on Survival in Metastatic Breast Cancer at Presentation"	NCT00193778	Randomized	LRT (mastectomy or breast conserving surgery accompanied by full axillary lymph node dissection) versus no LRT	**3-year overall survival** HR = 1.04; 95% CI (0.81–1.34)
Soran, 2018	MF07-01 "Local Surgery for Metastatic Breast Cancer"	NCT00557986	Randomized	LRT (complete excision of the primary tumor) followed by systemic therapy versus systemic therapy alone	**3-year overall survival** Noted no difference between groups **5-year overall survival** HR = 0.66; 95%CI (0.49–0.88)
Khan, 2020	ECOG 2108 "A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients With Metastatic Breast Cancer"	NCT01242800	Randomized	Among stage IV patients who did not progress during 4–8 months of optimal systemic therapy, patients were randomized to LRT for the intact primary tumor versus no LRT	**3-year overall survival** HR = 1.09; 90%CI (0.80–1.49)
King, 2016	TBCRC 013 "A Prospective Analysis of Surgery in Patients Presenting With Stage IV Breast Cancer"	NCT00941759	Observational (Non-Randomized)	Elective surgery versus no surgery among responders to first line therapy	HR not reported 30-month survival was similar between the surgery and no surgery arms (overall survival: 77% vs 76%)

LRT-Locoregional Treatment; HR – hazard ratio; CI – confidence interval.

follow-up between groups is a desired attribute to address immortal-time bias in study design if possible. Where such a design is not feasible, analytic approaches that address immortal-time bias using available observational data should be implemented. In this section we discuss three analytic approaches to address immortal-time: exclusion, time-dependent treatment classification, and the landmark approach.

As a baseline reference, we consider the naïve misclassification of immortal-time in Fig. 2A; this approach was most common in the early breast surgery studies, and can still be found in more recent publications. By misclassifying immortal-time to the surgery group (e.g., count person-time as exposed to surgery prior to surgical resection), we artificially inflate the person-time attributable to the surgery group, making it appear that this group lived longer with fewer events. As we have covered up to this point, there are many questions to be raised with this approach, and studies making such naïve comparisons should be subject to further scrutiny.

The first approach to mitigate immortal person-time bias involves excluding the immortal-time from the treatment group (Fig. 2B). In this approach, the date of treatment is the start of follow-up for patients who receive treatment. This approach may seem attractive at a glance, but we have just disregarded person-time from our analysis and will still overestimate the event rate in the untreated group. The results from this approach will still be biased, but typically less so than not doing anything (naïve misclassification). A limitation to this approach is the difficulty justifying why the study outcome would be measured differently between groups. While this approach does partially mitigate immortal-time bias, it is not recommended. This approach can be seen in studies which form their cohorts based on identifying treatments as the time

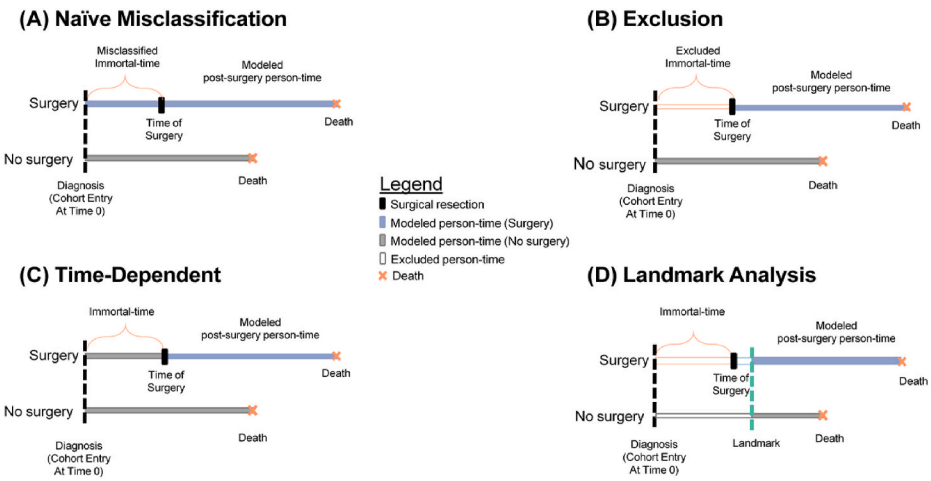

Fig. 2. Illustration of (a) naive missclassification, (b) exclusion, (c) time-dependent, and (d) landmark-based approaches to addressing immortal-time.

point of entry into the cohort. For example, surgery patients enter the surgery cohort at the date of their surgery, where the remainder of patients would form the non-surgery cohort and their start of follow-up would be defined using some arbitrary event (e.g., diagnosis date) [18].

The second approach to mitigate immortal person-time bias is the time-dependent approach (Fig. 2C). This approach allows a patient's exposure status to change over time, allowing them to switch from the non-surgery to surgery arm. Person-time before treatment is included as unexposed, and time after treatment is included as exposed [26]. Of note, date of treatment is required in order to correctly classify time in this manner. This approach can be used to both answer an "ever vs. never" question (i.e. by allowing patients to undergo surgery at any point during follow-up) or during a pre-specified window (e.g. only including surgery occurring within the first six months). Both approaches address immortal-time bias, but answer different clinical questions.

