Original paper

# Influence of gross specimen sampling on the incidence of incidental prostatic carcinoma in cystoprostatectomy specimens of patients with bladder carcinoma

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Reported prostate cancer incidence rates vary greatly among cystoprostatectomy samples. We investigated how the thoroughness of prostate sampling influences prostatic carcinoma incidence in bladder cancer patients. In a retrospective study, 313 cystoprostatectomy cases of urinary bladder carcinoma were analysed for the presence of concurrent prostatic carcinoma. Patients were divided into two groups: patients who had undergone the operation before and after 2007, when a policy of preferably complete prostate sampling in cystoprostatectomy specimens was introduced at our institution. Cases processed after the 2007 recommended sampling changes had a significantly higher rate of incidental prostatic carcinoma and clinically significant prostatic carcinoma than the pre-2007 group ($p < 0.0001$ and $p = 0.003$, respectively). Complete prostate processing in cystoprostatectomy specimens results in a higher incidence of incidental prostatic carcinoma than with partial processing. More patients with clinically significant prostate cancer are consequently discovered. In conclusion, we believe that complete prostate sampling should be mandatory.

**Key words:** prostatic neoplasms, urinary bladder neoplasms, cystoprostatectomy, surgical pathology.

## Introduction

Prostatic carcinoma is the most common non-cutaneous malignant neoplasm in Slovenian male patients. Its incidence has been increasing in recent years, being approximately 130/100,000 in Slovenia, while it is 160/100,000 in the United States. As a result of prostate specific antigen (PSA) determination and earlier detection, the overall 5-year survival of prostatic carcinoma patients has significantly increased [1, 2, 3]. The median age at diagnosis in the United States is currently 67 years and has been dropping since the introduction of PSA determination in the early 1990s [4, 5]. Primary risk factors for disease occurrence are age, race and family history, with age having the strongest impact [6]. Radical prostatectomy is the preferred option for patients with localised disease and long life expectancy. Other options are external beam radiotherapy and brachyradiotherapy. In locally advanced disease, adjuvant androgen deprivation therapy is recommended. In metastatic disease, luteinising hormone releasing hormone agonists are the primary treatment, with chemotherapy in castration-resistant cases [7, 8]. The exact choice of treatment modality (or non-treatment) is dependent upon multiple factors, including Gleason score, stage at diagnosis, PSA, physical performance and patient's choice [5, 7, 8, 9].

Bladder carcinoma is the second most common malignancy of the urinary tract, with an incidence in Slo-

venia of approximately 20/100,000; it is 4 times more frequent in males than females. Median age at diagnosis is 69 years for males and 71 years for females [1, 10, 11]. Risk factors involved in bladder carcinoma, in contrast to prostatic carcinoma, are predominantly environmental, especially smoking, arsenic, aromatic amines and infection with *Schistosoma* [11]. About 80% of patients are diagnosed with the disease limited to the mucosa. These can be managed by transurethral resection, followed by intravesical chemotherapy or bacillus Calmette-Guérin (BCG) instillation. Radical cystoprostatectomy is the gold standard for treatment of patients with disease limited to the mucosa and failure of primary therapy and of patients with muscle-invasive bladder carcinoma, with exceptions that will not be discussed further here [12, 13].

Due to both cancers predominantly occurring in older men and prostatic carcinoma having a high incidence, there is a significant risk of an incidental concurrent prostatic carcinoma in a cystoprostatectomy specimen of a patient with bladder carcinoma. Herein, we assess the frequency of incidental prostate carcinoma in such patients and the influence of the two methods of specimen processing on the incidence and clinical significance of incidentally discovered prostatic carcinoma.

## Material and methods

In a retrospective study, documentation of 313 consecutive cystoprostatectomy specimens of patients treated for bladder carcinoma between March 1996 and April 2015 was reviewed. All cases were scored according to the 2005 revised Gleason scoring system and the 2015 reccomendations on new grading system [14, 15]. Cases diagnosed prior to 2005 were reviewed and re-scored according to this system. Information was gathered on the presence of concurrent prostatic carcinoma, its Gleason score, stage, number of prostatic samples, as well as the histological type of bladder carcinoma and stage. The volume of prostatic carcinoma was not determined. We divided patients into two groups:

- cystoprostatectomy cases diagnosed before 2007, when four to eight samples were taken from each prostate;
- cases diagnosed after 2007, when complete prostate sampling, with approximately 3 mm thick slices, was started.

