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Contents

Review

Original Articles

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BEST REVIEWER of ISSUE
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Review

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Contemporary Role of Active Surveillance in Prostate Cancer: To Whom, When, How?

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Abstract

Due to the widespread use of prostate-specific antigen testing and the increase in the elderly population, many asymptomatic patients have started to be diagnosed with prostate cancer (PCa). This leads to the reality of overdiagnosis and overtreatment of PCa. Since most of the initial diagnoses are clinically insignificant, a concept called active surveillance (AS) has emerged in the treatment of PCa, especially for patients in the low-risk group. Some authors also recommend this approach to selected intermediate-risk group patients. The main goal of AS is to prevent the negative effects of radiotherapy and surgery. Several well-known clinicians reported their results on AS, and their criteria appear to differ in terms of patient selection and follow-up. We aimed to review the criteria for patient selection, follow-up principles, and the outcomes of AS.
Keywords: Prostate cancer, active surveillance, treatment

Introduction

Prostate cancer (PCa) is the most common cancer among men and the second most common cause of cancer-related death among men (1). The probability of developing invasive PCa from birth to death is 1 in 8 (1). With the widespread use of prostate-specific antigen (PSA), advances in prostate biopsy (PB) techniques, and the increase in the elderly population, many asymptomatic patients have started to be diagnosed with PCa. Although this situation reduces deaths due to PCa, it causes overdiagnosis and overtreatment issues (2). PCa is a predominantly biologically slow-progressing pathology and does not affect survival or cause lifelong symptoms in a group of patients. Additionally, many incidental PCa are detected in autopsy studies. Estimated mean PCa prevalence was found to increase non-linearly in autopsy studies from 5% under 30 years of age to 59% over 79 years (3). For this reason, it was thought that many patients with PCa could be followed up with active surveillance (AS). In a prospective AS study of grade group (GG) 1 PCa patients, the cumulative incidence of PCa-specific mortality or metastasis was 0.1% at 10 and 15 years (4). Moreover, 10 and 15-year cancer-specific survival (CSS) were observed as 98.1% and 94.3% in patients in AS (5). Patients with AS die from reasons other than PCa, such as cardiovascular causes, and the 15-year CSS and overall survival (OS) were 99.9% and 69%, respectively (6).

Simply put, AS is meant to avoid overtreatment and to provide proper treatment to patients with localized PCa at the appropriate time with a curative intent (7). AS also aims to protect patients from treatment-related side effects. The impact of AS on cancer-specific quality of life is noticeably less than the other two treatment options. The effects of radical prostatectomy (RP) on urinary and sexual function, and radiotherapy (RT) on bowel function, are well known, whereas these are not affected in AS (8). Urinary incontinence, erection, and sexual dysfunction are more common in patients with RP (9).

All of these facts have caused the use of AS to increase over time. In the USA, the use of AS and watchful waiting (WW) in low-risk prostate cancer (LRPCa) patients increased from 14.5% to 42.1% from 2010 to 2015, while the use of local curative treatments, RP and RT, dramatically decreased (10). According to European Association of Urology (EAU) guidelines, AS aims to delay or prevent unnecessary treatment and unnecessary

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treatment-related side effects in clinically localized PCa patients with a life expectancy of more than 10 years (11). It also aims to ensure the right timing for curative treatment. So, it is important for patients receiving AS to know that PSA monitoring, clinical examination, imaging, and repeat biopsies should be performed in a pre-planned follow-up strategy. As a result of these reassessments, patients may need to receive radical curative treatment. In this review, we aimed to review guidelines and protocols used in AS and we report the criteria of patient selection, follow-up principles and the outcomes of AS.

Which Patients are Eligible for Active Surveillance in Prostate Cancer?

AS is not WW; it aims to protect patients from the side effects of treatment, but also provides the right curative treatment if necessary at the appropriate time. It is still not clear how to identify patients with clinically insignificant PCa. Studies on AS are generally observational, and there are no strict criteria for patient selection and follow-up schedules (Table 1) (5,12-14). However, certain features look similar in describing eligible patients such as LRPCa patients with a Gleason score (GS) of 3+3, a PSA level less than 10 ng/mL, and a clinical stage less than or equal to cT2a. Initially, AS should be recommended to patients with localized PCa in LRPCa (15). Some studies also included intermediate-risk prostate cancer (IRPCa) patients. However, AS in intermediate-risk patients is a controversial issue and appropriate patient selection remains unclear. This topic is discussed in detail later.

Selection of eligible patients is critical in AS. Enrolling eligible patients will protect them from the side effects of unnecessary treatment and increase the success of AS. For example, a study that selects PSA <10 ng/dL as the AS selection criteria; and a study that selects PSA <15 ng/dL will have patients with different characteristics (5,16). These small differences lead to heterogeneity of patients in the studies. Iremashvili et al. (17) compared five different AS protocols with RP pathologies in patients whose initial diagnosis was GG 1 in PB. There was Gleason 4/5 cancers in 30% of the RP specimens. Overall, 75% of patients met the criteria of at least one protocol and only 23% met the criteria for all protocols (17). One should keep in mind that the majority of LRPCa patients selected for AS treatment will not be included if we select stricter criteria. On the other hand, enrolling intermediate or higher-risk patients in AS treatment could lead to treatment failure.

In AS for selecting patients, the main idea is to have a small tumor (low number of tumor-positive cores and percentage of positive tumor), low-grade positive biopsy-proven PCa low PSA level and low PSA density in early stage [in digital rectal examination (DRE)]. The prediction of clinically insignificant PCa patients meeting this condition was defined for the sextant biopsy scheme according to the Epstein criteria (clinical stage T1c, PSA density ≤0.15 ng/mL/cm^3, GS ≤6 or stage group 1, ≤2 positive PB cores and ≤50% tumor percentage in positive PB cores) (18). However, the number of tumor-positive cores and the percentage of tumors in the cores are found to be at higher rates in 12-core PB than in sextant PB (19). 12-core PB has become the standard biopsy scheme in clinical practice over the years. Although the sextant PB scheme has a high sensitivity in detecting clinically insignificant PCa according to Epstein's criteria, 12-core PB has shown better results than sextant PB (19,20).

EAU guidelines state that the most frequently published criteria are ISUP GG 1, clinical stage cT1c or cT2a, PSA <10 ng/mL, and PSA-D <0.15 ng/mL/cc, based on systematic biopsy schemes (11). National Comprehensive Cancer Network (NCCN) defines patients with cT1c, GG 1, PSA level <10 ng/mL, <3 PB fragments/cores positive, ≤50% cancer in each fragment/core, and PSA density <0.15 ng/mL/g as very low-risk prostate cancer (vLRPCa) (21). In the 2024 guidelines, the NCCN recommends AS or observation depending on life expectancy, as the only treatment option in vLRPCa patients, owing to no difference in survival with radical treatment and to prevent the side effects of radical treatment (21). NCCN also defines patients with cT1-cT2a, GG1, and PSA <10 ng/mL as LR-PCa and recommends AS as an alternative to radical treatments (21).

How to Follow-up the Patients in Active Surveillance?

AS is a management approach for people who are diagnosed with localized PCa. It is important to provide early radical curative treatment when a higher risk or higher volume disease develops in the follow-up. Patients in AS are followed according to a scheduled follow-up protocol. Regular tests are used for monitoring, such as through PSA tests, DRE, regular biopsies, and multiparametric prostate magnetic resonance imaging (mpMRI), in recent years. The follow-up criteria of some studies are shown in Table 1. There are some differences between the follow-up protocols in the studies.

Patients may be misclassified in PB. There may be an upgrade in the pathologies of patients who are under AS according to PB pathology. In a study, 29.7% of patients with PB pathology GG 1 had higher GG in RP pathologies (22). In another study, 21.8% of patients in the LRPCa, and 13.1% of the patients in the very LRPCa experienced pathological upgrades in RP (23). Confirmation biopsy is recommended to avoid these reclassification mistakes. We define confirmation biopsy as a repeat biopsy performed within 6-12 months to exclude sampling error, especially in patients who have not undergone MRI before biopsy (11). Confirmation PB is performed soon after the first PB in AS. Compliance with the first repeat PB was estimated to be 81% in patients under AS (12). NCCN guidelines strongly recommend AS consideration within the first 6 to 12 months for patients (21).

There are differences in the timing between confirmation PB and follow-up PB in studies. Studies recommend early confirmation of PB in order to select the most appropriate patient group and not delay the treatment of unsuitable patients for AS (24). Some studies follow-up with annual PB of patients by performing a confirmatory PB in the first 3 months (24). There are also studies in which patients undergo a 2-year PB with a confirmatory PB at 6-12 months (5). In some studies, no confirmation biopsy was performed, and patients were followed up with annual prostate biopsies (25). The NCCN recommends that all patients should undergo PB within 1-2 years of their diagnostic PB (21). Analyses of four active follow-up cohort studies showed a delay of 3 to 5 months in detecting upgrading with biennial PB

Table 1. Selection criterias and follow-up strategy of active surveillance protocols

