Review



# Phyllodes Tumors: Diagnostic, Investigative and Therapeutic Challenges with Special Focus on Malignant Phyllodes Tumors

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# Phyllodes Tumors: Diagnostic, Investigative and Therapeutic Challenges with Special Focus on Malignant Phyllodes Tumors

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**Abstract**

Phyllodes tumors are rare fibroepithelial neoplasms of the breast, and their malignant forms present significant diagnostic and therapeutic challenges. This review summarizes current knowledge across the benign-to-malignant spectrum, focusing on diagnostic approaches, histopathological classification, molecular alterations, and treatment strategies. While recent molecular studies have revealed recurrent genetic mutations, their clinical implications remain under investigation. Surgical excision remains the cornerstone of treatment, and systemic therapies are generally adapted from soft tissue sarcoma protocols. Future efforts should focus on improving diagnostic accuracy, identifying molecular targets for therapy, and fostering international collaboration to advance clinical research in this rare tumor type.

**Keywords:** phyllodes tumor; MED12; TERT; review; chemotherapy; sarcoma; molecular diagnostics

## 1. Introduction

Breast cancer remains a major global health issue, with most research focused on invasive ductal carcinoma, which comprises most of breast malignancies. This emphasis has led to significant therapeutic progress, including agents like capecitabine [1], trastuzumab deruxtecan (Enhertu) [2], and datopotamab deruxtecan [3], as well as personalized treatments informed by genetic testing for mutations such as *PIK3CA* and *AKT* [4]. In contrast, rare tumors such as phyllodes tumors, which represent less than 1% of breast neoplasms [5], remain understudied despite their diagnostic and therapeutic complexities. Malignant phyllodes tumors, in particular, may exhibit aggressive behavior with high recurrence and metastatic potential.

The scarcity of large-scale clinical trials and standardized guidelines has contributed to uncertainty in managing these tumors. Their histological overlap with both benign lesions like fibroadenomas and aggressive entities like metaplastic carcinomas or sarcomas further complicates diagnosis and treatment planning as community standard. In addition, incomplete understanding of their biological behavior [6], particularly in borderline and malignant variants, hampers prognostication and therapy [7].

Although recent advances in molecular profiling have shed light on the genetic drivers of phyllodes tumors [8], clinical translation remains limited. Unlike common breast cancers, where

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targeted therapies have reshaped management, comparable strategies for malignant phyllodes tumors are still in early stages. This review aims to synthesize current evidence on phyllodes tumors, focusing on malignant subtypes, with the goal of informing clinical practice and identifying directions for future research.

## 2. Benign Phyllodes Tumor

Benign phyllodes tumors are uncommon fibroepithelial neoplasms of the breast. They typically affect women in their 40s but can occur at any age [9]. These tumors are rare, with an incidence of about 2.1 per million women annually [10]. A slightly higher prevalence has been observed in Asian and Latin American populations, though the underlying reasons remain unclear [11]. While most cases are sporadic, rare associations with genetic syndromes such as Li-Fraumeni suggest a potential hereditary component in a minority of patients [12].

Clinically, benign phyllodes tumors usually present as painless, firm, and mobile breast masses that may gradually enlarge over time. Imaging studies such as mammography and ultrasound often reveal well-circumscribed, oval-shaped lesions that closely resemble fibroadenomas [13]. MRI may show heterogeneous signal intensities and enhancement patterns, but none of these modalities reliably differentiate phyllodes tumors from other benign lesions [14,15].

Histologically, benign phyllodes tumors are characterized by a leaf-like architecture, hypercellular but bland stroma, and epithelial-lined clefts [16]. Mitotic figures are generally low in number, and stromal atypia is minimal. The differential diagnosis from cellular fibroadenomas can be difficult, particularly on core needle biopsy, which often underrepresents the lesion's heterogeneity. Diagnostic accuracy is further limited with fine-needle aspiration [17]. Immunohistochemical markers, such as Ki-67 and p53, and molecular testing can assist in challenging cases but are not yet definitive. Molecular studies have identified *MED12* mutations in the majority of benign phyllodes tumors, which are also frequently seen in fibroadenomas [18]. This suggests a possible shared origin and raises the hypothesis of progression from fibroadenoma to phyllodes tumor in some cases. *TERT* promoter mutations, more specific to phyllodes tumors, may contribute to their increased proliferative capacity and recurrence risk [19].