The $\chi^2$ test was used for comparison of the prostate cancer incidence in the two groups. The Student t-test for independent samples was used for determination of the association of patient age with the presence of incidental prostatic carcinoma, and possible age discordance between the pre-2007 and post-2007 groups. The Mann-Whitney test was used for comparison of the number of prostate samples in both groups. We used SPSS, version 17.0 (IBM, Armonk, NY, United States) for statistical analysis. A level of $p < 0.05$ was considered statistically significant.

## Results

There were 164 cystoprostatectomy samples between March 1996 and December 2006 and 149 samples between January 2007 and April 2015. The average number of samples taken in partially and completely sampled prostates was 6.5 (range 2-17)

**Table I.** Characteristics of bladder pathology in 313 specimens of patients who had undergone cystoprostatectomy for bladder cancer

| Type of bladder pathology | Number (%) |
|---|---|
| Urothelial carcinoma | 247 (79.0) |
| Squamous cell carcinoma | 13 (4.2) |
| Adenocarcinoma | 3 (1.0) |
| Neuroendocrine carcinoma | 3 (1.0) |
| Clear cell carcinoma | 1 (0.3) |
| Mucinous adenocarcinoma | 3 (1.0) |
| Sarcomatoid carcinoma | 6 (2.0) |
| Anaplastic carcinoma | 4 (1.3) |
| Signet ring cell carcinoma | 1 (0.3) |
| No residual cancer | 26 (8.3) |
| Low-grade urothelial intraepithelial neoplasia | 3 (1.0) |
| Leiomyosarcoma | 1 (0.3) |
| Nephrogenic adenoma | 1 (0.3) |
| **pT stage of bladder carcinomas** | **Number (%)** |
| Tis | 5 (1.6) |
| Ta | 3 (1.0) |
| T1 | 26 (8.4) |
| T2a | 29 (9.3) |
| T2b | 40 (12.9) |
| T3a | 82 (26.3) |
| T3b | 42 (13.5) |
| T4a | 53 (17.0) |
| T4b | 2 (0.6) |
| ypT0 | 26 (8.4) |
| Low-grade urothelial intraepithelial neoplasia | 3 (1.0) |
| **pN stage of bladder carcinoma** | **Number (%)** |
| N0 | 173 (55.3) |
| N1 | 33 (10.5) |
| N2 | 49 (15.7) |
| N3 | 11 (3.5) |
| No tissue for evaluation (Nx) | 47 (15.0) |

**Table II.** Grading and staging of prostatic carcinomas in relation to complete and incomplete sampling

| Gleason score | Incompletely sampled prostate | Completely sampled prostate |
|---|---|---|
| 6 (3 + 3) | 9 | 29 |
| 7 (3 + 4) | 1 | 8 |
| 7 (4 + 3) | 0 | 4 |
| 8 (4 + 4) | 1 | 2 |
| 9 (4 + 5) | 0 | 1 |
| 9 (5 + 4) | 1 | 1 |
| pT stage of prostate carcinoma | | |
| T2a | 10 | 28 |
| T2b | 0 | 1 |
| T2c | 0 | 12 |
| T3a | 0 | 2 |
| T3b | 1 | 0 |
| T4 | 0 | 2 |

and 17.4 (range 11-36), respectively. This difference was statistically significant ($p < 0.0001$). The median age at cystoprostatectomy in our study was 64.2 years (range 36–79 years). The characteristics of urinary bladder carcinomas are presented in Table I. Patients with prostatic carcinoma in our study were younger than patients without it ($p = 0.043$), but the age difference was small (median 62.6 vs. 64.6 years). The median age of pre-2007 patients was 66.5 years while the median age of the post-2007 group was 62.9. This difference, although small, was statistically significant ($p = 0.004$). In a group comparison, cases processed after the 2007 policy change had a significantly higher rate of incidental prostatic carcinoma than the pre-2007 group (45 vs. 11 and 30.2% vs. 6.7%, $p < 0.0001$). There were three cases (27.3%) of pT3a stage or higher and/or Gleason score 7 or higher in the pre-2007 group, while 18 (40%) cases were identified in the post-2007 group ($p = 0.003$). Of the two pre-2007 cases one had a Gleason score of 7 or more and another had a Gleason score of 8, while also invading the seminal vesicles. Thirteen of the post-2007 cases had a Gleason score of 7 or more, one was stage pT3a and three both had a Gleason score of 7 or more and were pT3a or higher. In an additional post-2007 case the carcinoma had invaded the surgical margin. The characteristics of partially and completely sampled prostates are presented in Table II and Figs. 1 and 2. Examples of moderately differentiated and poorly differentiated prostatic carcinoma are shown in Fig. 3.

