Prospective evaluation of prostate cancer stage at diagnosis in Poland – multicenter study

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KEY WORDS

prostate cancer ◗ diagnosis ◗ clinical stage

ABSTRACT

Introduction. Prostate cancer (PCa) is one of the most common cancers diagnosed in men. Its presentation has evolved substantially since the introduction of prostate-specific antigen (PSA) measurement in blood. The incidence of organ confined PCa has increased. Locally advanced cases are currently found rarely. However, there is still little knowledge concerning prostate cancer stage at diagnosis in many countries all over the world, including Poland. It is known that every other man diagnosed with PCa dies from this disease here. Therefore, this multicenter study was conducted prospectively to address PCa clinical stage defined at diagnosis, in Poland.
The aim of the present study is to evaluate prospectively the clinical stage of newly diagnosed prostate cancer in selected institutions in Poland.
Material and methods. Data of men who were subjected to prostate biopsy from 1st July 2007 to 30th July 2008 in selected institutions in Poland were analyzed.
Results. Prostate biopsy was performed in 747 men aged between 34 and 93 years (mean age – 67.4). PCa was found in 52.7% of cases. Clinically organ-confined prostate cancer (cT ≤2) was diagnosed in 83.5% of them.
Conclusions. Clinically organ-confined prostate cancer was diagnosed in most of the patients. However the results of the study indicate the presence of high incidence of locally advanced PCa at diagnosis.

INTRODUCTION

Prostate cancer (PCa – *prostate adenocarcinoma*) is one of the most common cancers diagnosed in men. In 2005 the greatest PCa age-adjusted incidence was found in US and it amounted to 150.5/100,000 [1]. It has almost doubled since introduction of prostate specific antigen (PSA) testing [1]. The test allows for earlier recognition of PCa, long before symptoms and signs occur. Their presence is usually associated with advanced disease.

In more than 90% of newly diagnosed cases on US, PCa is confined to the prostate (cT ≤2 N0 M0) [2]. The major way of treatment of men with more than 10 years of life expectancy in whom cancer in this stage is found is radical prostatectomy (RP) or radiotherapy. At the beginning of the 90's of the previous century a significant increase in the number of radical prostatectomies performed in the USA was noted [3]. It probably resulted from the wide spread of PSA testing allowing for earlier PCa recognition and increased the number of younger men diagnosed with localized disease but also from greater popularity of the procedure itself. However, cancer specific mortality has continuously decreased throughout the recent years in the USA, suggesting a favorable impact of serum PSA measurement in a wide population of men [4].

PCa accounted for 7,154 cancer cases in Poland in 2006 [5]. It is the second most common cancer diagnosed in men in this country. Its incidence and mortality have continuously increased [6]. It amounted to 12.2 and 10.1 in 1991 and to 18.7 and 12.6 in 2000, respectively.

The current status of the stage of newly diagnosed prostate cancer and its previous variations come mainly from countries with known, wide spread of PSA testing. Data concerning PCa stage at diagnosis in Poland are very sparse. Recently published retrospective and single center experience showed that almost 1/3 of newly diagnosed PCa cases are locally advanced [7]. There is no registry in Poland that would address the issue of cancer stage that is epidemiologically relevant. The present study is designed to prospectively collect data from major centers in Poland regarding prostate cancer stage established at diagnosis.

MATERIAL AND METHODS

The data of all consecutive men subjected to prostate tru-cut biopsy (*tru-cut core Bx*) from 1st of July 2007 to 30th of June 2008 in 4 Departments of Urology (Postgraduate Medical Education Center, Międzylesie Hospital in Warsaw, Medical University in Warsaw, Collegium Medicum of the N. Copernicus University in Bydgoszcz, Regional Hospital named Dr. J. Biziel in Bydgoszcz) were prospectively collected and evaluated. The biopsy was indicated in cases of increased (≥4.0 ng/ml) and/or increasing PSA and/or abnormal digital rectal examination (DRE) and/or abnormal transrectal ultrasound (TRUS) findings. If PSA was the only indication, a so called "mapping biopsy" under TRUS guidance was done during which 6 to 20 cores from different areas of the prostate were obtained and the number of cores was adjusted to the prostate volume. In cases of abnormal DRE and/or TRUS, lesion-guided biopsies were performed, usually with cores taken from other "normal" sites of the prostate in men being potential candidates for radical therapy and with serum PSA of less than 10 ng/ml.

