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肾母细胞瘤的预后危险因素研究进展

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摘　要

肾母细胞瘤(Wilms tumor)是小儿最常见的肾脏恶性肿瘤，经常需要手术与放化疗结合的系统性综合治疗。随着目前医学技术的进展，肾母细胞瘤患儿的远期预后有了极大的改善，但仍存在某些特性类型的肾母细胞瘤患儿具有较差的预后，且对化疗以及放射性治疗反应性不佳。因此，利用临床上的预后危险因素对预后不佳的患儿进行早期识别显得十分重要。本文通过对国内外的肾母细胞瘤研究文献进行总结和归纳，对目前主要的肾母细胞瘤预后危险因素作一综述。

关键词

肾母细胞瘤，预后，危险因素

Research Advances of Prognostic Risk Factors of Wilms Tumor

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Abstract

Wilms tumor is the most common renal malignant tumor in children and it often needs systematic comprehensive treatment of surgery combined with radiotherapy and chemotherapy. Thanks to

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recent advances in medicine technology, the long-term prognosis of Wilms tumor patients has been greatly improved, but there are still certain types of Wilms tumor, whose response to chemotherapy and/or radiotherapy is not effective, and those patients have a relatively poorer prognosis. Therefore, it is of great importance to identify poor-prognosis patients using clinical risk factors in early stage. This article reviews the current prognostic risk factors by summarizing research articles on Wilms tumor at home and abroad.

Keywords

Wilms Tumor, Prognosis, Risk Factors

1. 引言

肾脏恶性肿瘤约占小儿恶性肿瘤的6%，其中约90%为肾母细胞瘤。关于肾母细胞瘤的治疗方案，目前采用多学科的协作联合治疗，通过数十年来的研究进展，使得肾母细胞瘤患儿的总体生存率突破了90% [1]。然而，对于某些特殊类型，如病理组织学提示预后不良型、分期较晚、双侧或者复发型肾母细胞瘤的患儿，即使在经过联合治疗后，他们的临床结局也并不总是乐观的；另外，对于少部分经过系统性治疗的患儿，后期也表现出了早发性的肾功能不全等不良事件，最终影响预后。因此，在临床上，早期识别可能会导致不良预后的危险因素，并根据其进行个性化调整治疗方案是很重要的。本文就影响肾母细胞瘤预后危险因素的相关研究进展作一综述。

2. 预后危险因素介绍

2.1. 肿瘤分期

肿瘤的分期是研究最早也是最透彻的预后影响因素。根据诊断时的情况，肾母细胞瘤分为局限(I~III期)、转移(IV 期)以及双侧肿瘤(V)期[2]。通常来说，随着分期提高，患儿的预后也会随之变差。然而，随着治疗方案的进展，部分分期较高的患儿生存率较以往有了较大的改善。在北美儿童肿瘤协作组(Children’s Oncology Group, COG)主持的AREN0532研究中，Fernandez等人对总共535名分期为III期的肾母细胞瘤患儿进行随访研究，最后的4年无事件生存率为88%，总体生存率为97% [3]。对于预后良好型且分期为IV 期(伴有肺转移)的患儿，Dix等人采用长春新碱/放线菌素D/多柔比星(DD4A)结合肺部放疗的治疗方案，使得总体生存率由既往研究的84.0%提升到了95.6% [4]。然而，除单纯的分期外，患儿的生存期还受到其他多种因素的制约，同样是分期为III期预后良好型的患儿，若淋巴结活检为阳性，且存在1p/16q杂合性丢失的话，4年无事件生存率就只有74% [3]。总体来说，术前根据临床资料准确分期，术后再根据手术情况视必要性重新分期，并根据分期结果制定对应的后续治疗方案十分关键，根据分期的不同，术后治疗方案有很大的区别，部分患儿可以完全不需后续治疗，也有患儿需要放化疗结合治疗[5]。另外，即使在同一个分期，肿瘤的预后也会有不同。Ehrlich 等人进行的全国肾母细胞瘤瘤研究-5 (National Wilms Tumor Study-5, NWTS-5)的一项回顾性研究发现，使得肿瘤分期为III期的各种因素(手术切缘阳性、淋巴结阳性、肿瘤破裂、腹膜种植等)对肿瘤的复发有着不同的影响，而且影响通常是叠加性

