PREVALENCE AND DETERMINANTS OF ACUTE ADVERSE EFFECTS OF EXTERNAL BEAM RADIATION THERAPY AMONG PATIENTS ON TREATMENT FOR HIGH RISK PROSTATE CANCER

THIS DISSERTATION IS SUBMITTED AS PART FULFILMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE (UROLOGY), UNIVERSITY OF NAIROBI

BY;

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DECLARATION

This project is my original work and has not been submitted anywhere else for consideration for publication or for the award of another degree.

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DEPARTMENTAL APPROVAL

This Dissertation has been presented at the Department of Surgery meeting and is hereby approved for presentation to the Kenyatta National Hospital Ethics and Research Committee.

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Finally, I thank the Almighty God for the strength that He has given me to complete this study.

DEDICATION

This dissertation is dedicated to my wife Elizabeth and my son Nathan who have provided the support, love and encouragement to complete this journey.

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To my father Joseph and my late mother Joyce who have consistently believed in me and have always provided a firm pillar that has motivated me to get fulfillment out of this God given life.

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LIST OF ABBEVIATIONS

ADT-	Androgen Deprivation Therapy
CAp-	Cancer of the prostate
EBRT-	External Beam Radiation Therapy
ERC-	Ethics Review Committee
KNH-	Kenyatta National Hospital
KRCHN-	Kenya Registered Community Health Nurse
MRI-	Magnetic Resonance Imaging
NCCN-	National Comprehensive Cancer Network
PSA-	Prostate Specific Antigen
RTOG-	Radiation Therapy Oncology Group
SPSS-	Statistical Package for Social Sciences
UON-	University Of Nairobi
ECOG-	Eastern Cooperative Oncology Group
GLOBOCAN-	Global Burden of Cancer study
HFRT-	Hypo Fractionated Radiotherapy
SADT-	Short acting Radiotherapy
CAPRA-	Cancer of the Prostate Risk Assessment score
LDRT-	Low Dose Radio Therapy
IGRT-	Image Guided Radio Therapy
3D-CRT-	3 Dimensional Conformal Radio Therapy

ABSTRACT

BACKGROUND

Prostate cancer is a malignancy of marked importance and causes significant mortality and morbidity in the male population. It is commonly diagnosed in the 7th decade after 65yrs. It is rarely diagnosed in men younger than 50 years old, accounting for only 2% of all cases(1). Global incidence rates have shown that it is the 5th common malignancy worldwide in men, though the incidence and mortality rates vary significantly between countries regions and races, 19% in developed countries, and 5.3% in developing countries. Studies have also shown that 60-70% of CAp originates in the gland's peripheral zone, 10–20% in the transition zone, and 5–10% in the central zone. CAp contributes 11.7% of new cancer cases overall (2).

The important variables considered for risk stratification before determining treatment are; age, PSA, Gleason score and measure of tumor volume by clinical tumor (T) stage and/or extent of biopsy core involvement. This risk stratification avoids under-treatment of high risk disease and over-treatment of low risk disease(2).

Among the available treatment modalities, radiotherapy contributes an important alternative to radical surgery alone to achieve cure in high risk prostate cancer management and it has been shown that external beam radiotherapy treatment offers similar survival benefits as surgery(3). In this respect, Intensity-modulated radiotherapy (IMRT) with/without IGRT, is currently the gold standard for external beam radiotherapy(4), though currently not available within the local set-up. Of note is that other modalities e.g. 2 dimensional and 3 dimensional conformal radiotherapy currently applied in limited resource setting. In as much as the treatment is geared towards beneficial outcomes, this modality is not without significant morbidity to the patient. This includes both short and long term adverse effects on skin and subcutaneous tissues, urinary system, gastro-intestinal system and musculo-skeletal system, which may in severe cases necessitate cessation of treatment(5). Most cases of prostate cancer present late in our set-up thus making radiotherapy a very important modality to be utilized in management of these cases which may not be amenable to surgery. The study seeks to determine prevalence and determinants of acute adverse effects of ERBT for the high risk CAp.

STUDY PURPOSE

CAp is one of the highly prevalent cancers in elderly males both locally and globally, and imparts significant morbidity and mortality. It is also the prominently seen cancer in elderly men in Kenya. The advent of radiotherapy i.e. both internal and external radiation (EBRT), as part of a combined treatment modality of prostate cancer has been associated with better clinical responses, albeit this is not without adverse clinical events. Though there is a demonstrated high potential for clinical benefit in the administration of EBRT, both acute and late adverse events related to the therapy cause an increased morbidity during management and thus a disrupted quality of life and treatment process. There is therefore a need to assess the prevalence and determinants of acute adverse clinical effects of EBRT among patients with high risk CAp in order to thoroughly make sure that treatment complications will not decrease the quality of life more than the disease would have done. This will also help facilitate the development of local management protocols that would better pre-empt these adverse events and optimize clinical outcomes and patient QOL.

OBJECTIVE

To determine the prevalence and determinant of acute adverse effects of EBRT among patients on treatment for high risk prostate cancer.

STUDY DESIGN

A descriptive cross-sectional study.

SETTING

Kenyatta National Hospital, Texas Cancer Center.

PATIENTS AND METHODS

The study was conducted between December 2016 and July 2017, it involved 48 patients with high risk CAp undergoing EBRT at Kenyatta National Hospital and Texas Cancer Center who fulfilled the inclusion criteria thereafter gave informed consent. Convenient sampling method was used to recruit patients into the study.

Patients had an initial pre-radiotherapy assessment, mid-radiotherapy and end of radiotherapy assessment. This duration was approximately 6 week per recruited patient from start to end. The presence of the adverse effects of radiotherapy involving the skin, genitourinary and Lower

gastro-intestinal systems were assessed, graded and recorded before beginning the EBRT, at the end of the third week of EBRT i.e. corresponded to mid-radiotherapy and at the end of the sixth week of administering EBRT i.e. end-radiotherapy.

RESULTS AND ANALYSIS

In this study, 48 patients were recruited. The cases comprised of male patients who were on treatment for high risk cancer of the prostate undergoing EBRT. The patients' ages ranged from 43 to 78 years. The mean age of males undergoing EBRT was 65.9 years (SD ± 6.5). The median age being 66.5 years. Majority of the patients (43) (87.5%) had a form of formal education (87.5%) i.e. primary, secondary or tertiary. Only 6 patients (12.5%) had no form of formal education. 28 (65.8%) patients had an ECOG classification of 1 and below. 29 patients (60.4%) had co-morbidities i.e. diabetes (27.6%), hypertension (75.9%), HIV (3.5%) and respiratory disease (3.5%). 40 patients (83.3%) were undergoing androgen deprivation therapy while 8 patients (16.7%) were not. Overall rate of EBRT adverse events was 100% with all 48 patients reporting or having at least one of the adverse events i.e. skin changes, lower genito-urinary symptoms and lower GIT symptoms associated with the treatment during the study period. None of these events resulted in hospitalization and all patients were supportively treated and recovered.

Data collected was entered and analyzed using Statistical Package for Social Sciences (SPSS) for Windows Version 21. P values were generated and results were presented in tables, figures and graph.

CONCLUSION

The results of our study indicated that external beam radiotherapy is commonly associated with low grade acute adverse effects which included skin effects, genito-urinary and gastro-intestinal effects. Despite these events, EBRT shows effective management choice in male men having high risk CAp though it is important to recognize the presence of these adverse effects in order to effectively counsel these patients prior to therapy. The majority of these complications were grade 1 and below at a radiation dose of 60Gy.

INTRODUTION

Prostate cancer is a malignancy of marked importance and causes significant mortality and morbidity in the male population. The median age of CAp diagnosis is 68 years, and 63% are diagnosed after 65yrs. It is rarely diagnosed in those men who are below the age of 50yrs, accounting for only 2% of all cases(1). Global incidence rates have shown that CAp is the 5th commonest malignancy among all cancers and the 2nd most common cancer in men globally, though the mortality and incidence rates can vary significantly between geographical regions. It has been found to contribute up to 11.7% of new cancer cases, 5.3% in developing countries and 19% is seen in developed countries. Studies have also shown that 60% to 70% of CAp originates in the peripheral prostate gland zone, 10% to 20% is seen in the transition zone and a further 5% to 10% in the central zone(2).

The important variables considered for risk stratification before determining treatment are; PSA level, Gleason score and measure of tumor volume by clinical tumor (T) stage and/or extent of biopsy core involvement. This risk stratification avoids under-treatment of high risk disease and over-treatment of low risk disease(2).

