

Stage pT0 Prostate Cancer: A Single-Center Study and Literature Review

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What's known on the subject? and What does the study add?

Stage pT0 prostate cancer (PCa) after radical prostatectomy is a rare phenomenon with unclear significance. Patients with a Gleason score of 6 and tumors in a single core and length of <2 mm in the biopsy have a higher risk of stage pT0 PCa.

Abstract

Objective: To report our experience with biopsy positive T0 prostate cancer (PCa) and perform a literature review to determine the frequency, clinical outcomes, and predictors of pT0 PCa after radical prostatectomy (RP).

Materials and Methods: The records of 497 patients who underwent robot-assisted RP at our institution between 2015 and 2020 were retrospectively reviewed. No patients were diagnosed after the transurethral prostate resection or received preoperative hormone therapy. Clinicopathological features including age, prostate-specific antigen (PSA), body mass index, digital rectal examination, biopsy results, clinical T stage, D'Amico risk, prostate weight, prostatectomy pathology, and follow-up data were analyzed.

Results: Overall, 3 patients were classified as pT0 on pathologic examination of the RP. The biopsy re-evaluation revealed that 1 patient did not have PCa. Subsequently, the entire RP specimens were re-analyzed, wherein 2 cases were signed out with no identified carcinoma. The incidence of the pT0 PCa was 0.4% in our series. The median age of patients was 64 years. The median PSA was 14.27 ng/mL. Biopsy Gleason score of 2 patients was reported as 3 + 3. All patients had a tumor in only one core and all were in clinical stage T1c. No biochemical recurrence was found in a mean 21-month follow-up. Eleven studies were identified involving 26,228 patients, wherein 122 (0.46%) were reported with pT0 cases. Most patients with stage pT0 have been reported to have a Gleason score of <7, only one positive core biopsy, and a tumor length of <2 mm.

Conclusion: Patients with a Gleason score of 6 and tumors in a single core and length of <2 mm in the biopsy should be informed about the risk of stage pT0.

Keywords: Prostate cancer, residual cancer, surgical pathology, prostatectomy

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men and is also second-ranked cancer that results in death in the United States (1). Currently, radical prostatectomy (RP) remains the gold standard surgical treatment for localized PCa. Widespread use of prostate-specific antigen (PSA) screening has resulted in an increased number of patients diagnosed with small-volume and low-grade tumors. Correspondingly, the volume of residual cancer in RP specimens has decreased

(2). In some cases, no demonstrable cancer is identified in the entire RP specimen despite prior positive biopsy. The inapparent cancer after the RP has been referred to as the 'vanishing cancer phenomenon' that was first described by Goldstein et al. in 1995 (3). The vanishing cancer phenomenon is defined as stage pT0 according to the Tumor, Node, and Metastasis classification. The rate of pT0 cystectomy specimens has ranged between 5.1% and 20.1% (4). However, the unusual event occurs in <1% of all RPs (5). Patients who have had neoadjuvant hormonal therapy or prior transurethral resection of the prostate (TURP) experience

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more commonly pT0 disease after the RP (2,6). The finding of pT0 disease following the RP is a challenging situation with unclear significance.

This study aimed to report the results of pT0 tumors after the RP at our institution. Additionally, the literature review was performed to determine the incidence, clinicopathological characteristics, and follow-up data of no residual cancer following RP.

Materials and Methods

Study Population

After the local institutional review board approval (approval number: 2021-007), we retrospectively identified the prospectively maintained robotic surgery database records of 497 patients who underwent robot-assisted RP (RARP) between March 2015 and June 2020 in our institution. The study was approved by Antalya Training and Research Hospital Ethics Committee (approval number: 2021-007). Patients who received hormonal therapy before the surgery (n=2) or who were diagnosed with PCa after TURP (n=4) were excluded from the study.

Acquisition and Definition of Data

For each case, patient age, PSA level, body mass index, digital rectal examination (DRE) finding, prostate biopsy results (number of biopsy core, number of positive core, length of positive core, percentage of cancer, and Gleason score), clinical T-stage, D'Amico risk group, prostate weight, prostatectomy pathology results (pathological N stage, RP diagnosis), last visit PSA level, and follow-up time were recorded.

