SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Radiotherapy

Diagnostic, Therapeutic and Evolutionary Characteristics of High Risk Prostate Cancer Managed In Department of Radiotherapy, Mohamed V Military Teaching Hospital - Rabat In Morocco

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DOI: 10.36347/sasjm.2021.v07i12.007 | **Received:** 21.08.2021 | **Accepted:** 27.09.2021 | **Published:** 12.12.2021

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Abstract **Original Research Article**

Purpose: the aim of this study was to rapport the experience of Military Teaching Hospital Mohammed V and specifically the radiotherapy department in the management of high risk prostate cancer. ***Materials and Methods:*** This is a retrospective descriptive and analytical study, involving 149 patients followed for high risk prostate cancer proven histologically, in the radiotherapy department of HMIMV in Rabat between April 2009 and December 2018. All patients with low or intermediate risk prostate cancer were excluded. ***Results*:** The mean age is 68.1 years ± 6.4; screening is performed in 29.5% of cases. Urinary signs were the most frequent symptoms (obstructive syndrome 16.7%, irritative 37.5%), the initial median PSA 22ng / ml [11.1- 40]; histological evidence was obtained by prostate biopsy in 87.24% of cases. Evaluation of locoregional extension by pelvic MRI was performed in 99.3% of patients. Treatment: 132 patients (88.59%) benefited from a combination of external beam radiotherapy and androgen deprivation therapy (LH-RH analogues) for long duration (2 to 3 years), 17 patients (11.41%) underwent radical prostatectomy coupled with ilio-obturator dissection (in 14 patients); all these patients received postoperative radiotherapy (adjuvant or salvage) ± hormone therapy. Evolution: With a follow-up of 117 months, 14 of our patients (9.39%) presented a recurrence: 2 biochemical relapses (1.34%), 5 locoregional relapses (3.35%) and 7 systemic relapses (4.69%); The univariate and multivariate analyzes made it possible to retain the level of PSA Nadir (P = 0.022) and lymph node invasion (P = 0.049) as predictors of relapse. ***Conclusion:*** High risk prostate cancer is a group at high risk of specific mortality linked to progression after treatment. Hence the interest of a multidisciplinary consultation meeting management to define the optimal therapeutic strategy for these patients.

Keywords: radiotherapy, histologically, HMIMV, obstructive syndrome, prostate cancer.

INTROCDUCTION

Prostate cancer is the most common neoplasia in men over 50 [1], as the risk of getting this androgen-dependent cancer increases with age; all men can be exposed. It represents a real public health problem because of its incidence and its high mortality and ranks 4th in overall mortality after broncho-pulmonary, gastric as well as colorectal cancer [2]. The cause of this cancer remains unknown, but ethnicity and family history of prostate cancer (ca P) are the main established risk factors [3], as well as dietary factors, work activities, behaviors, and certain lifestyles [4]. For the past ten years, the diagnostic and therapeutic approach to this cancer has been revolutionized by advances in screening and treatment tools and by perfect knowledge of the natural history of this cancer. The term "advanced prostate cancer" includes situations that are life-threatening to the patient in the medium or short term. It may be a localized cancer but at high risk of progression according to the D'Amico classification, cancer in biological or clinical progression after treatment, or a metastatic cancer.

High-risk prostate cancer is defined biologically as the acquisition of metastatic power and resistance to treatment, leading to an uncontrolled and potentially fatal course. This risk of progression is assessed on data for clinical stage T, the initial PSA value and the Gleason score, as defined by the classification of D'Amico *et al*., In 1998 [5]. The early detection of ca P represents a challenge aimed at reducing its morbidity and mortality and which is essentially based on physical examination (TR), assay

of PSA. Its prognosis is generally good because of the fairly slow progression of this cancer, unlike other cancers. Prostate cancer treatments have changed, with treatments that are increasingly personalized and adapted to patients' prognosis. The aim of our study is to describe the epidemiological, clinical, paraclinical, therapeutic and progressive aspects of high-risk prostate cancer through our institution experience then to determine different predictive prognostic factors for recurrence.

MATERIALS AND METHODS

This is a descriptive and analytical retrospective epidemiological study (series of cases) of epidemiological, clinical, paraclinical, therapeutic and evolutionary data on 149 patients carried out in the radiotherapy department of the Mohammed V military hospital in Rabat, spread over a period of nine years and nine months between APRIL 2009 and DECEMBER 2018.

Using the files of patients with a caP-HR and who had benefited from numerous therapies, namely: radiation therapy, surgery, androgen deprivation therapy.

