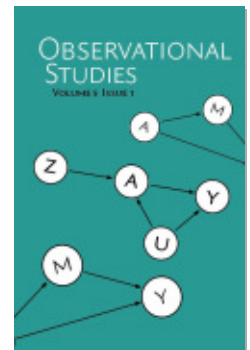# PROJECT MUSE®

Instrumental variable approach for estimating a causal hazard ratio: application to the effect of postmastectomy radiotherapy on breast cancer patients

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Instrumental variable approach for estimating a causal hazard ratio: application to the effect of postmastectomy radiotherapy on breast cancer patients

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Abstract

The use of postmastectomy radiotherapy (PMRT) on women with AJCC (American Joint Committee on Cancer) pT1-2pN1 breast cancer is controversial in practice. Huo et al. (2015) found that PMRT was associated with longer survival among a high-risk subgroup of AJCC pT1-2pN1 patients using a Cox model on data from the National Cancer Database. To address unmeasured confounding in this observational study, we consider the variation among facilities in the use of PMRT as an instrumental variable (IV). Recently, there has been widespread use of the two-stage residual inclusion (2SRI) method offered by Terza et al. (2008) for nonlinear models, and 2SRI has been the method of choice for analyzing proportional hazards model using IV in clinical studies. However, the causal parameter using 2SRI is only identified under a homogeneity assumption that goes beyond the standard assumptions of IV, and Wan et al. (2015) demonstrated that under standard IV assumptions, 2SRI could fail to consistently estimate the causal hazard ratio for compliers. In this paper, following Yu et al. (2015), we apply a model-based IV approach (Imbens and Rubin, 1997; Hirano et al., 2000) which allows consistent estimation of the causal hazard ratio for survival outcomes with a proportional hazards model specification under standard IV assumptions while flexibly incorporating the restrictions imposed by IV assumptions. Simulation studies show that when there is unmeasured confounding, both 2SRI and the standard Cox regression could provide biased estimates of the causal hazard ratio among compliers, while this model-based IV approach provides consistent estimates. We apply this IV method to the breast cancer study and our IV analysis did not find strong evidence to support the benefit of PMRT on survival among the targeted patients. In addition, we develop sensitivity analysis approaches to assess the sensitivity of causal conclusions to violations of the exclusion restrictions assumption for IV.

Keywords: Instrumental variable, Proportional hazards model, Sensitivity analysis

1. Introduction

1.1 Effect of PMRT on AJCC pT1-2pN1 breast cancer patients

Women with American Joint Committee on Cancer (AJCC) pT1-2pN1 breast cancer are the patients with 1-3 positive axillary lymph nodes and tumors $\leq$ 5 cm in size. Using the data from the National Cancer Database (NCDB), a clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society which captures more than 70% of newly diagnosed cancers in the United States, Huo et al. (2015) identified 93,793 women with AJCC pT1-2pN1 breast cancer who underwent mastectomy between 1998 and 2008. Among those patients, 21.5% of them received postmastectomy radiotherapy (PMRT). PMRT is currently recommended care for more advanced breast cancer patients who are with 4 or more positive nodes and with primary tumor > 5 cm in size. For AJCC pT1-2pN1 breast cancer patients, however, the use of PMRT remains controversial in practice (Harris et al., 1999; of Health Consensus Development Panel, 2001; Recht et al., 2001). In the late 1990s, three randomized trials demonstrated the survival benefit of PMRT on women with AJCC pT1-2pN1 breast cancer (Overgaard et al., 1997, 1999; Ragaz et al., 2005). However, concerns have been raised about the external validity and generalizability of the trials' findings. Those trials recruited patients before 1990 when the systemic therapies were not as advanced as the current ones, and the trials were criticized for various issues including the removal of a low number of axillary nodes (Recht et al., 1999; Katz et al., 2000; Taghian et al., 2004; Wallgren et al., 2003; Recht and Edge, 2003; Overgaard et al., 2007). Given the need of new studies with broader generalizability, Huo et al. (2015) assessed the effectiveness of PMRT using observational data from NCDB between 1998 and 2008, and found that PMRT was associated with a reduced mortality among a high-risk subgroup of AJCC pT1-2pN1 patients with two positive lymph nodes and tumors 2-5 cm in size or with three positive nodes. Their analysis was conducted using the Cox proportional hazards model (Cox, 1972) adjusting for measured confounders described in Section 5. However, there are unmeasured confounders such as molecular subtype, Ki67, and lymphovascular invasion that could potentially bias the result. The aim of this paper is to use instrumental variable (IV) method to obtain unbiased inference of the causal effect of PMRT on survival for the high-risk subgroup of AJCC pT1-2pN1 breast cancer patients using the same observational data in Huo et al. (2015).

1.2 Instrumental variable approach

Instrumental variable methods are being increasingly adopted in clinical studies (Basu et al., 2007; Lu-Yao et al., 2008; Gore et al., 2010; Hadley et al., 2010; Tan et al., 2012) to control for both measured and unmeasured confounding that is not addressed by regular regression and propensity score methods. An IV is a variable that (i) is associated with the treatment, (ii) has no direct effect on the outcome (i.e., exclusion restrictions), (iii) is independent of unmeasured confounders conditional on the measured ones. IV methods extract variation in the treatment that is free of the unmeasured confounding and utilize variation that is free of unmeasured confounding to obtain consistent estimation of the causal effect of the treatment on the outcome of interest. Together with (iv) the stable unit treatment value assumption that a subject's potential outcomes cannot be affected by other individuals'

treatment status, and (v) the monotonicity assumption that there are no defiers (see (1)), Angrist et al. (1996) showed that IV identifies the average treatment effect for the compliers, i.e. subjects who would take the treatment only if encouraged to do so by the IV.

The instrumental variable we consider is the variation among facilities in the use of PMRT, quantified by the predicted rate of receiving radiotherapy after mastectomy among patients with AJCC pT1-2pN1 breast cancer at the facility where the patient was treated based on the rates of use of PMRT in treating other types of breast cancer at the facility. The IV we use in this paper is a preference-based IV, assuming that different facilities or groups of facilities have different preferences dictating how medical procedures are used (Brookhart and Schneeweiss, 2007). The preference-based IVs have been widely applied in medical studies (Brooks et al., 2003; Johnston, 2000; Brookhart et al., 2006; Yang et al., 2014). The rate of receiving PMRT is predicted using logit regression with three predictors describing the facilities' use of PMRT for breast cancer patients other than stage pT1-2pN1: (i) the rate among breast cancer patients other than stage pT1-2pN1, (ii) the rate among breast cancer patients with pN0&pT1-2 (i.e., no positive axillary lymph nodes and tumors ≤ 5 cm in size), and (iii) the rate among breast cancer patients with pN2-3 (i.e., 4 or more positive axillary lymph nodes) or pT3 (i.e., tumors > 5 cm in size). The idea is that a patient may receive PMRT not because of anything unique to her but simply because she went to a facility which has a high use of PMRT. The proposed instrument extracts the naturally occurring variation in the use of PMRT at the facility level and describes the preference of each facility to use PMRT rather than anything about a particular high risk pT1-2pN1 patient. We follow Baiocchi et al. (2014); Guo et al. (2014) to further dichotomize this instrument into a binary variable according to its median. A patient with IV value 1 indicates that the patient was treated in a facility with higher than typical predicted rate of PMRT for pT1-2pN1 breast cancer patients, which is a facility that makes more extensive use of PMRT for breast cancer patients other than the pT1-2pN1 group; and a patient with IV value 0 indicates that the patient was treated in a facility with lower than typical predicted rate of PMRT for pT1-2pN1 breast cancer patients, which is a facility that utilizes PMRT less frequently for breast cancer patients other than the pT1-2pN1 group.

