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ORIGINAL ARTICLE

Histomorphological Comparison of Initial and Residual Prostate Cancer Chips at Muhimbili National Hospital, Tanzania

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ABSTRACT

Background: Residual prostate chips, after initial sampling provide an opportunity to examine potential differences in histomorphological features of prostate cancer. This study compared the histomorphological characteristics of prostate cancer in the partially sampled versus the residual prostate chips.

Methodology: This was a cross-sectional analytical laboratory-based study of archived slides of initial samples and residual tissue at the Muhimbili National Hospital's Central Pathology Laboratory (MNH-CPL).

Results: A total of 162 cases of Transurethral resection of the prostate were included in the analysis. The mean age of the selected cases with transurethral resection of prostate was 69.19 (±9.14) years. In initial specimen, out of 162 selected cases, 42 (25.9%) were prostate cancer. The specific diagnoses included benign prostatic hyperplasia (BPH) (72.8%), adenocarcinoma (25.3%), *Schistosomiasis* (1.2%) and Squamous Cell Carcinoma (SCC) (0.6%). For residual specimen, 31.5% were prostate cancer. The specific diagnoses included BPH (66%), adenocarcinoma (30.9%), *Schistosomiasis* (1.2%) and SCC (0.6%). In both initial (43.9%) and residual (53.8%) specimens, Grade group 5 was prevalent. Most of the initial specimen showed tumor volume of 81 to 90% and most of the residual tumor volume was greater than 90%. Overall agreement in histological diagnoses between initial specimen and residual prostate chips was 93.2% with a kappa strength (κ) 0.79. For specific diagnosis the agreement was 97.6%, 91.5%, 100% and 100% for adenocarcinoma, BPH, schistosomiasis and SCC Grade 1 with *Schistosomiasis* respectively. With exception of Grade group 5, the rest of the Grade group had low Kappa value of 0.12. Agreement of tumor volumes was 83.3% with a kappa strength (κ) of 0.79.

Conclusions: This study showed that there are notable histomorphological differences between initial and residual prostate chips with regard to prostate cancer. Further research with a larger group of patients and follow-up is recommended to validate these initial findings and their implications for prostate cancer management.

BACKGROUND

Globally, Prostate cancer (PCa) is one of the most commonly diagnosed solid-organ cancers and the second most prevalent malignancy in men, with an incidence of 14.1 per 100,000 and ranking sixth in male cancer-related deaths.[1,2] In 2020, PCa accounted for 375,304 deaths worldwide, ranking eighth in overall cancer mortality.[3] Compared to 2018, the incidence increased from 13.5 to 14.1 per 100,000 in men.[1,2]

In Africa, PCa was the third most common cancer in 2020, with an incidence of 8.4 per 100,000 and 47,249 deaths.[4] The burden is significantly higher among African descent, often due to underreporting, poor screening, limited healthcare access, genetics and environmental factors.[5] Men of African ancestry, include those in the Caribbean, Sub-Saharan Africa and the USA, have the highest PCA mortality rates.[6,7] Genetic predisposition such as altered androgen receptor signaling and genomic instability may contribute to more aggressive disease.[8] Delayed diagnosis and limited treatment access further worsen outcomes.[9,10]

Sub-Saharan Africa reports a PCa mortality rate of 7.7 per 100,000 and an incidence of 9.6 per 100,000 the highest among men in the region.[11]both sexes, all ages Total: 801 392 Breast 129 415 (16.1% Trend analysis by Seraphin et al. showed varying increase across 12 SSA populations between 1990-2018 with the Seychelles and Harare having the highest growth rates. Other rising trends have been observed, with annual increase of 2-10% in countries like Kenya, Zimbabwe and South Africa from 1995-2018.[12]