Were included in the study patients with caP-HR according to the prognosis groups of D'AMICO proven histologically and treated with a combination hormone therapy and radiotherapy or surgery followed by adjuvant or salvage radiotherapy during the period of study and were excluded from the study patients with low or intermediate risk prostate cancer according to the same classification.

The loco-regional and distant extension workup was based on a careful physical examination, prostate MRI, bone scintigraphy, thoraco-abdomino-pelvic CT, and/or choline PET.

For statistical analysis of the data collected, IBM SPSS STATISTICS version 26 software for Windows was used.

The analysis of our data used a descriptive analysis which is based on the calculation of means and percentages, all depending on the nature of the variable (Qualitative or Quantitative).

The quantitative variables are described as mean +/- standard deviation or a median with interquartile (IQR). The choice is made according to the normality of the variable (mean +/- its standard deviation for the Gaussian variables; and median IQR for the asymmetric variables). For a Qualitative variable: it is described by the number and the percentage.

Univariate and multivariate analyzes were carried out in search of predictive prognostic factors significantly associated with a risk of recurrence with a 95% confidence interval. All variables were entered using a binary logistic regression model. To analyze and calculate the overall and relapse survival rate, the Kaplan-Meier method was used.

RESULTS

During the period of the study spread over almost 10 years, 149 patients with high risk prostate cancer were treated in the radiotherapy department of our hospital. The average age was 68, 1 ± 6, 4 years. A family history of prostate cancer was found in only 2, 68% of cases. The diagnosis was revealed by an urinary symptom in 61, 07% of patients, by screening in 29, 54% and incidentally in 9, 35%. The average consultation time was 10 months and the revealing signs were irritative syndrome in 37,58%, obstructive one in 16,77% and the association of both in 12,75% of cases while almost 30% of patients were asymptomatic. The median rate of initial PSA was 22 ng/ml.

Histologically, it was an adenocarcinoma in all patients of our series and the diagnosis was made with a prostatic biopsy in 82, 24%, and a transurethral resection in 8, 05%. The Gleason score was mostly ⩾ 8 in 30, 2 % of patients. The loco-regional spread was assessed by a pelvic MRI in all cases and a staging lymphnode dissection in 5, 37% of patients. The distant spread was assessed by bone scan and thoracoabdominal tomodensitometry. The pet-choline was realized in 2, 68% only. The TNM classification found mostly a T2c in 34, 22% and N+ in 16% us shown in table 1.

Concerning therapeutic management, 132 patients (88.59%) underwent external radiotherapy associated with androgen deprivation therapy for 2 to 3 years while 17 patients (11.41%) underwent radical prostatectomy with pelvic lymph node dissection.

For patients treated by external beam radiotherapy, the VMAT technique was the most used in 85.23% in normal fractionation with IGRT control at a dose of 72.73 (Grays) ± 3.26. The treatment was marked by a good clinical tolerance with the main acute complication being grade 2 pollakiuria, found in 40% of cases. The median PSA nadir was 0.01 ng / ml obtained after a median delay of 11 months [8; 18]. Androgen deprivation therapy associated with radiotherapy of 36 months was responsible of hot flashes in 57% of cases.

All the operated patients underwent adjuvant or salvage radiotherapy at an average dose of 60 gray. Indeed, the surgical margins were reached in 71% of cases, the seminal vesicles were tumorous in 30% of cases. It should be noted that the anatomo-pathological report revealed the presence of a perinervous sheath in 41.18% and capsular rupture in 18.8%. The median postoperative PSA in our patients was 0.09 ng / ml and an urinary incontinence was noted in 30% of cases.

With a follow-up of 117 months, only one patient (0.7%) died, 28 patients (18.7%) were lost to follow-up, and 120 patients (80.53%) are still alive and well followed. In our series, 120 patients (80.53%) were in good locoregional control and 14 of our patients, or 9.39%, presented a recurrence. Among these relapses, 3.35% were locoregional, 1.34% a biochemical relapse and 4.69% were distant metastatic relapses mainly at the bone level. The median time to relapse was 24 months [12; 25] and the median PSA at relapse was of 6 ng / ml [2.4; 92.7]. The late complications of treatment was mainly erectile dysfunction and chronic cystitis, us shown in table 2. Thus, the 10-year overall survival rate was 98.8% and the relapse-free survival was 94, 2%, 90,2% and 88,5% respectively at 2, 5 and 10 years (Figure 1 & 2).

