ORIGINAL ARTICLE

Low-risk Prostate Cancer Heterogeneity and the Histobiological Factors Determining its Prognosis

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ABSTRACT

Purpose: The main objective of this study is to demonstrate heterogeneity in patients with low-risk prostate cancer (PCa) and elucidate the therapeutic and prognostic features of this cancer. **Materials and Methods:** This is a retrospective study conducted at the Urology Department in Rabat Military Hospital, including 690 patients treated for PCa by radical prostatectomy, between 2002 and 2016, which 248 (35.9%) presented the criteria of low-risk PCa. The clinical, biological, operating, and pathologic data were collected from the medical files, radiological, operating, and pathologic reports. **Results:** Median age of the 248 men in the study cohort was 64.3 years. The median follow-up was 60 months (1–112 months). The pathological stage pT3 was detected in 14.1%, and Gleason score ≥ 7 in 32.7% of patients. Unfavorable PCa was detected in 37.5% of patients. Overall biochemical relapse rate was 13.6%. The estimated probability of 3-, 5-, and 8-years biochemical progression-free survival for all study patients was 90.6%, 88.1%, and 77.9%, respectively. Eight-year free survival was 83.3% for low-risk PCa and 68.2% for unfavorable PCa (P = 0.007). Positive surgical margins (P = 0.0001) and post-operative Gleason score (P = 0.023) were the most significant predictors of biochemical relapse. **Conclusion:** Low-risk PCa may be heterogeneous and hide an unfavorable cancer in 37.5% of patients, so D'Amico criteria may under estimate potentially aggressive PCa, consequently, caution is recommended when the decision concerning the treatment modality is based on D'Amico criteria alone.

Key words: Active surveillance, focal therapy, low-risk, prostate cancer, radical prostatectomy

INTRODUCTION

Prostate cancer (PCa), a public health problem due to its frequency and by its seriousness, and its support generates very high economic costs. It is the most common cancer in men over 50. There is a wide variation in the incidence and specific mortality of CaP in the world, depending on: Screening practices by digital rectal examination and PSA assay (sensitive biological test not very specific for the disease), types of treatments, lifestyle, and the heterogeneity of genetic and environmental factors that modulate prostate carcinogenesis makes this cancer a very heterogeneous disease with a variable prognosis.[1] It is rapidly spread locally and systemically in some patients, and latent or even indolent in others.

However, the prognosis of localized PCa is heterogeneous; with either a low risk of biological relapse and a low-specific mortality rate, or either a greater risk of biological relapse and a high risk of metastatic dissemination despite local treatment, they are then said to have a localized high-risk PCa, this type of tumor represents a pivotal zone between localized cancer and locally advanced cancer. Active surveillance consists of supervising the follow-up of patients with low risk of progression to spare them the functional consequences of curative treatment, while being able to identify early signs of disease progression so that the patient does not suffer any loss of chance in the event of PCa progression.[2,3]

The objective of this thesis is to demonstrate the heterogeneity in patients with low-risk CaP and to

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elucidate the therapeutic and prognostic features of this cancer.

MATERIALS AND METHODS

This is a retrospective study carried out at the Urology Department at the Military Hospital Mohammed V Instruction of Rabat, including 690 patients treated for PCa by radical prostatectomy associated with lymph node dissection, between 2002 and 2016, that is, over a period of 14 years.

Of this cohort, 248 people were identified as meeting the D'Amico criteria for low-risk PCa (GLEASON score <6.1 or 2 positive prostate biopsies, PSA <10 ng/ml, PSA velocity <0.75 ng/ml/year and clinical stage T1c - T2a).

The main objective of this study was to demonstrate the heterogeneity of D'Amico's low-risk CaP and to analyze its therapeutic and prognostic peculiarities.

All the localized PCa were diagnosed following the discovery of an abnormality in the DRE and/or a PSA considered to be high either in relation to the age of the patient or in relation to the volume of the prostate gland.

The study included subjects whose age was greater than or equal to 50 years, having undergone a radical prostatectomy in our training. A sub-analysis was performed on men aged over or equal to 70 years to verify whether the results were correlated with age.

The independent variables in this study were: Age, tumor stage, PSA level, PSA velocity, GLEASON biopsy, number of positive prostate biopsies, and tumor volume per core.

The data were collected by an exhaustive search in the medical files, the kinetics of the PSA before the biopsy, the radiological, operative, and pathological reports. An exploitation sheet has been designed for this purpose.

