

Undergrading and Understaging in Patients with Clinically Insignificant Prostate Cancer who Underwent Radical Prostatectomy

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ABSTRACT

Purpose: The aim of our study is to evaluate the undergrading and understaging rates in patients with clinically localized insignificant prostate cancer who underwent radical prostatectomy.

Materials and Methods: Between July 2005 and July 2008, 406 patients underwent radical prostatectomy for clinical localized prostate cancer in our hospital. Based on preoperative data, 93 of these patients fulfilled our criteria of non-significance: Gleason score < 7, stage T1c, PSA < 10 ng/mL and percentage of affected fragments less than 25%. The pathologic stage and Gleason score were compared to preoperative data to evaluate the rate of understaging and undergrading. The biochemical recurrence free survival of these operated insignificant cancers were also evaluated.

Results: On surgical specimen analysis 74.7% of patients had Gleason score of 6 or less and 25.3% had Gleason 7 or greater. Furthermore 8.3% of cases showed extracapsular extension. After 36 months of follow-up 3.4% had biochemical recurrence, defined by a PSA above 0.4 ng/mL.

Conclusions: Despite the limited number of cases, we have found considerable rates of undergrading and understaging in patients with prostate cancer whose current definitions classified them as candidates for active surveillance. According to our results the current definition seems inadequate as up to a third of patients had higher grade or cancer outside the prostate.

Key words: *prostate neoplasms; Gleason score; prostatectomy*
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INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed malignancy among males in western countries. Autopsy studies estimate that 30% of men over 50 years harbors histological PC (1,2), but the chance of clinical diagnosis is much lower, being approximately 11% during lifetime (3), meaning that not all PC needs curative treatment. According to Epstein et al. (4), 16% of nonpalpable PC diagnosed by screening techniques is insignificant and may be safely managed conservatively.

For this reason, active surveillance protocols have been proposed as an option for patients with both low grade and stage, and several studies to date have shown the feasibility of treating localized PC by expectant or conservative procedures with good results (5). These studies reported a dropout rate of 25 to 30% driven mainly by tumor progression or patient and physician anxiety.

The main factor determining success in active surveillance protocols is the proper selection of patients. Due to the large PC heterogeneity, it is of paramount importance to distinguish the patients with

biologically aggressive tumors that need definitive treatment from those with an indolent tumor that benefits more by active surveillance (5,6).

Currently, the patients are selected accordingly to specific findings at biopsy and clinical stage, but the criteria of clinical non-significance are variable. The most widely accepted is the Epstein criteria, which consist of prostatic specific antigen (PSA) density 0.1-0.15, low or intermediate cancer grade, core involvement less than 3 mm and involvement of only one needle biopsy core (4). These criteria are used to predict the presence of clinically insignificant tumor, defined by Gleason patterns less than 4, tumor volume less than 0.5 cm³ and organ-confined disease (4).

However, one should not forget the known existence of understaging and undergrading for any neoplasm which can erroneously engage patients in expectant management when local treatment was the best option.

The incorrect staging and grading is a real threat to any active surveillance protocol. A study evaluating surgical specimens of patients with PSA less than 10 ng/mL, which is associated with lower stages, showed extra-capsular extension or seminal vesicle involvement in 10% and 3% of cases respectively (7).

Furthermore, Gleason score discordance between biopsy and surgical specimen has been estimated to vary between 47 to 69% (8,9). A meta-analysis involving over 14,000 patients, found that the Gleason graduation of prostatectomy was correctly anticipated by the biopsy in 63% of the patients. Interestingly, among all patients with high-grade tumor in the surgical specimen, 67% had tumors of low or moderate grade in the biopsy, indicating a higher risk of undergrading for these patients (10).

In conclusion, these studies reflect the inaccuracy of current staging and grading regarding the true insignificance of PC, meaning that selection of patients is of crucial importance in active surveillance protocols. The aim of this study was to compare data of prostate biopsy with the results of surgical specimen of patients with clinically insignificant operated PC, in order to evaluate the rate of undergrading and understaging. We also evaluated the biochemical recurrence free survival for these patients.

