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肿瘤间质比在妇科肿瘤中的预后价值

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摘　要

肿瘤间质比(tumor-stroma ratio, TSR)作为反映肿瘤微环境中上皮与间质成分比例的定量指标，近年来在多种实体瘤中被证实与患者预后相关。在妇科肿瘤中TSR也与预后存在显著关联，但不同肿瘤类型间呈现异质性。子宫内膜癌中，间质丰富与无复发生存期下降显著相关，但TSR的独立预后价值可能受分子分型影响。卵巢癌中，间质贫乏患者无进展生存期显著延长，且可预测铂类化疗耐药和免疫治疗反应。宫颈癌中TSR的预后价值存在争议，单纯TSR可能不如间质质量特征重要；单细胞和空间转录组学揭示宫颈腺癌与鳞癌具有截然不同的肿瘤微环境景观，间质丰富在腺癌中常伴随免疫抑制，在鳞癌中可能伴随免疫活化，这可能是TSR预后意义不确定的根本原因。TSR作为低成本、高可行性、高可重复性的病理指标，在妇科肿瘤中具有预后价值，但存在显著的肿瘤类型和组织学亚型异质性。临床应用中需结合分子分型、组织学类型和间质质量特征综合解读。

关键词

肿瘤间质比，宫颈癌，卵巢癌，子宫内膜癌，预后

Prognostic Value of Tumor-Stroma Ratio in Gynecologic Tumors

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Abstract

The tumor-stroma ratio (TSR), as a quantitative indicator reflecting the ratio of epithelial to stromal components in the tumor microenvironment, has been confirmed to be related to the prognosis of

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patients in various solid tumors in recent years. In gynecological tumors, TSR is also significantly associated with prognosis, but heterogeneity is presented among different tumor types. In endometrial cancer, stromal abundance is significantly associated with a decreased recurrence-free survival period, but the independent prognostic value of TSR may be affected by molecular typing. In ovarian cancer, the progression-free survival of patients with stromal poverty is significantly prolonged, and platinum-based chemotherapy resistance and immunotherapy response can be predicted. The prognostic value of TSR in cervical cancer is controversial. Simple TSR may not be as important as interstitial quality characteristics. Single-cell and spatial transcriptomics have revealed that cervical adenocarcinoma and squamous cell carcinoma have distinct tumor microenvironment landscapes. Rich stroma is often accompanied by immunosuppression in adenocarcinoma, while it may be accompanied by immune activation in squamous cell carcinoma. This may be the fundamental reason for the uncertain prognostic significance of TSR. As a low-cost, highly feasible and highly reproducible pathological indicator, TSR has prognostic value in gynecological tumors, but there is significant heterogeneity in tumor types and histological subtypes. In clinical applications, a comprehensive interpretation should be made in combination with molecular typing, histological types and interstitial quality characteristics.

Keywords

Tumor-Stroma Ratio, Cervical Cancer, Ovarian Cancer, Endometrial Cancer, Prognosis

1. 前言

妇科恶性肿瘤是全球女性健康的重要威胁，其中子宫内膜癌、卵巢癌和宫颈癌作为三大常见妇科肿瘤，其流行病学特征和影响因素各具特点。子宫内膜癌是发达国家最常见的妇科恶性肿瘤，近年来发病率呈上升趋势，与肥胖、人口老龄化和生育模式改变密切相关[1] [2]。卵巢癌的发病率虽低于子宫内膜癌，但病死率居妇科肿瘤之首，其早期症状隐匿、缺乏有效筛查手段，约 70%的患者确诊时已为晚期[3]。宫颈癌则是低中收入国家女性癌症死亡的主要原因，2023 年数据显示，低收入国家中宫颈癌死亡率仍居女性癌症首位[4]。尽管 HPV 疫苗和筛查技术的推广使部分国家宫颈癌发病率下降，但全球疾病负担分布极不均衡[5]。

肿瘤微环境(Tumor microenvironment, TME)是肿瘤细胞生存的“土壤”，其组成包括成纤维细胞、免疫细胞、血管内皮细胞及细胞外基质等。Hanahan 于 2022 年提出的癌症新特征中，将“重塑细胞外基质”和“促进免疫逃逸”列为肿瘤进展的核心标志，进一步凸显了 TME 在肿瘤发生发展中的关键作用[6]-[9]。肿瘤–间质比(Tumor-stroma Ratio, TSR)作为反映肿瘤–间质相互作用的定量指标，近年来受到广泛关注[10] [11]。TSR 是指苏木精–伊红染色(Hematoxylin-Eosin staining, HE)切片中肿瘤细胞与间质部分的比例，通常以肿瘤细胞占整体肿瘤组织的比例来表示，评估时在 10 倍物镜视野下，选取肿瘤浸润最前沿区域，排除坏死区域，目测评估肿瘤上皮与间质组织的面积百分比。每例标本至少评估 3 个视野，取平均值。经培训后的病理医师观察者间一致性良好。这一方法已在结直肠癌、乳腺癌等实体瘤中得到广泛验证[12] [13]。

