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RESEARCH ARTICLE

HIGH RISK PROSTATE CANCER: COMPARISON OF RADICAL PROSTATECTOMY VERSUS RADIATION THERAPY: EXPERIENCE OF MILITARY HOSPITAL RABAT

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Abstract

Context: To date, there is no Level 1 evidence comparing the efficacy of radical prostatectomy and radiotherapy for patients with clinically-localized prostate cancer.

Objective: to evaluate overall survival (OS) and relapse free survival of high risk prostate cancer (PCa) treated either with external beam radiotherapy (EBRT) associated with androgen deprivation therapy (ADT) or radical prostatectomy (RP) with adjuvant or salvage radiotherapy and ADT. Also, it is very interesting to compare different acute and late toxicity of the both approach.

Materials and Methods: During a period of 10 years from April 2009 and December 2018, 149 patients with high-risk prostate cancer were admitted to the radiotherapy department of the Mohammed V military hospital in Rabat (HMIMV). Among these patients, 17 underwent surgery followed by EBRT and ADT: this is the experimental arm (Group I) and 34 patients who had benefited from treatment with EBRT with ADT were selected from the other patients by a 1: 2 matching method who will represent the reference group (Group II) to allow a comparison with the experimental arm with the minimum possible bias.

Results: The overall survival (OS) at 5 and 10 years was 100 % in the both arms while relapse free survival at 5 years was 91,7 % and 93,1% respectively in group I and II and at 10 years 91,7% in the group multimodal approach and 88,9 % in the EBRT+ADT group without any significant difference. We note more toxicities in the surgical group with more urinary incontinence ($p=0,001$) and more erectile dysfunction.

Conclusion: RP with adjuvant EBRT and EBRT+ADT provided similar long-term cancer control for patients with high-risk prostate cancer but with different toxicity profiles.

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Introduction:-

Following the introduction of prostate cancer (PCa) screening, there has been a rise in the number of men diagnosed with clinically nonmetastatic PCa. Nevertheless, 17–31% of these men present with high-risk localized or locally advanced disease [1]. The optimal treatment for these patients remains unknown. Historically, men with high-risk

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PCa have been managed most commonly with external beam radiotherapy EBRT, androgen deprivation therapy ADT, or both, while radical prostatectomy RP has been discouraged in this setting, due to concerns about side effects and inadequate disease control. However, no randomized data are available to evaluate RP versus EBRT + ADT in terms of survival outcomes and/or toxicity, but the ongoing randomized SPCG-15 trial will provide us with valuable information on this matter [2]. Until these results are available, Patients should at all times be fully informed about all available options, and the likelihood of a multimodal approach including the potential side effects of both local and systemic treatment. The aim of our study is to compare two treatment modalities at high risk prostate cancer concerning oncological outcome and toxicity profile.

Materials and Methods:-

This is a retrospective study comparing two therapeutic modalities in patients with high-risk prostate adenocarcinoma: EBRT associated to ADT versus surgery followed by radiotherapy “multimodal treatment”.

During a period of 10 years from April 2009 and December 2018, 149 patients with high-risk prostate cancer were admitted to the radiotherapy department of the Mohammed V military hospital in Rabat (HMIMV). Seventeen patients (Group I) underwent radical prostatectomy with pelvic lymphadenectomy. EBRT in association with LH-RH analogues was indicated in patients with adverse features (positive margins, T3, post-operative detectable PSA, high grade). EBRT was delivered in 32 – 33 fractions with a total dose of 64 -66 Gray using volumetric modulated arc therapy technique VMAT to prostate fossa. Thirty four patients (Group II) with a ratio 2:1 were selected in the basis of clinical features (similar to group I) and treated with EBRT with long course ADT. EBRT was delivered to pelvis with a total dose of 46 – 50 Gy with a boost to prostate of 24 – 26 Gy using VMAT.

Statistical analysis of the data was performed by IBM SPSS 26 software. Propensity-score matching was performed. Kaplan–Meier survival analysis was used to compare overall survival and free failure survival. Univariate and Multivariate analysis was used.

