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ABOUT THE JOURNAL

Aims and Scope

Asian Archives of Pathology (AAP) is an open access, peer-reviewed journal. The journal was first published in 2002 under the Thai name “วารสารราชวิทยาลัยพยาธิแห่งประเทศไทย” and English name “Journal of the Royal College of Pathologists of Thailand”. The journal is a publication for workers in all disciplines of pathology and forensic medicine. In the first 3 years (volumes), the journal was published every 4 months. Until 2005, the journal has changed its name to be “Asian Archives of Pathology: The Official Journal of the Royal College of Pathologists of Thailand”, published quarterly to expand the collaboration among people in the fields of pathology and forensic medicine in the Asia-Pacific regions and the Western countries.

The full articles of the journal are appeared in either Thai or English. However, the abstracts of all Thai articles are published in both Thai and English languages. The journal features letters to the editor, original articles, review articles, case reports, case illustrations, and technical notes. Diagnostic and research areas covered consist of (1) **Anatomical Pathology** (including cellular pathology, cytopathology, haematopathology, histopathology, immunopathology, and surgical pathology); (2) **Clinical Pathology (Laboratory Medicine)** [including blood banking and transfusion medicine, clinical chemistry (chemical pathology or clinical biochemistry), clinical immunology, clinical microbiology, clinical toxicology, cytogenetics, parasitology, and point-of-care testing]; (3) **Forensic Medicine (Legal Medicine or Medical Jurisprudence)** (including forensic science and forensic pathology); (4) **Molecular Medicine** (including molecular genetics, molecular oncology, and molecular pathology); (5) **Pathobiology**; and (6) **Pathophysiology**.

All issues of our journal have been printed in hard copy since the beginning. Around the late 2014, we developed our website (www.asianarchpath.com) in order to increase our visibility. We would like to acknowledge that our journal has been sponsored by the Royal College of Pathologists of Thailand. We have the policy to disseminate the verified scientific knowledge to the public on a non-profit basis. Hence, we have not charged the authors whose manuscripts have been submitted or accepted for publication in our journal.

On the other hand, if any authors request a printed copy of the journal issue containing the articles, each of the copied journals costs 450 bahts for Thai authors and 30 United States dollars (USD) for international authors.

Publication Frequency

Four issues per year

Disclaimer

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ORIGINAL ARTICLE

Cytomorphological and Biochemical Profile of Serous Effusions

Goyal B^{*}, Baral A, and Shrestha AR

College of Medical Sciences, Bharatpur-10, Chitwan, Nepal.

* Correspondence to: Dr. Binita Goyal Associate Professor, Department of Pathology, College of Medical Sciences, Bharatpur-10, Chitwan, Nepal, Phone no: +977986016774, Email: binitagoyal@yahoo.com

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Abstract

Background: Serous effusions are commonly encountered clinical problem with a varied non-neoplastic and neoplastic etiologies. In neoplastic processes, they can represent an advanced stage of disease. Their analysis serves both for diagnostic as well as prognostic purpose.

Objectives: To see protein concentration of these effusions, classify them as transudate and exudate and compare with cytomorphological findings.

Materials and methods: 96 serous effusions received from 1st June to 15th August, 2023 were analyzed.

Results: There were 52 (54.2%) cases of peritoneal, 43 (44.8%) cases of pleural and 1 (1.0%) case of pericardial fluid. Total protein ranged from 0.06 to 5.96 g/dl with mean \pm SD of 2.65 ± 1.03 g/dl. There were 42 (43.8%) exudates and 54 (56.2%) transudates. Total cell count (TC) ranged from 10 – 22720 cells/cu mm. There was significant correlation between total protein and total count (Pearson correlation coefficient 0.525 and p value < 0.001). There was statistically significant difference between exudate and transudate in total protein, TC, mesothelial, lymphocyte and neutrophil percentage with higher total protein, TC and neutrophil percentage in exudates. 93 (96.9%) cases were negative for malignancy. 1 (1.0%) case each was atypia of undetermined significance, suspicious for malignancy and positive for malignancy.

Conclusion: Exudative effusions require manual microscopic examination.

Key words: cytomorphology; effusion; exudate; serous; transudate

Introduction

The pleural, pericardial and peritoneal cavities are serous cavities lined by a single layer of mesothelial cells, which normally contain a very small amount of fluid enough to lubricate the surfaces⁽¹⁾. When the fluid collected is larger than normal, it is termed effusion, which may be a presentation in systemic and local pathological processes which need to be investigated both for diagnosis and management⁽¹⁻²⁾.

Clinically, these effusions may be classified as transudates and exudates which can be differentiated biochemically based on protein estimation of these effusions. Transudates result due to imbalance in hydrostatic and oncotic pressures in conditions like congestive heart failure, cirrhosis and nephrotic syndrome and have low protein concentration, low specific gravity and little or no cellular debris. Exudates result due to injury to mesothelium in conditions like malignancy, infections, autoimmune diseases, pulmonary infarction and trauma and have higher protein and more cellular debris^(1,3).

The biochemical analysis of these effusions along with clinical information helps in arriving at differential diagnosis⁽²⁾. Cytological examination is also commonly performed as it helps in differentiating benign from malignant disease and has an advantage of being minimally invasive, easy availability and cost effectiveness⁽⁴⁾. Biochemical analysis is equally important as further cytological examination may not necessary in transudative effusion as malignancy results in exudate⁽⁵⁾.

Hence, this study is aimed to see protein concentration of these effusions, classify them as transudate and exudate and compare with cytomorphological findings.

Materials and Methods

This cross-sectional study was conducted in Department of Central Clinical Laboratory in College of Medical Sciences. Ethical approval was obtained from Institutional Review Committee (Reference no. COMSTH-IRC/2023-19). 96 serous effusions received in a time duration of two and a half months from 1st June to 15th August, 2023 were analyzed. Peritoneal, pleural and pericardial fluids were included. Recurrent cases were excluded. Total protein estimation was done on fully automatic biochemistry analyzer Biosystems BA 400 (Barcelona, Spain) based on spectrophotometry principle. Total cell count (TC) was done on improved Neubauer chamber in the ruling in 4 corners. 5 ml of fluid was centrifuged at 2500 revolutions per minute for 5 minutes. Sediment was poured on two glass slides and spread in circular manner. One slide was air dried and fixed in 90% ethanol and stained with Giemsa stain⁽⁶⁾. Another slide was wet fixed in 90% ethanol and stained with Papanicolau stain⁽⁷⁾. Differential count (DC) and cytomorphological evaluation were performed under 40X magnification by a pathologist. Cytological diagnosis was categorized according to international system for reporting serous fluid cytopathology⁽⁸⁾. Age, gender, type of fluid, total protein, TC, DC and cytological diagnosis was noted in a predesigned proforma. Fluid was categorized as

transudate if total protein was $< 3\text{g/dl}$ and exudate if protein was $\geq 3\text{g/dl}$ ⁽³⁾. Data was entered in software Statistical Package for Social Sciences (SPSS) 20. Continuous variables were expressed as mean \pm Standard deviation (SD). Categorical variables were expressed as frequency and percentages. Correlation between total protein and TC was done and Pearson correlation coefficient was calculated and p value < 0.05 was considered statistically significant at 95% confidence interval. Total protein, TC and DC was compared in transudates and exudates using non parametric Mann Whitney test and U value was calculated and p value < 0.05 was considered statistically significant at 95% confidence interval.

Results

This was a cross-sectional study conducted on 96 consecutive samples of serous effusions received in a time duration of 2 and a half months from 1st June to 15th August, 2023. Majority were peritoneal fluid comprising 52 (54.2%) cases (Fig 1).

