BMC Cancer

RESEARCH ARTICLE

Open Access

Timing of adjuvant chemotherapy initiation and mortality among colon cancer patients at a safety-net health system

Yan Lu[1], Aaron W. Gehr[1], Rachel J. Meadows[1,2], Bassam Ghabach[3], Latha Neerukonda[3], Kalyani Narra[3] and Rohit P. Ojha[1,2*]

Abstract

Background: Prior studies reported survival benefits from early initiation of adjuvant chemotherapy for stage III colon cancer, but this evidence was derived from studies that may be sensitive to time-related biases. Therefore, we aimed to estimate the effect of initiating adjuvant chemotherapy ≤8 or ≤ 12 weeks on overall and disease-free survival among stage III colon cancer patients using a study design that helps address time-related biases.

Methods: We used institutional registry data from JPS Oncology and Infusion Center, a Comprehensive Community Cancer Program. Eligible patients were adults aged < 80 years, diagnosed with first primary stage III colon cancer between 2011 and 2017, and received surgical resection with curative intent. We emulated a target trial with sequential eligibility. We subsequently pooled the trials and estimated risk ratios (RRs) along with 95% confidence limits (CL) for all-cause mortality and recurrence or death at 5-years between initiators and non-initiators of adjuvant chemotherapy ≤8 or ≤ 12 weeks using pseudo-observations and a marginal structural model with stabilized inverse probability of treatment weights.

Results: Our study population comprised 222 (for assessing initiation ≤8 weeks) and 310 (for assessing initiation ≤12 weeks) observations, of whom the majority were racial/ethnic minorities (64–65%), or uninsured with or without enrollment in our hospital-based medical assistance program (68–71%). Initiation of adjuvant chemotherapy ≤8 weeks of surgical resection did not improve overall survival (RR for all-cause mortality = 1.04, 95% CL: 0.57, 1.92) or disease-free survival (RR for recurrence or death = 1.07, 95% CL: 0.61, 1.88). The results were similar for initiation of adjuvant chemotherapy ≤12 weeks of surgical resection.

Conclusions: Our results suggest that the overall and disease-free survival benefits of initiating adjuvant chemotherapy ≤8 or ≤ 12 weeks of surgical resection may be overestimated in prior studies, which may be attributable to time-related biases. Nevertheless, our estimates were imprecise and differences in population characteristics are an alternate explanation. Additional studies that address time-related biases are needed to clarify our findings.

Keywords: Adjuvant chemotherapy, Timing, colon cancer, Quality of care, Prognosis, Mortality, Disease-free survival

Introduction

Adjuvant chemotherapy following surgical resection of colon cancer is intended to eliminate micrometastatic disease and increase overall and disease-free survival [1]. Evidence from randomized controlled trials (RCTs) established that adjuvant chemotherapy increased

*Correspondence: rojha@jpshealth.org

[2] Department of Medical Education, TCU School of Medicine, 3430 Camp Bowie Blvd, Fort Worth, TX 76107, USA
Full list of author information is available at the end of the article

survival among stage III colon cancer patients, [2–4] and thus adjuvant chemotherapy for stage III colon cancer is standard of care. In addition, evidence suggests that early initiation of adjuvant chemotherapy may improve survival among colon cancer patients, [5–8] and timing of adjuvant chemotherapy initiation is included in quality of care guidelines [9, 10]. Nevertheless, the evidence for timing of adjuvant chemotherapy was derived from observational studies, which may be sensitive to time-related biases [11, 12].

In contrast to RCTs, where the design ensures alignment of key elements such as treatment allocation, eligibility, and follow-up at a common starting point (i.e., time zero) to minimize time-related biases, this alignment requires additional methodologic considerations in observational studies [11, 12]. For example, prior studies [5–8] included comparisons of survival between patients who initiated adjuvant chemotherapy ≤8 weeks and patients who initiated adjuvant chemotherapy >8 weeks following surgical resection. Such comparisons are problematic because patients must survive a specified duration before initiating treatment, and analyses that do not properly account for this duration will incur immortal time bias [11, 13–17]. Several studies have illustrated severe overestimation of treatment effects on survival in observational studies of cancer patients, which was attributable to immortal time bias [18–20]. Immortal time bias has not been addressed in the context of timing of adjuvant chemotherapy initiation for colon cancer survival and could have implications for current quality of care guidelines. Therefore, we aimed to estimate the effect of initiating adjuvant chemotherapy for stage III colon cancer within an interval of interest (8 or 12 weeks) following surgical resection on survival using a study design that helps align time zero and reduce immortal time bias.

