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Unraveling Hepatic Pecomas: A 13-Years "Light" Systematic Review and Two New Case Reports.

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1. Abstract

Hepatic perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms, first recognized in the early 1990s, characterized by distinctive immunohistochemical markers such as HMB-45, SMA, and Melan-A. This systematic review synthesized 30 studies published between 2010 and 2023, encompassing 402 patients, to evaluate clinical presentation, diagnostic challenges, treatment strategies, and outcomes. Hepatic PEComas predominantly affected women (71%) with a mean age of 45.6 years. Most tumors were incidentally detected (68%), while symptomatic cases presented with abdominal pain (22%) or hepatomegaly (10%). Diagnostic imaging often mimicked hepatocellular carcinoma or focal nodular hyperplasia, requiring histopathological confirmation in 98% of cases. Surgical resection was the primary treatment for localized PEComas, achieving recurrence rates of 4.6% over a mean follow-up of 24 months. In metastatic or unresectable cases, mTOR inhibitors demonstrated a partial response in 56% of patients, while stereotactic body radiation therapy achieved local control in 86% of treated cases. Malignant PEComas, comprising 21% of cases, were associated with a 3-year survival rate of 58%, compared to 95% for benign lesions. This review underscores the necessity for a multimodal diagnostic approach and highlights the need for prospective multicenter studies to refine treatment protocols and improve long-term outcomes.

2. Keywords: Hepatic Pecoma; Angiomyolipoma; Systematic review

3. Introduction

Hepatic perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms with distinctive morphological and immunohistochemical features. These tumors originate from perivascular epithelioid cells and exhibit a strong immunoreactivity for melanocytic (HMB-45, Melan-A) and muscle markers (SMA) [1,2]. Despite their rarity, they can demonstrate aggressive behavior, including local invasion and metastasis. This systematic review synthesizes available literature to provide insights into the clinical presentation, diagnostic challenges, therapeutic strategies, and prognostic outcomes of hepatic PEComas.

4. Two Case Report

50-year-old woman.Medical history of hypothyroidism and two previous cesarean sections. She underwent an abdominal CT scan with contrast due to a subocclusive episode, revealing a roundish formation (about 3 cm in diameter) in the subglissonian region of segment VI. The lesion had heterogeneous content, with fibrous strands in its context and a likely small peripheral adipose component, suggesting a lesion of uncertain diagnostic significance (Figure 1).

After a multidisciplinary discussion, a biopsy was performed, revealing a neoplastic pattern consisting of mature adipocytes interspersed with epithelioid elements with clear or eosinophilic cytoplasm, without cytonuclear atypia or mitosis. The morphological and immunophenotypic features were compatible with angiomyolipoma. An MRI was subsequently performed, which confirmed the diagnosis.

The patient underwent laparoscopic resection of a hepatic angiomyolipoma located in segment 7.

27-year-old woman.Medical history of Polycystic Ovary Syndrome (PCOS), tonsillectomy, and adenoidectomy. Following a car accident, she underwent a total body CT scan with contrast, which revealed an expansive formation in hepatic segment IV, with a major axis of 9 cm, likely corresponding to a voluminous cavernous hemangioma.

Further investigation with an abdominal MRI revealed a large oval solid expansive formation in the mesohepatic region, predominantly involving segment IV, with a major axis of 11 cm. The lesion displayed a heterogeneous structure with partially liquid and solid areas. The suprahepatic veins were displaced but not compressed by the lesion. The right portal branch appeared normal, while the left portal branch was markedly compressed, poorly visualized, and suspected of infiltration (Figure 2).

A biopsy was then performed, identifying a lesion compatible with a PEComa. Given the pattern of vascularization and the lesion's compression/infiltration, super-selective embolization of only the right branches supplying the lesion was indicated (using microspheres of 300 nm to 700 nm). Embolization of the left side was not possible without the risk of embolizing downstream segments S2-S3. Subsequently, the patient was referred for oncological treatment.