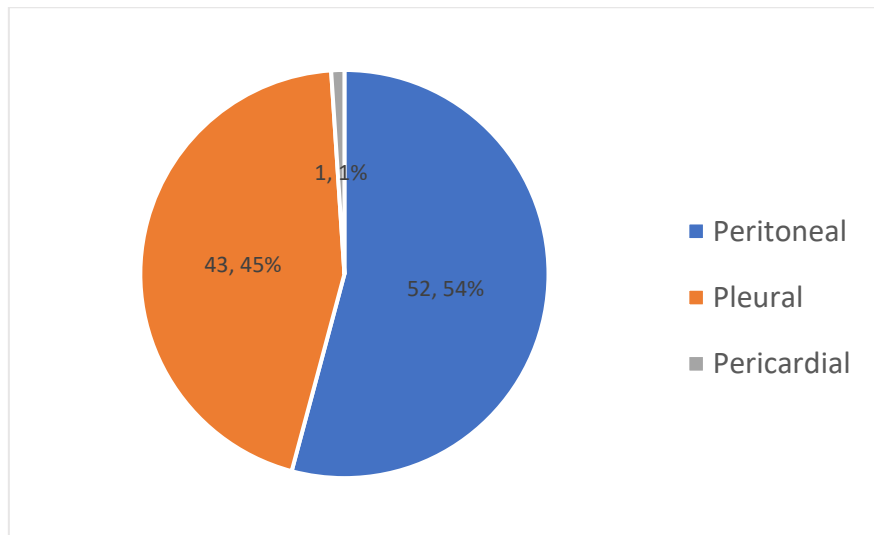


Figure 1. Pie chart showing types of effusion

Age ranged from 16 to 87 years with mean \pm SD of 55.4 ± 17.4 years and maximum 23 (24.0%) cases in 51 – 60 years age group (Fig 2). There were 56 (58.3%) males and 40 (41.7%) females with male female ratio 1.4:1.

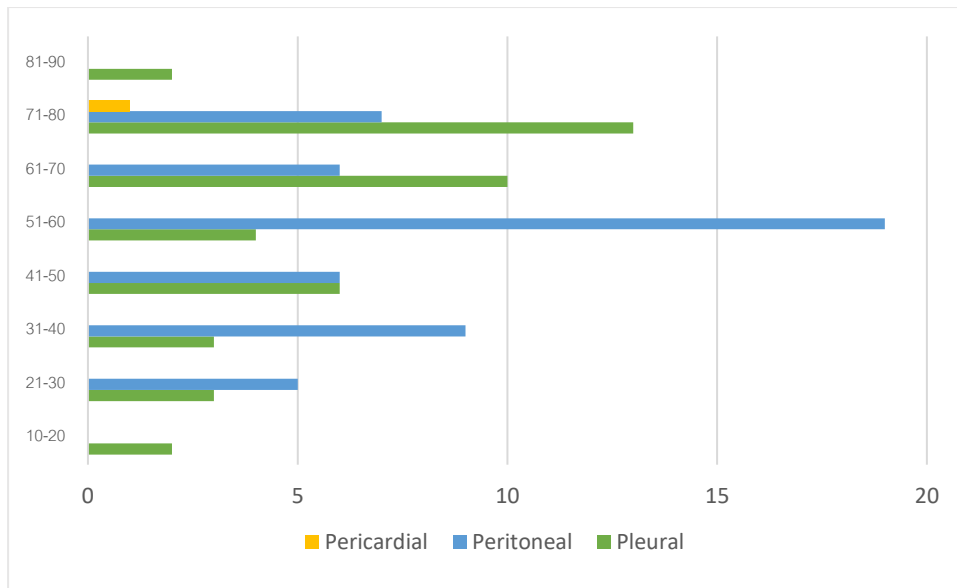


Figure 2 Bar diagram showing age distribution in various types of fluid

Total protein ranged from 0.06 to 5.96 g/dl with mean \pm SD of 2.65 ± 1.03 g/dl. There were 42 (43.8%) exudates and 54 (56.2%) transudates (Table 1).

Table 1. Distribution of exudate and transudate in different types of fluid (n = 96)

Type of fluid	Exudate n (%)	Transudate n (%)	Total
Pleural	27 (28.1)	16 (16.6)	43 (44.8)
Peritoneal	14 (14.6)	38 (39.6)	52 (54.2)
Pericardial	1 (1.0)	0 (0)	1 (1.0)
Total	42 (43.8)	54 (56.2)	96 (100)

TC ranged from 10 – 22720 cells/cu mm with mean \pm SD of 1407.15 ± 3639.21 cells/cu mm. There was significant correlation between total protein and total count as Pearson correlation coefficient was 0.525 and p value was < 0.001 at 99% confidence interval.

In 42 cases of exudates, DC showed presence of mesothelial cells in 36 (85.7%) cases, lymphocytes in 40 (95.2%) cases, neutrophils in 27 (64.3%) cases, histiocytes in 30 (71.4%) cases and eosinophils in 3 (7.1%) cases. In 54 cases of transudates, DC showed presence of mesothelial cells in 53 (98.1%) cases, lymphocytes in 54 (100%) cases, neutrophils in 17 (31.5%) cases and histiocytes in 47 (87.0%) cases. On Mann Whitney test, there was statistically significant difference between exudate and transudate in total protein, TC, mesothelial, neutrophil and histiocyte percentage (Table 2) with higher total protein, TC and neutrophil percentage in exudates. 93 (96.9%) cases were negative for malignancy. 1 (1.0%) case each

was atypia of undetermined significance, suspicious for malignancy (Fig 3) and positive for malignancy (Fig 4), all were exudates in nature.

Table 2. Comparison of Total protein, TC and DC in exudates and transudates (n = 96)

Parameter		Exudate	Transudate	U value	p value*
Total Protein (g/dl)	Range	3.0 – 5.96	0.06 – 2.90	< 0.001	< 0.001
	Mean rank	75.50	27.50		
Total count (cells/cu mm)	Range	128 – 22720	10 – 410	52.00	< 0.001
	Mean rank	74.26	28.46		
Mesothelial cells (%)	Range	0 – 72	0 – 70	815.00	0.018
	Mean rank	40.90	54.41		
Lymphocytes (%)	Range	0 – 100	9 – 96	938.50	0.149
	Mean rank	43.85	52.12		
Neutrophils (%)	Range	0 – 84	0 – 4	626.00	< 0.001
	Mean rank	60.60	39.09		
Histiocytes (%)	Range	0 – 73	0 – 35	853.00	0.037
	Mean rank	41.81	53.70		
*Significance (2-tailed)					

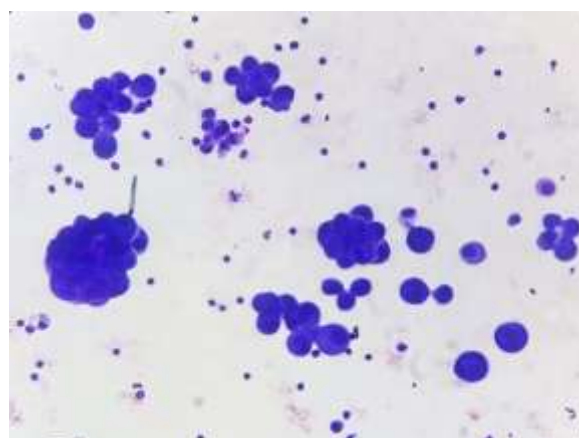


Figure 3. Suspicious for malignancy (Giemsa x100X)

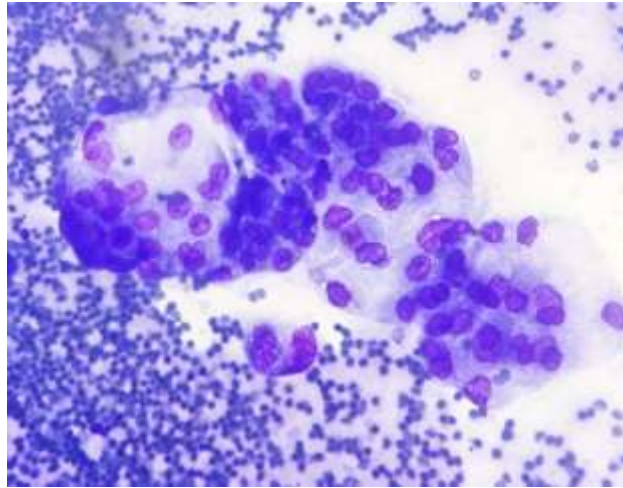


Figure 4. Positive for malignancy (Giemsa x 400X)

Discussion

The serous body cavities (pleural, peritoneal and pericardial) are lined by visceral and parietal layers which are collapsed in normal state and contain a very small amount of fluid inside enough for frictionless free movement of enclosed organs within during activities like respiration, peristalsis and heart beats⁽¹⁾. Increased amount of fluid known as effusion sufficient for tapping indicates a pathological process. Effusion may result from various mechanisms like increased hydrostatic pressure, decreased colloid oncotic pressure, increased vascular permeability, lymphatic obstruction and secretion by tumor cells⁽⁹⁾. The effusion may be a transudate with low protein content (< 3g/dl) and little cellular debris resulting from imbalance between hydrostatic pressure and colloid oncotic pressure or it may be an exudate with high protein content (> 3g/dl) and higher cellular content resulting from damage to the capillaries^(1,9-10). If on biochemical analysis, the effusion turns out to be transudate, then further line of management is to treat the underlying cause and if exudate, then finding out the aetiology whether inflammatory or malignant is necessary for which cytological examination becomes necessary⁽⁹⁾.