PubMed, Web of Science, Scopus/Science Direct, Wiley Online, and Google Scholar databases were scanned for the literature review. Scanning the literature was performed using the keywords: vanishing cancer, pT0, PCa, and no residual tumor.

Surgical Technique and Follow-up

Radionuclide bone scans were performed in symptomatic patients and patients with PSA levels of >10 ng/mL. The multiparametric magnetic resonance imaging was performed in all patients. All patients had a clinically localized PCa at the time of surgery. All patients underwent RARP. Our surgical technique of RARP has been described (7). Bilateral pelvic lymphadenectomy was performed in all high-risk and selected intermediate-risk patients according to the Briganti nomogram. Patients were followed up postoperatively with PSA every 3 months for the first year, every 6 months for the second year, and annually thereafter. The biochemical recurrence (BCR) was defined by two consecutive PSA levels of ≥ 0.2 ng/mL.

Pathological Examination

All RP specimens were sampled and examined using a standard protocol (8,9). Prostate needle biopsies were re-evaluated when no residual tumor was found following the histological review. After excluding false-positive prostate needle biopsy, entire RP specimens are re-analyzed. The slides of the surgical specimens were reviewed for residual cancer by a dedicated pathologist. The remaining prostate tissue was processed in toto if the RP specimen was not embedded. Three additional deeper sections of the RP tissue block corresponding to the tumor area of the biopsy were re-cut. After block-flipping, additional deeper sections were prepared. Immunohistochemical analysis was done if a lesion suspicious for cancer was present. The RP specimen was signed out as showing no residual cancer if cancer is not found after all of these steps. Cases were included in this study after confirmation of no residual tumor (pT0).

Statistical Analysis

Our study performed no statistical analysis due to insufficient data groups requiring statistical analysis. The data of patients were expressed as mean, minimum-maximum, and percentage.

Results

The clinical data of all cases with a postoperative pT0 stage were extracted from the database, wherein 3 cases were identified. All prostate biopsies corresponding to the pT0 tumors were reviewed by a second pathologist, and PCa diagnosis was not confirmed in 1 patient. After excluding this patient, RP specimens of 2 patients were re-analyzed. No residual tumor was found. The patient characteristics are listed in Table 1. The median age of patients was 64 years (range, 62-66). No abnormal findings were detected in the DRE of these patients. The median PSA was 14.27 ng/mL (range, 3.93-24.62). In all cases, PCa was diagnosed in the first biopsy. Prostate needle biopsy Gleason score of 2 patients was reported as 3 + 3. All patients had a tumor in only one core and all were clinical stage T1c. The final pathology was reported as high-grade prostatic intraepithelial neoplasia in patient 1, whereas nodular hyperplasia in patient 2. (Figure 1,

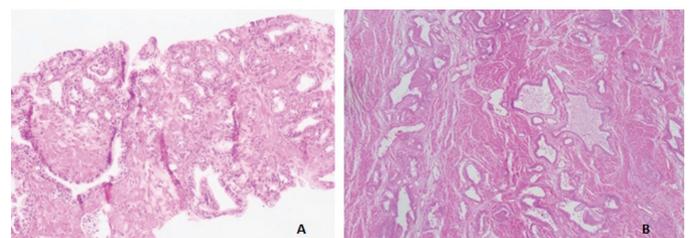


Figure 1. A- Crowded small glands of prostatic adenocarcinoma have amphophilic cytoplasm and enlarged nuclei with prominent nucleoli on needle core tissue. (Gleason score 3+3=6). B- Invasive tumor has not been determined at radical prostatectomy of the same patient

Figure 2) The mean prostate weight was 118 g (range, 110-126). The BCR was not detected in any patient.