1.3 IV methods for estimating the causal hazard ratio among compliers

IV methods have been well developed to estimate the causal hazard ratio among compliers under proportional hazards models (Loeys et al., 2005; Cuzick et al., 2007) in the context of randomized trials with non-compliance. However, those methods have limited generalizability to observational studies. Loeys et al. (2005) assumes the strong assumption of no access of control arm subjects to experimental treatment , i.e. no contamination, which is generally not true in observational studies where patients may choose the treatment even if not encouraged by their IV values (i.e. always takers). Although Cuzick et al. (2007) allows covariates to be correlated with the compliance status (compliance behavior with respect to IV encouragement, defined precisely in Section 2), however, their procedure relies on the unconditional randomization of treatment assignment which is not a valid assumption in most observational studies where an IV is plausibly valid only by conditioning on the measured confounders.

For observational studies, recently, there is a widespread use of two-stage residual inclusion (2SRI) method proposed by Terza et al. (2008) for nonlinear models, and 2SRI has been the method of choice for analyzing proportional hazards model using IV in clinical studies (Gore et al., 2010; Hadley et al., 2010; Tan et al., 2012; Bekelman et al., 2015). However, the causal parameter using 2SRI is only identified under a homogeneity assumption (i.e., the effects are the same across different compliance groups) that goes beyond the assumptions of IV, and a recent article, Wan et al. (2015), demonstrated that under standard IV assumptions (i)-(v) discussed in Section 1.2, 2SRI could fail to consistently estimate the causal hazard ratio among compliers. In the breast cancer study, the homogeneity assumption may not hold because the status of compliance may be related to tumor burden while magnitude of the treatment effectiveness also depends on tumor burden. Patients with large primary tumor and positive lymph nodes are more likely to be treated with PMRT regardless of the facilities' general preference of using PMRT and they are more likely to be always takers. Previous studies have showed that the effect of radiotherapy is stronger for patients with large tumor and high number of positive lymph nodes because these patients have higher risk of local regional recurrences (Group et al., 2006; Recht et al., 2001; Huo et al., 2015). Tchetgen Tchetgen et al. (2015) developed an IV approach under an additive hazards model and showed that the analogous estimation strategies can be used under a proportional hazards model, however, only when the event is rare. This method also couldn't be applied to our study because death is not a rare event among the high-risk pT1-2pN1 breast cancer patients. In our data, the proportion of patients that were followed up to death is 26.6%. Among them, 39.0% died within three years, and 65.8% died within five years. When the additive instead of the proportional hazards model is of interest, an alternative method is provided in Li et al. (2015).

Adopting a model-based IV approach (Imbens and Rubin, 1997; Hirano et al., 2000), Yu et al. (2015) developed a method under semiparametric linear transformation models for survival outcomes which contains the Cox proportional hazards model as a member. This model-based approach flexibly incorporates the restrictions on the joint distribution of the observable variables imposed by the IV assumptions and allows consistent estimation of the causal hazard ratio among compiers. In this paper, we consider a special case as in Yu et al. (2015). We will focus on the most commonly used Cox proportional hazards model and directly model the ratio of the hazard functions. We assume that baseline covariates affect hazard functions directly as well as through its effects on latent compliance classes but there is no additional interactions between covariates and latent compliance classes on hazard functions. And further, to address the potential concern that the facilities that prefer PMRT or not may affect time to death outcome in ways other than through the treatment PMRT, we develop sensitivity analysis approaches to assess the sensitivity of causal conclusions to violations of exclusion restrictions assumption for IV.

2. Notation and Assumptions

2.1 Notation

We adopt the potential outcomes framework(Neyman, 1923; Rubin, 1974) to define causal effects. Suppose that there are N subjects. We use the vector $\mathbf{X}_i$ to denote the values of measured covariates for subject i, and $\tilde{\mathbf{X}}_i$ to denote the corresponding covariates of subject

i with intercept, i.e. $(1, \mathbf{X}_i^T)^T$. The measured covariates in the breast cancer study describe both patients' characteristics and facilities' characteristics which are listed in details in Section 5. We let Z_i be the binary IV for subject i; 1 for being encouraged to the treatment, i.e., being treated in a facility that utilizes PMRT more often than typical, and 0 otherwise. We use $\mathbf{Z}$ to denote the vector of the IV values for all subjects, i.e., $\mathbf{Z} = (Z_1, ..., Z_N)$. Let $D_i(\mathbf{z})$ be the potential binary treatment that would be received under IV assignments $\mathbf{z}$; 1 if would be treated with PMRT after mastectomy and 0 if would not. We let $h_{it}(\mathbf{z})$ denote the potential hazard at time t under IV values $\mathbf{z}$ and $S_i(\mathbf{z})$ denote the potential survival time under IV assignments $\mathbf{z}$. Let $C_i(\mathbf{z})$ denote the potential censoring time for subject i under IV assignments $\mathbf{z}$. We define $T_i(\mathbf{z}) = \min\{S_i(\mathbf{z}), C_i(\mathbf{z})\}$ to be the potential follow-up time, and define $\Delta_i(\mathbf{z}) = I\{S_i(\mathbf{z}) \leq C_i(\mathbf{z}))\}$ as the potential indicator of death for subject i under IV values $\mathbf{z}$; 1 if death would occur before censoring and 0 otherwise. We use D_i, T_i, Δ_i to denote the actually observed treatment received, the observed follow-up time, and the observed indicator of death in the study.

2.2 Assumptions

We assume the following assumptions hold. The first five assumptions are the standard assumptions of IV as assumed in Angrist et al. (1996). The last assumption relates to the censoring mechanism.

Assumption 1 *Stable unit treatment value assumption (SUTVA). Let $\mathbf{z}$ and $\mathbf{z}'$ be any two possible IV assignments. If $z_i = z_i'$, then $D_i(\mathbf{z}) = D_i(\mathbf{z}')$, $S_i(\mathbf{z}) = S_i(\mathbf{z}')$, $C_i(\mathbf{z}) = C_i(\mathbf{z}')$, $T_i(\mathbf{z}) = T_i(\mathbf{z}')$ and $\Delta_i(\mathbf{z}) = \Delta_i(\mathbf{z}')$.*

SUTVA means that there is a single version of each treatment and that a subject's potential outcomes won't be affected by other individuals' IV assignments. And therefore, the potential outcomes for any individual i do not vary with the IV assignments of other individuals, so we can write $D_i(\mathbf{z}), S_i(\mathbf{z}), C_i(\mathbf{z}), T_i(\mathbf{z}), \Delta_i(\mathbf{z})$ as $D_i(z_i), S_i(z_i), C_i(z_i), T_i(z_i)$ and $\Delta_i(z_i)$, respectively. This assumption is plausibly satisfied for the breast cancer study since a patient's outcomes are unlikely to be affected by other patients' facilities proclivity of treating patients with PMRT.