## Discussion

Incidental prostate cancer has been described in more than 40% of autopsy cases of men older than 60 years and 60% of men older than 80 years [16]. A report of higher incidence of prostate cancer in patients with bladder cancer has been published, in which the authors tried to avoid the bias of urologic examinations and diagnostic procedures [17].

Prostate cancer is a common disease and a non-negligible proportion of samples managed for any condition will harbour incidental prostatic carcinomas. While small (volume less than 0.5 $cm^3$), low-risk carcinomas, defined as stage T2N0M0 or less, Gleason score of 6 or less and no invasion of the surgical margin, are less of a concern and may have little or no influence on post-cystoprostatectomy outcome, clinically significant prostate cancer is associated with a higher incidence of disease relapse and can establish

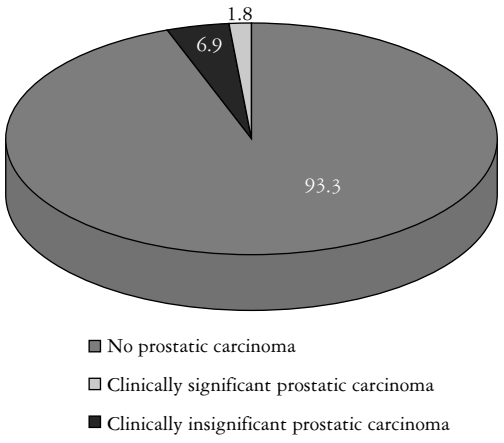


**Fig. 1.** Proportions of clinically significant and insignificant incidental prostatic carcinoma in partially sampled prostates of 164 patients with cystoprostatectomy for bladder cancer

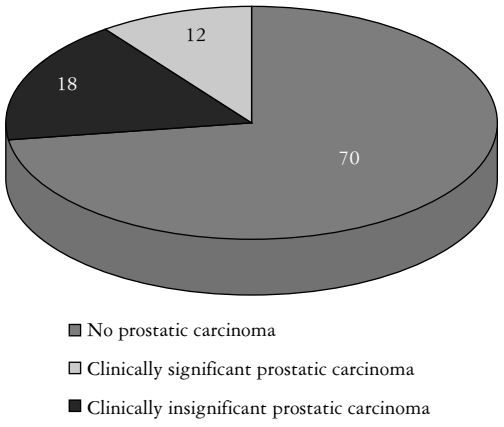


**Fig. 2.** Proportions of clinically significant and insignificant incidental prostatic carcinoma in completely sampled prostates of 149 patients with cystoprostatectomy for bladder cancer