Methods

Study population

We used institutional registry data from JPS Oncology and Infusion Center (JPS), an accredited Comprehensive Community Cancer Program. The center is part of an urban safety-net health system, which is the primary source of care for socioeconomically marginalized populations in Tarrant County, TX. Eligible patients were diagnosed with first primary stage III colon cancer between 2011 and 2017, aged 18–79 years at cancer diagnosis, received surgical resection with curative intent, and received at least part of the first course treatment at JPS. We excluded patients for whom adjuvant chemotherapy was contraindicated.

Variables

Our primary outcome of interest was 5-year overall survival (i.e., complement of all-cause mortality) and secondary outcome of interest was 5-year disease-free survival (i.e., complement of recurrence or mortality [21]). These outcomes were selected because adjuvant chemotherapy is intended to improve overall and disease-free survival [1]. In addition, the American Society of Clinical Oncology statement about clinically meaningful outcomes defines overall survival as the primary outcome of interest [22]. Our exposure (intervention) of interest was initiation of adjuvant chemotherapy within 8 or 12 weeks of surgical resection (i.e., initiators vs. non-initiators within 8 weeks in one analysis and initiators vs. non-initiators within 12 weeks in a separate analysis). We also extracted baseline information from the registry including age at diagnosis, sex, race/ethnicity, insurance coverage, marital status, comorbidities, body mass index, tumor grade, and surgical procedure.

Data analysis

We emulated a sequence of observational "trials," [11, 23–25] where study eligibility criteria were applied and intervention status was defined within a sequence of trials based on 2-week intervals through 8 or 12 weeks from surgical resection. One exception was that the interval for the first trial was 4 weeks because no one initiated adjuvant chemotherapy within 2 weeks of surgical resection. Baseline (i.e., time zero) for the first trial was the date of surgical resection. For the first trial, patients were classified as initiators if adjuvant chemotherapy was initiated ≤4 weeks (i.e., 28 days) of surgical resection, and as non-initiators if adjuvant chemotherapy was not initiated ≤4 weeks. We applied the eligibility criteria and initiator definition for sequential 2-week intervals, where time zero for each trial was the beginning of each interval. Consequently, patients could have been eligible for up to three trials for evaluating initiation ≤8 weeks and five trials for evaluating initiation ≤12 weeks of surgical resection but were no longer eligible for subsequent trials if adjuvant chemotherapy was initiated, the patient died, had recurrence (for disease-free survival), or were lost to follow-up in a previous trial.

We subsequently pooled data from all three (for evaluating initiation ≤8 weeks of surgical resection) or five trials (for evaluating initiation ≤12 weeks of surgical resection), which allowed for reducing variance [11, 23–25]. We fit a logistic regression model to compute stabilized inverse probability of treatment weights (IPTW) [26] for adjuvant chemotherapy initiation. Stabilized IPTW were based on a minimal sufficient set of covariates to reduce confounding bias identified using

the back-door criterion in a directed acyclic graph of dependency assumptions [27–29] between adjuvant chemotherapy initiation and mortality or recurrence. The minimal sufficient set of covariates included baseline measurements of age, sex (male or female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or non-Hispanic other), insurance coverage (uninsured without JPS Connection [a hospital-based medical assistance program for eligible individuals without insurance], uninsured with JPS Connection, or commercial/public insurance), marital status (single/never married, married, or divorced/separated/widowed), comorbidities classified by the National Cancer Institute [30] (0 or > 0), body mass index (BMI; BMI < 25, 25 ≤ BMI < 30, or BMI ≥ 30), tumor grade (well/moderately differentiated or poorly differentiated/undifferentiated), and surgical procedure (partial colectomy/segmental resection or hemicolectomy/subtotal/total colectomy). The standardized mean differences for covariates between initiators and non-initiators of adjuvant chemotherapy did not suggest meaningful imbalance after weighting except for one category of marital status in the 8-week analysis (Supplementary Table S1 and S2) [31].

We adjusted Kaplan-Meier estimators using stabilized IPTW [32] to generate marginal overall and disease-free survival for initiation and no initiation of adjuvant chemotherapy ≤8 or ≤ 12 weeks of surgical resection. For 5-year overall survival, patients were followed from date of surgical resection until death, loss to follow-up, or end of study, whichever occurred first. For 5-year disease-free survival, patients were followed from date of surgical resection until recurrence, death, loss to follow-up, or end of study, whichever occurred first. We also applied these weights in generalized linear models with pseudo-observations [33, 34] to construct marginal structural models [35] for estimating risk ratios (RR) for all-cause mortality and recurrence or death at 5 years comparing initiators and non-initiators of adjuvant chemotherapy ≤8 or ≤ 12 weeks of surgical resection. We estimated 95% confidence limits (CL) for RRs using clustered standard errors to account for repeated eligibility. Unlike Cox proportional hazard regression, the pseudo-observation approach does not require the proportional hazards assumption and allows estimating effect measures other than the hazard ratio, which is widely misinterpreted, has built-in selection bias, and no causal interpretation [36–40]. We estimated RR to provide a direct comparison of risk, which is easier to interpret than hazard [36, 38, 40].