Based on subjects' potential compliance behavior, we can partition the population into four groups with compliance status

$$U_i = \begin{cases} n, & \text{if } D_i(1) = D_i(0) = 0 \\ c, & \text{if } D_i(1) = 1, \ D_i(0) = 0 \\ a, & \text{if } D_i(1) = D_i(0) = 1 \\ d, & \text{if } D_i(1) = 0, \ D_i(0) = 1 \end{cases} \tag{1}$$

where n, c, a and d represent never taker, complier, always taker, and defier, respectively. Since $D_i(1)$ and $D_i(0)$ are never observed jointly, the compliance status of a subject is unknown without further assumptions. The causal parameter of interest is the log causal hazard ratio among compliers, $\log(h_{it}(1|U_i = c, \mathbf{X_i} = \mathbf{x_i})/h_{it}(0|U_i = c, \mathbf{X_i} = \mathbf{x_i}))$.

Assumption 2 *Nonzero average causal effect of Z on D:* $E(D_i(1) - D_i(0)) \neq 0$.

Table 1: Possible compliance classes given the combinations of (Z_i, D_i)

Z_i	D_i	Principal strata
1	1	Always taker *or* Complier
1	0	Never taker
0	1	Always taker
0	0	Never taker *or* Complier

This assumption is satisfied for the breast cancer study because the facilities' proclivity of using PMRT affects whether a patient will be treated with PMRT or not.

Assumption 3 *Independence of the IV from unmeasured confounders conditional on the measured ones: conditional on* $\mathbf{X}_i$, *IV is independent of the random vector* $(D_i(1), D_i(0), S_i(1), S_i(0), C_i(1), C_i(0), T_i(1), T_i(0), \Delta_i(1), \Delta_i(0))$.

The IV for the breast cancer study describes the proclivity of the facility to treat patients with PMRT, the value of which tells one little or nothing about the health of a particular pT1-2pN1 breast cancer patient. Table 3 shows that this facility level IV is well balanced across important observed prognostic factors for breast cancer as well as facilities' experiences and skills of dealing with breast cancer patients measured by the volume of breast cancer patients and facility type.

Assumption 4 *Monotonicity assumption:* $D_i(1) \geq D_i(0)$. *Under the monotonicity assumption, there are no defiers.*

This assumption is plausible for the breast cancer study because if a patient would not be treated with PMRT in a facility that prefers PMRT, then she probably will not be treated with PMRT in a facility that utilizes less PMRT. Under the monotonicity assumption, we have partial information about subjects' compliance status. Table 1 list the possible compliance status of subjects given the observable combinations of (Z_i, D_i).

Assumption 5 *Exclusion restrictions among never takers and always takers:* $h_{it}(1) = h_{it}(0)$, $S_i(1) = S_i(0)$, $C_i(1) = C_i(0)$, $T_i(1) = T_i(0)$, $\Delta_i(1) = \Delta_i(0)$ *if* $U_i = n$ *or* a, *meaning that the IV only affects the outcomes through treatment.*

The exclusion restrictions assumption is plausible for the breast cancer study because facilities' tendencies to treat patients with PMRT is unlikely to have a direct effect on the outcome not through using PMRT. But it is possible that the facilities that prefer PMRT treat patients differently in unknown ways other than PMRT compared with the facilities that do not prefer PMRT, we carry out a sensitivity analysis for violations of the exclusion restriction in our data analysis.

Assumption 6 *Independent censoring. The distribution of* $S_i(z)$ *is independent of the distribution of* $C_i(z)$ *conditional on observed covariates* $\mathbf{X}_i$ *and compliance status* U_i. *In addition,* $C_i(z)$ *is independent of the compliance status* U_i *conditional on* $\mathbf{X}_i$.

In the breast cancer study, patients diagnosed between 1998 and 2008 were included and followed until the end of 2011. Through national death index and other venues, the follow-up was quite complete. The main reason of censoring is arbitrary in 2011 and thus it is mostly likely independent of survival distribution.

3. Model and Estimation

3.1 Model

Following Yu et al. (2015), we adopt a model-based IV approach by incorporating the compliance classes into a parametric model (Imbens and Rubin, 1997; Hirano et al., 2000). As pointed out in Hirano et al. (2000), by incorporating the compliance classes into a parametric model, this model based IV approach simplifies the process of imposing the monotonicity assumption and the exclusion restrictions assumption, and also allows modeling causal effect among compliers directly.

We use a multinomial logistic model for compliance class U given covariates $\mathbf{X}$, and a proportional hazards model for survival outcomes (T, Δ) given covariates $\mathbf{X}$ and compliance class U.

Model for compliance class:

$$P(U_i = n \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}}) = \frac{1}{1 + \exp{(\tilde{\mathbf{x}}^T \delta_a)} + \exp{(\tilde{\mathbf{x}}^T \delta_c)}} \tag{2}$$

$$P(U_i = c \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}}) = \frac{\exp{(\tilde{\mathbf{x}}^T \delta_c)}}{1 + \exp{(\tilde{\mathbf{x}}^T \delta_a)} + \exp{(\tilde{\mathbf{x}}^T \delta_c)}}$$

$$P(U_i = a \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}}) = \frac{\exp{(\tilde{\mathbf{x}}^T \delta_a)}}{1 + \exp{(\tilde{\mathbf{x}}^T \delta_a)} + \exp{(\tilde{\mathbf{x}}^T \delta_c)}}$$

Model for hazard functions:

$$h_{it}(z) = \exp(\mathbf{x}^T \alpha + \xi_n \cdot I(U_i = n) + \xi_a \cdot I(U_i = a) + \gamma \cdot I(U_i = c) \cdot z)\lambda_0(t) \tag{3}$$

where $I(\cdot)$ is the indicator function. Model (3) specifies a proportional hazards model with $\lambda_0(t)$ being the hazard for compliers with baseline covariates when not encouraged to receive the treatment by IV. Under Assumption 5, $h_{it}(z)$ does not vary with z for never takers ($U_i = n$) and always takers ($U_i = a$). Notice that for compliers, $D_i = Z_i$, thus the log causal hazard ratio among compliers is γ which is our causal parameter of interest. Parameters ξ_n and ξ_a describe the survival behaviors of never takers and always takers, respectively, relative to untreated compliers, where ξ_n is interpreted as the log hazard ratio comparing never takers with untreated compliers and ξ_a is interpreted as the log hazard ratio comparing always takers with untreated compliers.

3.2 Estimation

The conventional method to estimate parameters in a proportional hazards model is by maximizing a partial likelihood (Cox, 1972) which is free of the unspecified baseline hazard

function $\lambda_0(t)$. However, for the IV setup where the compliance status for subjects are only partially known, the partial likelihood method is no longer able to avoid having to deal with $\lambda_0(t)$. Consider a subject i who was encouraged to take the treatment and received the treatment ($Z_i = D_i = 1$), this subject is either an always taker or a complier (see Table 1). Let h_{it}^a be the hazard at time t for subject i conditional on that the subject is actually an always taker, according to (3), $h_{it}^a = \exp(\mathbf{x}^T \alpha + \xi_a)\lambda_0(t)$. Similarly, let h_{it}^c be the hazard at time t for subject i conditional on that the subject is actually a complier and received the treatment, according to (3), $h_{it}^c = \exp(\mathbf{x}^T \alpha + \gamma)\lambda_0(t)$. Given the uncertainty of this subject's compliance class, the unconditional hazard at time t for subject i is a weighted sum of h_{it}^a and h_{it}^c, weighted by the probabilities of being in each corresponding compliance class given that the subject i is at risk at time t: $\frac{P(U_i=a)\cdot P(S_i(1)\geq t|U_i=a)}{P(U_i=a)\cdot P(S_i(1)\geq t|U_i=a)+P(U_i=c)\cdot P(S_i(1)\geq t|U_i=c)}$. $h_{it}^a + \frac{P(U_i=c)\cdot P(S_i(1)\geq t|U_i=c)}{P(U_i=a)\cdot P(S_i(1)\geq t|U_i=a)+P(U_i=c)\cdot P(S_i(1)\geq t|U_i=c)} \cdot h_{it}^c$. Due to the existence of the survival probabilities in the weight, the partial likelihood function will inevitably involve the baseline hazard function $\lambda_0(t)$ unless no survival effects are associated with compliance status (i.e. $\xi_a = \gamma, \xi_n = 0$) as discussed in Cuzick et al. (2007). The partial likelihood method under the IV setup is no longer superior to the full likelihood method, and the estimation using partial likelihood will be even more complicated. To estimate parameters in models (2)-(3), we resort to full likelihood which doesn't involve dealing with the ever changing probability of being in each compliance class given at risk at varying time t.

