11-19-2020

Impact of treatment modality on overall survival in localized ductal prostate adenocarcinoma: A national cancer database analysis

Chandler Bronkema

Sohrab Arora

Jacob Keeley

Nikola Rakic

Akshay Sood

See next page for additional authors

Authors

Chandler Bronkema, Sohrab Arora, Jacob Keeley, Nikola Rakic, Akshay Sood, Deepansh Dalela, Marcus Jamil, James O. Peabody, Craig G. Rogers, Mani Menon, and Firas Abdollah

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 000 (2020) 1−8

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Impact of treatment modality on overall survival in localized ductal prostate adenocarcinoma: A national cancer database analysis

Chandler Bronkema, B.S.[a,b,#], Sohrab Arora, M.Ch.[a,#], Jacob Keeley, M.S.[a], Nikola Rakic, B.S.[a,b], Akshay Sood, M.D.[a], Deepansh Dalela, M.D.[a], Marcus Jamil, M.D.[a], James O. Peabody, M.D.[a], Craig G. Rogers, M.D.[a], Mani Menon, M.D.[a], Firas Abdollah, M.D.[a,*]

[a] *VCORE − Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation, Henry Ford Hospital, Detroit, MI*
[b] *Wayne State University School of Medicine, Detroit, MI*

Received 11 July 2020; received in revised form 2 October 2020; accepted 6 November 2020

Abstract

Purpose: Ductal adenocarcinoma is considered a rare histological variant of prostate adenocarcinoma (PCa). Given the rarity of this subtype, optimal treatment strategies for men with nonmetastatic ductal PCa is largely unknown. We aimed to describe the impact of surgery, radiotherapy, systemic therapy, and observation on overall survival (OS) in men with nonmetastatic ductal PCa.

Materials and methods: We selected 1,656 cases of nonmetastatic ductal PCa, diagnosed between 2004 and 2015, within the National Cancer Database. Covariates included age, race, Charlson comorbidity score, clinical T stage, clinical lymph node stage, serum prostate specific antigen (PSA), income, hospital type, insurance status, year of diagnosis, and location of residence. Cox regression analysis tested the impact of treatment (surgery, radiotherapy, systemic therapy, and observation) on OS.

Results: In men with nonmetastatic ductal PCa, median (interquartile range [IQR]) age and PSA were 67 (60−73) years and 6.2 (4.2 −10.7) ng/ml, respectively. Advanced local stage (≥cT3a) was most frequently observed in patients initially treated with systemic therapy (34.8%), followed by those treated with radiotherapy (18.1%), surgery (7.1%) and observation (6.4%, $P< 0.001$). Serum PSA at presentation was highest in the systemic therapy cohort (median 16.0 ng/ml, IQR: 4.9−37.7), followed by the radiotherapy cohort (median 7.2 ng/ml, IQR: 4.1−12.2), observation cohort (median 7.0 ng/ml, IQR: 4.3−13.3) and surgery cohort (median 5.9 ng/ml, IQR: 4.3−9.2, $P< 0.001$). Multivariable analysis showed that in comparison to men treated surgically, OS was significantly lower for patients receiving radiotherapy (*HR 2.2; 95% CI: 1.5−3.2*), under observation (*HR 4.6; 95% CI: 2.8−7.6*) and receiving systemic therapy (*HR 5.2; 95% CI: 3.0−9.1*) as an initial course of treatment.

Conclusions: While limited by its retrospective nature, our study shows that starting treatment with surgery is associated with more favorable long-term OS outcomes than radiotherapy, systemic therapy or observation.

Keywords: Ductal adenocarcinoma; National Cancer Database; Prostatic neoplasms; Survival; Treatment

1. Introduction

Prostate cancer is the most common malignant tumor in American men, and on histology, over 90% of prostate cancer neoplasms are categorized as acinar adenocarcinoma [1]. However, according to the American Joint Committee on Cancer, 6 rare histological variants of prostate adenocarcinoma (PCa) exist. Among these, ductal is the most common subtype [2−4].

Several reports have shown that men with ductal PCa often present with more aggressive clinical features and have a less favorable prognosis when compared to those with acinar adenocarcinoma [2−6]. Even in patients presenting with nonmetastatic disease, ductal PCa still displays less favorable survival outcomes when comparted to acinar

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

Competing interest statement: Dr. Firas Abdollah is a consultant for DecipherDx Biosciences. All other authors have no competing interests to report.

[#]Authors contributed equally

*Corresponding author. Tel: +1 (313) 916-7129; fax: +1 (313) 916-1462.
E-mail address: fabdoll1@hfhs.org (F. Abdollah).

https://doi.org/10.1016/j.urolonc.2020.11.013
1078-1439/

PCa [2]. That said, a comprehensive analysis assessing optimal treatment strategies for men diagnosed with localized ductal PCa is lacking, and the rarity of this histological variant precludes the possibility of a future trial.

This void in contemporary literature poses a challenge for clinicians in both developing an ideal therapeutic plan and accurately counseling patients diagnosed with ductal PCa. Hence, using the National Cancer Database (NCDB), our aim was to describe the impact of surgery, radiotherapy (RT), systemic therapy (ST), and observation as initial treatment on overall survival (OS) in men with nonmetastatic ductal PCa.

2. Materials and methods

2.1. Data source

The NCDB is a clinical oncology database sponsored by the American College of Surgeons and the American Cancer Society. It comprises hospital registry data collected in more than 1,500 Commission on Cancer-accredited facilities. Data in this registry represents approximately 70% of newly diagnosed cancer cases nationwide across the US [7].

