GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF RADIOLOGY/ONCOLOGY AND RADIOTHERAPY

OUTCOMES AND DETERMINANTS OF PSA BASED HIGH RISK PROSTATE CANCER PATIENTS TREATED WITH CURATIVE RADIATION AT KORLE BU TEACHING HOSPITAL ACCRA, GHANA.

DISSERTATION SUBMITTED TO THE FACULTY OF RADIOLOGY/ONCOLOGY AND

RADIOTHERAPY IN PARTIAL FULFILMENT OF REQUIREMENT FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF PHYSICIANS (FGCP)

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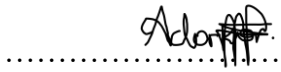
DECLARATION

I, Naa Adorkor Aryeetey declare that ‘‘I have wholly undertaken this dissertation therein under supervision and that except portions where references have been duly cited, this dissertation is the outcome of my research.’’

This dissertation has not been submitted for any degree, examination or journal.

Naa Adorkor Aryeetey



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CERTIFICATION

This is to certify that this research proposal work on

"Outcomes and determinants of PSA based high risk prostate cancer patients treated with curative radiation at Korle Bu Teaching Hospital'', was written by Naa Adorkor Aryeetey.

I have examined and endorsed it for acceptability by the Ghana College of Physicians and Surgeons.

Dr Verna Vanderpuye

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ABSTRACT

BACKGROUND: Prostate cancer (CAP) is one of the commonest male cancers worldwide. Usually described as a slow growing malignancy, treatment outcomes are often favourable with five-year overall survival quoted at 80% even in the metastatic setting of disease. Risk categorisation prior to treatment using several parameters including but not limited to prostate specific antigen (PSA), Gleason score, clinical stage and recently molecular features allows for tailored treatment predicated on life expectancy and the risk of recurrence. Local treatment is with radical prostatectomy, external beam radiotherapy and brachytherapy. The management of high risk localised prostate cancer patients with high PSA remains a challenge as there is paucity of data on treatment outcomes. External beam radiotherapy (EBRT) to doses above 70Gy with peri-radiotherapy androgen deprivation therapy (ADT) in the neoadjuvant, concurrent and adjuvant setting for 2-3 years is the recommended standard treatment for high risk disease. Partial implant brachytherapy, low dose rate permanent implant of radioactive isotopes (I^{125}, Cs-131 and Pd ^{103}), augmented with EBRT (45Gy-50Gy) is an alternative for local treatment of high risk disease. High dose rate brachytherapy (Ir-192 and Co-60) currently in use delivers doses upwards of 12Gy per fraction to the prostate gland. This can be used in the stead of low dose rate brachytherapy. Both options allow for dose escalation with reduced side effects to organs at risk. Treatment outcomes for patients with increasing PSA maybe inferior compared to those with low pre-treatment PSA levels represented by short time to biochemical failure and high biochemical failure rates, assuming the suspicion that patients with high pre-treatment PSA harbour early micro metastatic disease holds true. With evidence suggesting improved outcomes for localised treatment even in the presence of clinically evident metastasis, treatment outcomes are expected to be improved irrespective of pre-treatment PSA. The question though is whether outcomes will differ with increasing PSA levels.

Aim: To compare the treatment outcomes of localised high risk prostate cancer patients treated with curative intent using radiation therapy based on their pre-treatment PSA levels and the effect of a Gleason grade of 5 as primary grade on treatment outcomes

METHODOLOGY: In this retrospective chart review that combined descriptive and inferential study design, a cohort of patients treated from January 2010 to December 2014 were described for their demographic, tumour and treatment characteristics. A core group with localised high risk prostate cancer based on their PSA levels between 20-200ng/ml treated with curative intent with external beam radiotherapy alone (EBRT) or brachytherapy augmented by external beam radiotherapy(BRACHY+EBRT) with or without androgen deprivation therapy (ADT) were

grouped based on their pre-treatment PSA levels. Group A had PSA 20-49.9 ng/ml Group B 50-99.9ng/ml and C 100-200ng/ml and followed up from date of diagnosis to 31st December 2020. The patients were analysed using inferential statistic for treatment outcomes; biochemical and overall survival using Kaplan Meier curves and compared using log rank test. Patients were also compared for biochemical and overall survival outcomes based on their primary Gleason grade and combined Gleason score. Kruskal Wallis test of means was used for univariate analysis of non-parametric data and Cox regression analysis for multivariate analysis.

RESULTS: Eighty three percent of patients seen were evaluable for descriptive statistics (486 of 584). The median age at presentation was 67 years (range of 44-85 years). Adenocarcinoma was the commonest histology forming more than 99.6% of histologically diagnosed patients. The median PSA at presentation was 31.9ng/ml (interquartile range 20ng/ml-95ng/ml). Clinical stage T2N0 was the modal stage at diagnosis. Combined Gleason score was available for all but one patient with localised disease but only 88% of the patients had primary and secondary Gleason grades recorded.

Majority of the patients seen had high risk disease (53%), 7% low risk, 21% intermediate risk and 18% patients with metastatic disease. Data was inadequate to risk categorise 1% of the patients. Approximately half of patients with localised disease did not receive their intended curative treatment. High risk patients had the highest default rate of 58%.

External beam radiotherapy was the most used treatment modality. The mean dose for EBRT only was 72.42Gy, mean D90 was168.68Gy for brachytherapy only and for combination therapy the mean D90 of 109.60Gy and 45.35Gy for brachytherapy and EBRT respectively. Mean duration of treatment was for EBRT only was 8.9 weeks for the intended 7.5 weeks. Medical castration was the most used form of ADT. ADT was used for a mean of 14.6 months mainly in the high risk group. Four patients had bilateral total orchiectomy as lifelong ADT while 2 patients had radiotherapy concurrent with diethylstilbesterol (DES) and then for a total of 36 months.

The core group was followed up for a median of 7.25 years (range 4-10.5 years). There was a statistically significant difference in biochemical failure free survival when patients were stratified on pre- treatment PSA with p-value of 0.033. Based on combined Gleason score, biochemical failure free survival approached statistical significance with a p-value of 0.083.

There was no difference in biochemical failure free survival when compared based on primary Gleason grade

The 5 and 10-year biochemical free survival ranged from 46-68% and 36%-62% respectively, highest for Group B. Group C did not reach the 10 year mark for follow-up. Stratified for primary Gleason grade, biochemical failure free survival was about 55% at 10 years for primary Gleason grade 2-3. Primary Gleason 5 had biochemical failure free survival of 52% at 10years. Gleason 4 did not reach the 10-year follow-up mark but it was below that for Gleason 5 at 6 years, 38%. The curves were not statistically significantly different from each other with a pvalue of 0.311.

Nadir PSA value was found to be statistically significant for predicting biochemical failure free survival on both univariate and multivariate analysis. A Receiver operator characteristic (ROC) curve drawn to predict 4 year biochemical failure free survival based on the nadir PSA found 0.07ng/ml as the threshold PSA (p-value 0.047).

Estimated overall survival rates were above 70% at 10 years irrespective of patient stratification; pre-treatment PSA, primary Gleason grade or combined Gleason score. Overall survival showed a trend towards statistical significance when patients were assessed based on their combined Gleason score (p-value 0.06). This was not the case for pre-treatment PSA or primary Gleason grade. The biochemical failure free survival for group A, did not translate into overall survival benefit.

A planned systematic analysis to predict PSA cut off for curative treatment for localised high risk prostate cancer was abandoned due to the lack of difference in overall survival outcomes when patients were grouped based initial PSA.

CONCLUSION: Demography (age) and histological types of prostate cancer patients seen at the hospital compares to the rest of the world. Survival outcomes for localised high risk prostate cancer patients treated with radiotherapy and ADT at the National Radiotherapy Oncology and Nuclear Medicine Centre (NRONMC) of the Korle Bu Teaching Hospital (KBTH) is also comparable to existing published datasets. In our analysis a high initial presenting PSA up to 200ng/ml influenced biochemical outcomes in favour of low initial PSA. There was no difference in overall survival outcomes. This suggests all patients should receive curative treatment irrespective of pre-treatment PSA (up to 200ng/ml) provided there is no clinical or radiologic evidence of metastasis. There were no predictors of overall survival but nadir PSA

was found to statistically significantly predict biochemical failure free survival on univariate and multivariate analysis. A threshold nadir PSA of 0.07 predicts 4 years biochemical failure free survival. There was also a trend towards improved biochemical failure free survival (bffs) and overall survival (os) when patients were compared based combined Gleason score.

This study was limited by its retrospective nature as well as small numbers of patients studied.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND AND PROBLEM STATEMENT

Prostate cancer remains one of the most common male malignancies. It is the commonest visceral tumour in males worldwide although regional differences exist (Ferlay, 2019). In Ghana, prostate cancer is the second commonest solid cancer after hepatocellular carcinoma in men as per GLOBOCAN 2020. The Kumasi cancer registry data recorded it as the most common male cancer (Laryea *et al.*, 2014). The Accra cancer registry is expected to show a similar pattern. At the national centre for radiotherapy and nuclear medicine, prostate cancer is the most diagnosed male cancer and has been for over 12 years.

The advent of PSA testing has over the past 3 decades altered the presentation of the disease worldwide from mainly advanced and symptomatic metastatic disease at presentation to the diagnosis of early localised disease(Otis W Brawley, 2012). The benefit of population based screening of prostate cancer using PSA is controversial with several studies suggesting reduction in mortality at the risk of over diagnosis, over treatment, cost implications and risk of adverse events from treatment (Andriole *et al.*, 2012). Most of these studies have been performed in western countries where there is under representation of indigenous Africans. With evidence suggesting a stark difference in incidence, characteristics as well as clinical course of prostate cancer with worse treatment outcomes in blacks, an African study is long overdue to establish the role of prostate cancer screening in African men (Boring, C.C, Squires,T.S., Tong, 1994).

The use of PSA testing in the setting of diagnosed prostate cancer is however less controversial and well established. It is vital in the decision making for taking biopsies in patients undergoing active surveillance, risk categorisation of prostate cancer prior to start of treatment and in the post treatment surveillance.

Management decisions are based on several factors including, but not limited to, PSA levels, Gleason score, clinical stage, percentage positive cores, age and life expectancy of patients based on their co-morbidities.

Risk categorisation is the standard treatment decision making tool for management of prostate cancer. It recognises the heterogeneity in prostate cancer and aids clinicians in choosing the appropriate treatment. Based on PSA level, primary and secondary Gleason score,

combined Gleason score, clinical stage, percentage positive cores patients may be at low risk, intermediate or high risk of tumour recurrence and mortality from the disease (Rodrigues *et al.*, 2011) with several other permutations as evidenced by the different urological societies. These risk categorisation methods formed by combinations of the prognostic factors have been found to be highly reproducible in their ability to predict clinical endpoints in the management of prostate cancer. Table 6 shows some of the risk categorisations used worldwide (Gnanapragasam*et al.*, 2016).

High risk prostate cancer based on 2010 NCCN risk categorisation is PSA levels>20ng/ml or Gleason score more or equal to 8 or primary Gleason score of 5 and clinical stage T2B-3A. Treatment of patients with high risk disease using radiotherapy aims at delivering tumoricidal doses of radiation to the cancer while limiting dose to surrounding organs to reduce side effects. External beam radiotherapy (EBRT) to doses of 70-84 Gy with peri-radiotherapy androgen deprivation therapy (ADT) in the neoadjuvant, concomitant and adjuvant setting or using permanent implant low dose rate brachytherapy (BRACHY) to doses of 110Gy supplemented EBRT to 45Gy also with peri-radiotherapy ADT are considered adequate treatment. High dose rate (HDR) brachytherapy using Ir-192 and Co-60 are currently in use delivering doses upwards of 12Gy to the prostate gland is an alternative. This circumvents problems of substandard dosimetry which occurs with low dose rate brachytherapy due to seed loss or seed misplacement. In situ catheters at planning ensures optimized dosimetry for HDR brachytherapy. Radiotherapy is delivered within minutes minimising changes in position.(Mendez and Morton, 2018). High dose brachytherapy however may require multiple insertions which is less convenient compared to low dose rate brachytherapy. Both options allow for dose escalation with reduced side effects to organs at risk. The relationship between radiotherapy dose and cure probability increases to doses of up to about 86Gy beyond which it is known to plateau. Beyond this plateau, additional radiotherapy only worsens toxicity without any additional tumour kill. Dose escalation trials conducted in the early part of the 2000s found dose escalation to 78Gy from 70Gy to be beneficial in high risk prostate cancer based on the NCCN risk categorisation(Schulz and Kagan, 2011).

Current radiological investigations including bone scan, CT scan, MRI, MRI diffusion weighted imaging scans, prostate specific membrane antigen (PSMA) scans, positron emission tomography scan (PET scan) and choline PET scan, all have significant inadequacies in diagnosing micro metastatic disease at the pre-treatment stage. There is therefore a risk of

classifying patients with micro-metastatic disease as non-metastatic and vice versa. As a consequence, non-metastatic patients are at risk of not receiving curative treatment while metastatic patients may receive excessive treatment with the aim of cure when treatment should actually be palliative. Patients may thus be under treated or over treated respectively. It is difficult however to determine what under or overtreatment is in the management of prostate cancer as evidence builds for survival benefit with more intensified treatment even in the metastatic setting.

The CHARTERED trial has given high level evidence of survival benefit using chemotherapy or radiotherapy in addition to ADT compared with standard ADT alone in the setting of metastatic disease (Kyriakopoulos*et al.*, 2020). Radiotherapy treatment in addition to ADT for newly diagnosed metastatic disease without prior curative treatment has also been shown to improve overall survival in a select group of patients with low metastatic tumour burden at baseline (Parker *et al.*, 2018).

The evolution of prostate cancer from localised disease, often curable, to metastatic disease (the cause of morbidity and mortality) requires several processes from accumulation of genetic defects, the formation of abnormal cells, loss of cell-cell adhesion, entry to the blood stream and migration of tumour cells to distant sites (Hanahan and Weinberg, 2011). Circulating tumour cells (CTCs) which are free abnormal cells therefore appear in peripheral blood well before clinically evident metastases. An opportunity to determine patients with high burden of disease who may fail current treatment protocols could easily be identified using CTCs for intensified or palliative treatment. The number of CTCs in the peripheral blood and the analysis for genetic alterations can help determine prognosis and predict response to drugs providing a non-invasive means for disease characterization. This has enormous potential to promote precision and inch us closer to more personalised oncology (Maas *et al.*, 2019) especially when PSA levels have not consistently been found to accurately reflect response to treatment. Although the number of CTCs and their molecular characterization are useful for prognostication and provision of predictive markers for high risk prostate cancer patients, the evidence for its use as a biomarker outside metastatic castrate resistant prostate cancer is limited. In metastatic prostate cancer, CTC levels of ≥5 in 7.5 mL by CellSearch has been validated as a prognostic marker (Bono *et al.*, 2008)(Pienta, Raghavan and Heller, 2010).

While the use of CTC is awaiting approval and subsequent validation for the identification of patients with higher risk of disease progression and patients at risk of failure

after curative treatment, a very high PSA, defined in this study as PSA levels greater than or equal to 50ng/ml, is often considered a suggestion of occult metastatic disease with evidence suggesting adverse treatment outcomes compared to lower PSA lower levels (Wiebe et al., 2008). As we observe benefit of tumour directed radiotherapy for oligometastatic prostate cancer visible on radiological investigations (Deeket al., 2019), could these patients be best managed with curative intent?

Although there are several established and developing factors; clinical, radiological and pathological including molecular for risk categorisation and thence for treatment decision making, their shortfalls means that even within the various risk groups, there remains significant heterogeneity resulting in differing treatment outcomes. The effect of high PSA alone in background of other high risk factors in newly diagnosed prostate cancer patients is of importance especially in countries with low screening rates such as Ghana where patients continue present with high PSA levels with no clinical or radiological evidence of metastatic disease and also because of the paucity of data available in published literature for this subset of patients.

1.2 JUSTIFICATION/RATIONALE

Very high PSA levels may be a suggestion of occult disease outside of the prostate gland; in lymph nodes or distant metastatic sites. Patients with very high PSA are often excluded from clinical trials making choice of and outcomes of their treatment outcomes difficult to predict. Treating them with palliative intent without evidence of metastasis seems inadequate while treating them with curative treatment may be considered over treatment if they harbour inapparent metastatic disease that soon becomes clinically relevant.

With the current absence of local data on the treatment outcomes for patients with very high PSA treated with curative intent using EBRT, this study will provide vital information to aid the treatment decision process for the majority of Ghanaian patients who continue to present with very high PSA levels. This study will also help determine the cut off PSA, if any, beyond which curative treatment in the setting of very high PSA with other adverse prognostic features may offer no additional benefit in high risk prostate cancer.

1.3 AIM

To compare time to biochemical failure, biochemical failure rate biochemical failure free and overall survival in patients with high risk CAP with no clinical or radiological evidence of metastasis who are treated with curative intent using radiotherapy based on pre-treatment PSA levels.

To determine if there is a threshold PSA level beyond which curative treatment of patients with high risk prostate cancer using radiotherapy provides no additional clinical benefit.

1.4 OBJECTIVES

1. To determine the demographic characteristics of patients with high risk prostate cancer treated at the National Centre for Radiotherapy and Nuclear Medicine

2. To determine the level of presenting PSA (PSA trends) in patients with high risk prostate cancer treated with curative intent using radiotherapy at the National Centre for Radiotherapy and Nuclear Medicine. Accra Ghana,

3. To determine biochemical failure rate, time to biochemical failure, biochemical failure free and overall survival in high risk prostate cancer treated with curative intent based on their pretreatment PSA using radiotherapy at the National Centre for Radiotherapy and Nuclear Medicine.

4. To determine the proportions of primary Gleason 5 in Ghanaian PSA based high risk prostate cancer patients seen at the National Centre for Radiotherapy and Nuclear Medicine. Accra. Ghana.

5. To determine the biochemical failure free and overall survival rate of prostate cancer patients treated with curative intent based on their primary Gleason score and combined Gleason score using radiotherapy at the National Centre for Radiotherapy and Nuclear Medicine.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 THE PROSTATE GLAND

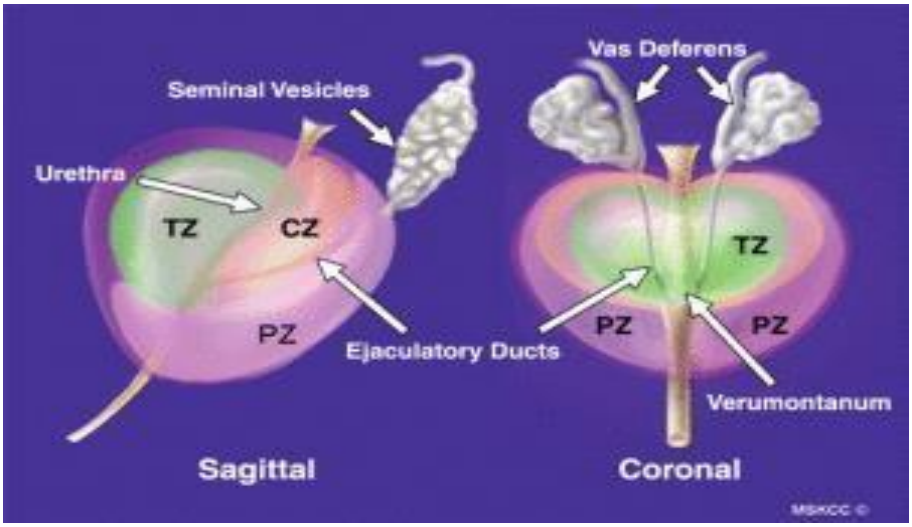
The prostate gland is a walnut shaped organ in pelvis of males with sexual and reproductive function. It is the largest accessory gland in humans. It lies sub-peritoneal above the pelvic diaphragm. It is located posterior to the pubic symphysis, anterior to the rectum and inferior the bladder surrounding the proximal urethra, the prostatic urethra. It is composed of fibrous, glandular and muscular components and covered by an adherent fibrous capsule which is continuous with the stroma.

It has a base that is attached to the neck of the bladder, an apex which lies on the superior surface of the urogenital diaphragm, an anterior surface which relates the pubic symphysis, a posterior surface which is anterior to the anterior rectal wall separated from it by the Denoviller's fascia as well as inferior lateral surfaces which relate the levator ani muscles. The paired seminal vesicles relate it posterior-superiorly.

The gland has several zones; the anterior fibromuscular stroma zone forms the convexity of the external surface, a central zone surrounds the ejaculatory ducts, a transition zone lies lateral to the urethra and a peripheral zone which is largest part (70-80%) of the gland and is the part accessible by digital rectal examination (DRE). Figure 1 shows a diagrammatic representation of the zones of the gland.

The gland is highly innervated receiving parasympathetic fibres from the hypogastric and pelvic nerves and sympathetic from the peripheral hypogastric ganglion. These nerves play a significant role in erection. The main function of the gland is the production of a fluid composed of proteins and non-protein components which adds to seminal fluid and may have a role in activating sperms for eventual fertilization with an ovum.

FIG 1.0: PZ- PERIPHERAL ZONE, TZ-TRANSITIONAL ZONE, CZ-CENTRAL ZONE



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2.2. PROSTATE CANCER

The prostate gland is a common site for disease in adult men with benign prostatic hyperplasia (BPH) and prostate cancer (CAP) the most relevant.

Prostate cancer is a disease of older men with a median age at diagnosis of 68 years. An increased number of patients were diagnosed in the early 1980's with the upsurge in the use of TURP for the management of benign prostatic hyperplasia (BPH) and in the early 1990's with the advent of use of prostate specific antigen (PSA) as a screening tool (O. W. Brawley, 2012).

The clinical course of CAP ranges from indolent disease with no consequence for patient to rapidly advancing disease which causes death. Determining the clinical course of diagnosed prostate cancer remains a challenge although prognostication is possible for the selection of patients for watchful waiting through active surveillance to management using single to multimodality treatment.

Appropriate treatment based on current evidence for non-metastatic disease is high dose EBRT or brachytherapy or a combination of the two with or without ADT or radical

prostatectomy (Andersson *et al.*, 2012). The best treatment selection employs a risk stratified criteria using several tools which allows for tailored treatment based on extent of disease and the likelihood of recurrence. D'Amico categorisation which has been validated by randomised studies (Hernandez *et al.*, 2007) and previously adopted by Harvard, American urological association(AUA) and European urological association (EUA) ,CAPRA as well as the SloanKettering risk assessment tool for prostate cancer are some of the other most commonly used ones.

The risk assessment tools utilize the pre-treatment PSA level, the Gleason score and the clinical stage in various combinations. Current tools also make use of the percentage positive cores in determining the risk category.

2.2.1. INDOLENT PROSTATE CANCER

Autopsy studies show about one-fifth of men over the age of 50 years have evidence of CAP on histology. Majority of these cases remain clinically insignificant (Hølund, 1980)

Whether indolent prostate cancer is formed at the beginning of the process of carcinogenesis and will remain so throughout its life or an indolent prostate cancer has the ability to develop into a more aggressive one is a matter of debate. One hypothesis is that genetic alterations that initiate carcinogenesis determine the clinical course of cancer. Others hypothesize that genetic alterations acquired during the life of the cancer can alter the clinical cause(Bernards and Weinberg, 2002). In a Swedish study conducted in the 1970s with over 21 years follow-up, prostate cancer specific mortality increased with prolonged follow up especially after 15 years for both cancers diagnosed with on DRE, representing clinically evident disease and those diagnosed following TURP for BPH representing clinically insignificant disease. This suggests that aggressive phenotype is acquired during the life of a cancer that may have started out as an indolent one (Johansson *et al.*, 2004).

For patients with indolent cancers and especially patients who have competing comorbid diseases, observation maybe an appropriate way to manage them.

2.2.2. CLINICALLY RELEVANT PROSTATE CANCER

2.2.2.1. NON-METASTATIC PROSTATE CANCER

Localised prostate cancer presents a good opportunity for curative treatment. The advent of PSA screening has resulted in increased numbers of cancers that are diagnosed while localised(Constantinou and Feneley, 2006), making curative treatment with emphasis on reduced side effects imperative.

Some seemingly localised cancers metastasize within 5 years of definitive treatment of the primary cancer (Hernandez *et al.,* 2007). Even so conservatively managed patients have been found to die from other causes without any morbidity incurred from their cancer (Anderssone*t al.,* 2012). The difficulty scientists currently have is identifying features that predict clinically significant cancers from those that are inconsequential.

Treatment options include EBRT, BRACHY or radical prostatectomy with or without the use of ADT. Failure after treatment often requires further interventions based on whether the recurrence is biochemical only or with evidence of metastatic disease as well as whether disease is castrate resistant or hormone sensitive.

2.2.2.2. METASTATIC PROSTATE CANCER

Currently metastatic prostate cancer is an incurable disease whether diagnosed de novo or following treatment of previously localised disease. Several studies including the STAMPEED and CHAARTED suggest more aggressive treatment especially in de novo metastatic disease using multimodality treatment such as combination of chemotherapy or radiotherapy with ADT improve overall survival (Parker *et al.*, 2018) (Kyriakopoulos *et al.*, 2020).

2.3. DIAGNOSING PROSTATE CANCER

Clinical and radiological diagnosis confirmed by pathological diagnosis is often required. Currently molecular testing has also become important for selecting treatment.

2.3.1. PROSTATE SPECIFIC ANTIGEN

Prostate specific antigen is a glycoprotein produced by the ductal epithelial cells in the prostate gland. It was purified in 1979 by Wang et al even though its discovery is surrounded by controversy (Rao, Motiwala and Karim, 2007). High levels of PSA is detectable in semen and in the serum of men with inflammation or enlargement of the prostate gland. Its levels are high in prostate cancer patients because of absence of basal cells in the prostate and the destruction of ductal architecture leading to its increased leakage into serum (Mizokami *et al.*, 2017).

