AN AUDIT AND REVIEW OF HISTOPATHOLOGICAL REPORTING OF PROSTATE CANCER ON PROSTATIC TISSUE SPECIMENS IN KENYATTA NATIONAL HOSPITAL

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DECLARATION

PRINCIPAL INVESTIGATOR

A declaration is hereby made that this work is original and has not been presented for examination in any other University or Institution of higher learning

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DEDICATION

This work is dedicated to my family for their moral support and encouragement.

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LIST OF ABBREVIATIONS

PSA: Prostate specific antigen

KNH: Kenyatta National Hospital

UoN: University of Nairobi

ERC: Ethics and Review Committee

GLOBOCAN: Global Cancer Incidence Mortality and Prevalence

WHO: World Health Organization

MYC: Myelocytoma

BRCA: Breast Cancer gene

HPC: Hereditary Prostate Cancer

TMPRSS: Transmembrane Protease Serine

ETS: E26 Transformation Specific

HGPIN: High Grade Prostatic Intraepithelial Neoplasia

CAP: College of American Pathologists

RCPA: Royal College of Pathologists of Australasia

ADASP: Association of Directors of Anatomic and Surgical Pathology

ICCR: International Collaboration on Cancer Reporting

TURP: Transurethral Resection of the Prostate

TRUS: Trans rectal Ultrasonography

VACURG: Veterans Administrative Cooperative Urological Research Group

H&E: Hematoxylin and Eosin

ISUP: International Society of Urological Pathology

AJCC: American Joint Committee on Cancer

SPSS: Statistical Package for the Social Sciences

ABSTRACT

Background

Cancer of the prostate is the second most frequent cancer in males globally and commonest in Kenya. The gold standard of diagnosis is histopathology. A complete report is required for patient management. Auditing of histopathology reporting is a key element of the quality assurance programme to ensure the generation of a reliable report. Studies have established that there have been significant changes in patient grading using the new modification of Gleason system and that there is observer variability in grading using this system. This study evaluated the completeness of prostate cancer reporting using the College of American Pathologists prostate cancer reporting protocol, to identify changes in grading with the 2014 modifications and to assess the level of inter-observer variability in grading.

Objective: The main objective was to audit and review histopathological reporting of prostate cancer on prostatic tissue specimens in Kenyatta National Hospital.

Study Design: A retrospective descriptive study.

Study Area: KNH/University of Nairobi (UoN) histopathology laboratory.

Study Population: A total of 137 prostatic tissue specimens previously reported as prostatic adenocarcinoma were audited.

Method: All consecutive request forms, reports and blocks for cases previously reported as prostate cancer were retrieved. Information from the request form and reports was then entered into the data collection tool which incorporated the CAP reporting protocol. Histological sections were prepared and stained using Hematoxylin and Eosin. The diagnosis and grading were reviewed using the International Society of Urological Pathologists 2014 Gleason system by the principal investigator and two consultant pathologists. The initial Gleason grades and grade groups were compared with the review findings.

Results: Age was indicated in 84.7% of all cases. The patient name and hospital number were

the only parameters provide in all cases. Other request form details including date of procedure, type of procedure, date specimen received in the laboratory, PSA level, clinician's details, clinical history and diagnosis were inconsistently indicated. Few macroscopic features were also inconsistently mentioned. The histological type in all cases was prostate adenocarcinoma not otherwise specified. In the initial report, 97.1% of cases were completely graded. Tumour volume was provided in 48.2% of cases. The other microscopic features were inconsistently reported. In the review, 94.2% of cases were graded. The predominant Gleason score sum was 9 while the grade group was 5. Gleason scores were upgraded in 51.8% of cases in the review whereas grade groups were upgraded in 43.1% of cases. The level of agreement was fair for the primary pattern (*k* 0.25), poor for the secondary pattern (*k* -0.31) and slight for the Gleason score sum (*k* 0.20).

Conclusions: Histopathologic request forms for histopathology of prostatic tissue specimens are not adequately filled. Completeness of reporting of tumour characteristics compares well with other studies done elsewhere. The presence and use of a standard reporting protocol that is inclusive of all required features ensures complete capture of all these essential parameters. There was an upward shift in Gleason grades and grade groups with the use of the ISUP 2014 modified Gleason system. The strength of agreement between the initial and review Gleason grades and scores ranged from poor to fair.

Recommendations: Sensitization of the clinicians on the importance of providing adequate information on the request forms. This can be done through continuous medical education sessions and clinico-pathological conferences. Use of the CAP cancer reporting protocol to enable the generation of a concise report with all the necessary features. There is need for institution of measures aimed at reducing observer variability in grading using the Gleason system. These include consensus grading of difficult cases, use of reference images and continuous training on any new changes in the system.

1.0 INTRODUCTION

Cancer of the prostate is the second commonest cancer and the sixth leading cause of cancer deaths in men globally (1,2,3). It is common in elderly males with the majority presenting after 65 years (4). In Kenya, it is the most common cancer among men and in the years 2004-2008 and 2013 the prevalence was 15.6% and 17.3% respectively (4,5).

The definitive diagnosis of prostate cancer is made on histopathology examination of biopsies. This is done following clinical suspicion and subsequent laboratory findings of elevated prostate specific antigen in blood (6). There is need to have a complete and accurate histopathology report as this will influence patient management. One of the goals during microscopy of prostatic core biopsies is to grade lesions positive for carcinoma. Gleason grading system is the universally accepted and widely used histological grading system. It has undergone various modifications over the years to suit current guidelines of patient care (7). Two major modifications were done in 2005 and 2014 by the ISUP. These led to changes in the criteria used to define the specific patterns and also on the general reporting guidelines. The aim was to come up with a more objective and clear means of grading that would be understood by all pathologists globally.

Gleason grading plays a significant role in determining the modalities of treatment and in prognostication. For this reason, it is important for grading to be done accurately. It is simple and easy to use but has been shown to have limitations that cause observer variations in interpretation (3,8,9,10). The degree of variation should be reasonable enough to sustain the validity of this system.

In this study, we audited the histopathological reporting of prostatic tissue specimens, assessed the variations and changes in grading with the new ISUP 2014 modified system and determined the level of inter-observer variability in grading at KNH.

2.0 LITERATURE REVIEW

2.1 Incidence and prevalence of cancer of the prostate

Worldwide, cancer of the prostate accounts for 15% of cancer in males and it is the second most frequent. It is the sixth cause of cancer deaths in males as of 2012 (1,11,12). It has variable incidence rates with the highest (69.5 per 100,000) in developed countries including Europe, Northern America, Oceania and some Caribbean nations (1,12). The higher rates of incidence in these areas has been attributed to the uptake of PSA screening. In developing countries the incidence is lower (14.5 per 100,000) but typically increasing (1,13,14). According to the Global Cancer Incidence Mortality and Prevalence and the World Health Organisation databases, in 2012, there were 1 million new cases with the majority in developed countries. It is predicted that there will be 20.3 million new cases of prostate cancer by the year 2030 (1).

The highest mortality tends to occur in low to medium resource countries and this is attributed to most cases being diagnosed in the late stages (1,11). In many developed nations, death rates for cancer of the prostate are decreasing with 307,000 deaths reported in 2012 (1).

According to GLOBOCAN database the incidence rate in Kenya was 31.7 - 55.1 per 100,000 in 2012. In 2013, the Nairobi cancer registry documented prostate cancer as the commonest cancer in males with a prevalence of 17.3% (5).

2.2 Anatomy and Histology of the normal prostate gland

The prostate is an exocrine gland of the male reproductive system. It weighs approximately 20-30g and measures 4x3x2 centimetres in an adult (15). It lies posterior to the pubic symphysis and anterior to the rectum (16,17).

The gland is divided into zones which include transition zone, central zone and peripheral zone (18,19). Age related benign prostatic hyperplasia commonly develops in the transition zone. The

peripheral zone is the largest portion occupying 70% of the glandular tissue and is the site of origin of 80% of adenocarcinomas.

Histologically, the prostate is composed of glands (70%) and stroma (30%) lined by a capsule (20,21).The glandular element is in the form of branching (papillary-like) convoluted glands that are irregularly shaped. The epithelium is composed of two cell layers (luminal and basal) with a surrounding basement membrane. The luminal secretory cells are tall columnar cells with prominent round basal nuclei and pale staining cytoplasm. The underlying basal cells are small, low cuboidal mucus secreting cells with eosinophilic cytoplasm. The basal cells are reserve cells and are most prominent in prostatic hyperplasia while are absent in carcinomas. The stroma is dense and composed of collagen, fibroblasts and smooth muscle fibres.

2.3 Risk factors, Pathogenesis and Histopathological features of cancer of the prostate

Risk factors for cancer of the prostate include old age, race, family history of prostate cancer and acquired somatic mutations (1). It is a disease of the aging male as its incidence increases with advancing age with the average age of diagnosis being 70 years (1,4,22,23). Racial predilection for men of African descent is well documented but the reason behind this is not clearly understood. Some authors suggest genetic susceptibility with a variant genome near the *MYC* oncogene on chromosome 8q24 (1). There is a strong familial predisposition more so in first degree relatives and this factor contributes to 5-10% of cases (1).

Somatic acquired mutations have been implicated in initiation of cellular transformation by dysregulation of cell survival and apoptosis (24). Mutations in BRCA genes, the androgen receptor, the HPC gene 1 and TMPRSS2 gene/ETS family have been linked to prostate cancer (1,24).

Prostate intraepithelial neoplasia is reported as the most likely precursor for development of invasive carcinoma (25). Another precursor lesion is atypical small acinar proliferation (25). The disease course begins with an initiating event that leads to dysplasia then malignant transformation to invasive carcinoma. Invasive carcinoma spreads locally to involve nearby organs like the urethra, bladder neck, seminal vesicles and rectum. It spreads to regional lymph nodes via the lymphatic system. Haematogenous dissemination follows with the bones being the commonest site of distant metastases. Lung, liver, and adrenal metastases have also been documented (26).

The predominant type of prostate cancer is adenocarcinoma which accounts for 95% of all prostate cancers with the acinar type comprising 95% and ductal type 5% (27). The remaining types of prostate cancer account for 5% (28). Microscopic features of prostate adenocarcinoma are divided into major and minor criteria (27,29,30). The three major criteria include change in architectural pattern, presence of a single cell layer and nuclear atypia (30). The minor criteria include intraluminal blue mucin, pink secretions and crystalloids, mitotic figures (extremely rare except in high grade tumours), adjacent high grade prostate intraepithelial neoplasia and amphophilic cytoplasm (30).

2.4 Audit and review in histopathology

A pathology laboratory based audit is a quality improvement procedure that aims to advance care and clinical outcomes through standard review of laboratory services against established principles with subsequent enforcement of change (31). Laboratory auditing is part and parcel of the continuous quality improvement process and a key element of a quality assurance programme (31). Audits compare and examine current practice against a set standard procedure and published guidelines. In the laboratory, audits are done to provide evidence on the quality of services and evidence that quality requirement processes are being met (32). Laboratory audits are of benefit to

both the patients and health professionals (32). They also provide an opportunity for pathologists to collaborate in patient care and may occasionally reveal diagnostic disagreements that need to be reconciled to prevent confusion or patient harm. Laboratory data have been found to influence over 70% of medical diagnoses thus it is pertinent to carry out regular auditing (31).

The audit process is cyclical and is done in the following stages; identifying the problem or area that needs auditing, defining criteria/standards that should be evidence based, data collection on current practice, comparing current practice with the criteria/guidelines and implementing any necessary changes. The final phase is re-auditing to monitor and sustain the new improvements (31,32). All elements in the pre-analytical, analytical and post-analytical phases should be analysed to provide a complete picture of the processes (33,34,35,36).

Auditing techniques employed in histopathology laboratories include examining consensus of cases, evaluating observer variation and checking diagnostic accuracy. The reviews are mostly blinded and random, a technique that has been demonstrated to be realistic, fair and excellent with a sensitivity of >99% to detect errors (42,43,39).

The significance and effectiveness of carrying out audits and re-audits in cancer reporting has been demonstrated in a number of studies. Onerheim *et al* showed a greater degree of completeness of reporting of breast cancer with an overall improvement from 0.9% to 20.5% between the first and second audits (40). After a departmental audit, Imperato *et al* also demonstrated an improvement in reporting of breast and prostate cancer that ranged from 12.6% to 19.9% and 1.4% to 23.9% respectively (40). This improvement was attributed to the first audit process which revealed the areas of deficiencies that were corrected before the subsequent re-audit.

In KNH, three audit studies in surgical pathology department have been done in the past. A study by Ndegwa in 2006 on auditing of histopathology reporting of mastectomy specimen revealed

there was a gap in clinical and microscopic information and he recommended the use of a standard proforma to ensure completeness of reporting (41). Another study by Maingi in 2009 on auditing of histopathological reporting of retinoblastoma revealed that ophthalmologists do not adequately fill request forms and that pathologists do not adequately document gross examination findings and some important prognostic features. He recommended the need to use standard reporting formats (42). The macroscopic details commonly missed out included tumour size, number, appearance and consistency. This study was followed by another retinoblastoma re-audit study done in 2016 by Midigo that revealed a better outcome in that there was more provision of adequate clinical information and the pathology reporting improved with the use of the CAP proforma (43).

2.5 Audit studies in prostate cancer pathology reporting

In a CAP Q-Probes study on adequacy of surgical pathology reporting of cancer, prostate cancer was found to have the highest percentage (88.4%) of inclusion of all required elements (40). The missing elements in descending order included extent of invasion (6%), extraprostatic extension (4.8%), seminal vesicle invasion (2.2%), margins (1%), secondary Gleason pattern (1%), and primary Gleason pattern (0.5%) (40). The study recommended and endorsed the use of checklists like CAP cancer reporting protocols to improve reporting. An audit report on prostate core biopsies provided by the West of Scotland cancer network based on Royal College of Pathologists of Australasia reporting guidelines demonstrated a high conformity of over 94.9%. In this study, the performance targets provided for exclusion of cases where it wasn't possible to report all the required elements due to specimen size and this may have contributed to a few cases that were not completely reported (44). The network advised for institution of systems that monitor pathology reports for completeness and provide feedback to the pathologists.

In a study by Aumann *et al* on radical prostatectomy specimen an overall of 48% of the reports had all the essential data that were determined based on RCPA, CAP and Professional association of German pathologists. This study also classified the reports on the basis of the reporting method and essential data were reported in 2.7% of the descriptive reports, 43.5% of structured reports and 97.2% of template based synoptic reports (45).

