Research Article

Annals of Urology (ISSN 2767-2271)

Effectiveness of surgical castration by bilateral sub-capsular orchiectomy as monotherapy for the treatment of advanced prostate cancer.

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Received Date : August 03, 2024
Accepted Date : August 04, 2024
Published Date : September 14, 2024

INTRODUCTION

Prostate cancer is the most common malignancy in men and the second cause of death due to cancer [1]. Treatment of prostate cancer has been a field of many progresses, but the discovery of the role of androgen in the genesis of prostate cancer by Hugins and Hodges is really a milestone in the treatment of advanced prostate cancer [2]. In patients with advanced prostate cancer, options for androgen ablation include bilateral orchiectomy, therapy with luteinizing hormone-releasing hormone (LHRH) analogues and antagonists, and combined androgen blockade (typically a LHRH analogue plus a first-generation anti-androgen). Although orchiectomy remains the historical gold standard for androgen ablation, LHRH therapy is considered to be equivalent therapeutically. Medical castration has the advantage to induce less psychological effects comparatively to the surgery, reason why in developed countries patients are managed with medical therapy [3].

However, LHRH agonists cannot induce a complete castration levels of testosterone in some patients [4]. Instead, surgical castration can completely eliminate remaining testosterone produced by the Leydig cells in testes [5]. According to the latest recommendations of the European Association of Urology (EAU), androgen deprivation therapy (ADT) is the first-line indication in patients with advanced and metastatic PCa [6]. This first line is made of LHRH agonists, surgical castration representing the second line [7] And Several techniques of surgical castration have been described with comparable results in terms of patient survival and quality of life, but the sub-capsular technique of preserving testicular albuginea and epididymis is the most commonly used [8]. The relatively high cost of chemical castration is a constraint in the therapeutic choice in developing countries [9]. Therefore, surgical castration is an interesting alternative because of its simplicity and affordability in patients, most of whom have no health insurance. In Togo, most patients diagnosed with prostate cancer are at the metastasis stage, and surgical castration is often used as first-line treatment [10]. The aim of this study was to assess the biological and clinical effectiveness of surgical castration as the sole treatment in patients with advanced prostate cancer.

PATIENTS AND METHODS

Study settings

University teaching hospital of Kara is located in the north part of Togo, it is the reference center for three regions over five that counts the country. People are in majority farmers and the minority is represented by government employers. Therefore, our study has been conducted in a resources constraint environment, on patients with a low income and having no insurance. The mean amount of medical castration was around 80,000 CFA monthly and that of surgical costed 50,000 once.

Patients Inclusion

We conducted a prospective and descriptive study in the urology-andrology department of the teaching hospital of Kara over a period of 24 months, from January 2020 to December 2021. The population of the study was represented by all the patients treated in the department during this period for prostate cancer. Thirty (30) patients selected to be treated by surgical castration in mono therapy were consecutively

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included. The sample size has been determined randomly by the length of the study. The first criteria was the diagnosis of advanced prostate cancer (T3NxM1) or locally advanced prostate cancer in case patients were not eligible for neither radical prostatectomy nor radiotherapy. The second criteria was the fact that pulpectomy might be the only treatment for the patient, thus all the patients treated by pulpectomy associated to any other method of androgen deprivation therapy were excluded. All the patients selected underwent a bilateral subcapsular orchiectomy using local anesthesia in ambulatory.

Technique of sub capsular orchiectomy

The orchiectomy was performed under local anesthesia using xylocaine 2%. The spermatic cord was the site of infiltration, after what a transverse scrotal incision was made, and the different envelopes incised up to the vaginal. Then we carried out an opening of the albuginea of the testicle. The testicular pulp was beaten in full. Testicular pedicle haemostasis was made by a suture in polygalactin 0; the albuginea was then seamed with polygalactin 0. Envelopes were stitched up in a single plane by separated points with polygalactin 2/0 and scrotal skin with nylon 3/0. After the surgery, patients were discharged the same day whit oral prescription of analgesic and amoxicillin for seven days. The scrotal wound has been treated for ten days, delay for ablation of sutures.