PSA is by no means prostate specific. It has been identified in pancreatic tissue and salivary gland via immunohistochemistry in women (Elgamal et al., 1996). It is found in serum bound to alpha-1-antichymotrypsin and alpha-2 macroglobulin. Even though more sensitive compared to digital rectal examination in diagnosing prostate cancer, the non-specific nature of PSA test has resulted in several variations being investigated with the aim to improve sensitivity. The cancer detection rate is 3.2% for digital rectal examination, 4.6% for PSA and 5.8% for the 2 methods combined for PSA levels above 4ng/ml (Catalona *et al.*, 1994).

There is no cut off PSA below which the risk of prostate cancer is negligible. Table 1 shows the probability of prostate malignancy for various PSA levels. To improve the sensitivity and positive predictive value of PSA, several variations including Free PSA, complexed PSA, PSA B, pro PSA, PSA velocity and PSA density are a few of the variations of PSA tests that have been investigated.

TABLE 1: PROBABILITY OF CANCER BASED ON PSA

(Catalona *et al.*, 1998)

PSA(ng/ml)	CANCER PROBABLITY
0-2	1%
2-4	15%
4-10	25%
>10	50%

Serum molecular forms of PSA; free, complexed and total PSA have been investigated for use as screening tool for prostate cancer. Low levels of free PSA (FPSA) and high complexed to total PSA were both associated with prostate malignancy. In a study, a median FPSA of 9.2% for normal sized prostate and 15.9% for enlarged prostate was found in patients with prostate cancer compared to 18.8% FPSA in men with BPH (Elgamal*et al.*, 1996). Table 2 shows percentage of FPSA and cancer probability.

TABLE 2: PROBABILITY OF CANCER BASED ON PERCENTAGE FPSA

(Catalona *et al.*, 1998)

%FPSA	CANCER PROBABLITY
1%-10%	56%
10%-15%	28%
15%-20%	20%
20%-25%	16%
>25%	8%

The rate of rise of PSA levels over a period, the PSA velocity (PSAV), has also been identified as being more predictive of a cancer diagnosis. PSA rise rate of more than 0.75ng/ml /per year has been associated with prostate malignancy for PSA of more than 4ng/ml while a value of 0.45ng/ml/per year was more predictive for PSA less than 4ng/ml(Smith, D. S., & Catalona, 1994) although several studies including ERSPC trial, a trial by Thompson and colleagues as well as one by Swedish group, Malmo preventive medicine group, all found PSAV not to correlate on multivariate analysis with prostate cancer diagnosis. (Fitzpatrick, Banu and Oudard, 2009) .

PSA density (PSAD) is quotient of serum PSA level and prostate volume as calculated on trans-rectal ultrasound scan (TRUS). Introduced by Benson et al, it is suggested that it may be more useful in distinguishing BPH from prostate cancer. It is based on the fact that PSA levels are proportional to the volume of malignant prostate cancer cells thus a high PSAD is associated with malignancy (Benson *et al.*, 1992). Jue

et al found PSAD as a useful predictor of malignancy for patients with PSA of 410ng/ml and those with PSA of more than 10ng/ml. PSAD was more useful prior biopsy although it also had some use in those with prior biopsy. They concluded that PSAD may be a useful predictor of malignancy than PSA as PSA levels increase. There was however a 4-8% risk of missing patients with malignancy while sparing 15% of patients from needless biopsy when PSAD cut off of 0.15ng/ml/cc was used (Joshua *et al.*, 2017)

The Prostate Health Index (PHI) test combines free and total PSA and the (-2) pro-PSA isoform (p2PSA). The PHI aims at reducing unnecessary prostate biopsies using a blood test in PSA tested men. In prospective multicentre studies, the PHI improved prediction of clinically significant prostate cancer in men with a PSA of 2 or 4 ng/mL to 10 ng/mL (Mottet *et al.*, 2015)

2.3.2. DIGITAL RECTAL EXAMINATION (DRE)

The prostate gland is related posteriorly to the rectum allowing for its examination via the rectal route. The peripheral zone, the commonest site of prostate cancer, is the part that is examined per the rectum.

DRE examines the lobes to assess for size, induration and nodularity, to determine the presence or absence of the median sulcus, the seminal vesicles for infiltration and fixity to the rectal mucosa. Used alone, DRE has several deficiencies from discordance amongst examiners to low sensitivity, specificity and positive predictive value (Smith, Ph and Catalona, 1995) (Jones *et al.*, 2018).

An analysis of a subset of the patients enrolled in the European Randomized Study of Screening for Prostate Cancer (ERSPC) was analysed to assess the effectiveness of DRE, TRUS and PSA alone and in combination in identifying prostate cancers. The large randomized trial provided numbers that reduced biases and sufficient statistical power to obtain reliable data. Data were obtained from the prevalence screen in the Rotterdam section of ERSPC for a 33-month period starting on July 1, 1994. The screening algorithm used was applied in a prospective fashion as part of the original protocol (Schro *et al.*, 1998).

This study showed an overall detection rate of prostate cancer when PSA level measurement, DRE, and TRUS are used to be 4.5%. Overall, 970 biopsies were used to diagnose 264 cancers (55.8% of all cancers) with a positive predictive value (PPV) of 27%; 82 (17.3%) cancers would have remained undetected by PSA-based screening alone. In this study about 4.8 biopsies found 1 prostate cancer. The PPV is dependent on PSA levels. This is evidenced by the rather low average PPV of 12.8% for PSA levels between 0-3.9ng/ml. The positive predictive value increases to 49.6%, nearly four times that for lower PSA levels, when PSA levels are more than 4ng/ml. This meant two biopsies must be done to find one cancer with PSA of 4 and above (Schro*et al.*, 1998).

Table 3 shows positive predictive value for combination of DRE and PSA as a screening tool.

TABLE 3: POSITIVE PREDICTIVE VALUE OF DRE AND PSA IN A MULTICENTER SCREENING TRIAL(Schro *et al.*, 1998)

DRE	PSA (ng/ml)	PPV
Abnormal	Any	21.4%
Any	<4->10	31.5%-52.9%
Normal PSA	<4	24.4%
Abnormal SA	<4->10	10.0%- 69.1%

2.3.3. RADIOLOGICAL IMAGING

Radiological imaging has no established role currently in the screening of prostate cancer. Multi-parametric prostate MRI (mpMRI) has gained popularity and is the basis for PI-RADS (Prostate Imaging–Reporting and Data System) a formalized reporting system for suspected prostate cancer in treatment naive prostate glands. The mpMRI images which are based on particular property of tissue water include apart from the anatomic T2-weighted images, other sequence such as diffusion-weighted imaging (based on tissue microstructure) and dynamic contrast images (based on blood flow and vessel wall permeability) as well as spectroscopic imaging. DWI currently provides the strongest prediction of prostate cancer volume (Bourne and Panagiotaki, 2016). It has been found to be useful as a modality for triaging prostate cancer patients by reducing the number of patients without clinically significant prostate who would have needed biopsy. By combining mpMRI findings with template prostate mapping (TPM) biopsy, NCCN guidelines recommends mpMRI in patients undergoing active surveillance if anterior and/or when aggressive cancer is suspected, when PSA increases and systematic prostate biopsies are negative.

TRUS guided biopsy has been used over several decades to assist in the taking biopsies for suspected prostate cancer when PSA is high during screening, however the risk of determining nonsignificant cancers is high resulting in overtreatment.

Post diagnosis of prostate cancer, radiological imaging assesses the extent of local disease within the prostate gland, capsular involvement, spread to seminal vesicle and extension to surrounding organs such as the urinary bladder, rectum, regional lymph nodes and presence of distant metastasis. Generally speaking, the role of imaging in prostate in the presence of low PSA, which often corresponds to low and intermediate risk disease, is nearly non-existent.

In high risk cases of prostate cancer, imaging has confirmatory significance. MRI is effective for assessing soft tissue extent of tumour while CT scans can give useful information on tumour extent and bony involvement (Tabatabaei *et al.*, 2011). No statistically significant difference was seen when CT scan and MRI was compared for non-invasive assessment of lymph node in prostate cancer. A sensitivity and specificity

was calculated for CT scan and MRI of 0.42 and 0.8 as well as 0.39 and 0.8 respectively (Heesakkers *et al.*, 2008).

Bone scans using Technetium 99 is often requested when PSA of more than 20ng/ml. Sensitivity increases with increasing PSA levels more than 20ng/ml. In a study that reviewed 23 articles, bone scan detection rate was 2.3% below 10ng/ml compared to16.2% for PSA 20-49.9 and 73% for >100ng/ml.(Abuzallouf, Dayes and Lukka, 2004)

PET scans have gained popularity over the past decade and have seen rapid improvement.

Initial choline scans have given way to sodium fluoride scan which is good at detecting bone involvement to the more recent fluciclovine F18 (axumin) which includes Gallium 68 PET PSMA scan. They have found the most use in biochemical recurrence.

2.3.4 BIOPSY

Histologic diagnosis is necessary for histologic type and Gleason score. For some patients, the diagnosis of prostate cancer may follow review of prostate gland removed via TURP for symptomatic BPH. For majority of patients however, an abnormal DRE or high PSA may result in biopsy often employing a trans-rectal ultrasound guided (TRUS) biopsy. TRUS biopsy has the ability to differentiate the various zones of the prostate gland. Ultra-sonographic changes frequently seen is a hypoechoic region when cancer is present. The peripheral zone (PZ) is echogenic relative to the central zone (CZ). The transition zone (TZ) is echo poor. In healthy adults, TZ is not easily distinguished from CZ.

The percentage volume of each zones changes with increasing age. When taken appropriately in a systematic manner, TRUS biopsy should be representative of the whole prostate gland except the inner gland which rarely harbours cancer (Harvey *et al.*, 2012). Sensitivity of about 70% has been calculated for 4 or more widely spaced biopsies. Sensitivity increases with higher numbers of cores biopsied albeit with an increase in the risk of side effects. A systematic biopsy of both lobes of the prostate gland using the combination of sextant approach suggested by Hodge and his colleagues from Stanford and the peripheral approach resulted in a cancer detection rate

of 96%. Targeting hypoechoic areas alone had a cancer yield of only 56% (Djavan and Margreiter, 2007). An analysis by Eichler et al of 87 studies which included over 20,698 patients reported that schemes of 12 cores that included posteriorly and laterally directed cores struck a balance between detection rate and adverse events (Djavan and Margreiter, 2007). The location and orientation (central or peripheral end) of each core should be separately identified so the pathologist can report the extent and grade of cancer in each core as well as the percentage volume of core involved by tumour, presence of any peri-neural invasion or extracapsular extension. These are useful for prognostication as it allows for calculation of PPC (Gordon *et al.*, 2000).

The use of multi parametric magnetic resonance imaging (mpMRI) guided biopsy that has been employed reduces the risk of biopsy of clinically insignificant cancers with a 4% risk of missing clinically significant prostate cancer. (Hendriks *et al.*, 2018)

2.3.5 GLEASON GRADE AND COMBINED SCORE

Gleason score is a component for risk categorisation. It is a grading system describing morphological changes in the glandular architecture of the prostate gland under light microscopy. The original 1966 system was refined several times and by 1977 a five point system was adopted for use based on the average morphological features. (Shah, 2005) The grading system has since been endorsed by WHO and is known for its prognostic significance in all stages of prostate cancer (Eble, Epstein and Sesterhenn, 2004).

Gleason score can be reported in a variety of ways; primary Gleason grade which describes the most predominant morphological type represented in more than 50% of the sample examined under a light microscope and a secondary Gleason grade which describes the second most common morphologic type, a total Gleason score which is the a sum of 2 scores. Higher sums correlate with higher probability of extracapsular extension, spread to pelvic lymph nodes, and distant metastases. A tertiary score, recently described, is the third highest/worse score pattern. Other ways include a modified Gleason score which takes into account all three scores, primary, secondary and tertiary scores (Rodrigues *et al.*, 2012). The significance of tertiary Gleason score is yet to be ascertained although worse outcomes have been described

when the tertiary Gleason score is 5 in patients with combines Gleason score of 7. If this tertiary pattern occupies more than 5% of cores submitted, it replaces the secondary Gleason score in the combined score (Gordetsky and Epstein, 2016).

Any Gleason grading of 5 has been suggested as conferring poor treatment outcomes. The revised 2014 NCCN guidelines reflects this by upstaging patients with Gleason score of 5 to very high risk disease. Five or more cores with combined Gleason 8-10 are also classified as very high risk group. A study by Sundi et al identified this group of patients, the very high risk group due to a pattern 5 in their Gleason score, had poor surgical outcomes, and may need multimodal treatment to improve outcomes(Sundi *et al.*, 2014).

In a retrospective study by Narang et al, patients treated from 1993-2006 with radiotherapy and ADT, very high risk patients were found to have inferior outcomes of treatment using the revised NCCN risk categorisation. The down side to this study was the use of treatment techniques, doses and ADT that do not reflect current standard of care(Narang *et al.*, 2016).

2.3.6 CLINICAL STAGING

Clinical staging using the best available imaging and clinical examination has improved over the years. American Joint Commission on Cancer (AJCC) staging method is frequently used where tumour extent is designated T, node involvement N and evidence of metastasis M. The staging system has undergone a few changes since 1997. The 2008 staging manual was used in this study and is found in table 4. The Jewett staging uses various combinations of the TNM staging to describe four stage groups. In this system, "A" and "B" describe confined to the prostate. The letter "C" for cancers outside the prostate gland but without lymph nodes spread or spread to other sites. And the letter "D" refers to metastasis to lymph nodes or to other sites but this staging system is historical and rarely used. The clinical stage of the disease is required for risk assessment.

TABLE 4: TNM STAGING

T- TUMOR N-NODE M- METASTASIS

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histologic finding in ≤5% of tissue resected (at time of transurethral resection of the prostate [TURP])
T1b	Tumour incidental histologic finding in >5% of tissue resected (at time of TURP)
T1c	Tumour identified by needle biopsy (because of elevated prostate specific antigen [PSA] level)
T2	Tumour confined within prostate (tumours found in 1 or both lobes by needle biopsy but not palpable on DRE or reliably visible by imaging are classified as T1c)
T2a	Tumour involves one-half of 1 lobe or less
T2b	Tumour involves more than one-half of 1 lobe but not both lobes

T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule (invasion into the prostatic apex, or into—but not beyond—the prostatic capsule is classified as T2
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invading seminal vesicle(s)
T4	Tumour fixed or invades adjacent structures other than seminal vesicles (eg, bladder, levator muscles, and/or pelvic wall)

athologic (pT)

pT2	Organ confined
pT3	Extraprostatic extension
pT3a	Extra-prostatic extension or microscopic invasion of the bladder neck
pT3b	Seminal vesicle invasion

pT4	Tumour is fixed or invades adjacent structures other than the seminal vesicles (eg, bladder, rectum)

There is no pathologic T1 classification.

Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

Regional lymph nodes (N)

Clinical (cN)

NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Pathologic (pN)

pNX	Regional nodes not sampled
pN0	No positive regional nodes

pN1	Metastases in regional nodes(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
If more than 1 site of metastasis is present, use the most advanced category.	

2.3.7 PERCENTAGE POSTIVE CORES (PPC)

This is a more recent addition to factors used for risk categorisation in the management of prostate cancer. Studies by D'Amico et al found percentage positive core calculated as a percentage of the number of cores found to be involved by tumour to the total number of cores sampled to have prognostic significance. Patients with PPC of less than 35% with intermediate risk factors had outcomes that were similar to low risk disease compared to those with PPC of more than 50% whose outcomes were similar to high risk disease. A study of 473 men with intermediate risk CAP men on cox regression multivariate analysis found PPC to have relevant clinical information regarding PSA outcomes while accounting for other established risk groups (D'Amico *et al.*, 2001).

Kestin et al reviewed 160 patients prospectively treated with EBRT to 46 Gy supplemented by trans-peritoneal interstitial iridium high dose rate implant from 19911999 and found PPC and Gleason score on univariate analysis to be significant for clinical failure. PPC was significant for biochemical and clinical failure whether analysed for subgroups or as a continuous variable. Patients with PPC scores of 33% or lower have the best biochemical control rates of 83% and 5 year clinical failure rate of 7% only compared to biochemical control rate of 57% and 5 year clinical failure rate of 25% when PPC is more than 67% (kestin LL et al., 2002).

2.4 RISK CATEGORISATION AND PROSTATE CANCER MANAGEMENT

2.4.1. TRENDS IN PROSTATE CANCER PROGNOSTICATION

Prostate cancer is a heterogeneous disease ranging from indolent disease which will have no clinical significance for a patient even without treatment to one which is inherently aggressive rapidly becoming fatal after developing resistance to all available treatment options. The decision to offer treatment is best made using validated risk assessment tools that allow for treatment that is tailored to the individual patient. The risk categorisation is useful for reporting outcomes of studies and for clinical trial design. It also provides a common nomenclature for easy interaction and discussions. (Rodrigues *et al.*, 2012).

Risk categorisation in prostate cancer management has a long history. Studies by D'Amico and his colleagues resulted in the initial risk categorisation which was adopted by NCCN following validation by several studies. This risk categorisation tool used pre-treatment PSA levels, Gleason score and clinical stage. Patients were grouped as low risk (LR), intermediate risk (IR) or high risk (HR). Several groups have different risk categorisation criteria and are represented in table 5.

The inadequacies of this initial categorisation was evidenced by the differences in clinical outcomes even within the same risk groups. Further studies by D'Amico et al found percentage positive core calculated as a ratio of the number of cores with tumour to total number of core as useful for the subdivision of intermediate risk patients to low and high risk based. Percentage positive score of below 33% was associated with treatment outcomes similar to low risk disease while those 50% and above has outcomes similar to high risk disease (ref) The new NCCN risk categorisation introduced in 2017 recognises the importance of sub-categorisation of intermediate risk into favourable and unfavourable groups as well as the separation of high risk and very high risk groups. The University of California, San Francisco Cancer of the Prostate Risk Assessment (UCSF-CAPRA) score considers the percentage of positive prostate biopsies (<34% or ≥34%) and patient age (<50 or ≥50 y) in addition to three previous risk factors to improve prediction of risk.

An analysis by Lughezzani et al found the CAPRA score outperforms the other models, D'Amico risk stratification scheme and the Stephenson nomogram in a European cohort of RP patients when decision curve analysis and calibration were used as benchmarks(Lughezzani *et al.*, 2010). In an analysis for the prediction of biochemical recurrence a similar outcome was found by Tamblyn et al. compared the performance of the CAPRA score and the Kattan and Stephenson nomograms in an Australian cohort; for the prediction of biochemical recurrence, with better c-indices for the CAPRA score and the Stephenson nomogram(Tamblyn *et al.*, 2011).

TABLE 5: Organizational pre-treatment prostate cancer risk stratification systems

(Rodrigues *et al.*, 2012)

Institution/organization	**Low risk**	**Intermediate risk**	**High risk**
Harvard (D'Amico) AUA EAU	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10–20 not low-risk	≥T2c or PSA >20 or GS 8–10
GUROC NICE	T1-T2a and GS ≤6 and PSA ≤10	T1-T2 and/or Gleason ≤7 and/or PSA ≤20 not low-risk	≥T3a or PSA >20 or GS 8–10
CAPSURE	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10–20 not low-risk	T3-4 or PSA >20 or GS 8–10
NCCN	T1-T2a and GS 2–6 and PSA ≤10 not very lowrisk AND very-low risk category: T1c and GS ≤6 and PSA <10 and Fewer than 3 biopsy cores positive and ≤50% cancer in each core	T2b or T2c and/or GS =7 and/or PSA >10–20 not low-risk	T3a or PSA >20 or GS 8–10 not very high risk AND very high-risk category: T3b-4
ESMO	T1-T2a and GS ≤6 and PSA <10	Not high risk and not low risk (the remainder)	T3-4 or PSA >20 or GS 8–10

AUA-American urological association, EUA-European urological association, European society of clinical oncology, NCCN- national comprehensive cancer network, CAPSURE-university of California San Francisco department of urology

2.4.2 CLINICO-GENOMIC RISK CLASSIFICATION OF PROSTATE CANCER

The ability to deliver treatment tailored to the individual patient has numerous advantages. It requires selecting patients who are predetermined based on specific tumour genetic characteristics (biomarkers) that predict response to and outcomes of treatment.

Genetic testing of patients allows not only a means for risk prediction for development of cancers and the prognosis of the cancer but also provides an assessment of an individual's polymorphisms in the key enzymes involved in metabolizing cancer drugs (pharmacogenomics).

Risk stratification enables for groups with similar characteristics to be classified and best evidence based management options proffered for them. It is also true that each risk category may be highly heterogeneous resulting in treatment outcomes that may differ, sometimes significantly, from each other. The incorporation of genomic factors in the current risk stratification holds the promise to provide a better prognostication method of treatment outcomes. The same has the ability to help cull out patients with poor prognosis for intensified treatment, as a cohort for studies into new therapies or for de-escalated of treatment.

Several molecular panels have been developed over the years to further improve with prognostication of prostate cancer as has been used in cancers of different sites including breast cancer. Table 6 lists some currently available molecular panels and their use.

The integration of these tests into commonly used risk stratification groups is however lacking. Decipher is a validated genomic test by Dechipher Biosciences San Diego captures 22 RNA markers that predicts treatment outcomes (metastasis and cancer specific mortality) after radical prostatectomy(Dalela *et al.*, 2016).

Spratt and his colleagues in a multi-institutional study, used the 22 gene Decipher scores to identify, characterize and validate a clinic-genomic risk grouping system in (n=991) retrospectively selected group of patients. They then performed reclassification analysis in two additional cohorts (n=5973) of patients. They developed a six tier categorisation in the training cohort which was eventually amalgamated into a three tier categorisation. After 8 years of follow- up, the c-indices of the clinico-genomic classification were improved over the NCCN and CAPRA methods of classification. C-indices for the

clinical-genomic risk grouping system (0.84; 95% CI, 0.61 to 0.93) were improved over NCCN (0.73; 95% CI, 0.60 to 0.86) and Cancer of the Prostate Risk Assessment (0.74; 95% CI, 0.65 to 0.84), and 30% of patients using NCCN low/intermediate/high would be reclassified by the new three-tier system. If the six tier system was used, 67% of patients would be reclassified from NCCN six-tier (very-low– to very-high–risk) by the new six-tier system.

A Study by Nguyen et al found decipher was able to predict metastasis and prostate cancer specific mortality at 6 years in intermediate and high risk patients treated radiotherapy following biopsy for CAP(Nguyen *et al.*, 2017).

Table 6 below shows various molecular tests and their use in prostate cancer management.

TABLE 6: MOLECULAR PANELS FOR PROGNOSIS AND RISK STRATIFICATION

NaDiA® ProsVue™	Beckman Coulter	Blood	Total serum PSA	Management post-RP
Decipher™	Dechipher Biosciences	RP	Transcriptomic microarray profiling of 22 gene markers	Management post-RP

Oncotype DX®	Genomic Health	Prostate tissue	Quantitative PCR for 12 PCa-related genes and 5 housekeeping controls	Active surveillance or treatment initiation
Prolaris®	Myriad Genetics	Prostate tissue	Quantitative PCR for 31 cell cyclerelated genes and 15 housekeeping controls	Active surveillance or treatment initiation
ProMark®	Metamark	Prostate tissue	*In situ* measurement of 8 protein biomarkers by automated image analysis	Active surveillance or treatment initiation

2.5. CURRENT MANAGEMENT RECOMMENDATIONS FOR HIGH RISK PROSTATE CANCER

Post biopsy and diagnosis of prostate cancer, risk stratification allows for selection of treatment based on clinical and more recently molecular stratification of patients.

The choice of investigations and therapy is tailored to patients risk group. Table 7 shows NCCN recommendations for workup based on patient risk group.

TABLE 7: RISK STRATIFICATION AND STAGE WORKUP (Source: NCCN clinical practice guidelines in oncology: Prostate cancer version 2, 2018)

Risk Group	Clinical/Pathologic Features	Imaging	Molecular Testing of Tumor	Genetic Testing of Tumor
Very low	All of the following: • T1c • Gleason score ≤6/grade group 1 • PSA <10ng/mL • <3 prostate biopsy fragments/ cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g	Not indicated	Not indicated	Consider if there's a strong family history
Low	All of the following: • T1-T2a • Gleason score ≤6/grade group 1 • PSA <10ng/mL	Not indicated	Consider if life expectancy is ≥10 years	Consider if there's a strong family history
Intermediate-favorable	Any of the following: • T2b-T2c • Gleason score 3+4=7/grade group 2 • PSA 10-20 ng/mL PLUS percentage of positive biopsy cores <50%	• Bone imaging: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Consider if life expectancy is ≥10 years	Consider if there's a strong family history
Intermediate-unfavorable	Any of the following: • T2b-T2c • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 • PSA 10-20 ng/mL	• Bone imaging: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider if there's a strong family history
High	Any of the following: • T3a • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 • PSA >20 ng/mL	• Bone imaging: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider
Very high	Any of the following: • T3b-T4 • Primary Gleason pattern 5 • >4 cores with Gleason core 8-10/ grade group 4 or 5	• Bone imaging: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider
Regional	Any T, N1, M0	Already performed	Consider tumor testing for: • homologous recombination gene mutations • MSI/dMMR	Consider
Metastatic	Any T, any N, M1	Already performed	Consider tumor testing for: • homologous recombination gene mutations • MSI/dMMR	Consider

Several developments including adoption of newer radiotherapy delivery techniques including three dimensional conformal radiotherapy, intensity modulated radiotherapy, image

guided radiotherapy and brachytherapy have improved the accuracy of delivery, allowing for safe dose escalation. This is in line with evidence of dose response relationship between prostate cancer and treatment outcomes to doses just under 90Gy. Treatment with curative intent is premised on evidence of organ confined disease to doses just above. Ultrahigh PSA levels in patients with organ confined disease are often under represented or excluded from randomised trials, unfortunately, this group commonly includes many patients of African descent.

