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review Article

Varnishing prostate cancer acinar (adenocarcinoma of the prostate gland pt0) in prostate biopsy specimen which subsequently becomes diagnosed as no prostate cancer or pt0 prostate cancer in a prostatectomy specimen: review and update

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Abstract:

Taking into consideration the increased undertaking of screening tests for serum prostate-specific antigen (PSA), it would be envisaged that the diagnosis of prostate cancer at an early clinical stage and small tumour-size had been appreciably increased over recent years and as a consequence, the volume of tumour within radical prostatectomy (RP) specimens had decreased in size. Pathological stage pT0 is referred to as no evidence of residual tumour within a radical prostatectomy (RP) specimen from a patient in whom biopsy-proven prostate carcinoma had been histologically confirmed as a diagnosis. This entity was given a terminology of the "vanishing cancer phenomenon" by Goldstein and associates. The pT0 stage of prostate cancer had been noted ensuing hormone therapy or prior transurethral resection of the prostate (TURP) for benign prostatic hyperplasia before the undertaking of RP. Even though much research had addressed these two scenarios of pT0 stage prostate cancer, patients that manifest with pT0 status in cases other than the aforementioned two scenarios occur on very rare occasions which had been iterated to be in between 0.2% and 0.8% of all prostate cancer patients). Only few studies had examined such patients. The clinical significance of pT0 staging has remained not to be clear. Nevertheless, many reports had documented that that pT0 stage patients do portend a highly satisfactory clinical outcome. pT0 at RP is extremely rare. Although most pT0 patients had tended to have low serum PSA levels, low clinical stage, low biopsy Gleasson Score (GS), and only one positive biopsy core, those with more aggressive characteristics could still harbour pT0 at RP. In order to prevent the undertaking of unnecessary treatment of such clinically insignificant cancers, it would be important to ascertain preoperative clinical and pathologic characteristics which might help the Urologists and oncologist to pre-operatively ascertain patients with a high probability of pT0 staging upon RP specimens. The ensuing article has discussed general overview aspects as well as miscellaneous narrations and discussions from some case reports, case series and studies related to the varnishing prostate cancer in order to provide recent educative material on the varnishing prostate cancer to all readers.

keywords: varnishing prostate cancer; adenocarcinoma of prostate; pt0; prostate biopsy; histopathology; immunohistochemistry; prostatectomy; recurrence; no tumour

Introduction

It has been iterated that carcinoma of prostate gland (prostate cancer) is the commonest malignancy which afflicts males within the western world, and that adenocarcinoma of prostate gland had often tended to be treated by the undertaking of radical prostatectomy (RP). [1] It had furthermore been iterated that with regard to rare cases of primary adenocarcinoma of prostate gland, no demonstrable cancer had been found within the radical prostatectomy (RP) specimen upon thorough pathology examination despite previous pathology examination features which had confirmed positive biopsy of prostate features of adenocarcinoma of prostate gland. It had been iterated in a number of

published documentations that the incidence of pT0 disease or "vanishing cancer" or the finding of no evidence of prostate cancer upon subsequent examination of radical prostatectomy specimens examined pursuant to treatment of the prostate cancer as treatment of curative intent is very low and that the prevalence rates had ranged from 0.2% to 0.8% [1] [2], [3], [4] It has also been documented that varnishing prostate cancer had been associated with neoadjuvant hormonal therapy, but varnishing prostate cancer may also occur outside of this setting [1] [4]. The finding of no evidence of prostate cancer or absence of prostate cancer within a radical prostatectomy specimen might represent a challenging situation as an enigma to both, the patient and the Urologist. Despite the rarity of the varnishing prostate cancer, considering that occasional cases of the varnishing prostate had been reported on sporadic occasions, it is important for the Urologist to ascertain, factors that may emanate in or be associated with the finding of the varnishing prostate cancer or the future finding of no evidence of prostate cancer as well as what needs to be done under such scenarios. The ensuing article on the Varnishing prostate cancer has been divided into two parts: [A] Overview of the varnishing adenocarcinoma of prostate cancer and [B] Miscellaneous narrations and discussions related to some case reports, case series, and studies related to the varnishing acinar adenocarcinoma of prostate gland.

Aim

To review and update the literature on the varnishing adenocarcinoma of prostate gland.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: the varnishing prostate cancer; the varnishing acinar adenocarcinoma of prostate gland; no evidence of prostate cancer in radical prostatectomy specimens following a previous positive prostate cancer confirmation in a prior prostate biopsy specimen. Forty-one (41) references were identified which was used to write the ensuing article which has been divided into two parts: [A] Overview of the varnishing adenocarcinoma of prostate cancer and [B] Miscellaneous narrations and discussions related to some case reports, case series, and studies related to the varnishing acinar adenocarcinoma of prostate gland.

Results

[A] Overview

Definition / general statements [5]

- It has been iterated that first described in 1995, vanishing cancer is a terminology that indicates no evidence of residual tumour found within radical prostatectomy specimen despite pre-radical prostatectomy confirmation of prostate cancer tumour within needle biopsy of prostate specimen. [6]
- It has been pointed out that sometimes, only high grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation suspicious for but not diagnostic of cancer ASAPP has tended to be found in some cases of the varnishing prostate cancer [5]

Essential features

The essential features of acinar ductal adenocarcinoma of the prostate gland that is referred to as the varnishing prostate cancer had been summated as follows:[5]

- It has been iterated that the contemporary incidence of vanishing cancer is 0.2% of radical prostatectomy specimens and that it was higher a decade or two ago when prostatectomy was being undertaken for smaller / lower grade cancers of the prostate gland.
- It has been stated that the incidence of the varnishing prostate cancer is higher within large prostates or in preoperatively treated ones
- It has been iterated that the resolution of dilemma of the varnishing prostate cancer does entail complete tissue submission of the prostate specimen, cancer specific immunohistochemistry stains, utilisation of second pathologist opinion, consideration of flipping blocks to other surface as well as it has been iterated that some residual cancers simply cannot be detected after the above efforts had been undertaken

Epidemiology

The epidemiology of the varnishing prostate cancer acinar adenocarcinoma of the prostate gland has been summated as follows: [5]

- It has been iterated that the most recent incidence of varnishing prostate cancer at prostatectomy was 0.2% of 160,532 with clinically localized cancer based upon Surveillance, Epidemiology and End Results (SEER) database (2004 - 2015) [7]
- It has been iterated that the aforementioned recent incidence of varnishing prostate cancer is lower than the incidence of vanishing cancer of 0.6% up to 4.9% of prostatectomy specimens a decade earlier, [8] [9] [10] [11] [12]
- Variation in rate is probably due to the institution and time of the study; however, the recent decrease may reflect upward stage and grade migration at prostatectomy, due to increased acceptance of active surveillance for low grade cancer [13]
- Predictors of vanishing cancer included a prostate weight ≥ 60 g or patients with prostate specific antigen (PSA) < 20 ng/ml, with biopsy GS < 7, patients with < clinical T2 disease and < 2 positive biopsy cores, [7] [10]

Aetiology [5]

- Most often, the phenomenon is attributed to the fact that routine histologic sections cannot evaluate every cubic millimetre of prostate volume, so small cancer foci remain in the paraffin block [5]
- Rarely, prostate cancer may have been ablated by the biopsy or transurethral resection procedure [14]
- Currently, more patients are receiving preoperative androgen deprivation, such as enzalutamide, that shrinks the cancer [15]
- It had also been proposed that a minute cancer focus at the edge of the prostate may be inadvertently left behind in the overzealous attempt to perform a nerve sparing procedure [11]

Diagnosis [5]