This study was conducted on 96 serous effusions. 54.2% were peritoneal fluids followed by 44.8% pleural and 1.0% pericardial fluids. Age of the patient ranged from 16 to 87 years with mean 55.4 years. Transudates were more common comprising 56.2% cases and exudates 43.8% cases. Similarly, in a study conducted by Anita B and Ahuja JM on serous effusions, most common was peritoneal comprising 48.5%, 44.3% were pleural and 7.1% were pericardial fluids. Age ranged from 8 to 90 years with a mean of 50.36 years. However, 52.9% cases were exudative and 47.1% were transudative⁽¹¹⁾. In study conducted by Chandan et al., more common were 64.7% cases of pleural fluid followed by 32% cases of peritoneal fluid. Mean age was 53.3 years. They also had higher 60.7% cases as transudate and 39.3% cases exudate⁽¹⁰⁾.

The first manifestation of ovarian or lung malignancy and mesothelioma may be an effusion whereas, in others effusion may occur in the course of disease, hence guide in prognosis. The cells which may be seen in an effusion may be lymphocytes, neutrophils, eosinophils, macrophages, mesothelial cells and malignant cells⁽⁹⁾. In present study, TC ranged from 10 – 22720 cells/cu mm with mean \pm SD of 1407.15 ± 3639.21 cells/cu mm. 93 (96.9%) cases were negative for malignancy. 1 (1.0%) case each was atypia of undetermined significance, suspicious for malignancy and positive for malignancy, all were exudates in nature. In study conducted by Anita B and Auja JM, TC ranged from 57 – 1,50,000/cu mm with a higher mean \pm SD of 3151.5 ± 17974.06 and 7.14% cases were malignant which was higher as compared to present study. All the malignant cases were exudative in nature in their study too⁽¹¹⁾. Also, in a study conducted by Sulbha VS and Dayanand BS, all 10 cases of malignant effusion were exudative in nature⁽¹²⁾. In study conducted by Chandan et al., malignancy was seen in much higher 18.7% cases. Moreover, 6 out of 28 (21.4%) malignant cases were transudative in their study⁽¹⁰⁾. In a study conducted by Ryu et al., 3.1% cases of malignant effusions were transudative. However, they found no clinical implication of cytology in transudative effusions in their study⁽¹³⁾. Though malignant pleural effusions are mostly exudative in nature, this is not always the case. Transudative effusions may also result because of pleural seeding, lymphatic obstruction by malignancy or by exacerbation of coexisting medical disease due to malignancy⁽¹⁴⁾. Cytological examination of effusion is an important diagnostic tool in malignant effusion and may even be superior to pleural biopsy⁽¹⁵⁾.

Conclusion

Biochemical and cytomorphological examination of serous effusions are important diagnostic tool in their evaluation. Malignant effusions are generally exudative. Decision to requirement of cytological analysis should not be based alone on exudative or transudative nature and should take clinical information also in account.

Acknowledgement

Not applicable.

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ORIGINAL ARTICLE

The Impact of Opposing Core Needle Biopsy Tumor Volume Quantification Methods on Prostatic Adenocarcinoma Active Surveillance Eligibility

Allison Kaye L. Pagarigan, MD* and Dennis Jose S. Carbonell, MD

National Kidney and Transplant Institute, Metro Manila, Philippines.

* Correspondence to: Allison Kaye L. Pagarigan, MD. Section of Anatomic Pathology, Department of Pathology and Laboratory Medicine, Ground Floor, Main Building, National Kidney and Transplant Institute, East Avenue, Quezon City, Metro Manila, Philippines. Phone No. (+63)917-863-6471 and (02)-8981-0300 local 114, E-mail: akpagarigan.md@gmail.com

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Abstract

Background: Tumor volume quantification is critical in determining eligibility for active surveillance in prostatic adenocarcinoma, however, pathologists have yet to arrive at a consensus regarding the optimal method for measuring tumor extent on core biopsies with spatially separated tumor foci.

Objective: This study aims to determine if a significant difference exists in the number of patients deemed eligible for active surveillance following use of opposing methods of tumor volume quantification on prostate core biopsies and to determine which method correlates better with histopathologic parameters on subsequent matched radical prostatectomy specimens.

Materials and Methods: Patient inclusion was confirmed through a review of histopathology records and retrieved tissue slides. Microscopic measurements were taken using microscope imaging software.

Results: When tested against radical prostatectomy tumor volume parameters, core biopsy values determined through the continuous method exhibited a low to moderate positive

correlation and an overall higher degree of association ($r = 0.3$ to 0.4) than the negligible correlation coefficients of the discontinuous method. As high as 40.63% ($p = 0.0005$) of cases initially considered eligible by the discontinuous method were eliminated after quantification using the continuous method. Active surveillance ineligibility by continuous measurement was significantly associated with presence of multifocal tumor ($p = 0.033$) and Gleason pattern 5 ($p = 0.028$) on definitive surgery.

Conclusion: Despite causing a steep decrease in active surveillance eligibility, the continuous method is recommended as it correlates better with tumor volume determinations on radical prostatectomy and significantly associates with tumor multifocality and presence of severe Gleason pattern.

Keywords: active surveillance, core biopsy, prostatic adenocarcinoma, radical prostatectomy, tumor volume quantification

Introduction

Prostatic tumor volume quantification, though considered an important criterion in eligibility for active surveillance (AS) protocols ⁽¹⁾, has never been standardized. In the most recently published outcomes of the International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma, no consensus guidelines were provided for tumor quantification on core needle biopsies (CNB) ⁽²⁾. In practice, tumor volume quantification follows either a continuous or discontinuous method. In the discontinuous method (DM), the linear extent of each discrete focus of carcinoma is measured in millimeters, the sum of which is then divided by the total CNB length to yield the percentage of tumor involvement of a particular tissue core ^(3,4). In the continuous method (CM), measurement encompasses the tumor foci located closest to each extreme end of the CNB and all intervening benign tissue. This measurement in millimeters is again divided by the total CNB length to arrive at the percentage of tumor involvement of a particular prostatic tissue core ^(3,4). These differing methods arise from a divide among pathologists who consider discrete tumor foci as representative of a multifocal carcinoma, against those who believe them to represent areas the same tumor weaving in and out of the plane of section.

The few published large-scale studies that aimed to resolve which method of prostatic CNB tumor volume quantification correlates better with findings on radical prostatectomy (RP) have had inconsistent conclusions. A recent systematic review undertaken by Lu, et.al. favored CM be more accurately predictive of RP pathologic findings. This study supported the notion of CNB discontinuous tumor involvement being the result of undersampling of a larger homogenous tumor nodule as opposed to tumor multifocality or multiclonality ⁽⁵⁾. In contrast, Patel, et.al. applied digital slide scanning technology to examine 78 CNBs and subsequent RPs. DM was found to be predictive of prostate cancer volume on RP and that CM measurements tended to overestimate tumor volume ⁽³⁾. Bsirini, et.al. concluded in favor of DM being more precise in predicting actual tumor extent at RP and other histologic outcomes such as Gleason score, risk of extraprostatic extension, and positive surgical margins ⁽⁴⁾. Fontugne, et.al. postulated that discordance in ERG and SPINK1 expression of spatially separated tumor foci confirmed the multiclonal nature of the tumor. Multiclonality, and therefore multifocality, was confirmed in approximately 25% of the cases, raising the possibility of a significant number of patients being excluded from AS protocols via CM.6 Similar findings were reported by Arias-Stella, et.al. who claimed that as high as 78% of discontinuous tumors seen on CNBs tend to arise from a single tumor focus in the same prostatic region. In contrast to Fontugne, Arias-Stella and colleagues recommended CM, citing that measurements made using this method often associate with a tumor focus of equivalent size on RP. Their recommendation is strengthened by the finding of only one patient meeting criteria for clinically insignificant cancer at RP out of the forty patients included in the study ⁽⁷⁾. Schultz, et.al. likewise favored CM with the observation that discontinuous foci on core biopsies likely represented

undersampling of a more extensive, irregular tumor. Moreover, discontinuous foci were also likely to be associated with positive surgical margins⁽⁸⁾.