In a large non-randomised study of high risk organ confined patients with ultrahigh PSA, radiotherapy and radical prostatectomy were found to be associated with prolonged survival. In this study, Tai P.M et al, reviewed the provincial registry and compared treatment outcomes for two groups of patients; those with PSA 20-49.9 and those with PSA equal or more than 50 treated between 1990 and 2001. Of the 1534 patients who had PSA of ≥20 ng/ml, 995 patients with PSA 20 to 49.9 ng/ml, 85 had radical prostatectomy (RP), and their 5- and 10-year causespecific survivals (CSS) were 95% and 84%, respectively. The 497 patients treated with radiotherapy (RT) had 5- and 10-year CSS of 92% and 71%. For the 332 patients with PSA 50–99.9 ng/ml, RT was associated with 5- and 10-year CSS of 81% and 55%. For the 207 patients with PSA of ≥100 ng/ml, RT was associated with 5- and 10-year CSS of 80% and 54 % (Davies *et al.*, 2013).This study suggests outcomes that are similar irrespective of pretreatment PSA level and the need for treating these patients with curative intent. The outcomes for this group of patients is expected to improve as technology advances resulting in accurate pre-treatment assessment of the extent of disease as well as improved radiotherapy delivery and surgical treatment (robotic surgery and improved skills).

A Swedish study conducted between January 1996 and December 2010 with prostate cancer and other cause mortality as the primary end point, data from the national prostate cancer register found that in the patients with very high risk disease which included patients with PSA 50ng/ml, ADT alone was associated with triple the hazard of death compared to radically treated cohort for both matched and unmatched patients(Sooriakumaran *et al.*, 2017).

In another Swedish study that investigated influence of curative treatment on cancer specific survival, men who met the inclusion criteria; all prostate cancer patients 75 years or less with localised disease without evidence of distant metastasis and PSA of between 20ng/ml100ng/ml, the cumulative 10-year prostate cancer-specific mortality was 36% for patients treated with palliative intent compared to 13% for those who received curative treatment. For the 74% patients who had curative treatment with PSA levels from 20 to 50

ng/mL at diagnosis, the hazard ratio for death from prostate cancer was 0.23 (95% confidence interval 0.19–0.27) compared with those given palliative treatment which was 0.22 (95% confidence interval 0.17– 0.30) for patients with PSA levels from 51 to 100 ng/ml after adjusting for age, co-morbidity, T category, PSA level and Gleason score (Ladjevardi *et al.*, 2012)

The SPCG-7/SFUO-3 trial conducted in Norway, Sweden and Denmark was an open randomised phase III trial included patients with PSA of less than 70ng/ml. This study which looked at the use of endocrine therapy with or without the use of radiotherapy in the management of locally advanced prostate cancer showed a 50 % reduction in prostate cancer specific mortality with acceptable side effects. After a median follow-up of 6 years, the cumulative incidence at 10 years for prostate-cancer-specific mortality was 23·9% in the endocrine alone group and 11·9% in the endocrine plus radiotherapy group (difference 12·0%, 95% CI 4·9–19), for a relative risk of 0·44 (0·30–0·66).

At 10 years, the cumulative incidence for overall mortality was 39·4% in the endocrine alone group and 29·6% in the endocrine plus radiotherapy group (difference 9·8%, 0·8–18·8%), for a relative risk of 0·68 (0·52–0·89). Cumulative incidence at 10 years for PSA recurrence was substantially higher in men in the endocrine-alone group (74·7% *vs* 25·9%, p<0·0001; HR 0·16; 0·12–0·20). After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus radiotherapy group (Widmark *et al.*, 2009).

A similar trial conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group whose inclusion criteria was later expanded to include patients with PSA of more than 20ng/ml also found the addition of RT to ADT improved overall survival at 7 years (74%, 95% CI 70–78 *vs* 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033) (Dignam *et al.*, 2019).

There is overwhelming evidence both from prospective and retrospective studies on the benefit of treating patients with localised but advanced prostate cancer with ultrahigh PSA with curative intent.

2.6. CLINICAL OUTCOMES OF TREATMENT FOR PROSTATE CANCER

Cancer of the prostate has prolonged survival even for metastatic disease. This situation presents some difficulty when conducting studies that assess interventions as long follow-up (10-15yrs) is required to determine an impact.

The most important treatment outcome end point for cancer treatment is overall survival. Disease free survival though an important endpoint is considered a surrogate. Quality of life, tumour response and tumour marker levels are endpoints applied in the non-curative setting.

For prostate cancer where survival outcomes may occur several years after intervention (or no intervention), biochemical failure becomes an important surrogate as a good predictor of survival outcomes.

2.6.1 BIOCHEMICAL FAILURE DEFINITION

Acquiring a precise definition for biochemical failure is essential to allow for easy comparism of clinical trial results as well as for patient stratification for interventions and for selection of therapy based on that risk stratification. Determining Biochemical failure following curative treatment for localised prostate cancer is a difficult task mainly because of several definitions based on initial treatment received. Post prostatectomy, up to 53 different definitions were found during a search. The AUA definition the most used. It defines post prostatectomy biochemical failure as PSA of more than 0.2ng/ml measured 6-13 weeks post prostatectomy followed by another test as confirmatory. Diagnosis of biochemical failure post radiotherapy and ADT yielded 99 different definitions. The most common employed by majority was the ASTRO definition (Paller and Antonarakis, 2013).

The ASTRO definition of biochemical failure for men who received EBRT only is defined as three consecutive PSA rises after a nadir is achieved. The proposed date of incidence of recurrence is halfway between the date of the nadir PSA and the date of first PSA increases or any rise great enough to provoke initiation of treatment. This definition requires backdating which is prone to scientific errors. The Phoenix definition is he PSA nadir+2 points and is more predictive of treatment outcomes even

for patients treated with ADT and BRACHY. In simple terms it is defined as any increase in PSA of at least 2ng/ml from the lowest PSA reading.

A study conducted between 1987 and 2001 that compared the two definitions found the Phoenix definition diagnosed fewer patients with biochemical failure however is was more robust in determining treatment outcomes after 71 months of follow-up. The Phoenix definition was more than a100 times (307 compared to 26) more accurate at predicting prostate cancer death and nearly 3 times (173 compared to 63) more predictive of distant metastasis compared to the ASTRO definition making the Phoenix definition more robust (Abramowitz *et al.*, 2007). By having above characteristics, time to biochemical failure serves as a good surrogate for assessment of treatment outcomes.

2.6.2. THE ROLE OF SURROGATE OUTCOMES IN THE MANAGEMENT OF PROSTATE CANCER

Surrogates endpoints have become important as they help determine the effectiveness of an intervention earlier than traditional endpoint such as overall survival. It is important that a surrogate endpoint which is a set of clinical signs or biochemical measurements used as a substitute for a clinical endpoint is differentiated from prognostic factors which are physical signs or measurements that determine the outcome of a disease process (Ladjevardi *et al.*, 2012). Not all prognostic factors make good surrogates.

Biochemical failure and time to biochemical failure have been investigated and adopted as surrogate endpoints in assessing clinical outcomes for prostate cancer management. In the NRG/RTOG 9202 study of 1520 patients, interval free time to biochemical failure (IBF) satisfied surrogacy criteria for prostate cancer specific survival (PCS) and overall survival (OS) in patients with locally advanced prostate cancer treated with curative intent using long course or short course ADT in combination with radiotherapy and thus provides an opportunity for determining outcomes of interventions earlier than traditionally possible (Dignam *et al.*, 2019).

CHAPTER THREE

3.0 METHODOLOGY

3.1 STUDY DESIGN

This is a retrospective cohort study that was both descriptive and inferential in design. It reviewed the charts of prostate cancer patients seen from January 2010-December 2014 to collect demographic, tumour and treatment factors and to evaluate biochemical and overall survival outcomes for high risk non-metastatic prostate cancer patients categorised in a PSA based manner and treated with curative radiotherapy at the National Centre for Radiotherapy and Nuclear Medicine. They were followed up till December 2020.

3.2 STUDY SITES

The National Radiotherapy Oncology and Nuclear Medicine Centre formerly the National Centre for Radiotherapy and Nuclear Medicine of the Korle Bu Teaching hospital is the larger of two national cancer treating centres in Ghana. It was established in 1997 and based on its location in Accra, it caters for the southern part of the country which has an estimated population of 10 million according to the 2010 population and housing census. The other centre is in the Ashanti region located in the middle belt of the country attracts patients from the northern part of the country. These are mainly based on proximity to the centres. Majority of the patients are referred from the Genito-urinary department of the same hospital and other hospitals including the Accra Regional Hospital, 37 Military Hospital, Tema General Hospital and University of Ghana Hospital.

Patients from neighbouring countries, Francophone and Anglophone West Africa without access to radiotherapy and oncology expertise tend to seek cancer treatment from the centre.

The centre reviews about 1600-2000 new cases every year and conducts follow-up clinics. Services include radiation and medical oncology for adult solid tumours as well as radiotherapy services for paediatric and haematological malignancies. A cancer registry office which collects cancer data for Greater Accra region has recently become operational with intention to expand into a population based registry. .

Until 2007 when a treatment planning system was acquired, prostate cancer patients were treated with 2-dimensional technique which relies on bony landmarks with the aid of a

simulator based on physician interpretation of CT imaging results. Treatment was delivered via a cobalt-60 machine. Over the past 3 years, since July 2019, a 6 mega volt volumetric modulated arc therapy (VMAT) LINAC machine and a modern cobalt 60 machine are available for treatment. Both 3DCRT and IMRT techniques are employed for the delivery of treatment to most cancer sites. Doses between 68-78Gy are considered curative for EBRT only treatment for prostate cancer.

Permanent interstitial implant LDR brachytherapy is the other available option for treating prostate cancer. I-125 seeds are inserted trans-perineal under ultrasound guidance using intra-operative preplanning and dynamic dose calculation method. Dose calculations are based on the AAPM TG 43 formalism. Doses of up to 160Gy are considered adequate for single modality treatment in low and intermediate risk prostate cancer while doses of 130 is adequate for partial implant brachytherapy with EBRT doses between 40-50Gy

3.3 SAMPLE POPULATION

Using judgement sampling, all men between the ages of 40-85 years with histologically confirmed non-metastatic (based on bone scan pelvic CT scan and MRI findings) adenocarcinoma of the prostate and categorized as high risk based on the D'Amico/ NCCN 2010 stratification with pretreatment PSA of 20ng/ml -200ng/ml who received curative radiotherapy and followed up at the NRONMC of the KBTH were included for the analysis of the study.

TOTAL ENUMERATION

The number of patients seen at the center over the period from January 2010 to December 2014 were described while those who fit the inclusion criteria with available medical records were studied for biochemical and overall survival outcomes till December 2020.

3.3.1 INCLUSION CRITERIA

All males with non-metastatic disease and PSA of more than or equal to 20ng/ml but less than or equal to 200ng/ml treated with curative intent using radiotherapy (EBRT only or EBRT+ BRACHY) with and without ADT.

3.3.2 EXCLUSION CRITERIA

All men with metastatic prostate cancer.

Prostate cancer patients treated with palliative intent

All high risk patients with PSA more than 200ng/ml

Post prostatectomy patients receiving adjuvant or salvage radiotherapy

All high risk prostate cancer patients treated with brachytherapy only

3.4 DATA COLLECTION AND MEASUREMENT

3.4.1 DATA COLLECTION

The primary source of data was from paper-based patients records. Information relevant to the study for all prostate cancer patients seen from 2010-2014 was gleaned by the meticulous review of all data captured by the treating physician. A research assistant who is a trained radiographer was responsible for data collection. I supervised the exercise and cleaned up the data.

Data on demographic and tumour factors were from patient's notes and included age, occupation, date of diagnosis, pre- treatment PSA. All patients were staged using the 2008 AJCCC staging guideline with the aid digital rectal examination, CT scan, MRI and technetium bone scan where indicated. Descriptive statistics were derived and described for all prostate cancer patients seen over the period.

Patients were risk categorised based on the D'Amico/NCCN classification with low risk as PSA<10 and Gleason <7 and T1-T2A. Intermediate risk was any patient with PSA between 10 and 20, or Gleason 7 or T2B-T2C and high risk as any patient with PSA> 20 or Gleason score of 8-10 and T3-T4 disease. Descriptive statistics were conducted on them.

The core group analysed were the patient group with prostate cancer PSA 20ng/ml200ng/ml treated with radiation therapy to delivered doses in excess of 6800cGy. They were to be divided into 3 groups based on their pre-treatment PSA levels as follows;

Group A were patients with initial PSA of 20-49.9 ng/ml

Group B were patients with PSA of 50-99.9ng/ml

Group C were patients with PSA of 100-200ng/ml

For the curative treatment of prostate cancer, 3D conformal radiotherapy was employed. CT scan captured images of the pelvis for tumour delineation to define the clinical target volume (CTV) which includes the prostate gland and the proximal 1cm of the seminal vesicle, expanded by a set of predefined linear expansions to develop a planning target volume (PTV), 0.8-1cm margin circumferentially with the posterior margin set to 0.6-0.8cm. This allows for physiologic movement and set up errors

Organs at risk within the treated area (rectum, bladder, femoral head and small bowel) was also contoured followed by the arrangement of radiation beams which are optimised to deliver tumoricidal doses of radiation to the prostate gland and the lowest possible doses to the organs at risk via forward planning. A dose range of 68-76Gy delivered dose to 95% isodose line was considered adequate.

Some patients were prescribed and received regional pelvic nodal irradiation based on the risk of lymph node involvement of >15% or more. This was calculated using roach's formula and was at the discretion of the treating physician.

Roach formula-{2/3 X PSA + (GS-6) X10}

Partial implant brachytherapy with targeted D90 of 130Gy (based on AAPM task group 43 formalism) supplemented by EBRT also delivered by 3DCRT to 45Gy was the alternative treatment. The choice of treatment was at the discretion of the physician and affordability. Prostate brachytherapy using iodine 125 is more expensive than EBRT only treatment

The duration of ADT used as part of curative treatment was assessed for all patients with available data.

3.4.2 OUTCOME MEASURES (FOLLOW UP)

All patients who fit the inclusion criteria were intended for follow up with PSA every three months for the first year post treatment and 6 monthly after that. At five years, patients were followed up yearly with PSA. Imaging was requested based on patient reported symptoms using CT scans, MRI scans and bone sans as required. Biochemical and mortality outcomes for patients were noted from patient's medical records. Where patients were not followed up at the National radiotherapy Oncology and Nuclear medicine Centre (NROMC), they were called via telephone to ascertain their status and to ask about biochemical outcomes if followed up elsewhere usually by genito-urinary surgeon (GU surgeons) or primary care physicians. Patients were then encouraged to attend the clinic at NRONMC for a final review with PSA within January 2021 as the last date for assessment as 31st December 2020 was the date of final review. A few patients who were not followed up were also encouraged to attend the follow up clinic where biochemical outcomes were estimated from PSA results presented.

For patients whose record of death was unavailable in their medical records, a call to the next of kin was made and date of death determined. Cause of death was not readily available for majority making cause specific survival analysis unfeasible.

3.5 DATA HANDLING

Data collected for the study was handled in the following way:

1. Patients' identification was recorded using their folder numbers.
2. Variables gleaned from the database was be entered into a password secured computer owned by the principal investigator.
3. Back up information was be stored on hard drive.
4. Registry records will be retained for 3 years after the completion of the study.
5. All study related documents will be made available for monitoring, audit and inspection by IRB, government regulatory bodies, and any quality assurance body

3.6 STATISTICAL ANALYSIS

Demographic, tumour and treatment factors were put in an excel document from where descriptive statistics were outlined using tables, graphs and central measures. Windows 2019 was the operating system of choice.

Biochemical and overall survival outcomes derived from data recorded by reviewing physician such as nadir PSA date, the date when the lowest PSA was recorded in patient's records, date of biochemical failure determined to be date when nadir PSA+2 was recorded, time to biochemical failure calculated from the date of completion of definitive radiotherapy to date of nadir+2 and overall survival calculated from date of diagnosis to date of last contact or death were calculated or the 31st of December 2020 (late date of follow-up) , date of death as stated in the folder or stated by next of kin . These were used for time to event analysis on SPSS version 25.

Biochemical failure rates, time to biochemical failure and biochemical failure free survival also known in some literature as biochemical recurrence free survival analysis were estimated using Kaplan Meier estimates and compared for all groups previously described using log rank tests. Five and ten year overall survival were estimated and compared in a similar manner.

Univariate analysis was with Kruskal Wallis test of means for nonparametric data while Cox regression model was used for multivariate analysis of factors predictive of biochemical and overall survival. Factors included age, T stage, initial PSA, time to nadir, nadir PSA value, and duration of ADT use, radiotherapy dose, Gleason score and time to biochemical failure.

The biochemical failure free survival and overall survival for patients based on primary Gleason grade and combined Gleason score were estimated with Kaplan Meier curves and compared with log rank test.

3.7 DISSEMINATION OF RESULTS

The result of the study is to be presented as part of requirements for the Ghana College of Physicians and Surgeons fellowship training. Results will also be published in a peer reviewed journal.

3.8 ETHICAL APPROVAL PROCESS

Ethical Approval – Study was conducted after ethical clearance has been granted by the KBTH Ethical Review Board. Letter in appendix. Due to the retrospective nature of the study, informed patient consent was not sought. Patients who were called to ascertain their status at the end of the study period were informed about the study. All study subjects were anonymized and identified by hospital folder number and data collected securely saved in a password accessible laptop. Appendix 2 shows scientific review and ethical clearance.

CHAPTER 4

4.0 RESULTS

4.1 RESULTS FOR ALL PROSTATE CANCER CASES

The data of patients seen over a 5-year period, from January 2010 to December 2014 was collected. A core group who received curative treatment for high risk prostate cancer based on their PSA were followed up until 31st December 2020 for time to event analysis; biochemical failure and overall survival outcomes. A total of 584 patients were seen with a diagnosis of prostate cancer. Data of 486 patients were successfully retrieved and analysed albeit with some missing information. Appendix 1 shows the data collection tool for the study. Figure 2 is a patient selection chart that describes the patients seen, the risk categories and treatment received.

DEMOGRAPHY

AGE DISTRIBUTION

Patients' ages ranged from a minimum of 44 years to a maximum of 85 years with a median age at diagnosis of 67 years. Table 8 shows central measures of age with mean, median and modal ages for all patients reviewed. Fig 3 is the age histogram.

TUMOR CHARECTERISTICS

HISTOLOGICAL TYPES

Report on histological types of cancer was available for 450 of the 486 patients seen. This represents 92.2% of the total number of patients who had records available for the study period. There was no histological diagnosis for 34 patients, 32 of whom were metastatic at presentation. They all presented with very elevated PSA and radiological evidence of distant metastatic disease. Two could not be risk categorised. Adenocarcinomas was the commonest histological type representing 99.6% of histological diagnosis. One of two patient each had transitional cell carcinoma and small cell carcinoma of the prostate.

HISTOLOGICAL GRADE

The Gleason grade represented the degree of differentiation of the tumour. Only one of 448 patients diagnosed histologically as adenocarcinoma did not have their combined Gleason score recorded. The individual primary and secondary Gleason grade patterns were available for 367 of 448 representing 82% of the cohort.

The modal primary Gleason grade was 3. A primary Gleason grade of 5 was recorded for 34 high risk patients with localised disease, 13 received curative radiotherapy treatment.

Other pathological features that portend bad prognosis including percentage positive cores, tertiary Gleason score and percentage volume of core involved by tumour was not consistently recorded and was therefore not used for this analysis

FIG 2: PATIENT SELECTION CHART

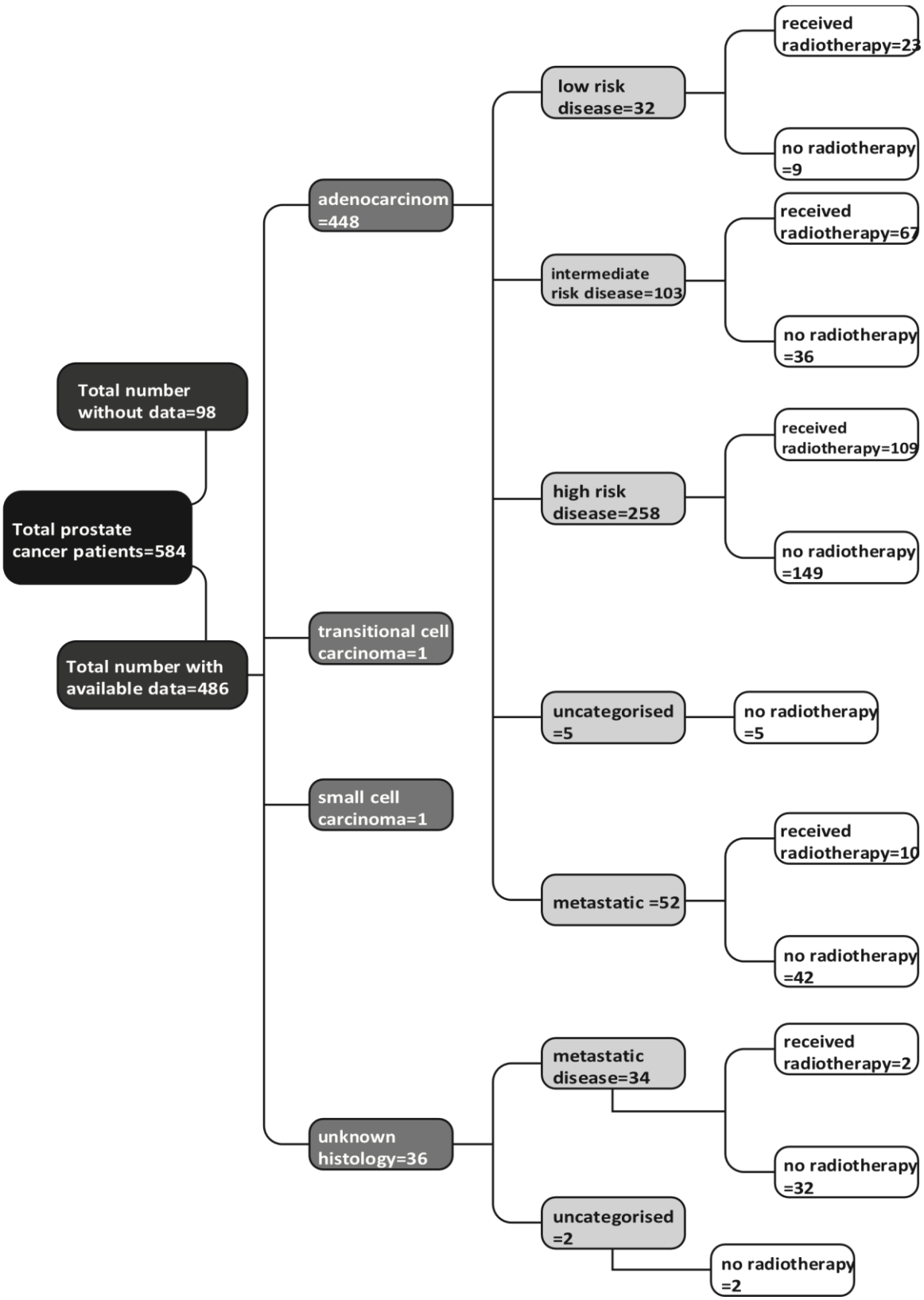


TABLE 8: AGE (MEDIAN, MEAN AND MODE)

Age at Initial Rx	
Mean	66
Median	67
Mode	71
Standard Deviation	7.592020578
Minimum	44
Maximum	85
Count	486

FIGURE 3: AGE DISTRIBUTION HISTOGRAM

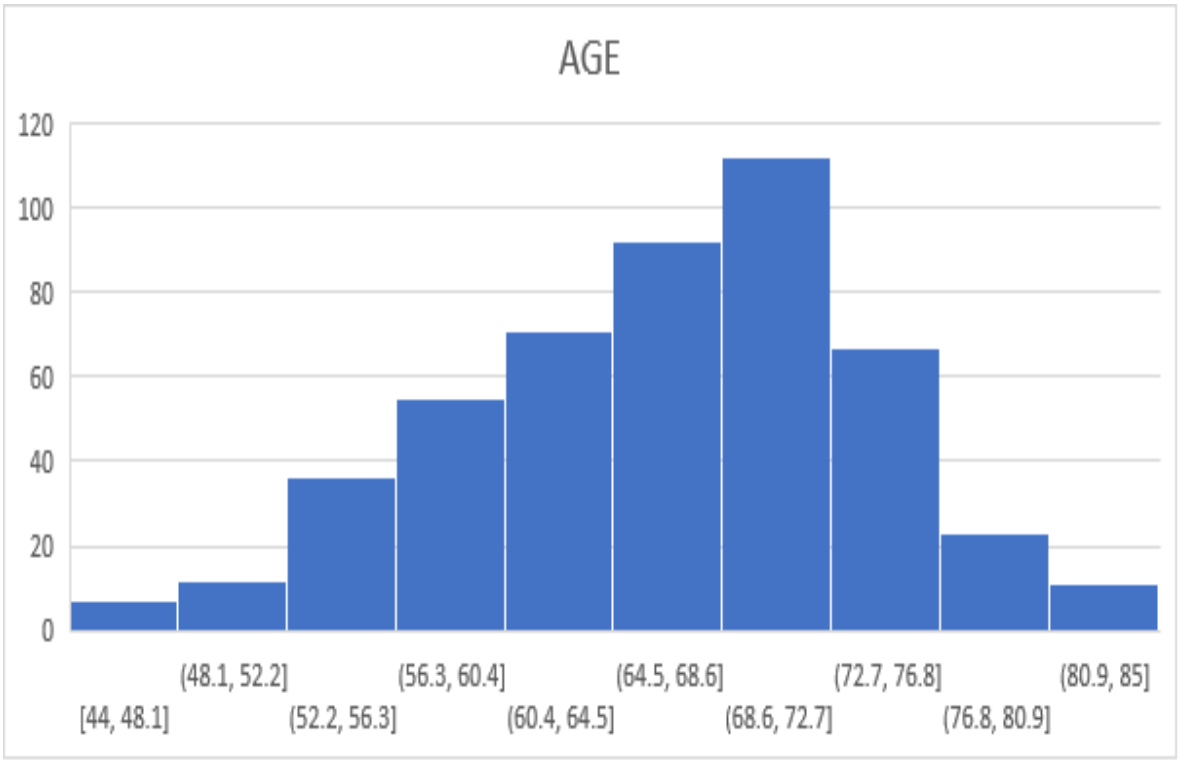


TABLE 9: DISTRIBUTION OF PRIMARY GLEASON GRADE IN PATIENTS WITH ADENOCARCINOMA

Primary Gleason grade	*Count*	*%age*
2	13	4%
3	186	51%
4	129	35%
5	39	11%
Count	367	100%

