

Synchronous bladder and prostate cancer specimens obtained from radical cystoprostatectomy: A single-center retrospective analysis

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Abstract. The aim of the present study was to analyze incidence, histopathological features and clinical outcomes of patients undergoing radical cystoprostatectomy (RCP) for bladder cancer, in which incidental prostate cancer (PCa) was found. How these types of cancer impacted the patients' management and whether prostate-sparing cystectomy could be an option for these patients was determined. The current study retrospectively analyzed the data of a cohort of patients from 'Umberto I' Hospital of Nocera Inferiore who underwent RCP for bladder transitional cell carcinoma. Patients with a preoperative diagnosis or clinical suspicion of PCa were excluded. Patients affected by incidental PCa in the RCP specimens were identified, and then their demographic, histopathological and clinical outcome data were collected. Overall, it was revealed that of the 303 patients undergoing RCP for bladder cancer, 69 (22.7%) had incidental PCa, with a median age of 71.6 (age range, 54–89 years). In total, 23 (33.33%) of the 69 patients with incidental PCa were considered to have clinically significant prostate disease. In conclusion, it was relatively common to identify incidental PCa in RCP specimens but no preoperative predictive factors were identified that were able to determine 'non-aggressive' PCa status. Therefore, the present results demonstrate the need for a careful and complete prostate removal during RCP. Nevertheless, since organ-sparing surgeries are widely performed in young population, due to the impossibility of predicting aggressive prostate cancer, these patients require close monitoring through lifelong PSA

surveillance, particularly focusing on the possible relapse of PCa after RCP.

Introduction

Prostate cancer (PCa) is a common cancer and the second cause of cancer-related mortality in men (1,2). Nonetheless, PCa prevalence at the histological level is higher than the clinically detected disease rates. During autopsy studies, prostatic adenocarcinoma has been histologically detected in >30% of men older than 50 years. These tumors are usually small and clinically indolent, with the ability to exist for several years before presenting any change, such as accelerated cell proliferation, tumor metastasis and clinical detection. More importantly, accumulating evidence has shown that, in patients affected by primary bladder cancer (BC) undergoing radical cystoprostatectomy (RCP), there is a higher incidence of PCa (3,4). RCP specimens from patients affected by diseases other than PCa can be a random sample from the prostates of asymptomatic men, offering a unique opportunity to study the incidence and morphological features of these incidental prostatic tumors. In terms of randomness, this cohort shows similarities to that of the autopsy studies, but differs in the reported higher PCa incidence in men with BC (3,4). According to the European Association of Urology guidelines, for patients affected by muscle-invasive bladder cancer (MIBC) or any high-risk, recurrent and non-invasive BC, the RCP procedure with bilateral pelvic lymphadenectomy and various types of urinary diversion is the gold standard of therapy (5). The standard RCP in men is based on the removal of the bladder along with prostate, seminal vesicles, a part of the vasa deferentia and distal ureter, including regional lymphadenectomy (in order to provide an effective local treatment of the disease), which can have a high incidence of sexual complications and urinary incontinence. Whereas alternative techniques can be considered in highly selected cases in which it is desired to preserve potency, fertility and urinary function. In the modern era of orthotopic bladder substitution after RCP for

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BC, sparing the entire prostate or a portion of it has become controversial in recent years. However, these techniques, in an effort to maintain sexual and urinary functions, have raised concerns regarding the oncological outcomes due to two potential risks: urothelial cancer local invasion of the prostate and a probable association with incidental PCa (6). PCa is complex: on one hand, numerous patients with PCa receive unnecessary treatment as their disease will never become clinically significant or result in death. On the other hand, some prostatic tumors require immediate treatment, which are known as clinically detected PCa. For this reason, incidentally identified PCas are divided in two groups: clinically significant and clinically insignificant. The aim of the present single-center retrospective study was to: i) assess incidence, histopathological features and clinical significance of incidentally identified prostatic tumors in RCP specimens obtained from patients affected by bladder cancer, but with clinically normal prostates; ii) examine patients' age, preoperative rectal examination findings and prostate specific antigen (PSA) values, in order to evaluate whether such features can help with the prediction and treatment of significant PCas; iii) establish whether prostate sparing-cystectomy could represent a feasible option for these patients.