The likelihood function in terms of the observed data is given by

$$
\begin{aligned}
L_{obs} &= \prod_{i=1}^{N} f(T_i = t_i, \Delta_i = \delta_i, D_i = d_i \mid Z_i = z_i, \mathbf{X}_i = \mathbf{x}_i) \\
&= \prod_{i:\{d_i=1,z_i=0\}} P(U_i = a \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = a, \mathbf{X_i} = \mathbf{x}_i) \\
&\quad \times \prod_{i:\{d_i=0,z_i=1\}} P(U_i = n \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = n, \mathbf{X_i} = \mathbf{x}_i) \\
&\quad \times \prod_{i:\{d_i=1,z_i=1\}} [P(U_i = a \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = a, \mathbf{X_i} = \mathbf{x}_i) \\
&\qquad + P(U_i = c \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = c, \mathbf{X_i} = \mathbf{x}_i)] \\
&\quad \times \prod_{i:\{d_i=0,z_i=0\}} [P(U_i = n \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = n, \mathbf{X_i} = \mathbf{x}_i) \\
&\qquad + P(U_i = c \mid \mathbf{X}_i = \mathbf{x}_i) \cdot f(T_i(z_i) = t_i, \Delta_i(z_i) = \delta_i \mid U_i = c, \mathbf{X_i} = \mathbf{x}_i)].
\end{aligned}
$$

Under Assumption 6,

$$
\begin{aligned}
f(T_i(z_i) &= t_i, \Delta_i(z_i) = \delta_i \mid U_i, \mathbf{X}_i = \mathbf{x}_i) \\
&= [f(S_i(z_i) = t_i \mid U_i, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i} \\
&\quad \cdot [P(C_i(z_i) \geq t_i \mid \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [f(C_i(z_i) = t_i \mid \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i}.
\end{aligned}
$$

Therefore,

$$L_{obs} \propto \prod_{i:\{d_i=1,z_i=0\}} P(U_i = a \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = a, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = a, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i}$$

$$\times \prod_{i:\{d_i=0,z_i=1\}} P(U_i = n \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = n, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = n, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i}$$

$$\times \prod_{i:\{d_i=1,z_i=1\}} \{ P(U_i = a \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = a, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = a, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i}$$

$$+ P(U_i = c \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = c, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = c, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i} \}$$

$$\times \prod_{i:\{d_i=0,z_i=0\}} \{ P(U_i = n \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = n, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = n, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i}$$

$$+ P(U_i = c \mid \mathbf{X}_i = \mathbf{x}_i) \cdot [f(S_i(z_i) = t_i \mid U_i = c, \mathbf{X}_i = \mathbf{x}_i)]^{\delta_i} \cdot [P(S_i(z_i) > t_i \mid U_i = c, \mathbf{X}_i = \mathbf{x}_i)]^{1-\delta_i} \}.$$

Given the hazard model specified in (3), we have that

$$P(S_i(z_i) > t_i \mid U_i, \mathbf{X}_i = \mathbf{x}_i)$$

$$= \exp\{-\exp[\mathbf{x}_i^T \alpha + \xi_n \cdot I(U_i = n) + \xi_a \cdot I(U_i = a) + \gamma \cdot I(U_i = c) \cdot z_i] \cdot \int_0^{t_i} \lambda_0(t) dt\},$$

and,

$$f(S_i(z_i) = t_i \mid U_i, \mathbf{X}_i = \mathbf{x}_i)$$

$$= \exp(\mathbf{x}_i^T \alpha + \xi_n \cdot I(U_i = n) + \xi_a \cdot I(U_i = a) + \gamma \cdot I(U_i = c) \cdot z_i) \cdot \lambda_0(t)$$

$$\times \exp\{-\exp[\mathbf{x}_i^T \alpha + \xi_n \cdot I(U_i = n) + \xi_a \cdot I(U_i = a) + \gamma \cdot I(U_i = c) \cdot z_i] \cdot \int_0^{t_i} \lambda_0(t) dt\}.$$

The likelihood function L_{obs} has a specific mixture structure because U_i is only partially observed for subjects with $Z_i = D_i$. To address this missing data problem which complicates the estimation of the parameters, we adopt the expectation-maximization (EM) algorithm to obtain maximum likelihood estimates (MLEs) of parameters by viewing the compliance status as a latent variable. The consistency of the MLE estimator for model-based IV approach under semiparametric linear transformation models for survival outcomes was proved in Yu et al. (2015). The details of the EM algorithm are given in Appendix A.

3.3 Sensitivity Analysis

In this subsection, we describe an approach to quantify the sensitivity of the causal conclusions to a certain plausible violation of the untestable exclusion restrictions assumption (i.e., Assumption 5).

Consider a possible direct effect of the IV on the survival in addition to its effect through the treatment, we modify the model for the hazard as follows:

$$h_{it}(z) = \exp(\boldsymbol{\alpha}^T \boldsymbol{x} + \xi_n \cdot I(U_i = n) + \xi_a \cdot I(U_i = a) + \gamma \cdot I(U_i = c) \cdot z + \kappa z) \lambda_0(t) \qquad (4)$$

where κ encodes the extent of the direct effect of the IV on the survival with κ being 0 for the model under the exclusion restrictions assumption. In this set of modified models (models (2), (3) and (4)), κ is a sensitivity parameter that is not identified, however, for a fixed value of κ, the MLEs of the remaining parameters could be obtained by extending our ECM algorithm for the original models. Sensitivity analysis could then be conducted by obtaining the estimates of γ for various assumed values of κ.

4. Simulation

We conduct simulation studies to compare the performance of the model-based IV approach with the commonly used 2SRI and the standard Cox regression approaches under various data generation scenarios. Consider a simple context of a single covariate X_i which follows a standard normal distribution N$(0, 1)$ where IV assignment Z_i is generated with $P(Z_i = 1 \mid X_i = x_i) = \text{logit}^{-1}(0.5 - 0.2x_i)$, resulting in around 60% of subjects being encouraged to the treatment. We consider the following five scenarios,

Scenario 1. $\delta_a^T = (-0.2, 0.2)$ and $\delta_c^T = (0.4, -0.5)$; $\alpha = 1$, $\xi_n = 0$, $\xi_a = 0.3$, and $\gamma = 0.3$; the baseline hazard is Exponential with $\lambda_0(t) = 0.1$; the underlying censoring time C_i follows a Weibull distribution $P(C_i = t) = 0.02 \cdot 1.2 \cdot t^{1.2-1}$ and also the subjects with the survival time $S_i > 100$ are further censored to mimic the censoring due to the end of study.