Tanzania is adding more cancer treatment facilities as a result of rising cancer incidence and death. Out of the 40,464 new cases in 2020, the trends show as follows: cervical (25%), breast (10%) and prostate (9%).[14,15] Mortality makes it stand at third with 7.4

per cases in 2020.[16] A retrospective hospital based study done from 2006 to 2015 for the cancer mortality pattern in Tanzania conducted by Lyimo E. et al[17] revealed that PCa was one of the most common and largest contributors to cancer mortality in all zones in Tanzania with a mortality of 13.6 per 100,000 cases among men. Western zone showed to produce most of the burden.[17]

Patients who exhibit prostate cancer signs clinically undergo procedures like Transurethral Resection of the Prostate (TURP) done by the surgeon; where by the obstructive or irritating symptoms of the lower urinary tract are relieved. The tissue is then taken to the laboratory where it is used to exclude prostatic or other malignancies, and confirm disease origin.

Prostate chip specimens pose a diagnostic challenge, as malignant lesions are often not apparent on gross examination. Microscope evaluation remains essential for accurately estimating tumor burden. To avoid underdiagnosis, it is crucial for pathologists to ensure adequate and representative sampling of the tissue. When only portion of the prostate chips obtained from a biopsy or surgical resection are processed and examined under a microspore, this is known as Partial sampling. This necessitates that the pathologist follow stringent guidelines such as provided by the College of American Pathologists, Royal College of Pathologists and Royal College of Pathologists of Australasia.[18,19] Human resources, turnaround time and reduction of costs (consumables, reagents and bills) contribute to the practice of partial sampling.

If detected, prostate cancer is assigned a grade and stage followed by a risk group determination for consideration of therapy. Prostate cancer grading has traditionally been performed according to the Gleason Grading system. In this two-number system, the first number is assigned to the predominant focus of tumor and the second, to the second more predominant pattern; each is graded on a scale of 1-5 and the sum of the two is the overall grade.[20]

Under sampling of prostate tissue can result in missed prostate cancer diagnosis, and a pathologist may run into this problem if they decide to gross the remaining prostate chips again.

To our knowledge, no data is available from our region showing us the difference between partially sampling vs complete sampling. This study compared diagnosis of the initial and residual sampling.

METHODS

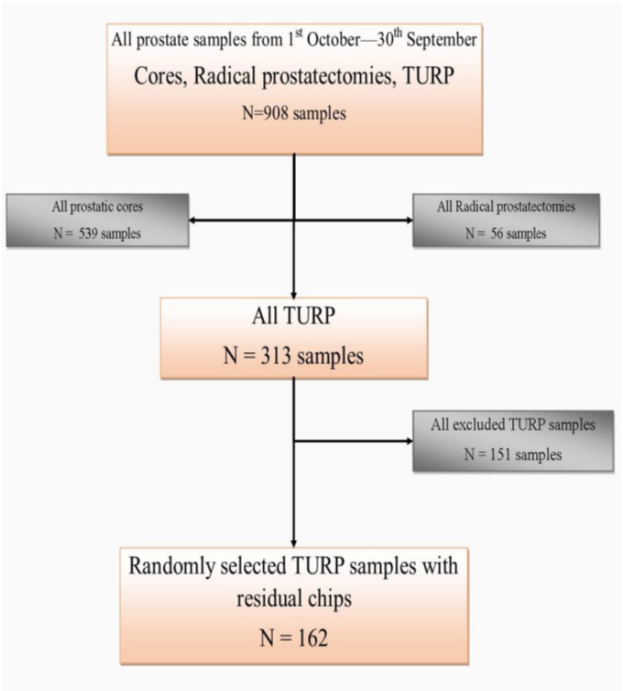
Study Design, Setting and Participants

This was a cross-sectional analytical, laboratory-based study conducted at the Central Pathology Laboratory of Muhimbili National Hospital (MNH-CPL) in Dar es Salaam, Tanzania. Muhimbili National Hospital (MNH) is the largest tertiary referral hospital in Tanzania and serves as the national referral and teaching hospital for the Muhimbili University of Health and Allied Sciences (MUHAS). Muhimbili National Hospital has a bed capacity of 1,500 and receives referrals from across the country. The CPL at MNH is one of the most advanced and well-resourced pathology laboratories in Tanzania. It provides a full range of diagnostic histopathology and cytopathology services processing thousands of tissue and cytology specimens annually.

