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Clinical-Bladder cancer

Propensity-matched analysis of stage-specific efficacy of adjuvant chemotherapy for bladder cancer

Felix V. Chen, MD[a], Tulay Koru-Sengul, PhD[b,c], Feng Miao, MS[c], Joshua S. Jue, MD[a], Mahmoud Alameddine, MD[a], Devina J. Dave, MD[b], Sanoj Punnen, MD, MS[a,c], Dipen J. Parekh, MD[a,c], Chad R. Ritch, MD, MBA[a,c], Mark L. Gonzalgo, MD, PhD[a,c,*]

[a] *Department of Urology, University of Miami Miller School of Medicine, Miami, FL*
[b] *Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL*
[c] *Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL*

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Abstract

Background: Contemporary randomized controlled trials exploring adjuvant chemotherapy (AC) for bladder cancer (BCa) have yielded inconsistent results due to premature termination and/or poor patient accrual.

Objective: To compare efficacy of AC vs. observation after radical cystectomy stratified by disease stage in a propensity-matched cohort.

Design, setting, and participants: We performed a retrospective study that included patients who underwent radical cystectomy for any pT, N0-1, M0 BCa from the National Cancer Data Base (2004−2014). Patients who underwent AC were 1:1 propensity matched with patients who received observation only.

Outcome measurements and statistical analysis: Overall survival was assessed with multivariable Cox regression models where adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) were calculated.

Results and limitations: After coarsened exact 1:1 propensity matching, 3,066 patients (AC 1,533; observation 1,533) were included in the analysis. There were no significant differences in patient-, facility-, or tumor-level characteristics among cohorts. Compared with patients who underwent observation, recipients of AC had improved overall survival (aHR 0.67; 95% CI 0.61−0.74). Patients with pT2-4, pN1 disease significantly benefited from AC. Among the pN0 cohort, improved survival from AC was observed only in stages pT3 (aHR 0.67; 95% CI 0.55−0.83) and pT4 (aHR 0.70; 95% CI 0.50−0.98).

Conclusions: AC was associated with improved survival in locally advanced (pT3-4, pN0) and regionally advanced (pT2-4, pN1) chemotherapy-naive BCa. © 2019 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Adjuvant chemotherapy; Perioperative chemotherapy; National Cancer Data Base

1. Introduction

Bladder cancer (BCa) is a leading cause of cancer-related mortality, and accumulates nearly 180,000 new diagnoses per year in the United States and European Union alone [1]. Over 25% of these diagnoses demonstrate evidence of muscle-invasive disease on initial presentation, which is often treated with immediate radical cystectomy (RC). Despite the potentially curative nature of this surgery, nearly half of patients develop metastatic recurrence and die from BCa [2−4]. Significant effort has been devoted to improving outcomes of RC by integrating perioperative chemotherapy into a multimodal treatment protocol. While neoadjuvant chemotherapy has consistently demonstrated level-1 evidence supporting its use, its adoption into practice has only recently begun to rise [5,6]. Conversely, despite the role of adjuvant chemotherapy (AC) in locally advanced BCa remaining controversial, these same studies have revealed that AC is implemented more frequently.

Randomized controlled trials (RCTs) have explored the effect of AC in locally advanced and/or pelvic lymph

*Corresponding author. Tel.: (305) 243-3246; fax: (305) 243-6597.
E-mail address: m.gonzalgo@miami.edu (M.L. Gonzalgo).

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node-positive BCa [7–14]. Unfortunately, none of these studies have definitively shown a survival benefit with AC use due to significant limitations in patient accrual in all contemporary studies [11–14]. A recently updated meta-analysis of 9 RCTs reports a risk reduction in overall mortality (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.55–0.99) and disease-specific mortality (HR 0.66; 95% CI 0.45–0.91). However, these findings are accompanied with concern over their generalizability due to low trial accrual [15]. As such, the National Comprehensive Cancer Network (NCCN) currently classifies AC in patients with high-risk pathology as a category 2A recommendation [16].

Observational investigations have attempted to supplement the existing prospective evidence surrounding the use of AC for muscle-invasive BCa. In this study, we performed a coarsened exact propensity-matched analysis of the efficacy of AC by stage of BCa. Based on the available evidence, we hypothesized that RC + AC would reduce the risk of overall mortality in locally advanced (pT3-4, pN0) and regionally advanced (pT2-4, pN1) disease compared to RC alone.

