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ORIGINAL ARTICLE

Incidental prostate cancer prevalence at radical cystoprostatectomy—importance of the histopathological work-up

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Abstract The reported incidental prostate cancer prevalence rates at radical cystoprostatectomy cover a range from 4 to 60 %. We investigated the influence of the histopathological work-up on prostate cancer prevalence rates. We identified 114 patients who had undergone cystoprostatectomy for bladder cancer between 2000 and 2012. Complete histopathological assessment was defined as follows: (i) complete embedding of the prostate gland, (ii) sectioning of 15 or more prostate sections, and (iii) processing as whole mount slides. Prostate cancer prevalence rates derived from complete and incomplete histopathological assessments were compared. The overall prostate cancer prevalence rate was 59.6 %. A mean of 14.4 macroscopic tissue sections (thickness 3–5 mm) were sectioned. Sectioning ≥15 sections resulted in a prostate cancer detection rate of 75 %, compared to 42.6 % when sectioning <15 sections ($p<0.001$). Complete embedding yielded a prostate cancer detection rate of 72.3 and of 23.1 % for partly embedded prostates ($p<0.0001$). Prostate cancer was detected in 68.8 % of the whole mounted samples and in 38.2 % of the samples sectioned as standard slides ($p<0.01$); according to the criteria described by Epstein and Ohori, 44.1 % of the detected prostate cancers were clinically significant. The quality of the histopathological work-up significantly influences prostate cancer detection rates and might at least partially explain the highly variable reported incidental prostate cancer prevalence rates at cystoprostatectomy (CP). The high proportion of significant prostate cancer found in our series calls for a careful surgical approach to the prostate during CP.

Keywords Incidental prostate cancer · Bladder cancer · Radical cystoprostatectomy · Histology

Introduction

With a proportion of 24.4 % of male malignancies, prostate cancer represents the most common solid neoplasm among men [28]. Bladder cancer makes up 6.3 % of all cancers among men in Europe and ranks as the 4th most common cancer for men, with approximately 95,000 newly diagnosed cases each year [13, 28]. The prevalence of both prostate and bladder cancers increases in the aging population. As radical cystoprostatectomy (CP) is performed mostly in elderly patients, the coincidental detection of both tumors is not uncommon. Highly variable prevalence rates of incidental prostate cancer at radical CP have been reported, ranging from 4 [30] to 60 % [29]. Importantly, the histopathological work-up of the prostate, more specifically, the macroscopic section thickness [3, 11] and the embedding technique [3, 14], is known to influence prostate cancer detection rates. Here, we assessed the prevalence rate of incidental prostate cancer in CP specimens in a highly industrialized town area and compared our findings to the reported rates worldwide. Furthermore, we analyzed the histopathological characteristics, their potential clinical relevance, and the influence of the histopathological technique on the detection of incidental prostate cancer.

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Materials and methods

This retrospective study was approved by the local ethics committee (EKBB). One hundred thirty-nine patients having undergone radical CP for bladder cancer (n=133) and other indications between 2000 and 2012 were identified by searches in the archives of the Departments of Urology and Pathology at University Hospital Basel and by searches in the accounting systems. Twenty-five of these patients did not qualify for the analysis because either prostate cancer had been diagnosed prior to surgery or they had been treated for other reasons (n=6) than bladder cancer like low-capacity bladder or contracted, nonfunctional bladder after radiation therapy. Finally, 114 men who had undergone radical CP for bladder cancer were included in the analysis. The medical reports were reviewed for individual patient characteristics. The histopathology reports were screened for the TNM classification of bladder and prostate cancers and for tumor histology, including Gleason score, surgical margins, maximal tumor diameter, complete or partial sampling, and number of macroscopic sections. All histological samples were reviewed according to the current classifications (i.e., TNM 2009, WHO 2004, ISUP 2005).

To determine the maximal tumor diameter, the edges of each tumor were outlined and the resulting distances were measured in millimeters; if a tumor was present in consecutive sections, the greatest measurement in all three dimensions (length, width, or depth) was considered the maximum diameter. In patients with complete transurethral resection of bladder (TUR-B) tumors and no evidence of tumors in the bladder at cystectomy, the final histology at TUR-B before the cystectomy was noted. Radical CP samples were processed in accordance with the descriptions in the guidelines of the Swiss Society of Pathology [12]. For histopathological grading, the 2004 WHO classification was used.