This study included archival of histopathology slides and residual prostate tissue obtained from TURP specimens collected between October 1, 2021 and September 30, 2022.

A total of 162 TURP cases were selected based on predefined inclusion and exclusion criteria (Figure 1)

FIGURE 1: Flow Chart for Case Selection



Sample Size Calculation

The sample size was obtained by using Conchran's formula considering a study by Vollmer et al which reported a difference of 12% between partially versus complete sampling. With the 95% confidence level and acceptable margin of error of 5%, the estimated sample size was 162 cases.

Inclusion Criteria

All TURP cases with residual tissue

Exclusion Criteria

All TURP cases that do not have residuals tissues for further histopathological evaluation

Laboratory Procedures

Tissue slides and block for Hematoxylin and Eosin

All TURP cases that have residual tissue from 1st October 2021 to 3th September 2022 were marked. Their respective initial slides were retrieved from the archive, reviewed and the initial diagnoses recorded. All residual tissues were taken from the archive, weighed and sampled completely into appropriate blocks then passed through tissue processing. The slides were stained with routine

hematoxylin and Eosin.

Slide Review
The residual slides were examined under a microscope by principal investigator who was the primary reader then reviewed by the junior pathologist and finally confirmed by senior pathologist. The histological diagnoses, grade group, and tumor volume were recorded in the data collection tool.

Data Collection Method
All prostate cases at MNH were reviewed and each case was given a special number and entered into a data collection sheet which included Hospital number, age, number of slides, initial histopathological diagnosis, tumor volume, Gleason score and grade group. The percentage of the prostate that the tumor occupies in prostate cancer patients is known as the tumor volume.

Date Analysis
Collected data was entered in Microsoft Office 2013 spreadsheet file, cleaned and edited for consistency and analyzed by SPSS Version 27 IBM Corpotation Chicago, USA. For categorical data, descriptive analysis was performed using frequency and proportion, and for continuous variables, means and standard deviations. Cohen's kappa correlation statistics was performed to determine level of agreement between initial and the residual tissues of the reported cases. The value of $P<.05$ was considered statistically significant.

Ethical Issues
Ethical clearance was granted by the Research and Publication Committee of Muhimbili University of Health and Allied Sciences (Ethical clearance reference number MUHAS-REC-12-2022-1469). Administrative permission was obtained to conduct the study at Muhimbili National Hospital (CPL) in accordance with the hospital's management protocols with reference MNH/TRCU/Perm/2022/097.

RESULTS
A total of 908 prostate samples were received and processed at MNH-CPL from 1st October 2021 to 30th September 2022. Prostatic cores were 539 (59.4%), 313 (34.5%) TURP, and 56 (6.2%) radical prostatectomies. Of the 313 TURP samples, 162 cases with residual samples were selected based on the inclusion and exclusion criteria. The mean age of the selected 162 cases was 69.19 (±9.1) years, age range from 49 to 87 years (Table1).

In the initial samples, 42 (25.9%) cases were prostate cancer and 120 (74.1%) other benign prostatic conditions. The specific diagnoses were 118 (72.8%) Benign Prostatic Hyperplasia (BPH) cases, 41 (25.3%) adenocarcinoma cases, 2(1.2%) *Schistosomiasis* and 1(0.6%) squamous cell carcinoma case.

For the residual samples of prostatic chips, the percentage distribution of diagnosis was as follows: 51(31.5%) cancer cases and 111 (68.5%) benign conditions. The diagnoses were 109(67.3%) BPH cases, 50(30.9%) Adenocarcinoma cases, 2(1.2%) *Schistosomiasis* cases and 1(0.6%) Squamous Cell Carcinoma cases. Percentage distributions for specific diagnoses are indicated in Table 1.

Lack of documentation was observed on some variables. Grade groups were not documented in 4 (9.8%) of the prostate cancer cases, and record for tumor volume was missing in 29 (70.7%) of the cancer cases (Table1).

