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INCIDENCE AND CLINICAL COURSE OF INCIDENTAL PROSTATIC ADENOCARCINOMA: A PROSPECTIVE INDIAN STUDY

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HOW TO CITE THIS ARTICLE:

Bikram Rout, Susanta Meher, Satyajit Rath, Rakesh Sharma, Jayanta Kumar Biswal, Chandan Kumar Ray Mohapatra. "Incidence and Clinical Course of Incidental Prostatic Adenocarcinoma: A Prospective Indian Study". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 42, October 19, 2015; Page: 7230-7240, DOI: 10.18410/jebmh/2015/981

ABSTRACT: BACKGROUND: Incidental Prostatic adenocarcinoma (IPC or Prostatic Incidentalomas) are early stage cancers which are clinically silent and are incidentally diagnosed at histopathological study of operated specimens of benign prostatic disease or screen-detected in asymptomatic individuals. This study investigates the incidence of IPC in operated specimens of patients with benign prostatic hyperplasia and their clinical behaviour. **MATERIALS AND METHODS:** Operated specimens (both Open Prostatectomy and Transurethral Resection of Prostate [TURP] of all patients with benign prostatic hyperplasia treated in VSS medical college between 2010-2015, were studied prospectively for evidence of IPC on histopathology and the cases were followed up to a period of five years. **RESULTS:** The incidence of IPC came out to be 6% (12 out of 200 cases). Eight cases (66.67%) were found in the 8th decade. The average IPSS (International Prostate Symptom Score) score of cases with IPC was 18, compared to 13.76 in cases with BPH. All the cases with IPC had a serum PSA (Prostate Specific Antigen) value more than 10ng/ml while, only 10.6% (20 out of 198) of cases with BPH had values more than 10ng/ml. Average weight of the enucleated specimens in cases of IPC was 37gm whereas that of cases with BPH was 44.58gm. Again, the average weight of TURP specimens in cases of IPC was 35 gm whereas that of cases with BPH was 27.88gm. In none of the cases of IPC there was any evidence of local recurrence or metastases during this follow up either clinically or radiologically or by other laboratory investigations. **CONCLUSION:** A majority of these patients with incidentally diagnosed disease having carcinomatous focus in the enucleated prostate, do not exhibit disease progression and therefore these patients do not necessarily require any specific therapy other than a "wait and watch" policy.

KEYWORDS: Benign Prostatic Hyperplasia; Incidental Prostatic Adenocarcinoma; Lower Urinary Tract Symptoms, Prostate Specific Antigen, International Prostate Symptoms Score, Trans Urethral Resection of Prostate.

INTRODUCTION: Carcinoma of prostate is the third most common malignancy among males worldwide.⁽¹⁾ The incidence of prostate carcinoma has increased in most industrial countries, with a decreasing trend in overall mortality.⁽²⁾ This is probably because of increased use of screening methods used for early detection of cancer and improvement in health care.⁽²⁾ Incidental prostatic adenocarcinoma (IPC) is a form of early stage cancer not detected on clinical examination whereas latent prostatic carcinoma is a form of early stage cancer which don't show any symptoms and are incidentally detected in autopsy specimens.⁽³⁾ About 15-20% of prostatectomies done for BPH

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reveals incidental carcinoma of prostate. Studies have shown a relatively lower incidence of incidental prostatic adenocarcinoma among Asian countries.⁽²⁾ In an Indian study done by Desai et al in 2002, the incidence of latent carcinoma was found in only 6.8% of Indian men.⁽⁴⁾

