Advances in Clinical Medicine 临床医学进展, 2025, 15(4), 2969-2989
Published Online April 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1541263

Hans汉斯

神经内分泌肿瘤的非手术治疗进展

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收稿日期：2025年3月24日；录用日期：2025年4月19日；发布日期：2025年4月27日

摘　要

神经内分泌肿瘤(NENs)是一类起源于神经内分泌细胞的高度异质性肿瘤，以胃肠胰和肺部为主要发病部位。诊断需整合影像学、病理学评估(核分裂象计数、Ki-67指数及坏死特征)及分子标志物检测，三者协同支持精准分级与分期。治疗策略以个体化为核心：局部病灶首选手术切除，非手术治疗涵盖多模式干预。生长抑素类似物(如奥曲肽、兰瑞肽)可有效控制功能性肿瘤的激素分泌症状；分子靶向药物通过调控信号通路抑制肿瘤增殖；化疗方案适用于高增殖活性或进展期患者；肽受体放射性核素治疗(PRRT)对SSTR阳性肿瘤展现出精准杀伤优势。免疫治疗在Merkel细胞癌及小细胞肺癌亚型中疗效显著，但对多数NENs响应有限。此外，放射治疗在特定解剖部位(如头颈部、垂体及胸部)肿瘤中发挥局部控制作用。本文系统综述了神经内分泌肿瘤的个体化非手术治疗策略，以期为临床诊疗实践提供参考。

关键词

神经内分泌肿瘤，非手术治疗，生长抑素类似物，肽受体放射性核素治疗

Advances in Non-Surgical Management of Neuroendocrine Neoplasms

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Received: Mar. 24th, 2025; accepted: Apr. 19th, 2025; published: Apr. 27th, 2025

Abstract

Neuroendocrine tumors (NENs) are highly heterogeneous tumors originating from neuroendocrine cells, mainly in the stomach, pancreas and lungs. Diagnosis requires the integration of imaging, pathological evaluation (mitogram count, Ki-67 index, and necrotic features), and molecular marker

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文章引用: 倪寇, 陈怡帆, 胡涵光. 神经内分泌肿瘤的非手术治疗进展[J]. 临床医学进展, 2025, 15(4): 2969-2989.
DOI: 10.12677/acm.2025.1541263

detection to support accurate grading and staging. The treatment strategy is individualistic: surgical resection of local lesions is preferred, and non-surgical treatment includes multi-mode intervention. Somatostatin analogues (such as octreotide, lanretide) can effectively control the hormone secretion symptoms of functional tumors. Molecular targeted drugs inhibit tumor proliferation by regulating signaling pathways; Chemotherapy regimen is suitable for patients with high proliferative activity or advanced stage. Peptide receptor radionuclide therapy (PRRT) shows a precision killing advantage for SSTR-positive tumors. Immunotherapy is effective in Merkel cell carcinoma and small cell lung cancer subtypes, but the response to most NENs is limited. In addition, radiation therapy provides local control of tumors at specific anatomical sites, such as the head and neck, pituitary gland, and chest. In this paper, the individualized non-surgical treatment strategies for neuroendocrine tumors are reviewed in order to provide reference for clinical practice.

Keywords

Neuroendocrine Neoplasms, Non-Surgical Treatment, Somatostatin Analogues, Peptide Receptor Radionuclide Therapy

1. 引言

神经内分泌肿瘤(Neuroendocrine Neoplasms, NENs)是一种异质性罕见肿瘤，起源于肽能神经元以及神经内分泌细胞，具有神经内分泌分化特性并表达神经内分泌标志物，常见于胃肠道和肺部[1] [2]。这些肿瘤可以根据是否分泌激素导致特定的临床综合征而区分为功能性或非功能性[3]-[5]。国内外研究表明，NENs 的发病率有显著上升趋势[6]-[12]。有研究估计 NENs 年发病率为 3~5/10 万人年，约占所有恶性肿瘤的 0.5% [7]。现代流行病学趋势研究中认为 NENs 在美国的患病总人数小于 20 万[12]，但 1973 至 2012 年间报告增长了 6.4 倍，达到了 6.98/10 万人年[7]，从 1996 年到 2015 年，中国台湾 NET 发病率从 0.244/10 万人年上升到 3.162/10 万人年[6]。