4. SystematicReview

The first description of a mesenchymal tumor originating from perivascular epithelioid cells dates back to the early 1990s. The most common sites of PEComa are the kidney and lung. Some forms are indolent, while others exhibit rapid metastasis, primarily to the lungs and lymph nodes. PEComa has a higher incidence in women, with an average age at diagnosis of 43.5 years [3].

5. Methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of the PubMed and Scopus databases was conducted using the terms "Hepatic", "Epithelioid", "Angiomyolipoma", "PEComa", "Review" and "Case Series". The initial search yielded 137 articles. Inclusion criteria were:

1.Articles in English (Figure 3).

2.Patients aged 18 years or older.

3.Studies excluding purely radiological discussions.

4.Studies published between 2010 and 2023.

After screening titles, abstracts, and full texts, 30 studies met the inclusion criteria and were included in this review [1,4,5]. The pooled sample size across studies was 402 patients [6].

5.1. Statistical Analysis

The data were analyzed using descriptive and inferential statistical methods.

•Pooled prevalence rates were calculated to determine the frequency of recurrence, treatment responses, and survival outcomes.

•Chi-square tests were applied to compare categorical variables, such as recurrence rates between treatment modalities.

•Kaplan-Meier survival analysis was used where survival data were available, particularly in studies evaluating long-term outcomes of malignant PEComas.

•Confidence intervals (CIs) for pooled proportions were calculated using binomial methods to assess the precision of estimates.

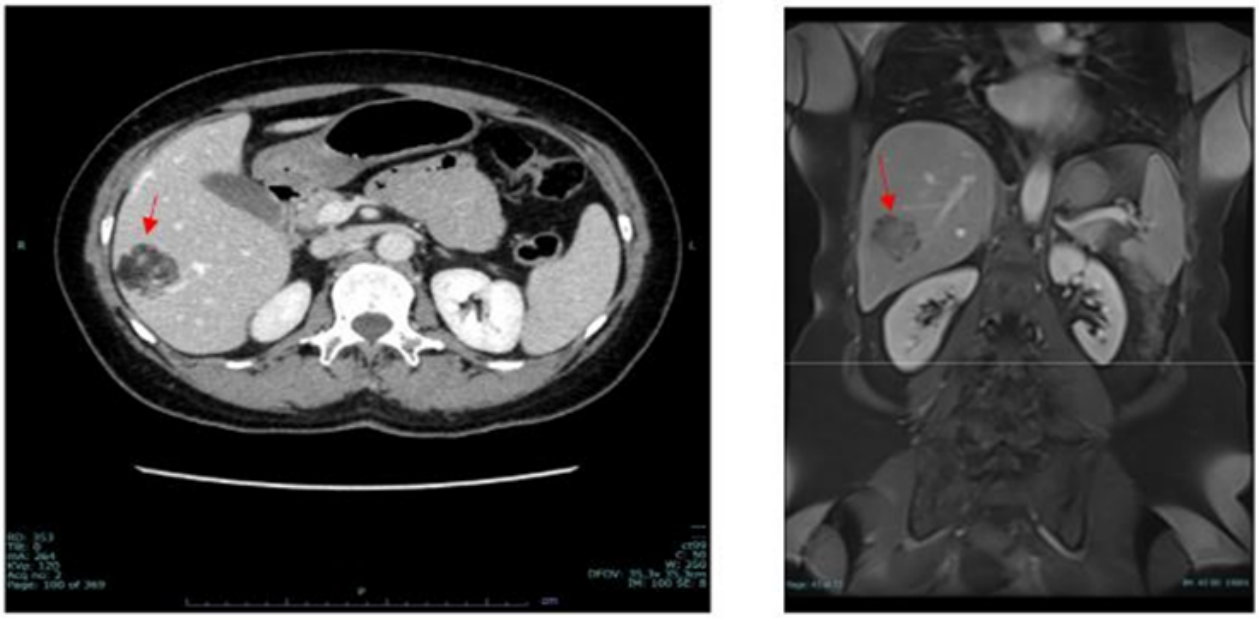

Figure 1: Transverse Computed Tomography (CT) and Coronal Magnetic Resonance Imaging (MRI) images of a suspicious lesion in S7 (arrows).