Scenario 2. $\delta_a^T = (-0.2, 0.2)$ and $\delta_c^T = (0.4, -0.5)$; $\alpha = 1$, $\xi_n = 0$, $\xi_a = 1.75$, and $\gamma = 0.5$; the baseline hazard is Weibull with $\lambda_0(t) = 0.02 \cdot 0.9 \cdot t^{0.9-1}$; the underlying censoring time C_i follows an exponential distribution with rate $0.008 \cdot \exp(0.3 \cdot X_i)$.

Scenario 3. $\delta_a^T = (-0.2, 0.2)$ and $\delta_c^T = (0.4, -0.5)$; $\alpha = 1$, $\xi_n = 0$, $\xi_a = 1.75$, and $\gamma = 0.5$; the baseline hazard is Weibull with $\lambda_0(t) = 0.02 \cdot 0.9 \cdot t^{0.9-1}$; the underlying censoring time C_i follows an exponential distribution with rate $0.04 \cdot \exp(0.3 \cdot X_i)$.

Scenario 4. $\delta_a^T = (-0.2, 0.2)$ and $\delta_c^T = (0.6, -0.5)$; $\alpha = 1$, $\xi_n = 1.5$, $\xi_a = -0.75$, and $\gamma = -1$; the baseline hazard is Weibull with $\lambda_0(t) = 0.01 \cdot 1.5 \cdot t^{1.5-1}$; the underlying censoring time C_i follows an Weibull distribution with $P(C_i = t) = 0.01 \cdot 1.1 \cdot t^{1.1-1}$.

Scenario 5. $\delta_a^T = (-0.1, 0.2)$ and $\delta_c^T = (-0.45, -0.2)$; $\alpha = 1$, $\xi_n = 1.5$, $\xi_a = -0.75$, and $\gamma = -1$; the baseline hazard is Weibull with $\lambda_0(t) = 0.01 \cdot 1.5 \cdot t^{1.5-1}$; the underlying censoring time C_i follows an Weibull distribution with $P(C_i = t) = 0.01 \cdot 1.1 \cdot t^{1.1-1}$.

Among the above five scenarios, scenario 1 is a case of no unmeasured confounding where the survival experience of never takers is the same as that of compliers when taking the control ($\xi_n = 0$), and the survival experience of always takers is the same as that of compliers when taking the treatment ($\xi_a = \gamma$). In the absence of unmeasured confounding, the model-based IV method, 2SRI as well as the standard Cox regression without IV are all expected to provide consistent estimates of the causal hazard ratio. In contrast, unmeasured confounding is present in scenarios 2 to 5 since $\xi_n \neq 0$ or/and $\xi_a \neq \gamma$ and the differences between principal strata are attributable to the unmeasured confounding (Cai et al., 2011). In those scenarios, the 2SRI and Cox regression could fail to provide consistent estimates of the causal hazard ratio under assumptions 1 to 6. Scenario 2 and 3 differ in their censoring rates, the censoring rate in scenario 2 is around 30% whereas the censoring rate in scenario 3 is much higher, which is around 60%. Scenario 4 and 5 differ in their proportions of compliers, compliers consist of 50% of the population in scenario 4 and consist of 25% of the population in scenario 5. The proportion of compliers reflects the strength of the instrument, stronger (i.e. larger proportion of compliers) IV is expected to result in higher precision in the estimate of the causal hazard ratio. Those five scenarios include cases of constant (scenario 1), decreasing (scenarios 2 and 3) and increasing (scenarios 4 and 5) hazards, and various different models for censoring are considered.

We considered sample sizes of 5000, a moderate sample size in observational studies, and 1000, a small sample size in observational studies, and simulated 1000 data sets for each of

Table 2: Simulation results under scenarios 1 to 5

Scenario	Sample size	Parameters	True values	Model-based IV method		2SRI		Cox	
				Mean	SD	Mean	SD	Mean	SD
S.1	n=5000	α	1	1.001	0.023	1.000	0.021	1.000	0.020
		ξ_n	0	0.000	0.084				
		ξ_a	0.3	0.298	0.080				
		γ	0.3	0.302	0.076	0.300	0.074	0.299	0.034
	n=1000	α	1	1.005	0.052	1.001	0.046	1.000	0.046
		ξ_n	0	-0.001	0.191				
		ξ_a	0.3	0.302	0.187				
		γ	0.3	0.297	0.172	0.295	0.169	0.298	0.075
S.2	n=5000	α	1	0.999	0.024	1.023	0.022	1.025	0.021
		ξ_n	0	0.001	0.096				
		ξ_a	1.75	1.753	0.086				
		γ	0.5	0.500	0.078	0.304	0.085	0.965	0.036
	n=1000	α	1	1.002	0.054	1.025	0.050	1.027	0.049
		ξ_n	0	-0.001	0.211				
		ξ_a	1.75	1.752	0.194				
		γ	0.5	0.498	0.177	0.303	0.195	0.965	0.085
S.3	n=5000	α	1	1.001	0.030	1.045	0.028	1.054	0.027
		ξ_n	0	0.002	0.139				
		ξ_a	1.75	1.752	0.114				
		γ	0.5	0.503	0.118	0.354	0.107	1.121	0.048
	n=1000	α	1	1.006	0.066	1.047	0.062	1.056	0.060
		ξ_n	0	-0.014	0.326				
		ξ_a	1.75	1.750	0.280				
		γ	0.5	0.497	0.285	0.336	0.256	1.125	0.112
S.4	n=5000	α	1	1.000	0.023	0.996	0.024	0.960	0.022
		ξ_n	1.5	1.502	0.065				
		ξ_a	-0.75	-0.753	0.072				
		γ	-1	-1.003	0.065	-0.601	0.079	-1.450	0.038
	n=1000	α	1	1.009	0.054	1.003	0.051	0.967	0.048
		ξ_n	1.5	1.503	0.153				
		ξ_a	-0.75	-0.757	0.170				
		γ	-1	-1.006	0.152	-0.605	0.180	-1.455	0.093
S.5	n=5000	α	1	1.000	0.023	0.893	0.024	0.903	0.021
		ξ_n	1.5	1.505	0.078				
		ξ_a	-0.75	-0.750	0.079				
		γ	-1	-0.999	0.112	-0.253	0.169	-1.699	0.044
	n=1000	α	1	1.009	0.054	0.897	0.056	0.907	0.050
		ξ_n	1.5	1.514	0.189				
		ξ_a	-0.75	-0.753	0.188				
		γ	-1	-0.993	0.262	-0.229	0.400	-1.705	0.098

the scenarios described above. Table 2 presents the means and standard deviations for the estimates of parameters in the outcome model across 1000 simulated data sets using the model-based IV method, 2SRI and the standard Cox regression. All three methods provide estimates of the association parameter for covariate α and the log causal hazard ratio γ, but only this model-based IV method could further provide understanding about the survival behaviors of never takers and always takers by allowing estimates of the log hazards ratio comparing never takers with untreated compliers ξ_n and the log hazards ratio comparing always takers with untreated compliers ξ_a .

