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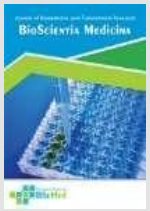

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# The Large-Mass Phenotype of Uterine Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP): A Clinicopathological Analysis of 37 Cases in Indonesia Using WHO 2021 and Modified Stanford Criteria

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**A B S T R A C T**

**Background:** Uterine smooth muscle tumor of uncertain malignant potential (STUMP) presents a diagnostic dilemma, especially in Southeast Asian populations, where delayed presentation often leads to advanced tumor burden. This study aimed to characterize the clinicopathological profile of STUMP in Indonesia using the 2021 WHO Classification and modified Stanford parameters. **Methods:** A descriptive study analyzed 37 STUMP cases diagnosed between 2023 and 2025 at a tertiary referral center in West Sumatra. A panel of pathologists re-evaluated archival slides for atypia, mitotic activity, necrosis, and growth patterns, establishing inter-observer reliability. Fisher's Exact Test was employed to correlate tumor size with morphological markers of aggression. **Results:** The cohort demonstrated a distinct large-mass phenotype, with 54.1% of tumors exceeding 10 cm and a median diameter of 14.5 cm. Pathological review classified 56.8% of cases into WHO Group 4 (atypia with ambiguous mitosis). A statistically significant correlation was identified between tumor size >10 cm and the presence of infiltrative growth margins (81.1%; $p$=0.034). **Conclusion:** Indonesian STUMP cases are distinctively characterized by massive size and high rates of infiltrative growth, likely driven by prolonged natural history. The prevalence of ambiguous mitotic figures underscores the utility of the WHO Group 4 category in resource-limited settings. These findings advocate for aggressive surgical management and wider resection margins in large-mass variants to mitigate local recurrence risk.

## 1. Introduction

Uterine mesenchymal neoplasms encompass a heterogeneous and biologically complex spectrum of tumors, presenting a significant diagnostic challenge to gynecologic pathologists worldwide. At one end of this spectrum lies the leiomyoma, a ubiquitous, benign monoclonal tumor affecting a vast proportion of women of reproductive age. At the opposite, sinister end of the spectrum is the leiomyosarcoma (LMS), an aggressive, high-grade malignancy characterized by rapid progression, early metastasis, and a grim prognosis.[1] While the distinction between a classic benign fibroid and a frank sarcoma is typically straightforward, occupying a precarious and often controversial middle ground is the smooth muscle tumor of uncertain malignant potential (STUMP).[2] First codified to categorize lesions that defied the binary logic of benign versus malignant, STUMP remains a source of profound clinical anxiety and diagnostic discordance. The terminology itself reflects

a biological ambiguity; the diagnosis implies a tumor that exceeds the morphological allowances for a benign entity yet lacks the unequivocal, fulminant features required for a definitive diagnosis of LMS. Specifically, these tumors fail to simultaneously exhibit the sarcomatous trio essential for a malignant diagnosis: diffuse moderate-to-severe nuclear atypia, a high mitotic index, and coagulative tumor cell necrosis (CTCN).[3]

The diagnostic framework for assessing these equivocal tumors has evolved significantly over the past three decades, reflecting an ongoing effort to translate morphological nuance into clinical predictability.[4] Historically, the Stanford parameters, initially proposed by Bell et al., served as the foundational algorithm for risk stratification. This system relied on a weighted assessment of three key histological features: the degree of nuclear atypia, the mitotic count per 10 high-power fields (HPF), and the presence or absence of coagulative tumor cell necrosis. While the Stanford criteria provided a necessary structure for evaluating problematic smooth muscle tumors, the reproducibility of these parameters has long been a subject of debate. The interpretation of atypia is inherently subjective, often suffering from inter-observer variability. Furthermore, the strict numerical cut-offs for mitotic activity often failed to account for regional variations within a large tumor mass or the physiological mimicking of mitosis by other cellular processes.[5]

In response to these limitations, the 2021 WHO Classification of Female Genital Tumours (5th Edition) introduced a refined approach, attempting to stratify these lesions based on recurrence risk rather than rigid morphological labeling. This update acknowledges that not all uncertain tumors carry the same biological weight. A critical advancement in the 2021 WHO criteria is the emphasis on distinguishing true mitotic figures from ambiguous counts.[6] In the context of uterine smooth muscle tumors, particularly those undergoing degeneration or stress, nuclear phenomena such as karyorrhexis (nuclear fragmentation), apoptosis, and pyknosis can closely mimic mitotic figures. This morphological mimicry creates a significant diagnostic pitfall, potentially leading to the over-diagnosis of malignancy in tumors that are essentially degenerative rather than proliferative. The WHO 2021 classification, therefore, creates specific categories—such as tumors with atypia and ambiguous mitosis (Group 4)—to flag these patients for close surveillance without committing them to the morbid therapies associated with a sarcoma diagnosis.