Among the available treatment modalities, radiotherapy contributes an important alternative to radical surgery alone to achieve cure in high risk prostate cancer management and it has been shown that external beam radiotherapy treatment offers similar survival benefits as surgery(3). In this respect, IMRT (+/-IGRT), is currently the standard of care for external beam radiotherapy(4), though currently not available within the local set-up. Of note is that other modalities e.g. 2 dimensional and 3 dimensional conformal radiotherapy currently applied in limited resource setting. In as much as the treatment is geared towards beneficial outcomes, this modality is not without significant morbidity to the patient. This includes both short and long term adverse effects on skin and subcutaneous tissues, urinary system, gastro-intestinal system and musculo-skeletal system, which may in severe cases necessitate cessation of treatment(5). Most cases of prostate cancer present late in our set-up thus making radiotherapy a very important modality to be utilized in management of these cases which may not be amenable to surgery. We seek to determine prevalence and determinants of acute adverse effects of ERBT during management of high risk carcinoma of the prostate.

LITERATURE REVIEW

Prostate Cancer

Cancer is a great burden worldwide and over the recent past a global focus on it has led to a shift in thinking away from communicable to non-communicable diseases in order to control this looming crisis. An estimated new cancer diagnosis of 14.1 million cancer cases, cancer death totaling 8.2 million and 32.6 million people being cancer afflicted was noted worldwide in 2012 (6)(7). CAp incidence and mortality rates in 2008 were 2nd and 6th among cancers affecting males globally(8). CAp is also rated the 5th leading cause of cancer death among men accounting 6.6% of the total men's death, with over 1.1 million cases and 300,000 deaths estimated globally in 2012. These cases were approximately 15% of all cancers diagnosed in men. Majority of these cases were seen to occur in more developed regions though more deaths as a result of CAp were seen in less developed. There have been estimated to be 27,540 deaths as a result of this disease in the USA within the year 2015(9). CAp is shown to be common of the newly diagnosed cancer cases and deaths in blacks within the USA according 2016 estimates(10).

In Africa, CAp contributes significantly to the public health burden, but unfortunately this burden is not yet well quantified due to the absence of good data. Davis Adeyole et al made a significant attempt to define the estimate of the incidence of CAp in Africa by analyzing available records from January 1980 to June 2015. They estimated a CAp incidence in Africa of 22/100,000 population and there was a trend of increasing incidence with advancing age. Highest CAp incidence was 39.0/100,000 population that was estimated in men of 70yrs and above. Even with these figures, they demonstrated a low research level of CAp incidence in the African continent as a whole thus providing a vast opportunity in research to mitigate this finding(11). The 2012 GLOBOCAN reported that the CAp incidence and mortality rates in Africa were 23.2 and 17.0/100,000, respectively(6).

The disease burden locally is significant according to the National Cancer Report in Kenya 2004-2008, with incidence rates of CAp being remarkably high in men over 65 years. CAp was shown to have a steadily increasing incidence with advancing age. In Nairobi over the period of 2004-2008, a total of 3889 cancer cases had been reported. CAp cumulative incidence was at 5.2% making a total number of 606 CAp cases reported within the said period. Cancer of the esophagus came in second with 333 cases reported with a cumulative incidence of 1.8%(12).

CAp has been seen to be the leading cancer affecting men within the country followed by cancer of the esophagus(12).

The trend of these cancers have been similar in earlier registries within the country though some cancers affecting males have shown an increase in incidence which may be due to better registries as opposed to an increase cancer occurrence e.g. CAp in the 2000-2003 registry had a frequency of 11% as opposed to 15.9% in the 2004-2008 registry. Population coverage of the cancer registries within the country is still low and according to some studies was at 2.3% of the population in Kenya with most of these records being from urban areas(13)(12). Low incidence rates that are reported in the African continent may be due to inadequate diagnosing and poor reporting, as a result of poorer access to screening and diagnostic facilities, and/or lack of national cancer registries. According to a study done by Wasike et al at Kenyatta National Hospital (KNH) in Kenya on CAp, a hospital incidence of 76.5 patients/ 100,000 patients was described. Most of these cases were elderly i.e. peak incidence at 66-70yrs and presented late with clinically advanced disease (87.5% of the patients)(14). This may be attributed to the health seeking behavior (especially in the rural areas), concentration of screening services in urban areas, absent diagnostic protocols in the primary centers (rural) as the primary doctors are not urologists and low numbers of qualified specialists I.e. urologists.
Like most tissue malignancies, cancer of the prostate is staged in order to assess how far the tumour has spread so as to institute appropriate management for the appropriate stage of the disease thus relating to a potential for cure or palliation. A commonly utilized staging system is the TNM system. This is based on primary Tumour (T) clinical stage, regional lymph nodes (N) which are divided into both clinical and pathological (pN) stage and distant metastasis (M) stage.(2). T-staging assessment is done based on various modalities which include;

1. Digital Rectal Exam (DRE)
2. PSA which has been seen to increase with advancing stage of tumour (though is not accurate in depicting the clinical and pathological tumour stage)
3. Prostate biopsy findings i.e. percentage of tissue found to have cancer is the main predictor for having post-surgery positive margins and
4. Imaging modalities as Multi-parametric MRI of the prostate(4)

Beyond the staging of CAp, patients are further classified based on their risk groups which include; very low risk CAp, low risk CAp, intermediate risk CA , high risk and very high risk CAp group. Several risk group classifications exist e.g. D'Amico, National Comprehensive Cancer Network (NCCN), CAp Risk Assessment Score (CAPRA score), American Urological

association classification (AUA), RTOG and EUA classification(4)(15)(16). For purposes of this study, the D'Amico classification will be utilized.

High Risk CAp

The exact definition of high risk cancer of the prostate is debated widely though it entails a heterogeneous group of patients with varying prognoses(17). Currently, high risk CAp diagnosis accounts for 15% of all CAp diagnosis(18). Literature published on high-risk CAp is extensive and increasing every year. D'Amico classification, various parameters are utilized to define high risk cancer of the prostate. These include a PSA level of > 20 ng/mL, Gleason score (GS) > 7, or clinical T stage of T2c-3a(4). Current treatment modalities available include; surgery, RT, primary ADT, chemotherapy and immunotherapy (still under research). Either of these treatment will result in good outcomes but can also fail with subsequent disease progression(18)(19). Various factors that include medical factors, some patient preferences, and the resource availability may alter the decision on which choice of treatment to utilize(18).Regardless of the cost incurred with these modalities outcomes do tend to be similar and this may be necessary information to inform policy when choosing treatment options(20). Though from research, a combination of both hormonal therapy and radiotherapy in localized CAp has been shown significantly reduce the mortality of patients(21).

As regards radiotherapy, modalities utilized in treatment of high risk CAp include EBRT, internal radiation therapy i.e. Brachytherapy or a combination of both(22). When considering which modality of treatment to use, one should put into consideration the patient's life expectancy and the significant morbidity that the treatment will bring along with it(23).

Radiotherapy

Radiation therapy or radiotherapy (RT) is utilization of ionizing radiation in therapy to treat cancer cells with the aim of controlling their spread or killing them. This use of energy that causes changes in abnormal body tissues is what results in therapeutic irradiation. Various cancers respond to this therapy in varying ways(24). Radiotherapy is a commonly used modality of treatment in patients with CAp and its benefits on cancer survival have been demonstrated(4). This demonstrated radio-sensitivity is the response of tumour cells to the irradiation and is measured by the extent of regression, rapidity of response, and response durability(25). Two main modalities of radiotherapy that are described in literature include: EBRT and Brachytherapy also termed as internal radiation therapy(26). EBRT was introduced by Bagshaw in the 1950s, has been among the main modalities of radiotherapy utilized in the treatment of patients with CAp. He also showed that disease free survival is achievable by prostate irradiation(3). Radiotherapy remains an important option for curative therapy in localized CAp(4). Various radiation regimens for CAp have been in use though the optimal regimen for localized CAp lacks consensus(27).

External beam radiation treatment

This method of radiation delivery is applied to the human body from external sources. This modality is available to patients with localized CAp, and is appropriate especially in those whom incomplete resection with radical prostatectomy is a possible risk of management(28). Good long term rates of survival among the patients with localized CAp have been described with this mode of therapy(29)(30)(31). The dose of radiation has consistently been seen to determine the freedom from biochemical failure in retrospective, randomized and sequential prospective studies.

Various EBRT technique are described. These include; Conventional box-technique, 3D-CRT, IMRT, IGRT and Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy(28)(32)(33). Over the years, a great need arose for techniques that would safely deliver the radiation dose and increase the local control of Cap (34)(35). 3D-CRT utilized computerized Tomography (CT) scanning to better localize the beam to the prostate(34). This is currently available within the country. In other studies, rectal and bladder symptoms were reduced as a result of utilizing these conformal techniques but increase in the dose of radiation delivered increased these events(36)(31). IMRT is a further developed improvement on the 3D-CRT and has shown potential to give increased irradiation to the prostate gland with less

irradiation acute and late effects(37)(35). This however is currently not available within the country. Various radiation regimens have been documented and these include; high and low dose RT, LDRT+ short- or long-term ADT, hypo fractionated radiotherapy, and HFRT+SADT(27). In these regimens various RT techniques were utilised. These included; IMRT, 3D-CRT, with a dose range of 55Gy to 80 Gy. Some studies utilized conventional dose fractions of 1.8-2Gr while others utilized hypo fractions of 2.7-4.5Gr fractions. Both of these regimens showed no superiority between each other(38). Among all regimens HFRT + ADT was shown to have been the most efficacious for localized Cap though it also has the worst toxicity(27).

