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Incidence of insignificant prostate cancer using free/total PSA: results of a case-finding protocol on 14,453 patients

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Table 1. Overall incidence of PCa in patients with tPSA \leq 10 ng/mL and prevalence of cancer in 2123 men submitted to prostate biopsy

PSA ng/mL	PCa (n)	Overall Incidence	Prevalence
< 2.5	14	0.2%	29.1%
2.6 - 4	49	1%	37.4%
4.1-10	396	17.1%	28%

Table 2. Gleason score (GS) values in 459 patients with PCa (PSA \leq 10 ng/mL) submitted to primary prostate biopsy.

tPSA ng/mL	GS 3 + 3	GS 3 + 4	GS 4 + 3	GS 8	GS 9	GS 10
< 2.5	10	2	2	-	-	-
2.6-4	22	18	5	4	-	-
4.1-10	257	58	23	38	19	1
Total	289 (63%)	78 (17%)	30 (6.6%)	42 (9.1%)	19 (4.1%)	1 (0.2%)

Table 3. Clinical findings and pathological stage (pTN) of 419 patients with tPSA \leq 10 ng/mL submitted to radical retropubic prostatectomy and pelvic lymphadenectomy

No of pts	Median age (range)	Median tPSA	pT	GS [°]	psm*	N+
1	58	4.8 ng/mL	pT0	-	-	-
9	60 (52-73)	5.2 ng/mL	pT2a	5 (3 + 2)	-	-
54	58 (53-73)	3.5 ng/mL	pT2a	6 (3 + 3)	-	-
48	59 (55-72)	4.8 ng/mL	pT2b	6 (3 + 3)	-	-
83	61 (54-73)	6.3 ng/mL	pT2c	6 (3 + 3)	18	-
20	58 (50-71)	7.1 ng/mL	pT2c	7 (3 + 4)	12	-
13	63 (52-73)	6.5 ng/mL	pT2c	7 (4 + 3)	9	-
74	62 (50-74)	5.8 ng/mL	pT3a	6 (3 + 3)	17	-
65	65 (52-73)	6.8 ng/mL	pT3a	7 (3 + 4)	20	4
13	63 (50-72)	8.7 ng/mL	pT3a	7 (4 + 3)	8	-
13	65 (50-72)	8.5 ng/mL	pT3a	8 (4 + 4)	10	3
9	63 (50-73)	8.3 ng/mL	pT3b	7 (3 + 4)	7	3
4	66 (58-74)	8.5 ng/mL	pT3b	7 (4 + 3)	4	3
11	67 (59-74)	9.2 ng/mL	pT3b	8 (4 + 4)	8	5
2	65 (64-66)	9 ng/mL	pT3b	9 (5 + 4)	2	2

*psm: positive surgical margins; [°]GS: Gleason score; N+: positive nodes

Introduction

The widespread use of the PSA test along with the introduction of mass screening protocols in Europe (1) and in USA (2) have increased the detection rate of prostate cancer (PCa), that is nowadays the most frequently diagnosed cancer in older men. At the same time, a drop in PCa-related mortality has been reported (3,4); recently, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a 20% reduction of mortality in the screened arm with an estimated rate of overdiagnosis as high as 50% (1). Overdiagnosis as well as the high prevalence of adverse side-effects related to unnecessary treatments make unclear the overall benefit of PSA mass screening. Unclear benefits but reliable healthcare costs: Heijnsdijk et al. (5) using MISCAN model to simulate PCa growth and detection in a cohort of 100,000 men (representative of standard European population) over 25 years estimated that the cost of overdiagnosis equals to 39% of total costs. Thus, the main concern in early diagnosis of PCa is to reduce the risk of overdiagnosing pathologically insignificant PCa (pIPCa), defined as cancer volume <0.5 ml and a Gleason score (GS) < 7 in radical prostatectomy (RP) specimens (6), by using more accurate clinical indications for biopsy as well as nomograms and PSA derivatives.

Our aim is to report retrospectively the incidence of pIPCa in a selected population of men with total serum PSA (tPSA) ≤ 10 ng/mL enrolled in a case-finding protocol for the early diagnosis of PCa, whose preliminary results were published elsewhere (7).

