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Prostate Cancer

Sensitivity and Detection Rate of A 12-Core Trans-Perineal Prostate Biopsy: Preliminary Report

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Abstract

Objectives: The various prostate biopsy methods are usually compared in terms of the diagnosis rate of prostate cancer. However, the prevalence of cancer in patients with a negative prostatic biopsy is not usually known. We determined the sensitivity and detection rate of 12-core transperineal biopsies in patients not previously investigated for prostate cancer.

Methods: We performed prostate biopsy in 63 patients (median age 67 years) before radical cystoprostatectomy for high-grade bladder cancer. We then assessed the relationships between biopsy result, prostate cancer in the surgical specimen, and other variables.

Results: 17.2% of patients had a positive biopsy and 54% had prostate cancer on definitive histology. Biopsy sensitivity was 32.3% overall, 75% for clinically significant cancers, and 11% for non-significant cancers. Median PSA was 1.2 ng/ml, PSA levels did not correlate with the presence of prostate cancer, the presence of clinically significant cancer, bioptic diagnosis, or prostate volume. Age correlated with risk of cancer.

Conclusions: According to autopsy series, the prevalence of prostate cancer is greater than 50% in males older than 60, yet low PSA levels do not reliably indicate disease absence. The sensitivity of double sextant biopsy is unsatisfactory overall (32%), but acceptable (75%) for diagnosing clinically significant cancer.

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1. Introduction

In 1989 random transrectal sextant biopsy was proposed as the gold standard for prostate cancer detection [1]. Since then, several alternative random sample techniques have been proposed [2,3], most of which increase the number of samples or change the sampling pattern in the hope of increasing the rate of diagnosis. Transrectal ultrasound-guided biopsy is the recommended diagnostic method with a minimum of 6–10 systematic, laterally directed cores [4].

A much less widespread alternative to the transrectal approach is the transperineal approach. The actual technique employed, transrectal or transperineal, is probably much less important than where the needles are placed in the prostate [5]; a high cancer detection rate can be achieved by 12-core transperineal prostate biopsy in patients with PSA >4 ng/ml [5], even though the false negative rate of the procedure is still unclear.

The aim of the present study was to determine the false negative rate of a 12-core transperineal prostatic biopsy in order to evaluate sensitivity and negative predictive value in a series not previously investigated for prostate cancer.

2. Materials and methods

2.1. Patients

From May 2002 to October 2004, 63 consecutive patients underwent radical cystoprostatectomy, 41 at the European Institute of Oncology and 22 at the Department of Clinical Urology, University of Milan, for infiltrating or superficial high-grade bladder cancer that was not amenable to conservative treatment. All patients gave informed consent to the pre-surgical biopsy and the use of the surgically removed material for the purposes of this study. Before the operation, digital rectal exploration (DRE) was performed, and PSA levels in the blood were determined by microparticle enzyme immune assay (MEIA) using an Axsym analyser (Abbott).

Patients were prepared and positioned for surgery according to Emiliozzi et al. [5]. Immediately after induction, transrectal ultrasonography (BK ultrasound, 7.5 MHz probe) was performed. Twelve-core transperineal prostate biopsy was then performed by two urologists (BR and MF) under ultrasound guidance using a Fast-Gun biopsy pistol (Sterylab, Rho, Italy) with a 16-gauge needle. Biopsy cores were nominally 20 mm long. Only the peripheral region of the gland was sampled with six cores per side (Fig. 1). This scheme was adopted based on observations of cancer development within the prostate [6].

2.2. Pathological evaluation

Biopsy material was fixed in 10% formalin, paraffin-embedded, longitudinally sectioned, and stained with hematoxylin and eosin. Length and Gleason score were determined for each core.

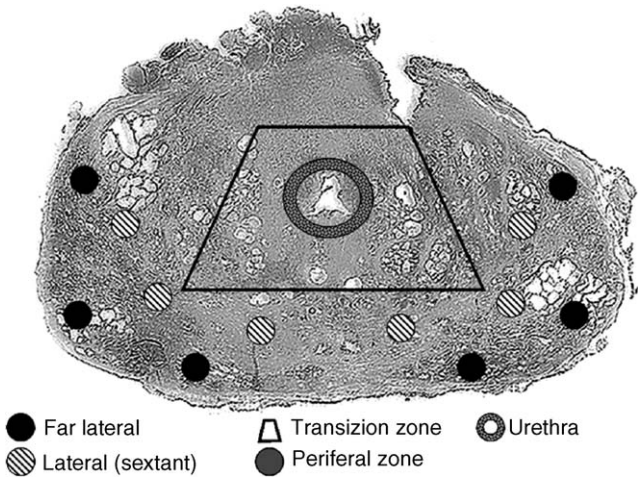

Fig. 1 – Coronal prostate section. Diagram illustrating core sites: 3 far lateral and 3 paramedian bilaterally.