Different prognostic factors were included in a univariate and multivariate analysis (table 3). On the univariate analysis, the initial PSA level in the relapsed group (73.66 ng / ml ± 90.45) was higher compared to the non-relapsed group (33.51ng / ml ± 58.90) with a statistical tendency towards significance (p = 0.056). In contrast, the Nadir PSA level dosed was very significantly different between the two groups. (p = 0.002). Lymph node invasion was statistically significant between the 2 groups (p = 0.043).The statistical analysis of the Gleason score between the 2 groups was significant for a score = 4 + 3 (p = 0.048), as well as a trend towards significance for a Gleason score = 3 + 4 (p = 0, 06). During multivariate analysis (logistic regression), the level of PSA Nadir (p = 0.022) and lymph node invasion (p = 0.049) appeared as predictive factors for the onset of relapse with a statistically significant difference between the 2 groups.

Table 1: TNM staging distribution

Stade T	**Number**	**pourcentage (%)**
T2a	**6**	**4,02**
T2b	**8**	**5,4**
T2c	**51**	**34,22**
T3a	**41**	**27,51**
T3b	**37**	**24,83**
T4	**3**	**2,01**
Unknown	**3**	**2,01**
N	**Number**	**pourcentage (%)**
N0	**123**	**82,6**
N+	**24**	**16,1**
Unknown	**2**	**1,3**

Table 2: Late complications of treatment

Toxicities		**Number**	**pourcentage (%)**
Late gastrointestinal toxicity	**Chronic proctitis**	2	1 ,3
	None	132	88,6
	Unspecified	15	10,1
Grade	**0**	132	88,6
	2	2	1,3
	unspecified	15	10,1
Genitourinary toxicity	**Urinary incontinence**	3	2,01
	Erectile dysfunction	33	22,14
	Chronic cystitis	20	13,42
	Urinary stenosis	37	24,83
	None	42	28,18
	unspecified	14	9,4
Grade	**0**	86	57,7
	1	1	0,7
	2	26	17,4
	3	17	11,4
	4	5	3,4
	unspecified	14	9,4

