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Should active surveillance in prostate cancer patients be based on a single histological assessment?

Łukasz Nyk[1], Tomasz Golabek[2], Jakub Dobruch[1], Michał Andrzej Skrzypczyk[1], Tomasz Dzik[3], Maciej Wysocki[4], Piotr L. Chłosta[2], Andrzej Borówka[1]

[1]*Postgraduate Medical Education Centre, Department of Urology, European Health Centre, Otwock, Poland*
[2]*Department of Urology, Collegium Medicum of the Jagiellonian University, Cracow, Poland*
[3]*Department of Urology and Pathomorphology, Central Railway Hospital, Warsaw, Poland*
[4]*Postgraduate Medical Education Centre, Department of Pathomorfology – Bielański Hospital, Warsaw, Poland*

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Correspondence
Tomasz Golabek,
Department of Urology,
18, Grzegorzecka Street
31–531 Cracow, Poland
phone: +48 12 424 79 50
elementare@op.pl

Introduction Active surveillance (AS) is always associated with a degree of uncertainty, whether or not prostate biopsy (TRUSBx) results indeed can be relied on for evaluation of cancer stage and histological grade, as the most commonly observed limitations of TRUSBx are undergrading, understaging and underestimating true prostate cancer (PCa) volume. We evaluated prostate cancer characteristics in men who could have been offered active surveillance based on clinical features and TRUSBx results, and compared them with the same patient's histology results following their radical prostatectomy (RP). Moreover, we assessed the level of consistency in reporting TRUSBx and RP specimens by the same pathologist on two separate occasions, as well as by another independent pathologist.

Material and methods All patients who underwent RP between 2005 and 2008 had their medical records reviewed retrospectively. All histological specimens were prospectively re–evaluated by the same pathologist, as well as by a second to assess for intra– and interobserver variability, respectively.

Results Eight out of a total of 124 patients who underwent RP could have been offered AS on the basis of initial microscopic reports. However, there was significant intra– and interobserver variability. The differences in the histological grade of the specimens obtained from TRUSBx and RP, reported by the same pathologist and by the second pathologist were apparent in 6 and 4 cases, and in 7 and 6 patients, respectively.

Conclusions We recommend that the decision about AS should be made after at least two pathologists have jointly reviewed and agreed on the TRUSBx histology results.

Key Words: intraobserver variability ‹› interobserver variability ‹› prostate biopsy ‹› cancer involvement

INTRODUCTION

Prostate cancer is one of the most commonly diagnosed malignancies in men [1, 2]. In the USA and several Western European countries, the incidence rates of PCa have exceeded the remaining malignant neoplasms in males [3, 4]. It is the second most prevalent malignancy after lung cancer in Poland [4]. There were 9,273 new PCa diagnoses recorded nationwide, according to the National Polish Cancer Register Statistics from 2010 [5].

The diagnosis of PCa is based on transrectal ultrasound–guided multiple core prostate biopsy results in view of raised serum prostate–specific antigen (PSA) levels and/or abnormal digital rectal examination (DRE), and/or the presence of TRUS–confirmed hypoechogenic foci within the marginal zone of the prostate gland, all of which are suggestive of malignancy. The clinical stage of PCa is evaluated from the DRE and TRUSBx results. The histological grade of the disease is given a score on the 10–point Gleason

scale, which has been widely used since 1966 [6, 7]. The Gleason score (Gl.s.) is a sum of two individual numbers, representing the two predominant (out of five possible) histological PCa grades.

The prevalence of PCa is now on the rise. Additionally, there has been a sharp increase of early stage and low–grade neoplasms diagnosed in younger men [8]. These trends closely reflect the frequency of PSA testing, as well as advances in TRUSBx techniques. As a result, the proportion of relatively young men with organ–confined PCa has risen.

The combination of PSA <10 ng/ml and Gl.s ≤6 correlates well with small tumour volume, evidenced by a small amount of PCa tissue in no more than two samples obtained during TRUS biopsy. PCa characterised by the aforementioned features is referred to as a low risk tumour [9, 10]. Some low–risk prostate cancers meet the criteria of a clinically insignificant disease, one which is unlikely to be the cause of the patient's death [11, 12]. Hence, some low–risk PCa men may never need active treatment and can be offered an active surveillance approach. AS is based on interval PSA testing, DRE and yearly TRUSBx, unless an increase in PSA or any abnormal DRE are reported. The rationale behind AS is to avoid unnecessary radical treatment with its potential risks to the patient, and also to monitor disease progression to the point where the patient can still be cured. Unfortunately, AS criteria have not yet been uniformly defined [13–16].

This study was undertaken to evaluate PCa characteristics based on clinical features and TRUSBx results, obtained from low–risk PCa patients as potential candidates for active surveillance, and to compare them with the same patients' histology results following their radical prostatectomy. The secondary objective was to assess the level of consistency in reporting TRUSBx and RP specimens by the same pathologist on two separate occasions, as well as by another independent pathologist.