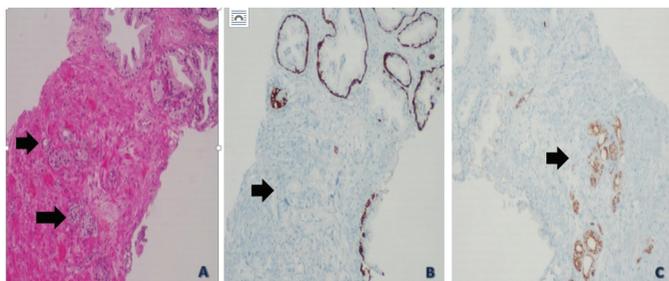


Figure 2. A- Small glands of adenocarcinoma (arrow), compared with benign glands (above) B- Basal cells of benign glands reactive with high-molecular weight cytokeratin (HMWK). Tumoral glands (arrow) do not express HMWK because basal cells are absent in invasive adenocarcinoma of the prostate. C- Neoplastic prostatic epithelial cells show over-expression of AMACR (arrow)

	Patient 1	Patient 2
Age, years	62	66
BMI, kg/m ²	29.74	28.40
Abnormal DRE	No	No
PSA, ng/mL	24.62	3.93
Biopsy Gleason score	3+3	3+3
Total number of cores, n	10	12
Number of positive core, n	1	1
Length of positive core, mm	2	1
Percentage of cancer, %	5	1
Preoperative stage	T1c	T1c
D' Amico risk group	High	Low
Specimen weight, g	126	110
Final pathology result	HGPIN	Nodular hyperplasia
Pathological N-stage	N0	Nx
Follow-up, months	24	17
BCR	No	No
Last visit PSA, ng/mL	0.02	<0.0008

BMI: Body mass index, DRE: Digital rectal examination, PSA: Prostate-specific antigen, HGPIN: High-grade prostatic intraepithelial neoplasia, BCR: Biochemical recurrence

Discussion

The absence of residual tumor in RP specimens is called the "vanishing cancer phenomenon" (pT0) (3). This phenomenon, which is very rare and challenging for both clinicians and patients, is also important from a medicolegal perspective. The incidence of stage pT0 PCa ranges from 0.1% to 2.12% (10-26). The frequency of pT0 PCa in our cohort was 0.4%. This incidence is higher in patients diagnosed with incidental PCa during TURP

or open prostatectomy performed to treat benign prostatic hyperplasia or patients who receive neoadjuvant hormonal therapy (17,27). In these patients, a small tumor focus may be removed during a surgical procedure or obscured by hormonal therapy. The final true incidence rate is 0.1%-1.3% in patients diagnosed with PCa on prostate needle biopsy and who do not receive preoperative hormonal therapy (10,12,13,15,16,18-20,23-25). The incidence and clinical outcomes of this group of patients are summarized in Table 2. Patients with tumors detected after the re-evaluation of RP specimen and prostate needle biopsy were not included in Table 2. Thus, the final true incidence was determined.

Most patients with stage pT0 have been reported to have lower PSA levels, biopsy Gleason scores, and tumor burden. Park et al. (15) compared patients with and without stage pT0 and revealed that patients with pT0 had significantly lower Gleason scores, a smaller number of positive cores, smaller tumor length, and larger prostate volume. Another study noted lower Gleason scores, a higher rate of lower-risk disease, and fewer positive cores in patients with pT0 (11). A study that compared patients with stage pT0 with a control group revealed statistically significantly lower Gleason scores, tumor length in the biopsy, and the number of positive cores in the pT0 group. Prostate volume was significantly larger (13). Schirmacher et al. (21) compared patients with and without stage pT0 and reported that Gleason scores, tumor length, and the number of positive cores were significantly lower in patients with pT0. Moreira et al. (17) showed that the PSA level of patients with pT0 was significantly lower than that of the control group. No comparative analysis was performed in our study. The mean PSA level of patients was 14.27 ng/mL. Based on previous studies, a high mean PSA level can be associated with the fact that one of the two patients had a PSA of 24.62 ng/dL. Two patients had a Gleason score of 6. In addition, the tumor was detected in a single core in both. The mean tumor length in the positive core was 1.5 mm.

