Malays J Pathol 2022; 44(3): 469 – 475

ORIGINAL ARTICLE

Cost analysis of pathology services comparing conventional 6-core transrectal biopsy versus transperineal saturation biopsy in diagnosing prostate cancer

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Abstract

Introduction: Patients who are suspected of having prostate cancer from screening tests require a tissue biopsy to confirm the presence of cancer. This study aims to compare the cost and cancer detection rate of two different biopsy protocols: 6-core transrectal (TR) approach, and transperineal (TP) saturation biopsy. Methods: In this descriptive, retrospective study, we selected all prostate biopsies received by the diagnostic pathology department of a tertiary hospital in Malaysia in the year 2020, from adult patients for analysis. Data on demographics, specimen preparation processes, and final histopathological diagnosis was extracted from the Laboratory Information System (LIS). The cost incurred for each biopsy diagnosed as cancer was calculated with the cost prices referenced from laboratory documentation. Statistical analysis was performed using SPSS, version 28. Results: The total cost for detection of cancer using TR biopsy ranged from RM11.22 – RM271.02 with mean of RM47.53. The standard deviation, s is RM43.45. For TP biopsies, the total cost ranged from RM112.20 – RM349.56 with mean of RM160.85, standard deviation of RM80.37. TR biopsies had a detection rate of 43.2%, while TP biopsies had a 24.2% cancer detection rate. There is a 3.38-fold increase in costs between TR and TP biopsy. Conclusion: The results show a 3.38-fold increase in costs and a reduction in cancer detection rate when comparing TR and TP biopsy. The reason for the reduced detection rate is unascertained in this study.

Keywords: costing, laboratory, prostate cancer, prostate biopsy

INTRODUCTION

According to the Malaysian National Cancer Registry Report (MNCR) 2012 – 2016[1], prostate cancer was the third most common cancer among all Malaysian males. It is primarily a disease of the elderly, with a peak incidence in Malaysian males occurring within the age of 70 – 74 years age group. Prostate cancer recorded the highest increase in incidence among all other cancers in the last 10 years.

At present, there is no national mass screening program for prostate cancer in Malaysia. A Ministry of Health (MOH) initiated Health Technology Assessment (HTA) Report in 2011[2] concluded the following:

- A mass screening program was not viable due to an increased risk of over detection and overtreatment, which invariably leads to physical and psychological iatrogenic complications.
- Selective screening of asymptomatic men above the age of 40 was recommended if they had a positive family history.
- Serum Prostate Specific Antigen (PSA) levels may be used for screening, with digital rectal examination (DRE) as an adjunct.

Other recommendations in the HTA were regarding patient education, informed consent, organizational issues, and standard guidelines in screening.

Keeping the conclusions above in mind, the MNCR 2012 – 2016 also reports that out of the 4,189 registered cases, 1,682 cases had staging data available where 15.4% and 53.2% of these cases were diagnosed at Stage III and IV respectively.[1] Compared to the South-East-Asian (SEA) regional incidence (Age-standardised rate) of 12.7 per 100,000; Malaysia appears to have a lower rate of 7.7 per 100,000.[3]

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Patients who are suspected of having prostate cancer from screening tests require a diagnostic test to confirm the presence of cancer. This usually takes the form of a prostate biopsy resulting in a tissue sample which is evaluated by the histopathologist.

A landmark study in 1989 by Hodge *et al*[4], showed that random digitally (finger)-guided biopsies were inferior to a transrectal ultrasound (TRUS) guided biopsy. Since then, many more advancements were made in techniques and imaging devices. In Hospital Kuala Lumpur (HKL), two main methods are used, which are:

i) A transrectal (TR) method where systematic biopsies are obtained from 6 locations: in the parasagittal plane of both the right and left lobes of the prostate gland at the base, mid-gland, and apex regions.
ii) A transperineal (TP) systematic approach using a "template", which results in more tissue cores, with the aim of saturating the entire area of the prostate gland, detecting smaller suspicious lesions in the prostate. HKL uses a Modified Barzell Zone template for TP biopsies, covering 20 anatomical locations within the prostate.