Materials and methods

The data of 303 male patients who underwent RCP with bilateral pelvic lymphadenectomy and different urinary diversion for BC at our Department of Urology were retrospectively reviewed. Data from the pre-operative digital rectal exam (DRE) and PSA assays were analyzed in patients diagnosed with incidental PCa, for a total of 69/303 (22.7%) patients. Treatment and prognosis of muscle invasive bladder cancer (MIBC) are determined by tumor stage and grade. So, before any curative treatment, it is essential to evaluate the presence of distant metastases. For this reason, all patients enrolled in the current study underwent CT of the chest, abdomen and pelvis, as well as MRI of the abdomen and pelvis. This staging showed that none of the patients had distant metastases or neoplastic disease of the prostate. The selection criteria were as follows: i) no previous history of PCa; ii) no previous history of chemotherapy or radiotherapy; iii) no evidence of PCa in the imaging evaluation; and iv) age ≥ 40 years old. Routine pathological examination was performed as by routine on bio-specimens. Beyond evaluation of the bladder, it was considered i) the presence of PCa; the stage of any detected prostatic adenocarcinoma following the 2002 TNM classification (7) and its Gleason score according to the World Health Organization system (8) and ii) the surgical margin status (a positive surgical margin was recorded upon detection of tumor cells at the stained margin of the specimens). Prostate involvement in bladder cancer was also assessed. The intact RCP specimens were immersed in 10% buffered formalin solution. Then, the prostate including seminal vesicles and vas deferens, was cut out from bladder, weighed and stained with Indian Ink. Sectioning was performed by cutting at 5-mm interval sections transverse to the long axis, which were then embedded in paraffin for H&E staining and examination. PCa was defined as clinically significant when any of the following criteria was met: Gleason Score ≥ 4 , stage $\geq pT3$, extracapsular

Table I. Clinicopathological characteristics of bladder tumors in patients with incidentally diagnosed prostate cancer.

Variables	Value (n=303)
Age (years), median (min-max)	71.6 (54-89)
Histological type (n, %)	
Urothelial (TCC)	275 (90.8%)
Other	28 (9.2%)
pT stage (n, %)	
Organ-confined ($<pT3$)	184 (60.7%)
Locally-advanced ($\geq pT3$)	119 (39.3%)
pN status (n, %)	
N0	206 (68%)
N+	97 (32%)
M status (n, %)	
M0	299 (98.7%)
M+	4 (1.3%)
Surgical margins (n, %)	
R0	288 (95%)
R+	15 (5%)
Intraprostatic urothelial proliferation (n, %)	
Yes	0
No	303 (100%)

extension (ECE), lymph node metastasis (LNM) or positive surgical margins (SM).

Results

In order to undergo surgery, all patients enrolled in our study underwent DRE and MRI of the abdomen and pelvis to specifically evaluate the prostate both clinically and instrumentally. Both examinations did not reveal any prostate abnormalities such as to require a prostate biopsy. Of the 303 RCP specimens, incidental PCa was detected in 69 patients (22.7%), with a median age of 71.6 years (age range, 54-89 years). We performed orthotopic bladder substitution in 29 (42%) patients, ileal conduit procedure in 14 patients (20.2%) and ureterocutaneostomy in 26 patients (37.7%). *Bladder cancer features.* Table I shows the histopathological features of BC. All tumors were of high grade. *PCa features.* The histopathological features of PCa identified within the RCP specimens are reported in Table II. Whereas Fig. 1 reports the preoperative PSA value and its distribution together with the age distribution. In 69 patients with incidental PCa, 23 of these cancers (33.33%) were regarded clinically significant. In this group of patients, only seven (for a percentage equal to 10.1%) were affected by locally advanced prostate cancer on histopathological examination. From the retrospective analysis, moreover, these patients presented a bladder tumor which invaded the trigone and the bladder neck. For this reason, the differential diagnosis between primary prostate tumor and bladder infiltration of the prostate was very difficult. *Incidence and characteristics of PCa stratified according to age.* Patients were subdivided into three age groups based

Table II. Clinicopathological characteristics of prostate tumors from radical cystoprostatectomy specimens.