After prostatic biopsy, cystoprostatectomy was performed. On the fresh surgical specimen, the individual organs were measured in three dimensions, 10% neutral buffered formalin was then injected into the bladder until fully distended, and the entire specimen was fixed in 5–10 volumes of 10% neutral buffered formalin for 18–24 hours.

After fixation and before inking the surface, the prostate was examined macroscopically for post-surgical clefts in peri-prostatic tissue, which were noted to avoid their misinterpretation as surgical margins. The prostate was then inked with different colours to facilitate left and right side recognition. The specimen, while still wet, was then briefly immersed in Bouin's fixative and air dried.

The prostate was sampled using the whole-mount section method. Coronal lengths, labelled progressively, were cut perpendicular to the urethral major axis at 0.3 cm intervals from the apex to the junction with seminal vesicles. The first apical length was cut para-sagittally (parallel to the major axis of the urethra) into 0.2–0.3-cm thick sections, labelling the right and the left sides. The lengths were placed in inclusion cassettes and moulds and embedded in paraffin. From the blocks, consecutive 0.3-μm thick sections were cut, stained in hematoxylin and eosin, and evaluated microscopically. The greatest diameter of each tumour focus was obtained by marking the tumour contour on the glass slide and measuring this distance with a ruler. If tumour size was <0.5 cm, an ocular micrometer was used for measurement The volume of carcinoma in the entire prostate was determined using the grid method [7,8] and was the sum of the volumes of individual tumour foci. The sum of each area was multiplied by the thickness of the average slice, and the sum of these volumes was multiplied by 1.25 to correct for tissue shrinkage during processing.

2.3. Data analysis

We analysed the correlation between patient age, PSA, prostate volume, biopsy, and surgical specimen outcome.

Biopsy false negative rate was then calculated to define sensitivity and negative predictive value of the procedure.

We assessed sensitivity and negative predictive value even in the subgroup of patients with clinically significant disease, as defined by Epstein et al. in 1998 (non-organ confined disease or Gleason pattern 4 or 5 or tumour volume >0.5 cc) [9].

Qualitative data are presented as frequencies or percentages; continuous data are provided as medians and range and compared using the Kruskal-Wallis test. Exact 95% confidence intervals (95% CI) for proportions were calculated using the binomial distribution. Associations were considered significant for two-sided p values of ≤ 0.05.

3. Results

Mean age of the 63 patients was 67 years (range 48–82); 1 of 63 had positive DRE. Mean PSA of the population was 1.2 ng/ml (range 0.2–9.1) and 7 of 63 had PSA >4 ng/ml. Mean prostatic volume was 34.9 cc (range 11.9–134.8) (Table 1).

Fifty-one (81%, 95% CI, 69–85%) of the 63 patients had a negative biopsy, 11 (17.5%; 95% CI, 9–29%) had a positive biopsy for adenocarcinoma, and 1 (1.5% 95% CI, 0.04–8.5%) had atypically proliferating small acini (ASAP). Urothelial invasion was present on the surgical specimen in two patients with a negative biopsy.

Nominal length of the core was 22 mm. The real median length was 11.2 mm (range 7–20 mm). The median length of the core for positive biopsies was 11.3 mm (range 4–20 mm) for negative biopsies 11.2 mm (range 7–13 mm).

Pathological analysis of the surgical specimen showed 25 (40%; 95% CI, 28–53%) patients without prostate carcinoma, 34 (54%; 95% CI, 41–67%) with prostate carcinoma, and 4 (6%; 95% CI, 2–15%) with high-grade III prostatic intraepithelial neoplasia (PIN).

Median PSA and median prostate volume did not correlate with the presence of prostate cancer in the biopsy or in the surgical specimen, whereas a higher median age of the patients was associated with the presence of cancer in the biopsy and in the surgical specimen.

