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Contemporary clinicopathological characteristics of pT0 prostate cancer at radical prostatectomy: A population-based study

Sophie Knipper, M.D.[a,b,*], Derya Tilki, M.D.[a,c], Elio Mazzone, M.D.[b,d], Francesco A. Mistretta, M.D.[b,e], Carlotta Palumbo, M.D.[b,f], Angela Pecoraro, M.D.[b,g], Zhe Tian, M.S.[b], Alberto Briganti, M.D.[d], Fred Saad, M.D.[b,h], Markus Graefen, M.D.[a], Pierre I. Karakiewicz, M.D.[b,h]

[a] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany*
[b] *Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Quebec, Canada*
[c] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany*
[d] *Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[e] *Department of Urology, European Institute of Oncology, Milan, Italy*
[f] *Urology Unit, ASST Spedali Civili of Brescia. Department of Medical and Surgical Specialties, Radiological Science and Public Health, University of Brescia, Italy*
[g] *Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Turin, Italy*
[h] *Division of Urology, University of Montréal Hospital Center, Montréal, Québec, Canada*

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Abstract

Background: The incidence of pT0 prostate cancer (CaP) at radical prostatectomy (RP) is extremely rare. We performed the first population-based analysis of pT0 CaP at RP.

Methods: Within the Surveillance, Epidemiology, and End Results database (2004–2015), we tested for clinical and pathological characteristics according to pT0 vs. non-pT0 CaP and included a multivariable logistic regression model.

Results: pT0 was identified in 358 (0.2%) out of 160,532 clinically localized RP patients. The majority of pT0 patients presented with initial prostate-specific antigen (PSA) <10 ng/ml (82.4%), harboured biopsy Gleason score (GS) 6 (69.8%) and cT1 disease (78.1%). Nonetheless, pT0 was identified in 13 (3.6%) patients with PSA ≥20 ng/ml, in 69 (19.3%) patients with biopsy GS ≥7 and in 78 (21.8%) patients with ≥cT2 disease. In a subset of patients with available number of biopsy cores, pT0 was identified in 34 (33.3%) patients with ≥2 positive biopsy cores. Age, race, marital status, hospital region, population density, PSA, as well as number of biopsy cores did not discriminate between pT0 and non-pT0 cases. Analyses according to annual rates (2004–2015) of pT0 did not vary between the years (0.2%–1.6%, estimated annual percent change: −1.6%, $P = 0.3$). Neither did the rates vary according to geographic region.

Conclusions: pT0 at RP is very rare. Even though, most pT0 patients have low PSA, low clinical stage, low biopsy GS, and only one positive biopsy core, those with more aggressive characteristics can still harbour pT0 at RP.

Keywords: pT0; Vanishing cancer; Prostate cancer; SEER database

1. Introduction

Prostate cancer (CaP) is the most common male malignancy in the western world, often treated with radical prostatectomy (RP). In rare cases, no demonstrable cancer is found in the RP specimen despite prior positive biopsy. The incidence of pT0 disease or "vanishing cancer" is very low and prevalence rates range from 0.2% to 0.8% [1–3]. It has been associated with neoadjuvant hormonal therapy, but may also occur outside of this setting [3]. Absence of CaP in the RP specimen may represent a challenging situation for both, the patient and the clinician. In order to

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*Corresponding author. Tel.: +49 (0)40 7410-51300; fax: +49 (0)40 7410-51323.

E-mail address: a.knipper@uke.de (S. Knipper).

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identify risk factors predicting pT0 at RP, a number of institutional analyses were performed [1,4−7]. However, the most contemporary patients included in existing reports were diagnosed up to 2007 [1,2,5,7,8] and only 1 institutional report included patients until 2013 [4]. Moreover, sample size was limited in these institutional reports with 9 to 62 patients [5,9]. Unfortunately, no population-based analyses capable of providing a sufficiently large patient pool from within which pT0 CaP patients could be identified has been reported to date.

