The Comparison of Survival Between Active Surveillance or Watchful Waiting with Focal Laser Ablation in Patients with Low-Risk Prostate Cancer

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Primary research

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Abstract

Introduction

Prostate cancer (PCa) is the second most common cancer in men. Some trials of focal laser ablation (FLA) in men with PCa have shown exciting results. Both active surveillance or watchful waiting (AS/WW) and FLA can avoid the complications caused by radical treatment, how to choose between them in clinical practice needs further study. Therefore, this study aims to compare and analyze the effects of them based on the overall survival (OS) and cancer-specific survival (CSS) for obtaining better long-term benefits.

Method

We included patients with low-risk PCa from the Surveillance Epidemiology and End Results database of 2010-2016. Multivariate Cox's proportional hazard analysis were conducted of OS and CSS in two groups. For eliminating bias, this study applied a serious of sensitive analyses. Moreover, Kaplan-Meier curves were plotted for survival status.

Result

Totally 18,841 patients with low-risk PCa were included with median 36.00 months follow-up time. According to the multivariate Cox proportional hazard regression, FLA group presented inferior survival benefits in OS than AS/WW group (HR 2.13, 95% CI 1.37-3.33, $p < .05$). After adjusting for confounders, the result consisted with before (HR 1.69, 95% CI 1.0- 2.81, $p < .05$). In sensitivity analysis, the inverse probability of treatment weighing model indicated the same result in OS.

Conclusion

Compared with standard treatment, AS/WW and FLA had the advantages of less side effects and avoiding over treatment. For patients with low-risk PCa, our study suggested that AS/WW could obtain more survival benefits. More relevant researches and more data will be need for further researches.

1 Introduction

Prostate cancer (PCa) is the second-most frequent cancer, and the fifth-highest mortality for men. It was estimated that there were nearly 1.3 million new prostate cancer cases and 359,000 related deaths worldwide in 2018. It is also the most diagnosed cancer among men in more than half of the world (105 out of 185 countries)(1). By the end of 2020, it is estimated that approximately 606,520 Americans will die of cancer, of which 321,160 will be male, and prostate cancer will be ranked second in mortality. Among the estimated new cases, prostate cancer ranks first in male patients (2).

During this same period, because of the high adoption of prostate-specific antigen (PSA) screening, the global diagnosis of cases with low-risk and medium-risk PCa has increased (3). From 2004 to 2014 in the

United States, 34.26% of all patients with PCa were diagnosed with low-risk PCa (4). As this represents a large proportion of affected patients, it is thus very important to ensure effective manage and treatment of these cases.

Conventionally, most patients with low-risk PCa receive either radical prostatectomy or radiotherapy (5, 6). However, the side effects of these treatments, such as urinary incontinence, erectile dysfunction, postoperative infection, hematuria, and pain, may be more detrimental to the patient versus the benefit of treatment itself (7–9). In addition to radiotherapy and radical prostatectomy, active surveillance (AS) was recommended as another standard treatment for patients with low-risk localized PCa (5, 6). Several studies have consistently suggested that men with low-risk PCa should consider AS as a valid treatment option (7, 10, 11). AS and watchful waiting (WW) are collectively referred to as conservative or deferred treatment in guidelines and in research (12–15), and the aim of both is to reduce overtreatment.

Another new treatment is local therapy; an approach centered on retaining key structures and ensuring stable urogenital function. It specifically destroys known tumor areas, and maintains the survival benefits of aggressive treatments (16). Several energy therapies, including focal laser ablation (FLA), cryotherapy, and photodynamic therapy, have been developed to promote the local treatment of low- and medium-risk PCa (17). FLA has undergone significant development as a focus therapy model, and the process is often guided under MRI (18, 19). Based on results of Phase II trials, FLA was associated with greater beneficial tumor prognosis in the short term, and in addition, FLA-treated patients did not show significant urinary, sexual, or intestinal side effects (20). Further, a small-scale research study reported that FLA as a treatment modality exhibited early tumor control and resulted in fewer complications and improved quality of life (21). A larger retrospective study showed that 83% of patients undergoing FLA had no relapse in one year, and no obvious changes were observed of sexual and urinary function after undergoing FLA (22). In addition, several other trials of FLA have shown encouraging short-term results, with the overall conclusion that FLA is a realistic treatment option (21, 23–25). Despite the encouraging potential of FLA based on these findings, the present trials investigating FLA as a treatment modality for PCa do not have a double-arm design and are not collecting long-term oncology results namely, outcomes of overall survival (OS) and cancer-specific survival (CSS).