- Diagnostic resolution should include these steps in the following order: [7]
    - If the prostatectomy tissue has been partially submitted, complete submission should be pursued
    - Get a second pathologist, particularly a urologic pathologist, to reread the resection slides
    - Review the biopsy that was diagnostic of cancer, if slides are available
    - Immunohistochemistry stains
    - Flip tissue in some or all of the paraffin blocks and have the opposite surfaces of the tissues cut
    - DNA identity analysis can be performed if specimen switching is suspected

Laboratory [5]

- Vanishing cancer patients typically have lower serum PSA [7]

Gross description [5]

- Larger prostates with an average size of 74 g are more likely to exhibit no residual tumour [10]

Positive stains [5]

- **P504S racemase** is positive in cancer; get immunohistochemistry stains on deeper levels, on areas initially suspicious for cancer
- **Negative stains [5]**
- **p63 or CK903** negative in cancer
- Molecular / cytogenetics description [5]
- Microsatellite analysis can be performed on the prostatectomy and biopsy specimens to confirm specimen identity; this very rarely shows a specimen switch (1 in 10 cases of vanishing cancer was attributed to specimen mix-up) [2]
- This is particularly indicated if there is high grade or high-volume cancer on the biopsy [2]
- Differential diagnosis [5]

- **Biopsy specimen switch: [5]**
  - Specimen mix-up with another patient must be excluded if the biopsy showed high grade or high-volume cancer and no cancer is seen in the resection
  - Molecular analysis can be performed [2]
- **Biopsy false positive: [5]**
  - Correct diagnosis of cancer on the prior biopsy should be confirmed
  - Immunohistochemistry stains (AMACR+ / p63, HMCK-) can be used if not previously performed

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to The Varnishing Prostate Cancer

Goldstein et al. [6] stated the following:

- Early detection efforts do identify prostate cancer at lower clinical and pathology stages, often resulting in smaller volumes of tumour within radical prostatectomy specimens.
- In some cases, complete sampling of the radical prostatectomy specimen for biopsy-proven adenocarcinoma does demonstrate minimal or no residual cancer.

Goldstein et al. [6] evaluated the clinical and pathology examination findings in 13 such cases in an effort to document this finding, which they had referred to as the "vanishing cancer phenomenon." Goldstein et al. [6] reported that the mean number of prostate-slides they had examined per case was 79 and the number of prostate-slides they had examined had ranged from 34 slides to 248. Goldstein et al. [6] summarised their results as follows:

- Carcinoma was absent in two cases, present in a single focus in eight cases, and present in two foci in three cases.
- The mean cancer volume in the 10 cases with residual tumour was 0.019 cc and the cancer volume had ranged between 0.003 cc and 0.038); the largest single dimension of any tumour focus was 3 mm.
- All cancers were upon examination found to be well-differentiated or moderately -differentiated within the biopsy specimen and prostatectomy specimen.
- Their results had indicated that in some cases cancer might be extremely difficult or impossible to find or identify within the prostatectomy specimen despite exhaustive sampling.
- The incidence of this "vanishing cancer phenomenon" was probably increasing because more low-stage cancers were being treated by the treatment option of prostatectomy.
- The inability to identify cancer in a prostate gland which had been removed for needle biopsy-proven carcinoma might not indicate technical failure.
- Knipper et al. [7] stated that the incidence of pT0 prostate cancer (CaP) at radical prostatectomy (RP) is very rare. Knipper et al. [7] stated that they had undertaken the first population-based analysis of pT0 CaP at radical prostatectomy (RP). With regard to the methods of their study, Knipper et al. [7] reported that within the Surveillance, Epidemiology, and End Results database (2004-2015), they had tested for clinical and pathological characteristics according to pT0 versus. non-pT0 CaP and included a multivariable logistic regression model. Knipper et al. [7] summarised the results as follows:
- pT0 was identified in 358 (0.2%) out of 160,532 clinically localized radical prostatectomy (RP patients).
- The majority of pT0 patients had manifested with serum initial prostate-specific antigen (PSA) levels <10 ng/ml (82.4%), they had harboured biopsy Gleason score (GS) 6 (69.8%) and cT1 disease (78.1%).
- Nevertheless, pT0 was identified in 13 (3.6%) patients with serum PSA level ≥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, serum PSA level, 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 had not varied 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.

Knipper et al. [7] made the ensuing conclusions:

- The finding of pT0 at RP is very rare.
- Although, most pT0 patients had low serum PSA levels, low clinical stage, low biopsy Gleasson Score, and only one positive biopsy core, those who had more aggressive characteristics could still harbour pT0 at radical prostatectomy (RP).
- Korarac et al. [8] stated that: "Vanishing carcinoma phenomenon" (VC) had been defined as the finding of minute or no cancer within radical prostatectomy specimens after a positive biopsy of prostate cancer. Korarac et al. [8] discussed their experience with VC and recommended guidelines for its detection as follows.
- One thousand seven hundred forty-one radical prostatectomy specimens (2004-2009), which they had processed by whole-mount section procedure had yielded 21 (1.2%) cases with VC and 6 (0.34%) cases with minimal carcinoma (≤ 2 mm) within the radical prostatectomy specimen.
- To find the eluding carcinoma in VC cases or more carcinoma in minimal carcinoma cases, the following was undertaken: 3 levels of all the paraffin blocks were obtained; if negative, the paraffin blocks were melted, the tissue was flipped, and 3 levels were prepared. The tumour bank frozen tissue was also processed for routine pathology examination.

- Korarac et al. [8] summarised the results as follows:
- Three deeper levels within the radical prostatectomy specimen of 21 VC cases had failed to demonstrate malignancy; nevertheless; the flipping and recutting of the tissue had yielded a focus of carcinoma (1-5 mm) in 16 of 21 cases and in 3 of 16 cases in the saved frozen tissue.
- In 1 of the 6 cases with minimal carcinoma, subsequent recuts of the flipped tissue had displayed carcinoma (2 foci of tumour, <1 mm each).

Korarac et al. [8] made the ensuing conclusions:

- In VC they had recommended the following: (a)Pathologists embed and process any remaining prostatic tissue including any saved fresh-frozen tissue; (b) Pathologists should obtain 3 levels of each paraffin block; if results are negative, then (c) pathologists should melt and flip the tissue and obtain 3 more levels.
- Following the above guidelines, a hidden carcinoma might be detected in the majority of the cases of VC.
- Mazzucchelli et al. [9] stated the following:
- The reported incidence of no residual prostate cancer (i.e. pathological stage pT0) on radical prostatectomy had ranged from 0.07% to 4.2%.
- The incidence is higher pursuant to neoadjuvant endocrine treatment.