A full decade has elapsed since Karram, et.al. published the first study on this controversial matter by posing the question: “Should intervening benign tissue be included in the measurement of discontinuous foci of cancer on prostate needle biopsy?”⁽⁹⁾ Although this pioneering investigation concluded in favor of CM, several succeeding studies with varying definitions and methodologies have challenged these findings. To date, no research endeavor has focused solely on the subpopulation most greatly affected by discrepancies in tumor volume quantification brought about by opposing methods in practice. The accurate estimation of tumor volume on prostatic CNBs becomes paramount in determining which patients may be eligible for AS in that the finding of greater than 50% involvement in a single tissue core effectively excludes a patient who otherwise meets all other criteria for such treatment protocols. The non-standardized methods of tumor quantification present a daily dilemma in the practice of surgical pathology. This diagnostic divide has to be settled unequivocally to provide clinicians with consistent and reliable data on which they can build therapeutic decisions.

As such, the general objective of this paper is to determine if a significant difference exists in the number of patients deemed eligible for active surveillance based solely on histopathologic criteria following prostate core biopsy tumor volume quantification using the continuous versus discontinuous method. Specifically, it aims to identify which method more closely correlates with the largest dimension of matched biopsy-site specific tumor and overall estimated extent of prostatic involvement by carcinoma on subsequent RP. Furthermore, it aims to investigate if cases deemed ineligible for active surveillance are significantly associated with the presence of the following histologic parameters on subsequent RP: tumor multifocality, positive involvement of surgical margins, presence of extraprostatic extension, and presence of Gleason patterns 4 and 5.

Materials and Methods

Study Design

An analytic cross-sectional study design is employed.

Study Population

All sextant prostatic core needle biopsies with subsequent radical prostatectomies performed at the National Kidney and Transplant Institute (NKTi) from the years 2015 to 2021, adhering to the stringent selection criteria outlined in Table 1.

Table 1. Selection criteria.

Inclusion Criteria	Exclusion Criteria
Single prostatic region involvement of prostatic acinar adenocarcinoma, Gleason score 6 (ISUP 2014), exhibiting spatially separated tumor foci (at least 1.0 mm apart) involving less than 50% of one to two tissue cores (at least 1.2 cm total core length) measured via discontinuous method	Discrepant patient identity inferred from records provided in core biopsy and prostatectomy histopathology requests
Tumor volume difference of at least 5% in measurements made using continuous and discontinuous methods	Damaged slides for which recut sections cannot be provided due to unavailable or damaged paraffin blocks
Prostatectomy performed within one year of core biopsy with no hormonal, radio/chemotherapeutic or surgical interventions initiated on interval	Unorientable or fragmented prostatectomy specimens for which laterality and region-specific disease cannot be assigned

A systematic review of international AS guidelines supports that there is currently no single optimal and universally accepted management strategy for clinically-localized, early-stage disease. Assessing these guidelines against the Appraisal of Guidelines for Research and Evaluation instrument identified the US National Comprehensive Cancer Network and New Zealand Prostate Cancer Task force guidelines as the most restrictive among current protocols.⁽¹⁰⁾ The definitions of low-risk AS eligibility for both protocols include maximum stage T2a disease, Gleason score 6, PSA less than 10 ng/mL, PSA density less than 0.15 mg/mL/g and cancer in less than 3 biopsy cores with less than 50% cancer in any core⁽¹¹⁻¹²⁾.

Studies have yet to arrive at a solid definition for discontinuous tumor foci with required measurements of intervening benign prostatic tissue ranging from 0.5 mm⁽⁴⁾ to 2.0 mm⁽⁷⁾ in research methodologies. For the current study, intervening benign tissue measuring at least 1.0 mm is inferred to ascertain the unequivocal spatial separation of malignant foci. Few studies have also investigated the ideal CNB length that allows for optimal detection of malignancy but results have been consistent at 12 mm⁽¹³⁻¹⁴⁾.

Prostatic adenocarcinoma has long been considered a slow-growing malignant entity especially in the setting of low-grade lesions despite a lack of reliable data on the actual neoplastic cell doubling time. Flow cytometric analysis placed maximum proliferative cell doubling time at 0.6 to 3.6 months, however, apoptotic rate could not be accounted for⁽¹⁵⁾. The significance of PSA doubling time (PSADT) has been more widely explored, with recent data suggesting a median PSADT of 20 months for localized, Gleason 6 tumors⁽¹⁶⁾. The required interval between CNB and RP is arbitrarily set at a maximum of one year in an attempt to eliminate significantly confounding tumor progression.

Methods

Sample Size and Sampling Method

Fontugne, et.al. and Arias-Stella, et.al. found that adenocarcinoma multifocality on RP are present in as high as 25% of prostatic core needle biopsies bearing spatially distinct tumor foci⁽⁶⁻⁷⁾. This value translates to the possibility of a significant number of patients being excluded from AS by CM. Assigning a value of 25% as the prevalence of the condition under investigation (p), together with a 95% confidence interval (z), 5% margin of error% (ϵ), and an average of 36 (n) in-house malignant prostate CNBs with subsequent RPs recorded per year, a sample size of approximately 33 is derived by applying the formula for sample size for proportions in a finite population. Given the very specific population being targeted, a purposive total enumeration sampling method was executed.

Data Collection

A review of histopathology logbooks from 2015 to 2021 showed an average of 248 CNBs and 64 RPs per year. Of these, an annual average of 36 matched malignant CNBs with subsequent RPs were documented. The initial assessments for study eligibility were conducted by accessing reports uploaded to the laboratory database. Patient demographics, clinical data and histologic findings were recorded.

A total of 36 cases progressed to microscopic assessment, of which, one had no available paraffin block nor slide warranting exclusion. Microscopic measurements were obtained using the ruler function of the Olympus cellSensTM Life Sciences Imaging Software linked to a BX53 Olympus light microscope (Evident Corporation, Tokyo, Japan). Three cases showed less than 1 millimeter distance between tumor foci, corresponding to a less than 5%

difference in tumor volume using either method and thus, were also excluded. General data categories included patient age, highest serum PSA and interval in days between CNB and RP. CNB data categories included sextant region, number of cores with carcinoma, total length of selected core for analysis, tumor volume quantification using both CM and DM, and AS eligibility using CM measurements. RP data categories included tumor focality, largest dimension of tumor in millimeters, estimated overall extent of organ involvement by carcinoma in percentage, surgical margin status, presence of extraprostatic extension, T-stage, and presence of Gleason patterns 4 and 5.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequencies and proportions were determined for categorical variables while means and standard deviations were computed for continuous variables. Independent sample T-test, Pearson Chi-square test and Pearson correlation coefficient were executed to determine the difference of mean of parametric continuous variables, frequency for the categorical variables and relationship between tumor volumes on biopsy and radical prostatectomy, respectively, between the two tumor volume quantification methods. All statistical tests were two tailed tests. Missing values were neither estimated nor replaced. Null hypotheses were rejected at 0.05 alpha level of significance.

Ethical Clearance

This research protocol adheres to international ethical standards as provided by the ICHGCP guidelines and NEGHR 2017 with approval from the ethical review committee of the NKT Clinical Trial and Research Unit. The committee likewise waived informed consent. All data is retrospectively obtained and anonymized for this non-interventional study. The full text and data sets for this endeavor contain no identifying information.

Results

Thirty-two matched prostate CNBs and RPs were analyzed with a summary of demographic and histopathologic characteristics detailed in Table 2.

