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ORIGINAL PAPER

Relevance of prostate cancer in patients with synchronous invasive bladder urothelial carcinoma: A monocentric retrospective analysis

Lucio Dell'Atti

Department of Urology, University Hospital "S. Anna", Ferrara, Italy.

Summary ***Objectives: We retrospectively reviewed data of patients with incidental prostate cancer (PCa) who underwent radical cystoprostatectomy (RCP) for invasive bladder cancer and we analyzed their features with regard to incidence, pathologic characteristics, clinical significance, and implications for management.***
Material and Methods: Clinical data and pathological features of 64 patients who underwent standard RCP for bladder cancer were included in this study. Besides the urothelial carcinoma of the urinary bladder, the location and tumor volume of the PCa, prostate apex involvement, Gleason score, pathological staging and surgical margins were evaluated. Clinically significant PCa was defined as a tumor with a Gleason 4 or 5 pattern, stage ≥ pT3, lymph node involvement, positive surgical margin or multifocality of three or more lesions. Postoperative follow-up was scheduled every 3 months in the first year, every 6 months in the second and third year, annually thereafter.
Results: 11 out of 64 patients (17.2%) who underwent RCP had incidentally diagnosed PCa. 3 cases (27.3%) were diagnosed as significant PCa, while 8 cases (72.7%) were clinically insignificant. The positive surgical margin of PCa was detected in 1 patient with significant disease. The prostate apex involvement was present in 1 patient of the significant PCa group. Median follow-up period was 47.8 ± 29.2 (range 4-79). During the follow-up, biochemical recurrence occurred in 1 patient (9%). Concernig the cancer specific survival there was no statistical significance (P = 0.326) between the clinically significant and clinical insignificant cancer group.
Conclusions: In line with published studies, incidental PCa does not impact on the prognosis of bladder cancer of patients undergoing RCP.

KEY WORDS: Bladder cancer;; Urothelial Carcinoma; Prostate cancer; Cystoprostatectomy; Incidental.

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INTRODUCTION

Radical cystoprostatectomy (RCP) remains the golden standard for muscle invasive bladder cancer or recurrent superficial urothelial carcinoma at high risk (1). The majority of cystectomy patients are in 6th-7th decade and therefore it is not surprising that in some patients prostate carcinoma (PCa) is detected incidentally on histological examination of the excised specimen (2). Following its initial description, this operation has undergone progressive refinement with the current application of nerve-sparing techniques, extended pelvic lymphadenectomy, and orthotopic bladder substitution (3, 4). However, this procedure is invariably associated with high incidence of sexual complications. Alternative techniques have recently been suggested for younger patients, in whom the prostate apex, prostate capsule or even the whole the prostate is preserved, with the aim of improving urinary continence and erectile function (5). These techniques to preserve sexuality raised some concerns because of two essential risks: local invasion of the prostate by the urothelial cancer and a possible association with incidental PCa (6). In this study we retrospectively reviewed data of patients with incidental PCa who underwent RCP for invasive bladder cancer and our aim was to analyze their features with regard to incidence, pathologic characteristics, clinical significance, and implications for management.

MATERIALS AND METHODS

The clinical data and pathological features of 64 patients who underwent standard RCP for bladder cancer at our institution from January 2006 to May 2013 were retrospectively reviewed. Bladder cancer was histologically diagnosed by transurethral resection. The indication for RCP included muscle invasive bladder cancer, carcinoma in situ of the bladder refractory to intravesical *bacillus Calmette-Guèrin* therapy and recurrent multifocal high-grade superficial bladder cancer uncontrollable by repeat transurethral resection. Standard pelvic lymphadenectomy including the obturator and iliac nodes was performed for all patients. The preoperative assessment included digital rectal examination (DRE), prostate-specific antigen (PSA), chest radiographies and computed thomography (CT) urography and/or magnetic resonance imaging were used for clinical staging. Patients with an abnormal result of DRE or PSA suspicious of PCa and finally confirmed by prostate biopsy before the sur-

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gery were already excluded from the study. All the pathological examination was performed in the same institution. Cystoprostatectomy specimens were immersed intact in formalin solution. The prostate and seminal vesicles were removed en bloc from the bladder, and the entire circumference of each resected prostate gland was inked. Complete transverse sections were taken from apex to base at 4 mm intervals. All pathological examinations were performed according to the 2002 TNM classification system. Besides the urothelial carcinoma of the urinary bladder, the location and tumor volume of the PCa, prostate apex involvement, Gleason score, pathological staging and surgical margins were evaluated. Clinically significant PCa was defined as a tumor with a Gleason 4 or 5 pattern, stage ≥ pT3, lymph node involvement, positive surgical margin or multifocality of three or more lesions. Postoperative follow-up was scheduled at 3-month intervals after the surgery, then every 3 months the first year, every 6 months the second and third year, annually thereafter. Serum PSA, creatinine and blood chemistry to assess the renal function, urinalysis, abdominal ultrasonography, and chest X-ray constitute the essentials of a follow up visit. In case of node-positive disease, CT scans and bone scintigraphies were performed at regular intervals. A biochemical recurrence was defined as a second confirmatory level of serum PSA of > 0.2 ng/ml.

