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垂体神经内分泌肿瘤术后复发的因素研究进展

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摘　要

垂体神经内分泌肿瘤是一种常见的颅内肿瘤，治疗方式主要为经蝶或经颅垂体瘤切除术，对于手术治疗的患者，术后是否复发会影响患者后续治疗方案以及生存预后，其中侵入鞍上或鞍旁区域的PitNET由于术中难以完全切除，术后12%~58%的患者会出现复发(本文复发定义采用2019年中国复发性垂体腺瘤诊治专家共识中的定义：垂体腺瘤切除术后已消失的症状体征再次出现；内分泌指标达到缓解标准后再次升高；影像学检查再次出现肿瘤生长)，即使瘤体被完全切除，10%~20%仍会在5~10年内复发。肿瘤的复发给患者带来经济和心理负担的同时降低了其生活质量。本文主要从影像学特征、病理学因素及其他因素三方面对术后PitNET复发的因素进行综述，以及对临床中PitNET的治疗方式提出个人建议，旨在为该病的临床治疗提供参考。

关键词

垂体神经内分泌肿瘤，各式垂体病损切除术，复发，因素，治疗

Research Advances on Factors of Postoperative Recurrence of Pituitary Neuroendocrine Tumors

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Abstract

Pituitary neuroendocrine tumor is a common intracranial tumor, and the treatment is mainly transsphenoidal or transcranial pituitary tumor resection. For patients undergoing surgical treatment,

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whether postoperative recurrence will affect the follow-up treatment plan and survival prognosis of the patients. Among them, the PitNET that invaded the suprasellar or parasellar area was difficult to be completely removed during surgery, and recurred in 12%~58% of patients after surgery. (In this paper, the definition of relapse was adopted in the expert consensus on diagnosis and treatment of recurrent pituitary adenoma in China in 2019: symptoms and signs that had disappeared after pituitary adenoma resection reappeared; Endocrine indexes increased again after reaching the remission standard; Tumor growth reappears on imaging.) And even if the tumor is completely removed, 10%~20% will recur within 5 to 10 years. The recurrence of tumors brings financial and psychological burden to patients and reduces their quality of life. This article mainly reviews the factors of postoperative recurrence of PitNET from three aspects: imaging features, pathological factors and other factors, and puts forward personal suggestions on the clinical treatment of PitNET, aiming at providing references for the clinical treatment of this disease.

Keywords

Pituitary Neuroendocrine Tumor, Pituitary Tumor Resection, Recurrence, Factors, Treatment

1. 引言

垂体神经内分泌肿瘤(pituitary neuroendocrine tumor, PitNET)是一种常见的颅内肿瘤，约占所有颅内肿瘤的15%~20%，是除神经胶质瘤和脑膜瘤后第三常见的颅内肿瘤[1]。目前PitNET的主要治疗方法是经蝶或经颅垂体瘤切除术，且一般术后患者症状缓解较为明显，然而，仍有部分PitNET表现出较强的侵袭性，导致术后出现复发，其中侵入鞍上或鞍旁区域的PitNET由于术中难以完全切除，术后12%~58%的患者会出现复发(本文复发定义采用2019年中国复发性垂体腺瘤诊治专家共识中的定义：垂体腺瘤切除术后已消失的症状体征再次出现；内分泌指标达到缓解标准后再次升高；影像学检查再次出现肿瘤生长)。即使瘤体被完全切除，10%~20%仍会在5~10年内复发[2]。随着肿瘤复发，患者死亡率也随之升高，因此，为了改善PitNET患者术后的生存质量，研究PitNET术后复发的因素具有重要意义。本文就影响PitNET术后复发的部分因素从影像学特征、组织病理学特征、生物标记物及其它因素四个方面进行综述，旨在为该病的临床治疗提供参考。

2. 影响因素

2.1. 影像学特征

2.1.1. 肿瘤术后残余

既往的多项研究表示肿瘤切除程度是影响复发最主要的因素。一项Meta分析根据患者术后有无肿瘤残余将患者分为两组(一组为未检测到术后残留肿瘤的患者；二组为肿瘤残留患者)，其中术后一组复发率为12%，二组复发率为46%，且一组术后5年、10年生存率较有二组明显较高[3]。在另外一项对142名患者的研究中，肿瘤完全切除的患者有24%出现复发，5年、10年、15年复发率分别为18%、32%、34%。而肿瘤术后有残余的患者中47%的患者术后残余的大小逐渐增加。5年、10年、15年复发率分别为30%、48%、70% [4]。