神经内分泌肿瘤的异质性较高，可起源于多个组织和器官，其最常见的部位是胃肠胰(约 60%) [13]，其次是肺部(>占 20%) [14]，其余较少出现的部位包括胰腺、胸腺、垂体、甲状腺、甲状旁腺、皮肤、肾上腺、生殖泌尿器官等[15]-[18]。胰腺和直肠是亚洲人群最常见的发病部位[9]，而欧美白人中，小肠和胰腺是最常见的发病部位[7]。

NENs 的临床症状因肿瘤位置和功能性而异。功能性 NENs 如类癌综合征，可能表现为潮红、腹泻和心脏病[19]，而非功能性 NEN 的症状通常与肿块效应或转移相关[3]-[5]。

NENs 的高度异质性决定了其诊断的困难和复杂性，为确定疾病的原发与累及部位并优化治疗管理，除了临床症状，还需包括超声(Ultrasound, US)、计算机体层成像(Computed Tomography, CT)、磁共振成像(Magnetic Resonance Imaging, MRI)等常规影像学检查，特殊的生物标志物、内窥镜(endoscopy)、超声内窥镜(Endoscopic Ultrsonography, EUS) [20] [21]、以及各种分子影像学检查如单光子发射计算机断层显像(Single Photon Emission Computed Tomography, SPECT)和正电子发射计算机断层显像(Positron Emission Tomography Imaging, PET)进行综合诊断，尤以生长抑素受体(Somatostatin Receptor, SSTR)显像、18F-FDG PET/CT、18F-DOPA PET/CT、68Ga-DOTA-exendin-4 有较高诊断价值[19] [22]-[26]。目前神经内分泌肿瘤诊断的金标准仍是病理学诊断。同一组织或器官起源的 NENs 在分类、分级不同时，亦有显著不同的

生物学行为，不同部位的 NENs 亦有不同的病理学命名、分类和分级，2022 年世界卫生组织(World Health Organization, WHO)发布了上皮型 NENs 的统一分类和分级标准[27]，该标准总体上把 NENs 分为分化好的神经内分泌瘤(Neuroendocrine Tumour, NET)和分化差的神经内分泌癌(Neuroendocrine Carcinoma, NEC)，而分化好的 NET 则根据核分裂象和 Ki-67 增殖指数分为 G1、G2 和 G3 共 3 个级别。该标准特别关注与肿瘤增殖活性相关的 3 个指标：核分裂象、Ki-67 增殖指数和肿瘤性坏死(表 1) [19]。

Table 1. Classification of epithelial NENs at different anatomical sites [19]
表 1. 不同解剖部位上皮型 NENs 的分类标准[19]

部位	类型	分级/亚型	诊断标准
胃肠胰和肝胆	NET	G1	<2 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＜3%
		G2	2~20 个核分裂象/2mm^2 和(或) Ki-67 增殖指数为 3%~20%
	NEC	G3	>20 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20%
		SCNEC	>20 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20% (常>70%，具有 SCNEC 的形态特征)
		LCNEC	>20 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20% (常>70%，具有 LCNEC 的形态特征)
上呼吸道、上消化道	NET	G1	<2 个核分裂象/2mm^2 和没有坏死，以及 Ki-67 增殖指数 ＜20%
		G2	2~10 个核分裂象/2mm^2 和(或)坏死，以及 Ki-67 增殖指数 ＜20%
	NEC	G3	>10 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20%
		SCNEC	>10 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20% (常>70%，具有 SCNEC 的形态特征)
		LCNEC	>10 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞20% (常>55%，具有 LCNEC 的形态特征)
肺和胸腺	NET	TC/NET，G1	<2 个核分裂象/2mm^2 和没有坏死
		AC/NET，G2	2~10 个核分裂象/2mm^2 和(或)坏死(通常是点状坏死)
		伴核分裂象和(或) Ki-67 增殖指数增高的类癌 (相当于 NET，G3)	具有 AC 形态，但>10 个核分裂象/2mm^2 和(或) Ki-67 增殖指数 ＞30%
	NEC	SCNEC	>10 个核分裂象/2mm^2，常伴坏死和 SCNEC 的形态
		LCNEC	>10 个核分裂象/2mm^2，几乎总伴坏死和具有 LCNEC 的形态
甲状腺	MTC	低级别 MTC	<5 个核分裂象/2mm^2 和没有坏死，以及 Ki-67 增殖指数 ＜5%
		高级别 MTC	下列 3 个指标中至少有 1 个：① ≥5 个核分裂象/2mm^2；② 出现坏死；③ Ki-67 增殖指数 ≥5%