Although AS/WW and FLA avoid complications caused by overtreatment, how to choose between them in clinical practice needs further study. In particular, a long-term tumor prognosis trial for patients with low-risk PCa is lacking. Furthermore, there has been no direct comparison between FLA and AS/WW. Therefore, the aim of this study was to verify the efficacy of FLA and AS/WW in patients with low-risk PCa. To evaluate long-term benefits of these approaches, OS and CSS were analyzed and compared in our patient cohort.

2 Materials And Methods

2.1 Patient Selection

In 2018, a new dataset was released containing AS/WW data from the Surveillance, Epidemiology, and End Results (SEER) Program in the United States (26), from which we identified known cases of low-risk PCa from 2010 to 2016. Our initial study cohort consisted of 57,631 patients, which underwent further evaluation based on inclusion and exclusion criteria. Our inclusion criteria included patients with low-risk PCa, which was defined as a clinical tumor stage between T1 to T2a, a Gleason score < 7, and PSA level < 10 ng/mL (5, 6). Exclusion criteria were as follows: 1) tumor had a different histology or unknown histology from adenocarcinoma; 2) absence of positive histological confirmation; 3) patients who rejected active treatment or WW as the treatment modality or patients without doctor's advice to take that treatment; and 4) patients who underwent treatment other than by AS/WW or FLA. Based on these criteria, our final cohort consisted of 18,841 patients. The evaluation process for screening patients is shown in Fig. 1. All information was downloaded from the SEER database.

2.2 Propensity Score Matching

Because baseline characteristics would influence treatment choice, we used propensity score matching (PSM) with a ratio of 1:4 and caliper width of 0.05 standard deviations. Our intent was to ensure that the FLA and AS/WW groups had similar baseline characteristics. In addition, we applied logistic regression to adjust for differences between groups (27). The process was executed according to the nearest neighbor matching principle, and the matching process was considered balanced when $p > 0.05$.

2.3 Data Analyses

Baseline indicators were contrasted before and after matching in FLA and AS/WW groups. We applied 2-tailed sample t-test, Chi-square test, Kruskal–Wallis test, rank sum test, and Fisher’s exact test for the respective variables. Kaplan–Meier survival curves were generated to estimate OS and CSS of patients in our two groups. Based on baseline characteristics, we also compared the two treatment options (FLA or AS/WW) for patients during 2010–2016 using a line chart. In addition, we performed multivariate Cox proportional hazard model to analyze pre- and post-PSM cohorts of our FLA and AS/WW groups. OS and CSS are expressed by hazard ratio (HR) with 95% confidence interval (CI). We also performed subgroup analyses based on race, age, tumor stage, and PSA level.

To verify the reliability of the main results, we conducted the following series of sensitivity analyses: (a) OS and CSS analyses after correcting for imbalanced covariates between the AS/WW group and FLA group; (b) CSM analysis after adjusting propensity scores; (c) PSM double-adjustments for multivariate Cox proportional hazard model; and (d) application of inverse probability of treatment weighing (IPTW) model after PSM. All data analyses were performed using R packages and EmpowerStats (28, 29). P-values less than 0.05 were considered statistically significant.

3 Results

Our study cohort consisted of 18,841 patients with low-risk PCa between 2010 and 2016 from the SEER database. It includes 18,611 patients undergoing AS/WW and 230 patients undergoing FLA. The median

follow-up time of this study was 36.00 months. Baseline characteristics of our cohort are presented in Table 1. We found that patients undergoing FLA were older than those undergoing AS/WW ($p < 0.001$), and that patients receiving FLA had a lower PSA level ($p < 0.05$) and longer survival rate ($p < 0.001$) compared with those found in patients receiving AS/WW. In addition, these two groups had differences in the baseline characteristics of insurance status ($p < 0.05$) and year of diagnosis ($p < 0.001$; Table 1). From 2010 to 2016, the overall trend of patients choosing AS/WW treatment increased, whereas the number of patients choosing FLA was small and exhibiting a slight downward trend (Fig. 2).