We addressed this unmet need and relied on the Surveillance, Epidemiology and End Results (SEER) database. We hypothesized that we might identify predictors of pT0 probability at RP. We also postulated that despite best precautions at risk stratification, occasional cases of pT0 may still be identified, even in individuals with intermediate and high risk criteria.

2. Patients and methods

2.1. Study population

The SEER database samples 26% of the United States and approximates the United States in terms of demographic composition, as well as of cancer incidence [10]. Within the SEER database (2004−2015), we identified patients ≥18 years with histologically confirmed CaP diagnosis at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9) who underwent RP ($n = 184,970$). Patients with unknown metastatic status (MX, $n = 1,062$) or known metastases (M1, $n = 465$), as well as lymph node metastases (N1, $n = 5,190$) were excluded. Subsequently, patients with unavailable prostate-specific antigen (PSA) value ($n = 17,705$), as well as clinical stage T0- patients ($n = 16$) were excluded. This resulted in a final cohort of 160,532 clinically localized RP patients.

Several variables were used for purpose of discrimination between pT0 and non-pT0 patients. These included age at diagnosis (continuously coded), year of diagnosis (continuously coded), race (Caucasian vs. African-American vs. other), marital status (married vs. unmarried), SEER-region (West vs. Midwest vs. North-East vs. South), population density (urban vs. rural), PSA (continuously coded, as well as categorized), number of biopsy cores (continuously coded), number of positive biopsy cores (1 vs. 2 vs. ≥3), biopsy Gleason grade groups (GGG) [11], defined as GGG I (Gleason score 3 + 3), GGG II (Gleason score 3 + 4), GGG III (Gleason score 4 + 3), GGG IV (Gleason score 8) and GGG V (Gleason score 9−10), as well as Gleason score (GS) sum (6 vs. 7 vs. 8 vs. 9 vs. 10) and clinical T-stage (cT1 vs. cT2−4).

2.2. Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The chi-square tested the statistical significance in proportions differences. The *t* test and Kruskal-Wallis test examined the statistical significance of means and median differences. Life table analyses were used to calculate the number of events at specific intervals of follow-up.

In subgroup analyses, focusing on patients with available biopsy information (number of biopsy cores and number of positive biopsy cores available since 2010), univariable and multivariable logistic regression models (MLR) tested the relationship between pT0 and several variables. Discrimination of the model was tested using the Harrell's concordance index (c-index), the confidence interval (CI) of the c-index was derived from 2,000 bootstraps. Since the number of positive biopsy cores might be affected by the number of cores taken, an interaction term consisting of the number of biopsy cores taken and the number of positive cores was tested. R software environment for statistical computing and graphics (version 3.4.3) was used for all statistical analyses. All tests were 2 sided with a level of significance set at $P < 0.05$.

3. Results

Of all 160,532 clinically localized RP patients within the SEER (2004−2015), pT0 was identified in 358 (0.22%, 95%CI: 0.20−0.24, Table 1). The majority of pT0 patients presented with initial PSA <10 ng/ml (82.4%), harboured biopsy GS 6 (69.8%), and cT1 disease (78.1%). Nonetheless, pT0 was identified in 13 (3.6%) patients with PSA ≥20ng/ml, in 53 (14.8%) patients with biopsy GS 7, in 16 patients with biopsy GS 8−10 (4.5%) and in 78 (21.8%) patients with ≥cT2 disease.

In a subset of patients with available information on number of biopsy cores ($n = 45,159$, 28.1%), 68 pT0 patients had only 1 positive biopsy core (66.7 vs. 15.5% in non-pT0, $P < 0.001$) vs. 34 pT0 patients with ≥2 positive biopsy cores (33.3 vs. 84.5% in non-pT0, $P < 0.001$, Table 2). Age, race, marital status, hospital region, population density, PSA, as well as number of biopsy cores did not discriminate between pT0 and non-pT0 cases in the overall cohort, as well as in the subset of patients. Further details on pT0 patients with GS 7 and available information on number of biopsy cores ($n = 24$) are provided in Table 3.