Variations of these techniques exist, with the usual number of anatomical sites biopsied ranging from 2-24; in certain cases, up to 34. In addition to the systematic areas, additional suspicious areas identified using imaging methods can also be biopsied.

At HKL, biopsies from each anatomical region (from 1 to up to 34 locations) are individually submitted in its own container. Usually, the urologist obtains 1-3 cores from each anatomical region, resulting in 12 – 102 tissue cores per case.

Upon receipt, the tissue cores from each anatomical site are macroscopically examined and subsequently placed in one cassette for each anatomical region and processed in a tissue processor. This results in a high number of cassettes to be processed, where the cassettes from prostate biopsies alone can equal or exceed the sum of biopsied tissues sent by all other clinical departments in the hospital for a given day.

After processing, the prostate tissue cores are embedded within paraffin wax and sectioned into 3-4 micrometre (μm) thick sections. The tissues are then mounted on glass slides and stained with haematoxylin and eosin (H&E) for microscopical examination. A diagnosis can sometimes be made at this point. However, some specimens require extra steps before a diagnosis is attained, namely: additional tissue sections, immunohistochemical (IHC) stains, or special stains.

In some cases, the biopsy may not reveal a malignant picture despite convincing clinical and screening results. To rule out false negatives, repeated biopsies will be done for the patient, resulting in additional hospital visits for the patient.

Due to the high number of prostate tissue cores requiring processing, it would be useful to know the relative difference in costs to the laboratory between the biopsy methods favoured by clinicians. Combined with knowledge of the cancer pickup rate, this study can provide meaningful data to justify or plan for biopsy protocols used by clinicians and tissue processing protocols used in the laboratory.

METHODS

Case Search

The target population included all adult (≥18 years of age) inpatients and outpatients who had prostate biopsy specimens submitted to the histopathology laboratory of Hospital Kuala Lumpur (HKL) in the year 2020.

Using the newly implemented Laboratory Information System (LIS), a list of all prostate specimens tagged with the SNOMED-CT Topology code "T-92000 (Prostate)" was generated. This yielded approximately 490 entries (inclusive of prostate biopsies, Trans-Urethral Resection of prostate (TURP) and prostatectomy specimens.

Study Selection

Using the generated list, archived histopathological reports were reviewed. TURP, prostatectomies and exenterations, and any cases diagnosed with metastatic carcinoma were excluded from the study. Paediatric samples and samples aberrantly labelled with the wrong Topology code were also omitted.

The final list, consisting of only prostate diagnostic biopsy specimens, numbered 309 cases. A further 4 cases were excluded due to inability to access the case record in the LIS due to technical issues. 305 cases were included in the final list for analysis.

Data Extraction

LIS data and the text of the histopathological

report were reviewed for the 305 cases. Relevant data extracted from the cases include number of targeted locations biopsied, initial number of H&E slides prepared, additional H&E slides requested, number and types of immunohistochemical (IHC) stains requested, and final diagnosis (benign pathology vs primary prostate cancer).

Cost Estimation

The cost of processing and preparing H&E and IHC slides, were obtained from documents used to determine the cost of laboratory tests/services before implementing a Full-Paying Patient (FPP) service in 2016 (Table 1).

The total cost of a specimen to the laboratory is calculated as follows:

- RM4 x no. of Tissue blocks + RM1.61 x H&E-Stained slides + RM29.67 x no. of IHC slides

Human Resource Estimation

Besides material cost, there are time and human labour costs incurred to the laboratory which depend on several factors. As stated above, HKL practices sending of specimens from each individual biopsy sites in its own container. This results in the laboratory processing tissue cores from each container into its own paraffin block and slide. A Medical Laboratory Technologist (MLT) would need time and effort to process, embed, section, and stain a slide before microscopical assessment of the slide can be performed by the pathologist. In short: the more containers/sites biopsied, the more material, time and labour costs are incurred in preparation of the tissue before analysis is even done.