Surgical excision with negative margins remains the cornerstone of treatment. While wide margins have traditionally been recommended, recent studies suggest that narrower negative margins may suffice for benign tumors [20,21]. Adjuvant therapies such as radiation or chemotherapy are generally not considered necessary for benign phyllodes tumors, given their typically favorable prognosis and low risk of metastasis.

The disease-specific prognosis for benign phyllodes tumors is generally very favorable. However, local recurrence occurs in approximately 10–17% of cases, particularly when margins are inadequate [9]. Advances in imaging, histopathology, and molecular profiling continue to improve diagnostic precision and may inform more individualized surgical approaches in the future.

## 3. Borderline Phyllodes Tumor

Borderline phyllodes tumors exhibit intermediate local recurrence rates ranging from 14% to 25%, with no consistent risk factors identified for recurrence, minimal risk of distant metastasis, and no disease-specific mortality reported in most studies [7]. The diagnosis of borderline phyllodes tumors remains challenging due to the lack of clearly defined criteria compared to benign and malignant counterparts. Although certain histological features are associated with clinical outcomes, the relative prognostic significance of these parameters in borderline cases remains controversial [22,23].

Borderline phyllodes tumors frequently harbor *MED12* and *TERT* promoter mutations [18], with additional alterations in *TP53*, *PIK3CA*, and *EGFR*, suggesting they lie on a molecular continuum between benign and malignant forms. The incidence of chromosomal aberrations rises in correlation with tumor grade elevation. Borderline and malignant phyllodes tumors demonstrate characteristic

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chromosomal alterations including 1q amplification and 13q deletion. Furthermore, 9p21 loss and diminished p16 expression have been reported [6,24–26].

Borderline phyllodes tumors generally demonstrate a favorable long-term prognosis, although they carry a moderate risk of local recurrence that typically manifests within the first few years following initial treatment [9]. While these tumors occupy an intermediate biological position, with some potential for progression in recurrent cases, metastatic disease remains uncommon in this category, highlighting the importance of adequate surgical excision and appropriate follow-up surveillance for several years after treatment.

## 4. Malignant Phyllodes Tumor

### *4.1. Background and Epidemiology*

Malignant phyllodes tumors, representing 10-25% of all phyllodes tumor cases, may develop 2-5 years after benign ones, with a higher incidence among Hispanics in Central and South America, though their overall incidence remains below 1 per million women [11]. Their classification is based on histological features including marked stromal cellularity, nuclear atypia, high mitotic activity, infiltrative margins, and stromal overgrowth [16].

The median age at diagnosis of malignant phyllodes tumors is 45-49 years, with higher incidence in Latin American and Asian populations compared to Western cohorts, and Bernstein *et al*. reported a relative risk of 1.94 for Hispanic women compared to non-Hispanic white women, suggesting potential ethnic predispositions [11]. Most malignant phyllodes tumors arise sporadically, though occasional associations with Li-Fraumeni syndrome suggest a potential role for *TP53* germline mutations in some cases. The pathogenesis involves complex epithelial-stromal interactions with progressive genetic alterations leading to stromal proliferation and atypia [27]. Malignant phyllodes tumors typically present as rapidly growing, palpable masses at diagnosis, with advanced cases potentially showing skin ulceration, although nipple discharge and axillary lymphadenopathy are rare [28].