From Table 2 we see that when there is no unmeasured confounding as in Scenario 1, all three methods provide unbiased estimates with standard Cox regression being most efficient as we expected. However, when unmeasured confounding is present as in Scenarios 2 to 5, simply applying standard Cox regression without addressing unmeasured confounding issue or incorrectly assuming homogeneity assumption that goes beyond IV assumptions 1-5 by using 2SRI give us biased estimates of the log causal hazard ratio, whereas the model-based IV method still provide approximately unbiased estimates. Comparisons between scenarios 2 and 3, and between scenarios 4 and 5 demonstrate that besides the sample size, the censoring rate and the proportion of compliers also impact the estimation efficiency on the log causal hazard ratio, with lower censoring rate and larger proportion of compliers having smaller standard deviations.

5. Data Analysis

The data is from NCDB between 1998 and 2008 which involved 1744 facilities and describes 24941 high risk subgroup (i.e., 3 positive nodes or 2 positive nodes and tumors 2-5 cm in size) of AJCC pT1-2pN1 breast cancer patients who were treated with mastectomy. The end point we are interested in is all cause mortality; we use T_i to represent the follow up time of the ith patient in the data set. The censoring rate is 73.4%. We view breast cancer patients that received radiotherapy after mastectomy as the treatment group ($D_i = 1$), whereas the ones that did not receive radiotherapy after mastectomy as the control group ($D_i = 0$). The proportion of patients that received post-mastectomy radiotherapy is 33.7% in this data set. Figure 1 presents the Kaplan-Meier curves for all cause mortality among those high risk subgroup of AJCC pT1-2pN1 breast cancer patients in each treatment group. This unadjusted analysis shows that breast cancer patients who received radiotherapy after mastectomy were associated with a lower risk of all cause mortality than those who did not receive radiotherapy. The five year survival probabilities for patients treated with radiotherapy and without radiotherapy after mastectomy were 85.1% (95% CI [84.3%, 86.0%]) and 76.7% (95% CI [76.0%, 77.4%]), respectively.

The vector of measured confounders $\mathbf{X}_i$ contain a rich set of variables that describe patients' characteristics as well as facilities' characteristics. Measured patients' characteristics include age at diagnosis, race/ethnicity, number of positive lymph nodes, number of lymph nodes examined, tumor size, histologic grade, histologic type, estrogen receptor, hormonal therapy, chemotherapy, laterality of mastectomy, extent of mastectomy, comorbidity index, insurance and year of diagnosis. Measured facilities' characteristics include facility type and volume of breast cancer patients. Although those confounders could be controlled using standard Cox regression, unmeasured confounders such as molecular sub-

Figure 1: Kaplan-Meier curves for all cause mortality among the high risk subgroup of AJCC pT1-2pN1 breast cancer patients.
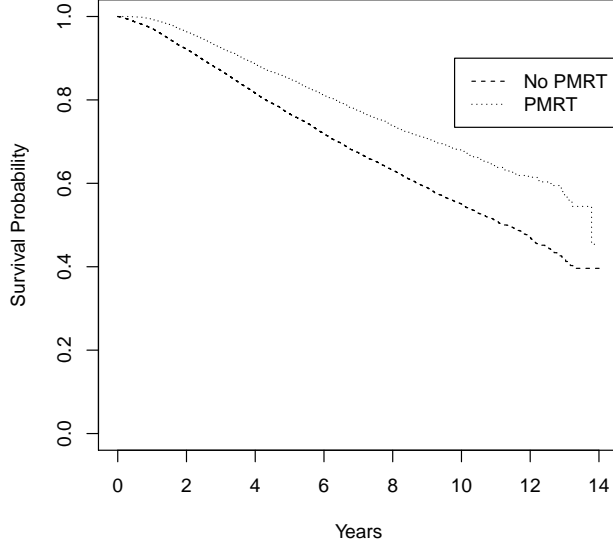
type and lymphovascular invasion are still a concern. The second column of Table 3 shows the imbalance of important observed prognostic factors for breast cancer and facilities' characteristics between breast cancer patients treated with (i.e., $D = 1$) versus without (i.e., $D = 0$) PMRT. The imbalance is measured by the standardized difference which is the difference in means between the two groups in units of the pooled standard deviation. The two groups of patients have very different characteristics, for instance, patients treated with PMRT are substantially younger on average compared to patients not treated with PMRT, which raises concerns about possible associations between the treatment and unmeasured confounders. To control for unmeasured confounding, we apply the IV method. We use Z_i to denote the IV value for the ith patient, with Z_i being 1 indicating that the patient was treated in a facility with higher than typical predicted rate of PMRT for pT1-2pN1 breast cancer patients. Table 3 shows that those important prognostic factors and facilities' characteristics are well balanced by the IV ($Z = 1$ for facilities preferring PMRT vs. $Z = 0$ for facilities not preferring PMRT). However, note that the standardized differences only measure the imbalance among observed covariates, which do not necessarily imply the associations between unobserved confounders with the treatment or with the proposed IV. A sensitivity analysis will be presented below to examine how the estimates will change if the IV has a direct effect on the survival, i.e., IV being associated with the survival through channels other than the use of PMRT.

Using model (2) for compliance class, the proportions of never takers, always takers and compliers can be estimated by $\frac{1}{N} \sum_{i=1}^{N} \hat{P}(U_i = n \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}})$, $\frac{1}{N} \sum_{i=1}^{N} \hat{P}(U_i = a \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}})$,

Table 3: Imbalance in important observed prognostic factors for breast cancer and facilities' characteristics across levels of the treatment and levels of the IV.[1]

Characteristic X	Standardized Difference $(D = 1$ *vs.* $D = 0)$	Standardized Difference $(IV = 1$ *vs.* $IV = 0)$
Tumor size (mm)	0.14	0.00
Three positive lymp nodes	0.21	0.01
Histologic grade		
well differentiated	-0.06	0.03
moderately differentiated	-0.05	0.03
poorly or undifferentiated	0.09	-0.04
Age at diagnosis	-0.46	-0.07
Positive estrogen receptor	0.17	0.07
Facility volume	0.04	0.10
Facility type		
community cancer program	-0.04	-0.07
comprehensive community cancer program	0.01	0.06
academic/research program	0.03	-0.01
other	-0.02	0.00

[1] Both the applications of the standard Cox regression analysis and the IV analysis to this data have their own limitations. The standard Cox regression does not address the potential concern of unmeasured confounding, whereas the IV is not particularly strong in this specific application, see Section 6 for discussions. The results presented in this table does not indicate that the IV analysis should be preferred. And the standardized differences only measure the imbalance among observed covariates, which do not necessarily imply the associations between unobserved confounders with the treatment or with the proposed IV. For the specific bias from failing to adjust a measured covariate, please refer to Brookhart and Schneeweiss (2007), Jackson and Swanson (2015), and Zhao and Small (2018).

Table 4: Estimates and 95% confidence intervals for the log hazard ratio among compliers (γ) for the breast cancer study using the model-based IV method, 2SRI and standard Cox regression.