TSR 不仅反映肿瘤微环境的细胞构成，还间接表征其物理特性。间质的丰富程度直接影响肿瘤组织的基质硬度与间质流体压力。研究证实，基质硬度升高可通过整合素–黏着斑激酶(FAK)-Yes 相关蛋白

(YAP)/转录共激活因子 PDZ 结合基序(TAZ)等机械传导信号通路，促进肿瘤细胞增殖、上皮－间质转化及化疗耐药[14]-[16]。间质占比较高的肿瘤中胶原纤维沉积增加，细胞外基质交联增强，形成物理屏障阻碍药物渗透，同时通过激活机械敏感性离子通道调控肿瘤细胞侵袭行为[17] [18]。

目前 TSR 在头颈癌、乳腺癌、胃癌、结直肠癌等实体瘤中均被证实具有预后价值[19]-[22]。在妇科肿瘤中也有相关文献报道了其对于预后的预测价值，本文将对 TSR 在妇科三大肿瘤中的研究进展进行综述，并探讨其与肿瘤微环境的关联。

2. TSR 在子宫内膜癌中的应用

2.1. 研究现状

在 Christensen 等的研究中，TSR 与子宫内膜癌预后存在显著关联，间质丰富是患者无复发生存期缩短的独立危险因素[23]。该研究以 10%为界，将患者分为间质丰富(TSR ≤ 10%)组与间质贫乏组(TSR > 10%)，这远低于其他实体瘤中常用的 50%阈值。这可能反映了即使是间质丰富的子宫内膜癌肿瘤，其绝对间质比例也可能低于其他癌种。这提示 TSR 的阈值设定可能存在肿瘤类型特异性。

子宫内膜癌的 TCGA 分子分型已被证实具有独立的预后价值[24]。De Nola 等的研究进一步发现，在低拷贝数型肿瘤中，WHO 分级是独立预后因素；而在微卫星不稳定型肿瘤中，肿瘤出芽具有显著预后意义[25]。TSR 在高度微卫星不稳定型肿瘤(Microsatellite Instability-High, MSI-H)中未显示独立预后价值，提示 TSR 的临床应用需与分子分型相结合，在特定亚型中发挥补充作用。

2.2. 机制探讨

子宫内膜癌中的间质可能富含促瘤性癌相关成纤维细胞(Cancer-associated Fibroblast, CAFs)，而非抑瘤性间质。CAFs 可分泌 C-C 基序趋化因子配体 2 (C-C motif chemokine ligand 2，CCL2；又称单核细胞趋化蛋白-1，monocyte chemotactic protein-1，MCP-1)和 C-X-C 基序趋化因子配体 12 (C-X-C motif chemokine ligand 12，CXCL12；又称基质细胞衍生因子-1，stromal cell-derived factor-1，SDF-1)等趋化因子，招募肿瘤相关巨噬细胞(Tumor-associated macrophage, TAM)和髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)，形成免疫抑制微环境。同时，CAFs 表达配体程序性死亡配体 1 (programmed death-ligand 1, PD-L1)和程序性死亡配体 2 (programmed death-ligand 2, PD-L2)，可直接抑制细胞毒性 T 淋巴细胞(Cytotoxic T Lymphocyte, CTL)的细胞毒性功能。间质丰富区域可能与免疫抑制细胞的富集相关，形成免疫耐受微环境[25]-[27]。这些机制共同解释了为何间质丰富的子宫内膜癌患者预后更差。子宫内膜癌肿瘤的病理类型差异较大，高侵袭性肿瘤可能诱导强烈的结缔组织增生反应，形成促瘤微环境[28]。

上述子宫内膜癌中间质丰富导致免疫抑制的机制，在卵巢癌中也存在类似现象。CAFs 分泌趋化因子招募免疫抑制细胞是妇科肿瘤中相对保守的间质－免疫交互模式。然而，不同癌种间也存在差异：子宫内膜癌中间质阈值远低于其他实体瘤，这可能反映了子宫内膜癌基线间质含量较低，或间质质量(如 CAFs 功能亚群)在其中的作用更为突出。