In cases of DRE and TRUS being highly suggestive of locally advanced PCa, a so called "formal" biopsy was done (^{FL}coreBx). The aim of this kind of biopsy was only the formal confirmation of cancer presence. In contradistinction to ^{FL}coreBx, the rest of the men were subjected to multiple core biopsy (^{TRUS}coreBx).

The data was analyzed *post factum*. The data routinely collected during biopsy were registered at the individual biopsy protocols elaborated for the purposes of our study and thereafter transmitted

Table 1. Age (in years) of men subjected to the prostate biopsy.

Age range	Number of men	Rate
30 – 39	1	0.1%
40 – 49	16	2.1%
50 – 59	122	16.4%
60 – 69	276	36.9%
70 – 79	283	37.9%
80	48	6.5%
Not known	1	0.1%
All	747	100%

Table 2. Indications for transrectal core biopsy of the prostate.

	Number of subjects			
	TRUScoreBx	FLcoreBx	All	Rate
DRE(+) only	19	–	19	2.5%
¬s.PSA only	344	–	344	46.1%
TRUS(+) only	–	–	–	0
DRE(+) and ¬s.PSA	145	4	149	19.9%
DRE(+) and TRUS(+)	6	1	7	0.9%
¬s.PSA and TRUS(+)	50	–	50	6.7%
¬s.PSA and DRE(+) and TRUS(+)	142	36	178	23.8%
All	706	41	747	–
Symbols used: DRE(+) – abnormal digital rectal examination suggesting prostate cancer; TRUS(+) – transrectal ultrasound findings suggesting prostate cancer; ¬s.PSA – elevated serum PSA level				

Table 3. Numbers and rates of men diagnosed with prostate cancer (^{TRUS}coreBx – random, targeted or random and targeted biopsies; ^{FL}coreBx – "formal" – all carried out under TRUS guidance) and positive predictive value (PPV) associated with biopsy indication.

	Number of PCa diagnosis				
	TRUScoreBx	FLcoreBx	All		
DRE(+) only	11	–	11	2.8%	57.9%
¬s-PSA only	116	–	116	29.4%	33.7%
TRUS(+) only	–	–	–	–	
DRE(+) and ¬s.PSA	84	4	88	22.3%	59.1%
DRE(+) and TRUS(+)	5	1	6	1.5%	85.7%
¬s-PSA and TRUS(+)	25	–s	25	6.3%	50.0%
¬s-PSA and DRE(+) and TRUS(+)	113	36	149	37.8%	83.7%
All	354	41	395	100.0%	
Symbols used as in table II					

from local institutions into the central data base. There was no additional factor that had to be applied in order to be enrolled into the study. Therefore there was no need to apply for an ethics committee approval.

Comparison among different clinicopathological features was performed with chi-square and Student t-tests. Test with $p \leq 0.05$ was considered significant.

RESULTS

Prostate biopsy was done in 747 consecutive men, aged from 34 to 93 years (mean – 67.4, median – 68). The most numerous group of men were those aged between 70 and 79 years. The age structure of biopsied men is presented in table 1.

In the majority of men (706 – 94.5%) ^{TRUS}coreBx was carried out. In the remaining 41 (5.5%) cases ^{FL}coreBx was performed. Biopsy indications are presented in table 2. Most frequently, the biopsy was done due to elevation of serum PSA only. It was found in 344 cases (46.1%). DRE abnormality as a single indication was observed in only 19 men (2.5%). Among those qualified to biopsy because of increased PSA (50 men), abnormal TRUS (6.7%) was also found.

PCa was diagnosed in 394 men (52.7%) including all cases subjected to ^{FL}coreBx and 353 (50%) were subjected to ^{TRUS}coreBx

Table 4. Comparison of mean age (years), s-PSA (ng/ml), PSAD (ng/ml/cm^3) and prostate volume (cm^3) in men diagnosed with prostate cancer [PCa(+)] and in men in whom prostate biopsy did not reveal any cancer cells [PCa(-)]; (p = level of significance).