Of the 34 patients with prostate carcinoma on the surgical specimen 20 (58%) were pT2a, 12 (35%) were pT2c, two had extraprostatic extension, one pT3apN1, and one pT4N1 (AJCC TNM 6th ed, March 2002) both diagnosed by transperineal biopsy. Gleason score was ≤6, in 27/34 (79%), 7 in four cases, and >7 in the remaining three patients, two of whom had prostate cancer lymph node metastases. Only one patient with Gleason score >6 had a negative prostate biopsy.

Median tumour volume was 0.2 ml (n = 34, range 0.001–9.6); None of the 34 patients had cancer located solely in the prostate transition zone.

The sensitivity of prostate biopsy in identifying specimen-confirmed cancer was 32.3% (95% CI, 17–50%), specificity was 100% (95% CI, 86–100%) and negative predictive value was 52.1% (95% CI, 37–67%) (Table 2). The likelihood ratio of prostate cancer for a negative test was 0.68.

Research was also extended to the subgroup of patients with clinically significant cancer according to Epstein's criteria [9].

Twelve (20%; 95% CI 10.2–31%) of the 63 patients had clinically significant cancers. Nine of these were identified by biopsy, thus biopsy sensitivity was 75% (95% CI, 43–94%); specificity was 95.7% (95% CI, 85–99%); and negative predictive value was 93.7% (95% CI, 83–99%). Prostate biopsy was positive in two (9% of total; 95% CI, 1–29%) of the 22 patients with clinically insignificant prostate cancer.

Distribution of prostate cancer volume is reported in Fig. 2. Median PSA did not differ between those with (1.55 ng/ml) and without (1.19 ng/ml) clinically significant disease or those without prostate cancer (1.11 ng/ml) (Kruskal-Wallis, p = 0.87) (Fig. 3). However, these three groups differed in age distribution

Table 1 – Relevant patient characteristics related to biopsy and surgical specimen outcome

Patient characteristics		BxP −	BxP +	Kruskall-Wallis	Pca −	Pca +	Kruskall-Wallis
No. Pts	63	51[a]	11[a]		25[b]	34[b]	
Median age	67 years (48–82)	64	72	p = 0.008	63	67.5	p = 0.022
Median PSA	1.2 ng/ml (0.2–9.1)	1.5 (0.2–9.1)	0.95 (0.4–6.8)	p = 0.44	1.1 (0.2–9.1)	1.2 (0.4–6.8)	p = 0.44
PSA >4 ng/ml		6/63	1/63		4/63	3/63	
DRE		0/63	1/63		0/63	1/63	
Median Prostate volume	34.9 ml (11.9–134.8)	33.5 (11.9–134.8)	39.5 (23–60)	p = 0.32	33.5 (15.3–66.4)	35.6 (11.9–134.8)	p = 0.98

Bxp −: negative biopsy; Bxp +: positive biopsy; Pca −: absence of prostate cancer on the surgical specimen; Pca +: presence of prostate cancer on the surgical specimen.
[a] 1 patient had ASAP.
[b] 4 patients had PIN III.

Table 2 – Overall and clinically significant[a] prostate cancer detection

	Overall	CI 95%	Clinical significant[a]	CI 95%
Sensitivity	32.3%	17–50%	75%	43–94%
Negative predictive value	52.1%	37–67%	93.7%	83–99%
Detection rate	17.5%		14.2%	

[a] According to Epstein [9], clinically significant prostate cancer is defined as (volume ≥0.5 ml or Gleason score >6 or presence of pattern 4).

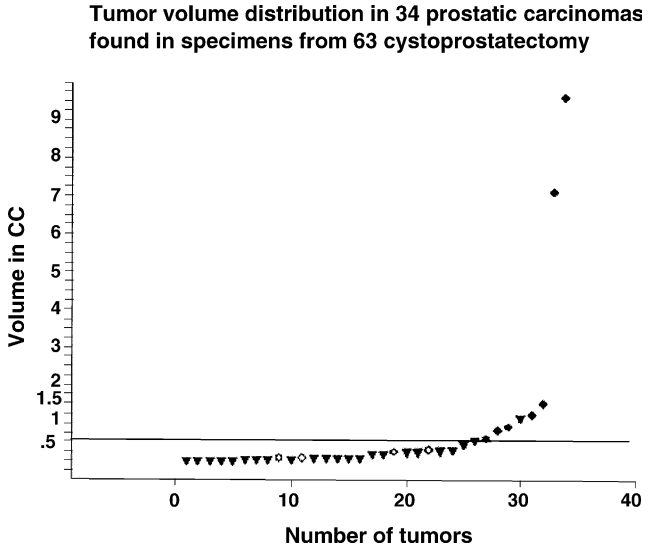

Fig. 2 – Distribution of prostate cancer volume in the 34 patients (in a series of 63 undergoing cystoprostatectomy) in whom prostate cancer was found. Circles indicate a negative biopsy, triangles a positive biopsy; a solid symbol indicates tumour volume <0.5 ml and an open symbol indicates tumour volume ≥0.5 ml.