As described earlier, this modality of treatment is not without both acute and late adverse effects, thus patient counseling regarding the potential toxicity and QOL post radiotherapy is crucial. This is to ensure that the patient makes informed decision concerning their management and the possible morbidity outcomes related to the therapy(39)(40).

Acute side effects of radiotherapy (RT) do pose an additional morbidity to the patient receiving the therapy. These effects can be mild or severe and occur during RT and in the immediate post radiotherapy period which is within two to six weeks with some persisting to chronicity(41)(39)(42). Normal or cancerous tissue will tolerate the radiation delivered differently thus determining the adverse effects. This mainly depends on the characteristics of the radiation being delivered. (41)(25)(29)(35)(5)(31)(43)(27). Studies have also shown that combination of ADT with RT during management may be associated with a reduction of risk in acute toxicity as compared with giving RT alone. Giving the high dose radiation showed to have more efficacy though this was at the expense of more side effects (27). Among the described effects or radiotherapy are both local and systemic. These acute adverse effects can be graded based on Toxicity criteria of the RTOG and the EORTC. This enables one to well grade the effect and its severity(44)(41)..

Acute adverse effects of radiotherapy among prostate cancer patients

Acute adverse effects following EBRT have been described to occur during the treatment, and are low grade to intermediate grade in severity. They usually resolve within 4 to 6 weeks following completion of the treatment. They result from the effects of radiation exposure on rapidly dividing cells, which in CAp patients will include; the mucosal epithelium of the rectum, bladder, and prostatic urethra. Among the acute side effects of EBRT described from

literature include local skin effects, genitourinary system and lower gastro intestinal system, and these can be graded based on their severity(5)(44)(41). These are described to occur from the period of radiotherapy delivery to four months post treatment. Many factors can predict the adverse effects of radiotherapy and these include; prior surgery and presence of pre-treatment symptoms(5).

Genitourinary side effects of radiotherapy described include; hematuria i.e. both macroscopic and microscopic, urgency, nocturia, dysuria, bladder spasm and acute urine retention(44). These can occur in varying grade of severity. The lower gastrointestinal acute effects described include; change in quality and increased frequency of bowel, diarrhea, mucous discharge, rectal and abdominal pain, hematochezia, acute obstruction and tenesmus (44). Skin complications described include; erythema, epilation, dry desquamation, edema, tenderness, ulceration, hemorrhage and necrosis(44). The acute effects occur in varying grades of severity which can be assessed utilizing the RTOG criteria of describing these effects(5). All the above occurrences are described among the acute adverse effects of EBRT. This study aimed to describe these acute side effects as they occur in patients receiving EBRT during management.

PROBLEM STATEMENT AND JUSTIFICATION OF THE STUDY

CAp is one of the highly prevalent cancers in elderly males both locally and globally, and greatly affects men's health. It is the 5th commonest cancer in male and female cancers combined worldwide and the 2nd commonest malignancy in men. Its incidence rises as age advances among men. It is also the leading cancer in elderly men in Kenya. Given the increased life expectancy, increased diagnostic acumen and better documentation in cancer registries, the incidence and prevalence of cancer of the prostate have been found to increase over the years. The mainstay of treatment of CAp in Kenya has been the use of various treatment modalities including androgen deprivation therapy (ADT), surgery and radiotherapy (RT). All these methods utilized to treat cancer of the prostate (CAp) with an intent to cure have different adverse effects. The advent of radiotherapy i.e. both internal and external radiation, as part of a combined treatment modality has been associated with better clinical responses, albeit this is not without adverse clinical events.

Though there is a demonstrated high potential for clinical benefit in the administration of EBRT, both acute and late adverse events related to the therapy cause an increased morbidity during management and thus a disrupted quality of life and treatment process. There is therefore a need to assess the prevalence and determinants of acute adverse clinical effects of EBRT among patients with high risk CAp in order to thoroughly make sure that treatment complications will not decrease the quality of life more than the disease process would have done. This will also help facilitate the development of local management protocols that would better preempt these adverse events and optimize the clinical outcomes of patients and adherence to the management plans during follow up their patient quality of life.

RESEARCH QUESTION

1. What is the prevalence and determinant of acute clinical adverse effects of EBRT among patients on treatment for high risk CAp?

OBJECTIVES

General Objective

To determine the prevalence and determinant of acute adverse effects of EBRT among patients on treatment for high risk CAp.

Specific Objectives

1. To determine the prevalence of acute adverse effects of EBRT among patients on treatment for high risk CAp.
2. To determine the total dose of radiation given to each patient during treatment.
3. To determine the modality of EBRT utilized in treatment.
4. To determine the association between total dose of radiation, the modality of EBRT utilized and the acute adverse effects.

MATERIALS AND METHODS

STUDY AREA

The study was performed at two centers: The Kenyatta National Hospital (KNH) radio-oncology clinic and the Texas Cancer Center. KNH, a tertiary referral hospital in Kenya remains one of the largest hospitals in East and Central Africa. It forms one of the convergence points of patients in the public health care system in Kenya and offers specialized cancer care services. KNH is at the apex of the public health system, thus the results of this study brought external validity to the majority of the male population of Kenya affected by high risk cancer of the prostate, who receive EBRT in the public health system.

Texas Cancer Center is a private healthcare institution within the country offering cancer care services. It has become a separate nidus of confluence for patients with various cancers seeking specialized care. Given the increased access to this facility by patients who seek health care services in the private sector, having these patients participate in the study obtained results that provided insight into the situation among patients undergoing management for high risk prostate cancer in the private health care system in Kenya.

By having participants from both the public and private health care systems in Kenya, this study provided crucial information that will enable development protocols that take both these populations into account, thereby enhancing the potential for optimization the management of high-risk CAp in Kenya. Basing this study within the facilities also contributed crucial information concerning radiation treatment adverse effects among patients undergoing management for high risk prostate cancer.

STUDY DESIGN

A descriptive cross-sectional study designed to facilitate the description of the acute adverse effects of EBRT among patients on treatment for high-risk CAp.

STUDY POPULATION

The study population comprised male patients who were on treatment for high risk CAp. High risk CAp in this study was defined as the presence of at least one of the following three criteria: a Gleason score equal to or greater than 7, PSA level greater than 20 ng/ml, clinical staging of cT2c-3a. (D'amico classification).

Inclusion criteria

1. Male patients diagnosed with of high-risk CAp and utilizing EBRT as a treatment modality.
2. Willingness to participate in the study and signing an informed consent.

Exclusion criteria

1. Presence of any other co-existing malignancy other than cancer of the prostate.
2. Patients who had undergone previous radiotherapy for other malignancies.
3. Patients who declined to sign and give informed consent.
4. Patients who withdraw willingly due to the acute adverse effects.

SAMPLING

Sampling Method

Convenient sampling procedure was used to recruit patients into the study. All patients who fulfilled the eligibility criteria were consecutively enrolled until the full sample size was achieved.

Sample size calculation

The basis for the calculation of the sample size was derived from data from the following. According to medical records data from the facilities in the study, approximately 200 CAp cases are seen annually. This is similar to prostate cancer figures reported in the Nairobi cancer report 2004-2008(5). This study was conducted over an 8 month period and the accessible population within the period was 48 patients due to a few unforeseen limitations. The nitial study period calculated was 4 months with a study population of 50 patients.

A representative sample was drawn from this population and the sample size calculation was obtained using the formula for finite population (Daniel, 1999). The calculation was as follows:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$ Where

n' = sample size with finite population correction,

N = size of the target population = 50

Z = Z statistic for 95% level of confidence = 1.96

P = Estimated proportion of patients with acute adverse effects after EBRT

d = margin of error = 5%

Substituting into the formula, Incidence for acute effects as seen by Peeters et al (2005)

A minimum of 44 patients were to be sampled to estimate prevalence of acute adverse effects within 5% level of precision.

CLINICAL METHODS

Eligible patients were first seen by the radio-oncologist as the initial step. Medical images i.e. CT scans and MRI scans were reviewed to assess tumour location and burden. The selected patient was then sent for radiotherapy planning. Radiographic simulation was done to visualize the region to be irradiated and produce an image of the same. The patient was then marked externally on the skin with i.e. a permanent marker to act as a guide. Patient then was sent to the machine room where continuity of this planning took place. The patient lay supine on the machine bed, arms over chest/arms behind the head, legs were placed straight and adducted, and the pelvic region then exposed. Machine parameters were set to the marked field.

