Clinical Significance of Incidental Prostatic Carcinoma on Radical Cystectomy Histology Specimens: a Clinicopathological and Survival Analysis

Dharma Ram¹ · Suhas K. Rajappa¹ · Sudhir Rawal² · Amitabh Singh² · Kailash Chand Sharma¹ · Ajay Kumar Dewan¹

Received: 27 July 2017 / Accepted: 10 April 2018 / Published online: 21 April 2018
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Abstract

Incidental prostatic carcinoma on radical cystectomy histology specimens is not an uncommon entity and managing such cases is still controversial. Classification into clinically significant and insignificant cancers by Epstein based on the assumption that one is more likely to affect the survival than the other is not universally accepted. We conducted this retrospective analysis with the aim to find out the role of dichotomization of incidental prostatic cancer into such classification. Patient's data were retrospectively reviewed from January 2013 to December 2014. A total of 175 patients underwent radical cystectomy during the study duration and amongst them, 38 specimens showed incidental prostatic cancer. Their data pertaining to demographic profile, clinicopathological details, treatment received, complications and follow-up data was recorded. On comparative analysis, the disease-free survival in csPCa (clinically significant prostatic cancer) group was 60.82% and cisPCa (clinically insignificant prostatic cancer) 62.68% at 2.3 years (p 0.566), while OS was 55.68% for csPCa and 87.5% for cisPCa respectively (p 0.814). The mean duration to recurrence was also comparable (19.4 months csPCa and 17 months cisPCa). None of the patients developed PSA elevation on follow-up and none of the recurrence or death were attributed to prostatic cancer. The stage of bladder cancer was the only factor, which had a significant impact on overall survival. The distinction between clinically significant and insignificant is not relevant according to our analysis.

Keywords Incidental · Carcinoma prostate · Carcinoma bladder · Clinically significant · Epstein criteria

Introduction

Prostate cancer (PCa) is the second most common cancer in men and the fifth leading cause of cancer-related death in men (6.6% of the total men deaths) and the incidence of PCa is rising in India and projection data shows that the number of cases will be doubled by 2020 [1]. Incidental prostatic

cancer (IPCa) is defined as one diagnosed by clinical examination, investigation, surgical intervention like TURP (transurethral resection of the prostate)/radical cystectomy or autopsy [2]. One distinct subset of these incidental cases includes post-radical cystectomy for bladder cancer which has a very limited literature available and there are no specific recommendations for managing these cases. The growing acceptance of total prostate sparing or prostatic apex sparing radical cystectomies has made this question relevant again. To the best of our knowledge, this is the first series from India analyzing this largely unexplored problem. We are presenting our experience of these cases with clinicopathological and survival attributes and comparing the oncological impact of clinically significant and insignificant PCa with the goal to find out whether the term clinically significant or insignificant has any prognostic value in this subset of incidental prostate cases.

✉ Dharma Ram
drdharmapoonia@gmail.com

¹ Department of Surgical Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi 110085, India

² Department of Uro-Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi 110085, India

Method and Materials

The present study was conducted at Rajiv Gandhi Cancer Institute, New Delhi, India, from January 2013 to December 2014. A total of 175 patients underwent radical cystectomy during the study duration and amongst them, 38 specimens showed incidental prostatic cancer. We excluded the patients where complete data was not available, patients with diagnosed prostate cancer and who underwent radical cystectomy for a nonmalignant cause. We analyzed the records of these cases pertaining to their clinical profile, bladder cancer characteristics, prostate cancer characteristics, and follow-up details.

As per institutional protocol, the prostate specimens were serially sectioned at 5-mm intervals perpendicular to the long axis. The cut specimens were fixed for an additional 24 h and then dehydrated in graded alcohols, cleared in xylene, embedded in paraffin, and examined histologically as 5- μ m-thick, whole-mount, hematoxylin and eosin-stained sections. In a case of low-volume disease and diagnostic dilemma, immunohistochemical (IHC) analysis with AMACR was done to confirm the final diagnosis. In the case of node positivity, confirmation of primary pathology was done using IHC.

Pathological details like histology, tumor volume, tumor location, T stage, perineural invasion (PNI), lymphovascular invasion (LVSI), extra prostatic extension, seminal vesicle extension, and margin status were noted. Patients were classified into clinically significant and insignificant based on Epstein criteria which include total tumor volume, 0.5 cm³ or more; Gleason grade, 6 or more; extraprostatic extension; seminal vesicle invasion; lymph node metastasis (of PCa); or involved margins [3]. All the relevant details were recorded on a spreadsheet and analyzed using SPSS version 24.