2. Patients and methods

2.1. Data source

The National Cancer Data Base (NCDB) is a hospital-based, comprehensive clinical surveillance oncology dataset that encompasses 70% of all cancer diagnoses across the United States. The database includes information on patient demographics, insurance status, comorbidity status, disease stage, and disease treatment compiled from patient records and death registries. Patient disease course and therapy are recorded according to the American College of Surgeons' Facility Oncology Registry Data Standards. This study was exempt from institutional review board approval since only deidentified patient information is used. No financial support or grant funding was received to conduct this research.

2.2. Study population

We included patients diagnosed from 2004 to 2014 with urothelial cell carcinoma of the bladder who

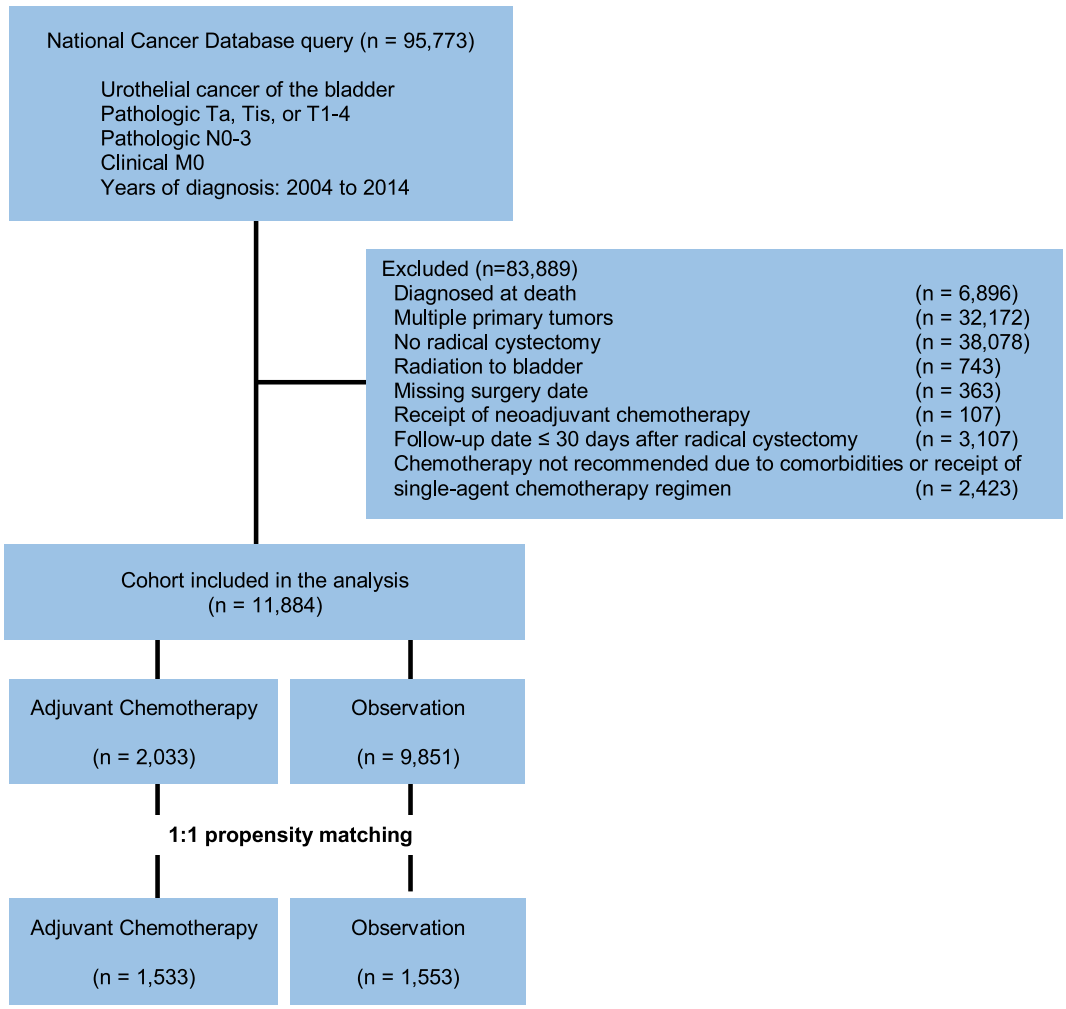

Fig. 1. Study cohort flow diagram.

