RESEARCH ARTICLE

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Causal Inference Methods Based on Pseudo-Observations: A Comparative Analysis of Treatment Types for Iranian Gastrointestinal Cancer Patients

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Abstract

Objective: This study investigates the effects of different treatments on the survival of patients with gastrointestinal cancer. One of the methods for causal inference, the doubly robust estimator, is easy to apply with complete data, but becomes complex with incomplete or censored data. To overcome these challenges, we used pseudo-observations. **Methods:** This historical cohort study included 602 patients residing in the provinces of Mazandaran and Golestan. The patients were followed up over a period of approximately 11 years. To evaluate the effects of surgical, radiotherapeutic, and chemotherapeutic treatments on survival, we used inverse probability weighting and the doubly robust estimator using pseudo-observations. The survival and pseudo packages of the R software were used for model fitting. The efficacy of the doubly robust estimator and inverse probability weighting was assessed by comparing survival estimates derived from both methods across different treatment types. **Result:** In this study, there were 441 cases (73.26%) of deaths from gastrointestinal cancer. Our analysis included three time points: the first year, the eighth year and the fifteenth year. The results showed that the survival of patients with gastrointestinal cancer varied depending on the treatment method. In particular, surgical treatment showed a significant impact on survival at all three time points. In contrast, radiotherapy only showed a significant correlation at the first time point, while no significance was found at the two subsequent time points. A significant correlation was found for chemotherapy at all three time points. **Conclusion:** Using a doubly robust estimator with pseudo-observations is more efficient and simpler. Causal inference methods can serve as evaluation tools for different treatments in patients with gastrointestinal cancer.

Keywords: Causal inference- Inverse Probability Weighting- Doubly Robust- Pseudo-observations

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Introduction

Gastrointestinal cancers, including colorectal, stomach, and esophageal cancers, represent a significant medical and financial burden and cause the most new cases and deaths worldwide each year. According to the latest data, gastric cancer ranks fourth in overall mortality rate and fifth in age-standardized incidence rate globally, with approximately 1.1 million new cases occurring each year, making it the fourth most common form of malignancy worldwide [1]. In Asia, including Iran, the burden of gastrointestinal cancers is particularly pronounced. For instance, the Iranian Ministry of Health reports that cancer is the third leading cause of mortality in Iran, with gastrointestinal cancers accounting for over 60% of cancer-related deaths. In developing countries, colorectal cancer is the most common gastrointestinal cancer, while esophageal and stomach cancers are more prevalent in Western countries. However, due to the increasing burden of certain risk factors, esophageal and stomach cancers are on the rise again in Western countries. At the same time, significant shifts in the prevalent types of stomach cancer are observed in countries undergoing economic transition, including regions within Iran. It is worth noting that all cancers of the gastrointestinal tract can be identified by precancerous lesions, and their development is strongly linked to individual lifestyle habits [2]. Golestan Province in northern Iran is recognized as a high-risk area for gastrointestinal cancer, where these cancers often present asymptomatically in their early stages and are diagnosed at advanced stages, leading to poor prognoses [3, 4]. Early mortality is a critical indicator used to evaluate screening programs, early detection efforts, and prognostic factors [5]. In recent years, substantial information has been gathered regarding the epidemiology and burden of cancer in various regions of Iran, aimed at examining cancer trends across the country and designing strategic programs for the health system [6]. This disease represents a significant

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public health problem and profoundly impacts individuals, families, and communities. The survival time of cancer patients is typically measured as the time from diagnosis to death, based primarily on clinical characteristics observed in previous years and physicians' medical expertise. Studies in this area often focus on assessing the temporal aspects of significant events, including patient mortality, response to treatment, and disease recurrence [7]. In conclusion, while gastrointestinal cancers pose a global challenge, it is essential to highlight the specific context of Asian countries like Iran, where these cancers contribute significantly to morbidity and mortality. Addressing this issue requires targeted public health strategies and increased awareness of the risk factors associated with these diseases.

A major obstacle in analyzing time-to-event data is the occurrence of incomplete or censored data, which can bias the results. Survival analysis techniques are commonly employed to handle such censored observations [8]. Among these, nonparametric estimators like the Kaplan-Meier estimator are frequently used to assess the survival function of populations receiving treatment. When treatment allocation is not random and depends on individual prognosis and baseline characteristics, potential biases arise. In observational studies, the subgroup receiving a particular treatment may exhibit notable differences compared to the overall population [9]. To address confounding factors, regression models such as the Cox regression model are often utilized. While these models can control for confounding, they primarily provide conditional causal effects; researchers may be more interested in average or marginal causal effects. Two widely used methods for estimating marginal causal effects are inverse probability weighting (IPW) and the g-formula. The IPW method adjusts for the probability of receiving a specific treatment, while the g-formula incorporates both confounding variables and treatment variables in a time-event model [10–14]. For cancer studies, various statistical methods have been applied, including those mentioned above along with others tailored to specific types of cancer. The validity of IPW relies on accurately modeling all relevant intervening factors. Doubly robust estimators that integrate both the g-formula and IPW can enhance validity if at least one model is correctly specified [15–17]. Another fundamental assumption in survival analysis is the constancy of proportional risks over the study duration. If this assumption cannot be demonstrated, alternative methods must be employed. While implementing doubly robust methods for complete data is relatively straightforward, it becomes complex for incomplete or censored data. Pseudo-observations can help overcome these challenges by allowing conventional causal inference methods to be applied at specified time points where no participants are censored [18].