Data collection

Patients were monitored weekly for one month, then monthly for six months and quarterly until the eighteenth month. No complications occurred during the period. The studied parameters were the initial rate of PSA, the Gleason score (obtained on previous prostatic biopsies), the TNM stage, the evolution of the patient's quality of life one month after castration comparatively to the patient's state before the procedure, testosterone value at 1 month, PSA at 1, 3 and 6 months after surgical castration, and patient survival. Quality of life was assessed using the Expanded Prostate Cancer Composite Index score (EPIC) which takes into account urinary comfort, digestive symptoms, sexual disorders and vitality. EPIC score is based on a questionnaire made by ten items, each question is given a value accordingly to the patient response and the maximum is 60. All the questions of the questionnaire are relative to the last four weeks. Values obtained after patient response are added together to get the final score and this one is linked to quality of life (QoL) of the patient. The survival has been assessed using the Kaplan-Meier method.

Statistical analysis

Data were analyzed by Excel; the quantitative variables were expressed as mean and standard deviation and the qualitative variables as percentage. Chi square test was used to assess the correlation between the different parameters. The significance threshold was 0.05.

Ethical consideration

Consent was obtained from all patients enrolled in the study, and the data were processed confidentially.

RESULTS

Patients' characteristics

Thirty patients were included over a period of twenty-four months. The average age of patients was 68.9 (the extremes are 54 and 79 years). The mean initial PSA was 2597.3ng/ml (extremes of 35.45 and 25205ng/ml); the median initial PSA was 429.5ng/ml (standard deviation 5347.4). The Gleason score ranged from 6 to 9 (5+4); 4 patients (13.3%) were classified as ISUP 1, 10 (33.3%) ISUP 2, 5 (16.7%) ISUP 3, 6 (20%) ISUP 4 and 5 (16.7%) ISUP 5. According to the 2017 TNM classification, the lowest stage was T3N0M1a while the highest was T4N1M1c. Metastasis sites were preferentially bones and nodes and the majority of patients had multiple metastasis. Characteristics of patients are summarized in **Table 1**.

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Table 1

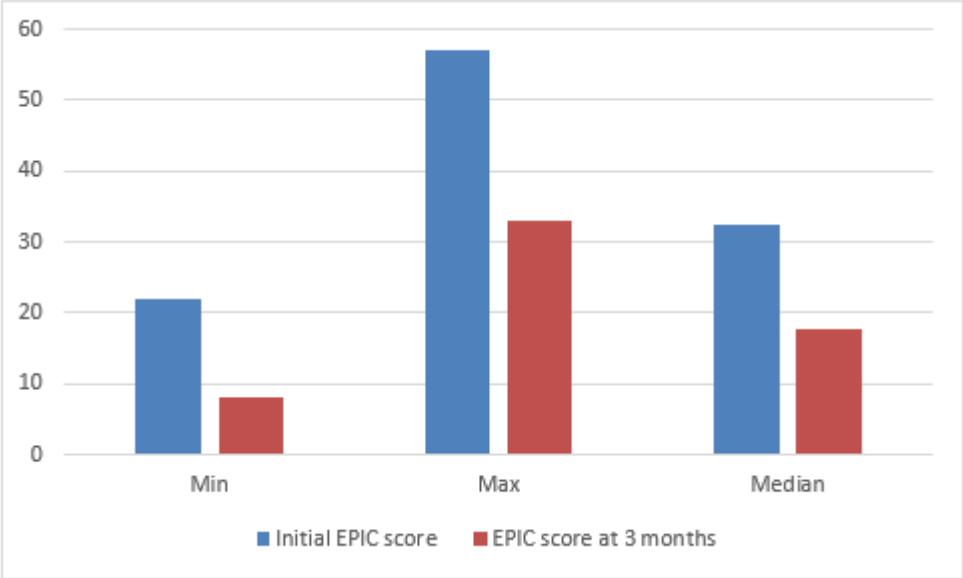
	Median	Min	Max
Age	68.9	54	79
PSA initial	429.5	35.4	25205
Gleason score		6	9(5+4)
Stade TNM			
	Effectif	**Percentage**	
T3N0M1a	3	10	
T3N0M1b	5	16.7	
T3N1M1a	3	10	
T3N1M1b	10	33.3	
T3N1M1c	2	6.7	
T4N1M1b	4	13.3	
T4N1M1c	3	10	