Results:-

Patient’s Characteristics

The frequency of multimodal approach in our series is 11, 4%. The epidemiological, clinical, paraclinical, and histological characteristics can be summarized in Table 1.

		Group I	Group II	p
AGE (years)		65.41 ± 5,7	68.24 ± 6,7	0,147
Initial PSA (ng/ml)		10.0 [7.3 - 20.7]	16.1 [9.5 - 23.5]	0,135
Urinary symptoms n (%)		7 (41,2)	17(50)	0,76
Histological diagnosis modality	Biopsy n (%)	16(94,1)	31(91,2)	0,813
	RTUP n (%)	10(5,9)	3(8,9)	0,813

Table 2:- The Gleason score of the two arms is summarized.

Gleason score	Group 1	Group 2	P
<7	47.1%	20.6%	0,242
3+4	29.4%	29.4%	
4+3	5.9%	17.6%	
>=8	17.6%	32.4%	

Table 3:- The TNM classification of our patients in the two groups is shown.

	Group 1		Group 2		P
	N	%	N	%	
T2a	0	0	1	2,9	0,66
T2b	2	11,8	4	11,8	
T2c	13	76,5	19	55,9	
T3a	1	5,9	7	20,6	
T3b	1	5,9	3	8,8	

T4	0	0	0	0	
N0	17	100	30	88,2	0,288
N+	0	0	4	11,8	

Surgery in Group I patients consisted of radical prostatectomy associated with lymph node dissection in 82.4% and radical prostatectomy alone in 17,6 %. Histopathological data on the operative part showed that the gleason score was greater than that found on the biopsy since an ISUP 4/5 was noted in 23.5% versus 17.6%, The surgical margins were reached in 70.6 %, capsular breach was found in 17.6%, the seminal vesicles were affected in 29.4% and perineural sheath was noted in 41.2%. As for lymph node dissection, lymph node involvement was found in 14.3% of patients.

The postoperative PSA median was 0.09 ng / ml [0.04-0.32].

Oncological Outcomes

The overall survival (OS) at 5 and 10 years was 100 % in the both arms while relapse free survival at 5 years was 91,7 % and 93,1% respectively in group I and II and at 10 years 91,7% in the group multimodal approach and 88,9 % in the EBRT+ADT group without any significant difference us shown in the survival curves (figure 1)

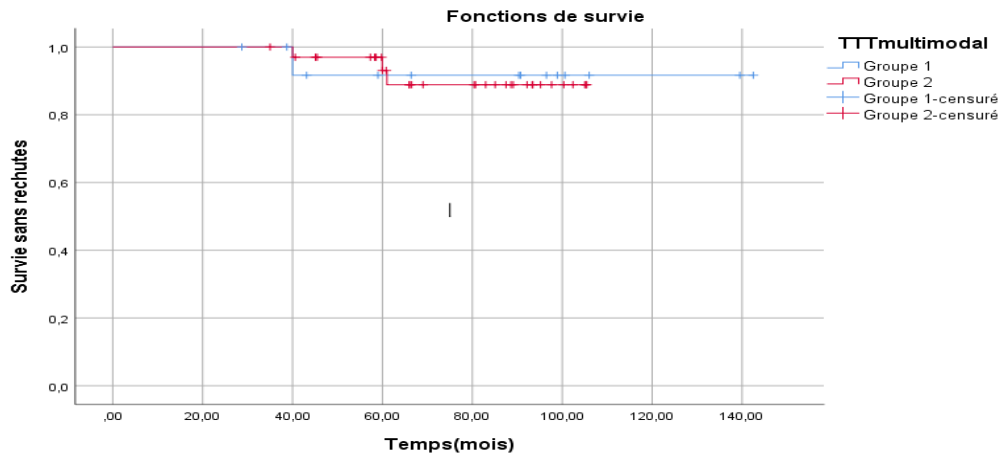


Table 4:- Concerning relapses of our patients, we can summarize the results in the following Table.