The aim of this study is to apply causal inference methods — in particular the inverse probability weighting method and the doubly robust method using pseudo-observations of the survival function in the survival time data of gastrointestinal cancer patients (gastric, esophageal or colorectal cancer) to calculate the marginal probability of survival and obtain the marginal survival curve. Additionally, this study aims to compare different treatment methods to assess their effectiveness in improving survival outcomes for these patients.

Materials and Methods

This study used data from patients diagnosed with gastrointestinal cancer (colorectal cancer, esophageal cancer and stomach cancer) who were followed up until July 2017. These patients were enrolled between March 2002 and March 2007 in Mazandaran and Golestan provinces. Data were obtained from the National Institute of Health Research of Iran. The ward in which each patient was living at the time of diagnosis was documented. In 2002, there were fifteen wards in Mazandaran and eleven in Golestan. Ultimately, the study included a total of 602 patients. Variables examined included age at diagnosis, gender, place of residence (rural vs. urban), smoking habits, race (Turkmen vs. other), treatment modalities (chemotherapy, radiotherapy and surgery) and type of cancer (gastric, esophageal or colorectal). However, it is important to note that the disease stage was not included in the initial data collection due to limitations in accessing comprehensive medical records. Patients were contacted by telephone for follow-up. Initially, only the age at diagnosis, sex, place of residence and type of cancer were recorded as variables. Therefore, patients or their families were interviewed at the end of the follow-up period to obtain additional information. Any patients who could not be reached or whose families were unresponsive were excluded from the study. This approach ensured that all patients diagnosed with gastrointestinal cancer between 2002 and 2007 were followed up until 2017. To be eligible for this study, the patient had to have lived in one of the districts of Mazandaran or Golestan at the time of diagnosis and have been diagnosed with gastrointestinal cancer between 2002 and 2007.

Statistical analysis

The IPW and DR approaches and the use of pseudo-observations are some of the important components that we combine in our approach in this section. The software used is R, specifically version 4.3.2. The packages utilized include pseudo, geepack, and survival. A significance level of 0.05 was considered.

Inverse Probability Weighting and Doubly Robust estimator

The objective of causal inference is to assess the average causal effect within a population, particularly by examining the variations in average outcomes across different treatment levels. Specifically, we define the Average Causal Effect (ACE) as follows:

$$ACE = E(Y^1) - E(Y^0) \quad (1)$$

Assuming our treatment consists of two levels, the potential outcomes for each subject i (where i=1,2,…, n.) are denoted as Y_i^0 and Y_i^1.

The underlying mathematical framework for establishing both assumptions and statistical models in

causal inference is based on the concept of potential outcomes. In this framework, we consider that each subject i in the target population has two possible values for the outcome variable: Y_i^1 , which represents the outcome that would occur if the subject received treatment 1, and Y_i^0 , which indicates the outcome under treatment 0. Since each subject can belong to only one treatment group, at least one of these potential outcomes remains counterfactual and cannot be observed. Consequently, the individual causal effect, typically expressed as $Y_i^1 - Y_i^0$, is unobservable. Therefore, causal inference often centers on estimating the average causal effect across the entire population.

Consistency, positivity and conditional exchangeability are the three necessary conditions to obtain a causal effect in observational studies. The simplest method for dealing with missing data is to restrict the analysis to complete cases. A widely used technique to mitigate this bias is IPW. First, propensity scores are derived by fitting an appropriate model:

$$ps_{1i} = P(H_i = 1 \mid Q_i) \quad (2)$$

Assume that the response variable y_i for patient i is represented as a function of a binary treatment indicator, H_i , where H_i takes the value 0 for the control group and 1 for the active treatment group. Q_i represent counfounding variables. The IPW estimator:

$$\widehat{IP_1} = \frac{1}{n}\sum_{i=1}^{n} \frac{H_i y_i}{ps_{1i}} \quad (3)$$

Finally, the average causal effect is calculated using the following formula [18].

$$\widehat{ACE}_{IPW} = \frac{1}{n}\sum_{i=1}^{n} \frac{H_i y_i}{ps_{1i}} - \frac{1}{n}\sum_{i=1}^{n} \frac{H_i y_i}{ps_{0i}} \quad (4)$$

The doubly robust method can be implemented utilizing the IPW estimator and outcome regression (OR model) that refers to a statistical approach used to adjust for confounding factors in the analysis of time-to-event data, defined as $E(y_i \mid H_i, V_i) = m(D_i)(V_i, \beta)$ specifically for the variables y_i, H_i, and V_i. Here, V_i represents a collection of covariates associated with subject i. The term $m(D_i)(V_i, \beta)$ indicates the expected outcome for subject i given their covariates V_i and parameters β, conditional on their treatment assignment D_i.