The prognosis of patients with stage pT0 is assumed to be satisfactory. Several studies have indicated no local recurrence or clinical progression in the follow-up period (10,12-16,20,23,24). This study observed no BCR or disease progression in any patients during the mean follow-up period of 21 months. In a population-based study conducted by Knipper et al. (11), cancer-specific death was observed in only 3 patients with pT0 during a 9-year follow-up period. The cancer-specific survival rate in the 9 years was 99.5% in patients with pT0; however, it was 98.8% in those without pT0. In a study including 62 patients with pT0, 7 (11%) had disease relapse during the median of 10.9 years of follow-up (17). However, all these patients had received treatment before surgery. Compared with patients without pT0, those with pT0 were reported to have longer recurrence-free survival. Prayer-Galetti et al. (26) reported PSA progression in

3 (12.5%) patients in their pT0 cohort study that included 24 patients. All patients who experienced PSA progression had undergone preoperative hormonal therapy. The absence of PSA progression in studies including patients who did not receive preoperative hormonal therapy indicates a favorable prognosis in these patients. However, caution must be exercised in the follow-up of these patients. Patients with pT0 PCa should be followed up routinely. Thwaini et al. (28) reported that bone metastasis was detected during the follow-up of a patient with pT0 who did not receive hormonal therapy before the surgery.

Some researchers have investigated variables that can be used to predict stage pT0 before RP. In the study by Park et al. (15), no multivariate logistic regression analysis could be performed, as the number of patients was low. However, they chose four criteria to predict pT0 disease: (1) Gleason score of ≤ 6 , (2) positive cores of ≤ 2 , (3) tumor size in biopsy of ≤ 2 mm, and (4) prostate volume of ≥ 30 cm³. When these four criteria were combined, they calculated that the sensitivity of pT0 in predicting the disease was 88.8%, specificity was 93.4%, positive predictive value (PPV) was 12.7%, and negative predictive value

Table 2. Literature data of patients with pT0 prostate cancer

References	Study period	Total, n	pT0, n	Incidence, %	Follow-up	Oncological outcomes	Predictors of pT0
Bessede et al. (10)	1991-2010	2462	19	0.77	Median follow-up of 41 months	No clinical or biochemical recurrence	N/A
Bream et al. (12)	1991-2011	1635	2	0.12	Ranging 3 months to 10 years follow-up	No clinical or biochemical recurrence	N/A
Descazeaud et al. (13)	1996-2005	1950	11	0.56	Mean follow-up of 30 months	No clinical or biochemical recurrence	One positive core only, overall tumor length of ≤ 2 mm, biopsy Gleason score of < 7 , and prostate weight of 60 g. A combination of 4 variables had a sensitivity of 82% and a specificity of 99%. The PPV value was 31% and the NPV was 99%.
Park et al. (15)	2004-2008	702	9	1.3	Mean follow-up of 23.6 months	No clinical or biochemical recurrence	Gleason score of 6 or less, two or fewer positive cores, a tumor size of 2 mm or less, and prostate volume of ≥ 30 cm ³ . A combination of the 4 criteria had a sensitivity of 88.8% and a specificity of 93.4%. The PPV value was 12.7% and the NPV was 99.8%.
Bessède et al. (16)	1998-2006	7693	30	0.39	Median follow-up of 82 months	No clinical or biochemical recurrence	N/A
Mazzucchelli et al. (18)	1995-2006	1328	3	0.22	N/A	N/A	N/A
Kosarac et al. (19)	2004-2009	1741	5	0.28	N/A	N/A	N/A
Trpkov et al. (20)	2000-2005	1351	9	0.67	Mean follow-up of 714 days	No clinical or biochemical recurrence	N/A
Mehta et al. (23)	1998-2010	1060	11	1	Median follow-up of 64 months	No clinical or biochemical recurrence	N/A
Herkommer et al. (24)	1990-2004	3609	13	0.36	Median follow-up of 62 months	No clinical or biochemical recurrence	N/A
Duffield and Epstein (25)	2005-2007	2200	8	0.36	N/A	N/A	N/A
Present study	2015-2020	497	2	0.4	Mean follow-up of 20.5 months	No clinical or biochemical recurrence	N/A
Total		26.228	122	0.46			