Table 1
Comparison of baseline variables between AC and observation groups in the original and matched data sets

	Original data set							Matched data set				
	All patients		AC		Observation		*P*value	AC		Observation		*P* value
All	11,884	(100.0)	2,033	(17.1)	9,851	(82.9)		1,533	(50.0)	1,533	(50.0)	
Age at diagnosis							<0.0001					0.4467
17< to 64	4,884	(41.1)	1,096	(53.9)	3,788	(38.5)		717	(46.8)	696	(45.4)	
64< to high	7,000	(58.9)	937	(46.1)	6,063	(61.5)		816	(53.2)	837	(54.6)	
Mean	66.4		62.9		67.2		<0.0001	64.7		65.2		0.1535
SD	10.7		10		10.7			9.2		9.5		
Median	67		63		68			65		66		
Range	22-90		22-88		27-90			34-88		35-86		
Sex							0.4534					1.0000
Female	3,637	(30.6)	608	(29.9)	3,029	(30.7)		428	(27.9)	428	(27.9)	
Male	8,247	(69.4)	1,425	(70.1)	6,822	(69.3)		1,105	(72.1)	1,105	(72.1)	
Race							0.4713					0.9496
White	10,740	(90.4)	1,847	(90.9)	8,893	(90.3)		1,458	(95.1)	1,456	(95.0)	
Black	721	(6.1)	121	(6.0)	600	(6.1)		45	(2.9)	47	(3.1)	
Other	277	(2.3)	40	(2.0)	237	(2.4)		9	(0.6)	8	(0.5)	
Unknown	146	(1.2)	25	(1.2)	121	(1.2)		21	(1.4)	22	(1.4)	
Hispanic							0.5298					0.8466
No	10,755	(90.5)	1,825	(89.8)	8,930	(90.7)		1,397	(91.1)	1,411	(92.0)	
Yes	326	(2.7)	51	(2.5)	275	(2.8)		19	(1.2)	18	(1.2)	
Unknown	803	(6.8)	157	(7.7)	646	(6.6)		117	(7.6)	104	(6.8)	
Primary payer							<0.0001					1.0000
Private insurance	4,154	(35.0)	900	(44.3)	3,254	(33.0)		672	(43.8)	672	(43.8)	
Medicaid/other government	673	(5.7)	141	(6.9)	532	(5.4)		47	(3.1)	47	(3.1)	
Medicare	6,381	(53.7)	876	(43.1)	5,505	(55.9)		773	(50.4)	773	(50.4)	
No insurance	418	(3.5)	80	(3.9)	338	(3.4)		32	(2.1)	32	(2.1)	
Unknown status	258	(2.2)	36	(1.8)	222	(2.3)		9	(0.6)	9	(0.6)	
Academic/research program							<0.0001					1.0000
Yes	5,748	(48.4)	848	(41.7)	4,900	(49.7)		658	(42.9)	658	(42.9)	
No	6,136	(51.6)	1,185	(58.3)	4,951	(50.3)		875	(57.1)	875	(57.1)	
Comorbidity							<0.0001					1.0000
No	8,455	(71.1)	1,522	(74.9)	6,933	(70.4)		1,164	(75.9)	1,164	(75.9)	
Yes	3,429	(28.9)	511	(25.1)	2,918	(29.6)		369	(24.1)	369	(24.1)	
Pathological T Stage							<0.0001					1.0000
NMIBC	1,893	(15.9)	36	(1.8)	1,857	(18.9)		20	(1.3)	20	(1.3)	
2	4,035	(34.0)	331	(16.3)	3,704	(37.6)		233	(15.2)	233	(15.2)	
3	4,384	(36.9)	1,166	(57.4)	3,218	(32.7)		932	(60.8)	932	(60.8)	
4	1,572	(13.2)	500	(24.6)	1,072	(10.9)		348	(22.7)	348	(22.7)	
Pathological N stage							<0.0001					1.0000
Negative	8,709	(73.3)	661	(32.5)	8,048	(81.7)		579	(37.8)	579	(37.8)	
Positive	3,175	(26.7)	1,372	(68.5)	1,803	(18.3)		954	(62.2)	954	(62.2)	
Surgical margins status							<0.0001					1.0000
Negative	10,862	(91.4)	1,714	(84.3)	9,148	(92.9)		1,346	(87.8)	1,346	(87.8)	
Positive	1,022	(8.6)	319	(15.7)	703	(7.1)		187	(12.2)	187	(12.2)	

AC = adjuvant chemotherapy; SD = standard deviation; NMIBC = nonmuscle invasive bladder cancer.
Data are given as no. (%) unless otherwise noted.

underwent RC. Only BCa patients with pathologic stage Ta/Tis/T1-4, N0-1, M0 disease were included. Patients diagnosed at death or autopsy, died within 30 days of cystectomy, or receipt of single-agent chemotherapy, or any radiation were excluded from the patient population. Patients who received neoadjuvant chemotherapy or with missing data regarding the timing or administration of chemotherapy were also excluded. Receipt of neoadjuvant chemotherapy was defined by receipt of any chemotherapy prior to RC. The AC cohort was defined by receipt of multiagent chemotherapy within 90 days after RC.