DR estimator can be constructed as [15].

$$\frac{1}{n}\sum_{i=1}^{n} \frac{y_i H_i - (H_i - ps_{1i}(\hat{\gamma}))m_1(V_i, \hat{\beta})}{ps_{1i}(\hat{\gamma})} \quad (5)$$

pseudo-observations

The pseudo-survival probability for all individuals at time t_0 is obtained:

$$\hat{S}_h^i(t) = n\hat{S}_h(t) - (n-1)\hat{S}_h^{-i}(t) \quad (6)$$

Where h is treatment indicator and $\hat{S}_h(t)$ and $\hat{S}_h^{-i}(t)$ are the Kaplan-Meier estimator calculated with the complete dataset, alongside the Kaplan-Meier estimator derived from the dataset with individual i excluded [19].

Inverse Probability Weighting and Doubly Robust estimator based on pseudo-observations

The IPW estimator can be constructed by substituting y_i by $\hat{S}_h^i(t)$ in (2) and yielding the following estimator:

$$\widehat{IP_1} = \frac{1}{n}\sum_{i=1}^{n} \frac{\hat{S}_h^i(t) H_i}{ps_{1i}} \quad (7)$$

Similarly, to construct a DR estimator [20] substitute y_i by $\hat{S}_h^i(t)$ in (5).

$$\frac{1}{n}\sum_{i=1}^{n} \frac{\hat{S}_h^i(t)\, H_i - (H_i - ps_{1i}(\hat{\gamma}))m_1(V_i, \hat{\beta})}{ps_{1i}(\hat{\gamma})} \quad (8)$$

Results

We used the doubly robust estimator and the inverse probability weighting method to analyze data on gastric, esophageal, and colorectal cancers obtained from the Iran National Institute of Health Research in Mazandaran and Golestan provinces of Iran. Our aim was to compare three treatment methods: surgery, radiotherapy, and chemotherapy, with their respective comparison groups for the treatment of patients with gastrointestinal cancers. Since the treatments were not randomized, a direct comparison of the treatment groups may not be possible. For each treatment method, we defined comparison groups as follows:

1. Patients who received surgery compared to those who did not receive surgery.
2. Patients who received radiotherapy compared to those who did not receive radiotherapy.
3. Patients who received chemotherapy compared to those who did not receive chemotherapy.

Baseline covariates included in the dataset were age at diagnosis, sex, place of residence (rural vs. urban), smoking habits, race (Turkmen vs. other), and type of cancer (gastric, esophageal, or colorectal). Either the IPW or the proposed DR approaches were applied to these covariates to adjust the survival curve estimates.

In this study involving 602 patients, the average age at diagnosis was 62.61 years, with a standard deviation of 13.84 years. Among the patients, 285 had gastric cancer (47.33%), 175 had esophageal cancer (29.07%), and 142 had colorectal cancer (23.59%). In total, there were 441 deaths attributed to gastrointestinal cancer, representing 73.26% of the study cohort.

In the full dataset, the surgery group included 364 patients, while the comparison group for surgery consisted of 238 patients. The radiotherapy group comprised 203 patients, with its corresponding comparison group containing 399 patients. Lastly, the chemotherapy group included 374 patients, and the comparison group for chemotherapy comprised 228 patients.

Table 1. Patient Characteristics at Diagnosis: Frequencies and Percentages by Treatment Modality (Surgery, Radiotherapy, Chemotherapy)

