

Monotherapy of androgen deprivation therapy versus radical prostatectomy among veterans with localized prostate cancer: comparative effectiveness analysis of retrospective cohorts

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Background: This retrospective cohort study aimed to examine the comparative effectiveness of monotherapy of primary androgen deprivation therapy or radical prostatectomy.

Methods: Male patients with localized prostate cancer (T1-T2, N0, M0) were identified in the Veterans Affairs Veterans Integrated Service Network 16 data warehouse (January 2003 to June 2006), with one-year baseline and at least three-year follow-up data (until June 2009). Patients were required to be 18–75 years old and without other recorded cancer history. The initiation of primary androgen deprivation therapy or monotherapy of radical prostatectomy within six months after the first diagnosis of prostate cancer was used as the index date. Primary androgen deprivation therapy patients were matched to the radical prostatectomy patients via propensity score, which was predicted from a logistic regression of treatment selection (primary androgen deprivation therapy versus radical prostatectomy) on age, race, marital status, insurance type, cancer stage, Charlson comorbidity index, and alcohol and tobacco use. The overall survival from initiation of index treatment was then analyzed using the Kaplan–Meier and Cox proportional hazards model.

Results: The two cohorts were well matched at baseline (all $P > 0.05$). During a median follow-up of 4.3 years, the cumulative incidence of death was 13 (10.57%) among 123 primary androgen deprivation therapy patients and four (3.25%) among 123 radical prostatectomy patients ($P < 0.05$). The overall three-year survival rate was 92.68% for primary androgen deprivation therapy and 98.37% for radical prostatectomy ($P < 0.05$). Patients who received primary androgen deprivation therapy had almost three times as high a mortality risk as those using radical prostatectomy (hazards ratio 3.388, 95% confidence interval 1.094–10.492, $P = 0.034$).

Conclusion: After propensity score matching, overall three-year survival rate following radical prostatectomy among patients with localized prostate cancer was significantly higher than that after primary androgen deprivation therapy.

Keywords: prostate cancer, primary androgen deprivation therapy, radical prostatectomy, survival rate

Introduction

Prostate cancer is the most common malignancy in men.¹ In 2009, new cases of prostate cancer were estimated over 190,000, and the disease also causes approximately 30,000 deaths per year in the United States.² Approximately 80% of patients with prostate cancer were diagnosed at clinically localized or regional stages.³ They are often treated with active surveillance, surgery, androgen deprivation therapy, or radiation. We note that the National Comprehensive Cancer Network practice guidelines for management

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include all of the above except for androgen deprivation therapy as monotherapy.⁴

Despite the lack of support, primary androgen deprivation therapy has become a common choice for clinically localized patients. According to the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, 14.4% of clinically localized patients received primary androgen deprivation therapy.⁵ The common use of primary androgen deprivation therapy in patients with localized prostate cancer may be because several studies support the use of androgen deprivation therapy in patients with metastatic disease or with high-risk cancer, in combination with radiation therapy or as adjuvant therapy for node-positive patients after radical prostatectomy.^{6–9} While the optimal timing of androgen deprivation therapy also remains controversial,¹⁰ no randomized controlled studies have evaluated androgen deprivation monotherapy in patients with low-risk cancer. Further, large population-based studies observed inferior survival following primary androgen deprivation therapy compared with watchful waiting.^{11,12}

On the other hand, radical prostatectomy is a commonly used cure attempt for clinically localized patients, with an estimate of 60,000 radical prostatectomies performed annually in the United States.¹³ Its clinical benefit in patients at an early stage has been demonstrated in Scandinavian Prostate Cancer Group Study Number 4.¹⁴ However, the patients were not typically detected by prostate-specific antigen screening in this study. These results might or might not apply to today's patients in the United States, who are identified primarily by prostate-specific antigen-induced prostate biopsies. Ongoing studies are evaluating surveillance as a control group in this setting and require prolonged periods of follow-up to draw a conclusion.^{13,15}

There is no randomized controlled trial to compare primary androgen deprivation therapy with radical prostatectomy in the literature, and no such study is ongoing to our knowledge. In this retrospective cohort study, we examined the overall survival rate of localized prostate cancer using either primary androgen deprivation therapy or radical prostatectomy as monotherapy in the Veterans Affairs health system.