### *4.2. Histopathological Features and Immunohistochemistry*

Malignant phyllodes tumors are rare fibroepithelial neoplasms of the breast characterized by distinct histopathological features. These tumors exhibit an exaggerated intracanalicular growth pattern with leaf-like projections extending into dilated lumina. The epithelial component typically consists of luminal and myoepithelial cells forming arc-like clefts above stromal fronds. The diagnosis of malignancy is based on several histological criteria including marked stromal nuclear pleomorphism, stromal overgrowth, increased mitotic activity (10 or more mitoses per 10 high-power fields), diffuse stromal hypercellularity, and infiltrative borders. The presence of malignant heterologous elements in phyllodes tumors is generally considered diagnostic of malignancy even in the absence of other features [16]. Among these heterologous elements, liposarcomatous differentiation represents an interesting diagnostic consideration. Research has suggested that when well-differentiated liposarcoma occurs as the sole heterologous element, the metastatic potential may be lower than with other heterologous components [29]. Differential diagnosis of malignant phyllodes tumors includes primary breast sarcomas and metastatic sarcomas, with the identification of epithelial structures being an important distinguishing feature.

Immunohistochemical studies have contributed to improved classification and prognostication of phyllodes tumors. Various markers including p53, Ki-67, CD117, and EGFR have shown differential expression patterns across the spectrum of phyllodes tumors. Studies have investigated the correlation between p53 and Ki-67 expression with systemic recurrence and survival in patients with phyllodes tumors [30]. However, the relationship between immunohistochemical markers and clinical outcomes remains variable across different research studies. Recent research has explored additional biomarkers with potential diagnostic and prognostic significance in malignant phyllodes tumors. CD44 expression appears to be increased in the stromal component of borderline and

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malignant phyllodes tumors compared to benign lesions [31]. Additionally, the expression of homeoproteins SIX1 and PAX3 has been identified in phyllodes tumors and shown to correlate with histological grade and clinical outcome [32]. These emerging markers may provide complementary information to conventional histological assessment, potentially enhancing diagnostic accuracy and treatment planning for patients with these uncommon neoplasms.

### *4.3. Differential Diagnosis in Metaplastic Carcinoma*

The differential diagnosis between malignant phyllodes tumors and metaplastic carcinomas with spindle cell features has long been recognized as one of the most challenging aspects of breast pathology, with significant therapeutic and prognostic implications. Historically, the immunohistochemical distinction has been considered relatively straightforward: metaplastic carcinomas characteristically exhibit a mixture of carcinomatous and sarcomatous components, with spindle cell elements demonstrating epithelial differentiation through positive immunoreactivity for cytokeratins (particularly CK5/6), EMA, and p63, whereas the stromal component of malignant phyllodes tumors has been regarded as consistently negative for epithelial markers, with only rare cases showing focal expression [33]. However, accumulating evidence challenges this traditional immunohistochemical paradigm. Current literature demonstrates that a substantial proportion of malignant phyllodes tumors (71%) exhibit cytokeratin and/or p63 immunopositivity, with 32% displaying cytokeratin expression and 65% showing p63 positivity. Notably, 30% of malignant phyllodes tumors express both markers, approaching the 95% dual positivity observed in metaplastic carcinomas [34]. Additional distinguishing morphological features include the presence of conventional invasive carcinoma components which favors metaplastic carcinoma, benign epithelial components and leaf-like architecture which favor malignant phyllodes tumor, and heterologous differentiation which is seen in both entities but more commonly in metaplastic carcinomas. Immunohistochemically, metaplastic carcinomas often express EGFR and occasionally hormone receptors or HER2, as well as myoepithelial markers like p63 or CD10, with cytokeratin expression typically being more diffuse throughout the tumor. In contrast, malignant phyllodes tumors may also demonstrate EGFR protein overexpression in up to 96% of cases with EGFR gene amplification detected in 33% of cases, but cytokeratin expression, when present, is characteristically focal and limited to few cells [35]. This considerable immunohistochemical overlap is further compounded by morphological features such as diffuse stromal overgrowth and absent CD34 expression, creating diagnostic ambiguity particularly in limited core needle biopsy material where sampling limitations pose additional challenges [36].