Authors reference	Article	Year	N	Age	Selection criteria						Follow-up strategy				
				Median (min-max)	Gleason score	Clinical stage	Positive core number	Single-core positivity	PSA (ng/mL)	PSA density (ng/mL)	Prostate biopsy	PSA measurement	DRE	Prostat MRI	
Tosoian et al. (25)	Active surveillance program for prostate cancer: an update of the Johns Hopkins experience	2011	769	66 (45-92)	≤6	cT1c	≤2	≤50%	<10	<0.15	Annualy	Semiannually	Semiannually	None	
Bul et al. (12)	Active surveillance for low-risk prostate cancer worldwide: the PRIAS study	2013	2494	65.8 (61-71.4)	≤6	cT1/T2	≤2	Not recorded	≤10	<0.2	1, 4, 7 years	3 months (first 2 years) / 6 months (after 2 years)	None	None	
Selvadurai et al. (16)	Medium-term outcomes of active surveillance for localised prostate cancer	2013	471	66 (51-79)	≤6 or 7 (older than 65 patients)	≤cT2a	None	≤50%	<15	Not recorded	2 years	3 months (first 2 years) / 4 months second year / 6 months (after 2 years)	3 months (first 2 years) / 4 months second year / 6 months (after 2 years)	None	
Tosoian et al. (6)	Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer	2015	1298	66 (62-69)	≤6	cT1c	≤2	≤50%	Not recorded	<0.15	Annualy	In every 6 month	Semiannually	None	
Klotz et al. (5)	Long-term follow-up of a large active surveillance cohort of patients with prostate cancer	2015	993	67.8 (41-89)	≤6 or 7 (older than 70 age patients)	≤cT2a	None	None	<10 or <15 (older than 70 age patients)	<0.15	Confirmation biopsy and 3-4 years	3 months (first 2 years) / 6 months (after 2 years)	None	None	
Godtman et al. (57)	Long-term results of active surveillance in the göteborg randomized, population-based prostate cancer screening trial	2016	244 (51%)	66 (63-68)	≤6	T1c	≤2	≤50%	<10	<0.15	Confirmation biopsy and 2-3 years	3-12 months	Semiannually	Yes, in 18 month	
			126 (27%)		≤6	T1c	Not recorded	Not recorded	<10	Not recorded					
			104 (22%)		7	T1-2	Not recorded	Not recorded	<20	Not recorded					
Tosoian et al. (4)	Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort	2020	1293	66 (61-69)	≤6	cT1c	≤2	≤%50	<10	<0.15	Confirmation biopsy and Annualy*	Semiannually	Semiannually	Yes, in 18 month	*If PIRADS 3 ≤ in prostat mr , fusion biopsy after 2014
			525	67 (62-71)	≤6	≤cT2a	None	None	≤10	None					

Table 1. Continued

Authors reference	Article	Year	N	Age	Selection criteria						Follow-up strategy				
				Median (min-max)	Gleason score	Clinical stage	Positive core number	Single-core positivity	PSA (ng/mL)	PSA density (ng/mL)	Prostate biopsy	PSA measurement	DRE	Prostat MRI	
Carlsson et al. (13)	Long-term outcomes of active surveillance for prostate cancer: the memorial sloan kettering cancer center experience	2020	2664	62 (57-68)	≤6	≤cT2b	Core Positivity = any	No restriction on number of positive biopsy cores	PSA= any	Any	Confirmation biopsy and in every 2-3 years	Semiannually	Semiannually	Yes, in 18 months	
Herden et al. (14)	Active surveillance for incidental (cT1a/b) prostate cancer: long-term outcomes of the prospective non-interventional HAROW study	2021	68	69.9 (63.6-72.5)	≤6	≤cT1a/b	≤2	Not recorded	≤10	≤0.2	First year and then after every 3 year	3 months (first 2 years) / 6 months (after 2 years)	3 months (first 2 years) / 6 months (after 2 years)	None	

PSA: Prostate specific antigen, DRE: Digital rectal examination, MRI: Magnetic resonance imaging

starting after a first confirmatory PB compared with annual biopsies (26). Despite this delay, biopsy frequencies do not seem to have a significant effect on survival among studies. Therefore, as an alternative to annual biopsies in suitable patients, biopsy frequencies may be reduced and semiannual PB follow-up may be appropriate (26).

The use of mpMRI contributes clearly to the detection of clinically significant PCa in PB. However, if biopsies were performed based solely on MRI progression findings during follow-up, approximately two-thirds of biopsies would be avoided, but 40% of patients with histological progression would be undetected (11). Therefore, protocol-based repeat PB should be performed. Studies recommend follow-up PB in AS despite differences in the timing of PB among studies. Some studies perform annual PB, while others do PB at intervals of 2-3 years (12,16,25). Although follow-up PB is recommended by AS protocols, some authors stated that repeat PB may be omitted in some patients with low PSA density (<0.15) because there is a very low risk of progression, especially in low-grade stable MRI findings (27).

PSA monitoring and DRE at an average of 3-6 month intervals are recommended by many studies in the follow-up conducted. There is no single accepted protocol for follow-up in the studies. It seems suitable for clinicians to recommend a patient-specific follow-up protocol on the basis of evidence-based medicine. The most appropriate approach is to individualize the intensity of the patient's follow-up protocol in AS according to the patient's life expectancy and re-classification risk (21).

Is Active Surveillance in Intermediate Risk Prostate Cancer Patients an Appropriate Approach?

Utility of AS in the IRPCa is controversial, and studies in this perspective are limited (16,28,29). However, in very selected patients, it might have a role (30). Unfortunately, a similar problem with the selection criteria and follow-up protocols also happens here (31). Nyame et al. (32) reported their findings in a cohort of localized PCa patients with AS. Although they prefer to restrict AS management to localized PCa patients with vLRPca and LRPca as described by NCCN criteria, they also offer AS to IRPCa and high-risk PCa patients with a life expectancy of less than 20 years. Authors report the 5- and 10-year survival rates of all intermediate and high-risk patients as 98% and 94%, respectively. Similarly, Bul et al. (33) reported a 10-year survival rate for LRPCa and IRPCa as 99.1% and 96.1% with no statistically significant difference. However, in another study, survival and metastasis-free survival rates at 5-year follow-up were similar between LRPCa and IRPCa; but worse in the IRPCa at 10-year follow-up (31). Mukherjee et al. (34) found that the 5-, 10-, and 15-year treatment-free survival rates, 5- and 10-year metastasis-free survival rates, and 5-year OS rates were similar in IRPCa and LRPCa patients, but the 5-, 10-, and 15-year CCS rates, long-term OS rates (10 and 15 years), and metastasis-free survival rate (15 years) were significantly lower in IRPCa.

It should be taken into consideration that IRPCa patients are heterogeneous. High core involvement and the presence of Gleason 4 pattern in these patients are indicators of an increased risk of progression (35). In a study of patients with LRPCa and

IRPCa, the data support the use of AS in Gleason 6 patients, but not in Gleason 7 patients (36). AS for intermediate risk PCa patients has increased over time. The rate of AS in NCCN favorable IRPCa patients increased from 13% to 45% from 2012 to 2020 (37). The 5-year treatment-free rate in AS patients was 73% for GG 1 disease and 57% for GG 2 disease. In these patients, delayed surgery resulted in 46% adverse pathology compared with immediate RP, but there was no difference in biochemical recurrence between the groups at short-term follow-up (37). A meta-analysis evaluating AS studies in IRPCa found that 10-year treatment-free survival was similar, but metastasis-free survival, cancer-specific survival, and OS were worse compared with LRPCa (38). Selected patients (only GG ≤2) had better metastasis-free survival (38). In the study, it was emphasized that unselected IRPCa patients experienced higher metastasis and cancer mortality compared to LRPCa patients; the importance of optimizing patient selection criteria in IRPCa was stated (38).

The EAU guidelines recommend that AS in IRPCa be offered with a weak recommendation to favorable patients with low-grade ISUP GG 2 (<10% pattern 4, PSA <10 ng/mL, ≤cT2a, low disease extent on imaging, and low extent of tumor in biopsies: ≤3 positive cores with GS 3+4 and ≤50% cancer involvement per core) who have a life expectancy of more than 10 years. Alternatively, it can be offered patients with another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, with an explanation of the increased potential risk of metastatic progression (11). The NCCN defines patients with GG 1 or 2, <50% biopsy cores positive, (e.g., <6 of 12 cores) and one intermediate risk factor (cT2b-cT2c, GG 2 or 3, PSA 10-20 ng/mL) as favorable IRPCa and recommends AS as an alternative to radical treatments (21). If AS is considered in favorable IRPCa patients, then especially patients with low percentage of 4 Gleason pattern, low tumor volume, low PSA density, and low genomic risk may be suitable (21).

As a result, AS will be an appropriate treatment for IRPCa patients. But we do not yet know exactly which IRPCa patients will be suitable for AS. It will be necessary to use different diagnostic methods for the selection of suitable IRPCa patients. The use of mpMRI may be beneficial in selecting appropriate IRPCa in the future.

Use of Multiparametric Prostate Magnetic Resonance Imaging in Active Surveillance Patients

mpMRI and mpMRI fusion biopsy increase the detection of clinically significant PCa in patients (39,40). Detection of clinically significant PCa in mpMRI fusion PB was shown to be statistically significantly higher (38% vs. 26%) (41). The use of mpMRI both in the first PB and follow-up biopsies in patients with previous negative biopsy increase detection of clinically significant PCa and it has been emphasized that prostate MRI can reduce the need for PB in patients (42). MRI-targeted biopsies detect more clinically significant PCa compared to standard PB (49.5% for systematic PB, 67% for targeted PB and 75.7% for targeted+systematic PB) (43). So, MRI-fusion biopsies are useful in detecting ISUP Grade 1 patients with higher accuracy. This will reduce the likelihood of detecting GS upgrade in AS follow-up. In a meta-analysis of 6 studies also showed that cancer upgrade (Gleason ≥3+4) was observed in 27% of patients when MRI-targeted + systematic biopsies were used (44). EAU guidelines recommend that mpMRI is performed prior to the initial PB or confirmation PB (11).

There are two important benefits of using mpMRI in AS. Initially, with the use of mpMRI before the first PB, the detection rate of clinically important PCa will increase. In one study, 10% of patients were found ineligible for AS according to the results of mpMRI-targeted PB compared to standard PB (45). In this way, patients will receive earlier diagnosis and treatment, and a more appropriate patient group will be selected for AS. This will increase the rate of success in AS. Secondly, it is thought that the use of prostate MRI in the follow-up of patients under AS can reduce the number of follow-up biopsies. It is also possible to use mpMRI in combination with other clinical information to detect clinically significant PCa. Based on PSA concentration, age, PI-RADS score, lesion length, and DRE findings, the Turkish Urooncology Association nomogram provides 75.6% sensitivity and 74.8% specificity in detecting clinically significant PCa in patients undergoing mpMRI fusion biopsy (46). The use of mpMRI may improve patient management and reduce unnecessary PB by contributing to the diagnosis of clinically significant PCa with high sensitivity and specificity. In recent years, follow-up protocols including mpMRI have also been used. Patients are selected using mpMRI-based selection criteria and follow-up protocols for some studies that have started in the past and are still ongoing (47).

It is thought that mpMRI may replace systemic repeat biopsies in the near future, but we need studies with a large patient cohort with long-term results. While mpMRI is a useful test in AS, it still cannot replace PB, and integration requires further research (48). In addition, ensuring optimal image quality in MRI, standardization of radiological findings in MRI and expertise in mpMRI reporting are crucial.