Mazzucchelli et al. [9] undertook a study, to search for residual cancer on radical prostatectomy (RP) specimens when an initial sampling had failed to find the cancer in patients who had tumour positive biopsy. Mazzucchelli et al. [9] reported that they had reviewed their database of 1,328 consecutive patients whose biopsies and RP specimen were both examined at the Polytechnic University-United Hospitals of the Marche Region between March 1995 and June 2006. Mazzucchelli et al. [9] also reported that the radical prostatectomies were grossly completely sampled and examined with the whole mount technique. Mazzucchelli et al. [9] summated the results as follows:

- They had identified eight patients (i.e. 0.6%; three untreated and five hormonally treated preoperatively, i.e. 0.3 and 0.8%, respectively, of the total number of RPs included in the study) with positive biopsy and with no residual cancer within the initial routine histological examination of the RP. The RP of this group of eight was subjected to additional sectioning and evaluation of the paraffin blocks of the prostatectomy, also after block-flipping, immunostaining with an antibody against CAM 5.2, p63, PSA, and alpha-methylacyl-CoA racemase, and DNA specimen identity analysis. There were no cases with a false positive biopsy diagnosis, and cancer was not overlooked or missed in the initial routine histopathology examination of any of the 8 pT0 RPs.
- A minute focus of cancer (the diameter was always below 2.0 mm) was found on the additional sections in five. In particular, cancer was identified after block-flipping in one of them. In an additional case, cancer was eventually discovered after immunohistochemistry staining tissue sections for cytokeratin CAM 5.2, for p63 and PSA.
- In the remaining two cases (one untreated and the other hormonally treated), cancer was not identified or found (0.15% of the 1,328 RPs included in the study).
- Their review of the description of the macroscopic or gross appearance of the RP and of its slides had demonstrated or revealed that part of the peripheral zone corresponding to the site of the positive biopsy was missing, i.e. not removed from the patient at the time of the operation at least in one of the two.
- DNA specimen analysis had confirmed the identity of the biopsy and prostatectomy within both.
- An extensive search for residual cancer had reduced the number of pT0 RPs pursuant to a positive biopsy from 0.6 to 0.15%.

Mazzucchelli et al. [9] made the ensuing additional conclusions and recommendations:

- It is recommended to have the needle biopsy reviewed, carefully look again at the radical prostatectomy, do deeper sections and then flip certain paraffin blocks.
- In addition, atypical foci should be stained for basal cell markers and often AMACR, especially in hormone-treated cases.
- If a block is missing part of the peripheral zone (capsular incision), this should be commented upon.
- DNA analysis for tissue identity should be undertaken when the other steps had been taken without finding cancer.

Duffield et al. [10] iterated that radical prostatectomy (RP) specimens occasionally contain no carcinoma within the initial slides of an entirely submitted specimen, but no protocol had been established to assess for carcinoma in the remainder of the specimen. Duffield et al. [10] evaluated 34 cases with no carcinoma in the initial slide review of the entirely submitted RP over a 2-year interval out of 2200 RPs. Duffield et al. [10] reported that their sequential protocol for cases with no initial tumour included the following: (1) to review the biopsy; (2) to undertake immunohistochemistry staining on suspicious foci; (3) to perform levels on blocks with high-grade prostatic intraepithelial neoplasia; (4) to perform 3 levels on the posterior sextant and adjacent sextant region where cancer was identified on biopsy; and (5) to flip the blocks within these regions and to perform 3 additional levels. Duffield et al. [10] summarised the results as follows:

- The mean age of the patients was 58.1 years and the ages of the patients had ranged between 41 years and 69 years, with a mean serum prostate-specific antigen level of 5.9 ng/mL (0.8 to 19 ng/mL).
- Upon review, all of the biopsies had carcinoma with a Gleason score (GS) of 3+3=6.
- The number of positive cores was 1 [n=29 (85%)], 2 (n=3), 3 (n=1), and 4 (n=1).
- Fifty-nine percent (20/34) of the biopsies had immunohistochemistry (IHC) for basal cells and/or alpha-methylacyl CoA racemase.
- The radical prostatectomy specimens (RPs) on average had weighed73.6 g (36 to 155 g).
- Out of the 34 cases with no initial cancer, cancer was found in 26 (76%), and 8 (24%) had no residual carcinoma despite extensive levelling in all cases and IHC in 1 case.
- IHC was undertaken on 12 of the 34 RP cases.
- Out of 26 RP cases with cancer, 22 had cancer on only 1 slide, and 4 had cancer on 2 slides.
- All of the cancers in the radical prostatectomies were Gleasson Score (GS) 6, and the GS agreed with the corresponding biopsy in all cases.
- In 83% (20/24) of cases that specified laterality within the biopsy, RP carcinoma was ipsilateral to carcinoma in the biopsy.
- In 93% (14/15) of the cases that specified sextant site in the biopsy, the location of the carcinoma in the RP was in the same or the adjacent inferior-superior sextant site.
- Out of the 29 cases that required levelling, in 7 cases cancer was found only after flipping the blocks and doing additional levels.

- Out of the 8 cases with no cancer, all biopsies had only 1 positive core with 6/8 having <10% of the core involved.
- Duffield et al. [10] made the ensuing conclusions:
- In about 1.5% of RP cases no tumour would be seen in the initially entirely submitted specimen.
- A methodical limited targeted approach to the identification of cancer could identify cancer in 73% of the cases with no initial cancer, yet there will still be 0.4% of all RPs where cancer is not been identified or detected.
- As cancer was seen in areas away from the biopsy site in some of their cases with minute tumour, levelling all the blocks might have identified cancer in some of the cases in which they found no tumour with their protocol.

Javali et al. [11] iterated the following:

- Widespread serum PSA (prostate specific antigen) screening had resulted in stage migration of prostate cancer.
- Smaller tumour volumes are being detected within radical prostatectomy specimens.
- This had coincided with increasing reports about the 'vanishing cancer phenomenon.'
- In order to analyse the cases of robot assisted laparoscopic prostatectomy (RALP) within their institute in which the pre operative prostate biopsy was positive for adenocarcinoma but no tumour could be identified within the final histopathology, and they had reviewed the literature for possible reasons for such a phenomenon.
- With regard to the materials and methods of their study: Javali et al. [11] reported the ensuing:
- They had identified nine patients out of a total of 184 cases of RALP in which the final histopathology had not correlated with the initial biopsy report.
- The initial biopsy slides as well as the final histopathology slides were reviewed by a second pathologist.
- The specimens were processed in entirety and additional sections were taken until no tissue was left.
- Javali et al. [11] summarised the results as follows:
- Two patients had cancer diagnosed upon TURP (transurethral resection of prostate) chips, while the remaining patients had undergone TRUS biopsy for elevated serum PSA.
- The final histopathology examination diagnosis was benign prostatic hyperplasia in two patients, chronic prostatitis in four patients, and acute florid prostatitis in one patient, granulomatous prostatitis with glandular-stromal hyperplasia in one patient and TCC (transitional cell carcinoma) of prostate in one patient.

Javali et al. [11] made the ensuing conclusions:

- Majority of cases of pT0 are due to inability of routine histopathological analysis to identify minute tumour focus.
- Urologists need to be aware of this in view of the potential medico legal implications.
- Green et al. [12] retrospectively reviewed 1792 consecutive radical prostatectomies (RP) from 2003 to 2006 at a single institution in order to establish tumour volume reference values, to ascertain current trends in visually estimated prostate adenocarcinoma tumour volume, and to characterize cases with no residual cancer on RP. Green et al. [12] recorded tumour volumes and subsequently stratified them as very low, 0-1%; low, 1.1-10%; intermediate, 10.1-20%; high, 20.1-50%; and very high, >50%, with incidences of 11.7%, 52.1%, 21.5%, 13.2%, and 1.5%, respectively. Green et al. [12] summarised the results as follows:
- The incidence of very low volume tumours had increased within the time period (p=0.04).
- They had detected seminal vesicle involvement in 5.0% of cases and lymph node metastasis occurred in 1.4%.
- Volume categories had statistically correlated with seminal vesicle invasion (p=0) and lymph nodes metastases (p=0).
- They had identified eleven cases of no residual cancer (0.6%) with a non-statically significant increase during the study (p=0.07).
- Green et al. [12] made the ensuing conclusions and recommendations:
- The rising incidence of very low volume tumours should be considered by clinicians when discussing treatment options with patients.
- A discrete tumour volume should be provided for RP specimens as it might be an important prognostic factor.