Results

Our analyses were based on 222 evaluable observations after pooling 3 sequential trials for evaluating initiation ≤8 weeks and 310 evaluable observations after pooling 5 sequential trials for evaluating initiation ≤12 weeks of surgical resection. Table 1 summarizes the distribution of the baseline characteristics of these observations. The median age of the study population was 56 years (interquartile range [IQR]: 50–61), and the majority were female (56–57%), racial/ethnic minorities (64–65%), or uninsured with or without enrollment in our hospital-based medical assistance program (68–71%). Median time from diagnosis to surgical resection was 4 days (IQR: 1–28). Median time from surgical resection to adjuvant chemotherapy was 56 days (IQR: 46–78) for observations that initiated adjuvant chemotherapy in the 8-week analysis and 69 days (IQR: 51–86) for observations that initiated adjuvant chemotherapy in the 12-week analysis. For the 8-week analysis, 28% did not initiate adjuvant chemotherapy at any time, and for the 12-week analysis 34% did not initiate adjuvant chemotherapy at any time. The most common reason for not initiating adjuvant chemotherapy was patient refusal (71%). FOLFOX (including modified FOLFOX) was the most common adjuvant chemotherapy regimen (71–73%).

We observed 62 deaths and 57 recurrences within 5 years of surgical resection among observations in the 8-week analysis, and 84 deaths and 79 recurrences among observations in the 12-week analysis. Figures 1 and 2 illustrate the marginal overall and disease-free survival curves for initiators and non-initiators of adjuvant chemotherapy ≤8 or ≤ 12 weeks of surgical resection. The crude risk of all-cause mortality was 17% lower (RR = 0.83; 95% CL: 0.46, 1.51) and the crude risk of recurrence or mortality was 7% lower at 5 years (RR = 0.93; 95% CL: 0.55, 1.57) for patients who initiated adjuvant chemotherapy ≤8 weeks compared with patients who did not initiate adjuvant chemotherapy ≤8 weeks of surgical resection. The crude risk of all-cause mortality was 14% higher (RR = 1.14; 95% CL: 0.77, 1.68) and the crude risk of recurrence or mortality was 22% higher at 5 years (RR = 1.22; 95% CL: 0.85, 1.76) for patients who initiated adjuvant chemotherapy ≤12 weeks compared with patients who did not initiate adjuvant chemotherapy ≤12 weeks of surgical resection.

The adjusted risk (i.e., after weighting) of 5-year all-cause mortality was 4% higher for patients who initiated adjuvant chemotherapy ≤8 weeks compared with patients who did not initiate adjuvant chemotherapy ≤8 weeks of surgical resection, but our data were compatible with 43% lower risk or 92% higher risk of mortality (RR = 1.04, 95% CL: 0.57, 1.92). The adjusted risk of recurrence or mortality at 5 years was 7% higher for patients who initiated adjuvant chemotherapy ≤8 weeks compared with patients who did not initiate

Table 1 Characteristics of study populations with stage III colon cancer eligible for adjuvant chemotherapy following surgical resection

Characteristics	Study population for adjuvant chemotherapy initiation ≤ 8 weeks of surgical resection (*n* = 222) n (%)	Study population for adjuvant chemotherapy initiation ≤ 12 weeks of surgical resection (*n* = 310) n (%)
Age (years)		
Median (Interquartile range)	56 (50–61)	56 (50–61)
Sex		
Female	126 (57)	175 (56)
Male	96 (43)	135 (44)
Race/Ethnicity		
Non-Hispanic White	77 (35)	112 (36)
Non-Hispanic Black	67 (30)	87 (28)
Hispanic	57 (26)	87 (28)
Non-Hispanic other	21 (9.5)	24 (7.7)
Insurance coverage		
Uninsured without hospital-based medical assistance program	50 (23)	73 (24)
Uninsured with hospital-based medical assistance program	107 (48)	137 (44)
Insured[a]	65 (29)	100 (32)
Marital status		
Single	89 (40)	124 (40)
Married	70 (32)	99 (32)
Divorced/Separated/Widowed	63 (28)	87 (28)
Body Mass Index (BMI)		
BMI < 25	56 (25)	78 (25)
25 ≤ BMI < 30	59 (27)	87 (28)
BMI ≥ 30	107 (48)	145 (47)
NCI comorbidity index		
0	168 (76)	235 (76)
> 0	54 (24)	75 (24)
Tumor grade		
Well/Moderately differentiated	191 (86)	265 (85)
Poorly differentiated/Undifferentiated	31 (14)	45 (15)
Surgery procedure		
Partial colectomy/Segmental resection	106 (48)	143 (46)
Subtotal/Hemicolectomy/Total colectomy	116 (52)	167 (54)
Timing of adjuvant chemotherapy initiation		
Initiation ≤ 8 weeks of surgical resection	81 (36)	N/A
No initiation ≤ 8 weeks of surgical resection	141 (64)	N/A
Initiation ≤ 12 weeks of surgical resection	N/A	150 (48)
No initiation ≤ 12 weeks of surgical resection	N/A	160 (52)