(median ages 73, 64.5, and 63, respectively; Kruskal-Wallis, $p = 0.003$).

Among the 56 patients with no pre-operative suspicion of prostatic disease (PSA 0–4 ng/ml; negative DRE), 10 (17.8%) had a positive biopsy and 8 of these (14.2% of 56; 95% CI, 6.4–26.2%) had clinically significant disease; 31 (55%, 95% CI: 41.5–68.6%) had cancer in the surgical specimen, and 11 of these (19.6% of 56; 95% CI 10.2–32.4%) had clinically significant disease.

4. Discussion

The detection rate of prostatic cancer in sextant biopsy samples is about 25% in patients with PSA >4 ng/ml [10]. However, repeated biopsies or computer simulations indicate that sextant biopsy is associated with false negative rates of 15–34% [11–15]; autopsy series show prostate cancer in 27% of men aged 30–40, and in more than 60% of men older than 80 [16]. Clearly, sextant biopsy fails to detect a significant proportion of prostate cancers. Also, although the proportion that develops clinically significant disease is considerably lower than the autopsy prevalence, clinically significant prostate cancers cannot be distinguished from clinically insignificant ones before surgery.

A more pressing clinical problem is the frequent discordance between PSA findings and prostate biopsy findings. Urologists commonly propose a repeated biopsy in patients with negative biopsy histology but high PSA, a proposal justified by the high false negative rate of biopsies. In a recent study Djavan et al. [17] reported that among cancers identified at second biopsy in patients with negative initial biopsy, the proportion that was clinically significant was the same as the proportion of clinically significant cancers identified by the first bioptic set [18]. Assessing the diagnostic accuracy of these modalities is therefore very useful.

In this study we chose the less common transperineal approach because biopsy cores, taken along

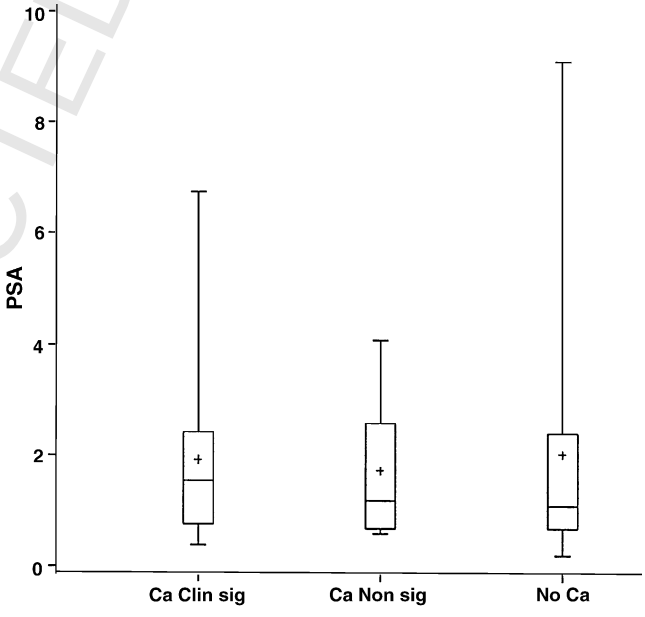

Fig. 3 – Box plots showing distribution of PSA levels (ng/ml) according to disease status and clinical significance as defined in text. The crosses indicate the means. Ca Clin sig = clinically significant cancer. Ca Non sig = clinically non significant cancer. No Ca = no cancer. Note the large overlap of PSA concentrations.

a longitudinal plan parallel to the rectum, enable us to sample only the peripheral zone, whereas in the transrectal technique a part of adenoma happens to also be sampled even in biopsies directed only at the peripheral zone [19]. We chose a 16-gauge needle because detection rate and complications seemed to be proved the same as with an 18-gauge [20], and we are assessing whether there may be advantages in terms of inclusion and cut of the cores. Although the nominal length was 20 mm, the overall mean core length was 11.2 mm, about 3 mm less than the length published by Iczkowski et al. [21] (despite their use of an 18-gauge needle), who had shown a correlation between core length and prostate cancer detection rate with the sextant technique. The difference can probably be partly explained by the fact that Iczkowski calculated the core length summing up to three fragments, while we gave only the length of the longest core of each sample.