Preisser et al. [13] stated the following:

Two recent European studies had demonstrated an increasing proportion of non-organ-confined (NOC; pathologic stages T3-4) prostate cancer (PCa) in radical prostatectomy (RP) specimens. Preisser et al. [13] undertook a study, to ascertain if the trend for NOC and pT3-4 PCa is also evident among contemporary North American patients. With regard to the design, setting, and participants. Preisser et al. [13]: reported the following: Within the Surveillance, Epidemiology, and End Results database (2010-2014), they had identified 58 558 patients with clinically localized PCa which had been treated with RP. Preisser et al. [13] included only patients with clinical stage T1-2 and biopsy Gleason grade group (GGG) 1-3 prostate cancer (PCa). Preisser et al. [13] iterated the following:

- With regard to the Outcome measurements and statistical analysis, the annual trend analyses and multivariable logistic regression models had focused on the rate of NOC PCa, the rate of primary pathologic Gleason ≥4 PCa, and the rate of either NOC PCa and/or primary pathology Gleason ≥4 PCa.
- Adjustment was made for clinical tumour characteristics (serum prostatic specific antigen [PSA] level, clinical stage of the tumour, and biopsy GGG).
- Preisser et al. [13] summarised the results and limitations as follows:
- The rate of NOC PCa had increased during the study period (18.7% versus 24.2%; p=0.002) and had remained significant after adjustment (16.9% versus 22.3%; p=0.001)
- Similarly, the rate of pathology primary Gleason score ≥4 PCa had increased during the study period (16.8% versus 23.0%, p=0.001) and had remained significant after multivariable adjustment (10.8% versus 14.2%; p=0.002).
- Furthermore, virtually the same findings were recorded when both endpoints were combined.
- Their results were confirmed in multivariable logistic regression analyses in which year of diagnosis was modelled as a continuous variable or a categorical variable or when a cubic spline approach was used.
- Preisser et al. [13] made the ensuing conclusions as well as patient summary:
- Rates of NOC PCa and primary Gleason ≥4 PCa had increased over time among contemporary North American patients who were treated with RP.

- This finding might be related to better acceptance of active surveillance and watchful waiting by North American patients.
- In their report, they had looked at pathology outcomes for contemporary North American patients who had undergone treatment with radical prostatectomy for prostate cancer.
- They found an increase in non-organ-confined and more aggressive prostate cancer.

Iczkowski et al. [15] stated that they had performed the first evaluation of the effects of the 5-alpha-reductase inhibitor class of drugs on cancer histopathologic features at radical prostatectomy in a placebo-controlled multi-centre trial. Iczkowski et al. [15] analysed prostatectomy slides in a blinded manner from 17 men who had been treated with dutasteride, an inhibitor of types 1 and 2 isoenzymes of 5-alpha-reductase, and 18 men who had been treated with placebo for 5 to 11 weeks before undergoing radical prostatectomy. The histopathology examination features of benign epithelium, high-grade prostatic intraepithelial neoplasia, and cancer were recorded, and the treatment effect was also scored. Digital imaging analysis was utilised to measure the stroma/epithelium ratio and epithelial height, as well as the nuclear area in cancer. Iczkowski et al. [15] summated the results as follows:

- In benign epithelium, treatment had caused distinctive cytoarchitectural changes of atrophy and a decrease in the epithelial height ($P = 0.053$).
- The peripheral zone demonstrated the most marked response to treatment.
- Within cancer tissue, the tumour volume was significantly lower in the dutasteride-treated men than in the placebo-treated men (mean 15% versus 24%, respectively, $P = 0.025$), the percentage of atrophic epithelium was increased ($P = 0.041$), and the stroma/gland ratio was doubled ($P = 0.046$).
- The treatment alteration effect score was doubled ($P = 0.055$) and had not correlated with any Gleason score changes.
- Iczkowski et al. [15] made the ensuing conclusions:
- Pursuant to a short-term dutasteride treatment, benign epithelium had shown involution and epithelial shrinkage, and prostate cancer tissue had demonstrated a decrease in epithelium relative to stroma.
- These findings had suggested that dutasteride induces significant phenotypic alterations in both the benign and the neoplastic prostate, supportive of a chemo-preventive or chemo-active role.

Montgomery et al. [16] stated the following:

- Prostate cancer is dependent upon androgen receptor (AR) activation.
- Optimal AR antagonism might effectively cytoreduce local disease and suppress or eliminate micro-metastases.
- They had evaluated neoadjuvant therapy prior to the undertaking of prostatectomy with the potent AR antagonist enzalutamide (enza) either alone or in combination with dutasteride (dut) and leuprolide (enza/dut/luteinizing hormone-releasing hormone analogues [LHRHa]).
- With regard to the experimental design and results of their study, Montgomery et al. [16], reported the following:
- Forty-eight of 52 men with intermediate or high-risk localized prostate cancer had proceeded to undergo prostatectomy after neoadjuvant enzalutamide or enza/dut/LHRHa for 6 months.
- They had assessed pathology assessment complete response (pCR), minimal residual disease (MRD; ≤3 mm maximum diameter of residual disease), residual cancer burden (RCB), and expression of PSA and serum and tissue androgen concentrations.
- They had compared the proportion of patients with pCR in each treatment arm with a historical control rate of 5%, based on previous reports of flutamide with LHRHa.
- In the enzalutamide arm, none of the 25 patients achieved pCR or MRD.
- Within the enza/dut/LHRHa arm, one of 23 patients (4.3%) achieved pCR and 3 of 23 (13.0%) achieved MRD.
- The median RCB was higher in the enzalutamide arm than in the enza/dut/LHRHa arm (0.41 cm3 vs. 0.06 cm3, respectively).
- Tissue testosterone and dihydrotestosterone levels correlated with RCB.
- No adverse events leading to study drug discontinuation were reported.
- Montgomery et al. [16] made the ensuing conclusions:
- Combination therapy with enza/dut/LHRHa had resulted in pCR and MRD rates comparable with historical controls.
- Evidence of continued AR activity in residual tumour had indicated that AR signalling might contribute to survival.
- Strategies to more effectively ablate AR activity are warranted in order to ascertain whether more substantial antitumor effects are observed.

Kalampokis et al. [17] stated that following the undertaking of radical prostatectomy (RP), the absence of a demonstrable tumour on the specimen of a previously histologically proven malignancy is known as the pT0 stage. Kalampokis et al. [17 undertook a study to perform a narrative review of current literature in order to ascertain the frequency and oncology outcomes in patients with pT0 disease. Kalampokis et al. [17] undertook a narrative review of all available literature. Kalampokis et al. [17] summated the results as follows:

- The incidence of pT0 had ranged between 0.07% and 1.3%.
- Predictors of the pT0 stage were only a single biopsy core with low-grade cancer, a cancer length not exceeding 2 mm and a high prostate volume.
- Biochemical recurrence had ranged between 0 and 11%.
- Kalampokis et al.: [17] made the ensuing conclusions and recommendations:
- The absence of malignancy in the RP specimen despite a previous positive biopsy is a rare and unpredictable finding.
- Even though the prognosis is considered to be excellent in majority of the cases, a continued close follow-up is warranted.

Osunkoya et al. [17] iterated that one would expect cases with small foci of cancer at radical prostatectomy to be associated with correspondingly favourable (Gleason score < or = 6, < 3 positive cores, no core with greater than 50% cancer) biopsy and preoperative clinical findings. Osunkoya et al. [17] identified radical prostatectomies from The Johns Hopkins Hospital (July 2004 to July 2006) with only 1 to 3 slides involved by 3+3=6 adenocarcinoma of the prostate gland with no focus of cancer measuring greater than 2 mm in dimension. Osunkoya et al. [17] summarised the results as follows:

- They had obtained one hundred fifty-one radical prostatectomy specimens with cancer involving 1 slide in 69 cases (45.7%), 2 slides in 61 cases (40.4%), and 3 slides in 21 cases (13.9%).