[a] Commercial or public insurance

adjuvant chemotherapy ≤8 weeks of surgical resection, but our data were compatible with 39% lower risk or 88% higher risk of recurrence or mortality (RR = 1.07, 95% CL: 0.61, 1.88). The results were similar for initiation of adjuvant chemotherapy ≤12 weeks of surgical resection (Table 2).

Discussion

Our analysis aimed to align time zero and reduce immortal time bias, which were sources of error in prior studies about timing of adjuvant chemotherapy initiation for stage III colon cancer patients < 80 years. Our results suggest that the overall and disease-free survival benefits

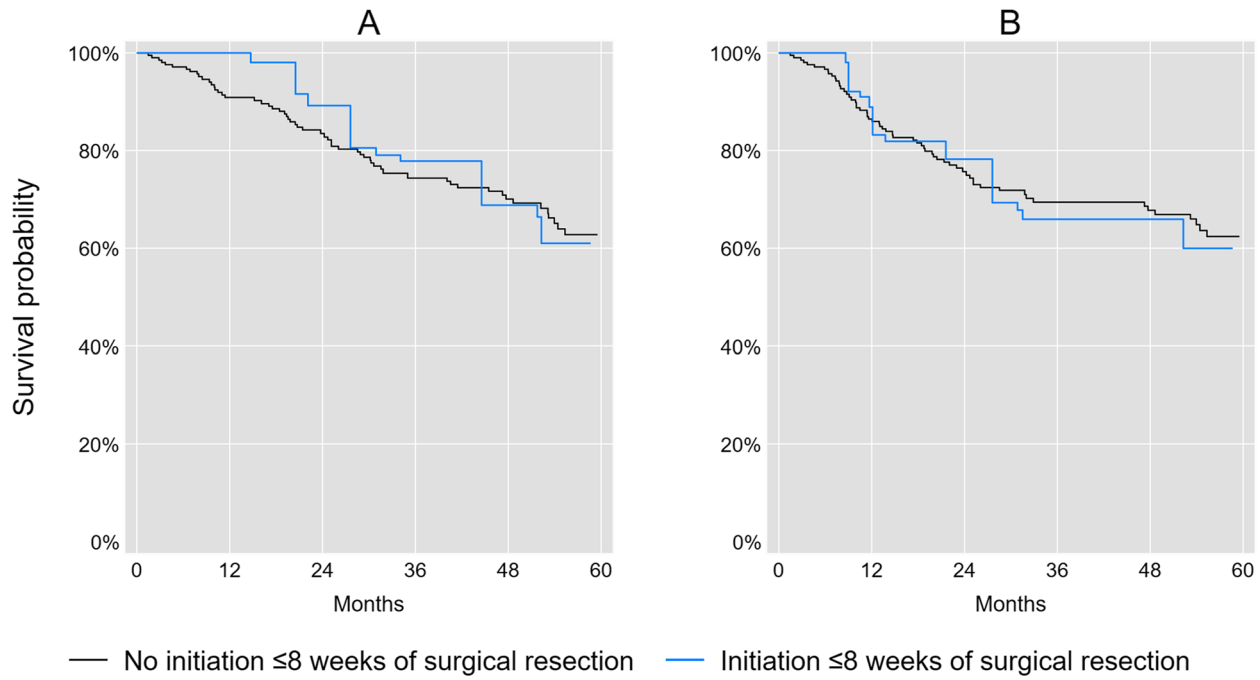

Fig. 1 Marginal survival curves[a] for initiation or no initiation of adjuvant chemotherapy ≤8 weeks of surgical resection for stage III colon cancer patients. **A** Overall survival. **B** Disease-free survival. (Adjusted for age, sex, race/ethnicity, insurance status, marital status, National Cancer Institue comorbidity index, body mass index, tumor grade, and surgical procedures)