Covariate		Total	Surgery		p.value	Radiotherapy		p.value	Chemotherapy		p.value
			No	Yes		No	Yes		No	Yes	
Sex	Male	392 (65.12%)	150 (63.03 %)	242 (66.48 %)	0.385	257 (64.41%)	135 (66.50%)	0.611	147 (24.42%)	245 (65.51%)	0.796
	Female	210 (34.88 %)	88 (36.97 %)	122 (33.52%)		142 (35.59%)	68 (33.50%)		81 (13.46%)	129 (34.42%)	
City	Rural	319 (52.99%)	146 (61.34%)	173(47.53%)	<0.001	213 (53.38%)	106 (52.22%)	0.786	132 (57.89%)	187 (50.00%)	0.060
	Urban	283 (47.01%)	92 (38.66%)	191 (52.47%)		186 (46.62%)	97 (47.78%)		96 (42.11%)	187 (50.00%)	
History	No	391 (64.95%)	160 (67.23%)	231 (63.46%)	0.345	257 (64.41%)	134 (66.01%)	0.698	151 (66.23%)	240 (64.17%)	0.608
	Yes	211 (35.05%)	78 (32.77%)	133 (36.54%)		142 (35.59%)	69 (33.99%)		77 (33.77%)	134 (35.83%)	
Smoking	No	464 (77.08%)	171 (71.85%)	291 (80.39%)	0.014	303 (75.94%)	161 (79.31%)	0.353	175 (76.75%)	289 (77.73%)	0.883
	Yes	138 (22.92%)	67 (28.15%)	71 (19.61%)		96 (24.06%)	42 (20.68%)		53 (23.25%)	85 (22.73%)	
Race	Turkmen	65 (10.80%)	46 (19.33%)	19 (05.22%)	<0.001	49 (08.14%)	16 (07.88%)	0.103	35 (15.35%)	30 (08.02%)	0.006
	Other	537 (89.20%)	192 (80.67%)	345 (94.78%)		350 (58.14%)	187 (92.12%)		193 (84.65%)	344 (91.98%)	
Surgery	No	238 (39.53%)	238 (39.53%)	0	<0.001	183 (45.86%)	55 (27.09%)	<0.001	138 (60.53%)	100 (26.74%)	
	Yes	364 (60.47%)	0	364 (60.47%)		216 (54.14%)	148 (72.91%)		90 (39.47%)	274 (73.26%)	
Radiotherapy	No	399 (66.28%)	183 (76.89%)	216 (59.34%)	<0.001	399 (66.28%)	0		211 (92.54%)	188 (50.27%)	<0.001
	Yes	203 (33.72%)	55 (23.11%)	148 (40.66%)		0	203 (33.72%)		17 (07.46%)	186 (49.73%)	
Chemotherapy	No	228 (37.87%)	138 (57.98%)	90 (24.73%)		211 (52.88%)	17 (08.37%)	<0.001	228 (37.87%)	0	<0.001
	Yes	374 (62.13%)	100 (42.02%)	274 (75.27%)		188 (47.12%)	186 (91.63%)		0	374 (62.13%)	
Esophageal	Yes	175 (29.07%)	137 (57.56%)	290 (79.67%)	<0.001	303 (75.94%)	124 (61.08%)	<0.001	158 (69.30%)	269 (71.93%)	0.491
	Others	427 (70.93%)	101 (42.44%)	74 (20.33%)		96 (24.06%)	79 (38.92)		70 (70.30%)	105 (07.28%)	
Colorectal	Yes	142 (23.59%)	9 (03.78%)	231 (63.46%)	<0.001	310 (77.69%)	150 (73.89%)	0.299	206 (90.35%)	254 (67.91%)	<0.001
	Others	460 (76.41%)	229 (96.22%)	133 (36.54%)		89 (22.31%)	53 (26.11%)		22 (9.65%)	120 (32.09%)	
Age	Mean±SD	62.61±13.84	68.30±11.69	58.89±13.92	<0.001	64.36±13.08	59.19±14.66	<0.001	68.27±10.93	59.16±14.29	<0.001

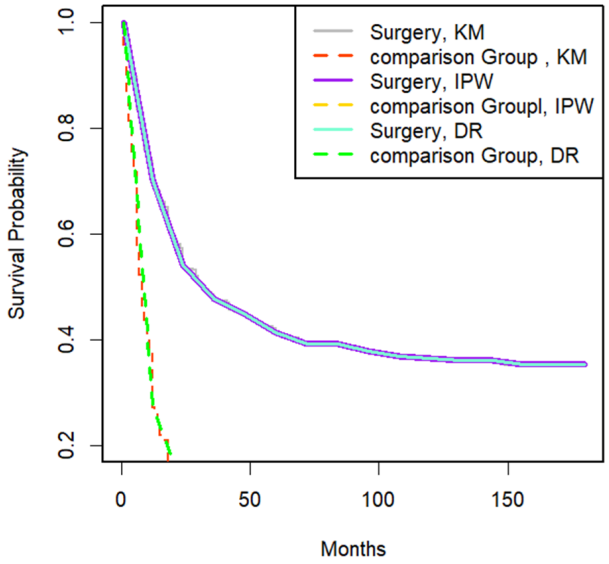

Figure 1. Adjusted Survival Curves for the Surgery Group and Comparison Group (who did not receive surgery) Using Inverse Probability Weighting (IPW) and Doubly Robust (DR) Methods Compared to Unadjusted Kaplan-Meier (KM) Curves