Dose calculation was done and time required to deliver the effective daily dose was calculated. The dose rate varied according to the machine in use. Approximately 1-2 minutes were required to deliver the 2Gy dose per session. 1Gy from posteriorly and 1Gy from anteriorly. Total time from patient positioning to completion of dose delivery took approximately 5 minutes. These sessions continued daily for 5 days, followed by 2 days of rest until full completion of the treatment dose. The entire process during assessment and management took approximately 6 weeks per patient. The pre-radiotherapy data was collected before radiotherapy, the mid-radiotherapy assessment data was collected at the end of week three of EBRT and the end-radiotherapy assessment data was collected after the final week six of EBRT.

DATA COLLECTION

Data collection was done using a standard questionnaire after consent was sought from the respondents. Data was collected by a trained research assistant through interviewing subjects as well as a physical examination. The trained research assistants had a minimum qualification of Kenya Registered Community Health Nurse (KRCHN) or equivalent, with experience in handling oncology patients collected the data.

The eligibility of inclusion was ascertained by verification from the recorded data and decisions made in the files of the patients, in addition to the information provided by the patient. The pre-radiotherapy PSA levels were obtained from patient laboratory assessment done during the diagnosis of the prostate cancer. Tumour stage was obtained from a staging CT scan, MRI or clinical staging done during the diagnosis of the CAp. This information was sought from the

patients' medical records. The patients' observations i.e. BP, pulse rate, temperature were taken by the research personnel after consent was sought.

The patients who fulfilled the study inclusion criteria were invited into a separate room within the facility. The purpose and objectives of the study were introduced and discussed. Both verbal and written consent was sought. A baseline physical examination was performed at the time of recruitment, the study questionnaire was administered in private and confidentiality assured. A follow-up examination was performed at mid-point of EBRT and at the end of EBRT. The participants'/ care-takers' telephone numbers were recorded in order to facilitate ease of follow-up by reminding the patients about their follow-up appointments.

Data Collection Instrument

Data was collected using a structured questionnaire that focused on the following areas based on the objectives of the study:

1. Demographic factors
2. Acute adverse clinical effects
3. Treatment dynamics e.g. total dose of radiation and modality of EBRT

QUALITY ASSURANCE:

All aspects of this study were subjected to strict quality control. There was strict adherence to the inclusion criteria in order to avoid collecting irrelevant data. Observation of the ethical considerations while handling the study participants was paramount. The primary investigator verified each questionnaire to confirm that responses were filled correctly.

DATA MANAGEMENT

Once data collection was completed, the database was password protected for security and to prevent tampering or alterations. Regular file back-up was done to avoid any loss; some back up files were stored in flask discs.

DATA ANALYSIS

Statistical analysis was performed in SPSS version 21.0. Patients' socio-demographic and clinical information was summarized into percentages and means/medians for categorical and continuous variables respectively. Acute adverse effects of EBRT were analyzed and presented as percentages with 95% confidence intervals. The total dose given to the patient was calculated

and presented. Associations between total dose of radiation, modality of EBRT and acute adverse effects were tested using Chi square test for categorical independent variables and Student's t test to compare means. Statistical tests were interpreted at 5% level of significance (p value less or equal to 0.05). Study findings were presented in tables, figures and graphs.

ETHICAL CONSIDERATIONS

This proposal was subjected to review by the KNH/UON ERC as well as the relevant administrative review personnel at the Texas Cancer Center. The data collected from this study is to be used to provide information geared towards development of protocols that would help optimize treatment outcomes for patients who have high-risk CAp.

Consent was sought before administration of the questionnaire. The study was fully voluntary and affected men would leave without giving any reason or due to the acute adverse effects and this did not affect the quality of care that they received.

The findings were treated with utmost confidentiality, for the purpose of this research only.

Management of Adverse Effects

During the course of EBRT, patients who developed acute adverse effects were supportively managed at the facilities respective multidisciplinary clinics though none required any form of hospitalization.

RESULTS

Sample Characteristics

This was a prospective descriptive study. In this study, 48 patients were recruited. The cases comprised of male patients who were on treatment for high risk CAp undergoing EBRT.

Section A- Socio Demographic Characteristics

The patients' ages ranged from 43 to 78 years. The mean age of males undergoing EBRT was 65.9 years (SD ± 6.5). The median age being 66.5 years (Table 1). Majority of the patients (43) (87.5%) had a form of formal education i.e. primary education (43.8%), secondary education (33.3%) and post-secondary education (10.4%). Only 6 patients (12.5%) had no form of formal education. 32 patients (66.7%) resided in a rural residence while16 patients (33.3%) came from an urban residence. 45 patients (95.8%) were found to have an immediate family member as a primary care giver which necessitated their consistent follow-up while undergoing EBRT. 2 patients (4.2%) who had a relative as a primary care giver were unable to have timely therapy.

Section B: Pre-Radiotherapy Assessment (Time 0 before radiotherapy)

Table 2 shows that according to the bother score of 1 to 10 which was assessing whether the prostate cancer limited the patient's daily activities, 32 patients (66.6%) reported a score of below five while 16 patients (33.4%) had a score of above 5. 28 (65.8%) of patients had an ECOG classification of 1 and below. Majority of the patients had minimally affected pre-disease performance, were fully active, or were restricted to perform heavy duties. This classification did no significantly change during the course of therapy. Table 3 and figure 1.
9 patients (18.8%) had a urethral catheter during the pre-treatment assessment though only 1 utilised a catheter during subsequent therapy. 29 patients (60.4%) had co-morbidities i.e. diabetes (27.6%), hypertension (75.9%), HIV (3.5%) and respiratory disease (3.5%). 40 patients (83.3%) were undergoing androgen deprivation therapy while 8 patients (16.7%) were not.

The mean PSA was 370.2ng/ml while the mean Gleason score was 8.1 (SD ± 1). 23 (51.1%) of the cases had a TNM tumour stage of III, 18 patients (40%) had stage IV. This was mainly attributed to financial constraints of these patients.

On assessment of the pre-radiotherapy acute effects on the systems concerned i.e. skin, genito-urinary and skin, using the RTOG criteria, the following was noted; all 48 patients (100%) were found with grade 0 on the GIT and skin assessment. Only 3 patients (6.3%) reported grade 1 on genitourinary system which was attributed to the pre-treatment urethral catheterisation.

TABLE 1: SOCIODEMOGRAPHIC CHARACTERISTICS

Variables	**Count (%)**
Age	
Mean (SD)	65.9 (6.5)
Median (IQR)	66.5 (62.0-70.0)
Min-max	43.0-78.0
Education level	
No formal education	6 (12.5)
Primary education	21 (43.8)
Secondary education	16 (33.3)
Post-secondary education	5 (10.4)
Usual residence	
Urban	16 (33.3)
Rural	32 (66.7)
Marital status	
Single	1 (2.1)
Married	39 (81.3)
Widowed/divorced	8 (16.7)
Primary home care giver	
Immediate family member	46 (95.8)
Relative	2 (4.2)

TABLE 2: PRE-RADIOTHERAPY ASSESSMENT

Variable	Count (%)
Effects of prostate cancer on patient's daily activities, n=46	
0	2 (4.2)
1	7 (14.6)
2	7 (14.6)
3	5 (10.4)
4	2 (4.2)
5	9 (18.8)
6	3 (6.3)
7	2 (4.2)
8	4 (8.3)
9	2 (4.2)
10	3 (6.3)
Presence of urinary catheter	
Yes	9 (18.8)
No	39 (81.3)
Presence of other co-morbidities, n=29	
Hypertension	22 (75.9)
Diabetes	8 (27.6)
Respiratory infection	1 (3.5)
HIV	1 (3.5)
On combination treatment with ADT	
Yes	40 (83.3)
No	8 (16.7)
Level of PSA	
Mean (SD)	370.2 (1118.3)
Median (IQR)	68.0 (33.1-272.0)
Min-max	5.2-7100.0
Gleason score	
Mean (SD)	8.1 (1.0)
Median (IQR)	8.0 (7.0-9.0)
Min-max	6.0-10.0
Tumor stage (TNM), n=45	
IIB	4 (8.9)
III	23 (51.1)
IV	18 (40.0)

TABLE 3: ECOG PERFORMANCE STATUS CLASSIFICATION

Grade	n	0 (%)	1 (%)	2 (%)	3 (%)
Pre-radiotherapy	41	6 (14.6)	21 (51.2)	12 (29.3)	2 (4.9)
Mid-radiotherapy	36	7 (19.4)	19 (52.8)	8 (22.2)	2 (5.6)
End- radiotherapy	37	5 (13.5)	21 (56.8)	9 (24.3)	2 (5.4)