Materials and methods

Data source

This study was a retrospective analysis of patients with prostate cancer in the Veterans Integrated Service Network (VISN) 16. VISN 16 is one of the 23 VISNs of the Department of Veterans Affairs, serving veterans in Arkansas, Louisiana, Mississippi,

Oklahoma, and parts of Alabama, Florida, Missouri, and Texas. The database contains demographic data, inpatient and outpatient activities, pharmacy prescriptions, laboratory results, and mortality information (date of death) for each patient treated within the network. A tumor registry, which captures data on cancer stage and therapies in the network, is also available. The data warehouse is updated monthly and maintained by the VISN 16 Information Technology Development Group. Data covering the period from January 1, 2002, to June 30, 2009, were extracted. Both Tulane and Veterans Health Administration institutional review boards and Veterans Health Administration Research and Development approved this study protocol. All patient identifiers were removed. Data format and content were in compliance with the Health Insurance Portability and Accountability Act requirements.

Sample selection

Figure 1 summarizes the sample selection process. Patients were included in the study if they had at least one diagnosis of prostate cancer (International Classification of Disease-9-Clinical Modification [ICD-9-CM] 185.xx). Prostate cancer diagnoses were confirmed by the inclusion of patients in the VISN 16 cancer registry. The participants were required to have records of clinically localized prostate cancer patients (T1-T2, N0, M0). Further inclusion criteria included: initiation of androgen deprivation therapy or radical prostatectomy between January 1, 2003 and June 30, 2006 to ensure one-year study baseline and at least three years follow-up (until June 30, 2009); either androgen deprivation therapy or radical prostatectomy as monotherapy was initiated within six months after first diagnosis of prostate cancer; age 18–75 years; and no documented cancer history before prostate cancer diagnosis. Patients who had ever received radiation therapy were excluded from this study.

Treatments

Androgen deprivation therapy was identified utilizing a reported algorithm,¹⁶ including the Healthcare Common Procedure Coding System [HCPCS] codes for orchiectomy: 54520, 54521, 54522, 54530, 54535 or ICD-9-CM code of 62.4, and the HCPCS codes for luteinizing hormone releasing hormone (LHRH) agonists: J1950, J9202, J9218, or J9219. radical prostatectomy was identified using the HCPCS codes: 55821, 55801, 55810, 55812, 55815, 55831, 55840, 55842, 55845 or ICD-9-CM code: 60.3, 60.4, 60.5, 60.6, and 60.62.¹⁷

Outcome

Survival was defined as the interval from the initiation of treatment to the date of death. Patients were followed from