TABLE 1: General Study Population Characteristics

Variable	Initial Prostate Tissue n (%)	Residual Prostate Tissue n (%)
Age: Mean (SD) in years	69.19 (±9.14)	
Age group (years)		
30 - 49	2(1.2)	
50 - 69	80(49.4)	
70 - 89	80(49.4)	
Cancer status		
Cancer	42(25.9)	51(31.5)
No cancer	120(74.1)	111(68.5)
Diagnosis		
Adenocarcinoma	41(25.3)	50(30.9)
BPH	118(72.8)	109(67.3)
Schistosomiasis	2(1.2)	2(1.2)
SCC Grade 1 with *Schistosomiasis*	1(0.6)	1(0.6)
Grade group		
1	2(4.9)	8(15.4)
2	5(12.2)	6(11.5)
3	2(4.9)	2(3.8)
4	10(24.4)	8(15.4)
5	18(43.9)	28(53.8)
Not documented	4(9.8)	0(0)
Tumour volume (%)		
1 - 5	0(0.0)	10(19.6)
6 - 10	0(0.0)	7(13.7)
11- 20	0(0.0)	4(7.8)
31 - 40	2(4.9)	0(0.0)
61 - 70	2(4.9)	2(3.9)
71 - 80	2(4.9)	6(11.8)
81 - 90	4(9.8)	9(17.6)
Greater than 90	2(4.9)	13(25.5)
Not documented	29(70.7)	0(0.0)

SCC: Squamous Cell Carcinoma

Histological Diagnosis of Initial Sample Versus Residual Prostate Chips.
The overall concordance was 93.2%, kappa statistic strength (κ) 0.79 and CI (-0.68 – 2.18). For specific diagnosis, the agreement was 97.6%, 91.5%, 100% and 100% for adenocarcinomas, BPH, *Schistosomiasis* and squamous cell carcinoma with *Schistosomiasis*, respectively (Table 2).

Grade Group of Initial Sample Versus Residual Prostate Chips.
The overall concordance was 50% with a kappa strength of 0.12; CI (-0.04 – 0.27). For specific Grade group, the agreement was 100% in Grade group 5 (Table 3).

Tumuor Volume of Initial Sample Versus Residual Prostate Chips.
Records for tumor volume was missing in 72.7% of the cases in the initial samples. Overall agreement was

83.3% with a kappa strength of 0.786; CI (0.47 – 1.09) (*P* value=.00). Percentage agreement per specific tumor volume is indicated in Table 4.

TABLE 2: Agreement of Histological Diagnosis Between Initial and Residual Prostate Chips

	Residual Prostate Chips			
	AdenoC n(%)	BPH n(%)	Schisto n(%)	SCC Grade 1 with Schisto (%)
Initial Prostate Chips				
AdenoC	40(97.6)	1(2.4)	0(0.0)	0(0.0)
BPH	10(8.5)	108(91.5)	0(0.0)	0(0.0)
Schisto	0(0.0)	0(0.0)	2(100)	0(0.0)
SCC Grade 1 with Schisto	0(0.0)	0(0.0)	0(0.0)	1(100)

P value=.000; Fisher's exact test

TABLE 3: Agreement of Grade Group Between Initial and Residual Prostate Chips

	Residual prostate chips n (%)		
	2	4	5
Initial prostate chips			
1	2(100)	0(0)	0(0)
2	0(0)	4(66.7)	2(33.3)
3	0(0)	2(100)	0(0)
4	0(0)	0(0)	8(100)
5	0(0)	0(0)	18(100)

