

Prevalence and Pathological Analysis of Adenocarcinoma Prostate Discovered Incidentally in Radical Cystoprostatectomy Specimen: An Indian Center Experience

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ABSTRACT

Introduction: Potency-preserving techniques of radical cystectomy raise concern because of a possible association with incidental prostate adenocarcinoma. Cystoprostatectomy specimen provides a unique opportunity to estimate the prevalence and to define the morphological features of silent (incidental) adenocarcinoma of the prostate.

Aim: To determine the prevalence and histopathological features of incidental prostate carcinoma detected in radical cystoprostatectomy specimens taken for muscle invasive bladder cancer.

Materials and Methods: A retrospective chart review of patients who underwent radical cystoprostatectomy for infiltrating bladder tumors during the period between 2003 and April 2014 was done. The histopathology slides of these patients were reviewed.

Results: Fourteen incidental prostate cancers were identified in 113 radical cystoprostatectomies. The mean patient's age

was 65 years (range 48-75 years). The median Gleason Score was 3+3 (3+3, 4+3). Nine patients (64%) had Gleason 6 and five (36%) had Gleason 7 disease. Pelvic lymph node metastasis from prostate adenocarcinoma was detected in four patients. On mean follow up of 2.5 years for three patients with node positive disease there was no evidence of biochemical recurrence. For patients with node negative disease, six patients had no evidence of recurrence on a follow up of 3.5 years.

Conclusion: Percentage of incidentally detected prostate cancer in cystoprostatectomy specimen at our clinical center is much lower (12.4%) than reported rates in the world until now (23-68%), which can be attributed to varying methods of pathological examination and regional difference in prostate cancer. It would be prudent to do digital rectal examination (for clinical prostate evaluation) and Prostate-Specific Antigen (PSA) testing along with bladder cancer work up.

Keywords: Bladder, Cancer, Incidental, Prostate, Radical cystectomy

INTRODUCTION

Radical cystoprostatectomy represents the most effective treatment for muscle-invasive non-metastatic bladder cancer [1]. The high incidence of sexual complications has been one of the reasons for development of alternative procedures like cystectomy with partial prostatectomy [2] cystectomy with adenoma enucleation [3] and cystectomy preceded by transurethral resection of prostatic tissue with preservation of the prostatic capsule. These potency-preserving techniques raise concern because of two essential risks: (a) involvement of the prostate by the urothelial cancer; (b) a possible association with incidental prostate cancer [1-3].

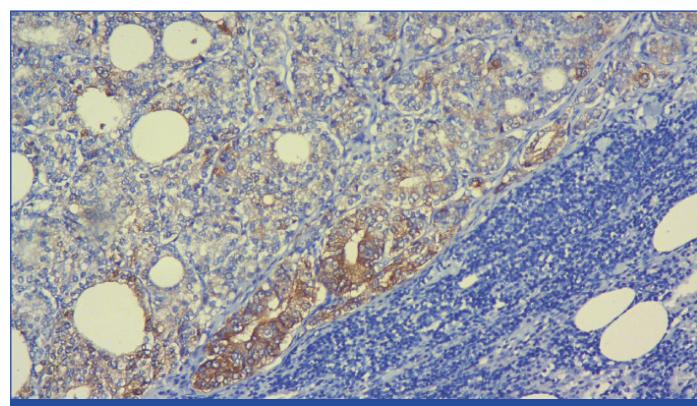
The frequency of incidentally detected prostate cancer is nearly 42% in men older than 50 years of age, and higher than 80% in men older than 80 years [4]. A large proportion of prostate cancer remains undiagnosed or clinically insignificant resulting in high frequency of autopsy detected cases. Cystoprostatectomy specimen obtained from patients with bladder cancer provides a unique opportunity to estimate the prevalence and to define the morphological features of silent (incidental) adenocarcinoma of prostate. The aim of this study was to determine prevalence and histopathological features of incidental prostate carcinoma detected in radical cystoprostatectomy specimens for muscle invasive bladder cancer.

MATERIALS AND METHODS

A retrospective chart review of patients who underwent radical cystoprostatectomy for infiltrating bladder tumors during the period between 2003 and April 2014 was done in our Department. A total of 123 patients underwent radical cystectomy for invasive bladder cancer at our Institute. Of these, 113 patients were males. Patients

who underwent PSA screening, desired prostate sparing surgery or had any surgical procedure for benign prostate disease were excluded from the study.