2.3. Patient characteristics

Demographic and clinical characteristics such as age at diagnosis, sex, race, ethnicity, insurance status, treatment at an academic/research program, comorbidity, pT stage, and surgical margin status were recorded. Race and academic/research program were defined by the NCDB. A

comorbidity status was derived from the NCDB Deyo-Charlson comorbidity score to increase the number of propensity-matched patients. A comorbidity status of "no" indicates a Deyo-Charlson comorbidity score of 0, while "yes" consists of comorbidity scores ≥1. Pathologic stage was determined using the American Joint Committee on Cancer Staging Manual edition in use at the time of diagnosis. Baseline characteristics between AC and observation cohorts were compared by the number and percentage of patients in each category using the chi-square test. Patients in the AC cohort were coarsened exact propensity matched to patients in the observation cohort on a 1:1 basis, based on the previously described demographic and clinical characteristics. The final matched cohorts were used for the remainder of our analyses.

2.4. Statistical analyses

Unadjusted and adjusted HR, 95% CI, and *P*values were calculated from fitting univariable and multivariable Cox proportional hazard regression models to compare overall survival (OS) between the AC and observation cohorts. All patient demographic and clinical characteristics included in propensity matching were included as variables in the hazard regression models. The HR for age at diagnosis was calculated as risk per year increase. OS was defined as the elapsed time between diagnosis and death or last follow-up for living patients. Subanalyses within each cohort were conducted in a similar manner to identify significant predictors of worse OS for patients undergoing RC + AC and RC alone, respectively. Forest plots encompassing data from the cohort-specific multivariable Cox proportional hazard regression models were created to compare the stage-specific efficacy of RC + AC and RC alone. Type-I error rate was set to 5%, where *P*values <0.05 were considered statistically significant. All statistical analyses were performed using SAS v9.4 statistical software for Windows (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient characteristics

A total of 2,033 patients met criteria for the AC cohort and 9,851 patients for the observation cohort (Fig. 1). The majority of patients within each group were white males treated at nonacademic/research institutions. Patients receiving AC most commonly had private insurance, while those receiving only RC most commonly had Medicare. There were also significantly more patients treated at nonacademic programs with higher stages of disease and positive surgical margin rates in the AC group compared to the observation group (*P*< 0.0001). After propensity matching, a total of 1,533 patients were present in each cohort, with no significant differences between the 2 cohorts (Table 1).

Table 2
Multivariate Cox regression analysis for overall survival in the matched data set

Prognostic factors	Adj. HR (95% CI)	*P* value
Chemotherapy		
Observation	Ref	
Adjuvant chemotherapy	0.67 (0.61−0.74)	<0.001
Age at diagnosis		
Per year increase	1.01 (1.01−1.02)	<0.001
Sex		
Male	Ref	
Female	1.00 (0.90−1.11)	0.967
Race		
White	Ref	
Black	1.24 (0.95−1.63)	0.114
Other	0.73 (0.37−1.43)	0.352
Unknown	0.66 (0.44−1.01)	0.057
Hispanic		
No	Ref	
Yes	0.99 (0.66−1.47)	0.943
Unknown	0.98 (0.82−1.16)	0.783
Insurance		
Private insurance	Ref	
Medicaid/other government	1.41 (1.07−1.87)	0.016
Medicare	1.06 (0.93−1.21)	0.365
No Insurance	1.19 (0.89−1.59)	0.235
Unknown status	0.74 (0.39−1.38)	0.342
Academic/research program		
Yes	Ref	
No	1.13 (1.03, 1.24)	0.010
Comorbidity		
No	Ref	
Yes	1.25 (1.13−1.39)	<0.001
Pathological T stage		
2	Ref	
Ta/Tis/T1	0.76 (0.47−1.21)	0.247
3	1.84 (1.59−2.13)	<0.001
4	2.75 (2.33−3.25)	<0.001
Pathological N stage		
Negative	Ref	
Positive	2.03 (1.83−2.24)	<0.001
Surgical margins status		
Negative	Ref	
Positive	1.47 (1.27−1.69)	<0.001

Ref = reference group; Adj. HR = adjusted hazard ratio; CI = confidence interval.