According to Jewett-Whitmore American clinical staging system IPC is represented as stage A. A1 being focal and involving less than 5% of the specimen and A2 being diffuse and involving more than 5% of the specimen. The TNM counter staging being T1a and T1b. Stage 1c being screen detected in asymptomatic individuals because of raised PSA.⁽³⁾ Though age specific prevalence of benign prostatic hyperplasia (BPH) is similar to IPC but BPH presents at an earlier age and there is no statistical cross-correlation between them.⁽⁵⁾ The cancer originating in the prostate proper has no relation with the adenoma as it invades the adenomatous areas afterwards. BPH arises in the inner periurethral groups of glands whereas the outer zone of peripheral glands are the primary sites for origin of cancer and in this zone BPH is very much uncommon.⁽⁶⁾ Most of the IPC originate in the peripheral zone where cancer predominates.⁽⁵⁾

Prostatic Intraepithelial Neoplasia (PIN) are architecturally benign prostatic acini or ducts lined by cytologically atypical cells and classified as low-grade or high-grade neoplasias.⁽⁷⁾ Patients with low-grade PIN at needle biopsy are at no greater risk of having invasive carcinoma on repeated biopsy than men with benign biopsy findings.⁽⁸⁾ On the contrary, high-grade PIN is a precursor to many peripheral intermediate to high-grade invasive adenocarcinoma.

Recent studies after 2000, on incidence and clinical behaviour of incidentally detected carcinoma of prostate are very few. Whatever studies has been done almost all are from western countries. Literature regarding the incidence and clinical behaviour of IPC from India are scanty. The purpose of this study was to find out the incidence of IPC among Indian males with BPH and to study their clinical behaviour over time.

MATERIALS AND METHODS: This was a prospective observational study done in a tertiary care hospital placed in a remote area of eastern India. Ethical clearance was taken from the institutional review board before the commencement of this study.

Study Population: The study comprised of all cases of clinically diagnosed BPH with age above 50 years; admitted to the department of General Surgery and department of Urology, V.S.S Medical College and Hospital, Burla, Sambalpur, Odisha during the years 2010-2015. All patients were subjected to thorough clinical examination, routine and special investigations and were provisionally diagnosed as cases of senile enlargement of prostate.

Sample Removal and Processing: The specimens obtained after TURP or enucleated during open prostatectomy were studied for gross pathological anatomy and dispatched for histopathological assessment.

Histopathological Assessment: The operated specimens were sent for histopathological examination to the Pathology department of this institution where the specimens were cut into 120-200 serial sections. Every fifth section was stained by haematoxylin and eosin stain and examined thoroughly. Slides with evidences of malignancy were staged as per TNM staging and graded as per Gleason's grading systems.

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Clinico pathological Correlation and Follow-up: Detailed operative findings of the prostate, bladder and if any difficulty during enucleation were noted followed by a correlation of pathology with intraoperative findings. All the patients in this series were followed up till their convalescence in the hospital and after discharge till five years of post-operative period. Patients were discharged with advice to attend regular post-operative check-up once every month for 3 months and once every 3 months subsequently.

Statistics: Descriptive statistical analysis was done using SPSS software version 16, and the values were noted as percentage and average with standard deviation.

OBSERVATION AND RESULTS: After through clinical evaluation and investigation 200 patients, provisionally diagnosed as having BPH underwent surgery. Out of 200 cases, transurethral resection of prostate (TURP) was done in 72 patients (36%) whereas Enucleation was done in 128 patients (64%). The mean age of the patients included in the study was 67.3 years (52-86 years) with a standard deviation (SD) of 7.59 years. Table 1 illustrates the various parameters of the patients evaluated in the pre-operative and peri-operative period.

IPSS Score: International Prostate Symptoms Score; PSA: Prostate Specific Antigen; PVRU: Post Void Residual Urine; TURP: Transurethral Resection of Prostate; BHP: Benign Prostatic Hyperplasia; IPC: Incidental Prostatic Adenocarcinoma.