For macroscopic tissue sectioning, a mean of 14.4 (median 15, range 2–37) sections with a thickness between 3 and 5 mm were used. Of the total 114 processed samples, 26 (23.1 %) had been partially and 83 (76.1 %) had been completely embedded. For five samples, no information on the completeness of the embedding was available. Eighty (70.2 %) samples were prepared as whole mount sections, and 34 (29.8 %) samples were processed as standard specimen slides.

We applied the following most commonly used criteria for nonsignificant prostate cancer [22]: (i) Gleason score ≤6 without Gleason pattern 4 or 5, (ii) organ-confined disease, and (iii) tumor volume <0.5 cm^3.

To determine the maximal tumor diameter, the edges of each tumor were outlined and the resulting distances were measured in millimeters; if a tumor was present in consecutive sections, the greatest measurement in all three dimensions (length, width, or depth) was considered the maximum diameter. Pathological reports did not encompass tumor volume but did indicate tumor diameter. Based on the mathematical formula of spherical volume ($4/3\ \pi r^3$), we calculated the diameter for a tumor with a volume of 0.5 cm^3 and concluded that a tumor with a diameter larger than 1 cm would therefore be defined as significant.

All statistical inference testing and data visualization were performed using R 3.0.1. [24]. For continuous data, Wilcoxon rank sum tests were used, and for categorical data, Fisher's exact tests or Pearson's chi-squared tests were applied as indicated. The clinical follow-up information regarding PSA course, survival, progression, or recurrence was incomplete, and the data quality did not allow for further statistical analysis. P values lower than 0.05 were considered statistically significant.

Results

Detailed characteristics for all 114 bladder cancer patients are given in Table 1. Most of the detected bladder cancers were diagnosed as urothelial carcinomas (n=108; 94.7 %), while the remaining diagnoses were small cell carcinoma, sarcomatoid carcinoma, squamous cell carcinoma, mixed carcinoma, and urothelial dysplasia.

Incidental prostate cancer was identified in 68 (59.6 %) of the 114 CP specimens. The patient characteristics for the patients with incidental prostate cancer are given in Table 2. All prostate cancers were histologically classified as adenocarcinomas. In three patients, high-grade prostatic intraepithelial neoplasia (PIN) was diagnosed. Median age of patients with prostate cancer was comparable to that of the whole investigated population, and no significant difference in age between patients with (69.4 years) and without (69.7 years) prostate cancer was observed. Four (5.9 %) had a Gleason score of 4. The majority of patients (n=45) exhibited a Gleason score of 5–6 (66.2 %), and 19 patients (27.9 %) had Gleason scores ≥7. Sixty-one (89.7 %) of the 68 tumors displayed organ-confined growth, while extra-capsular extensions were observed in 7 (10.3 %). Of note, none of the 67 prostate cancer patients for whom the lymph node status had been determined demonstrated lymph node metastases. The mean number of resected lymph nodes was 15.5 (median 13.5; range 2–37). Overall, 62 (91.2 %) of the specimens showed tumor-free surgical margins (R0), and 6 (8.8 %) displayed positive margins (R1). Positive margins were identified dorsally (n=1), laterally (n=1), in the apex (n=2), and the basis (n=2).

PSA had been tested prior to surgery for 32 patients and upon follow-up for 20 patients. The mean PSA prior to surgery was 2.78 ng/ml (median 1.55 ng/ml, range 0.03–12 ng/ml). The mean preoperative PSA value of the groups with prostate cancer (3.3 ng/ml) and without detected prostate cancer (1.1 ng/ml) was significantly different (Fig. 1, p<0.05,

Table 1 Descriptive characteristics of bladder cancer detected in cystoprostatectomy specimens

Number of patients	114	
age (years)		
median	69.7	
range	44–88	
T stage	*n*	%
Ta	1	0.9
cis	7	6.1
T1	13	11.4
T2	40	35.1
T3	2	1.8
T3a	18	15.8
T3b	15	13.2
T3 total	35	30.7
T4 total	18	15.8
Concomitant Cis	20	17.5
Grade		
G2	18	16.8
G3	96	84.2
pN stage		
N0	83	72.8
N1	18	15.8
N2	12	10.5
Nx	1	0.9
Distant metastases		
M0	100	87.7
M1	1	0.9
Not reported	13	11.4
Resection margin		
R0	101	88.6
R1	13	11.4
Histology		
Urothelial carcinoma	108	94.7
Others	6	5.3