MATERIALS AND METHODS

Between July 2005 and July 2008 a group of 406 men diagnosed with localized PC underwent radical prostatectomy at our institution. From this group, we selected the patients whose tumor was diagnosed by an extended biopsy protocol and who fulfilled the following criteria of non-significance: preoperative PSA less than or equal to 10 ng/mL, staging clinical T1c, transrectal prostate biopsy with Gleason grading less than or equal to 6, no pattern Gleason 4 or 5 and percentage of affected fragments less than or equal to 25% (Table-1). Patients who received hormone therapy before surgery were excluded. Considering these criteria, 93 patients were selected for this analysis.

The following surgical pathology data was recorded: Gleason score, pathological staging, seminal vesicle invasion, microvascular and perineural invasion, extracapsular invasion, bladder neck invasion, positive margin and total weight of prostate. Unfortunately, tumoral volume, an important predictor of biological behavior, is not a parameter routinely measured in our institution and was not recorded.

We compared the Gleason score concordance between biopsy and surgical specimen and the percentage of patients with locally advanced disease, attempting to estimate the number of patients erroneously classified as candidates to active surveillance. The biochemical recurrence free survival was calculated considering recurrence as a PSA above 0.4 ng/mL.

Statistical Analyses

The chi-square test was employed to evaluate the difference of the Gleason score between biopsy

Table 1 – Definition of clinically insignificant prostate cancer.

PSA preoperative	< 10 ng/mL
Clinical stage	T1c
Gleason score in biopsy	≤ 6
% of positive cores in biopsy	≤ 25%

PSA = protein-specific antigen.

Table 2 – Demographic data.

Variable	N. of Patients
Total	93
Age (mean)	65.7 years (range 48 - 79)
PSA preoperative (mean)	6.03 ng/mL (2.5 - 9.7)
N. of cores in biopsy (mean)	12.01 (10 - 18)
% of positive cores (mean)	14.6 % (5.6 - 25%)

PSA = prostatic specific antigen.

Table 3 – The comparison of Gleason scores between biopsy and surgical specimen in 87 cases.

	Surgical Specimen					Total
	4	5	6	7	8	
Biopsy	4	5	6	7	8	Total
4	0	0	1	1	0	2
5	0	0	2	2	0	4
6	0	2	60	16	3	81
Total	0	2	63	19	3	87

Chi-square $p < 0.001$

and surgical specimen and a p value < 0.05 was considered statically significant. For other variables the statistical methods consisted of descriptive and categorical analyses.

RESULTS

The average age of patients was 65.7 years and the mean PSA was 6.03 ng/mL. The average percentage of positive fragments on biopsy was 14.6%. The complete demographic data is depicted in Table-2.

The comparison of Gleason score between biopsy and surgical specimen was possible in 87 cases and the results are displayed in Table-3. According to this table, 77.9% of cases showed the same Gleason score, while upgrading and undergrading occurred in 19.5% and 2.6% of cases, respectively. Employing the Chi-square test, a significant difference ($p < 0.001$) of Gleason score between radical prostatectomy specimen and biopsy was observed, being important to note that 25% of clinically insignificant PC showed Gleason score higher than 6 at surgery.

Regarding the pathological stage, data was available for 84 patients of which 90.4% had organ confined disease (Table-4). Additional surgical pathology data is showed in Table-5.

After 36 months of follow-up only three patients (3.4%) had biochemical recurrence defined as a PSA greater than or equal to 0.4 ng/mL.

COMMENTS

The discrepancy between the Gleason score observed at the biopsy and surgical specimen may

Table 4 – Pathological stage (TNM) of patients.

Pathological Stage	N. of Patients
T0	3 (3.6%)
T2	73 (86.9%)
T3	8 (9.5%)
Total	84 (100%)

TNM = tumor, node, metastasis.

Table 5 – Pathological characteristics of surgical specimens of radical prostatectomy.

