Title: **Comparison of the Therapeutic Efficacy and Patient Satisfaction of Three Techniques of Bilateral Orchidectomy in Prostate Cancer Patients of a Nigerian Sub-population (TEPSO)**

NCT No: **Not yet assigned**

Date: **30th of July, 2018**

Study location and population

The study was conducted among patients of the Urology Division of the University College Hospital, Ibadan with locally advanced and metastatic PCa.

Study design

It was a randomized experimental study. Ethical approval for the study was obtained from the UI/UCH Ethical Committee.

Sample size calculation

The **minimum** sample size in each group was calculated using the formula shown below [116, 117]:

$$n = 2\,\frac{[(a + b)^2 s^2]}{(\mu_1 - \mu_2)}$$

where,

n = the sample size in each group

μ_1 = population mean in treatment Group 1

μ_2 = population mean in treatment Group 2

$\mu_1 - \mu_2$ = the difference the investigator wishes to detect = 10%

s = standard deviation (SD) = 9.7[11]

a = conventional multiplier for alpha = 0.05

= 1.96

b = conventional multiplier for power = 0.80

= 0.842

$$n = \frac{2[(1.96 + 0.842)^2\, 9.7^2]}{10^2}$$

n = 14.7

n is approximately 15 per group

To account for 10% attrition,

n = 15/ 0.9

= **17 per group**

Thus, the total minimum sample size for entire sampled population was **51**.

Subject recruitment and sampling

Proficiency in the prosthetic techniques was gained from March 2015. Recruitment was between March 2016 and November 2017. The three-month post-operative assessment ended in March, 2018. The study spanned 23 months. Informed consent was obtained from the patients by the researcher or another medical doctor.

Inclusion criteria

- Consecutive consenting patients with histologically confirmed locally advanced or metastatic PCa who have accepted to have an orchidectomy

Exclusion criteria were:

- Patients who have had bilateral orchidectomy
- Those who opted for medical castration
- Non-consent

The patients were randomized into three groups by ballotting: Bilateral simple orchidectomy, B**SO**; Bilateral subcapsular orchidectomy, **BSCO;** and Bilateral epididymal – sparing orchidectomy, **BESO**. The ballot was done by an observer in the theatre suite. The patient was blinded to the surgical procedure undertaken. A research bag with a total of fifty one labelled choices, comprising 17 labels each for BSO, BSCO and BESO was prepared. These ballots were exhausted and refilled for extension of the sample size.

Study protocol

Preoperative component

- Informed consent was obtained
- Socio-demographic data and information on the patient's symptoms, performance score and co-morbidities was obtained using a proforma, Fugl Meyer Questionnaire (FMQ) and the Expanded Prostate Cancer Index Composite (EPIC) 2.2002 demographic questionnaire
- The preoperative testicular volume was estimated with a Prader orchidometer
- Pre- operative blood samples were taken for PSA and testosterone
- The FMQ and the EPIC-26 were administered

Perioperative component

- A preoperative antibiotic was administered [112]
- The scrotal skin was prepared and isolated with sterile drapes.
- 0.5% lignocaine with adrenaline was used to infiltrate the median raphe, the proposed incision site, and block the spermatic cord. Some patients required sedation with a combination of Pentazocine, an opioid, and Diazepam, a barbiturate.
- Samples for serum testosterone and PSA were taken at 0 hour (immediately after removing both testes or testicular parenchyma), 1, 2 and 3 hours post-operatively.

The surgical technique

A median raphe scrotal incision was made and deepened to expose the TV on one side. The testis, with the TV covering it, was delivered into the wound. The TV was incised and retracted proximally over the testis, epididymis and cord structures via pledget dissection.[112,122] Subsequent steps depended on the castration technique employed.

Simple orchidectomy

The spermatic vessels were isolated from the vas deferens, double clamped proximally, singularly clamped distally, and divided. A free tie was applied proximal to the proximal clamp and suture ligation done distal to that, using 1 vicryl. The vas deferens was clamped and ligated separately with 2/0 vicryl. [112,122] Haemostasis was ensured.