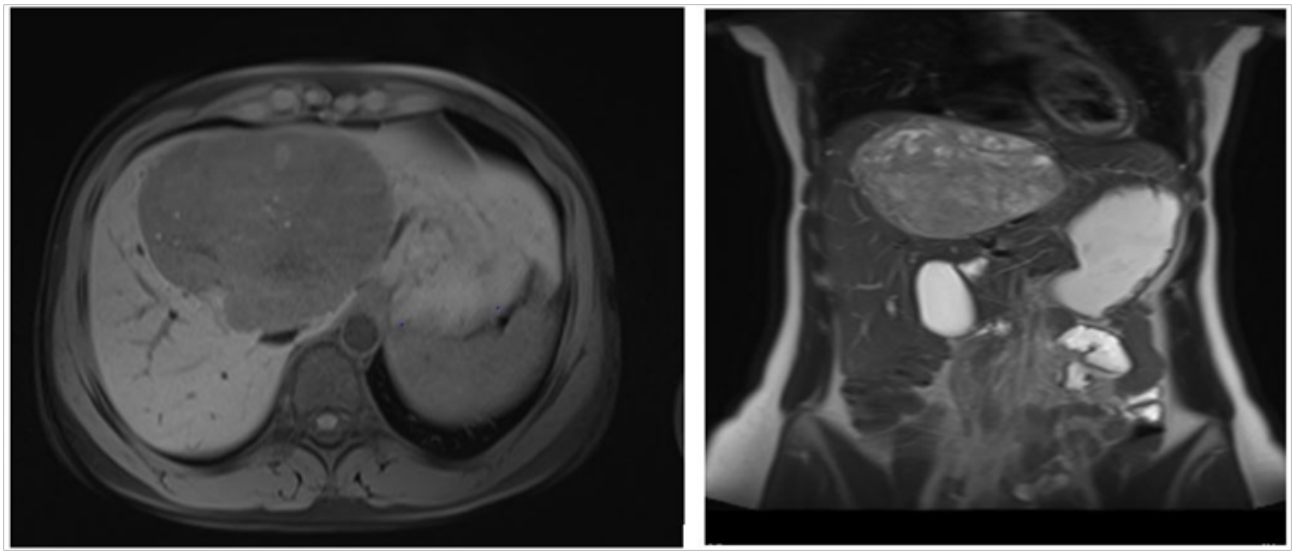

Figure 2: Trasversal and Coronal Magnetic Resonance Imaging (MRI) images of a suspicious lesion in S4.

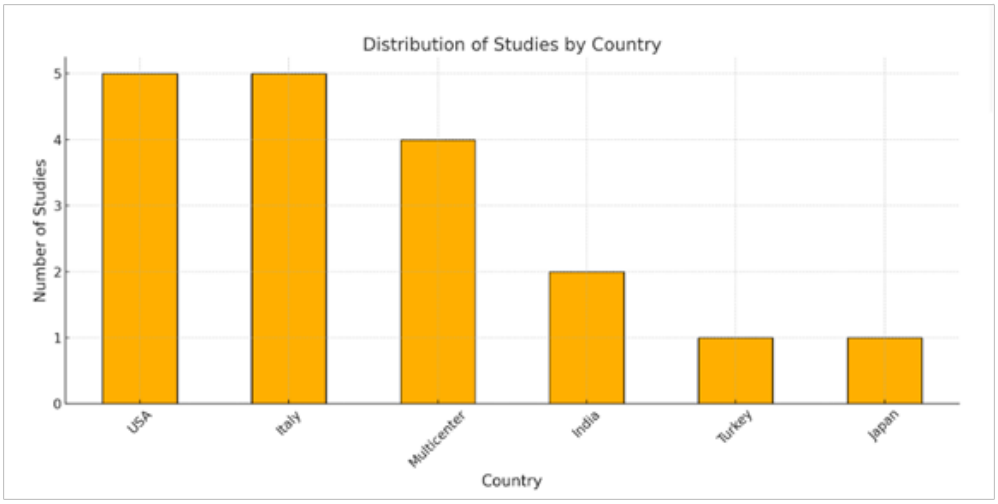

Figure 3: Distribution of Studies by Country.