Based on Kaplan–Meier survival curves (Fig. 3), we found increased OS in patients from the AS/WW group compared with the FLA group ($p < 0.05$), and no statistical difference in CSS between the two groups ($p = 0.32$). Next, using multivariate Cox proportional hazard regression analysis, we found that patients from the FLA group have worse survival benefits in OS compared with patients from the AS/WW group (HR, 2.13; 95% CI, 1.37–3.33; $p < 0.05$). Regarding CSS, no obvious difference between groups was observed before adjustments (HR, 1.96; 95% CI, 0.27–14.32; $p = 0.51$). After adjusting for age, insurance status, year of diagnosis, race, tumor stage, and PSA level, we similarly found worse OS in the FLA group compared with the AS/WW group (HR, 1.69; 95% CI, 1.0– 2.81; $p < 0.05$) and no significant difference in CSS between groups (HR, 1.97; 95% CI, 0.27–14.58; $p = 0.51$; Table 2). We then performed subgroup analysis and found that differences in race, age, PSA level, and tumor stage between the two groups exerted varying effects on OS and CSS. However, in spite of these findings, we found no evidence of an interaction on OS or CSS in our cohort ($p > 0.05$; Table 3)

Next, we performed PSM matching 177 patients undergoing FLA with 708 patients undergoing AS/WW in a 1:4 ratio. Age, race, tumor stage, PSA level, and insurance status were chosen as covariates; the difference in PSA level was negated after PSM. All baseline variables are shown in Supplementary Table 1. Following PSM, we analyzed the matched cohorts using regression analysis and unexpectedly found that the CSS of patients receiving FLA was significantly worse compared with that of patients receiving AS/WW (HR, 17.76, 95% CI, 1.15–275.02; $p < 0.05$), whereas no obvious difference was observed in OS between the two groups ($p > 0.05$). As there may be baseline differences after PSM, we performed a double-adjustment with PSM. After adjusting for age, race, tumor stage, and insurance status, we found that the results were consistent with those after PSM, but before double-adjustment (CSS: HR, 19.48; 95% CI, 1.03–369.49; $p < 0.05$; OS: $p > 0.05$; Supplementary Table 2). To further verify the robustness of our findings, we then used IPTW after PSM, and found that OS was lower in the FLA group compared with the AS/WW group, a result consistent with the main finding of our study. Details regarding PSM and IPTW analyses are available in Supplementary Table 2.

4 Discussion

Based on our study cohort of 18,841 patients with low-risk PCa from 2010 to 2016 from the SEER database, the main finding of our study was that OS of patients receiving AS/WW treatment was better compared to patients receiving FLA treatment. In a median follow-up of 36.00 months, we found that both OS and CSS showed similar results after model adjustments, PSM, and sensitivity analysis. Using

available data, we further examined data of the AS/WW group, which included patients receiving either AS or WW treatment. Although some guidelines and researchers have collectively grouped AS and WW (12, 30–33), and they are treated as a single variable in SEER data, there are important differences between the two approaches. AS is a monitoring strategy for patients with low-risk PCa, allowing patients to delay active treatment without cancer progression. Its purpose is to achieve treatment of progressive diseases without losing the therapeutic window (34). In contrast, WW is a conservative treatment of patients who are considered unsuitable for treatment from the beginning. It requires observation of patients and palliative treatment according to symptoms to maintain quality of life (30). Although we applied many methods to eliminate bias between AS/WW and FLA in our groups, it is still important to consider potential intragroup differences within AS/WW.

