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Survival and oncological outcomes for young men (≤ 55 years) undergoing radical prostatectomy for localized prostate cancer

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Summary

Objectives: *This research aimed to compare the prostate cancer (PCa) features, survival rate, and functional outcomes after open suprapubic Radical Prostatectomy (RP) between younger men (≤ 55 years) and older men (> 55 years).*

Methods: *In this retrospective cohort study, we studied 134 patients with clinically localized PCa who underwent RP at our centers between 2011 and 2019, with 26 (19.40%) patients aged ≤ 55. Pathological parameters, survival rate (at 5 and 10 years), and functional outcomes such as erectile function and continence rate (at two years from RP) were evaluated retrospectively, and the two groups were compared. The Chi-square test, Kaplan-Meier, and Cox proportional hazards method were used for statistical analysis.*

Result: *Men aged ≤55 had greater rates of organ-confined tumors, lower D'Amico risk grouping and pathologic Gleason grade than their older counterparts (all $p < 0.05$). The median follow-up was 81 months. The survival rate at five and ten years were higher in younger men versus older counterparts (96.15% vs. 93.47% and 92.15% vs. 82.13%) but difference was not statistically significant ($p = 0.1539$). Five-year biochemical recurrence-free and metastasis-free survival rates in younger men versus older counterparts were 96.2% vs. 81.5% and 75.7% vs. 51.5%. Men > 55 years were associated with worse BCR-free and metastasis-free survival in univariate analysis and with worse BCR in multivariate analysis. The continence rate was significantly better in men aged ≤ 55 compared to older counterparts (OR: 5.08; 95% CI: 1.61-22.61; $p = 0.013$). However, erectile function was not statistically significant between groups [for moderate ED: (OR: 1.08; 95% CI: 0.43-2.79, $p = 0.865$), for severe ED (OR: 1.60; 95% CI: 0.35-11.50, $p = 0.579$)].*

Conclusions: *Our study showed that survival rates were similar in younger men (≤ 55 years) and their older counterparts. However, older patients who underwent RP had more advanced disease, worse BCR-free survival, and a worse continence rate. For localized prostate cancer patients under 55 years of age, radical prostatectomy is an excellent treatment option with excellent long-term survival outcomes. Given the relatively small number of patients younger than 55, a large cohort study with long-term postprocedural follow-up is needed to validate this observation.*

Key words: *Radical prostatectomy; Survival outcome; Oncological outcomes; Young men.*

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Introduction

Prostate cancer (PCa) is a male malignancy seen mainly in the older population. Eighty percent of cases are diagnosed after the age of 65 years, yet PCa identification in younger males aged less than 50 has risen from 1% in the 1970s to 5% (1). Various autopsy investigations show a considerable rate of latent PCa in the third, fourth, and fifth decades of life, ranging between 20% and 30% (2). In younger men, latent PCa prevalence varies in autopsy series reports, ranging from 34% occurrence in the United States to 27% occurrence in Hungary and 2.6% occurrence in the Greek series (3-5). The increasing prevalence of PCa detection at a young age raises concerns about the natural course of this disease and treatment options. In low-risk, elderly PCa patients with a Gleason score of about (6), active surveillance is a good option (6). This is not the case with patients under the age of 55, who might require urgent intervention in the majority of instances due to the more aggressive behavior of the disease in younger patients, which leads to an increased number of patients undergoing *radical prostatectomy* (RP) (7).

The data regarding the outcomes of young men who suffered from PCa are contentious. According to *Tjaden et al.*, the disease in younger patients is more aggressive, with worse prognoses (8). However, recent studies mentioned that young men with low-risk PCa have better outcomes after RP (9, 10). A common limitation in these surveys was the use of *prostate-specific antigen* (PSA) relapse to measure the endpoint of the oncological outcome. At the same time, the progression of the disease or mortality seems to be the optimal outcome for reaching a better judgmental conclusion. In this article, we studied PCa patients who underwent RP and compared the pathological findings, oncological outcomes, and survival rates between younger men (≤ 55 years) versus older patients.