Wilcoxon rank sum test). In the low PSA group (PSA <4 ng/ml), prostate cancer was detected in 20 (70.4 %) of the 27 patients; 7 (41.2 %) cases were significant. Prostate cancer was detected in all five patients with a PSA >5 ng/ml. The comparison of the PSA values prior to surgery (n=31) correlated positively with the tumor diameter (p=0.0071, Spearman rho=0.58, R^2=0.33). After surgery, the PSA dropped to a mean of 0.034 ng/ml (median <0.03, range <0.03–0.09). Additionally, 30 (44.1 %) of the 68 detected prostate cancers fulfilled the criteria for a significant carcinoma. Eighteen tumors had a Gleason pattern of 4 or higher, 23 featured a diameter greater than 10 mm, 7 were not organ confined, and 13 met several of the criteria for clinical significance (Table 3). The mean preoperative PSA in the subgroup of insignificant prostate cancer (1.4 ng/ml) was significantly lower than the mean PSA in the subgroup of significant prostate cancer (5.4 ng/ml, p=<0.01) (Fig. 1).

Table 2 Descriptive characteristics of incidentally detected prostate cancer

Number of patients	68	%
Histology		
Adeno-ca	68	100
T stadium		
T2	2	2.9
T2a	34	50
T2b	4	5.9
T2c	21	30.9
T2 total	61	89.7
T3	1	1.5
T3a	6	8.8
T3 total	7	10.3
pN stage		
N0	67	98.5
N1	0	0
Nx	1	1.5
Resected LN (n=36)		
Mean	15.5	
Median	13.5	
Range	2–37	
Distant metastases		
M1	0	0
M0	57	83.8
Unknown	11	16.2
Gleason score		
Median	6	
2+2	4	5.9
2+3	6	8.8
3+2	5	7.4
3+3	34	50
3+4	10	14.7
7	1	1.5
3+5	1	1.5
4+3	5	7.4
4+5	1	1.5
5+3	1	1.5
Tumor diameter (mm)		n=68
Mean	9.6	
Median	8	
Range	1–44	
Tumor volume (cm^3)		n=68
Mean	0.268	
Range	0.0005–44.6	

In the group with incidental prostate cancer, a mean of 16.4 (median 17, range 5–34) tissue sections were sectioned. Fewer than 15 sections were used for 54 (47.4 %) of the prostates, and 15 or more sections were used for 60 (52.6 %) prostates.

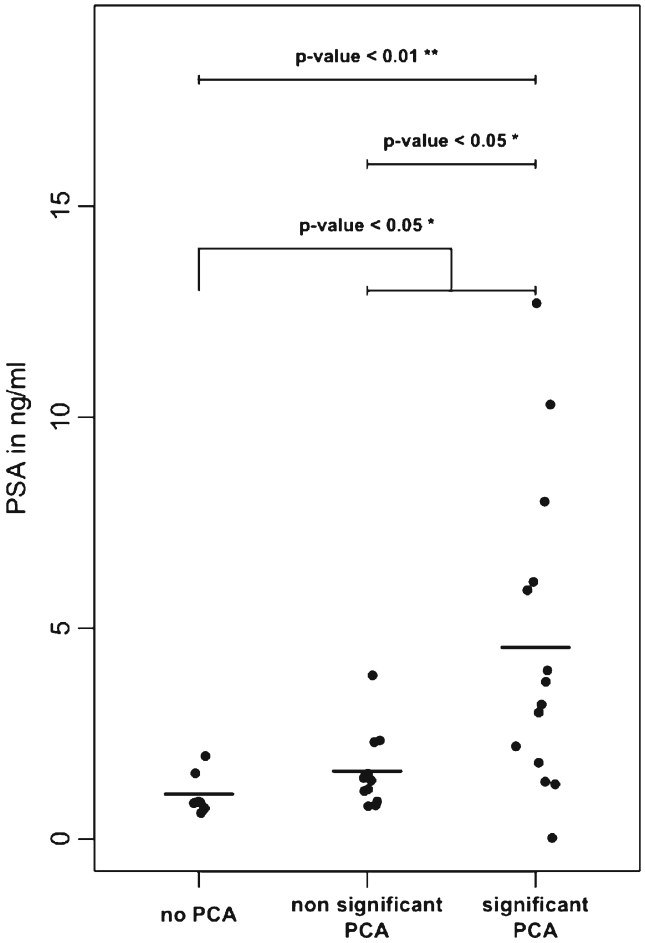

Fig. 1 Comparison of preoperative PSA values in the groups without, with nonsignificant, and with significant prostate cancer