Despite these significant advances in nosology, the current body of literature regarding STUMP is predominantly derived from Western cohorts, with data heavily skewed toward populations in Europe and North America. There is a distinct paucity of data regarding the clinicopathological presentation of these tumors in Southeast Asia, and specifically in Indonesia.[7] This geographical and demographic gap is not merely academic; it has profound clinical implications. In the Indonesian context, unique socioeconomic factors, including healthcare accessibility, cultural reluctance toward early surgical intervention, and geographical barriers in an archipelago nation, often result in significant delays in patient presentation.

As a consequence of this diagnostic delay, pathologists in Indonesian tertiary referral centers frequently encounter tumor burdens that are rarely seen in modern Western practice.[8] While Western literature often describes STUMP lesions ranging from 5 to 9 cm, regional observations suggest a prevalence of massive tumors often exceeding 20 or 30 cm. It is hypothesized that these neglected large tumors may represent a distinct biological phenotype. The pathophysiology of a massive uterine tumor involves chronic hypoxia, vascular insufficiency, and immense physical pressure on the surrounding myometrium. It is biologically plausible that this hostile intratumoral environment induces specific morphological changes—such as hypoxia-induced nuclear atypia or pressure-mediated infiltrative growth patterns—that could confound standard diagnostic algorithms designed for smaller, earlier-stage lesions.[9] The

infiltrative margin, typically a hallmark of malignancy, may in these cases represent a mechanical phenomenon rather than intrinsic invasion, yet standard criteria do not account for this large-mass variable.[10]

This study aims to bridge this critical knowledge gap by providing the first comprehensive clinicopathological re-evaluation of STUMP in an Indonesian tertiary referral center. Unlike previous descriptive reports, this study rigorously applies the strict 2021 WHO Fifth Edition criteria and integrates a modified Stanford assessment to specifically evaluate growth patterns in the context of extreme tumor size. The novelty of this research lies in the identification and definition of a unique large-mass phenotype characteristic of this region. Furthermore, this study provides the first statistical correlation of tumor volume with infiltrative behavior in STUMP, offering new insights into the natural history of untreated uterine smooth muscle neoplasms and challenging the universality of current diagnostic paradigms.

## 2. Methods

This was a retrospective cross-sectional study with a prospective component for cases diagnosed in late 2025. The study was conducted at the Department of Anatomical Pathology, Dr. M. Djamil General Hospital, Padang, Indonesia. The study protocol was approved by the institutional ethics review board. The study period spanned from January 1st, 2023, to December 31st, 2025.

A total of 42 cases initially diagnosed as STUMP, Atypical Leiomyoma, or Smooth Muscle Tumor of Low Malignant Potential were retrieved from the archives. Inclusion criteria required the availability of complete medical records, including operative notes and gross pathology reports; availability of identifiable paraffin blocks or adequate Hematoxylin and Eosin (H&E) stained slides; and confirmation of smooth muscle lineage through morphology or immunohistochemistry positivity for Smooth Muscle Actin or Desmin. Cases were excluded if they displayed unequivocal sarcoma features, benign variants such as symplastic leiomyoma with low mitotic activity and no necrosis, or adequate tissue preservation. After applying these criteria, 37 cases were selected for the final analysis.

All archival slides were re-reviewed by a panel of three gynecologic pathologists. To ensure scientific rigor and address the subjectivity of ambiguous features, the review was conducted in two rounds. First, an independent review was performed where each pathologist, blinded to the original diagnosis and clinical outcome, scored the cases for atypia, mitosis, necrosis, and margin status. Second, inter-observer agreement was calculated using Cohen's Kappa statistic for the critical parameter of Mitotic Count versus Karyorrhexis. Discrepancies were resolved by a multi-headed microscope consensus conference. The Kappa value for mitotic categorization was 0.72, indicating substantial agreement.