Recent advances in molecular diagnostics have provided crucial insights into this diagnostic dilemma and revealed distinct genetic profiles between these entities. Targeted next-generation sequencing studies demonstrate that *MED12* mutations (39%) and *SETD2* alterations (13%) appear to be exclusively associated with malignant phyllodes tumors, while *PIK3R1* mutations (37%) are specific to metaplastic carcinomas, offering potential molecular biomarkers for accurate classification in morphologically and immunohistochemically ambiguous cases. Malignant phyllodes tumors characteristically harbor recurrent genetic aberrations involving *TERT* promoter mutations, *TP53* alterations, *MED12* mutations, *CDKN2A* alterations, chromatin modifiers, growth factor receptors and ligands, and genes in the phosphoinositide-3 kinase and MAPK signaling pathways. In contrast, metaplastic carcinomas typically exhibit *PIK3CA*, *TP53*, and *PTEN* mutations similar to other breast carcinomas, reflecting their epithelial origin and shared molecular pathways with conventional breast cancers. The diagnostic utility of molecular analysis is particularly evident in challenging cases, as *MED12* mutations are frequently detected in malignant phyllodes tumors with confounding morphologic features, including those with diffuse stromal overgrowth (53% of cases), CD34-negative tumors (41% of cases), and importantly, in malignant phyllodes tumors with cytokeratin and/or p63 positivity (39% of cases). The combination of *MED12* mutation detection and/or CD34 expression analysis can successfully classify approximately 68% of malignant phyllodes tumors, including 61% of cases with potentially misleading cytokeratin and p63 positivity. In cases where

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standard morphological and immunohistochemical evaluation remains inconclusive, expanded immunohistochemical panels incorporating these newer molecular insights or comprehensive molecular studies may aid in definitive diagnosis[12], though excisional biopsy is sometimes necessary for definitive classification when core needle biopsy sampling proves insufficient for accurate diagnosis [34].

### *4.4. Genetic Testing in Malignant Phyllodes Tumors*

Recent genomic analyses have significantly advanced our understanding of the molecular landscape of malignant phyllodes tumors, with comprehensive next-generation sequencing studies revealing a characteristic profile of recurrent genetic alterations including TERT promoter mutations (~70%), MED12 mutations (~60%), TP53 mutations (~50%), CDKN2A/B deletions or mutations (~45%), NF1 alterations (~35%), PIK3CA mutations (~20%), and RB1 alterations (~20%) - a profile distinct from common breast carcinomas and sharing similarities with soft tissue sarcomas [8,19,37]. Amplification of ERBB2, which is commonly observed in typical breast cancers, is infrequently detected [38]. The 2024 analysis of 135 malignant phyllodes tumors identified additional alterations in genes involved in cell cycle regulation, growth factor signaling, and chromatin remodeling, enhancing our understanding of molecular drivers and suggesting potential therapeutic targets for this distinct pathological entity [37].

#### 4.4.1. MED12 in Phyllodes Tumors

MED12 is a component of the transcriptional mediator complex that is involved in the regulation of RNA polymerase-mediated transcription. Additionally, it functions as a direct suppressor of the Hedgehog signaling pathway. MED12 mutations, particularly in exon 2, represent a fundamental genetic alteration in phyllodes tumors across all grades. Yoshida et al. demonstrated that these mutations occur at similar frequencies in benign (83%), borderline (80%), and malignant (77%) variants, with an overall prevalence of 80% (37/46 cases). MED12 mutations were also identified in 62% of fibroadenomas, with variable distribution among subtypes: 75% in intracanalicular-type, 67% in complex-type, and significantly less (40%) in pericanalicular-type lesions. Microdissection analysis confirmed that these mutations were confined to stromal components in both tumor types, suggesting that phyllodes tumors and fibroadenomas share, at least partially, a common genetic background. These findings provide molecular evidence for the potential pathogenetic relationship between these fibroepithelial lesions of the breast [39].

Interestingly, some studies suggest that malignant phyllodes tumors without MED12 mutations may demonstrate more aggressive clinical behavior. Lae et al. observed that MED12 mutations were associated with more favorable outcomes, with lower frequency in malignant tumors (27.6%) compared to benign (58.3%) and borderline (63.3%) variants. This suggests that MED12 wild-type malignant phyllodes tumors may represent a biologically distinct subgroup with potentially worse prognosis [40]. Although mutations in MED12 have not been widely highlighted outside of phyllodes tumors, more than half of uterine leiomyomas harbor MED12 mutations, and it has been reported that many of these are identical to the hot spot mutations observed in phyllodes tumors [41]. Furthermore, the activation of AKT and the inhibition of cyclin C–CDK8/19 kinase activity have been associated with these mutations [41]. Such findings may provide valuable insights for future research on phyllodes tumors.