Material and methods

The study comprises 14,453 Caucasians patients, aged between 40 and 73 years (median 60.5 years) with a life expectancy >10 years, who were enrolled from February 2002 to October 2009. Most of them- 10,329 (71.5%) - were referred to our outpatient Clinic for evaluation of lower urinary tract symptoms (LUTS). All patients underwent digital rectal examination (DRE) and blood sample was taken for tPSA and percent free PSA (%f-PSA) assay (Roche II). Patients were divided in 3 age-groups (< 50, 50-65 and > 65 yrs). The indications for a prostate biopsy were: suspicious DRE, tPSA > 10 ng/mL, tPSA \leq 2.5 ng/mL with %f-PSA < 15%, tPSA between 2.6 and 4 ng/mL with %f-PSA < 20% and tPSA between 4.1 and 10 ng/mL with %f-PSA < 25% (7). Extended prostate needle biopsy was accomplished in all cases under antibiotic prophylaxis in a transperineal way with a tru-cut 18 G needle through a GE Logiq 500 PRO ecograph supplied with a biplanar transrectal probe (5-6.5 MHz), previous local anaesthesia or under sedation. A median of 18 cores (range 15-22) and 26 cores (range 20-38) were taken in case of primary (8) and repeated biopsy (9). Among other biopsy findings presence of microfocal PCa, defined as a single microfocus (5% or less) of GS \leq 6, was also reported.

In patients diagnosed with PCa, radiotherapy or radical retropubic prostatectomy (RRP) with bilateral pelvic lymphadenectomy were proposed as curative forms of treatment; in selected cases, an active surveillance (AS) protocol was suggested as a conservative management .

Prostatectomy specimens were processed as follows. After inking the specimen, the apical and basal parts were removed by a transversal cut at 4-mm from the distal and proximal margins, respectively. The apical and proximal parts were sectioned parasagittally at 4-mm intervals and perpendicularly to the inked surface. The specimen was step-sectioned at 4-mm intervals perpendicularly to the apical-basal axis of the gland. The presence of extraprostatic extension (EPE), seminal vesicle involvement (SV+) and surgical margin (SM) status were recorded. The

volume of cancer was reported as the percentage of cancer in the entire specimen according to Bostwick et al.(10); moreover, incidence of pIPCa was recorded (6).

Results

The median tPSA was 3.2 ng/mL (range: 0.1-645 ng/mL); overall, 6,795 (47%), 11,466 (79.3%), 13,782 (95.3%) and 671 (4.7%) patients had a tPSA level ≤ 2.5 ng/mL, ≤ 4 ng/mL, ≤ 10 ng/mL and >10 ng/mL, respectively. According to our protocol criteria, 2,328 patients (16.1%) were eligible for prostate needle biopsy: 205 (8.9%) refused it and 2123 (91.1%) underwent biopsy. Except for 534 men with tPSA >10 ng/mL, 1589 patients (74.8%), submitted to biopsy as primary procedure, had a tPSA ≤ 10 ng/mL: in 48 (3%) tPSA was ≤ 2.5 ng/mL, in 131 (8.2%) and 1410 (88.8%) equal to 2.6-4 ng/mL and 4.1-10 ng/mL, respectively.

Indication for biopsy was based on PSA values only in 1,411 (88.8%) cases, on suspicious DRE in 19 (1.2%) and on PSA values plus DRE in 159 (10%) cases; in the 48, 131 and 1410 patients with tPSA ≤ 2.5 ng/mL, included between 2.6-4 or 4.1-10 ng/mL DRE was abnormal in 20 (45.4%), in 22 (16.7%) and 136 (9.6%) cases, respectively.

PCa was found in 777 out of 2123 (36.6%) biopsies, HGPIN in 17 (0.8%), ASAP in 9 (0.4%) and benign histology in 1320 cases (62.2%); 459/777 patients with PCa had a tPSA ≤ 10 ng/mL and we will refer only to this patient subgroup. According to age-groups PCa was found in 6/550 (1%) cases (< 50 yrs), in 168/9480 (1.7%) cases (50-65 yrs) and 285/3752 (7.6%) cases (> 65 yrs).

