
**eFigure 1.** Flowchart Describing the Selection of Patients Who Received Neoadjuvant Chemotherapy and Radical Cystectomy Followed by Adjuvant Chemotherapy vs Observation for pT3/T4 and/or pN⁺ Urothelial Carcinoma of the Bladder in the National Cancer Data Base (2006-2012)

**eFigure 2.** Utilization of Adjuvant Chemotherapy vs Observation for Patients With pT3/T4 and/or pN⁺ Urothelial Carcinoma of the Bladder Who Received Neoadjuvant Chemotherapy and Radical Cystectomy

**eFigure 3.** Effect of Inverse Probability of Treatment Weighting Adjustment on the Baseline Characteristics Distribution of Patients Who Received Neoadjuvant Chemotherapy and Radical Cystectomy Followed by Adjuvant Chemotherapy vs Observation for pT3/T4 and/or pN⁺ Urothelial Carcinoma of the Bladder

**eFigure 4.** Kernel Density Plots Showing the Distribution of Propensity Scores in the Neoadjuvant Chemotherapy and Radical Cystectomy Followed by Adjuvant Chemotherapy vs Observation Groups Before (A) and After (B) Inverse Probability of Treatment Weighting Adjustment

**eAppendix.** Stata Codes for the National Cancer Data Base (2006-2012) Analysis of the Comparative Effectiveness of Adjuvant Chemotherapy vs Observation for Patients With Adverse Features at Radical Cystectomy Who Previously Received Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Carcinoma of the Bladder

This supplementary material has been provided by the authors to give readers additional information about their work.
**Figure 1.** Flowchart Describing the Selection of Patients Who Received Neoadjuvant Chemotherapy and Radical Cystectomy Followed by Adjuvant Chemotherapy vs Observation for pT3/T4 and/or pN+ Urothelial Carcinoma of the Bladder in the National Cancer Data Base (2006-2012)

UCB: urothelial carcinoma of the bladder; AC: adjuvant chemotherapy; NAC: neoadjuvant chemotherapy; RC: radical cystectomy
**eFigure 2.** Utilization of Adjuvant Chemotherapy vs Observation for Patients With pT3/T4 and/or pN+ Urothelial Carcinoma of the Bladder WhoReceived Neoadjuvant Chemotherapy and Radical Cystectomy
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**Covariates for population selection**

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eAppendix. Stata Codes for the National Cancer Database (2006-2012) Analysis of the Comparative Effectiveness of Adjuvant Chemotherapy vs Observation in Patients With Adverse Features at Radical Cystectomy Who Previously Received Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Carcinoma of the Bladder

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**Covariates for population selection**

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//Metastasis
destring TNM_CLIN_M, gen(metastasis)

//clinical T stage
encode TNM_CLIN_T, gen(clinT)
recode clinT (1 2 13 14=1 NMIBC) (3 4 5=2 cT2) (6 7 8=3 cT3) (9 10 11=4 cT4) (else=5 unknown), gen (ctstage)

//cN stage
encode TNM_CLIN_N, gen(clinN)
recode clinN (1=0 cN0) (2/4=1 cN1) (else=2 cNx), gen (cnstage)

//Histology
recode HISTOLOGY (8130 8120 = 1 urothelial) (8070 8071 8052 8051 8074 8072 8076 8073 8075 8084 = 2 squamous) (8041 8045 8044 = 3 smallcell) (8131 = 4 micropapillary)/* (8246 8013 = 5 neuroendocrine) (8490 = 6 signet-ring) (8122 8032 8980 8981 8318 8033 = 7 sarcomatoid) (8140 8480 8260 8310 8481 8255 8323 8574 8144 8261 8263 = 8 adenocarcinoma) */ (else = .), gen (histology1)
recode histology1 (1=0 urothelial) (2/8=1 non-urothelial) (else=2 unknown), gen (urothelial)

//pT stage
encode TNM_PATH_T, gen(pathT)
recode pathT (1 2 13 14=1 NMIBC) (3 4 5=2 pT2) (6 7 8=3 pT3) (9 10 11=4 pT4) (else=5 unknown), gen (ptstage)