- Predominantly transition zone cancer was identified in 1 patient (0.66%).
- The mean age of the patients was 57.1 years and their ages had ranged between 41 years and 73 years.
- Twenty-two patients that amounted to 14.6% of the patients had a suspicious digital rectal examination.
- Mean serum prostate-specific antigen (PSA) and percentage free PSA were 5.2 ng/dL (0.3 to 16.7 ng/dL) and 15.5% (8% to 36%), respectively.
- Out of 146 men, 127 men that amounted to 87% of men with available information had PSA density of less than 0.15.
- The mean number of cores obtained was 12 (4 to 27 cores) and all were Gleason 3+3=6 cancers upon biopsy.
- One hundred fourteen cases that amounted to 75.5% of the cases had 1 core positive, 28 cases (18.5%) 2 cores, and 9 cases (6%) had 3 or more cores positive.
- One hundred forty-eight cases that amounted to 98% of the cases had cancer involving 50% or less of 1 core; 2 of these cases with greater than 50% cancer were discontinuous foci.
- Osunkoya et al. [17] concluded that:
- Even though, typically, biopsy and clinical pre-operative findings associated with very limited cancer at radical prostatectomy are correspondingly favourable, exceptions occur in terms of biopsy cancer extent, serum PSA measurements, and digital rectal examination findings.

Truskinovsky et al [18] characterized minute prostate cancer seen at radical prostatectomy and they stated that with aggressive screening and more extensive biopsy sampling, they had increasingly seen these cancers at radical prostatectomy. Truskinovsky et al. [18] examined radical prostatectomy specimens submitted in total for minute cancer. Truskinovsky et al. [18] summarised the results as follows:

- During the preceding 1.5 years, 78 prostates (5.2%) had either no cancer (2 cases) or contained between one and six foci of organ-confined carcinoma (76 cases) measuring 6 mm or less, with a Gleason score of 6 or less.
- The mean pre-biopsy serum prostate-specific antigen level was 5.8 ng/mL, and 84.6% of the patients had undergone biopsy because in view of an elevated prostate-specific antigen level.
- Out of these patients, 40% had had either benign or atypical diagnoses on prior biopsies, and 43% had only minute (0.5 mm or less) foci of carcinoma on biopsy.
- The radical prostatectomy specimens had a mean of two cancer foci that measured, on average, 3 mm in the greatest dimension.
- In 85% of the cases, the side of the positive biopsy had matched the side of the carcinoma found at radical prostatectomy; 81.5% of cases had high-grade prostatic intraepithelial neoplasia immediately adjacent to the cancer.
- Truskinovsky et al. [18] made the ensuing conclusions:
- The incidence of minute carcinoma of the prostate had increased from 0.5% in 1988 to 5.2% in their current study.
- The patients often had moderately increased prostate-specific antigen levels and minute foci of carcinoma upon prostate biopsy.
- These small tumours at radical prostatectomy were usually identified by fortuitous biopsy which had often been preceded by other biopsies with noncancerous diagnoses.

Truskinovsky et al. [18] concluded that patients who had the above clinical and biopsy findings should be counselled about the possibility of finding only minute foci of carcinoma at radical prostatectomy and they might want to consider watchful waiting.

Epstein et al. [19] stated that they had identified information critical for patient treatment on prostate needle biopsies diagnosed with prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma. Epstein et al. [20] undertook a search utilising the MEDLINE database and referenced lists of relevant studies to obtain articles addressing the significance of finding PIN or atypical foci suspicious for carcinoma on needle biopsy. Epstein et al. [19] summarised in their results that there were certain results concerning PIN as follows:

- (1) Low grade PIN should not be documented in pathology reports due to poor interobserver reproducibility and a relatively low risk of cancer following re-biopsy.
- (2) The expected incidence of HGPIN upon needle biopsy was between 5% and 8%.
- (3) Even though the diagnosis of HGPIN is subjective, inter-observer reproducibility for its diagnosis was fairly high among urological pathologists, and yet only moderate among pathologists without special expertise in prostate pathology.
- (4) The median risk recorded in the literature for cancer following the diagnosis of HGPIN on needle biopsy was 24.1%, which was not much higher than the risk that had been reported in the literature for repeat biopsy following a benign diagnosis.
- (5) The majority of publications which had compared the risk of cancer in the same study following a needle biopsy diagnosis of HGPIN to the risk of cancer following a benign diagnosis on needle biopsy had shown no differences between the 2 groups.
- (6) Clinical and pathological parameters do not help stratify which men with HGPIN are at increased risk for a cancer diagnosis.
- (7) A major factor which had contributed to the decreased incidence of cancer following a diagnosis of HGPIN on needle biopsy in the contemporary era is related to increased needle biopsy core sampling, which detects many associated cancers on initial biopsy, such that re-biopsy, even with good sampling, does not detect many additional cancers.
- (8) It was recommended that men do not need routine repeat needle biopsy within the first year following the diagnosis of HGPIN, while further studies were required to confirm whether routine repeat biopsies should be undertaken several years following a HGPIN diagnosis upon needle biopsy.
- There were certain results concerning atypical glands suspicious for carcinoma as follows: 1) An average of 5% of needle biopsy pathology reports are diagnosed as atypical glands suspicious for carcinoma. 2) Cases that are diagnosed as atypical have the highest likelihood of being changed upon expert review and urologists should consider sending such cases for consultation in an attempt to resolve the diagnosis as definitively benign or malignant before subjecting the patient to repeat biopsy. 3) Ancillary techniques utilising basal cell markers and AMACR (alpha-methyl-acyl-coenzyme A racemase) can decrease the number of atypical diagnoses, and yet one must use these techniques with caution since there are numerous false-positive and false-negative results. 4) The average risk of cancer following an atypical diagnosis is about 40%. 5) Clinical and pathological parameters do not help predict which men with an atypical diagnosis do have cancer upon repeat biopsy. 6) Repeat biopsy should entail

increased sampling of the initial atypical site, and adjacent ipsilateral and contralateral sites with routine sampling of all sextant sites. In view of this, it is critical for urologists to send or submit needle biopsy specimens in a manner in which the sextant location of each core could be determined. 7) All men who have an atypical diagnosis need re-biopsy within 3 to 6 months.

Epstein et al. [19] made the ensuing conclusions:

- It is critical for urologists to differentiate between a diagnosis of HGPIN and that of atypical foci suspicious for cancer upon needle biopsy.
- These 2 entities do suggest different risks of carcinoma on re-biopsy and different recommendations for follow-up assessments.

Cao et al. [2] iterated the ensuing:

- With more vigilant screening for prostate cancer, there had been an associated increase in patients with little or no residual cancer at radical prostatectomy pursuant to an initial diagnosis of minute cancer upon needle biopsy.
- This raises a critical question as to whether the biopsy and subsequent radical prostatectomy in these patients were obtained from the same patient.
- They had utilised PCR-based microsatellite marker analysis to undertake identity test in 46 men (35 with minute cancer and 11 with no residual cancer).
- Out of them, 41 were interpretable, including 31 with minute cancer and 10 with no residual cancer.
- All 31 interpretable cases with minute cancer had shown match between the initial biopsy and radical prostatectomy specimens.
- Nine of the 10 interpretable cases with no residual cancer had shown match and 1 had shown mismatch. The remaining 5 cases (4 with minute cancer and 1 with no residual cancer) were considered uninterpretable due to technical problems.
- The initial biopsy of the mismatched case had high-grade cancer (Gleason score 4 + 4 = 8) that measured 9.6 mm in length with perineural invasion.
- Cao et al. [2] made the ensuing conclusions:
- Their results had confirmed that, in majority of cases of "vanishing cancer" in radical prostatectomy specimens, it does reflect a chance sampling of a minute cancer and not a switch in specimens.
- Nevertheless, specimen switch can rarely occur, and if there is high grade or a lot of cancer upon the biopsy with no or very minimal cancer in the radical prostatectomy specimen, one should evaluate for patient identity.