As for the choice of 12-core sampling, this is in line with the guidelines [4] and with current common clinical practice: according to Descazaud et al, up to 70% of urologists sample 10–12 cores [22].

Analysing the results of the pathological specimen, we found that more than 50% of the subjects had prostate cancer, a result in line with autopsy studies. In particular, focusing on the 6th, 7th, and 8th decades, representing 94% (59 of 63) of our population, our series revealed a prostate cancer prevalence of 42.8%, 54.5%, and 63.6%, respectively. Sakr et al. analysed autopsy prostate specimens of 525 men who died of trauma. Of these 211 were Caucasian and the prevalence of prostate cancer in this group was 44%, 65%, and 83% in the 6th, 7th, and 8th decades, respectively [23]. Similarly, in a recent autopsy series Soos et al. found in 139 men without history of urological disease 32.1%, 50%, and 64.7% of prostate cancer in the same age ranges [24].

We then assessed the data obtained with the prostatic biopsy.

The diagnostic rate was much lower than with other 12-core transperineal techniques such as that of Emiliozzi et al, which had a detection rate of 51% with 12 cores, in a population with PSA >4 ng/ml [5] and Ficarra et al, who had a detection rate of 42.1% in a population of patients with mean PSA of 7.6 ng/ml [25]. Our data were closer (17.5% vs. 15.2%) to those obtained by Thompson et al. who used, in most subjects examined, the transrectal sextant technique [26].

The two significant tumours undetected by biopsies were localised in the peripheral zone, in the parenchymatous areas, usually sampled with our technique. With respect to this, the needle tract unfortunately skims over the neoplastic area without reaching the tumour (Fig. 4). Notwithstanding, we found that the sensitivity of our biopsy technique was 32.3% and the negative predictive value 52.1%. We compared our data with those of Terris [27], who carried out a similar study performing transrectal sextant prostate biopsy before cystoprostatectomy. Our figures are much lower than the 60% and 89.2%, respectively, reported in a smaller series of similar age (43 patients, median 71.5 years, range 52–83) to ours (63 patients, median 67 years, range 48–82) but characterised by higher PSA levels (median 4.1 ng/ml, range 0.7–10 vs. our 1.2 ng/ml, range 0.2–9.1) and fewer patients with prostate cancer (23% compared to our 54%). Furthermore, Terris's series was characterized by larger tumour volumes, which facilitate bioptic diagnosis, thereby reducing the false negative rate and increasing the negative predictive value. Six of Terris's 10 cases had tumours >2 ml, while only 2 of our 34 cases had similar volumes (7.1 and 9.6 ml). These data may explain the greater sensitivity and lower false negative rate found in the sextant biopsy series compared to our series, which theoretically used a more exhaustive biopsy technique. However, our biopsy method identified clinically significant (sensitivity 75%) more efficiently than total cancers (sensitivity 32%).

PSA values in our entire series were low, with median levels <4 ng/ml in all groups, and there were no significant differences between them. This somewhat anomalous finding is nevertheless consistent with the results of the recent study by Thompson et al. [26], which found that more than 15% of 2,950 men with negative DRE and PSA <4 ng/ml had prostate cancer on sextant biopsy

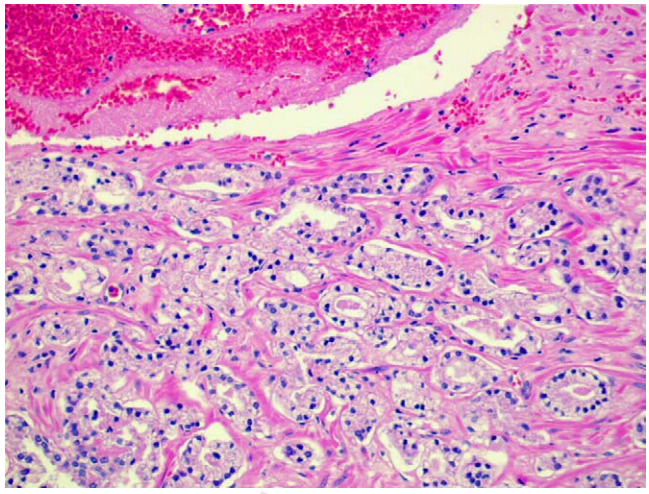

Fig. 4 – Haemorrhagic area contiguous to clinically significant tumour, where neoplastic glands are only grazed by the needle tract.