TC：典型类癌(Typical Carcinoid)；AC：不典型类癌(Atypical Carcinoid)。乳腺 NEN 目前无统一的分级标准，常采用 Nottingham 分级系统分级，临床中与其他部位(女性生殖、泌尿系统和男性生殖等)参考 GEP-NENs 分类和分级标准。

分化好的 NET 即使出现远处转移，亦能获得较长生存期，可长达 5 年甚至 10 年。而分化差的 NEC 其预后远差于同部位的其他恶性肿瘤，文献报道的中位生存期仅 12~19 个月[19]。因此，鉴别高分化的 NET 和低分化的 NEC 有着极为重要的意义。需从细胞形态、组织结构和免疫组织化学(Immunohistochemistry,

IHC) 3 个方面综合考量[28]。病理学形态特征是诊断 NENs 的关键，高分化的 NETs 由卵圆形细胞核和颗粒状染色质组成，具有“盐和胡椒”的外观，低分化的 NEC 常见为均一的少细胞质(Small Cell NEC, SCNEC)或显著细胞质(Large Cell NEC, LCNEC)，呈“片状”生长。有研究认为 NETs 的神经内分泌标志物表达水平较 NECs 更高[29]。而确认神经标志物的表达则要求在形态学基础上利用 IHC 染色确认肿瘤具有神经内分泌分化。推荐应用包括突触素(Synaptophysin, Syn)、嗜铬粒蛋白 A (chromogram A, CgA)和胰岛素瘤相关蛋白 1 (Insulinoma-Associated Protein 1, INSM1)在内的多个抗体染色以明确诊断[30]。诊断时还需鉴别混合性神经内分泌－非神经内分泌肿瘤(Mixed Neuroendocrine Non-Neuroendocrine Neoplasms, MiNENs)，这是一种同时含有神经内分泌和非神经内分泌成分的混合型上皮肿瘤，约占 NENs 的 5%，在形态学和免疫表型中两种成分独立，且每种成分至少占 30%，常表现为腺癌和神经内分泌癌的组合[31]。

NENs 的治疗被认为以内镜治疗[32] [33]、外科治疗[34]、介入治疗[35]等手术方案为主。内镜手术在低级别、病灶局限的消化道神经内分泌肿瘤(Gastrointestinal Neuroendocrine Neoplasms, GI-NENs)中作为首选治疗方式，对于无内镜手术指征的低级别 GI-NENs，胰腺 NENs，支气管肺和胸腺 NENs、默克尔细胞癌(Merkel Cell Carcinoma, MCC)、除泌乳素瘤外的垂体神经内分泌肿瘤(Pituitary Neuroendocrine Tumors, PitNETs)、副神经节瘤/嗜铬细胞瘤(Pheochromocytoma and Paraganglioma, PPGLs)、甲状腺髓样癌(Medullary Thyroid Carcinoma, MTC)、以外科手术作为首选治疗方式[19]，同时新辅助治疗或术前转化治疗可尝试选择化疗、抗血管生成靶向治疗及肽受体放射性核素治疗(Peptide Receptor Radionuclide Therapy, PRRT) [36]。

NET 的术后辅助治疗适用于接受根治性手术但术后复发风险较高的 GEP-NETs 患者及 AC 患者，常有肿瘤分级较高、分期较晚、切缘阳性等特点，常应用 CAPTEM 方案(卡培他滨 + 替莫唑胺)或替莫唑胺单药辅助治疗。对各部位 NEC，推荐行术后化疗(EP 或 EC 方案等)和(或)放疗[19]。MCC 术后或可考虑免疫治疗作为辅助治疗方案[37]。PitNETs、PPGLs、MTC 的术后辅助治疗尚缺乏证据。

然而，近几十年来，许多非手术治疗方法有了相当大的发展，涵盖全身治疗[38]、内分泌治疗[39] [40]、靶向治疗[41]、放射治疗[42]、PRRT [43]等手段扩大了这些肿瘤的治疗选择。