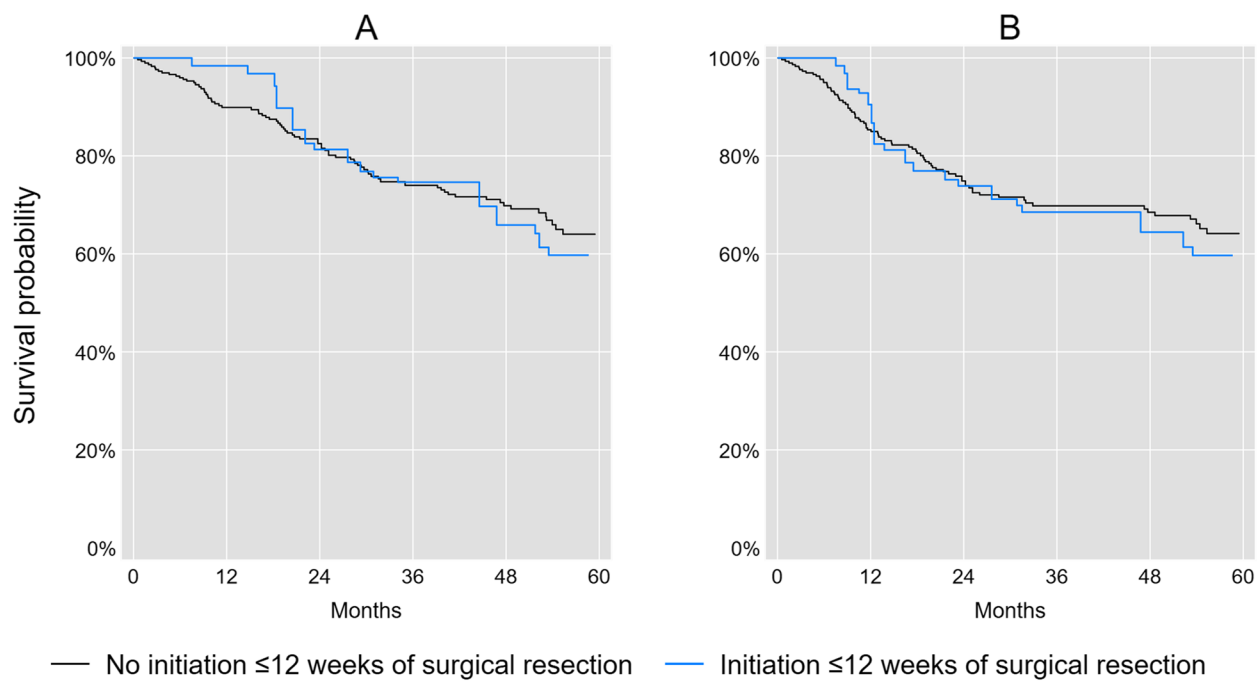

Fig. 2 Marginal survival curves[a] for initiation or no initiation of adjuvant chemotherapy ≤12 weeks of surgical resection for stage III colon cancer patients. **A** Overall survival. **B** Disease-free survival. (Adjusted for age, sex, race/ethnicity, insurance status, marital status, National Cancer Institue comorbidity index, body mass index, tumor grade, and surgical procedures)

Table 2 Risk ratios (RRs) for all-cause mortality and recurrence or mortality at 5-years between initiators and non-initiators of adjuvant chemotherapy ≤8 or ≤12 weeks of surgical resection for stage III colon cancer patients

	Crude RR (95% CL[a])	Adjusted RR (95% CL[a])
5-year mortality		
Initiation ≤8 weeks	0.83 (0.46, 1.51)	1.04 (0.57, 1.92)
Initiation ≤12 weeks	1.14 (0.77, 1.68)	1.11 (0.74, 1.67)
5-year recurrence or death		
Initiation ≤8 weeks	0.93 (0.55, 1.57)	1.07 (0.61, 1.88)
Initiation ≤12 weeks	1.22 (0.85, 1.76)	1.12 (0.76, 1.67)

[a] *CL* Confidence limits

of initiating adjuvant chemotherapy ≤8 or ≤12 weeks of surgical resection may be overestimated in prior studies. Nevertheless, our data were compatible with either meaningful benefit or harm of initiation within specified intervals. Imprecision and potential sources of error require further consideration when interpreting our results.