Outcomes after sub capsular orchiectomy

1. Quality of Life

There was a significant improvement in life quality four weeks after pulpectomy, especially in patients with bone symptomatology. The 3-month EPIC rating (minimum, maximum, average) compared to the initial values showed a clear decrease. The median of EPIC score decreased from 32.5 initially to 17.8 three months after pulpectomy (Figure 1).

Figure 1. Comparison of initial EPIC Score and 3 months after castration



Min = minimal EPIC Score; Max = maximal EPIC Score; Median = median EPIC Score

2. Testosterone

Amount of testosterone was below castration level (mean 0.05 ng/ml or 50 ng/dl) in all patients, one month after treatment.

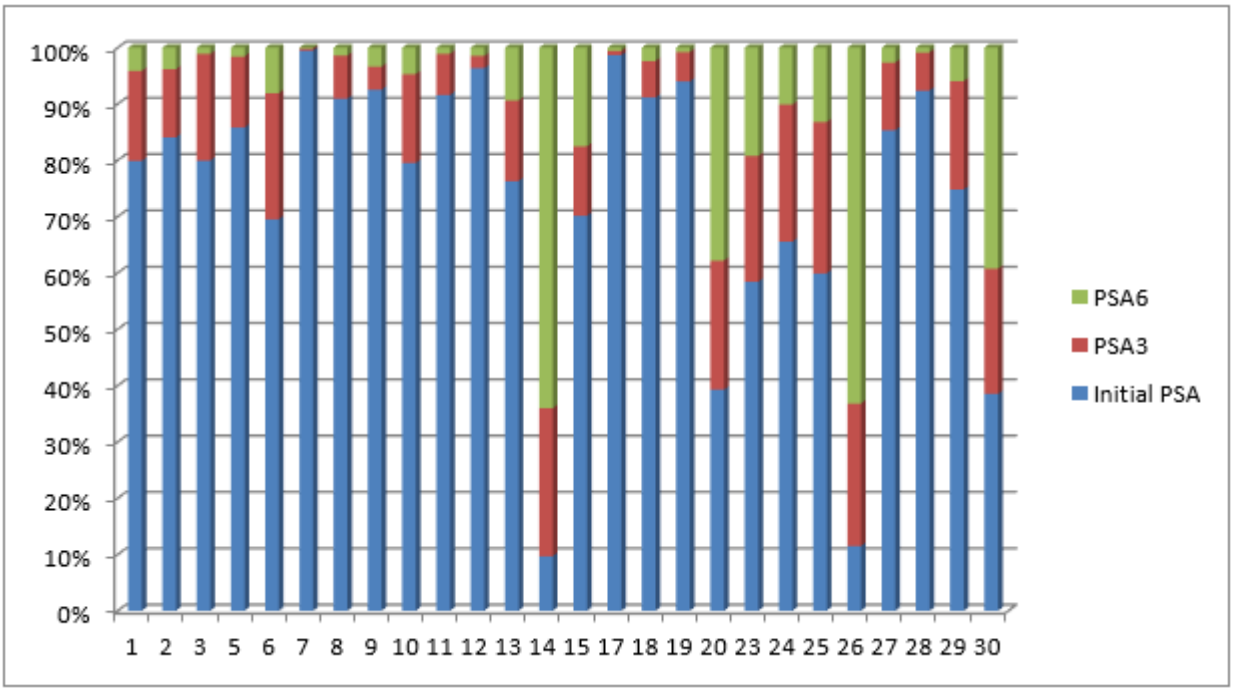
3. PSA

After six months follow-up, the PSA rates were below the initial values (Figure 2). The decrease of PSA levels was estimated to 70% in more than 2/3 of the patients and that decrease was significant (P= 0.02). There was resistance to the castration in 4 patients (15.3% of surviving patients), defined by two consecutive increasing PSA levels after a nadir obtained after 8 weeks in 1