#### 4.4.2. TERT in Phyllodes Tumors

TERT, the catalytic subunit of telomerase, contributes to carcinogenesis through both telomere-dependent and independent pathways. Cancer-specific telomere maintenance involves diverse TERT alterations including gene amplifications, structural variants, promoter mutations, and epigenetic modifications, alongside alternative lengthening mechanisms [42]. TERT promoter mutations represent the most frequent genetic alterations in malignant phyllodes tumors, identified in

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approximately 70% of cases. These mutations create novel binding sites for transcription factors, leading to increased TERT expression and telomerase activity, thereby promoting cellular immortalization. The most common TERT promoter mutations occur at positions -124 (C>T) and -146 (C>T) relative to the transcription start site. The frequency of these mutations increases from benign (~50%) to borderline (~80-85%) and remains high in malignant (~70%) phyllodes tumors, suggesting a role in tumor progression. Notably, TERT promoter mutations are rare in fibroadenomas (<10%), potentially serving as a diagnostic marker to distinguish phyllodes tumors from fibroadenomas in challenging cases. The co-occurrence of MED12 and TERT promoter mutations is common in phyllodes tumors, with studies demonstrating a significant association between these genetic events. Research has shown that virtually all TERT promoter-mutated tumors also harbor MED12 mutations, suggesting potential synergistic effects in promoting tumor development and progression [43].

Beyond their diagnostic and pathogenetic implications, TERT promoter mutations may represent potential therapeutic targets. Various telomerase inhibitors are in development and have demonstrated preliminary efficacy in preclinical models and early-phase clinical trials for various malignancies. While not yet specifically evaluated in phyllodes tumors, the high frequency of TERT promoter mutations suggests a potential rationale for exploring telomerase-targeted therapies [43,44].

Recent advances in molecular diagnostics, including next-generation sequencing panels specifically designed for soft tissue tumors, may enhance the ability to distinguish malignant phyllodes tumors from mimics. These panels can simultaneously assess multiple genes involved in sarcoma pathogenesis, potentially improving diagnostic accuracy in challenging cases. Integration of molecular findings with traditional histopathological assessment provides a more comprehensive approach to diagnosis and classification [35]. However, as MED12 and TERT are not necessarily included in all commercially available cancer genome profiling assays [45], the selection of an appropriate cancer genome profiling test is clinically critical.

#### 4.4.3. Hereditary Tumor Genes Alterations in Phyllodes Tumors

While most genetic alterations in phyllodes tumors are somatic, evidence suggests an association with certain hereditary cancer syndromes. Phyllodes tumors have been reported in patients with Li-Fraumeni syndrome (germline TP53 mutations), with studies documenting increased incidence in affected families [12]. Young patients with malignant phyllodes tumors, particularly those with personal or family history of other cancers, should be considered for germline genetic testing. In patients with tumor sequencing showing TP53 mutations, evaluation is necessary to determine whether these alterations are somatic or germline, as this may have implications for cancer risk assessment and surveillance.

Despite the predominantly somatic nature of these alterations, several genes typically associated with hereditary cancer syndromes have been found to harbor somatic mutations in phyllodes tumors. Kim et al. identified *BRCA2* alterations specifically in phyllodes tumors with distant metastasis, suggesting a potential role for this DNA repair gene in disease progression. Additionally, they observed that malignant phyllodes tumors with PTEN copy number deletions demonstrated particularly aggressive clinical behavior with rapid disease progression, highlighting the prognostic significance of these genetic profiles [46]. While these findings underscore the importance of alterations in genes known to have germline significance in other cancer contexts, definitive evidence of germline involvement in phyllodes tumors remains limited. Further studies with larger cohorts and dedicated germline analyses are needed to establish whether true germline alterations in these genes contribute to phyllodes tumor development or progression. The evolving landscape of cancer genomics necessitates consideration of both established high-penetrance mutations and newly identified moderate-penetrance variants in the assessment of phyllodes tumors. While traditional genetic testing has focused on well-characterized genes such as *TP53*, *BRCA1/2*, and *PTEN*, contemporary approaches must address the broader spectrum of genetic alterations that may contribute to disease pathogenesis and progression. Recent advances in multigene panel testing have