With the development of technology and increased accessibility, different diagnostic methods are increasingly used in PCa. One study reported that PSMA-PET-MRI improved the negative predictive value and sensitivity in the diagnosis of clinically significant PCa (49). The use of PSMA PET/CT may also improve patient selection for AS (50). However, these are clinical studies in small patient groups, and we need more data to make more precise comments on this issue (11).

Outcomes of Active Surveillance and Conversion to Treatment

AS is offered to patients as an alternative to RP and RT. The success rate is very high, especially in low-risk localized disease. In a study comparing patients with AS and those receiving curative treatment (RP or RT), no statistically significant difference was observed between 10-year CSS rates (<1% in all three groups); however, fewer disease metastases (<1% in all three groups) were observed in the treatment group (51). In another study, no difference was observed in the 10-year cumulative PCa mortality (AS 0.4% vs. RP 0.5%) between the treatment strategies (52). Outcomes from AS Protocols are shown in Table 2. Studies show that CSS and metastasis-free survival rates are

Table 2. Outcomes from active surveillance protocols

Authors reference	Article	Year	No curative treatment (%)	Median follow-up (years)	Disease specific survival (%)	Metastasis-free survival (%)	Overall survival (%)
Tosoian et al. (25)	Active surveillance program for prostate cancer: an update of the Johns Hopkins experience	2011	54	2.7	100	100	98.2
Bul et al. (12)	Active surveillance for low-risk prostate cancer worldwide: the PRIAS study	2013	75.6	1.6	100	2 cases	97.1 (2-years) 86.5 (4-years)
Selvadurai et al. (16)	Medium-term outcomes of active surveillance for localised prostate cancer	2013	68.8	5.7	96 (5-years)	2 cases	96 (5-years)
Tosoian et al. (6)	Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer	2015	63 (5 years) 50 (10 years) 43 (15 years)	5	99.9 (10 years) 99.9 (15 years)	99.4 (10 years) 99.4(15 years)	93 (10 years) 69 (15 years)
Klotz et al. (5)	Long-term follow-up of a large active surveillance cohort of patients with prostate cancer	2015	75.7 (5 years) 63.5 (10years) 55.0 (15years)	6.4	98.1 (10 years) 94.3 (15 years)	98.7	80 (10 years) 62 (15 years)
Godtman et al. (52)	Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial	2016	43	6.3	99.5 (10 years) 96 (15 years)	99 (10 years) 93 (15 years)	80 (10 years) 51 (15 years)
Tosoian et al. (4)	Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort	2020	48	5	99.9 (10 and 15 years)	99.9 (10 and 15 years)	93.2
Carlsson et al. (13)	Long-term outcomes of active surveillance for prostate cancer: the memorial sloan kettering cancer center experience	2020	58	15	100 (10 years)	99.4 (10 years)	94 (10 years)
Herden et al. (14)	Active surveillance for incidental (cT1a/b) prostate cancer: long-term outcomes of the prospective noninterventional HAROW study	2021	46.8	7.7	100	98.4	83.8

over 95% in patients under AS. Research indicates that AS is a safe and appropriate treatment approach in localized PCa. The risk of delaying patients' treatment is another concern. The EAU guidelines emphasize that for clinically localized low/intermediate-risk disease, no treatment modality is superior to another or to deferred active treatment (11).

CSS and OS are evidently good in eligible patients who are followed up in AS. Men can choose to stay in AS as long as they want, provided the disease remains stable, and life expectancy is over 10 years. However, it is known that more than one third of these patients require curative treatment due to Gleason upgrade, disease extent increase, disease stage, progression, or patient request (11). Different tests were used in the studies to evaluate the progression and stage of AS in the follow-up. The following tests include: PSA increase, PSA doubling time, PSA density, upgrade in repeat PB (reclassification), and DRE.

Progression of the disease in AS, and exclusion of the patient from the criteria for AS are the main reasons to recommend radical curative treatment (6). Crossing a PSA threshold, an increase in GG on repeat biopsy, or a change in T-stage findings on imaging or clinical examination is a reason for switching to active curative treatment during AS. In some studies, radical curative treatment was given to patients with a PSA doubling time of less than 3 years, GS upgrade (histologic reclassification) or clinical progression (5,53). It should not be overlooked that re-classification in PB and transition to radical curative treatment is more likely when patients have an increased number of positive cores and PSA density (12,54). In a meta-analysis, high PSA-D, >2 positive cores (in systematic biopsies), and African-American origin were found to be highly associated with re-classification (55). However, PSA kinetics alone are not sufficiently reliable in predicting adverse pathology and should not be used in place of annual biopsies in AS (56). Thus, in patients with elevated PSA alone or short PSA doubling time, it is recommended to make a decision by re-evaluation with repeat MRI and repeat biopsy instead of directly changing treatment (11).

The most common reason for patients to switch to active curative treatment is a GS upgrade (reclassification) during follow-up (21,25,53). Increase in tumor volume, a rise in PSA density, and patient anxiety are other factors (21). The stress of

living with cancer also creates a desire for treatment in patients. In a study involving the patients, it was shown that the most common reason (53%) for curative treatment was an increase in disease volume with GS upgrading (histologic reclassification) (57). In addition, curative treatment was given to 2% of patients for anxiety (57). After 10 years of follow-up, 41% of patients discontinued AS because of AS protocol-based reclassification, and 5% of patients discontinued AS due to anxiety or a patient request (47). In another study, 73.4% of the patients received curative treatment due to the AS protocol progression criteria and 8.9% because of anxiety (12). It should be kept in mind that providing psychological support to patients in AS may help reduce anxiety levels.

There is growing evidence that some gene mutations, for instance BRCA2 mutations, are more likely to be associated with aggressive cancer even when there is clinically LRPCa, so active treatment may be preferable to AS for these patients with genetic risk factors (58). In the near future, germline test results and findings of certain somatic mutations on biopsy tissue will determine the appropriate candidates for AS.

Conclusion

AS is an appropriate approach to protect patients from the side effects of curative treatments in PCa. It is recommended as an alternative to RP and radical RT with high survival rates in patients with LRPCa. AS is a safe and reasonable option for patients with clinically localized LRPCa. The NCCN guidelines even recommend it as the only treatment option in patients with vLRPCa. Data on AS in the IRPCa are limited. There is a need for studies with a large number of patients and long-term follow-ups on AS in IRPCa. AS may be preferred in the favorable IRPCa group. AS should be followed very carefully and the patients should be well informed about the risks in this group. mpMRI increases the detection of clinically important PCa. More appropriate patients are selected for AS with the use of mpMR. In addition, it is thought that the use of mpMRI may reduce the number of repeat prostate biopsies in follow-ups. However, there is no standard protocol for AS that includes prostate MRI. In light of future studies, it seems that mpMR-based follow-up protocols will be created. Also, genetic biomarkers will be used to select the most valid PCa patients for AS in the near future.

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Footnotes

Authorship Contributions

Concept: G.Ö., Y.T., H.K.Ç., Design: G.Ö., Y.T., H.K.Ç., Data Collection or Processing: G.Ö., Y.T., H.K.Ç., Analysis or Interpretation: G.Ö., Y.T., H.K.Ç., Literature Search: G.Ö., Y.T., H.K.Ç., Writing: G.Ö., Y.T., H.K.Ç.

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Original Article

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Association of Pelvic Lymph Nodes Inclusion with Late Side Effects in Prostate Cancer Patients Undergoing Curative Radiotherapy

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Abstract

Objective: Curative radiotherapy is one of the two leading definitive treatment options for prostate cancer, along with surgery. The inclusion of pelvic lymph nodes in curative radiotherapy for prostate cancer is controversial. In our study, we aimed to investigate the association of pelvic lymph node irradiation with late gastrointestinal system (GIS) and genitourinary system (GUS) side effects in intermediate and high-risk prostate cancer patients who underwent curative radiotherapy.

Materials and Methods: Patients who underwent curative radiotherapy for intermediate and high-risk prostate cancer between 2015 and 2022 were evaluated retrospectively. GIS and GUS side effects were graded according to the Radiation Therapy Oncology Group scale. Patients were divided into 2 groups: those who received treatment of the pelvic lymph node (group 1) and those who received treatment of the prostate and seminal vesicle (group 2). We analyzed whether there was a difference in late GIS and GUS side effects between the groups. The independent samples t-test was used to compare late side effects between the groups. A p-value of $p<0.05$ was considered statistically significant.

Results: Seventy-one patients treated for intermediate and high-risk prostate cancer were analyzed. Thirty seven patients received a radiotherapy regimen in group 1, and 34 patients received a radiotherapy regimen in group 2. Intermediate risk patients received radiotherapy in group 2, and high-risk patients received radiotherapy in the group 1 regimen. The mean age of the patients was 70 years and the mean follow-up period was 39 months. All patients received hormone therapy. Late GUS and GIS side effect rates were found to be extremely low. There was no statistically significant difference between the groups in terms of side effect rates.

Conclusion: In localized prostate cancer, including pelvic lymph nodes in the treatment area does not increase long-term GIS and GUS side effects.

Keywords: Prostate cancer, radiotherapy, side effect, pelvic lymph node irradiation

Introduction

Curative radiotherapy is one of the two leading definitive treatment options in prostate cancer along with surgery. The different side effect profiles of the applied modalities play a role in the choice of treatment (1,2). Gastrointestinal system (GIS) and genitourinary system side effects that may develop after curative treatments for localized prostate cancer are possible complications and may cause morbidity in the patient's life (3-5). The inclusion of pelvic lymph nodes in curative radiotherapy for localised prostate cancer is a controversial issue. Although some studies have found that pelvic radiotherapy is not beneficial, other studies have found that it may increase progression-free survival (PFS), disease-free survival (DFS) and biochemical recurrence-free survival (BRFS). Studies suggest that the practice of including pelvic lymph nodes based on the risk of lymph node involvement has gained prominence (6-9). To assess the risk of lymph node involvement, the Roach formula has been used (10). If the risk is above 15%, the inclusion of pelvic lymph nodes is recommended. When including pelvic lymph nodes, the question that the treatment-related side effect profile may increase comes to mind. In our study, we aimed to investigate the relationship between pelvic lymph node irradiation and late GIS and GUS side effects in intermediate and high-risk prostate cancer patients who underwent curative radiotherapy.