Siddiqui *et al* in 2010 in an audit of prostate core biopsy reports, found that in most cases pathologists provided essential information which included Gleason grading with total sum, total percentage of tumour and perineural invasion. The number of cores positive for tumour, was the only element that wasn't reported consistently (46). A re-audit was done in 2013 and found that information on number of cores involved by tumour was given in almost all cases (46). The improvement in reporting was partially related to the use of synoptic reporting system based on RCPA dataset.

Hobday *et al* in a review of prostate biopsies found a concordance rate of reporting of 78%. The discordance in the 22% was based on the Gleason grade and the tumour volume both of which changed after the review. They carried out a re-audit in 2015 where they assessed the change in Gleason grade, volume percentage change of >5% and perineural invasion discrepancy. The Gleason grade, perineural invasion and tumour volume changed in 18.2%, 4.9% and 4.9% of cases respectively (47). The study recommended that prostate cancer cases should at least be reviewed by a lead uropathologist and that there should be frequent self and laboratory audits.

2.6 Observer variation in Gleason grading

2.6.1 Methods of assessing observer variability

The most commonly reported measure of level observer variation in medical literature is the kappa statistic (48). It has the advantage of minimizing the possibility that the agreement between

observers was just by chance (49). When the observed agreement exceeds chance kappa is positive. Kappa value of 1 indicates perfect agreement whereas kappa value of 0 indicates agreement less by chance. The magnitude of positivity reflects the strength of agreement. Different scales have been proposed to classify the strength. One commonly used scale was proposed by Landis and Koch (50). Another technique for assessing observer variability is joint-probability of agreement (48). It is estimated as the percent agreement and is calculated by taking the number of ratings that are in agreement divided by total number of ratings with conversion of the end result into a percentage. It is the simplest method but does not take into account the fact that agreement may happen solely based on chance thus may lead to overestimation.

2.6.2 Gleason grading observer variability studies

Studies have been done to assess the level of observer variation in grading using the Gleason system. Many have shown a fairly acceptable level of observer variation. In the 1980s, Bain *et al* in 1982 demonstrated an inter-observer exact agreement rate of between 47-60% (k 0.605-0.836) whereas Rousselat in 1986 and de las Morenas in 1988 found inter-observer agreement rates of 65% and 66% respectively (51,54,55). In 1996 Ozdamar *et al* found overall intra-observer and inter-observer reproducibility rates of 78.1% and 70.8% respectively (54). In their study there was no statistical difference between intra- and inter- observer variations ($p>0.05$). McLean *et al* in 1997 found the extent of inter-observer variation (weighted kappa) for the raw Gleason scores (2-10) as 0.16-0.29 (poor to fair) with a total agreement rate of 9.9% and total disagreement rate of 43.7% (53). In 2001 Allsbrook *et al* found an overall kappa (k) coefficient for inter-observer agreement as 0.435 (moderate agreement) with a k range from 0.00 to 0.88 (52). Coard C. *et al* in 2004 demonstrated a 60% overall concordance in consensus Gleason scores (9). Melia J. *et al* in 2006 found an overall intra-observer agreement of 77%, k 0.66 and inter-observer agreement of

78%, k 0.54 (8). In 2011 Rodriguez-Urrego *et al* demonstrated an inter-observer agreement of κ = 0.72 (excellent) for the Gleason primary grade and for the other parameters κ ranging from 0.36 to 0.55 which was fair (55). Abdollahi A. *et al* in 2010 demonstrated a fair inter-observer agreement of k 0.29 and an almost perfect intra-observer reproducibility rate of 85.2% (58,3). Salmo *et al* in 2015 demonstrated complete agreement in 72% of cases that were reviewed (56).

2.6.3 Causes and implications of variation in grading

According to Allsbrook *et al,* the variability is attributed to; inherent subjectivity, differences in training, varying experience, volume of practice and familiarity with the Gleason system (54,59). The common sources of problems encountered by pathologists in grading include tumours with low grades, tumours with small circumscribed cribriform pattern and tumours that are borderline between the classical patterns (54,59,10). Discrepancies in Gleason grading can affect patient management and this was documented by Harbias *et al* in a collaborative study on implications of observer variability (58). In another study by Sooriakumaran *et al*, 19% of patients had their grading reviewed to a level that affected their clinical risk and 94% of the ones changed had their prognosis worsened (59). They compared Gleason grades between their referral hospital based pathologist and the referring facility's pathologist. The danger posed by the change in prognosis was that these patients would have received inaccurate information regarding their prognosis or they may have missed opportunities for appropriate radical treatment (59).

Other general factors that affect the quality of reporting include the quality and quantity of surgical specimen, technical processing of the tissue and clinico-pathological consultation (60).

2.6.4 Methods of reducing observer variation

Mechanisms that have been studied as means of minimizing this observer variability include centralised review of cases, education and training on application of Gleason system, and use of a diagnostic protocol with the criteria clearly outlined (9,55,62). Diagnostic protocols also help in ensuring there is complete reporting of all tumour characteristics by use of a checklist system.

2.7 Completeness of a pathology report and use of cancer reporting protocols

The completeness or adequacy of a histopathology report requires that the information given in the report should not only include the diagnosis but should also include pathological features of both prognostic and predictive significance (34). All scientifically validated features that directly influence choice of therapy should form part of the complete report.

Cancer reporting protocols consist of a checklist or dataset of features that are required or recommended in order to give out a complete report. These protocols have been in use over time to report tumours and also as audit tools (34). Examples of cancer reporting guidelines with standard reporting protocols in use include CAP, RCPA, ADASP and ICCR protocols (38,39,40,41).

The significance of protocols cannot be overemphasized as it has been proven superior in a vast majority of studies. Their use ensures completeness of reporting.

A multi-institutional study by Idowu *et al* demonstrated that centres which regularly utilized checklists reported all the necessary elements as opposed to those that did not use (88% versus 34%). Srigley *et al* demonstrated a higher rate of completeness of reporting using checklist based system (96.2%) in contrast to narrative based system (50.8%). It is important to also note that the presence and use of a checklist by itself does not warrant a sufficient report if they are not fully completed and verified (40).

2.8 Components of a complete histopathology request form

Adequate clinical information has been shown to affect the accuracy and completeness of pathology reports. Clinicians need to give adequate demographic and clinical information that will have an impact on the diagnostic process or affect its interpretation.

In a study done by Zuk *et al* about one fifth of all request forms had inaccurate or absent demographic and clinical details (66). Nutt *et al* in a study of extent and impact of incompletely filled request forms at a tertiary hospital, found that the most incomplete parameters were the clinician's contacts and the patient's current treatment. The diagnosis was not indicated in 39.1% of the forms analysed. The study recommended use of electronic requesting rather that manual so as to minimize errors (67).

Alagoa *et al* also demonstrated that clinicians do not always fill in the request forms properly. In their study only the patient name and investigation required were filled in all forms. All the other parameters including age, gender, hospital number, clinicians' details, working diagnosis, date of collection and nature of specimen were incompletely filled (68). Histopathology audit studies that have been done in KNH have shown similar findings of inadequacy in filling request forms (41,42). On the contrary, Siddiqui *et al* in an audit of prostate core biopsies found that clinical information provided was satisfactory except for digital rectal examination findings (69).

A complete prostate cancer histopathology request form should therefore contain the following parameters (64,65,66);-

- Patient health identifiers; patient name, age, hospital number and geographical location.
- Date when the procedure was performed and when the specimen was received in the laboratory.

- Relevant clinical information including brief clinical history, clinical diagnosis, prior biopsies, previous treatment, pre biopsy total/free PSA level, type of operative procedure, nature of specimen and the clinical stage.
- Name, signature, contact details of the requesting clinician.

The patient identifiers should match with the details on the specimen container in order to avoid mix ups and to facilitate comprehensive storage. Inclusion of the date helps in assessment of the turnaround time as a quality measure. The requesting clinician can be contacted to provide information regarding the clinical picture and for further patient follow up (70). Type and nature of specimen needs to be recorded as this cannot be determined in the laboratory if there is fragmentation of the specimen.

Information about prior biopsies or treatment helps in interpretation of the microscopic findings within an appropriate clinical context in order to get an accurate pathological diagnosis. In patients with prior biopsies Gleason grade and score should be indicated by the clinician to allow assessment of any advancement of the tumour to a higher grade and thus help in prognostication (71). Radiotherapy causes changes that may lead to misinterpretation. These changes include nuclear enlargement and nucleolar prominence in benign acinar epithelium, cytological atypia, nuclear enlargement and nuclear smudging in basal cells and increased stromal fibrosis that resembles tumour-induced desmoplasia (72). Androgen deprivation therapy may induce morphological changes in both prostate cancer and benign tissue (72). Indicating the pre biopsy PSA level helps in risk stratification in the process of patient prognostication (41,39).

2.9 Components of a complete prostate cancer histopathology report

2.9.1 Macroscopic information

Required and recommended grossing information include:

- Specimen identification.
- Specimen description.
- Gross tumour description (larger specimens) including presence or absence of lesion, location, size and consistency of the lesion.

Specimen identification entails assigning a pathology laboratory accession number to the specimen which will also appear on the request form, paraffin blocks, microscopy slides and the final report. This number aids in tracking and proper record keeping. The patient details on the request form should match with the details on the labelled specimen container in order to process the right specimen for the right patient. Identify and record nature and type of specimen. Specimen gross description before sectioning depends on the type. Needle core biopsies should be counted and measured (39,41). Current consensus recommendations from CAP, ISUP, RCPA and ADASP, urologists should submit a core per container and each should be processed as a separate specimen. In cases where there are two or more cores or if there is fragmentation, it becomes hard to determine number of cores and to quantify tumour in each core and yet these are prognostic indicators that need to be included. In such scenarios a pathologist ought to consult the clinician to seek clarification on the sampling so as to avoid giving wrong information (64).

TURP specimen (prostatic chips) should to be counted, measured and weighed. Prostatectomy specimen should be weighed and measured in three dimensions. In the radical prostatectomy specimen, any additional organs attached including vasa deferentia, seminal vesicles and bladder neck should be mentioned. The tumour should be measured and described when it is grossly

visible. Lymph nodes, if submitted, should be counted and described in terms of their size, appearance and anatomical location.

2.9.2 Microscopic information

Following an adequate gross description a thorough microscopic review is required arrive at an accurate diagnosis. It is important to mention the prognostic and predictive factors that will help in patient management (73). The microscopic details to be included are histologic type, Gleason grade, tumour volume, percentage of patterns 4 and 5, tumour location, extra prostatic extension, seminal vesicle invasion, perineural invasion, lymphovascular invasion, resection margins, lymph node status, intraductal carcinoma, any additional findings and pathologic stage.

Histologic type

Carcinomas other than adenocarcinoma are uncommon. The rare types of carcinoma if present should be recorded because some carry a poorer prognosis (65). Assigning of the tumour type usually follows the WHO classification scheme as highlighted in table 1.

Table 1: 2016 WHO classification of prostate tumours

Epithelial tumours	Other tumours

Glandular neoplasms Acinar adenocarcinoma • Atrophic • Pseudohyperplastic • Microcystic • Foamy gland • Mucinous (colloid) • Signet ring-like cell • Pleomorphic giant cell • Sarcomatoid Prostate intraepithelial neoplasia, high-grade Intra-ductal carcinoma Ductal adenocarcinoma • Cribriform • Papillary • Solid Urothelial carcinoma **Squamous neoplasms** Adenosquamous carcinoma Squamous cell carcinoma **Basal cell carcinoma**	Neuroendocrine tumours Mesenchymal tumours Hematolymphoid tumours Miscellaneous tumours Metastatic tumours Tumours of the seminal vesicles

Histologic grade; Gleason Grading System.

It was developed in 1966 by Donald. F. Gleason, a pathologist in Minnesota in collaboration with the VACURG. It was based on a study of 270 patients enrolled from 1959 to 1964 (68,69,70). The assessment was done on H&E stained tissue sections derived from larger specimens including prostatectomy and TURP specimens(76). The observations were done on low power (x4, x10) (74). The fundamental basis was on the degree of glandular differentiation and the architectural pattern of tumour growth in the stroma (77). Up to nine architectural patterns were described then characterized into five grades (1-5) (77). These grades are reported in decreasing differentiation

order but increasing in number. It was a general observation that prostate adenocarcinoma had heterogeneous patterns. Therefore, in the reporting the most predominant pattern was assigned as the primary grade while the second most common pattern in the same sample was assigned as the secondary grade. A final Gleason sum/score was then derived by adding up the two grades like a mathematical equation (for example Gleason 1+1=2). When there is one grade it is doubled to give the score. The scores range from 2-10. The original Gleason grading system has been refined and modified first by Gleason et al in 1974 and 1977 then by the IUSP in 2005 and 2014. It is the most recommended system by WHO since 1993 (54). Gleason grading plays a major role in determining treatment modality, risk stratification and patient prognostication (7).

Traditional Original Gleason grading system as established in 1960s-1970s

Gleason pattern (grade) 1

This is a rare pattern and it is the most well-differentiated (77). The glands are uniform, round to oval, single, separate, closely packed (back-to-back) and medium-sized. They are separated by thin stromal rims that don't exceed one gland diameter. The glands do not infiltrate into adjacent benign prostatic tissue (75). This pattern is usually seen in carcinomas arising from the transition zone (77).

Gleason pattern (grade) 2

This pattern consists of glands that are more loosely arranged with variable intermediate sizes and shapes. There is a slight increase in stroma between the glands and minimal stromal invasion (75). This pattern is usually seen in carcinomas arising from the transition zone and occasionally in the peripheral zone (77).

Gleason pattern (grade) 3

Pattern three is moderately differentiated and is the most common pattern in all prostatic adenocarcinomas. The glands are intermediate sized and are variably shaped; some angular, elongated or twisted. Each gland has an open lumen and is discrete and distinct with surrounding stroma (69,71). In the original Gleason system this pattern also included cribriform, papillary and glomeruloid glands (77).

Gleason pattern (grade) 4

The glandular architectures in pattern four include cribriform, papillary, fused/poorly defined and hypernephromatoid glands (77). The fused glands have no clear lumen

Gleason pattern (grade) 5

This pattern comprises of solid sheets, nests, cords, trabeculae or individual cells that invade through stroma (77). There is no trace of gland formation (75). Pattern five also includes comedonecrosis that is surrounded by papillary, cribriform, or solid glands.