This resulted in the detection of 23 (42.6 %) and 45 (75 %) incidental prostate cancers ($p<0.001$; Fisher's exact test), respectively, as presented in Fig. 2. Eighty-three (76.1 %) of the total 114 prostates were embedded completely, and 26 (23.9 %) were embedded partially. For five prostates, the embedding technique was not reported. Prostate cancer was detected in 60 (72.3 %) of the 83 completely embedded samples and in 6 (23.1 %) of the 26 partially embedded samples ($p<0.0001$; Fisher's exact test; Fig. 2). Significant prostate cancer was detected in 28 (33.7 %) of the 83 completely embedded samples and in 1 (3.8 %) of the 26 partially embedded samples ($p<0.01$; Fisher's exact test).

Table 3 Further criteria for the clinical relevance of prostate cancer (n = patients with prostate cancer fulfilling the indicated criteria)

	Number	Percent
Gleason score including a pattern ≥4	18	26.5
pT stage ≥T3	7	10.3
Max tumor diameter >10 mm	23	33.8
More than one criterion for relevant cancer	13	19.1
<60 years	13	19.1
≥60 <75 years	35	51.5
≥75 years	20	29.4
Total clinical relevant tumors	30	44.1

We compared the rates of complete embedding with the detection rate of prostate cancer in the periods between 2000 and 2006 and 2007 and 2012. The rates of completely embedded samples in the two periods were 55.3 and 91.9 %, respectively. The first period yielded an overall prostate cancer prevalence rate of 50 %, and the second period yielded 67.7 %.

Whole mount sections were used for 80 (70.2 %) samples, and standard slides were used for 34 (29.8 %) samples. In 55 (68.8 %) of the whole mount sections and in 13 (38.2 %) of the standard slides, prostate cancer could be detected ($p<0.01$; Fisher's exact test; Fig. 2).

Discussion

Here, we explored the prevalence of incidental prostate cancers in CP specimens in a highly industrialized town area, where most of the CP specimens are processed centrally at a single pathology institute. Comparison of complete versus incomplete specimen processing indicated prostate cancer prevalence rates reaching up to 75 % for completely processed specimens.

Based on previous publications, including a total of 11,553 patients, the mean prevalence rates of prostate cancer at radical CP in Europe and globally were 25.2 and 26.5 %, respectively (Table 4). Detection rates are influenced by technical variables [3, 11], study populations [3], and geographic [23, 28] factors; e.g., studies from Asia generally reported lower rates than those from the USA and Europe (Table 4). Compared to these previously reported rates, the 59.6 % in our study represent one of the highest published prevalence rates of incidental prostate cancer in CP specimens (Table 4). Generating a best-case scenario and analyzing the subgroup of 53 patients with complete embedding, the use of 15 or more sections and whole mount sections results in a prevalence rate of 75.5 %. This extraordinary high proportion is unlikely to be greatly biased by the retrospective nature of the study because our study was based on a consecutive series of CP specimens. Our high prevalence of incidental prostate cancer also clearly exceeded the rates of most previous autopsy series [7]. Only Sakr et al. discovered unexpected prostate cancer at a similarly high rate of 55 and 64 % of autopsied patients who had died in their 6th and 7th decades, respectively, after a histological examination of their whole prostates [25].