Analyses according to annual rates (2004−2015) showed no significant differences of pT0 rates between the years (0.2%−1.6%, estimated annual percent change: −1.6%, $P = 0.3$). Virtually the same results were recorded within each of the four examined SEER regions (all $P > 0.1$).

In analyses focusing on the subset of patients with available information on number of biopsy cores, MLR were performed (Table 4). In MLR predicting pT0, number of biopsy cores represented an independent predictor (Odds ratio [OR]: 1.1). Moreover, number of positive cores and biopsy GS also represented independent predictors. Specifically, 1 positive core (OR: 11.3), as well as biopsy GS ≤6 (OR: 1.7) reached independent predictor

Table 1
Descriptive characteristics of 106,532 clinically localized prostate cancer patients treated with radical prostatectomy within the Surveillance, Epidemiology, and End Results (2004−2015) database, stratified according to pT-stage (pT0 vs. non-pT0)

Variables	pT0 *n* = 358 (0.2%)	non-pT0 *n* = 160,174 (99.8%)	*P* value
Age at diagnosis, years			
Median	61	61	0.6
Interquartile range	56−66	56−66	
Year of diagnosis			
Median	2009	2009	0.4
Interquartile range	2007−2011.8	2007−2012	
Region, n (%)			
West	180 (50.3)	83,792 (52.3)	0.3
Midwest	39 (10.9)	16,844 (10.5)	
North-East	71 (19.8)	25,996 (16.2)	
South	68 (19.0)	33,542 (20.9)	
Prostate-specific antigen (PSA), ng/ml			
Median	5.7	5.6	0.7
Interquartile range	4.4−8.3	4.4−8.0	
Biopsy Gleason sum, n (%)			
<6	3 (0.8)	872 (0.5)	<0.001
6	250 (69.8)	61,350 (38.3)	
7	53 (14.8)	75,102 (46.9)	
8	9 (2.5)	9,945 (6.2)	
9	6 (1.7)	5,116 (3.2)	
10	1 (0.3)	226 (0.1)	
Unknown	36 (10.1)	7,563 (4.7)	
Clinical T stage, n (%)			
cT1a	8 (2.2)	457 (0.3)	<0.001
cT1b	3 (0.8)	417 (0.3)	
cT1c	266 (74.3)	103,027 (64.3)	
cT1- not specified	3 (0.8)	274 (0.2)	
cT2	76 (21.2)	52,625 (32.9)	
cT3	1 (0.3)	2,704 (1.7)	
cT4	1 (0.3)	115 (0.1)	
Unknown	0 (0)	555 (0.3)	
D'Amico risk group, n (%)			
low risk	186 (52.0)	41,634 (26.0)	<0.001
intermediate risk	90 (25.1)	72,123 (45.0)	
high risk	34 (9.5)	31,410 (19.6)	
Unknown	48 (13.4)	15,007 (9.4)	
Pathological N stage, n(%)			
pN0	151 (42.2)	93,551 (58.4)	<0.001
pNX	205 (57.3)	66,410 (41.5)	

status. The accuracy of the model to discriminate between pT0 and non-pT0 patients was 79% (CI: 75.8% −85.3%). No statistically significant interaction between number of biopsy cores and number of positive cores was identified.

In life table analyses at 9 years of follow-up, 3 cancer-specific deaths were recorded in pT0 patients, which resulted in a 9-year cancer-specific survival rate of 99.5%. The 3 cancer-specific deaths occurred in 1 low risk (PSA 3.1 ng/ml, GS 6, cT1c), 1 intermediate risk (PSA 6.9 ng/ml, GS 7, cT2a) and 1 high-risk patient (PSA 5.5 ng/ml, GS 7, cT4). Follow-up in these patients was between 72 and 107 months. At 9-year follow-up, 1,327 cancer-specific deaths were recorded in non-pT0 patients, which resulted in a 9-year cancer-specific survival rate of 98.8%.