ISUP 2005 Modified Gleason grading system

There were varied advancements in prostate cancer diagnosis and management from the time of development of the original Gleason system. The use of PSA testing as a screening tool enabled patients to be diagnosed earlier when the tumour volume and stage are low as opposed to the pre-PSA era where diagnosis was made in advanced stages with greater tumour volumes when Gleason established this system (74). The methods of obtaining specimen were also modified in that Gleason used 14 gauge needles to obtain a few thick biopsies and was not site specific but this has since changed to use of 18 gauge needles to give thin multiple biopsies (up to 9-12) with a systematic and site specific (apex, mid, base) sampling (74). Radical prostatectomy was not a common procedure in the 1960s and processing of the prostates was not as extensive as is currently undertaken (74). With these greater sampling techniques there was need to update Gleason grading

system accordingly (76). Immunohistochemistry staining for basal cells has led to the discovery that Gleason's original 1+1=2 tumours would be currently identified as adenosis. In addition Gleason's original cribriform pattern 3 would currently be regarded as cribriform HGPIN or intraductal carcinoma of the prostate (68,69,70). A number of new variants of prostate adenocarcinoma were also discovered and thus needed grading (68,72). It was also noted that there was a subtle difference in application of the system among pathologists based on their own understanding and interpretation of the original Gleason system therefore the need to have a consensus to arrive at a common view (68,69). Because of these reason there was need to refine and modify the traditional Gleason system.

In March 2005, a group of 80 urological pathologists met in San Antonio Texas with an aim of standardizing the use of Gleason grading system (74). A consensus was arrived at when two-thirds of the group agreed. Changes were made and new findings were included in the system as highlighted below (7,68,69,70,72,73,74).

The general applications of the system and the specific architectural features of each pattern were re-defined. A general resolution was that a diagnosis of Gleason patterns 1 and 2 should not be made on core biopsies and that Gleason score 1+1=2 should not be diagnosed in any specimen except for very rare occasions. Pattern 1 was basically eliminated. Gleason score 3-4 (1+2, 2+1 and 2+2) on needle biopsies remained controversial given its poor reproducibility and poor correspondence on later radical prostatectomy. It was also agreed upon that Gleason scores 3-4 should not be assigned on core biopsies except only "rarely, if ever", on specimen from transition zone and this should be done with expert consultation.

In Gleason pattern 3 changes made included removal of individual cells as part of the features and to move large cribriform growths into pattern 4. Cribriform pattern 3 diagnosis was made in rare

occasions given the new stringent criteria which included well-circumscribed, smooth and rounded glands the size of normal glands with evenly spaced lumina and even thickness of interconnecting cellular bridges. However with additional data combined with experiences accumulated in larger centres, they proposed that cribriform glands should be considered Gleason pattern 4. Definition of pattern 4 was widened to include ill-defined glands with poorly formed lumina.

Gleason pattern 5 remained as described but comedonecrosis was re-defined to include presence of necrotic cellular debri within the lumen and/or karryohexis. A summary of the architectural patterns 1-5 as modified in the 2005 IUSP is as shown below in table 2 below.

Table 2: 2005 Modified Gleason system

Pattern	**Description**
1	Circumscribed nodule of closely packed, but separate, uniform, rounded to oval, medium-sized acini
2	Fairly circumscribed, more loosely arranged, not quite as uniform Minimal infiltration at the edge of the tumor nodule
3	Discrete smaller glandular units of marked variation in size and shape Small smoothly circumscribed cribriform nodules Infiltrates in and amongst non-neoplastic acini
4	Fused microacinar glands Ill-defined glands with poorly formed glandular lumina. Large cribriform glands Cribriform glands with an irregular border Hypernephromatoid
5	No glandular differentiation. Solid sheets, cords, or single cells. Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

The features and recommendations for grading variants of prostate adenocarcinoma were also redefined by the consensus. Modifications were also made in the general reporting. Presence of a

limited quantity (<5% of tumour) of a lower grade secondary pattern should be ignored in all specimens. In this case the primary pattern should be doubled to give a score. On the contrary, presence of a higher grade secondary pattern even of a lower quantity (<5%) must be included as part of the score in core biopsies. In the event of presence of three patterns in needle biopsies, the overall score is obtained by adding the most predominant pattern with the worst (highest) pattern. In radical prostatectomy specimens, a tertiary pattern of higher grade should be reported separately (i.e. 3+3=6 with tertiary pattern 4). Needle biopsies that show different grades and which have been submitted in separate containers and localized anatomically should each be awarded its own score or optionally an overall score can still be given. In the event that cores are fragmented or submitted in one container, a general overall score should be awarded. For radical prostatectomy specimens that show varied grades in separate nodules, each dominant nodule should be awarded a score.

ISUP 2014 Modified Gleason grading system

Further modifications of the Gleason patterns with a proposal of a new grade grouping system were done in November 2014 at an IUSP conference that was held in Chicago, and which included pathologists, clinical specialists in urology, radiation and medical oncology (80). There were a few unresolved issues from the 2005 modified Gleason system that was in part due to lack of sufficient data (80). They arrived at a consensus on many issues. They resolved that in needle core biopsies Gleason patterns 1 and 2 and therefore Gleason scores 2-5 should not be made because they lack reproducibility and do not correlate well with subsequent radical prostatectomy grades (7).

It was agreed that the grading of mucinous (colloid) variant be based on the underlying glandular architecture. All cribriform glandular patterns and glomeruloid pattern should all be considered Gleason pattern 4 (76). Intraductal carcinoma shouldn’t be assigned a grade in the absence of

invasive component but a statement should be made to denote that its presence is invariably associated with aggressive carcinoma (73,74). It was recommended that the amount (percentage) of pattern 4 in score 7 particularly Gleason score 3+4=7, should be indicated because it has great implications in treatment approach (80). The characteristics of each pattern as of 2014 are summarised in table 3.

Table 3: 2014 Gleason pattern criteria

Gleason Pattern	**Criteria**
Pattern 3	Discrete well-formed individual glands with clear lumen Variably sized and shaped Some glands with infolding and branching
Pattern 4	Poorly formed, fused glands Ill-defined glands with poorly formed glandular lumina All cribriform glands Glomeruloid glands
Pattern 5	Sheets of tumour Individual cells Cords of cells Solid nests of cells with vague microacinar or only occasional gland space formation Comedonecrosis with central necrosis surrounded by cribriform or solid nests

A major consensus was the proposal of a new prognostic grade grouping system (69,72,73,74,75,76). This was on the basis that in practice scores 2-5 were no longer being awarded and the least score was 6 with a score range of 2-10. This could give patients a false impression that their cancer is mild and could even cause overtreatment of indolent disease (82). Another concern was that some centres were using inaccurate grade combinations for making therapeutic decisions and prognostication (82). Gleason scoring system was notably complex because with a combination of two numbers you could have 25 different scores. For these reasons the new grade

grouping of prostate carcinoma was proposed and it was based on a study done in John Hopkins Hospital (80). The 5 grade groups and histological features are outlined in table 2 (82). This new system has been found to be advantageous by providing a more simple and accurate stratification. It also provides the potential for reducing overtreatment of indolent cancer given that the lowest grade is 1 (74,76). The WHO accepted this new system in the year 2016 and recommended that it should be reported together with the usual Gleason grading system[for example; Gleason score 3+3=6(Grade Group 1)] (82).

The prognostic grade grouping system has been validated in a number of studies. In a study by Berney *et al* this system was validated using biochemical relapse as an outcome in radical prostatectomy whereas Epstein *et al* validated it using prostate cancer disease specific death as an outcome (83).

Table 4: Grade grouping system

Grade group	**Gleason score**	**Features**
1	2-6	Individual distinct, discrete well-formed glands
2	3+4=7	Well-formed glands with lesser component of poorly-formed/fused/cribriform
3	4+3=7	Poorly formed/fused/cribriform glands with lesser component of well-formed
4	4+4=8 3+5=8 5+3=8	Only poorly-formed/fused/cribriform glands
5	4+5=9 5+4=9 5+5=10	Lacks gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

Tumour extent/quantitation

Tumour volume, as documented in studies, is significant in predicting prognosis of prostate cancer although data are conflicting as to its independent prognostic significance (77,78). Most agree that tumour quantity has value in predicting metastasis, biochemical recurrence and disease-specific death (84). A study by Bostwick *et al* revealed that tumour volume is a useful prognostic factor and may be a valuable adjunct to staging (86). They assessed the utility of tumor volume in predicting progression of early prostate cancer based on composite published evidence from nine pathologic studies. Logistic regression was used to show how tumor volume is a good positive predictor of progression. They found that there was a 10% probability of capsular invasion, 10% probability of seminal vesicle invasion and 10% probability of metastases in tumors measuring about 0.5 cm^3, 4.0 cm^3 and 5.0 cm^3 respectively.

On the contrary Salomon *et al* and Kikuchi *et al* demonstrated that tumour volume doesn't give added information more so following radical prostatectomy (80,81). However, in the absence of other better prognosticators tumour quantity can provide guidance in prognostication (84).

There are different ways of estimating the tumour volume. In needle biopsies techniques employed include counting of the number of cores positive for tumour versus total number of cores, estimating the percentage of tumour in each core or measuring the linear tumour extent (63,62). In TURP specimen tumour volume is determined by estimating the percentage of prostatic tissue that is involved by the tumour or counting the number of positive chips versus the total number of chips. Additionally in TURP specimen, the percentage involvement is used to determine the clinical T1 sub stage, with ≤5% involvement being T1a and >5% being T1b (62). Tumour quantity in prostatectomy specimens is obtained by estimating the percentage through visual inspection or two dimensional measurement of a dominant nodule. Other people advocate for indication of number of tumour positive blocks out of the all the blocks received (70).

Percentage of Gleason patterns 4 and 5

Recording of percentage of Gleason patterns 4 and 5 is applicable to Gleason scores of ≥7. This was recommended during the 2014 conference and was found to play added role in prognostication of patients (62). The percentage of pattern 4 can either be limited (<10%) or extensive (>75%). Identification of percentage of pattern 4 in all cases of Gleason score 7 has been shown to influence therapeutic strategies in that some patients with limited pattern 4 in GS 3+4=7 can be good candidates for active surveillance (62).

Tumour location

The location of the tumour in the different prostate lobes has been found to play two main roles including influencing the choice of treatment and prognostication. It is not an independent prognostic variable but it is still applicable in association with the other prognosticators (70,85). Studies have shown that transitional zone tumours carry a more favourable prognosis than peripheral zone tumours (85). As regards the influence on choice of treatment, transitional zone tumours could be treated with a more conservative approach than the rest. In addition mentioning the specific location finds value when correlating the core biopsy findings and the imaging findings (70).

Extra prostatic extension (EPE)

Refers to the presence of tumour outside the prostate gland in the periprostatic fat (70). EPE has been shown to be a fundamental predictor of recurrence in node negative patients (70). It could be focal or extensive both of which carry a sufficiently greater risk of recurrence at both 5 and 10 years (70). It's also important to state the location of the EPE.

Seminal vesicle invasion (SVI)

Seminal vesicle invasion is an independent and an unfavourable prognostic factor and determinant of disease recurrence (64,78,82). It is defined as extension of the cancer into the wall of the seminal vesicle outside the prostate gland (70). Seminal vesicle invasion suggests that the tumour may be stage pT3b (65).

Bladder neck involvement

Bladder neck invasion refers to presence of neoplastic glands in the bladder neck smooth muscle at the prostatic base with no benign prostatic tissue (71) and is a fundamental predictor of PSA-recurrence (70). When there is bladder neck invasion in radical prostatectomies it is grouped as stage pT3a and in this scenario it has same biochemical recurrence free survival and cancer specific survival to patients with SVI or EPE.

Perineural invasion

Perineural invasion in core biopsies is linked to EPE in consecutive radical prostatectomies and it therefore has a prognostic significance (62). Perineural invasion can also independently predict an unfavourable outcome in patients treated with external beam radiation (62). It does not have prognostic significance in radical prostatectomy specimens (38,77).

Lymphovascular invasion (LVI)

Lymphovascular invasion refers to presence of tumour cells within endothelial-lined spaces with no or only thin underlying muscular walls (72). Presence of LVI has been associated with reduced time to biochemical progression, distant metastases and overall survival after radical prostatectomy (72). However a multivariate analysis by Jonathan *et al* concluded that studies are inconsistent on the value of LVI in independently predicting biochemical recurrence (90). This inconsistency could be due to difference in definition of LVI and that some studies used a few

number of patients who already had nodal metastases and SVI both of which influenced the stratification of patents (72).

Resection margins

During grossing the outer surface should be inked entirely to enable subtle assessment of surgical margins (62). The surgical margins are positive if the neoplastic cells touch the inked margin (62). Margins are designated negative if the neoplastic cells are near but not in contact with the inked surface. Positive surgical margins increase the chances of disease progression after radical prostatectomy and are also linked with a 2.6-fold increased likelihood of mortality (70).

Lymph node status

Lymph node invasion is an independent unfavourable prognostic factor (72). During microscopy it is important to indicate the anatomical location, if provided, and the number of positive nodes out of the total number of nodes submitted.

Intraductal carcinoma of prostate (IDC-P)

Intraductal carcinoma is defined as a well-circumscribed lesion composed of malignant cells surrounded by an intact basal cell layer (84). It is found in about 17% of radical prostatectomy specimens and is its presence is associated with invasive cancer (72). Its presence is also independently linked to increased risk of biochemical recurrence, lymph node metastases and reduced cancer specific survival rate (84). It is not common in needle biopsies.

Additional pathological findings

Other important findings that should be mentioned if present include presence of HGPIN, adenosis, benign nodular hyperplasia and inflammation (39,64).

Pathological stage

It is required to provide the TNM (Tumour, Node, Metastases) stage for radical prostatectomy specimens because it carries high value in determining the next treatment action and prognostication of the case. Pathologic staging is done after resection of the primary tumour. The tumour stage should be classified based on the pathologic AJCC TNM system (8th edition currently) which is as shown below (72).

Primary Tumour (pT)

pT2: Organ confined

pT3: Extraprostatic extension

pT3a: EPE (unilateral or bilateral) or microscopic invasion of bladder neck

pT3b: Tumour invades seminal vesicle(s)

pT4: Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional Lymph Nodes (pN)

pNX: Regional lymph nodes cannot be assessed

pN0: No positive regional nodes

pN1: Metastases in regional node(s)

Distant Metastasis (pM) (required only if confirmed pathologically)

pM1: Distant metastasis

pM1a: Non regional lymph nodes(s)

M1b: Bone(s)

M1c: Other site(s) with or without bone disease

2.10 Impact of modification of Gleason grading system

Studies have been done to demonstrate the effect of modification of Gleason system on the overall patient grades and also the impact it has on patient stratification during prognostication. A number have made a comparison between the old traditional Gleason system versus the ISUP 2005 modified system. In all these studies there was shift towards a higher grade and a decrease in the number of lower grades when the 2005 modified system was used. In a meta-analysis by Chen *et al*, one study documented an increase of scores 7-10 from 59% to 72% and a decrease in scores 2-5 from 27% to 0% in core biopsies (75). Another study documented an increase of scores 7 from 25.5% to 67.9% with a resultant increase in high risk category tumours from 31.3% to 41% on core biopsies (75). In one study assessing radical prostatectomies there was a 34% upgrade of score 6 to 7 or 8 (75).