2.1.2. 肿瘤大小

肿瘤大小目前也被认为是垂体瘤术后复发的一项独立危险因素。体积较大的肿瘤常常会加大手术全切的难度，从而导致术后肿瘤残余，进一步引起肿瘤术后复发[5]-[8]。Kyle Juraschka 等人在一项关于影响垂体瘤切除程度的研究中明确指出，最大肿瘤直径是垂体瘤切除程度的影响因子，当肿瘤按直径 3~4 cm、4~4.9 cm 和≥5 cm 分组时，肿瘤切除程度分别为 89%、80.6%和 73.4%，具有统计学意义[9]。Ferreira 等人的研究中也发现，肿瘤越大，所需要的外科手术次数也就越多，随着肿瘤大小的增加，患者伴随垂体功能减退症的可能性也就越大[10]。

2.1.3. 肿瘤侵袭程度

PitNET 一般呈良性生长，但仍有部分会表现出侵袭周围组织、生长迅速、对常规治疗有抵抗和多次复发的行为[11]。一些作者也提出肿瘤体积和海绵窦侵犯是影响 PitNET 全切除术的重要因素[12]-[15]。其中在 Chuzhong Li 等人的研究中，Knosp ≤ 2 级的患者，实现全切的概率为 90.6%，Knosp ≥ 3 级的患者仅为 63.9%。不伴随骨质侵犯的患者全切率为 83.4%，而伴随骨侵犯的患者仅为 30.8% [12]。并且对于侵袭方向不同，全切的难度也不同，横向侵入的肿瘤(海绵窦等)比垂直侵入的肿瘤(鞍上窦、蝶窦等)更难切除。可能是由于蝶窦的骨骼结构可以通过电钻去除，以扩大暴露以达到完全去除，而海绵窦累及许多血管和神经，很难获得足够的手术暴露，从而导致术后复发[15]。

2.1.4. 肿瘤 MRI 参数

对于 PitNET 术后的复发，目前有些研究发现，肿瘤在 MRI 中的参数可预测肿瘤的复发程度。一些 MRI 质地参数，比如在 MRI 非增强冠状 t1 加权 MRI 图像中，包括平均数灰度值、灰度值中值、最小和最大灰度值与 NFPA 术后复发或进展密切相关，无论是在切除完整性、Ki67 指数和年龄调整之前还是之后。平均灰度值高于中值的肿瘤更容易复发或进展[16]。

2.2. 组织病理学特征

2.2.1. 肿瘤分型

2022 年新的 WHO 分类基于肿瘤细胞谱系、细胞类型和相关特征将 PitNET 分为 PIT1 谱系 PitNETs、TPIT 谱系 PitNETs。SF1-谱系 PitNETs 和无确切细胞谱系的 PitNETs 四种类型以及十余种亚型[17]。尽管新的肿瘤分类不支持任何分级系统或预后分层建议，仅考虑某些肿瘤类型和亚型，但是未成熟 PIT1 谱系肿瘤，Crooke 细胞肿瘤，无细胞肿瘤，嗜酸性粒细胞干细胞肿瘤，稀疏颗粒状的生长激素和无生化功能的“沉默”皮质性肿瘤往往更具有更高的侵袭性和复发风险[18]。这些特点在多项[8] [19] [20]研究中均得到证明。B W Scheithauer 也在他的研究中发现无症状的促皮质腺瘤表现为侵袭性，常常伴随海绵窦侵袭，且伴有高复发率[21]。相反的是，Piotr Sumislawski 等人在他们的研究中提出了不同的观点，他们在对一项显微镜下经蝶骨术后 62 例病历的临床和组织学分析中提出在不同组织学分组中，缓解率和复发率之间没有统计学意义差异[22]。产生这种结果的原因可能是由于研究方法的不同和一些亚型比较少见。

2.2.2. 激素水平

PitNET 中亦有部分肿瘤表现为激素分泌异常，根据分泌的激素不同又可分为不同类型的肿瘤。对于这些带有分泌功能的肿瘤，据研究[23]-[25]，术前或术后激素水平可以在一定程度上预测术后复发的情况。在 Liu Yifan 对库欣病经蝶术后复发的因素的研究中，术后早晨血清皮质醇最低点以及术后和术前早晨促肾上腺皮质激素水平与复发显着相关[24]。在一项研究中也表示，术后短暂性肾上腺功能不全和昼夜皮质醇分泌节律恢复预示着较低复发率[7]。在一项 meta 分析中显示，较低的术后基础泌乳素浓度和促甲状腺激素试验的正常化是与永久治愈相关的有利临床因素。肢端肥大症患者术后生长激素浓度低，或促甲状