Incidence and prevalence of PCa in the population under study is listed in Table 1; 311/459 PCa (67.8%) were non palpable (cT1c) with an higher prevalence in patients with tPSA included between 2.6-4 ng/mL (65.4%) and 4.1-10 ng/mL (74.5%) in comparison with PSA ≤ 2.5 ng/mL (28.6%) ($P = 0.0001$). GS values in patients with PCa and tPSA ≤ 10 ng/mL are listed in Table 2.

One hundred-fifty men were submitted to repeated biopsy; in 35 (23.3%) of them a PCa was found: 8 (22.8%), 18 (51.5%) and 9 (25.7%) had tPSA values included between 2.6-4 ng/mL, 4.1-10

ng/mL and > 10 ng/mL, respectively. PCa in the 26 patients with tPSA \leq 10 ng/mL had a median GS of 6.1 (range: 6-7).

A microscopic neoplastic focus was found in 46 (10%) and in 10 (38.5%) patients with tPSA \leq 10 ng/mL, who underwent primary and repeated biopsy, respectively.

Among 459 men with PCa diagnosed by primary biopsy, 40 patients underwent radiotherapy and 419 (91.3%) opted for RRP; no one accepted the AS program proposed in 67 cases.

On 419 prostatectomy specimens, an organ-confined PCa was found in 244 (58.3%) cases and a locally advanced PCa in the remaining 175 (41.7%) with a median GS equal to 6.4; overall, positive SM, SV+ and positive nodes were found in 115 (27.4%), 26 (6.2%) and 20 (4.7%) cases, respectively (Table 2).

In the 26 patients with PSA \leq 10 ng/ml submitted to RRP after repeated biopsy, 18 (69.2%) had an organ-confined disease (4 pT2aN0; 3 pT2bN0; 11 pT2cN0) and 8 (30.8%) a locally advanced PCa (8 pT3aN0) with a median GS of 6; positive SM were found in 2 cases (7.7%).

Surgical specimens showed a pIPCa in 6 (1.4%) and 2 (7.7%) patients submitted to primary and repeated biopsy, respectively; in details in 6 (13%) out of 46 cases and 2 (20%) out of 10 men who underwent RRP with a diagnosis of microscopic cancer focus. In 6 patients the cancer volume was < 0.5 ml and in 2 cases no tumour at all was found (pT0); median GS was 5.7 (range: 5-6).

Discussion

The aim of any protocol for early detection of PCa should not be to pick up as many cancers as possible, but to detect only those that need to be treated before they become life threatening.

The results of the ERSPC (1) have shown, at a median follow-up of 9 years in men aged 55-69 years at the time of randomization, a 20% reduction of PCa-related mortality with an estimated risk of overdiagnosis/overtreatment equal to 50% in the screened arm. These figures are exceedingly elevated if compared with screening results for colorectal, breast and cervical cancers.

In PLCO (Prostate Lung Colon Ovarian) screening (2), after a median follow-up of 7 years, no reduction of PCa mortality was reported, although many bias have been suggested to explain these contradictory results (i.e., short follow up, previous PSA test in all men enrolled in the screening arm).

The prevalence of PCa in various protocols for early diagnosis (4,6,11) varies in relation to the inclusion criteria (number of biopsy cores, cut-off PSA values for biopsy, etc.) but conclusive data on the risk of overdiagnosis have not reported.

Up to now, no imaging modality is able to detect the actual clinical stage of PCa and a certain number of patients will undergo unnecessary treatments with an high incidence of adverse side effects; alternatively, these men could be enrolled in AS programs, deferring curative treatment at disease progression (rapid PSA rise, increase of GS or extent of tissue involvement at repeat biopsy) according to the patient's age, the coexistence of comorbidities and the patient's ability to cope with the psychological stress related to frequent follow-up and to the awareness of the disease.