Variables	Value (n=69)
Age, years, median (range)	
Clinically significant PCa group	72 (55-89)
Clinically insignificant PCa group	72.5 (54-85)
Preoperative PSA, ng/ml, median (range)	
Clinically significant PCa group	3.83 (0.68-18.6)
Clinically insignificant PCa group	3.56 (0.68-9.9)
pT stage (n, %)	
Organ-confined disease (\leq pT2)	62 (89.9%)
Locally advanced disease (\geq pT3)	7 (10.1%)
pN status (n, %)	
N0	69 (100%)
N+	0 (0%)
Gleason score (n, %)	
<6	24 (34.8%)
7 (3+4)	26 (37.7%)
7 (4+3)	14 (20.3%)
>7	5 (7.25%)
Surgical margins (n, %)	
R0	60 (87.0%)
R+	9 (13.0%)

PCa, prostate cancer; PSA, prostate specific antigen.

on the 33 and 66% age quantiles (<70, between 70-75 and >75 years of age) and then evaluated. For both TNM stage and Gleason score no significant difference in the mean value of the respective parameter between the three age categories was identified. *Aggressiveness of PCa*. In total, 46 (66.66%) of 69 patients presented a 'non-aggressive' PCa. The incidence of aggressive tumor categorized by age group is shown in Fig. 2. None of the pre-operative factors, namely PSA level and age, were predictive factors for non-aggressive PCa. Comparisons of the mean values and rank order for age and PSA level between the patients with aggressive PCa and the patients who had non-aggressive tumor by means of unpaired t-tests and Mann-Whitney U tests did not result in any significant difference as can be seen in Table III.

Discussion

Incidental PCas identified in RCP samples, derived from patients who underwent BC surgery but had no preoperative evidence of prostatic disease, show histological and morphological features similar to those of latent tumors identified in several autopsies (9-11). According to the literature, the frequency variability of incidentally discovered PCa in cystoprostatectomy specimens is extremely high, ranging from 17-70% (12,13), owing to various factors. The first of these is the different definition of clinically significant cancer in published studies (14). Over the past two decades, the emerging concept of 'insignificant' PCa has progressed to indicate

Table III. Parametric and non-parametric difference in the mean values and rank order of age and PSA level between the clinically significant PCa group and the clinically insignificant PCa group.

A, Age	
Test	Result
Welch two sample t-test	
t	-0.298
df	40.629
p	0.768
95% confidence interval	-4.6,3.4
Mann-Whitney U test	
W	496
p	0.679
B, PSA	
Test	Result
Welch two sample t-test	
t	-0.255
df	28.317
p	0.801
Mann-Whitney U test	
W	481
p	0.545