Billis *et al* compared concordance of pattern and change of prognostic groups for the conventional and 2005 modified Gleason system and comparing the two there was agreement in 83.1%, 63.3% and 68.0% for Gleason primary pattern, secondary pattern and score respectively. In this study, there was a shift to a lower grade in 2.3% and to a higher grade 26.7% of the cases (91). In a review by Epstein *et al* on the impact of the 2005 ISUP modification, they documented a shift towards assigning higher Gleason scores on both biopsy and prostatectomy specimens (91). The overall shift in grading has been attributed to limiting the definition of pattern 3 and expanding the definition of pattern 4. In addition there was a decline in assigning scores of 2-4 on core needles biopsies (92).

Studies comparing the 2005 modification and the 2014 modification have also demonstrated an equally upgrade of the scores. Shah *et al* documented a marked decrease (80%) in Gleason score 6, a 28.57% decrease in Gleason score 8 and 60% increase in Gleason score 9 due to the new

criteria for pattern 4 (93). They also reported that the grade group offered a much precise, well defined and better means of prognostication as compared to the old risk stratification system.

2.11 College of American Pathologists

CAP is a leading organization of board-certified pathologists, serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. For 70 years, the CAP has fostered excellence in laboratories and advanced the practice of pathology and laboratory science (94).

The CAP Cancer protocols provide consistent and meaningful information that enable health care professionals to manage clinical data necessary in improving patient care. CAP cancer protocols are used by thousands of pathologists and other medical professionals to provide complete and uniform reporting of malignant tumours including current AJCC staging (95).

2.11 JUSTIFICATION

Prostate cancer is the commonest cancer in males in Kenya. There are at least 1000 new reported cases yearly with 850 deaths annually (4). High mortality has been attributed to late presentation in advanced stages that is caused in part by lack of access to proper health services including pathology laboratory services. Early diagnosis with a complete histopathology biopsy report would help in institution of early and proper treatment. Auditing of histopathology reporting is therefore

crucial as part of quality control and quality assurance in generating this reliable report. It is standard practice to have comprehensive reports that will help the clinician manage the patient totally.

Grading is one of the important features in determining the biologic behaviour of the tumour and the treatment choice. It is thus pivotal to have a high degree of precision and accuracy in reporting of the same specimen among pathologists.

Studies have been done elsewhere and have demonstrated that Gleason grading like in other histologic grading systems suffers from subjectivity. This system has also undergone a number of modifications that have been shown to have an influence on the grading and on patient prognostication.

No study has been done in KNH to audit the reporting of prostate cancer, to evaluate if there is an observer variability in grading and to assess the effect that the 2014 modification has had on Gleason grading and on patient prognostication.

This study therefore sought to evaluate the coverage and completeness of prostate cancer reporting using the CAP protocol, to identify changes in grading with the 2014 modifications and assess the level of inter-observer variability. Data from this study will also provide a basis for which future audits on prostate cancer can be done.

2.12 RESEARCH QUESTIONS

1. Are the request forms completely filled with adequate information?
2. Do the histopathology reports for prostate cancer contain all clinical, macroscopic and microscopic information?

3. What are the Gleason scores, grade groups and their changes from the initial report using the ISUP 2014 modified Gleason system?
4. What is the level of inter-observer variability in Gleason scores between the initial and review findings in the years 2016 and 2017?

2.13 OBJECTIVES

2.13.1 BROAD OBJECTIVE

To audit and review histopathological reporting of prostate cancer on prostatic tissue specimens in Kenyatta National Hospital.

2.13.2 SPECIFIC OBJECTIVES

1. To determine the completeness of information provided in the request forms.
2. To determine the completeness of documentation of macroscopic and microscopic features using the CAP reporting protocol.
3. To determine the Gleason scores, grade groups and their changes from the initial report using the ISUP 2014 modified Gleason system.
4. To determine the inter-observer variability in Gleason scores between the initial and review findings in the years 2016 and 2017.

3.0 MATERIALS AND METHODS

3.1 Study Design

This was a retrospective descriptive study.

3.2 Study Area

The study was conducted at the KNH/UoN histopathology laboratory.

3.3 Study Population

Prostatic tissue specimen including core biopsies, TURP specimen, simple prostatectomy and radical prostatectomy specimen previously reported as prostate cancer starting from September 2013 to January 2017.

3.4 Selection criteria

3.4.1 Inclusion criteria

Prostatic tissue specimen including core biopsies, TURP specimen, simple prostatectomy and radical prostatectomy specimen which were histologically confirmed to have prostate cancer from September 2013 to January 2017.

3.4.2 Exclusion criteria

Cases in which the request forms, reports and paraffin blocks were missing.

3.5 Sample size determination

The sample size was calculated using the agreement rate of 9.9% obtained from an audit study by McLean et al on inter-observer variation in prostate cancer Gleason scoring where they found an

overall agreement rate of 9.9% on raw Gleason scores(96). Fisher's formula was applied as shown below with a 95% confidence interval (97).

$$n = \frac{Z^2 \times P (1-P)}{d^2}$$

n – Sample size

Z – 1.96 (95% confidence interval)

P – Estimated prevalence 9.9%

d – Margin of error (precision error) = ±5%

Substituting into the formula,

$$n = \frac{1.96^2 \times 0.099 \times 0.901}{0.05^2}$$

n =137.06

n = 137

3.6 Sampling Method

All consecutive reports and paraffin blocks for prostatic tissue specimen including core biopsies, TURP specimen, simple prostatectomy and radical prostatectomy specimen, which were histologically confirmed to have prostate cancer from September 2013 to January 2017 were retrieved and included in the study.

3.7 Data Management

3.7.1 Data collection

1. The principal investigator selected reports that met the inclusion criteria from the records office. Each case was assigned a unique study number that corresponded to the laboratory number.
2. Clinical and demographic information was obtained from the request forms and entered into the data collection tool.
3. Macroscopic and microscopic information from the initial reports was entered into respective sections in the audit data collection tool that was derived from the CAP protocol.
4. The corresponding specimen paraffin wax embedded blocks were retrieved from the histopathology department for sectioning and H&E staining according to the recommended standards.
5. All the prepared slides were reviewed and reported by the principal investigator and thereafter confirmed by the two supervisors (consultant pathologists). The final Gleason scores and grade groups for the review were then derived using the ISUP 2014 Gleason system. The supervisors were blinded on the initial report microscopy findings. The initial and review report histological grade and grade group were then compared to assess the changes.

3.7.2 Data Analysis

Data was collected, cleaned, verified and entered into a Microsoft excel worksheet. The worksheet was imported into the statistical analysis software- SPSS version 20. It was presented as frequencies and percentages on tables, charts and graphs. Photomicrographs were also presented.

The level of agreement in Gleason grading between initial and review reports for 2016 and 2017 was calculated using Cohen kappa (k) statistic and interpreted using the scale shown in table 5.

Table 5: Interpretation of kappa values

Kappa value	Kappa agreement
<0.00	Poor (less than chance) agreement
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-1.00	Almost perfect agreement

3.8 Quality control and quality assurance.

3.8.1 Pre-analytical stage

- Proper report and tissue block identification; the lab number on the request forms was matched with the one on the tissue block.

- Relevant data from the request forms and reports was carefully entered into the audit data collection tool to avoid mix-up and transcription errors.
- The slides were clearly labelled and given a study number that corresponded to the lab number.
- The processing including sectioning, staining and mounting was carried out using a standard operating procedure availed at the work station and care was taken not to induce artefacts. Stains were kept covered and daily filtering was done before use. Contamination of slides was avoided by using standard staining rack.

3.8.2 Analytical stage

The principal investigator carefully screened the prepared slide sections and then reported them with two separate qualified pathologists.

3.8.3 Post-Analytical stage

All data was entered correctly into the computer database without transcription errors.

3.9 Ethical considerations

Ethical approval for the study protocol was sought and obtained from KNH/UoN-ERC before the study was conducted. Permission to carry out the processing and analysis in the laboratory was obtained from the head of KNH-UoN Histopathology laboratory. Patient confidentiality was maintained in all stages.

3.10 Results dissemination

A scientific paper will be published in a peer review journal.

4.0 RESULTS

This study was done between December 2018 and April 2019. A total of one hundred and thirty seven (137) cases were analyzed. Table 6 illustrates the distribution of the cases per year.

Table 6: Distribution of cases studied per year (n=137)

Year	**Frequency**	**Percentage (%)**
2013	47	34.3
2014	53	38.7
2015	21	15.3
2016	9	6.6
2017	7	5.1
TOTAL	**137**	**100**

The highest (47, 34.3%) and lowest (7, 5.1%) number of cases were reported in the years 2013 and 2017 respectively. Fifty three (38.7%), twenty one (15.3%) and nine (6.6%) cases were reported in the years 2014, 2015 and 2016 respectively.

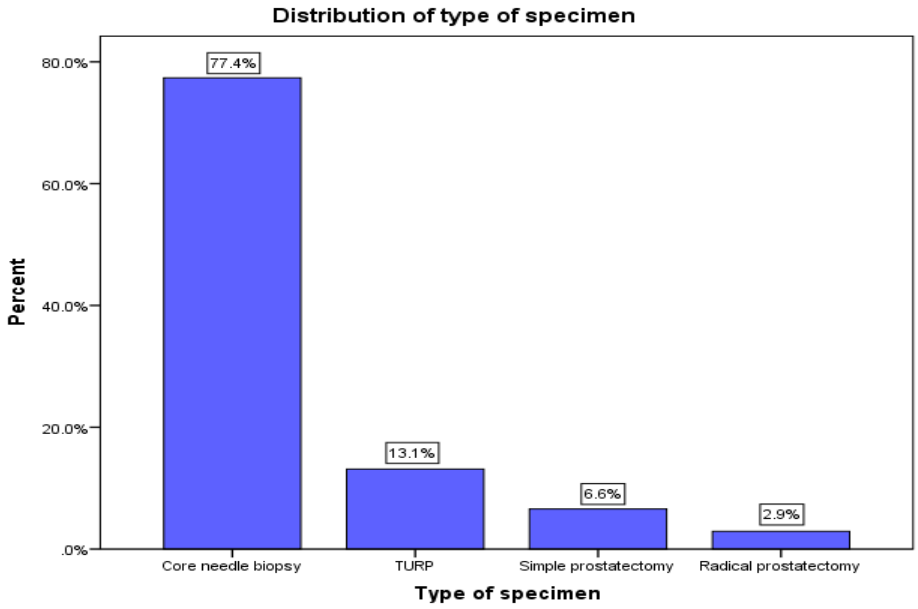


Figure 1: Distribution of type of specimen

The distribution of specimen type in all the years is as shown in figure 1. Majority of the specimens were core biopsies (106) accounting for 77.4% followed by TURP specimen (18 cases, 13.1%). Prostatectomy specimens were the least with nine (9) simple and four (4) radical prostatectomy specimens accounting for 6.6% and 2.9% of all specimens respectively.

4.1 Completeness of information provided in the request forms

Age

Out of the 137 cases a total of 116 (84.7%) had the age indicated whereas in 21 (15.3%) it was not indicated on the request forms. The mean age was 59 with a range of 25-90 years. Peak age was 71-80 years. Figure 2 shows the age distribution.

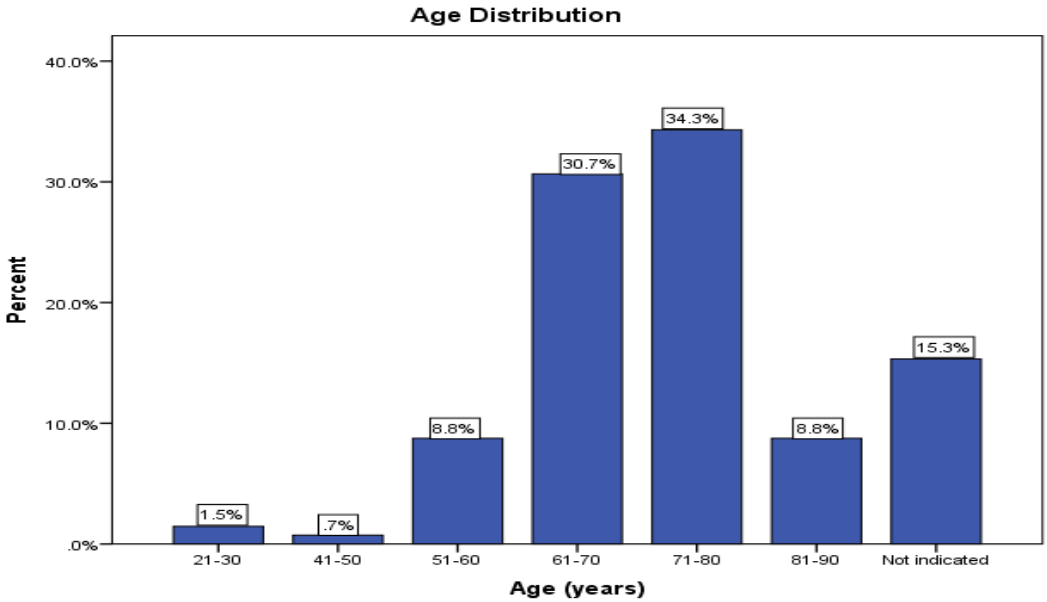


Figure 2: Age distribution

Hospital number, name, dates and clinical information

The patient name and hospital number were included in all the request forms (137). The date when the surgical procedure was done was indicated in 80 cases (58.4%). The type of procedure done was indicated in 107 cases (78.1%). In 127 cases (92.7%) the date when the specimen was received in the laboratory was indicated on the request form. The clinical history was indicated in 62 cases (45.3%). In 100 cases (73%) the clinical diagnosis was indicated. In all the cases (137) there was no information on the history as regards any cancer related therapy. The PSA level was indicated in 27 cases (19.7%). The clinician's details including name and signature were indicated in 128 (93.4%).

Table 7: Request form details.

	Indicated n (%)	Not indicated n (%)	Total n (%)
Hospital number	137 (100)	-	137 (100)
Patient name	137 (100)	-	137 (100)

Date of procedure	80 (58.4)	57 (41.6)	137 (100)
Date specimen received	127 (92.7)	10 (7.3)	137 (100)
Clinical history	62 (45.3)	75 (54.7)	137 (100)
Clinical diagnosis	100 (73)	37 (27)	137 (100)
Type of procedure	107 (78.1)	30 (21.9)	137 (100)
PSA level	27 (19.7)	110 (80.3)	137 (100)
Clinician details	128 (93.4)	9 (6.6)	137 (100)

4.2 Completeness of documentation of macroscopic and microscopic features

Completeness of documentation of macroscopic features

Table 8: Number and length of core biopsies

	Number of cores n (%)	Length of cores n (%)
Provided	100 (94.3)	98 (92.3)
Not provided	6 (5.7)	8 (7.7)
Total	106 (100)	106 (100)

Table 7 shows information on the number and length of core biopsies. The number of cores was provided in 100 cases (94.3%). The length of cores was provided in 98 cases (92.3%).

