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Adequacy of Sampling Transurethral Resection of Prostate for Accurately Evaluating Incidentally Detected Prostatic Carcinoma

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ABSTRACT
Incidental detection of prostate cancer in transurethral resection of prostate (TURP) samples has increased over the past decade. There are no definite guidelines for sampling TURP specimens when incidental carcinoma is detected and practices vary between institutions. The aim of this study was to identify a reasonable sampling approach to accurately evaluate TURP samples with incidentally detected carcinoma without compromising quality of the report. We evaluated thirty nine TURP samples received in our department over a period of 5 years, with clinically presumed benign hyperplasia, in which incidental carcinoma was identified in the initial samples and which were subsequently submitted entirely and examined. Gleason score and tumour volume in the initial and additionally sampled chips were analyzed. The main finding from our study was that after complete sampling, Gleason score and percentage of initially estimated tumour volume remain unchanged. We also found that we face an average loss of Rs. 2592 per case following complete sampling. We conclude that initial random sampling as per established CAP protocol is sufficient to accurately evaluate the Gleason score and tumour stage in the entire resected TURP chips when an incidental prostate cancer is detected and the additional expenses, manpower and delay in turnaround time can be avoided with partial sampling.

INTRODUCTION

Prostate cancer is the second most common malignancy in men and is the fifth most common cause of death due to malignancy in men[1]. Highest incidence of prostate carcinoma is reported in northern Europe and lowest in South Central Asia[1,2]. Epidemiological studies have shown that there is age, geographical and racial differences in incidence of prostatic carcinoma[3]. The number of cases has increased over the past decades due to higher life expectancy, dietary habits and life style such as smoking, overweight and physical inactivity[4]. The Gleason grading system is recommended for use in all prostatic specimens containing adenocarcinoma, with the exception of those showing treatment effects, usually in the setting of androgen withdrawal and radiation therapy.

TURP has been the undisputed reference standard for elderly men with lower urinary tract symptoms caused by prostatic enlargement and obstruction[5] and is used as both diagnostic and treatment modality. Detection rate of prostatic carcinoma by TURP is around 3-4% and it has a greater chance for detection of clinically unsuspected and low-grade prostatic carcinoma. Carcinoma that is unsuspected clinically is referred to as stage T1 disease, subdivided into T1a and T1b. These are not detected clinically because amount of carcinoma in the gland is very small. Moreover, a carcinoma that infiltrates the prostate without much induration or tumours located more anteriorly and centrally, may not be detected during digital rectal examination. Stage T1b refers to tumour occupying >5% of the specimen and progression rate of these tumours is higher, compared to stage T1a tumours occupying <5% of the specimen. Therefore, stage T1b tumours are treated definitively with surgery or radiotherapy, whereas most stage T1a tumours require no further invasive treatment, can be kept under active surveillance particularly in patients older than 60 years[4]. However, young patients with stage T1a disease are treated with radical prostatectomy because of their long-term risk of progression. Therefore, it is important for pathologist to accurately substage T1 tumors since it mandates different patient care.

Quantity of TURP chips received in the pathology laboratory varies. Recommendations by the College of American Pathologists (CAP) require submission of specimens weighing 12g or less in their entirety, usually in 6-8 cassettes[6]. For specimens greater than 12 g, the initial 12 g should be submitted and thereafter, one cassette for every additional 5 g is submitted. The CAP Cancer Committee recently added a recommendation that “if an unsuspected carcinoma is found in the tissue submitted and if it involves 5% or less of the tissue examined, the remaining tissue may be submitted for microscopic examination". However, controversy exists as to how much additional sampling is required to ensure an accurate tumour volume estimate and to ascertain the Gleason score in the resected specimen when unsuspected cancer is identified.

The aim of this study was to identify a reasonable sampling approach to accurately evaluate transurethral resection of prostate samples with incidentally detected carcinoma without compromising quality of the report. The secondary objective was to evaluate the yield and cost of additional tissue sampling.