low-grade, small-volume and organ-confined prostatic tumors that are likely slowly progressing, and these, although might not need urgent therapeutic treatment, are eligible for active surveillance (3). Currently, the pathological assessment of the lesion indicates further patient management (15). Generally, PCa is diagnosed as 'insignificant' when all these criteria are met: i) the disease has a Gleason score <7 (without a Gleason pattern of 4 or 5); ii) it is confined to the organ (stage pT2); and iii) the tumor mass has a <0.5 cm³ volume. Here, only tumor stage and grade could be taken into account to cancer aggressiveness as tumor volume was not available on the pathological report. Our results showed that 46 (66.66%) of the incidentally diagnosed PCas were considered as 'non-aggressive' as they were organ-confined or with a Gleason score of <7 (4+3). Then, an association between BC and PCa was suggested by several previous studies (16,17). A previous study on a Japanese cohort showed that the relative risk to develop PCas was 9x higher in patients with BC (18). Moreover, Kantor and McLaughlin (19) reported a 3-fold excess risk of PCa within a year after the diagnosis of BC. Mersheimer *et al* (20) also observed that the combination of BC and PCa was common, being the second in frequency after skin and colon cancers co-occurrence. However, the association between BC and PCa can be explained as a possible detection bias, associated with more detailed clinical assessment and thorough pathological examination. For example, once a diagnosis of BC has been made, a complete investigation of the entire genitourinary system is