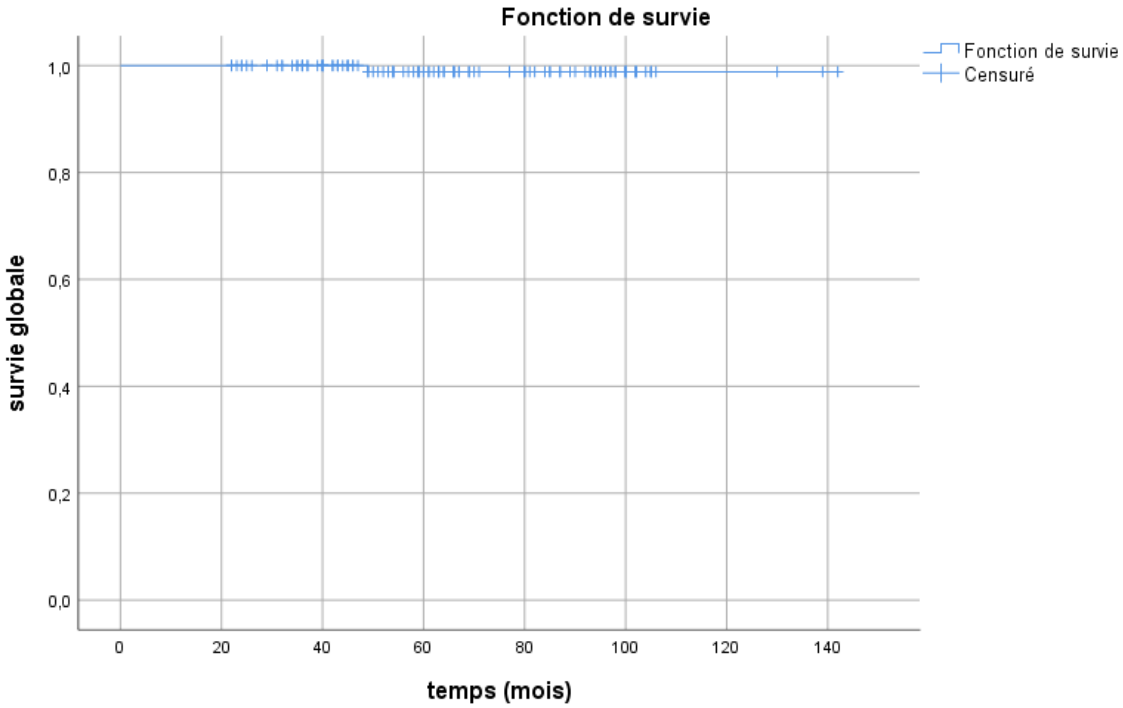

Figure 1: Overall survival curve

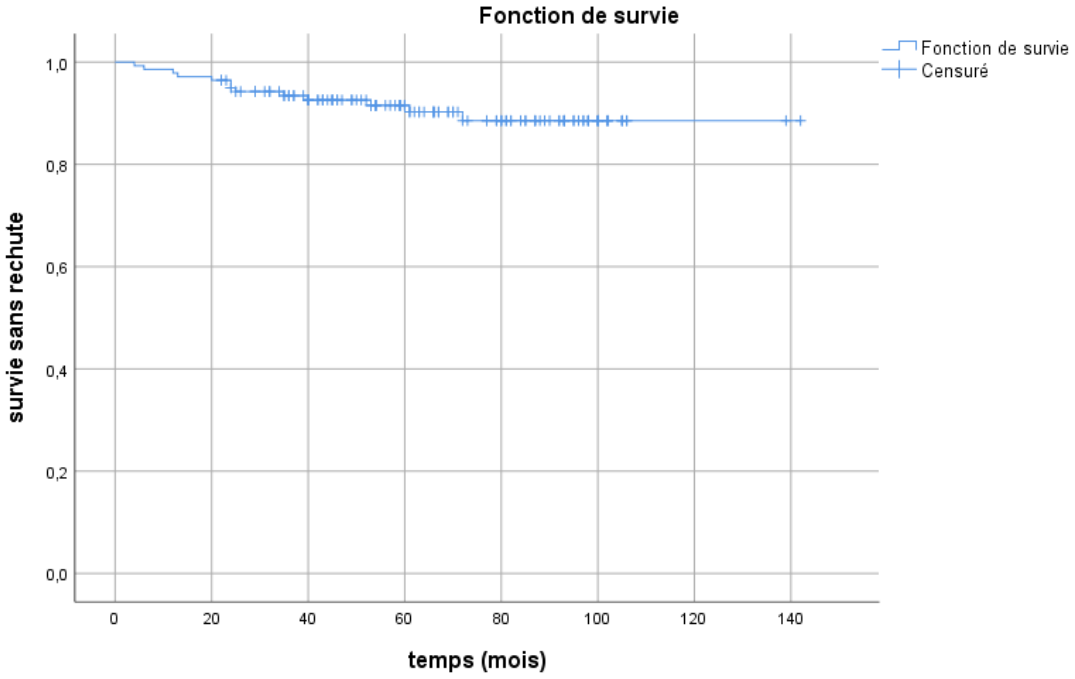

Figure 2: Relapse free survival curve

Table 3: Univariate and multivariate analysis

Characteristics	Relapse		Univariate analysis			Multivariate analysis		
	Oui	Non	OR	IC (95%)	p	OR	IC (95%)	p
1-Age	65,64 ± 6,59	68,65 ± 5,80	1,026	[0,94 ; 1,12]	**0,559**	1,064	[0,94; 1,19]	0,312
2-Initial PSA	73,66 ±90,45	33,51 ± 58,90	0,994	[0,98 ;1]	**0,055**	0,997	[0,98; 1,01]	0,458
3-PSA NADIR	0,61 ± 1,36	0,02 ± 0,05	0,01	[0,00 ; 0,76]	**0,002**	0,004	[0,00 ; 0,45]	**0,022**

4-perineural sheath	Oui	64,3%	40,7%	0,398	[0,12 ; 1,28]	**0,124**	0,226	[0,03 ; 1,73]	0,152
	Non	35,7%	59,3%	R					
5-radiotherapy plan	SIB	30,8%	9,9%	0,437	[0,11 ; 1,83]	**0,258**	0,735	[0,08 ; 6,24]	0,778
	SEQUENTIEL	69,2%	90,1%	R					
6-surgery	Oui	7,1%	11,7%	1,71	[0,20 ; 14,14]	0,999			
	Non	92,9%	88,3%	R					
7-lymphatic spread	N0	64,3%	85,7%	R					
	N+	35,7%	14,3%	3,52	[1,04; 11,91]	**0,043**	12,22	[1,02 ; 147]	**0,049**
8- Gleason score	<7	15,4%	28%	R					
	3+4	7,7%	26,4%	4,5	[0,91 ;22,33]	**0,06**	0,55	[0,05 ;6,05]	0,627
	4+3	7,7%	17,6%	8 ,48	[1,02 ;70,69]	**0,048**	1,47	[0,11 ;21 ,32]	0,777
	>8	69,2%	28 %	5,65	[0,67 ;47,78]	0,111	5,15	[0,42 ;63,71]	0,202
9-**T clinical stage**	T2a	0%	4%	R					
	T2b	7,7%	4,8%	3		0.999			
	T2c	23,1%	36%	7 ,5	[0,12 ;73,64]	0,501	0,547	[0,004 ;85,30]	0,815
	T3a	23,1%	30,4%	6,33	[0,52 ;108,28]	0,139	5,925	[0,079 ;414,81]	0,419
	T3b	38,5%	32,2%	2,9	[0,43 ;91,70]	0,176	2,332	[0,32 ;169,36]	0,698
	T4	7,7%	1,6%	2	[0,219 ;38,32]	0,419	8,157	[0,12 ;591,032]	0,337
10-famiy history of caP	Oui	0%	100%			1			
	Non	96,6%	3,4%	R					