TABLE 10: COMBINED GLEASON SCORE FOR ADENOCARCINOMA HISTOLOGY

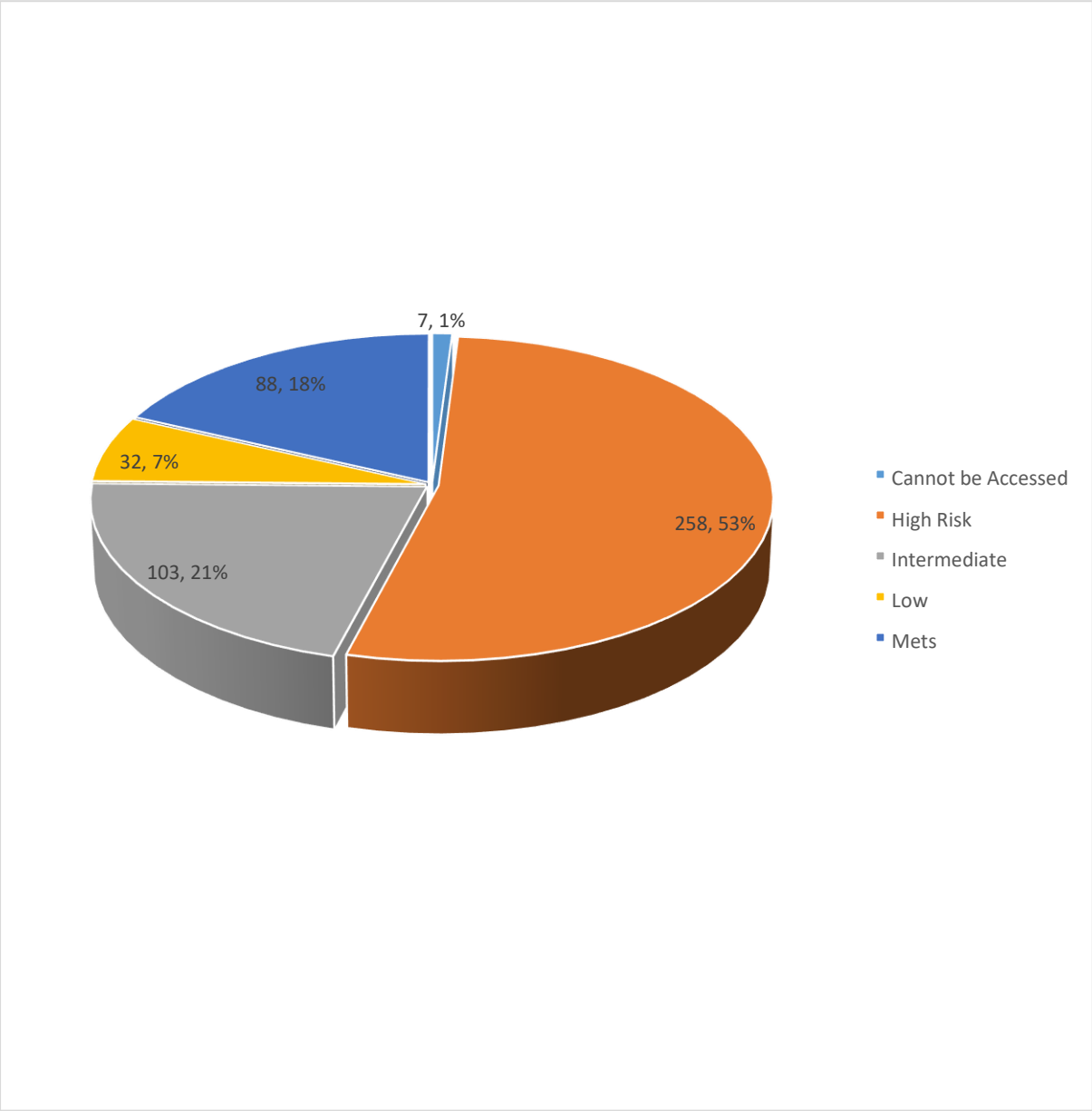
Gleason score	Count of Combined Gleason Score	Percentage %
4-6	160	35.79
7	146	32.66%
8-10	141	31.54%
Grand Total	447	99.99%

RISK GROUP DISTRIBUTION

A total of 32 patients forming about 7% of the population studied had low risk disease, 103 patients had intermediate risk disease making 21% while 258 representing 53% were categorised as high risk. The percentage of patients who had metastatic disease at presentation

was 18.0%. The information available was inadequate for the risk categorisation of 5 histologically diagnosed and 2 who had no histopathology diagnosis. This represents 1% of the patient population studied as shown in figure 4.

FIGURE 4: RISK CATEGORISATION FOR ALL PATIENTS



PSA LEVELS AT PRESENTATION.

The highest PSA reading prior to initiation of treatment was recorded for all patients. The median was 31.9ng/ml with a range of 0.87-23046 ng/ml. The central measure statistics for PSA of the various risk categories are represented in table 11 while figure 4 shows a box plot of same.

FIGURE 5: BOX PLOT OF PRE-TREATMENT PSA

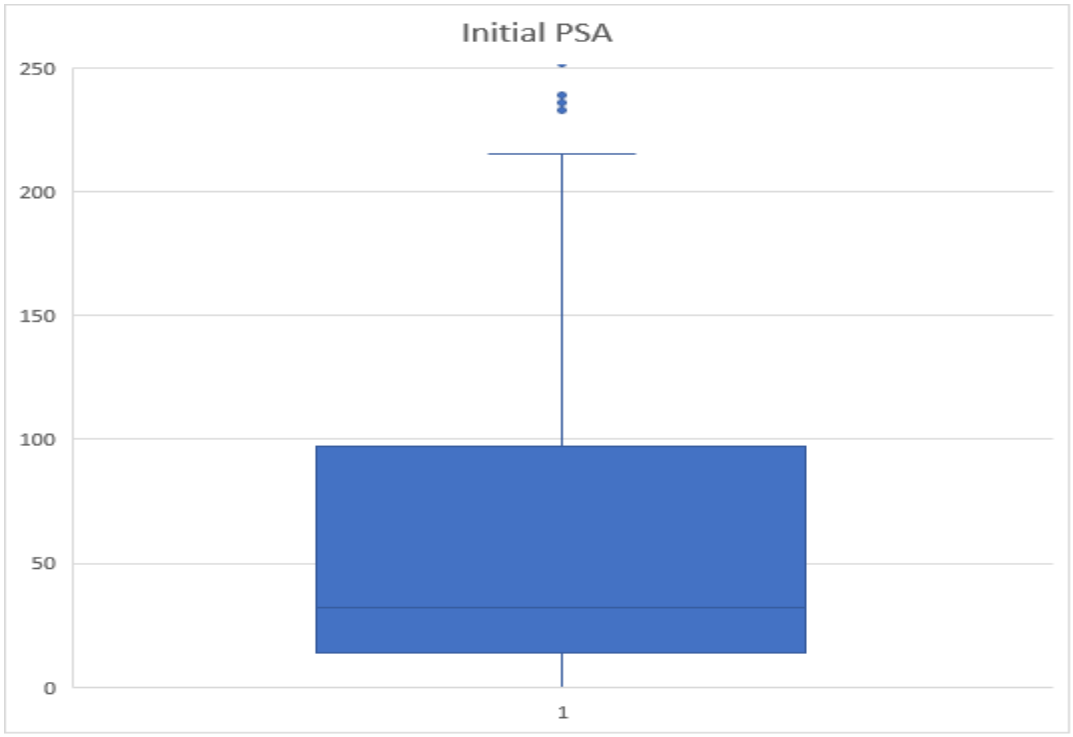


TABLE 11: PSA STATISTICS FOR ALL PATIENTS SEEN

STATISTIC	ALL PATIENTS	LOW RISK	INTERMEDIATE RISK	HIGH RISK	METASTASIS
Mean (PSA)	312.40	6.92	12.90	319.38	990.8
Median (PSA)	31.90	7.06	12.35	49.25	141.64
Mode (PSA)	100	5.20	18.00	100	
Standard Deviation	1,482.37	2.14	3.91	1,653.82	2,083.91
Sample Variance	2,197,422.64	4.59	15.31	2,735,127.52	4,342,682.04
Standard Error	70.43	0.38	0.40	103.57	278.47
Minimum	0.87	0.87	5.56	2.5	1.04
Maximum	23,046	10.00	20.00	23,046	11,702
Count	443	32	98	255	56

TREATMENT RECEIVED

RADIOTHERAPY

A total of 391 out of the 448 which forms 87.2% of the total number of patients with adenocarcinoma of the prostate reviewed over the period had localised disease however only 199 accounting for 50.9% of them received their intended curative treatment. The percentage of patients who received intended treatment for localized disease based on risk categorisation was 71.88% for low risk, 67% for intermediate risk and 42% for high risk disease. Table 12 describes the various treatments received.

EBRT as sole treatment was the commonest modality used in all risk groups seen. The mean dose delivered was 72.42Gy for all patients treated including patients who received salvage and adjuvant radiotherapy.

Brachytherapy alone was the treatment used for nearly half of the patients with low and intermediate risk adenocarcinoma, 65% for low risk and nearly 50% for intermediate risk. One high risk patient had brachytherapy only. The minimum D90 dose was 155.88Gy and a maximum of 221.98Gy and the mean dose was 168.68Gy for full implant brachytherapy treatments.

For patients who had partial implant brachytherapy as boost for EBRT, the mean D90 dose was 106.6Gy and the mean EBRT dose 45.35Gy. Appendix 3 shows a picture of brachytherapy insertion, appendix 4 a D90 prescription for one of the patients.

Appendix 5 shows the treatment field for EBRT while appendix 6 is a dose volume histogram (DVH) for a patient treated with EBRT.

ANDROGEN DEPRIVATION THERAPY (ADT)

In total 133 patients treated with curative intent received ADT as part of their treatment however the information on type and duration of use was available for106 of them. Medical castration with gonadotropin releasing hormone (GNRH) agonists was the most common means of attaining androgen deprivation. GNRH agonist was used in 81 out of 109 high risk patients. Two patients had the nonsteroidal oestrogen diethylstilboestrol (DES). Surgical castration was used in 4 high risk patients. Nineteen patients with intermediate and low risk disease had information on duration of ADT use.

The average duration of ADT use was 14.6 months for the whole group treated with curative radiotherapy excluding the patients who had BTO as lifelong ADT. Intermediate and low risk groups had an average of 10.57 months of ADT while high risk patients had an average of 17.16 months.

TABLE 12: TREATMENT RECEIVED BY ALL PATIENTS SEEN OVER THE 5 YEARS.

		RT TYPE					
Histology	**Risk Category**	**Brachy Only**	**EBRT Only**	**EBRT + Brachy**	**Palliative**	**No Radiation**	**Grand Total**
Adeno Ca	High Risk	1	91	17		149	258
	Intermediate	33	34			36	103
	Low	15	7	1		9	32
	Mets				10	42	52
	Cannot be Accessed					3	3
Adeno Ca Total		**49**	**132**	**18**	**10**	**239**	**448**
Unknown	Mets				2	32	34
	Cannot be Accessed					2	2

Unknown Total					**2**	**34**	**36**
small cell carcinoma	Mets					1	1
small cell carcinoma Total						**1**	**1**
TCC	Mets				1		1
TCC Total					**1**		**1**
Grand Total		**49**	**132**	**18**	**13**	**274**	**486**

4.2 STATISTICAL ANALYSIS FOR CORE GROUP (PSA BASED HIGH RISK PROSTATE CANCER PATIENTS)

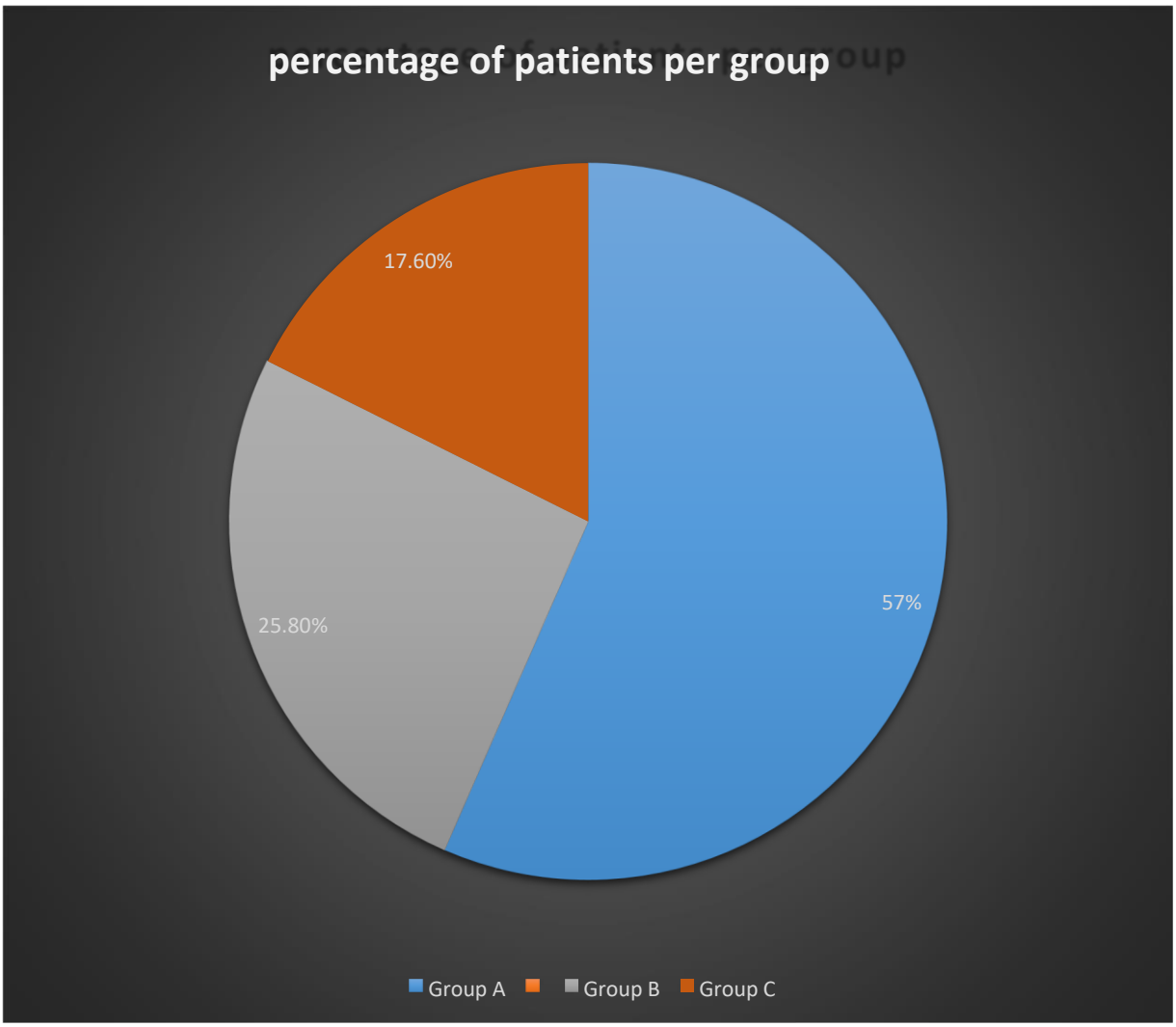
The core group studied were high risk localised prostate cancer who received curative treatment with PSA between 20ng/ml and 200ng/ml. There were 109 patients who were treated for high risk prostate cancer based on the D'Amico categorisation. This represented 42.56% of patients so categorised. In a PSA based manner, 85 patients fit the inclusion criteria. Nine patients were excluded because they had PSA less than 20ng/ml. One patient was excluded because he had brachytherapy alone as treatment and another three because of prior prostatectomy. The rest, 9, were excluded because of inadequate data or because their initial PSA was more than 200ng/ml. The 85 patients represent 78% of 109 high risk patients. They were subdivided into:

Group A - patients with initial PSA of 20-49.9 ng/ml

Group B -patients with PSA of 50-99.9ng/ml

Group C - patients with PSA of 100-200ng/ml

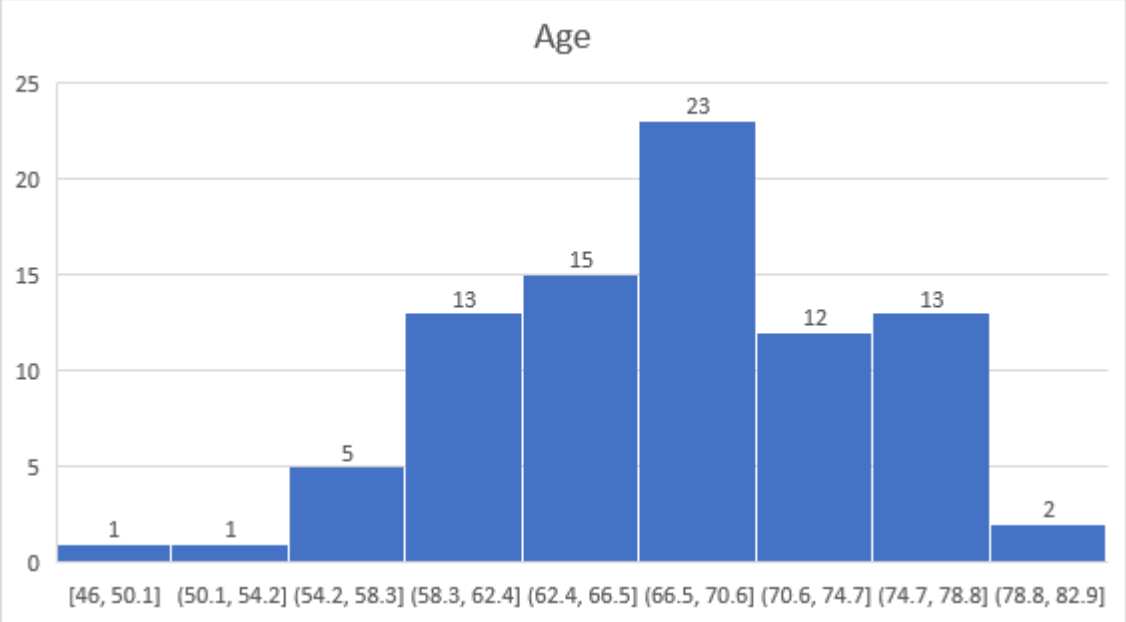
FIG 6: PIE CHART SHOWING DISTRIBUTION OF PATIENTS PER GROUP



AGE DISTRUBUTION

The mean age at diagnosis for the whole group was 67.08 (sdv. 6.83). The statistics on the age at presentation of the Groups A, B, and C, and their standard deviation are in table 15 which summarises demographic and tumour features. Group A had the highest mean age followed by group C. Figure 7 is an age histogram distribution.

FIG. 7-AGE HISTOGRAM



CO-MORBID FACTORS

Hypertension and diabetes mellitus were recorded as co-morbid conditions for the high risk patients. Hypertension was the most common chronic disease seen followed by diabetes mellitus. Fifteen patients had both hypertension and diabetes.

TABLE 13: CO-MORBIDITIES HYPERTENSION AND DIABETIES

Group	Hypertension	Diabetes
A 20-49.99	12	3
B 50-99.9	26	7
C100-200	16	6
Total	54	16

MARITAL STATUS

Information on the marital status of 85 patients representing 89.4% of the patients were married at presentation.

Table 14: MARITAL STATUS

STATUS	married	Not stated	Unmarried/divorced	widowed
NUMBER	76	8	0	1

TUMOR FACTORS

METHOD OF DIAGNOSIS

All the patients had trans-rectal ultrasound guided biopsy and had their histological report in their patient's record. The date of diagnosis, the date of pathology report, was available for all patients.

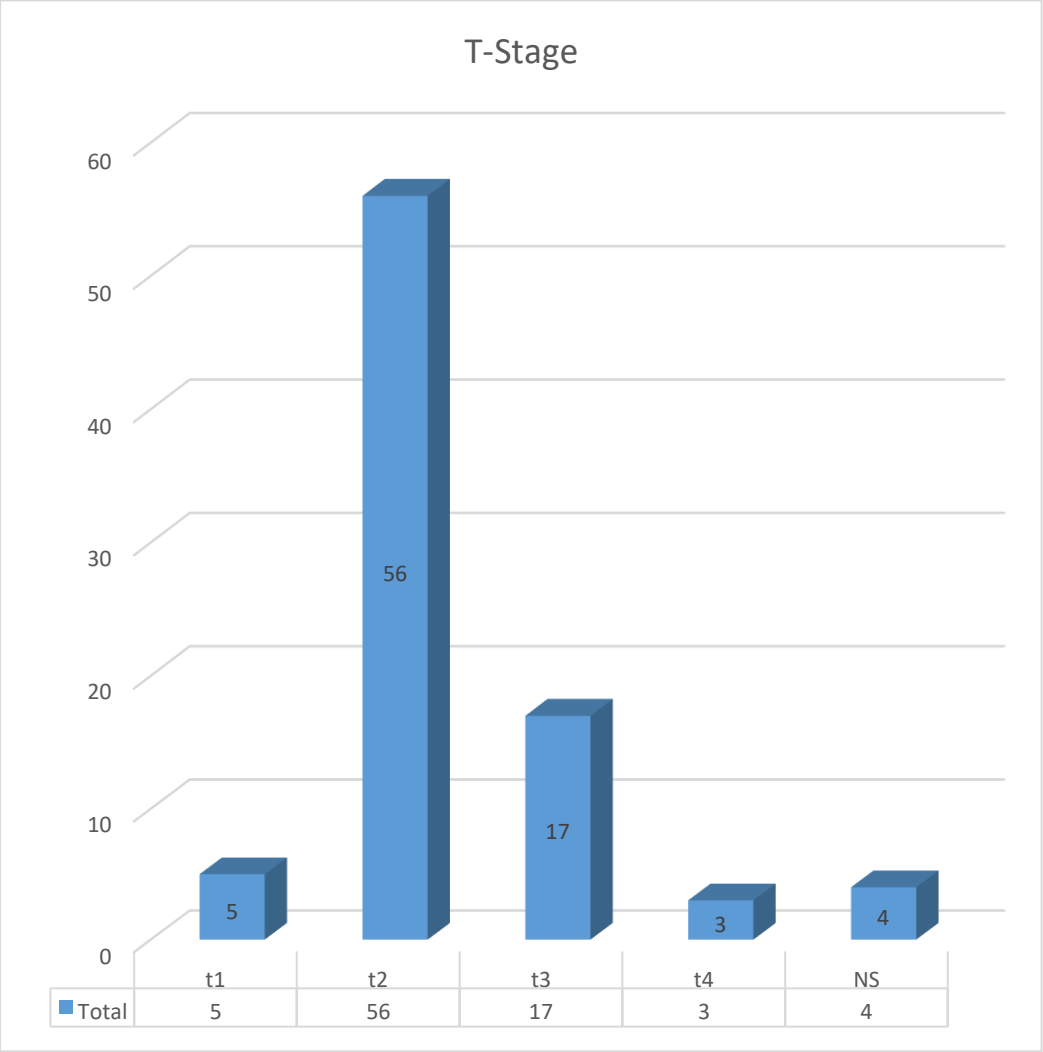
INITIAL PSA AT PRESENTATION

The median initial PSA at diagnosis was 58.59 with a range of 20.86ng/ml-191.15ng/ml. Table 15 shows the median PSA at presentation for the various groups.

CLINICAL STAGE AT PRESENTATION

Clinical staging was based on the 2008 TNM staging classification. The T stage was assessed on digital rectal examination without sub classification to A, B OR C for purposes of this analysis as they were not consistently captured in the patients' record. The T stage information for the three groups at presentation is also in table 15. T stage information was not available for 4 patients. Majority of the patients presented with clinical T2 as depicted in the bar chart in figure 8.

FIG 8: DISTRIBUTION OF T STAGE



TREATMENT FACTORS.