P value=.001; Fisher's exact test

FIGURE 3: Photomicrograph Illustrating the Gleason Patterns

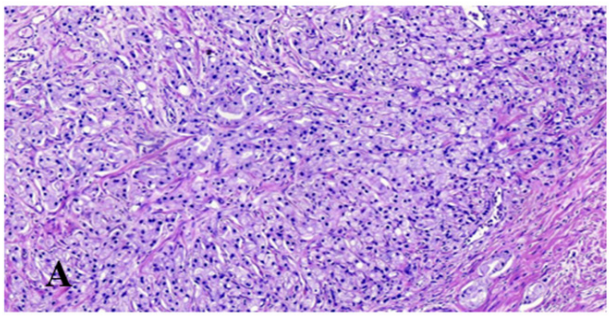


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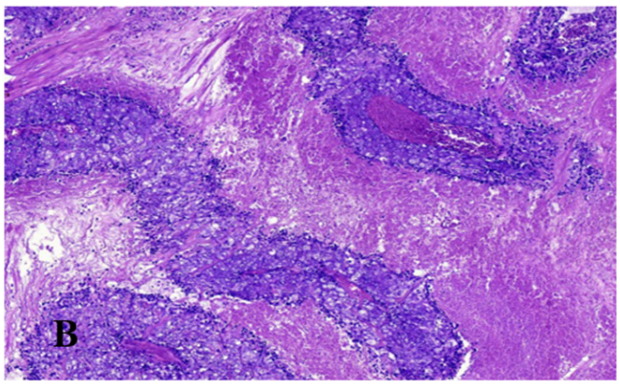
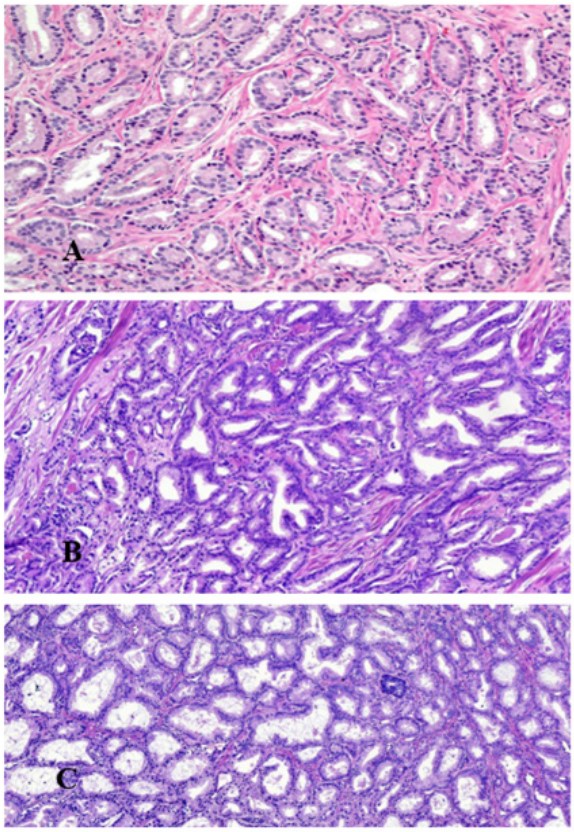
FIGURE 3: Continued



Routine H&E-stained sections. A: Solid sheets, Gleason pattern 5 (×100). B: Comedo necrosis, Gleason pattern 5 (×100)