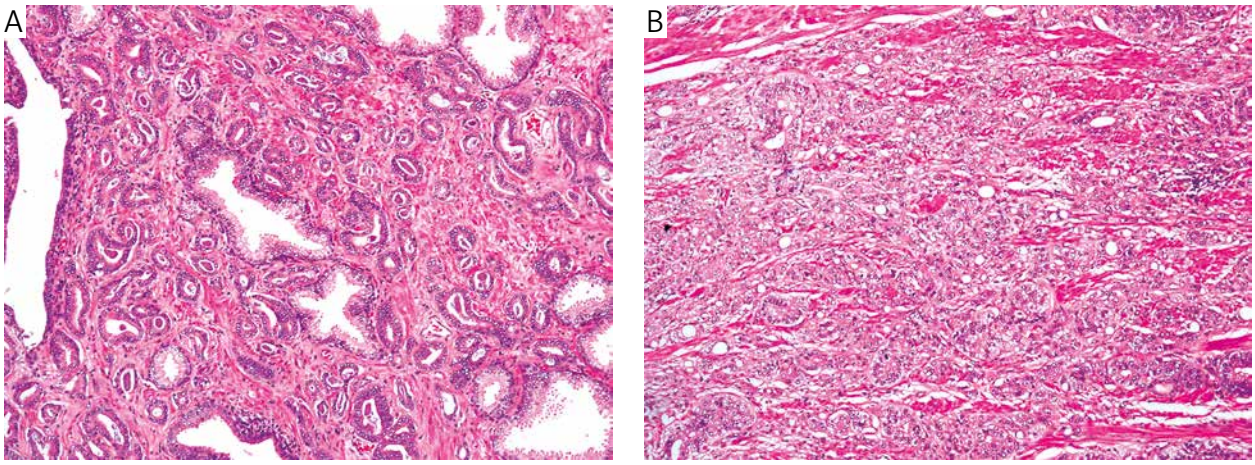


**Fig. 3.** A) An example of Gleason 6 (3 + 3) prostatic carcinoma (HE, original magnification 100×). B) An example of a Gleason 9 (4 + 5) prostatic carcinoma (HE, original magnification 100×)

a requirement for more stringent patient monitoring, possible adjuvant radiotherapy or androgen deprivation therapy [18, 19].

There are two possible methods of prostate assessment in radical cystoprostatectomy specimens. One consists of processing the entire prostate, while the other involves only representative sampling, with a variable number of samples and slice thickness among institutions. In the past few years, several reports have been published that indicate a higher diagnostic accuracy of completely processed prostates in cystoprostatectomy specimens of patients with bladder carcinoma [20, 21, 22, 23].

Different approaches to prostate sampling in terms of completeness and slice thickness in cystoprostatectomy specimens are adopted at different institutions and also by pathologists at the same institution. To date, the reported rates of incidental prostate cancer in cystoprostatectomised patients have been in the range of 14-45% in studies with partial sampling and 3-72% in those with complete sampling [23, 24, 25, 26]. Recent evidence shows that complete prostate processing results in a substantially higher rate of finding the carcinoma. In a study by Fritsche *et al.*, it was shown that 19% of partially processed prostates harbour cancer, while the rate was twice as high (40%) after complete processing [20]. In another study, by Wetterauer *et al.*, the rates were 23% and 72% for partially and completely sampled prostates, respectively [23]. In our study, the incidence of prostate cancer in completely processed prostates was approximately 4.5 times higher (6.7% vs. 30.2%) than the incidence in partially sampled prostates.

Significant prostate cancer in radical prostatectomy or cystoprostatectomy specimens is most often considered to have one or more of the following characteristics: Gleason score 7 or more, stage pT3a or more, presence of prostatic tumour in resection margins, tumour volume of 0.5 $cm^3$ or more and lymph node involvement [7, 20, 27, 28]. Four percent to 57% of prostate specimens included in studies with partial processing harboured clinically significant cancer [23, 24]. In our study, 21 out of 56 (37.5%) incidental prostate cancers had a Gleason score of 7 or more and/or a stage of pT3a or more and/or invasion of the surgical margin. Twenty-seven percent of the partially sampled cases fulfilled one of those two criteria, while 40% did so in cases with complete embedding. In keeping with these results, it has been shown by two previous studies that the rate of clinically significant incidental prostate cancer is much higher in completely as opposed to partially processed prostates (18% vs. 9% and 44% vs. 4%, respectively) [20, 23]. Patients with incidental prostatic carcinoma were slightly younger in our study, as compared to those without it. This is probably due to the combination of a slightly rising incidence of bladder cancer in younger patients (less than 60 years old) in Slovenia and the 2007 policy change to complete prostate embedding [1]. The post-2007 group had a larger population of relatively young patients and, in addition, more thoroughly sampled prostates.

Two of the three largest studies to date, which included more than 1100 and almost 4300 cases of incidental prostatic carcinoma in radical cystoprostatectomy samples, did not identify any impact of incidental carcinoma on survival [29, 30]. However, the largest study did identify a 1.9% relapse rate of prostatic carcinoma, and another large study, including more than 1400 patients, identified a higher risk of mortality in patients with concurrent incidental prostatic carcinoma [30, 31]. Prostate cancer, while in most instances an indolent disease when discovered early, can pose a risk of mortality when not discovered but, at the same time, being a significant disease as defined by the criteria discussed above. In these instances, appropriate measures (more frequent follow-up, radiotherapy or androgen deprivation ther-

apy) that could have resulted in a higher rate of recurrence and metastatic disease would not have been undertaken.

To conclude, in our opinion, these data show that complete sampling should be mandatory. In cases when this is not possible due to financial constraints, it should be as thorough as possible.

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*The authors declare no conflict of interest.*

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