4. Discussion

The incidence of pT0 disease after prior positive biopsy in RP patients is very low with prevalence rates ranging from 0.2% to 0.8% [1−3]. Of all available studies describing pT0 disease, none are based on population-based data repositories. Additionally, most contemporary institutional reports only included patients diagnosed until 2007 [1,2,5,8] and only 1 institutional report included patients diagnosed until 2013 [4]. Moreover, all institutional reports are limited in sample size, as evidenced by the numbers of pT0 cases that ranged from 9 cases out of 1,950 patients to 62 cases out of 20,222 patients [5,9].

Based on these limitations of the existing literature, we performed a population-based analysis, that relied on the

Table 2
Descriptive characteristics of the subset of 45,159 prostate cancer patients treated with radical prostatectomy, with available number of biopsy cores taken and number of positive cores within the Surveillance, Epidemiology, and End Results database (2004−2015), stratified according to pT-stage (pT0 vs. non-pT0)

Variables	pT0 *n* = 102 (0.2%)	non-pT0 *n* = 45,057 (99.8%)	*P* value
No. of cores (categorical), n (%)			
<12	13 (12.7)	8,505 (18.9)	0.3
12	61 (59.8)	25,337 (56.2)	
> 12	28 (27.5)	11,215 (24.9)	
No. of positive cores (categorical), n (%)			
1	68 (66.7)	7,006 (15.5)	**<0.001**
2	12 (11.7)	7,342 (16.3)	
≥3	22 (21.6)	30,709 (68.2)	
Prostate-specific antigen (ng/ml)			
Median	5.5	5.8	0.3
Interquartile Range	4.4−8.1	4.5−8.3	
Prostate-specific antigen category, n (%)			
<2.5 ng/ml	6 (5.9)	1,686 (3.7)	0.5
≥2.5 to <4 ng/ml	12 (11.8)	4,437 (9.8)	
≥4 to <10 ng/ml	69 (67.6)	31,217 (69.3)	
≥10 to <20 ng/ml	14 (13.7)	5,829 (12.9)	
≥20 ng/ml	1 (1)	1,888 (4.2)	
Biopsy Gleason sum, n (%)			
<6	0 (0)	38 (0.1)	**<0.001**
6	68 (66.7)	17,222 (38.2)	
7	24 (23.5)	21,539 (47.8)	
8	4 (3.9)	3,803 (8.4)	
9	4 (3.9)	1,633 (3.6)	
10	0 (0)	80 (0.2)	
Unknown	2 (2)	742 (1.6)	

Table 3
Descriptive characteristics of the subset of 24 pT0 prostate cancer patients treated with radical prostatectomy, with available number of biopsy cores taken and number of positive cores within the Surveillance, Epidemiology, and End Results database (2004−2015) who had biopsy Gleason score sum 7

Variables	pT0 with Gleason score 7 *n* = 24
Age at diagnosis	
Median	62
Interquartile range	56−68
Prostate-specific antigen, ng/ml	
Median	6.6
Interquartile range	5−9.3
Prostate-specific antigen category, n (%)	
<2.5 ng/ml	1 (4.2)
≥2.5 to <4 ng/ml	4 (16.7)
≥4 to <10 ng/ml	14 (58.3)
≥10 ng/ml	5 (20.8)
No. of cores (categorical), n (%)	
<12	3 (12.5)
12	16 (66.7)
> 12	5 (20.8)
No. of positive cores (categorical), n (%)	
1	11 (45.8)
2	4 (16.7)
≥3	9 (37.5)

most contemporary patients in whom Gleason grading was attributed according to the International Society of Urological Pathology consensus [12] and where potentially a substantially higher number of pT0 cases could be identified. Within that cohort, we hypothesized that we might identify predictors of pT0 probability at RP. We also postulated that despite the best precautions at risk stratification, occasional instances of pT0 may still be identified, even in individuals with intermediate or high risk CaP criteria. Our analyses demonstrated several noteworthy observations.