Similarly, in our consideration of AS/WW, there are a number of considerations regarding FLA. It is a new protector therapy for PCa, in which thermal ablation using a laser fiber can lead to cell death by raising the temperature above 60 ℃. The intent behind FLA is to reduce complications as well as improve quality of life of patients, albeit having no effect on tumor control (25, 35). To date, a small number of studies with a maximum follow up of one year reported the clinical application of FLA, but they lack long-term evidence (23, 25, 36, 37). Nevertheless, it was determined that FLA provided benefits for patients with low-risk PCa, and furthermore, concluded that FLA was a feasible and safe minimally invasive treatment for patients eligible for AS and radical treatment. However, van Luijtelaar et al. took the position that FLA should not be applied to candidates of AS and patients receiving FLA should be closely followed (38). Therefore, the FLA and AS groups were comparable for clinical use, and the findings match those from our study. OS did differ between patients with low-risk PCa from the AS/WW-treated and FLA-treated groups.

It is not unreasonable to consider that prognostic differences exist for different treatments. A study (39) showed that in a series of men who received AS with selective deferred therapy, many patients who eventually received radical prostatectomy were found to have advanced disease. It was also reported that short-term oncology results of FLA are promising, in which 50% of patients have no evidence of a tumor in the postoperative biopsy and 67% of patients have no tumor in the resection area (40). Such differences may be reflected in the survival and prognosis between these two treatments. As shown in our study, although no statistical differences were observed in CSS, we still found distinguishing characteristics between the AS/WW and FLA groups. Our main results show an obvious and robust difference in OS between the two groups; a finding that suggests the treatment approach of AS/WW is superior to that of FLA. In addition, we conducted a series of sensitivity analyses to evaluate stability and reliability, and found that CSS significantly differed between our groups after PSM. Although this finding was not identical with the main result of our investigation, it is still aligned with the fact that AS/WW improved survival status significantly over FLA. Furthermore, our findings following IPTW analysis confirm this conclusion by identifying differences in OS between groups.

To our knowledge, this investigation is the first comparative study of FLA and AS/WW in prostate cancer. In addition, our study had a number of advantages. First, we were able to recruit a large cohort with over

18,000 patients with low-risk PCa. Second, in contrast to present studies that have focused on short-term tumor control, our cohort had a medium-term follow-up and we also investigated long-term survival. Finally, we used a robust array of statistical analysis methods to eliminate bias. Although the findings from our study warrant further research, there were some limitations. Despite the attempt to randomize our study using statistical methods, a retrospective study cannot have the same level of evidence as a randomized controlled trial. In addition, because of limitations of the SEER database, the baseline data of patients is not comprehensive, and therefore, there may be latent confounders. Although we used PSM to address these limitation, we cannot avoid the possibility of potential bias in the AS/WW group. Further, patients with a long life expectancy would lack long-term AS/WW data.

In conclusion, compared with standard treatment, AS/WW and FLA have the advantage of fewer side effects and the benefit of avoiding overtreatment. The findings from our study show that treatment using AS/WW confers survival benefits to patients with low-risk PCa. We call for further research to investigate the clinical applicability of these treatment modalities toward ensuring that the best treatment is available for patients with low-risk PCa.

Abbreviations

AS, active surveillance; CI, Confidence interval; CSS, cancer-specific survival; FLA, focal laser ablation; HR, Hazard ratio; IPTW, inverse probability of treatment weighing; OS, overall survival; PCa, prostate cancer; PSA, prostate-specific antigen; PSM, Propensity score matching; SEER, Surveillance, Epidemiology, and End Results; WW, watchful waiting.

5 Declarations

5.1 Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

5.2 Ethics Statement

The study was approved by the Ethics Committee of West China Hospital in Chengdu, China.

5.3 Author Contributions

Jiakun Li wrote the main manuscript text. Shi Qiu, Yige Bao, Lu Yang and Qiang Wei modified the manuscript text. Jiakun Li, Kun Jin and Shi Qiu analyzed the data. Boyu Cai, Qiming Yuan and Xingyu Xiong prepared figures. Liansha Tang, Di Jin, Xianghong Zhou and Cong Chen prepared tables. All authors have read and approved the manuscript.

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5.6 Consent for publication

Written informed consent for publication was obtained from all participants.

5.7 Availability of data and materials

The datasets analysed for this study can be found in the National Cancer Institute. https://seer.cancer.gov/seerstat/databases/prostate-ww/index.html. Please see the Data Availability section of the Author guidelines for more details.