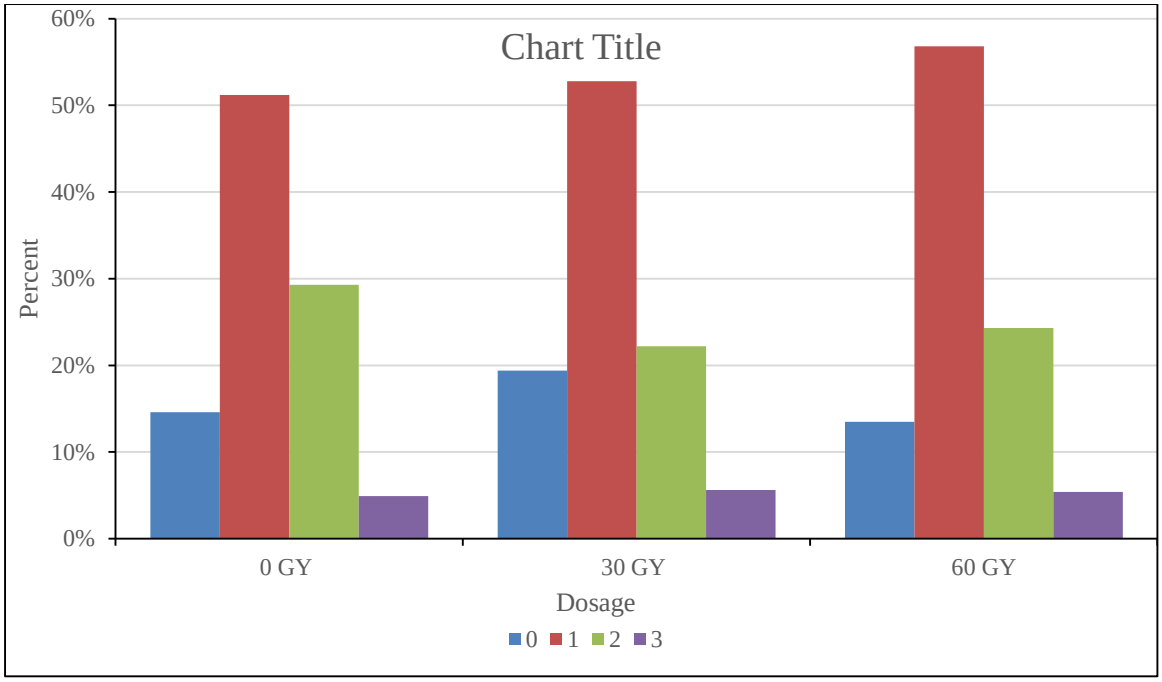

FIGURE 1: ECOG ACCORDING TO DOSAGE

TABLE 4:PRE-RADIOTHERAPY RTOG GRADE ASSESSMENT

Grade	n	0 (%)	1 (%)	2 (%)	3 (%)
Skin assessment	47	47 (100.0)	0	0	0
Genitourinary	47	44 (91.7)	3 (6.3)	0	0
Gastro-intestinal/pelvis assessment	47	47 (100)	0	0	0

Section C: The Acute Adverse Effects of EBRT among Patients on high-risk CAp treatment

It was noted generally that the rate of EBRT adverse effects was 100% with all 48 patients reporting or having at least one of the adverse events i.e. skin changes, lower genito-urinary

symptoms and lower GIT symptoms associated with the treatment during the study period. The prevalence of adverse effects is as shown on the table 5 below.

TABLE 5: PREVALENCE OF ADVERSE EFFECTS

	Mid		**End**	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Overall	41 (87.2)	76.6-95.7	46 (97.9)	93.6-100.0
Skin	26 (54.2)	40.4-68.1	44 (93.6)	87.2-100.0
Gastro intestinal/pelvis	20 (42.6)	27.7-57.4	39 (83.0)	70.2-93.6
Genito urinary	34 (72.3)	59.6-83.0	42 (89.4)	78.7-97.9

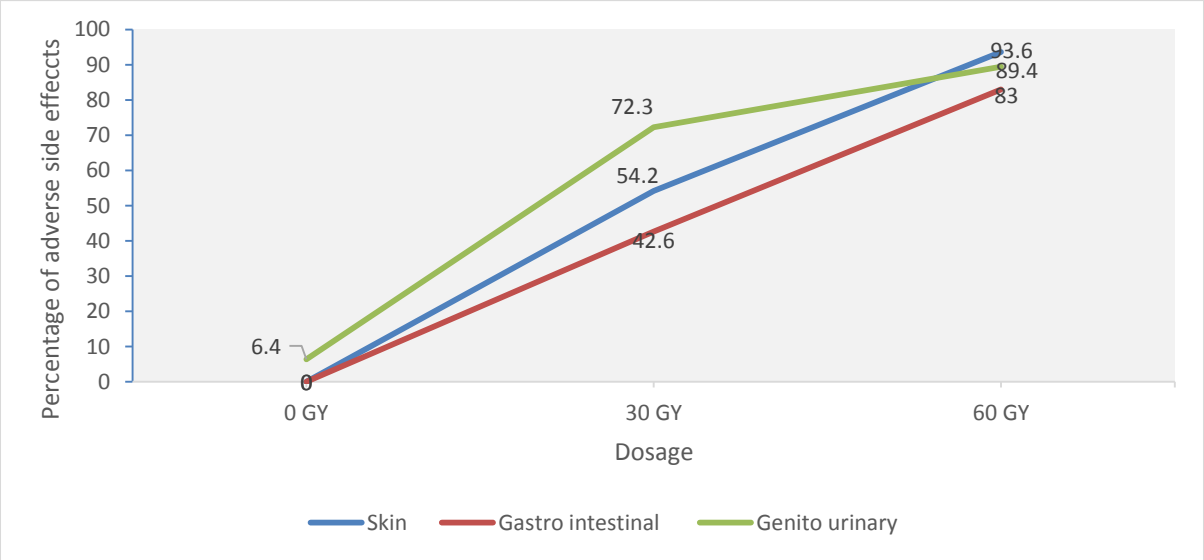

FIGURE 2: ADVERSE SIDE EFFECTS

From **figure 2** above, it was found that throughout the radiotherapy, the various adverse events were picked at the different assessment points i.e at time zero (pre-radiotherapy), end of third week after EBRT (mid-radiotherapy) and end of week 6 (end-radiotherpy). Genito-urinary effects had been notably higher than skin and lower gastro-intestinal adverse toxicity at mid-radiotherapy assessment (72.3%) though this pattern changed at the end of the radiotherapy where skin toxicity was highest at 93.6%.

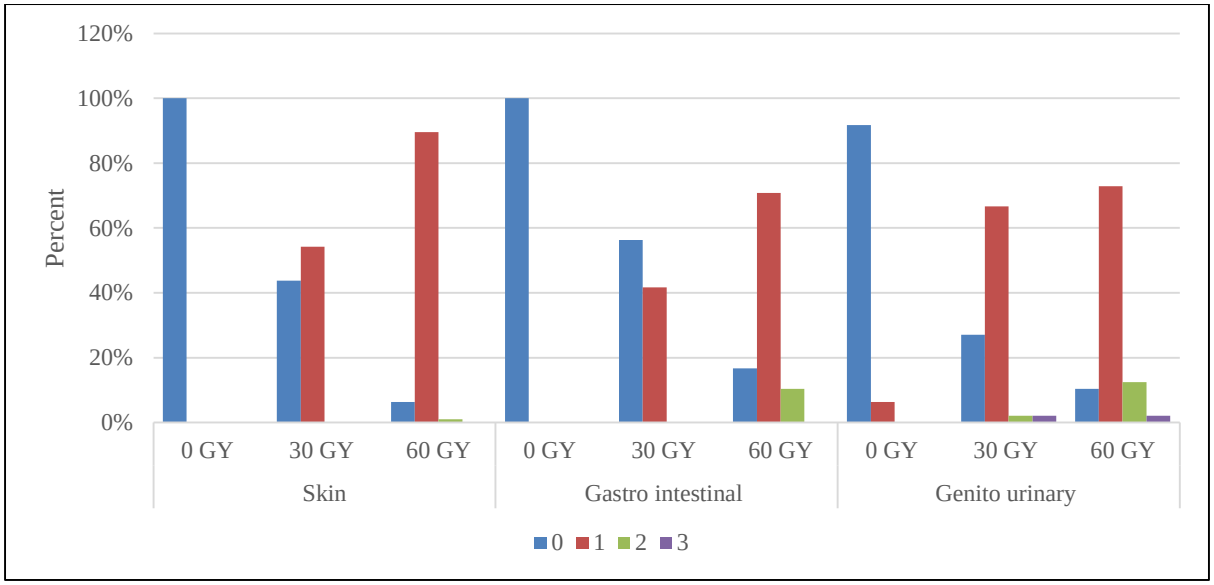

FIGURE 3: ADVERSE EFFECTS ACCORDING TO DOSAGE

From figure 3 illustrated above, at mid-radiotherapy (30Gy) majority of the adverse effects across all the systems undergoing assessment showed a predominant grade 1 for skin 26 (54.2 %) and genito-urinary systems 32 (66.7%) and predominant grade 1 skin toxicity 43 (89.6%) at end of radiotherapy.