First, within the overall population, the rate of pT0 was 0.2% (358 patients). This rate appears moderately lower than in most previous reports [1,3,6,9]. Specifically, Gross et al., performed a pooled analysis of 7 studies with overall 18,135 patients and reported a pT0 rate of 0.4% (74 patients, CI: 0.3%−0.5%) within this combined cohort [3]. In the most contemporary institutional report, Schirrmacher et al. initially reported on an incidence of 0.7% (28 patients, CI: 0.5%−1.0%) within 3,821 RP-patients, which was reduced to 0.5% (18 patients, CI: 0.3%−0.7%) after extensive pathological work-up to find CaP within the RP specimen in suspected pT0 cases [4]. Taken together, the comparison of pT0 rates and numbers between previous reports and the current report shows a very low proportion. Moreover, the rates of 0.4%−0.7% in historical reports that

Table 4
Multivariable logistic regression models in a subset of 45,159 prostate cancer patients, in which biopsy information was available, predicting the probability of pT0 at radical prostatectomy within the Surveillance, Epidemiology, and End Results (2004–2015) database

Predictors of pT0 variables	Odds Ratio (95% confidence interval)	*P* value
Age at diagnosis[a]	1.0 (1.0–1.0)	0.5
Year of diagnosis[a]	1.0 (0.9–1.1)	0.4
Race		
Caucasian	Ref.	
African-American	0.9 (0.4–1.5)	0.6
Other	0.8 (0.3–1.7)	0.6
Prostate-specific antigen at diagnosis[a]	1.0 (0.9–1.0)	0.4
Number of biopsy cores taken[a]	1.1 (1.0–1.1)	**0.008**
Number of positive cores		
No. of pos. cores ≥3	Ref.	
No. of pos. cores 1	11.3 (6.9–19.1)	**<0.001**
No. of pos. cores 2	2.1 (1.0–4.1)	0.05
Biopsy Gleason score sum		
>6	Ref.	
≤6	1.7 (1.1–2.7)	**0.03**
Unknown	1.7 (0.3–5.8)	0.9
Clinical T stage		
cT1	Ref.	
cT2–4	0.6 (0.4–1.0)	0.08

[a] continuously coded.

are based on substantially smaller populations than the current one must be interpreted with caution, since the effect of chance might have exaggerated the rate of pT0 cases as evidenced by wider CIs around their estimates.

Second, the stratification between pT0 and non-pT0 patients revealed important observations. Specifically, the vast majority of pT0 patients presented with a PSA <10 ng/ml (82.4%), harboured biopsy GS 6 (69.8%), cT1 disease (78.1%), and 1 positive biopsy core (66.7%). These characteristics are in agreement with previous reports [3,5]. However, as many as 33% of pT0 patients harboured more unfavorable clinical and/or pathological characteristics, such as PSA ≥20 ng/ml (3.6%), biopsy GS ≥7 (19.3%), ≥cT2 disease (21.8%), or ≥2 positive biopsy cores (33.3%). These observations indicate that a very important proportion of pT0 patients harbour highly favorable clinical and/or pathological characteristics. However, as many as 3.6% to 33.3% of pT0 patients may also harbour more aggressive clinical and/or pathological CaP variants. This corroborates previous descriptions of high risk cases within pT0 patients [7,9].

Third, no significant differences of pT0 rates between the years (2004–2015) were observed in analyses according to annual rates (0.2%–1.6%, estimated annual percent change: −1.6%, $P = 0.3$). Virtually the same results were recorded within each of the 4 examined SEER regions. These observations indicate that little, if any variability exists with respect to pT0 rates. Specifically, significantly higher or lower rates could not be identified according to time or region. The observed rates appeared to be randomly distributed within our patient cohort.