Materials and methods

Study design: In this retrospective cohort study, we studied 134 PCa patients who underwent retropubic RP in our referral teaching centers (*Ali-Asghar Hospital and Namazi Hospital, Shiraz, Iran*) between March 2011 and March 2019. The mean age of patients was 62.6 ± 9.2

years (range: 29.0-77.0 years). Twenty-six (19.4%) patients were aged ≤ 55 years, while 108 (80.6%) patients were aged > 55 years. The study was approved by the *Ethics Committee of Shiraz University of Medical Sciences* (ID: IR.SUMS.MED.REC.1398.493) and was conducted per the Declaration of Helsinki. Additionally, written informed consent was obtained from patients for participation in our study.

We included all patients diagnosed with localized PCa who underwent Radical Prostatectomy and filled the standardized self-administrated questionnaires before and one year after the surgery. Patients with missed information regarding clinical and paraclinical parameters were excluded. Patient characteristics, such as family history of disease, age, and clinical parameters, such as clinical stage, biopsy Gleason score, and PSA level, were gathered before surgery. After surgery, pathological data (surgical margin status, lymph node status, pathological stage, and Gleason score) were obtained. The PSA level was evaluated every three months in the initial year post-RP. This frequency was reduced to biannually for the subsequent two years, and from the fourth year onward, the check-ups were conducted annually. In two successive readings, *biochemical recurrence* (BCR) was defined as a PSA of more than 0.2 ng/ml. The RECIST criteria were used to evaluate the progression of the disease: CT, MRI, and bone scan were used to confirm skeletal lesions. Following the pathological analysis of *prostate cancer* (PCa), supplementary treatment, either *radiation therapy* (RT) or a combination of RT and androgen deprivation therapy, was given within four months post-RP. If BCR was identified, a rescue treatment, either RT alone or combined with androgen deprivation therapy, was administered.

We used histological examination following surgery or biopsy to confirm a local recurrence. The pathological result was evaluated using the AJCC 2002 staging system. From 1992 to 2005, we utilized the Gleason Grading system for tumor grading, and after 2005, we adopted the updated Gleason grading system (11). Urine continence was considered to use a 0-1 protective pad.

The evaluation of erectile function was carried out using a uniform questionnaire, which incorporated the *International Index of Erectile Function* (IIEF-5). Patients who had an IIEF-5 score greater than 16, indicating no erectile dysfunction or only mild erectile dysfunction, were classified as potent. We assessed clinical and pathological data, along with follow-up information (such as time to BCR, detected metastasis or local recurrence, urinary continence, and erectile function) comparing the two groups.

Statistical analysis

We utilized the mean ± *standard deviation* (SD) to represent the quantitative variables, and the frequency (percentage) was employed to describe the qualitative variables. Chi-squared tests were used to compare the characteristics of patients and tumors. Kaplan-Meier survival curves and Cox-proportional hazard methods were applied for univariate and multivariate BCR-free survival, metastasis-free survival, and overall survival analyses. Functional outcome (24-month continence and potency) was analyzed using multivariable logistic regressions. A p-value less than 0.05 was deemed statistically significant. All the data were processed using the SPSS version 20 software (*SPSS Inc., Chicago, IL, USA*).

Result

Patient and tumor characteristics

Table 1 presents all the cases' pathological and clinical features and compares age-related variables. Among our 134 cases, 26 (19.40%) patients were aged ≤ 55 years, while 108 (80.6%) patients were aged > 55.

Young patients had greater rates of organ-confined tumors, lower D'Amico risk grouping and pathologic Gleason grade group than their older counterparts (all $p < 0.05$). However, the younger group aged ≤ 55 years have a higher rate of positive family history of prostatic cancer ($p < 0.001$).