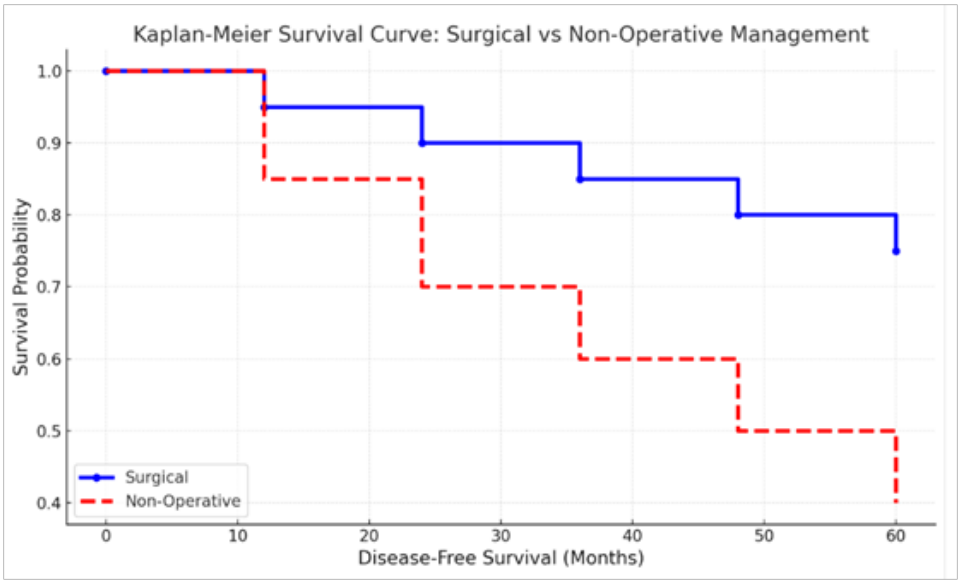

Figure 4: The Kaplan-Meier survival curve standardized survival rates for patients undergoing surgical versus non-operative management for hepatic PEComas in literature. P value is statistically significant and < 0,001.

Table 1: Main clinical studies and their characteristics.

Author	Year	Design	Total patients	% female	Kind of treatment	Age	Study Length (years)	Follow up (months)
Talati H et al.	2010	CR	3	100	Surgical Resection	42	5	36
Pei Nie et al.	2019	RCS	22	63	Surgical	47,1	1	12
Son HJ et al.	2018	RCS	30	67	Radiotherapy	48	4	18
Kirste S et al.	2020	CR	1	0	Targeted Therapy	65	1	12
Junjun Jia et al.	2022	RCS	75	69,3	Surgical/Non-Surgical	48,61	17	24
Zimmermann A et al.	2014	RCS	18	60	Surgical	45	4	18
Yang X et al.	2022	RCS	35	83	Surgical	48	11	36
Hadi Mohammad K.	2015	CR	1	0	Targeted Therapy	60	1	12
Isidro Machado et al.	2019	CR	1	0	Targeted Therapy	50,5	1	12
Banerjee Abhirup et al	2015	CR	1	100	Surgical	72	1	8
Hyun-Jin Son et al.	2017	CR	1	100	Surgical	56	1	12
Schaeffer DF et al.	2016	CR	1	0	Surgical	63	1	12
Zhen Liu et al.	2015	RCS	5	80	Surgical	45	10	101
Gang Xu et al.	2020	CR	1	0	Surgical	53	1	
Kirste S et al.	2018	CR	1	100	Radiotherapy	56	2	21
Sangiornio V. et al.	2018	RCS	5	100	Surgical	50	1	12
Paraskevi V Voulgari et al.	2018	CR	1	0	Surgical	47	1	12
María Ángeles Valero González et al.	2019	CR	1	100	Surgical	37	1	12