本综述的重点是为临床和基础研究科学家提供有关神经内分泌肿瘤非手术治疗的全面概述，以帮助他们理解 NENs 和选择治疗方式。

2. 药物治疗

神经内分泌肿瘤(NENs)因其组织学特征和生物学行为的显著差异，在临床治疗领域面临多重诊疗难题。为实现个体化治疗目标，临床决策需建立在对多维度参数的全面评估之上，具体包括：明确肿瘤原发部位及功能性分泌状态，鉴别组织分化程度与增殖指数，检测生长抑素受体(SSTR)显像结果，评估转移病灶分布范围，同时整合分子遗传学特征和疾病动态演变趋势。这种基于循证医学的多参数评估体系，可为 NENs 患者制定最优化的药物治疗策略提供科学依据。

NENs 的系统性药物治疗应遵循双重治疗目标：一方面通过调节受体介导通路改善功能性肿瘤(F-NENs)引发的内分泌紊乱及相关临床综合征；另一方面基于分子病理学特征抑制肿瘤增殖及转移进程[44] [45]。

2.1. 内分泌治疗

2.1.1. 生长抑素类似物

分子调控视角下，生长抑素作为多效性神经肽，通过配体－受体相互作用对内分泌网络产生双向调

节作用，尤其表现在胰高血糖素动态平衡及胰岛素分泌节律的精密调控。鉴于大多数 NENs 细胞表面特异性表达 SSTR 亚型，临床实践中长效缓释剂型生长抑素类似物(Long-Acting Somatostatin Analogs, SSAs)通过高亲和力受体结合介导信号通路双重调控：不仅实现对肿瘤源性激素模拟物(如血管活性肠肽、组胺等)的生物化学调控，同时展现对肿瘤增殖信号阻断效应，这使其成为功能性 NENs 症状控制的核心药理机制[46] [47]。SSAs 包括长效奥曲肽、兰瑞肽水凝胶及长效帕瑞肽，是改善大部分功能性 NENs，尤其是胸部及消化系统 NENs 激素相关症状的一线治疗[47]。分子层面上，SSTR 家族包含 SSTR1-5 五种亚型，其中奥曲肽和兰瑞肽主要选择性激活 SSTR2/SSTR5 信号轴，而帕瑞肽则展现出对 SSTR1/2/3/5 多亚型的广谱亲和力，其延缓 GEP-NET 和不明原发灶 NET 肿瘤进展的疗效分别在 SPINET 临床研究中得到证实，有效患者延长 PFS [40]。

临床给药方案需遵循受体动力学特征：推荐采用奥曲肽缓释微球制剂(20~30 mg/4 周，肌注)或兰瑞肽水凝胶缓释系统(90~120 mg/4 周，皮下注射)作为基础治疗方案。针对耐药性病例可采取剂量密集策略或剂量递增模式[48]。对于突发性激素危象，皮下按需注射短效奥曲肽可作为急性期干预手段[49]。当一线治疗失效时，可启用第二代广谱 SSAs——帕瑞肽长效制剂，初始剂量 40 mg/4 周，根据生物标志物应答情况阶梯式上调至 60 mg/4 周维持治疗[50]。第二代广谱 SSAs 还可以通过选择性激活 SSTR5 信号通路，可有效抑制 ACTH 异常分泌，以治疗 ACTH 瘤[51]。此外，在生长激素瘤与分泌促甲状腺激素的垂体神经内分泌肿瘤抑制激素分泌治疗中，SSAs 均是首选治疗方案[52] [53]。

SSAs 最常见的不良反应包括胆结石形成、血糖波动、和中度胃肠不适，如恶心和腹胀[54] [55]。因此，胰岛素瘤的 SSAs 应用全程应实施持续血糖监测，SSAs 通过 SSTR5 介导的 β 细胞超极化作用加剧低血糖风险[3]。常推荐联用二氮嗪，通过激活胰腺 ATP 敏感性钾通道抑制胰岛素释放[21]。

2.1.2. 生长激素受体拮抗剂

生长激素受体拮抗剂(Growth Hormone Receptor Antagonist)通过竞争性拮抗生长激素受体(GHR)的活性，可有效降低血清胰岛素样生长因子-1 (IGF-1)水平，代表药物为培维索孟(Pegvisomant) [56]。其治疗方案需遵循个体化原则：起始阶段推荐采用负荷剂量(40 mg，皮下注射)，随后调整为每日 10 mg 维持治疗，后续剂量需根据 IGF-1 的动态监测结果进行优化调整。在生长激素瘤的疗效评估中，需定期联合检测随机血清生长激素(GH)浓度及 IGF-1 水平以综合评价生化缓解状态。值得注意的是，培维索孟的作用机制并非抑制 GH 分泌，而是特异性阻断 GH 与受体的结合，从而削弱其下游信号传导[52]。因此，当 GH 与 IGF-1 水平出现分离现象时(如 GH 水平持续升高而 IGF-1 正常化)，建议以 IGF-1 作为疗效判断的主要指标。