MATERIALS AND METHODS

We conducted a combined prospective and retrospective study, on 39 transurethral resected specimens of prostate received in our department of Pathology, over a period of 5 years (April 2017 to May 2022). TURP specimens are sampled in our department according to the College of American Pathologists (CAP) protocol[6]. When unsuspected carcinoma is identified in the initial sample, remaining tissues are examined in entirety to ensure an accurate diagnosis in terms of Gleason score and tumour volume. All samples with clinically presumed benign hyperplasia in which incidental carcinoma was identified in the initial samples and which were subsequently submitted entirely and examined formed the study group. All submitted chips were examined by 3 pathologists (1 trainee + 2 consultants) blindly. A consensus opinion of Gleason score and tumour volume in the initial and additionally sampled chips were recorded on score sheets and analyzed. Fisher’s exact and Mann-Whitney tests were used for statistical analysis for qualitative and quantitative variables respectively. A cost analysis for additional tissue sampling was performed. TURP samples received from patients with known case of carcinoma prostate, specimen weighing less than 12g and TURP with tumours other than adenocarcinoma were excluded.

RESULTS

In this study, the age of patients ranged from 54-83 years, majority being 66-70 years, with average age of 72.5 years (Fig. 1). Prostatic hyperplasia (BPH) was the common clinical presentation (66.7%). Majority of the patients had grade 2 (43.6%) and grade 3 prostatomegaly (35.9%). Mean PSA in our study group was 11 ng mL^{-1} with standard deviation of 25.64 (Fig. 2). Twenty six out of the thirty nine cases (66.7%) of the incidental prostate carcinoma in this study were stage T1a and only 33.3% cases were stage T1b (Fig. 3). The difference in age distribution between T1a and T1b cases was not statistically significant (p = 0.984). There was no statistically significant difference in PSA level between T1a and T1b stages (p-0.174), although 66.7% patients with PSA values >10 ng mL^{-1} were stage T1b.