腺激素输注后生长激素反常升高正常化，均代表着一个术后肿瘤较低的复发率[26]。

2.3. 生物标记物

2.3.1. 基质金属蛋白酶

基质金属蛋白酶(matrix metalloproteinase, MMPs)是细胞外基质降解所需的主要分泌酶，作用于伤口愈合、胚胎植入、肿瘤侵袭、转移和血管生成等各种生理和病理组织重建过程中，既可以促进侵入周围组织，又可以参与新生血管形成，所以曾被认为是恶性神经胶质瘤的一个重要因素[27]。在一项研究[28]中发现，侵入性较强的 PitNET 中 MMP-9 的阳性表达率显着高于非侵入性 PitNET，而非侵入性 PitNET 中金属蛋白酶 1 组织抑制剂 TIMP-1 的阳性表达率相对较高。此外，一项研究对 55 例经鼻蝶腺瘤切除术后的库欣病患者进行回顾性研究，发现 ACTH 腺瘤患者 MMP-9 水平越高，复发率越高，复发间隔越短，提示 MMP-9 可作为预测 ACTH 腺瘤复发的有效工具[29]。

2.3.2. 人类垂体转化基因

人类垂体转化基因(pituitary tumor transforming gene, PTTG)是有丝分裂中后期的检查点基因，也是促进细胞周期进程的原癌基因[30]，PTTG 在垂体中过表达会导致有丝分裂中姐妹染色单体被拉到同一极，从而产生非整倍体子细胞[31]。一项研究对 74 个垂体瘤样本进行了免疫组织化学分析。结果表示 PTTG 表达与年龄呈负相关，与 PA 大小、再生长和 Ki-67 指数呈正相关、PTTG 的阳性率与 PitNET 的鞍上范围和体积呈正相关[32]，这不仅提示 PTTG 的过度表达常常会诱导肿瘤生长从而导致更高的术后复发率，也标志着 PTTG 在未来可能作为 PitNET 的药物治疗靶点。

2.3.3. 免疫检查点分子

免疫检查点是指连接到免疫系统中的大量抑制途径，这些途径对于维持自我耐受和调节外周组织中生理免疫反应的持续时间和幅度至关重要，然而，部分肿瘤可通过选择某些免疫检查点通路以避免被识别与破坏[33]。例如程序性细胞死亡蛋白 1 (Programmed Cell Death Protein 1, PD-1)，它主要位于活化的 T 细胞、B 细胞、单核细胞、自然杀伤(NK)细胞和树突状细胞的表面。它有两个配体：程序性死亡配体 1 (programmed cell death ligand 1, PD-L1)和程序性死亡配体 2 (programmed cell death ligand 2, PD-L2)，肿瘤可以通过抑制 PD-1 和 PD-L1，损害 T 细胞激活、识别和消除癌细胞的能力，从而通过绕过抗肿瘤免疫监视来不受控制地生长[34]。而 CD-80 和 CD-86 是通过在免疫环境中充当共刺激分子，从而在 T 细胞与 CD28 结合时激活 T 细胞，或在 T 细胞与 CTLA-4 结合时使 T 细胞失活[35]。目前已有许多关于免疫检查点分子的研究，一项在 60 份垂体样本的研究中发现，侵袭性垂体腺瘤中 PD-L2 ($p < 0.0001$)、CD-80 ($p = 0.0035$)和 CD-86 ($p = 0.004$)的 mRNA 水平显著升高[35]。然而，侵袭性垂体腺瘤和正常垂体样本之间的 PD-1、PD-L1 mRNA 水平没有显着差异[35]。同时也发现 PD-L1 的 mRNA 水平在 Ki67 较高的肿瘤中显着升高[35]。Shinsuke Uraki [36]、Zhou [37]等人也在自己的研究中提出了类似的观点。

2.3.4. 表皮生长因子受体

表皮生长因子受体(EGFR)是一种跨膜糖蛋白，EGFR 信号通路对细胞的生长、增殖和分化等生理过程发挥重要的作用。目前已发现 EGFR 定位于几种人类肿瘤中，并已证明与腺癌的发生和患者的预后具有显着的相关性[38]。Rai Ashutosh 等人研究了复发性无功能性垂体腺瘤(NFPA) ($n = 47$)和非复发性 NFPA ($n = 55$)中 pEGFR 的表达，发现与非复发性 NFPA 相比，复发性 NFPA 中 pEGFR T693 阳性率明显更高(95.7% vs 81%, $p = 0.02$) [39]。这项研究中还采用染色强度和阳性染色细胞数量的乘(H 值)表示表达程度[39]，研究发现复发性 NFPA 的 H 值也显着更高(122.1 ± 6 vs 81.54 ± 3.3, $p < 0.0001$)。表明 pEGFR T693