的，在单因素分析中淋巴结活检是否阳性对患儿无事件生存率(p = 0.66)以及总体生存率(p = 0.057)没有显著差异，但多因素分析中淋巴结受侵犯与肿瘤切缘阳性叠加使得患儿的无事件生存率(p = 0.008)与远期生存率(p = 0.07)存在差异[6]。一项单中心的临床回顾研究发现，分期同为 III 期及以上的患儿，存在术前肿瘤破裂的患儿相比不存在术前肿瘤破裂的患儿具有更高的转移复发几率(p = 0.031)，不过远期预后并无显著的差异(p = 0.256) [7]。

2.2. 组织分型

国际儿科肿瘤协会(The International Society for Pediatric Oncology, SIOP)及 COG 均认同在肿瘤组织中找到间变细胞是预后不良的标志[2] [8]。间变细胞常表现为明显增大的细胞核，直径常大于相邻非间变同类细胞的 3 倍，同时伴有核深染以及多倍体的病理性核分裂相[9]。间变细胞的出现与肿瘤分期及组织学分类没有明显关联，含有间变细胞的肾母细胞瘤又可分为局灶间变型和弥漫间变型，通常来说，间变细胞预示着肿瘤对于放化疗有着更强的抗性，同时发生转移和复发的危险性也更高，局灶间变型的危险性介于非间变型和弥漫间变型肾母细胞瘤之间[10]。然而，目前研究认为，间变细胞所带来的不良预后可以通过提高化疗药物的强度来克服。Daw 等人发现，对于 I 期间变型肾母细胞瘤，使用时长 25 周的长春新碱 + 放线菌素 D + 多柔比星，结合放疗可以使患儿的无事件生存率从既往研究的 77.5%提升到 97.2% [11]。Fajardo 等人则发现，对于 1 期弥漫间变型肾母细胞瘤，28 周 DD4A 化疗方案不结合放疗亦可以达到相似效果，同时也省去了儿童放疗所带来的潜在危险[12]。

胚芽细胞是肾母细胞瘤中分化程度最低的非间变细胞成分，在瘤体中常常表现为无明显排列规律的原始细胞。因此 SIOP 认为胚芽为主型的肾母细胞瘤常常预示着更差的预后，在术前化疗的危险度评估中分为高危组[13]，Pasqualini 等发现在 IV 期肾母细胞瘤患儿中，病理为胚芽为主型的患儿与弥漫间变型的患儿五年无事件生存率无明显统计学差异(p = 0.09) [14]。因此，术后病理诊断确认为胚芽为主型的患儿也预示着更差的远期预后，常常需要强化的后续治疗方案。

2.3. 年龄

COG 将年龄纳入肾母细胞瘤患儿危险度分层的影响因素之一，并且认为年龄增加会导致更糟糕的预后和更高的复发几率[15]。对这种趋势的一种解释认为，年龄较大的患儿诊断时常常处于较高的临床分期，并且年龄较大的患儿中间变型肾母细胞瘤所占的比例较高[16]。然而也有研究者认为除开这些因素外，年龄也是一项独立影响预后的因素[17]，Pritchard-Jones 等发现对于预后良好型肿瘤，年龄较大患儿的预后也不及年龄较小患儿，该年龄分界线在 4 岁左右较为明显[18]。目前，关于适合手术的最佳年龄段尚有争议，COG 危险度分层中将年龄 < 2 岁作为较低危的一个因素[19]。然而，日本肾母细胞瘤研究(Japan Wilms Tumor Study, JWiTS)的一项针对 128 例肾母细胞瘤患儿的预后分析中，以 2 岁为年龄分界线，小于 2 岁患儿的总体生存率为 88%，大于 2 岁患儿则为 78%，未见显著统计学差异(p = 0.275) [20]。无论如何，早诊断早治疗仍是基本的治疗原则。

2.4. 遗传学及分子标志物

2.4.1. 染色体 1p 和 16q 的杂合性丢失(Loss of Heterozygosity, LOH)

杂合性丢失是指父母其中一方的遗传物质由于染色体缺失，基因转换，有丝分裂重组等原因出现丢失，导致等位基因失衡，被认为会导致恶性肿瘤的发生及进展。LOH 被认为有可能会增强肿瘤的复发能力，提升肿瘤的耐药性，从而导致不良预后事件发生[21]。Mengelbier 等人认为这是因为 16q 的杂合性丢失会导致 IRX3 基因的表达下调，而 IRX3 系列基因的表达在肾脏发育和形成，尤其是肾小管的成熟过程