Events	Group I		Group II		P
	N	%	N	%	
Good locoregional control	16	94,1	31	91,3	0,834
Biochemical relapse	0	0	1	2,9	
Locoregional relapse	1	5,9	1	2,9	
Metastatic relapse	0	0	1	2,9	

Non Oncological Outcomes

Regarding toxicity after surgical treatment with adjuvant radiotherapy and EBRT-ADT, no statistically significant difference was noted concerning acute toxicity us shown in **Table 5** while more late complications was noted in the group treated with combining surgery and EBRT-ADT with a p=0,001 for urinary incontinence and a p=0,027 which tends toward a significance concerning erectile dysfunction (**Table 6**).

		Group TMM		Group H-RT		P
		N	%	N	%	
Gastrointestinal toxicity	Anal pain	1	7,1	4	12,9	1,0
	diarrhea	1	7,1	3	9,7	
	Rectal bleeding	0	0	0	0	
	Any	12	85,7	24	77,4	
Grade	0	8	88,9	13	65	0,547

	1	0	0	3	15	
	2	1	11,1	4	20	
	3	0	0	0	0	
	4	0	0	0	0	
Genitourinary toxicity	Dysuria	3	21,4	3	9,4	0,464
	Mictionnel Burns	2	14,3	11	34,4	
	Pollakiuria	7	50	11	43,8	
	Any	2	14,3	14	12,5	
Grade	0	2	16,7	4	11,5	0,556
	1	1	8,3	3	11,5	
	2	8	66,7	20	76,9	
	3	1	8,3	0	0	
	4	0	0	0	0	

		Group TMM		Group H-RT		P
		N	%	N	%	
Late gastrointestinal complications		0	0	0	0	-
Late genito-urinary complications	Urinary incontinence	6	35,4	0	0	0,001
	Erectile dysfunction	9	52,9	7	20,5	0,027
	Chronic cystitis	0	0	4	11,7	0,28
	Utheral stenosis	1	5,9	10	29,4	0,075
	Any	1	5,9	13	38,4	0,019
Grade	0	2	14,3	21	67,7	0,00
	1	0	0	1	3,2	
	2	2	14,3	6	19,4	
	3	6	42,9	3	9,7	
	4	4	28,6	0	0	

Discussion:-

Multimodal approach for high risk prostate cancer historically treated with external beam radiotherapy and androgen deprivation therapy is an emergent option and subject of a large debate. It is defined by the association of surgery based on radical prostatectomy and pelvic lymph node dissection followed by adjuvant or salvage radiotherapy with or without ADT [3]. At diagnosis, prostate cancer is usually classified into major risk categories based on TNM clinical stage, biopsy Gleason score, and pretreatment PSA levels. The definition of high risk group is cT2c or ISUP grade 4/5 (Gleason > 7) or PSA > 20 ng/ml according to the D'Amico classification and the European association of urology (EAU) while the NCCN group define this category by cT3 or ISUP grade 4/5 (Gleason > 7) or PSA > 20 ng/ml [4]. However, High-risk prostate cancer is an extremely heterogeneous disease and a clear definition of prognostic subgroups based on combinations of unfavorable risk factors is mandatory to dictate the optimal management. So, very studies tried to stratify the high risk patients in prognostic categories like the study of Steven Joniau et al. [5] which show that survival varied from 49 to 80% at 5 years according to risk stratification. In fact, there is no large-scale randomized study and the retrospective studies present a lot of bias in particular the heterogeneity of high risk patients, the use of adjuvant treatment, the dose and technique of radiotherapy, the duration of ADT and functional, urinary and sexual status before treatment. It is worth noting that the retrospective series to date that have compared outcomes after surgery and radiation for high-risk tumors have demonstrated widely disparate results, with several groups reporting improved outcomes after radical prostatectomy, others reporting better results after radiation and a few trials noting equivalent efficacy. We start with some institutional comparative studies like this one [6] including 2380 patients with high risk prostate cancer and revealed that the group treated with RP had a lower risk of metastatic progression and a better specific survival. However, an American group of Washington included 6692 high risk prostate cancer [7] and compared overall and specific survival of three arms, RP, brachytherapy and EBRT; the results were in favor of EBRT. Also, a series of Mayo Clinic including 1847 patients [8] find an equivalent specific survival and overall survival at 10 years in the two