3.2. Survival analyses

Multivariable Cox proportional hazards regression models that included all patients were constructed to identify predictors of OS (Table 2). Receipt of AC was associated with improved OS when compared to observation (HR 0.67; 95% CI 0.61−0.74). Patient level characteristics associated with worse OS included age at diagnosis (1.01; 1.01−1.02), Medicaid insurance (1.41; 1.07−1.87), treatment at a nonacademic center (1.13; 1.03−1.24), and comorbidity (1.25; 1.13−1.39). As expected, worse survival was also found with pT3 stage, pT4 stage, pN+ stage, and positive surgical margins (HRs, 1.84, 2.75, 2.03, 1.47, respectively).

Table 3
Multivariate Cox regression analysis for overall survival—adjuvant chemotherapy vs. observation

	Adjuvant Chemotherapy		Observation	
Prognostic factors	Adj. HR (95% CI)	*P* value	Adj. HR (95% CI)	*P* value
Age at diagnosis				
Per year increase	1.01 (1.00–1.02)	0.081	1.02 (1.01–1.03)	<0.001
Sex				
Male	Ref		Ref	
Female	0.97 (0.83–1.14)	0.697	1.03 (0.89–1.19)	0.733
Race				
White	Ref		Ref	
Black	1.47 (0.99–2.18)	0.055	1.12 (0.78–1.62)	0.526
Other	1.33 (0.63–2.84)	0.455	0.38 (0.13–1.12)	0.080
Unknown	0.80 (0.43–1.51)	0.497	0.61 (0.35–1.04)	0.071
Hispanic				
No	Ref		Ref	
Yes	1.13 (0.69–1.86)	0.636	0.88 (0.50–1.55)	0.666
Unknown	1.07 (0.84–1.36)	0.570	0.88 (0.69–1.13)	0.321
Insurance				
Private insurance	Ref		Ref	
Medicaid/other government	1.30 (0.83–2.05)	0.248	1.50 (1.06–2.12)	0.023
Medicare	1.11 (0.92–1.33)	0.273	1.02 (0.85–1.23)	0.808
No insurance	0.87 (0.54–1.40)	0.567	1.51 (1.05–2.19)	0.028
Unknown status	1.05 (0.58–1.88)	0.875	0.51 (0.17–1.48)	0.213
Academic/research program				
Yes	Ref		Ref	
No	1.04 (0.91–1.19)	0.590	1.20 (1.05–1.37)	0.006
Comorbidity				
No	Ref		Ref	
Yes	1.25 (1.08–1.46)	0.004	1.26 (1.09–1.45)	0.002
Pathological T stage				
2	Ref		Ref	
Ta/Tis/T1	0.45 (0.15–1.33)	0.148	1.00 (0.61–1.62)	0.985
3	1.76 (1.42–2.17)	<0.001	1.90 (1.56–2.31)	<0.001
4	2.66 (2.10–3.38)	<0.001	2.84 (2.27–3.56)	<0.001
Pathological N stage				
Negative	Ref		Ref	
Positive	1.91 (1.65–2.22)	<0.001	2.11 (1.84–2.42)	<0.001
Surgical margins status				
Negative	Ref		Ref	
Positive	1.38 (1.12–1.68)	0.002	1.57 (1.27–1.92)	<0.001

Ref = reference group; Adj. HR = adjusted hazard ratio; CI = confidence interval.

Nonmuscle invasive disease status and gender were not found to be significant predictors of survival.

The relationship between demographic and tumor-related characteristics and survival stratified by treatment is shown in Table 3. Within the AC group, worse OS was associated with the presence of comorbidities (HR 1.25 95% CI 1.08–1.46), node positivity (1.91; 1.65–2.22), and positive surgical margins at RC (1.38; 1.12–1.68). Among recipients of AC, worse OS was also associated with stages pT3 (1.76; 1.42–2.17) and pT4 (2.66; 2.10–3.38) in comparison to stage pT2. Of note, patient age at diagnosis, insurance type, and treatment at an academic/research program were not significant predictors of survival in the AC cohort. Within the observation group, age at diagnosis, Medicaid insurance, no insurance, treatment at a nonacademic program, presence of comorbidity, node positivity, and positive surgical margins were predictors of worse OS. Similarly, among patients under observation, worse OS was found with stages pT3 (1.90; 1.56–2.31) and pT4 (2.84; 2.27–3.56). Adjusted HRs were compared by stage between the AC and observation cohorts in a Forest plot (Fig. 2) and as adjusted survival curves (Fig. 3) from Cox proportional hazard models.