3. TSR 在卵巢癌中的应用

3.1. 研究现状

高级别浆液性卵巢癌患者中，间质贫乏患者的无进展生存期显著延长[29] [30]。Lou et al.的研究以间质在肿瘤组织中的占比来表征 TSR，基于卵巢癌患者 TSR 中位数 30%为界进行划分，同时发现 TSR 在原发性肿瘤中的预后价值高于转移性肿瘤。多项研究以 50%为界进行划分，这些研究显示，间质丰富是患者复发和死亡的独立危险因素[31] [32]。卵巢癌中，高级别浆液性癌是最常见的组织学类型，有研究发

现高级别浆液性癌根据分子特征可分为免疫反应型、分化型、增殖型、间质型，其中间质型与最差的预后相关[33] [34]。TSR 作为反映间质比例的指标，可能与间质型高级别浆液性癌存在关联，但目前缺乏直接证据。此外，BRCA1/2 基因突变状态(BRCA mutation status)和同源重组缺陷是卵巢癌重要的治疗预测标志物[35] [36]，TSR 与这些分子标志物的关系值得进一步探索。

3.2. 预测治疗反应

根据 Lou *et al.*研究，高 TSR 患者出现化疗耐药的概率是低 TSR 患者的 2.86 倍，同时发现在卵巢癌患者中间质数量比间质表型特征更具有预后意义[31] [32] [37]。这提示间质丰富患者在初诊时即可被识别为铂类化疗潜在耐药人群，可考虑加强化疗方案、早期引入维持治疗、临床试验入组。

3.3. 机制探讨

CAFs 可分泌肝细胞生长因子(hepatocyte growth factor, HGF)和成纤维细胞生长因子(fibroblast growth factor, FGF)等生长因子，激活肿瘤细胞内的磷脂酰肌醇 3-激酶/蛋白激酶 B (phosphoinositide 3-kinase/protein kinase B, PI3K-Akt)信号通路，直接抑制细胞凋亡[38]，通过重塑细胞外基质，增加胶原沉积和交联，形成物理屏障阻碍药物渗透间接介导化疗耐药[39] [40]，并通过自噬和糖酵解为肿瘤细胞提供代谢支持，如分泌乳酸和酮体，促进肿瘤细胞在化疗压力下存活[41] [42]。高 TSR 肿瘤中可见 CD8 阳性程序性死亡受体 1 阳性 T 细胞(CD8$^+$PD-1$^+$T 细胞)和间质增殖性 CD8 阳性 Ki-67 阳性 T 细胞(CD8$^+$Ki-67$^+$T 细胞)富集[43]，由于其间质成分较少，免疫效应细胞更容易浸润肿瘤核心，同时，这些肿瘤本身可能具有更高的免疫原性，对免疫检查点抑制剂更敏感。

与子宫内膜癌和宫颈癌不同，卵巢癌中 TSR 的预后价值更为明确，这可能与其特殊的解剖位置有关。卵巢癌常以腹膜播散方式转移，富含间质的原发性肿瘤可能更易于在腹膜腔中形成转移灶。此外，间质贫乏肿瘤中效应 T 细胞浸润增加的现象，与子宫内膜癌中 MSI-H 型肿瘤(常呈间质贫乏)对免疫治疗敏感相一致，提示“间质贫乏–免疫活化”模式在妇科肿瘤中可能具有普适性。

4. TSR 在宫颈癌中的应用

4.1. 研究现状

与子宫内膜癌和卵巢癌相比，TSR 在宫颈癌中的研究结论存在争议。早期宫颈癌患者中，间质丰富是患者死亡和复发的独立危险因素[44]，该研究未对不同病理类型进行亚组分析。一项纳入了鳞癌和腺癌患者的研究中，TSR 与任何临床病理特征或无疾病和总体生存期没有相关性，而反应性间质表型与更短的无复发生存期和总生存期相关[45]，该研究特别指出，肿瘤浸润淋巴细胞(tumor-infiltrating lymphocytes, TILs)和间质变化是独立的微环境重塑特征，遵循不同的癌变通路。Zong 等(2020)对 384 例 2018 FIGO IIIC 期宫颈鳞癌患者的分析显示，间质贫乏患者的总生存期和无病生存期均显著优于间质丰富患者。多因素分析证实，间质丰富是独立不良预后因素[46]。在宫颈腺癌中，低 TSR 与深部间质浸润、宫旁浸润等侵袭性病理特征显著相关，且与更短的总生存期相关，但不具备独立预后意义[47]。