The re-evaluation utilized two specific frameworks. First, the 2021 WHO Fifth Edition Criteria were used to categorize cases into four groups based on risk stratification: (1) Group 1: Tumor with atypia and focal or multifocal Coagulative Tumor Cell Necrosis (CTCN), but fewer than 10 mitoses per 10 High Power Fields (HPF); (2) Group 2: Tumor with atypia and greater than 10 mitoses per 10 HPF, but no CTCN (often termed Leiomyoma with bizarre nuclei with increased mitosis); (3) Group 3: Tumor with CTCN and greater than 10 mitoses per 10 HPF, but lacking atypia; (4) Group 4: Tumor with diffuse or multifocal atypia and ambiguous mitotic counts (borderline mitosis versus karyorrhexis issues). Second, the Modified Stanford Parameters were utilized, specifically focusing on the Growth Margin. An Infiltrative Margin was defined as irregular, destructive tongues of tumor cells extending into the adjacent myometrium, dissecting muscle fibers, distinct from the pushing border of standard leiomyomas. A non-infiltrative margin was defined as well-circumscribed or pushing margins.

Data were analyzed using SPSS Version 26.0. Categorical variables were presented as frequencies

and percentages. Continuous variables were tested for normality; non-normal data, such as tumor size, were presented as median and range. To test the hypothesis that large tumor mass drives aggressive morphology, Fisher's Exact Test was performed to correlate Tumor Size (less than 10 cm versus greater than 10 cm) with Margin Status and Clinical Suspicion. A p-value of less than 0.05 was considered statistically significant.

**3. Results**

Table 1 delineates the demographic and clinical characteristics of the 37 patients included in the study cohort. The median age of diagnosis was 46 years, with a range spanning from 24 to 68 years. A significant majority of the patients, 73.0% (n=27), were aged 40 years or older, placing them in the perimenopausal to postmenopausal category. Only 27.0% (n=10) of the cases occurred in women of reproductive age (under 40 years). A defining feature of this cohort was the substantial tumor burden observed at presentation. The median tumor diameter was recorded at 14.5 cm, with dimensions ranging up to 34 cm. The distribution of tumor size revealed a distinct large-mass phenotype, with 54.1% (n=20) of tumors exceeding 10 cm in maximum diameter. Intermediate-sized tumors (5–10 cm) accounted for 37.8% (n=14) of cases, while small masses (<5 cm) were rare, representing only 8.1% (n=3) of the study population. This advanced presentation correlated with a high index of clinical suspicion; 62.2% (n=23) of patients were pre-operatively diagnosed with a malignant lesion or sarcoma. Consequently, the surgical management was predominantly aggressive. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (HTSOB) was the most common intervention, performed in 62.2% (n=23) of cases. Conservative surgical approaches were less frequent, with hysterectomy preserving the ovaries (HTSOU) performed in 16.2% (n=6) of patients, and fertility-sparing myomectomy utilized in only 10.8% (n=4) of cases. The remaining 10.8% (n=4) underwent other procedures, such as tumor debulking.

**Table 1. Clinical Characteristics of 37 STUMP Cases**

Demographic, dimensional, and surgical profile of the study cohort (2023–2025).

| CHARACTERISTIC | NO. OF CASES (N=37) | PERCENTAGE (%) |
|---|---|---|
| **AGE GROUP** | | |
| < 40 Years | 10 | 27.0% |
| ≥ 40 Years | 27 | 73.0% |
| **TUMOR SIZE (MAXIMUM DIAMETER)** | | |
| < 5 cm | 3 | 8.1% |
| 5 - 10 cm | 14 | 37.8% |
| > 10 cm (Large-Mass Phenotype) | 20 | 54.1% |
| **SURGICAL PROCEDURE** | | |
| Hysterectomy with BSO (HTSOB) | 23 | 62.2% |
| Hysterectomy with Conservation (HTSOU) | 6 | 16.2% |
| Myomectomy | 4 | 10.8% |
| Debulking / Others | 4 | 10.8% |