To the best of our knowledge, this is the first report on the prevalence of incidental prostate cancer in CP specimens in Switzerland. It could be speculated that the high prevalence in an industrialized town area may be due to an increased exposure to potential carcinogenic factors that drive prostate cancer. However, to date, there has been no published evidence

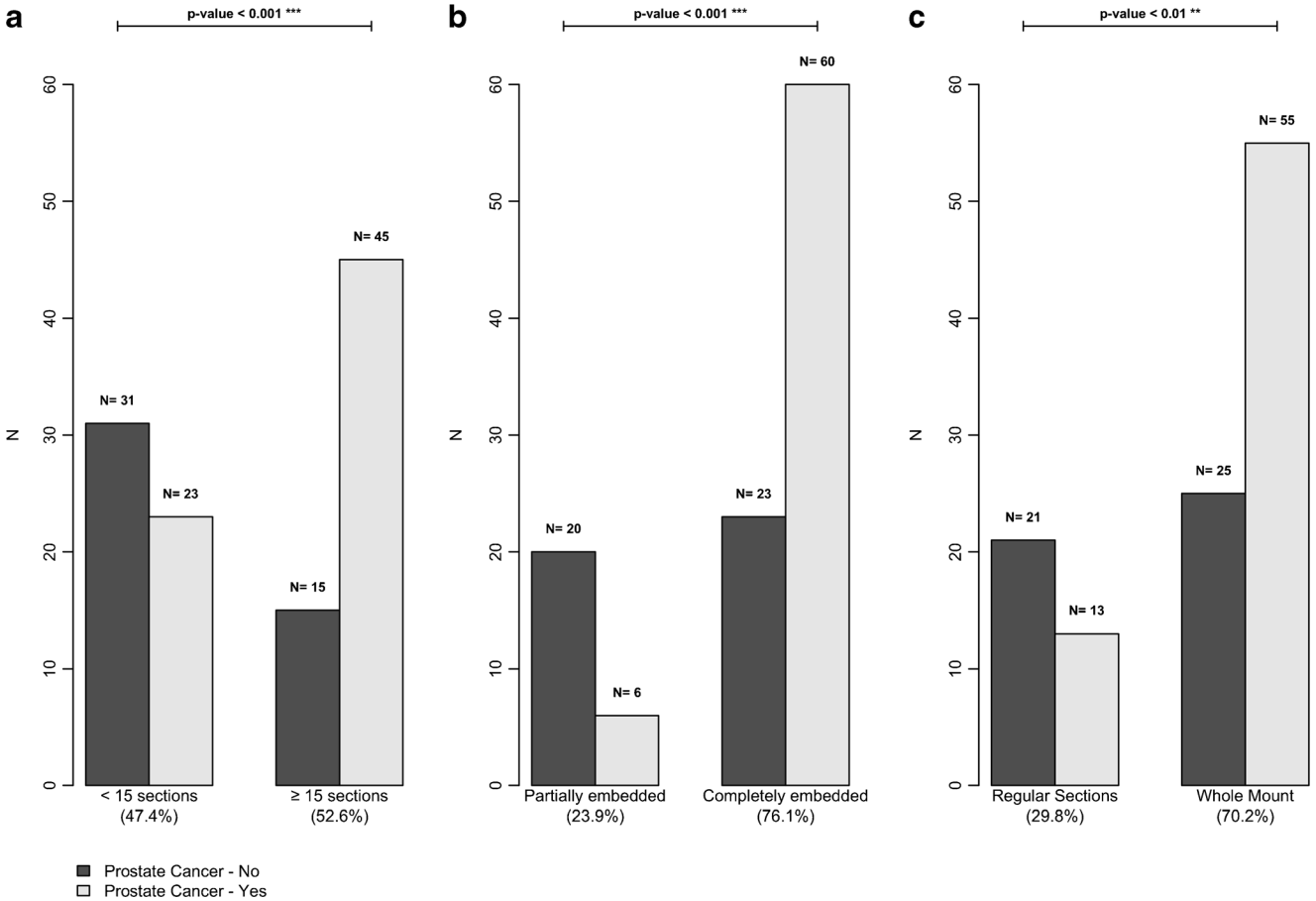

Fig. 2 Detection rates of incidental prostate cancer, according to the pathological work-up. **a** <15 versus >15 prostate sections. **b** Complete versus partial embedding. **c** Regular slides versus whole mount slides. The numbers in *brackets* indicate the percentage of specimens in each indicated group

that a high prevalence of incidental prostate cancer could be driven by exposure to carcinogens in the context of the substantial presence of chemical and pharmaceutical industries or by other, as yet undefined, exposures in our region.