Oncological outcome

Biochemical recurrence occurred in 21 (16%) patients over a median of 44 months [Min: 23 - Max: 65 months] of follow-up, with no statistically significant difference between groups (p = 0.0588) (Figure 1). During a follow-up of 84.6 ± 23.1 months (median: 81 [min: 27 - max: 120]), metastases were discovered in 32 (23.9%) patients, with no sig-

Table 1.
Demographics and tumor characteristics stratified by patient age groups.

Variables	Subgroup	Total (n = 134)	Age ≤ 55 (n = 26, 19.4%)	Age > 55 (n = 108, 80.6%)	P-value
Age (year)	Mean (SD)	62.6 (9.2)	47.0 (7.0)	66.3 (4.7)	< 0.001
Family history of prostatic cancer	Negative	127 (94.8)	20 (76.9)	107 (99.1)	< 0.001
	Positive	7 (5.2)	6 (23.1)	1 (0.9)	
Gleason grade group	≤ 6	34 (25.4)	17 (65.4)	17 (15.7)	< 0.001
	7	66 (49.3)	7 (26.9)	59 (54.6)	
	≥ 8	34 (25.4)	2 (7.7)	32 (29.6)	
PSA (ng/ml)	< 10	29 (21.6)	15 (57.7)	14 (13.0)	< 0.001
	10-20	52 (38.8)	11 (42.3)	41 (38.0)	
	> 20	53 (39.6)	0 (0.0)	53 (49.1)	
D'Amico risk classification	Low risk	36 (26.9)	11 (42.3)	25 (23.1)	0.007
	Intermediate	41 (30.6)	11 (42.3)	30 (27.8)	
	High risk	57 (42.5)	4 (15.4)	53 (49.1)	
Surgical margin	Negative	102 (76.1)	24 (92.3)	78 (72.2)	0.057
	Positive	32 (23.9)	2 (7.7)	30 (27.8)	
Lymph node invasion	No	93 (69.4)	23 (88.5)	70 (64.8)	0.035
	Yes	41 (30.6)	3 (11.5)	38 (35.2)	
Pathologic confined	Organ confined	74 (55.2)	21 (80.8)	53 (49.1)	0.007
	non-Organ confined	60 (44.8)	5 (19.2)	55 (50.9)	

PSA: prostate-specific antigen.
Boldface indicates a statistically significant result (p < 0.05).

Figure 1.
Mortality-free survival stratified by age groups.

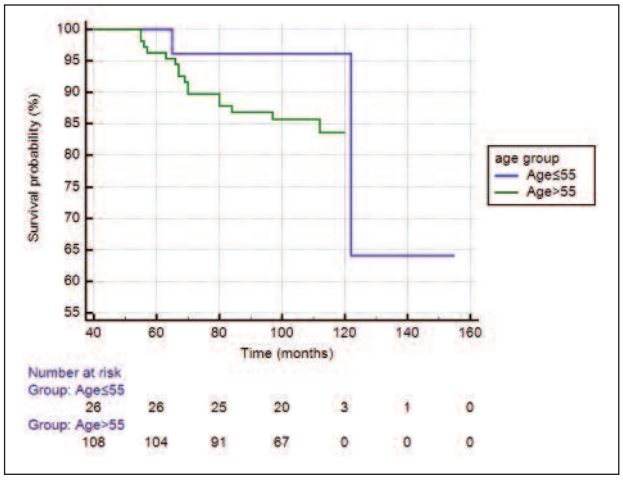


Figure 2.
Biochemical recurrence-free survival stratified by age groups.