The histopathology slides of these patients were reviewed. Gleason Score (GS), seminal vesicle invasion, extracapsular extension, type of tumour (ductal/acinar) and lymph nodal involvement by adenocarcinoma prostate, confirmed by Immunohistochemistry (IHC) staining for PSA [Table/Fig-1] was determined. Associated or isolated Atypical Small Acinar Proliferation (ASAP) and High Grade Prostatic Intraepithelial Neoplasia (HGPIN) were also noted. Specimens with adenocarcinoma prostate fulfilling all the following criteria were defined as insignificant: (a) GS<=6 without Gleason pattern 4 or 5; (b) Organ confined disease; (c) tumour volume <0.5cc (dominant nodule) [5,6].



[Table/Fig-1]: Photomicrograph showing tumour cells positive for Prostate Specific Antigen (PSA) staining on Immunohistochemistry (IHC) in a background of lymphoid tissue.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean \pm standard deviation, whereas categorical variables were expressed as frequency and percentage.

RESULTS

Adenocarcinoma prostate was detected in 14 out of 113 specimens with an overall prevalence of 12.4%. Eight of these patients had received neoadjuvant chemotherapy with Gemcitabine and Carboplatin for bladder cancer. The mean patient's age was 65 years (range 48-75 years). The median Gleason Score was 3+3 (3+3, 4+3); (64%) had GS of 3+3, three patients (22%) had a GS of 3+4 and two (14%) had GS 4+3. As per Tumour (T) stage, seven patients (50%) had T2c and four patients (29%) had T2a disease. Three patients had locally advanced disease, one with seminal vesical invasion (GS 3+3) and two patients with extra prostatic extension [Table/Fig-2].

Pelvic lymph node metastasis from adenocarcinoma prostate was detected in four patients, which was confirmed with PSA staining of the nodes [Table/Fig-1]. None of these patients had evidence of metastatic lymph nodes on Computerized Tomography of abdomen and pelvis (CT). Two of these patients had GS 3+4, with T2b and T3a disease respectively. One patient had GS 4+3 and T2c disease. One patient with LN metastasis had GS 3+3 with SV invasion on one side. Two of these patients had received neoadjuvant chemotherapy with gemcitabine and carboplatin [Table/Fig-2]. Four patients had ASAP and 1 had diffuse high grade PIN with no evidence of carcinoma prostate. 10 out of 14 patients with Carcinoma prostate (CaP) had associated diffuse high grade PIN on HPE. As per the definition of significant tumour given by Ohori and Epstein et al., 64% of all incidental CaP were significant in our study [Table/Fig-3] [5,6].

One patient expired in the post-operative period due to ureteric anastomotic leak leading to sepsis and Multi Organ Dysfunction (MODS). 3 out of 4 patients with Lymph Node (LN) positive CaP underwent medical or surgical castration (as per patient preference) and followed up 6 monthly with PSA. On a mean follow-up of 2.5 \pm 1.2 years, these patients had no evidence of disease progression (clinical or biochemical). One patient with LN positive CaP was followed up with serial PSA (patient refused therapy) and underwent castration after one year when there was PSA rise. Two patients lost to follow up. Of the remaining seven patients, one developed

Age (years)	T staging (UB)	Operative procedure	HGPIN/ ASAP	Nodal status	Total nodes dissected	Peri-op CT
70	T3a	RC+IC	ASAP	N0	13	Y
60	T3a	RC+ONB	ASAP	N0	19	Y
72	T1	RC+IC	ASAP	N0	12	N
62	T3a	RC+IC	HGPIN	N0	14	N
62	T1	RC+IC+ URETHRECTOMY	ASAP	N0	18	Y

[Table/Fig-3]: Isolated ASAP/HGPIN patient details.

HGPIN: High grade prostate intraepithelial neoplasm; ASAP: Atypical small acinar proliferation; RC: Radical cystectomy; ONB: Orthotopic neobladder; IC: Ileal conduit, CT: Chemotherapy

adenocarcinoma stomach after 2 years. He underwent surgery and adjuvant chemotherapy for stomach cancer. On a mean follow-up of 3.5 \pm 1.5 years, the other six patients had no evidence of disease progression (clinical or biochemical) [Table/Fig-4].

Node Positive (PSA positive) patients			
Total	Hormone Therapy	Mean BCR free survival (n=4)	
4	3 (one patient refused)	2.5 years	
Node negative patients			
Total	Lost to follow up	Mortality	Mean BCR free survival (n=6)
10	2	2 (One non prostate cancer specific mortality)	3.5 years

[Table/Fig-4]: Follow-up of patients stratified as per pathological nodal status.