4. Discussion

RCTs are the gold-standard for building evidence in comparing treatment efficacy, yet they are not without limitations. RCTs exploring the role of AC in BCa have been historically difficult to conduct due to poor accrual [13,14]. As a result, conclusive evidence for the current guideline

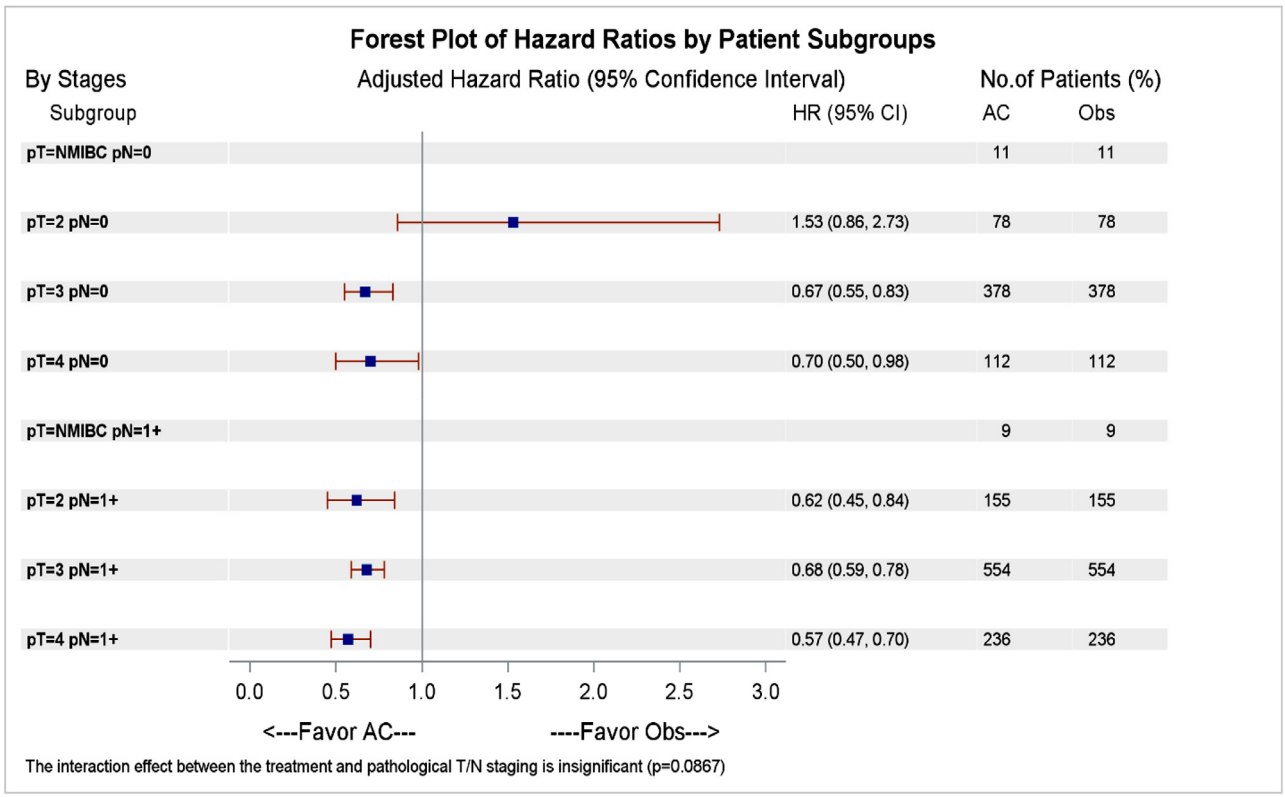

Fig. 2. Forest plot of impact of adjuvant chemotherapy (AC) on overall survival in disease subgroups. CI = confidence interval; HR = hazard ratio; Obs = observation.

recommendations on the role of AC in BCa are lacking. In this investigation, we used observational, retrospective population-based cancer registry data to supplement the questions answered by RCTs. Our results are consistent with the current recommendations made by the NCCN guidelines for AC in BCa patients and provide information regarding stage-specific efficacy of AC.