Skin Acute Adverse Effects of ERBT

Table 6 shows that during mid-radiotherapy assessment, which corresponded to a radiation dose of 25 to 30Gy delivered, 26 patients (54.2%) were found to have grade 1 adverse effects on RTOG assessment. These included a single symptom or combination of faint follicles or dull erythema, skin epilation, skin desquamation and a decreased in sweating on the skin. 21 patients (43.8%) were not found to have symptoms during assessment. Assessment at the end of EBRT which corresponded to a final radiation dose of 50 to 60gy showed a significant increase in symptomatology among the patients whereby; 43 patients (89.6%) had grade 1 RTOG adverse effect i.e. a rise of 35.4%. 1 patient (2.1%) was found to have grade 2 adverse effects. 3 patients (6.3%) remained with a grade 0 RTOG assessment. None of the patients developed adverse skin effects above grade 2 RTOG assessment. None of the patients developed adverse genito-urinary events beyond grade 3. (Figure 2 and 3).

TABLE 6: RTOG SKIN ASSESSMENT

RTOG Grade	n	0 (%)	1 (%)	2 (%)	3 (%)
Pre-radiotherapy	47	47 (100.0)	0	0	0
Mid-radiotherapy (30Gy)	47	21 (43.8)	26 (54.2)	0	0
End- radiotherapy (50-60Gy)	47	3 (6.3)	43 (89.6)	1 (2.1)	0

Genito-Urinary Acute Adverse Effects of EBRT

As shown in Table 4 and 7, 3 of the 47 patients had RTOG grade 1 symptomatology prior to EBRT. However during mid-radiotherapy RTOG assessment, 32 patients (66.7%) developed grade 1 adverse effects which included a single symptom or a combination of i.e. Frequency, dysuria or urgency. This was a rise of 60.4%. After a dose delivery of 50-60Gy at end of radiotherapy, 35 patients (72.9%) had RTOG grade 1 effects (a rise of 6.2% from mid-radiotherapy assessment), 6 patients (12.5%) developed grade 2 adverse effects which included; Frequency that is < every hour, Dysuria, presence of urgency, spastic bladder requiring treatment. 1 patient developed grade 3 effects i.e. pelvic pain and severe urgency.

TABLE 7: RTOG GENITO-URINARY ASSESSMENT

RTOG Grade	n	0 (%)	1 (%)	2 (%)	3 (%)
Pre-radiotherapy	47	44 (91.7)	3 (6.3)	0	0
Mid-radiotherapy (30Gy)	47	13 (27.1)	32 (66.7)	1 (2.1)	1 (2.1)
End- radiotherapy (50-60Gy)	47	5 (10.4)	35 (72.9)	6 (12.5)	1 (2.1)

Lower Gastro-Intestinal Acute Adverse Effects of EBRT

Table 4 and 8 shows pre-radiotherapy RTOG grade of 0 on all patients. During mid-radiotherapy assessment 20 patients (41.7%) developed RTOG grade 1 symptoms which included a single symptom or a combination of frequency or altered quality of bowel movement that does not require treatment and rectal discomfort that does not require pain medication. After the full therapeutic dose was given, 34 patients (70.8%) had RTOG grade 1 effects and 5 patients (10.4%) showed RTOG grade 2 effects which included diarrhea that requires treatment, mucous discharge not requiring sanitary pads and rectal or abdominal pain that would require pain medication. 8 patients (16.7%) remained asymptomatic throughout the treatment period. None of the treated patients had symptoms beyond RTOG grade 2.

TABLE 8: GASTRO INTESTINAL/PELVIS ASSESSMENT

RTOG Grade	n	0 (%)	1 (%)	2 (%)	3 (%)
Pre-radiotherapy	47	47 (100.0)	0	0	0
Mid-radiotherapy (30Gy)	47	27 (56.3)	20 (41.7)	0	0
End- radiotherapy (50-60Gy)	47	8 (16.7)	34 (70.8)	5 (10.4)	0

Adverse Effects Associated With Co-Morbidities

Hypertension

Occurrence of adverse effects were associated with hypertension (p>0.05). Adverse effects on the skin was 90.9% in the hypertensive patients and was not significantly different from 96% reported among those with normal blood pressure (p=0.593). Gastro-intestinal adverse effects were 72.7% in hypertensive patients and 92% in non-hypertensive patients (p=0.123). Similarly, 90.9% of hypertensive patients had genito-urinary adverse effects compared to 88% of those with normal blood pressure (p=1.000).

TABLE 9: ADVERSE EFFECTS ASSOCIATED WITH HYPERTENSION

	HTN (%)	No HTN (%)	P value
Skin			
Yes	20 (90.9)	24 (96.0)	0.593
No	2 (9.1)	1 (4.0)	
Gastro intestinal			
Yes	16 (72.7)	23 (92.0)	0.123
No	6 (27.3)	2 (8.0)	
Genito urinary			
Yes	20 (90.9)	22 (88.0)	1.000
No	2 (9.1)	3 (12.0)	

Diabetes

As shown in the table 10, there was no significant association between diabetes and occurrence of adverse effects (p>0.05). All diabetic patients experienced adverse effects on the skin compared to 92.5% reported among the non-diabetic patients (p=1.000). Gastro-intestinal adverse effects were reported in 71.4% of the diabetic patients while the non-diabetic reported 85% (p=0.585). Similarly, 85.7% of diabetic patients had genito-urinary adverse effects compared to 90% in the non-diabetics (p=0.571).

TABLE 10: ADVERSE EFFECTS ASSOCIATED WITH DIABETES

	Diabetic (%)	Non-Diabetic (%)	P value
Skin			
Yes	7 (100.0)	37 (92.5)	1.000
No	0	3 (7.5)	
Gastro intestinal			
Yes	5 (71.4)	34 (85.0)	0.585
No	2 (28.6)	6 (15.0)	
Genito urinary			
Yes	6 (85.7)	36 (90.0)	0.571
No	1 (14.3)	4 (10.0)	

DISCUSSION

CAp is one of the highly prevalent cancers in elderly males both locally and globally. CAp is currently the leading cancer in elderly men in Kenya. The mainstay of treatment of high risk CAp in Kenya has been the use of various treatment modalities including androgen deprivation therapy (ADT) and radiotherapy (RT). Radiotherapy is a commonly used modality of treatment in patients with CAp and its benefits on cancer survival have been demonstrated(3). All these methods utilized to treat cancer of the prostate (CAp) have different degrees of adverse effects. The advent of radiotherapy i.e. both internal and external radiation, as part of a combined treatment modality has been associated with better clinical responses, albeit this is not without adverse clinical adverse events. The clinician should thus be aware of the acute adverse clinical effects of EBRT among patients with high risk CAp in order to thoroughly make sure that treatment complications will not decrease the quality of life more than the disease would have done.

In this prospective study, fourty-eight patients were recruited into the study. The mean age of the patients undergoing the procedure was 65.9 years with a range of 43 to 78 years. This age was similar to a study done by Wasike et al at Kenyatta National Hospital (KNH) in Kenya on CAp, Most of these cases were elderly i.e. peak incidence at 66-70yrs (14). In this study it was found that 83.3% of patients were on combination adjuvant hormonal ADT therapy during the treatment of high risk prostate cancer which indicated that the current evidence based combination clinical management of high risk CAp was being instituted. According to Bria E. et.al, hormone suppression with radiation therapy significantly decreases mortality and recurrence in patients with localized CAp, without altering the toxicity (21).

It was found in our study that the acute adverse effects increased with an increase in the radiotherapy dose i.e figure 2 and 3, which was in keeping with Padraig Warde et.al observation on RT for localized CAp and dose effect on adverse events. He noted that the severity of the reaction varies according to the total radiation dose given and the time it is given among other important factors(29). Patients in our study were exposed to radiation at a maximal dose level of 60Gy given in 2Gy fractions by the end of the EBRT. Most patients had some form of grade 1 acute toxicity, be it skin- 43patients (89.6%), lower gastro-intestinal- 34 patients (70.8%) and genito-urinary 35 patients (72.9%). Although direct comparison is difficult due to differences in study population, CRT mapping and delivery method used, our overall adverse effect rate

was high compared with that of a study done by Michalski JM et.al. Which showed that the acute toxic effects was low, with about 53 to 54% of the patients presenting with either no or grade 1 toxicity at dose levels I (68.4 Gy) and II (73.8 Gy). 62% of a second group of patients had either none or grade 1 toxicity at either dose level. In our study it was also found that 0-2.1% of patients developed grade 3 of bowel or urinary bladder toxicity which was similar to the Michalski JM et.al study that showed 0-3% patients experienced a grade 3 acute bowel or bladder toxicity. One late high grade bladder reaction in their grouped series at 73.8Gy was recorded as was seen in our study where 1 patient developed grade 3 bladder toxicity. There was no toxicity above grade 3 in our study which was similar to the Michalski JM et.al study that showed there were no grade 4 or 5 toxicities at the above radiation levels(45).