Subcapsular orchidectomy

The TA was incised longitudinally and its edges held with haemostats. Haemostasis was secured. The testicular parenchyma was scraped off the TA by pledget dissection moving towards the hilus, was secured with 3/0 vicryl. Water-tight closure of the TA ensued with continuous sutures using 2/0 vicryl.[11,112,122]

Epididymal – sparing orchidectomy

A vasectomy was done and the vas ligated with 2/0 vicryl. The plane between the epididymis and the testis was developed [122] The caudal, middle and superior epididymal vessels as well as the spermatic artery to the testis were clamped and ligated with 3/0 vicryl.[112] The testis was then excised. The epididymis was folded on itself to create a pseudotesticle and a continuous suture with 3/0 vicryl used to complete the epididymoplasty.[34]

The dartos muscle layer was closed with a continuous suture using 3/0 vicryl. The procedure was repeated on the contralateral side. Subcuticular skin closure was done with 3/0 vicryl. Firm scrotal dressing with scrotal support was applied.[112,122]

Postoperative component

- Day 3
    - Wound review
    - Further reviews were dictated by the state of the wound at initial review
- Day 7
    - Samples for serum testosterone and PSA would be taken
- Three months post-operatively
    - The QoL would be assessed with the FMQ and EPIC-26
    - Each patient would assess their scrotal appearance with a graduated VAS, on a scale from 0 – 100 % satisfaction [118]
    - Prader orchidometric pseudotesticular volume estimation was done for all patients in the BSCO and BESO groups

Technique of serum assay

Enzyme-linked Immunosorbent Assay (ELISA) was used for the quantitative determination of serum testosterone levels. Two millilitres of blood was collected, centrifuged and the serum (supernatant) decanted off. This was the test sample. It was stored at -80^{o}C. This process was carried out by a laboratory scientist and myself. Further processing would be done by another more specialized medical laboratory scientist and myself.

3.5.5.1 Serum testosterone assay

Enzyme immunoassay Bio-Inteco test kit (Inteco, Beechwood, Egland, QC16-885) was used. Ten microliter of controls, standards and samples were places on the wells. 50µl of anti-

testosterone antibodies and 100µl of conjugate reagent were added. This was incubated at 37^0C for 90 minutes. A wash buffer was diluted at a ratio of 50 to 1, and used to rinse the wells to remove any unbound material. A resultant blue colour change was observed, the intensity of which was inversely proportional to the testosterone concentration in the antibody-testosterone-conjugate complex. 100µl of substrate was then added. It was incubated for another twenty minutes. A stop solution (Hydrochloric acid) was added to terminate the reaction. The colour change was measured in terms of absorbance using a microtitre plate reader. Reliability of test results was increased by running controls with each batch of samples, use of distilled water to rinse the unbound materials off, avoiding bubbles in the microwells and using reagents at room temperature.[123]

The optical density of the absorbance was converted to serum testosterone in mg/dl by using the using calibration curves. The values obtained were multiplied by 28.85 to convert to nmol/l.

3.5.5.2 Serum PSA assay

An Enzyme Immunoassay test kit for total PSA (Rapid Labs, Essex, United Kingdom, LOT: 1701020, B031568-01) was used. Twenty microliters of controls and samples, and 100µl of anti-PSA peroxidase conjugate were inserted in the microwells. This was agitated gently. The microwell was covered by a plate sealer and incubated for 30 minutes at 30^0C. A buffer was h solution was diluted 1:25, and used to rinse the microwells, which were dried. To each microwell was added 50µl of two substrates, with a colour change. It was agitated gently, covered, and incubated for 15 minutes longer. Sulphuric acid (50 µl) was added as a stop solution. The optical density of the microwells was obtained using a plate reader at 450nm. Calibration curves were used to calculate the PSA concentration in ng/ml.