(NPV) was 99.8%. Similarly, Descazeaud et al. (13) identified four criteria (i.e., single positive core, total tumor length in the biopsy of ≤ 2 mm, Gleason score of < 7 , and prostate volume of ≥ 60 g). The sensitivity of the combination of these criteria was 82%, specificity was 99%, PPV was 31%, and NPV was 99%. In a population-based study, the number of biopsy cores taken, a Gleason score of ≤ 6 , and the detection of tumors in a single core was shown as independent variables in multivariate logistic regression analysis to predict pT0 disease (11). In a study of 20,222 patients, a multivariate analysis determined low PSA levels, low Gleason score, and preoperative hormonal therapy as independent variables in predicting pT0 disease (17). In this study, the Gleason score of two patients was 6. The tumor was detected in a single core in both patients, and the tumor length was < 2 mm. Our results are also consistent with the multivariate logistic regression analysis (11). Although the patient's PSA level is high, it should be considered that there is a risk of pT0.

Several reasons may be present for the absence of residual tumor in RP specimens following positive biopsy results. The possibility of a false-positive result on prostate needle biopsy should be considered first. Prostate needle biopsy tissue should be re-examined by a second pathologist, and the diagnosis of PCa should be confirmed. Another possibility is that the diagnosis of the RP specimen is a false negative. The specimen should be examined again for an overlooked residual tumor. If a tumor is still absent, the entire prostate tissue should be sampled. Further deeper re-cutting should be performed in the prostate tissue corresponding to the areas with positive biopsy results. Immunohistochemical staining should be used for minimal residual tumor and suspected foci. This step is critical to detect the tumor that has become a small focus as a result of preoperative hormonal treatment. As these steps were followed meticulously, tumors were detected in some patients with pT0. When the RP specimens of 8 patients with pT0 were examined closely, it was determined that 6 of them had tumors (18). Similarly, in one study, no residual tumor was detected in 28 patients in the first examination, whereas the second examination revealed the presence of tumor in 10 patients (21). In a study by Duffield and Epstein (25), among 2,200 patients who underwent RP, 34 showed to have pT0 in the first pathological examination and a further examination revealed that 8 patients have pT0. In our study, both biopsy tissue and prostatectomy specimen results were meticulously reviewed and false positivity was noted in one patient biopsy result. Another possibility for the vanishing cancer phenomenon is the diagnostic treatment of the tumor. Tumor focus might have been removed during TURP and open prostatectomy. Moreover, a small tumor area might be completely regressed with hormonal therapy. However, this is unclear in prostate biopsy. Kommu introduced the curative biopsy theory and claimed that the malignancy focus might be completely removed by biopsy (29). Some researchers argue that necrosis may develop in tumor tissue due to vasospasm or

hematoma and the tumor may disappear after a biopsy (30,31). Evidence on this issue is insufficient. The last possible reason for the absence of a residual tumor is misnomenclature or confusion regarding the specimen. To eliminate this possibility, some researchers performed DNA analysis of the biopsy and surgical specimens (3,10,20,22). DNA mismatch was detected in only 1 of the patients in these studies. No DNA analysis was performed in our study.

Study Limitations

Our study has some limitations. First, the study has a retrospective design. Furthermore, the number of patients in our study was small, and the follow-up period was relatively short. Owing to the small number of patients, no regression analysis could be performed for variables that could be used to predict pT0. Finally, the needle biopsy and RP pathology reports were verified by a second pathologist; however, no DNA analysis was performed.

Conclusion

No residual tumor after RP is extremely rare. Consensus about its clinical importance is unclear; however, patients should be routinely followed up. Patients with a Gleason score of 6 and tumors in a single core and length of < 2 mm in the biopsy should be informed about the risk of stage pT0, and active surveillance option should be explained.

Ethics

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Ethics Committee (approval number: 2021-007).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ., K.Y., M.A., Ş.Y., Concept: K.K., M.T.Ö., M.A., Design: K.K., M.T.Ö., M.A., Data Collection or Processing: K.K., K.Y., O.A., Analysis or Interpretation: K.K., M.T.Ö., K.Y., O.A., Ş.Y., Literature Search: K.K., E.İ., Writing: K.K., M.T.Ö., E.İ., Ş.Y.

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