In other studies done by Michalski JM et.al, checking on toxicity after 3D-RT for CAp with dose level 74Gy at 2Gy fractions, 79.2 Gy being given at 1.8 Gy fraction or 78 Gy being given at 2.0Gy fractions which was a much higher dose than our treatment plan, the following was observed. The acute toxic effect at dose Level 78 Gy was low, with Grade 3 acute effects reported in only 4% or less of their patients. In our study, patients were assigned to be treated with 60Gy at 2Gy fractions with none of the patients developing grade 4 or 5 toxicity. They reported no grade 4 or 5 toxicity even with a higher dose compared to our study(46)(47).

Bagshaw M, et.al described various results in their study of CAp cases whose intention was treatment with cure. They found that 24% of patients presented with genital and urinary symptomatology and 43% showed gastrointestinal adverse effects, Most of which were minor toxicities. We found similar toxicities in our study most of which were minor grade 1 though percentage of affected patients was much higher i.e. genitourinary 35 (72.9%) and gastro-intestinal 34 (70.8%). Diabetes as a co-morbidity was not associated with an increase witht e rate and grade of adverse events. Severe acute adverse effects of the urinary and GIT that require a halt in therapy are not common and these effects were shown in 2.5% of all treated patients various series.

CONCLUSION

Our study demonstrates that,

1. External beam radiotherapy is commonly associated with low grade acute adverse effects which include skin effects, genito-urinary and gastro-intestinal effects. Despite these events, EBRT is a relatively safe and an effective treatment mode in male patients with high risk CAp though it is important to recognize the presence of these adverse effects in order to effectively counsel these patients prior to therapy.
2. The majority of adverse events arising from EBRT are grade 1 and below at a radiation dose of 60Gy.
3. A large number of patients undergoing EBRT for high-risk CAp will get a form of adverse event i.e. skin related, gastro-intestinal and/or genito-urinary.

STUDY LIMITATION

1. A medical strike involving public health institutions and spanning a period of approximately 5 months greatly limited timely data collection and follow-up of patients initially recruited to the study.
2. Patients' information regarding how their current disease affected them was very subjective.
3. Patient numbers with high risk cancer of the prostate were few and far between thus achieving the required patient size.

APPLICATION OF RESULTS

These results will be disseminated to scientific fora and stake holders in the health sectors. It will help inform decisions geared towards improvement of high-risk CAp management as concerns EBRT. The study is also expected to serve as a baselinefor those who may wish to make further research on the area.

RECOMMENDATIONS

1. There is need to develop local protocols within radiotherapy departments for patients undergoing EBRT for high risk cancer of the prostate that include a patient information guide as to the type and grade of the adverse events that they should expect with this treatment modality.

2. Further larger multicenter prospective studies are recommended to evaluate the acute adverse events occurring as a result of this modality of treatment within Kenya.

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APPENDICES

APPENDIX A: INFORMED CONSENT FORM (ENGLISH):

This Informed Consent form is for male patients with high risk cancer of the prostate attending external beam radiotherapy treatment sessions and will be administered to the eligible patients or patient's next of kin. We are requesting these patients to participate in this research project whose title is **"THE PREVALENCE AND DETERMINANTS OF ACUTE ADVERSE EFFECTS OF EBRT AMONG PATIENTS ON TREATMENT FOR HIGH RISK CAp"**.

Principal Investigator: Dr. Samuel Kagiri Maingi

Institution: Department of Surgery, School of Medicine, University of Nairobi.

This Informed Consent Form has three parts:

1) Information Sheet (to share information about the research with you).
2) Certificate of Consent (for signatures if you agree to take part).
3) Statement by the researcher/person taking consent.

You will be given a copy of the full informed consent form.

PART I: Information Sheet

Introduction

My name is Dr. Samuel Kagiri Maingi, a post graduate student in Urology at the University of Nairobi. I am carrying out a research to determine the acute adverse effects of external beam radiation therapy among patients on treatment for high risk cancer of the prostate.

Purpose of the research

Prostate cancer is one of the most common cancers affecting men within our country and globally. Various treatment methods are used to manage the disease process which currently are recommended to be done in combination rather than singly. Various studies have shown benefits to this approach. Among the treatment methods includes using radiation therapy. This radiation therapy may have acute side effects during treatment and the purpose of this study is to describe these effects if and as they occur. I will provide information to you and let me know what you don't understand understand. After receiving the information concerning the study, you are encouraged to seek clarification in case of any doubt.

Type of Research Intervention

This research will involve asking relevant questions, examination of your body and medical records with your doctor's permission [or their representative] to obtain the symptoms arising from the radiation treatment. This assessment will be done before, during and immediately after your scheduled radiotherapy sessions.

Voluntary participation

Your participation is entirely voluntary. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. You have a right to refuse or withdraw your participation in this study at any point.

Confidentiality

The information obtained will be treated with confidentiality and only be available to the principal investigator and the study team. Your name will not be used. Any information about you will have a number on it instead of your name. We will not be sharing the identity of those participating in this research.

Sharing the results

The knowledge that we get from this study will be shared with the policy makers in the Ministry of Health and doctors through publications and conferences. Confidential information will not be shared.

Benefits

You may get no direct benefit from the information you provide for this study. However, the results will greatly contribute towards the advancement of health science by providing knowledge on the acute effects of radiotherapy in our setups and better management of patients undergoing a similar treatment process such as yours.

Risks

There are no direct risks anticipated in this study as it only seeks to describe the acute effects of the treatment that you are receiving.

Cost and compensation

There will be no extra cost incurred for participating in this study nor will there be any compensation offered. This proposal has been reviewed and approved by UoN/KNH Ethics Committee.

PART II: Certificate of Consent

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Signature of Participant _____

Date _____

If Non -literate:

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Thumb print of participant

Signature of witness _____

Date _____

PART III: Statement by the researcher

I have accurately read out the information sheet to the participant, and to the best of my ability made sure that the participant understands that the following will be done:

- Refusal to participate or withdrawal from the study will not in any way compromise the care of treatment.
- All information given will be treated with confidentiality.
- The results of this study might be published to facilitate better understanding of the acute effects of radiotherapy.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Name of researcher/person taking consent _____

Signature of researcher/person taking consent _____

Date_____

Who may you contact if need be;

1. Principal Researcher:
   Dr. Samuel Kagiri Maingi,
   P.O. Box 19676 KNH, Nairobi 00202.
   Mobile no. 0721686039

2. University of Nairobi Supervisors:
   1) DR. CATHERINE NYONGESA
      MB.ChB (UON), M.MED RAD ONC-Witwatersrand, FC RAD ONC (SA)
   2) DR. FRANCIS A. OWILLAH,
      MBCH.B, M.MED (GEN SURG.), FCS (ECSA), CERT UROL. (KCMC),
      Consultant Urologist/lecturer, Department of surgery, University of Nairobi.

If you have any ethical concerns, you may contact:
Secretary, UON/KNH-ERC,
P.O. Box 20723- 00202,
KNH, Nairobi.
Tel: 020-726300-9
Email: KNHplan@Ken.Healthnet.org

APPENDIX B: FOMU YA MAKUBALIANO.

Fomu hii ya makubaliano itaidhinishwa na wagonjwa wanaume au jamaa zao, wenye hatari kubwa ya kuugua saratani ya tezi kibovu (prostate cancer) ambao wanapokea matibabu ya miale ya mionzi (external beam radiotherapy). Tunakusihi kushiriki katika uchunguzi huu wa maarifa ambao anwani yake ni: "**athari za utabibu wa miale ya mionzi kwa wagonjwa walio na hatari kubwa ya saratani ya tezi kibovu."**

Mtafiti mkuu: Dkt. Samuel Kagiri Maingi

Chuo Kikuu cha Nairobi,

Kitivo cha utabibu.

Fomu hii ina sehemu tatu:

1) Habari itakayo kusaidia kukata kauli
2) Fomu ya makubaliano (utakapo weka sahihi)
3) Ujumbe kutoka kwa mtafiti

Utapewa nakala ya fomu hii.

SEHEMU YA KWANZA: Ukurasa wa habari

Kitambulizi

Mimi ni daktari Samwuel Kagiri Maingi, anayesomea uzamili katika idara ya upasuaji Chuo Kikuu cha Nairobi. Ninafanya utafiti kwa anwani ya: "**THE PREVALENCE AND DETERMINANTS OF ACUTE ADVERSE EFFECTS OF EXTERNAL BEAM RADIATION AMONG PATIENTS ON TREATMENT FOR HIGH RISK CANCER OF THE PROSTATE."**

Lengo kuu la utafiti.

Saratani ya tezi-kibovu ni mojawapo ya maradhi makuu yanayowaathiri wanaume katika nchi yetu na dunia nzima. Kunao aina nyingi ya matibabu asilia ambazo hutumika kukabili maradhi haya, ijapo kwa wakati mwingi hutumika kwa jumuisho. Mojawapo ya aina za tabibu ni miale ya mionzi. Utabibu huu unaweza kuwa na athari zake wakati mgonjwa anapoupokea ndiposa utafiti huu ukalenga kuzipekua kwa kina. Nitakupa ujumbe kuhusu utafiti huu kasha nikupe fomu utakayoijaza kama kibali cha kujiunga kwa utafiti. Iwapo kuna baadhi ya mambo hutaelewa, una uhuru wa kuuliza kwa maelezo zaidi.