Table 9: Macroscopic findings in TURP specimen

	Number of chips n (%)	Weight of chips n (%)	Dimension n (%)
Provided	11 (61.1)	10 (55.6)	12 (66.7)
Not provided	7 (43.1)	8 (44.4)	6 (33.3)
Total	18 (100)	18 (100)	18 (100)

Out of the 18 TURP cases reported, 11 cases (61.1%) had the number of chips provided. The weight measured in grams was provided in 10 cases (55.6%) whereas the dimension measured in millimetres was provided in 12 cases (66.7%).

Table 10: Weight and dimensions of prostatectomy specimens

	Weight n (%)	Dimensions n (%)
Provided	12 (92.3)	11 (84.6)
Not provided	1 (7.7)	2 (15.4)
Total	13 (100)	13 (100)

The weight measured in grams of the prostatectomy specimens was provided in 12 cases (92.3%) whereas the dimensions measured in millimetres was provided in 11 cases (84.6%). There was no mention of the colour and presence of nodules in the dissected surface in all the prostatectomy cases.

Table 11: Seminal vesicles, lymph nodes in radical prostatectomies

	Provided n (%)	Not provided n (%)	Total
Seminal vesicles	3 (75)	1 (25)	4 (100)
Lymph nodes	1 (25)	3 (75)	4 (100)

Three (3, 75%) out of four radical prostatectomies were presented with seminal vesicles. Lymph nodes were submitted by the surgeons in only one (1, 25%) case.

Completeness of documentation of microscopic features in the initial report

Histologic type

All the one hundred and thirty seven cases (137, 100%) were diagnosed as prostate adenocarcinoma not otherwise specified.

Gleason grade

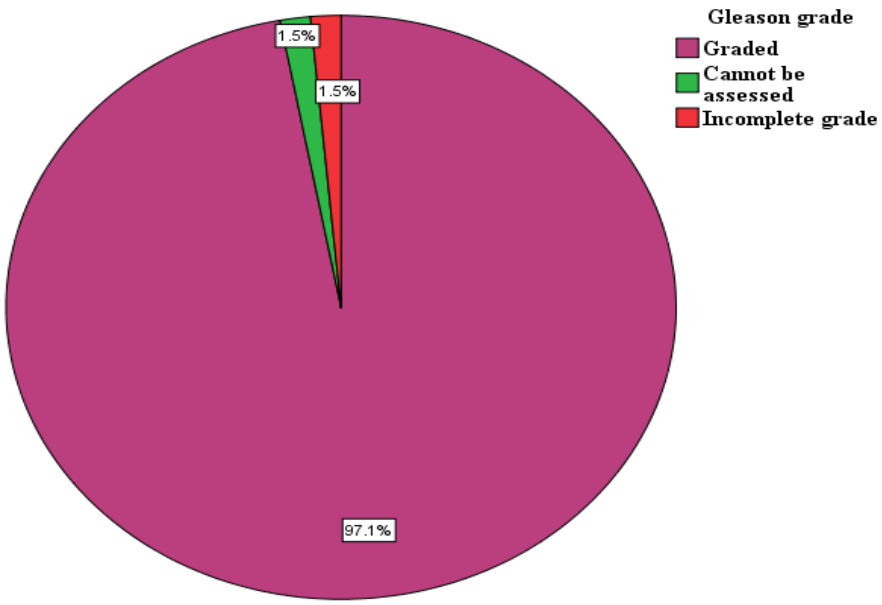


Figure 3: Gleason grading in the initial report.

Figure 3 illustrates the Gleason grading. 133 cases (97.0%) were graded completely. Two cases (1.5%) could not be assessed. These were cores which were small and fragmented. Two cases (1.5%) were incompletely graded in that there was a final score given but no mention of the primary and secondary patterns.

Table 12: Distribution of the primary and secondary patterns in the initial report

Pattern	Primary n (%)	Secondary n (%)
2	9 (6.6)	7 (5.1)
3	53 (38.7)	32 (23.4)
4	44 (32.1)	58 (42.3)
5	27 (19.7)	36 (26.3)
Not provided	2 (1.5)	2 (1.5)
Cannot be assessed	2(1.5)	2 (1.5)
Total	137 (100)	137 (100)

Table 12 illustrates the distribution of the primary and secondary Gleason patterns. The predominant primary pattern was 3 accounting for 38.7% (53 cases). Pattern 4 was the predominant secondary pattern accounting for 42.3% (58 cases).

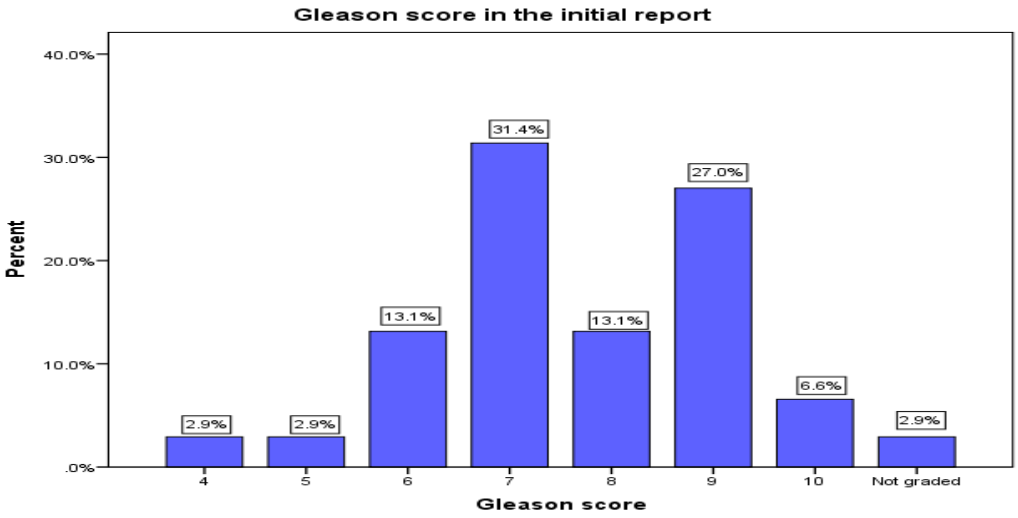


Figure 4: Distribution of final Gleason scores in the initial report

Figure 4 shows the distribution of the Gleason scores. The predominant Gleason score was 7 accounting for 31.4% (43 cases) of all the scores. Least predominant scores were 4 and 5 both with four cases (2.9%) each. Scores 6, 8, 9 and 10 accounted for 13.1% (18 cases), 13.1% (18 cases), 27.7% (38 cases) and 6.6% (9 cases) respectively.

Tumour volume

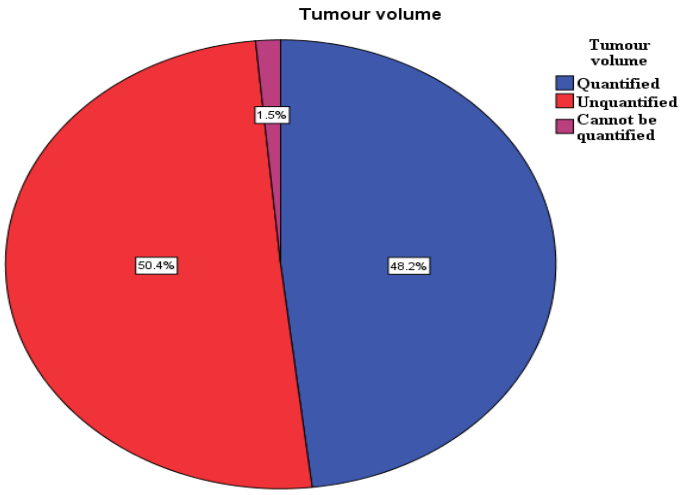


Figure 5: Tumour volume

Figure 5 illustrates the tumour volume. Out of the 137 cases tumour volume was quantified in 69 cases (50.4%). In 66 cases (48.2%) tumour volume was not mentioned. Tumour volume could not be quantified in two cases (1.5%). There was no mention of the reasons why in the two cases the volume could not be quantified.

Lymphovascular, perineural invasion and extra-prostatic extension.

Table 13: Findings on lymphovascular invasion, perineural invasion and extra-prostatic extension.

	Lymphovascular invasion		Perineural invasion		Extra-prostatic extension	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Present	15	10.7	26	18.6	6	4.4
Not identified	23	16.4	23	16.4	8	5.8

Not mentioned	99	70.7	88	62.9	123	89.8
Total	137	100	137	100	137	100

Lymphovascular invasion was present in 15 cases (10.7%) and was not identified in 23 cases (16.4%). It was not recorded in 99 cases (70.7%). Perineural invasion was identified in 26 cases (18.6%) and was not recorded in 23 cases (16.4%). It was not noted in 88 (62.9%) cases. Extra prostatic extension was identified in 6 cases (4.4%) and it was not identified in 8 cases (5.8%). It was not recorded in 123 cases (89.8%).

Urinary bladder neck invasion, seminal vesicle invasion and lymph node involvement

There was no record on the presence of urinary bladder neck invasion in all the radical prostatectomy specimens (4 cases, 100%). There was no seminal vesicle invasion identified in the three (75%) radical prostatectomy specimens which had the seminal vesicles. The submitted lymph node in one of the specimens turned out to be soft tissue and therefore there was no report of lymph node involvement by tumour.

Margins and pathologic stage

Table 14: Margins and pathologic stage

	Indicated n (%)	Not indicated n (%)	Total n (%)
Margin status	3 (75)	1 (25)	4 (100)
Pathologic stage	3 (75)	1 (25)	4 (100)

Table 14 shows the resection margin status and pathologic stage. Three cases (75%) out of the four radical prostatectomy specimen had positive margins. Only one case (25%) out of the four had the involved margin specified which was the anterior margin. In one case (25%) there was no record

on the margin status. Three cases (75%) out of the four radical prostatectomy specimens had the pathologic stage indicated all of which were pT2NxMx. In one case (25%) there was no record of the pathologic stage.

Additional pathological findings

Table 15: Additional pathological findings

	Frequency	Percentage (%)
None identified	121	88.4
Nodular prostatic hyperplasia	8	5.8
Inflammation	7	5.1
HGPIN	1	0.7
Total	137	100

There were no additional pathological findings in 121 cases (88.4%). Nodular prostatic hyperplasia was identified in 8 cases (5.8%). Chronic inflammation was identified in 7 cases (5.1%) while HGPIN was detected in 1 case (0.7%).

4.3. Gleason grades, grade groups and their changes using the ISUP 2014 system

Gleason grades and grade groups using the ISUP 2014 system

Figure 6: Gleason grading in the review

Figure 6 shows the Gleason grading in the review. 129 cases (94.2%) were graded in the review. 8 cases (5.9%) were not graded on account of discrepant diagnoses. In one of the TURP specimens the review diagnosis was a high grade papillary urothelial carcinoma. In one simple prostatectomy and six core biopsies, the review diagnosis was benign prostatic hyperplasia.

Table 16: Distribution of the primary and secondary patterns in the review

Pattern	Primary n (%)	Secondary n (%)
3	23 (16.8)	26 (19.0)
4	74 (54.0)	40 (29.2)
5	32 (23.4)	63 (46.0)
Not graded	8 (5.8)	8 (5.8)
Total	137 (100)	137 (100)

Table 16 shows the distribution of the primary and secondary patterns in the review. The predominant primary pattern was grade 4 (74 cases) and the least was grade 3 (23 cases) accounting for 54% and 16.8% respectively. The predominant secondary pattern was grade 5 (63 cases) and the least was grade 3 (26 cases) accounting for 46% and 19% respectively.

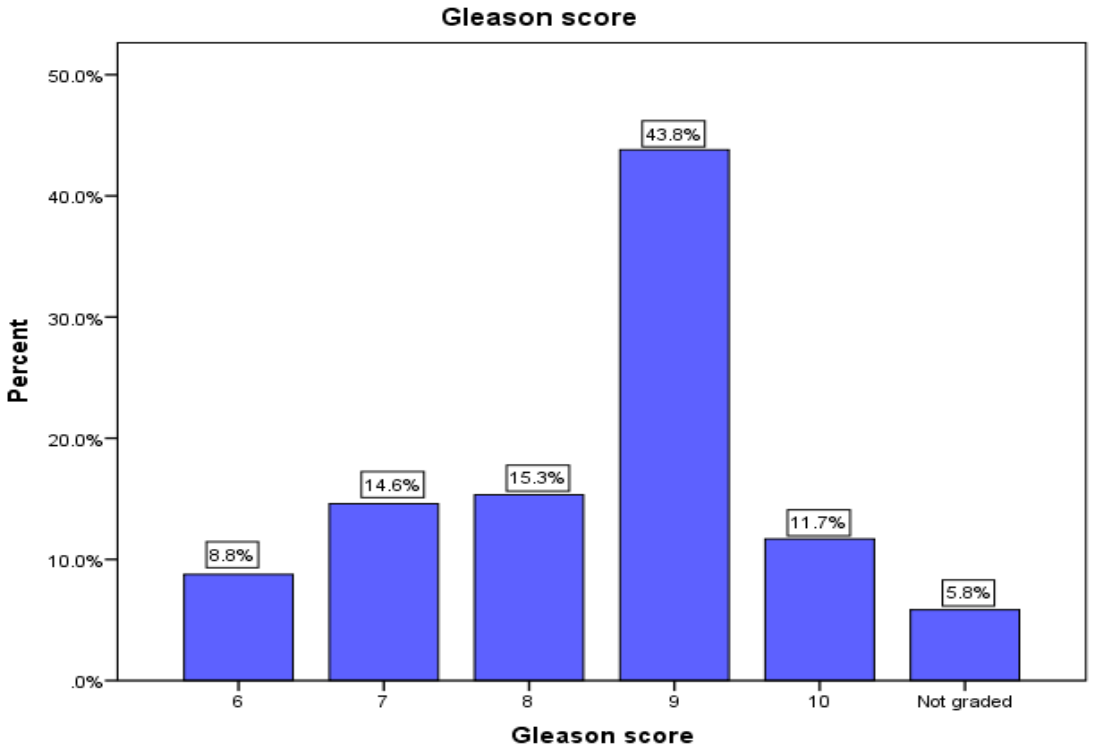


Figure 7: Distribution of Gleason scores in the review

Figure 7 illustrates the distribution of the final Gleason scores in the review. The predominant Gleason score was 9 with 60 cases (43.8%). The least score was 6 with 12 cases (8.8%). Scores 7, 8, and 10 comprised of 14.6% (20 cases), 15.3% (21 cases) and 11.7% (16 cases) respectively.