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Materials and Methods

The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep City Hospital (approval number: 32/2024, date: 26.6.2024). Patients who underwent curative radiotherapy for intermediate and high-risk prostate cancer between 2015 and 2022 were retrospectively evaluated. Patients who received postoperative-adjuvant radiotherapy, as well as those with low-risk prostate cancer, lymph node involvement, or distant metastasis, were excluded from the study. GIS and GUS side effects were graded according to the Radiation Therapy Oncology Group (RTOG) scale (Table 1). Toxicities were graded and recorded by the physicians during outpatient follow-up. Side effects 6 months after the end of radiotherapy were defined as late side effects. Patients were divided into 2 groups: those who received treatment to the pelvic lymph node (group 1) and those who received treatment to the prostate and seminal vesicle (group 2). Intermediate risk patients received radiotherapy in group 2 and high-risk patients received radiotherapy in group 1 regimen. As per our department policy, all high-risk patients underwent pelvic irradiation, and intermediate-risk patients underwent prostate and seminal vesicle irradiation. In group 1, obturator, external iliac, internal iliac, and distal common iliac lymph nodes were included in the treatment area. All patients received radiotherapy with the intensity-modulated radiation therapy (IMRT). Quantitative Analysis of Normal Tissue Effects in the Clinic dosimetric limitations were followed in radiotherapy planning. We analyzed whether there was a difference in late GIS and GUS side effects between the groups.

Statistical Analysis

A normal distribution test was performed with the Kolmogorov-Smirnov test. Independent samples t-test was used to compare the late side effects between the groups. P<0.05 was accepted for statistical significance. SPSS version 23.0 was used for the statistical analysis of this study.

Results

Seventy-one patients treated for intermediate and high-risk prostate cancer were analyzed. Thirty seven patients received radiotherapy regimen in group 1 and 34 patients in group 2. The mean age of the patients was 70 years (52-85) and the mean follow-up period was 39 months (9-79). Mean pretreatment prostate-specific antigen (PSA) (ng/mL) was 27.3 (range: 5-188), and mean testosterone was 3.2 (ng/dL). The mean prostate size before radiotherapy was 47 cubic centimeters (11-128), and there was no significant difference between the groups. The mean positive quadrant ratio in prostate biopsy was 46% (7-100) and was significantly higher in the high-risk group (p<0.01). Half of the patients had no comorbidities before treatment, while the most common comorbidities were hypertension, coronary artery disease, and diabetes mellitus. None of the patients had bowel disease before radiotherapy. Patient characteristics are shown in Table 2. Patients in group 1 received 46 Gy to the pelvis, 54 Gy to the prostate + seminal vesicle, and 78 Gy to the prostate. Patients in group 2 received 54 Gy to the prostate and seminal vesicle and 76-78 Gy to the prostate. The mean PSA value within 1 month after radiotherapy was 0.55 (range: 0-12), and there was no significant difference between the groups. All patients received hormone therapy, and the mean duration of hormone therapy was 24 months (6-72). Neoadjuvant hormone therapy was administered to 32% of the patients. There was no significant difference in side effect rates between patients who received neoadjuvant hormone therapy and those who did not. The rates of late GUS and GIS side effects are shown in Figures 1 and 2, and were found to be extremely low. Observed grade 2 GUS side effects were nocturia and dysuria, while GIS side effects were rectal bleeding and tenesmus. It is noteworthy that a grade 3 GUS side effect was seen in only 1 patient, and the patient underwent surgery because of urethral stenosis. A Grade 3 GIS side effect was not observed. There was no statistically significant difference between the groups in terms of side effect rates.

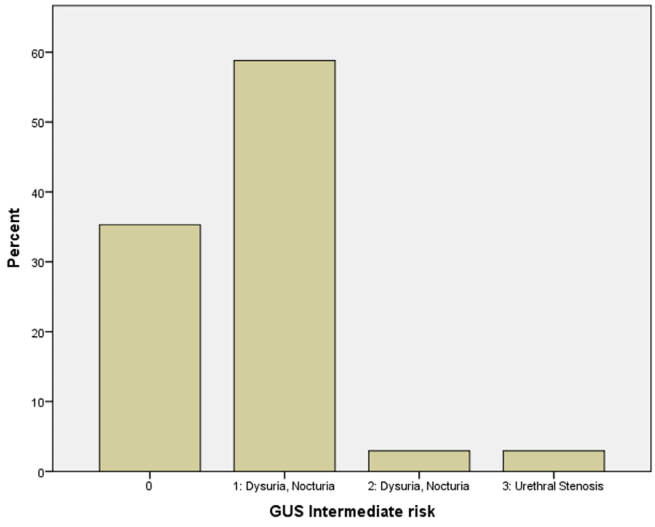
Table 1. RTOG late toxicity grading

0: No symptoms
1: Mild symptoms that do not require treatment
2: Symptoms that improve with local - non-invasive treatment and do not significantly affect daily life
3: Serious symptoms that do not require immediate intervention; hospitalization may be required
4: Life-threatening symptoms
5: Death due to side effects
RTOG: Radiation Therapy Oncology Group

Table 2. Patient characteristics

Patients number	Group 1	37
	Group 2	34
Age	Group 1	70.8 (49-88)
	Group 2	70.2 (57-81)
Follow-up	Group 1	42.6 (13-62)
	Group 2	34.8 (9-79)
Comorbidity (%)	Group 1	51.3
	Group 2	47
Pretx PSA (ng/dL)	Group 1	43.6 (5-188)
	Group 2	10 (3.4-18.4)
Pretx testosterone (ng/dL)	Group 1	3.5 (1-12)
	Group 2	3 (1.3-5.5)
Pretx prostate size (cc)	Group 1	43.8 (11-88)
	Group 2	51.7 (18-128)
Positive quadrant ratio in Bx (%)	Group 1	68.3 (7-100)
	Group 2	35.9 (7-80)
ADT duration (m)	Group 1	41(15-66)
	Group 2	6 (6-9)
Neoadjuvant ADT	Group 1	37.8%
	Group 2	26.5%
Radiotherapy dose (Gy)	Group 1	78
	Group 2	76 (76-78)

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy, Bx: Biopsy



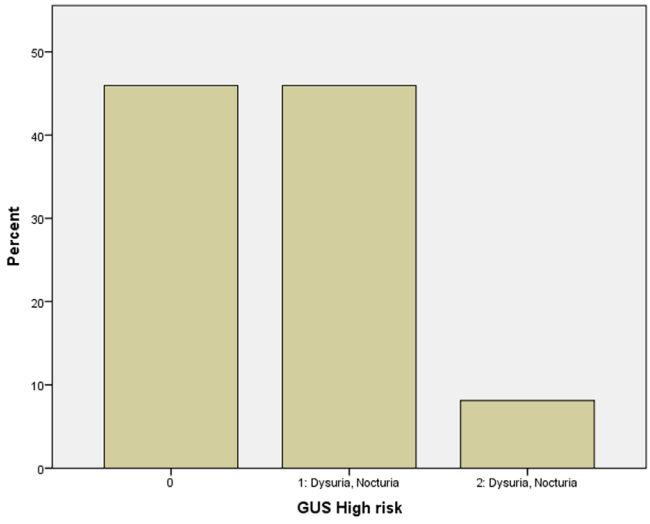
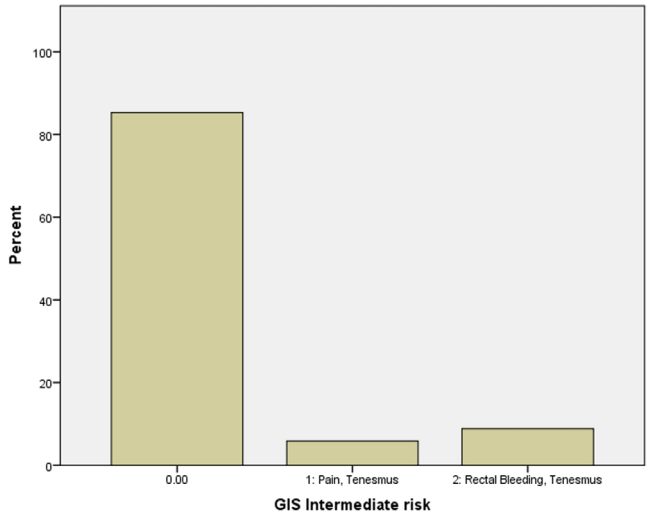


Figure 1. Late GUS side effect rates

GUS: Genitourinary system



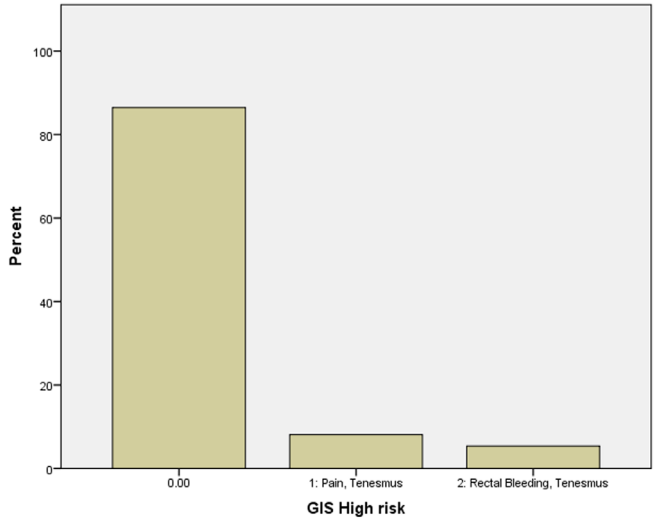


Figure 2. Late GIS side effect rates

GIS: Genitourinary system

Discussion

Elective pelvic field irradiation in localized prostate cancer radiotherapy is controversial. In the RTOG 9,413 study, patients with a risk of lymph node involvement >15% were included (6). There is a 2x2 study design defined by hormone therapy initiation time (neoadjuvant-adjuvant) and radiotherapy area (pelvic lymph node included and prostate-only irradiation group). As a result of the study, PFS was higher in the group that received neoadjuvant hormonotherapy + pelvic lymph node treatment; than in the group that received neoadjuvant hormonotherapy + prostate-directed radiotherapy; and adjuvant hormonotherapy + pelvic lymph node radiotherapy. In the Gastrointestinal Tumor Study Group-01 study, no benefit of pelvic lymph node irradiation was found (7). In the POP-RT study, it was found that BRFS and DFS rates increased with pelvic lymph node irradiation in the patient group with an estimated lymph node involvement risk ≥20 percent (8). In the systematic review by De Meerleer et al., (9) it was reported that pelvic lymph node irradiation was beneficial in patients with a lymph node involvement risk of ≥35% according to the Roach formula. In the literature, according to Roach's formula, pelvic lymph node irradiation may be beneficial considering the risk of lymph node involvement. In our study, pelvic radiotherapy was applied to high-risk patients according to our clinical protocol, but not to intermediate-risk patients.