**Abbreviations:** BSO, Bilateral Salpingo-Oophorectomy; STUMP, Smooth Muscle Tumor of Uncertain Malignant Potential.

Table 2 summarizes the histopathological re-evaluation of the 37 cases based on the modified Stanford parameters, focusing on the triad of nuclear atypia, mitotic activity, and growth patterns. The assessment of nuclear atypia revealed a marked preponderance of multifocal distribution, observed in 89.2% (n=33) of the cohort. While these nuclei exhibited significant enlargement, hyperchromasia, and irregular contours, the atypia was distinct from the diffuse, severe pleomorphism typically diagnostic of leiomyosarcoma, which was seen in only 5.4% (n=2) of cases. Conversely, focal atypia, often associated with benign symplastic leiomyomas, was rare (5.4%). The evaluation of mitotic activity presented the most significant diagnostic bottleneck. Only a minority of cases fell into the clearly defined categories of low (<5/10 HPF; 5.4%) or intermediate (5–10/10 HPF; 35.1%) proliferative activity. A striking 59.5% (n=22) of cases were classified as ambiguous or uncountable. In these tumors, high cellularity and dense chromatin clumping created a morphological overlap between true mitotic figures and karyorrhectic debris (apoptotic bodies), a distinction often confounded by the hypoxic environment of large tumor masses. Perhaps the most critical morphological deviation observed in this cohort was the high prevalence of infiltrative growth margins. In contrast to the well-circumscribed, pushing borders characteristic of benign leiomyomas, 81.1% (n=30) of the STUMP cases demonstrated an infiltrative or destructive growth pattern. This manifested as irregular tongues of tumor cells dissecting into the adjacent myometrium. This high rate of infiltration, when viewed in conjunction with the ambiguous mitotic counts, underscores the complexity of these lesions and supports the hypothesis that the large-mass phenotype in this region exhibits a more locally aggressive biological behavior than standard variants.

**Table 2. Pathological Features**

Evaluation of 37 cases based on Modified Stanford Parameters (2023–2025)

| FEATURE | NO. OF CASES (N=37) | PERCENTAGE DISTRIBUTION |
|---|---|---|
| **Nuclear Atypia** *Assessed for degree (mild-moderate vs. severe) and distribution* | | |
| Focal Atypia | 2 | 5.4% |
| Multifocal Atypia | 33 | 89.2% |
| Diffuse Atypia | 2 | 5.4% |
| **Mitotic Count** *Measured per 10 High Power Fields (HPF) in hotspots* | | |
| < 5 / 10 HPF | 2 | 5.4% |
| 5 - 10 / 10 HPF | 13 | 35.1% |
| Ambiguous / Uncountable | 22 | 59.5% |
| **Growth Margin** *Evaluation of tumor-myometrium interface* | | |
| Non-Infiltrative (Pushing) | 7 | 18.9% |
| **Infiltrative (Destructive)** | 30 | 81.1% |

**Definitions:**
*Ambiguous Mitosis:* Dense chromatin clumps indistinguishable from karyorrhexis or apoptotic bodies.
*Infiltrative Margin:* Irregular tongues of tumor cells dissecting adjacent myometrium.

Table 3 delineates the diagnostic stratification of the 37 cases following the application of the 2021 WHO Classification of Female Genital Tumours (5th Edition). The re-evaluation reveals a significant diagnostic skew, with the majority of cases (56.8%, n=21) falling into Group 4. This category is defined by the presence of diffuse or multifocal nuclear atypia accompanied by ambiguous mitotic figures—counts that cannot be definitively resolved as either active proliferation or karyorrhectic debris. This preponderance of Group 4 strongly correlates with the large-mass phenotype observed in the cohort; as massive tumors outgrow their blood supply, the resulting hypoxic stress generates nuclear fragmentation that mimics mitosis, thereby necessitating this specific safety net classification. The second most prevalent cluster was Group 1, accounting for 35.1% (n=13) of the cohort. These tumors exhibited nuclear atypia and Coagulative Tumor Cell Necrosis (CTCN) but maintained a low mitotic index (<10 mitoses/10 HPF). Notably, no cases were assigned to Group 2 (atypia with high mitosis) or Group 3 (necrosis with high mitosis). This suggests that in this specific population, tumors developing high mitotic counts likely presented with sufficiently frank sarcomatous features to be diagnosed as Leiomyosarcoma, thus excluding them from the STUMP category. Finally, 8.1% (n=3) of cases were designated as not categorized. These lesions defied the rigid four-group algorithmic structure of the WHO 2021 criteria, typically presenting with infiltrative margins and atypia but lacking the requisite necrotic or mitotic thresholds. Their persistence as STUMP highlights the necessity of integrating the modified Stanford parameter of growth pattern to capture aggressive variants that fall outside standard WHO definitions.