Data analysis

Data analysis was with the Statistical Package for Social Sciences Version 20 (SPSS 20) and STATA version 12. Measures of central tendency and dispersion were used to analyse the quantitative parameters. The qualitative parameters were ranked. Variation in serum testosterone and PSA, sociodemographic and technical parameters, pre- and post-operative testicular volumes, cosmetic appeal and HRQoL parameters were compared between the three groups and analysed using univariate (ANOVA) and multivariate analyses, student t-test for the continuous and Wilcoxon rank-sum test for the non-parametric measures. A repeated measures ANOVA with Greenhouse-Geisser correction was modeled for the average log testosterone and PSA concentration declines. A Post-hoc test, the least significant difference (LSD) was applied to the curves. Kaplan-Meier analyses of the PSA and testosterone kinetics and patient survival were plotted. The level of statistical significance, p, used was ≤ 0.05. The groups were dichotomised into those with and without prostheses, and the associations re-evaluated.

3.7 Ethical Considerations

This study was conducted in compliance with the guidelines of the Nigerian Code of Health Research Ethics.

Costs to participants: Participation in the study did not increase the financial cost of care for the participants. The serum testosterone and PSA estimations were funded by the lead researcher. The patients funded the surgery. There was no increase in the frequency of hospital visits because of the study as the routine scheduled visits for all patients who have had orchidectomies as per our unit protocol was adhered to.

Benefits: The participants did not have to pay for the routine pre- and post-operative serum testosterone or PSA assessments. Participants may benefit from the aesthetic outcome of the technique used, however, this would be determined by the results of the study. Information

obtained from the study would be beneficial to future patients with prostate cancer. Medical personnel would be able to objectively state which type of orchidectomy gives the most patient satisfaction and what the levels of efficacy are.

Confidentiality: All information collected was de-identified with code numbers which cannot be linked to the participants in anyway.

Voluntariness: The patients' participation in this research was entirely voluntary. The participants were informed that they could withdraw from the research at any time. No undue coercion or incentives were used. Non-consent did not jeopardise patient care.

Non-maleficence to participants: There was minimal undue harm to be borne by the patient for participating in this study. It was explained that orchidectomy, irrespective of the technique, may be complicated by wound infection, haematoma, seroma, wound dehiscence, operative site pain, breast pain, breast swelling, hot flashes and loss of sexual drive. The entire blood sample required for the study amounted to a volume of 32 ml over a three month period. This did not cause undue harm. The participants were informed that some of the questions asked required introspection and may broach sensitive topics.

Compensation: There was no monetary compensation for participating in this research. However, the burden of your perioperative serum testosterone investigations which are routinely done would be borne by the primary investigator.

Translation of protocol to the local language: The informed consent and questionnaires were translated to Yoruba, the indigenous language of Ibadan.

CONSENT FORM

IRB Research approval number: UI/EC/15/01/2008a

Title of research: Comparison of the therapeutic efficacy and patient satisfaction of three techniques of bilateral orchidectomy in prostate cancer patients of a Nigerian sub - population

Name and affiliation of researcher: Dr I. N. Chibuzo of the University College Hospital, Ibadan is the primary investigator, supervised by Professor Linus I. Okeke and Dr Augustine O. Takure. This project would be done in part fulfilment of Part II dissertation for the National Postgraduate Medical Council of Nigeria.

Sponsor of research: The study is self-sponsored.

Purpose of research: The purpose of this research is to compare the therapeutic efficacy of bilateral total orchidectomy with endogenous testicular prosthetic techniques of subcapsular and epididymal – sparing orchidectomy and to determine which technique is associated with a higher level of patient desirability.

