



OVERRATING HIGH RISK PROSTATE CANCER ON TRANSRECTAL ULTRASOUND NEEDLE BIOPSY VS RADICAL PROSTATECTOMY SPECIMEN

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Prostate cancer is one of the leading causes of cancer-specific mortality. Prostate biopsy is essential for diagnosis, risk stratification and therapeutic management of disease. The Gleason score is the key parameter and plays a vital role. The retrospective study consisted of 1799 transrectal ultrasound-guided biopsies carried out in 2012–2015 including 332 cases of high risk disease. In 63.8% of cases Gleason score was downgraded to Gleason 7. Concordance between needle biopsy and radical prostatectomy specimen was present in 31.7%. Patients with both Gleason 8 or higher on needle biopsy and after radical prostatectomy had local extended disease (pT_{3a}– 26.1 % and pT_{3b} – 21.7%) totalizing 47.8%. Positive margins were observed in 8% of the analyzed cases. Organ confined disease was frequently encountered in the downgraded group (pT_{2c} representing 21.7% from the total of 63.8 %). Over half of contemporary Gleason 8 on prostate needle biopsy are downgraded on surgical pathology. Over treatment may contribute to a statistically significant increase of erectile dysfunction and also determine increased intra and postoperative complications. The use of new criteria and investigations are needed to reduce the gap between Gleason score on biopsy and the radical prostatectomy specimen.

Key words: prostate biopsy, Gleason score, high risk prostate cancer, radical prostatectomy, PSA.

INTRODUCTION

Prostate cancer is one of the leading causes of cancer-specific mortality. Prostate biopsy is essential for diagnosis, risk stratification and therapeutic management of disease. The European Association of Urology as well as the American Association of Urology recommend a 10–12 core systematic ultrasound guided biopsy as the gold standard for primary diagnosis for both suspected areas identified in digital rectal exam and through ultrasonography. The majority of patients today present with non-palpable, cT_{1c}, tumors and prostate specific antigen < 10 ng/ml^{1,2}. The Gleason score of the biopsy material is the key parameter and plays a

vital role in evaluation, prognostic and management decisions.

In 2005 the International Society of Urological Pathology revised its recommendations in interpreting and reporting of morphological patterns. To improve the agreement between needle biopsy and radical prostatectomy specimen the biopsy may always include the highest Gleason grade. Tendency to assign higher Gleason scores for needle biopsy specimens has been observed in the past decades³. According d’Amico criteria, high risk prostate cancer is defined as Gleason Score >7 or PSA >20 or cT_{2c}, resulting an increased risk of treatment failure. In recent series of patients treated by surgical monotherapy approximately 4–12% were Gleason 8 or higher at biopsy^{2,4}.

The Gleason grading system has also a significant amount of deficiencies that have an impact on patient care. For example treatment decisions using a simplified Gleason 7 fail to recognize that 4 + 3 and 3 + 4 (well-differentiated cancer with a lesser component of poorly differentiated cancer) have significant prognostic differences⁵. In 2013 a new grading system based on data from Johns Hopkins Hospital was proposed to address the inherent in the Gleason system. A five group division using the original Gleason scale was made – Group 1: Gleason 6, Group 2 (Gleason 3 + 4 = 7), Group 3 (Gleason 4 + 3 = 7), Group 4 (Gleason 8) and Group 5 (Gleason 9–10)⁶.

As a result the risk of overtreatment the low-risk prostate cancer is reduced and also there might appear a better patient compliance by reducing the “fear” of advanced cancer. On the other hand, the prostate cancers included in the “high risk” group are aggressively treated because have significant higher cancer-specific mortality compared with low and intermediate risk patients^{7,8}.

The aim of this paper is to highlight the needle biopsy overrating tendency in patients with high-risk prostate cancer and also to stress out the risk of overtreatment in this category of patients by analyzing the agreement between Gleason score, risk stratification at biopsy followed by radical prostatectomy in our clinic.