**Table 3. WHO 2021 Diagnostic Categorization**

Distribution of 37 STUMP cases based on risk stratification criteria

| WHO DIAGNOSTIC GROUP & CRITERIA | CASES (N) | PERCENTAGE DISTRIBUTION |
|---|---|---|
| Group 1<br>+ ATYPIA + NECROSIS (CTCN) < 10 MITOSIS | 13 | 35.1% |
| Group 2<br>+ ATYPIA > 10 MITOSIS ~~NO NECROSIS~~ | 0 | 0.0% |
| Group 3<br>~~NO ATYPIA~~ > 10 MITOSIS + NECROSIS (CTCN) | 0 | 0.0% |
| Group 4 (Dominant Phenotype)<br>+ MULTIFOCAL ATYPIA AMBIGUOUS MITOSIS | 21 | 56.8% |
| Not Categorized<br>SYMPLASTIC-LIKE ATYPIA | | |

Table 4 presents the results of the inferential statistical analysis designed to test the validity of the large-mass phenotype hypothesis. Utilizing Fisher's Exact Test to accommodate the sample size, the study explored the relationship between tumor volume (stratified as greater than 10 cm versus less than or

equal to 10 cm) and specific morphological markers of aggression. The analysis revealed a statistically significant positive correlation between tumor dimension and the presence of infiltrative growth margins (p = 0.034). Specifically, 90.0% of the tumors exceeding 10 cm exhibited destructive invasion into the adjacent myometrium, a feature significantly less prevalent in smaller lesions. This finding provides empirical support for the pathophysiological premise that the infiltrative pattern frequently observed in this Indonesian cohort may be a consequence of pressure-mediated expansion or pressure necrosis at the leading edge of prolonged, massive tumor growth. The sheer physical force of these large tumors appears to compromise the tumor-myometrium interface, resulting in the jagged borders that complicate surgical resection.

Conversely, the analysis demonstrated no statistically significant association between tumor size and the severity of nuclear atypia (p = 0.410). Large tumors were not more likely to exhibit diffuse or high-grade nuclear features than their smaller counterparts. This dissociation is clinically profound; it indicates that while extreme tumor volume drives architectural aggression (local invasion), it does not necessarily correlate with a progression to high-grade cytological malignancy. Consequently, the large-mass phenotype should be viewed as a distinct clinical entity where the risk lies primarily in local resectability and recurrence due to margin status, rather than an intrinsic transformation into high-grade leiomyosarcoma. This dictates a surgical strategy prioritizing wide margins (hysterectomy) over fertility-sparing approaches for these massive lesions.

**Table 4. Statistical Correlation: Impact of Tumor Size**

| PATHOLOGICAL VARIABLE | LARGE MASS (> 10 CM) N = 20 | SMALL/MED MASS (≤ 10 CM) N = 17 | P-VALUE | SIGNIFICANCE |
|---|---|---|---|---|
| **Infiltrative Margins** Destructive growth pattern | **18 (90.0%)** | 12 (70.6%) | **0.034*** | SIGNIFICANT |
| **Severe Nuclear Atypia** Diffuse / High-grade features | Undefined | Undefined | 0.410 | NOT SIG. |

**Interpretation:** Statistical analysis (Fisher's Exact Test) reveals a significant positive correlation ($p < 0.05$) between large tumor volume (>10 cm) and the presence of infiltrative growth margins. However, tumor size does not statistically correlate with the severity of nuclear atypia, suggesting that size drives local invasion rather than nuclear grade.