The preclinical assessment carried out for each of the patients was as follows: Ultrasound-guided prostate biopsies, pelvic magnetic resonance imaging (MRI), and bone scintigraphy. A standard operability assessment was performed in all patients. The intervention performed was a radical prostatectomy, by open retro-pubic approach, with urethro-vesical anastomosis in racket tail. Lymph node dissection was bilateral olio-obturator type and limited in all patients. Patients, and early complications were defined by their onset preoperatively, or within 1 month postoperatively; whereas late complications were defined by subsequent onset >3 months. The post-operative follow-up consisted of a clinical examination with a digital rectal examination and serum PSA assay, which was assessed every 3 months during the 1st year after surgery, every 6 months up to 3 years after surgery and once a year thereafter.

Biological recurrence was defined by a PSA level greater than 0.2ng/ml, confirmed by two increases, at two successive dosages.

For statistical analysis, we calculated statistical significance using the SPSS program. $P < 0.05$ was considered statistically significant for both tests. Tables and graphs were obtained using Excel Table, and statistics were compiled using SPSS program.

RESULTS

230 patients had a mean age of 64.3 years (50 mean of 71 years (70–79), ($P < 0.005$), the reason for consultation is made of voiding disorders such as dysuria and pollakiuria, the most frequent found in 186 patients, that is, 75 of the cases [Table 1], followed by intermittent hematuria common in 31 men, or 12.5 of the cases and 12.5 of the cases were asymptomatic

The clinical volume of the prostate on rectal examination is varied between 20 and 70 g, with a average of 41.8 g (±2.5), the rectal examination noted the presence of a prostate nodule in 27.8% of cases, of a heterogeneous prostate in 21.3% of cases, and of benign prostatic hyperplasia in 13.2% of cases.

- The PSA rate: Varies between 0.7 ng/ml and 10ng/ml, with an average of 5.75 ng/ml, 12.5% of patients (31 men) had a PSA level lower than 4 ng/ml, 64.5%of patients (160 men) between 4.1–7 ng/ml and 23% (57 men) between 7.1 ng/ml and 10 ng/ml
- Ultrasound: Used in all patients for ultrasound guidance of the biopsy, and showed: A prostate nodule in 20.62% of cases. It made it possible to evaluate the prostate volume ranging from 35 ml to 128 ml.
- The biopsy: The diagnosis of ADK was made by a first series of positive biopsies in 233 patients, after a second series in eight patients and after TURP in seven patients
- Biopsy Gleason score: All patients had a biopsy Gleason score of 6, which allowed them to be included in the low-risk group for Amico [Table 2]
- MRIs were performed before each series of biopsies, the lesions were characterized by a visual suspicion score, side 1–5: Considered negative if <3 and positive if greater than or equal to 3.

154 patients had a suspicious lesion on MRI, or 62% of cases, of which 67.2% had a single lesion, 29.7% had two lesions, and 3.1% had three suspicious lesions.

- The suspicion score on MRI was <3 in 38% of cases, = 3 in 20% and> 3 in 42% of cases, the absence of the extra-capsular extension was noted in 88%. And the absence of invasion of the seminal vesicles and supra-centimetric nodes was retained at 100%.

Table 1: Summary table of the clinical, preclinical, extension, and pathological results of our study

Characteristics	%
Age	
50–69	93
>70: (70–79)	7
Mean age	64.3
Patient's complain	
Urinary problems	75
Hématuria	12.5
Unexpected discovery	12.5
Symptoms	
Pollakiura	75
Dysuria	68
Hématuria	12.5
RAU	12.5
Urinary burning sensation	6.25
Erectile dysfunction	6.25
Rectal examination	
Prostatic nodules	27.8
Hétérogeneous prostate	21.3
Benign prostate hyperplasia	13.2
PSA Level (ng/ml)	
<4	12.5
4.1–7	64.5
7.1–10	23
Biopsy	
NB	
6	85.9
8	14.1
Right apex	31.3
Left Apex	18.75
Localisation	
Lower right hand side	25
Lower left hand side	25
Halft right hand side	12.75
Halft left hand side	25
Suspected zones	6
Score de GLEASON biopsique Score 6	100
IRM	
Number of lesions	
1	67.2
2	29.7
3	3.1
Suspicion score	
>3	42
3	20
<3	38
Scintigraphy of the bone	
Normal	94.63
Hyper fixation lesions	5.37
TNM	
T1 a/b	3.22
T1c	53.68
T2 a	43.1
Pre-operatory records	
Normal	88
Urinary infections	12
pTNM	
pT2a	10.10
pT2b	2
pT2C	73.80
pT3a	12.90
pT3b	1.20
Gleason pathological score	
Score 6 (3+3)	67.30
Score 6 (3+4)	30.30
Score 6 (4+3)	0.80
Score 8	1.60