	Range		Mean		Median		
	PCa (+)	PCa (-)	PCa (+)	PCa (-)	PCa (+)	PCa (-)	
Age	34-93	45-86	68.3	66.5	69.5	66	<0.05
s-PSA	1.05-2650,00	0.24-80.30	41.9	10.7	10,2	8.2	<0.05
Pv	14.9-268.0	18.9-219	47.5	62.8	42.0	58.5	<0.05
PSAD	0.02-53.2	00.1-7.2	1.39	0.23	0.24	0.15	<0.05

Table 5. Local, clinical stage of prostate cancer (cT).

	^{TRUS}coreBx		^{FL}coreBx		Total	
	Number	Rate	Number	Rate	Number	Rate
T1c	116	32.8%	–	–	116	29.4%
cT2a/b	188	53.1%	5	12.2%	193	48.9%
cT2c	16	4.5%	5	12.2%	21	5.3%
cT3	34	9.6%	31	75.6%	65	16.5%
All	354	100%	41	100%	395	100%

Table 6. Range, mean and median values of PSA in association with clinical stage of prostate cancer.

	s.PSA (ng/ml)		
	Range	Mean	Median
T1c	2.4 – 55	11.2	8.0
cT2a-b	1.05 – 97.31	13.5	9.6
cT2c	4.9 – 74.5	21.2	15.0
cT3	2.05 – 1000	95.2	24.0

Table 7. Rates of clinically organ-confined prostate cancers diagnosed in men being outside screening programs.

Countries	Authors	Years		Cancer confined to the prostate	
				Number	Rate
USA	Catalona WJ and al. [12]	1993	no data	20	42.5%
Western Europe	Rietbergen JB [10]	1999	no data	2824	60%
Poland	Dobruch J [7]	2006	854	326	65.6%
Poland	Gołąb A and al. [8]	2002	690	277	40%
Western Europe	Postma R and al. [9]	2006	no data	229	49.4%

(Tab. 3). The most frequent cancer diagnosis referred to the group of men with ↑s.PSA, DRE(+), and TRUS(+) (PPV 83.7%) and also to the group of DRE(+) and TRUS(+) (PPV 85.7%), but because the latter group comprised only 7 cases it should be neglected. Interestingly, elevated serum PSA as single indication to biopsy was associated with the lowest probability (PPV 33.7%) of PCa finding (Tab. 3).

Mean age, serum PSA, prostate volume and PSA density were all significantly lower in patients in whom PCa was found than in men with negative biopsy (Tab. 4).

Cancer clinically confined to the prostate was diagnosed in 330 (83.5%) cases. It was mainly classified as cT2a or cT2b PCa (48.9%), (Tab. 5). Among men subjected to ^{TRUS}coreBx those with organ confined disease predominated (90.4%) whereas the majority of men subjected to ^{FL}coreBx were diagnosed as having locally advanced disease (75.6%).

Locally advanced disease was mainly diagnosed in men in their 8th decade of life. Half of the cases were attributable to this age range (Fig. 1). As age increased, the number of locally advanced disease also increased.

Serum PSA increased with clinical stage of the prostate cancer. Mean values of PSA in men in whom PCa in T1c, T2a-b, T2c and T3 stage was found were 11.2 ng/ml, 13.5 ng/ml, 21.2 ng/ml, and 95.2 ng/ml, respectively (Tab. 6).

DISCUSSION

This study is aimed to evaluate the clinical stage of newly diagnosed prostate cancer in Poland. The analyzed data were collected prospectively in four different institutions to establish in a more accurate manner the character of PCa in the modern era. The rate of cancers clinically confined to the prostate is surprisingly high and amounts to 83.5% of cases. According to our previous single center analysis and an analysis done in a different Polish area, the rate was significantly lower and ranged from 32% to 65.6% [7, 8] (Tab. 7). A similarly low rate ranging from 42.5% to 60% was noted in Western Europe and the USA in men being outside prostate cancer screening programs [9, 10]. It was mainly found in white men being over 70 years of age.

Table 8. Rates of clinically organ-confined prostate cancers (PCa) diagnosed in men subjected to screening programs.