2.2. Study population

We identified 2,209 patients diagnosed with ductal PCa, between 2004 and 2015. Histologically confirmed primary prostate malignancies diagnosed by biopsy and transurethral resections were identified using International Classification of Diseases in Oncology (ICD-O-3) diagnosis codes 8500/3-8503/3. All other variants of PCa were not included in our initial cohort. Individuals with absent database follow-up information ($n = 215$), missing sufficient data regarding treatment ($n = 122$), and those individuals presenting with cM1 disease were excluded ($n = 216$), yielding a total sample of 1,656 men. *The inclusion and exclusion criteria are depicted in* Fig. 1.

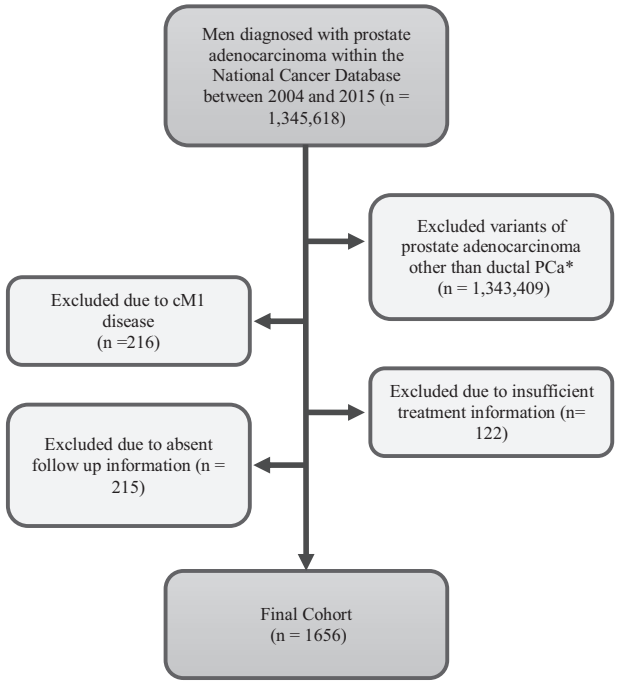


Fig. 1. Inclusion and exclusion criteria of patient sample. *Excluded variants of prostate adenocarcinoma include acinar, neuroendocrine, mucinous, signet ring cell, sarcomatoid, and adenosquammous.

2.3. Covariates

Patient-specific variables consisted of age at diagnosis, race (non-Hispanic white, non-Hispanic black, other), and baseline Charlson Comorbidity Index category (0,1 or ≥2), location (metropolitan, urban, or rural county), and insurance status (not insured, private insurance/managed care, Medicare, Medicaid, or other). We estimated socioeconomic variables using household income quartiles. Additional variables include hospital type, and disease-specific characteristics, namely, year of diagnosis, serum prostate specific antigen (PSA), clinical tumor stage (cT1-T4, or missing), and clinical lymph node stage (cN0, cN1, or cNx). Of note, Gleason grade data was absent in over 30% of the NCDB cohort, and the reporting on ductal PCa was change in 2010 to where the overwhelming majority of ductal PCa cases are categorized as Gleason 4 by definition [8]. Due to this lack of uniformity in reporting over the study period and absent database information, Gleason score was not included as a covariate.

Treatment modality was also abstracted as follows: any patient with receipt of prostatectomy was assigned to the surgery cohort. Patients primarily receiving treatment in the form of beam radiation, radioactive implants, radioisotopes, or radiation not otherwise specified composed the RT cohort. Individuals in the ST cohort were those men treated with one or more of the following therapies as their primary course of therapy: single-agent chemotherapy, multiagent chemotherapy, and hormone therapy. All other patients were assigned to the observation cohort.

2.4. Endpoints

We examined 2 main endpoints: (1) disease characteristics at presentation, (2) OS, defined as time from PCa diagnosis to death from any cause or last available follow-up.

2.5. Statistical analyses

Median and interquartile ranges (IQRs) were reported for continuous variables, while frequencies and proportions were reported for categorical variables. The Mann-Whitney-U and chi-square tests were used to compare medians and proportions, respectively.

For our statistical analysis, Kaplan-Meier depicted survival in all patients ($n = 1,656$), after stratifying them based on treatment type. A similar Kaplan-Meier was depicted for

men with cN0 disease (1,329). The very limited sample size of men with cN1 disease ($n = 41$) precluded the possibility of separately analyzing these individuals. Cox regression analysis tested the impact of treatment modality on OS, after adjusting for all covariates. To assess the impact of unobserved confounders on our regression analysis, we performed sensitivity analyses without assumptions using the method described by Ding and VanderWeele [9]. This method estimates the magnitudes of the joint bounding factor for various combinations of the likelihood of receiving initial RT, ST, or observation in the presence of unmeasured confounders ($OR_{RT\text{-}U}$, $OR_{ST\text{-}U}$, and $OR_{obs\text{-}U}$, respectively) and the likelihood of mortality in the presence of unmeasured confounders ($HR_{mortality\text{-}U}$), as compared to surgery (reference variable).

Additionally, regression analyses were performed in a subanalysis of cN0 men. Since recent reports have concluded that ductal PCa is associated with compromised survival outcomes and earlier time to biochemical recurrence following RP [5,6,10], this subanalysis was conducted to assess the efficacy of ST and RT in treating men with cN0 disease as compared to surgery. Further, an additional subanalysis was performed excluding men who underwent initial observation since this is a population treated outside of the guidelines and are likely unfit for surgery [11,12]. Of note, since the sensitivity analyses consisted of a limited patient cohort, hospital type, location, year of diagnosis, and insurance status were not included.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Two-sided statistical significance was defined as a P-value <0.5.