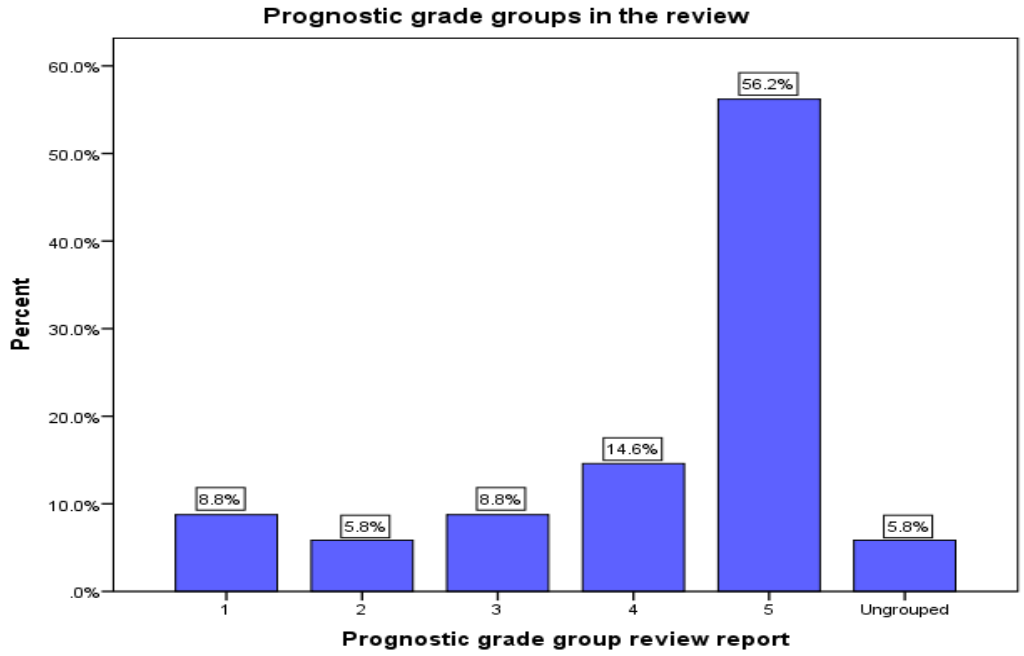


Figure 8: Prognostic grade groups in the review.

Figure 8 illustrates the prognostic grade groups in the review. The predominant prognostic grade group was 5 with 77 cases (56.2%). The least was group 2 with 8 cases (5.8%). Prognostic grade groups 1 (12 cases), 3 (12 cases) and 4 (20 cases) accounted for 8.8%, 8.8% and 14.6% respectively.

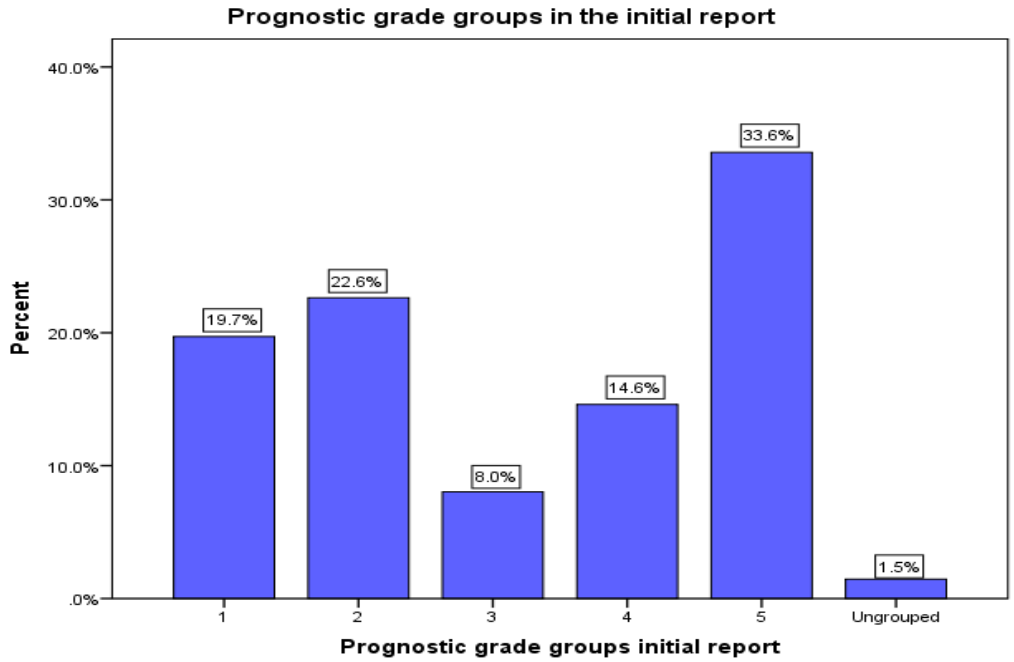


Figure 9: Prognostic grade groups in the initial report

Figure 9 illustrates the prognostic grade groups in the initial report. The predominant grade group was group 5 with 46 cases (33.6%). The least was group 3 with 11 cases (8.0%). Prognostic grade groups 1 (27 cases), 2 (31 cases) and 4 (20 cases) accounted for 19.7%, 22.6% and 14.6% respectively.

Changes in Gleason grades and grade groups between the initial and the review findings.

Table 17: Changes in Gleason scores between initial and review findings

	Frequency	Percentage (%)
Unchanged	44	32.1
Upgraded	71	51.8
Downgraded	14	10.2
Changed diagnosis	8	5.8
Total	137	100

Table 17 shows the changes in Gleason scores between the initial and review findings. A total of 44 cases (32.1%) remained unchanged upon re-classification with the ISUP 2014 system. Majority, 51.8% were upgraded. 10.2% of cases were downgraded.

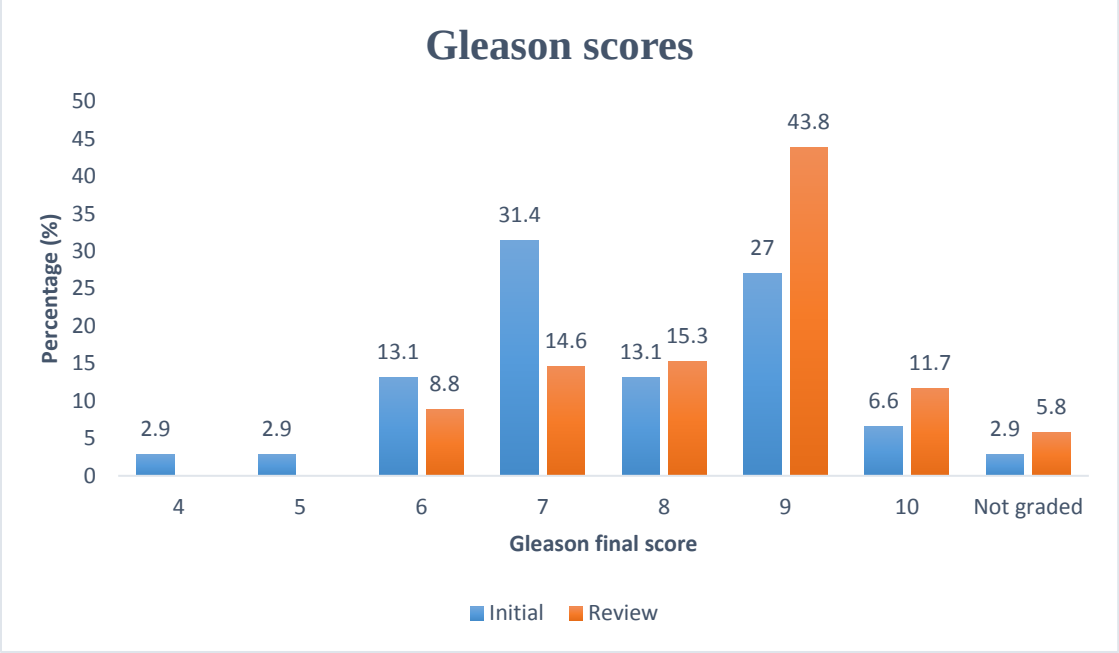


Figure 10: Gleason scores in the initial and review findings.

Figure10 illustrates the Gleason scores in both the initial and review findings. There was no score 4 and 5 in the review findings. There was a rise in the diagnosis of score 9 from an initial of 2.7% to 43.8%. Scores 8 and 10 were slightly increased in the review. The decline was on the diagnosis of score 6 and 7 from an initial of 13.1% to 8.8% and 31.4% to 14.6% respectively.

Table 18: Changes in the grade groups between the initial and review findings

	Frequency	Percentage (%)
Unchanged	60	43.8
Upgraded	59	43.1
Downgraded	10	7.3
Changed diagnosis	8	5.8
Total	137	100

Table 18 illustrates the changes in grade groups between the initial and review findings. The prognostic grade group in 60 cases (43.8%) remained unchanged. It was upgraded in 59 cases (43.1%) and downgraded in 10 cases (7.3%).

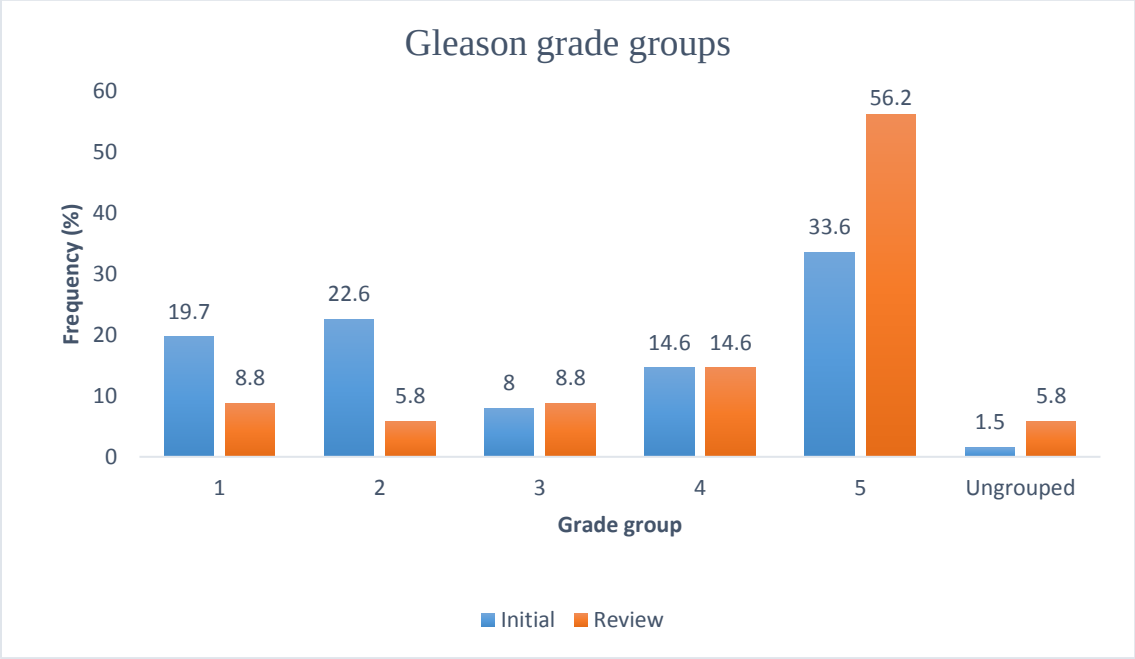


Figure 11: Grade groups in the initial and review findings

Figure 11 illustrates the grade groups in both the initial and review findings. There was a rise in cases of group 5 from an initial of 33.6% to 56.2%. Groups 1 and 2 were decreased in the review from an initial of 8.8% to 19.7% and 5.8% to 22.6% respectively. There was a slight increase in group 3 from 8 to 8.8%. Group 4 remained the same in both the initial and review findings.

4.4 Inter-observer variability between initial and review Gleason scores for 2016/2017

Table 19: Level of agreement between initial and review Gleason grade for 2016/2017

	Percent agreement (%)	kappa	Strength of agreement	p value
Primary pattern	46.7	0.25	Fair	0.043
Secondary pattern	20.0	-0.13	Poor (less than chance agreement)	0.806
Gleason score	33.3	0.20	Slight	0.026

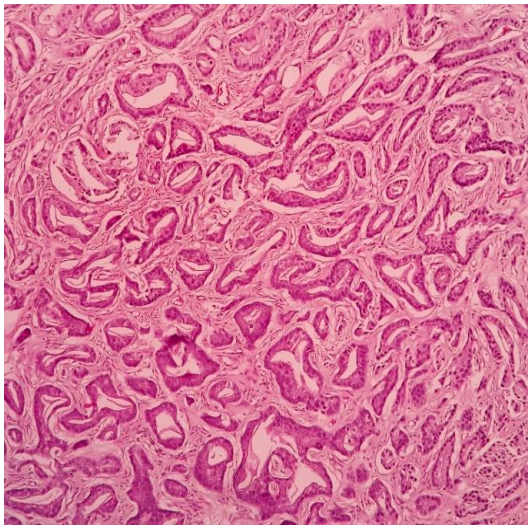
The primary pattern had a fair agreement (*k* 0.25). The secondary pattern had poor agreement (*k* -0.13). The level of agreement in Gleason score sum was slight (*k* 0.20).

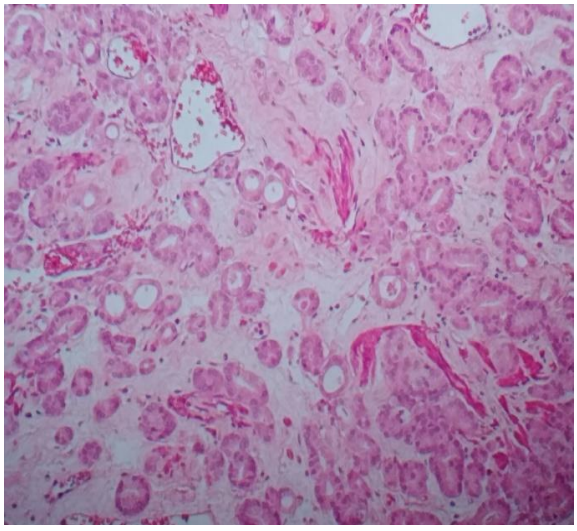
4.5 Examples of photomicrographs showing the different Gleason patterns

Gleason pattern 3

Pca 44: Variably sized discrete glands with well-formed lumina separated by stromal rims.

Pca 69: Small sized glands with well-formed lumina. Some are branching.