Procedure of the research: You are being asked to participate in this study because you have locally advanced or metastatic prostate cancer and have consented to an orchidectomy under local anaesthesia. If you agree to participate in the study, the following will be required of you:

1. One of our members of staff will ask you about yourself, your work, your lifestyle, your health condition, your symptoms, especially those related to urinary, bowel and sexual function. We will obtain information of the treatments that you are receiving or have received and how these treatments have affected your bodily function and/ or lifestyle. The information would be recorded in a form called a questionnaire.

2. 2 ml blood samples would be taken each for serum testosterone and Prostate specific antigen (PSA) before the surgery. You would be selected to have one of three types of orchidectomy: either a **bilateral total orchidectomy**, in which both testes are removed or a **subcapsular orchidectomy** that removes the tissue within the testes and leaves the covering or an

epididymal – sparing orchidectomy that removes the testis but leaves the epididymis behind. The volume of your testis would be measured before surgery using a meter designed for this purpose. At surgery, four 2 – ml samples would be required: at orchidectomy (0 hour), then at 1, 2 and 3 hours after the surgery for serum testosterone estimation. Another would be required seven days after the surgery for serum testosterone estimation. Three months following the surgery, serum PSA would be assessed again via a 2 – ml sample of blood.

3. At this visit, you will be asked to tell us how satisfied you are with the surgery and the appearance of your scrotum. Measurements of the post – operative prosthetic volume for those concerned would be taken. Another doctor would also assess the appearance of the scrotum at this visit.

4. A questionnaire on your symptoms as well as urinary, bowel and sexual function would be administered at this visit.

This marks the end of your participation in the study.

Expected duration of study and participants' involvement in the research: The duration of this study will be 12 months during which we expect to enroll at least 24 patients. However, your active participation in this study will be over a three month period. We may call to remind you of your appointments.

Risks: There is minimal undue harm to be borne by you for participating in this study. Orchidectomy, irrespective of the technique, may be complicated by wound infection, haematoma, seroma, wound dehiscence, operative site pain, breast pain, breast swelling, hot flashes and loss of sexual drive. The entire blood sample required for the study amounts to a volume of 16 ml over a three month period. This would not cause undue harm.

Costs to participants: Your participation in this research will not cost you anything other than your time as mentioned above. There would be no increase in the frequency of hospital visits

because of the study. We shall adhere to the routine scheduled visits for all patients who have had orchidectomies as per our unit protocol.

Benefits: Your participation in this study may not be of direct benefit to you, however, information obtained would be beneficial to other patients with prostate cancer in future. Medical personnel would be able to objectively state which type of orchidectomy had the most patient satisfaction and what the levels of efficacy are.

Confidentiality: The data collected in this study will be used for the purpose stated above. All information collected will be de - identified with code numbers which cannot be linked to you in anyway. Reports or publications from this study would not bear your name or any form of identification traceable to you. Information may be obtained from your medical records only for the purpose of the study. To ensure this study is conducted properly, representatives of the UI/UCH HREC and National Postgraduate Medical Council of Nigeria may have access to these records.

Voluntariness: Your participation in this research is entirely voluntary. If you choose not to participate, this will not affect your treatment in this hospital in any way. You can also choose to withdraw from the research at any time.

Compensation: You will not be paid any fees for participating in this research. However, the burden of your peri – operative serum PSA and testosterone investigations which are routinely done would be borne by the primary investigator.

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information, including about risks and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____ SIGNATURE: _____

NAME: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

Detailed contact information including contact address, telephone, e-mail and any other contact information of researcher(s) and the institutional HREC:

This research has been approved by the Health Research Ethics Committee of the University of Ibadan and the Chairman of this Committee can be contacted at Biode Building, Room T10, 2nd Floor, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Telephone: **08032397993**, E-mail: uiuchirc@yahoo.com. In addition, if you have any question about your participation in this research, you can contact the principal investigator, Dr Chibuzo at the Department of Surgery, University College Hospital, Ibadan. The contact phone number is **08065819167**.

PLEASE KEEP A COPY OF THE SIGNED INFORMED CONSENT