Countries	Authors	Years		Number (rate) of:	
				PCa diagnosis	Organ confined PCa
USA	Smith DS [19]	1994	NA	1.114 (NA)	1.080 (97%)
Canada	Labrie F [20]	1996	1.366	244 (17.9%)	173 (70.9%)
USA	Crawford ED [21]	1996	906	322 (35.5%)	286 (88.9%)
USA	Smith DS [22]	1997	866	284 (32.8%)	268 (94%)
USA	Smith DS [22]	1997	2.466	606 (24.6%)	596 (98%)
USA	Smith DS [22]	1997	198	50 (25.2%)	50 (100%)
Europe	Rietbergen JB [10]	1999	2.262	474 (21%)	340 (78%)

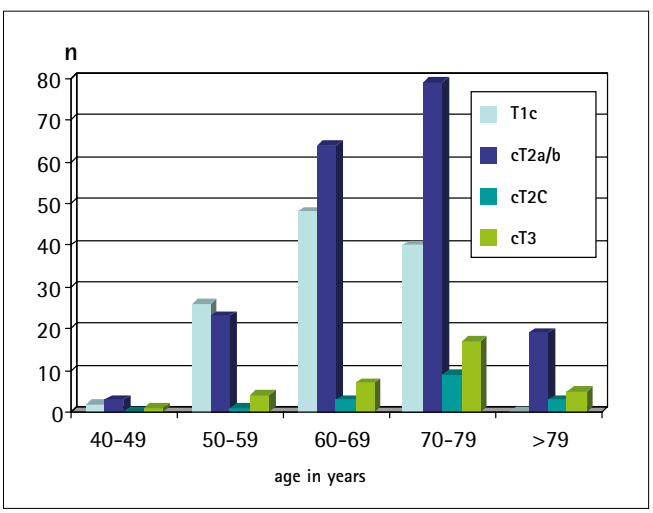

Fig. 1. Clinical stage and the number of men diagnosed with prostate cancer in relation to patients' age.

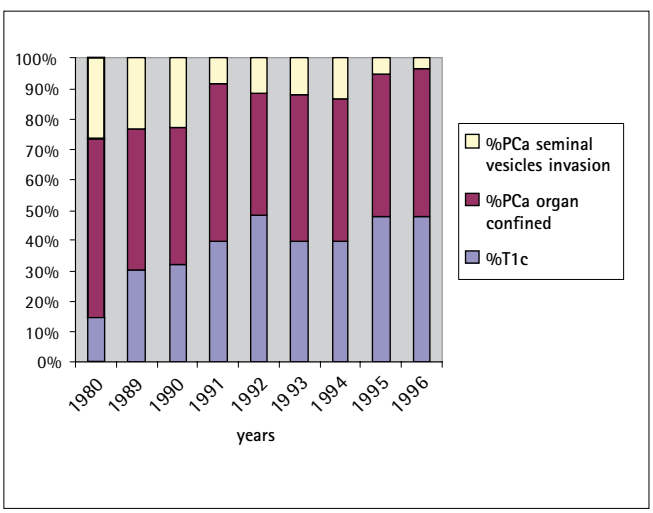

Fig. 2. Trends in pathological stage of prostate cancer in USA from 1988 to 1996 [14].

Introduction of PSA testing has produced enormous changes in presentation of the disease. A significant downward trend in age and mean PSA at diagnosis has been observed, concomitant with a downward shift in stage of disease (stage migration) at diagnosis, which started with the advent of the PSA era in the late 1980s [11, 12, 13]. The rate of organ confined prostate cancer diagnosed before the PSA era has increased more than twofold in the USA [11, 14] (Fig. 2).