DISCUSSION

The frequency of incidentally discovered CaP in radical cystoprostatectomy specimens is extremely variable among the most relevant published series. In our study we noted the prevalence to be 12.4%. This is much lower than overall mean frequency in other series (range 23-68%) [7,8]. This variability can be explained by different pathological sampling protocols used. Ruffion et al., found a 51.0% rate of incidentally detected CaP, advocating the use of 2.5 mm prostate slices [8]. Similar results were seen in the study by Abbas et al., who examined prostatic tissue from 40 radical cystoprostatectomy specimens with serial step slices taken at 2 to 3-mm intervals [9]. On the other hand, variability can also be noted when considering those using a different pathologic examination protocol with 5-mm sections. Yang et al., reported rate

Age (yrs)	T Staging (UB)	Operative Procedure	GS	T Staging (CaP)	Nodal Status	Significant Tumour	Diffuse HGPIN	Peri-op CT	Total Nodes	PSA** (ng/ml)	Bone scan
63	T2a	RC+IC	3+3	T2a	N0	N	Y	N	15	0.03	NA
71	T2b	RC+ONB	3+4	T2c	N1(PSA)	Y	Y	N	16	0.2	Negative
67	T1	RC+IC	3+3	T3b	N1(PSA)	Y	Y	N	15	0.1	Negative
75	yT0	RC+IC	3+4	T3a	N1(PSA)	Y	Y	Y	16	0.01	Negative
58	T1G3	RC+IC	3+3	T3a	N0	Y	Y	Y	14	0.05	NA
70	yT0	RC+IC	3+4	T2c	N0	Y	N	Y	11	0.001	NA
48	T4a	RC+IC	3+3	T2a	N0	N	N	Y	15	0.035	NA
49	T2a	RC+NB	3+3	T2a	N0	N	N	N	17	0.004	NA
73	T2b	RC+IC	3+3	T2a	N0	Y	Y	Y	13	0.1	NA
73	T4a	RC+IC	3+3	T2a	N0	N	Y	N	11	0.02	NA
71	T4a	RC+CU	3+3	T2c	N0	Y	Y	Y	7	0.1	NA
72	T1	RC+IC	3+3	T2c	N0	N	Y	N	12	0.008	NA
64	T3a	RC+CU	4+3	T2c	N0	Y	Y	Y	16	0.12	NA
58	T1	RC+ONB	4+3	T2c	N1(PSA)	Y	Y	Y	15	0.1	Negative

[Table/Fig-2]: Characteristics of carcinoma prostate diagnosed incidentally in radical cystoprostatectomy specimen.

UB: Urinary bladder; GS: Gleason score; CaP: Carcinoma prostate; HGPIN: High grade prostate intraepithelial neoplasm; RC: Radical cystectomy; ONB: Orthotopic neobladder; IC: Ileal conduit; CU: Cutaneous ureterostomy; CT: Chemotherapy; PSA: Prostate specific antigen; NA: Non applicable

**After surgery

of incidentally detected CaP as 21%. At our center, we routinely sample the prostate taking 5 mm cut [10].

In our study majority of patients (64%) had low-grade disease with GS 3+3. On basis of the criteria to define significant tumour by Ohori et al., and Epstein et al., 64% of all tumours were significant in our study. Revelo et al., reported a 41% rate of unsuspected CaP, with 48% being considered clinically significant [11]. In a series of 141 cystoprostatectomies by Delongchamps et al., 30% were considered insignificant [12]. Montironi et al., concluded that incidentally detected CaP is less aggressive than CaP clinically detected with regard to stage, Gleason score, and surgical margin status. The same group investigated the expression of some of the markers of aggressiveness i.e., nuclear and nucleolar size, proliferation activity assessed as Ki-67 index, HER2 gene amplification, HER2 protein expression, endothelin-1 in incidental cancer. They pointed out that incidental cancers are different from clinical ones in terms of marker expression, having cell features of less aggressiveness [13]. The proportion of clinically significant cancers in various series published previously varies from 10% to 70% [12]. Such wide variability could be related to different criteria adopted to define clinically significant cancer, different pathological techniques and the population under investigation. In conclusion, there is no consensus in defining clinically insignificant prostate cancer.

Total four cases of node positive disease (28%) were confirmed to be of prostatic origin using PSA staining. Nodal involvement by incidental carcinoma prostate has not been reported by most of the other series in the past. These CaP patients had Gleason pattern 4 on HPE or seminal vesicle invasion/extra capsular spread. Abdelhady et al., in their review of 58 radical cystoprostatectomy specimen reported a relatively higher rate of extra capsular extension (20%) and Gleason grade 4 (21%) than previously noted (3-11%) [14]. We found evidence of diffuse HGPN in 10 out of 14 patients (71%) with incidental carcinoma prostate. There was only one radical cystoprostatectomy specimen with diffuse HGPN without any evidence of incidental CaP. In the study by Wiley et al., incidental PC was found in 22 of 48 cystoprostatectomy cases and HGPN was found in 21 (95%) of these 22 cases. Conversely, there was only one incidental PC in the eight prostates without HGPN (13%). They concluded that HGPN is a marker for concurrent PC, and that the risk depends more on the volume of HGPN than on its absolute presence [15].