Park et al. [1] provided the ensuing iterations:

- Considering the increased utilisation of screening tests for serum prostate-specific antigen (PSA), diagnosis of prostate cancer at an early clinical stage and small tumour size had over recent years increased, and as a consequence, tumour volume in radical prostatectomy (RP) specimens had been reported to have decreased with regard to size [21] [22].
- The pathology stage pT0 had been defined as no evidence of residual tumour within an RP specimen from a patient in whom biopsy-proven prostate carcinoma had been confirmed histologically to be diagnosed.
- This terminology of the "vanishing cancer phenomenon" was coined by Goldstein and associates [6].
- The pT0 stage of prostate cancer had been identified as ensuing hormone treatment or the undertaking of previous transurethral resection of the prostate (TURP) for benign prostatic hyperplasia before RP [22] [23] [24] [25]] [26].
- Even though much research had addressed these two scenarios of pT0 stage prostate cancer [27] [28] [29], patients manifesting with pT0 status in cases other than these two scenarios do occur on very rare occasions, in about 0.2% to 0.8% of all prostate cancer patients, as well as few studies had examined such patients [4] [30] [31].
- The clinical importance of pT0 staging had remained not clarified. Nevertheless, many reports had indicated that pT0 stage patients do portend a highly satisfactory clinical outcome [4] [31].
- In a 10-year follow-up study of 38 pT0 patients, neither tumour recurrence nor progression had been identified observed in any patient. Therefore, in order to avoid the undertaking of unnecessary treatment of such clinically insignificant cancers, it is pivotal to identify pre-operative clinical and pathological characteristics which would help in the detection of patients who have a high probability of pT0 staging upon RP specimens.
- It had been pointed out that due to the fact that the pT0 stage of prostate cancer is rarely found, only a few studies of the preoperative features of such patients had been published [4] [6] [30] [31] [32].
- Furthermore, few reports had been documented upon the characteristics of pT0 Asian patients.
- It has been reported that, in comparison with Western countries, Asian populations had demonstrated a lower incidence of prostate cancer, but that Asians do have high-grade prostate cancer (Gleason score above 7) and a smaller prostate volume [33] [34] [35]. Hence, considering this ethnic difference, simple adaptation of the predictive measures of prostate cancer pT0 stage that is used within the Western countries to Asian populations might be inappropriate.
- Therefore, in their reported study, they had analysed preoperative clinical and pathologic characteristics of patients in whom pT0 staging was confirmed after diagnosis of prostate cancer on prostate needle biopsy and RP.
- Patients who underwent hormone treatment or who were diagnosed with prostate carcinoma when receiving TURP for benign prostatic hyperplasia before RP were not included in their reported study which follows.

Park et al. [1] analysed 702 patients who had prostate cancer and who had undergone radical prostatectomy (RP) within their institution between January 2004 and July 2008. They excluded patients who had received preoperative hormone treatment (68 cases) or who were diagnosed as having prostate carcinoma by undergoing trans-urethral resection of prostate (TURP) for benign prostatic hyperplasia before undergoing RP (13 cases) were excluded from the analysis. Park et al. [1] reported that all of the patients had clinically localized prostate cancer that had been assessed based upon digital rectal examination, endorectal ultrasonography, and magnetic resonance imaging (MRI). All of the patients had undergone retro-pubic RP and pelvic lymph node dissection. Park et al. [1] re-examined and retrospectively analysed the ensuing clinical as well as pathological factors: age, serum PSA level, digital rectal examination result, Gleason score, number and length of positive cores within the prostate needle biopsy, and tumour volume of the RP specimen. The pathology pT0 stage was assigned when no residual tumour was identified within the RP specimen. Each RP specimen, which was examined by two genitourinary (GU) pathology specialists within

their institution, was completely fixed and cut into 3 mm slices. When areas with possible prostate cancer were identified, these regions were examined by the undertaking of immunochemistry staining utilising AMACR (1:40; BIOCARE, Walnut Creek, USA) and anti-p63 (1:100; DAKO, Glostrup, Denmark). The prostate needle biopsy tissue was re-examined only when residual tumour was not identified. When prostate cancer was however, identified within the biopsy during re-examination, the RP tissue block corresponding to the tumour area of the biopsy was serially sectioned and the block was turned upside down to create more serial sections. Slides were screened by pathology fellows or residents and they were further examined for cancer by the two GU pathology specialists. Park et al. [1] stated that all RP specimens of stage pT0 were examined by at least three pathologists. Park et al. [20] compared patients who had pT0 stage prostate cancer with a control group, which consisted of the remaining 693 prostate cancer patients who had undergone treatment within their institution during the same period. Park et al. [1] examined preoperative clinical and pathology characteristics including: patient age, serum PSA level, digital rectal examination data, Gleason score, the number and length of positive cores on the prostate needle biopsy, prostate volume on endorectal ultrasonography, and the size of tumour the RP specimen in all patients. Prostate volume was evaluated by utilising the ellipsoid formula, $\pi/6$ x prostate width x height x depth. Park et al. [20] analysed these features in a search for characteristics predictive of the pT0 stage of prostate cancer. Park et al. [1] calculated the cutoff value of clinical and pathological factors that were significantly correlated with pT0 staging and also investigated the sensitivity and specificity of such factors. In order to compare patients with pT0 prostate cancer with the control group, Park et al. [1] utilised the chi-square test to analyse categorical variables (digital rectal examination), and the Mann-Whitney U test was used when consecutive variables (age, preoperative PSA level, number and length of positive cores on preoperative needle biopsy, Gleason score on needle biopsy) were examined. p-values of <0.05 were considered to reflect a statistically significant difference. SPSS, version 12.0, was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). Park et al. [1] summarised the results as follows:

- In their reported study, 9 (1.3%) of the 702 patients were post-operatively diagnosed as having prostate cancer of pT0 stage.
- The mean age of the nine patients was 66.4 years and their ages had ranged, from 61 years to 73 years, and their average serum PSA level was 8.1 ng/ml, as well as the serum PSA level had ranged between 5.0 and 24.4 ng/ml.
- Of the nine patients, six (66.7%) were of clinical stage T1c, and three (33.3%) were of stage T2. Eight patients (88.9%) had a biopsy Gleason score of 6 and one patient a score of 7 (4+3).
- Among the eight patients that amounted to 88.9% of the patients who had two or fewer positive biopsy cores, seven had only one positive core. The other patient had two positive cores.
- The mean length of the positive biopsy cores was 3 mm, and the length of the cores had ranged between 1.0 mm and 14.0 mm.
- Except for the one patient in whom the tumour length was noted to be 14 mm and the one patient in whom the tumour length was not known, a tumour size of 2 mm or less was found in the remaining seven patients.
- The mean prostate volume was 54.1 cm3, and the prostate volume had ranged between 23 and 82 cm3), and, except for one patient whose tumour volume, was 23 cm3, the prostate gland volume of all pT0 patients was at least 30 cm3.
- Out of the nine patients, four had high-grade prostatic intraepithelial neoplasia (HGPIN) (see Table 1).
- During the mean follow-up period of 23.6 months, no biochemical prostate cancer recurrence had occurred in any patient.