The influence of PSA on men diagnosed with PCa as well as its characterization may be followed by the results of studies dedicated to prostate cancer screening programs. According to the European Randomized Study of Screening for Prostate Cancer (ERSPC) and North American studies the rates of organ confined PCa diagnosed within screening programs ranged from 70.9% to 100% (Tab. 8). Comparing data coming from Tirol in Austria and the USA in 1994–1998 with data collected 10 years before show that the number of men who could be qualified for radical therapy has doubled [15, 16, 17]. Data published recently showed that the rate of subjects diagnosed with locally advanced and generalized disease decreased from 14.1% and 19.2% in 1988 to 3.3% and 4.4% in 1998 [11]. Taken together the data strongly emphasize the role of wide spread use of PSA on PCa presentation. It has driven the decision to perform prostate biopsy in the majority of the studied cases. However, the rate of locally advanced disease is greater in our study than in the screened group of ERSPC (16.5% *vs.* 14.6%). Moreover, according to other series addressing the issue of PCa screening the rate of locally advanced disease was not necessarily so high (Tab. 8).

The median values of PSA found in men diagnosed with PCa were 10.2 ng/ml in the present study and 4.9 ng/ml in ERSPC suggesting significant underestimation of cancer stage in our study.

The local stage of PCa is usually estimated in clinical practice based on results of DRE and TRUS, as it was in our study. These examinations are frequently imperfect. According to comparison of clinical and pathological stage of PCa in men subjected ultimately to radical prostatectomy, in almost half of the cases the local stage of the tumor was underestimated [18]. Sub-analysis of presented data according to 4 different centers showed that the rates of locally advanced PCa differed substantially and amounted to 6.1%, 12%, 25.3% and 37.8%. The mean PSA and mean age of patients with organ confined cancer was 15.3 ng/ml and 66 years, 13.8 ng/ml and 62 years, 16.2 ng/ml and 70.2 years, and 11.5 ng/ml and 70.1 years. It has to raise the issue of underestimation and imperfect instruments used to define the stage by the members of our cooperating groups.

The risk of prostate cancer is strongly associated with PSA and age of biopsied men. The incidence of PCa is highest among men over 70 years of age [23]. In comparison to subjects with negative biopsy, mean age of men with PCa was significantly greater (68.3 *vs.* 66.5). However, the most abundant group of biopsied men in this study were subjects over 70 years old. According to our previous analysis [7] the mean age of patients with biopsy confirmed PCa was 69.8 and the rate of men with organ confined disease was 65.6%. In the present study the number of locally advanced cases was the greatest among men over 70 years of age.

To our knowledge this study is the first multi-institutional survey performed in Poland to evaluate the PCa stage at diagnosis. This study has several limitations. The data have been collected in different centers and PCa stages estimated by different urologists. During analysis of the data we have found that practice concerning

the prostate biopsy technique is not always satisfactory – simply speaking prostate biopsy was quite often performed under DRE guidance without using TRUS. Therefore, as the methods used to evaluate the stage of PCa were imperfect, they raised suspicion that estimation of local advancement of PCa was imperfect in some portion of the patients. At the end of this trial we were convinced that rules of defining the clinical stage of PCa should be based on European Association of Urology (EAU) Guidelines concerning PCa [24] approved by the Polish Urological Association (PUA). Surprisingly, our belief seemed to be false in relation to one cooperating center.

Moreover, the number of men subjected to biopsy is too low to accurately predict the stage of prostate cancer diagnosed in Poland. This limitation is the result of small amounts of biopsy protocols provided by the two centers offering their full contribution in completing our program.

The number of PCa cases registered in our country in 2006 has reached 7,154 [5]. If we admit that the number of men newly diagnosed with PCa increases yearly 3-5%, we can roughly estimate that the mean number of men in whom PCa developed during the time of our trial has increased from 7,400 to 7,500. Therefore, the number of men diagnosed with PCa in frames of our study constitutes, probably, not more than 5% of all newly diagnosed prostate cancers during this period of time.

Our study has found that in the majority of PCa cases are organ confined and potentially curable. Nevertheless, it is hard to believe that the real rate of men with organ confined PCa is so big in Poland. It clearly indicates that further studies should be carried out to improve our knowledge of the real PCa stage at diagnosis.

CONCLUSIONS

Our study indicated that clinically organ-confined prostate cancer has been diagnosed in most of the patients submitted to core biopsy of the prostate.

This – first to our knowledge – multi-institutional trial suggests that credibility of assessment of the prostate cancer's clinical stage at diagnosis is limited in our country and convinces us that conducting such trials in our circumstances is difficult despite its' inclusion into the frames of financially granted studies.

The results of the presented study should be redefined.

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