Survival in localized prostate cancer is long and GIS and GUS side effects related to definitive radiotherapy may affect the quality of life of patients (3-5). Whether long-term GIS and GUS toxicities are increased in patients who receive pelvic lymph node irradiation compared to patients who receive prostate-only radiotherapy, is a question that needs to be answered. In our study, no increase in long-term toxicity was found with pelvic radiotherapy. In a retrospective study conducted by Deville et al. (11) on patients who received definitive radiotherapy using IMRT, no difference was observed in late GIS and GUS toxicities, although an increase was observed in rectal and bladder dosimetric parameters in the pelvic lymph node

irradiated group compared to the other group. In the study conducted by Ogino et al., (12) the rate of serious toxicities was found to be very low in both groups and no significant difference was found between the toxicity rates the groups. In this study, volumetric-modulated arc therapy (VMAT) was used as the planning technique. It was emphasized that it would not be correct to omit pelvic radiotherapy in high-risk prostate cancer considering the toxicities. In a retrospective dosimetric analysis by Guckenberger et al. (13) using the IMRT technique, it was concluded that pelvic lymph node irradiation did not increase bladder and rectal toxicity, although it could increase normal organ doses. In Takemura et al.'s (14) retrospective study including 112 high-risk prostate cancer patients who received pelvic field radiotherapy, late GIS and GUS side effects were found to be extremely low. In this study, VMAT was used for radiotherapy planning. In studies comparing different radiotherapy techniques in prostate cancer, it is noteworthy that in terms of normal organ sparing is better with IMRT and VMAT than with 3-dimensional-conformal radiotherapy (15,16). In curative radiotherapy for localized prostate cancer using IMRT and VMAT, including the pelvic area in the treatment does not increase long-term toxicities. The result obtained in our study is consistent with the literature data. Based on the results of our study, we conclude that if we use advanced radiotherapy techniques, there is no need to avoid pelvic radiotherapy for localized prostate cancer.

Study Limitations

The retrospective nature and the relatively small number of patients are among its limitations.

Conclusion

In curative radiotherapy for localized prostate cancer using IMRT and VMAT, including the pelvic lymph nodes in the treatment area does not increase long-term toxicities. It is not a logical approach to omit pelvic lymph node treatment because of increased side effects.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep City Hospital (approval number: 32/2024, date: 26.6.2024).

Informed Consent: Retrospective study.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

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Original Article

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Differences Between Patients with and without Persistent PSA after Radical Prostatectomy in Clinically High-risk and/or Locally Advanced Prostate Cancer

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Abstract

Objective: This study aimed to identify preoperative and postoperative factors associated with persistent prostate-specific antigen (PSA) following radical prostatectomy (RP) in patients with clinically high-risk and/or locally advanced prostate cancer. Understanding these factors can guide early postoperative management decisions, including adjuvant treatment strategies.

Materials and Methods: A retrospective analysis was conducted on 183 patients who underwent RP for locally advanced prostate cancer between 2009 and 2023. Patients were divided into two groups: those with persistent PSA at 1 month postoperatively (group 2, n=43), and those without (group 1, n=140). Preoperative and postoperative variables, including PSA levels, clinical stage, biopsy grade group, tumor volume, and pathological findings, were compared between groups.

Results: Patients in group 2 had significantly higher preoperative PSA levels (24.6±19 ng/mL vs. 15±15.5 ng/mL, p<0.001), advanced clinical stage (≥T2B: 52.6% vs. 32.1%, p=0.032), and higher percentage of positive biopsy cores (p=0.011). Postoperative findings demonstrated a higher tumor volume (20.2±14.1 cc vs. 10.7±10.5 cc, p=0.002), tumor density (p=0.005), and positive surgical margins (86% vs. 70%, p=0.025) in group 2. Patients in group 2 had higher rates of lymph node dissection, adjuvant therapy, and early salvage radiotherapy.

Conclusion: Preoperative PSA levels, biopsy grade group, positive surgical margins, and advanced pathological stage are critical predictors of persistent PSA after RP. Early identification of high-risk patients enables personalized management plans, including timely initiation of adjuvant therapies, to improve outcomes. Further prospective studies are needed to refine risk stratification models and personalize treatment strategies.

Keywords: Prostate cancer, persistent PSA, radical prostatectomy, prostate-specific antigen

Introduction

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide. While localized prostate cancer can often be effectively managed with definitive therapies such as radical prostatectomy (RP), the management of locally advanced disease presents significant therapeutic challenges (1). RP, as an initial step in a multimodal treatment approach, plays a pivotal role in these cases. However, persistent prostate-specific antigen (PSA) levels following RP may indicate residual disease and are associated with poorer oncological outcomes (2).

The identification of factors that predict persistent PSA after surgery is critical for optimizing patient management. Understanding these predictors not only facilitates more tailored postoperative surveillance but also informs decisions regarding adjuvant therapies, such as radiotherapy (RT) or androgen deprivation therapy, to enhance patient outcomes. Despite improvements in surgical techniques and the availability of effective adjuvant treatments, the incidence of persistent PSA remains a significant concern in patients with locally advanced prostate cancer (3).

In this study, we aimed to identify the preoperative and postoperative factors associated with persistent PSA following

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RP in patients with clinically high risk and/or locally advanced prostate cancer. By clarifying these predictive factors, we aim to contribute to the development of more personalized and effective treatment strategies for this challenging patient population.

Materials and Methods

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from, İzmir Bozyaka Research and Educational Hospital Ethics Committee, reference number 03 (date: 17.01.2018). After obtaining approval from the hospital's ethics committee, we retrospectively evaluated data from 183 patients who underwent open retropubic RP for clinically high risk and/or locally advanced prostate cancer between 2009 and 2023. Patients were included in the study if they had complete data for preoperative and postoperative evaluations, including PSA levels at 1 month post-surgery. Exclusion criteria included incomplete clinical or pathological data, history of prior prostate cancer treatments (such as RT or androgen deprivation therapy), or the presence of metastatic disease at the time of surgery. Of the 191 eligible patients, only those with available PSA data from the first postoperative month were included in the study.

The postoperative 1-month PSA level was chosen as the threshold for determining persistent PSA based on its widespread use in clinical practice, and its predictive value for identifying residual disease early. Because the half-life of PSA is approximately 3.15 days, serum PSA values of 50 ng/mL should be undetectable within 4 weeks after RP. PSA persistence defined at 1-month postoperatively is strongly associated with adverse oncological outcomes, including biochemical recurrence and metastatic progression. This timeline ensures early detection of residual disease, enabling timely initiation of adjuvant therapies to improve patient outcomes (4).

The patients' demographic characteristics, PSA levels, prostate biopsy findings, RP pathology results, and follow-up data were analyzed. The cohort was divided into two groups: those with no evidence of persistent PSA at 1 month post-RP (group 1) and those with persistent PSA (group 2). The collected data were compared between these two groups. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 23. Descriptive statistics for parametric variables were presented as mean and standard deviation, while non-parametric variables were expressed as median and range (minimum-maximum) or counts and percentages. The normality of distribution for continuous variables was evaluated using the Kolmogorov-Smirnov test. For comparisons of normally distributed quantitative data, the Student's t-test was employed. The Mann-Whitney U test was used for non-normally distributed quantitative variables. Categorical variables were compared using the chi-square and Fisher's exact test. A p-value of less than 0.05 was considered statistically significant within a 95% confidence interval.

Results

The mean age of the 183 patients included in this study was 66.9 years, and the mean preoperative PSA level was 17.3 ng/mL. The clinical and pathological characteristics of the patients are summarized in Table 1. At the 1-month postoperative evaluation, 43 patients were found to have persistent PSA levels, while 140 patients had PSA levels below 0.1 ng/mL. A comparison of the results between the persistent PSA group (group 2, n=43) and the non-persistent PSA group (group 1, n=140) is provided in Table 2.

Preoperative data revealed that the mean PSA level in group 1 (15±15.5 ng/mL) was significantly lower than that of in group 2 (24.6±19 ng/mL) ($p<0.001$). Additionally, patients with clinical stage cT2B or higher were more frequently observed in group 2 compared to group 1 ($p<0.05$). When preoperative transrectal ultrasound-guided biopsy data were analyzed, the biopsy grade group and percentage of positive biopsy cores were significantly higher in patients with persistent PSA (group 2) ($p<0.05$).

Postoperative findings demonstrated that the tumor volume and tumor density (calculated as the ratio of tumor volume to prostate volume) were significantly higher in group 2 ($p<0.05$). Similarly, pathological T-stage and positive surgical margins were more frequently observed in group 2 ($p<0.05$). The rates of lymph node dissection, adjuvant therapy, and adjuvant or early salvage RT were also higher in this group (Table 3). Key predictors between group 1 and group 2 are summarized in Figure 1, providing a visual comparison of significant variables identified in our analysis.

Discussion

Persistent PSA after RP remains a significant concern in the management of locally advanced prostate cancer. In this study, we identified several preoperative and postoperative factors associated with persistent PSA, aligning with current literature that emphasizes the multifactorial nature of this outcome.