4.2. 机制探讨

宫颈癌的两种主要组织学类型具有完全不同的肿瘤微环境，这可能是 TSR 预后意义存在争议的核心原因。在腺癌中，间质丰富往往伴随免疫抑制，这与子宫内膜癌、卵巢癌相似；而在鳞癌中，间质丰富可能伴随免疫活化，提示不同组织学来源的肿瘤对间质信号的响应存在根本差异。单纯 TSR 无法区分这两种截然不同的生物学状态[45]。在最具有侵袭性的宫颈腺癌中，肿瘤与间质之间存在双向通信和协调性重

塑，导致间质主动参与恶性进程，单纯 TSR 无法区分侵袭性与非侵袭性肿瘤在间质数量上可能相似，但间质表型特征截然不同[48]-[50]。比较而言，病理类型多为腺癌的子宫内膜癌和以高级别浆液性癌为主的卵巢癌中观察到的“间质丰富–不良预后”关系更接近于宫颈腺癌模式，而非宫颈鳞癌模式。这提示组织学类型可能是决定 TSR 预后意义的重要因素，未来研究应关注间质响应差异的根本机制。

5. 结语与展望

TSR 作为反映肿瘤微环境中上皮与间质成分比例的定量指标，在妇科三大常见肿瘤中的预后价值已得到广泛关注，但其临床意义呈现显著的肿瘤类型和组织学亚型异质性。在子宫内膜癌中，现有证据显示间质占比超过 10%预示着更短的无复发生存期，但 TSR 的独立预后价值可能受分子分型影响，提示 TSR 需在分子病理背景下综合解读。在卵巢癌中，TSR 的预后价值最为明确，间质贫乏与无进展生存期延长显著相关，且可预测铂类化疗耐药和免疫治疗反应。宫颈癌中 TSR 的预后意义存在组织学异质性，鳞癌中间质丰富提示不良预后，腺癌中则需结合间质质量特征综合评估。单细胞和空间转录组学研究表明，宫颈腺癌与鳞癌具有截然不同的肿瘤微环境景观，腺癌中间质丰富常伴随免疫抑制，而鳞癌中间质丰富可能伴随免疫活化，这从根本上解释了 TSR 预后意义的组织学异质性。此外，宫颈癌中间质的“质量特征”(如反应性表型、CAFs 功能亚群)可能比单纯的“数量”(TSR)更具预后价值。TSR 作为基于常规 HE 染色切片的病理指标，具有成本低廉、可行性高和可重复性高的优点，与现有病理工作流程兼容。在临床实践中，TSR 可作为现有预后因素的补充指标，为患者风险分层提供额外信息。

TSR 在妇科三大肿瘤中的预后意义呈现出子宫内膜癌–卵巢癌–宫颈腺癌趋同，宫颈鳞癌相对趋异的模式。通用机制方面，CAFs 介导的免疫抑制微环境形成、细胞外基质重塑导致的物理屏障效应以及 CAFs 分泌生长因子激活的增殖/抗凋亡信号通路，是解释间质丰富促进肿瘤进展的共同生物学基础。差异机制方面，各癌种特有的间质基线水平、解剖转移方式及组织学来源共同决定了 TSR 预后意义的肿瘤特异性。未来研究应在统一标准化评估体系下，开展多癌种头对头比较，以期阐明 TSR 作为泛妇科肿瘤预后标志物的统一理论框架。

TSR 临床转化的首要前提是评估方法的标准化。目前不同研究采用的阈值(10%、30%、50%)各异，评估区域亦不统一。建议统一采用浸润前沿区域，以 50%为阈值，并进行多中心验证。未来应借鉴国际 TSR 工作组在结直肠癌领域的经验，建立妇科肿瘤 TSR 评估的共识指南，明确切片选择标准、坏死区排除规则、阈值设定的肿瘤类型特异性、观察者培训与质量保证方案。

现有研究以回顾性单中心研究为主，证据等级有限。未来需开展前瞻性、多中心队列研究，在统一的标准化评估体系下验证 TSR 的独立预后价值。TSR 作为单一指标存在固有局限性，未来应探索 TSR 与分子分型、免疫微环境标志物、间质表型特征的联合应用[51]。

TSR 以其低成本、高可及性的独特优势，有望成为妇科肿瘤精准病理的实用工具。然而，其临床转化之路仍面临标准化、验证和机制阐释等多重挑战。未来需在肿瘤类型特异性框架下，将 TSR 与分子分型、免疫微环境特征和间质质量评估相结合，从单纯的“数量”走向“数量 + 质量”的综合评估，才能真正释放这一简易指标在妇科肿瘤精准诊疗中的潜在价值。随着单细胞和空间组学技术的普及，TSR 有望从形态学指标升华为功能生物学标志物，最终服务于临床实践，为妇科肿瘤患者提供更精准的预后信息和治疗指导。

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