External beam radiotherapy alone was the most frequently used form of radiation treatment, 85% of all the patients receiving radiation, to a mean dose of 7265.43cGy (SD 230.27). The mean D90 dose for those who had partial implant brachytherapy was 121.97Gy with the mean supplementary EBRT dose of 4529.88cGy.Table 16, 17 and 18 show the proportions of patients who received the two types of treatment in each of the groups, the mean dose of supplementary EBRT and D90 doses as well as the mean dose for EBRT. The prescribed dose for EBRT only was intended to be delivered over a period of 7.5 weeks. The mean duration time for treatment was 8.9 weeks.

TABLE 15: SUMMARY OF DEMDEMOGRAPHY AND TUMOR CHARACTERISTICS

Group	Number(per centage)	Mean age	Co-morbid conditions	Tumour stage	Median initial PSA (range)ng/ml
A 20-49.99	48(56.5%)	69.41 (SD 6.51)	HPT-26 DM-7	T1-2 T2-36 T3-7 T4-2 NS-1	30.85(20.86-49.25)
B 50-99.9	22(37.9%)	66.31 (SD7.28)	HPT-12 DM-3	T1-2 T2-14 T3-3 T4-1 NS-2	68(50.27 - 97.23)
C100-200	15(17.6%)	68(SD 4.93)	HPT-15 DM-6	T1-2 T2-7 T3-5 T4-0 NS-1	129.63 (100 – 200)

TABLE 16: TYPE OF RADIATION RECEIVED

Pre PSA Group(ng/ml)	Number BRACHY+EBRT	Number EBRT ONLY	Grand Total
A20 - 49.9ng/ml	7	41	48
B50 - 99.9ng/ml	3	19	22
C100-200ng/ml	2	13	15

TABLE 17: MEAN DOSE OF RADIATION FOR BRACHYTHERAPY+EBRT

Pre PSA Group(ng/ml)	BRACHY(N)	MEAN BRAC DOSE(Gy)	sdv of BRAC DOSE(Gy)	MEAN EBRT DOSE(Gy)	sdv of EBRT DOSE
A20 - 49.9	7	119.46	9.27	4500.00	0
B50 - 99.9	3	127.09	4.03	4500.00	0
C100-200	2	129.36	0.31	4500.00	0

TABLE 18: MEAN DOSE OF RADIATION FOR EBRT ONLY

EBRT DOSE ONLY			
Pre PSA Group	**Number EBRT**	**MEAN EBRT DOSE(Gy)**	**Sdv EBRT DOSE(Gy)**
A (20 - 49.9)	41	7269.00	240.61
B (50 - 99.9)	19	7252.63	174.00
C (100-200)	13	7330.39	146.28

ANDROGEN DEPRIVATION THERAPY (ADT) USE

Hormonal manipulation was consistently employed for nearly all patients treated, 95% of patients. The most common method of castration was with GNRH agonist zoladex. Four patient had surgical castration and their mean ADT duration was estimated from date of BTO to date of last follow up. Their mean duration of use was 57 months. One patient received stilbesterol in the neoadjuvant, concurrent and adjuvant setting for 36 months while another did not have use of ADT stated. The median duration of use of GNRH agonist was 16.64 months for the whole group. Group A had a mean duration of about 13.42 months, group B a mean duration of 14.32 months and Group C a mean duration of 17.44 months.

TABLE 19: SUMMARY OF TREATMENT FACTORS

Group	(N) EBRT ONLY	(N) B+EBRT	B+EBRT B (D90 Gy)	B+EBRT EBRT DOSE Gy	MEAN RT DOSE GY EBRT ONLY	MEAN DURATION OF TREATMENT (WEEKS)	MEAN DURATION OF ADT MONTHS (SD)(INCLUDING DES)
A(20-49.9)	41	7	119.46	4500.00	7269.00	8.9	13.42(15.84)
B(50-99.9)	19	3	127.09	4500.00	7252.63	9.3	17.43(10.26)
C(100-200)	13	2	129.36	4500.00	7330.39	7.2	19.07(8.98)

BIOCHEMICAL OUTCOMES.

BIOCHEMICAL FAILURE RATES

Date of PSA only failure, biochemical failure, was recorded for all patients followed up using the Phoenix definition Nadir+2. The proportion of patients who failed as well as those censored for the various groups are represented in table 20, the average time to biochemical failure in table 21, while the median and mean follow up times for biochemical outcomes for each of the four groups is in table 22. The median follow up was 87months with a range of 70125 months. A graph showing the percentage of patient who failed biochemically during follow up is presented in fig 9.

TABLE 20: BIOCHEMICAL FAILURE EVENTS FOR GROUPS AND PERCENTAGE CENSORED.

				Censored	
Pre PSA Group	Total N	N of Events	% of failure	N	Percent
A(20 - 49.9)	48	14	29.1%	34	70.8%
B(50 - 99.9)	22	11	50.0%	11	50.0%
C(100-200)	15	10	58.0%	7	41.2%

TABLE 21: AVERAGE TIME TO BIOCHEMICAL FAILURE IN MONTHS

PRE PSA GROUP	Count	Average(months)	sdv
A(20 - 49.9)	14	38.57	20.00
B(50 - 99.9)	11	32.45	19.30
C(100-200)	10	35.90	25.38

TABLE 22: MEAN AND MEDIAN SURVIVAL TIMES FOR THE GROUPS

Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confiden Interval				95% Confidence Interval	
pre_grp	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
100-200	54.078	8.032	38.335	69.820	48.000	17.663	13.380	82.620
20 - 49.	93.019	6.939	79.419	106.618	.	.	.	.
50 - 99.	65.686	10.667	44.779	86.593	46.000	17.842	11.029	80.971
Overall	80.583	5.543	69.718	91.448	87.000	.	.	.

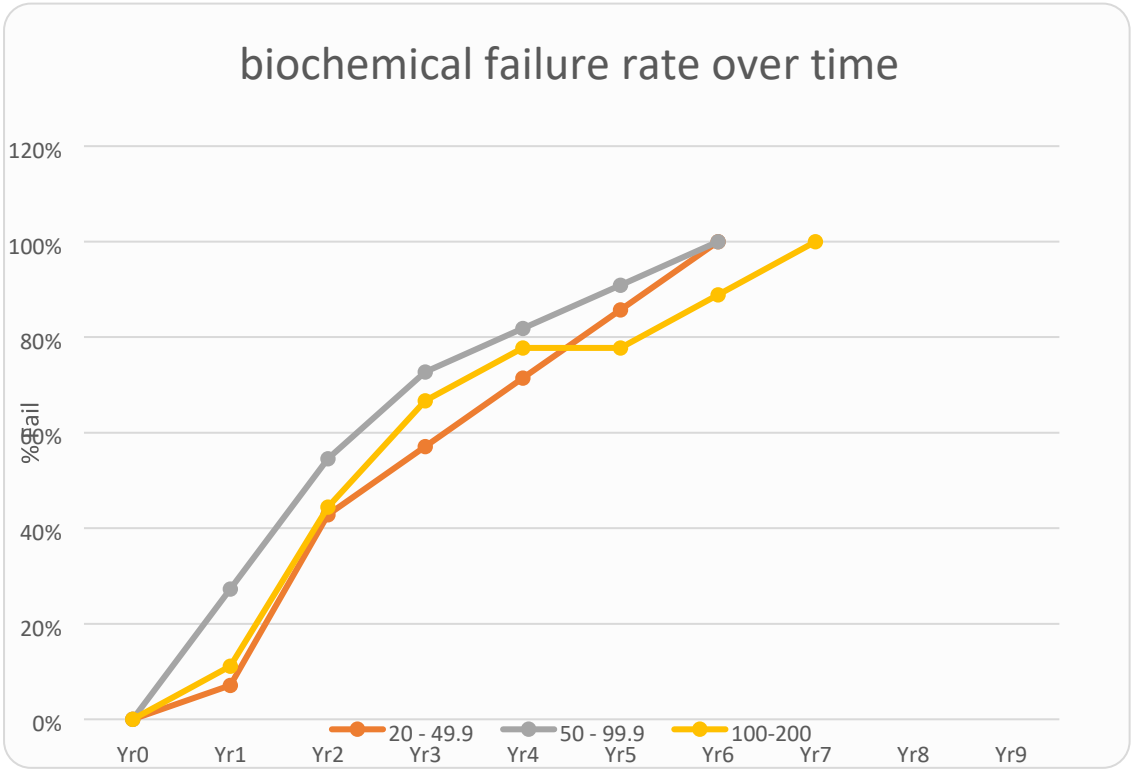
TIME TO BIOCHEMICAL FAILURE

Time to biochemical failure was calculated from date of completion of radiotherapy or brachytherapy whichever is later to date of nadir+2.

The mean time to biochemical failure calculated for the groups were; for group A 38.57 months, for group B 32.45months and for group C 35.87 after a median follow-up of 87months. There was no statistically significant difference in the mean time to biochemical failure amongst groups studied.

Figure 9 is a graphical representation of biochemical failure rate over the study period. By the third year post treatment which is the commonest time to biochemical failure for high risk disease, group A had 57% failure, group B had 67% failure and group C 73% failure. All the patients in Group A and B had all failed by the 6th year while 100 percent failure occurred in the 7th year in group C.

FIG 9: BIOCHEMICAL FAILURE RATE STRATIFIED BY PSA GROUP



BIOCHEMICAL FAILURE FREE SURVIVAL ANALYSIS (bffs)

Patients were followed up for estimation of biochemical failure free survival outcomes using date of completion of EBRT or brachytherapy which ever was later to date of failure, date of censor (date of last follow up) or date of death. The last date of follow up was 31st December 2020.

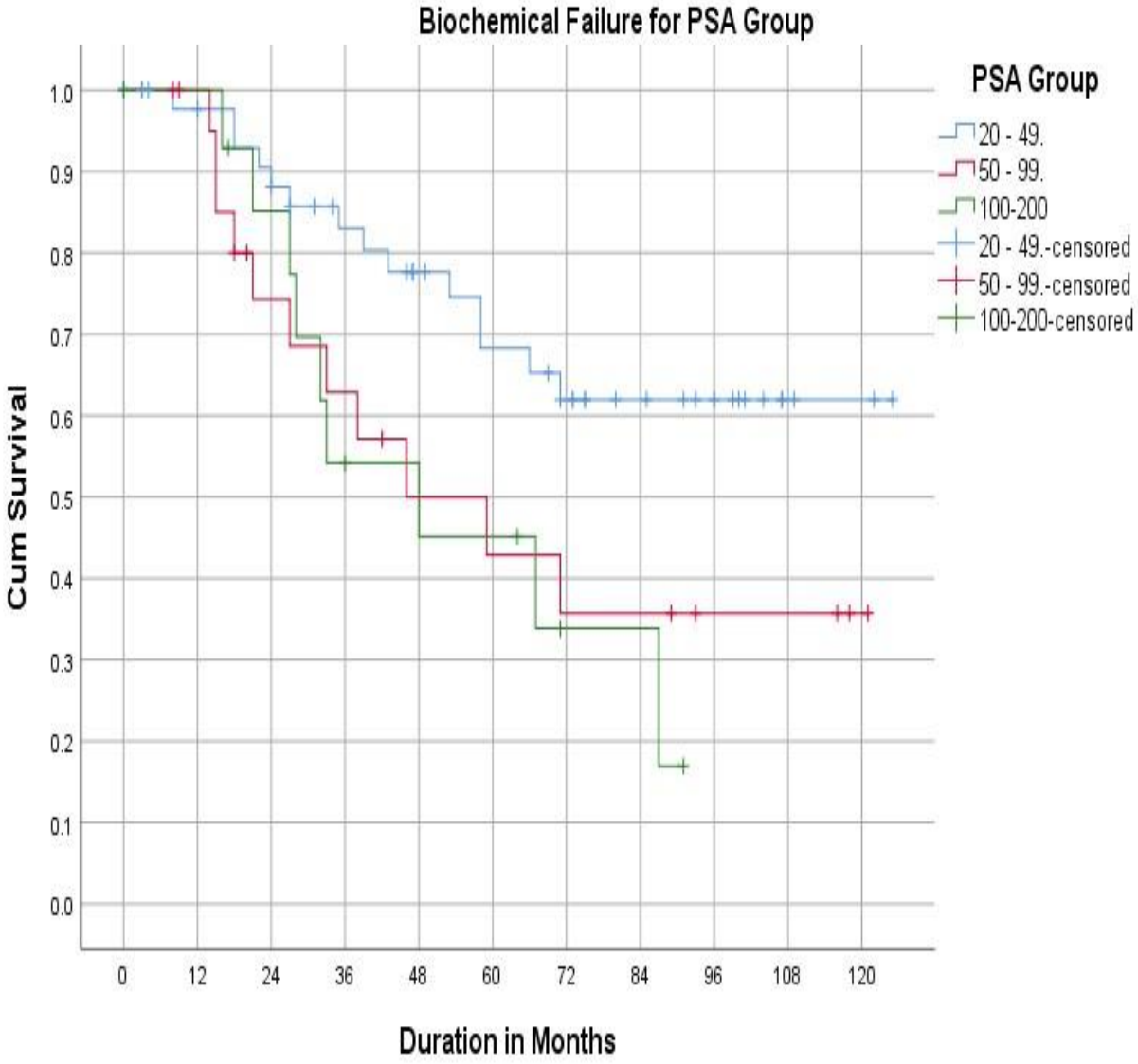
A Kaplan Meier estimate was used to plot survival curves. The median survival was not reached, 46 months and 48 months for group A, B and C respectively. The median survival as stated previously is 87months. The bffs at 5 years were 68%, 44% and 46% while the 10 year bffs was 62%, and 36% for group A and B respectively. Group C did not reach the 10 year mark. Log rank test to compare the curves showed a statistically significant difference in biochemical failure free survival in favour of group A with a p value of 0.033 as shown in table 23 and represented graphically in figure 10

TABLE 23: SIGNIFIANCE ANALYSIS COMPARING BIOCHEMICAL FAILURE FREE SURVIVAL CURVES

verall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.826	2	.033

Test of equality of survival distributions for the different levels of pre_grp.

FIG 10: KAPLAN-MEIER CURVE OF BIOCHEMICAL FAILURE FREE SURVIVAL



PREDICTORS OF BIOCHEMICAL FAILURE

Age, T stage, nadir PSA value, the duration of use of ADT and type of radiation therapy received were assessed on univariate and multivariate analysis using Kruskal-Wallis test of means and cox regression analysis respectively for predictors of biochemical outcomes.

Table 23 shows Kruskal-Wallis estimated p-values for some predictors of biochemical failure. Test of means of nadir PSA was statistically significant with a p-value of 0.00. Post hoc pairwise comparism showed statistically significant difference in mean nadir PSA values amongst all the groups. Table 24 shows the results of the pairwise analysis which showed that the difference in mean nadir PSA value differed between all the groups. Nadir PSA remained statistically significant at predicting biochemical failure free survival on multivariate analysis, Cox regression analysis (p value 0.000) with an inverse correlation between nadir PSA and biochemical failure free survival as shown by the positive b co-efficient of 2.45. WALD of 21.8 shows a strong correlation. Table 27 shows the Cox regression analysis output.

TABLE 24: KRUSKAL-WALLIS TEST OF MEANS FOR PREDICTORS OF BIOCHEMICAL FAILURE

PREDICTOR	Test statistic	DF	P VALUE
Time to nadir PSA	1.7015	3	0.6366
Nadir PSA value	74.053	3	0.0000

TABLE 25: PAIRWISE COMPARISM BETWEEN THE GROUPS FOR NADIR PSA **Multiple Comparison**

Pairwise Comparison		P-value	Decision
Group A	Group B	2.27E-10	Significant Difference
	Group C	1.08E-08	Significant Difference
Group B	Group C	6.24E-07	Significant Difference

TABLE 26: SIGNIFICANCE ANALYSIS FOR PREDICTORS OF BIOCHEMICAL FAILURE (OMNIBUS TESTS)

Omnibus Tests of Model Coefficients[a]

	Overall (score)			Change From Previous Step			Change From Previous Block		
-2 Log Likelihood	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
222.258	38.301	7	.000	22.632	7	.002	22.632	7	.002

a. Beginning Block Number 1. Method = Enter

TABLE 27: COX REGRESSION ANALYSIS FOR PREDICTORS OF BIOCHEMICAL FAILURE

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
pre_grp			7.101	2	0.029			
pre_grp(1)	-1.199	0.497	5.816	1	0.016	0.302	0.114	.799
pre_grp(2)	-.303	0.506	0.358	1	0.550	0.739	0.274	1.992
RT Type	.117	0.323	0.131	1	0.717	1.124	0.596	2.119
Nadir PSA	2.458	0.526	21.803	1	0.000	11.682	4.163	32.778
ADT Duration	.000	0.017	0.000	1	0.999	1.000	0.968	1.033
Age	-.011	0.031	0.116	1	0.733	0.989	0.931	1.052
Combine Gleason Score	.139	0.166	0.704	1	0.401	1.149	0.831	1.590

OVERALL SURVIVAL ANALYSIS

Overall survival was calculated from date of diagnosis stated on the pathology report, to date of last follow up, or death or 31st December 2020 which was when the study was closed.

The 5 year overall survival for group A was 93.5% and at 10 years nearly 82%.it remained so for over 16 years. The 5 year and 10 year overall survival was 100% for groups B and continued at 100% to year 13. Group C had a drop to 93% by the 2nd year but this was maintained through to year 12. Figure 11 shows the Kaplan-Meier survival estimate curves for the groups. There was no statistically significant difference in the overall survival when survival was compared using the log rank test. (P-value 0.26)

TABLE 28: CASE PROCESSING SUMMARY FOR OVERALL SURVIVAL

Case Processing Summary

pre_grp	Total N	N of Events	Censored	
			N	Percent
>100	15	1	14	93.3%
20 - 49.	48	5	43	89.6%
50 - 99.	22	0	22	100.0%
Overall	85	6	79	92.9%

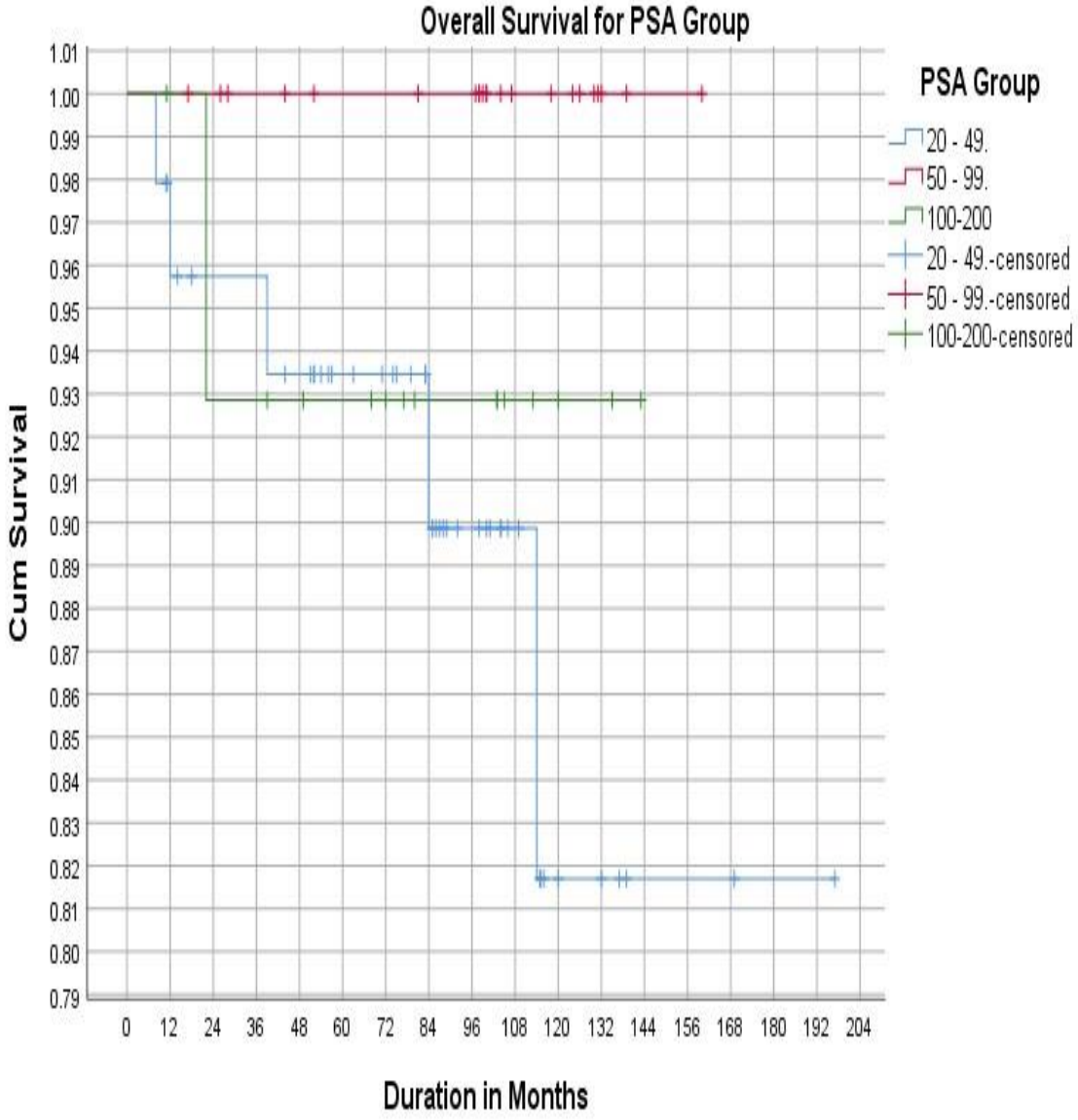
TABLE 29: SIGNIFICANCE ANALYSIS FOR OVERALL COMPARISONS FOR OVERALL SURVIVAL BASED ON PSA GROUPS

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.690	2	0.261

Test of equality of survival distributions for the different levels of pre_grp.

FIG 11: KAPLAN-MEIER ESTIMATE OF OVERALL SURVIVAL BASED ON PSA GROUPS



PREDICTORS OF OVERALL SURVIVAL

As was done with biochemical failure free survival, predictors of overall survival was checked. The included RT type, nadir PSA, duration of ADT use, combined Gleason score and time to biochemical failure.

Table 30 shows factors that were assessed as well as the statistics using Cox regression for multivariate analysis. None of the factors studied including time to biochemical failure showed a statistically significant ability to predict overall survival.

TABLE 30: SIGNIFICANCE ANALYSIS FOR OVERALL SURVIVAL

Omnibus Tests of Model Coefficients[a]

	Overall (score)			Change From Previous Step			Change From Previous Block		
-2 Log Likelihood	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
7.892	8.272	7	0.309	14.239	7	0.047	14.239	7	0.047

a. Beginning Block Number 1. Method = Enter

TABLE 31: COX REGRESSION ANALYSIS FOR PREDICTORS OF OVERALL SURVIVAL

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
RT Type	7.721	149.538	0.003	1	0.959	2255.607	0.000	4.369E+130
Nadir PSA	-2.781	6.521	0.182	1	0.670	0.062	0.000	22030.228
ADT Duration	-.127	.145	0.768	1	0.381	0.881	0.662	1.170
Initial PSA	-.145	.109	1.781	1	0.182	0.865	0.698	1.071
Combine Gleason Score in Groups			0.004	2	0.998			
Combine Gleason Score in Groups(1)	-3.518	223.102	0.000	1	0.987	0.030	0.000	2.383E+188
Combine Gleason Score in Groups(2)	9.084	145.407	0.004	1	0.950	8815.873	0.000	5.196E+127
Time to biochemical failure	-.113	.079	2.063	1	0.151	0.893	0.766	1.042

SURIVAL ANALYSIS BASED ON PRIMARY GLEASON GRADE AND COMBINED GLEASON SCORE

Both biochemical failure free survival and overall survival was compared for patients based on their primary Gleason grade, 2-3, 4 and 5. This analysis was limited by the low numbers of patients with primary Gleason grade of 5. Similar studies were done with patient grouped based on their combined Gleason score; </=6, 7 and 8-10 to represent well differentiated, intermediate and poorly differentiated cancer respectively. Figures 12 and 13 show the Kaplan-Meier curves for the patients grouped based on their primary Gleason grade for biochemical failure free survival and overall survival while figures 14 and 15 describes the biochemical failure free survival and overall survival based on combined Gleason score respectively. Comparism of survival curves using log rank test showed a trend towards biochemical failure free survival and overall survival benefit in favour of combined Gleason 6 with p-value of 0.08 for biochemical failure free survival and 0.06 for overall survival. This are shown in table 37 and 39 respectively.