The correlation coefficients of acquired CNB and RP tumor volume measurements were computed for and compared in Table 3. Results show a low to moderate positive correlation (~0.3 to 0.4) between CM CNB and RP tumor volume measurements while there is a low to negligible positive correlation when DM is employed. Overall, both methods display a linear positive relationship with RP tumor quantification parameters, however, CM CNB measurements exhibits a higher degree of association with RP measurements as demonstrated by the computed correlation coefficients.

Table 2. Population characteristics.

Population Characteristics (n=32)	Frequency (%) or Mean+/-SD
Demographics and Clinical Data	
Age (years)	66.8+/-5.5
Interval from biopsy to prostatectomy (days)	103.1+/-95.6
Pre-operative serum prostate specific antigen (ng/mL)	13.2+/-7.4
Prostatic Core Needle Biopsy Histologic Parameters	
Length of tissue core (mm)	14.6+/-2.6
Core tumor length (mm)	
Discontinuous Method	1.8+/-1.3
Continuous Method	6.4+/-4.4
Estimated extent of core involvement by carcinoma (%)	
Discontinuous Method	12.17+/-8.65
Continuous Method	42.62+/-24.19
Discontinuous tumor on CNB corresponds to:	
Large unifocal tumor nodule	9 (28.13%)
Multifocal tumor	23 (71.88%)
Active surveillance eligibility based solely on tumor volume quantification:	
Discontinuous Method	32 (100%)
Continuous Method	19 (59.38%)
Radical Prostatectomy Histologic Parameters	
Tumor volume (%)	25.09+/-24.92
Greatest tumor dimension (mm)	10.7+/-7.0
Positive prostatectomy margins	7 (21.9%)
Present extraprostatic extension	4 (12.5%)
Present Gleason pattern 4	15 (46.9%)
Present Gleason pattern 5	3 (9.4%)
Pathologic stage pT2	32 (100%)

Table 3. Comparison of correlation coefficients of tumor volume quantification parameters on core biopsy and radical prostatectomy.

Core Biopsy Tumor Volume Quantification Method	Matched Biopsy Site-Specific Tumor on Radical Prostatectomy	
	Estimated Tumor Volume (%)	Greatest Tumor Length (mm)
Discontinuous Method	0.0818001	0.1225633
Continuous Method	0.3749671	0.2914902

Table 4 examines the impact of CNB tumor volume measurement methods on eligibility for AS. A significant difference ($p < 0.05$) exists between the proportion of patients deemed eligible for AS based solely on histopathologic criteria following CNB tumor volume quantification using opposing methods.

Table 4. Eligibility for active surveillance based on core biopsy tumor volume quantification (%).

Core Biopsy Tumor Volume Quantification Method	Eligible ($< 50\%$)	Ineligible ($\geq 50\%$)	<i>P</i> -value
Discontinuous Method	32 (100%)	0 (0%)	0.000053674
Continuous Method	19 (59%)	13 (41%)	

In Table 5, a comparison of RP outcomes between AS eligible and ineligible groups determined via CM discloses significant associations between AS ineligibility and presence of tumor multifocality and Gleason pattern 5 on RP. No significant association is identified with regard to surgical margin involvement, presence of extraprostatic extension and Gleason pattern 4.

Table 5. Comparison of radical prostatectomy outcomes between active surveillance eligible and ineligible groups determined via the continuous method of biopsy tumor volume quantification.

Active Surveillance Eligibility	Tumor Focality		
	Unifocal	Multifocal	<i>P</i> -value
Eligible	8	11	0.0334637
Ineligible	1	12	
Surgical Margin Status			
	Negative	Positive	<i>P</i> -value
Eligible	16	3	0.3140688
Ineligible	9	4	
Extraprostatic Extension			
	Absent	Present	<i>P</i> -value
Eligible	16	3	0.4963671
Ineligible	12	1	
Gleason Pattern 4			
	Absent	Present	<i>P</i> -value
Eligible	12	7	0.1691476
Ineligible	5	8	
Gleason Pattern 5			
	Absent	Present	<i>P</i> -value
Eligible	19	0	0.0278360
Ineligible	10	3	

Discussion

The stringent clinical and histopathologic criteria for AS eligibility serves to accurately identify patients with low-level involvement by prostatic adenocarcinoma with the objective of delaying the onset of adverse effects commonly associated with certain medical and surgical oncologic interventions.⁽¹⁰⁾ CNB tumor volume quantification plays a crucial role in establishing patient eligibility for AS. The fact that two methods of tumor volume quantification exist with no consensus as to the validity of one over the other in predicting outcomes at radical surgery makes for a dilemma on the part of the clinician who has to

decide whether to place a patient under AS or to proceed with more aggressive treatment modalities.

With focus placed solely on histologic variables, statistical analysis proved that CM CNB measurements more closely correlates with corresponding RP tumor volume parameters. The drawback of favoring CM, however, is a steeply significant decrease in AS eligibility. Whereas Fontugne, et.al. placed the difference at 25% when methods were compared against each other, the current study reflects a 40.63% decrease in eligibility when CM is utilized. Of the existing theories behind discontinuous tumor foci on CNBs, matched site-specific tumor irregularity with wide area involvement was consistently observed, supporting the claims of Arias-Stella and Schultz.

Interestingly, a significant association between CM AS ineligibility and discrete multiregional involvement was discovered. In fact, 92.3% of cases with $\geq 50\%$ CNB adenocarcinoma involvement were proven to be multifocal at RP. Overall, 78% of assessed RPs were classified as multifocal. These values do not largely deviate from the known prevalence of prostatic adenocarcinoma multifocality reported to range from 60% to 90%.⁽¹⁷⁾ Multifocality is theorized to result from the genetic and molecular heterogeneity of prostatic epithelial malignancies allowing for several distinct clones to co-exist within foci of the same primary tumor.⁽¹⁸⁾ Another core finding of this study is the concurrent accuracy of CM in assigning all RP cases with true low-level cancer involvement – that is, unifocal tumors involving $\leq 5\%$ of the entire prostate with complete absence of negative prognostic indicators – as AS eligible.

With the current evidence presented, it appears most prudent to measure prostatic adenocarcinoma CNB involvement in accordance with the continuous method especially for tumors of single histologic type. It also cannot be emphasized enough that CNB histologic findings have to be assessed in the context of the clinical criteria for AS eligibility as tumor volume alone fails to associate with most negative prognostic indicators.

Conclusion

A significant difference exists in the number of patients deemed eligible for active surveillance based solely on histopathologic criteria following prostate core biopsy tumor volume quantification using the discussed opposing methods. Despite the increased rate of case elimination for active surveillance, uniform use of continuous method is recommended as it correlates better with tumor volume determinations on subsequent radical prostatectomy and shows significant associations with tumor multifocality and presence of severe Gleason patterns.

Given the extremely specific target population and limited sample of this single-center investigation, a prospective multi-institutional approach is recommended for future studies. Immunohistochemistry can be utilized to identify foci of adenocarcinoma that are not readily

evident by morphology. Measurement of greatest tumor dimensions on whole-mount or mapped prostatectomy histologic sections can overcome the limitation of cassette size for tissue processing.

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CASE REPORT

Malignant phyllodes tumour of the breast with focal rhabdomyosarcomatous area: Gross examination vigilance.

Sumitra Sivakoti^{1*}, Ashutosh Rath¹, Tushar Mohanlal Parmeshwar², Anvitha L Joshi¹, Shrinivas B Somalwar¹ and Shailaja Prabhala¹

1 Department of Pathology and Lab Medicine, All India Institute of Medical Sciences, Bibinagar, Telangana, India.

2 Department of General Surgery, All India Institute of Medical Sciences, Bibinagar, Telangana, India.

* Correspondence to: Sumitra Sivakoti, Department of Pathology and Lab Medicine, All India Institute of Medical Sciences, Bibinagar, Telangana, India.

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Abstract

Mammary phyllodes are less common fibroepithelial tumours of the breast, and malignant entities in phyllodes are even rarer. Malignant phyllodes are diagnosed on nuclear pleomorphism and stromal growth or the presence of malignant heterologous elements irrespective of size. Concerning the overspreading development of stroma uncontrollably, the heterologous areas are identified after examining multiple sections with a diligent sampling of the tumour areas. We present a case of malignant phyllodes in an older woman with a huge mass in her right breast showing predominantly borderline histological stromal features and a focal rhabdomyosarcomatous area at the lesion's periphery.