During microscopical review of the case, the pathologist will have to review all slides prepared. A diagnosis can be made using only the initial H&E slides if the case is straightforward, i.e., the histopathology diagnosis is not controversial. In some cases, IHC stains are required for a variety

Table 1: Costing of tissue blocks and slides

Tissue Block Preparation	**Cost (RM)**
Wax	0.51
Alcohol	0.94
Xylene	0.88
10% Neutral Buffered Formalin (NBF)	0.64
Dye	0.12
Cassette	0.17
Cold Paper	0.67
Foam Pad	0.07
Total	**4.00 (per block)**

H&E Staining and Slide Preparation	
Alcohol	0.13
Xylene	0.13
Mounting medium	0.10
Blade	0.47
Coverslip	0.30
Glass Slide (Conventional)	0.01
Haematoxylin	0.23
Eosin	0.24
Total	**1.61 (per slide)**

IHC stains	
Diamino benzidine (DAB) Detection Kit	28.00
Superfrost Slides	1.67
Total	**29.67 (per slide)**

of purposes. The common stains used include High Molecular Weight Cytokeratin (HMWCK) or p63 to demonstrate the basal layer of the prostate glands; Alpha-methalacyl-Coenzyme-A Racemase (AMACR) which is overexpressed in prostatic adenocarcinoma. Other IHC such as Pan-Cytokeratin (Pan-CK) are occasionally required for even more complex specimens where such ancillary information is required to determine the origin of visualised suspicious cells.

We categorised the complexity of cases, based on the above reasoning which also relates to time spent working-up and reviewing the histopathology of the cases, into the following levels:

- Level 1: Straightforward case, no additional levels or IHC needed
- Level 2: Medium Case, requires 1 round of basic IHC (HMWCK, p63 or AMACR) to confirm diagnosis or requires more H&E levels to confirm diagnosis.
- Level 3: Multiple rounds of H&E or IHC needed for diagnosis.

Due to the limitation of the LIS, it was not possible to extract the amount of time spent preparing the extra slides nor the sequence in which the extra slides (IHC or H&E) were requested. Therefore, only cases requiring "non-routine" IHC stains (for prostate biopsies) such as Pan-CK will be classified as Level 3.

Statistical Analysis

Laboratory data was exported from the LIS into Microsoft Excel 2109 build 14430.20306 (Microsoft, USA). The data obtained were cleaned and analysed using IBM Statistical Package for the Social Sciences v28 (SPSS Inc., Chicago, USA (http://www.spss.com). Simple descriptive analysis such as frequencies and measures of central tendency were applied for an overview of the sample cases. Variables were compared using Independent-Samples t-test where all p values <0.05 were considered statistically significant.

Ethical Considerations

Approval for this study was obtained from the Medical Research & Ethics Committee (MREC) of the National Medical Research Register (NMRR) (Reference No**.:** NMRR-21-1488-58412) and from the Medical Research Ethics Committee of University of Malaya Medical Centre (Reference No.: 202179-10355)

RESULTS

The lab received 309 cases of diagnostic prostate tissue biopsies in 2020. Data for four cases were not included due to technical errors with the LIS data.

Of the 305 cases with valid data, a total of 2709 prostate biopsy tissue paraffin blocks were processed, 2808 H&E and 178 IHC slides were prepared. The total expenditure for tissue blocks, H&E and IHC stains per case are described below in Table 2.

Out of 305 cases, the breakdown of type of biopsy and histopathology result of the biopsy are shown in Table 3: 243 (79.7%) were TR biopsies, 62 (20.3%) were TP biopsies. The overall cancer detection rate for both biopsy strategies (combined) was 39.3% (120/305); TR biopsies had a detection rate of 43.2% (105/243), while TP biopsies had a 24.2% (15/62) cancer detection rate.