TABLE 32: CASE PROCESSING SUMMARY FOR ESTIMATION OF BIOCHEMICAL FAILURE FREE SUTVIVAL BASED ON PRIMARY GLEASON GRADE

Case Processing Summary

Primary Gleason Score	Total N	N of Events	Censored	
			N	Percent
2-3	48	17	31	64.6%
4	24	11	13	54.2%
5	11	4	7	63.6%
Overall	83	32	51	61.4%

TABLE 33: LOG RANK TEST FOR COMPARISM OF KAPLAN MEIER CURVES FOR BIOCHEMICAL FAILURE FREE SURVIVAL BASED ON PRIMARY GLEASON GRADE

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.333	2	0.311

FIG 12: KAPLAN MEIER ESTIMATE GRAPH OF BIOCHEMICAL FAILURE FREE SURVIVAL BASED ON PRIMARY GLEASON GRADE

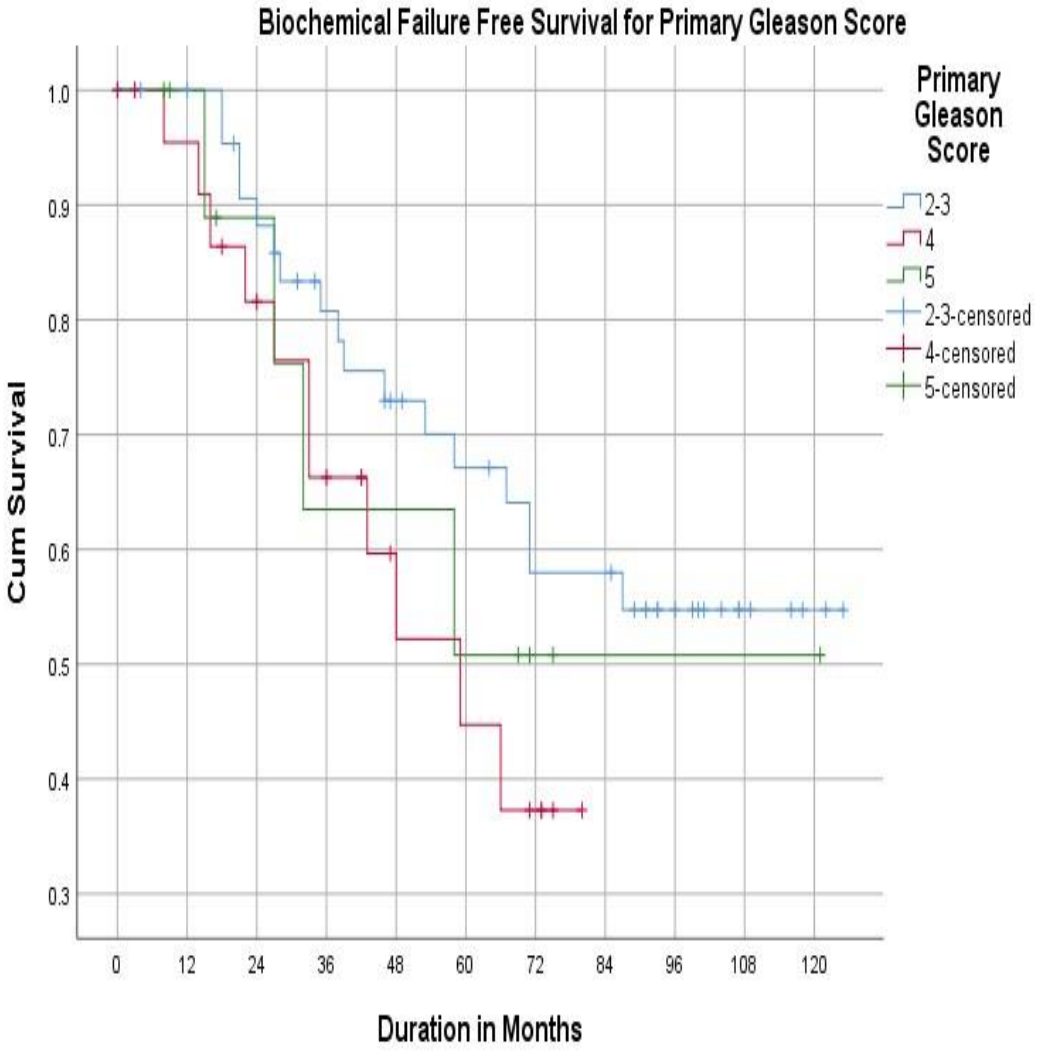


TABLE 34: CASE PROCESSING SUMMARY FOR OVERALL SURVIVAL BASED ON PRIMARY GLEASON GRADE

Case Processing Summary

Primary Gleason Score	Total N	N of Events	Censored	
			N	Percent
2-3	48	5	43	89.6%
4	24	0	24	100.0%
5	11	1	10	90.9%
Overall	83	6	77	92.8%

TABLE 35: LOG RANK TEST COMPARISM OF KAPLAN MEIER CURVES FOR BIOCHEMICAL FAILURE FREE SURVIVAL BASED ON PRIMARY GLEASON GRADE

verall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.999	2	0.368

Test of equality of survival distributions for the different levels of Primary Gleason Score.

FIGURE 13: KAPLAN MEIER CURVES FOR OVERALL SURVIVAL BASED ON PRIMARY GLEASON GRADE

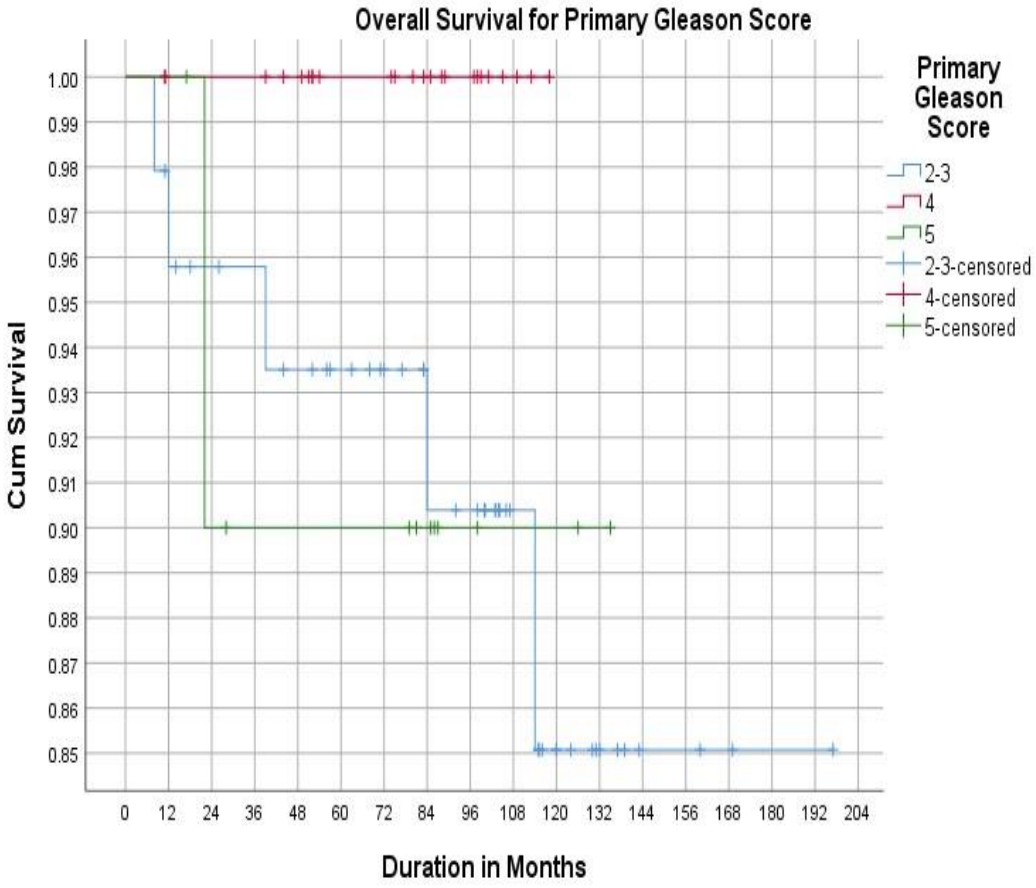


TABLE 36: CASE PROXESSING SUMMARY FOR ESTIMATION OF BIOCHEMICAL FAILURE FREE SUTVIVAL BASED ON COMBINED GLEASON SCORE

Case Processing Summary

Combine Gleason Score in Groups	Total N	N of Events	Censored	
			N	Percent
<=6	24	6	18	75.0%
7	34	17	17	50.0%
8-10	27	11	16	59.3%
Overall	85	34	51	60.0%

TABLE 37: LOG RANK TEST COMPARISM OF KAPLAN MEIER CURVES FOR BIOCHEMICAL FAILURE FREE SURVIVAL BASED ON COMBINED GLEASON SCORE

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.973	2	0.083

Test of equality of survival distributions for the different levels of Combine Gleason Score in Groups.

FIGURE14: KAPLAN MEIER ESTIMATE CURVES OF BIOCHEMICAL FAILURE FREE SURVIVAL BASED ON COMBINED GLEASON SCORE

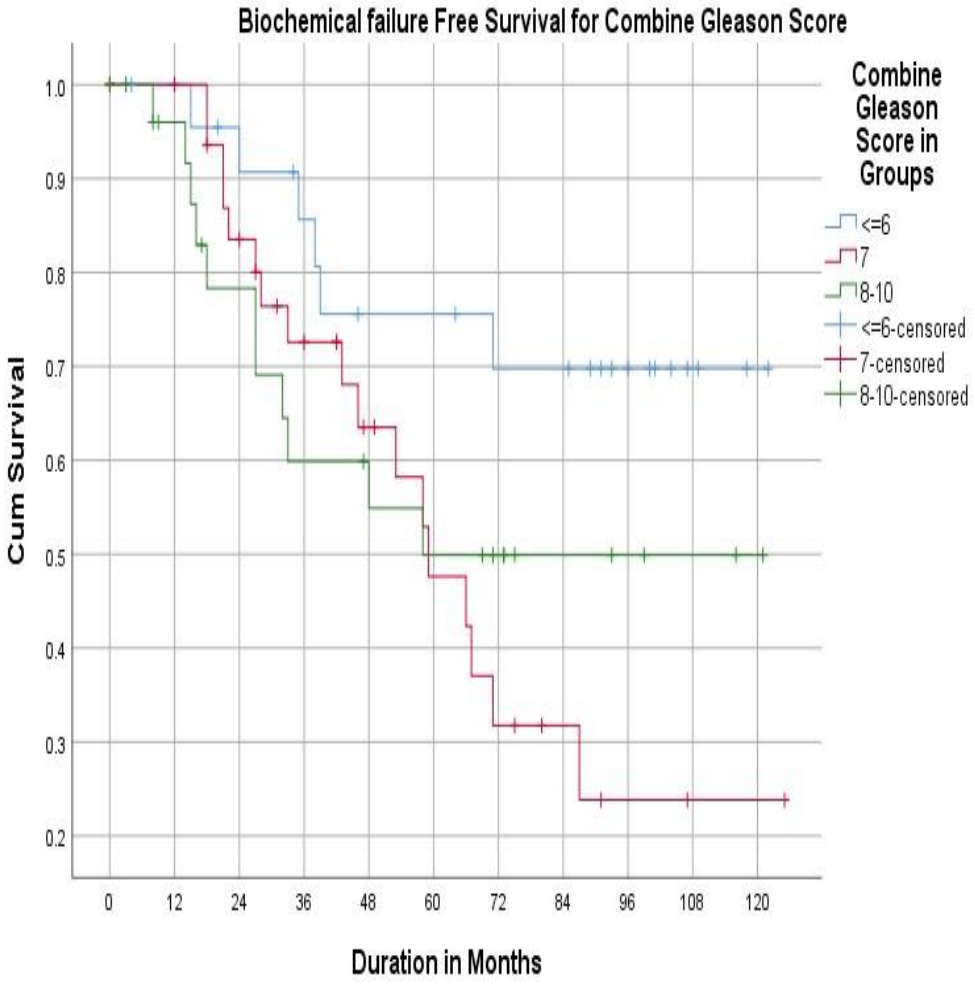


TABLE 38: CASE PROCESSING SUMMARY PROCESSING FOR OVERALL SURVIVAL BASED ON COMBONED GLEASON SCORE

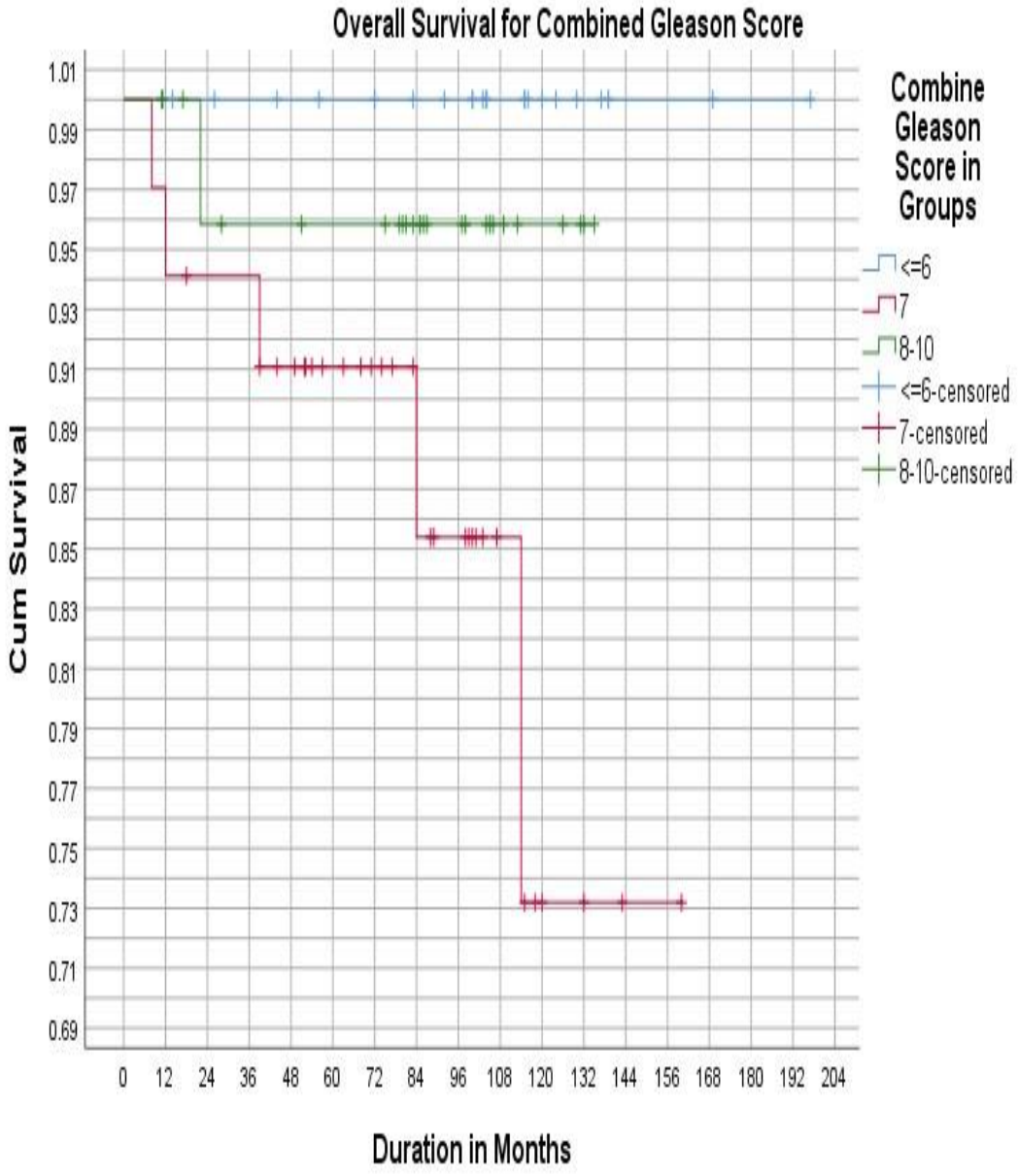
ase Processing Summary				
			Censored	
Combine Gleason Score in Groups	Total N	N of Events	N	Percent
<=6	24	0	24	100.0%
7	34	5	29	85.3%
8-10	27	1	26	96.3%
Overall	85	6	79	92.9%

TABLE 39: LOG RANK TEST FOR COMPARING OVERALL SURVIVAL BASED ON COMBINED GLEASON SCORE

O verall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.640	2	0.060

Test of equality of survival distributions for the different levels of Combine Gleason Score in Groups.

FIGURE 15: KAPLAN MEIER ESTIMATE CURVE OF OVERALL SURVIVAL BASED ON COMBINED GLEASON SCORE



An ROC curve for predicting risk of 4 year biochemical failure free survival probability in high risk prostate cancer patients identified in this study cohort was conducted. Figure 16 shows the ROC curve. A cut off point of 50% where true positive and false positive have an equal chance of occurring was chosen for prediction. A critical nadir PSA was of 0.07 was identified as significantly predicting biochemical recurrence with a p-value of 0.047. The accuracy, sensitivity, specificity and precision is in table 40

FIG 16: RECEIVER OPERATING CHARACTERISTIC CURVE FOR PREDICTING BFFS AT 4 YEARS USING NADIR PSA

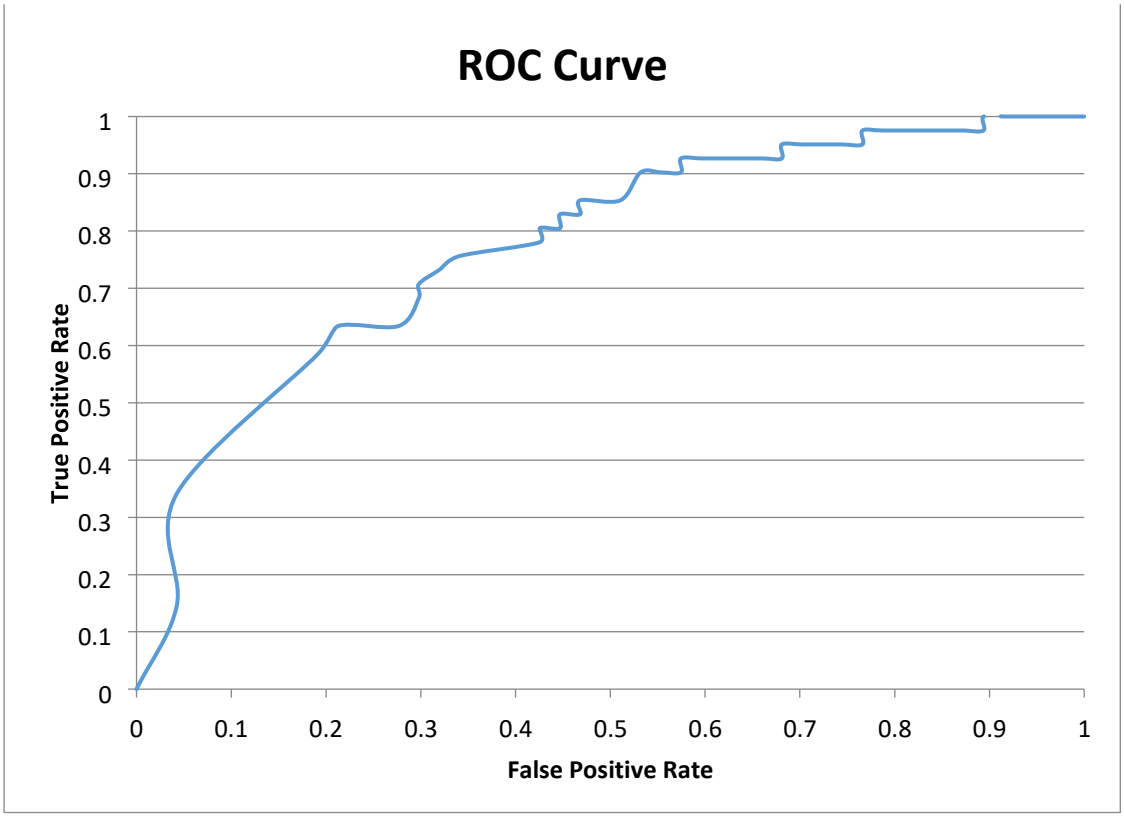


TABLE 40: RESULTS OF SYSTEMATIC ANALYSIS AT 0.5 CUTOFF

Accuracy	0.68
Sensitivity	0.83
Specificity	0.55
Precision	0.62

CHAPTER 5

DISCUSSION

This retrospective cohort study sought to conduct an audit to describe patient and tumour characteristics for all patients with prostate cancer seen at the Korle Bu Teaching hospital Radiotherapy Oncology and Nuclear Medicine Centre from 2010-2014.

It was hypothesised that patients with high risk localised prostate cancer will benefit from curative radiotherapy plus ADT given irrespective of their pre-treatment PSA level provided there was no evidence of distant metastasis at presentation. Treatment outcomes were expected to be favourable maybe even similar amongst the three groups irrespective of PSA levels as overall survival benefit for the use of localised treatment even in the presence of oligo metastatic disease and clinically evident metastatic disease has been shown (Rusthoven *et al.*, 2014).

Over the period of 5 years during which the study was conducted, prostate cancer was the commonest male malignancy seen at the institution and has remained so to date. This is representative of national trends where prostate cancer is second only to liver cancer as the commonest male malignancy. The centre does not manage liver cancers hence prostate cancer being the commonest. The average number of patients seen per year was 117 patients (range of 101-138) with each year showing a steady rise in number of cases. Prostate cancer according to GLOBOCAN 2020 statistics is the second commonest male cancer after lung cancer worldwide and is currently number 6 cause cancer mortality (Sung *et al.*, 2021). A study by Odedina et al reported men of west African descent have a disproportionately high incidence of prostate cancer (Odedina *et al.*, 2009). It is therefore not surprising the number 1 position of prostate cancer as the commonest seen at the centre.

Research into the global trends of prostate cancer show declining or stabilized incidence and mortality. These could be attributed to a drop in PSA screening following studies that show conflicting results for overall survival benefit and subsequent recommendation by several groups against screening especially in men with normal risk(Culp *et al.*, 2020). More so, there is improvement in therapy and lower morbidity after both radical prostatectomy and radiotherapy and life prolonging treatment after failure of localised treatment. The yearly increase in number of cases seen over the years may be a reflection of the low screening rate amongst the population. Ann W Hsing et al, reviewed 1037 Ghanaian men randomly selected

in Accra, the capital of Ghana, a 5.8-6.6% (based on 2.5ng/ml PSA cut off) screen detected prostate cancer prevalence was found. This is three and two times higher than the prevalence found in African American men investigated in south Carolina and Michigan in the united states of America respectively(Hsing *et al.*, 2014) who represent a screened African population.

All consecutive patients with prostate cancer were identified for the study. A total of 486 of 584 (88%) patients with a diagnosis of prostate cancer had their medical records available for review. Figure 2 describes the process of patient selection.

It is a disease of old age with majority of cases occurring after 65 years (Rawla, 2019). As was the case in this study more than 50% of patients were 65 years or older at presentation. The median age at diagnosis for this study was 67 years (range of 44-86 years) a figure comparable to world statistics which states a median age of 68 years. A median age of 66 years was quoted in a study that followed up a larger group of prostate cancer patients of which this current study sample is a subset (Asamoah *et al.*, 2018). Figure 3 shows an age histogram for the study sample.

Initial PSA was recorded for 443 patients evaluable. Table 11 shows the PSA statistics. The median PSA at diagnosis for the whole group was 31.90ng/ml with a range of 0.87-23046.00 ng/ml.

Diagnosis was confirmed by biopsy in more than 92% of all cases identified. There were 36 patients without histological diagnosis. Thirty-four had metastatic disease while 2 could not be categorised. The commonest metastatic site was bone. They presented with elevated median PSA level of 141.6 (range 1.04-11702).

Adenocarcinoma was the most common histological type representing 99.6% of cases. One of two patients each had histology of TCC and small cell carcinoma a variant of adenocarcinoma. This compares to other published data on the histological variants of prostate cancer. Other less common histological types are ductal and sarcomatiod (Humphrey, 2012).

Risk categorisation presents an objective assessment based on clinico-pathologic and increasingly clinico-genetic factors for prognostication and for deciding choice of treatment. These tools have consistently been validated. Out of a total of 448 with localised adenocarcinoma, risk categorisation based on the D'Amico classification showed majority of patients presenting with high risk disease (53%). This may represent the disproportionately high levels of aggressive disease described in West African men by Odedina et al (Odedina *et*

al., 2009). Lack of screening may also be a reason. Low and intermediate risk formed 48% cases. A total of 18 cases which represents 1% of prostate adenocarcinoma could not be categorised due to inadequate data. The rest had metastatic disease. Figure 3 is a pie chart showing the risk groups.

Treatment modalities available to the patients at the time were full implant brachytherapy using I-125 to D90 of 160 Gy and 3DCRT using a Co-60 machine for low and intermediate group patients to doses above 68Gy. Three dimensional conformal EBRT to doses 68-76GY was used for treatment of high risk disease as was partial implant brachytherapy with D90 dose of 130Gy supplemented by 3DCRT to 45Gy-50 Gy to the prostate for the purpose of dose escalation. Dose escalation trials show a direct relationship between radiation therapy dose and tumour control for prostate cancer to doses 74-86.4Gy. This is associated with low rates of biochemical failure and absence of viable tumour at biopsy (Zelefsky *et al.*, 2011). This biochemical control benefit however has not translated into overall survival benefit. The use ADT and other hormonal treatment concomitant with radiotherapy presents opportunity for improved overall survival.

The percentage of patients with localised adenocarcinoma who received their intended curative treatment were 50% (199 out of 391). Asamoah and his colleagues reported lower default rate of 46% in prostate cancer patients who were followed up at the same centre (Asamoah *et al.*, 2018). High attrition was also seen in a study by Dadzie et al that followed up patients with cancer of the vulva where a third of patients defaulted treatment.(Dadzie, Aidoo and Vanderpuye, 2017). High default rate for cancer patients has been observed for several other tumour sites including breast and cervical cancer in Ghana.

In studies of cancer patients in low middle income countries where access to treatment remains a challenge, a high attrition rate can be envisaged. In a study conducted in Rwanda a country with similar socioeconomic set up as Ghana, only 58% of patients with curable breast cancer received intended chemotherapy, surgery and hormonal therapy, the full complement of treatment(O'Neil *et al.*, 2017). Cost implication of treatment and the use of alternative and complementary medication may explain the high default rate.

Table 12 shows all the patients with available records, the various risk groups, proportions of patients who received curative treatment and the type of treatment received by the various risk groups.

Brachytherapy alone was used more commonly in low and intermediate risk patients at 65.22% and 49.2% respectively. One high risk patient opted for brachytherapy alone. A 10 year review of experience of brachytherapy use in managing prostate cancer for the KBTH has been published(Mensah *et al.*, 2016).