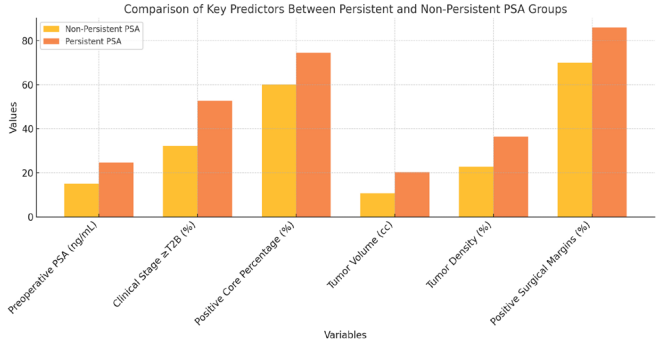

Figure 1. Comparison of key predictors between persistent and non-persistent PSA groups

PSA: Prostate-specific antigen

Table 1. Demographic, clinical, and pathological data of the patients		
		n=191
Age (years)		66.9±6.3 (46-81)
PSA (ng/mL) (n=182)		17.3±16.7 (2.6-100)
Clinical stage, (n=152)	T1C-T2A	95 (62.5%)
	T2B	27 (14.1%)
	≥T2C	30 (19.7%)
Biopsy grade group, (n=185)	1	45 (24.3%)
	2	51 (27.6%)
	3	32 (17.3%)
	4	42 (22.7%)
	5	15 (8.1%)
Number of PCa positive cores (n=155)		5.4±3.6
Percentage of PCa positive cores (n=143)		63.6±30.7%
RP grade group, n	1	14 (7.3%)
	2	45 (23.6%)
	3	55 (28.8%)
	4	44 (23%)
	5	33 (17.3%)
Pathological stage, (n=190)	T3A	103 (54.2%)
	T3B	84 (44.2%)
	T4	3 (1.6%)
Tumor volume (cc)		13.3±12.1
Tumor density		25.9±20.3
Positive surgical margins, n		141 (73.8%)
Lymph node dissection, n		158 (82.7%)
Mean number of LN removed (n=134)		13.8±8.7
Lymph node metastasis, (n=134)		36 (26.9%)
Mean number of positive LNs (n=134)		0.66±1.35
Number of positive LNs, (n=36)	1 LN+	12 (33.3%)
	2 LN+	10 (27.8%)
	≥3 LN+	14 (38.9%)
Follow-up duration (months)		33.4±20.9
Persistent PSA post-RP, (n=183)		43 (23.5%)
Biochemical recurrence, (n=184)		31 (16.8%)
Adjuvant therapy, n		111 (58.1%)
Adjuvant therapy, (n=111)	RT	23 (20.7%)
	RT + LHRH	76 (68.5%)
	RT + LHRH + AA	1 (0.9%)
	LHRH	11 (9.9%)
Radiotherapy, (n=100)	Adjuvant	62 (62%)
	Early salvage	19 (19%)
	Salvage	19 (19%)

PSA: Prostate-specific antigen, PCa: Prostate cancer, RP: Radical prostatectomy, LN: Number of positive lymph node, RT: Radiotherapy, LHRH: Luteinizing hormone-releasing hormone, AA: Androgen ablation

Our finding that higher preoperative PSA levels are predictive of persistent PSA is consistent with previous studies. For instance, Preisser et al. (4) found that elevated preoperative PSA, alongside other clinical variables such as advanced T-stage, significantly increased the likelihood of biochemical persistence (2). Additionally, the percentage of positive biopsy cores was also highlighted as, a crucial predictor, a finding corroborated by Milonas et al. (5), who demonstrated that patients with a higher proportion of positive cores were at greater risk for PSA persistence (3).

Surgical margin status was another key postoperative factor linked to PSA persistence. This relationship is well-established in the literature. Wiegel et al. (6) showed that positive margins, particularly in combination with extracapsular extension and seminal vesicle invasion, significantly increase the risk of biochemical recurrence and PSA persistence (2,3). Similarly, Shiota et al. (7) observed that patients with positive margins are more likely to benefit from early salvage RT, underscoring the importance of identifying these high-risk patients early (3).

Pathological stage, particularly ≥pT3b disease, was also a strong predictor of persistent PSA in our cohort, consistent with studies by Fossati et al. (8) and Bartkowiak et al. (9), which highlighted the prognostic impact of advanced pathological stage on the likelihood of PSA persistence and long-term oncologic outcomes (3). These findings emphasize the need for more aggressive adjuvant treatment strategies in patients with advanced stage disease.

Our findings have significant implications for clinical decision-making, particularly regarding adjuvant and salvage radiotherapy strategies. Adjuvant radiotherapy (RT) involves treating some patients who might never develop recurrent cancer, potentially exposing them to unnecessary side effects. On the other hand, salvage RT, which is reserved for patients with confirmed recurrence, may delay treatment in high-risk patients, increasing the risk of progression to metastatic disease. Although the ARO 96-02 trial showed that early salvage radiotherapy improves relapse-free and overall survival in patients with persistent PSA, especially in clinically high-risk and/or locally advanced prostate cancer, as an indicator of residual disease, has been strongly associated with worse oncological outcomes, emphasizing the importance of earlier and individualized intervention (6-8,10).

Pre-operative predictors such as high PSA levels and advanced clinical stage could guide pre-surgical counseling and decision-making. For patients identified as high risk for persistent PSA, discussions regarding alternative treatment modalities, such as primary RT combined with androgen deprivation therapy, or multimodal treatment may be warranted. This approach could avoid the risks associated with delayed adjuvant interventions. Additionally, the early identification of high-risk patients may streamline decisions for immediate adjuvant RT and androgen deprivation therapy in the postoperative period, allowing these treatments to be initiated without waiting for biochemical recurrence (5,7,10,11).

Postoperative factors like positive surgical margins and advanced pathological stages further highlight the need for aggressive management in patients at high risk of persistent PSA levels.

In such cases, the integration of imaging modalities like PSMA PET/CT may be bypassed to expedite the initiation of adjuvant therapy, particularly in settings where PSA monitoring indicates a high likelihood of disease progression. Recent studies have shown that timely adjuvant RT, particularly when combined with androgen deprivation therapy, significantly improves metastasis-free survival and reduces biochemical recurrence. This approach could benefit patients with pathological risk factors, irrespective of early postoperative PSA levels, ensuring better long-term outcomes (7,9,11,12).

Our findings also underline differences in adjuvant treatment preferences between groups, with the persistent PSA group

Table 2. Comparative results of clinicopathological data in patient groups with and without postoperative persistent PSA

		No persistent PSA (n=140)	Persistent PSA (n=43)	p-value
Age (years)		66.7±6.1	67.9±6.2	0.372
PSA (ng/mL)		15±15.5	24.6±19	**<0.001**
Clinical stage, n (n=147)	**T1C-T2A**	74 (67.9%)	18 (47.4%)	**0.032**
	T2B	15 (13.8%)	12 (31.6%)	
	≥ T2C	20 (18.3%)	8 (21%)	
Biopsy grade group, n (n=178)	**1**	40 (29.6%)	3 (7%)	**0.025**
	2	36 (26.7%)	12 (27.9%)	
	3	23 (17%)	8 (18.6%)	
	4	26 (19.3%)	15 (34.9%)	
	5	10 (7.4%)	5 (11.6%)	
Number of PCa positive cores (n=151)		5.1±3.7	6.3±3.3	0.054
Percentage of PCa positive cores (n=139)		60.1±30.8	74.4±28.1	**0.011**
RP grade group, n	**1**	10 (7.1%)	2 (5%)	0.490
	2	35 (25%)	7 (17.5%)	
	3	41 (29.3%)	13 (32.5%)	
	4	29 (20.7%)	14 (35%)	
	5	25 (17.9%)	7 (17.5%)	
Pathological stage, (n=182)	**T3A**	83 (59.7%)	14 (32.6%)	**0.003**
	T3B	53 (38.1%)	29 (67.4%)	
	T4	3 (2.1%)	0 (0%)	
Tumor volume (cc)		10.7±10.5	20.2±14.1	**0.002**
Tumor density		22.8±17.9	36.4±25.3	**0.005**
Positive surgical margins, n		98 (70%)	37 (86%)	**0.025**
Lymph node dissection, n		110 (78.6%)	41 (95.3%)	**0.006**
Positive lymph node metastasis, n		24 (17.1%)	12 (27.9%)	0.120
Mean number of positive LNs (n=129)		0.54±1.05	1.02±1.9	0.351

PSA: Prostate-specific antigen, PCa: Prostate cancer, LNs: Number of positive lymph nodes

Table 3. Adjuvant therapy status in patients with and without persistent PSA

		No persistent PSA (n=140)	Persistent PSA (n=43)	p-value
Adjuvant therapy, n		70 (50%)	38 (88.4%)	**<0.001**
Adjuvant therapy, (n=108)	**RT**	16 (22.8%)	6 (15.8%)	0.399
	RT + LHRH	48 (68.6%)	26 (68.4%)	
	RT + LHRH + AA	0 (0%)	1 (2.6%)	
	LHRH	6 (8.6%)	5 (13.2%)	
Radiotherapy (n=97)	**Adjuvant RT**	37 (57.8%)	22 (66.7%)	**0.04**
	Early salvage RT	10 (15.6%)	9 (27.3%)	
	Salvage RT	17 (26.5%)	2 (6%)	

PSA: Prostate-specific antigen, RT: Radiotherapy, LHRH: Luteinizing hormone-releasing hormone, AA: Androgen ablation

demonstrating significantly higher rates of adjuvant therapy, including adjuvant RT (88.4% vs. 50%, p<0.001). This reinforces the role of persistent PSA as a decisive factor in postoperative management, supporting a more proactive approach in initiating adjuvant therapies. By incorporating persistent PSA predictors into routine practice, clinicians can better stratify patients for adjuvant treatments, optimize the timing of interventions, and potentially improve oncological outcomes.

Study Limitations

This study has several limitations. First, its retrospective design may introduce selection and recall biases, potentially impacting the generalizability of the findings. Second, the data were obtained from a single institution, which may limit the applicability of the results to broader populations. Additionally, some variables, such as genetic markers, were not included; their inclusion could provide a more comprehensive risk stratification in predicting persistent PSA.

Conclusion

Our findings are consistent with existing literature, reinforcing that both preoperative and postoperative factors, such as preoperative PSA levels, the percentage of positive biopsy cores, positive surgical margins, and advanced pathological stage, are critical in predicting persistent PSA after RP. Early identification of these high-risk patients is essential for tailoring postoperative management strategies, including the timely use of salvage radiotherapy and adjuvant treatments. Further prospective studies are warranted to refine risk stratification models and optimize individualized treatment pathways.

