

Research Article

Treatment Option in Patients with nmCRPC

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Introduction

In Latin America, prostate cancer (CaP) is the third most common tumor (after lung and breast), and the most common among men, reaching the highest mortality rate among all cancers [1].

It was shown that about 10% to 20% of patients with CaP will develop castration-resistant prostate cancer (CRPC) within 5 years of follow-up. When high risk factors, such as a PSA duplication time (PSA DT) <10 months are present in patients without evidence of metastasis at the time of diagnosis of CRPC, 33% of these patients are expected to be able to develop metastatic disease in the next 2 years [2] and 60% in the next 5 years, directly impacting quality of life [3]. Today, these men are considered to have non-metastatic castration resistant CaP (nmCRPC).

In 2018, the FDA approved the use of Enzalutamide and Apalutamide for the treatment of this group of patients with nmCRPC and in 2019 Darolutamide was approved for this same group of patients.

Currently, medical practice guidelines do not include radical prostatectomy as a treatment option in this group of patients.

The aim of this study is to evaluate salvage radical prostatectomy as another treatment option in patients with nmCRPC who previously received radiation therapy.

Materials and methods

This is a retrospective, descriptive and observational study. We analyzed the results obtained from patients with diagnosis of nmCRPC who had received radiation therapy as initial local treatment, who were performed salvage radical prostatectomy + extended lymphadenectomy in the Hospital of Clinics "José de San Martín" between June 2014 and December 2020. Demographic, preoperative, intraoperative and postoperative variables were evaluated.

We defined nmCRPC as an increase in PSA greater than 25% of the confirmed PSA nadir value in a second determination made at least three weeks later and with PSA value >2 ng/mL, keeping the patient testosterone levels in castration range (<50 ng/mL) and without evidence of radiological metastases by conventional imaging methods (Computed tomography and bone scan) [4].

Inclusion criteria: All patients with non-metastatic castration-resistant prostate cancer operated in our hospital were included, defining this group as those with 2 registries of PSA greater than 2 ng/ml on the value of PSA nadir with testosterone levels in castration range (< 50 ng/mL), who had previously received radiation therapy and had no evidence of metastases.

The other criterion was to present a PSA DT <10 months.

Exclusion criteria: The presence of bone or visceral metastases targeted by bone scan and/or positron emission tomography (PET) - choline were considered exclusion criteria.

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Results

Thirteen patients who met the inclusion and exclusion criteria were part of the study.

The average age at the time of diagnosis of the disease was 56 years (r: 50-65). The median time from the start of hormonal therapy to the development of castration resistance was 76 months (r: 60-84).

We all undergo salvage radical prostatectomy with enlarged lymphadenectomy at our center once confined organ disease is confirmed.

The average age at the time of salvage surgery was 63 years (r: 55-70). The average duration of surgery was 135 minutes (r: 100-180). The estimated blood loss was 500 ml. The median internment time was 4 days (r: 3-10). As an anatomopathological result, six patients obtained one pT3a and seven patients obtained one pT3b. Five of the thirteen patients had a pN1. Postoperative complications have been classified according to the Clavien-Dindo scale, two patients (Clavien-Dindo I), by infection of the surgical site. A patient (Clavien-Dindo II), for requiring endovenous antibiotic treatment. A patient (Clavien-Dindo VIC), who evolved with a urinary fistula and was tested for radiation (Table 1).

Of the thirteen patients, eight developed urine incontinence. Erectile sexual dysfunction was observed in all patients, clarifying that it was already present in patients prior to surgery, objectified by the IIEF-5.

A PSA <0.2 ng/ml post salvage surgery was achieved in six of the thirteen patients.

At a median follow-up of 38 months (r: 20-66), four patients remained without evidence of disease, six patients developed biochemical relapse, currently on treatment with an HRML analogue without castration resistance and three patients evolved with metastatic disease.