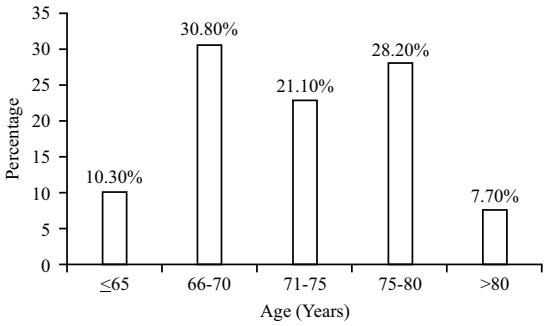

Fig. 1: Distribution of age

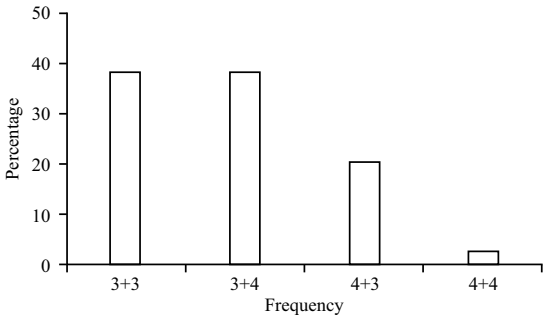

Fig. 4: Distribution of Gleason pattern

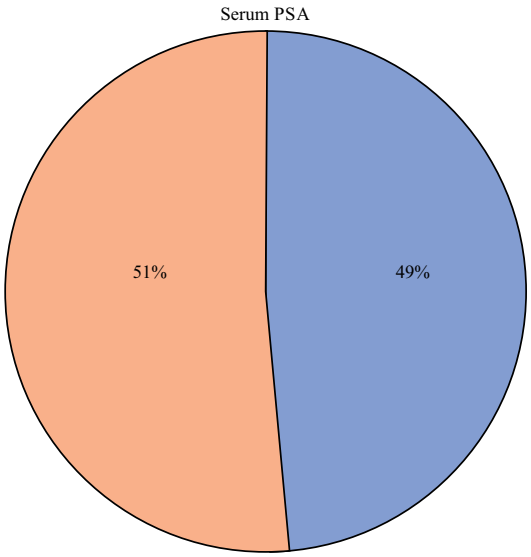

Fig. 2: Distribution of Serum PSA

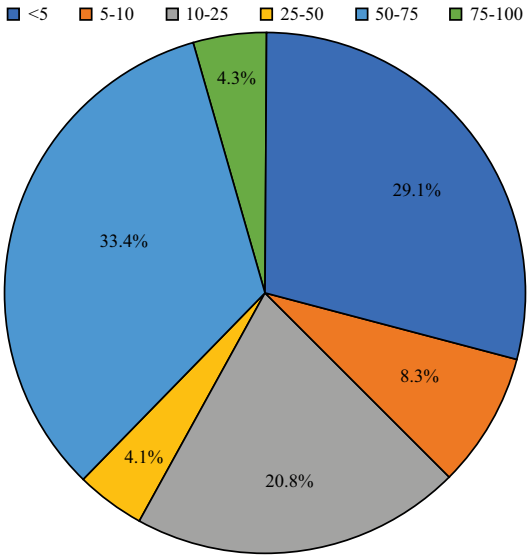

Fig. 5: Percentage of pattern 4

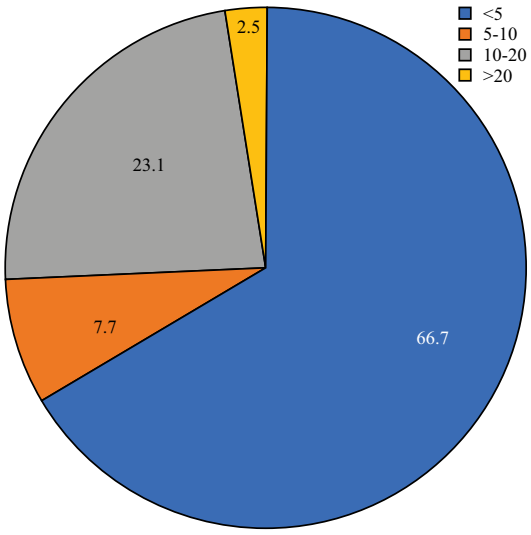

Fig. 3: Distribution of tumour volume (%)

Gleason pattern 3+3, grade group1 and 3+4, grade group 2 were the most frequent grades in these incidental tumours (Fig. 4). Twenty four cases (61.5%) had pattern 4, majority (62.3%) as secondary component. Only 9 cases (37.7%) had pattern 4 as primary component (Fig. 5). Amongst 26 stage T1a cases,15 cases (57.6%) were Gleason pattern 3+3, grade group 1. Secondary pattern 4 was present in 30.4% cases. On the other hand, amongst 13 stage T1b cases, 12 cases (92.2%) were Gleason pattern 3+4, grade group 2 and Gleason pattern 4+3, grade group 3. One case showed Gleason pattern 4+4, grade group 4. None of the T1b tumours had Gleason pattern 3+3, grade group 1 (Table 1, Fig. 6).

Table 1: Comparison of gleason score between stage T1a and stage T1b

Gleason score	T1a stage (n = 26)	T1b stage (n = 13)	Total (n = 39)	p-value
3+3	15 (100.0%)	0 (0.0%)	15	0.001
3+4	8 (53.3%)	7 (46.7%)	15	
4+3	3 (37.5%)	5 (62.5%)	8	
4+4	0 (0.0%)	1 (100.0%)	1	
5+3, 3+5	0 (0.0%)	0 (0.0%)	0	

Table 2: Comparison of perineural invasion between stage T1a and stage T1b

Perineural invasion	T1a stage (n = 26)	T1b stage (n = 13)	Total (n = 39)	p-value
Absent	26 (78.8%)	7 (21.2%)	33	0.0008
Present	0 (0.0%)	6 (100%)	6	