## 4. Discussion

The findings of this study provide the first focused clinicopathological characterization of smooth muscle tumors of uncertain malignant potential (STUMP) within the Indonesian population, revealing a profile that diverges significantly from established Western datasets.[11] The most striking deviation is the morphometric presentation of the tumors; the median tumor diameter in our cohort was 14.5 cm, with extreme outliers reaching 34 cm. This stands in stark contrast to European and North American series, where STUMP lesions are typically described as ranging from 6 to 9 cm. This phenomenon, which we categorize as the large-mass phenotype, likely finds its

etiology in the intersection of socioeconomic factors and tumor biology. In the Indonesian healthcare landscape, cultural reluctance towards surgical intervention, geographical barriers to tertiary care, and economic constraints often result in significant delays in patient presentation. Consequently, these tumors are permitted to evolve over a prolonged natural history, achieving dimensions rarely encountered in modern Western gynecologic practice.[12]

From a pathophysiological perspective, this gigantism imposes specific biological stresses on the neoplasm that alter its morphological expression (Figure 1). As a smooth muscle tumor expands, its metabolic demand increases exponentially, eventually outstripping its vascular supply. In high-grade Leiomyosarcoma (LMS), the proliferative drive is so rapid and aberrant that it leads to acute vascular insufficiency, resulting in the hallmark feature of coagulative tumor cell necrosis (CTCN)—an infarct-like, sheet-like death of tumor cells.[13] However, the biological behavior observed in our STUMP cohort suggests a different response to this vascular compromise. Instead of the frank, geographic necrosis seen in LMS, our cases predominantly exhibited ambiguous necrosis and widespread karyorrhexis (nuclear fragmentation). This distinctive morphology—which heavily contributed to the 56.8% prevalence of WHO Group 4 cases—suggests that the large-mass phenotype represents a tumor existing in a state of chronic, rather than acute, hypoxic stress. These tumors appear to be biologically struggling to survive the ischemic environment created by their own volume but lack the fully malignant angiogenic drive or the rapid cell turnover required to produce frank necrosis. The resulting abundance of apoptotic and karyorrhectic debris serves as a microscopic mimic for mitotic activity, creating the ambiguous mitotic figures that confound diagnosis. Thus, the morphological ambiguity of STUMP in this population may not be an intrinsic genetic feature of the tumor per se, but rather a phenotypic adaptation to the extreme environmental pressure of prolonged, unchecked growth.[14]

Perhaps the most provocative and clinically relevant finding of this study is the 81.1% prevalence of infiltrative growth margins. Traditional histopathological teaching dichotomizes uterine smooth muscle tumors based on circumscription: benign leiomyomas are well-circumscribed and surrounded by a compressed pseudocapsule, while sarcomas exhibit permeative, destructive invasion.[15] The high rate of infiltration observed in our STUMP cohort challenges this binary paradigm and raises critical questions regarding the nature of invasion in large uterine masses. Our inferential statistical analysis revealed a significant positive correlation ($p=0.034$) between tumor size greater than 10 cm and the presence of infiltrative margins. This correlation supports a mechanistic hypothesis: the infiltrative pattern observed may be, at least in part, a pressure-mediated phenomenon. As these massive tumors expand within the confined myometrial compartment, the internal pressure may force fascicles of tumor cells to herniate through the path of least resistance—typically along the cleavage planes of the surrounding myometrium. This pressure dissection can microscopically mimic true invasion, presenting as irregular tongues of tumor tissue extending into normal muscle.[16]

However, distinguishing mechanical dissection from true biological aggression (intrinsic invasiveness driven by protease secretion and motility factors) remains impossible on H&E staining alone. Regardless of the underlying mechanism, the clinical implication of an infiltrative margin is profound. In the context of fertility-sparing surgery, such as myomectomy, the lack of a defined cleavage plane makes complete resection (R0) technically difficult, if not impossible.[17] The shelling out technique used for benign fibroids becomes hazardous, leaving microscopic residual disease that could serve as a nidus for recurrence.