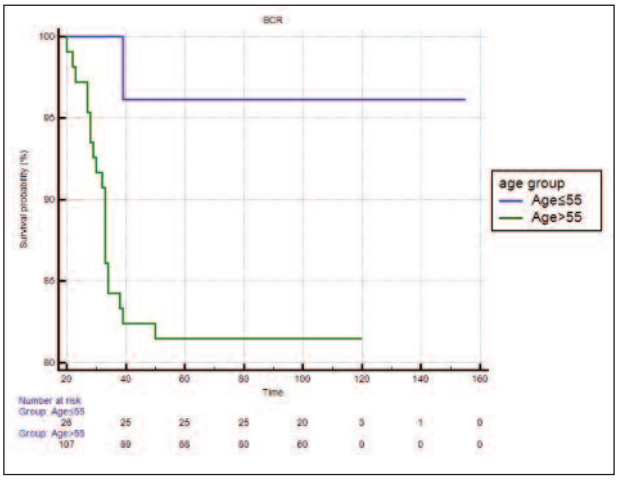
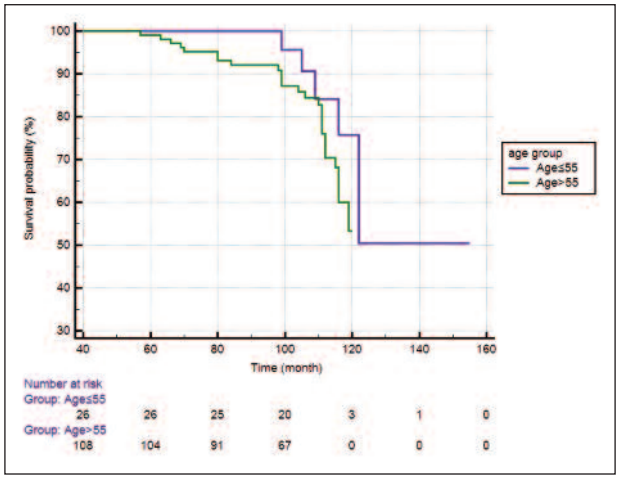


Figure 3.
Metastasis-free survival stratified by age groups.



nificant difference between groups (p = 0.1539) (Figure 2). Five-year biochemical recurrence-free and metastasis-free survival rates in younger men versus older counterparts were 96.2% *vs.* 81.5% and 75.7% *vs.* 51.5%. Median survival was 87 months (95% CI: 81-90 months). The disease's progression time was 82.8 ± 24.7 months (median: 80 [min: 27 - max: 120 months]) and did not differ significantly between groups (p = 0.1348) (Figure 3).

The survival rate for the age group ≤ 55 years at five and ten years was 96.15% (95% CI: 89.04%-100.0%) and 92.15% (95% CI: 82.27%-100.0%). The survival rate for the age group > 55 years at five and ten years was 93.47% (95% CI: 88.92%-98.3%) and 82.13% (95% CI: 3.76%-91.4%). The Kaplan-Meier analysis showed a similar biochemical progression-free survival (BPFS) rate without statistically significant difference (log-rank p = 0.152). The uni- and multivariable Cox-regressions analysis showed that in univariate analysis, older patients were more likely to develop BCR (HR: 26.04; 95% CI: 8.42-80.54, p < 0.001) and metastasis (HR: 2.60; 95% CI: 1.02-6.60, p = 0.045).

The multivariable Cox-regressions analysis showed that nearly all parameters, both before and after surgery, were similar except for biochemical recurrence (HR: 88.70; 95% CI: 14.19-554.43, p < 0.001) and was a predictor for disease progression. However, after adjusting for further prognostic factors (Gleason score, preoperative PSA, lymph node status, surgical margin, pathologic stage), patients' age (≤ 55 *vs* > 55 years) was not a statistically significant predictor for mortality (p = 0.949) (Table 2).