Pca 44 (x10) Pca 69 (x10)

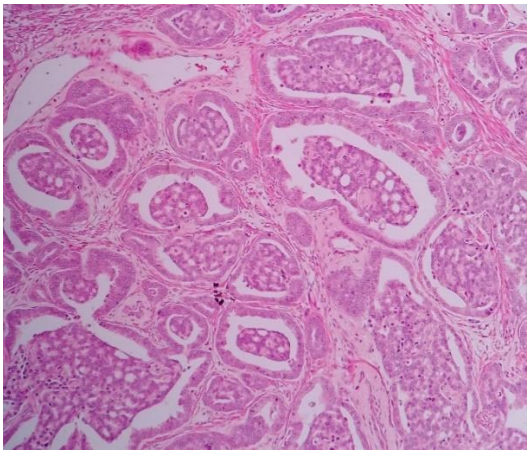
Gleason pattern 4

Pca 104a: Glomeruloid glands.

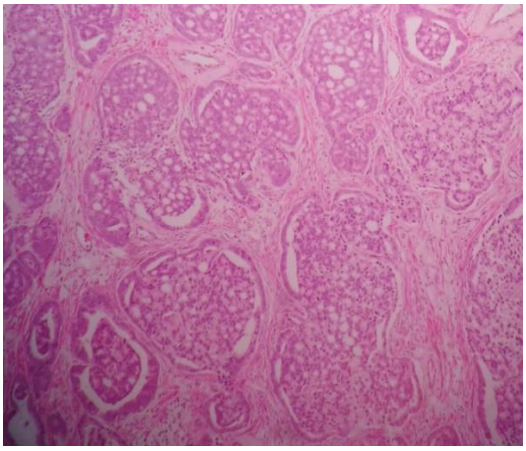
Pca 104b: Cribriform glands.

Pca 69: Ill-defined glands with poorly formed glandular lumina (“rosette-like feature”).

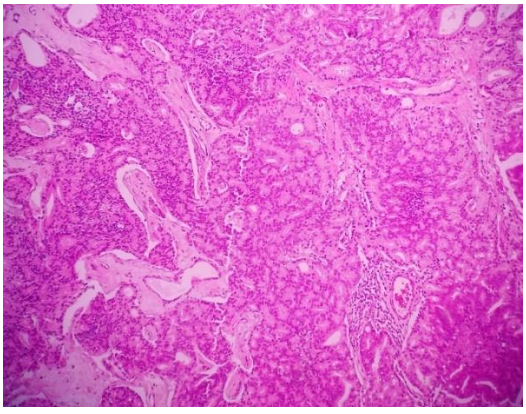
Pca 09: Poorly formed and fused glands.



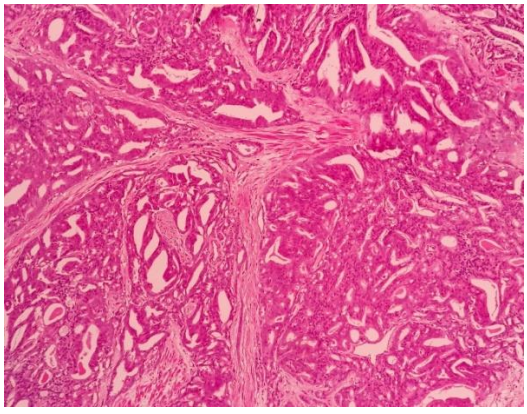
Pca 104a (x10)



Pca 104b (x10)



Pca 69 (x10)



Pca 09 (x10)

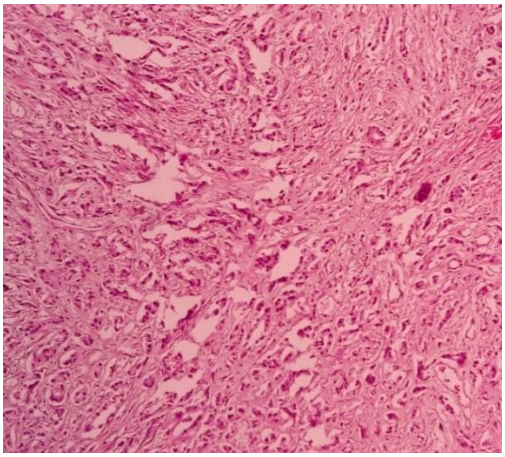
Gleason pattern 5

Pca 44: Individual cells and cords of cells.

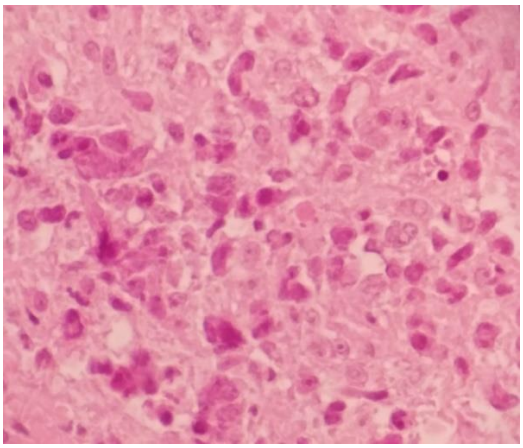
Pca 131: Individual cells at a higher power.

Pca 09a: Solid nests/sheets. Perineural invasion is also noted.

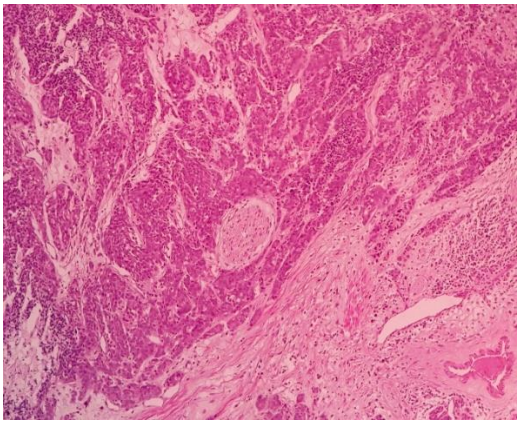
Pca 09b: Comedonecrosis with central necrosis surrounded by cribriform glands.



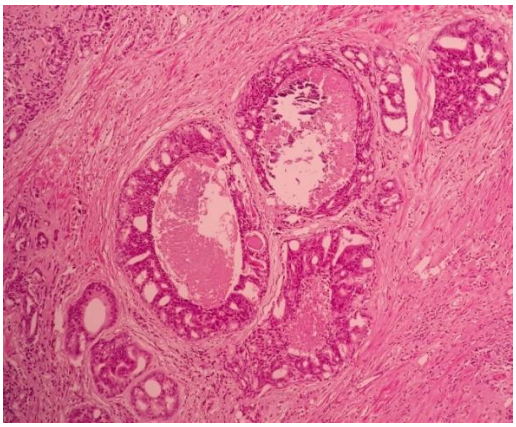
Pca 44 (x10)



Pca 131 (x40)



Pca 09a (x10)



Pca 09b (x10)

5.0 DISCUSSION

In this study, we audited the histopathological reporting of prostatic tissue specimens, assessed the variations and changes in grading with the new ISUP 2014 modified system and determined the level of inter-observer variability in grading at KNH. A total of 137 request forms with their histopathology reports were selected and corresponding paraffin blocks obtained for analysis. Clinical and demographic information obtained was generally inadequate in some cases. Likewise some macroscopic features were missing in a few cases. A number of microscopic features were equally not captured in the initial report. The shift in Gleason grades and prognostic grade groups in this study corresponded to findings in other studies done elsewhere. The level of observer

variability in this study ranged from poor to fair and the postulated reasons behind this finding are explained later in the text.

The pre-laboratory pre-analytical phase in the total testing process is majorly dependent on the clinician who is charged with the duty of filling a laboratory request form. The value of having a completely filled in request form with relevant and pertinent information cannot be underrated. Omission of information that is key to patient diagnosis will have a negative ripple effect on patient management.

Demographic parameters help identify the patient and also permit correlation with any previous reports. The hospital number and the patient name were the only consistent parameters included in all the forms. This correlates well with a study done by Alagoa *et al* in Nigeria where all the request forms had the patient name indicated (68). All the other parameters were incomplete. The patient's age was missing in 15.3% of all the cases. This is a similar finding to other studies however slightly higher than in studies by Alagoa *et al* and Nutt *et al* who found age missing in 11.5% and 3.7% of cases respectively (67,68). The date when the surgical procedure to obtain the specimen was done wasn't indicated in 41.6% of cases. This is higher compared to the study by Nutt *et al* which had 3.3% of cases missing the date. This date is important for assessing the general turnaround time from the time of specimen collection. The date of receipt of the specimen in the laboratory also contributes to measuring the turnaround time as a quality indicator. Most of the forms (92.7%) had this date indicated. It is of utmost importance to indicate the type of procedure performed and thence the specimen type obtained. This helps in proper handling of the specimen and avoidance of identification errors. This was missing in 21.9% of cases. This finding is similar to the study by Alagoa *et al* who found 11.0% of request forms having no information on the type of specimen. Adequate clinical history and clinical diagnosis contributes heavily to the

interpretation of laboratory findings. Sufficient clinical information helps the pathologists to interpret the report in the clinical context. It may also determine whether further analysis like special staining and immunohistochemistry, may be needed. In this study clinical history was lacking in 54.7% whereas the diagnosis was missing in 27% of the cases. This is comparable to findings by Alagoa *et al* and Burton *et al* who found that 16.5% and 6.1% respectively had no clinical history (98). A study by Nutt et al also had a similar outcome where 19.1% of request forms had no clinical diagnosis. The PSA level plays role in prognostication and also gives guidelines or pointers to the diagnosis during reporting of the surgical specimens. The PSA level was not indicated in 80.3% of cases. Details of the requesting clinician including name, signature and contact details are very important. It makes it possible to get more clinical information from the clinicians also convey to them critical findings. In 6.6% of cases the clinician's details were not provided. This is comparable to the finding of 6.5% in the study by Nutt *et al*. Previous cancer related therapy including hormonal and radiotherapy has been found to influence the interpretation of histological findings thus knowledge of this will help in appropriate assessment of findings. In all the cases (137) there was no mention of any previous therapy probably because it wasn't offered or may be deemed not important for interpretation of histopathological findings. Generally, lack of adequate details in the request forms may be because of unawareness among the clinicians on the importance of these parameters in the generation of a histopathology report, patient follow-up and intervention.

The importance of adequate reporting of macroscopic features cannot be overemphasized. It is the first step in formulating a histopathological diagnosis. Counting and measuring core biopsies helps in assessing the adequacy of sampling by the surgeon and also in determining the quantity of tumour. In this study number of cores was given in 94.3% and the length was indicated in 92.3%

of all cases. This is unlike the finding by Siddiqui *et al* where the number and length was given in 100% of all 101 cases in their study (46). This was attributed to the use of a standard reporting protocol. There was incomplete assessment of TURP specimens. The number of prostatic chips was indicated in only 61.1%. The weight of chips was indicated in 55.6% and the dimensions were indicated in 66.7%. The weight and dimensions of prostatectomy specimens was missing in one and two specimens respectively. When the tumour is seen grossly it is paramount to describe its features including the size, appearance, consistency as these features will aid in assessment during microscopy. Accompanying structures removed during radical prostatectomies including seminal vesicles, vas deferentia, bladder neck and lymph nodes should be indicated if submitted. This will help when assessing for tumour extension. In this study seminal vesicles were provided in 75% of the cases. A single lymph node was submitted with one radical prostatectomy specimen.

During microscopy it is important to report all features including those that affect the treatment choice and prognosis of the patient. In this audit study to assess the completeness of reporting, we used a standard reporting guideline from the College of American Pathologists that has included all the features that have been documented to be paramount in management. There was complete assessment of the histologic type in all the 137 cases (100%). All were diagnosed as prostate adenocarcinoma not otherwise specified. This concurs with findings in a study by Idowu *et al* in which there was 100% inclusion of the histologic type in prostate cancer specimens (40). The histologic type plays role in determining the grade and in patient prognostication. Other histologic types apart from acinar adenocarcinoma bear a poor prognosis, the degree of which depends on the specific type. The Gleason grade guides the treatment choice and the risk stratification of patients. 133 cases (97.0%) were graded completely with the primary, secondary and final Gleason score. This is unlike in the study by Siddiqui *et al* where there was indication of the grade in 100%

of cases (46). They assessed a total of 101 core biopsies. There was incomplete grading in two cases (1.5%) in which the final score was given without indication of the primary and secondary patterns. This compares to the study by Idowu *et al* who found primary pattern missing in 0.5% and secondary pattern in 1% (40). The grade in two cases could not be assessed. These specimens were both core biopsies and possibly not assessable due to specimen related issues including the quality and quantity of the tissue. There was no indication of the primary and secondary patterns in two cases both of which were also core biopsies. Other prognostic and predictive factors for prostate cancer that were inconsistently reported included tumour quantity, lymphovascular invasion, perineural invasion, extra prostatic extension, margins and pathological stage. In the study by Idowu *et al* the missing elements included extent of invasion, tumour volume, and lymphovascular invasion (40). In another study by Aumann *et al* the inconsistently reported features in descriptive reports included resection margin status extraprostatic extension, seminal vesicle invasion, perineural invasion, lymphovascular invasion and pathologic stage(45). Tumour quantitation especially in core biopsies and TURP prostatic chips is an important prognostic indicator linked to pathologic and clinical end points. Tumour quantitation was done in 48.2% of cases. In two cases it was not assessable. Lymphovascular invasion status was not recorded in 70.7%. Perineural invasion was missing in 62.9% while extraprostatic extension was missing in 89.8% of cases. In the study by Siddiqui *et al* there was 100% reporting of these elements and this again was attributed to the use of a standard reporting protocol. In radical prostatectomy specimens the other features to include are urinary bladder neck invasion, seminal vesicle invasion, lymph node involvement, margin status and pathological stage. In this study there was no mention of urinary bladder neck invasion in all the prostatectomies and this could be because the bladder neck was not dissected with the specimen. There was no seminal vesicle invasion in all. The lymph

node submitted with one of the specimens turned out to be soft tissue therefore there was no mention of lymph node involvement. The resection margin status in 25% was not stated. 75% of cases were staged.

In this audit the reports assessed were descriptive in nature hence the possibility of missing out of some elements as reported in previous studies. This is unlike the presence and use of a standard protocol with a checklist that lists out the exact features to report.

Ever its inception in the 1960s, Gleason grading system has remained one of the most powerful tool in management of patients with prostate cancer. It has maintained a great impact on the reporting, prognosis of prostate cancer and prediction of local recurrence and distant metastases. It however has its own systemic flaws that has contributed to poor reproducibility in many studies. It has therefore been a subject of wide discussion and has been modified to suit current trends in care. Two major modifications were done in 2005 and 2014 by the ISUP. The 2014 modification was done to overcome the flaws of the 2005 one. The 2014 system has redefined patterns three and four and introduced prognostic grade groups which have been found to be more accurate and useful. In this study we reviewed the cases and re-classified them using the 2014 criteria.