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patient, 9 weeks for the second one and 14 and 15 weeks for the last two patients. In these patients there was no exacerbation of clinical manifestations such as pain or other symptoms. These four patients underwent new generation Androgen Receptor (AR) pathway inhibitors, using Abiraterone associated to glucocorticoids.

Figure 2. Comparison between initial PSA rates, at 3 months and 6 months after castration in patients surviving at six months.

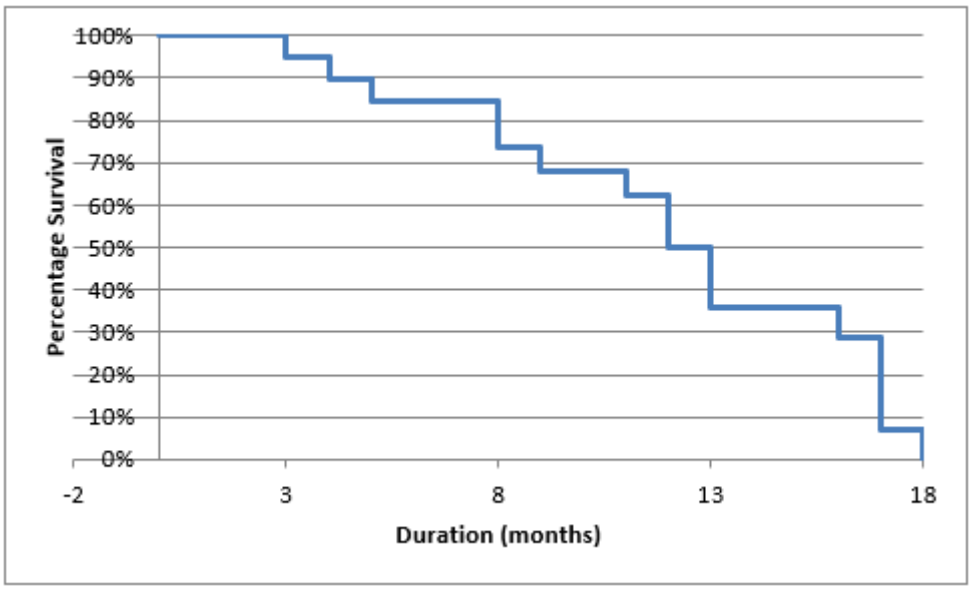


PSA3 = PSA rate at three months; PSA6 = PSA rate at six months

4. Survival

The average length of participation to the study of all patients was 8.06 months. In terms of survival, the cumulative overall survival at 6, 12 and 18 months were respectively 83.3%, 50% and 13.3% as shown in figure 3.

Figure 3. Survival curve according to Kaplan-Meir



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DISCUSSION

The aim of this study was to evaluate the effectiveness of sub capsular orchiectomy in patients with an advanced prostate cancer. Although the study focused on a small series, our results allow us to emphasize the effectiveness of surgical castration by sub capsular orchiectomy, this in addition to its low cost. Patients included in the study was characterized by a great heterogeneity, both biologically (PSA levels and Gleason score) and morphologically, with a very variable prognosis. Despite this disparity, the results obtained after orchiectomy were almost all in favor of a gain in terms of quality of life. Survival appears to be poor over 18 months, but the absence of a control group makes it impossible to draw a precise conclusion. Castration resistance was observed in all patients in the ISUP 5 group, thus underlining the major prognostic role of Gleason score.