3. Results

3.1. Patient characteristics

Detailed descriptive data of our cohort stratified by treatment modality are provided in Table 1. Overall, 1,030 (62.2%) men received surgical treatment, 348 (21.0%) were treated with radiation, 89 (5.4%) with ST, and 189 (11.4%) with observation. There were 1329 individuals with cN0 disease and 41 with cN1 disease at presentation. Median age at presentation for the entire cohort was 67 years old (IQR: 60−73). Men treated surgically were the youngest at presentation (median: 64, IQR: 58−68), while men in the ST cohort were oldest (median: 78, IQR: 67−85).

Advanced stage disease (≥cT3a) was observed in 34.8% of patients receiving ST, 18.1% of those treated with radiation, 7.1% of men treated surgically, and 6.4% who underwent observation (P<0.001). Serum PSA at presentation was highest in men treated with ST (median 16.0 ng/ml, IQR: 4.9−37.7), followed by men treated with RT (median 7.2 ng/ml, IQR: 4.1−12.2), those who underwent observation (median 7.0 ng/ml, IQR: 4.3−13.3), and men treated surgically (median 5.9 ng/ml, IQR: 4.3−9.2) (P<0.001).

3.2. Survival analysis

In our cohort, median (IQR) follow-up period was 55.0 months (30.4−84.7). At ten years, OS was 62.4% for the entire cohort, 77.9% for the surgery group, 51.0% for the RT group, 31.1% in the observation group, and 23.6% in the ST group (Fig. 2A; P<0.001). Similar rates were observed for patients with cN0 disease (Fig. 2B).

At multivariable regression analysis of the entire patient cohort (Table 2), treatment modality was an independent predictor of mortality. Specifically, men treated with ST, those in the observation cohort, and those treated with RT had a *5.2, 4.6, and 2.2*-fold higher mortality risk than their counterparts treated surgically (all P<0.001). Other independent predictors of OS included age, Charlson Comorbidity Index score, clinical lymph node stage, and hospital type. Ding-VanderWeele analysis magnitudes of the joint bounding factor for various combinations of $OR_{RT\text{-}U}$, $OR_{ST\text{-}U}$, or $OR_{obs\text{-}U}$ and $HR_{mortality\text{-}U}$ are reported in Supplementary Tables 1a-1c. For the OS benefit of surgery versus RT, ST, or observation to be explained solely by unmeasured confounders, $OR_{RT\text{-}U}$, $OR_{ST\text{-}U}$, or $OR_{obs\text{-}U}$ and $HR_{mortality\text{-}U}$ would need to meet specific estimates where the joint bounding factor would suggest the opposite (red area) or nonsignificant (yellow area) treatment effect. Over half of these joint bounding factor values did not exist in our analysis comparing RT versus surgery, and over $^3/_4$ did not exist when comparing ST or observation versus surgery. Thus, the sensitivity analysis without assumptions suggested a minimal influence of unknown confounders, if any, on our study findings (blue area).

Furthermore, our sensitivity analysis focusing exclusively on patients with cN0 disease (Table 3) confirmed treatment method as an independent predictor of OS, after adjusting for age, race, comorbidities, clinical T stage, PSA, and income. In this cohort, men treated with ST, those in the observation cohort, and those treated with RT had a 9.1, 5.4, and 2.7-fold higher mortality risk than their counterparts treated surgically (P<0.001). Similarly, our sensitivity analysis excluding men who underwent initial observation displayed similar findings and treatment modality was shown to be an independent predictor of OS (Supplementary Table 2, P<0.001).

4. Discussion

Ductal adenocarcinoma is a rare subtype of PCa, and the vast majority of literature surrounding ductal PCa outlines the aggressive nature and unfavorable prognosis this malignancy displays as compared to nonvariant PCa [2,4−6]. However, studies assessing the effect of certain treatment modalities on survival outcomes in men diagnosed with ductal PCa stem primarily from case series studies with small patient samples due to the rarity of this variant. Thus, using the NCDB, we sought to describe the impact of