MATERIAL AND METHODS

In this study, all procedures have been carried out in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983. All patients who underwent open radical prostatectomy between 2005 and 2008 had their clinical data, as well as both TRUSBx and surgical sample histology reports, analysed retrospectively. Subsequently, all low–risk PCa cases, eligible for active surveillance, were identified. The inclusion criteria for AS were as follows: (i) PSA <10 ng/ml; (ii) Gl.s. ≤6; (iii) a total PCa percentage (%PCa) within the prostate biopsy sample of ≤25%. The TNM classification from 2002 was used for PCa clinical staging, and where cancer is limited to the prostate (T2), it is subdivided into either T2a (the tumor is in half or less than half of one of the prostate gland's two lobes) or T2b (the tumor is in more than half of one lobe, but not both), or T2c (the tumor is in both lobes) [17]. The evaluations of PCa burden, based on clinical stage and histological grade, were performed prospectively by two independent pathologists, where one examined pre–operative core needle biopsies and post–operative surgical samples, then re–examined them at later stage. The second pathologist additionally examined the same specimens obtained from biopsy and RP. Both pathologists had no access to each other's reports.

Table 1. *Prostate cancer clinical tumour stage (cT) in patients treated with radical prostatectomy*

cT	Number of patients (n)	(%)
cT1c	32	25.8
cT2a	55	44.4
cT2b	20	16.1
cT2c	12	9.7
cT3a	5	4
Total	124	100

Table 2. *Serum PSA level (PSA), PSA density (PSAD), prostate cancer histological grade (Gl.s.) in 8 low–risk men eligible for active surveillance*

Variables	Mean	Range
PSA (ng/ml)	5.39	2.44–8.0
PSAD (ng/ml/cm3)	0.13	0.07–0.28
Gl.s. (number of positive biopsies)	4.37	4–6

RESULTS

Between 2005 and 2008 there were 124 RPs, with a mean patient age of 62.7 years (range, 47 to 74 years). In 119 cases, the cancer was limited to the prostate (cT ≤2 N0, M0) (Table 1).

The low–risk PCa inclusion criteria were fulfilled in 8 patients (6.45%), and subsequently, these men could have been offered AS. Features of malignancy, within single core biopsy samples, were found in five men, and within three and two cores in one and two patients, respectively. Cancer positive core biopsies were obtained from the same prostate lobe and did not exceed 25% of total specimen volume. Histologically, Gl.s. 4 (2+2) was present in five men, whereas Gl.s. 5 (2+3) in three cases, respectively. The oncological variables of selected low–risk PCa patients are presented in Table 2.

The tumour stage, determined by the histological examination of radical prostatectomy samples, was originally reported as pT2a, pT2b and pT3a in 4, 3 and 1 patients, respectively. One patient was found to have a positive surgical margin, while two had extracapsular extension of cancer.

Overall, the reporting concordance of core biopsy specimens, re–examined by the same pathologist (the time between the initial and subsequent examination ranged from 1 to 5 years) and then by the second pathologist, with regard to the number of PCa positive core biopsies, as well as PCa positive radical prostatectomy specimens, was low. Similarly, differences were found in reporting the specimens obtained during RP. The disagreement in reporting the Gleason score for the specimens obtained from TRUSBx and RP was apparent in 6 and 4 patients, in the second examination by the same pathologist, and in 7 and 6 cases in the examination performed by the second pathologist, respectively (Table 3).

DISCUSSION

Prostate cancer trigger factors remain unknown and the natural history of PCa is unpredictable [18, 19]. Recently, there have been more prostate cancer cases diagnosed at an earlier stage and in younger men from developed countries [1]. Consequently, this increases the number of potential candidates for the active surveillance approach. According to the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database, which included 1,884 Americans with PCa, 16.4% of men met active surveillance criteria and thus might have avoided early radical treatment [20]. Patients who undergo radical prostatectomy following a period of active surveillance have the same biochemical–free and cancer specific survival as those men who are operated on without delay [21]. However, active surveillance can trigger a feeling of anxiety in both patient and doctor. Patients are mainly concerned about the continuous need for necessary disease monitoring and prostate biopsies, as well as the fear of impending cancer progression. From the urologists' perspective, active surveillance is always associated with a degree of uncertainty, whether or not TRUSBx results indeed can be relied on in terms of cancer stage and histological grade. In fact, the most commonly observed limitations of TRUSBx are undergrading, understaging and underestimating true PCa volume [22, 23].

In this prospective analysis of data from 124 PCa patients who underwent RP, 8 (6.45%) could have been offered (based on TRUSBx results) AS instead. The proportion of men eligible for active surveillance reported by others varies, and can reach up to 57% depending on the inclusion criteria and population used [17, 24, 25].