The distribution of case complexity against histopathology results (Table 4) showed that the majority, 226 (74.1%) cases, were of Level 1 complexity, while 76 (24.9%) were Level 2. Only 3 (1.0%) cases were of Level 3. For Levels 1 & 2, no malignancy was reported in 137 (60.6%) and 47 (61.8%) cases respectively, while prostate cancer was reported in 89 (39.4%) and 29 (38.2%) cases respectively. Of the three Level 3 cases, 1 (33.3%) case had no malignancy while the other 2 (66.7%) were prostate cancer.

Comparing TR and TP biopsies diagnosed

Table 2: Material cost per case of prostate biopsy in this study

	Cost of Tissue Blocks (RM)	Cost of H&E Stain (RM)	Cost of IHC stains (RM)	Total Overall Cost (RM)
Mean	35.25	14.82	17.32	67.39
Std. Deviation	24.22	10.10	46.73	60.67
Minimum	4.00	1.61	0.00	5.61
Maximum	112.00	48.30	356.04	457.02

Note: All costs are per case.

Table 3: Type of biopsy by final histopathology result

		TR Biopsy		TP Biopsy	
		N	%	N	%
Histopathology result	Benign	138	56.8%	47	75.8%
	Cancer	105	43.2%	15	24.2%
	Total	243	100.0%	62	100.0%

with cancer (Table 5), most TR biopsies diagnosed with cancer have Level 1 complexity (82 cases, 78.1% of all TR cancer cases). TP biopsies with cancer tend to be distributed evenly between Level 1 and 2 with 7 cases (46.7%), and 8 cases (53.3%) respectively. Only 3 TR cases had Level 3 complexity. No Level 3 cases were encountered in the TP biopsies.

The total cost for detection of cancer using TR biopsy ranged from RM11.22 – RM271.02 with mean of RM47.53. The standard deviation, s, is RM43.45. For TP biopsies, the total cost ranged from RM112.20 – RM349.56 with mean of RM160.85, standard deviation of RM80.37. There is a statistically significant ($p<0.01$) 3.38-fold increase in costs between TR and TP biopsy (Table 6).

Table 4: Case complexity (level) by final histopathology result

		Complexity (Level)					
		1		2		3	
		N	%	N	%	N	%
Histopathology result	Benign	137	60.60%	47	61.80%	1	33.30%
	Cancer	89	39.40%	29	38.20%	2	66.70%
	Total	226	100.00%	76	100.00%	3	100.00%

Table 5: Type of biopsy strategy by case complexity level (cancer only)

		TR		TP	
		N	%	N	%
Complexity level	1	82	78.10%	7	46.70%
	2	21	20.00%	8	53.30%
	3	2	1.90%	0	0.00%
Total		105	100.00%	15	100.00%

Table 6: Descriptive statistics of total cost of biopsy strategies

	TOTAL COST	
	TR	TP
Mean	47.5316	160.8520
Std. Deviation	43.45544	80.37358
Minimum	11.22	112.20
Maximum	271.02	349.56
Difference from cost of TR biopsy	100%	338%
Fold change from cost of TR biopsy	x 1.0	x 3.38

DISCUSSION

We estimated that the total material cost for detection of cancer using TR biopsy ranged from RM11.22 – RM271.02 with a mean of RM47.53 per case. For TP biopsies, the total cost ranged from RM112.20 – RM349.56 with a mean of RM160.85 per case. This estimated cost only covers the laboratory expenditure in terms of consumables/materials. Due to the more extensive sampling in TP biopsies, and departmental policy to process each anatomical site as a separate tissue block with no "combining", the total cost to the laboratory will always be directly proportional to the number of samples.

It is generally recommended that all prostate biopsies are submitted to the laboratory with site-specific labels.[5] This allows for more granular information regarding the location of the tumour to be derived from the biopsy samples. In turn, detailed knowledge about the tumour "geography" allows more precise treatment modalities to be used, such as high-intensity focused ultrasound and laser ablation.[6] Although published evidence exists stating that there is low positive predictive value (PPV) for extracapsular extension using individually positive cores, the negative predictive value (NPV) for extracapsular extension is 96.9%.[7] This information might not enable the clinician or surgeon to have a highly accurate "map" of the prostate in mind, but it does give a general idea of where potential extracapsular extension is not likely to occur and assist in planning surgery, re-biopsies or other therapy.