Clinical data					Biopsies				HGPIN in RP specimen
Patient number	Age (years)	Clinical stage	PSA (ng/ml)	Prostate volume (cm^3)	Gleason score	P/T	Length of cancer (mm)	Location	
1	61	T2	5	68	6	1/8	1	Left postero-lateral	Yes
2	71	T1c	8	82	6	1/12	1	Right postero-lateral	No
3	71	T1c	5.9	23	7	4/13	14	Both postero lateral	No
4	61	T2	7.2	36	6	1/12	1	Left apical	No
5	73	T1c	6.2	36	6	1/12	2	Right apical	Yes
6	67	T2	5.6	65	6	2/17	2	Right postero lateral	Yes
7	65	T1c	5	80	6	1/12	1	Left midline	Yes
8	68	T1c	24.4	35	6	1/12	1	Right postero lateral	No
9	61	T1c	5.2	63	6	1/12	1	Left	No

Table 1: Characteristics of nine pT0 patients.

PSA: prostate-specific antigen, P/T: positive / total cores, HGPIN: high grade prostatic intraepithelial neoplasia, RP: radical prostatectomy. Reproduced from [1] under the Creative Commons Attribution license.

- In a comparison between the two groups (the 9 patients with pT0 staging and the remaining 693 patients with tumours seen in RP specimens), no significant differences were found with regard to the mean age (66.4 vs. 65.0 years, p=0.500), PSA level (8.1 vs. 11.2 ng/ml, p=0.447), or abnormality in the digital rectal examination (33.3% versus. 38.3%, p=0.464).
- Nevertheless, a significant difference was found when preoperative biopsy Gleason score was examined (≤6/>6; 88.9/11.1% in those with pT0 disease versus. 53.3/46.7% in the control group, p=0.042).
- Another significant difference that was found was that two or fewer positive cores were seen in patients with pT0 staging (88.9% in pT0 disease versus. 48.4% in the control group, p=0.018).
- The size of the tumour upon biopsy had also differed significantly between the two groups. It was 2 mm or less in length in 88.9% of those with pT0 disease versus. 23.0% of the control group (p<0.001).
- Finally, the mean prostate volume was 54.1 cm3 in pT0 patients but 37.5 cm3 in the control group, showing that pT0 patients had a larger prostate volume (p=0.015) (see Table2).

	pT0 group (n=9)	Control group (n=693)	p-value
Mean age (year)±SD	66.4±4.7 (61-73)	65.0±6.6 (41-79)	0.500
Mean preoperative PSA (ng/ml)±SD	8.1±6.2 (5.0-24.4)	11.2±12.5 (3.2-162)	0.447
Abnormal DRE rate (%)	33.3	38.3	0.464
Gleason score on biopsy (≤6/>6, %)	88.9/11.1	53.3/46.7	0.042
No. of positive cores (≤2/>2, %)	88.9/11.1	48.4/51.6	0.018
Tumor length on biopsy (≤2/>2 mm, %)	88.9/11.1	23.0/77.0	<0.001
Mean prostate volume (cm^3)±SD	54.1±21.8 (23-82)	37.5±20.1 (8-275)	0.015

Table 2: Comparisons between the pT0 group and the control group.

SD: standard deviation, PSA: prostate-specific antigen, DRE: digital rectal examination. Reproduced from [1] under the Creative Commons Attribution license.

- For the prediction of pT0 staging of prostate cancer, they had chosen four criteria such as a Gleason score of 6 or less, two or fewer positive cores, a tumour size of 2 mm or less on preoperative biopsy, and a prostate volume of 30 cm3.
- Combining the four criteria had revealed a sensitivity of 88.8%, a specificity of 93.4%, a positive predictive value of 12.7%, and a negative predictive value of 99.8% (see Table 3).
- In Table 4, they had reviewed previous studies in the literature on the incidence and characteristics of pT0 stage patients and compared them with their results.

	pT0 patients	Control group	Total
4 criteria combined	8	55	63
4 criteria not combined	1	638	639
Total	9	693	

Table 3: Number of patients satisfying the four characteristics.

4 Criteria, Pre-operative Gleason Score ≤6, Number of positive cores ≤2, Tumour length ≤2mm, Prostate volume ≥ 30 cm3 Reproduced from [1] under the Creative Commons Attribution license.

	No. of patients	Study period	Race	Incidence (%)	Predictor of pT0 prostate cancer
Bostwick and Bostwick [11], 2004	6,843	1966-1995	Caucasian (American)	0.6	Not identified
Descazeaud et al [12], 2006	1,950	1996-2005	Caucasian (French)	0.5	Gleason score <7 Positive biopsy core ≤1 Tumor length on biopsy <2 mm Prostate weight >60 g
Herkommer et al [13], 2004	3,609	1990-2003	Caucasian (German)	0.8	Not identified
Bessede et al [18], 2010	7,693	1998-2006	Caucasian (French)	0.4	Not identified
Present study	702	2004-2008	Asian (Korean)	1.3	Gleason score ≤6 Positive biopsy cores ≤2 Tumor length on biopsy ≤2 mm Prostate volume >30 cm^3

Table 4: Literature Review: Reproduced from [1] under the Creative Commons Attribution license.

New Reference numbers for current literature [11 now reference 30] [12 now reference 4] [13 now reference 31], [18 reference 37]

Park et al. [1] made the ensuing detailed educative discussions:

- Previous studies had noted that, after patients who received preoperative hormone therapy and who were diagnosed with prostate cancer when undergoing TURP for treatment of benign prostatic hyperplasia were excluded, the incidence of pT0 staging after RP was extremely low (0.2-0.8%) [4] [30] [31] [36].
- Many explanations are possible for patients being staged as pT0 after RP. Firstly, the tumour might have been completely removed during the preoperative biopsy.
- A very small tumour might have been eliminated during specimen workup procedures, such as paraffin block preparation.
- Secondly, the preoperative biopsy might have yielded a false-positive result. Such false-positives could arise as a result of pathologist error.
- Thirdly, the pathological examination of an RP specimen might have resulted in a false-negative finding due to a very small tumour volume, in which the tumour could be easily undetected by the pathologist, or due to an inflammatory reaction.
- Finally, specimen mix-up or a mislabelled specimen might result in a false-positive diagnosis of prostate cancer.
- DNA identity testing is available and could be utilised if the original diagnostic material is available [32].
- It had been iterated that pathology examination plays an important role in the diagnosis of small tumours.
- In a study that was undertaken by Kollermann and colleagues, in which four GU pathology experts had re-examined RP specimens from 20 pT0 patients, small residual tumours (≤0.2 ml in volume) were discovered in 13 patients [28].