Variables	Subgroup	Total (n = 134)	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Age group	Age ≤ 55	26 (19.4)	-		-	
	Age > 55	108 (80.6)	4.13 (0.55-31.19)	0.169	1.08 (0.11-11.04,)	0.949
Gleason score	≤ 6	34 (25.4)	-		-	
	7	66 (49.3)	1.13 (0.73-1.76)	0.577	0.89 (0.56-1.44)	0.646
	≥ 8	34 (25.4)	0.73 (0.43-1.24)	0.243	0.67 (0.36-1.25)	0.207
PSA (ng/ml)	< 10	29 (21.6)	-		-	
	10-20	52 (38.8)	0.87 (0.54-1.42)	0.581	0.73 (0.42-1.29)	0.281
	> 20	53 (39.6)	1.41 (0.87-2.30)	0.168	1.07 (0.57-2.00)	0.837
Surgical margin	Negative	102 (76.1)	-		-	
	Positive	32 (23.9)	0.70 (0.44-1.11)	0.128	0.82 (0.47-1.46)	0.506
Lymph node invasion	No	93 (69.4)	-		-	
	Yes	41 (30.6)	0.87 (0.57-1.32)	0.507	1.06 (0.61-1.84)	0.844
Pathologic confined	Organ confined	74 (55.2)	-		-	
	non-Organ confined	60 (44.8)	0.90 (0.62-1.30)	0.577	0.70 (0.45-1.08)	0.107
Biochemical recurrence	No	113 (84.3)	-		-	
	Yes	21 (15.7)	26.04 (8.42-80.54)	< 0.001	88.70 (14.19-554.43)	< 0.001
Metastasis	No	102 (76.1)	-		-	
	Yes	32 (23.9)	2.60 (1.02-6.60)	0.045	2.16 (0.62-7.52)	0.225

PSA: prostate-specific antigen, CI: confidence interval, HR: hazard ratio.
Boldface indicates a statistically significant result (p < 0.05).

Table 2.
Uni- and multivariable Cox-regressions predicting mortality-free survival.

Table 3.
Postoperative continence and potency rates stratified by age groups.

Variables	Subgroup	Age ≤ 55 (n = 26, 19.4%)	Age > 55 (n = 108, 80.6%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Erectile function	Potent	13/26 (50%)	56/108 (51.8%)	-		-	
	Moderate	11/26 (42.3%)	42/108 (38.8%)	0.89 (0.36-2.21)	0.792	1.08 (0.43-2.79)	0.865
	Severe	2/26 (7.6%)	10/108 (9.2%)	1.16 (0.26-8.14)	0.858	1.60 (0.35-11.50)	0.579
Continence	Continence) (0 to 1 pad/day	23/26 (88.5%)	66/108 (61.1%)	-		-	
	Incontinence (> 1 pad/day)	3/26 (11.5%)	42/108 (38.9%)	4.88 (1.57-21.47)	0.014	5.08 (1.61-22.61)	0.013

OR: odds ratio, CI: confidence interval.
Boldface indicates a statistically significant result (p < 0.05).

Functional outcome biochemical progression-free survival
Regarding postoperative functional outcome, the continence rate was significantly influenced by age in univariate analysis (OR: 4.88; 95% CI: 1.57-21.47, p = 0.014) and multivariate analysis (OR: 5.08; 95% CI: 1.61-22.61; p = 0.013). The erectile function was more improved in younger age [2 (16.7%) *vs.* 10 (83.3%)]. However, the rate was not statistically significant in univariate [for moderate: (OR: 0.89; 95% CI: 0.36-2.21, p = 0.792) and for severe (OR: 1.16; 95% CI: 0.26-8.14, p = 0.858)] or multivariate analysis [for moderate: (OR:1.08; 95% CI: 0.43-2.79, p = 0.865), for severe (OR: 1.60; 95% CI: 0.35-11.50, p = 0.579=)] (Table 3).

Discussion

Age at cancer diagnosis is a well-known prognostic factor in the majority of malignancies. Although few studies have found a worse prognosis in earlier high-stage PCa patients (12-15), Interestingly, evidence from recent research has also revealed that early diagnosis of PCa in younger cases is related to lower stage and grade or perhaps to better results (9, 10, 16). A recent comprehensive review also discovered that younger age was associated with positive clinicopathological features and a more favorable prognosis for BCR in patients with low to intermediate risk. However, in high-risk groups, younger patients often experienced notably poorer oncological results (17). In this research, we examined the characteristics of PCa, functional results, and survival outcomes in young men 55 years old or below after RP and then compared these findings with those of men older than 55.