Prior studies have suggested a benefit from AC. In a meta-analysis consisting of 945 patients from 9 RCTs published in 2014 evaluating AC for ≥ pT2 stage disease, Leow et al. [15] reported improved OS (HR 0.77; 95% CI 0.59−0.99) and disease-free survival (HR 0.66; 95% CI 0.45−0.91) with AC. These findings are consistent with a previous meta-analysis published in 2005 [17]. Our study adds to prior meta-analyses by utilizing a robust study size to evaluate the impact of AC by disease stage. In an observational study following patients from 2003 to 2006, Galsky et al. [18] similarly demonstrated improved survival with AC in pT3-4 stage disease with little difference in HR between subgroups defined by age, sex, lymph node status, or number of lymph nodes removed. Our study builds upon Galsky et al. by including patients diagnosed up to 2014 to reflect the impact of the category 1 recommendation for neoadjuvant chemotherapy. Despite these guideline changes, a significant percentage of BCa patients continue to miss out on preoperative therapy and would benefit from AC. Although these findings add to the confidence in the benefit of AC, its validity continues to be limited by small sample sizes and heterogeneity among published results [17]. Our investigation adds to existing literature by using a large cohort from a registry that encompasses the majority of cancer diagnoses in United States and provides stage-specific outcomes for AC.

Baseline demographics of the unmatched cohort in Table 1 reflect the current selection criteria for recipients of AC. Recipients of AC were younger and had fewer comorbidities than patients under observation following RC. This trend supports the finding that patient performance status may be a primary determinant driving recommendations for AC [19,20]. Table 2 shows that a per year increase of age at diagnosis weakly, but significantly, correlates with mortality. Interestingly, the impact of age is lost when stratified by receipt of AC (HR 1.01; 95% CI 1.00−1.02; $P < 0.081$) vs. observation (HR 1.02; 95% CI 1.01−1.03; $P< 0.001$). The impact of age on adjuvant therapy administration and outcomes should be closely analyzed in future studies to better delineate this relationship.

Socioeconomic status and insurance type have been shown to influence treatment options [21−23], which significantly varied between the 2 cohorts in Table 3. Among patients under observation, worse outcomes were associated with patients with Medicaid (HR 1.50; 95% CI 1.06−2.12) or no insurance (HR 1.51; 95% CI 1.05−2.19) compared to patients with private insurance. Prior studies have shown