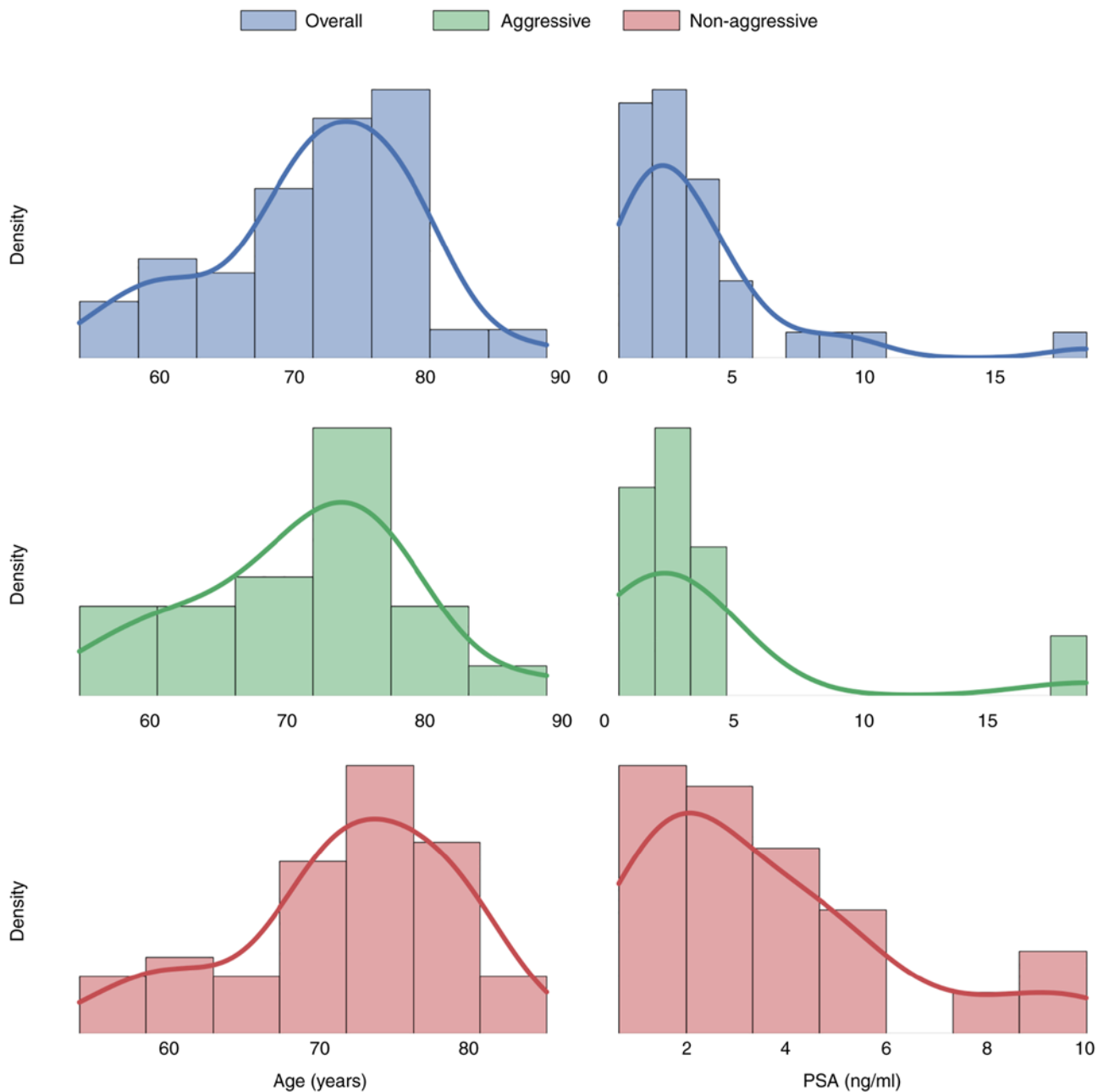


Figure 1. Histogram and kernel density estimate of patient age and PSA level. PSA, prostate specific antigen.

likely to occur (21). Indeed, BC patients in the clinical practice are more actively screened for prostatic tumors compared with the general population. Kurokawa *et al* (22) examined a case cohort of 106 patients for BC (case cohort) in comparison with a 1,060 age-matched control cohort of men who were subjected to PCa screening. They found a PCa rate of 12.3% in the cohort of BC patients vs. 1.5% in the control cohorts, thereby confirming that the risk of developing PCa in patients affected by BC could be higher. In this regard, however, it is important to note that the prognosis of patients bearing both PCa and BC is not considered to be worse than the prognosis of patients bearing only one of these two cancer types; rather, it is the stage of BC that impacts the prognosis. The risk of death by the more aggressive tumor type is not altered by the presence of other tumors in patients undergoing radical pelvic surgery.

The different detection rate of PCa in RCP specimens may be influenced by the thickness of the prostate histological slices, because pathologists might focus more to the bladder. Indeed, Kouriefs and colleagues (23) reasoned that the lower PCa incidence observed in their study (18%) was possibly caused by thick gland sections, indicating that thinner sectioning is recommended (≤ 10 mm). Consistently, Abbas *et al* (24) found a 45% incidence rate using 2-3-mm-thick slices and Moutzouris *et al* (25) a 27% of PCa using 5-mm slices. The current study used 5-mm slices and the observed 22.7% incidence rate of PCa supported the aforementioned hypothesis, indicating that thin tissue sectioning should be used to optimize cancer detection. Finally, genetic and environmental factors may influence the variability of the findings from different countries. In the present study, the majority of prostatic tumors were well differentiated. Our data are consistent