Keywords: malignant phyllodes, rhabdomyosarcomatous area, heterologous areas

Introduction

Phyllodes tumours (PT) are uncommon but relatively well-circumscribed large fibroepithelial breast tumours. They are classified into three grades, benign, borderline and malignant tumours, based on histological features like cellularity, atypia and proliferative index⁽¹⁾. Benign phyllodes behave like benign fibroadenoma, with a propensity to recur locally. Malignant phyllodes account for 10-20% of all breast phyllodes tumours; recurrence rate and distinct metastasis are more common in malignant phyllodes⁽²⁾.

Heterologous sarcomatous differentiation in a Malignant phyllodes tumour (MPT) is a rare phenomenon, with the cases reported showing differentiation mostly towards liposarcoma, fibrosarcoma, angiosarcoma, osteosarcoma, or chondrosarcoma⁽¹⁾. MPT with rhabdomyosarcomatous differentiation is extremely rare, with only a few reported in the literature⁽³⁾. They have an overall dismal prognosis, with the metastatic ones carrying an inferior prognosis. The local recurrence rate of malignant phyllodes within 2-3 years of diagnosis is 23%-30%, whereas distant metastases occur in 2% of tumours within 5-8 years⁽⁴⁾. Not much data is available on the prognosis of MPT with rhabdomyosarcomatous differentiation. Breast conservative surgery can be acceptable with wide location excision of the tumour.

The masses of phyllodes are thought to occur ten times more than the size of ductal carcinoma. Detailed examination of gross pathology and meticulous sampling of abnormal areas on gross is advised. Malignant Phyllodes with rhabdomyosarcomatous differentiation is an unusual and rare entity. Pathologists should be aware of heterologous differentiation.

Case Report

A 56-year-old female presented with a lump of 10x9 cm occupying all four quadrants of the right breast for two years. There was no significant past or family history. On examination, a well-defined round, painless mass without nipple discharge or overlying skin was expected, and no axillary lymphadenopathy.

Cytology and Core needle biopsy revealed atypical fibroepithelial lesion and Borderline Phyllodes tumour, respectively. The mass showed a good surface smoothness and was easily detachable from the adjacent parenchyma, enucleated and sent for histopathological examination.

On gross examination, a well-circumscribed globular mass measured 110 mm X 95mm X 90 mm was noted with a smooth external surface. The cut surface showed a pearly white solid group having well-defined margins. Small haemorrhagic foci in the periphery of the lesion were noted. (Fig 1a)

Most areas showed a fibroepithelial tumour with stromal expansion, forming leaf-like projections into the dilated lumen (figs. 1b and c). Increased stromal cellularity was noted, predominantly around the epithelial component, with marked atypia, bizarre multinucleated tumour giant cells, and mitoses of 11-13/10 hpf. A small haemorrhagic focus at the periphery

of the nodule revealed non-cohesive colonies and sheets of high-grade tumour cells. These cells were polygonal with well-defined cytoplasmic borders, abundant eosinophilic cytoplasm, and vesicular nuclei resembling the morphology of rhabdomyoblasts (fig 1d). Immunohistochemistry for desmin showed strong and intense positivity in rhabdomyoblasts, confirming the diagnosis of malignant phyllodes with rhabdomyosarcoma (fig 1e and f).

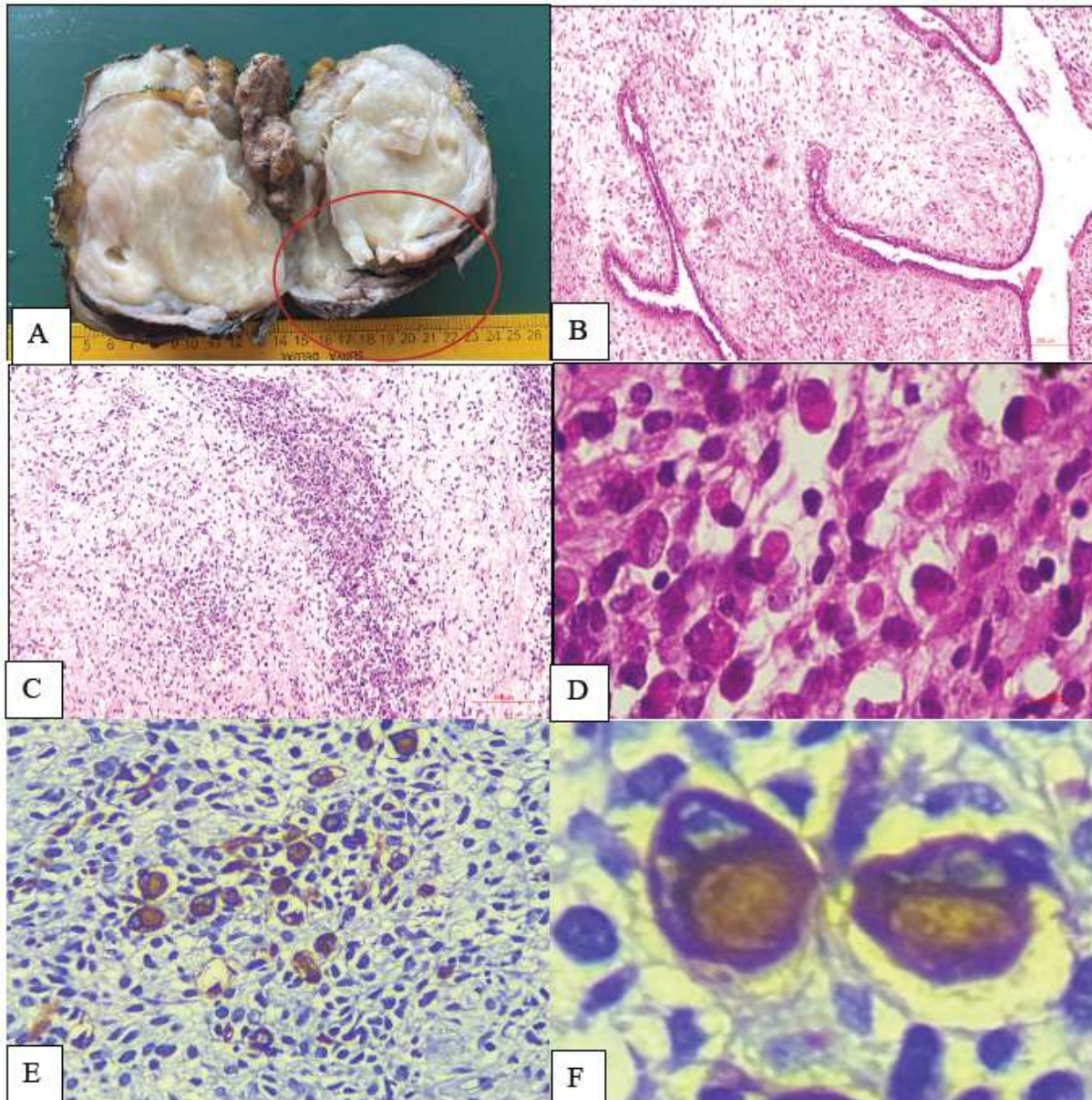


Fig A: The Cut surface of the round lesion shows predominantly solid grey-white areas with haemorrhagic foci at the periphery. **B:** Leaf-like projection of epithelial component with stromal expansion (H&E 4x) **C:** Island of heterologous element (H&E,10x) **D:** Rhabdomyoblasts cells. (H&E,40x), **E&F:** Strong positivity with Desmin immunohistochemistry (DAB, 40X &100X).

Discussion

Phyllodes tumours form a spectrum from absolutely benign to borderline to frankly malignant tumours based on histological characteristics comprising the degree of stromal cellularity, atypia, mitoses, presence of stromal overgrowth, malignant heterologous element and tumour borders ⁽¹⁾. Heterologous sarcomatous elements include angiosarcoma, chondrosarcoma, leiomyosarcoma, osteosarcoma, and rhabdomyosarcoma, are rarely encountered in malignant phyllodes tumours.