MATERIAL AND METHODS

The retrospective study consisted of 1799 transrectal ultrasound-guided PBP carried out in 2012–2015 including 332 cases of high risk disease. 41 patients with high grade prostate cancer, diagnosed by PBP candidates for radical prostatectomy underwent surgical treatment in our hospital, the rest followed oncology treatment (antiandrogenic associated with GnRH analogue) due to old age at diagnosis (> 78 years) and locally advanced clinical stage (cT3b). In determining the therapeutic conduct the D’Amico predictive model was used.

Radical prostatectomy was made within 3 months from biopsy so potential grade progression between procedures was not an issue. Biopsies were transrectal ultrasound guided using an 18-gauge needle. Only 12 core biopsies that underwent the surgical treatment were included in this retrospective study. The cores were stored using BioChip that permitted a better understanding of the topography and the volume of the disease. The analyzed data consisted of the pathological report of both procedures that were introduced in a table that also contained clinical stage of the disease, PSA value, number of cores, age. They were statistically analyzed using SPSS version 22.

Table 1

Statistical means of variables within the studied population

	Gleason Score after PNB	Gleason Score after RP	PSA	AGE
Mean	8.30	7.3478	171.63	71.02
Median	8.00	7.0000	50.00	71.00
Std. Deviation	.476	.98205	484.815	8.844
Minimum	8	6.00	5	44
Maximum	10	9.00	5800	90

Biopsy and surgical specimens were reviewed by the same uropathology laboratory. Radical prostatectomy specimens were step-sectioned at 3 mm intervals and included “in toto” for the examination of tumor volume, percentage of each Gleason pattern, surgical margins and staging (TNM). Samples were post-operatively fixed in 10% formaldehyde, reduced to paraffin, marked with China ink, microtome sectioned at 2–3 microns

standard colored with HematoxylinEozin and Van Gieson.

Upgrade was defined as any increase of pathological Gleason score as a total sum of primary and secondary pattern at surgical specimen referring to needle biopsy. Downgrade was defined as any decrease of pathological Gleason score as a sum of primary and secondary pattern between ultrasound guided biopsy a radical prostatectomy.

RESULTS

The main characteristics of the study group are shown in table 1. 332 patients were diagnosed with high risk disease out of which 41 underwent radical prostatectomy in our clinic. Both classic retropubic prostatectomy and the laparoscopic approach were included in our study. The mean age at the moment of biopsy was 71.92 years (patients aged between 44 and 90 years old) and a medium PSA value of 171 ng/ml (PSA range between 5–5800 ng/ml). According to D’Amico criteria we defined high risk prostate cancer those cases which had PSA > 20 ng/ml or GS > 7 or cT2c. The clinical stage was evaluated by digital rectal exam before the needle biopsy. The majority of our patients in the high risk disease presented PSA value between 21 and 100 (135 cases) followed by those with PSA level > 20 (104 cases). Gleason 8 was encountered in 237 representing 71.39% cases while Gleason 9 (both 4 + 5 and 5 + 4) was observed in 92 cases. Only 3 cases presented Gleason 10 but they have not been taken into account (the pathological examination could not exclude a small cell component).

Table 2

Cross tabulation of population by grouped age and Gleason score after PNB

		Gleason Score after PNB			Total
		8	9	10	
Age of studied population grouped	< 70	114	46	1	161
	71–80	93	25	1	119
	> 81	30	21	1	52
Total		237	92	3	332

Most patients in our group followed oncological treatment due to associated pathology and the local progression of the disease at diagnosis moment. All patients performed CT/MRI scan after biopsy result to accomplish a better therapeutic management.

41 patients diagnosed with high risk prostate cancer underwent radical prostatectomy. The surgical specimens were analyzed in our pathology department. In 63.8% of cases Gleason score was downgraded from high risk (Gleason 8 or 9) to Gleason 7 or less. Concordance between needle biopsy and radical prostatectomy specimen was present in 31.7%. Due to high risk prostate cancer at moment of diagnosis neurovascular bundles were sacrificed for oncological safety. Also for better

oncological outcome extended lymph node dissection was performed.