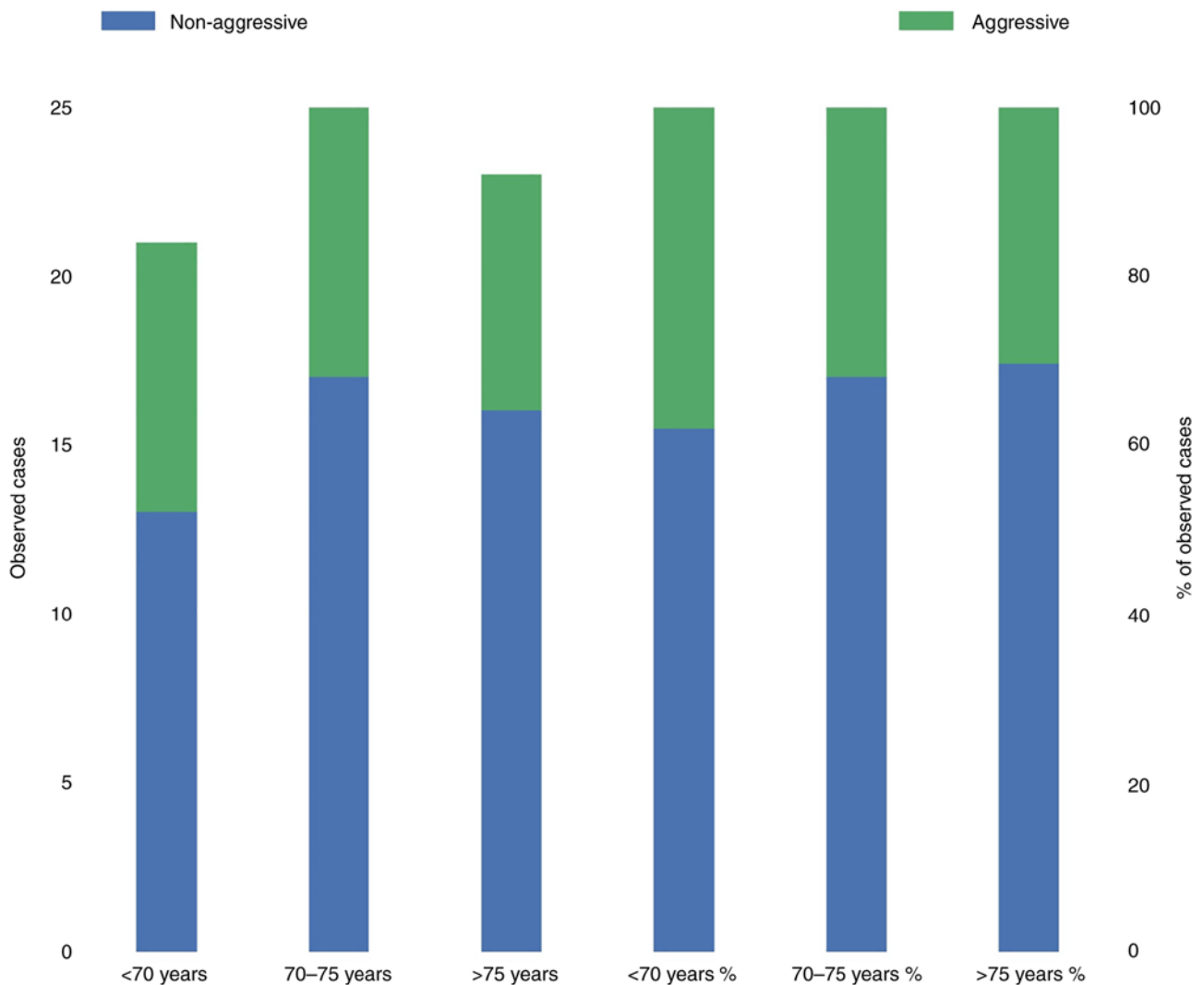


Figure 2. Cancer significance distribution between age categories.

with what reported in other studies in which most of detected tumors were not clinically significant, with only few patients requiring therapeutic treatment (10,11,24). The preservation of continence and erectile function, as well as guaranteeing excellent oncological results, remain the primary goals of the treatment of BC with RCP. Various techniques can help to preserve postoperative continence and erectile function, such as leaving the apex or the entire tissue of the prostate; however, the potential risk of not removing the synchronous PCa can be problematic. By contrast, the probability that patients undergoing RCP and have PCa will not die from prostatic disease is high. Determining whether patients are suitable for prostate-sparing surgery can be difficult due to the wide variability of both cancer rates. In this regard, the RCP findings obtained in a study by Moutzouris *et al* (25) raise further concerns, showing apical involvement by PCa in the 31% of cases and the presence of multifocal PCa in the 31% of patients (25). Moutzouris *et al* (25) claimed that apical involvement by PCa indicates the need of a complete prostate resection. Indeed, a patient within their cohort bearing PCa in the apex had recurrent prostatic disease in the urethro-ileal anastomosis of an orthotopic bladder substitute. Similarly,