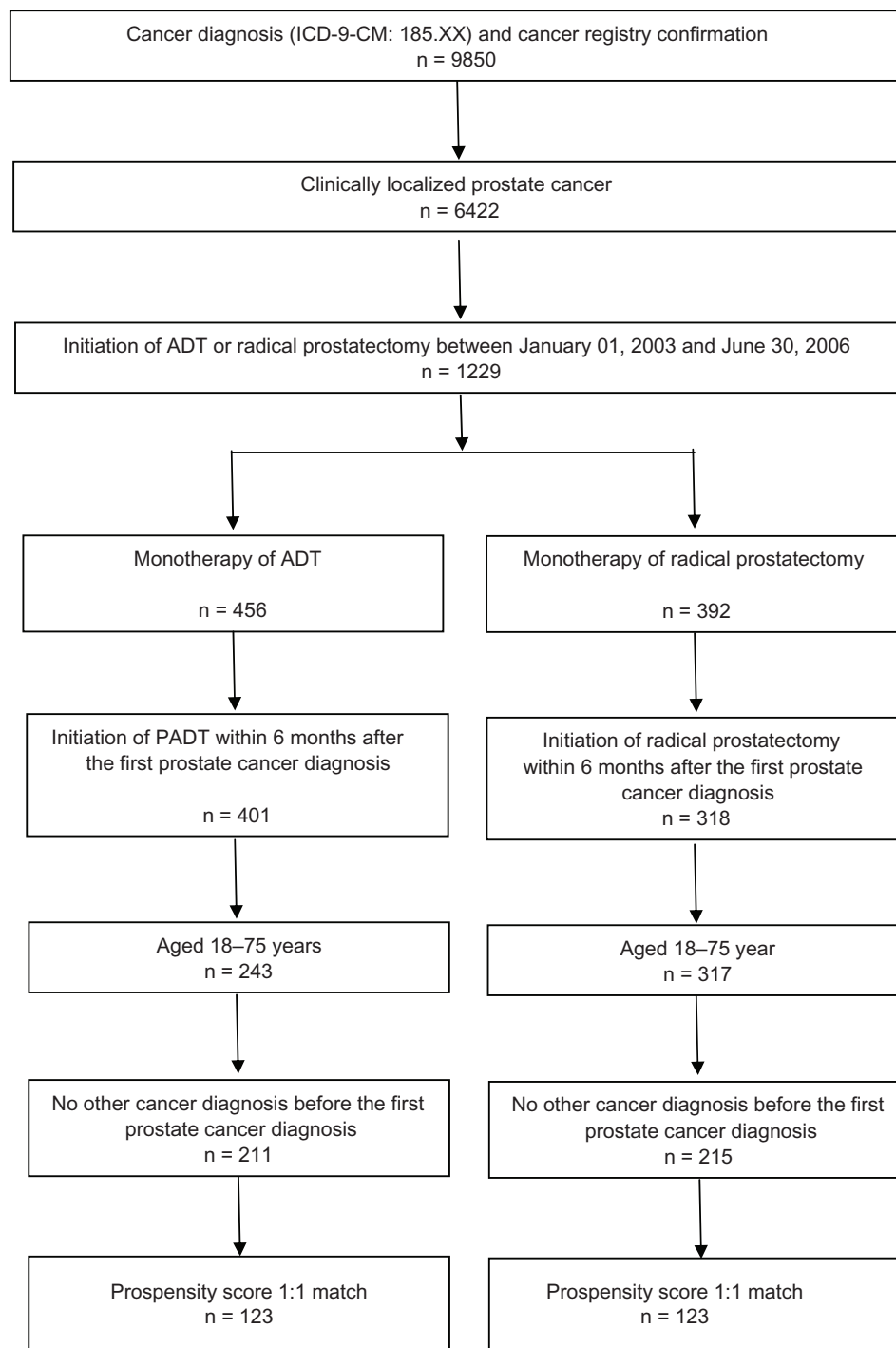


Figure 1 Flow chart for selection of patients with clinically localized prostate cancer.

Abbreviations: ADT, androgen deprivation therapy; PADT, primary androgen deprivation therapy.

their treatment initiation date to death, or were censored at the end of data availability (until June 30, 2009).

Statistical analyses

Propensity score matching was used to adjust for treatment selection bias, which is expected in observational studies due to lack of randomization.¹⁸ After matching, two cohorts with

comparable baseline information were expected, and this was, in fact, obtained. Specifically, the propensity scores were assessed from a logistic regression that estimated the probability of receiving primary androgen deprivation therapy versus radical prostatectomy, using age at the first prostate cancer diagnosis, race, marital status, insurance type, cancer stage, Charlson comorbidity index,¹⁹ and alcohol and tobacco

use as the explanatory variables. A radical prostatectomy patient was then matched with a primary androgen deprivation therapy patient if their predicted probability were the closest, with a maximum distance tolerance of 0.1.¹⁸ Chi-square tests for categorical variables and paired *t*-tests for continuous variables were used to verify that the baseline characteristics were comparable after matching.

Overall survival rate was analyzed using the Kaplan–Meier method, and hazard ratios were estimated using Cox proportional hazard regression, adjusted for age at first prostate cancer diagnosis, race, marital status, insurance type, cancer stage, Charlson comorbidity index, and tobacco and alcohol use.