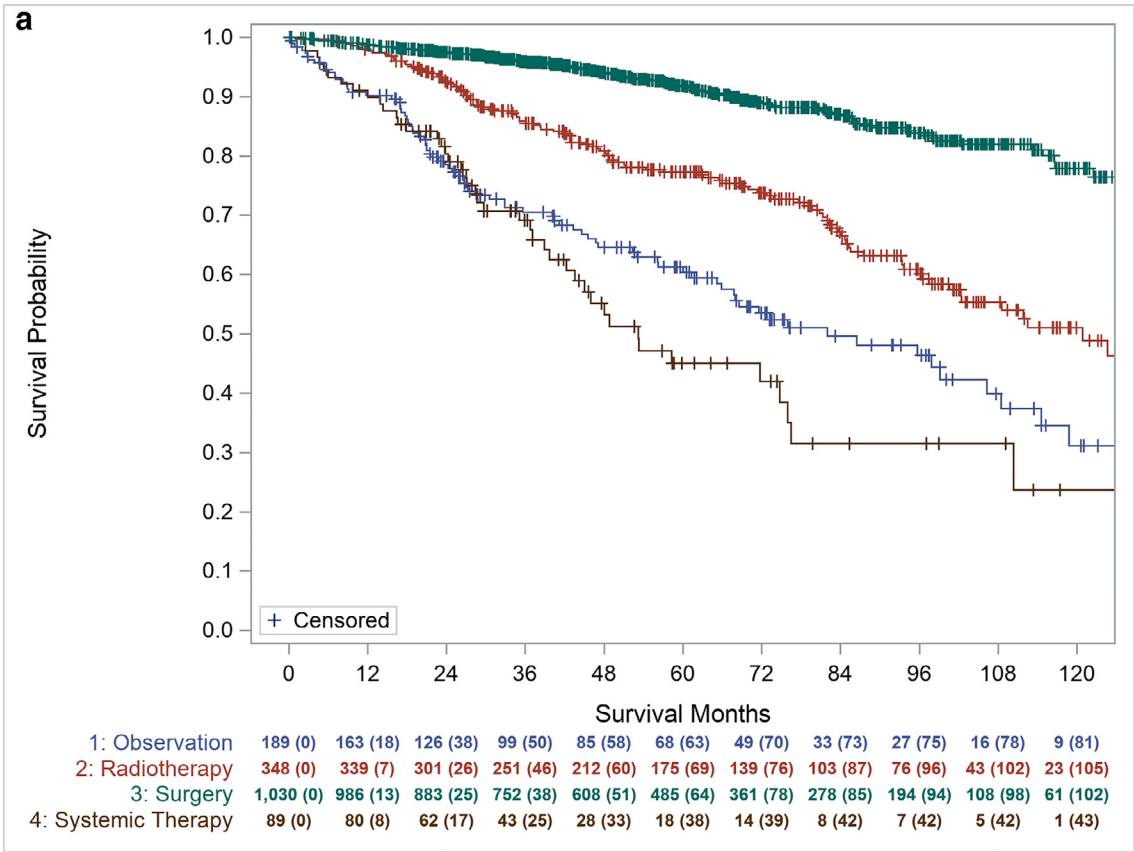
Table 1
Descriptive characteristics of 1656 patients diagnosed with nonmetastatic ductal prostate adenocarcinoma between 2004 and 2015 within the National Cancer Database, stratified by treatment modality

	All Patients ($n = 1656$)	Surgery ($n = 1030$)	Radiotherapy ($n = 348$)	Systemic therapy ($n = 89$)	Observation ($n = 189$)	*P* value
Age, years, median (IQR)	67 (60-73)	64 (58-68)	73 (67-78)	78 (67-85)	77 (67-84)	<0.001
Race, *n* (%)						
White	1369 (82.7)	859 (83.4)	281 (80.8)	72 (80.9)	157 (83.1)	
Black	193 (11.7)	113 (11.0)	46 (13.2)	11 (12.4)	23 (12.2)	
Others	72 (4.4)	43 (4.2)	17 (4.9)	6 (6.7)	6 (3.2)	0.7
Charlson comorbidity score, *n* (%)						
0	1322 (79.8)	823 (79.9)	276 (79.3)	65 (73.0)	158 (83.6)	
1	287 (17.3)	182 (17.7)	61 (17.5)	18 (20.2)	26 (13.8)	
2 or more	47 (2.8)	25 (2.4)	11 (3.2)	6 (6.7)	5 (2.7)	0.2
Clinical T stage, *n* (%)						
T1	775 (46.8)	509 (49.4)	149 (42.8)	31 (34.8)	86 (45.5)	
T2	475 (28.7)	307 (29.8)	102 (29.3)	20 (22.5)	46 (24.3)	
T3/T4	179 (10.8)	73 (7.1)	63 (18.1)	31 (34.8)	12 (6.4)	
cTx/missing	227 (13.7)	141 (13.7)	34 (9.8)	7 (7.9)	45 (23.8)	<0.001
Clinical lymph node involvement, *n* (%)						
N1	41 (2.3)	11 (1.1)	13 (3.7)	17 (19.1)	0 (0)	
N0	1329 (80.3)	855 (83.0)	293 (84.2)	57 (64.0)	124 (65.6)	
Nx	270 (16.3)	159 (15.4)	41 (11.8)	14 (15.7)	56 (29.6)	<0.001
Serum PSA, ng/ml, median (IQR)	6.2 (4.2-10.7)	5.9 (4.3-9.2)	7.2 (4.1-12.2)	16.0 (4.9-37.7)	7.0 (4.3-13.3)	<0.001
Income¥, *n* (%)						
Quartile 1	262 (15.8)	160 (15.5)	47 (13.5)	12 (13.5)	43 (22.8)	
Quartile 2	372 (22.5)	229 (22.2)	83 (23.9)	15 (16.9)	45 (23.8)	
Quartile 3	421 (25.4)	256 (24.9)	102 (29.3)	26 (29.2)	37 (19.6)	
Quartile 4	589 (35.6)	379 (36.8)	114 (32.8)	35 (39.3)	61 (32.3)	0.058
Hospital type, *n* (%)						
Community Cancer Program	88 (5.3)	29 (2.8)	31 (8.9)	6 (6.7)	22 (11.6)	
Academic/Research Program	899 (54.3)	652 (63.3)	128 (36.8)	37 (41.6)	82 (43.4)	
Integrated Network Cancer Program	159 (9.6)	89 (8.6)	42 (12.1)	8 (9.0)	20 (10.6)	
Comprehensive Community Cancer Program	508 (30.7)	258 (25.1)	147 (42.2)	38 (42.7)	65 (34.4)	<0.001
Insurance status, *n* (%)						
Not Insured	22 (1.3)	13 (1.3)	6 (1.7)	2 (2.3)	1 (0.5)	
Medicaid	37 (2.2)	24 (2.3)	10 (2.9)	1 (1.1)	2 (1.1)	
Medicare	802 (48.4)	401 (38.9)	233 (67.0)	54 (60.7)	114 (60.3)	
Other Government	17 (1.0)	10 (1.0)	3 (0.9)	1 (1.1)	3 (1.6)	
Private/Managed Care	710 (42.9)	577 (56.0)	83 (23.9)	20 (22.5)	30 (15.9)	<0.001
Year of diagnosis, *n* (%)						
2004-2006	290 (17.5)	148 (14.4)	84 (24.2)	22 (24.7)	36 (19.1)	
2007-2009	497 (30.0)	309 (30.0)	108 (31.0)	18 (20.2)	62 (32.8)	
2010-2012	507 (30.6)	334 (32.4)	96 (27.6)	25 (28.1)	52 (27.5)	
2013-2015	362 (21.9)	239 (23.2)	60 (17.2)	24 (27.0)	39 (20.6)	<0.001
Location, *n* (%)						
Metropolitan county	1338 (80.8)	835 (81.1)	290 (83.3)	72 (80.9)	141 (74.6)	
Urban county	245 (14.8)	153 (14.9)	43 (12.4)	14 (15.7)	35 (18.5)	
Rural county	23 (1.4)	9 (0.9)	10 (2.9)	2 (2.3)	2 (1.1)	<0.001
10-year estimated overall survival*, (%)	62.4	77.9	51.0	23.6	31.1	<0.001