Table 3

Cross tabulation of population by grouped PSA values and Gleason Score after PNB

		Gleason Score after PNB			Total
		8	9	10	
PSA values grouped	<20	81	23	0	104
	21–100	88	35	2	125
	>101	68	34	1	103
Total		237	92	3	332

There was no statistically significant correlation between age, PSA value and the concordance of Gleason score before and after radical prostatectomy. Patients with both Gleason 8 or higher on needle biopsy and after radical prostatectomy had local extended disease (pT_{3a} – 26.1 % and pT_{3b} – 21.7%) totalizing 47.8%. Positive margins (pR₁) was observed in 8% of the analyzed cases. Organ confined disease was frequently encountered in the downgraded group (pT_{2c} representing 21.7% from the total of 63.8%).

Table 4

Descriptive statistic of high risk prostate cancer

	Frequency	Percent
8	237	71.4
9	92	27.7
10	3	.9
Total	332	100.0

Overall 63.8% patients were downgraded to Gleason 7 or less and most of them had organ confined disease. From the high risk prostate cancer group represented by 31.7 % almost half had local progression present. Due to better oncological outcome neurovascular bundles were sacrificed and extended lymph node dissection was performed. As a result, overtreatment was present in 63.8 % of cases.

DISCUSSIONS

Moussa *et al.* studied in 2009 the variables that predict significant grading changes in patients with

intermediate and high risk prostate cancer⁹. He concluded that men with high volume cancer, perineural invasion are more likely to be upgraded while men with low volume prostate and low volume cancer are to be downgraded.

A study made in Mayo Clinic and published in Japanese Journal of Clinical Oncology in 2010 outlined the importance of radical prostatectomy staging because over 25% of cT₃ cases with a Gleason score of 8 or higher were actually organ confined disease¹⁰.

Basically, a sample of prostatic tissue collected by PNB cannot be representative for the entire gland, therefore the scores will be different from the one of the radical prostatectomy.

Contemporary imagistic techniques play an important role in the diagnosis, treatment management and follow-up of the patient with prostate cancer. Better view of lesions, discovering low volume cancer and more accurate biopsy promise to narrow the gap between Gleason score before and after surgical treatment. A series of new imagistic techniques that combine both multiparametric RMN and transrectal ultrasound (fusion targeted biopsy) are available and recent studies have shown promising results. One of the main disadvantages is that these new techniques are very expensive which makes them unavailable for some countries that are in the developing process.

Radtke *et al.* studied multi-parametric magnetic resonance (MRI) and MRI-trans-rectal ultrasound fusion biopsy for index tumor detection: correlation with radical prostatectomy specimen concluding that use of saturation biopsy combined with MRI-trans-rectal ultrasound fusion biopsy and multiparametric MRI find more significant cancer than any other alone, using trans-perineal saturation biopsy as a reference test¹¹. To increase the sensibility and specificity of these late techniques and for a better standardization for worldwide interpretation the PI-RADS v1 was elaborated in 2008 and PI-RADS v2 in 2015. Woo *et al.* published that preoperative MRI is a significant predictor for downgrade in patients with Gleason score 7¹². Further refinement of the PI-RADS scoring system or comprehensive interpretation with other MRI and clinical-pathological factors may be needed for its successful implementation.

As any new method, there is a learning curve that must be outdated, but most of all, the time test will offer all the necessary answers.

Progress for more accurate diagnosis prior surgical intervention for a better stratification and a

better management of high risk prostate cancer is needed specially to overcome the overtreatment with all its implications.

CONCLUSIONS

Over half of contemporary Gleason 8 on prostate needle biopsy are downgraded on surgical pathology. Overtreatment in these cases may contribute to a statistically significant increase of erectile dysfunction following radical prostatectomy due to unnecessary resection of neurovascular bundles. Also may determine increased intra and postoperative complications due to extended lymph node dissection and an increase in overall intervention time. There is also an economic impact that should not be neglected – high risk cancer needs more investigations (for example bone scan at the moment of diagnosis) extending the time between diagnosis and surgical intervention.

The use of new criteria and investigations are needed to reduce the gap between Gleason score on biopsy and the radical prostatectomy specimen.

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