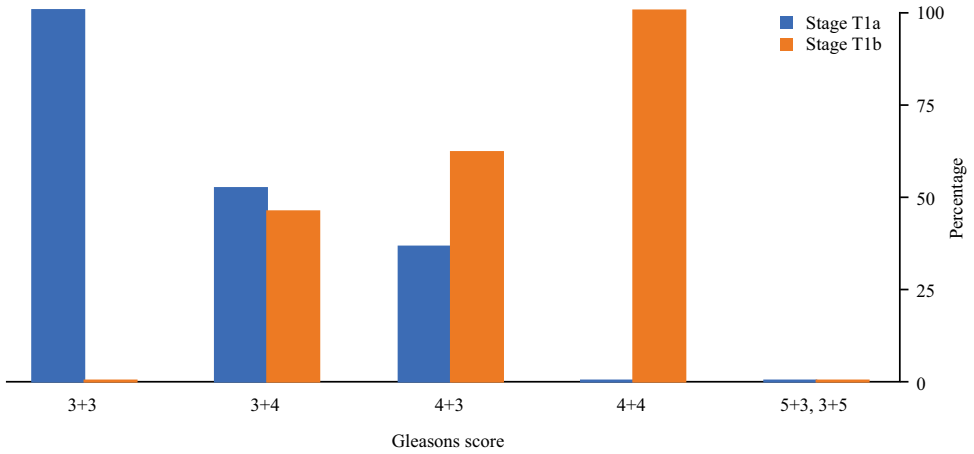

Fig. 6: Comparison of Gleason score between stage T1a and stage T1b

Table 3: Relationship between gleason score (pattern 4) and perineural invasion

	Perineural invasion			
Gleason score	Absent (n = 33)	Present (n = 6)	Total (n = 39)	p-value
3+3	15(100%)	0 (0%)	15	0.02
3+4	12(80%)	3 (20%)	15	
4+3	6 (75%)	2 (25%)	8	
4+4	0 (0%)	1 (100%)	1	

Table 4: Comparison of gleason score between partial and complete sampling

		Sampling		
Gleason score	Grade group	Partial	Complete	p-value
3+3	1	15(38.4%)	15 (38.4%)	1.000
3+4	2	15 (38.4%)	15 (38.4%)	
4+3	3	8 (20.7%)	8 (20.7%)	
4+4	4	1 (2.5%)	1 (2.5%)	

Table 5: Comparison of tumour volume between partial and complete sampling

Tumour volume	Partial sampling	Complete sampling	p-value
T1a	26 (66.7%)	26 (66.7%)	1
T1b	13 (33.3%)	13 (33.3%)	

Table 6: Comparison of cost between partial and complete sampling

Cost	Mean	SD	p-value
Partial sampling	2420	0.000	0.000
Complete sampling	5012	1238	

The difference in perineural invasion between T1a and T1b stage was found to be significant ($p<0.05$). T1b stage cases showed perineural invasion more frequently (100%) compared to T1a stage cases (0.0%) (Table 2). Similarly, relationship between Gleason score and perineural invasion was also found to be significant ($p<0.05$), lower in cases with Gleason score 3+3 (0.0%) and 3+4 (20%) compared to the cases with Gleason score 4+3 (25%), 4+4 (100%) (Table 3).

When we compared Gleason score and grade group after complete sampling, they remained exactly the same and none of the tumours were upgraded after complete sampling ($p>0.05$) (Table 4). Similarly, the tumour volume remained the same after complete sampling which means none of the cases were upstaged from T1a to T1b after complete sampling ($p>0.05$) (Table 5).

On comparison of the cost between partial and complete sampling, we found that the cost is significantly higher in complete sampling (Rs. 5012±1238) compared to partial sampling (Rs. 2420±0.000) with an average additional cost of Rs. 2592 for complete sampling (Table 6).