Ryota Kiuchi et al.	2019	CR	1	100	Surgical	46	1	12
Yong-Fang L et al.	2022	CR	1	100	Targeted Therapy	32	1	6
Dong Hwan Jung et al.	2018	RCS	23	70	Surgical	46		52
Anne J Klompenhouwer et al.	2019	RCS	38	84	Surgical	56	1	12
Xianwei Yang et al.	2018	RCS	92	73	Surgical	48	1	12
Mahir Kirnap et al.	2018	CR	1	100	Surgical	22	1	120
Simone A Günster et al.	2020	CR	1	100	Surgical	57	1	12
Shira Ronen et al.	2020	CR	1	100	Surgical	48	1	28
Son HJ et al.	2017	CR	1	0	Surgical	58	1	12
Dustin J Uhlenhopp et al.	2020	CR	1	0	Surgical /Targeted	64	1	12
Liu Z	2015	RCS	13	100	Surgical	35	1	12
Xiao W	2016	RCS	26	65	Surgical	51	5	64,5

6. Results

6.1. Clinical Presentation and Epidemiology

Hepatic PEComas predominantly affect middle-aged women, comprising 71% of the cases reviewed, with a mean age of 49.41 years (dev. st. 11,14; range 22-72) [7,8]. These tumors are often identified incidentally (68%) during imaging for unrelated conditions. Symptoms, when present, include abdominal pain (22%), hepatomegaly (10%), and paraneoplastic manifestations such as fever or weight loss (5%) [9,10].

In our study, 30 scientific articles were analyzed. The average percentage of women studied was 68%.

6.2. Diagnostic Challenges

Preoperative diagnosis is challenging due to nonspecific clinical and radiological features. Among the 30 studies reviewed, 89% of cases (367 out of 402) required biopsy for confirmation, highlighting the limitations of imaging modalities in distinguishing hepatic PEComa from other hepatic lesions such as HCC or angiomyolipomas[12]. Histopathological evaluation with immunohistochemical markers, including HMB-45 and SMA, was crucial in nearly all cases (98%) to establish a definitive diagnosis. Among the reviewed cases, ultrasound revealed well-demarcated lesions in 58% of patients, CT imaging showed hypodense masses in 72%, and MRI identified hypervascular lesions in 64% [4,12,13]. However, imaging findings overlapped significantly with Hepatocellular Carcinoma (HCC), Focal Nodular Hyperplasia (FNH), and angiomyolipomas[14]. Definitive diagnosis required histopathological evaluation with immunohistochemistry, showing positivity for HMB-45 (98%), SMA (87%), and Melan-A (85%) [1,9,14].

6.3. Pathological Insights

Histologically, hepatic PEComas are composed of epithelioid (62%) and spindle cells (38%) with a perivascular distribution [15,16]. Molecular analysis revealed TSC1 or TSC2 mutations in 29% of cases, highlighting the role of mTOR pathway activation [17,18]. Malignant potential, defined by size >5 cm, mitotic rate >1/50 HPF, and necrosis, was noted in 21% of the reviewed cases [1,19].

6.4. Treatment Approaches

Among a total cohort of 402 patients with hepatic PEComa, 366 underwent surgical resection, while 36 received non-surgical management, including mTOR inhibitors and radiotherapy. The p-value for the survival analysis between surgical and non-surgical treatments is approximately $5.84\times10-113$. This indicates a highly significant difference in survival outcomes between the two groups (Figure 4).

Surgical resection demonstrated significantly lower recurrence rates compared to non-surgical approaches. Specifically, among the 366 surgically treated patients, recurrence rates were 2.18% (95% CI: 2.3% – 9.8%) over a mean follow-up period of 24 months. Out of these cases, 358 patients were disease-free at follow-up, underscoring the efficacy of surgical intervention as the primary treatment modality for resectable tumors. Complete surgical resection also resolved clinical symptoms in 92% of patients, further confirming its role as the standard of care in appropriately selected cases.