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Tables

Table 1. Baseline Demographic and Clinicopathologic Characteristics by AS/WW versus FLA. AS/WW = Active Surveillance or Watchful Waiting; FLA = Focal Laser Ablation; PSA = Prostate-specific Antigen; SD = Standard Deviation.

Treatment group	All patients	AS/WW	FLA	SD	P-value
	Mean+SD / N(%)				
Number of patients	18841	18611	230		
Age at diagnosis (year)	64.09 ± 7.59	64.05 ± 7.58	67.77 ± 7.96	0.48 (0.35, 0.61)	<0.001
PSA (ng/ml)	5.61 ± 1.89	5.62 ± 1.88	5.18 ± 2.21	0.21 (0.08, 0.34)	0.002
Survival months	36.00 ± 23.55	35.92 ± 23.53	41.99 ± 24.48	0.25 (0.12, 0.38)	<0.001
Insurance status				0.21 (0.08, 0.34)	0.034
Insured	14303 (75.91%)	14145 (76.00%)	158 (68.70%)		
Insured/No specifics	2554 (13.56%)	2516 (13.52%)	38 (16.52%)		
Any Medicaid	570 (3.03%)	560 (3.01%)	10 (4.35%)		
Uninsured	218 (1.16%)	217 (1.17%)	1 (0.43%)		
unknown	1196 (6.35%)	1173 (6.30%)	23 (10.00%)		
Year of diagnosis				0.30 (0.17, 0.43)	<0.001
2010	1881 (9.98%)	1840 (9.89%)	41 (17.83%)		
2011	2389 (12.68%)	2352 (12.64%)	37 (16.09%)		
2012	2489 (13.21%)	2456 (13.20%)	33 (14.35%)		
2013	3048 (16.18%)	3018 (16.22%)	30 (13.04%)		
2014	2773 (14.72%)	2743 (14.74%)	30 (13.04%)		
2015	2946 (15.64%)	2914 (15.66%)	32 (13.91%)		
2016	3315 (17.59%)	3288 (17.67%)	27 (11.74%)		
Race				0.08 (-0.05, 0.21)	0.754
White	14788	14606	182		

	(78.49%)	(78.48%)	(79.13%)		
Black	2545 (13.51%)	2512 (13.50%)	33 (14.35%)		
Other	1034 (5.49%)	1025 (5.51%)	9 (3.91%)		
Unknown	474 (2.52%)	468 (2.51%)	6 (2.61%)		
T stage				0.89 (0.76, 1.02)	<0.001
T1a	51 (0.27%)	0 (0.00%)	51 (22.17%)		
T1b	8 (0.04%)	0 (0.00%)	8 (3.48%)		
T1c	17386 (92.28%)	17235 (92.61%)	151 (65.65%)		
T1NOS	76 (0.40%)	68 (0.37%)	8 (3.48%)		
T2a	1320 (7.01%)	1308 (7.03%)	12 (5.22%)		
Gleason total				0.10 (-0.03, 0.23)	0.746
3	9 (0.05%)	9 (0.05%)	0 (0.00%)		
4	18 (0.10%)	18 (0.10%)	0 (0.00%)		
5	72 (0.38%)	72 (0.39%)	0 (0.00%)		
6	18742 (99.47%)	18512 (99.47%)	230 (100.00%)		

Table 2. Multivariate cox regression analyses for overall survival and cancer-specific survival in the total cohort. The adjusted model adjusted by age, insurance status, year of diagnosis, race, T stage and PSA level. AS/WW = Active Surveillance or Watchful Waiting; FLA = Focal Laser Ablation, CSS = Cancer-specific Survival; OS = Overall Survival.

	Non-adjusted, HR (95% CI) P-value	Adjusted, HR (95% CI) P-value
CSS		
AS/WW	1	1
FLA	1.96 (0.27, 14.32) 0.5092	1.97 (0.27, 14.58) 0.5050
OS		
AS/WW	1	1
FLA	2.13 (1.37, 3.33) 0.0009	1.69 (1.02, 2.81) 0.0430

Table 3. Subgroup analysis for overall survival and cancer-specific survival by Active Surveillance or Watchful Waiting versus Focal Laser Ablation. CSS = Cancer-specific Survival; OS = Overall Survival; PSA = Prostate-specific Antigen. The results were showed as “HR (95% CI) P-value”. Some of the results were not shown, because the number of people in the corresponding subgroup was too small to get.