2.1.3. 多巴胺受体激动剂

多巴胺受体激动剂(Dopamine Agonists, DA)是泌乳素瘤患者实现生化缓解的首选药物，其中溴隐亭(Bromocriptine)因其广泛可及性及明确疗效被国内指南列为一线治疗方案[57]。该药物的推荐使用剂量为每日 2.5~15.0 mg，建议采用个体化剂量滴定策略：初始日剂量为 2.5 mg，根据血清泌乳素(PRL)水平及肿瘤体积变化逐步调整至目标剂量。对于溴隐亭耐药(定义为 PRL 未达标或肿瘤缩小不足 50%)或药物不耐受患者，可转换为第二代 DA 卡麦角林(Cabergoline)。相较于溴隐亭，卡麦角林对多巴胺 D2 受体具有更高的亲和力及选择性，推荐剂量为每周 0.5~3.5 mg (分 1~2 次给药)，其临床缓解率及耐受性均显著优于传统 DA 药物。

2.1.4. 肾上腺皮质类固醇合成抑制剂及糖皮质激素受体拮抗剂

库欣综合征(Cushing’s syndrome)患者因促肾上腺皮质激素(ACTH)的持续高分泌状态，常继发肾上腺源性糖皮质激素过量释放，需联合应用肾上腺皮质类固醇合成抑制剂以阻断皮质醇生成通路。常用药物

包括：通过抑制 11β-羟化酶活性减少皮质醇合成的美替拉酮；兼具肾上腺皮质溶解作用及酶抑制效应的米托坦(Mitotane)；抑制胆固醇侧链裂解酶及 11β-羟化酶的酮康唑(Ketoconazole)以及新型 11β-羟化酶抑制剂奥西卓司他[58]。

对于存在肾上腺抑制剂可及性限制的患者，可选择口服米非司酮(Mifepristone)治疗，该药物通过竞争性拮抗糖皮质激素受体改善高皮质醇血症相关糖代谢异常[58]。但其疗效需通过血糖动态监测间接评估，且对皮质醇过量介导的低钾血症调控作用有限。

2.1.5 选择性雌激素受体调节剂(SERMs)

根据 2023 年《美国国立综合癌症网络(NCCN)指南》，雌激素受体阳性乳腺神经内分泌肿瘤(ER + NETB)的全身治疗策略与常规激素受体阳性乳腺癌(HR + BC)遵循相同原则，推荐将选择性雌激素受体调节剂(SERMs)或芳香化酶抑制剂(AIs)作为基础方案，绝经前高危患者需联用卵巢功能抑制(OFS)以增强疗效[59]。这一共识得到回顾性临床数据的支持：一项纳入 42 例 ER 阳性 NETB 患者的队列研究显示，接受他莫昔芬辅助治疗者的五年无病生存率(DFS)显著优于未治疗组(84% vs 65%, $p < 0.05$)，提示传统内分泌治疗在神经内分泌分化肿瘤中仍具明确抗增殖活性[60]。

目前临床研究仅支持他莫昔芬用于治疗神经内分泌肿瘤，乳腺癌内分泌治疗所常用的芳香化酶抑制剂(AIs)、雌激素受体下调剂(SERDs)、促性腺激素释放激素(GnRH)激动剂，对于乳腺神经内分泌肿瘤患者的预后是否有获益仍待进一步研究。

2.2. 分子靶向药物

2.2.1. mTOR 抑制剂

PI3K/AKT/mTOR 通路的异常活化是神经内分泌肿瘤(NETs)发生发展的关键致癌机制。作为该通路的核心靶点，mTOR 抑制剂依维莫司(Everolimus)通过阻断 mTORC1 复合物抑制肿瘤细胞增殖的生物学效应，在 RADIANT-3、RADIANT-4 研究中依维莫司显著提升了 NET 患者的 PFS [61] [62]。因此，推荐依维莫司用于进展期 G1/G2 级胃肠胰、肺及不明原发灶 NET 患者。