DISCUSSION

Prostate cancer continues to be detected incidentally in transurethral prostatic resection specimen especially in elderly patients inspite of routine PSA testing and advanced imaging modality. TNM staging system of American joint committee on prostate cancer, define T1 as clinically insignificant tumour, not palpable or visible by imaging and further classify T1a as tumour with incidental histological finding in <5% of tissue and T1b as tumour in >5% of tissue examined. This distinction is important because T1a tumour has better prognosis and behave like "non-cancerous lesion". High grade tumours in terms of Gleason score and tumour volume require definitive surgery or radiotherapy. So accurate evaluation of TURP sample is essential. CAP protocol does not give clear guidelines regarding how to sample TURP chips when small volume of incidental carcinoma is detected in patients undergoing transurethral resection for clinically unsuspected cancer.

Recent studies show that clinical disease progression rate of T1a tumours is low and varies from 8-27% with only 4% of patients progressing in 4 years while 16-25% will progress in 8 to 10 years after TURP[5-8]. In contrast, patients with T1b tumours, have much higher risk for disease progression (33%) and usually require additional treatment. Vollmer[9] reported in his studies that complete sampling of TURP specimens would not change the original diagnosis and is unnecessary. Murphy *et al.*[10] found that sampling 12 g of the randomly selected chips detected

almost 90% of all incidental carcinomas and that all clinically significant prostatic carcinomas (T1b tumors) would be detected if only 6 g of chips are sampled. McDowell *et al.*[11] recommended complete submission of remaining tissue only in cases with T1a tumor, but not T1b tumor, if detected in the initial blocks. This approach was justified based on one case upstaged in his studies and the low incidence of unsuspected T1a tumours requiring more than 9 blocks for complete sampling. Humphrey[12] and Humphrey and Walther[12,13] suggested that partial sampling may be sufficient for patients older than 60 years, while in younger patients, they recommended complete sampling because of the long term risk of progression of T1a tumours. In a study by Trpkov *et al.*[14] initial Gleason scores and tumour volume were not changed in any of the studied cases after partial and complete sampling. The main findings from our study were similar and after complete sampling, Gleason score and percentage of initially estimated tumour volume remained unchanged.

We also found a correlation between stage and Gleason score/grade group. All tumours with Gleason pattern 3+3, grade group 1 were T1a tumours. Primary Gleason pattern 4 was detected more in T1b tumours, compared to T1a tumours. Gleason pattern 5 was not detected in any of the tumours in this study (Table 1/ Fig. 6). This is comparable to study conducted by Nergiz *et al.*[15] where majority of cases (73%) in T1a were grade group 1. Perineural invasion was identified in only 6 (15.4%) T1b cases, all of which had pattern 4 as a component (Table 2,3).

There was no statistically significant difference in PSA levels between T1a and T1b stages although 66.7% patients with PSA values >10 ng mL^{-1} were stage T1b. This is comparable to study conducted by Masue *et al.*[16]. This indicates that PSA values have no correlation with tumour stage in early cancers.

In our lab, cost of TURP specimens is fixed at Rs 2420, based on the technical manpower and the pathologist fees. No additional fee is charged for complete sampling. Our study, thus, estimated the cost of additional tissue sampling at a rate of Rs. 126 per block (as followed in our lab) and found that we face an average loss of Rs. 2592 per case following complete sampling. The cost analysis for our laboratory may not be identical with other centers, however the cost of additional tissue sampling has to be taken into account in these situations.

There are some limitations to this study. The sample size is small. Patients with unavailable pre- and post- operative serum PSA values were not included in the study. Treatment and outcome could not be assessed because data related to the postoperative follow up were not available in all patients.

CONCLUSION

This study found that initial random sampling as per established CAP Protocol is sufficient to accurately evaluate the Gleason score and tumour stage in the entire resected TURP chip specimens. As there is no yield from additional sampling, complete sampling is not warranted and the additional expenses, manpower and delay in turnaround time can be avoided with partial sampling when an incidental prostate cancer is detected in TURP specimens.

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