Subgroups	Number of patients	CSS	OS
Race			
White	14788	1.33 (0.80, 2.19) 0.2709	1.18 (1.03, 1.35) 0.0163
Black	2545	-	1.03 (0.72, 1.48) 0.8557
Other	1034	-	-
Unknown	474	NA	-
P-value of interaction		0.8551	0.7331
Age at diagnosis			
<65	9402	-	0.93 (0.57, 1.53) 0.7812
≥65	9439	1.29 (0.78, 2.13) 0.3265	1.17 (1.02, 1.33) 0.0224
P-value of interaction		0.3853	0.3334
PSA			
<4	2785	2.71 (1.16, 6.31) 0.0208	1.33 (1.03, 1.73) 0.0314
≥4	16056	-	1.10 (0.95, 1.27) 0.2055
P-value of interaction		0.0547	0.2387
T stage			
T 1	17521	-	1.16 (1.03, 1.30) 0.0112
T 2	1320	2.39 (1.17, 4.89) 0.0166	1.12 (0.68, 1.87) 0.6551
P-value of interaction		0.1123	0.935

Figures

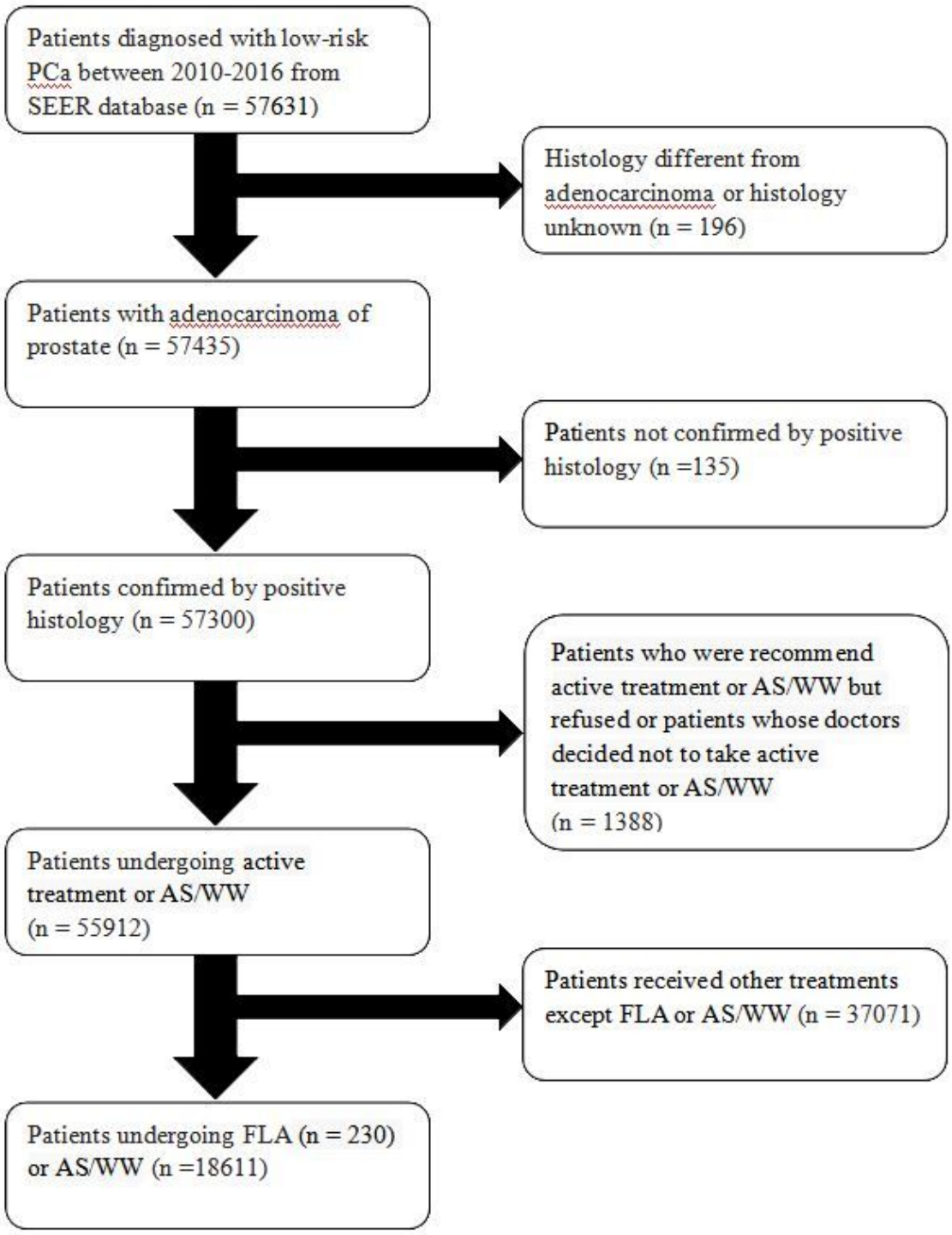

Figure 1

Flowchart of the patients selection. PCa = Prostate Cancer; SEER=Surveillance Epidemiology and End Results; AS/WW = Active Surveillance or Watchful Waiting; FLA = Focal Laser Ablation.