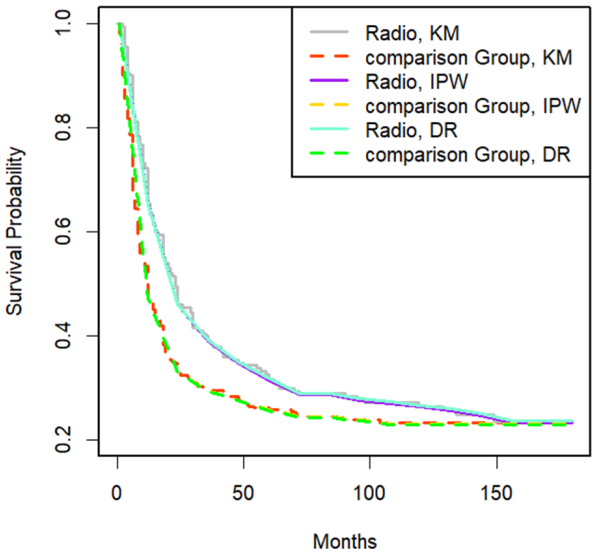

Figure 2. Adjusted Survival Curves for the Radiotherapy Group and comparison Group (who did not receive radiotherapy) Using Inverse Probability Weighting (IPW) and Doubly Robust (DR) Methods Compared to Unadjusted Kaplan-Meier (KM) Curves

Table 2. The Median Survival Times and Confidence Intervals (CI) Based on various Demographic Variables and Treatment Methods

Covariate		Deat	Median	Std.eror	95% confidence interval	Log-rank
Sex	Male	148 (70.5%)	18	2.129	(13.826,22.174)	0.130
	Female	293 (74.7%)	14	1.014	(12.012,15.988)	
City	Rural	252 (79.0%)	12	0.729	(10.570,13.430)	0.000
	Urban	189 (66.8%)	21	3.096	(14.932,27.068)	
History	No	289 (73.9%)	15	1.171	(12.705,17.295)	0.528
	Yes	152 (72.0%)	17	1.427	(14.204,19.796)	
Smoking	No	335 (72.2%)	15	1.043	(12.956,17.044)	0.326
	Yes	106 (76.8%)	16	1.831	(12.412,19.588)	
Race	Turkmen	55 (84.6%)	18	1.184	(15.679,20.321)	0.002
	Other	386 (71.9%)	11	1.612	(7.840,14.160)	
Surgery	No	217 (91.2%)	8	0.727	(6.574,9.426)	0.000
	Yes	224 (61.5%)	32	4.768	(22.655,41.345)	
Radiotherapy	No	292 (73.2%)	12	1.156	(9.734,14.266)	0.008
	Yes	149 (73.4%)	23	3.057	(17.008,28.992)	
Chemotherapy	No	181 (79.4%)	10	1.101	(7.843,12.157)	0.000
	Yes	260 (69.5%)	21	1.793	(17.486,24.514)	

Table 1 shows the Patient characteristics across the surgery and comparison groups, as well as the radiotherapy and comparison groups, and the chemotherapy and comparison groups. In the surgery group, significant covariates at the 5% level included age, place of residence, smoking habits, race, chemotherapy, radiotherapy and cancer type (esophageal and colorectal). In the radiotherapy group, the significant factors at the 5% level included age, chemotherapy, surgery and cancer type (esophageal cancer). In the chemotherapy group, the significant covariates at the 5% level were age, race, radiotherapy, surgery and cancer type (colorectal).

In this study, survival analysis was conducted using the log-rank test as presented in Table 2 to compare survival outcomes across different treatment groups. The results indicated that there were statistically significant differences between the two patient groups: Patients who received surgery compared to those who did not receive surgery Patients who received radiotherapy compared to those who did not receive radiotherapy., and Patients who received chemotherapy compared to those who did not receive chemotherapy(p-value<0.001). These

Table 3. Average Causal Effect (ACE) and Confidence Intervals (CI) Using Inverse Probability Weighting (IPW) and Double Robust Approach (DR) for Surgical, Chemotherapy, and Radiotherapy Treatments at Time Points T=1, 8, and 15

Treatment	Time	Methods	ACE	CI
Surgery	T=1	IPW	0.427	(0.3423,0.5137)
		DR	0.4278	(0.3344,0.5212)
	T=8	IPW	0.3232	(0.2513,0.3951)
		DR	0.3243	(0.2542,0.3943)
	T=15	IPW	0.3074	(0.2364,0.3783)
		DR	0.3085	(0.2395,0.3775)
Chemotherapy	T=1	IPW	0.1772	(0.0802,0.2741)
		DR	0.1799	(0.1067,0.2531)
	T=8	IPW	0.1407	(0.0656,0.2158)
		DR	0.1355	(0.0752,0.1958)
	T=15	IPW	0.132	(0.0558,0.2083)
		DR	0.1264	(0.0648,0.1881)
Radiotherapy	T=1	IPW	0.1841	(0.0136,0.3546)
		DR	0.1818	(0.0796,0.2840)
	T=8	IPW	0.0374	(-0.0262,0.1011)
		DR	0.0423	(-0.0261,0.1107)
	T=15	IPW	0.0014	(-0.0613,0.0640)
		DR	0.0067	(-0.0594,0.0727)