FIGURE 2: Photomicrograph illustrating the Gleason Patterns



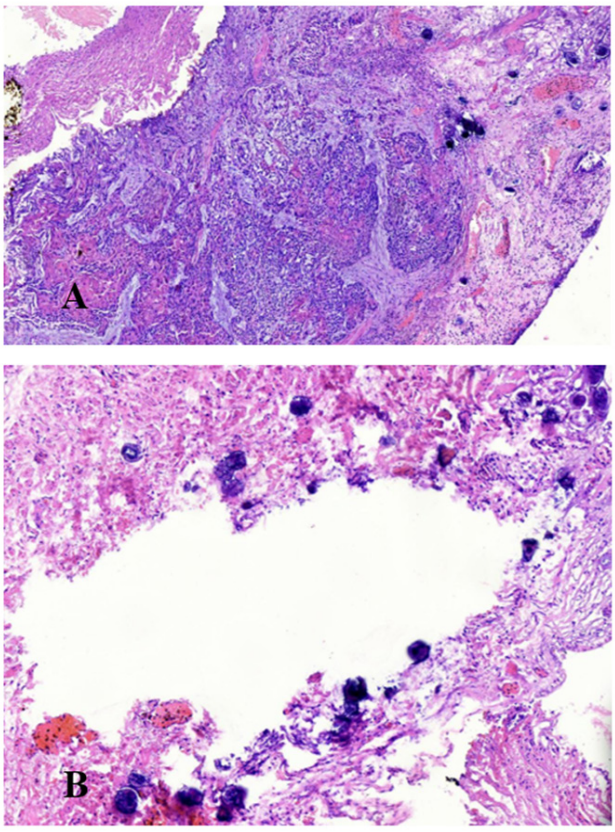
Routine H&E-stained sections. A: Discrete glands, Gleason pattern3 (×100). B&C: Poorly formed and fused glands, Gleason pattern4 (×100)

TABLE 4: Agreement of Tumour Volumes Between Initial and Residual Prostate Chips

	Residual Prostate Chips n (%)			
	61 - 70	71 - 80	81 - 90	>90
Initial Prostate Chips				
31 - 40	0(0)	0(0.0)	0(0)	2(100)
61 - 70	2(100)	0(0)	0(0)	0(0)
71 - 80	0(0)	2(100)	0(0)	0(0)
81 - 90	0(0)	0(0)	4(100)	0(0)
>90	0(0)	0(0)	0(0)	2(100)

P value=.000; Fisher's exact test

FIGURE 4: Photomicrograph Illustrating the Gleason Patterns



Routine H&E-stained sections. A: Squamous cell carcinoma with *schistosomiasis* (×100). B: Schistosoma eggs (×100)

DISCUSSION

The diagnosis and management of prostate cancer rely heavily on the accurate assessment of tumor characteristics obtained from prostate biopsy samples.[21,22]cells of epithelial and mesenchymal origin contribute to the structure and function of developing organs. However, these phenotypes are not always permanent, and instead, under the appropriate conditions, epithelial and mesenchymal cells convert between these two phenotypes. These processes, termed Epithelial-Mesenchymal Transition (EMTOur study was designed to answer few basic questions. Is there prostate cancer in residual chips that was not present in the initial partially sampled tissues? How grave is the difference? Is the difference significant enough to change patient management?

From this and previous studies, there can be very little doubt that some cancers of the prostate will go undetected unless all tissue from the transurethral prostatectomies is processed and examined microscopically; whether it will change the course of treatment or not that is another issue. We analyzed and detected a 6.1% point increase in new prostate cancer between the initial samples and the residual samples. This increase in prostate cancer percentage concurs with a study done by Vollmer R[23] and colleagues who found an increase of 12% between partial sampling and complete sampling.[23]

When focusing on the changes; no changes were found in130 (80.2%) of the cases. Interestingly one case had prostate cancer in the initial sample but no prostate cancer was found in the residual sample. Minimal changes were found in 10 (6.2%) of the cases. When reviewing, all those cases showed changes from grade group 4 to grade group 5.

Major changes were found in 18 (11.1%) cases. Ten (10) showed change from no prostate cancer to prostate cancer. Of those 10 cases; eight (8) cases were Grade Group 1, one (1) case was Grade Groups 2 and one (1) case was Grade group 3. All of them had tumor volume of less than 20%. The mean number of slides used for the 10 cases was 6 slides with a range of 2 to 22 slides. The low grades and the small tumor cancer volumes could maybe explain why the initial samples did not have prostate cancer as they were more probable to be unsampled.

Four (4) cases changed from (Grade group 2 to Grade group 4), 2 cases changed from (Grade group 2 to Grade group 5), and 2 cases changed from (Grade group 3 to Grade group 4). On the contrary, a study by Trpkov K. et al[24] showed otherwise; although prostate cancer was found in the residual specimens there was no difference in the grade groups. Our study and their study match on the aspect of no tumor volume difference between the initial vs. the residual sample.[24] This could be partly explained by the poor practice of underreporting tumor volume in our study hence the potentially not exact agreement found.