- In their reported study, after fixation, whole specimens were cut into 3 mm slices, and when no tumour was identified in these initial sections, additional tissue slides were prepared. Absence of residual tumour was confirmed by at least two Genito-urinary (GU) pathology specialists.
- Whilst the incidence of pT0 staging had been generally known to be under 1%, the frequency was 1.3% in their reported study [4] [30] [31].
- Majority of pT0 stage patients in their study had serum PSA levels less than 10 ng/ml, initial prostate needle biopsies with a Gleason score of 6 or less, two or fewer positive cores, a core length of 2 mm or less, and larger tumour volume.
- Descazeaud et al examined 11 patients who were diagnosed as pT0 stage after RP and reported that 90.9% of the patients had serum PSA levels less than 15 ng/ml, 81.8% had one positive core, and all had a Gleason score of 6 or less [4]. The pT0 stage group had also demonstrated a significant difference from the control group in prostate weight (72 grams versus. 51 grams).
- Given that a small tumour is more difficult to find within a large-volume prostate gland, the frequency of pT0 staging after RP might be associated with prostate volume.
- In their analysis of pre-operative characteristics in the two groups, a significant difference was found in those with a Gleason score of 6 or less, two or fewer positive cores, and core length of 2 mm or less. Also, four patients had HGPIN in the RP specimen.
- Mean prostate volume was also significantly larger in patients with pT0 staging in comparison with within the control group.
- Given that the prostate volume of Asians is smaller than that of Westerners, application of Western pT0 staging-predictive factors for prostate cancer to Asian populations would clearly be inappropriate.
- Utilisation of RP for the treatment of pT0 prostate cancer is controversial; in that it is not clear whether RP is appropriate or excessive.
- In a study on patients diagnosed with T1a prostate cancer after TURP, Epstein et al had claimed that a trace of disease progression within 8 years was found in only 16% of the reported patients [37].
- Nevertheless, according to Carter et al, advanced prostate cancer was identified pursuant to RP in 6% of T1a prostate cancer specimens and 32% of T1b specimens [38]
- It was evident that characteristics predictive of pre-operative pT0 staging would be helpful in deciding whether definitive treatment should be immediately implemented or whether watchful waiting might be a more appropriate treatment option.
- In their analysis of the features that are predictive of pT0 staging following RP, include: the combination of a Gleason score of 6 or less, two or fewer positive cores, a positive core length of 2 mm or less, and a prostate volume of 30 cm^3 or larger offered a sensitivity and a specificity of 87.5% and 93.1%, respectively.
- Within the control group, all patients who were identified by these criteria had low-grade pT2 prostate cancer (Gleason score of 6 or less).
- Few studies related to the characteristics predictive of pT0 stage after RP had appeared.
- Their study was particularly meaningful in that it was the first attempt to analyse features predictive of pT0 staging in an Asian population.
- Nevertheless, the most notable limitation of their study was the extremely low incidence of pT0 staging after RP.
- This low incidence was insufficient for the multiple logistic regression model that is required to investigate the predictive factors of pT0 stage after RP as in a previous study [4]
- In addition, data on the free/total serum PSA ratio and PSA velocity were not available in their study, so these variables had not been analysed as predictive factors of pT0 staging after prostatectomy.
- Hence, further multicentre research on the value of these predictive characteristics is required.
- Park et al. [1] made the ensuing conclusions:
- In their study of 702 patients who had undergone RP after being diagnosed with prostate carcinoma by biopsy, the rate of pT0 staging was 1.3%.
- They found that Gleason score, the number of positive cores, the positive core length, and the prostate volume were helpful in the prediction pT0 staging of prostate cancer in RP specimens.
- Considering the favourable outcomes of patients with pT0 prostate cancer, these predictive factors for pT0 prostate cancer would be useful for clinicians and patients when they decide on a treatment option.
- Gross et al. [20 undertook a literature review of current data to determine the frequency and correlates of pT0 prostate cancer after radical prostatectomy alone. Gross et al. [20] undertook a comprehensive search of MEDLINE and PUBMED. Gross et al. [20] identified seven studies involving 18,135 patients with 74 reported pT0 cases. The most frequent correlates from their pooled data of patients with pT0 specimens included preoperative serum PSA <10 ng/ml, only one positive core biopsy, and Gleason score <7.
- Bream et al. [39] stated the following:
- The pT0 stage of prostate cancer relates to the radical prostatectomy (RP) specimen where no cancer could be identified.
- Taking into consideration the known racial and geographic differences in prostate cancer incidence and survival, they had reviewed their experience with pT0 disease to determine applicability of these predictive features in an American population.
- They had undertaken a retrospective chart review for all RPs at one state tertiary care institution during a 20-year period between 1991 and 2011.
- They had collected as well as re-reviewed the clinicopathologic features of pT0 patients their relevant pathologic material.
- Bream et al. [39] summarised the results as follows:
- Of a total of 1,635 radical prostatectomies (RPs) undertaken, 4 (0.2%) not receiving neoadjuvant therapy or other prior prostate surgeries were stage pT0.
- Biopsies from 3 of 4 patients were re-evaluated and these confirmed a small focus, <1% of tissue, of Gleason score 3+3 adenocarcinoma; a fourth was not available for re-review.
- Their re-review of the RP slides had identified small foci of cancer in two of the four, thus yielding a final true pT0 incidence of 0.1%.
- Preoperative serum prostate specific antigen had ranged from 4.4 to 7.4 ng/ml, clinical stages were all T1c, and there was no evidence of recurrence at 3 months to 10 years of follow-up.
- Bream et al. [39] made the ensuing conclusion.
- Stage pT0 prostate cancer is very uncommon, which does occur with an incidence of 0.1%, and in their experience occurs only in clinical T1c patients with pre-biopsy prostate specific antigen < 7.5 ng/ml, with Gleason score 3 + 3 adenocarcinoma comprising < 1%, 1 mm of a single core biopsy, a stricter threshold than that seen in non-American populations.

- Kalampokis et al. [40] stated the ensuing:
- Over the preceding decades, the undertaking of a widely accepted screening program for the early identification of prostate cancer had been associated with even more patients being diagnosed as having low-grade, small in size malignancies.
- Pursuant to the undertaking of radical prostatectomy (RP), the absence of a demonstrable tumour within the specimen prostate gland of a previously histologically proven malignancy is referred to as the pT0 stage.
- It has been iterated that even though this is a well-known phenomenon for individuals receiving neoadjuvant hormonal therapy (NHT), the incidence of pT0 among patients who had been directly treated by the undertaking of radical prostatectomy (RP) without a preceding androgen deprivation therapy (ADT) is less than 2 percent (<2%) [2] [3] [6] [41].
- Even though the prognosis of pT0, is considered to be excellent in majority of the cases, a continued close follow-up of patients who have pT0 adenocarcinomas of the prostate gland needs to be emphasised and is warranted.

Conclusions And Lessons to Learn as Well As Reflect Upon

- The incidence of pT0 adenocarcinoma of prostate gland has ranged between 0.07% and 1.3%.
- Predictors of the pT0 stage are only a single biopsy core with low-grade cancer, a cancer length not exceeding 2 mm and a high prostate volume.
- Biochemical recurrence of tumour has ranged between 0 % and 11%.
- The absence of malignancy in the RP specimen despite a previous positive biopsy is a very rare and unpredictable finding.
- Even though the prognosis has been regarded to be excellent in majority of the cases, a continued close patient follow-up is necessary.
- The absence of malignant neoplasm within a radical prostatectomy specimen despite preceding positive finding of malignant tumour within the prostate gland biopsy specimen is an uncommon finding, which necessitates special management in view of the possible medico-legal repercussions.
- The finding of pT0 of the prostate gland, has tended to be associated with features of low-risk cancer and pre-operative hormonal treatment of prostate cancer.
- It is conjectural; nevertheless, perhaps, the active surveillance strategy option in relation to cases of low-risk localised adenocarcinoma of prostate gland instead of the undertaking of radical prostatectomy, may need to be encouraged.
- At the time of publication of this article, many models that serve the purpose of pre-operative predictors of pT0 staged prostate cancer had been promulgated, nevertheless, none of them had achieved wide global acceptance and adoption in the daily clinical practices, even the prognosis, attributable to pT0, had been considered to be excellent, with regard to the majority of cases and continued thorough follow-up assessments of individuals who are found to have pT0 prostate cancers had been recommended.

Conflict Of Interest – Nil

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