Cost, clinician and patient preference may have influenced choice between brachytherapy and EBRT for low and intermediate risk group patients. Previous TURP and large prostate volume also affects choice of therapy. Studies show comparable outcomes for brachytherapy only versus EBRT in low and intermediate risk prostate cancer (Goldner *et al.*, 2012) while other studies show superiority of brachytherapy for biochemical control(Grimm *et al.*, 2012).

EBRT alone was the most used local treatment (66.33%) in all cases but more so in the high risk group (84.49%). Combination of EBRT and brachytherapy was less frequently used.

The mean doses of each type of treatment were EBRT only 72.42Gy, full implant brachytherapy with a mean D90 dose of 168. 68Gy (range 155.88Gy- 221.98Gy). Table 17 shows the statistics for doses of partial implant radiotherapy and supplementary EBRT. The doses are at par with suggested doses in literature(Morris *et al.*, 2014)(Goldner *et al.*, 2012).

ADT was used with radiotherapy in about 66.83% of the patients mainly with intermediate and high risk patients (133/199). Data on type and of ADT was available for 106 patients. Medical castration with GNRH agonist was the most used means for ADT. Bilateral total orchiectomy was the means of lifelong castration for 4 patients who could not afford GNRH agonist. High level studies including meta-analysis have found surgical and medical castration to be comparable for controlling tumour(Seidenfeld *et al.*, 2005) .Two patients received diethylstilboestrol, a steroidal oestrogen with radiation. The reason for this choice was not stated but cost of GNRH agonist and the permanency of BTO may have prevented their use.

ADT use is associated with improved overall survival. Investigation on the duration of ADT suggest 24-36 months as the optimal duration for high risk patients(Lawton *et al.*, 2017) The benefit was in spite of dose escalation. ADT was given over a mean of 17.68 months for the high risk group who received about 82.73% of all ADT administered. Four to six months of short course ADT has been shown to improved overall survival for intermediate risk. The mean duration in the intermediate risk group for this cohort was about 10 months.

Co-morbid factors were recorded only for patients with high risk disease. Hypertension and type 2 diabetes mellitus were the most common co-morbid factors. This mimics the national picture where these two non-communicable diseases have the highest incidence and prevalence(Ministry of Health of the Republic of Ghana, 2012)

Patients with high risk prostate cancers are categorised as T2b/T3/T4 disease or PSA> 20ng/ml or Gleason score of 8-10 without evidence of distant metastasis. This describes a large pool of patients who inherently differ from each other with regards to clinical and pathological factors.

A total of 258 patients were categorised as having high risk disease. Sixty one percent of high risk disease patients did not receive their intended treatment for localised disease. Out of the 109 received curative treatment, a subset of 85 patients who fit the inclusion criteria were followed up for treatment outcomes. The number represents 78% of all patients seen with high risk disease and received curative treatment. The exclusions have previously been described.

Figure 9 shows a graph of percentage biochemical failure recorded over the follow up period for each of the groups described. Forty percent of patients seen (35 out 85) had recorded evidence of failed treatment at the end of the study on 31st December 2020.

The Phoenix definition of nadir+2 was selected over thr ASTRO definition because of its robustness(Abramowitz *et al.*, 2007).Biochemical failure appeared to occur early in patients with high initial presenting PSA of >50ng/ml. Time to biochemical failure, described in certain texts as interval to biochemical failure was calculated from date of completion of radiotherapy to the date of biochemical failure.

The average time to biochemical failure in months for each of the groups is represented in table 21. Group A had the longest average time to biochemical failure of 38.57 months followed by Group C with 35.90 months. Group B had the shortest time numerically but this was not statistically significantly different amongst the groups. While there was no failure in the first year for group A, group B and C had 27% and 11% failures respectively within the first year of treatment. In over 2234 patients followed up after brachytherapy with or without EBRT and ADT for all risk categories of prostate cancer, high risk patients had the highest rate of biochemical failure at 10 years with a the median time to failure was 2.8 years. Majority of the recurrences occurred within the first four years. Biochemical failure was defined as PSA > 0.40 ng/mL after nadir(Taira *et al.*, 2013). Our current study showed a range of 71-82 % at four years using the Pheonix definition.

Biochemical failure free survival analysis was done and compared for the groups using Kaplan-Meier estimate and is shown in figure 10. There was an improvement for biochemical failure free survival in patients with low PSA level, p value of 0.033. This was statistically significant. For the three groups, the 5 year bFFS ranged from 44%-68%. At 10 years it was 36%- 62%. Patients in group C were 100% censored by 7.5 years. Group A had the best biochemical failure free survival compared to the other two groups. The biochemical failure free survival was 68% and 62% at 5 and 10 years respectively.

A previous study by Asamoah et al showed biochemical disease free survival of 48% at 5 years(Asamoah *et al.*, 2018). This figure is on the lower spectrum for this study.

In a study by Brandli et al conducted in 2003 on patients with high PSA levels treated with radical prostatectomy, biochemical recurrence free survival after 54 months of follow up showed a median 5 year biochemical recurrence free survival (bRFS) of 50% (range, 35-60%) for the different PSA levels 20-29ng/ml, 30-39ng/ml, 40-49ng/ml and 50-100ng/ml (Brandli *et al.*, 2003). Bastide et al. after 64 months of following up 80 patients from Germany found bRFS of 50% for patients with PSA of >20ng/ml treated with radical prostatectomy.

A hundred and thirty-eight patients including those with distant metastasis and PSA of more than 50ng/ml treated using all modalities of treatment, after a median follow up of 51 months were reported on by Wiebe et al. The 5 year and 9 year bRFS was 53% and 0%. In our study, for all patients seen with PSA > 50ng/ml, a 5year and 10 year bffs ranged from 44%68%- and 36%-62% respectively. Our biochemical free failure survival is higher but this study included 63.2% of patients who had clinical and radiologic evidence of metastasis which may explain the difference in biochemical survival rate(Wiebe *et al.*, 2008) .Table 41 shows a summary of studies compared above.

TABLE 41: COMPARISM OF CURRENT STUDY WITH SIMILAR STUDIES FOR BIOCHEMICAL OUTSCOMES

Name of author (YEAR OF PUBLICATION)	**Country**	**No of patients**	**PSA (ng/ml)**	**TREATMENT**	**MEDIAN FF UP (months)**	**RESULTS**
Brandli et al(2003)	U.S.A	50	20-100	RP	54	5y bRFS 35-60%
Bastide et al(2006)	Germany	80	>20	RP	64	5y bRFS 58%
Wiebe el al(2008)	Canada	138(63% mets)	>50	RP,EBRT,ADT	51	5y bRFS 53%, 9y bRFS 0%
Guarneri et al(2012)	Germany	155	>20	EBRT+/- ADT	62	5Y bDFS 64.8%
Asamoah et al(2018)	Ghana	254	>= 20	EBRT(2D+3D) +/- ADT	43	5y bDFS 48%
Current study (2020)	Ghana	85	20-200	EBRT+/- ADT	87	5Y bffs 44-68% 10Y bffs 36-62% (PSA>100 did not reach 10 years 18%)

Dose escalation has been investigated in several randomised trials and have consistently been associated with improved biochemical outcomes. The Medical Research Council study RT01 randomised patients to 64Gy and 74Gy with 3-6 months of ADT in each of the arms. Biochemical recurrence was low in the 74Gy arm. The MD Anderson study randomised patients to 70Gy and 78Gy with similar outcomes for high risk prostate cancer. In the GETUG 06 trial dose escalation to 80Gy was associated with a decrease biochemical failure even in the absence of ADT compared to 70Gy. In the analysis of the patients studied, group C had the highest mean delivered dose of radiation to 73.36Gy compared to Group A and B for EBRT only treatment. Even when brachytherapy boost was used, group C had the highest mean dose of 129.36Gy. This may explain similarity in 5 year bffs between Group B and C. The mean duration of treatment was 9.3 weeks for an estimated 7.5 weeks of treatment in Group B may also have affected outcome resulting in the similarity between Group B and Group C at 5 years in spite of the lower presenting PSA.

Overall survival analysis based on pre-treatment PSA was estimated using KaplanMeier analysis. The status of about 32.3% of the cases followed up could not be determined and so patients were censored at date of last follow-up. Telephone calls were made to patients and their next of kin to help determine patient status. Some patients had wrong telephone numbers recorded in their patients' records while others had their phones switched off. Status of 65 patients was confirmed after this exercise.

In fig 11, the estimated 5 and 10 year overall survival was 100% for group B. That of group C remained at 100% for the first 2 years, dropped to about 93% and continued to about 13 years. Group A had the most variable overall survival over the follow up years. Overall survival at 5 years was 93.5% and 10 year survival was nearly 82%. It remained so for 16 years. The addition of ADT to EBRT is evidence based with several randomised control trials showing overall survival benefit. Several RTOG trials including RTOG 9212, EORTC trials the Quebec trial and Trans-Tasman radiation groups trials have compared no ADT ,short course ADT and long course ADT with all studies showing overall survival benefit of statistical significance with the use of long term ADT up to 36 months in high risk patients(Amini, Kavanagh and Rusthoven, 2016). The study by Nabid et al that suggested a similar outcome for 18 months ADT use is flaws by being underpowered(Nabid *et al.*, 2018). Group C which had the longest mean duration of ADT, nearly 3 month longer than group B also had overall survival at about 93% while group A with the shortest duration of ADT use had the worst overall survival although it did not reach statistically significant p value of 0.261.

In a review of 2 separate RTOG trials that fit the criteria of patients with high initial PSA levels of more than 50ng/ml, a total of 401 cases treated with EBRT and followed up for a median duration of 87.6 months, the 7 year overall survival was 52-69% for the different studies (Rodrigues *et al.*, 2011). In our study, the 7 year overall survival ranged from 93%100% for patients with PSA of more than 50ng/ml.

Patricia Tai reviewed 1534 Canadian patients retrospectively using the Saskatchewan provincial register. Patients were treated with all treatment modalities but mostly EBRT or ADT. Patients were stratified based on their pre-treatment PSA (20-49.9 50-99.9-100). After 67.2 months of median follow-up 5, 10, 15-year overall survival 65%, 28%, 9%(Tai *et al.*, 2012). With documented high level of evidence suggesting overall survival benefit with multimodality treatment the ADT only subgroup may have accounted for the low overall survival in this cohort compared to our study population.

A single institutional study by Alessia Guarneri and colleagues in university of Turin, Germany, that followed up high risk patients with PSA more than 20ng/ml, after a median follow-up time of 62 months, actuarial 5 year overall survival was 94.4 %. These patients were treated with EBRT with ADT(Guarneri *et al.*, 2013). The cohort is more comparable to the patients we studied who also received EBRT with ADT for definitive the treatment. The 5 year overall survival for our cohort ranged between 93-100%.

Table 42 shows comparism of overall survival were compared of this study with above quotes studies.

TABLE 42: COMPARISM OF CURRENT STUDY WITH SIMILAR STUDIES FOR OVERALL SURVIVAL OUTSCOMES

Name of author	**country**	**No of patients**	**PSA (ng/ml)**	**TREATMENT**	**MEDIAN FF UP (MONTHS)**	**RESULTS (OS 5Y:10Y)**
Tai et al(2012)	Canada	497 109 38	20-49.9 50-99.9 >100	EBRT	64 59 49	84%:58% 66%:32% 68%:34%
Rodrigues et al (RTOG)(2011)	USA/Canada	401	>50	EBRT	88	7Y 52%-69%:NS
Guarneri et al (2012)	Italy	155	>20	EBRT+ADT	62	94.4%:NS
Current study (2020)	Ghana	48 22 15	20-49.9 50-99.9 100-250	EBRT+ADT BRACHY+EBRT	Not reached 46 48	94%:82% 100%:100 86%

As part of the analysis, predictors of biochemical failure and overall survival were interrogated. Age, T stage, Gleason score, duration of ADT use, nadir PSA, time to Nadir PSA were studied for biochemical failure free survival. For overall survival, all the predictors of biochemical failure were studied in addition to time to biochemical failure. Duration of ADT use was not a predictor of bffs or overall survival outcomes.

Kruskal-Wallis test of means was used for univariate analysis to assess predictors of biochemical failure. The calculated p values for nadir PSA and time to nadir PSA as predictors of biochemical failure is shown in table 22. The mean nadir PSA values were statistically significant different (p-value-0.00). On post hoc pairwise comparism the difference in means was between all the three groups compared to each other. Table 23 shows results of the comparism. Only nadir PSA retained its statistical significance to predict biochemical failure free survival on multivariate analysis using Cox regression with a p-value maintained at of 0.00.

Several studies have found nadir PSA value to be a predictor of biochemical failure. In a group of 375 patients who were treated with EBRT to a dose of 72Gy and who received ADT for 3-36 months and studied by Geara et al, nadir PSA was one of three predictors of biochemical outcomes identified on multivariate analysis using cox regression. The receiver operating characteristic (ROC) curve showed a nadir PSA of 0.06 ng/ml as the cut off value significantly predicting the patients' risk of biochemical recurrence ($p < 0.001$)(Geara *et al.*, 2017). The others were T-stage and combined Gleason score. An ROC curve for predicting risk of 4 year biochemical failure free survival in this study cohort was conducted. Figure 16 shows the ROC curve and table 37 the confusion matrix. A cut off point of 50% where true positive and false positive have an equal chance of occurring was chosen for prediction. A critical nadir PSA was of 0.07ng/ml similar to the Geara study was identified as significantly predicting biochemical recurrence with a p-value of 0.047 when all high risk prostate cancer patients were studied.

Nadir PSA was also found to predict biochemical outcomes when other treatment modalities such as high intensity frequency ultrasound (HIFU). Ganzer et al found that nadir PSA after HIFU correlates in a statistically significant manner with treatment failure and

disease free survival rates (DFSR) (Ganzer *et al.*, 2008). The nadir PSA was found to have a p-value of 0.02 on multivariate analysis using Cox regression model.

Four patients opted for BTO as ADT and received curative radiotherapy. One of these patients was lost to follow up but the other three were alive at the close of this study in December 2020. They have no evidence of biochemical recurrence. BTO is a viable option in patients who cannot afford medical castration. Lifelong ADT does not improve biochemical failure free survival or overall survival when compared to long course GNRH agonist given for 36. BTO is a permanent procedure therefore the risk of biochemical failure and progression to castrate resistant prostate cancer will have to be explained in detail to all patients who opt for it as a choice of ADT. It also has fewer medial side effects.

Literature abounds with studies on ADT use and its adverse effects. GNRH agonist was the most used form of castration in more than 90% of patients treated for high risk prostate cancer at our centre. Similarly there is a body of evidence that suggests improved treatment outcomes in intermediate and high risk patients when treated with a combination of EBRT and ADT even with dose escalation(Schulz and Kagan, 2011)(Zelefsky *et al.*, 2011). Recent studies show GNRH antagonist with fewer cardiac effects relative to use of GNRH agonists with noninferiority established for controlling PSA levels. A recent meta-analysis by Abufarjah et al found no difference in PSA progression when GNRH agonist and GNRH antagonists were compared however there appeared to be lower overall mortality with GNRH antagonist use. Caveat emptor, this study has a relatively short follow- up(Abufaraj *et al.*, 2021).

An estimation of time to nadir was determined from date of completion of EBRT or brachytherapy whichever is later to date nadir PSA was recorded. Some studies have found it to predict biochemical failure. Time to nadir PSA was not found to be a predictor of biochemical failure in this cohort studied.

Primary, secondary and tertiary grades have all been shown to have significant prognostic implications and linked treatment outcome. It has been shown to be linked to development of metastasis and overall survival (Andrén *et al.*, 2006). Currently patients with Gleason score of 3+4 are grouped as group grade 2 and said to have better treatment outcomes compared to those with Gleason 4+3, group grade 3, thus stating individual Gleason score is helpful for prognostication as the primary score which describes the most abundant histological type is the driver of the natural history of the disease. Gleason score can also be used to grade variants of

the adenocarcinomas such as the small cell and ductal types. It is not useful for TCC of the prostate (Humphrey, 2004).

A record of individual primary and secondary Gleason grade in all patients studied. The modal primary Gleason score was 3 followed by pattern score 4. A few patients had primary Gleason score of 2 which is currently discouraged for samples attained on needle biopsies if there's a pattern 3 or 4 present(Epstein, 2000). Thirteen patients in the high risk group had primary Gleason score of 5 and received curative radiotherapy. Gleason grade 5 is represented by comedo necrosis and anaplastic cells which bear little resemblance to a normal prostate and portends worse treatment outcomes. It is an important prognosticator and is used for many risk assessment tools as shown in table 5 as a component for risk categorisation for various urological groups.

When biochemical failure free survival and overall survival outcomes were investigated for the patients based on their primary Gleason grade using log rank test, there was no difference in the curves estimated that was statistically significant. This comparism is however limited by the few number of patients with pattern 5 primary Gleason grade. Figures 12 shows biochemical failure free survival based on primary Gleason grade and figure 13 overall survival. P value calculated was 0.311 and 0.368 respectively.

An analysis was done for our patients based combined Gleason score groups as follows; less than or equal to 6, 7 and 8-10. The 5 years bffs was 76% for </=6 and 54% for 7 and 50% for Gleason score 8-10. The bffs curve of Gleason 7 was to the right of the curve for Gleason score 8-10 as was expected until the 5 year mark from where it crosses over to lie on its left with continued reduction in biochemical failure free survival till the end of the study period. At 10 years, the bffs were 70%, 24% and 50% for those with Gleason <=6, 7 and 8-10 respectively. A log rank comparism of the curves approaches statistical significance (p-value 0.08) in favour of patients with combined Gleason score of >/=6.

In this nonrandomised unmatched review, there is a risk of patients having multiple prognostic factors by chance or due to bias in choice and dose of treatment, their role as confounders and causing unexpected outcomes cannot be underestimated.

A further analysis of the Brandli et al study previously described, revealed a difference in outcome when patients in were stratified based on combined Gleason score. Gleason score of <8 had a 5 year biochemical recurrence free survival was of 57% compared to those with

Gleason score of >8 who had 38%.(Brandli *et al.*, 2003). Our 5 year biochemical failure free survival figures are higher than quoted in that study.

When stratified based on combined Gleason score and assessed for overall survival, both 5 and 10 year overall survival was above 90% except for Gleason 7 at 10 years which was just above 73%. The use of post treatment failure interventions including more ADT, Abiraterone and enzalutamide available currently for use in the metastatic castrate resistant setting could account for high overall survival even though biochemical failure rates were high.

In the study conducted in university of Turin, on multivariate analysis, only Gleason score was significantly associated overall survival: hazard ratio 2.6; p = 0.038 in favour of Gleason less than 7.

T staging and its potential impact on overall and biochemical failure free survival was analysed but limited by the lack of proper staging of the patients cohort reviewed. Proving it as predictor of treatment outcome is a tall order. On both univariate and multivariate analysis performed using the cox regression analysis, T stage appeared not to have a statistically significant ability to predict worse biochemical treatment outcomes. Several nomograms incorporate T staging for risk categorisation as shown in table 5. Proportion of stages T1, T2, T3 and T4 stages were described for all high risk prostate cancer and is represented in figure 8 by a bar chart.

In a systematic review by Thomas Van den Broeck and colleagues which investigated the Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer, after reviewing over 77 publications, 14 of which addressed differences in oncological outcomes between patients treated with EBRT as definitive treatment, high initial PSA was prognostic for overall mortality but was found to be prognostic in our study. Biochemical recurrence was also an independent risk factor for the development of distant metastasis and overall mortality(Van den Broeck *et al.*, 2019). The high biochemical free survival of group A did not translate into overall survival benefit in our analysis suggesting no influence of biochemical failure on overall survival although it must be stated that the difference in overall survival amongst the three groups did not reach statistical significance (pvalue 0.261). A short time to biochemical failure emerged as a strong predictor of poor overall survival in patients treated with EBRT (Van den Broeck *et al.*, 2019). Inherent in this factor are two other predictors of failure; nadir PSA and PSA doubling time. Inability to reach a low nadir PSA which may occur early and signify poor response to local treatment and fast

PSA doubling time due to recurrence of disease both of which have been found to predict poor overall survival could result in short time to biochemical failure hence its ability to predict poor overall survival(Van den Broeck *et al.*, 2019). Time to biochemical failure on multivariate analysis did not predict overall survival outcomes. In our study, group A which has the longest mean time to biochemical failure had the worst overall survival. Shorter duration of ADT use has been discussed as a possible cause.

Age did not statistically significantly impact biochemical or overall survival outcomes. Age however consistently had a direct relationship with overall survival/biochemical failure free survival with a negative beta value as seen in table 27. An increase in age is associated with poor biochemical failure free survival although this was not statistically significant. Competing factors acting as confounders; tumour stage and extent of treatment and co-morbid factors may have obscured its predictive ability.

Co morbid factors remain an important cause of the death in cancer patients. Cardiac disease is amongst the most important. Hypertension and diabetes mellitus were recorded for the patients reviewed. Hypertension was the most diagnosed co morbid factor. This compares to national trends which quote hypertension prevalence rates of 27%. The prolonged use of ADT ,18-36 ,given together with radiotherapy for high risk prostate cancer has been found to improve overall survive(Lawton *et al.*, 2017) but also has adverse quality of life effects including reduced libido and hot flushes several other medical complications mainly related to the metabolic syndrome exists.

In a meta-analysis by Lee et al, pre-existing DM was associated with a statistically significant risk of all-cause mortality but not prostate cancer specific mortality. Some of the patients had both hypertension and DM co-existing but comorbid factors, hypertension and DM were not on Cox regression analysis model to predict worse overall survival.

Charmie et al retrospectively reviewed 1031vetrans diagnosed with prostate cancer that was clinically localised from 1997-2004 in the Los Angeles area. Compared with patients no co-morbid conditions, there was a higher non-prostate cancer mortality for all stages of DM and patients with peripheral vascular disease(Chamie *et al.*, 2012). An attempt at incorporating co-morbid conditions in the decision making for prostate cancer patients especially with side

effects of treatment that may compound pre-existing patient conditions such as GNRH agonist or antagonist would is of critical importance.

PSA alone is inadequate for predicting survival outcomes. In our study it statistically significantly predicted biochemical failure free survival for PSA between 20-200ng/ml but not overall survival. Increasingly, clinico-genetic markers are being used to augment the prognostic abilities of various risk categorisation tools which combines multiple clinical and pathologic features. The Decipher test has proven itself a useful adjunct that has been validated in both radical prostatectomy patients and patients treated with EBRT as useful for predicting metastasis and death (Michalski *et al.*, 2018). Stratified on all other prognostic factors, this tool may actually help decipher the patients who require more intensified treatment due to high predicted risk of recurrence or de-escalation of treatment those who are likely to have a good prognosis.

CONCLUSION AND RECOMMENDATIONS

Prostate cancer remains an important public health concern and was the commonest male cancer seen at the hospital. The patients seen over the study period have similar demographic features to other parts of the world with a mean age of 67 years. Most of the patients were married. Hypertension and diabetes mellitus was the commonest co morbid factors.

Pathological diagnosis was available for 92.6 % of the patients followed up. More than 99% were adenocarcinoma. Combined Gleason score was available for 447 out of 448 patients with adenocarcinoma while the individual primary and secondary Gleason grade was reported for 367 of 448 patients representing 82% of histologically diagnosed adenocarcinoma of the prostate.

Majority of the Options for curative treatment are available and were employed in the management of patients resulting in biochemical failure free survival and overall survival comparable to what is found in literature.

In our analysis a high initial presenting PSA appeared to influence biochemical failure free survival with a p value of 0.033 depicting statistically significant benefit for low initial presenting PSA. Biochemical control did not seem to translate into overall survival benefit although salvage treatment.

Low nadir PSA levels when achieved predicts higher bffs although this has no consequence for disease outlook as was shown in the study.

Biochemical recurrence remains source of distress for patients and clinicians. Delayed biochemical recurrence will therefore have significant effect on the quality of life of patients. The ROC curve drawn for predicting bffs based on nadir PSA had low accuracy of 41% and was not fit for purpose.

Survival outcomes for patients treated with external beam radiotherapy and ADT at the National Radiotherapy Oncology and Nuclear Medicine Centre (NRONMC) of the Korle Bu Teaching Hospital (KBTH) is comparable to existing published datasets. When patients present with very high initial PSA at the start of treatment, this study shows benefit for curative treatment for PSA 20-200ng/ml evidenced by no difference in overall survival. The study suggests no threshold for withholding curative treatment based on pre-treatment PSA provided there is no evidence of distant metastasis.

When patients were stratified based on primary Gleason grade, there was no statistically significant difference in biochemical failure free survival or overall survival suggesting Gleason grade 5. There were few patients with primary Gleason grade of 5 in this study.

Stratified based combined Gleason score however, there was a trend towards statistical significance for both biochemical failure free survival and overall survival in favour of low grade tumour.

No other predictors of biochemical of overall survival outcomes were identified.

LIMITATIONS/STRENGTHS

This retrospect cohort study employed both descriptive and analytical methods to provide data on prostate cancer patients seen at the NRONMC of the KBTH, their demographics, tumour factors, treatment and follow up. Although plagued by some limitations stemming mainly from the retrospective study design, this study has several strengths.

Missing data was one of the most significant influencers of outcomes. Although 96 patients were effectively identified, not all information pertaining to their management was universally available for review. The absence of a data collecting tool prior to starting management means that data which could have been relevant to the study was not always captured or sometimes not captured in a manner that is useful for this study available as was the case with the staging of patients.

Patients were not matched for baseline characteristics which may have been a confounding factor. They may also not be representative of the general population because of lack of randomisation.

Treating clinician bias cannot be underestimated. Choice of treatment are influenced by several factors including both patient and doctor preferences. The choice of a D90 dose to 221Gy is not easily be explained.