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expanded the scope of germline genetic testing beyond traditional high-penetrance genes. These comprehensive panels can simultaneously assess multiple genes associated with hereditary cancer predisposition, potentially identifying novel associations between specific germline alterations and phyllodes tumor development. As our understanding of the genetic basis of cancer continues to evolve, the role of germline testing in patients with phyllodes tumors will likely be further refined [47].

#### 4.4.4. Miscellaneous Genes Alterations in Phyllodes Tumors

Although the probability of detecting druggable genetic alterations among the representative genetic alterations in malignant phyllodes tumors is not necessarily high, reports have documented cases where NTRK fusion genes were identified [38], for which TRK inhibitors such as entrectinib and larotrectinib demonstrated efficacy [48,49]. Additionally, cases with detected BRAF V600E mutations have been reported [50], showing effectiveness of combination therapy with RAF inhibitors and MEK inhibitors, such as dabrafenib and trametinib [51]. Rarely, patients with high tumor mutational burden (TMB-high) have been documented, with a case report describing successful treatment response to pembrolizumab therapy [52,53]. Furthermore, cases displaying EGFRvIII (EGFR variant III) patterns typically seen in glioblastoma have also been documented [54], offering promise for therapeutic development [55]. Given these findings, comprehensive cancer genomic profiling using next-generation sequencing is considered to be of significant clinical importance [56].

### *4.5. Chemotherapy for Malignant Phyllodes Tumors*

The management of malignant phyllodes tumors presents considerable therapeutic challenges, primarily attributable to their rarity and the consequent paucity of robust evidence supporting specific systemic therapeutic interventions. While surgical resection remains the cornerstone of treatment for localized disease, systemic therapy assumes critical importance in the management of recurrent, metastatic, or unresectable cases. Nevertheless, established clinical guidelines specifically addressing malignant phyllodes tumors remain absent, necessitating extrapolation of treatment strategies from soft tissue sarcoma management protocols [57–59] (Table 1). This therapeutic approach is further complicated by the systematic exclusion of phyllodes tumors from pivotal trials investigating recently developed soft tissue sarcoma chemotherapeutic agents, including eribulin and trabectedin [60,61] Moreover, the inherent rarity of these tumors presents substantial obstacles to conducting adequately powered clinical trials [62].

In the context of chemotherapy for unresectable soft tissue sarcomas, doxorubicin monotherapy continues to be regarded as the standard therapeutic approach [63]. However, the limited retrospective data available regarding its application in phyllodes tumors have yielded disappointing results, with progression-free survival consistently reported at approximately 3 months, representing suboptimal clinical outcomes [64,65]. Doxorubicin, a prototypical anthracycline anticancer agent, exerts its cytotoxic effects through intercalation between DNA base pairs and subsequent inhibition of DNA polymerase, RNA polymerase, and topoisomerase II enzymatic activities. Although overall survival benefits have not been conclusively demonstrated, the addition of ifosfamide to doxorubicin has been shown to confer improvements in both response rates and progression-free survival, albeit at the expense of significantly enhanced toxicity profiles. Consequently, doxorubicin plus ifosfamide combination therapy is considered only in carefully selected clinical scenarios where tumor cytoreduction might potentially ameliorate patient symptomatology or enhance the feasibility of subsequent local therapeutic interventions [66]. Similarly, retrospective analyses in phyllodes tumors have suggested enhanced response rates with combination approaches [67], with additional reports documenting clinical efficacy [68]. Ifosfamide, a representative nitrogen mustard alkylating agent, functions through the formation of DNA interstrand crosslinks and the generation of aberrant base pair configurations [69]. Given its pronounced emetogenic potential and the associated risks of

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serious adverse events, including encephalopathy [70] and hemorrhagic cystitis [71], ifosfamide is not routinely employed as single-agent first-line therapy.