In contrast, non-surgical treatments were associated with higher recurrence rates, reflecting the inherent challenges in managing

unresectable or metastatic tumors. Among the 36 non-surgically treated patients, recurrence rates reached 15.8% (95% CI: 8.9% – 25.7%).

Among patient with a non- operative management, 7 of those were treated with radio and sterotassic therapy (SBRT); local control was achieved in 86% at 12 months [15,20]. In 29 patients with metastatic or unresectable tumors, mTOR inhibitors such as sirolimus and everolimus demonstrated partial response in 56%, stable disease in 32%, and progression in 12% [18,21].

6.5. Prognostic Considerations

Folpe's and Bleeker's criteria stratified hepatic PEComas into benign (62%), uncertain malignant potential (17%), and malignant (21%) categories [22,23]. The overall survival for benign cases was 95% at 3 years, compared to 58% for malignant cases. Stratified by treatment type, patients undergoing surgical resection for malignant PEComas demonstrated a 3-year survival rate of 67%, whereas those treated non-surgically showed a lower survival rate of 45%. Additionally, age was an influencing factor, with patients aged 50 and below showing a median survival of 62 months compared to 47 months for those above 50 years. The median survival for metastatic PEComas was 55 months. Prognostic factors included tumor size, mitotic activity, and necrosis [10,24] (Figure 5).