Out of the 200 operated prostatic specimens, histopathological study revealed 172 (86%) cases of Predominant Adenomatous Hyperplasia suggesting benign pathology. Four cases had Adenomatous Hyperplasia with Inflammatory changes suggesting Prostatitis. Adenomatous Hyperplasia with Atypia in a single gland was found in 4 cases. Adenomatous Hyperplasia with Prostatic Intraepithelial Neoplasia was found in 8 (4%) cases. Invasive Adenocarcinoma (Incidental Prostatic Adenocarcinoma; IPC) was observed in 12 (6%) cases [Table 2].

Four slides with PIN were of low-grade, and the others were of high grade (with prominent nucleoli) [Figure 1]. Gleason score and TNM staging of the eight cases of IPC were 7 (3+4) and stage T1b with occasional ill-defined and fused glandular units. The other cases of IPC had a score of 6(3+3) and stage T1a with uniformly discrete glandular units with marked variation in shape and size [Figure 2].

Eight (66.7%) cases of IPC presented in the 8th decade and four (33.3%) in the 7th decade whereas the prevalence of BPH in the 8th decade was 8 out of 188 cases (4.2%), and in the 7th decade was 60 out of 188 cases (31.9%) [Figure 3]. Mean age of BPH in 188 cases was 64.42 years while that of the patients with IPC was 81 years.

Average IPSS score of patients with BPH was 13.76 whereas that of patients with IPC came out to be 18. Both BHP group and IPC group had moderate IPSS score (8-19) [Table 3]. Besides, other less common symptoms like dysuria, hematuria, dribbling and hesitancy were more common in cases of IPC compared to cases of BPH.

Only 10.6% (20 out of 188) of patients of BPH had a serum PSA level greater than 10ng/dl, whereas 100% of patients with IPC had values greater than 10 [Figure 4].

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Out of the 12 specimens of IPC four were obtained by Suprapubic Prostatectomy (SPP) by enucleation and the other 8 were TURP specimens. The average weight of all the enucleated specimens of BPH came out to be 44.58gm while that of the enucleated IPC specimen was 37gm. Average weight of the specimens of BPH obtained by TURP was 27.88gm, whereas the average weight of the specimens of IPC obtained by TURP came out to be 35gm [Figure 5]. In all cases of enucleated IPC specimens the median lobe and both the lateral lobes were enlarged. Whereas the median lobe and both the lateral lobes were enlarged in 72 out of 124 enucleated specimens of BPH (58.1%). The consistency of enucleated specimens of both IPC and BPH were firm in all cases. The enucleated IPC didn't have any nodularity, nor showed any inflammatory changes but there was some difficulty during the maneuver of enucleation.

During operation all the cases had moderate amount of blood loss except in 16 cases, eight cases each of SPP and TURP. In cases of SPP they were controlled by two figure-of-eight sutures at the prostatovesical junction in 5 and 7 o'clock positions. In cases of TURP they were controlled by electrocoagulation. All cases were maintained on traction by an overinflated perurethral Foley's catheter to prevent reactionary hemorrhage post-operatively. Cases with excessive bleeding required blood transfusion intra operative as well as post-operative period. Enucleation difficulty was encountered in three cases of BPH with IPC and BPH with PIN due to adhesions in the plane of cleavage. Two cases of BPH undergoing TURP had intra-operative urine extravasation which was managed by urethral catheterization and cessation of the operative procedure.

All the patients in this series were followed up till their convalescence in the hospital and after discharge up to five years of post-operative period. Few patients did not turn up at all. 1 case died in the hospital during the post-operative period (due to cardiovascular complications) and 2 other cases died subsequently after being discharged from the hospital. Few patients were lost in follow up as they did not respond and belonged to floating population.

Cases of incidentally detected adenocarcinoma were specifically followed up to detect any local recurrence of malignancy or any evidence of local or distant metastases. The patients were followed up with repeated clinical (Digital Rectal Examination), radiological (X-Rays and ultrasonography) and laboratory assessments (serial serum PSA assays) for evidences of progression of malignancy. In none of the cases irrespective of benign hyperplasia or incidental prostatic adenocarcinoma, any evidence of local or distant metastatic lesions of malignancy was observed either clinically or radiologically or by other investigations during this short span of follow up.