* *p* value from Kaplan Meier survival analysis. Regression analyses confirmed the above findings ¥ Zip code-based income quartiles.

surgery, RT, ST, and observation on OS in men with nonmetastatic ductal PCa.

In the present study, Kaplan-Meier survival analyses showed that, in terms of survival, great variation exists amongst patients undergoing surgery, receiving RT, ST, and undergoing observation as their initial course of treatment. Estimated 10-year OS was 77.9% in the surgery cohort, 51.0% in the RT cohort, 31.1% in the observation cohort, and 23.6% in the ST cohort (Table 1). These estimates, along with our multivariable analyses (Tables 2 and 3), show that patients initially treated surgically fare much better than those treated with other modalities. Notably, prior reports have shown that, following RP, men with ductal PCa have a greater chance of harboring adverse pathologic features such as, positive surgical margins, extraprostatic extension and seminal vesicle invasion [13,14]. Furthermore, several studies have elucidated that ductal PCa is associated with early biochemical recurrence and shorter survival following RP [5,10,11,15–19]. Comparative data regarding survival outcomes in surgically treated men diagnosed with ductal PCa is



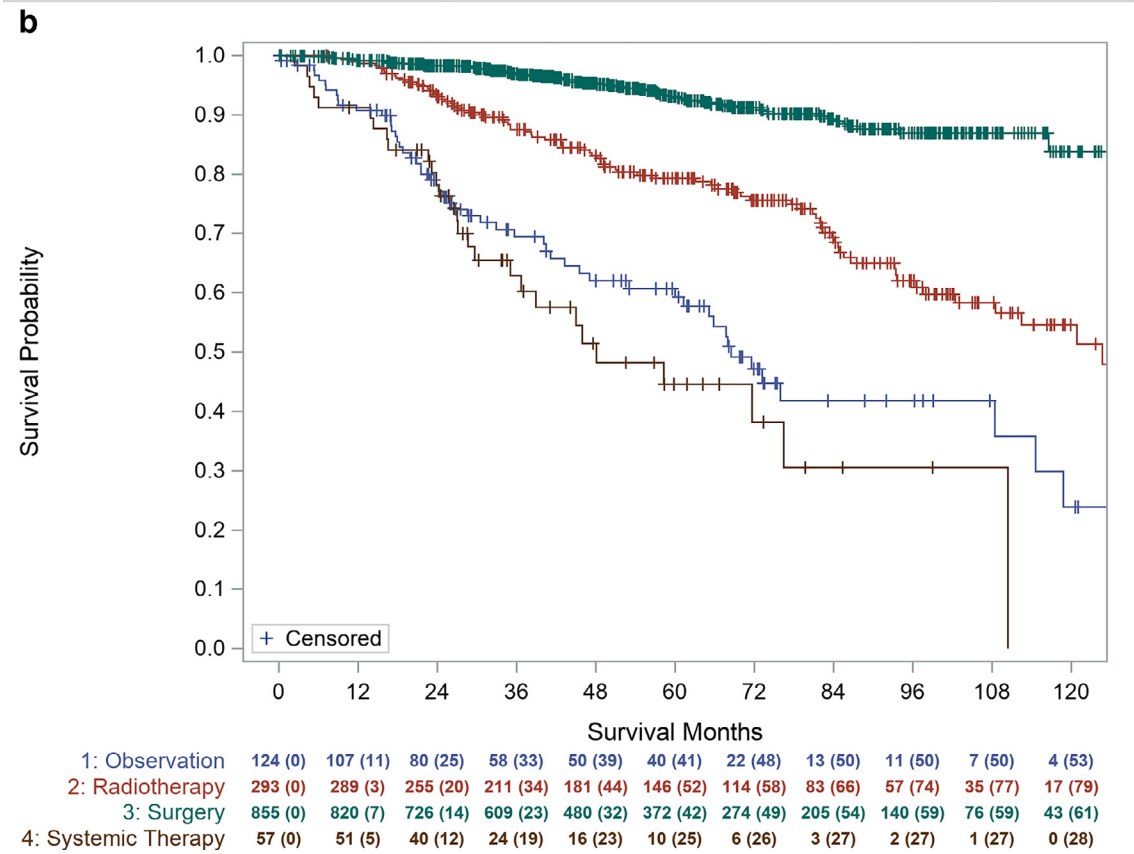


Fig. 2. A. Kaplan-Meier overall survival estimates of 1656 cM0 ductal prostate adenocarcinoma patients, diagnosed between 2004 and 2015, within the National Cancer Database, stratified based on treatment method. B. Kaplan-Meier overall survival estimates of 1329 cM0N0 ductal prostate adenocarcinoma patients, diagnosed between 2004 and 2015, within the National Cancer Database, stratified based on treatment method.

Table 2
Univariable and multivariable Cox proportional hazards regression analysis testing the effect of treatment modality on mortality in 1656 patients with nonmetastatic (cM0) ductal prostate adenocarcinoma diagnosed between 2004 and 2015 within the National Cancer Database

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment modality				
Surgery	Ref		Ref	
Radiotherapy	2.90 (2.21-3.79)		2.16 (1.49-3.15)	
Systemic therapy	7.50 (5.25-10.72)		5.20 (2.97-9.09)	
Observation	5.41 (4.06-7.26)	<0.001	4.58 (2.75-7.63)	<0.001
Age	1.10 (1.08-1.11)	<0.001	1.04 (1.02-1.06)	<0.001
Race				
White	Ref		Ref	
Black	0.92 (0.66-1.28)		1.18 (0.78-1.78)	
Others	0.37 (0.17-0.78)	0.031	0.50 (0.19-1.37)	0.3
Charlson comorbidity score				
0	Ref.		Ref.	
1	1.58 (1.21-2.06)		1.66 (1.18-2.35)	