after a seven year follow-up. Similarly, in a preliminary analysis of ERSPC data, Ciatto et al. [28] found that reduction of the biopsy referral threshold from 4 to 3 ng/ml did not result in a significant reduction in the biopsy diagnostic rate, and that even PSA levels in the 2–3-ng/ml range were associated with cancer diagnosis rates fairly similar to those in men with PSA $\geq$4 ng/ml. Ciatto et al. concluded that PSA levels in the 1–10-ng/ml range were not effective predictors of prostate cancer [28]. More recently, Stamey et al. [29] concluded that the role of PSA in prostate cancer diagnostics was over in the USA, emphasizing that serum PSA correlated well with prostate volume, but not with cancer risk.

Nevertheless, the widespread use of PSA testing has undoubtedly increased the prostate cancer diagnosis rate over the short term and has caused a marked stage migration. However, lowering the PSA threshold for biopsy may increase the proportion of indolent cancers identified; using tumour volume <0.5 cc with no high-grade components as a cut-off to identify indolent tumours, Epstein reported 9–29% of clinical insignificant diseases in T1c prostate cancer in patients with PSA >4 ng/ml [9], whereas Hautmann reported that 9% of insignificant cancers were found with transrectal sextant biopsy in a population of asymptomatic men with PSA <4 ng/ml [16].

In our study, 35.3% of the cancers identified in the surgical specimen were clinically significant, and the 12-core transperineal technique identified 75% of these, but only 11% of the clinically insignificant cancers. Considering only patients with PSA <4 ng/ml and negative DRE, our biopsy technique afforded a greater cancer detection rate (17.8%, 95% CI 6.4–26.2%) than reported by Hautmann et al. (5%, 95% CI 2–10%) using the standard transrectal sextant technique [16]; we also detected a greater proportion of clinically significant cancers: 8/10 (75% 95% CI 43–94%) vs. Hautmann et al.'s 3/11 (27%, 95% CI 6–61%). Moreover, in the Hautmann study, PSA levels (always <4 ng/ml) were significantly associated with the presence of prostate cancer; in our study there was no such association.

Finally, the increase in the incidence of prostate cancer in prostate biopsy and definitive surgical specimen in relation to age appears in line with the consolidated data in the literature [4,23].

Our study has several possible limitations: the small sample size seems to be the major limitation, therefore our data need to be considered preliminary.

4.1. *Population selection*

The only way to verify the rate of false negatives is to have a pathologic analysis of the prostate even when the biopsy is negative. One way to do this is to examine the whole prostate in cadavers following biopsy. Such an approach has not been described previously, and PSA levels are unlikely to be systematically available in autopsy cases. By contrast, use of cystoprostatectomy specimens from bladder cancer patients undergoing prostate biopsy is an established procedure [30], although such patients may not be representative of the general population. In our series this possibility seems unlikely because the frequency of prostate cancers diagnosed in the surgical specimen is closely similar to the autopsy prevalence of prostate cancer in subjects of similar age ranges [23].

4.2. *Two different operators*

The two urologists who performed the biopsies at different centres followed exactly the same biopsy protocol and achieved closely similar biopsy rates (7/41 or 17% at the European Institute of Oncology; 4/22 or 18% at Clinical Urology University of Milan; $p = 0.95$).

5. Conclusions

This study provides further evidence that prostate cancer is present in more than 50% of elderly males. It also seems to confirm that most of these cancers are not identified by prostate biopsy, even using a more exhaustive sampling technique than the standard sextant biopsy. Importantly, our preliminary data seem to indicate that 12-core biopsy is able to identify about 75% of clinically significant cancers, while only 11% of clinically insignificant cancers are diagnosed. Somewhat anomalously, PSA levels in our series were uninformative, correlating neither with the overall risk of prostate cancer nor with the risk of clinically significant disease. We are trying to collect further data to confirm these preliminary data.

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