DISCUSSION

High-risk disease accounts for approximately 15% of prostate cancer diagnoses, but the current definitions include a heterogeneous group of patients with a range of prognoses [6].

The optimal management of this patient sub-group is evolving. A refined classification scheme is needed to enable the early and accurate identification of high-risk disease so that more effective treatment paradigms can be developed. There has been clinical equipoise surrounding the issue of selecting optimal definitive therapy, as treatment paradigms have evolved to incorporate both upfront surgery and radiation approaches (2). Definitive therapy for newly diagnosed cases of high-risk disease now routinely includes radical prostatectomy (RP) followed by a consideration of adjuvant radiation (ART) and androgen deprivation therapy (ADT) or a combination of external beam radiation therapy (XRT) with androgen deprivation therapy (ADT) with or without the addition of brachytherapy (BT) [7]. The relative risk of PCa-related mortality in men with high-risk prostate cancer (HRPCa) is substantial despite optimal therapy, and has been estimated at 14.2% after radical prostatectomy and 14.3% after external beam radiation therapy (EBRT) [8].

In a landmark paper published in 1998, D'Amico *et al*., [9] established the most popular risk-stratification system for PCa based on clinical data obtained from 1872 patients who underwent radical prostatectomy or EBRT with curative intent. HRPCa was defined as having any of the following risk factors, predicting greater than 50% probability of cancer recurrence after local therapy: clinical stage T2c or higher, a pretreatment PSA greater than 20 ng/ml, or a biopsy Gleason score of at least 8. The American Urological Association and the UK National Institute for Health and Clinical Excellence have endorsed the D'Amico high-risk criteria [10, 11], whereas the European Association of Urology and National Comprehensive Cancer Network (NCCN) guidelines have narrowed the risk group by restricting the clinical stage criterion to T3a and above rather than T2c [3, 20]. The Radiation Therapy Oncology Group (RTOG) uses a risk-stratification scheme which consists of PSA 20–100 ng/ml, biopsy Gleason score at least 7, and any clinical T stage; or PSA below 100 ng/ml, Gleason score at least 8, and clinical stage T2c [12]. The Cancer of the Prostate Risk Assessment (CAPRA) score incorporates additional variables into the equation including age, PSA, clinical stage, biopsy Gleason score, and percentage of positive biopsy cores; a score of 6–10 represents HRPCa [13]. The Kattan preoperative nomogram uses a multivariate model that combines stage, grade, and PSA to generate an estimate of the risk of treatment failure following radical prostatectomy on a continuous scale [14]. Using this nomogram, one can apply any reasonable threshold to segregate high-risk from nonhigh-risk tumors.

The optimal management for patients with high-risk prostate cancer remains controversial. An increasing proportion of high-risk patients are treated with combined radiation and hormonal therapy, in light of evidence from randomized controlled trials demonstrating an advantage over radiation alone. Without clear evidence of superiority, radiation therapy combined with androgen-deprivation therapy (ADT) has become the standard-of-care treatment for patients with high-risk disease; however, increasingly patients are initially treated surgically. Surgery for high-risk disease, as part of multimodal therapy, has comparable

efficacy to radiotherapy with ADT; therefore, primary surgery, with or without adjuvant radiotherapy, is a viable treatment option.

CONCLUSION

Multimodal treatment utilizing combined androgen suppression and radiotherapy has improved survival rates for patients with high-risk prostate cancer. In addition, multiple randomized trials in patients treated with primary radical prostatectomy have demonstrated improved outcomes with the addition of adjuvant radiotherapy. Improved radiotherapy techniques that allow for dose escalation, and new systemic therapy approaches such as adjuvant chemotherapy, present promising future therapeutic alternatives for patients with high-risk prostate cancer.

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