Parameters	Proposed IV method		2SRI		Cox	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
γ	0.102	[-0.460, 0.750]	0.159	[-0.214, 0.503]	-0.144	[-0.204, -0.085]
ξ_n	0.253	[-0.336, 0.950]	-	-	-	-
ξ_a	0.075	[-0.474, 0.716]	-	-	-	-

and $\frac{1}{N}\sum_{i=1}^{N}\hat{P}(U_i = c \mid \tilde{\mathbf{X}}_i = \tilde{\mathbf{x}})$, respectively. In this breast cancer study, nearly 60% of the subjects were never takers, 26.3% were always takers, and 14.1% were compliers. Table 4 presents the estimates for the log hazard ratio among compliers as well as the 95% confidence intervals obtained using the model-based IV method, 2SRI and standard Cox regression. The 95% confidence intervals for the model-based method and 2SRI are obtained through bootstrap using 500 re-samples. Applying the standard Cox regression that is not designed to account for unmeasured confounders, the estimate is -0.144 with a 95% confidence interval [-0.204, -0.085], which shows that PMRT is associated with lower hazard of death therefore longer survival time among the high risk subgroup of AJCC pT1-2pN1 breast cancer patients. However, using the model-based IV method which is designed to account for both measured and unmeasured confounders under Assumptions 1-6, the estimated log hazard ratio among compliers is 0.102 with a 95% confidence interval [-0.460, 0.750] that covers 0, so we did not find strong evidence that PMRT benefits survival for the high risk subgroup of AJCC pT1-2pN1 breast cancer patients. The result of the 2SRI method reaches the same conclusion as the model-based method. But unlike 2SRI which assumes homogeneity effects, the model-based IV method does not make this strong assumption, and allows comparisons of survival experiences between untreated compliers and treated always takers, untreated never takers, respectively. Based on the estimates of ξ_n and ξ_a, there is not strong evidence that the survival experience of untreated compliers differs from that of treated always takers and untreated never takers.

For the breast cancer study, a potential concern about the validity of the proposed IV is that the facilities that prefer PMRT may treat patients differently also in ways other than using PMRT compared with the facilities that do not prefer PMRT. That is, the facilities' tendency to treat patients with PMRT may have a direct effect on the survival not through PMRT– a violation of the exclusion restrictions assumption. Given the discrepancy in the conclusions between the model-based IV method and the standard Cox regression, we are interested in knowing specifically that if some factor other than PMRT (e.g. a concomitant treatment or procedure) at high rate PMRT facilities had impact on survival, how the result would change. Figure 2 presents the sensitivity analysis results, showing how the estimates and the 95% CIs of the log causal hazard ratio γ vary with different values of the direct effect quantified by the parameter κ in model (4). According to our sensitivity analysis results, the 95% confidence interval for γ does not cover 0 until κ reaches 0.1, indicating that if there is a concomitant treatment or procedure which high rate PMRT facilities

Figure 2: Impact of a direct effect of the IV on the causal parameter log hazard ratio among compliers γ for the breast cancer study.
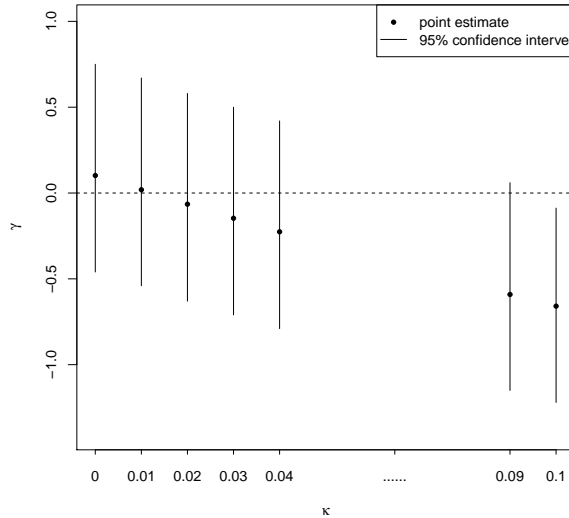
often implement whereas low rate PMRT facilities usually do not adopt, the concomitant treatment or procedure needs to have an effect of increasing the log hazard of death by at least 0.1 (i.e., corresponding to a hazard ratio 1.105) so that our conclusion will be changed to that there is a statistically significant benefit of PMRT on survival. To our knowledge, such a concomitant treatment is unlikely to exist.

6. Summary and Discussion

In this paper, we follow Yu et al. (2015) to use a model-based IV approach to obtain consistent inference on the causal hazard ratio among compliers under standard IV assumptions, and apply the method to an observational study of breast cancer. Different from the published result based on the standard Cox regression analysis (Huo et al., 2015) that PMRT is associated with longer survival among the high risk subgroup of AJCC pT1-2pN1 breast cancer patients, our IV analysis did not find strong evidence to support the benefit of PMRT on survival. One should interpret these results with care. On one hand, the published result based on the standard Cox regression analysis may suffer from unmeasured confounding; on the other hand, the IV in our analysis is not particularly strong with an estimated proportion of compliers being 14.1%, therefore, the effective sample size is drastically reduced, resulting in low power. Given the width of the confidence intervals for the IV estimates, the IV analyses cannot rule out meaningful benefit or harm from the treatment. Since there is no conclusive conclusion on the effect of PMRT on survival, to provide guidance for clinical practice, further studies with stronger IVs or randomized controlled trials are needed.

When there are a large number of covariates, dimension reduction in the measured confounders will be attractive and desired. The IV propensity score could be helpful in this case. Similar to the propensity score $P(D = 1 \mid \mathbf{X} = \mathbf{x})$, the IV propensity score is defined as $P(Z = 1 \mid \mathbf{X} = \mathbf{x})$. Cheng and Lin (2018) showed that as a balancing score, the IV propensity score retains key advantages of the usual propensity score such as dimension reduction, but different from the usual propensity score, it further deals with unmeasured confounders in addition to the measured ones. Future research will be conducted to utilize the IV propensity score for dimension reduction.

This model-based IV approach explicitly models the hazards for never takers, always takers and compliers under the monotonicity assumption that there are no defiers. And therefore, it can not be directly applied to scenarios where the violations of the monotonicity assumption are potentially severe. Considering study contexts in which the monotonicity assumption is likely to be violated, Small and colleagues (Small et al., 2017) introduced a stochastic monotonicity assumption which only requires a monotonic increasing relationship between the IV and the treatment among each subpopulation defined by a set of covariates. Under the stochastic monotonicity assumption, the authors showed that the standard Wald or the two stage least squares estimator for IV identifies a weighted average effect of the treatment for a so-called "strength-of-IV weighted population". We will explore how their framework can be extended to account for the censoring in the survival outcome in the future research.

Acknowledgments

Appendix A. Estimation Algorithm

Besides the partially known compliance status, another complication in the estimation is that $\lambda_0(t)$ is unknown and the form of its distribution is unspecified. To solve this problem, we follow the conventional approach proposed by Breslow (1974) of replacing the baseline hazard by the discrete maximum likelihood estimates. We let n_1 be the number of ordered distinct death times with $0 < t_{(1)} < t_{(2)} < \cdots < t_{(n_1)} < +\infty$, and $\phi_{(j)}$'s, $j = 1, ..., n_1$ be the discrete maximum likelihood estimates of $\lambda_0(t_{(j)})$. Then $\int_0^{t_i} \lambda_0(t) \, dt$ will be approximated by $\sum_{k=1}^{k=l_i} \phi_{(k)}$ where $t_{(l_i)} \leq t_i < t_{(l_i+1)}$.