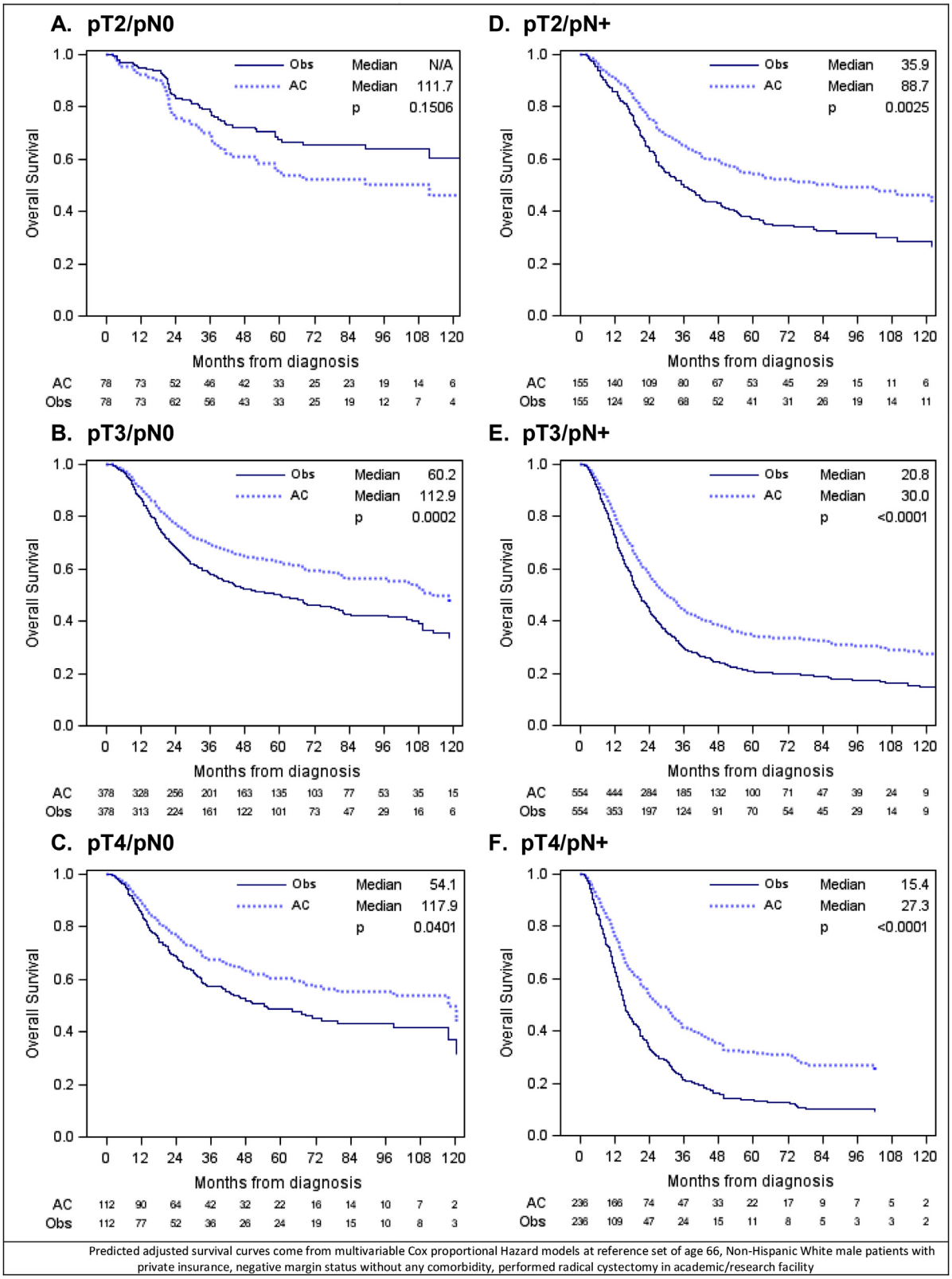

Fig. 3. Adjusted survival curves according to tumor stage and use of chemotherapy: (A–C) no nodal metastasis; (D–F) nodal metastasis. Obs = observation; AC = adjuvant chemotherapy.

that uninsured and Medicaid-insured patients present with later stage disease [24,25] and are independent predictors for increased comorbidities, longer postoperative hospitalizations, and complications [26]. Interestingly, among recipients of AC, survival outcomes were similar among all insurance types. Insurance type may influence access to care, but response to chemotherapy does not appear to differ among patients with different insurance types.

Adjusted survival curves with median survival in Fig. 3 demonstrate improved OS in patients with pT2/pN1 and all pT3-4 disease regardless of nodal status. Although not reaching statistical significance, patients with pT2/pN0 disease had worse outcomes with receipt of AC vs. observation ($P = 0.1506$; Fig. 3A). We believe that a likely explanation for this trend is that recipients of AC within the pT2/pN0 cohort may be collectively in worse health for reasons not captured by NCDB, thereby warranting AC in a disease stage not supported by existing guidelines.

Our findings should be interpreted within the limitations of the study design. First, the retrospective nature of this investigation inherently introduces selection bias. We attempted to minimize this with propensity score-based matching. Although propensity matching may be effective in minimizing the impact of observable confounders, it may not address unobservable confounders that could influence survival. Second, although the NCDB has well defined and standardized reporting protocols, the NCDB precludes details regarding certain demographic and clinical history, such as facility cystectomy volume, nodal count, or the exact type of chemotherapy that is administered. We addressed this by limiting inclusion criteria to "multi-agent chemotherapy only," but this does not differentiate between platinum-based or other guideline-driven regimens [16,27], nor discern level of adherence or appropriateness of chemotherapy cycles. Given these limitations, our study may support use of AC in certain BCa patients who did not receive preoperative chemotherapy, but cannot prove the efficacy of AC regimens as recommended by existing guidelines.

5. Conclusion

In conclusion, we report a survival benefit from AC in locally advanced (pT3-4, N0) and regionally advanced (pT2-4, N1) BCa patients who did not receive neoadjuvant chemotherapy. While neoadjuvant chemotherapy followed by RC remains the preferred approach based on level-1 evidence, patients who did not receive preoperative chemotherapy may benefit from AC. These findings are consistent with recommendations made by the NCCN guidelines for BCa.

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