//pN stage
encode TNM_PATH_N, gen(pathN)
recode pathN (1=0 pN0) (2/4=1 pN1) (else=2 pNx), gen (pnstage)

//pTN stage
gen ptnstage=.
replace ptnstage=0 if (ptstage==3 & pnstage==0)
replace ptnstage=1 if (ptstage==4 & pnstage==0)
replace ptnstage=2 if pnstage==1

//Chemotherapy
recode RX_SUMM_CHEMO (0 82 86 87=0 none) (1=1 unknown_agent) (2=2 single) (3=3 multiple) (else=.), gen (chemo)

//Radiation therapy
recode RX_SUMM_RADIATION (0=0 noradiation) (1/5=1 radiation) (else=.), gen (radiation_therapy)

//Surgery
recode RX_SUMM_SURG_PRIM_SITE (0=0 none) (50/80=1 cystectomy) (10 11 12 13 14 20 21 22 23 24 25 26 27=2 TURBT) (else=3 Other_unknown), gen(surgery)

//Surgical margins
recode RX_SUMM_SURGICAL_MARGINS (0=0 "Negative") (1 2 3 = 1 "Positive") (else=.), gen (margins)

***********************
**Population selection**
***********************

drop if YEAR_OF_DIAGNOSIS==2004 | YEAR_OF_DIAGNOSIS==2005 | YEAR_OF_DIAGNOSIS==2013
drop if urothelial!=0
drop if metastasis!=0 | cnstage!=0
drop if ctstage==1 | ctstage==5
drop if surgery!=1
drop if (radiation_therapy==. | radiation_therapy==1)
drop if ptnstage==. | ptnstage==5
drop if RX_SUMM_SYSTEMIC_SUR_SEQ==0
drop if RX_SUMM_SYSTEMIC_SUR_SEQ==3
| RX_SUMM_SYSTEMIC_SUR_SEQ==5 | RX_SUMM_SYSTEMIC_SUR_SEQ==6
| RX_SUMM_SYSTEMIC_SUR_SEQ==9 | RX_SUMM_SYSTEMIC_SUR_SEQ==. | RX_SUMM_SYSTEMIC_SUR_SEQ==.
drop if chemo!=3
drop if DX_LASTCONTACT_DEATH_MONTHS==0
| DX_LASTCONTACT_DEATH_MONTHS==
drop if (DX_LASTCONTACT_DEATH_MONTHS<=6 & PUF_VITAL_STATUS==0)

***********************
**Other Covariates**
***********************

//Race

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recode RACE (1=0 white) (2=1 Black) (3/98=2 Other) (else=.), gen (race_cat)

//CCI
recode CDCC_TOTAL (0=0 Zero) (1=1 One) (2=2 Two), gen (CCI)

//Insurance
recode INSURANCE_STATUS (1=0 Private) (2 4=1 Medicaid_other_gov) (3=2 Medicare) (0=3 Not_insured) (else=.), gen (insurance_cat)

//Incomes
recode MED_INC_QUAR_12 (4 3=0 High) (2 1=1 Low) (else=.), gen (income_cat)

//Education
recode NO_HSD_QUAR_12 (4 3=0 High) (2 1=1 Low) (else=.), gen (education_cat)

//County type
recode UR_CD_13 (1 2 3=0 Metro) (4 5 6 7=1 Urban) (8 9=2 Rural) (else=.), gen(county_cat)

//Distance
recode CROWFLY (min/12.4=0 first) (12.5/49.9=1 second) (50/max=2 third) (else=.), gen (dist)

//Facility type
recode FACILITY_TYPE_CD (3=0 Academic) (1 2 4=1 Non_Academic) (else=.), gen (facility_cat)

//Facility location
recode FACILITY_LOCATION_CD (1 2 3=0 Est) (4 5 6 7=1 Center) (8 9=2 West) (else=.), gen (location_cat)

*******************************************************************************
**Treatment variable**
*******************************************************************************
recode RX_SUMM_SYSTEMIC_SUR_SEQ (2=0 nac) (4=1 nacac), gen (seq)

*******************************************************************************
**Analyses**
*******************************************************************************
//Annual percent change
regress seq YEAR_OF_DIAGNOSIS