Replacing $\int_0^{t_i} \lambda_0(t)\,dt$ by $\sum_{k=1}^{k=l_i} \phi_{(k)}$ in the likelihood, had we observed the compliance class for subjects with $Z_i = D_i$, the log likelihood of complete data l_c is given by

$$
\begin{aligned}
l_c(\boldsymbol{\theta}) = & \sum_{i:\{d_i=1,z_i=0\}} \log P(U_i = a \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a + \log(\phi_{(l_i)})\right) \\
& + \sum_{i:\{d_i=0,z_i=1\}} \log P(U_i = n \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_n\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_n + \log(\phi_{(l_i)})\right) \\
& + \sum_{i:\{d_i=1,z_i=1\}} I(U_i = a)[\log P(U_i = a \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a + \log(\phi_{(l_i)})\right)] \\
& + \sum_{i:\{d_i=1,z_i=1\}} I(U_i = c)[\log P(U_i = c \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \gamma\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \gamma + \log(\phi_{(l_i)})\right)] \\
& + \sum_{i:\{d_i=0,z_i=0\}} I(U_i = n)[\log P(U_i = n \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_n\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_n + \log(\phi_{(l_i)})\right)] \\
& + \sum_{i:\{d_i=0,z_i=0\}} I(U_i = c)[\log P(U_i = c \mid \boldsymbol{X}_i = \boldsymbol{x}_i) - \exp\left(\boldsymbol{x}_i^T\boldsymbol{\alpha}\right) \cdot \sum_{k=1}^{l_i} \phi_{(k)} + \delta_i \cdot \left(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \log(\phi_{(l_i)})\right).
\end{aligned}
$$

In the E-step, we find the conditional expectation of $l_c(\boldsymbol{\theta})$, with respect to the conditional distribution of unknown U given $(T, \Delta, D, Z, \boldsymbol{X})$ under the current estimates of the parameters $\boldsymbol{\theta}^{(t)} = (\boldsymbol{\delta}_a^{(t)}, \boldsymbol{\delta}_c^{(t)}, \boldsymbol{\alpha}^{(t)}, \xi_n^{(t)}, \xi_a^{(t)}, \gamma^{(t)}, \phi_{(1)}^{(t)}, ..., \phi_{(n_1)}^{(t)})$ at the tth iteration, which is equivalent to calculate the following chances of being in each of the two possible compliance classes for subjects with $Z_i = D_i$: $\mathrm{E}_{U_i|T_i,\Delta_i,D_i,Z_i,\boldsymbol{X}_i,\boldsymbol{\theta}^{(t)}} I(U_i = a)$ and $\mathrm{E}_{U_i|T_i,\Delta_i,D_i,Z_i,\boldsymbol{X}_i,\boldsymbol{\theta}^{(t)}} I(U_i = c)$ for subjects with $Z_i = D_i = 1$, and $\mathrm{E}_{U_i|T_i,\Delta_i,D_i,Z_i,\boldsymbol{X}_i,\boldsymbol{\theta}^{(t)}} I(U_i = n)$ and $\mathrm{E}_{U_i|T_i,\Delta_i,D_i,Z_i,\boldsymbol{X}_i,\boldsymbol{\theta}^{(t)}} I(U_i = c)$ for subjects with $Z_i = D_i = 0$. For example, for subjects with $Z_i = D_i = 1$,

$$
\begin{aligned}
& \mathrm{E}_{U_i|T_i,\Delta_i,D_i,Z_i,\boldsymbol{X}_i,\boldsymbol{\theta}^{(t)}} I(U_i = a) \\
& = P(U_i = a \mid T_i = t_i, \Delta_i = \delta_i, D_i = 1, Z_i = 1, \boldsymbol{X}_i = \boldsymbol{x}_i, \boldsymbol{\theta}^{(t)}) \\
& = \frac{P(U_i = a \mid \boldsymbol{X}_i = \boldsymbol{x}_i) \cdot P(T_i = t_i, \Delta_i = \delta_i \mid U_i = a, Z_i = 1, \boldsymbol{X}_i = \boldsymbol{x}_i)}{\sum_{u=\{a,c\}} P(U_i = u \mid \boldsymbol{X}_i = \boldsymbol{x}_i) \cdot P(T_i = t_i, \Delta_i = \delta_i \mid U_i = u, Z_i = 1, \boldsymbol{X}_i = \boldsymbol{x}_i)} \\
& = \frac{\exp\left[-\exp(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a) \cdot \sum_{k=1}^{l_i} \phi_{(k)}\right]}{\exp\left[-\exp(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \xi_a) \cdot \sum_{k=1}^{l_i} \phi_{(k)}\right] + \exp[\boldsymbol{x}_i^T(\boldsymbol{\delta}_c^{(t)} - \boldsymbol{\delta}_a^{(t)}) - \exp(\boldsymbol{x}_i^T\boldsymbol{\alpha} + \gamma) \cdot \sum_{k=1}^{l_i} \phi_{(k)}] \cdot [\exp(\gamma - \xi_a)]^{\delta_i}}.
\end{aligned}
$$

In the M-step, given $Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}^{(t)}) = \mathrm{E}_{U|T,\Delta,D,Z,\mathrm{X}_i,\boldsymbol{\theta}^{(t)}} l_c(\boldsymbol{\theta})$ obtained in the E-step, we first obtain $(\boldsymbol{\delta}_a^{(t+1)}, \boldsymbol{\delta}_c^{(t+1)}) = \underset{\boldsymbol{\delta}_a,\boldsymbol{\delta}_c}{\arg\max} Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}^{(t)})$ by fitting a weighted multinomial logistic regression model. Then we conduct a conditional maximization given $\phi_{(j)} = \phi_{(j)}^{(t)}$, $j = 1..., n_1$ to obtain $(\boldsymbol{\alpha}^{(t+1)}, \xi_a^{(t+1)}, \xi_c^{(t+1)}, \gamma^{(t+1)}) = \underset{\boldsymbol{\alpha},\xi_a,\xi_c,\gamma}{\arg\max} Q(\boldsymbol{\delta}_a, \boldsymbol{\delta}_c, \boldsymbol{\alpha}, \xi_a, \xi_c, \gamma, \phi_{(1)}^{(t)}, ..., \phi_{(n_1)}^{(t)} \mid \boldsymbol{\theta}^{(t)})$ using Newton's method. Lastly, given $(\boldsymbol{\alpha}^{(t+1)}, \xi_a^{(t+1)}, \xi_c^{(t+1)}, \gamma^{(t+1)})$, we obtain $(\phi_{(1)}^{(t+1)}, ..., \phi_{(n_1)}^{(t+1)}) = \underset{\phi_{(1)},...,\phi_{(n_1)}}{\arg\max} Q(\boldsymbol{\delta}_a, \boldsymbol{\delta}_c, \boldsymbol{\alpha}^{(t+1)}, \xi_a^{(t+1)}, \xi_c^{(t+1)}, \gamma^{(t+1)}, \phi_{(1)}, ..., \phi_{(n_1)} \mid \boldsymbol{\theta}^{(t)})$. From the functional form of the complete data log likelihood l_c, it is easy to see that $(\phi_{(1)}^{(t+1)}, ..., \phi_{(n_1)}^{(t+1)})$ is a function of the current values of parameters in the model (3) for hazard functions, i.e., $(\boldsymbol{\alpha}^{(t+1)}, \xi_a^{(t+1)}, \xi_c^{(t+1)}, \gamma^{(t+1)})$,

and is not a function of the current values of parameters in the model (2) for compliance class, i.e., $(\boldsymbol{\delta}_a^{(t+1)}, \boldsymbol{\delta}_c^{(t+1)})$.

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