2 or more	4.33 (2.79-6.71)	<0.001	4.11 (2.21-7.66)	<0.001
Clinical T stage				
cT1	Ref		Ref	
cT2	1.24 (0.95-1.62)		1.23 (0.90-1.70)	
cT3/T4	1.85 (1.33-2.57)	0.001	1.65 (1.11-2.45)	0.046
Clinical lymph node involvement				
cN0	Ref		Ref	
cN1	1.96 (1.04-3.70)		1.35 (0.61-2.98)	
cNx	1.74 (1.38-2.21)	<0.001	2.20 (1.48-3.27)	<0.001
PSA	1.01 (1.01-1.02)	0.001	1.01 (0.99-1.01)	0.2
Income*				
Quartile 1	Ref		Ref	
Quartile 2	0.95 (0.68-1.32)		0.93 (0.59-1.45)	
Quartile 3	0.81 (0.58-1.13)		1.06 (0.66-1.69)	
Quartile 4	0.71 (0.52-0.97)	0.10	0.97 (0.61-1.55)	0.9
Hospital type				
Community Cancer Program	Ref		Ref	
Academic/Research Program	0.31 (0.21-0.45)		0.52 (0.32-0.86)	
Integrated Network Cancer Program	0.49 (0.30-0.80)		0.61 (0.33-1.12)	
Comprehensive Community Cancer Program	0.76 (0.52-1.11)	<0.001	0.80 (0.50-1.29)	0.027
Insurance status				
Not Insured	Ref		Ref	
Medicaid	1.92 (0.52-6.25)		5.52 (0.96-31.8)	
Medicare	1.88 (0.70-5.05)		3.72 (0.78-17.7)	
Other Government	2.26 (0.51-10.1)		6.04 (0.47-77.5)	
Private/Managed Care	0.65 (0.24-1.78)	<0.001	3.29 (0.70-15.5)	0.4
Year of diagnosis, *n* (%)				
2004-2006	Ref		Ref	
2007-2009	0.77 (0.59-1.01)		1.20 (0.82-1.74)	
2010-2012	0.82 (0.60-1.12)		1.27 (0.83-1.95)	
2013-2015	0.77 (0.48-1.21)	0.3	0.82 (0.41-1.64)	0.4
Location, *n* (%)				
Rural county	Ref		Ref	
Urban county	1.09 (0.47-2.53)		1.29 (0.30-5.54)	
Metropolitan county	0.80 (0.36-1.81)	0.10	1.16 (0.28-4.85)	0.8

* Zip code-based income quartiles

limited. However, in a population-based analysis, Knipper et al. [6] reported that in men treated with RP, 10-year cancer-specific survival rates were 92.0% versus 82.3% in men treated with other treatment modalities.

Taken together, although ductal PCa patients may have a greater chance of early relapse following RP, the findings in the present study in conjunction with that outlined by Knipper et al. support the notion that initial surgical treatment is associated with better long-term survival outcomes in men with nonmetastatic ductal PCa. Furthermore, our regression analysis of the entire patient cohort (cM0 only), along with our subanalysis of cM0N0 men displays that surgery offers a more favorable prognosis in both cohorts, but especially in cM0N0 men as displayed in Table 3. That

Table 3
Univariable and multivariable Cox proportional hazards regression analysis testing the effect of treatment modality on mortality in 1329 cM0N0 patients with ductal prostate adenocarcinoma diagnosed between 2004 and 2015 within the National Cancer Database