Instead, the extent of histological processing appears to be the most influential factor to explain the high prostate cancer prevalence (Fig. 2). Several published results have shown that lower section thickness increases prostate cancer detection rates [11, 30]. In our study, the prostates were processed into 3–5 mm tissue slices and paraffin blocks, and sections from 15 or more tissue blocks significantly raised the prostate cancer detection rates. Although the section number can depend on the size of the prostate gland, our results suggest that prostate cancer detection rates increased proportionally with the number of tissue blocks and sections. The same was true for complete versus incomplete embedding of the prostate, which is in line with other published series [3, 14]. Furthermore, complete embedding significantly improved ($p<0.01$) the detection of significant prostate cancer compared to partial embedding in our series. The use of the whole mount technique [19] resulted in a significantly ($p<0.01$) higher prostate cancer detection rate of 68.8 %, compared to the use of regular slides (38.2 %). As a caveat, 89.3 % of the prostates processed as whole mount sections, but only 26.5 % of those processed as regular slides were completely embedded. Finally, the overall prostate cancer prevalence rate of 67.7 % between 2007 and 2012, when most of the samples were embedded completely, indicates that a consequent use of complete embedding, the use of whole mount sections, and/or a high section number can significantly influence the prostate cancer prevalence rates in CP series.

The clinical relevance of incidental prostate cancers detected at radical CP remains questionable. Two studies demonstrated significantly worse survival after radical CP for patients with concurrent tumors [8, 27], while Pritchett found no difference in the mortality rates [11]. In a recent series of 1476 patients, 22 % of the detected prostate cancers were classified as significant. However, the most influential factor in this series was not the presence of relevant prostate cancer but prostatic infiltration of a urothelial carcinoma [6]. In our series, almost half of the prostate cancers met criteria for significant prostate cancer (Table 3) but none had detectable lymph node metastases (Table 2). Our rate of clinically significant prostate cancer is comparable to the other reported rates (Table 4), even though the reported rates are diverse, based on the different criteria being applied [22]. Elevated

Table 4 Worldwide reported rates of incidental prostate cancer in cystoprostatectomy specimens

Author	Region	Year	*N*	Mean age	Section thickness (mm)	Sampling	PCa total	PCa %	Significant PCa (%)
North America									
Winfield [3]	Iowa, USA	1987	80	63.7		Complete	22	27.5	11 (50 %)
Pritchett [11]	South Carolina, USA	1988	165	65		Partial	45	27.3	8 (17.8 %)
Montie [11]	Cleveland, USA	1989	84	62	4–5	Complete	39	46.4	6 (15 %)
Kabalin [3]	Standford, USA	1989	66	64	3	Complete	25	37.9	3 (12 %)
Abbas [11]	Miami, USA	1996	40	64.3	2–3	Partial	18	45	
Ward [3]	Rochester, USA	2004	129	69			30	23.3	18 (60 %)
Revelo [11]	Nashville, USA	2004	121	67.4	5	Complete	50	41.3	24 (48 %)
Abdelhady [3]	Ontario, Canada	2007	204	67		Complete	58	28.4	18 (31 %)
Weizer [3]	Michigan, USA	2007	35	65			16	45.7	4 (25 %)
Bruins [6]	Los Angeles, USA	2013	1476	69	3–5		559	37.9	123 (8.3 %)
Europe									
Moutzouris [11]	Athens, Greece	1999	59	66.5	5	Complete	16	27.1	
Conrad [11]	Hamburg, Germany	2001	133	60	3	Complete	58	43.6	11 (19 %)
Prange [3]	Hamburg, Germany	2001	85	64	4	Complete	41	49.0	4 (10 %)
Cindolo [3]	Naples, Italy	2001	165	69	3	Partial/complete	17	10.3	
Kouriefs [3]	Gillinghan, England	2005	128				23	18	
Delongchamp [11]	Paris, France	2005	141	62	4	Complete	20	14.2	14 (70 %)
Montironi [3]	Ancona, Italy	2005	132	61		Complete	55	42 %	
Ruffion [11]	Lyon, France	2005	100	62	2.5	Complete	51	51	6 (12 %)
Rocco [11]	Milano, Italy	2006	63	67	3	Complete	34	54	12 (35 %)
Winkler [29]	London, England	2007	97		2	Partial	58	60	31 (53 %)
Barbisan [5]	Marche, Italy	2008	248	68	3		123	49.6	23 (18.7 %)
Mazzuchelli [18]	Ancona, Italy	2009	248	68	3	Complete	123	49.6	23 (18.7 %)
Gakis [15]	Tübingen, Germany	2010	95	68	4–5		26	27.4	7 (27 %)
Buse [8]	Germany	2012	1122	65.6	2–5		200	17.8	
Fritsche [14]	Regensburg, Germany	2012	295	68	4	Partial/complete	91	30.8	41 (45 %)
Alsinnawi [2]	Dublin, Ireland	2012	108	64	4	Complete	35	32.4	10 (28.5 %)
Sruogis [27]	Vilnius, Lithuania	2012	81	61.3			27	33.3	13 (48.1 %)
Pignot [21]	France	2013	4251	70.2			905	21.7	
Wetterauer	Basel, Switzerland	2013	115	68.9	3–5	Partial/complete	68	59.6	40 (58.8 %)
Asia									
Lee [30]	Kweishan, Taiwan	2006	248	63	5	Complete	10	4	
Yang [30]	Thaijung, Taiwan	1999	49	67.8	3	Complete	16	32.6	
Nakagawa [20]	Tokyo, Japan	2009	349	65	5		91	26.1	68 (74.7 %)
Jin [16]	Hangzhou, China	2008	264	70.9	5	Complete	37	14	12 (32.4 %)
Zhu [30]	Shanghai, China	2009	92	67.1	5	Complete	3	3.3	1 (33.3 %)
Australia									
Ahmadi [1]	Sydney, Australia	2012	129				50	38.8	35 (70 %)
Middle east									
Aydin [3]	Turkey	1999	121	67.1			17	14	
Hosseini [3]	Theran, Iran	2007	50	62.5		Partial	7	14	4 (57 %)
Aytac [4]	Bursa, Turkey	2011	300	62	3–5	Complete	60	20	40 (66.7 %)
North America			2400				862	35.9	
Europe			7551				1903	25.2	
Asia			1002				157	15.7	
Australia			129				50	38.8	
Middle East			471				84	17.8	
Total			11,553				3056	26.5	