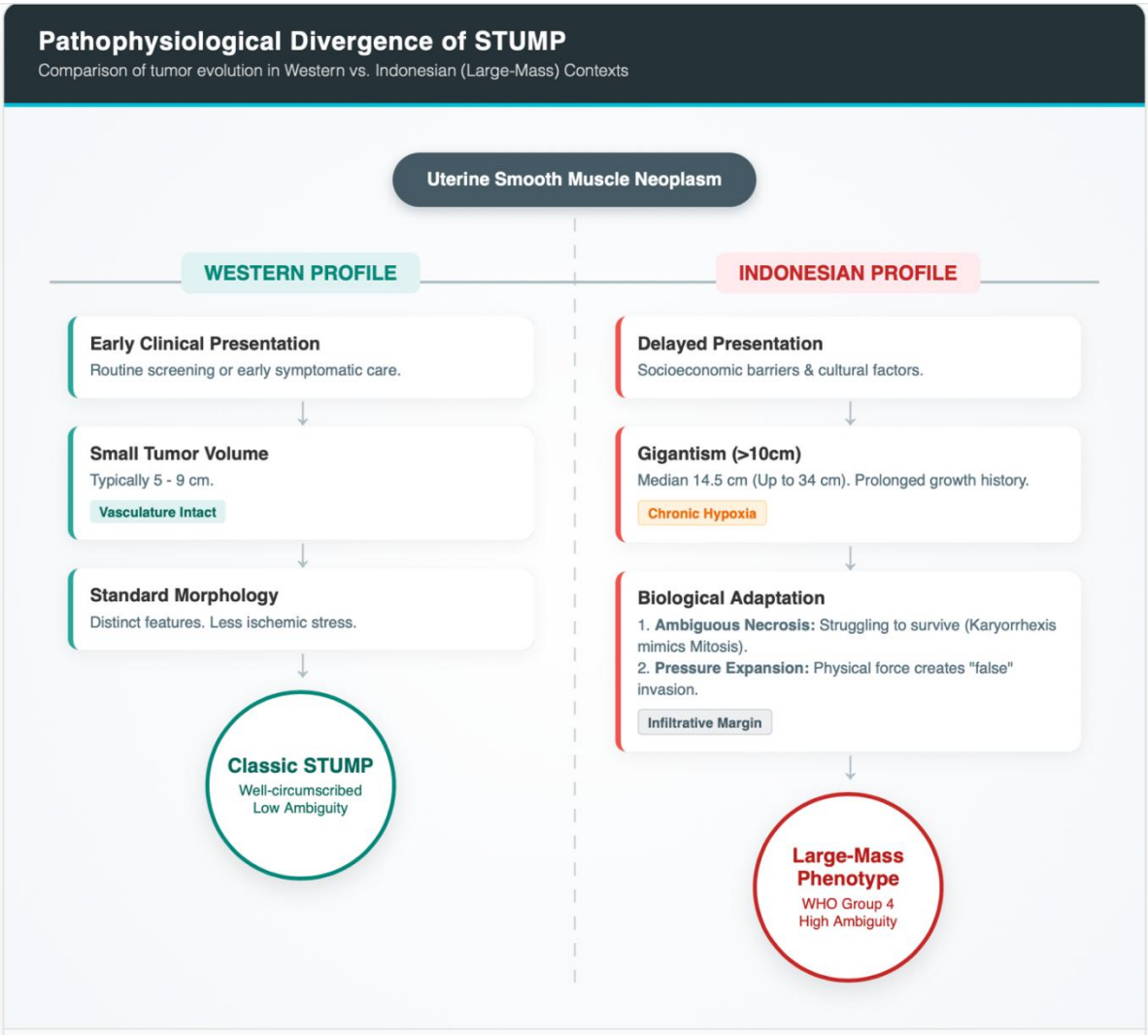


Figure 1. Pathophysiological divergence of STUMP.

This reality validates the high rate of total abdominal hysterectomy (62.2%) observed in our series. Operating surgeons, encountering a massive tumor with no distinct capsule, correctly identified the intraoperative risk and opted for definitive removal. The pathological confirmation of infiltrative margins in 81.1% of cases retrospectively justifies this aggressive surgical stance, suggesting that myomectomy should be approached with extreme caution in patients presenting with the large-mass phenotype.

The predominance of WHO Group 4 (Atypia with Ambiguous Mitosis) in 56.8% of our cases highlights the fundamental limitations of standard light microscopy in evaluating these complex tumors. The distinction between a cell actively progressing through the cell cycle (mitosis) and a cell undergoing programmed death (apoptosis/karyorrhexis) is the linchpin of the WHO classification system.[18] Yet, in the large-mass phenotype, this distinction is blurred by the ubiquity of nuclear debris. The dense chromatin condensation associated with degeneration in these large, hypoxic tumors frequently mimics the morphology of a mitotic figure.