Results

Among 1229 localized patients with prostate cancer, 456 (37.1%) received primary androgen deprivation therapy and 392 (31.9%) used radical prostatectomy. A total of 426 patients met all the study inclusion criteria, ie, 211 patients

in the primary androgen deprivation therapy group and 215 in the radical prostatectomy group. Before propensity score matching, patients in the primary androgen deprivation therapy group were older ($P < 0.001$), with a higher Charlson comorbidity index score ($P < 0.001$), less likely to be black ($P = 0.027$), less likely to have other insurance ($P < 0.001$), and less likely to be tobacco ($P = 0.008$) and alcohol users ($P = 0.020$). No difference in marital status ($P = 0.057$) and baseline cancer stage ($P = 0.127$) was found between the groups. Detailed information is available in Table 1.

After 1:1 propensity score matching, the final sample of this study was 246, ie, 123 patients in the primary androgen deprivation therapy cohort and 123 in the matched radical prostatectomy cohort. All 123 patients in the primary androgen deprivation therapy cohort used LHRH agonists in this study. The mean age was 62.9 ± 5.50 years in the primary androgen deprivation therapy patients, and 62.5 ± 4.95 years in the radical prostatectomy patients. Charlson comorbidity index

Table 1 Baseline characteristics of primary androgen deprivation therapy cohort versus radical prostatectomy cohort before and after propensity score match

	PADT (n = 211)	RP (n = 215)	P values before match	Matched PADT (n = 123)	Matched RP (n = 123)	P values after match
Age, years*	66.2 (6.07)	59.9 (6.15)	<0.001	62.9 (5.50)	62.5 (4.95)	0.386
Age, years			<0.001			0.678
<65	93 (44.08%)	171 (79.53%)		87 (70.73%)	84 (68.29%)	
≥65	118 (55.92%)	44 (20.47%)		36 (29.27%)	39 (31.71%)	
Race			0.027			0.655
White	121 (57.35%)	121 (56.28%)		72 (58.54%)	71 (57.72%)	
Black	58 (27.49%)	77 (35.81%)		42 (34.15%)	39 (31.71%)	
Others	32 (15.17%)	17 (7.91%)		9 (7.31%)	13 (10.57%)	
Marital status			0.570			0.796
Married	111 (52.61%)	119 (55.35%)		72 (58.54%)	70 (56.91%)	
Others	100 (47.39%)	96 (44.65%)		51 (41.46%)	53 (43.09%)	
Insurance other than VA			<0.001			0.523
Yes	71 (33.65%)	129 (60.00%)		56 (45.53%)	61 (49.59%)	
No	140 (66.35%)	86 (40.00%)		67 (54.47%)	62 (50.41%)	
Cancer stage			0.127			1.000
≤T2a	191 (90.52%)	203 (94.42%)		113 (91.87%)	113 (91.87%)	
>T2a	20 (9.48%)	12 (5.58%)		10 (8.13%)	10 (8.13%)	
CCI*	0.8 (0.64)	0.3 (0.21)	<0.001	0.6 (1.20)	0.5 (1.08)	0.821
CCI			<0.001			0.921
0	122 (57.82%)	174 (80.93%)		89 (72.36%)	87 (70.73%)	
I	53 (25.12%)	25 (11.63%)		21 (17.07%)	21 (17.07%)	
≥2	36 (17.06%)	16 (7.44%)		13 (10.57%)	15 (12.20%)	
Tobacco user			0.008			0.438
Yes	109 (51.66%)	138 (64.19%)		75 (60.98%)	69 (56.10%)	
No	102 (48.34%)	77 (35.81%)		48 (39.02%)	54 (43.90%)	
Alcohol user			0.020			0.691
Yes	59 (27.96%)	83 (38.60%)		43 (34.96%)	46 (37.40%)	
No	152 (72.04%)	132 (61.40%)		80 (65.04%)	77 (62.60%)	

Note: *Data presented as mean ± standard deviation.

Abbreviations: CCI, Charlson comorbidity index; RP, radical prostatectomy; PADT, primary androgen deprivation therapy; VA, Veterans Affairs.

was 0.6 ± 1.20 years in primary androgen deprivation therapy and 0.5 ± 1.08 years in radical prostatectomy patients. After matching by propensity scoring, all baseline variables were equivalent between the two groups (all P values > 0.05).