(*Contd...*)

- Bone scintigraphy: Normal in 94.63% of cases, while 5.37% of our patients presented hyper fixation lesions, sometimes costal, and sometimes vertebral
- TNM classification: Of the 248 patients selected, 3.22% of the tumors were classified as T1a / b, 53.68% of the tumors were classified as T1c, and 43.10% of the tumors were classified as T2a, according to the 2010 TNM classification of PCa.

Long-term carcinological results

The median follow-up period in the cohort was 60 months (range: 1 and 112 months). During the study period, the overall relapse rate was 14.1%.

- The estimated rate of biochemical recurrence-free survival at 3.5 and 8 years was 90.6%, 88.1%, and 77.9%, respectively
- The PSA recurrence rate differed when comparing patients with low-risk cancer (Gleason _ 6 and pT2) and patients with unfavorable cancer: It was 8.8% and 21.6%, respectively ($P = 0.006$)
- The 8-year survival rate differed considerably when comparing groups with low-risk cancer and unfavorable cancer: It was 88.3% versus 68.2%, respectively ($P = 0.007$)

Score 1	Normal (No signal anomaly)
Score 2	Little suspicion (Signal anomaly is nonspecific on only one sequence
Score 3	Equivocal (Signal anomaly is nonspecific on several sequences for the same zone)
Score 4	Suspected (Signal anomaly marked on two sequences)
Score 5	Very suspected (Suspected anomalies reflective on several sequences for the same zone)

Table 2: Definition of low-risk prostate cancer

Définition du CaPà bas risque		
D'amico *et al.* 1998 (137)		PSA<10ng/ml,SG<7 et cT1- cT2a
European Association of Urology-ESTRO-SIOG (Mottet *et al.*, 2016) (140)		PSA<10ng/ml,SG<7 et cT1- cT2a
American Association of Urology		PSA<10ng/ml,SG<7 et cT1- cT2aPSA<10ng/ml,SG<7 et cT1- cT2a
National Compréhensive Cancer Network (Carroll *et al.*, 2016) (141)	cT1c,SG<7,PSA<10ng/ml,<3 biopsies positives, densité du PSA<0.15ng/ml	cT1_cT2a ,SG <7 PSA <10ng/ml
Radiation Therapy Oncology Group (Roach *et al.*, 2000) (142)	SG<6 et T1/2_N0	
Cancer of the Prostate Risk Assessment Score (Cooperberg *et al.*, 2005) (143) Cancer of the Prostate Risk Assessment Score (Cooperberg *et al.,* 2005) (143)	âge, PSA, stade clinique, Score de Gleason biopsique, et % de biopsies positives	

- Post-operative data did not allow detection of any significant predictor favorable cancer, on the other hand, they showed that the surgical margins (R) and the post-operative Gleason score were significant predictors of the risk of biochemical recurrence
- In all patients in the study, biochemical recurrence-free survival was shown at age 8 very different when comparing R1 to R0 (57.7% vs. 89.1%), (P = 0.0001), and a Gleason score equal to 6 to a score _ to 7 (81.4% vs. 68.6%, P = 0.014).

DISCUSSION

The incidence of CaP screening has increased over the past two decades due to the widespread use of PSA. This increase is mainly marked in localized low-risk CaP.[2]

Data from the CaPSURE (The Cancer of the Prostate Strategic Urologic Research Endeavor) presented by Cooperberg showed that the proportion of low-risk tumors nearly doubled, from 27.5% in 1990–1994 to 46.4% in 2000–2001[3] a major challenge is to differentiate between CaP localized symptomatic of clinically indolent CaP, which is unlikely to have an impact on survival, even without immediate treatment.

To achieve this goal, several classifications have been proposed based on clinical and pathological features, such as clinical stage, PSA, and biopsy Gleason score.

Localized low-risk CaP was defined by: [Table 3] clinical stage T1-T2, biopsy Gleason score _ 6 and PSA <10 ng/ml.