Ethics

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Türkiye, İzmir Bozyaka Research and Educational Hospital Ethics Committee, reference number 03 (date: 17.01.2018).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ç., M.Ç., M.H.D., M.M., B.K., T.Ç., İ.H.B., B.G., T.D., Concept: A.E., B.K., Design: S.Ç., T.Ç., Data Collection or Processing: A.E., M.M., Analysis or Interpretation: A.E., S.Ç., Literature Search: M.H.D., İ.H.B., Writing: A.E., M.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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From First to Final: How Surgical Experience Affects Robotic Radical Prostatectomy Outcomes

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Abstract

Objective: To evaluate the impact of surgeon experience on surgical outcomes in robotic-assisted radical prostatectomy (RARP) by comparing the first and last 50 patients in a clinical setting.

Materials and Methods: This retrospective study analyzed the first and last 50 patients who underwent RARP for localized prostate cancer at a City Hospital between November 2022 and October 2024. Complications were classified using the Clavien-Dindo classification system. Oncological outcomes were evaluated by assessing surgical margins and postoperative prostate-specific antigen (PSA) levels at 4-8 weeks. Functional outcomes, including continence and potency, were defined as follows: full continence was reported when patients used 0 pads per day without anticholinergic therapy, while potency was defined as the ability to achieve an erection sufficient for sexual intercourse.

Results: A total of 100 patients diagnosed with localized prostate cancer were included in this study, divided into two groups: the first 50 patients and the last 50 patients who underwent RARP. The last 50 patients demonstrated significant improvements in perioperative outcomes, including shorter hospital stays (p=0.01), urethral catheter removal times (p=0.03), drainage catheter removal times (p=0.04), and operative times (p=0.02). Complication rates were lower in the last 50 patients, with no grade 5 complications observed in either group. Grade 3 complication rates were 12% in the first 50 patients and 2% in the last 50 patients (p=0.01). Oncological outcomes improved, with positive surgical margins decreasing from 22% to 6% (p=0.02) and undetectable PSA levels increasing from 76% to 90% (p<0.01). In terms of functional outcomes, the continence rate was 88% in the last 50 patients compared to 76% in the first 50 patients (p<0.05).

Conclusions: This study demonstrates that surgical experience significantly improves outcomes in RARP for localized prostate cancer. The later cohort exhibited reduced complications, shorter catheter durations, and enhanced oncological and functional results, highlighting the importance of proficiency in achieving optimal patient care.

Keywords: Robotic-assisted radical prostatectomy, surgical experience, complications, oncological outcomes, functional outcomes

Introduction

Robotic-assisted radical prostatectomy (RARP) has emerged as a preferred surgical technique for the treatment of localized prostate cancer, offering several advantages over traditional open and laparoscopic approaches (1). These benefits include reduced intraoperative blood loss, decreased postoperative pain, faster recovery times, and improved visualization of the surgical field (2,3). Furthermore, the use of robotic systems provides enhanced dexterity and precision for the surgeon, allowing for meticulous dissection and nerve-sparing techniques that can contribute to better functional outcomes, such as continence and potency (4,5). Despite these advantages, the success of RARP largely depends on the surgeon's experience, highlighting the significance of the learning curve in achieving optimal outcomes (6). As surgeons become more proficient with the robotic system, improvements in surgical efficiency, complication rates, and oncological outcomes are expected (7,8). Therefore, evaluating the impact of the learning curve on patient outcomes is essential to better understand how surgical expertise influences the results of RARP.

The concept of the learning curve in robotic surgery refers to the period during which a surgeon acquires proficiency in the technique, evidenced by a reduction in operative time, decreased complication rates, and improved clinical outcomes over time (9). Numerous studies have demonstrated that the

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learning curve in RARP can extend over the first 50 to 100 cases (10,11). During this period, surgeons typically experience a gradual reduction in operating time as they become more comfortable with the robotic platform, alongside a decrease in intraoperative complications and a trend towards better postoperative outcomes (12). However, the specific impact of this learning period on perioperative and oncological outcomes remains a subject of ongoing research. For instance, the learning curve may also influence the rates of positive surgical margins (PSM), which are crucial indicators of oncological efficacy (13). Understanding this relationship can provide insights into the time frame required for surgeons to achieve proficiency and maintain high standards in surgical practice.

By comparing the surgical outcomes of the first 50 and last 50 patients, this study aims to provide a clearer understanding of how increased surgical experience affects RARP outcomes.

Materials and Methods

Patient Characteristics

In this retrospective study, patients who underwent RARP for localized prostate cancer between November 2022 and October 2024 were evaluated. Ethical approval for the study was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2024-1173, date: 11.12.2024).

During this time period, the surgeries were performed by a surgical team. This team consisted of two surgeons who operated on the first 50 and the last 50 patients. The patients were not randomized regarding the type of surgery to be performed. The advantages and disadvantages of open, laparoscopic, and robotic surgery were explained to them. Following the informed consent process, the surgical approach was jointly decided by the physician and the patient.

The study compared the first 50 patients and the last 50 patients who underwent RARP. The first 50 patients were included in the study because the literature emphasizes that 50 cases are needed to complete the learning curve. The last 50 patients were selected as a comparison group to achieve similar statistical outcomes and to assess performance after the completion of the learning curve. This methodology is supported by existing literature indicating that at least 50 cases are needed to accurately analyze the learning curve in robotic surgery (14,15). Patients with locally advanced prostate cancer and those who had previously received radiotherapy were excluded from the study.

Patient demographic characteristics, tumor pathology findings, perioperative and postoperative outcomes and complications, American Society of Anesthesiologists (ASA) scores, and functional follow-up parameters such as continence and erectile function were retrospectively retrieved and evaluated from the hospital's medical records.

Surgical Technique

The da Vinci® X system was used to perform RARP. The patient was placed in the Trendelenburg position, and a pneumoperitoneum was created with an intra-abdominal pressure of 14-16 mmHg. Five ports were placed, consisting of four robotic ports and one assistant port. The subsequent steps were similar to the standard defined surgical procedure (16). All patients had a drainage catheter and a urethral catheter inserted.

Prophylactic antibiotic therapy was administered to all patients. All patients received enoxaparin prophylaxis for 5-7 days. If there were no contraindications, each patient was advised to use a phosphodiesterase type 5 inhibitor for penile rehabilitation during the first visit. Additionally, after mobilization, information on pelvic floor muscle exercises was provided, and patients were encouraged to perform them.

Outcome Measures

The Clavien-Dindo classification system was used to categorize the adverse events associated with the surgeries performed. In this classification system, complications of grade 3 or higher correspond to major complications. Grade 1 complications refer to any deviation from standard postoperative recovery that does not require treatment, except for specific medications (e.g., antiemetics, analgesics, and antipyretics). Grade 2 complications include situations that require various medical treatments or blood transfusions. Patients requiring intervention under general anesthesia are classified as grade 3, while complications related to Trendelenburg position and pneumoperitoneum are considered severe complications, and are corresponding to grades 4 and 5 (17).

Oncological outcomes were assessed using surgical margins and prostate-specific antigen (PSA) levels measured 4-8 weeks postoperatively.

Functional outcomes were evaluated at 3-month follow-up intervals after surgery. Complete continence was defined as situations, where the patient did not use any pads daily, and there was no need for medical treatment. Erectile function was defined as the ability to achieve sufficient erection for sexual intercourse.

Statistical Analysis

Statistical analysis was conducted using SPSS version 25.0 for Windows. The chi-square (χ^2) test was used to evaluate categorical variables, while Fisher's exact test was employed for assessing small sample sizes. The Mann-Whitney U test was used for the analysis of non-categorical data. A p-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 100 patients with localized prostate cancer were included in this study. Of these, the first 50 underwent RARP and the last 50 did as well. The mean age in the first 50, group was 68.2±3.5 years, and in the last 50, group, it was 69.1±4.0 years. The first 50 and last 50 groups had similar mean ages, pre-operative tumor characteristics, and ASA status. The baseline demographic characteristics, patient and tumor characteristics, and ASA statuses are summarized in Table 1.

Table 1. Baseline demographic patient and tumor characteristics			
Characteristic	**First 50 patients (n=50)**	**Last 50 patients (n=50)**	**p-value**
Age, mean (SD)	68.2 (3.5)	69.1 (4.0)	0.72
BMI, mean (SD)	27.5 (4.8)	27.2 (4.9)	0.65
Cardiovascular disease, n (%)	15 (30)	16 (32)	0.81
Diabetes, n (%)	12 (24)	13 (26)	0.79
PSA, mean (SD), ng/dL	7.3 (6.9)	7.5 (6.7)	0.67
Prostate weight, mean (SD), g	58.0 (22.5)	57.3 (21.0)	0.54
D'Amico clinical risk group, n (%)			0.78
Low	17 (34)	16 (32)	
Intermediate	25 (50)	26 (52)	
High	8 (16)	8 (16)	
Gleason grade group, n (%)			0.74
≤6	9 (18)	10 (20)	
7	28 (56)	27 (54)	
≥8	13 (26)	13 (26)	
Nerve-sparing status, n (%)			0.42
None	29 (58)	27 (54)	
Unilateral	15 (30)	17 (34)	
Bilateral	6 (12)	6 (12)	
Lymph node dissection,n (%)	38 (76)	37 (74)	0.89
ASA class, n (%)			0.56
Class 1	2 (4)	2 (4)	
Class 2	32 (64)	31 (62)	
Class 3	14 (28)	15 (30)	
Class 4	2 (4)	2 (4)	
SD: Standard deviation, BMI: Body mass index, PSA: Prostate-specific antigen, ASA: American Society of Anesthesiologists			

Perioperative Surgical Outcomes

In the last 50 patient group, the hospital stay duration (p=0.01), urethral catheter removal time (p=0.03), drainage catheter removal time (p=0.04), and operative time (p=0.02) were significantly shorter compared with the first 50 patient group. However, the estimated blood loss was similar between the groups. The perioperative surgical outcomes are summarized in Table 2.

Perioperative Adverse Events

No Clavien-Dindo grade 5 complications (death) were observed in either the first 50 patients or the last 50 patients. Newly diagnosed atrial fibrillation developed in one patient, who was among the last 50 patients. Grade 4 complications were not observed in any other patients in either group.