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//Multiple imputation
mi set flong
mi register imputed race_cat insurance_cat income_cat education_cat facility_cat location_cat county_cat margins
mi describe

set seed 29390

mi impute chained (logit) facility_cat margins (mlogit) race_cat insurance_cat location_cat county_cat (ologit) income_cat education_cat = c.AGE i.SEX i.CCI i.ptnstage i.PUF_VITAL_STATUS c.DX_LASTCONTACT_DEATH_MONTHS c.Intime, add (15) replace augment noisily

mi xeq: tab seq

save NACAC_imputed_15, replace

//IPTW
use NACAC_imputed_15.dta, clear

mi xeq: logit seq; predict ps0 , pr

mi xeq: logit seq c.AGE c.YEAR_OF_DIAGNOSIS i.SEX i.race_cat i.CCI i.insurance_cat i.income_cat i.education_cat i.county_cat i.facility_cat i.location_cat i.ptnstage i.margins; predict ps1 , pr

mi xeq: gen ipw= seq*(ps0/ps1) + ((1-seq)*((1-ps0)/(1-ps1)))

mi estimate, eform: logit seq c.AGE c.YEAR_OF_DIAGNOSIS i.SEX i.race_cat i.CCI i.insurance_cat i.income_cat i.education_cat i.county_cat i.facility_cat i.location_cat i.ptnstage i.margins

save NACAC_imputed_15_ipw, replace

//Median follow-up
use NACAC_unimputed, clear
stset DX_LASTCONTACT_DEATH_MONTHS [iw=ipw15], failure(PUF_VITAL_STATUS==1) scale(1)
stsum
stsum,by(seq)
sts test seq

//Baseline unweighted and weighted characteristics
use NACAC_imputed_15_ipw, clear
mi extract 1
tempfile d0

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save `d0', replace

forvalues i=2/15 {
    use NACAC_imputed_15_ipw, clear
    mi extract `i'
    tempfile d`i'
    save `d`i'', replace

    use `d0', clear
    append using `d`i''
    save `d0', replace
}

gen n = 1/15
gen ipw15 = ipw/15
save NACAC_unimputed, replace

sum AGE [aw=n], detail
sum AGE if seq==0 [aw=n], detail
sum AGE if seq==1 [aw=n], detail
tab age_cat seq [iw=n], col
tab YEAR_OF_DIAGNOSIS seq [iw=n], col
tab SEX seq [iw=n], col
tab race_cat seq [iw=n], col
tab CCI seq [iw=n], col
tab insurance_cat seq [iw=n], col
tab income_cat seq [iw=n], col
tab education_cat seq [iw=n], col
tab facility_cat seq [iw=n], col
tab location_cat seq [iw=n], col
tab county_cat seq [iw=n], col
tab ptnstage seq [iw=n], col
tab margins seq [iw=n], col

sum AGE [aw=ipw15], detail
sum AGE if seq==0 [aw=ipw15], detail
sum AGE if seq==1 [aw=ipw15], detail
tab age_cat seq [iw=ipw15], col
tab YEAR_OF_DIAGNOSIS seq [iw=ipw15], col
tab SEX seq [iw=ipw15], col
tab race_cat seq [iw=ipw15], col
tab CCI seq [iw=ipw15], col
tab insurance_cat seq [iw=ipw15], col
tab income_cat seq [iw=ipw15], col
tab education_cat seq [iw=ipw15], col
tab facility_cat seq [iw=ipw15], col

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tab location_cat seq [iw=ipw15], col
tab county_cat seq [iw=ipw15], col
tab ptnstage seq [iw=ipw15], col
tab margins seq [iw=ipw15], col

pbalchk seq AGE SEX race_cat CCI insurance_cat income_cat education_cat county_cat facility_cat location_cat YEAR_OF_DIAGNOSIS ptnstage margins, wt(n)
pbalchk seq AGE SEX race_cat CCI insurance_cat income_cat education_cat county_cat facility_cat location_cat YEAR_OF_DIAGNOSIS ptnstage margins, wt(ipw15) graph