The grade of the tumour plays a significant role in the tumour outcome ⁽²⁾. Malignant heterologous element places the tumour straight away into a malignant category, even without specific criteria required to fulfil the diagnosis. However, fewer authors have shown that surgical excision with at least a 1 cm tumour-free margin significantly reduces local recurrence ⁽⁵⁾. Recent literature suggests that liposarcoma as a heterologous component is no longer a histological criterion of malignancy because no tumour recurrences were seen in the MPT. They do not harbour MDM2 aberrations or CDK4 amplification ⁽⁶⁾. Not much data is available on the prognosis of MPT with rhabdomyosarcomatous differentiation.

Distant metastasis to bone and lung is most commonly seen with a dismal prognosis. A study done on 335 cases of phyllodes showed that death from phyllodes is due to preceded recurrence and distant metastasis ⁽⁷⁾. The grade progression can be seen in recurrent tumours due to the lack of proper sampling and tumour heterogeneity ⁽⁸⁾. The gross examination is a unique challenge in anatomical pathology because the tumour's final diagnosis, grade, prognosis and behaviour of the tumour depend on it. Gross examination with appropriate tissue submission for microscopic examination is crucial for accurate diagnosis and prognosis.

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APPENDIX 1

INFORMATION FOR AUTHORS

All authors listed in a paper submitted to Asian Archives of Pathology (AAP) must have contributed substantially to the work. It is the corresponding author who takes responsibility for obtaining permission from all co-authors for the submission. When submitting the paper, the corresponding author is encouraged to indicate the specific contributions of all authors (the author statement, with signatures from all authors and percentage of each contribution can be accepted). Examples of contributions include: designed research, performed research, contributed vital new reagents or analytical tools, analysed data, and wrote the paper. An author may list more than one type of contribution, and more than one author may have contributed to the same aspect of the work.

Authors should take care to exclude overlap and duplication in papers dealing with related materials. See also paragraph on Redundant or Duplicate Publication in “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” at <http://www.icmje.org/index.html>.

The submitted manuscripts will be reviewed by three members of the Editorial Board or three expert reviewers from different institutions. At the discretion of the Editorial Board, the manuscripts may be returned immediately without full review, if deemed not competitive or outside the realm of interests of the majority of the readership of the Journal. The decision (reject, invite revision, and accept) letter will be coming from the Editorial Board who has assumed responsibility for the manuscript’s review. The editor’s decision is based not just on technical merit of the work, but also on other factors such as the priority for publication and the relevance to the Journal’s general readership. All papers are judged in relation to other submissions currently under consideration.

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The letters to the editor are the reactions to any papers published in AAP. These letters will be reviewed by the Editorial Board and sent to the authors of the original paper with an invitation to respond. Letters and eventual responses will be published together, when appropriate.

- *Word Count: 300 – 500 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 10*
- *Figure or Table: Maximum of 1 (if needed)*

2. Original Articles

The original articles are the researches describing the novel understanding of anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. Systematic reviews, meta-analyses and clinical trials are classified as articles. The articles should be clearly and concisely written in the well-organised form (see ***Organisation of Manuscripts***): abstract; introduction; materials and methods; results; discussion; and conclusions. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two or more experts in the field.

- Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)
- Structured Abstract (see ***Organisation of Manuscripts***): 150 – 200 words
- References: Maximum of 150
- Figures or Tables: Maximum of 6

3. Review Articles

The review articles are generally invited by the Editor-in-Chief. They should focus on a topic of broad scientific interest and on recent advances. These articles are peer-reviewed before the final decision to accept or reject the manuscript for publication. Therefore, revisions may be required.

- Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)
- Unstructured Abstract: 150 – 200 words
- References: Maximum of 150
- Figures or Tables: Maximum of 4

4. Case Reports

AAP limits publication of case reports to those that are truly novel, unexpected or unusual, provide new information about anatomical pathology, clinical pathology (laboratory medicine) or forensic medicine (legal medicine or medical jurisprudence). In addition, they must have educational value for the aforementioned fields. The journal will not consider case reports describing preventive or therapeutic interventions, as these generally require stronger evidence. Case reports that involve a substantial literature review should be submitted as a review article. The submitted case reports will undergo the usual peer-reviewed process.

- Word Count: 1,200 – 2,000 words (excluding abstract, references, and figure or table legends)
- Unstructured Abstract: 150 – 200 words

- *References: Maximum of 20*
- *Figures or Tables: Maximum of 4*

5. Case Illustrations

Case illustrations are aimed to provide education to readers through multidisciplinary clinicopathological discussions of interesting cases. The manuscript consists of a clinical presentation or description, laboratory investigations, discussion, final diagnosis, and up to 5 take-home messages (learning points). Regarding continuous learning through self-assessment, each of the case illustrations will contain 3 – 5 multiple choice questions (MCQs) with 4 – 5 suggested answers for each question. These MCQs are placed after the final diagnosis and the correct answers should be revealed after the references. The questions and take-home messages (learning points) are included in the total word count. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two experts in the field.

- *Word Count: 1,000 – 2,000 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 10*
- *Figures: Maximum of 2*
- *Tables: Maximum of 5*

6. Technical Notes

The technical notes are brief descriptions of scientific techniques used in the anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. The submitted manuscripts are usually peer-reviewed.

- *Word Count: Maximum of 1,000 words (excluding references and figure or table legends)*
- *Abstract: Not required*
- *References: Maximum of 5*
- *Figures or Tables: Maximum of 2*

Organisation of Manuscripts

1. General Format

The manuscripts written in English language are preferable. However, Thai papers are also acceptable, but their title pages, abstracts, and keywords must contain both Thai and English. These English and Thai manuscripts are prepared in A4-sized Microsoft Word documents with leaving 2.54-cm (1-inch) margins on all sides. All documents are required to be aligned left and double-spaced throughout the entire manuscript. The text should

be typed in 12-point regular Times New Roman font for English manuscript and 16-point regular TH SarabunPSK font for Thai manuscript.

The running titles of English and Thai manuscripts are placed in the top left-hand corner of each page. They cannot exceed 50 characters, including spaces between words and punctuation. For the header of English paper, the running title will be typed in all capital letters. The page number goes on the top right-hand corner.

Footnotes are not used in the manuscripts, but parenthetical statements within text are applied instead and sparingly. Abbreviations should be defined at first mention and thereafter used consistently throughout the article. The standard abbreviations for units of measure must be used in conjunction with numbers.

All studies that involve human subjects should not mention subjects' identifying information (e.g. initials) unless the information is essential for scientific purposes and the patients (or parents or guardians) give written informed consent for publication.

2. Title Page

The title page is the first page of the manuscripts and must contain the following:

- The title of the paper (not more than 150 characters, including spaces between words)
- The full names, institutional addresses, and email addresses for all authors (If authors regard it as essential to indicate that two or more co-authors are equal in status, they may be identified by an asterisk symbol with the caption "These authors contributed equally to this work" immediately under the address list.)
- The name, surname, full postal address, telephone number, facsimile number, and email address of the corresponding author who will take primary responsibility for communication with AAP.
- Conflict of interest statement (If there are no conflicts of interest for any author, the following statement should be inserted: "The authors declare that they have no conflicts of interest with the contents of this article.")

3. Abstract

A structured form of abstract is used in all Original Article manuscripts and must include the following separate sections:

- *Background: The main context of the study*
- *Objective: The main purpose of the study*
- *Materials and Methods: How the study was performed*
- *Results: The main findings*
- *Conclusions: Brief summary and potential implications*

- *Keywords: 3 – 5 words or phrases (listed in alphabetical order) representing the main content of the article*

4. Introduction

The Introduction section should clearly explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

5. Materials and Methods

The Materials and Methods section must be described in sufficient detail to allow the experiments or data collection to be reproduced by others. Common routine methods that have been published in detail elsewhere should not be described in detail. They need only be described in outline with an appropriate reference to a full description. Authors should provide the names of the manufacturers and their locations for any specifically named medical equipment and instruments, and all chemicals and drugs should be identified by their systematic and pharmaceutical names, and by their trivial and trade names if relevant, respectively. Calculations and the statistical methods employed must be described in this section.