The rate of life-threatening complications, (grades 4 and 5) was 2.0% (1 out of the last 50 patients) in the last 50-patient group, and no grade 4 or 5 complications were observed in the first 50-patient group.

As a grade 3 complication, rectal injury requiring colostomy was observed in one patient from the first 50 patients (2.0%), along with anastomotic leaks requiring placement of a catheter with extra drainage holes at the proximal end of the balloon catheter in five patients (10.0%). In contrast, no anastomotic leaks were observed in the last 50 patients. One patient in the last 50 patients group, developed a hematoma that required endoscopic intervention (2.0%). The incidence of anastomotic leaks was significantly higher in the first 50 patients (p=0.01). Grade 3 and above complication rates were 12.0% (6/50) for the first group of 50 patients, and 2.0% (1/50) for the last group of 50 patients. There was a statistically significant difference in this parameter (p=0.01).

As a grade 2 complication, one patient in the last 50 patients group (2.0%) required erythrocyte suspension replacement due to port site-related bleeding. In the first group of 50 patients, two patients (4.0%) developed urinary tract infections, and one patient (2.0%) experienced epididymitis.

Pain requiring morphine, wound infection, lymphoedema, serum creatinine elevation, and portside hematoma were grade 1 complications that occurred at similar rates in both groups, and there was no statistical difference (p=0.08). The perioperative adverse events are summarized in Table 3.

Oncological Outcomes

The surgical margin was positive 11 patients (22.0%) in the first 50 patients, while this rate was 3 patients (6.0%) in the

Table 2. Perioperative surgical outcomes			
Outcome	**First 50 patients (n=50)**	**Last 50 patients (n=50)**	**p-value**
Hospital stay, median (d) (range)	4.5 (2-17)	3.0 (2-7)	**0.01**
Estimated blood loss, median (mL) (range)	110.0 (80-300)	90.0 (60-200)	0.10
Operative time, median (min) (range)	190.0 (190-320)	140.0 (120-180)	**0.02**
Urethral catheter removal time, median (d) (range)	12.0 (10-15)	8.0 (7-10)	**0.03**
Drainage catheter removal time, median (d) (range)	4.0 (2-6)	3.0 (2-4)	**0.04**

Table 3. Perioperative adverse events categorized according to the Clavien-Dindo classification system			
Clavien-Dindo classification	**First 50 patients (n=50)**	**Last 50 patients (n=50)**	**p-value**
Grade 1, n (%)			0.8
Pain requiring morphine	9 (18.0)	8 (16.0)	**0.01**
Fever	6 (12.0)	4 (8.0)	0.91
Wound infection	3 (6.0)	0 (0.0)	-
Lymphoedema	8 (16.0)	6 (12.0)	0.66
Serum creatinine elevation	3 (6.0)	0 (0.0)	-
Portside hematoma	0 (0.0)	1 (2.0)	-
Grade 2, n (%)			
Erythrocyte suspension replacement	0 (0.0)	1 (2.0)	-
Urinary tract infection	2 (4.0)	0 (0.0)	-
Epididymitis	1 (2.0)	0 (0.0)	-
Grade 3, n (%)			
Rectal injury (requiring colostomy)	1 (2.0)	0 (0.0)	-
Anastomotic leaks (requiring catheter placement)	5 (10.0)	0 (0.0)	**0.01**
Hematoma (requiring endoscopic intervention)	0 (0.0)	1 (2.0)	-
Grade 4, n (%)			
Atrial fibrillation	0 (0.0)	1 (2.0)	-
Grade 5, n (%)			
Death	0 (0.0)	0 (0.0)	-

last 50 patients. There was a statistically significant difference between the two groups (p=0.02). In the first 50 patients, undetectable PSA levels were present in 38 (76%), while in the last 50, 45 (90%) had undetectable PSA levels. There was a statistical difference between the two groups (p<0.01). The improvement in undetectable PSA levels from the first group to the last group is 14%. The oncological outcomes are summarized in Table 4.

Functional Outcomes

The rates of full continence (patient-reported 0-pad-per-day usage without anticholinergic therapy) were measured at 76% (38/50) in the first 50 patients' group and approximately 88% (44/50) in the last 50 patients' group. There was a statistically significant difference between the two groups (p<0.05). Both groups exhibited similar rates of potency for sufficient erection for intercourse, with the first group of 50 patients showing a rate of 22% (11/50) and the last group of 50 patients showing 24% (12/50). The functional outcomes are summarized in Table 5.

Discussion

The results of this study on RARP provide significant insights into the surgical outcomes, oncological efficacy, and functional recovery in patients with localized prostate cancer. The comparison of the first 50 patients with the last 50 patients highlights the importance of the learning curve associated with the RARP technique. The notable differences in perioperative outcomes, complication rates, and functional results between these two groups underscore the evolving nature of surgical expertise in robotic surgery.

Our study found that the hospital stay duration, urethral catheter removal time, drainage catheter removal time, and operative time were significantly shorter in the last 50 patients, compared to the first 50 patients. These findings are consistent with previous literature that emphasizes the learning curve's effect on improving surgical efficiency and reducing complications over time (18). As surgeons gain experience with robotic systems, they typically experience a gradual reduction in operating time, leading to shorter hospital stays and quicker recovery for patients (19). This aligns with the work of Bock et al. (20), who reported that with increased surgical experience, patients

Table 4. Oncological outcomes			
Outcome	**First 50 patients (n=50)**	**Last 50 patients (n=50)**	**p-value**
Positive surgical margin, n (%)	11 (22.0)	3 (6.0)	**0.02**
Undetectable PSA levels, n (%)	38 (76.0)	45 (90.0)	**0.01**
PSA: Prostate-specific antigen			

Table 5. Functional outcomes			
Outcome	**First 50 patients (n=50)**	**Last 50 patients (n=50)**	**p-value**
Full continence, n (%)	38 (76.0)	44 (88.0)	**0.05**
Potency for sufficient erection, n (%)	11 (22.0)	12 (24.0)	0.80

demonstrated a marked decrease in both operative time and postoperative complications.

The reduction in major complications observed in the group of the last 50 patients (of grade 3 and above complications) compared to the first group is particularly noteworthy. The incidence of such complications in the first group was 12.0%, whereas it dropped to 2.0% in the last group, reflecting the surgeon's enhanced proficiency and improved surgical technique over time. This reduction is corroborated by findings from several studies that illustrate how accumulating experience leads to lower complication rates in robotic surgeries (21).

In terms of oncological outcomes, the PSM rates and undetectable PSA levels exhibited significant improvements from the first group to the last group. The rate of PSM decreased from 22.0% in the first group to 6.0% in the last group, which is a crucial indicator of oncological success. This improvement is consistent with findings from the literature, which indicate that surgeons' experience correlates with reduced rates of PSM, enhancing overall oncological efficacy (22,23).

The increase in undetectable PSA levels from 76% in the first group to 90% in the last group further emphasizes the positive impact of surgical experience on oncological outcomes. The observed 14% improvement aligns with similar studies that document enhanced oncological results as surgical proficiency increases (4,5). However, it is essential to consider that while our study shows promising results, variations in patient selection, tumor characteristics, and follow-up durations among different studies may lead to disparities in findings.

Functional outcomes, including continence and potency, are critical for evaluating the success of RARP. In our study, the rates of full continence improved from 76% in the first 50 patients to approximately 88% in the last 50 patients, demonstrating a statistically significant difference between the groups. These findings are in line with the literature, which reports that robotic-assisted techniques can yield favorable functional outcomes compared to traditional approaches (5).

The improvement in potency rates was also noteworthy, while not statistically significant, with the first group exhibiting a potency rate of 22% compared to 24% in the last group. Although these rates appear modest, they reflect the surgeon's ongoing efforts to utilize nerve-sparing techniques effectively, which are pivotal in preserving sexual function postoperatively (24). It is important to note, that literature on functional outcomes in RARP often highlights variability based on patient characteristics, including age, comorbidities, and baseline sexual function, which may influence recovery rates differently across studies (4). The low rates of potency can be attributed to several factors: the patients' age over 65, their high comorbidity rates, and the selection of a strict criterion for the assessment of erectile function.

The results of this study corroborate many findings in the existing literature while also highlighting some differences. For instance, while our study demonstrates a significant decrease in PSM with experience, other studies have reported varying results, with some indicating minimal changes after a specific number of cases (22). This discrepancy may be attributed to differences in surgical techniques, patient demographics, and follow-up protocols.

Moreover, the improvement in functional outcomes in our study is comparable to findings from other institutions employing RARP; however, variations in definitions of continence and potency across studies may lead to inconsistencies in reported rates (4,5). Our operational definitions of continence as patient-reported zero-pad-per-day usage and potency as sufficient erection for intercourse are consistent with standards used in many similar studies (4,5).

This study is not without limitations. The retrospective design inherently carries the risk of bias, and the lack of randomization in selecting patients for RARP could impact the generalizability of our findings. Additionally, the relatively small sample size and limited follow-up duration may not sufficiently capture the long-term outcomes of RARP, including oncological and functional results. Validated forms were not used to assess functional outcomes. This may affect the reliability of the results, and we recommend the use of such forms in future studies involving a larger patient population. Future prospective studies with larger cohorts and extended follow-up periods are warranted to validate these findings and further explore the long-term effects of surgical experience on patient outcomes.

In conclusion, this study highlights the benefits provided by robotic surgery in the learning process. The significant improvements observed in surgical efficiency, complication rates, oncological efficacy, and functional recovery from the first to the last group underscore the importance of surgical experience in achieving optimal patient outcomes. These findings contribute to the growing body of literature advocating for the integration of robotic-assisted techniques in urology, emphasizing the need

for ongoing education and training to maximize the benefits of robotic surgery for patients.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2024-1173, date: 11.12.2024).

Informed Consent: Following the informed consent process, the surgical approach was jointly decided by the physician and the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.S., A.N.K., Concept: A.S., H.M.D., Design: A.S., O.B.K., F.Ç., Data Collection or Processing: O.B.K., F.Ç., Analysis or Interpretation: M.Y., K.S., A.L.S., Literature Search: H.M.D., A.L.S., Writing: A.S., H.M.D., A.N.K.,

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