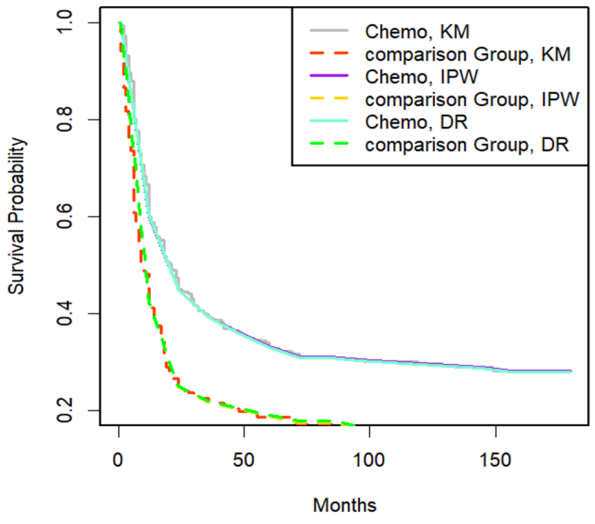

Figure 3. Adjusted Survival Curves for the Chemotherapy Group and comparison Group(who did not receive chemotherapy) Using Inverse Probability Weighting (IPW) and Doubly Robust (DR) Methods Compared to Unadjusted Kaplan-Meier (KM) Curves

results clearly demonstrate the positive impact of various treatments on patient survival and emphasize that these interventions significantly affect survival outcomes.

The Kaplan-Meier results indicate significant differences in survival among the various treatment groups. Notably, as presented in Table 2, the mean survival time for patients undergoing surgical treatment is reported to be 32 months with 224 deaths. In contrast, patients receiving chemotherapy have a mean survival time of 21 months with 260 deaths, while those who underwent radiotherapy experience a mean survival time of 23 months and 149 deaths. These results clearly demonstrate the positive impact of various treatments on patient survival and emphasize that these interventions significantly affect survival outcomes.

We used both the IPW and DR approaches based on pseudo-observations. First, we fitted a Cox model that included conditioning therapy and the variables in Table 1 as covariates to estimate the average causal effect on the three-year overall survival probability. We then calculated the pseudo-observations at 15 years for each patient and reported the three-year outcomes.

The time points T=1, T=8, and T=15 were chosen to represent three distinct phases in the study: the early phase (T=1), the middle phase (T=8), and the later phase (T=15). This approach allows us to capture changes in the risk of death at different stages of the follow-up period, providing a comprehensive understanding of how mortality risk evolves over time.

In Table 3, the confidence intervals in the surgery group were significant at all three time points. This observation emphasizes the significant impact of the surgical group on survival. The confidence intervals for the IPW and DR approaches in the radiotherapy group were significant at the first time point, but were not significant at time points 8 and 15. Interestingly, The confidence intervals in the chemotherapy group are significant at all time points.

The $\hat{S}_h^i(t)$ was calculated annually over a period of 15 years. Figures 1, 2 and 3 show the DR and IPW survival curves after surgery, radiotherapy and chemotherapy as well as the unadjusted curves (KM survival curves). The adjusted survival curves for the treatment groups

that received surgery and chemotherapy at all three time points, as well as for radiotherapy at the first time point, showed similarities with the unadjusted curves. In contrast, the adjusted survival curves for the control group were significantly lower than the unadjusted curves, indicating a significantly improved treatment effect after the adjustments. The second term ($m_1(V_t\beta^*)$) of the DR estimator in formula (8) had little effect on the estimates for either groups, so DR and IPW were quite similar. In cases where there are few common significant factors between the DR and IPW models, the influence of the second term may be negligible. In both models, only the colorectal factor in the surgical treatment, the chemotherapy factor in the radiotherapy treatment, and the colorectal and surgical factors in the chemotherapy treatment showed statistical significance at the 5 percent level. This observation may explain the similarity between the inverse probability weighting and the doubly robust estimates.

Discussion

In this paper, we propose the estimation of the treatment effect (surgery, chemotherapy and radiotherapy) using the IPW and the doubly robust DR approaches based on pseudo-observations. In fact, we proposed a method to eliminate confounding in the estimation of survival functions based on pseudo-observations. Because the application of the DR estimator to survival data can be complex and computationally intensive, we used pseudo-observations in our study. This study was conducted using data from patients with gastrointestinal cancer in Mazandaran and Golestan provinces in northern Iran, with a follow-up period of 15 years. We examined the risk of death in three different time periods: the first, eighth and fifteenth year. In the surgery group, the confidence intervals were significant in all three periods. In the radiotherapy group, the confidence intervals were only significant in the first period, while they were not significant in years 8 and 15. In the chemotherapy group, the confidence intervals were significant at all time points.