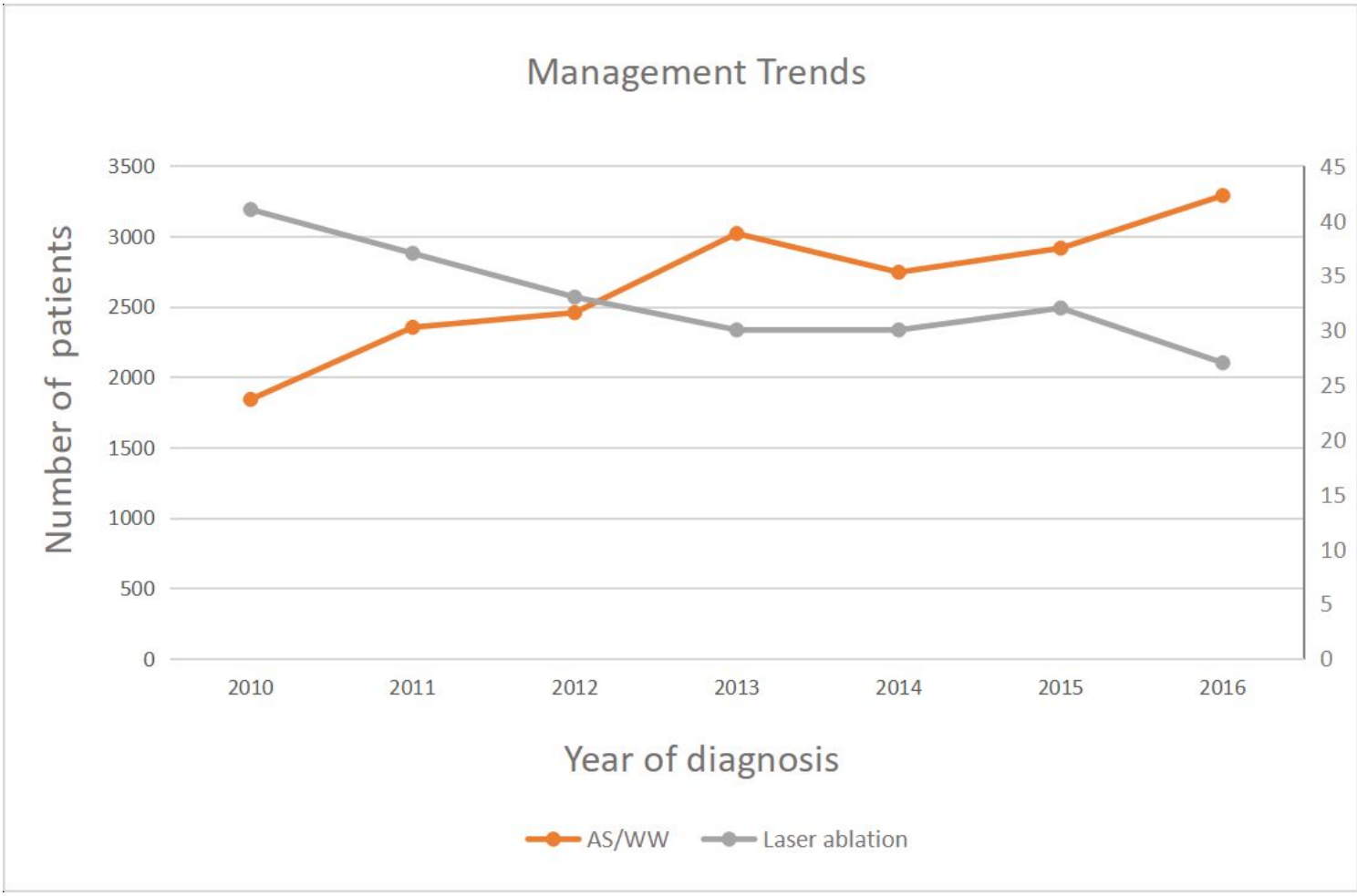

Figure 2

Initial management trends in people with low-risk prostate cancer from 2010 to 2016 in the Surveillance Epidemiology and End Results database. AS/WW = Active Surveillance or Watchful Waiting.

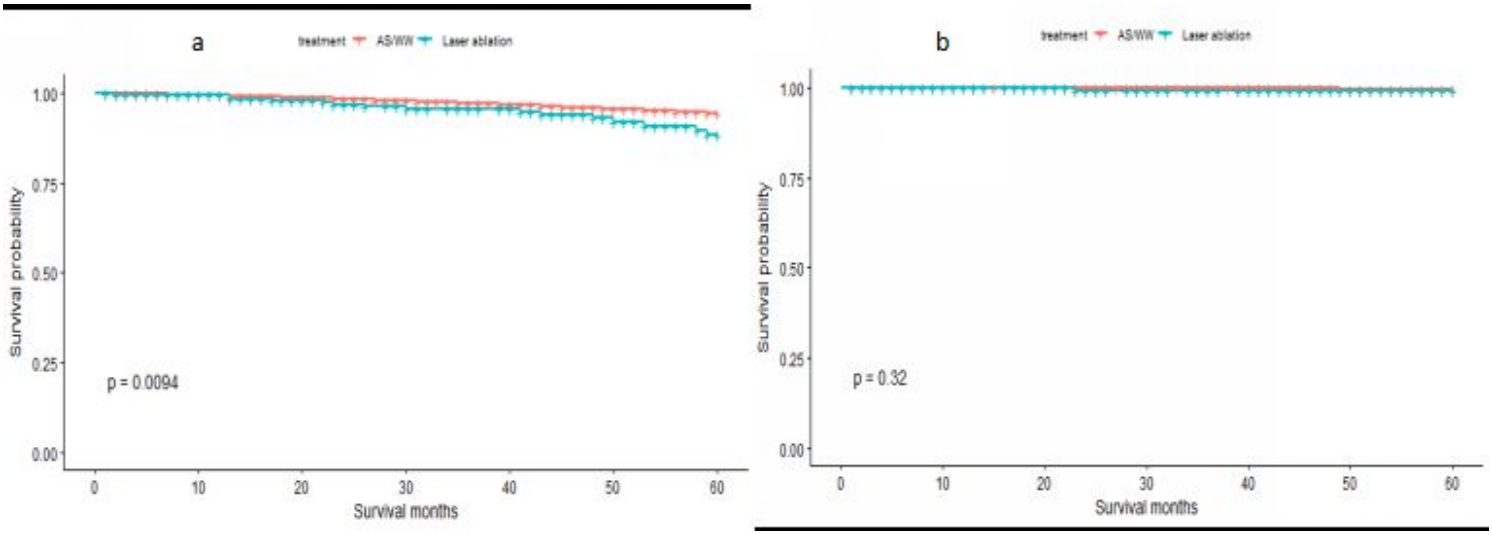

Figure 3

Kaplan-Meier Survival Curves of Active Surveillance or Watchful Waiting versus Focal Laser Ablation. a, Overall Survival; b, Cancer-specific Survival. AS/WW = Active Surveillance or Watchful Waiting.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaltable2.doc
- Supplementaltable1.doc