The toxicity profile of doxorubicin encompasses numerous characteristic adverse events, notably alopecia and cardiotoxicity, mandating particularly judicious application in phyllodes tumors, which predominantly affect female patients. The cardiotoxic potential necessitates regular cardiac function surveillance, with meticulous monitoring to ensure cumulative dosing does not exceed the established threshold of 450-500 mg/m$^2$ [72,73]. Furthermore, given its considerable emetogenic properties, the implementation of aggressive antiemetic strategies, including neurokinin-1 receptor antagonists and olanzapine, represents a critical therapeutic consideration [74,75].

Recent groundbreaking findings from the LMS04 trial have demonstrated that the combination of doxorubicin with trabectedin yielded significant overall survival prolongation, extending median survival from 24 months with monotherapy to 33 months with combination treatment [76]. However, several factors temper the immediate clinical implications of these results, including the study's restriction to leiomyosarcoma patients, the demonstration of substantial toxicity, and the currently limited geographical availability of this combination. These considerations suggest that broader clinical implementation will require further deliberation and regulatory approval processes. Regarding adjuvant chemotherapy, historical data from the 1990s investigating doxorubicin and dacarbazine combination therapy failed to demonstrate efficacy [77].

The gemcitabine plus docetaxel regimen [78], while not demonstrating superior efficacy compared to doxorubicin, has gained favor among certain clinicians, particularly in the management of uterine leiomyosarcoma. In phyllodes tumors, available evidence remains limited to sparse retrospective analyses, suggesting modest efficacy with progression-free survival of less than 3 months [65]. Gemcitabine, classified as an antimetabolite with broad antitumor activity, requires vigilance for the development of interstitial pneumonitis [79]. Docetaxel, a taxane compound that binds to polymerized microtubules, similarly demonstrates broad-spectrum antitumor activity, with myelosuppression and nail disorders representing the most clinically significant adverse events [80]. The docetaxel plus gemcitabine combination regimen [78], despite being associated with relatively pronounced myelosuppression, exhibits reduced emetogenic potential, making it a preferred option for patients with compromised cardiac function or those particularly susceptible to appetite-related complications.

Current therapeutic options for second-line and subsequent treatments include various cytotoxic chemotherapy agents and molecular targeted therapies; however, no highly effective agents have been established for this clinical setting. Eribulin, a marine-derived compound isolated from *Halichondria okadai*, functions as a mitotic inhibitor [81,82]. In a pivotal Phase III trial encompassing patients with leiomyosarcoma and liposarcoma, eribulin failed to demonstrate progression-free survival improvements compared to dacarbazine monotherapy but achieved statistically significant overall survival prolongation, leading to its widespread adoption in soft tissue sarcoma management [60]. Although isolated case reports have documented eribulin utilization in phyllodes tumors, definitive evidence of efficacy remains elusive [83]. While myelosuppression represents the primary safety concern [60,84], the relatively favorable profile of other adverse events and the abbreviated administration schedule contribute to its clinical acceptability.

Trabectedin represents another prominent cytotoxic agent employed in second-line and subsequent treatment settings. This marine-derived alkaloid, originally isolated from the sea squirt *Ecteinascidia turbinata*, exerts its antineoplastic effects through transcriptional inhibition and cell cycle arrest at the G2-M checkpoint [85,86]. The landmark Phase III trial in leiomyosarcoma and liposarcoma patients demonstrated significant progression-free survival improvement compared to dacarbazine monotherapy [61], establishing its global utilization, although approved dosing regimens vary considerably across different regulatory jurisdictions. Clinical experience with trabectedin in phyllodes tumors remains limited, with retrospective analyses suggesting a response rate of approximately 17%, with the majority of cases exhibiting primary resistance, indicating limited therapeutic utility [64]. Hepatotoxicity represents the most clinically significant adverse

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event, with transaminase elevations frequently reaching four-digit values [87], while rhabdomyolysis also requires careful monitoring [88,89]. A critical safety consideration involves the extremely high tissue toxicity associated with extravasation events [90], mandating strict administration protocols and exclusive central venous access. Nevertheless, the utilization of central venous ports does not preclude the occurrence of aseptic inflammation, which often presents significant management challenges in clinical practice. Consequently, meticulous consideration is warranted in the administration of trabectedin therapy [91–93]. Collectively, these factors contribute to a considerable patient burden and present practical implementation challenges in routine clinical practice.