	Present	Absent
Invasion of seminal vesicles	6 (7.1%)	78 (92.9%)
Extracapsular extension	7 (8.3%)	77 (92.0%)
Invasion of bladder neck	1 (1.2%)	83 (98.8%)
Positive margin	6 (7.1%)	78 (92.9%)

result in improper assessment of the disease and treatment, which can influence the prognosis of an individual patient, specially if active surveillance is proposed. Therefore, the correct stage and grade is of paramount importance in the treatment decision for any neoplasm.

In our series, we found a substantial Gleason score disagreement between biopsy and surgical specimen in patients that fulfilled active surveillance requirements ($p < 0.001$). Within a group of patients with non palpable tumors of low grade, 25% had Gleason score of 7 or greater in the surgical specimen, reflecting the inadequacy of grade prediction with the current employed methods.

The undergrading rate of 25% underscores the risk and consequence of incorrect grade evaluation at biopsy in a group of patients that would be assigned to conservative management. In accordance to our results, Müntener et al. evaluating 6625 patients found an identical Gleason score in biopsy and surgical specimens only in a third of patients (8). In a contemporary series of 1,455 men who underwent radical prostatectomy at John Hopkins, although the rate of undergrading was smaller than before, the disagreement between biopsy and radical prostatectomy Gleason score was seen in 24% of cases (11), a rate similar to that observed in our study.

An important aspect of our results is that PC diagnosis was made through extended biopsy protocols, which is known to improve diagnosis and reduce the sampling error that is intrinsic to the ultrasound-guided prostate biopsy. The better performance of extended biopsy when compared to fewer samplings schemes can be exemplified by the Nesrallah's study, who found PC detection rates of 75% and 88% when 6 or 14 cores were respectively sampled (12). However,

our undergrading rate was considered significant even when employing extended biopsy.

The precise staging is also important for adequate PC management. In our series of clinically insignificant patients, despite 3 cases that showed pT0, we found non organ confined disease in 9.5% of cases. This finding is a known negative prognostic factor in PC and does not qualify these tumors as being indolent.

A lower PSA is associated with organ confined tumor and is a common requisite of any clinically insignificant criteria, however there is sufficient data indicating that lower PSA is not always associated with indolent PC. A study evaluating surgical specimens of patients with PSA less than 4.0 ng/mL revealed extra-prostatic extension or positive margin in 8.3% of cases (13). Likewise, Geary et al. (7) found positive surgical margins in 13% of non palpable tumors with PSA between 4 and 10 ng/mL.

It is noteworthy, that in our series the error related to staging (9.5%) was lower than the error rate related to grade assignment (25%), a finding that was also observed by others (14), which indicates that new methods should be particularly developed to improve grade prediction in PC.

Considering the undergrading and understaging together, we observed that up to a third of our patients with clinically insignificant tumors displayed unfavorable findings at radical prostatectomy. In agreement with our results, Chun et al. evaluating patients with clinically insignificant tumor found that 33% had pathological Gleason score of 7 to 10 or non organ confined tumor at surgical specimen (15). Even when the cohort was restricted to patients who also had PSA < 10 and T1c clinical stage the rate of unfavorable cancer was 28% (15).

Similarly, D'Amico et al. evaluated 66 men with PC diagnosed on the basis of a single microscopic examination of adenocarcinoma, and found extracapsular extension in 4% and positive margin in 6% of cases (16). It is important to mention that 10% of these patients failed biochemically within 5 years after radical prostatectomy.

Even after a short follow-up period, we observed that three patients (3.4%) had biochemical recurrence. Likewise, a systematic review of operated small-volume cancer on biopsy showed biochemical recurrence in 8.6% of cases (range 6.1%-12.1%) (17). These data emphasize the fact that even clinically insignificant cancer may not be cured by radical prostatectomy.

We believe that active surveillance is an adequate treatment for PC, however a considerable proportion of patient candidates for this modality of treatment have "significant" features at surgical specimen. Our data indicates that current criteria to select patients for active surveillance seems inappropriate, as once up to a third of these patients clearly do not have insignificant tumors; in fact, they would be exposed to mortality by PC if the tumor was left untreated.