A limitation of this approach is related to time-varying confounding. In other words, is there enough information recorded about the patient's clinical characteristics, such as the development of new comorbidities, disease progression, or a decline in performance status, throughout follow-up to help us address non-random treatment assignment at time points beyond baseline? A patients' likelihood of initiating treatment changes over time with their evolving characteristics. For example, a surgical candidate may be strongly considered for immediate surgery when assessed at the time of diagnosis. Their blood pressure may fluctuate in response to initial cancer treatment, putting them at greater risk of anesthesia related complications, subsequently leading to the decision to delay surgery until their blood pressure can be better managed. Approaches have been developed to address this issue but require the appropriate time-dependent data and modelling assumptions to be interpreted adequately, and are beyond the scope of this text [27,28].

The third approach to mitigate immortal person-time bias is the landmark design (Fig. 2D). This approach involves classifying a patient's exposure according to whether they have initiated treatment by a specific time during follow-up (i.e. the landmark), at which point follow-up begins [29]. The Translational Breast Cancer Research Consortium study (King et al., Table 1), utilized this approach when conducting their prospective, observational cohort study; patients who responded to first-line systemic treatment were included in the treatment group if they underwent surgery within 6 months of diagnosis and follow-up for both surgical and non-surgical patients began after that date [8].

Another way to characterize a landmark design is to imagine that the exposure period (the period which treatment assignment is designated) is separated by the landmark from the outcome period (in which patients are assessed for whether they experience the outcome), or in other words, the exposure and outcome assessment windows are non-overlapping. Patients in either group who die before the landmark time point are excluded from the analysis, and patients exposed (or treated) after the landmark would still be categorized in the unexposed group for analysis.

This approach addresses immortal-time by synchronizing the ascertainment of treatment status and start of follow-up for both groups, but requires creating and justifying a clinically meaningful landmark. In the King et al. study, a 6-month landmark was chosen as a surrogate for the average time to response assessment after the 1st line of therapy [8]. Approaches have also been developed for landmark analyses when data on the timing of treatment is not known [30]. This analytic approach is most appropriate in situations where the exposure of interest is known to cluster early after diagnosis or start of follow-up (even if date of treatment is unknown). If receipt of treatment is uniformly distributed over a longer period of time, the choice of meaningful landmark is less clear. Additionally, using a landmark design can impact the generalizability of the results. For example, using a 6-month landmark means that you are estimating the impact of surgery *among those who survived at least* 6 months *after diagnosis*. If a meaningful percentage of patients die before the end of the landmark, your analytic cohort may not be representative of your initially defined target population [31]. If we require patients to remain alive for a period of time after the start of follow-up, the cohort may be restricted to a healthier population. This restriction may impact the internal or external validity of the estimates and should be considered when using this approach.

5. Discussion

Here we presented an example of a challenging question re-examined over time in the setting of evolving approaches to breast cancer surgical health services research, to highlight how the handling of immortal-time bias is key to the appropriate design and interpretation of both retrospective and prospective studies and affects results. We note that immortal-time bias itself does not explain the differences between the existing literature's findings from retrospective observational and prospective randomized studies. Patient selection, confounding, and immortal-time bias, among others act together to bias our study's estimates. Throughout, we provided suggestions to guide surgical health services researchers to evaluate, anticipate, and address immortal-time bias. Handling immortal-time is a challenge not only for researchers conducting studies, but also for peer reviewers, editors, and readers to recognize. We hope that through this example, the surgical health services researcher gains greater confidence to overcome these challenges and is equipped with an enhanced understanding of what immortal-time is, and how it can, has, and will continue to introduce bias if not adequately addressed.

To say that surgical health services research using observational data is challenging is an understatement. There are many opportunities for bias to affect study findings and their interpretation; in this manuscript we focused on immortal-time bias but others exist. In a more general sense, researchers can enhance the quality of their work in observational data using the following guidelines: (1) begin planning the study by soliciting input from methodologists, epidemiologists, or biostatisticians familiar with potential sources of bias in observational research studies; (2) incorporate approaches that limit the impact of immortal-time bias (and other forms of bias) into the study design by crafting a well-defined research question mapped to clinically relevant interventions, synchronizing eligibility, treatment assignment, and the start of follow-up; and (3) when presenting and publishing findings, explicitly state and justify your choice of analytic approach. If immortal-time bias remains a concern after taking these steps, descriptions of person-time and time to treatment should be presented, sensitivity analyses of alternative approaches to add robustness to the findings should be performed (e.g. primary analysis using the time-varying approach with sensitivity analysis using a landmark approach), and limitations sections should acknowledge the presence and potential impact of immortal-time bias on study findings. Similar approaches should also be used when addressing other potentially lingering forms of bias as well. These are but a few recommendations that will improve the rigor and quality of studies which contribute to our understanding of outcomes in surgical health services research.

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