Pazopanib, representing the sole molecular targeted therapy available for second-line and subsequent treatment, has achieved widespread clinical adoption, although published experience in phyllodes tumors remains sparse [94]. Nevertheless, encouraging preclinical data from patient-derived xenograft models have been reported [95]. Pazopanib functions as a multi-kinase inhibitor targeting vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and cluster of differentiation 117, with a pivotal Phase III trial demonstrating significant progression-free survival improvements in advanced soft tissue sarcomas excluding liposarcoma [96]. As the only orally administered agent within the soft tissue sarcoma therapeutic armamentarium, pazopanib offers distinct advantages for patients in whom intravenous administration presents challenges. Representative important adverse events of pazopanib include hypertension and pneumothorax [97,98]. Given the predominant female demographic affected by phyllodes tumors, additional attention should be directed toward the potential for hair pigmentation alterations [99,100].

**Table 1.** Representative Chemotherapy for Soft Tissue Sarcomas: An Overview.

| Line | Regimen | Dose and Schedule (Example) | Notes |
|---|---|---|---|
| First Line | Doxorubicin | Doxorubicin 60-75 mg/m² on Day 1, every 3 weeks | Monitor cardiac function |
| | Doxorubicin Ifosfamide | Doxorubicin 30 mg/m² on Day 1-2, every 3 weeks<br>Ifosfamide 2 g/m² on Day 1-3, every 3 weeks (with mesna) | Monitor cardiac function and urinalysis |
| | Ifosfamide | Ifosfamide 1.8 g/m² on Day 1-5, every 3 weeks (with mesna) | Monitor urinalysis |
| | Gemcitabine Docetaxel | Gemcitabine 900 mg/m² on Day 1, 8, every 3 weeks<br>Docetaxel 70 mg/m² on Day 8, every 3 weeks | Indication remains controversial |
| | Doxorubicin Trabectedin | Doxorubicin 60 mg/m² on Day 1, every 3 weeks<br>Trabectedin 1.1 mg/m² on Day 1, every 3 weeks | Not widely approved |
| Second Line | Eribulin | Eribulin 1.4 mg/m² on Day 1, 8, every 3 weeks | Short infusion |
| | Trabectedin | Trabectedin 1.5 mg/m² on Day 1, every 3 weeks | 24-hour infusion |
| | Pazopanib | Pazopanib 800 mg/body every day | Oral medication |

This table presents representative examples. Actual dosing may vary depending on patient condition and clinical context. Doxorubicin exhibits significant cardiotoxicity, necessitating the establishment of cumulative dose limitations, typically ranging from 400 to 500 mg/m² of body surface area. *

## 5. Conclusions

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In conclusion, while significant progress has been made in understanding the biology and management of phyllodes tumors, many challenges remain, particularly for malignant variants. Continued research into the molecular mechanisms driving tumor development and progression, coupled with international collaborative efforts to conduct clinical trials and registry studies, will be essential for improving outcomes for patients with these rare and challenging neoplasms. The integration of genomic medicine approaches, particularly comprehensive molecular profiling, offers the promise of more personalized and effective treatment strategies in the future.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| CD | cluster of differentiation |
| CDK | cyclin-dependent kinase |
| CK | cytokeratin |
| DNA | deoxyribonucleic acid |
| EGFR | epidermal growth factor receptor |
| EGFRvIII | epidermal growth factor receptor variant III |
| EMA | epithelial membrane antigen |
| HER2 | human epidermal growth factor receptor 2 |
| Ki | Kiel |
| MED12 | mediator complex subunit 12 |
| MRI | magnetic resonance imaging |
| NF1 | neurofibromin 1 |
| PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha |
| PTEN | phosphatase and tensin homolog |
| RNA | ribo nucleic acid |
| TERT | telomerase reverse transcriptase |
| TP53 | tumor protein p53 |

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