The current best practices aim to reduce the fragmentation of tissue, which complicates estimation of the number of positive cores and the volume of tumour within the core. The placement of more than one tissue core in each bottle is discouraged as the cores tend to fragment more easily when 2 or more cores are present in the container.[8] Multiple cores embedded within a paraffin block often results in uneven sectioning, and causes loss of visualized tissue on H&E.

Divergent opinions exist, where one centre noted that there was no statistical difference in the mean length of cores and cancer detection rate when up to 9 tissue cores were embedded within the same paraffin block.[9]

In the pursuit of pre-analytical perfection, we must keep in mind that workload and cost will become a significant bottleneck. With most healthcare expenditure in government owned hospitals being taxpayer funded in this country, the cost of processing and ancillary tests might not be immediately apparent to the patient or doctor.

Allowing only a single core in each slide can potentially double the workload of an institution which initially caters for a maximum of two cores in one slide. The challenge of embedding multiple tissue cores in parallel and similar depth in paraffin also increases exponentially with increasing number of cores.

The question of how many cores required to gain a representative picture about the health of the prostate gland is still under debate. A study involving 303 patients comparing 6-, 12-, 18-, and 21- systematic core biopsies demonstrated cancer detection rates of 22.7%, 28.3%, 30.7%, and 31.3%, respectively[10]; this showed an increase of 8.0% as number of biopsied cores increased from 6 to 18. However, only an increase of 0.6% occurred when the biopsied cores increased from 18 to 21. With the increase in number of tissue cores, more anatomical locations are sampled, and the tissue obtained becomes more representative of the condition of the entire prostate gland.

In our study, the overall observed cancer detection rate was 39.3%; while the rate for TR and TP biopsies was 43.2% and 24.2%. An increase in cores led to an apparent decrease in cancer detection rate (CDR). However, this may be due to selection bias as patients who have clinical, biochemical and/or radiological findings suspicious of a tumour will undergo TR biopsy as a first-line investigation. Patients with clear-cut, targetable lesions in the prostate might only be subjected to targeted biopsy (2-4 cores from the lesion only) as seen in some cases in our study. Patients with enlarged prostates and low clinical suspicion of a tumour undergo TP biopsy as it is hoped that sampling more areas from the prostate will aid in identifying tumours that are small and not apparent on imaging studies.

The overall CDR might be artificially inflated in our study, keeping in mind that this institution has a large pool of symptomatic and asymptomatic patients referred in from primary care, and other institutions without urology services.

The comparison of side effects regarding TR and TP biopsies shows some indication that TP biopsy is a safer method that induces less bleeding or infective side effects such as urinary tract infection (UTI), sepsis, prostatitis, and urosepsis.[11] This can be attributed to the relative cleanliness of the perineum after

adequate pre-procedure cleaning, compared to the rectum, which is rich in microbes and at risk of being introduced into the systemic circulation with every pass of a needle. However, evidence also shows that TP biopsy requires more time to perform, causes more pain, and requires additional anaesthesia.[12]

This study does not aim to support one biopsy method over the other, it provides some objective data on costs and human resource demands on the laboratory incurred by these biopsy-based protocols, which would be valuable in laboratory management considerations.

Acknowledgements: We thank Ms. Ting Jing Siew and Mr. Muhammad who provided valuable assistance in navigating the rough seas of the LIS. We also thank the Director General of Health Malaysia for giving us permission to publish the results of our findings.

Authors' contribution: Acquisition of data, conception & drafting of manuscript (TJH), supervision (RG and LLM), revision of manuscript (LLM)

Conflict of interest: The authors declare no conflict of interest.

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