The median follow-up was 4.3 years in the primary androgen deprivation therapy cohort and 4.2 years in the radical prostatectomy cohort. During the follow-up period, the cumulative incidence of death was 13 (10.57%) among 123 primary androgen deprivation therapy-treated patients and four (3.25%) among 123 radical prostatectomy-treated patients. According to the Kaplan–Meier curves (Figure 2), the overall three-year survival rate was 92.68% in primary androgen deprivation therapy cohort and 98.37% in the radical prostatectomy cohort ($P = 0.028$). The Cox proportional hazard regression results are presented in Table 2. Patients who underwent primary androgen deprivation therapy had almost three times mortality risk as those using radical prostatectomy (hazards ratio 3.388, 95% confidence interval = 1.094–10.492, $P = 0.034$). All other explanatory variables, including age, race, marital status, insurance, cancer stage, Charlson comorbidity index, tobacco use, and alcohol use, were not statistically significant (all P values > 0.05).

Discussion

Though prior data from studies have compared the utilization of early versus delayed androgen deprivation therapy

use¹⁰ and radiotherapy versus radiotherapy combined with androgen deprivation therapy,⁸ this is the first study which attempts to explore the comparative effectiveness between primary androgen deprivation therapy and radical prostatectomy among patients with localized prostate cancer.

According to our study, primary androgen deprivation therapy was related to a three-fold higher risk of death than radical prostatectomy.

Previous studies have also reported that higher death rates are associated with this form of therapy.¹⁷ Physiologic effects of primary androgen deprivation therapy, such as weight gain, muscle mass reduction, and changes in lipids may lead to exacerbation of potentially more serious conditions, such as hypertension, diabetes, and coronary artery disease.²⁰ Androgen deprivation therapy has also been related to a higher risk of fracture,¹⁶ diabetes, and possible coronary heart disease,²¹ and has adverse effects on quality of life.²² These results indicate that androgen deprivation therapy alone may not be an appropriate therapeutic choice for the population with localized prostate cancer. However, primary androgen deprivation therapy seems to be overutilized for patients with localized prostate cancer in Veterans Affairs during this period. Specifically, more than one third of the localized population received primary androgen deprivation therapy in the study, as compared with 14.4% in the CaPSURE database;²³ more people treated with primary

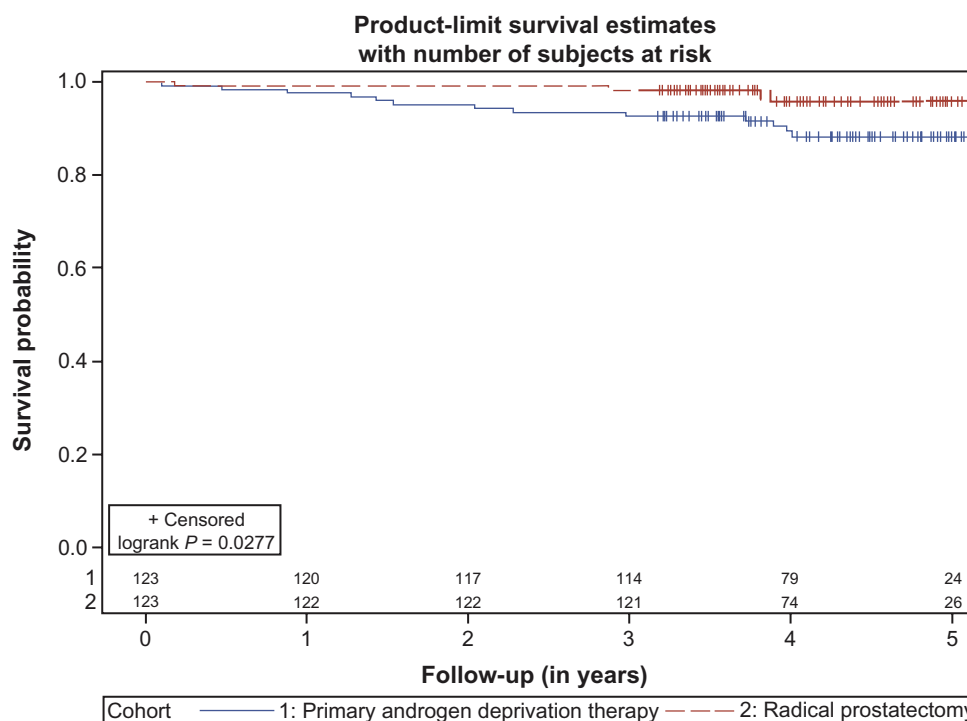


Figure 2 Overall survival in primary androgen deprivation therapy cohort versus radical prostatectomy cohort after propensity match.