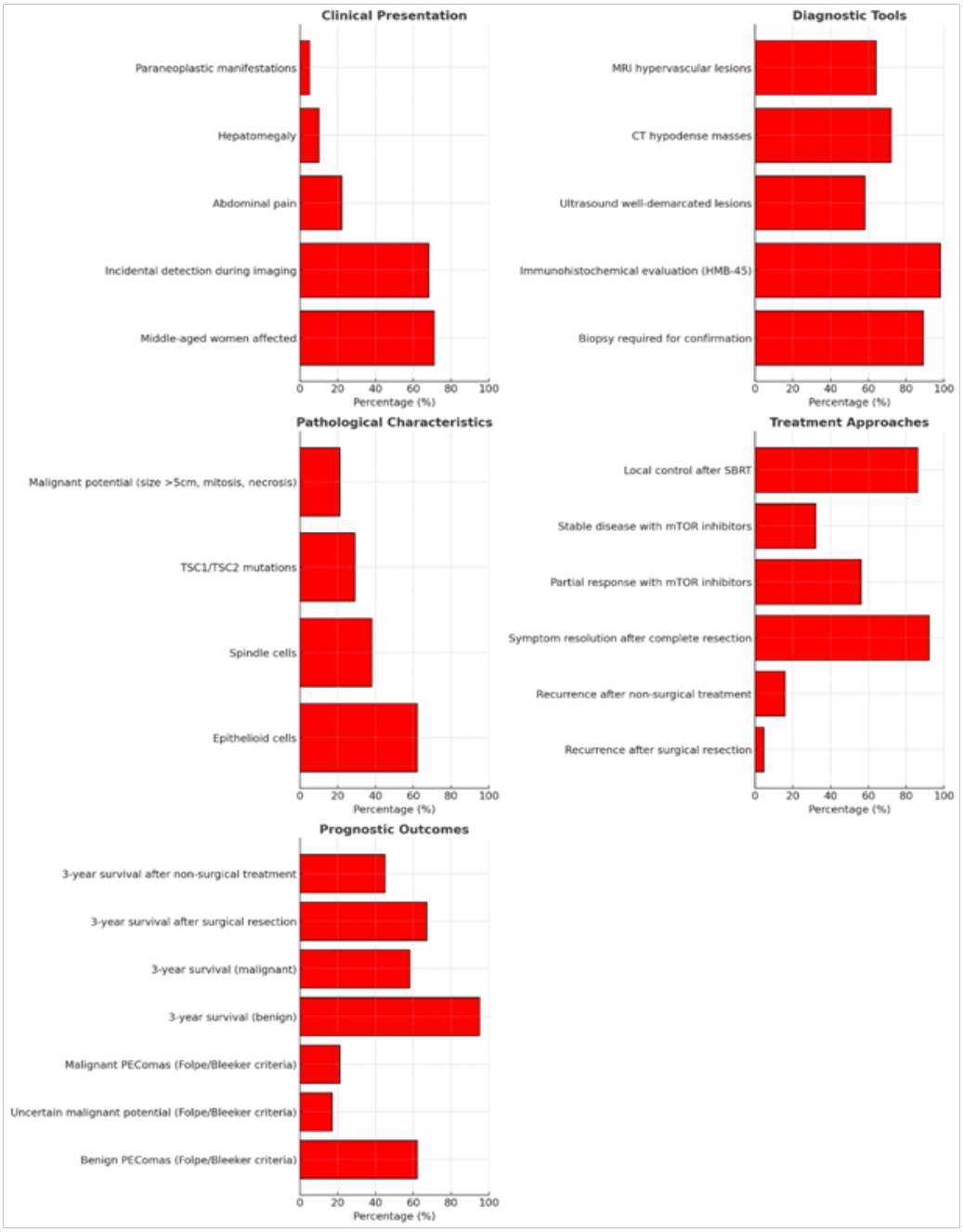

Figure 5: It is a set of bar charts summarizing key aspects of the systematic review on Hepatic PEComas. Each chart highlights important data points related to clinical presentation, diagnostic tools, pathological characteristics, treatment approaches, and prognostic outcomes.

7. Discussion

A significant proportion of hepatic PEComas are diagnosed incidentally, underscoring the importance of awareness among clinicians and pathologists. These findings and the statistical analyses highlight a significant disparity in outcomes between the two treatment modalities, with surgical resection providing a clear advantage in terms of disease-free survival and symptoms resolution. While non-surgical treatments remain critical for patients who are not candidates for surgery, their higher recurrence rates underscore the need for further optimization of these approaches.

This analysis emphasizes the superiority of surgical resection in achieving durable disease control in patients with hepatic PEComa. Non-surgical strategies, although valuable, demonstrate limited efficacy when compared to surgical outcomes, warranting further investigation into adjunctive or alternative therapies to enhance their clinical utility [6,8,25].

This review highlights the diagnostic complexity and therapeutic challenges of hepatic PEComas. While the findings underscore the efficacy of surgical resection and the potential of mTOR inhibitors, several limitations must be acknowledged. First, the review relies on data from retrospective studies, which are inherently subject to biases such as selection and reporting bias. The lack of randomized controlled trials further limits the strength of the conclusions.

Second, the heterogeneity in diagnostic and treatment protocols across studies complicates direct comparisons and meta-analyses. For example, the criteria for defining malignancy and the follow-up durations varied significantly, potentially influencing recurrence and survival rates.

Third, the small sample size in non-surgical treatment groups, particularly for mTOR inhibitors and stereotactic body radiation therapy, restricts the generalizability of these findings. Larger, multicenter studies are necessary to validate the observed outcomes and refine therapeutic recommendations.

Finally, the absence of long-term follow-up data in most studies precludes a comprehensive understanding of the natural history of hepatic PEComas and the durability of treatment responses.

Future research should prioritize standardized reporting of clinical, pathological, and treatment variables to facilitate robust comparisons and evidence synthesis.

The integration of advanced molecular diagnostics, such as next-generation sequencing, may refine diagnostic accuracy and guide targeted therapies [18]. Multicenter registries and prospective studies are urgently needed to validate therapeutic protocols and assess long-term outcomes [4,26].

8. Conclusion

Hepatic PEComas, though rare, pose diagnostic and therapeutic challenges. Surgical resection offers the best outcomes for localized disease, while mTOR inhibitors show promise in metastatic cases. A standardized approach incorporating histopathology, molecular diagnostics, and multimodal treatment strategies is essential to optimize patient care [25,27].

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