DISCUSSION: Prostate carcinoma can be considered as a combination of the different subtypes:

1) Clinically apparent carcinoma of prostate; in which clinical symptoms are apparent on examination, 2) Occult carcinoma of prostate; in which the disease do not manifests locally but patients have evidence of metastatic symptoms from carcinoma of prostate, 3) Incidental prostatic adenocarcinoma; in this subtype invasive carcinoma is detected on prostate biopsy specimen either following operative procedure or by screening methods, 4) Latent carcinoma of prostate; are carcinoma detected in autopsy specimen, this subgroup of patients do not show any evidence of symptoms during their life time.⁽³⁾ The incidence of prostate cancer varies significantly among various geographical distributions. Asian countries especially China shows are very low incidence

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of carcinoma of prostate including India.⁽²⁾⁽⁴⁾ The probable reason for this lower incidence are under reporting, unavailability of a central cancer registry and the presence of latent carcinoma of prostate or incidental prostatic adenocarcinoma which goes unnoticed due to their lack of their symptoms. The incidence of latent carcinoma of prostate is almost similar or slightly higher than that of incidental prostatic adenocarcinoma.

Studies have shown that incidence of latent carcinoma of prostate or IPC are higher in Western countries as compared to Asian countries. In our series 12 cases of IPC were detected out of 200 cases (6%). E. Hradec et al found 7.7% in their series of 891 cases.⁽⁹⁾ In 1993 Chancellor et al recorded an incidence of 34.2% (11 in their case series of 311 patients)⁽¹⁰⁾ [Table 4]. Recently Mosli et al found an incidence of 7.2% (15 out of 207 cases).⁽³⁾ Study from India has shown an incidence of 6.8% of incidentally detected carcinoma of prostate.⁽⁴⁾ Our study has shown a similar incidence of IPC with that of the Indian study. Table 5 and Table 6 illustrate the incidence of IPC or LPC among various Western countries and Asian countries.

According to E. Hradec, L. Jarolim and K. Motlik et al a statistically significant prevalence of carcinoma, in the medium sized prostates (30-40gms = 12.4%) as compared to smaller and longer prostates.⁽⁹⁾ Mosli et al found out the average weight of maximum incidence to be 35.4gm but their median weight was 29gm.⁽³⁾

Eight cases of IPC presented in the 8th decade (66.7%) and four in the 7th decade (33.3%) whereas the prevalence of BPH in the 8th decade was 8 out of 188 cases (4.2%), and in the 7th decade were 60 out of 188 cases (31.9%) [Table 7]. According to Hradec et al the maximum incidence of IPC was found in the age group 70-80 years and the next commonly found age group was 60-70 years, while Mosli et al recorded a maximum incidence in the 6th decade (53.3%)^(3,9). The observations in this series don't tally with the observations of other studies with respect to age incidence.

The average weight of all the enucleated specimens (both SPP and RPP) of BPH came out to be 44.58gm while that of the enucleated IPC specimen was 37gm [Figure 5]. According to Hradec et al a statistically significant prevalence of carcinoma was found in the medium sized prostates (30-40gms) well compared to smaller and larger prostates.⁽⁹⁾ Mosli et al found out the average weight of maximum incidence to be 35.4g but their median weight was 29g. Value in this study almost corresponds to the above studies.⁽³⁾

During a follow up period of up to five years no clinical, laboratory or radiological evidence of local recurrence or metastasis was found. Our present study, although has limitation of having a small sample size and short duration of follow up, but the results corresponds to the findings of other studies. This gives a conclusion that latent carcinoma after resection or enucleation is potentially not a danger to life, as the probability of recurrence or metastasis is not at all a frequent feature.