Loss to follow up is another limitation to the study. Access to patients was hampered by telecommunication challenges as described in the study. Wrong telephone number was the bane of following up the patients. Reasons for loss to follow-up was difficult to ascertain.

Limited data on outcomes of treatment for patients with high pre-treatment PSA means their treatment remains unstandardized. This study although retrospective has the strength of adding to published literature and suggests a hypothesis: there is no difference in os outcomes for patients based on pre-treatment PSA levels. This hypothesis can be tested in a randomised study.

A study with larger population is likely to help develop an ROC curve capable of predicting biochemical failure based on nadir PSA values. Similarly, a larger population may will validate the difference in biochemical failure free survival this study suggests and help detect predictors of survival if in fact more exists.

The use of the Co-60 machine did not influence treatment survival outcomes as the delivered doses were above 70Gy. A study that compares the side effects between Co-60 and LINAC due to differences in integral dose would enriched this study.

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APPENDIX 1

DATA COLLECTION FORM

TOPIC: OUTCOMES AND DETERMINANTS OF PSA BASED HIGH RISK PROSTATE CANCER PATIENTS TREATED WITH CURATIVE RADIATION AT KORLE BU TEACHING HOSPITAL.

OUTCOMES AND DETERMINANTS OF PSA BASED HIGH RISK PROSTATE CANCER PATIENTS TREATED WITH CURATIVE RADIATION AT KORLE BU TEACHING HOSPITAL.

Demographic Variables

a) Folder Number……..

b) Age…….

Marital Status

a) Married……

b) Single……

c) Divorced…….

Occupation

Level of Education

a) Basic……

b) Secondary……

c) Tertiary……..

b) None……

Religion

a) Christian
b) Muslim
c) Traditional religion

CLINCAL VARIABLES

a) Disease Stage

I. T1……

II. T2 a,b,c…… III. T3a,b…….

IV. T4……

V. N yes/no VI. iPSA

b) Treatment Variables

I. Neoadjuvant ADT YES/NO

II. Duration…….

III. Adjuvant ADT YES/NO

IV. Duration…….

d) EBRT dose

e) BRACHY dose

Whole pelvis yes/no

Prostate only yes/no

f) Date of nadir……

g) Date of biochemical failure ……

h) Date of last follow up or death…….

APPENDIX 2

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No. KBTH/MD/98/21
Your Ref. No......

KORLE BU TEACHING HOSI
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-(
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

6th January, 2021

DR NAA ADORKOR ARYEETEY
NATIONAL RADIOTHERAPY ONCOLOGY AND
NUCLEAR MEDICINE CENTER
KORLE BU

SCIENTIFIC AND TECHNICAL COMMITTEE APPROVAL
PROTOCOL IDENTIFICATION NUMBER: KBTH-STC 000168/2020

The Korle Bu Teaching Hospital Scientific and Technical Committee (KBTH-STC), on 6th January, 2021 approved your submitted study protocol.

TITLE OF PROTOCOL: "Outcomes and Determinants of PSA Based High Risk Prostate Cancer Patients Treated with Curative Radiation at Korle Bu Teaching Hospital"

PRINCIPAL INVESTIGATOR: Dr Naa Adorkor Aryeetey

This approval requires that you **forward your approved document to Korle Bu Teaching Hospital –Institutional Review Board (KBTH-IRB) for the ethical aspect of the proposal to be assessed before the project can be initiated.**

This STC approval is valid till 30th September, 2021
You may, however, request extension of the approval period, or renewal as the case may be, should the study extend beyond the stated period.

Upon completion, you are required to submit a final report on the study to the STC. This is to enable the STC ensure among others that, the project has been implemented as per the approved protocol. You are also required to inform the KBTH-STC and Research Directorate of any publications that may emanate from the research findings.

Kindly note that, should the need arise, the KBTH-STC or IRB may institute appropriate measures to satisfy itself that study is being conducted according to the highest scientific and ethical standards.

Please note that any modification to the study protocol without Scientific Technical Committee (STC) approval renders this approval invalid.

Sincere regards,

Prof. G. Obeng Adjei
Chairman, KBTH-STC

Cc: The Chairman, KBTH-IRB

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No. KBTH/NRD/1938/21
Your Ref. No......

KORLE BU TEACHING HOSPITAL
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Tel: +233 302 667759/673034-6
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5th May, 2021

DR NAA ADORKOR ARYEETEY
NATIONAL RADIOTHERAPY ONCOLOGY AND
NUCLEAR MEDICINE CENTER
KORLE BU TEACHING HOSPITAL

OUTCOMES AND DETERMINANTS OF PSA BASED HIGH RISK PROSTATE CANCER PATIENTS TREATED WITH CURATIVE RADIATION AT KORLE BU TEACHING HOSPITAL

KBTH-IRB /000168/2020

Investigator: Dr Naa Adorkor Aryeetey

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled: "Outcomes and Determinants of PSA Based High Risk Prostate Cancer Patients Treated with Curative Radiation at Korle Bu Teaching Hospital"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 31st March, 2022. You are to submit annual report for continuing review.

Sincere regards,

DR. DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB

Cc: The Chief Executive Officer, KBTH
The Director of Medical Affairs, KBTH

MEDICAL DIRECTORATE
KORLE BU TEACHING HOSPITAL

5th May, 2021

THE HEAD
NATIONAL CENTRE FOR RADIOTHERAPY AND
NUCLEAR MEDICINE
KORLE BU

LETTER OF INTRODUCTION – DR NAA ADORKOR ARYEETEY
"OUTCOMES AND DETERMINANTS OF PSA BASED HIGH RISK PROSTATE CANCER PATIENTS TREATED WITH CURATIVE RADIATION AT KORLE BU TEACHING HOSPITAL"

I have the pleasure to introduce to you the above named Investigator from National Centre for Radiotherapy and Nuclear Medicine, Korle Bu. Dr Naa Adorkor Aryeetey sought and has been granted approval to conduct a study entitled "Outcomes and Determinants of PSA Based High Risk Prostate Cancer Patients Treated with Curative Radiation at Korle Bu Teaching Hospital".

She is to contact you to discuss the commencement date of the study.

Please verify her identity with a Government issued National ID card and accord her the needed assistance.

Attached is the Scientific and Technical Committee and Institutional Review Board approval, which specifies the terms.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No.....
Your Ref. No.....

KORLE BU TEACHING HOSPITAL
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5th May, 2021

DR NAA ADORKOR ARYEETEY
NATIONAL RADIOTHERAPY ONCOLOGY AND
NUCLEAR MEDICINE CENTER
KORLE BU TEACHING HOSPITAL

INSTITUTIONAL APPROVAL: KORLE BU TEACHING HOSPITAL-SCIENTIFIC AND TECHNICAL COMMITTEE/INSTITUTIONAL REVIEW BOARD (KBTH-STC/IRB/000168/2020

Following approval of your study entitled "Outcomes and Determinants of PSA Based High Risk Prostate Cancer Patients Treated with Curative Radiation at Korle Bu Teaching Hospital." by the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board.

I am pleased to inform you that institutional approval has been granted for the conduct of your study in Korle Bu Teaching Hospital.

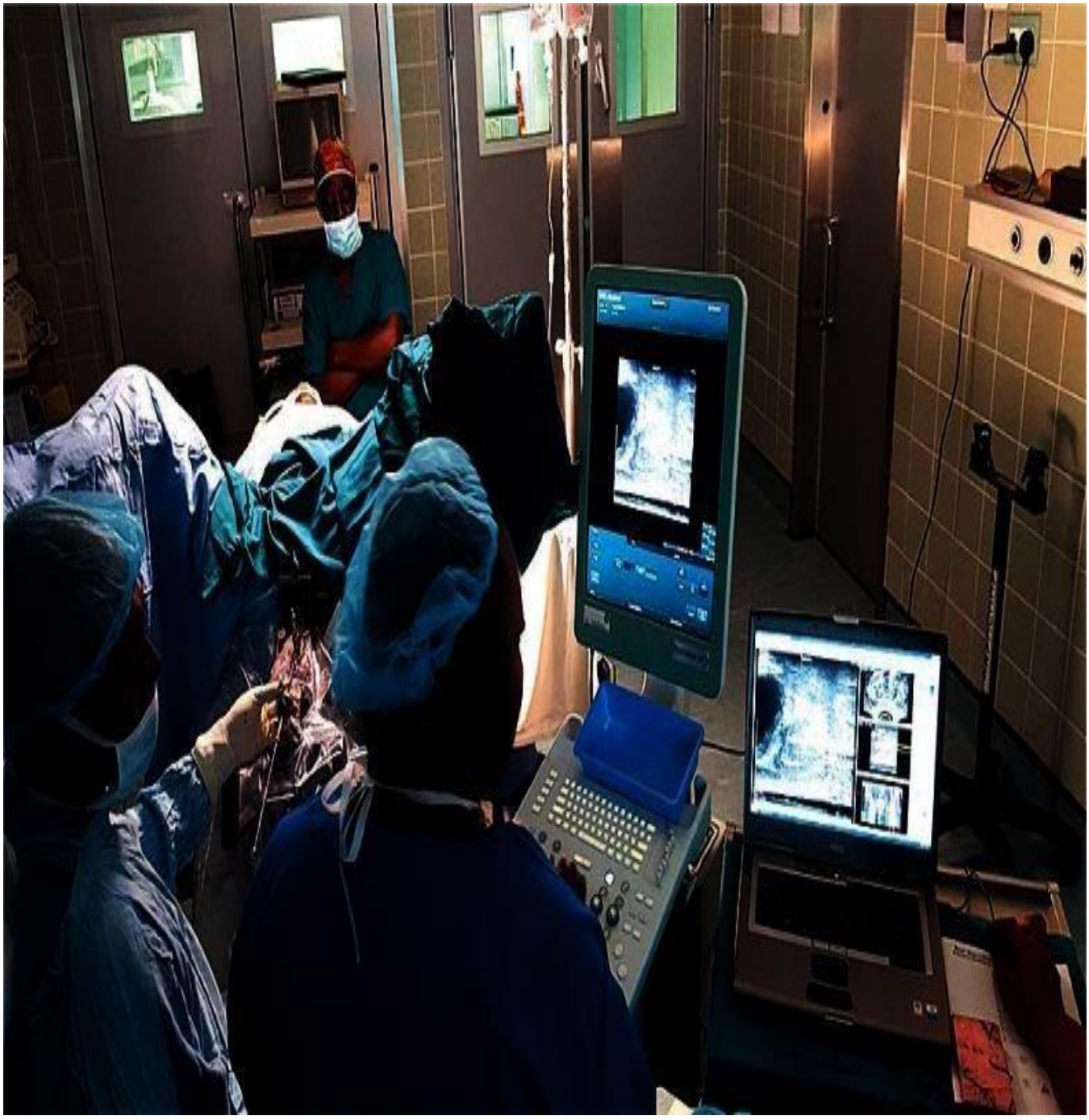
Please contact the Head of Department to discuss the commencement date of the study.

Please note that, this institutional approval is rendered invalid if the terms of the Institutional Reviewed Board/Scientific and Technical Committee approval are violated.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

APPENDIX 3



ProSeed™

DATE: 16th April 2011

BARD PROSEED™ RECORD SHEETFOR PROSTATE IMPLANTS

7													
6.5													
6													
5.5													
5													
4.5													
4													
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3					O			O	O	Ø			
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1				O	O	O		O	O	O			
	A	a	B	b	C	c	D	d	E	e	F	f	G

PLANNING DATA

ISOTOPE	I-125
PROSTATE VOLUME	
TOTAL ACTIVITY REQUIRED	
ACTIVITY PER SEED	
TOTAL NUMBER OF SEEDS	

PATIENT: AGC 43 AA

NO. OF SEEDS IMPLANTED: 45

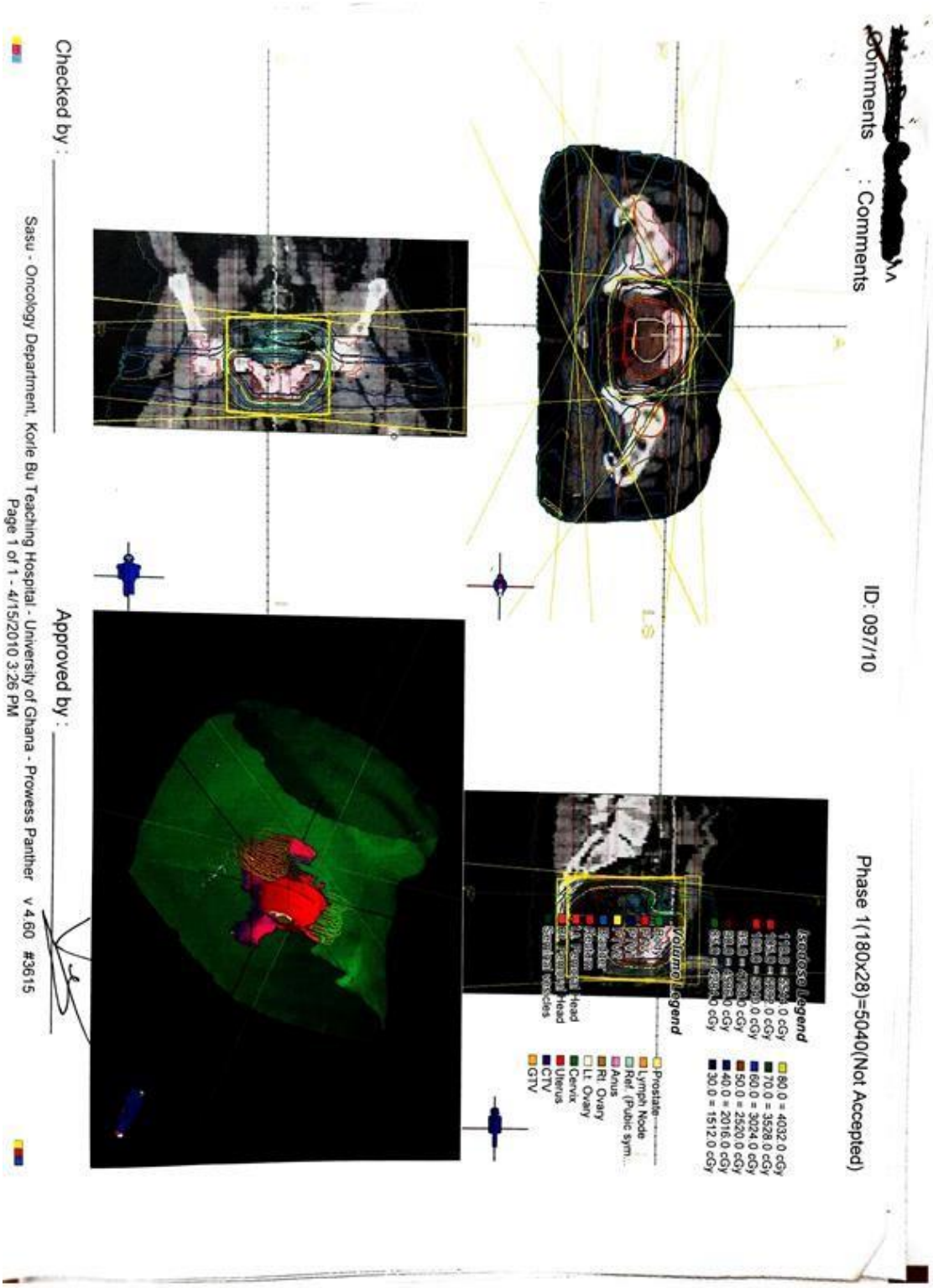
ACTIVITY IMPLANTED ______ mCi

1 2 3 4 5 6 7 8 9 10 11 12 13 14 (15)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 (15)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 (15)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Dp90: 182.21 Gy
Vp100: 96.06%
Dp150:
Dp200:
Du30: 129.15%
Vr100 : 5.00 cc

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	TOTAL
External	COLUMN	b	b	b	C	C	c	d	E	d	e	E	e	e					
	ROW	1	1.5	2.5	3	1	1	3	3	1	2.5	1	1	2					
	NO. OF SEEDS	3	3	3	2	4	4	3	3	3	1	4	4	3					
	TOTAL	3	6	9	11	15	19	22	25	28	29	33	37	40					
Internal	COLUMN	C	d	E															
	ROW	1.5	1.5	2															
	NO. OF SEEDS	2	1	2															
	TOTAL	42	43	45															

APPENDIX 4

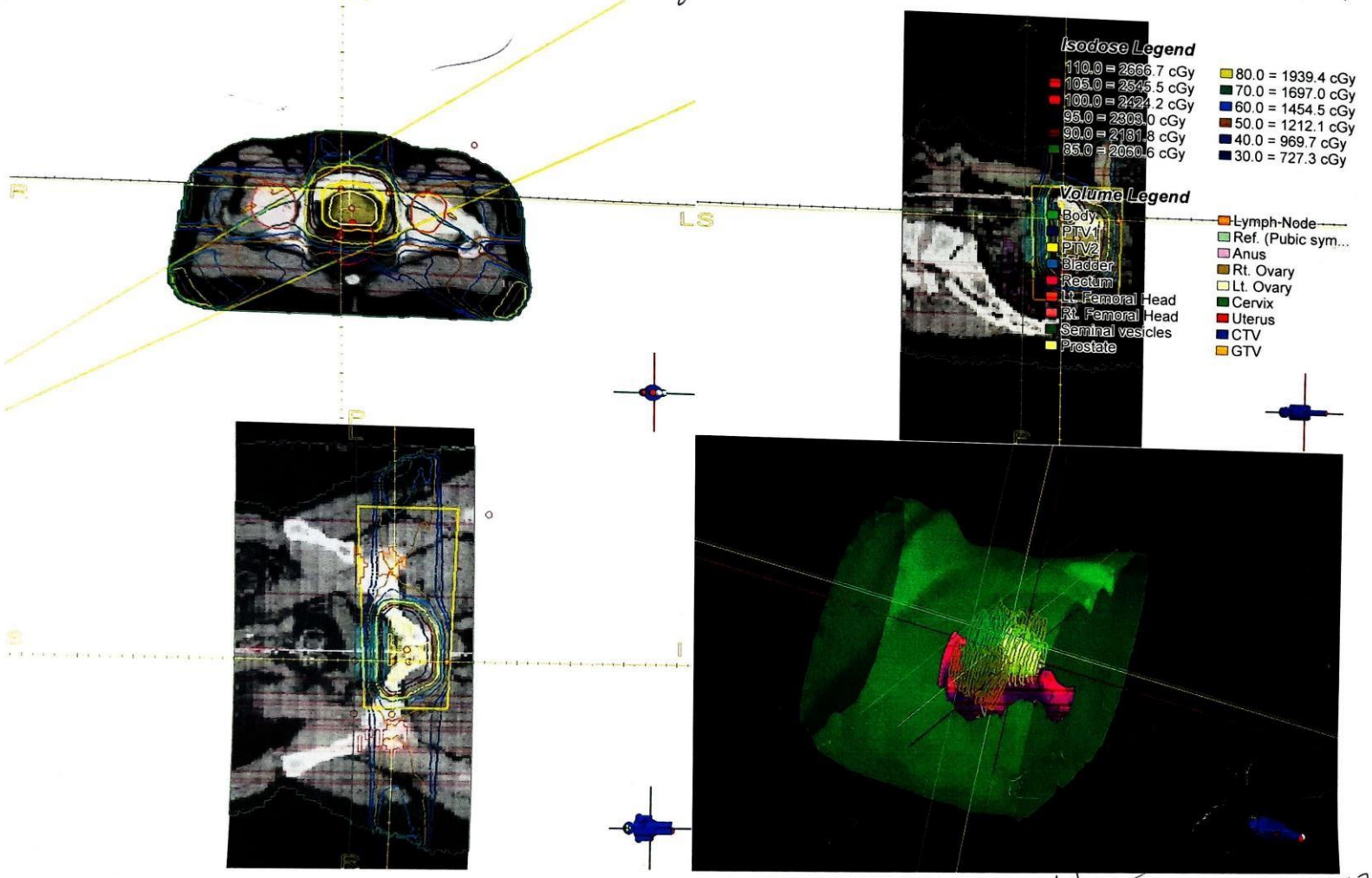

Comments : Comments
ID: 097/10
Phase 1(180x28)=5040(Not Accepted)
Isotoxic Legend
80.0 = 4032.0 cGy
70.0 = 3528.0 cGy
60.0 = 3024.0 cGy
50.0 = 2520.0 cGy
40.0 = 2016.0 cGy
30.0 = 1512.0 cGy
Volume Legend
Prostate
Lymph Node
Ref. (Pubic sym...
Anus
Rt. Ovary
Lt. Ovary
Cervix
Uterus
CTV
GTV
Checked by :
Approved by :
Sasu - Oncology Department, Korle Bu Teaching Hospital - University of Ghana - Prowess Panther v 4.60 #3615
Page 1 of 1 - 4/15/2010 3:26 PM

Comments : Comments

NB: New sime is 1·5cm inf the old sime

ID: 097/10

Copy of "Phase 2(200X12)=2400(Not Accepted)



Checked by : _____

Approved by : _____

200 X 12 = 2400

Dose Volume Histogram

Prowess Panther v 4.60

Patient Name: [redacted]^^^^
Patient ID: *097/10*
Physician: *Yarney*
Institution: *Oncology Department, Korle Bu Teaching Hospital*

Plan Name: *Phase 1(180x28)=5040*
Anatomical Site: *Pelvis*
Dosimetrist: *Planner*
Date: *4/15/2010*

Volume Name	PTV	Rectum	Lt. Femoral Head	Rt. Femoral Head	Seminal vesicles	Prostate
Volume Total (cc)	244.1	117.4	60.0	80.0	28.2	39.8
DLV at 100.0 cGy	244.1 cc 100.0 %	114.3 cc 97.4 %	60.0 cc 100.0 %	80.0 cc 100.0 %	28.2 cc 100.0 %	39.8 cc 100.0 %
D100	4563.7 cGy 90.5 %	26.4 cGy 0.5 %	870.5 cGy 17.3 %	685.9 cGy 13.6 %	4985.7 cGy 98.9 %	4669.2 cGy 92.6 %
D50	5059.3 cGy 100.4 %	4657.9 cGy 92.4 %	2872.2 cGy 57.0 %	2584.7 cGy 51.3 %	5090.7 cGy 101.0 %	5023.0 cGy 99.7 %
D25	5065.6 cGy 100.5 %	4967.9 cGy 98.6 %	3410.0 cGy 67.7 %	3322.6 cGy 65.9 %	5066.8 cGy 100.5 %	5047.7 cGy 100.2 %
V150	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %
V100	128.4 cc 52.6 %	19.6 cc 16.7 %	0.0 cc 0.0 %	0.0 cc 0.0 %	21.7 cc 76.9 %	15.7 cc 39.5 %
V95	232.6 cc 95.3 %	50.2 cc 42.7 %	0.0 cc 0.0 %	0.0 cc 0.0 %	28.2 cc 100.0 %	38.2 cc 96.0 %
Min Dose	4541.4 cGy 90.1 %	0.0 cGy 0.0 %	863.4 cGy 17.1 %	668.5 cGy 13.3 %	4961.0 cGy 98.4 %	4665.5 cGy 92.6 %
Max Dose	5264.3 cGy 104.5 %	5275.9 cGy 104.7 %	4488.0 cGy 89.0 %	4391.5 cGy 87.1 %	5188.0 cGy 102.9 %	5157.4 cGy 102.3 %
Mean Dose	5028.3 cGy 99.8 %	4136.8 cGy 82.1 %	2802.8 cGy 55.6 %	2735.5 cGy 54.3 %	5065.7 cGy 100.5 %	5004.1 cGy 99.3 %
EUD (cGy)	-	-	-	-	-	-

Checked by : _____

Approved by : _____

Dose Volume Histogram

Prowess Panther v 4.60

Patient Name: [redacted]^^^
Patient ID: *097/10*
Physician: *Yarney*
Institution: *Oncology Department, Korle Bu Teaching Hospital*

Plan Name: *Copy of "Phase 2(200X12)=2400*
Anatomical Site: *Pelvis*
Dosimetrist: *Planner*
Date: *6/1/2010*

Volume Name	PTV2	Rectum	Prostate	Ref. (Pubic symphysis)
Volume Total (cc)	88.9	117.4	39.8	12.6
DLV at 100.0 cGy	88.9 cc 100.0 %	82.1 cc 69.9 %	39.8 cc 100.0 %	12.6 cc 100.0 %
D100	2199.7 cGy 91.7 %	12.4 cGy 0.5 %	2237.0 cGy 93.2 %	907.2 cGy 37.8 %
D50	2410.6 cGy 100.4 %	793.2 cGy 33.0 %	2390.2 cGy 99.6 %	1824.1 cGy 76.0 %
D25	2430.8 cGy 101.3 %	1887.7 cGy 78.7 %	2413.4 cGy 100.6 %	2352.6 cGy 98.0 %
V150	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %	0.0 cc 0.0 %
V100	43.8 cc 49.2 %	0.1 cc 0.0 %	18.1 cc 45.3 %	2.6 cc 20.7 %
V95	86.5 cc 97.3 %	10.8 cc 9.2 %	38.7 cc 97.2 %	4.1 cc 32.8 %
Min Dose	2199.4 cGy 91.6 %	0.0 cGy 0.0 %	2230.5 cGy 92.9 %	899.1 cGy 37.5 %
Max Dose	2481.9 cGy 103.4 %	2410.5 cGy 100.4 %	2458.1 cGy 102.4 %	2472.2 cGy 103.0 %
Mean Dose	2390.5 cGy 99.6 %	976.5 cGy 40.7 %	2387.5 cGy 99.5 %	1889.7 cGy 78.7 %
EUD (cGy)	-	-	-	-

Checked by : _____

Approved by : _____