Imprecision in survival analysis is a function of number of events (i.e., death or recurrence in our analysis) and person-time. A larger sample size or longer follow-up (assuming more events) could provide more precise estimates, but our sample size was limited to available data. Precision is certainly important but only addresses random error. Quantification of effects with reduced systematic error (i.e., mitigated biases) is also critical. Our analysis prioritized mitigating key biases in prior studies that could mislead interpretation. Consequently, our estimates may be useful despite imprecision, [41, 42] particularly if estimates from multiple studies with similar approaches are summarized in a meta-analysis to improve precision [41].

As with any observational study, our estimates may be sensitive to violations of exchangeability [43, 44] (i.e., unmeasured confounding or selection bias). For example, data were unavailable to allow adjustment for frailty at diagnosis. Nevertheless, unmeasured confounding by frailty would create bias away from the null because we would expect an inverse relation between frailty and initiation of adjuvant chemotherapy ≤8 or ≤12 weeks of surgical resection (i.e., initiation may require additional time for frail patients) and frailty would increase mortality risk. Adjustment would thus move the estimate further toward the null [45]. In addition, the crude and adjusted 95% confidence limits for risk ratios were largely overlapping despite adjustment for multiple covariates, particularly for the more stable 12-week estimates. The lack of notable differences in crude and adjusted estimates suggests that confounding may not be as prominent of a concern once time zero is aligned, which is a phenomenon observed in prior studies that explored the effects of misaligned time zero [23, 46]. Lastly, survival could be affected by adherence to adjuvant chemotherapy [47, 48], but addressing adherence would change the question of interest and require a different study design [49]. Our study was designed to address the effect of initiating adjuvant chemotherapy, which is the question of interest relevant to quality of care guidelines and the basis of prior studies.

Our findings differ from prior studies [50–53], in which point estimates suggested 25–55% lower mortality hazards for initiation of adjuvant chemotherapy ≤8 weeks after surgical resection compared with later initiation or no initiation among colon cancer patients. Time-related biases [11, 12, 14, 15, 54] from misaligned start of eligibility, time of treatment assignment, and start of follow-up are a key consideration for effect heterogeneity between our study and prior studies. For example, immortal time bias is a concern in prior studies [50–53, 55] because follow-up time was measured from surgical resection, but adjuvant chemotherapy was initiated after follow-up time began. The consequence is misclassified person-time, where the time between start of follow-up and treatment initiation is considered "immortal." Several studies have reported substantial bias away from the null because of immortal time, [19, 20, 25, 56] and this bias can be more severe than unmeasured confounding [23, 46]. We used analytic methods to mitigate immortal time bias, [11, 57] which may partly explain why our point estimates are closer to the null than prior studies. In addition, prior studies [50–52] excluded patients who were eligible for but did not initiate adjuvant chemotherapy, which incurs selection bias [58]. Lastly, effect heterogeneity across studies may be related to clinical setting and population characteristics. For example, our study was conducted in a cancer center that provides care for socioeconomically marginalized populations. Our estimates may be closer to the null if adverse effects of social determinants of health override benefits of earlier treatment initiation [59, 60]. Consequently, our results may generalize to other safety-net settings but not necessarily academic cancer centers.

In summary, assuming no substantial effect of biases, our results suggest that initiating adjuvant chemotherapy ≤8 or ≤12 weeks of surgical resection for stage III colon cancer patients <80 years may not be as beneficial as reported in prior studies. Nevertheless, our results were imprecise and require confirmation. Future studies that also address time-related biases and have larger samples

or longer follow-up may provide greater precision. Alternatively, estimates from multiple similar studies may be combined in a meta-analysis to improve precision. Such evidence could be valuable considering that cancer care delivery organizations dedicate considerable resources to meet guidelines for timely care, but some guidelines may not be optimized for meaningful outcomes or for certain settings.

Abbreviations

RR: Risk ratio; CL: Confidence limits; RCT: Randomized controlled trials; BMI: Body mass index; IPTW: Inverse probability of treatment weights; IQR: Interquartile range.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-09688-w.

Additional file 1: Supplementary Table S1, S2.

Acknowledgements

Not applicable.

Authors' contributions

YL: investigation, formal analysis, data curation, visualization, writing – original draft, project administration. AWG: investigation, writing – review and editing. RJM: investigation, writing – review and editing. BG: investigation, writing – review and editing. LN: investigation, writing – review and editing. KN: investigation, writing – review and editing. RPO: conceptualization, investigation, methodology, formal analysis, supervision, writing – review and editing. All authors have read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The data analyzed for the current study are available on reasonable request to the corresponding author and review by the JPS Health Network External Data Governance Committee (research@jpshealth.org).

Declarations

Ethics approval and consent to participate

This study was approved by the North Texas Regional Institutional Review Board (IRB# 2017–19). Given the use of existing registry data, the need for informed consent was waived by the IRB.