Fourth, life table analyses revealed a cancer-specific survival rate of 99.5% at 9 years in pT0 patients. This rate was virtually the same as in the population of non-pT0 patients (98.8%). However, the absolute number of events in pT0 patients precluded any meaningful statistical comparisons and interpretations. Nonetheless, according to our findings the probability of cancer-specific mortality of pT0 patients is marginal at best. Nonetheless, lack of biochemical recurrence and metastatic progression data prevent us from addressing these earlier endpoints, which represented the focus of several previous pT0 analyses. For example, Moreira et al. described 62 pT0 patients, of whom 7 developed disease recurrence and one experienced systemic progression [9]. Thus, a small but non-negligible risk of progression remains.

Finally, we fitted a MLR to identify predictors of pT0 at RP. Within that model, 3 variables reached independent predictor status, namely number of biopsy cores taken, number of positive biopsy cores and Gleason score at biopsy. Nonetheless, the overall accuracy of the multivariable model was 79%, which implies an error margin of 21% when predictions are made. In consequence, such model is devoid of any clinical usefulness in the context of a pathological entity with a prevalence rate of 0.2%. In consequence, it can be safely concluded that accurate prediction of pT0 at RP cannot be accomplished, which is also in agreement with previous reports [5,9].

Several take home messages can be identified from within our results. First, the rate of pT0 is extremely low (0.2%). Second, most pT0 diagnoses are made in patients with favorable clinical and or/pathological characteristics, such as PSA <10 ng/ml, biopsy GS 6, cT1 disease or only 1 positive biopsy core. Third, up to 20% of pT0 patients can be diagnosed from among individuals with more unfavorable clinical and/or pathological characteristics. Finally, despite identification of general trends for higher pT0 prevalence, it is impossible to accurately identify individual patients who are at high risk of pT0 at RP.

Several limitations of our study need to be mentioned. First, all SEER based analyses are retrospective in nature. In consequence, lesser amount of details regarding clinical and/or pathological characteristics is available than in prospective institutional studies. Lack of detail is offset by significantly larger numbers of observations. Additionally, cancer-control endpoints can only be based on CSM and cannot address biochemical recurrence or metastatic progression. In consequence, comparisons regarding these characteristics cannot be made with other studies. Second, the pathological assessment of biopsy samples and RP specimens did not benefit of central pathological review. This said, it would be extremely unlikely that a pathologist would not invest all possible efforts to identify CaP in a RP specimen. Indeed, within the institutional study of Schirrmacher et al., the most thorough assessment of RP

specimen of pT0 patients resulted in an additional diagnosis of 10 CaP cases that lowered the original pT0 diagnosis rate from 0.7% to 0.5% [4]. In consequence, our findings illustrate the reality of pT0 rates in the community practice. Third, information about neoadjuvant hormonal therapy was not available within the SEER database. Neoadjuvant hormonal therapy can predispose to pT0 [3,13,14]. According to contemporary guidelines, it would be highly unlikely to administer neoadjuvant hormonal therapy to patients who in vast majority harboured extremely favorable clinical and pathological characteristics and in whom excessively rare instances of pT0 cases were identified [15]. However, according to a SEER-Medicare report approximately 5% of all RP patients (1992–2007) received neoadjuvant hormonal therapy [16]. Within such patients, the rate of pT0 increased up to 29% depending on the length of neoadjuvant hormonal treatment [13]. In consequence, some of the pT0 patients may have been treated with neoadjuvant hormonal therapy, even within our cohort. This might also explain the small, but non-negligible mortality rate within pT0 patients. Indeed, Miyata et al. found that neoadjuvant hormonal therapy stimulates cancer cell progression and promotes biochemical recurrence via up-regulation of lymphangiogenesis-related parameters in patients with low risk CaP [17]. Moreover, no information on completeness of prostate resection was available which may represent another explanation for pT0 at RP [18]. Last, imaging information, such as magnetic resonance imaging, number of biopsy session, prostate volume, PSA-density, or other markers such as free PSA were not available.

5. Conclusion

pT0 at RP is very rare. Even though, most pT0 patients have low PSA, low clinical stage, low biopsy GS, and only 1 positive biopsy core, those with more aggressive characteristics can still harbour pT0 at RP.

Conflict of interest

The authors declare that they have no conflict of interest.

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