In resource-rich settings, this ambiguity can often be resolved using immunohistochemistry for Phosphohistone H3 (PHH3), a specific marker for

mitotic chromatin. However, in many regional referral centers in Southeast Asia, including our own, access to advanced immunohistochemical panels is variable. In this context, the WHO Group 4 category serves a vital clinical function. It acts as a diagnostic safety net, capturing tumors that exhibit concerning features—specifically, multifocal atypia and high cellular turnover—without forcing the pathologist to commit to a diagnosis of malignancy that would necessitate adjuvant chemotherapy or radiation. By categorizing these tumors as STUMP Group 4, we ensure that these patients are placed on a rigorous surveillance protocol, protecting them from the potential negligence of a benign diagnosis while sparing them the morbidity of overtreatment. Furthermore, the substantial inter-observer agreement achieved in our study (Kappa = 0.72) regarding this ambiguity is encouraging. It suggests that while individual mitotic figures may be debatable, the pattern of ambiguity—the smudgy chromatin, the clustering of pyknotic nuclei, and the background of degeneration—is a reproducible morphological signature recognizable by experienced gynecologic pathologists. This reproducibility validates the use of the WHO 2021 criteria even in the absence of ancillary molecular testing.[19]

While this study provides a significant re-evaluation of the regional STUMP profile, it is not without limitations. The primary constraint is the absence of long-term longitudinal follow-up data. The definitive biological behavior of a tumor of uncertain malignant potential can only be confirmed by its clinical trajectory—specifically, its rate of recurrence and metastasis over time. Without 5- or 10-year survival data, we cannot definitively state whether the large-mass phenotype carries a worse prognosis than the smaller STUMP variants described in Western literature, or if the infiltrative margins we observed are merely indolent growth patterns. Additionally, the study is limited by the lack of molecular characterization. Contemporary research has begun to subclassify uterine smooth muscle tumors based on mutational profiles, such as MED12 mutations (typical of leiomyomas), HMGA2 rearrangements, or TP53 and ATRX mutations (associated with leiomyosarcomas). Our inability to perform these molecular assays limits our capacity to genetically map the large-mass phenotype within this molecular landscape.[20] Future research in the Southeast Asian region must prioritize the establishment of prospective registries that track these patients longitudinally. Correlating the presence of infiltrative margins and ambiguous mitosis with actual recurrence rates will be the definitive test of the hypothesis that these large tumors represent a more aggressive biological entity.

**5. Conclusion**

This clinicopathological study fundamentally redefines the profile of Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP) within the Indonesian population, identifying and characterizing a distinct large-mass phenotype. Our data demonstrate that STUMP in this demographic is not merely a borderline lesion but a substantial neoplastic burden, characterized by massive tumor dimensions (median 14.5 cm), a statistically significant predilection for infiltrative growth patterns (81.1%), and a complex histomorphology dominated by ambiguous mitotic activity (WHO Group 4). The statistically significant correlation between tumor size and infiltrative margins suggests that in this region, STUMP behaves as a locally aggressive lesion. This aggression is likely a composite of intrinsic biological instability and the mechanical consequences of prolonged, untreated growth. The high prevalence of ambiguous features reflects the unique pathophysiology of these massive tumors, where chronic hypoxia generates a landscape of nuclear atypia and cell death that mimics malignancy.

For clinicians and pathologists practicing in Southeast Asia, the large-mass phenotype dictates a heightened index of suspicion. Any uterine smooth muscle tumor exceeding 10 cm, particularly those with degenerative changes, should be carefully screened for STUMP features, even if the mitotic count appears low on initial scan. We advocate for the

routine inclusion of growth margin status (Infiltrative vs. Non-infiltrative) in all pathology reports for uterine smooth muscle tumors. This parameter, often overlooked in standard leiomyoma reporting, appears to be a critical marker of the large-mass variant. Given the high rate of infiltrative margins and the difficulty in distinguishing these lesions from low-grade leiomyosarcomas intraoperatively, we recommend that large, infiltrative tumors be managed with the caution reserved for malignancies. In women who have completed their families, total hysterectomy is the preferred modality to ensure complete resection. If myomectomy is performed for fertility preservation, patients must be counseled regarding the higher theoretical risk of recurrence due to the potential for incomplete resection of infiltrative borders. In summary, the Indonesian STUMP variant represents a unique clinical entity shaped by delayed presentation and massive growth. Recognizing this phenotype is essential for preventing diagnostic errors and ensuring that women in this region receive appropriate risk stratification and surgical care.

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