In our study, when comparing pre– and postoperative histology, it appeared that in five out of eight cases the PCa grade and stage were significantly underestimated and would not have allowed for AS. In three patients PCa was present in both lobes (pT2c), in two PCa extended beyond the prostate (pT3a), and in one the Gleason score was greater than 6.

Pineiro and colleagues, who compared the concordance of TRUSBx and surgical specimens histological examination findings, reported that out of a total of 164 radical prostatectomies, 36% of PCa cases were low–risk and could, therefore, be eligible for AS [24]. However, the analysis of the postoperative findings showed that Gl.s. >6, PCa extracapsular extension (pT >2) and the seminal vesicle invasion occurred respectively in 42.4%, 47.5% and 5% initially classed as low–grade PCa patients.

Table 3. *Gleason scores as per the first pathologist's first examination, the first pathologist's second examination and the second pathologist's examination of both TRUSBx and RP specimens*

	Number of patients								
	TRUSBx specimens								
	Gl.s. 4 (2+2)	Gl.s. 5 (2+3)	Gl.s. 5 (3+2)	Gl.s. 6 (3+3)	Gl.s. 6 (2+4)	Gl.s. 7 (3+4)	Gl.s. 7 (4+3)	Gl.s. 8	Gl.s. >8
$P1^1$	5	3	0	0	0	0	0	0	0
$P1^2$	1	1	0	6	0	0	0	0	0
P2	0	1	0	5	0	1	0	1	0
	RP specimens								
$P1^1$	2	3	1	0	1	1	0	0	0
$P1^2$	0	3	0	3	0	2	0	0	0
P2	0	1	0	2	0	5	0	0	0

TRUSBx – transrectal ultrasound–guided multiple core prostate biopsy, Gl.s.– Gleason score, RP– radical prostatectomy, $P1^1$ – the first pathologist's first examination, $P1^2$ – the first pathologist's second examination, (P2) – the second pathologist's examination

The influence of intra– and interobserver variability, in preoperative histological diagnosis of PCa, on the decision–making process regarding active surveillance, has not yet been reported in the literature. In our study, as in other reports, a proportion of the TRUSBx and surgical specimens re–examined by the same pathologist was reported differently from the initial reports [26, 27]. To better assess the possible impact of intraobserver variability on the decision for active surveillance, two reports by same pathologist were compared. Had the decision about active surveillance been made on the re–examined TRUSBx histology, 3 patients would not have been offered it due to a high total PCa percentage within the prostate biopsy specimen. In six reviewed reports the PCa was upgraded, but without altering patient management.

The interobserver variability in histology reporting has also been observed by several research groups previously [28, 29, 30]. In our study, in two out of eight cases (25%) active surveillance would not have been indicated if the decision was made based on the TRUSBx report reviewed by the second pathologist. Moreover, six out of eight surgical specimens reviewed by the second pathologist were also less favourably reported. Undoubtedly, TRUSBx and postoperative histology reports vary due to the sheer volume of the specimens being analysed. However, we have also noticed a marked intra– and interobserver variability in pre– and postoperactive histological evaluation of PCa. The observed differences in initial and subsequent assessments may result from the variation in the criteria for interpretation, the actual interpretation of the criteria, and expertise in interpreting the criteria [31, 32, 33]. One should, therefore, always be aware of prostate cancer understaging and undergrading by TRUSBx when deciding whether active surveillance is in patient's best interest.

The concept of active surveillance prior to radical treatment in patients with prostate cancer refers back to Whitmore's cornerstone questions: "Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?" [34]. This also reflects the trend to tailor PCa management to an individual patient's needs [35]. There is a large body of evidence which supports that in selected cases active surveillance is oncologically safe [36, 37]. We recommend, however, maintaining cautious monitoring of all PCa patients under active surveillance. Moreover, the decision about active surveillance should, ideally, be made after at least two pathologists have jointly reviewed and agreed on the TRUSBx histology results.

Strengths and limitations of the study

Our study has several methodological strengths, which are: (i) clearly defined inclusion criteria for active surveillance; (ii) a second, blinded histological evaluation by the same pathologist (intraobserver variability), as well as a second, blinded histological evaluation by a different pathologist (interobserver variability); (iii) histological reporting in accordance with the ISUP (International Society of Urological Pathology) 2005 guidelines.

The study was limited, however, by a small number of patients, partly retrospective study design, and the 6 to 8–core prostate biopsy.

CONCLUSIONS

The decision about active surveillance prior to radical prostatectomy, offered to low–risk prostate cancer patients, should be made with full awareness of the limitations associated with prostate biopsy. Our study has identified significant intra– and interobserver variability where PCa histology reports differed, and were often undergraded. Therefore, the decision about active surveillance of low–risk prostate cancer patients should be made carefully, taking into account all available clinical and histological data, and after at least two pathologists have jointly reviewed and agreed on the TRUSBx histology results. Further prospective studies with a larger number of patients need to identify the most adequate histological approach for an optimal selection of candidates suitable for active surveillance.

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