Consent for publication

Not applicable.

Competing interests

The authors have no financial or non-financial competing interests to disclose.

Author details

[1]Center for Epidemiology & Healthcare Delivery Research, JPS Health Network, 1500 S. Main Street, Fort Worth, TX 76104, USA. [2]Department of Medical Education, TCU School of Medicine, 3430 Camp Bowie Blvd, Fort Worth, TX 76107, USA. [3]Oncology and Infusion Center, JPS Health Network, 1450 8th Ave, Fort Worth, TX 76104, USA.

Received: 31 October 2021 Accepted: 24 May 2022
Published online: 31 May 2022

References

1. Grávalos C, García-Escobar I, García-Alfonso P, Cassinello J, Malón D, Carrato A. Adjuvant chemotherapy for stages II, III and IV of colon cancer. Clin Transl Oncol. 2009;11(8):526–33.
2. Laurie JA, Moertel CG, Fleming TR, Wieand HS, Leigh JE, Rubin J, et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The north central Cancer treatment group and the Mayo Clinic. J Clin Oncol. 1989;7(10):1447–56.
3. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990;322(6):352–8.
4. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med. 1995;122(5):321–6.
5. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087.
6. Petrelli F, Zaniboni A, Ghidini A, Ghidini M, Turati L, Pizzo C, et al. Timing of adjuvant chemotherapy and survival in colorectal, gastric, and pancreatic cancer a systematic review and meta-analysis. Cancers (Basel). 2019;11(4):550.
7. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305(22):2335–42.
8. Des Guetz G, Nicolas P, Perret GY, Morere JF, Uzzan B. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer. 2010;46(6):1049–55.
9. National Quality Forum Cancer Fall 2019 Cycle Measures. https://www.qualityforum.org/ProjectMeasures.aspx?projectID=86163&cycleNo=2&cycleYear=2019.
10. American Society of Clinical Oncology. QOPI Certification Track 2021 Measures Summary. 2020. https://practice.asco.org/sites/default/files/drupalfiles/QOPI-2021-Round-1-Measure-Summary-QCP-Track.pdf. Accessed 28 Mar 2022.
11. Hernan MA, Sauer BC, Hernandez-Diaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70–5.
12. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2020;29(9):1101–10.
13. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167(4):492–9.
14. Lash TL, Cole SR. Immortal person-time in studies of cancer outcomes. J Clin Oncol. 2009;27(23):e55–6.
15. Hanley JA, Foster BJ. Avoiding blunders involving 'immortal time'. Int J Epidemiol. 2014;43(3):949–61.
16. Platt R, Hutcheon J, Suissa S. Immortal time Bias in epidemiology. Curr Epidemiol Rep. 2019;6(1):23–7.
17. Yadav K, Lewis RJ. Immortal time Bias in observational studies. JAMA. 2021;325(7):686–7.
18. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963–9.
19. Weberpals J, Jansen L, van Herk-Sukel MPP, Kuiper JG, Aarts MJ, Vissers PAJ, et al. Immortal time bias in pharmacoepidemiological studies on cancer patient survival: empirical illustration for beta-blocker use in four cancers with different prognosis. Eur J Epidemiol. 2017;32(11):1019–31.
20. Emilsson L, Garcia-Albeniz X, Logan RW, Caniglia EC, Kalager M, Hernan MA. Examining Bias in studies of statin treatment and survival in patients with Cancer. JAMA Oncol. 2018;4(1):63–70.
21. U.S. Food & drug administration: clinical trial endpoints for the approval of cancer drugs and biologics. 2018.
22. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American society of clinical oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32(12):1277–80.
23. Hernan MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008;19(6):766–79.