Statistical analysis

Chi-square analysis (or *Fisher's exact test* for nonparametric variables) was used to analyze categoric variables and t test (or *Mann-Whitney test* for nonparametric variables) to analyze continuous variables. Patient age, tumor volume, and PSA level were treated as continuous variables, whereas Gleason scores, margin status, stage, multiplicity, and apical tumor involvement were treated as categoric variables. A $P < 0.05$ was considered to indicate statistical significance.

Results

In our study, primary tumors were transitional cell carcinoma (TCC) of the bladder in 62 patients (96.9%), sarcoma and adenocarcinoma of the bladder in the remaining two patients (3.1%), respectively. Carcinoma in situ and non invasive high-grade urothelial papillary carcinoma were seen in 6 (9.7%) and 2 (3.3%) patients, respectively. In 20 (32.3%), 18 (29%) and 13 (20.9%) patients, urothelial carcinoma had invaded the subepithelial connective tissue, muscolaris propria, and perivescical tissue, respectively. Stage pT4 (direct extension to the prostate) was seen in 5 patients (7.8%). 11 out of 64 patients (17.2%) who underwent RCP had incidentally diagnosed PCa. The mean age was 73.3 ± 7.2 years and 74.9 ± 6.9 years for patients with incidental PCa and without incidental cancer, respectively (P = 0.255). A preoperative median PSA in 11 cases with incidental PCa was 2.79 ± 1.94 ng/mL and in 53 patients without incidental cancer was 2.19 ± 1.88 ng/mL, which showed no significant difference (P = 0.144). Median tumor volume was 0.09 cm^3 (range 0.01 to 17.62 cm^3), and a tumor volume of more than 0.5 cm^3 was identified in 7 patients (7/11, 66.6%). Two patients were found to have apex involvement of PCa. The detailed characteristics of patients who underwent RCP were summarized in Table 1.

3 cases (3/11, 27.3%) were diagnosed as significant PCa, while 8 cases (8/11, 72.7%) were clinically insignificant. The positive surgical margin of PCa was detected in 1 patient with significant disease. The prostate apex involvement was present in 1 patient of significant PCa group. There was no statistical difference in pathological staging and the pelvic lymph node involvement of the bladder cancer between the two groups. High-grade prostatic intraepithelial carcinoma (HGPIN) was identified in 2 men (2/11, 18.2%) with incidental PCa and in 3 men (3/53, 5.7%) who underwent RCP without incidental PCa (P = 0.243). Table 2 summarizes the pathologic characteristics of the two groups of incidental PCa. Follow-up data were available for all 64 patients who underwent RCP. Median follow-up period was 47.8 ± 29.2 months (range 4-79). All 11 patients with incidental PCa had undetectable serum PSA levels 3 months after RCP. During the follow-up, biochemical recurrence occurred in 1 patient (9%) that was treated with androgen deprivation therapy. For adjuvant therapy, the 17 patients with bladder TCC received platinum-based combination chemotherapy. Of the 62 who underwent RCP with bladder TCC, 8 patients (8/62, 12.9%) experienced pelvic recurrence or distant metastasis from a bladder tumor, 1 patient in clinically insignificant PCa group (1/3, 33.4%) and 3 patients in clinically significant group (3/8, 37,5%). There was no PCa-related death in

Table 1.
Characteristics of patients who underwent cystoprostatectomy.

Patients characteristics (n = 64)	Patients with incidental PCa (n = 11)	Patients without incidental PCa (n = 53)	P value
Age (yrs), mean ± SD	73.3 ± 7.2	74.9 ± 6.9	NS
Primary tumor, (n)			NS
Bladder TCC	10	52	
Sarcoma bladder	1	0	
Adenocarcinoma bladder	0	1	
Pathological stage of bladder cancer (TCC):			NS
Carcinoma in situ	1	5	
pT1	3	17	
pT2	3	15	
pT3	2	11	
pT4	1	4	
Previous intravesical chemotherapy/BCG	8	39	NS
PSA level ng/mL, (range)	2.79 ± 1.94	2.19 ± 1.88	NS
HGPIN (n)	2	3	NS
Follow-up, (months)	46.9 ± 28.5	48.7 ± 27.9	NS

NS = not significant; PCa = prostate cancer; SD =standard deviation; TCC = transitional cell carcinoma; BCG = bacille Calmete-Guèrin.