CONCLUSION: A majority of these patients with incidentally diagnosed disease having carcinomatous focus in the enucleated prostate, do not exhibit disease progression and therefore these patients do not necessarily require any specific therapy other than a "wait and watch" policy. Unfortunately in a small proportion of cases the disease will progress but at present there is no way of detecting who they will be. As such these patients must be followed up at regular intervals

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with clinical, radiological and by other biochemical investigations for early detection of the features of progression of malignancy, and prompt institution of intervention, either medical or surgical whenever implied.

Authors' Contribution: Dr. Bikram, Dr. Susanta, Dr. Chandan and Dr. Jayanta planned the study design. Dr. Satyajit, Dr. Rakesh and Dr. Susanta collected the data. Dr. Bikram and Dr. Susanta prepared the manuscript. Dr. Jayanta critically revised the final manuscript. Dr. Bikram gave the statistical advice.

REFERENCES:

1. Hosseini SY, Danesh a. K, Parvin M, Basiri a., Javadzadeh T, Safarinejad MR, et al. Incidental prostatic adenocarcinoma in patients with PSA less than 4 ng/mL undergoing radical cystoprostatectomy for bladder cancer in Iranian men. *Int Braz J Urol*. 2007; 33(2): 167–78.
2. Zare-Mirzaie A, Balvayeh P, Imamhadi MA, Lotfi M. The frequency of latent prostate carcinoma in autopsies of over 50years old males, the Iranian experience. *Med J Islam Repub Iran*. 2012; 26(2): 73–7.
3. Mosli H a M. Incidental adenocarcinoma of the prostate: Frequency rate at a tertiary care hospital. *Ann Saudi Med*. 1997; 17(6): 662–4.
4. Desai SB, Borges AM. The prevalence of high-grade prostatic intraepithelial neoplasia in surgical resection specimens: An Indian experience. *Cancer*. 2002; 94(9): 2350–2.
5. Stamatiou K, Alevizos A, Natzar M, Mihos C, Mariolis A, Michalodimitrakakis E, et al. Associations among benign prostate hypertrophy, atypical adenomatous hyperplasia and latent carcinoma of the prostate. *Asian J Androl*. 2007; 9(2): 229–33.
6. Franks LM. Latent carcinoma of the prostate. *J Pathol Bacteriol* 1954; 68(2): 603–16.
7. Tarle M, Kraljic I. Free and total serum PSA values in patients with prostatic intraepithelial neoplasia (PIN), prostate cancer and BPH. Is F/T PSA a potential probe for dormant and manifest cancer? *Anticancer Res* 1997; 17(3A): 1531–4.
8. Arista-Nasr J, Gómez-Ramírez AM, Gonzáles-Romo M a., Maldonado-Martínez H a., Martínez-Benítez B, Lara C, et al. Frequency of high-grade prostatic intraepithelial neoplasia in Mexican population. *Rev Investig Clin*. 2007; 59(4): 234–8.
9. Hradec E, Jarolim L, Motlik K. Carcinoma of the prostate in specimens removed for benign hyperplasia. *Scand J Urol Nephrol Suppl* 1980; 55: 193–6.
10. Chancellor MB, VanAppledorn CA. Value of transrectal prostate ultrasonography pre-transurethral prostatectomy in screening for occult prostate carcinoma. *Urology* 1993 Jun; 41(6): 590–3.
11. Edwards CN, Steinthorsson E, nicholson D. An autopsy study of latent prostatic cancer. *Cancer* 1953; 6(3): 531–54.
12. Yatani R, Shiraishi T, Nakakuki K, Kusano I, Takanari H, Hayashi T, et al. Trends in frequency of latent prostate carcinoma in Japan from 1965-1979 to 1982-1986. *J Natl Cancer Inst* 1988 Jul; 80(9): 683–7.
13. Lee S-H, Chang P-L, Chen S-M, Sun G-H, Chen C-L, Shen B-Y, et al. Synchronous primary carcinomas of the bladder and prostate. *Asian J Androl* 2006; 8(3): 357–9.