Surgical castration by bilateral sub capsular orchiectomy has been introduced in 1942 by Riba, and therefore represented a credible option to the simple bilateral orchiectomy [11]. More recently, a less invasive method has been described. It consists of the use of the Burdizzo clamp which allows to cut the spermatic cord under local anesthesia without cutaneous opening [12]. Although this last technic has the advantage of being fast and providing fewer complications, the results are less good, with lower PSA and testosterone values decrease. In a study comparing efficacy, aesthetic outcome and patient satisfaction, total orchiectomy, sub-capsular orchiectomy (pulpectomy) and sub-epididymal orchiectomy had the same effect in terms of disease control; but the cosmetic result and patient satisfaction were much better with sub epididymal orchiectomy [13]. Nevertheless, subcapsular orchiectomy is a good alternative to the sub epididymal orchiectomy. By avoiding an empty scrotum, subcapsular orchiectomy induces less psychological impact on patients comparatively to total orchiectomy, without lessening oncologic effectiveness [14,15]. Technically, total orchiectomy is the easiest procedure, leading to the lower rate of complications even though both generally aren't responsible of noticeable complications.

Surgical castration represents an interesting androgenic suppression method, giving largely positive outcomes. In 2012 in Senegal, it was a method of choice for patients requiring castration in the series of Fall [9]. The cumulative survival rates were above ours. They were 77.3% and 52.3% at 24 months. Also, its low morbidity and lower cost were key arguments in the therapeutic choice in patients with low economic conditions. No complication was observed in our series, while in Fall's it was limited to a parietal suppuration, that occurred in 2.4%. The immediate action of surgical castration, as evidenced by testosterone levels at very low values as in our study, is also a significant benefit in these often-impaired patients. Compared to LHRH analogues, the lack of a "flare up" effect also favors it.

More recently, the place of surgical castration in the therapeutic options in patients having castration-resistant prostate cancer has been reviewed. Studies suggest that surgical castration could significantly delay (up to 24 months) the introduction of chemotherapy [16].

The choice between medical and surgical castration is not based only on the difference in efficiency, as both methods have the same ability to achieve testosterone castration levels [17,18]. Though, the last assertion is controversial, indeed in 2012, Van der Sluis and colleagues reported that LHRH agonist injections lowered testosterone more than surgical castration did in a short series (66 men) [19]. However, their study was limited by a cross-sectional design and a heterogeneous surgical intervention group that included both men undergoing sex-change operations and men with prostate cancer. A randomized trial comparing LH-RH agonist by 24-week depot Triptorelin injections, and sub capsular orchiectomy, results in the same conclusion which is that triptorelin induces a significantly lower testosterone levels [20].

But in terms of maneuverability, medical castration has the advantage of being able to be interrupted and reintroduced as needed, allowing intermittent treatment that can be beneficial in patients with disabling side effects. Other criteria can be taken in account, according to the geographic area; In a comparative study of 10,675 patients in the US, the criteria for choosing between the two methods of castration were strongly related to racial, ethnic and socio-economic factors but also to whether or not the patient had health insurance [21].

The survival rate in our series was lower than those in the literature, a randomized controlled trial comparing androgen deprivation therapy (ADT) and combination of ADT with local radical therapy, reported 3-year overall survival rates of respectively 70% and 88% [22]. Their series included only patients having oligometastatic prostate cancer, while all types of advanced prostate cancer were involved in our study. Local treatment of primary tumor seems to be beneficial for improvement of the overall survival, especially in patients with low metastatic burden [23].

This study had some limitations linked first to the small size of the sample; a longer study period may allow enrolling more than thirty patients. The selection criteria also could be improved by making more accurate indications for androgen deprivation therapy. In our context many other considerations such as socioeconomic level of patients may represent some particularities that must be taken in account when discussing the choice of treatment modalities.

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CONCLUSION

This study showed the beneficial role of surgical castration in the management of advanced prostate cancer. Bilateral sub capsular orchiectomy as monotherapy is an effective option for the management of advanced prostate cancer, providing clinical and biological improvement. This short series is a preliminary study to a more extensive and comparative one between medical and surgical castration in our context of limited resources.

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