	Univariable analysis		Multivariable analysis	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment modality				
Surgery	Ref		Ref	
Radiotherapy	3.50 (2.52-4.88)		2.70 (1.79-4.08)	
Systemic therapy	11.86 (7.55-18.62)		9.08 (4.86-16.93)	
Observation	8.42 (5.83-12.17)	<0.001	5.40 (3.02-9.64)	<0.001
Age	1.10 (1.09-1.12)	<0.001	1.03 (1.01-1.05)	0.004
Race				
White	Ref		Ref	
Black	1.08 (0.73-1.61)		1.20 (0.77-1.88)	
Others	0.34 (0.13-0.93)	0.095	0.41 (0.13-1.29)	0.2
Charlson comorbidity score				
0	Ref.		Ref.	
1	1.52 (1.10-2.10)		1.67 (1.14-2.44)	
2 or more	3.98 (2.38-6.67)	<0.001	4.14 (2.09-8.20)	<0.001
Clinical T stage				
cT1	Ref		Ref	
cT2	1.14 (0.85-1.54)		1.22 (0.86-1.73)	
cT3/T4	1.76 (1.19-2.60)	0.019	1.60 (1.00-2.56)	0.13
PSA	1.01 (1.01-1.02)	0.002	1.01 (0.99-1.02)	0.3
Income*				
Quartile 1	Ref		Ref	
Quartile 2	0.72 (0.49-1.07)		1.02 (0.64-1.63)	
Quartile 3	0.68 (0.46-1.00)		1.03 (0.63-1.69)	
Quartile 4	0.52 (0.36-0.76)	0.008	0.71 (0.44-1.14)	0.3

* Zip code-based income quartiles

said, the NCDB does not capture secondary treatments, which might have contributed to the better outcomes observed in the surgical cohort.

Unfortunately, the current available literature regarding the efficacy of different treatment modalities in ductal PCa is very limited in its validity and generalizability. For example, Lemberger et al. [20] found that, in a group of 39 men with ductal PCa, response to hormone therapy was similar to a comparable cohort of men with acinar adenocarcinoma. These findings were contradictory to what Dube et al. [21] observed in 1973. Additionally, to assess the efficacy of external-beam RT with adjuvant androgen deprivation in a small patient cohort ($n = 6$), Eade et al. [22] concluded that such treatment strategies may be effective since 4 out of 6 patients remained alive between 3.2 and 4.8 years from treatment. Likewise, an analysis of 11 men with localized ductal PCa by Orihuela and Green showed that a combination of radiation and endocrine therapy yielded adequate oncologic control [23]. However, extrapolation of the findings in the 3 aforementioned studies to present clinical practice is challenging since these reports are dated, limited, and lack comparative data to men treated with RP.

In addition to the covariates studied in the present report, other measures may be useful in clinical decision making for men with ductal PCa. For example, ductal PCa can occur as pure ductal or mixed with acinar adenocarcinoma [24], and the proportion of the ductal component may have an impact on survival [11,15]. Harkin et al. [15,25] and Jang et al. provided evidence that a high ductal component in mixed ductal PCa was a significant predictor of biochemical recurrence following RP, thus proposing the proportion of the ductal component on pathology may be a useful determinant for adjuvant RT. These findings may prove propitious in future clinical decision-making applications.

Interestingly, although contemporary reports have shown PSA to be similar or higher in men presenting with ductal PCa compared to pure acinar [2,4–6], this variable failed to predict OS on our multivariable analysis. This finding may imply that PSA is a less useful indicator of survival outcomes in the ductal variant, due to the variation in ductal features amongst patients diagnosed with this malignancy [24]. This notion is also supported by findings presented by Bronkema et al. [2] in which ductal PCa patients presented with a greater PSA range compared to pure acinar. Together, these findings highlight the prognostic inadequacy of PSA and need for additional valuable biomarkers in this subtype.

The present study addresses a subject that has been minimally studied, is representative of a contemporary patient cohort, and is a robust analysis, given the rarity of ductal PCa. Further, to our knowledge, this report is the first to compare outcomes in men diagnosed with ductal PCa initially treated with surgery versus RT versus ST versus

observation. Moreover, the results of our study are of substantial utility in clinical decision making and in counseling patients on their outcomes.

Despite these strengths, the present study is not devoid of limitations and should be interpreted within the framework of a retrospective study design which can lead to confounding. Further, certain variables that may have an impact on patient outcomes, such as surgeon experience, rate of positive margins, and pathological lymph node stage were not assessed in our analysis. In addition, the NCDB is not a population-based registry and only Commission on Cancer accredited institutions report to this database. Thus, our report may not be applicable to patients treated outside of such facilities. An additional limitation of our study is that the ductal PCa subtype lacks centralized pathological review, a void that risks consistency in diagnosing and staging this malignancy. Finally, the present study assessed OS, but we did not have access to other measurable endpoints such as cancer-specific mortality rates and cancer recurrence. Assessment of such endpoints would likely allow for a more accurate delineation of the effect of the different treatment modalities on patient outcomes.

5. Conclusion

While limited by its retrospective nature, our study shows that starting treatment with surgery is associated with more favorable long-term OS outcomes than RT, ST, or observation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.11.013.

References

[1] Seipel AH, Delahunt B, Samaratunga H, Egevad L. Ductal adenocarcinoma of the prostate: histogenesis, biology and clinicopathological features. Pathology 2016. https://doi.org/10.1016/j.pathol.2016.04.001.

[2] Bronkema C, Arora S, Sood A, Dalela D, Keeley J, Borchert A, et al. Rare histological variants of prostate adenocarcinoma: a national cancer database analysis. J Urol 2020. https://doi.org/10.1097/ju.0000000000001011.