Selecting candidates for radical prostatectomy is a challenging task for both the physician and the patient. The patient's life expectancy, the natural history and curability of prostate cancer, as well as the morbidity of treatment and deferred treatment, must all be carefully evaluated. Although the existing clinical data containing this information has inherent flaws, all these factors can be calculated with good precision. A concentrated effort should be made to present the patient with prognostic information that is appropriate for his age, health status, and the stage and grade of cancer. Because not all men who choose radical prostatectomy will require or benefit from surgical intervention, the patient must be fully involved in the decision-making process (18). In our study, it is probable that younger individuals underwent more intensive screening, resulting in more frequent diagnoses at an early stage of the disease. Furthermore, younger patients were more likely to prefer surgery over older patients.

It is crucial to seek a better understanding of the correlation between younger age and prostate cancer occurrence and progression, which will aid strategic approaches when treating younger prostate cancer patients in the PSA era (17). *Salinas et al.* observed that prostate cancer diagnoses in those under 55 are mainly localized. However, men in this age group are more likely to die from higher grade/stage disease, indicating a demographic difference between early-onset and older male prostate cancer patients (19). Similar to our study design, several studies on clinicopathological characteristics of prostate cancer chose the age of 55 as a cutoff point (13, 20, 21). However, there is no agreement on the age at which these tumors become most aggressive or on the characteristics that make these tumors more aggressive in young individuals. A recent meta-analysis suggested that age 50 is often used as the cutoff to separate younger and older patients in RP cohorts, which contradicts our choice of 55 as the cutoff (17). However, with our limited number of cases, choosing a lower age cutoff threshold of less than 55 years would result in an unbalanced sample size per group, increasing the possibility of mistakes during the matching and making statistical analysis challenging.

Family history, age, and race are all established risk factors for prostate cancer. While family history accounts for just 9% of cases, early-onset prostate cancer has a higher likelihood of being hereditary compared to late-onset prostate cancer. This increase in the risk of prostate cancer can be explained by the higher number of alleles in those patients (22, 23). Similarly, in our study, family history was found in 0.9% of older males (> 55 years) and 23.1% of younger men (≤ 55 years), which was statistically significant (< 0.001). Several other studies also show a strong link between family history and early-onset prostate cancer detection in young men (9, 12). Future research on rare cases is essential to finding additional risk alleles and better understanding the disease's etiology.

In this study, men aged ≤ 55 had greater rates of organ-confined tumors, lower D'Amico risk grouping, and pathologic Gleason grade than their older counterparts. The findings of this report were similar to *Milonas et al.* report, which mentioned younger men (≤ 55 years old) tend to have less aggressive clinical and pathological PCa characteristics than older men (24). According to several investigations, older men are more likely to have advanced malignancy features. *Ji and colleagues* analyzed the pathological characteristics of PCa patients divided into three age groups: 55 or younger, between 56 and 75, and older than

75. They found that the percentage of Gleason pattern five tumors varied significantly across the groups (44.4%, 32.3%, and 36.8%, respectively), indicating a significant difference ($\chi 2 = 11.641$, $p = 0.003$) (25). This study's bivariate regression analysis demonstrated that greater pathological GS were indicators of illness development. However, this conclusion might arise from the considerable imbalance in the patient group ages, with just 26 participants aged ≤ 55 and 108 patients aged 55-75. All of these data lead us to believe that preconceptions regarding cancer's aggressiveness at a young age play a significant influence in choosing a surgical treatment decision.