In agreement with Arterburn et al. [21], Güller et al. [22], Rodríguez et al. [23], and Aghcheli et al. [24] our study showed a significant association between surgical interventions and time of death at all time points. Consistent with the findings of Yang et al. [25] and Dixon et al. [26] patients who had not received radiotherapy had a higher risk of death than patients who had received radiotherapy. This is consistent with the results of the studies by Matthew et al. [27] Han K et al .[28] and Brink et al. [29] which found a significant association between radiotherapy and survival. In our study, although individuals who had not received radiotherapy had a higher risk of death in the first period, this association was no longer significant in later periods. Our study also found that individuals who had not received chemotherapy had a higher risk of death across all time points, similar to Kasuga et al. [30] , Graf et al. [31] and Smyth et al. [32]. and in contrast to the results of A Hern et al. [33].

Limitations of this study include the lack of access to precise information regarding the stage of the disease at diagnosis, which may lead to recall bias and inaccurate estimates of the relationship between treatment variables and survival. Additionally, the variables were collected from patients or their families at the end of the follow-up period, which may introduce information bias due to the long intervals between diagnosis and data collection. Therefore, it is suggested that future studies pay closer attention to clinical variables and disease stages to achieve more accurate and reliable results.

In conclusion, this study investigated the impact of various treatment methods, including surgery, radiotherapy, and chemotherapy, on the survival of patients with gastrointestinal cancer in Mazandaran and Golestan provinces. The findings indicate that surgery had a significant effect on the survival of patients at all follow-up time points, with surgically treated patients exhibiting better survival compared to non-surgical patients. Furthermore, radiotherapy showed a positive and significant effect on survival only in the first year, while in the eighth and fifteenth years, this effect significantly diminished and became insignificant. On the other hand, chemotherapy demonstrated a positive and significant relationship with patient survival, with chemotherapy patients showing higher survival rates.

Author Contribution Statement

SV: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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General

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Approval

It is part of an approved student thesis

Data Availability

The data analyzed in the study are not available due to privacy issues.

Ethical Declaration

This study was approved by the Biomedical Ethics Committee of Ahvaz University of Medical Sciences (approval number: IR.AJUMS.REC.1402.325), ensuring ethical research conduct with informed consent from all participants. The studies were conducted in accordance with the local legislation and institutional requirements.