Aina ya utafiti.

Utafiti huu utahusu kujibu maswali kupitia kwa dodoso, kukupima hali ya afya kulingana na ugonjwa wako wa saratani na pia kudurusu hifadhi ya jumbe za afya yako kulingana na hiari ya dakitari wako. Utafiti utafanywa kabla, wakati na baada ya kupokea utabibu wa miale ya mionzi.

Haki ya kukataa utafiti

Kushiriki kwako kwa utafiti huu ni kwa hiari yako. Una uhuru wa kukataa kushiriki, na kukataa kwako hakutatumiwa kukunyima tiba. Unayo haki ya kujitoa katika utafiti wakati wowote unapoamua.

Taadhima ya siri

Ujumbe kuhusu majibu yako yatahifadhiwa. Ujumbe kuhusu ushiriki wako katika utafiti huu waweza kupatikana na wewe na wanaoandaa utafiti na wala si yeyote mwingine. Jina lako halitatumika bali ujumbe wowote kukuhusu utapewa nambari badili ya jina lako.

Hatari unayoweza kupata

Hakuna hatari yoyote ambayo yaweza kutokea kwa sababu ya kuhusishwa kwa utafiti huu. Hatari ambazo zaweza tokana na upasuaji wenyewe zitaelezwa katika fomu ya kibali cha upasuaji,tofauti na hii.Aidha, kukataa au kujitoa katika ushiriki wako kwa huu utafiti kwa wakati wowote ule hakutakuletea hatari yoyote ya matibabu.

Hifadhi ya matokeo.

Matokeo ya utafiti huu yatachapishwa kwa nukuu mbali mbali za sayansi kupitia kwa idhini ya mtafiti mkuu. Nakala za chapisho zitahifadhiwa katika idara ya upasuaji, chuo kikuu cha Nairobi na katika maktaba ya sayansi za Afya, kitivo cha utabibu. Hivyo basi, matokeo ya utafiti huu hayatasambazwa kwa umma au jukwaa lisiloidhinishwa kihalali. Ujumbe ulio kwa dodoso hautahifadhiwa baada ya uchanganuzi wa matokeo.

Gharama au fidia.

Utafiti huu hautakugharimu zaidi ya matibabu yako ya kawaida. Vilevile, hakuna malipo yoyote au fidia utakayopokea kutokana na kujiunga kwako katika utafiti huu. Muda wako ndio utakaotumiwa wakati wa mahojiano.

SEHEMU YA PILI: Fomu ya makubaliano

Nimeelezewa utafiti huu kwa kina. NakubaIi kushiriki katika utafiti huu kwa hiari yangu. Nimepata wakati wa kuuliza maswali na nimeelewa kuwa iwapo nina maswali zaidi, ninaweza kumwuliza mtafiti mkuu au watafiti waliotajwa hapa juu.

Jina la
Mshiriki_____

Sahihi ya mshiriki
_____

Tarehe_____

Kwa wasioweza kusoma na kuandika:

Nimeshuhudia usomaji na maelezo ya utafiti huu kwa mshiriki. Mshiriki amepewa nafasi ya kuuliza maswali. Nathibitisha kuwa mshiriki alipeana ruhusa ya kushiriki bila ya kulazimishwa.

Jina la shahidi_____

Sahihi la shahidi_____

Tarehe _____

Alama ya kidole cha gumba cha mshiriki

SEHEMU YA TATU: Ujumbe kutoka kwa mtafiti

Nimemsomea mshiriki ujumbe kiwango ninavyoweza na kuhakikisha kuwa mshiriki amefahamu yafuatayo:

- Kutoshiriki au kujitoa kwenye utafiti huu hakutadhuru kupata kwake kwa matibabu.
- Ujumbe kuhusu majibu yake yatahifadhiwa kwa siri.
- Matokeo ya utafiti huu yanaweza chapishwa kusaidia utambuzi wa shida zinazotokana utabibu wa miale ya mionzi.

Ninathibitisha kuwa mshiriki alipewa nafasi ya kuuliza maswali na yote yakajibiwa vilivyo. Ninahakikisha kuwa mshiriki alitoa ruhusa bila ya kulazimishwa.

Mshiriki amepewa nakala ya hii fomu ya makubaliano.

Jina la mtafiti

_____

Sahihi ya Mtafiti

_____

Tarehe_____
___

Anwani za Wahusika

Ikiwa uko na maswali ungependa kuuliza baadaye, unaweza kuwasiliana na:

1. Mtafiti Mkuu:
   Dkt. Samuel Kagiri Maingi

   Idara ya upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi,

   SLP 19676 KNH, Nairobi 00202.

   Simu: 0721 686 039

2. Wahadhiri wahusika:

1) DKT. CATHERINE. NYONGESA
   MB.Ch.B, MMED-Radio/Onc. (Witwatersland, SA), FC-Radio/Onco. (ASCO).
2) DKT. FRANCIS A. OWILLAH,
   MBCH.B, M.MED (GEN SURG.), FCS (ECSA), CERT UROL. (KCMC), surgery-UON.

Wahusika wa maslahi yako katika Utafiti:

- Karani,
  KNH/UoN-ERC
  SLP 20723 KNH, Nairobi 00202
  Simu: +254-020-2726300-9 Ext 44355

Barua pepe: : uonknh_erc@uonbi.ac.ke

APPENDIX C: QUESTIONNAIRE

STUDY STAFF INITIALS:_____

DATE:_____

CONTACT:_____ IN PATIENT NUMBER_____

SECTION A: DEMOGRAPHIC DATA

Age? _____

What is your level of formal education?

No formal education

Primary education

Secondary education

Post-secondary education (Certificate, Diploma, Degree, Masters)

What is your usual residence?

Urban

Rural

Marital status

Single

Married

Other –widowed/divorced

Primary home care giver

Immediate family member/s

Relative

Friend

Other

SECTION B: PRE-RADIOTHERAPY ASSESSMENT

Does the prostate cancer limit the patient's daily activities? (CIRCLE)

Not 1 2 3 4 5 6 7 8 9 10 very

At all much

ECOG performance status classification (Grade 0, 1,2,3,4 or 5)

Vital signs

Blood pressure_____

Pulse_____

Temperature_____

Respiratory rate_____

Presence of urinary catheter (Urethral/Suprapubic)?

Yes

No

Presence of other co-morbidities?

No

Yes

If yes, indicate the co-morbidity_____

On treatment with Androgen deprivation therapy?

Yes

No

If no, indicate reason_____

Level of PSA _____

Gleason score_____

Tumour stage (TNM)_____

PRE-RADIOTHERAPY LOCAL SKIN ASSESMENT

FINAL GRADE_____

PRE-RADIOTHERAPY LOWER GASTRO INTESTINAL/PELVIS ASSESMENT

FINAL GRADE_____

PRE-RADIOTHERAPY GENITOURINARY ASSESMENT

FINAL GRADE_____

SECTION D: MID- RADIOTHERAPY ASSESSMENT

ECOG performance status classification (Grade 0,1,2,3,4 or 5)

Vital signs

Blood pressure_____

Pulse_____

Temperature_____

Respiratory rate_____

MID-RADIOTHERAPY LOCAL SKIN ASSESMENT

FINAL GRADE_____

MID-RADIOTHERAPY GASTRO INTESTINAL/PELVIS ASSESSMENT

FINAL GRADE_____

MID-RADIOTHERAPY GENITOURINARY ASSESMENT

FINAL GRADE_____

SECTION E: END- RADIOTHERAPY ASSESSMENT

ECOG performance status classification (Grade 0,1,2,3,4 or 5)

Vital signs

Blood pressure_____

Pulse_____

Temperature_____

Respiratory rate_____

END-RADIOTHERAPY LOCAL SKIN ASSESMENT

FINAL GRADE_____

END-RADIOTHERAPY GASTRO INTESTINAL/PELVIS ASSESSMENT

FINAL GRADE_____

END-RADIOTHERAPY GENITOURINARY ASSESMENT

FINAL GRADE_____

APPENDIX D: RTOG GRADING OF ADVERSE EFFECTS

The study variables will be as shown in the table below.

STUDY OBJECTIVE	OUTCOME VARIABLE (toxicity)	EXPOSURE VARIABLE	SOURCE OF DATA
Immediate adverse clinical effects among patients undergoing EBRT for High-risk cancer of the prostate	GU EFFECTS-grade 0,1,2,3,4,5 LOWER GI EFFECTS-grade 0,1,2,3,4,5 LOCAL SKIN CHANGES- grade 0,1,2,3,4,5	External beam radiotherapy treatment	Physical examination of patient Patient questionnaire-RTOG ACUTE Radiation Morbidity questionnaire

NB: For all: GRADE 0 = no symptoms, GRADE 5 = death directly related to radiation effects.