Revelo *et al* (26) reported a 25% of patients with apical PCa, of which about 2/3 were clinically significant. They found apical involvement of the prostate with BC in 16% of patients. Overall, they suggested that prostatic apex preservation was a feasible method to improve continence, but it was associated with the risk of incomplete cancer resection. In the attempt to overcome this risk, Revelo *et al* (26) suggested to perform a pre-operative prostate biopsy and freeze intraoperative sections. However, due to possible sampling error, a negative biopsy may not completely exclude apical involvement of PCa in subjects elected for apical sparing surgery. Hautmann *et al* (27) performed sextant biopsies of the prostate upon removal of RCP specimens and detected through this method PCa in only 5% of cases, showing that the biopsy detection rate was 1 out of 9 tumors. Therefore, while sextant biopsies seem not adequate to exclude clinically significant PCa, the optimal prostatic biopsy procedure still needs to be defined. So, routine biopsy has a certain degree of uncertainty regarding the ability to identify clinically significant PCa with high sensitivity when attempting to select patients for prostate-sparing cystectomy. For a successful radical cancer removal it remains crucial not to leave PCa in the apical

prostatic margin or residual tissue of PCa, which might be clinically significant. According to Pettus and colleagues (28), only age was a predictive factor for PCa (odds ratio=1.3, $P=0.046$). However, the present data suggest that patients' age was not a preoperative factor associated with a significant status of PCa. Likewise, the preoperative PSA level seems not significantly associated with the ability to incidentally discover PCa (3). In the present study, PSA values and DRE findings were available for all patients, but their results were not indicators for cancer. This finding suggests that preoperative PSA screening and DRE in RCP candidates provide no advantages in this setting, which was consistent with results of previous studies (24). Identifying that there was not a significant difference in PSA levels in men with clinically significant PCa and those with clinically insignificant PCa at the preoperative stage indicates that PSA is a weak predictor of significant disease, and there is no reliable PSA threshold having a 100% negative predictive value. Consistently, Gakis and colleagues (29) showed that no preoperative clinical value could formally exclude PCa in an RCP specimen. Overall, these studies indicate that it is currently not possible to adequately determine which patients can safely be selected for prostate-sparing cystectomy and that the mainstay of treatment, in cases of MIBC, remains RCP and the current study agrees with these findings.

In conclusion, the present study demonstrated that incidentally diagnosed PCa in specimens from RCP for BC was frequently found, resulting in a rate of ~23% of the current RCP specimens. As in other studies, also in the current report the majority of these prostatic tumors were not clinically significant, not requiring therapeutic treatment. This has increased the desire to preserve the continence and erectile function in patient undergoing RCP for bladder cancer; however, the risk of not removing the synchronous PCa should be considered. In effect, in our cohort, 33,3% of patients was affected by clinically significant prostate cancer. It was suggested that the differences in the incidence and behavior of prostatic disease were associated with the patient's age. However, in this study, no preoperative predictive factors (patient's age, PSA or DRE) were identified that were able to determine 'non-aggressive' PCa status, resulting in the inability to adequately determine which patients can be safely selected for prostate-sparing surgery. So, the present results demonstrate the need for a careful and complete prostate removal during RCP. Nevertheless, since organ-sparing surgeries are widely performed in young population, due to the impossibility of predicting aggressive prostate cancer and considering the 33,3% of clinically significant prostate cancer in our cohort, these patients require close monitoring through lifelong PSA surveillance, particularly focusing on the possible relapse of PCa after RCP. Finally, in our study the technique for cutting the prostate at 5-mm interval sections transverse to the long axis, allowing the detection of nearly 23% of PCA, supports the hypothesis that thin tissue sectioning should be used to optimize cancer detection (regardless of prostate volume which traditionally affects the number of biopsies to be taken).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RB made substantial contributions to conception and design and contributed to writing the manuscript. RB and GM made substantial contributions to acquisition of data and confirm the authenticity of all the raw data. CC, UM, OI, UP, CD, AC, FP, RS, RB and GM analyzed and interpreted the patient data regarding the urological disease. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Signed informed consent was obtained from all the patients for publication of this study and for processing their medical data.

Competing interests

The authors declare that they have no competing interests.

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