Discussion

Asymptomatic prostate cancer throughout its natural history is symptomatic with bone spread. Survival of a patient with localized prostate cancer is greater than 15 years, when spread is reduced to less than 5 years, and when resistant to castration is only 12 months [5,6].

Castration-resistant prostate cancer (CRPC) is an advanced form of prostate cancer characterized by disease progression after surgical or pharmacological castration (androgen deprivation). The prognosis for patients with CRPC is poor and survival is reduced.

Kirby et al in their review of 12 articles, described that between 10% and 20% of prostate cancer patients develop CRPC in 5 years of follow-up and that 16% of these patients show no evidence of bone metastasis in the diagnosis of CRPC. Of these patients with nmCRPC, 33% developed bone metastases in 2 years [2].

ClearMR et al. described in a randomized study that in the natural history of nmCRPC 30% will develop bone metastases and 20% will die within 2 years of diagnosis [7].

In July 2018 the use of Enzalutamide and Apalutamide was

Figure 1: Characteristics of patients at onset (preradotherapy), at the time of castration-resistant prostate cancer (preoperative) and postoperative.

Variable	Result
Initial Gleason Score (Biopsy)	
≤ 7	5
8	6
9	2
Radiation therapy performed, 3D-RT(n); IMRT(n)	8; 5
Time up to nmCRPC, medium (range)	76 months (60-84)
Age in ransom PR, average (range)	63 years (55-70)
PSA in Rescue PR, Median (Range)	14,5 ng/ml (3-37)
PSA DT (months)	<10
Enlarged lymphadenectomy (n)	13
Number of resected nodes, median (range)	11 (10-14)
Staging pT	
pT3a	6
pT3b	7
Staging pN	
pN0	8
pN1	5
FinalGleason Score	
7	5
8	6
9	2
Clavien-Dindo (n)	
I	2
II	1
IIIa	1

approved through PROSPER and SPARTAN [8,9] studies for the treatment of patients with nmCRPC and 2019 the use of Darolutamide is approved from the study ARAMIS [10], currently included in the clinical practice guidelines [11].

Salvage radical prostatectomy as a treatment option for this group of patients is currently not included in these referral guidelines. However Gontero et al. conducted a prospective study on the role of salvage radical prostatectomy in patients with NM-CRPC after primary radiation therapy, the only work published so far. He described that after 40.5 months of follow-up, three of the twelve patients included in his series had no evidence of disease, one had a biochemical relapse, two developed metastatic disease and six died from disease progression [12].

Analyzing this work it was seen that 30% of these patients could achieve healing.

In our series four patients of the 13 included are without evidence of disease, six patients had biochemical relapse, however they reversed resistance to castration, three developed meta-

static disease with a median follow-up of 38 months.

Daher C. Chade et al. in its review described the surgical complications, mentioning that rectal lesion occurred in 0 to 28% of patients, and the narrowness of anastomosis varied from 7% to 41%. Major complications (Clavien 3-5) occurred in 0-25% of patients, and estimated blood loss varied between 119 ml and 1000 ml. Most of the reported complications were managed conservatively (Clavien 1-2), ranging from 67% to 91%. Anastomotic stenosis was treated with endoscopic procedures (Clavien 3a). Treatment of intraoperat6ria rectal lesion was varied, most of the surgical descriptions refer to primary closure [13,14].

In our series the postoperative complications recorded have been classified according to the Clavien-Dindo scale, two patients (Clavien-Dindo I), by infection of the surgical site. A patient (Clavien-Dindo II), for requiring endovenous antibiotic treatment. A patient (Clavien-Dindo VIC), who evolved with a urinary fistula and was tested for radiation.

Conclusion

While we understand that the low number of patients as the short follow-up period were the limitations of this study, we consider that salvage radical prostatectomy in post-radiotherapy nmCRPC is an acceptable treatment option to consider in young patients, noting that it positively influences the natural history of these patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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