阳性可显着预测 NFPA 的复发(HR = 4.9, CI 2.8~8.8, p < 0.0001) [39]。

2.4. 其它因素

2.4.1. 年龄

年龄对于 PitNET 的复发是否有影响目前来看是具有争议的。一些作者认为年龄较小，肿瘤的复发率也就越高，在 Lyu W [40]的研究中发现，高龄可有效抑制肿瘤复发。MARCO LOSA M.D [5]和 Trott G [41]两人也在自己的文章中证实了这个观点，并且提出作为细胞增殖的标志物 Ki 67 与无功能垂体腺瘤患者的年龄呈负相关的观点，Anna K Watts [42]在研究中发现，患者每年轻一岁，复发的概率就降低 3%，41 岁及以下个体的再生率是 41 岁以上个体的 4.2 倍。但是也有一些作者在自己的研究中[1] [8] [43]发现年龄与 PitNET 的复发没有直接关系，产生这种不同研究结果的原因可能是由于这些研究中对于年龄无明显分组[8] [43]或各分组间样本量差距较大[1]。

2.4.2. 吸烟史及体重指数

目前关于吸烟史和身体质量指数(Body Mass Index, BMI)与 PitNET 的复发相关因素研究较少，CHENY [43]在研究中发现 BMI ≥ 25 kg/m² 和吸烟史是 PitNET 患者术后复发或进展的独立危险因素。超重患者的平均无进展生存期(Progress free survival, PFS)为 44.99 个月，而 BMI 健康患者的平均 PFS 为 53.6 个月。此外，与非吸烟者相比，有吸烟史的患者平均 PFS 较短(40.38 个月 vs 54.35 个月) [43]。此外，一些研究也证明吸烟[44]、BMI [45]-[47]和肿瘤的生长复发有关。

2.4.3. 术后放疗

术后放疗是目前常见的降低后期复发的治疗方案，常用于一些高复发风险患者的后续治疗。Chang Edward F 等人对 663 名 NFPA 患者术后进行了长期随访与分析，确定不进行放疗的次全切除(STR)与复发增加相关(HR 3.6, 95% CI 1.4~14; p = 0.01) [48]。发现术后放疗能减少接受 STR 的患者的肿瘤复发，但不能减少总切除的患者的肿瘤复发[48]。在 Park Paul 等人的研究中，对 258 例 NFPA 的随访中也发现，术后立即接受放疗的患者的 5 年和 10 年复发率分别为 2.3%和 2.3%，未接受放疗的患者的 5 年和 10 年复发率分别为 15.2%和 50.5% [49]。然而，放疗可能导致术后垂体功能缺陷以及长期脑血管意外风险的增加，故在采用放疗之前必须权衡个体患者的风险以及年龄、内分泌功能和残留肿瘤大小和位置等其它变量，以便为患者做出个性化决策[50]。

3. 结语

本文就影响 PitNET 术后复发的部分因素从影像学特征、组织病理学特征、生物标记物及其它因素四个方面进行综述，从而希望能帮助临床医师更有效地了解和治疗这些肿瘤，可惜的是 PitNET 的复发受到多项因素的影响。因此面对 PitNET 术后复发的问题，多学科诊疗(Multi-disciplinary Treatment, MDT)模式就显得较为重要，在复杂性 PitNET 的诊治过程中，应该联合神经内科、内分泌科、放射科、肿瘤科、病理科和眼科，从各专业角度出发，最终对于患者的诊治制定完善的诊疗方案，从而尽早开展规范化的个体化治疗。这种多学科协作模式改变了传统的单一学科诊疗模式，提高了诊断准确性、治疗的有效性，并且有助于长期随访和管理。并且神经外科医生在治疗中应当充分考虑患者的各方面情况，如在有条件的情况下尽量做到全切，针对易复发和残留的病人采取术后化疗，对于有复发的高危因素的患者，后期应加强随访等。并且 MDT 模式在垂体瘤术后患者的护理中也可以运用以降低术后并发症的风险。MDT 模式在垂体瘤治疗中的应用具有显著的优势，包括提高诊疗质量和效率、优化患者护理、促进医疗资源的合理利用以及提升医疗团队的专业能力。因此，MDT 模式是当前及未来垂体瘤及相关疾病诊疗的重要趋势。

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