Table 2.
Clinical data and pathological features of significant and insignificant incidental prostate cancer.

	Patients with significant PCa (n = 3)	Patients without insignificant PCa (n = 8)	P value
Age (yrs), mean ± SD	73.3 ± 7.2	74.9 ± 6.9	NS
Primary tumor, (n)			NS
Bladder TCC	10	52	
Sarcoma bladder	1	0	
Adenocarcinoma bladder	0	1	
Pathological stage of bladder cancer (TCC):			NS
Carcinoma in situ	1	5	
pT1	3	17	
pT2	3	15	
pT3	2	11	
pT4	1	4	
Previous intravesical chemotherapy/BCG	8	39	NS
PSA level ng/mL, (range)	2.79 ± 1.94	2.19 ± 1.88	NS
HGPIN (n)	2	3	NS
Follow-up, (months)	46.9 ± 28.5	48.7 ± 27.9	NS

NS = not significant; PCa = prostate cancer; SD =standard deviation; TCC = transitional cell carcinoma; BCG = bacille Calmete-Guèrin.

both groups during the follow-up. Concerning the cancer specific survival there was no statistical significance (P = 0.326) between the clinically significant and clinical insignificant cancer group.

Discussion

It is not infrequent that patient with muscle-invasive bladder cancer would also concomitantly have incidental PCa in RCP specimens (7). It was shown that both prostate and bladder cancers have similar genetic origins, and some suppressor genes play a significant role in both malignancies. In addition, prostatic stem cell expression has been shown in bladder carcinomas, thereby demonstrating the common genetic origin of those malignancies (8, 9). In 1993, *Stamey et al.* discovered unsuspected prostate cancer in 40% of an unselected group of cystoprostatectomy specimens (10). According to epidemiologic data only 8% of prostate cancers are clinically apparent cancers and that these must be the largest tumors, these investigators took 8% of the largest tumors identified in their series (sized 0.5-6.1) and concluded that any tumor over 0.5 cc must be clinically significant. The question is whether screening of these patients for PCa is necessary, because patients who are candidates for RCP with serum PSA determination and DRE have a risk of overdiagnosis for Pca (11) and because the diagnosis of PCa in a patient with muscle-invasive bladder cancer will probably not cause the death of a given patient, also as demonstrated by our study (p = 0.326).
Androulakakis et al. suggested that simultaneous finding of PCa and bladder cancer did not affect the prognosis of either disease. The patient's prognosis appears to be related to the characteristics of each tumor, separately (12). More recently it was reported no worse survival in patients with both cancers compared with those with bladder cancer alone (13). However, some authors emphasize the importance of diagnosis of PCA in patients with muscle invasive bladder cancer for a correct approach to surgical alternatives in order to preserve sexuality and urinary continence in young adult patients (14, 15). Considering the important role of prostate apex for urinary continence and the erectile function, the apex-sparing approach and/or the prostate capsule-preserving for improve urinary continence is suggested by several authors and has become a treatment of choice for muscle invasive bladder cancer (16). *Davila et al.* found that erectile function could be significantly preserved by prostate apex-sparing cystectomy (17). *Vallavicien et al.* advocated cystectomy preceded by transurethral resection of prostatic tissue with preservation of the prostatic capsule (15). *Muto et al.* combined cystectomy with adenoma enucleation according to *Millin* (18). In the present study of men having RCP, 17,2% of patients were diagnosed with incidental PCa; of those 27,3% were classified clinically significant and 1 patient (1/11, 9%) was found to have prostate apex involvement by prostate adenocarcinoma. Our study cohort was a homogenous group, a representative sample of Italian population. Incidental PCa detected in similar international studies ranges between 14 and 60%.
International differences in the incidence of PCa in cystoprostatectomy specimens could represent a racial variation in CaP prevalence (18). In our study, in line with published studies (19-21), incidental PCa does not impact on the prognosis of bladder cancer patients undergoing RCP.

Conclusions

However, is important to identify patients with high-risk PCa prospectively, so that they can be offered adjuvant treatment with view to longer-term risk reduction. Preoperative prostate assessment in those going for RCP may influence not only the decision but also technique used. Prostatic apical sparing for better continence or prostate capsule preserving for erectile function in neobladder formation should be considered only in carefully selected patients. Therefore, the real impact of prostate-sparing radical cystectomy on functional outcomes requires further investigation.

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Correspondence

Lucio Dell'Atti, MD, PhD (Corresponding Author)
dellatti@hotmail.com

Department of Urology University Hospital "S. Anna"
8 A. Moro Street - 44124 Cona, Ferrara, Italy