We analyzed disease-free survival and overall survival and compared oncological outcomes of clinically significant and insignificant PCa. Univariate Cox regression analysis was done to find out the impact of relevant variables for both the groups and hazard ratio was calculated to see the difference in disease-free survival (DFS) and overall survival (OS). A biochemical recurrence was defined as “two serial elevations of serum prostate specific antigen (PSA) of > 0.2 ng/ml” (PSA-free survival). In a case of disease recurrence, it was ensured to find out the origin whether it was from bladder or prostate cancer by using fine-needle aspiration or biopsy.

Results

Patient Characteristics

A total 38 patients were found suitable for analysis, which makes 21.7% of total radical cystectomy specimens during the study duration. The majority of bladder cancer patients

were stage 2–3 (81.6%) and histopathology was acinar adenocarcinoma in all the patients. Preoperative PSA value was not available for any patient. The most frequent Gleason score was 3 + 3 contributing to more than 60% of the patients, while 4 + 5 and 5 + 4 were found in one patient each. Tumor localized to peripheral zone was seen in 94.7% of the patients and more than 70% patients had 0.5cm³ or less tumor volume. The most frequent stage was T2a which was found in 44.7% of the specimens. All specimens were pN0 for PCa, while PNI and LVI were seen in 23.7 and 13.2% specimens respectively. Patient characteristics with their distribution in clinically significant prostatic cancer (csPCa) and clinically insignificant prostatic cancer (cisPCa) groups are depicted in Table 1.

Comparative Analysis csPCa and cisPCa

csPCa was found in 22 (57.9%) of the patients with incidental ca prostate, and the rest were cisPCa by using Epstein criteria. The mean age of presentation was 65 years (43–88). As depicted in Table 1, patient and bladder cancer characteristics were comparable in both the groups.

Follow-up

The median duration of follow-up was 19 months (range 11–28 months). At last follow-up, five patients had succumbed to the disease and other seven were alive with disease. The DFS and OS were 65.39 and 65.64% respectively (Table 2). On comparative analysis, the disease-free survival in csPCa group was 60.82% and cisPCa 62.68% at 2.3 years (p 0.566), while OS was 55.68% for csPCa and 87.5% for cisPCa respectively (p 0.814). The mean duration to recurrence was also comparable (19.4 months csPCa and 17 months cisPCa). None of the patients developed PSA elevation on follow-up and none of the recurrence or death were attributed to prostatic cancer.

We further evaluated survival using Cox univariate regression analysis in relation to variables including age, comorbidities, smoking, American Society of Anesthesiologists (ASA) score, neoadjuvant chemotherapy, bladder cancer stage, perineural invasion, and prostate cancer stage and these details are depicted in Table 3. The stage of bladder cancer was the only factor, which had a significant impact on overall survival while none of the factors studied had any effect either on OS or DFS (Figs. 1 and 2).

Discussion

Prostate cancer has a relatively less prevalence in the Indian subcontinent, but its incidence is on the rise [1, 4, 5]. Bladder cancer has an age-adjusted incidence rate of 0.6–6.8 per 100,000 population with the highest incidence rate in New Delhi and has an age-adjusted incidence rate of 7.4

Table 1 Clinicopathological characteristics of the patient with incidental prostatic cancer on radical cystectomy specimens. ASA (American Society of Anesthesiologists score), EP (extra prostatic) extension, HGPIN (high-grade prostate intraepithelial neoplasia), LVI (lymphovascular invasion), PNI (perineural invasion), PC (prostate cancer), SV (seminal vesicle), UC (urothelial carcinoma)

Factor	Clinically significant cases PC (csPCa)	Clinically insignificant cases PC (cisPCa)	<i>p</i> value	All cases
Bladder cancer findings and their distribution				
Subjects	22 (57.9%)	16 (42.1%)	–	38
Median age in years (mean ± SD)	64.5 (65.75 ± 10.01)	65 (64.54 ± 10.96)	0.731	65 (65.05 ± 10.45)
Smokers	10	14	0.452	24
Associated comorbidities	14	08	0.917	22
Median ASA (mean ± SD)	2 (2.41 ± 0.67)	2 (2.25 ± 0.58)	0.388	2 (2.34 ± 0.63)
NACT received	5	4	0.729	9
Stage 1 UC	2	3	0.380	5
Stage 2 UC	12	06	–	18
Stage 3 UC	8	5	–	13
Stage 4 UC	1	1	–	2
Incidental prostate cancer findings				
Gleason score				
3 + 3	–	–	–	24 (63.1%)
3 + 4	–	–	–	8 (21.1%)
4 + 3	–	–	–	4 (10.6%)
4 + 5	–	–	–	1 (2.6%)
5 + 4	–	–	–	1 (2.6%)
Tumor location				
Peripheral zone	–	–	–	36 (94.7%)
Transition zone	–	–	–	2 (5.3%)
Tumor volume				
0.5 cm ³ or less	–	–	–	27 (71.1%)
More than 0.5 cm ³	–	–	–	11 (28.9%)
Tumor laterality				
Unilateral	–	–	–	25 (65.8%)
Bilateral	–	–	–	13 (34.2%)
TNM Staging				
T2a	–	–	–	17 (44.7%)
T2b	–	–	–	6 (15.8%)
T2c	–	–	–	10 (26.3%)
T3a (EP extension)	–	–	–	3 (7.9%)
T3b (SV invasion)	–	–	–	2 (5.3%)
Nodal positivity	–	–	–	0
Other findings				
PNI + ve	6	3	0.450	9 (23.7%)
LVI + ve	3	2	0.124	5 (13.2%)
Pathological margin + ve	–	–	–	3 (7.9%)
HGPIN	2	1	0.235	3 (7.9%)