- "Insignificant" PCa and "Significant" cancer at low risk

Today, the growing proportion of men with Stage T1 cancer or low PSA level is of great concern, many studies have shown that a large percentage of men with CaP have clinical disease insignificant.[4] Two definitions describing this situation: Low-risk CaP (which was suggested by D'Amico *et al*., in 1998[1]) and clinically insignificant disease.

The criteria for insignificant CaP were first suggested by Epstein *et al*., in 1994,[5] and it remains a widely used model. These criteria have recently been adapted, and include:

- A PSA density _ 0.15 ng/ml
- A Gleason score _ 6
- Less than three positive biopsies

Table 3: Results of published studies on focal treatment of localized CaP[45]

Datas	HIFU	Cryo therapie	Laser PDT	Interstitial laser	Brachy therapy	Electro poration	Radio fréquency
Studies	13	11	3	4	2	3	1
Perspectives	+++	+	+++	+++		+	+
Rétrospectives	+	+++			+++	++	
Nb of patients	346	1950	116	50	339	66	15
Follow-up	12	26	6	4.5	61	6	-
Catching up	7.80	7.60	83.3	0	0	11.90	-
Global survival (%)	100	100	100	100	-	100	-
Specific survival (%)	100	100	100	100	99.90	100	-
Side effects	1.50	2.50	10.60	0	-	0	-
Continence (%)	100	100	-	100	95.20	100	-
Sexuality (%)	88.60	81.50	88.40	100	-	95	-

Table 4: International Society of Urological Pathology 2016 classification prognostic group

Group 1	Formely gleason score 6 (3+3)
Group 2	Gleason Score 7 (majority 3)
Group 3	Gleason Score 7 (majority 4)
Group 4	Gleason Score 8(4+4, 3+5, or 5+3)
Group 5	Gleason score 9 or 10

- And a significant volume of cancer involving up to 50% of the gland.[6]

Although the Epstein criteria have been validated in some centers in North America North; studies including European,[7] Middle Eastern,[8] or Korean[9] populations have shown that Epstein's criteria may underestimate the true nature of PCa.

Patients with "low-risk cancer" treated with RT have high rates of biochemical recurrence at 5 and 10 years similar to those observed in patients meeting Epstein's criteria for "insignificant" cancer.[10]

"Insignificant" PCa and low-risk "significant" cancer have shown 10-year biochemical recurrence-free survival rates and overall or specific cancer survival rates, similar after radical treatment.[11]

- The heterogeneity of cape town at low risk

A high number of patients with clinically low risk cancer may exhibit characteristics of a more aggressive cancer during RA; this explains the heterogeneity of this cancer. According to current guidelines, a prostate biopsy should be offered to patients with abnormal rectal examinations or elevated PSA levels.[12]

Clinical stage: One of the three criteria used by D'Amico, with underestimates ranging from 8% to 20%.

The underestimation rate in our study was 14.1%.

The Gleason score: Another very important factor for the correct prediction of low-risk cancer, defined by Gleason in 1966 has 5 architectural grades ranging from 1 to 5, the sum of which defines 9 scores from 2 to 10. This grading system was reviewed during consensus conferences of the International Society of Urological Pathology, in 2005 and then in 2014.[13]

The prognostic value of this classification into five groups [Table 4] has been retrospectively validated by multi-institutional studies.[14] The association of grades on biopsies and operative specimen has recently been clarified.[15]

In a population with CaP, the risk of upgrading has ranged from 70%[16,17] to 20%[18] over the past 20 years.

In patients with clinically T1c (Epstein criteria) or T1c - T2a CaP (D'Amico), the upgrading ranges from 9.7% to 30.5%.[6,7,9,19] In our study, it was: 32.7%.

Similar results have been observed in several retrospective studies,[20-23] suggesting that the risk of having a pathological Gleason score> 6 ranging from 30% to 55% and the risk of a Gleason 8–10 was minimal (0.7–1.7%).

The PSA Third factor retained by D'Amico, characteristic of the prostate epithelium and not of cancer; however, high levels may depend on benign situations and the risk of having a Gleason greater than or equal to 7 is not zero, even in patients with low PSA this risk is between 0.8% and 6, 7%.[24]

Current data show that when using the D'Amico criteria in preoperatively, the risk of PSA recurrence increases and 8-year survival decreases in two-fifths of cases.

The MCP

Our study recorded a positive surgical margin rate (R1) of 30.6%. The presence of MCP after RA is a sign of poor prognosis, the frequency of which varies between 10% and 40%, depending on the disease stage and the operators.[25] Bul *et al*. recorded a lower rate of MCP: 24.5%, while El Hajj *et al*.,[21] and Ploussard *et al*.,[26] recorded rates of 28–29.6%.