arms like results of our study since there was no statistically significant difference in 5 and 10 years survival as well as free failure survival between the two therapeutic groups. In the literature, there is many metaanalysis with divergent results, like this one [9] published on 2014 including 17 series showing benefice of RP versus EBRT concerning specific and overall survival but an equivalent biochemical free survival between the two groups. Also, a Swedish metaanalysis of observational studies between 1996 and 2010 [10] with an advantage for RP in patients with good general conditions. In fact, several of the meta-analyses of observational studies available demonstrate robust and statistically significant OS and SS benefits in favor of RP over RT-based approaches in all clinically localized disease [11, 12, 13, 14]. Indeed, there is a lack of true randomized trial comparing the two treatment modality in a homogeneous high risk population. Through our literature review, in this comparative study [15], long term outcomes appear similar among patients with high risk and very high risk prostate cancer deemed eligible for either RP or EBRT+ADT with similar local recurrence, distant metastasis failure and overall survival. Beyond this, there is equipose regarding the optimal treatment. Inference must still be drawn from retrospective single-institution studies, population-based studies, and multi-institutional registries, all of which contain inherent selection bias, limited reporting, and potential residual confounding errors, which are difficult to address even with the best propensity score, instrumental variable, or regression methods and the challenge faced when assembling evidence regarding surgical or radiation-based treatment efficacy for high-risk prostate cancer is the lack of randomized trials to provide sufficient power [16]. Fortunately, SPCG-15 [17] is a prospective, multi-center, open randomized phase III trial. Patients are randomized to either standard (EBRT and ADT) or experimental (RP with extended pelvic lymph-node dissection and with addition of adjuvant or salvage RT and/or ADT if deemed necessary) treatment. Each center follows guidelines regarding the timing and dosing of postoperative RT and adjuvant treatment such as ADT the primary endpoint is cause-specific survival. Secondary endpoints include metastasis-free and overall survival, quality-of-life, functional outcomes and health services requirements. Each subject will be followed up for a minimum of 10 years. Until available results of this interesting prospective study, despite ongoing uncertainty regarding optimal standard of care, NCCN and EAU guidelines list EBRT+ADT, EBRT+brachytherapy or RP+PLND combination as valid options for patients with >5 years expected survival. Finally, our study evaluated the effects of local treatment. In general, both radical and systemic treatments result in significant side effects. We can conclude that patients treated with RP experience mainly genitourinary toxicity and sexual dysfunction, while EBRT can result in gastrointestinal problems. Attention should be drawn to increases the risk of urinary incontinence and erectile dysfunction even no comparison was made between adjuvant and salvage radiotherapy or between open and robotic surgery. In our practice, we often underestimate the risk of toxicity and focus on oncological outcomes, however patient can recover from his disease but with a very hard toxicities impacting directly the life quality [18]. Surgery by itself significantly induces a risk of incontinence and deterioration of sexual function [19]. In three main trials of adjuvant radiotherapy, and increased risk of toxicity is consistently noted. In southwest Oncology Group (SWOG) trial [20], the risk of urinary incontinence fell from 2.8 % to 6.5% urethral stenosis from 9.5% to 17.8%. Similarly, in the EORTC and ARO trials, the grade 2 or 3 risk is significantly increased [21]. A partial analysis in the EROTC trial did not show difference in postoperative incontinence [22]. In summary, our study is not devoid of limitations. First, it includes patients treated with RP over a relatively long period of time. Because surgery has been considered as possible a possible first time treatment for selected high risk prostate cancer only in more recent years at our institution, the effective of patients in surgical arm is very low. Also, because most prostate deaths can occur over 10 years after initial treatment, further follow up is needed to provide more robust estimations of prostate cancer specific survival in both arms.

Conclusion:-

RP with adjuvant EBRT and EBRT+ADT provided similar long-term cancer control for patients with high-risk prostate cancer but with different toxicity profiles. No prospective data is available until now but the the ongoing randomized SPCG-15 trial will provide us with valuable information on this matter.

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