[3] Humphrey PA. Histological variants of prostatic carcinoma and their significance. Histopathology 2012. https://doi.org/10.1111/j.1365-2559.2011.04039.x.

[4] Marcus DM, Goodman M, Jani AB, Osunkoya AO, Rossi PJ. A comprehensive review of incidence and survival in patients with rare histological variants of prostate cancer in the United States from 1973 to 2008. Prostate Cancer Prostatic Dis 2012. https://doi.org/10.1038/pcan.2012.4.

[5] Meeks JJ, Zhao LC, Cashy J, Kundu S. Incidence and outcomes of ductal carcinoma of the prostate in the USA: analysis of data from the surveillance, epidemiology, and end results program. BJU Int 2012. https://doi.org/10.1111/j.1464-410X.2011.10520.x.

[6] Knipper S, Preisser F, Mazzone E, Mistretta FA, Tian Z, Briganti A, et al. Contemporary comparison of clinicopathologic characteristics and survival outcomes of prostate ductal carcinoma and acinar adenocarcinoma: a population-based study. Clin Genitourin Cancer 2019. https://doi.org/10.1016/j.clgc.2019.04.009.

[7] American College of Surgeons, American Cancer Society. National cancer database. Natl Cancer Database 2017.

[8] Epstein JI. An update of the gleason grading system. J Urol 2010. https://doi.org/10.1016/j.juro.2009.10.046.

[9] Dinga P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology 2016. https://doi.org/10.1097/eDe.0000000000000457.

[10] Packiam VT, Patel SG, Pariser JJ, Richards KA, Weiner AB, Paner GP, et al. Contemporary population-based comparison of localized ductal adenocarcinoma and high-risk acinar adenocarcinoma of the prostate. Urology 2015. https://doi.org/10.1016/j.urology.2015.07.009.

[11] Tu SM, Lopez A, Leibovici D, Bilen MA, Evliyaoglu F, Aparicio A, et al. Ductal adenocarcinoma of the prostate: clinical features and implications after local therapy. Cancer 2009. https://doi.org/10.1002/cncr.24326.

[12] Epstein JI. Prostatic ductal adenocarcinoma: a mini review. Med Princ Pract 2009. https://doi.org/10.1159/000252842.

[13] Amin A, Epstein JI. Pathologic stage of prostatic ductal adenocarcinoma at radical prostatectomy: Effect of percentage of the ductal component and associated grade of acinar adenocarcinoma. Am J Surg Pathol 2011. https://doi.org/10.1097/PAS.0b013e31820eb25b.

[14] Seipel AH, Wiklund F, Wiklund NP, Egevad L. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. Virchows Arch 2013. https://doi.org/10.1007/s00428-013-1385-5.

[15] Jang WS, Shin SJ, Yoon CY, Kim MS, Kang DH, Kang YJ, et al. Prognostic significance of the proportion of ductal component in ductal adenocarcinoma of the prostate. J Urol 2017. https://doi.org/10.1016/j.juro.2016.11.104.

[16] Christensen WN, Steinberg G, Walsh PC, Epstein JI. Prostatic duct adenocarcinoma. Findings at radical prostatectomy. Cancer 1991: doi:10.1002/1097-0142(19910415)67:8<2118::AID-CNCR2820670818>3.0.CO;2-G.

[17] Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. Am J Surg Pathol 1999. https://doi.org/10.1097/00000478-199912000-00004.

[18] Morgan TM, Welty CJ, Vakar-Lopez F, Lin DW, Wright JL. 244 Ductal adenocarcinoma of the prostate: increased mortality risk and decreased psa secretion. J Urol 2010. https://doi.org/10.1016/j.juro.2010.02.303.

[19] Kim A, Kwon T, You D, Jeong IG, Go H, Cho YM, et al. Clinicopathological features of prostate ductal carcinoma: matching analysis and comparison with prostate acinar carcinoma. J Korean Med Sci 2015. https://doi.org/10.3346/jkms.2015.30.4.385.

[20] Lemberger RJ, Bishop MC, Bates CP, Blundell W, Ansell ID. Carcinoma of the prostate of ductal origin. Br J Urol 1984. https://doi.org/10.1111/j.1464-410X.1984.tb06152.x.

[21] Dube VE, Farrow GM, Greene LF. Prostatic adenocarcinoma of ductal origin. Cancer 1973:doi:10.1002/1097-0142(197308)32:2<402::AID-CNCR2820320218>3.0.CO;2-Q.

[22] Eade TN, Al-Saleem T, Horwitz EM, Buyyounouski MK, Chen DYT, Pollack A. Role of radiotherapy in ductal (endometrioid) carcinoma of the prostate. Cancer 2007. https://doi.org/10.1002/cncr.22644.

[23] Orihuela E, Green JM. Ductal prostate cancer: contemporary management and outcomes. Urol Oncol Semin Orig Investig 2008. https://doi.org/10.1016/j.urolonc.2007.05.028.

[24] Zhou M. High-grade prostatic intraepithelial neoplasia, PIN-like carcinoma, ductal carcinoma, and intraductal carcinoma of the prostate. Mod Pathol 2018. https://doi.org/10.1038/modpathol.2017.138.

[25] Harkin T, Elhage O, Chandra A, Khan N, Kiberu Y, Frydenberg M, et al. High ductal proportion predicts biochemical recurrence in prostatic ductal adenocarcinoma. BJU Int 2019. https://doi.org/10.1111/bju.14831.