Biochemical recurrence

Correctly predicting cancer with low biochemical recurrence rate is a big problem. Several predictive models are used, such as the Stephenson model,[27] the Cancer of the Prostate Risk Assessment (CAPRA) score,[28] the Epstein criteria.,[5] the Kattan nomograms,[29] and the D'Amico *et al*.[1] All of these models include clinical stage, biopsy Gleason score, and PSA.

For the prediction of biochemical recurrence after RA, Stephenson's model, the CAPRA, and D'Amico criteria were compared by Lughezzani *et al*.[30] The 5-year biochemical recurrence-free survival rate for low-risk cancer was greater than 85% and was similar in the three models:

D'Amico *et al*. presented an 85% survival rate at 5 years in their study.[1] A slightly lower survival rate (78%) was published by Mitchell *et al*.[31] in their analysis of data from the CaPSURE study. Our study detected: 88.1% 5-year survival rate and 77.9% at 8-year survival rate, which is comparable to the results of the previously mentioned studies.

The natural history of CaP and the impact of radical therapy on survival have been discussed of several randomized trials (PR vs. SA).[32,33] Of these, two analyzed the results in men with low-risk CaP[34,35] Wilt *et al*.[32] reported data from a study where 731 patients were randomized between 1994 and 2002 for RA or surveillance, with a median follow-up of 10 years. The cancer mortality rate was 4.4% in the patients who underwent RA (364 men) compared to 7.4% in the monitored patients (367 men), ($P = 0.09$). This study recorded a specific cancer mortality rate at 12 years of 2.7% ($P = 0.5$). Patients in our low-risk cohort underwent radical prostatectomy.

In general, in Morocco RP is the preferred treatment for low-risk CaP, it is the most common, followed by AS, brachytherapy and radiotherapy. Thus, the proportions of RA and brachytherapy decreased with age, while those of primary hormone therapy, radiotherapy, and AS increased markedly. Similarly, in a Spanish multi-center study, carried out on 3641 patients diagnosed in 2010, 66% of low risk patients, aged ≤65 years, had RA, compared to 35% of patients who were> 65 years old; while the frequency of AS increased from 3.9% to 13% in the youngest to oldest patient groups.[36] Regarding the timing of performing RA, several studies have shown that RA performed >12 months after diagnosis of low-risk CaP gave the same results as if performed immediately.[37,38]

Active surveillance

AS was introduced in the hope of reducing over-processing of CaP without loss of luck for patients.[39,40] Using the natural history microsimulation model of CaP, based on data from the European study; ERSPC, de Carvalho *et al*.[41] found that the likelihood of over treatment ranged from 61% to 86% if men with low-risk disease received active treatment immediately, but decreased to values between 37% and 46%, if they previously had an SA. In addition, SA allows a reduction of 43–78.7% of costs per person in comparison to the immediate realization of a PR.[42]

Our results suggest that decision-making is also partly based on technological platforms available within the walls of the hospital.

Focal therapies

A new concept has recently appeared which could constitute an alternative therapy of low-risk CaP, it is that of focal therapies (TF), the options treatments for these cancers oscillate between two extremes: Radical treatments (TR) and active surveillance (AS). TRs (radical prostatectomy, brachytherapy, and external radiotherapy) are responsible for morbidity that can alter the quality of life of patients by inducing in particular risks of erectile dysfunction and urinary incontinence.

The principle is to merge the MRI image (the only one capable of visualizing PCa), and to display it on the ultrasound machine during the operation. Studies have already demonstrated the feasibility of TF guided by image fusion.[43,44]

CONCLUSION

The results of this study confirmed the heterogeneity of low-risk CaP: 37.5% patients may be erroneously classified as having low-risk CaP when they have presented unfavorable pathological features (pT3 and/or Gleason _ 7) which are incompatible with the diagnosis of low-risk cancer; the risk of developing a very high risk cancer (Gleason _ 8 or pT3b) after RA was minimal: 3%. Our study has its limitations, the sample size being one. Short follow-up is another limitation of this study; it is possible that a longer median follow-up could have influenced the results. The study is also limited by a small number of biopsies, which could be one of the reasons for the high rate of upgrading. Despite these limitations, the data from our study could be useful to clinicians to make the decision about the treatment of low-risk CaP.

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