In our study good agreement (93.2%; κ=.79) was found when comparing histological diagnoses from initial and residual specimens. The overall high agreement of the histological diagnoses between initial and residual specimen showed that both sampling methods yielded almost similar results regarding presence or absence of cancer. Like ours, several studies[25,26] have compared the histological diagnoses obtained through partial sampling and residual sampling methods, and they have consistently shown a high level of agreement between the two sampled specimens. This could be partly because of the representative nature of selecting the fragments in partial sampling. Although only a portion of the specimen is examined, careful selection of the fragments by an experienced pathologist aimed to capture areas that reflect the overall histopathological characteristics could potentially improve the agreement rates. Another factor could be the multifocal exhibition of prostate cancer in the several areas of the gland.

When comparing the grade groups between the initial and residual chips, the overall agreement was 50% (κ=.12). Our study also showed a change in grade groups in 8 (22.2%) of the cases from lower to higher grades in the initial and residual specimens, respectively.[27] A number of factors could be taken into consideration when assessing the grade groups; 1) Prostate cancer is known for its heterogeneity with various architectural patterns, if the selected samples do not capture the high-grades the assigned grade groups may be lower than the actual grade of the tumuor; 2) Depending on the sampling selection, there is a possibility of sampling bias where certain areas of higher or lower grade may be missed; 3) Accurate grading of prostate cancer can be challenging even with experienced pathologists. The subtle difference between grades and the subjective nature of interpretation can contribute to discordance in grade group assignment, particularly when examining limited sections in partial sampling.

The overall agreement of 72.7% (κ=.79) was seen when comparing the tumor volume between the initial specimens and the residual specimens. Tumor volume estimation in partial sampling is often correlated with the presence and extent of significant tumor findings. This correlation, along with selection of representative sections contributes to a high level of agreement with tumor volume estimated through residual sampling. The accuracy of tumor volume estimation relies on the expertise and experience of pathologists. Experienced pathologists are more likely to accurately estimate tumor volume, regardless of the sampling method used. It is also crucial to consider that accurate tumor volume estimation is important for treatment planning and assessing disease progression. Residual sampling is generally preferred in cases where precise tumor volume estimation is critical, as it provides a more comprehensive evaluation of the entire specimen.

Based on a combination of PSA levels, clinical stage, Grade group and other additional factors, healthcare provides can classify prostate cancer into risk categories, such as low-risk, intermediate-risk, or high-risk. These categories help guide treatment decisions. It's important to note that prostate cancer treatment decisions are individualized and should be made in consultation with healthcare professionals, considering the patient's unique medical history, preferences, and the latest medical guidelines.

This study, has shown that the prostate cancer increase in the residual specimen may be alarming. Although factors like cost effectiveness for human resources and supplies may come into play, it is important to provide accurate diagnosis which is in turn crucial for proper patient management. Perhaps putting in place standards for both sampling and reporting could potentially make it safer for patients.

Few of the limitations that were faced when conducting our study worth mentioning are: Lack of proper documentation of grade groups and tumor volumes. No known published data from our region to compare with showing the agreements of histomorphological features of prostate cancer between initial and residual prostate chips. To address these issues in the future studies, it is essential to standardize pathology reporting practices by ensuring consistent documentation of tumor grade and volume, Additionally, establishing local or national prostate cancer registries and promoting regional collaborative studies will help generate comparative data and improve the understanding of histological patterns in our settings.

CONCLUSION

In summary, this study demonstrates that there are notable histomorphological differences between initial and residual prostate chips with regard to prostate cancer. The study identified variations in histological diagnoses, tumor grade, and tumor volume. Partial sampling, when performed by experienced pathologists using representative sections, can provide reliable estimates of the above characteristics. Regardless of the cost prohibitive nature of entire blocking or extensive sampling of prostatic chips, for precise and comprehensive assessment, residual sampling remains the gold standard.

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