per 1,00,000 [6]. With an increased utilization of the radical cystectomy, the incidence of incidental prostate cancer on histological evaluation of the RC specimen has become a problem and their clinical relevance is sparingly described in the literature. The dichotomization into clinically significant and insignificant cancers was done by Epstein based

on the assumption that one is more likely to affect the survival than the other and is based on tumor volume, Gleason grade, extension, lymph node metastasis (of PCa), and margin status [3, 7].

Patients with bladder cancer are more likely to harbor prostatic cancer and incidence has been reported to be as many as

Table 2 Survival characteristics of the patients in both groups (csPCa and cisPCa)

Factor	Clinically significant cases	Clinically insignificant	P value	All cases
Status at median follow-up 19 months (11–28)				
Disease free	10	16		26
Alive with disease	3	4		7
Dead	2	3		5
Patients with PSA rise	0	0	—	0
Disease-free survival				
Mean duration to recurrence (range)	19.4 months (11–23)	17 months (11–24)		
DFS at 2.3 years	60.82%	62.68%	0.566	65.39%
OS at 2.3 years	55.68%	87.5%	0.814	65.64%

nine times compared to the general population and recent molecular genetic studies have shown a common stem cell origin of bladder and prostate cancer [8]. Few studies have shown a common pathway of pathogenesis using p53 and retinoblastoma (Rb) gene alteration but its clinical significance is yet to be seen [7, 9].

The incidence rate of PCa on radical cystectomy in the literature varies from 4 to 60% of the radical cystectomy specimens and this is closely linked with specimen mounting-sectioning technique and geographical distribution of prostate cancer. The specimen sectioning method is not uniformly defined and different centers use different methods [2, 10].

Studies using thinner serial sections (2–3 mm) have shown somewhat a higher incidence rate of PCa (10–60%), while the whole specimen mounting with 5-mm sectioning have reported 4–27% of incidental prostate cancer on radical cystectomy specimens [2, 11, 12]. Our analysis using 5-mm sectioning of the whole specimen from apex to base identified 21.7% of the specimen having PCa.

High-grade prostatic intraepithelial neoplasia (HGPIN) has been described as the harbinger of prostatic cancer and the prevalence of HGPIN in a radical cystoprostatectomy specimen is significantly lower in the Asian population (0–37.3%) when compared to Western studies (75–99%) [13]. The

Table 3 survival characteristics analysis using Cox regression univariate method showing hazard ratio (HR) and *p* value in both the study groups