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14. Labess M. Occult carcinoma in clinically benign hypertrophy of the prostate; a pathological and clinical study. J Urol 1952 Dec; 68(6): 893–6.

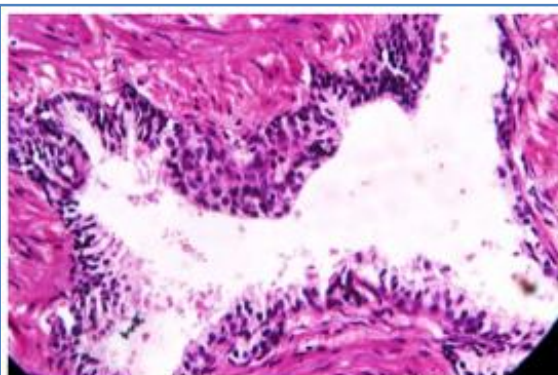


Fig. 1: Histopathological slide showing High Grade Prostatic Intraepithelial Neoplasia (HGPIN)

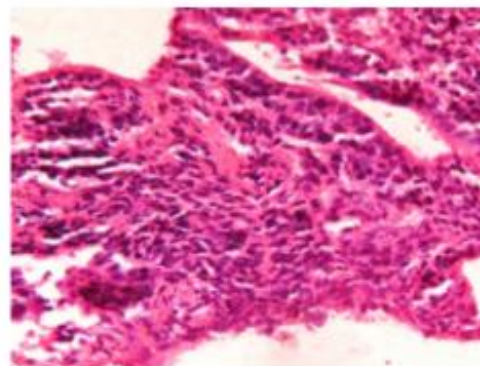


Fig. 2: Histopathological slide of incidental Carcinoma Prostate showing distorted glands and stromal invasion