中起到调控作用，从而影响肾母细胞瘤的预后[22] [23]。与组织分型相似，可以通过强化治疗方案来使得存在 LOH 的患儿达成更佳的预后。在 AREN0532/AREN0533 研究中，对于预后良好型且伴有 1p/16q LOH 的患儿，对于分期为 I~II 期的患儿采用 DD4A 方案化疗，对于分期 III~IV 的患儿采用 M 方案化疗(长春新碱、放线菌素 D、多柔比星/环磷酰胺 + 依托泊苷，结合放疗)，4 年无事件生存率分别为 87.3%、90.2% [24]。Park 等发现 1p 染色体的 LOH 更容易在年龄较小的患儿上被发现，且具有更低的无事件生存率(3 年生存率，73.7% vs. 91.1%，p = 0.037) [25]。

2.4.2. 染色体 1q 拷贝数增加(1qGain)

1q 拷贝数增加是肾母细胞瘤最常见的细胞遗传学异常之一，约在 30%的肿瘤中均可发现[26]。1q 拷贝数增加往往与肿瘤的高复发风险呈相关性，且与肿瘤分期无明显相关性，在各个临床分期的肿瘤中均可以发现，带有这种变异的肿瘤患儿具有更低的无事件生存率及总体生存率[27]。同时，有研究发现 1q 拷贝数增加可能与 1p/16qLOH 之间存在相关性，染色体 1p 和 16q 的易位可能会导致两种变异共同出现[28]。尽管现在与肾母细胞瘤相关的肿瘤基因已经发现了数十条，但与 1q 拷贝数增加相对应的驱动基因仍然未知，需要进一步的研究探索[29]。

2.4.3. 其它分子标志物

除外上面所提到的，还有大量的与肾母细胞瘤相关的分子标志物被不断发现，并且有希望被运用于临床上进行预后的预测[30] [31] [32]。通过高分辨率蛋白质组学分析，Ortiz 等人在肾母细胞瘤患儿的尿液中识别出高于正常水平的抗增殖蛋白(Prohibitin, PHB)。进一步研究发现，尿 PHB 的水平增高与肿瘤复发具有相关性，而且在预后良好及不良型肿瘤中均有升高。细胞实验发现，PHB 可能参与肿瘤生长与存活过程，可能与线粒体功能及凋亡相关；PHB 的异位高表达可能与肿瘤的耐药性有关联[33]。相关研究结果的发现，为临床上采用无创手段获得有价值的生物标志物指出了可行性，将有希望应用于更准确的危险度分层及治疗方案的制定上。

2.5. 对放化疗的敏感性

目前关于肾母细胞瘤患儿肿瘤切除术前是否需要进行新辅助化疗仍然存在争议。COG 认为，直接进行手术切除可以获得更准确的肿瘤分期，有助于指定术后的序贯治疗方案；而 SIOP 认为，对于分期较高的患儿，术前进行新辅助治疗，可以一定程度上降低肿瘤分期，减少肿瘤体积，减小术中瘤体破裂的风险，从而增加肿瘤切除手术的安全性，降低术后肿瘤复发的可能性[34]。Vujanic 等人对单侧非间变型肾母细胞瘤患儿进行的回顾性病例对照研究发现，经过术前化疗后，术后病理诊断为完全坏死型(CN-WT)及消退型(RT-WT)的患儿，手术后无事件生存率及总体生存率有所提高[35]。

肿瘤肺转移是肾母细胞瘤患儿最常见的转移方式。对于存在肺部转移灶的患儿，SIOP 的指南建议先行进行为期 6 周的 DD4A 方案化疗，若肺部结节对化疗药物表现为完全反应，则患儿可以不进行肺部放射治疗，而肺结节表现为不完全反应甚至无反应的患儿往往需要进一步放化疗来取得相对较好的治疗后生存期[36]。

3. 结论

随着相关研究的不断进展，各种肾母细胞瘤的预后影响因素被先后发现，它们有助于对疾病的危险度进行分层，以及根据各种危险因素进行更加个性化更加具有针对性的治疗方案。然而，对于其中某些危险因素的机理还需进一步深入探讨，部分预后因素如何更加有效地转化到临床应用上也需要更多的临床相关实验进行探究。

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