References

1. Xie Y, Shi L, He X, Luo Y. Gastrointestinal cancers in China, the USA, and Europe. Gastroenterol Rep. 2021;9(2):91–104. https://doi.org/10.1093/gastro/goab010
2. Moradpour F, Gholami A, Salehi M, Mansori K, Maracy MR, Javanmardi S, et al. Incidence, prevalence, and mortality rate of gastrointestinal cancer in Isfahan, Iran: Application of the MIAMOD method. Asian Pacific J Cancer Prev. 2016;17(S3):11–5. https://doi.org/10.7314/apjcp.2016.17.s3.11.
3. Jahani MA, Esmaeili R, Abbasi M, Nikbakht HA, Azarbakhsh H, Roshandel G, et al. Burden of upper gastrointestinal cancers in the east of Golestan province (Golestan cohort study). Cancer Rep. 2024;7(3):1–8. https://doi.org/10.1002/cnr2.2001.
4. Nikbakht HA, Sahraian S, Ghaem H, Javadi A, Janfada M, Hassanipour S, et al. Trends in Mortality Rates for Gastrointestinal Cancers in Fars Province, Iran (2005–2015). J Gastrointest Cancer. 2020;51(1):63–9. https://doi.org/10.1007/s12029-019-00204-1
5. Shadmani FK, Farzadfar F, Yoosefi M, Mansori K, Shadman RK, Haghdoost A. Premature mortality of gastrointestinal cancer in Iran : trends and projections 2001 – 2030. 2020;20(1):752. https://doi.org/10.1186/s12885-020-07132-5
6. Somi MH, Golzari M, Farhang S, Naghashi S, Abdollahi L. Gastrointestinal cancer incidence in east Azerbaijan, Iran: Update on 5 year incidence and trends. Asian Pacific J Cancer Prev. 2014;15(9):3945–9. https://doi.org/10.7314/apjcp.2014.15.9.3945
7. Xu L, Guo C, Liu M. A weighted distance-based dynamic ensemble regression framework for gastric cancer survival time prediction. Artif Intell Med. 2024;147:102740. https://doi.org/10.1016/j.artmed.2023.102740
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457-81.
9. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41–55. https://doi.org/10.1093/biomet/70.1.41
10. J Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an aids clinical trial with inverse probability of censoring weighted (ipcw) log-rank tests. Biometrics. 2000;56(3):779-88. https://doi.org/10.1111/j.0006-341x.2000.00779.x
11. Porter KE. The Relative Performance of Targeted Maximum Likelihood Estimators Under Violations of the Positivity Assumption. Int J Biostat. 2011;7(1):31. https://doi.org/10.2202/1557-4679.1308
12. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004;75(1):45–9. https://doi.org/10.1016/j.cmpb.2003.10.004
13. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med. 2005;24(20):3089–110. https://doi.org/10.1002/sim.2174
14. Robbins JM. A new approach to causal inference in mortality studies with extended exposure periods: application to control the health worker survivor effect. Math Mod. 1986;7:1393-512.
15. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. J Am Stat Assoc. 1994;89(427):846-66. https://doi.org/10.1080/01621459.1994.10476818
16. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: A comparative study. Stat Med. 2004;23(19):2937-60. https://doi.org/10.1002/sim.1903
17. Kang JD, Schafer JL. Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data. Stat Sci. 2007;22(4):523–39.
18. Wang J. A simple, doubly robust, efficient estimator for survival functions using pseudo observations. Pharm Stat. 2018;17(1):38-48. https://doi.org/10.1002/pst.1834
19. Graw F, Gerds TA, Schumacher M. On pseudo-values for regression analysis in competing risks models. Lifetime Data Anal. 2009;15(2):241-55. https://doi.org/10.1007/s10985-008-9107-z
20. Per K Andersen 1, Elisavet Syriopoulou 1 2 ETP. Causal inference in survival analysis using pseudo-observations. Stat Med. 2017;36(17):2669–81. https://doi.org/10.1002/sim.7297
21. Arterburn DE, Olsen MK, Smith VA, Livingston EH, Van Scoyoc L, Yancy Jr WS, et al. Association Between Bariatric Surgery and Long-term Survival. JAMA. 2015;313(1):62–70. https://doi.org/10.1001/jama.2014.16968
22. Güller U, Tarantino I, Cerny T, Schmied BM, Warschkow R. Population-based seer trend analysis of overall and cancer-specific survival in 5138 patients with gastrointestinal stromal tumor. BMC Cancer. 2015;15:557. https://doi.org/10.1186/s12885-015-1554-9
23. Rodríguez-Camacho E, Pita-Fernández S, Pértega-Díaz S, López-Calviño B SPT. Clinical-pathological characteristics and prognosis of a cohort of oesophageal cancer patients: a competing risks survival analysis. J Epidemiol. 2015;25(3):231–8. https://doi.org/10.2188/jea.JE20140118
24. Aghcheli K, Marjani HA, Nasrollahzadeh D, Islami F, Shakeri R, Sotoudeh M, et al. Prognostic factors for esophageal squamous cell carcinoma--a population-based study in golestan province, iran, a high incidence area. PLoS One. 2011;6(7):e22152. https://doi.org/10.1371/journal.pone.0022152
25. Yang D, Hendifar A, Lenz C, Togawa K, Lenz F, Lurje G, et al. Survival of metastatic gastric cancer : Significance of age , sex and race / ethnicity. J Gastrointest Oncol. 2011;2(2):77-84. https://doi.org/10.3978/j.issn.2078-6891.2010.025.
26. Dixon M, Mahar AL, Helyer LK, Vasilevska-Ristovska J, Law C, Coburn NG. Prognostic factors in metastatic gastric cancer: Results of a population-based, retrospective cohort study in ontario. Gastric Cancer. 2016;19(1):150-9. https://doi.org/10.1007/s10120-014-0442-3
27. McMillan MT, Ojerholm E, Roses RE, Plastaras JP, Metz JM, Mamtani R, et al. Adjuvant radiation therapy treatment time impacts overall survival in gastric cancer. IInt J Radiat Oncol Biol Phys. 2015;93(2):326-36. https://doi.org/10.1016/j.ijrobp.2015.05.025
28. Han K, Jung I. Restricted Mean Survival Time for Survival Analysis: A Quick Guide for Clinical Researchers. Korean

J Radiol. 2022;23(5):495–9. https://doi.org/10.3348/kjr.2022.0061
29. Brink C, Bernchou U, Bertelsen A, Hansen O, Schytte T, Hjelmborg JVB, et al. Causal relation between heart irradiation and survival of lung cancer patients after radiotherapy. Radiother Oncol. 2022;172:126-33. https://doi.org/10.1016/j.radonc.2022.05.002
30. Kasuga A, Hamamoto Y, Takeuchi A, Kawasaki K, Suzuki T, Hirata K, et al. Positive relationship between subsequent chemotherapy and overall survival in pancreatic cancer: meta-analysis of postprogression survival for first-line chemotherapy. Cancer Chemother Pharmacol. 2017;79(3):595–602. https://doi.org/10.1007/s00280-017-3263-3
31. Graf W, Påhlman L, Bergström R, Glimelius B. The relationship between an objective response to chemotherapy and survival in advanced colorectal cancer. Br J Cancer . 1994;70(3):559–63. https://doi.org/10.1038/bjc.1994.345
32. Smyth EC, Nilsson M, Grabsch HI, van Grieken NCT, Lordick F. Gastric cancer. Lancet. 2020;396(10251):635–48. https://doi.org/10.1016/S0140-6736(20)31288-5
33. A'Hern RP, Ebbs SR, Baum MB. Does chemotherapy improve survival in advanced breast cancer? A statistical overview. Br J Cancer. 1988;57(6):615–8. https://doi.org/10.1038/bjc.1988.140