The present results indicate that the percentage of incidentally detected prostate cancer in cystoprostatectomy specimens at our clinical center is much lower (12.5%) than reported rates in the world until now (25-68%). We assumed that the varying methods of histopathological examination of the prostate could be the main cause of these frequency differences. Also, regional differences in prostate cancer incidence rates can be related to environmental and racial factors. The clinical significance of these incidentally discovered cancers remain questionable because the outcome of the patients with both malignancies depends on the prognosis of the bladder tumor. None of the patients in our study showed evidence of progression on follow up. Node positive incidental CaP remained in remission following hormone therapy.

LIMITATION

The retrospective nature and small sample size are the main drawbacks of our study. A longer follow up period of patients with incidental carcinoma prostate would have given a better understanding of the natural history of these tumours.

CONCLUSION

The percentage of incidentally detected prostate cancer in cystoprostatectomies varies in different studies. This can be attributed to sampling techniques and possibly environmental and racial factors. The clinical significance of incidental prostate cancer is doubtful and prognosis depends on the aggressiveness of bladder tumour. It would be prudent to do digital rectal examination (for clinical prostate evaluation) and prostate-specific antigen (PSA) testing along with bladder cancer work.

REFERENCES

- [1] Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World Journal of Urology*. 2006;24:296-304.
- [2] Spitz A, Stein JP, Lieskovsky G, Skinner DG. Orthotopic urinary diversion with preservation of erectile and ejaculatory function in men requiring radical cystectomy for non urothelial malignancy: a new technique. *J Urol*. 1999;161(6):1761-64.
- [3] Muto G, Bardari F, D'Urso L, Giona C. Seminal sparing cystectomy and ileocapsuloplasty: long-term follow-up results. *J Urol*. 2004;172:76-80.
- [4] Hiroi M, Spahovic H, Selimovic M, Sadovic S. Incidental prostate cancer in patients undergoing radical cystoprostatectomy for bladder cancer. *Bosn J Basic Med Sci*. 2008;8(2):147-51.
- [5] Ohori M, Wheeler TM, Dunn JK, Stamey TA, Scardino PT. The Pathological features and prognosis of prostate cancer detectable with current diagnostic tests. *J Urol*. 1994;152:1714-20.
- [6] Epstein JI, Walsh PC, Brendler CB. Radical prostatectomy for impalpable prostate cancer: The John Hopkins experience with tumours found on transurethral resection (stages T1A and T1B) and on needle biopsy (stage T1C). *J Urol*. 1994;152:1721-29.
- [7] Pettus JA, Ahmadieh, Barocas DA, Koppie TM, Herr H, Dalbagni G. Risk assessment of prostatic pathology in patients undergoing radical cystoprostatectomy. *European Urology*. 2008;53(2):370-75.
- [8] Ruffion A, Manel A, Massoud W. Preservation of prostate during radical cystectomy: evaluation of prevalence of prostate cancer associated with bladder cancer. *Urology*. 2005;65:703-07.
- [9] Abbas F, Hochberg D, Civantos F. Incidental prostatic adenocarcinoma in patients undergoing radical cystoprostatectomy for bladder cancer. *Eur Urol*. 1996;30:322-26.
- [10] Yang X, Monn MF, Liu L, Liu Y, Su J, Lyu T, et al. Incidental prostate cancer in Asian men: high prevalence of incidental prostatic adenocarcinoma in Chinese patients undergoing radical cystoprostatectomy for treatment of bladder cancer and selection of candidates for prostate-sparing cystectomy. *Prostate*. 2015;75(8):845-54.
- [11] Revelo MP, Cookson MS, Chang SS. Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. *Journal of Urology*. 2004;171:646-51.
- [12] Delongchamps NB, Mao K, Theng H. Outcome of patients with fortuitous prostate cancer after radical cystoprostatectomy for bladder cancer. *European Urology*. 2005;48:946-50.
- [13] Montironi R, Mazzucchelli R, Santinelli A. Incidentally detected prostate cancer in cystoprostatectomies: pathological and morphometric comparison with clinically detected cancer in totally embedded specimens. *Human Pathology*. 2005;36:646-54.
- [14] Abdelhady M, Abusamra A, Pautler SE. Clinically significant prostate cancer found incidentally in radical cystoprostatectomy specimens. *BJU International*. 2007;99:326-29.
- [15] Wiley EL, Davidson P, McIntire DD, Sagalowsky AI. Risk of concurrent prostate cancer in cystoprostatectomy specimens is related to volume of HGPN. *Urology*. 1997;46:692-96.

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