Disease-free survival (DFS)						
	csPCa		cisPCa		All	
	HR	<i>p</i> value	HR	<i>p</i> value	HR	<i>p</i> value
Age	30.5 (0.6–1.5)	0.433			24.5(0.7–8.7)	0.444
Comorbidities	1.9 (0.3–11.1)	0.431	0.54 (0.8–3.3)	0.511	1.16 (0.3–3.6)	0.857
Smoking	1.02 (0.1–5.7)	0.975	0.42 (7–2.5)	0.422	0.60 (0.1–2.0)	0.413
ASA	1.64 (0.2–5.9)	0.587	0.03 (0.0–19.0)	0.623	1.01(0.21–4.7)	0.983
NACT	0.29 (0–48)	0.349	0.63 (0.6–5.8)	0.692	0.2 (.2–1.7)	0.148
UC stage	1.12 (.1–10.1)	0.919	14.4 (0.9–23.0)	0.059	2.0 (0.2–15)	0.508
UC PNI	0.9 (0.1–7.7)	0.929	0.60 (0.6–5.5)	0.659	0.8 (0.1–3.8)	0.807
PCa stage	0.63 (0.6–5.8)	0.511		0.341	1.02 (0.1–5.7)	0.646
Overall survival (OS)						
Age	71 (0.02–332)	0.436			27.6 (0.0–250)	0.569
	1.1 (0.7–19.0)	0.909	0.10 (0.0–120.0)	0.443	0.2 (0.3–2.5)	0.258
Comorbidities						
Smoking	0.6 (0.4–11.4)	0.791	0.72 (0.4–11.5)	0.817	0.39 (0.6–2.3)	0.316
ASA	0.27 (0.0–6.2)	0.830	0.036 (0.0–7.5)	0.802	0.031 (0–17.0)	0.535
NACT	2.5 (0.15–40.0)	0.512	3.4 (0.2–55.7)	0.381	1.9 (0.3–11.9)	0.469
UC stage	12.4 (0.6–21.0)	0.089	14.49 (0.90–231.7)	0.059	16.3 (2.2–116.0)	0.005
UC PNI	6.1 (0.5–69.0)	0.144	0.02 (0.0–66.4)	0.568	2.5 (0.2–16.4)	0.285
PCa stage	1.16 (0.3–3.6)	0.814	0.6 (0.4–11.4)	0.257	0.29 (0–48)	0.245

Fig. 1 KM survival curve depiction of disease-free survival. *CIS* clinically insignificant, *CS* clinically significant, *PCa* prostatic cancer

prevalence of HGPIN in our study was 7.8% of the specimens which is similar to other Asian series.

The role of perineural invasion (PNI) in prostate cancer is still unresolved and has been variably described as a factor predictive of advanced disease or poor PSA-free survival [14]. PNI positivity rate was comparable in both comparative arms in the present study and its role cannot be commented upon by current analysis. Lymphovascular invasion (LVI) is a significant predictor of outcome for bladder cancer but its role in the incidental ca prostate is not well defined [15]. Even though 13.2% of our patients had LVI, it did not affect the outcome.

Bladder cancer is an aggressive disease than prostate cancer which makes it difficult to identify the natural history of

prostate cancer in these cases. Few series have shown that IPCa is less aggressive when compared to other cases [16]. For patients with IPCa, their clinical relevance and management is debatable as many series have shown that they are an innocuous bystander while other have shown about this as a factor responsible for an increase in cancer-specific mortality [16]. The majority of published data have shown that prostate cancer-specific death is 0% and PSA failure is very low in such patients (< 5%) [17–21].

One of the largest series from Carver College of Medicine, University of Iowa, reported that one of their clinically insignificant PCa patients developed a biochemical failure with a PSA doubling time of 183 months while none of the cases

Fig. 2 KM survival curve depiction of overall survival. *CIS* clinically insignificant, *CS* clinically significant, *PCa* prostatic cancer

from the clinically significant group had a biochemical failure at a median follow-up of 40.3 months. This highlights the fact that even in a very good risk bladder cancer patient prostate cancer relevant surveillance may be important and the distinction between clinically significant and insignificant may not be relevant [17]. Similar conclusions have been suggested by the University of Southern California series analyzing their 37 years experience [18]. Bruins et al. highlight the importance of infiltration of the prostate by bladder cancer as a poor prognostic factor and not the presence of IPCa [18].

In contradiction, a few series have demonstrated poorer outcomes in patients with IPCa as compared to whom no associated IPCa [22, 23]. Overall, our analysis suggests that this distinction is mere futility and there is no survival or DFS difference noted in the patients of either group. Though the current analysis does not provide the strongest of the evidence, for or against, it does add an Indian perspective to the data already available in the world literature. The major drawbacks in the current study are the intermediate term follow-up and being a retrospective analysis. When it comes to prostate cancer-specific survival, there must be a long follow-up of 10–15 years, which is lacking in our series.

Only the prognostic variable impacting OS was the stage of bladder cancer similar to the few other series, which have mentioned the role of carcinoma bladder, stage affecting the outcome [23, 24].

In the current era where functional quality stands amongst priorities, total prostate sparing or prostatic apex sparing radical cystectomies has been proposed to preserve the urinary and sexual functions but it was questioned due to the presence of incidental PCa, in 1–6% of the cases. There is a differing opinion about acceptance of these approaches all across the globe, and this will continue until a strong evidence using randomized comparison with long-term follow-up becomes available. [5, 24]

Conclusion

Incidental prostatic cancer on radical cystectomy specimen is an increasingly frequent finding. High-grade prostatic intraepithelial neoplasia is comparatively less common in Indian patients than the Western population. They are mostly clinically insignificant and hardly dictate survival. The distinction between clinically significant and insignificant is not relevant according to our analysis, though at least baseline PSA may be done.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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