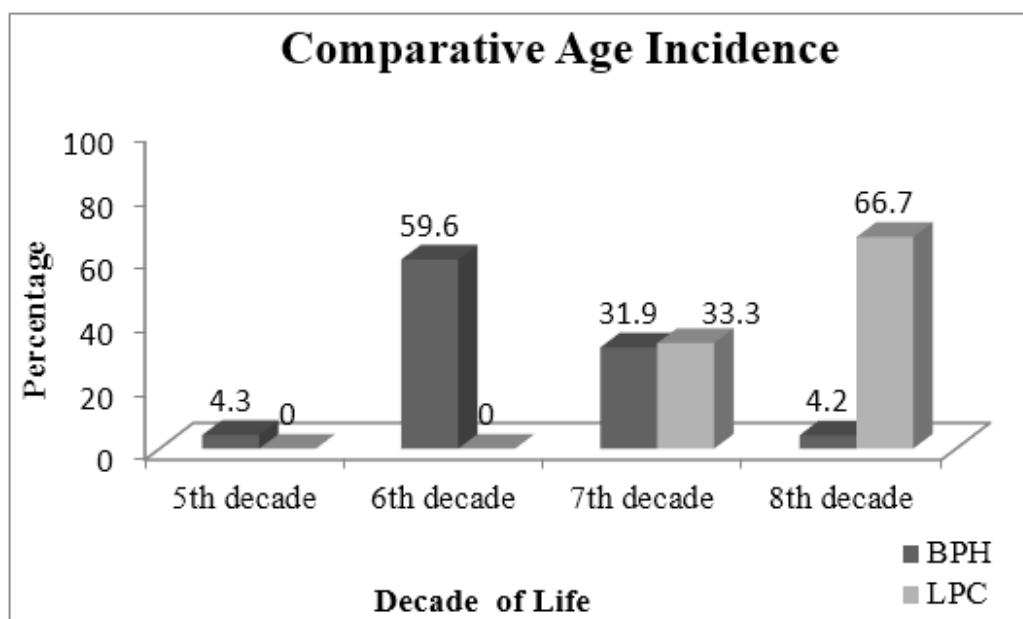


Fig. 3: Comparative Age Incidence of IPC and BPH

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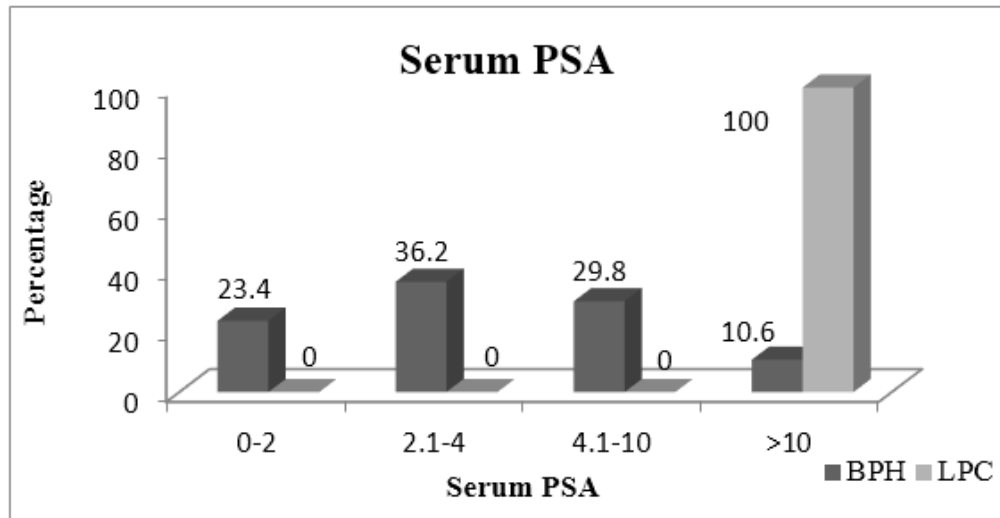


Fig. 4: Comparative Serum PSA levels between BPH and IPC patients

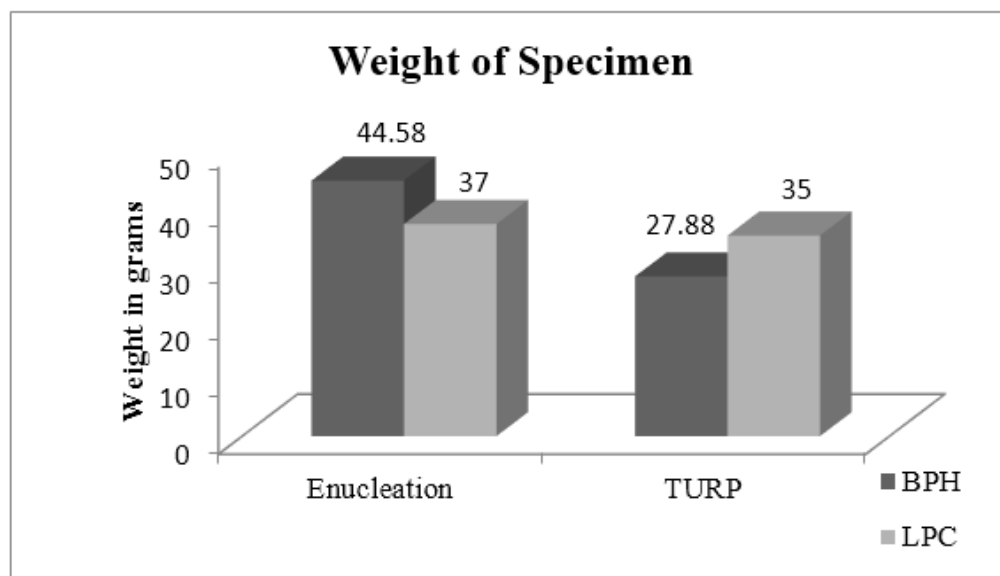


Fig. 5: Weight of prostatectomy specimens

Parameters	Average (Standard Deviation)	Range
Age (in years)	67.3 (7.59)	52-86
IPSS Score	14.02 (2.98)	9-21
Serum PSA (in ng/ml)	6.95 (13.82)	1-98.2
Prostate Volume (in ml)	49.54 (12.52)	35-85
PVRU (in ml)	60.44 (18.3)	30-100
Weight of Prostate (in gms)	38.7 (10.73)	20-58