At present, the main task of screening programs based on DRE and PSA derivatives is improving their accuracy in detecting only significant PCa as it is probably better to delay a diagnosis of cancer (provided that an opportunity of cure still exists) rather than to diagnose and treat a cancer that will not reduce the patient's life expectancy. It is well known that tPSA values ≤ 10 ng/mL have a low specificity; especially in men at first observation, %f-PSA has been introduced in clinical practice to improve accuracy reducing the number of biopsy sets and the incidence of indolent cancer (12). Hoffman et al., proposed a %f-PSA cutoff for biopsy of 25% in men with tPSA 4.0 to 9.9 ng/mL showing a sensitivity equal to 95% in detecting PCa, avoiding 20% of biopsies (13). Chun et al (14), on 2,323 patients enrolled in a PCa screening program, reported that half of men with no clinical evidence of cancer had PSA levels < 1.0 ng/mL and %f-PSA $> 25\%$; Capitanio et al (15), on 3,222 patients undergoing PCa screening, reported median tPSA and %f-PSA equal to 1 ng/mL and 26%, respectively.

In our case material, the overall incidence of PCa was 5.3%; in particular, 459 (3.3%) out of 13,782 patients with tPSA \leq 10 ng/mL had a PCa, that is, 28 % of the men submitted to primary biopsy. The relatively high detection rate of cancer in the lowest PSA groups demonstrated the appropriateness of the indications for biopsy: PCa prevalence in case of tPSA \leq 2.5 ng/mL (%f-PSA < 15%), 2.6-4 ng/mL (%f-PSA < 20%) and 4.1-10 ng/mL (%f-PSA < 25%) was equal to 29.1%, 37.4% and 28.8%, respectively. Median GS was 6 in 37% and greater than 6 in 73% of the patients, showing higher values if compared with ERSPC results (GS < 6 or equal to 6 in 73% and 37% of the cases, respectively) (1). Moreover, compared with our previous results (7), we have observed a higher incidence of T1c clinical stage tumours, PCa diagnosed with tPSA \leq 10 ng/mL and an increased number of microfocal PCa (59 % vs 51.1%, 67.8% vs 51.8%, 1.7% vs 0.9%, respectively), probably because a more extended biopsy protocol was introduced (18 vs 12 cores) (7).

Despite most of these patients fulfill D'Amico low risk criteria (16), 40.3% of 419 men submitted to RP after primary biopsy had a locally advanced disease with positive SM, SV+ and positive nodes in 115 (27.4%), 26 (6.2%) and 20 (4.7%) cases, respectively. Only in 6/419 (1.4%) and 2/26 (7.7%) men submitted to surgery after primary and repeated biopsy, a pIPCa was diagnosed: in details, in 6/8 cases a microfocal cancer was found at biopsy suggesting that the risk of overdiagnosis was very low in comparison with the estimated 50% risk of ERSPC (1).

Finally, our protocol allowed to spare 757 (25.3%) and 75 (33.3%) biopsies in case of primary and repeated biopsy, respectively, if a PSA cut-off of 4 ng/mL for prompting biopsy should be used; moreover, using the same cut-off 63 out of 459 (13.8%) PCa with PSA \leq 4 ng/mL would have been missed (17).

Some limitations of our study deserve mention: first, the majority (71,5%) of men enrolled in our protocol complained of LUTS introducing a selection bias that can affect the tPSA values and the true incidence of PCa. However, one-third of unselected adult male over 50 years of age suffers from LUTS (18) but these symptoms are not associated with an increased risk of PCa (19); second,

tPSA and %f-PSA cut-offs for biopsy have been arbitrary selected on the basis of a literature review. As a consequence; we are able to report only the detection rate for PCa in men submitted to biopsy not the number of cancer missed in men who did not undergo biopsy according to our inclusion criteria (the true prevalence of PCa in the selected population remains unknown); third, this is a retrospective study.

In conclusion, a PCa detection rate of 28.8% and a risk of detecting pIPCa equal to 1.4% (primary biopsy) and 7.7% (repeated biopsy) in patients with tPSA \leq 10 ng/mL should induce to add %f-PSA values in screening programs to reduce the risk of overdiagnosis; however, an unknown percentage of significant PCa could be missed in men who were excluded from biopsy according to these arbitrary guidelines.

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