In the review, the predominant primary pattern was 4 and the least was 3 accounting for 54% and 16.8% respectively. In the initial report pattern 3 was the predominant one accounting for 38.7% while pattern 4 accounted for 32.1%. The change from the initial report may be explained by the difference in criteria for patterns 3 and 4. All cribriform glands despite the sizes were re-classified as pattern 4. Branching and irregular glands as long as they had a clear lumen and stroma in between them were classified as pattern 3. Pattern 5 accounted for 23.4% of all the primary patterns. In the review, the predominant secondary pattern was 5 and the least was 3 accounting for 46% and 19%. In the initial report, pattern 4 was the most common secondary pattern followed

by pattern 5. The change from the initial report may be explained by the fact that the second pattern in the review was assigned to the worst pattern present as opposed to the old second predominant pattern. There may have been a second predominant pattern that was of a lower grade but this was not reported in the review. Pattern 4 accounted for 29.2% of all the secondary patterns.

There were no cases assigned scores 4 and 5 in the review whereas in the initial report these were present. This finding may be explained by the fact that no case was assigned patterns 1 and 2 as per the 2014 guidelines. The most common final score in the review was 9 accounting for 43.8% of all cases. These findings are similar to a study by Shah *et al* who found a predominance of score 9 accounting for 45.5% and they also did not have scores 4 and 5 (83). They classified their cases using the ISUP 2014 criteria. In the initial report score 9 accounted for 2.7%. In this study the least common score was 6 with 8.8% of cases which also compares with Shah's study where score 6 was the lowest accounting for 3%. In the initial report score 6 accounted for 13.1%. In the review Gleason scores 7, 8, and 10 accounted for 14.6%, 15.3% and 11.7% of all the scores.

The final Gleason score in a majority of cases (51.8%) were upgraded whereas only 10.2% of them were downgraded. There was an increase in number of cases scored 8, 9, 10 and a decline in scores 6 and 7. The differences are again attributed to the change in pattern and reporting criteria as earlier mentioned.

In the initial report, the commonest grade group was 5 (33.6%) with the least being 3 (8.0%). In the review findings, the commonest grade group was 5 (56.2%) while the least was 2 (5.8%). This correlates with the findings of Shah *et al* with a predominance of group 5 accounting for 48.5% (93). However in a study by Gupta *et al* the predominant grade group was 3 accounting for 41.7% (99).

The prognostic grade group in 43.8% of cases remained unchanged. The number of cases upgraded (43.1%) was more than those that were downgraded (7.3%). There was a 22.6% increase in cases of group 5 from an initial of 14.6% to 56.2% and a slight increase in group 3. Groups 1 and 2 were decreased in the review while group 4 remained unchanged. These changes in the grade groups were as a result of the increased reporting of higher Gleason scores and decreased reporting of lower scores in the review.

The primary pattern had a fair agreement (*k* 0.25) between the initial and review. This is comparable to Ozkan *et al* (*k* 0.34) (10). The secondary pattern had poor agreement (*k* -0.13). Ozkan *et al* had a fair agreement (*k* 0.37) (10). The level of agreement in Gleason score sum was slight (*k* 0.20). This is comparable to a study by Mc Lean *et al* (*k* 0.15-0.29) (96). Problematic factors that contribute to poor-fair agreement that have been documented and which also applied in this study, include difficulties in differentiating benign glandular structures that mimic pattern 3, small amount of tissue/tumor especially in core biopsies, tumors with patterns that fall in the interphase between two classic patterns and inherent subjectivity (10,3,9). This subjectivity is because Gleason grading is a qualitative parameter rather than a quantitative one and therefore inherently bound to have different interpretations by the pathologists. This may therefore not always be interpreted as an error (3). The quality of specimen is also another confounding factor. Core biopsies that are fragmented or have changes as a result of compression during processing have also been associated with difficulties in both assessing for the presence and grade of the tumor (3).

5.1 CONCLUSIONS

The histopathologic request forms for prostatic specimens were not adequately filled. There was sufficient reporting of macroscopic features in most cases. There was incomplete reporting of various microscopic tumour features owing to the nature of descriptive reporting. Presence and use of a standard reporting protocol ensures complete capture of all essential parameters required for diagnosis, management and prognostication of patients with prostate cancer. There was an upward shift in Gleason grades and grade groups with the use of the ISUP 2014 modified system. The strength of agreement between the initial and review Gleason grades and scores ranged from poor to fair and this was influenced by the nature of the specimen, equivocal patterns and inherent subjectivity of the Gleason system.

This study was therefore able to reveal the deficient areas starting right from the request form to the final histopathology report. In addition, we highlighted the changes that come with the use of the new modified Gleason system and also the level of agreement in grading that was previously unknown in KNH. The findings from this study form base for which a future re-audit can be undertaken.

5.2 STUDY LIMITATION

Histology slides used for the initial diagnosis were not available as they were not archived. While it would have been important to re-examine the previous slides especially where discrepancies in diagnoses were found in the review, the lack of the old slides made this impossible. Nonetheless, if the old initial slides were available, it would still have been challenging in a few cases to interpret them because of fading of the stain over time.

5.3 RECOMMENDATIONS

1. Sensitization of the clinicians on the importance of providing adequate information on the request forms. This can be done through continuous medical education sessions and clinico-pathological conferences.
2. Use of the CAP cancer reporting protocol to enable the generation of a concise report with all the necessary features.
3. The department of histopathology needs to establish a new system of archiving slides that can be sustainable over time.
4. There is need for institution of measures aimed at reducing observer variability in grading using the Gleason system. These include consensus grading of difficult cases, use of common ‘reference images’ showing the architectural patterns and continuous training of residents and consultant pathologists on any new changes in the system.

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APPENDICES

APPENDIX A: SECTIONING OF PARAFFIN BLOCKS

1. Release the brake and rotate the hand wheel until the handle is at 1 o'clock position and re-apply the brake.
2. Push the quick release lever of the cassette clamp backward, insert the cassette clamp backward, insert the cassette, release the lever and check that the cassette is firmly clamped.
3. Use the vertical and horizontal tilt controls to orientate the specimen correctly with the knife edge and lock the orientation head.
4. Release the brake and turn the coarse advance knob clockwise and anticlockwise to bring the tissue block closer or away from the cutting edge.
5. Trim the block using the coarse advance knob until the full face is attained.
6. Set the section thickness with thickness control knob.
7. Turn the hand wheel to cut the sections.
8. Pick the sections and float in warm water to remove the creases.
9. Fish the sections and mount on clean microscope slides. Label the slides with a lead pencil or diamond pencil.
10. Put the slides in a hot air oven at 56 degrees Celsius for 1hour. Remove the slides and stain.

APPENDIX B: H&E STAINING

Reagents

1. Eosin 1% aqueous solution.
2. Absolute alcohol.
3. Harris-haematoxylin solution.
4. Scott's tap water.

Procedure for staining

1. De-wax sections with two changes of xylene.
2. Re-hydrate sections with two changes of absolute alcohol and wash in running water.
3. Stain with haematoxylin solution for up to 5 minutes.
4. Wash in running tap water.
5. Differentiate in acid alcohol for approximately 5 minutes.
6. Wash in running tap water.
7. Blue in Scott's tap water for few seconds.
8. Wash in running tap water.
9. Stain with eosin for approximately for 5 minutes.
10. Wash in running tap water.
11. Dehydrate, clear and mount section.

APPENDIX C: AUDIT DATA COLLECTION TOOL

PART A: Demographic/Clinical information (tick/fill in as required)

Study number ☐ Lab number ☐ Age (years) ☐ Not indicated ☐

Date of procedure ☐ Not indicated ☐ Date specimen received in lab ☐ Not indicated ☐

Clinical history: Indicated ☐ Not Indicated ☐

Clinical diagnosis: Indicated ☐ Not Indicated ☐

Type of procedure: Radical prostatectomy ☐ TRUS ☐ TURP ☐ Not indicated ☐

Previous therapy: Radiotherapy ☐ Hormonal therapy ☐ Not indicated ☐

Serum PSA (prebiopsy) value: Numeric: ___ng/mL Not indicated ☐

Requesting clinician details: Name and Contact details; Indicated ☐ Not indicated ☐

PART B: Macroscopic details (tick/fill in as required)

Needle core biopsies

Number of cores submitted ☐ Cannot be determined ☐ Not provided ☐

Location of cores identified ☐ Specify ☐ Not provided ☐

Length of core ☐ mm AND/OR Length of Fragments ☐ mm Not provided ☐

TURP specimen specimen

Number of chips ☐ Not provided ☐ Weight of chips ☐ g Not provided ☐

Dimension ☐ mm Not provided ☐

Prostatectomy

Weight ☐ g Not provided ☐ Dimensions ☐ mm Not provided ☐

Seminal vesicles Absent ☐ Present ☐

Lymph nodes Absent ☐ Present ☐ Number ☐ Laterality ☐

Gross tumour description:

Tumour: Seen grossly…… Not seen grossly……

Location of tumour: Mentioned……. Not mentioned……

Size of tumour: Mentioned……Not mentioned……

Consistency of tumour: Mentioned……Not mentioned…….

PART C: Microscopic findings (CAP Protocol incorporated) (tick/fill in as required) for the initial report

Histologic Type (select all that apply)

___ Acinar adenocarcinoma ___ Ductal adenocarcinoma

___ Small-cell neuroendocrine carcinoma ___ Other histologic type not listed (specify): ___

Not indicated ___

Histologic Grade (Gleason)

Graded ___ Not graded ___ Incompletely graded ___ Cannot be assessed ___

Needle core biopsies

Primary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Secondary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Gleason Score ____ Not provided ____

TURP

Primary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Secondary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Gleason Score ____ Not provided ____

Prostatectomy

Primary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Secondary Gleason Pattern 1___ Pattern 2 ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 Not provided ___

Gleason Score ____ Not provided ____

Tumour Quantitation

Needle core biopsies

Number cores positive: ____ Total number of cores: ____ Cannot be determined ____

and percentage of prostatic tissue involved by tumour: ____% **or**

Number cores positive: ____ Total number of cores: ____ Cannot be determined ____

and Total linear millimetres of carcinoma (millimetres): ___ mm

Total linear millimetres of needle core tissue (millimetres): ___ mm

Percentage of prostatic tissue involved by tumour for core with the greatest amount of tumour: ____%

Unquantified ____ Cannot be assessed ____

TURP

Estimated percentage of prostatic tissue involved by tumour: ____%

Number of positive chips: ____ Total number of chips: ____

Unquantified ____ Cannot be assessed ____

Prostatectomy

Estimated percentage of prostate involved by tumor: ____% and/or Tumor size (dominant nodule, if present): Greatest dimension (millimetres): ___ mm Additional dimensions (millimetres): ___ x ___ Location of dominant nodule_____

Unquantified ____ Cannot be assessed ____

Extraprostatic Extension

Not identified ___ Present, focal ___ Present, nonfocal ___ Cannot be determined ___

Not mentioned ___

Urinary Bladder Neck Invasion

Not identified ___ Present ___ Not mentioned ___

Seminal Vesicle Invasion

Not identified___ Present ___ Right___Left ___Bilateral ___ No seminal vesicle present ___

Margins

Cannot be assessed ___ Uninvolved by invasive carcinoma ___

Involved by invasive carcinoma ___

___ Limited (<3 mm) ___ Non-limited (≥3 mm)

Location of Positive Margin(s) (select all that apply)

___ Right apical___ Right bladder neck ___ Right anterior___ Right lateral ___ Right postero-lateral (neurovascular bundle) ___ Right posterior

___ Left apical ___ Left bladder neck ___ Left anterior ___ Left lateral ___ Left postero-lateral (neurovascular bundle) ___ Left posterior

Not indicated ___

Treatment Effect (select all that apply)

___ No known presurgical therapy

___ Not identified

___ Radiation therapy effect present

___ Hormonal therapy effect present

___ Other therapy effect(s) present (specify): _____

___ Cannot be determined

Lymphovascular Invasion

Not identified ___ Present ___ Cannot be determined ___ Not mentioned ___

Perineural Invasion

Not identified ___ Present ___ Not mentioned ___

Regional Lymph Nodes (where applicable)

___ No lymph nodes submitted or found

Number of Lymph Nodes Involved: _____

___ Number cannot be determined (explain): _____

Specify Site(s): _____ Number of Lymph Nodes Examined: _____

Number cannot be determined (explain): _____

Size of Largest Lymph node Involved (centimeters): ___ cm Specify Site: _____

Pathologic Stage Classification pTNM (Radical prostatectomy)

Primary Tumor (pT) ___

Regional Lymph Nodes (pN) ___

Distant Metastasis (pM) (required only if confirmed pathologically in this case) ___

Specify site(s), if known: _____

Not indicated ___

Additional Pathologic Findings (select all that apply)

___ None identified

___ High-grade prostatic intraepithelial neoplasia

___ Inflammation (specify type): _____

___ Atypical adenomatous hyperplasia (adenosis)

___ Nodular prostatic hyperplasia

Prognostic grade group:……

PART D: Microscopic findings in the review

Histologic Grade (Gleason)

Graded ___ Not graded ___ Incompletely graded ___ Cannot be assessed ___

Needle core biopsies

Primary predominant Gleason Pattern ___ Pattern 3 ___ Pattern 4 ___ Pattern 5

Worst Remaining Gleason Pattern ___ Pattern 3 ___ Pattern 4 ___ Pattern 5

Secondary pattern if only two patterns are present___

Gleason Score: ____

TURP and Simple prostatectomy

Primary (Predominant) Gleason Pattern ___ Pattern 1 ___ Pattern 2 ___ Pattern 3

___ Pattern 4 ___ Pattern 5

Secondary (Worst Remaining) Gleason Pattern___ Pattern 1 ___ Pattern 2 ___ Pattern 3

___ Pattern 4 ___ Pattern 5

Total Gleason Score: ____

Radical prostatectomy

Primary Gleason Pattern ___ Pattern 1 ___ Pattern 2 ___ Pattern 3 ___ Pattern 4___ Pattern 5

Secondary Gleason Pattern ___ Pattern 1 ___ Pattern 2 ___Pattern 3___Pattern 4___Pattern 5

Tertiary Gleason Pattern ___ Pattern 3 ___ Pattern 4 ___ Pattern 5 ___ Not applicable

Total Gleason Score: ____

Prognostic grade group:……

Investigator……. Supervisor……. Supervisor……..

Sign…….. Sign…….. Sign…….

Date…… Date……. Date……...