24. Gran JM, Roysland K, Wolbers M, Didelez V, Sterne JA, Ledergerber B, et al. A sequential cox approach for estimating the causal effect of treatment in the presence of time-dependent confounding applied to data from the Swiss HIV cohort study. Stat Med. 2010;29(26):2757–68.
25. Karim ME, Gustafson P, Petkau J, Tremlett H, Long-Term B. Adverse effects of Beta-interferon for multiple sclerosis study G: comparison of statistical approaches for dealing with immortal time Bias in drug effectiveness studies. Am J Epidemiol. 2016;184(4):325–35.
26. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656–64.
27. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37–48.
28. Pearl J. Causality: models, reasoning, and inference. 2nd ed. Cambridge: Cambridge University Press; 2009.
29. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. J Clin Epidemiol. 2022;142:264–7. https://doi.org/10.1016/j.jclinepi.2021.08.001. Epub 2021 Aug 8.
30. National Cancer Institute. NCI Comorbidity Index Overview. 2021. https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html. Accessed 28 Mar 2022.
31. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661–79.
32. 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.
33. Andersen PK, Perme MP. Pseudo-observations in survival analysis. Stat Methods Med Res. 2010;19(1):71–99.
34. Andersen PK, Syriopoulou E, Parner ET. Causal inference in survival analysis using pseudo-observations. Stat Med. 2017;36(17):2669–81.
35. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550–60.
36. Hernan MA. The hazards of hazard ratios. Epidemiology. 2010;21(1):13–5.
37. Aalen OO, Cook RJ, Roysland K. Does cox analysis of a randomized survival study yield a causal treatment effect? Lifetime Data Anal. 2015;21(4):579–93.
38. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med Res Methodol. 2013;13:152.
39. Sutradhar R, Austin PC. Relative rates not relative risks: addressing a widespread misinterpretation of hazard ratios. Ann Epidemiol. 2018;28(1):54–7.
40. Trinquart L, Bill-Axelson A, Rider JR. Restricted mean survival times to improve communication of evidence from Cancer randomized trials and observational studies. Eur Urol. 2019;76(2):137–9.
41. Hernán MA. Causal analyses of existing databases: no power calculations required. J Clin Epidemiol. 2022;144:203–5.
42. Smith AH, Bates MN. Confidence limit analyses should replace power calculations in the interpretation of epidemiologic studies. Epidemiology. 1992;3(5):449–52.
43. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. Int J Epidemiol. 1986;15(3):413–9.
44. Greenland S, Robins JM. Identifiability, exchangeability and confounding revisited. Epidemiol Perspect Innov. 2009;6:4.
45. Mehio-Sibai A, Feinleib M, Sibai TA, Armenian HK. A positive or a negative confounding variable? A simple teaching aid for clinicians and students. Ann Epidemiol. 2005;15(6):421–3.
46. Maringe C, Benitez Majano S, Exarchakou A, Smith M, Rachet B, Belot A, et al. Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. Int J Epidemiol. 2020;49(5):1719–29.
47. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of adjuvant chemotherapy for stage III Colon Cancer. N Engl J Med. 2018;378(13):1177–88.
48. Lieu C, Kennedy EB, Bergsland E, Berlin J, George TJ, Gill S, et al. Duration of Oxaliplatin-containing adjuvant therapy for stage III Colon Cancer: ASCO clinical practice guideline. J Clin Oncol. 2019;37(16):1436–47.
49. Hernan MA. How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ. 2018;360:k182.
50. Bayraktar UD, Chen E, Bayraktar S, Sands LR, Marchetti F, Montero AJ, et al. Does delay of adjuvant chemotherapy impact survival in patients with resected stage II and III colon adenocarcinoma? Cancer. 2011;117(11):2364–70.
51. Massarweh NN, Haynes AB, Chiang YJ, Chang GJ, You YN, Feig BW, et al. Adequacy of the National quality forum's Colon cancer adjuvant chemotherapy quality metric: is 4 months soon enough? Ann Surg. 2015;262(2):312–20.
52. Becerra AZ, Aquina CT, Mohile SG, Tejani MA, Schymura MJ, Boscoe FP, et al. Variation in delayed time to adjuvant chemotherapy and disease-specific survival in stage III Colon Cancer patients. Ann Surg Oncol. 2017;24(6):1610–7.
53. Turner MC, Farrow NE, Rhodin KE, Sun Z, Adam MA, Mantyh CR, et al. Delay in adjuvant chemotherapy and survival advantage in stage III Colon Cancer. J Am Coll Surg. 2018;226(4):670–8.
54. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf. 2007;16(3):241–9.
55. Zeig-Owens R, Gershman ST, Knowlton R, Jacobson JS. Survival and time interval from surgery to start of chemotherapy among colon cancer patients. J Registry Manag. 2009;36(2):30–41 quiz 61-32.
56. Cui Y, Wen W, Zheng T, Li H, Gao YT, Cai H, et al. Use of antihypertensive medications and survival rates for breast, colorectal, lung, or stomach Cancer. Am J Epidemiol. 2019;188(8):1512–28.
57. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016;183(8):758–64.
58. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;15(5):615–25.
59. Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the United States: a blueprint for practice, research, and policy. CA Cancer J Clin. 2020;70(1):31–46.
60. Lu Y, Gehr AW, Narra K, Lingam A, Ghabach B, Meadows RJ, Ojha RP. Impact of prognostic factor distributions on mortality disparities for socioeconomically disadvantaged cancer patients. Ann Epidemiol. 2022;65:31–7.

Publisher's Note