//Kernel Density plot
***>Unweighted
use NACAC_unimputed, clear
tempvar fw
gen `fw' = round((n*1000),1)
twoway (kdensity ps1 if seq==0 [fw=`fw'], bw(0.02) lpattern(solid) lwidth(medthick) lc("0 64 115")) (kdensity ps1 if seq==1 [fw=`fw'], bw(0.02) lpattern(solid) lwidth(medthick) lc("220 169 31")), xtitle("Propensity Score", size (medlarge)) xlabel(0 "0" .2 "0.2" .4 "0.4" .6 "0.6" .8 "0.8") ytitle("Kernel Density", size (medlarge)) ylabel(0 "0" 1 "1" 2 "2" 3 "3" 4 "4", angle (horizontal)) legend(order (2 1) label(1 "Observation") label(2 "Adjuvant chemotherapy") cols (1)) legend(pos(2) ring(0)) graphregion(fcolor(white))

***>weighted
tempvar fw
gen `fw' = round((ipw*1000),1)
twoway (kdensity ps1 if seq==0 [fw=`fw'], bw(0.02) lpattern(solid) lwidth(medthick) lc("0 64 115")) (kdensity ps1 if seq==1 [fw=`fw'], bw(0.02) lpattern(solid) lwidth(medthick) lc("220 169 31")), xtitle("Propensity Score", size (medlarge)) xlabel(0 "0" .2 "0.2" .4 "0.4" .6 "0.6" .8 "0.8") ytitle("Kernel Density", size (medlarge)) ylabel(0 "0" 1 "1" 2 "2" 3 "3" 4 "4", angle (horizontal)) legend(order (2 1) label(1 "Observation") label(2 "Adjuvant chemotherapy") cols (1)) legend(pos(2) ring(0)) graphregion(fcolor(white))

//IPTW-adjusted Kaplan-Meier curves
use NACAC_imputed_15_ipw, clear
tempfile d0
save `d0', replace
qui{
    set more off
    forvalues i = 1/15 {
        tempfile d`i'
        use `d0', clear
        mi extract `i'
    }
}
```
stset DX_LASTCONTACT_DEATH_MONTHS [iw=ipw],
failure(PUF_VITAL_STATUS==0) scale(1)
sts graph if seq==0, outfile(`d`i''_0, replace)
sts graph if seq==1, outfile(`d`i''_1, replace)
use NACAC_imputed_15_ipw, clear
append using `d`i''_0, gen(seq_0)
append using `d`i''_1, gen(seq_1)
save avg_km, replace

} }

use avg_km, clear
gen _seq = cond(seq_0==1, 0 , cond(seq_1==1,1,.))
collapse (mean) survival , by(_t _seq)
sort _t
twoway scatter survival _t if _seq==0 & _t<=85 , c(stairstep) ms(i) lwidth(medthick)
lcolor("0 64 115") || scatter survival _t if _seq==1 & _t<=85, c(stairstep) ms(i)
lwidth(medthick) lcolor("220 169 31") xtitle("Time, months", size (medlarge))
xlabel(0(12)84) xmtick(0(3)84) ytitle("Overall Survival, %", size (medlarge))
ylabel(0 "0" .2 "20" .4 "40" .6 "60" .8 "80" 1 "100", angle(horizontal)) ymtick(0(.05)1)
legend(order(2 1) label(1 "Observation") label(2 "Adjuvant chemotherapy") cols(1))
legend(pos(2) ring(0)) graphregion(fcolor(white))

//IPTW-adjusted Cox model
use NACAC_imputed_15_ipw, clear
mi stset DX_LASTCONTACT_DEATH_MONTHS, failure(PUF_VITAL_STATUS==0) scale(1)
mi svyset [iw=ipw],
mi estimate, eform post: svy: stcox seq

//Power calculation
stpower logrank 0.2, n(788) hratio (0.78) nratio (0.7)

//Interaction terms
mi estimate, eform post: svy: stcox i.seq##c.AGE
mi estimate, eform post: svy: stcox i.seq##i.SEX
mi estimate, eform post: svy: stcox i.seq##c.CCI
mi xeq: recode ptnstage (0 1=0 pN0) (2=1 pN+), gen (ptnstage2)
mi estimate, eform post: svy: stcox i.seq##i.ptnstage2
mi estimate, eform post: svy: stcox i.seq##i.margins

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```