All studies involving animal or human subjects must abide by the rules of the appropriate Internal Review Board and the tenets of the recently revised Helsinki protocol. Hence, the manuscripts must include the name of the ethics committee that approved the study and the committee's reference number if appropriate.

6. Results

The Results section should concisely describe the findings of the study including, if appropriate, results of statistical analysis which must be presented either in the text or as tables and figures. It should follow a logical sequence. However, the description of results should not simply repeat the data that appear in tables and figures and, likewise, the same data should not be displayed in both tables and figures. Any chemical equations, structural formulas or mathematical equations should be placed between successive lines of text. The authors do not discuss the results or draw any conclusions in this section.

7. Discussion

The Discussion section should focus on the interpretation and the significance of the findings against the background of existing knowledge. The discussion should not repeat information in the results. The authors will clearly identify any aspects that are novel. In addition, there is the relation between the results and other work in the area.

8. Conclusion

The Conclusion section should state clearly the main summaries and provide an explanation of the importance and relevance of the study reported. The author will also describe some indication of the direction future research should take.

9. Acknowledgements

The Acknowledgements section should be any brief notes of thanks to the following:

- *Funding sources*
- *A person who provided purely technical help or writing assistance*
- *A department chair who provided only general support*
- *Sources of material (e.g. novel drugs) not available commercially*

Thanks to anonymous reviewers are not allowed. If you do not have anyone to acknowledge, please write “Not applicable” in this section.

10. References

The Vancouver system of referencing should be used in the manuscripts. References should be cited numerically in the order they appear in the text. The authors should identify references in text, tables, and legends by Arabic numerals in parentheses or as superscripts. Please give names of all authors and editors. The references should be numbered and listed in order of appearance in the text. The names of all authors are cited when there are six or fewer. When there are seven or more, only the first three followed by “et al.” should be given. The names of journals should be abbreviated in the style used in Index Medicus (see examples below). Reference to unpublished data and personal communications should not appear in the list but should be cited in the text only (e.g. A Smith, unpubl. Data, 2000).

- *Journal article*
 1. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia – eclampsia. Am J Obstet Gynecol 1990; 162: 1141 – 5.
- *Books*
 2. Remington JS, Swartz MN. Current Topics in Infectious Diseases, Vol 21. Boston: Blackwell Science Publication, 2001.
- *Chapter in a book*
 3. Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Bloom SL, Wenstrom KD. Hypertensive disorders in pregnancy. In: Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Brom SL, Wenstrom KD, eds. Williams Obstetrics, 22nd ed. New York: McGraw-Hill, 2005: 761 – 808.

11. Tables

The tables should be self-contained and complement, but without duplication, information contained in the text. They should be numbered consecutively in Arabic numerals (Table 1, Table 2, etc.). Each table should be presented on a separate page with a comprehensive but concise legend above the table. The tables should be double-spaced and vertical lines should not be used to separate the columns. The column headings should be brief, with units of measurement in parentheses. All abbreviations should be defined in footnotes. The tables and their legends and footnotes should be understandable without reference to the text. The authors should ensure that the data in the tables are consistent with those cited in the relevant places in the text, totals add up correctly, and percentages have been calculated correctly.

12. Figure Legends

The legends should be self-explanatory and typed on a separate page titled “Figure Legends”. They should incorporate definitions of any symbols used and all abbreviations and units of measurement should be explained so that the figures and their legends are understandable without reference to the text.

If the tables or figures have been published before, the authors must obtain written permission to reproduce the materials in both print and electronic formats from the copyright owner and submit them with the manuscripts. These also follow for quotes, illustrations, and other materials taken from previously published works not in the public domain. The original resources should be cited in the figure captions or table footnotes.

13. Figures

All illustrations (line drawings and photographs) are classified as figures. The figures should be numbered consecutively in Arabic numerals (Figure 1, Figure 2, etc.). They are submitted electronically along with the manuscripts. These figures should be referred to specifically in the text of the papers but should not be embedded within the text. The following information must be stated to each microscopic image: staining method, magnification (especially for electron micrograph), and numerical aperture of the objective lens. The authors are encouraged to use digital images (at least 300 d.p.i.) in .jpg or .tif formats. The use of three-dimensional histograms is strongly discouraged when the addition of these histograms gives no extra information.

14. Components

14.1. Letters to the Editor

The Letter to the Editor manuscripts consist of the following order:

- *Title Page*
- *Main Text*
- *References*
- *Table (if needed)*
- *Figure Legend (if needed)*
- *Figure (if needed)*

14.2. Original Articles

The Original Article manuscripts consist of the following order:

- *Title Page*
- *Structured Abstract*
- *Introduction*
- *Materials and Methods*
- *Results*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.3. Review Articles

The Review Article manuscripts consist of the following order:

- *Title Page*
- *Unstructured Abstract*
- *Introduction*
- *Main Text*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.4. Case Reports

The Case Report manuscripts consist of the following order:

- *Title Page*
- *Unstructured Abstract*
- *Introduction*

- *Case Description*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.5. Case Illustrations

The Case Illustration manuscripts consist of the following order:

- *Title Page*
- *Clinical Presentation or Description*
- *Laboratory Investigations*
- *Discussion*
- *Final Diagnosis*
- *Multiple Choice Questions (MCQs)*
- *Take-Home Messages (Learning Points)*
- *Acknowledgements*
- *References*
- *Correct Answers to MCQs*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

14.6. Technical Notes

The Technical Note manuscripts consist of the following order:

- *Title Page*
- *Introduction*
- *Main text*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

Proofreading

The authors of the accepted manuscripts will receive proofs and are responsible for proofreading and checking the entire article, including tables, figures, and references. These authors should correct only typesetting errors at this stage and may be charged for extensive alterations. Page proofs must be returned within 48 hours to avoid delays in publication.

Revised Manuscripts

In many cases, the authors will be invited to make revisions to their manuscripts. The revised manuscripts must generally be received by the Editorial Board within 3 months of the date on the decision letter or they will be considered a new submission. An extension can sometimes be negotiated with the Editorial Board.

APPENDIX 2

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APPENDIX 3

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- Step 4:** Click the “+ New Submission” button on the upper right-hand side of the page.
- Step 5:** Proceed to fill up the Submission Form online and follow the directions given therein.
- Step 6:** Upload your manuscript file (s).
- Step 7:** Re-check the content of your manuscript (s) and the uploaded file (s) more carefully prior to the submission. If you have submitted your manuscript file (s) incorrectly, you must contact Editor-in-Chief of Asian Archives of Pathology immediately. The Editor-in-Chief can clear the incorrect attempt and allow you another submission.
- Step 8:** Click the “Submit Manuscript” button under Important Notice.

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The Editorial Office of Asian Archives of Pathology

Department of Pathology, Floor 6, Her Royal Highness Princess Bejaratana Building
Phramongkutkloao College of Medicine
317 Rajavithi Road, Rajadevi, Bangkok 10400 Thailand

Telephone: +66 (0) 90 132 2047

Fax: +66 (0) 2 354 7791

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The Editorial Office of Asian Archives of Pathology

Department of Pathology, Floor 6, Her Royal Highness Princess Bejaratana Building

Phramongkutklao College of Medicine

317 Rajavithi Road, Rajadevi, Bangkok 10400 Thailand

Telephone: +66 (0) 90 132 2047

Fax: +66 (0) 2 354 7791

Email: editor@asianarchpath.com

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Assistant Professor Dr Chetana Ruangpratheep

MD, FRCPath (Thailand), MSc, PhD

Editor-in-Chief of Asian Archives of Pathology

ACADEMIC MEETINGS AND CONFERENCES

Announcements of academic meetings and conferences that are of interest to the readers of Asian Archives of Pathology (AAP) should be sent to the Editor-in-Chief at least 3 months before the first day of the month of issue. The contact information is shown below.

Assistant Professor Dr Chetana Ruangpratheep

The Editorial Office of Asian Archives of Pathology

Department of Pathology, Floor 6, Her Royal Highness Princess Bejaratana Building

Phramongkutklao College of Medicine

317 Rajavithi Road, Rajadevi, Bangkok 10400 Thailand

Telephone: +66 (0) 90 132 2047

Fax: +66 (0) 2 354 7791

Email: editor@asianarchpath.com

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