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	Number	Percentage
Clinical Grading of Prostate		
Grade I	4	2%
Grade II	104	52%
Grade III	76	38%
Grade IV	16	8%
Operative Procedure		
TURP	72	36%
Enucleation	128	64%
Average Post-Operative Stay		
BHP	15days	
IPC	16days	

Table 1: Patients Characteristics

IPSS Score: International Prostate Symptoms Score; **PSA:** Prostate Specific Antigen; **PVRU:** Post Void Residual Urine; **TURP:** Transurethral Resection of Prostate; **BHP:** Benign Prostatic Hyperplasia; **IPC:** Incidental Prostatic Adenocarcinoma.

Histopathological Finding	No. of cases	%
Predominant Adenomatous Hyperplasia	172	86
Adenomatous Hyperplasia with Inflammatory changes	04	02
Adenomatous Hyperplasia with Atypia	04	02
Adenomatous Hyperplasia with PIN	08	04
Invasive Adenocarcinoma (IPC)	12	06

Table 2: Histopathological Findings

IPSS Score	No. of BPH cases	%	No. of IPC cases	%
0-7	0	0	0	0
8-19	176	93.6	08	66.7
20-35	12	6.4	04	33.3
	Total cases= 188		Total cases = 12	

Table 3: Comparison of IPSS score among BPH and IPC patients

Author	No. of BPH cases	No. of IPC cases	%
Hradec et al ⁽⁹⁾ (1980)	891	69	7.7
Chancellor et al ⁽¹⁰⁾ (1993)	311	11	34.2
Mosli ⁽³⁾ (1997)	207	15	7.2
Present study	200	12	6

Table 4: Incidence of Latent Carcinoma in BPH according to different studies

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Country	Number of cases	% frequency	LPC or IPC	Author
Canada	173	16.7	LPC	Edward et al, 1953 ⁽¹¹⁾
England	-	33.6	LPC	Franks, 1954 ⁽⁶⁾
Saudi Arabia	207	7.2	IPC	Mosli, 1997 ⁽³⁾
Greece	212	18.8	LPC	Stamatiou, 2007 ⁽⁵⁾
Iran	149	9.4	LPC	Mirziae et al, 2012 ⁽²⁾

Table 5: Frequency of LPC or IPC in men over 50 years

Nation	Author	Procedure	Total number of cases	Mean age	Number of cases of LPC (%)
India	Desai et al ⁽⁴⁾	Cystoprostatectomy	44	54.7	3(6.8)
Japan	Yatani et al ⁽¹²⁾	Autopsy	576	NA	119(20.5)
Iran	Hosseini et al ⁽¹⁾	Cystoprostatectomy	50	62.5	7(14)
China	Lee et al ⁽¹³⁾	Cystoprostatectomy	248	63	10(4)
India	Present study	TURP or Open	200	67.4	12(6)

Table 6 Comparison of latent prostate carcinoma in different Asian countries

NA: Not Available.

Authors	50-60 years	60-70 years	70-80 years	80-90 years	90-100 years
Labess ⁽¹⁴⁾	-	-	44.5	33.3	22.2
Hradec ⁽⁹⁾	4.9	36.1	50.8	8.2	-
Mosli ⁽³⁾	20	53.3	20	6.7	-

Table 7: Age specific incidence of IPC in BPH according to different studies

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Date of Submission: 09/10/2015.
Date of Peer Review: 10/10/2015.
Date of Acceptance: 12/10/2015.
Date of Publishing: 13/10/2015.