PSA may be predictive of the presence of significant cancer and a large tumor diameter, as suggested by our comparison; however, the patient numbers are low, and the clinical data are insufficient for making final conclusions about these findings.

Srougi et al. proposed a cystectomy in combination with the enucleation of adenomas [3], and TUR-P with preservation of the capsule prior to cystectomy was reported as an option by Colombo et al. [10]. These techniques might be applicable for selected patients for whom the preservation of potency is paramount, but in light of our findings, they may stand against the principles of cancer surgery. If attempted though, it seems reasonable to perform prostate biopsy before such surgery as even low PSA values cannot exclude the presence of prostate cancer (Fig. 1). Given the high risk of prostate cancer in patients undergoing CP, special attention to the removal of the prostate seems advisable. Once the presence of prostate cancer has been confirmed after CP, specific oncologic follow-up may be indicated. At least in high-risk prostate cancer, the oncologic follow-up might include regular PSA monitoring in order to detect residual, recurrent, or metastatic disease.

It has been suggested that bladder cancer patients have an increased risk of being diagnosed with prostate cancer [17, 26]. In fact, a higher coincidence rate of bladder and prostate tumors compared to their presence in the general population has been reported [9]. Such a correlation may be explained partly by the relatively high age of patients and the fact that exposure of patients with either tumor type to urologists favors the detection of other urogenital cancers, if present. Finally, there is currently no compelling evidence for a common link between prostate and bladder cancers.

Several studies have reported the influence of specific pathologic sampling techniques on prostate cancer detection rates in CP specimen. To the best of our knowledge, we are the first to assess the influence of specific aspects of pathologic sampling within one series at a single Pathology Institute and to report the incidental prevalence rate of PCa at CP in Switzerland. Compared to the extremely variable reported rates of incidentally discovered prostate cancers, our reported rate of 59.6 % ranks among the highest published rates. Subgroup analysis of samples with complete embedding, the use of 15 or more sections, and whole mount sections resulted in prevalence rates of more than 75 % in our series.

Conclusions

We report a high prevalence of incidental prostate cancer at CP of 59.6 %. This is more than twice as high as the mean reported European and worldwide prevalence of 26.5 %. We demonstrate the paramount importance of a complete histopathological work-up for estimating the true prevalence of prostate cancer in a given population and for the detection of significant prostate cancer. Our results call for a careful surgical approach to the prostate at radical cystoprostatectomy.

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

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