Various studies have shown a high long-term *Biochemical-Free Survival Rate* (BFSR) in the young male group. For example, *Tan et al.* showed greater 5- and 10-year survival rates among younger individuals (97.9% vs. 95.9% and 94.9% *vs.* 85.3, respectively) (13). *Freedland and colleagues* examined 1.753 male patients post-RP in their research. They discovered that men under 50 had a significantly higher BFSR than other age groups.16 In contrast, *Milonas et al.* found that young men had a 5- and 8-year BFSR of 77.9% and 72.4%, although this difference was not statistically significant compared to males over 55 (12). *Song and colleagues* found that patients aged 55 or younger had better survival rates in the first year after treatment but poorer outcomes in the second, third, and fifth years compared to older age groups (20). In our study, the survival rate at five and ten years in younger men versus older counterparts was 96.15% *vs.* 93.47% and 92.15% *vs.* 82.13% but was not statistically significant ($p = 0.1539$). Five-year BCR-free and metastasis-free survival rates in younger men versus older counterparts were 96.2% *vs.* 81.5% and 75.7% *vs.* 51.5%, and men > 55 years were associated with worse BCR-free and metastasis-free survival in univariate analysis and worse BCR in multivariate analysis. However, the patient's age at surgery was not proven to be an independent predictor in multivariable analysis. Similarly, in most studies, the patient's age at surgery was not proven to be an independent predictor in multivariable analysis, indicating a significant role of other factors (12, 16).

In the current study, young individuals had less erectile dysfunction (16.7% *vs.* 83.3%), but it was not statistically significant in regression analysis. Our findings were similar to those of other studies in the literature. *Brajtbord and colleagues* studied the recovery of erectile function after RP in two age groups (≤ 60 years old and those older than 60). They found that older men were more likely to experience a notable decrease in sexual outcomes, specifically discomfort (26). In another study, *Alemozaffar et al.* also showed a correlation between increasing age and a lower chance of erectile function despite controlling for baseline performance (27). *Tilki et al.* reported the one-year sexual function after RP in patients aged less than 45 years, between 45-65 years, and over 65 years. They found that 75.6%, 58.6%, and 45.3% of patients had a potent sexual function, respectively (28). However, the better recovery of erectile function in our study might result from the differences in community settings and specialists.

Indeed, the restoration of continence should be viewed as a process. Although information on early continence is rare, it has been observed that most men regain continence three months post-RP. Furthermore, the recovery rate increases to approximately 90% after one year and continues improving (29, 30). A recent report by *Theissen et al.* investigated the factors impacting early continence in post-radical prostatectomy. The authors revealed reduced urine loss in younger patients or those with organ-confined tumors and those in whom the bilateral nerve-sparing technique was successfully used in RP. In the current study, younger individuals had statistically significantly better continence rates. Our findings were similar to those of other studies in the literature (31, 32).

Study limitations

Our research had some limitations. First, as a retrospective study with a small sample size, especially in the young age group (less than 55 years), it inherits some inevitable confounders related to these studies, which could cause gaps in clinical information. Second, due to limitations in the data archive, factors such as detailed treatments and multimodality treatments were not evaluated. We also could have benefited from a larger group of younger patients in our study to strengthen our results. As a result, more high-quality studies with larger sample sizes are required to validate our findings further.

Conclusions

Our study showed survival rates were similar in younger men (≤ 55 years) and their older counterparts. However, older patients who underwent RP had more advanced disease, worse BCR-free survival, and worse continence rate. For that, in localized PCa patients under 55 years, radical prostatectomy is an excellent treatment option with excellent long-term survival results. Given the modest number of patients under 55, extensive cohort studies with long-term post-procedural follow-up are necessary to validate this observation.

Declarations

Ethical approval: Registry and the Registration No. of the study/trial: Not applicable. All patient's parents or legal guardians provided written informed consent before enrolment.

Availability of data and material: All inquiries can be directed to the corresponding author.

Competing interests: The authors declare no conflict of interest.

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Authors' contributions: SZ and AM: designed the study and were involved in the record collection. FA and MA: wrote the manuscript. SZ and AA: edited the manuscript, and provided guidance, and formal analysis. AA: conceptualized the study, designed the study, edited the manuscript, provided guidance, and approved the final version of the manuscript.

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