Table 2 Hazard risk of death among localized prostate cancer patients according to Cox proportional hazard regression after propensity score match

	Hazards ratio	95% Confidence interval	P values
Treatment (reference RP)			0.034
PADT	3.388	(1.094, 10.492)	
Age (reference ≤ 65)			0.793
≥ 65	1.014	(0.916, 1.121)	
Race (reference, black)			
White	1.198	(0.409, 3.507)	0.742
Other race	0.000	NA	0.993
Marital status (reference, married)			0.127
Others	2.243	(0.795, 6.329)	
Insurance (reference, VA only)			0.448
Others	0.657	(0.222, 1.945)	
Cancer stage (reference $\leq T2a$)			0.659
$>T2a$	0.629	(0.081, 4.915)	
CCI (reference 0)			
1	1.284	(0.331, 4.982)	0.718
≥ 2	3.155	(0.850, 11.709)	0.086
Tobacco user (reference, no)			0.651
Yes	0.747	(0.212, 2.641)	
Alcohol user (reference, no)			0.446
Yes	1.595	(0.480, 5.304)	

Abbreviations: CCI, Charlson comorbidity index; RP, radical prostatectomy; NA, not available (because of the zero coefficient and a large P value); PADT, primary androgen deprivation therapy; VA, Veterans Affairs.

androgen deprivation therapy as compared with radical prostatectomy. The reason for the higher rate of primary androgen deprivation therapy in Veterans Affairs than in the CaPSURE population is unclear because no guideline has embraced this form of therapy. A recent study reported that decreased physician reimbursement was related to a reduction of androgen suppression therapy from 10.2% in 2003 to 6.1% in 2005 among low-risk prostate cancer patients.²⁴ In contrast with private practice, the Veterans Affairs system does not link drug usage to physician reimbursement incentives. The question of how to reduce the inappropriate use of androgen deprivation therapy remains a challenge in the Veterans Affairs system.

Radical prostatectomy patients achieved a comparatively high three-year survival rate in this study, both in univariate analysis and in multivariate analysis adjusted for other baseline variables. Further, randomized trials indicate that radical prostatectomy is a better choice than active surveillance in men with non-prostate-specific antigen-detected cancers. Previous studies have also reported that radical prostatectomy patients have a lower risk of death than watchful waiting patients, so radical prostatectomy is typically regarded as the “gold standard” for localized prostate cancer.²⁵ Despite being a known effective therapy, radical prostatectomy is also related to distinct patterns of adverse change in quality of life, particularly sexual and urinary health.^{25,26}

This study has several limitations. First, it was an observational study without randomization. Even though we balanced the baseline information between two cohorts using propensity score matching, selection bias may still be an issue due to unobservable variables. For example, important severity measures such as prostate-specific antigen and Gleason score were not available in the registry database. Second, cause of death was not recorded in the Veterans Affairs vital records. Prior studies clearly indicate high non-prostate cancer mortality among prostate cancer patients, even after failure of primary treatment.²⁷ But, overall survival rate is still one important aspect to compare two treatments, especially for a study population with an average age of 63 years. Third, localized prostate cancer patients typically have a high overall survival rate, and a substantial number of participants had only a relatively short-term follow-up in this study.

In conclusion, this preliminary comparative effectiveness analysis of overall three-year survival rate found that the cohort of patients with clinically localized prostate cancer and radical prostatectomy had significantly higher survival outcomes than the cohort of patients with primary androgen deprivation therapy. Further analyses of cause of death and longer-term follow-up are warranted to confirm the finding and to understand better the reasons for the mortality observed.

Disclosure

No potential conflicts of interest are disclosed. This study has been presented at the 16th annual meeting of the International Society for Pharmacoeconomics and Outcomes Research in Baltimore, MD, May, 2011 and also been reported in the media *Renal and Urology News*, August 2011.

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