In accordance to our conclusion, a recent validation of Epstein criteria in European men showed that 24% of the patients who fulfilled the criteria had unfavorable characteristics at radical prostatectomy (14). The authors conclude that the widely used Epstein criteria underestimate the true nature of PC and that caution is advised when treatment decisions are based solely on this single criterion (14).

Corroborating this observation, Goto et al. evaluated 170 surgical specimens whose data fulfill the Ohori criteria of non-significance, which are PSA density less than 0.1, clinical stage T1c and maximum length of cancer of 2 mm in any core, and found that 25% of specimens showed significant PC (18). These two series, along with ours, indicate that the undergrading and understaging rates are similar in clinically insignificant PC whatever the criteria employed.

It is important to note that the Epstein criteria were largely validated (14,19) and, although not perfectly accurate, remain the better alternative for prediction of clinically insignificant PC when

compared to other definitions (18,20). The Epstein criteria are more accurate, for example, than the Kattan nomogram whose accuracy is between 64% and 79% (20).

The addition of molecular biology data may add to the predictive accuracy of the existing criteria for clinical non-significance, as demonstrate by Kattan et al. that increased the accuracy of biochemical recurrence prediction by adding TGF- β e interleukin 6 levels in previous nomogram (21). The inclusion of PSA derivatives may also improve prediction and a study evaluating 163 radical prostatectomy specimens of stage T1c showed that the addition of free PSA increased the accuracy of Epstein criteria (22).

We recognize that our small patient population is a limitation to our conclusions, due to the fact that our institution is a tertiary health care center that receives the more complex and advanced cases. Therefore, only a few of our operated patients could be included in this analysis. Nevertheless, based in our results, other criteria should be developed in order to improve the non-significance factor and selection of PC patients, and to reduce the understaging and undergrading rates.

CONCLUSION

Although the expectant management for PC is a valid alternative treatment of properly selected cases, after analyzing our data we conclude that special care should be taken when including patients in this modality of treatment, because the risk of understaging and under grading seems substantial even in these properly selected cases.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this study, Santana de Oliveira et al. (1) report on how current criteria for clinically insignificant prostate cancer (PCa) work in their series which includes less than 100 cases. This is an important limitation to the study design; likewise, the paper is of interest since insignificant PCa is an important topic in daily practice. As shown by Santana de Oliveira et al. (1) we do not have a reliable model to predict insignificant prostate cancer in every single patient. Prediction of clinically insignificant prostate cancer (PCa) remains as a major problem in clinical practice. In the updated format, the contemporary Epstein criteria represent the most widely used tool for prediction of clinically insignificant prostate cancer, in spite of limitations. Of 217 patients with organ confined disease, 18 (7.6%) had Gleason sum 7 or higher in the series used to update the Epstein criteria. Therefore, 199 of 237 patients (83.9%) in the updated Epstein criteria series had both organ-confined disease and favorable (Gleason 6 or lower) prostate cancer grade. This finding indicates that the updated Epstein criteria underestimated disease stage and/or grade in 16% of North American patients and were accurate in 84%

of predictions. Conversely, the rate of Gleason sum 7 was substantially higher in Brazilian population (25.3%) which yielded substantially lower overall accuracy (74.7%) than the one reported in North America (84%); the Brazilian cohort refers to 12 (10-18) cores per case just similar to the Hopkins study that refers to 12 core biopsies. Therefore, it may be argued that the stage and grade migration that results in the detection of an increasing proportion of Gleason 6 prostate cancer may result in lower error rate of the Epstein clinically insignificant prostate cancer criteria, when these are compared with Brazilian findings (1-2). The authors (1) provide an in depth review of the various causes leading to failure of the contemporary Epstein's criteria. An important issue derived from the current study deserves a comment since it is related to the diagnostic rate of Gleason 7; this grade is heterogeneous and represents the most complex exercise in needle prostate biopsies sign out, and differences in the performance of the Epstein criteria between North America and Brazil may explain by itself the observed differences seen in the current study. The results by Santana de Oliveira et al. (1)

emphasize the need for continuing education activities concerning Gleason grading in order to achieve the maximum accuracy and reproducibility in daily practice of prostate pathology.

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