在 RADIANT-2 和 COOPERATE-2 研究中，依维莫司联合 SSAs 对进展期 pNET、胃肠及肺 NET 患者较 SSAs 未能提升 PFS，因此不推荐常规使用 SSAs 与依维莫司联用来控制肿瘤生长[63]-[65]。目前，无证据支持依维莫司在高级别 NENs 中的应用。

临床实践发现，标准剂量依维莫司(每天 10 mg)的耐受性较低，近 60%的患者需药物减量，常见不良反应为口腔溃疡、血糖血脂升高、机会性感染、非感染性间质性肺炎等[45]，推荐依维莫司每天 5 mg 作为起始剂量，每 1~2 周评估患者的不良反应，对可耐受者可考虑增量，不超过每天 10 mg。

2.2.2. 酪氨酸激酶抑制剂(TKIs)

靶向抑制血管内皮生长因子受体(VEGFR)及其下游信号传导已成为神经内分泌肿瘤(NET)领域的重要治疗策略。以舒尼替尼、索凡替尼和卡博替尼为代表的酪氨酸激酶抑制剂具有多靶点抑制特性，其作用机制涵盖抗血管生成和直接抗肿瘤效应。临床研究数据显示，舒尼替尼基于 III 期临床试验结果(中位无进展生存期 11.4 个月对比 5.5 个月)获批用于进展性胰腺神经内分泌肿瘤的治疗[66]；索凡替尼则经中国药监部门批准用于晚期胃肠胰神经内分泌肿瘤，其 SANET 系列研究显示客观缓解率达 19% [67]；卡博替尼在肺神经内分泌肿瘤的 II 期临床试验中表现出 68%的疾病控制率[68]。

在临床应用中，舒尼替尼和索凡替尼因其疗效显著而成为首选治疗方案。根据个体化治疗原则，推荐舒尼替尼初始剂量为每日 25 毫克，索凡替尼每日 200 毫克，并在治疗过程中持续监测甲状腺功能、24 小时动态血压及尿蛋白与肌酐比值等指标。此类抗血管生成药物常见不良反应涉及多个系统，包括高血

压、蛋白尿、腹泻、甲状腺功能减退、水肿、出血风险增加、消化道穿孔及瘘管形成、骨髓抑制、肝功能异常以及手足综合征等。

2.2.3. 细胞周期蛋白依赖性激酶 4/6 抑制剂

CDK4/6 属于靶向治疗药物，主要用于治疗激素受体阳性(HR+)、人表皮生长因子受体 2 阴性(HER2-)的乳腺癌，也探索性用于其他实体瘤治疗。目前有一项 II 期单臂试验(NCT02644460)提示晚期进展性胰腺 NET 中位 PFS 12.1 个月，ORR 8% [69]，仍需要进一步临床研究确定其疗效。

2.2.4. 靶向药物随访监测

值得注意的是，约 30%患者因药物毒性反应无法耐受标准剂量治疗，需进行剂量调整或暂停给药[70]。临床实践中需建立完善的随访监测体系，及时识别和处理药物相关不良反应，以平衡治疗效果与安全性。常采用的多维度监测包括：

1) 代谢监测

每月检测血常规、肝肾功能及电解质水平，使用 mTOR 抑制剂时需增加血脂、血糖监测频次。空腹血糖 ≥ 7.0 mmol/L 或随机血糖 ≥ 11.1 mmol/L 时，优先选用 DPP-4 抑制剂(如西格列汀)，出现酮症倾向(血酮 ≥3.0 mmol/L)需暂停靶向治疗，胰岛素强化干预[71]；心血管高风险患者 LDL-C ≤ 1.8 mmol/L 或甘油三酯 ≥5.6 mmol/L 时启用他汀类药物治疗[72]；低钾血症(K^+ < 3.5 mmol/L)时，口服氯化钾缓释片联合保钾利尿剂。

2) 影像学监测

治疗前基线 68Ga-DOTATATE PET/CT 显像，每 6~12 个月复查对比肿瘤负荷变化，同时监测骨密度。治疗应答评估采用 RECIST 1.1 联合 PERCIST 双标准[73]，骨密度检测 T 值 ≤ −2.5 时启用唑来膦酸 4 mg/6 月。

3) 心功能监测

对于使用舒尼替尼等 VEGFR 抑制剂患者，建议治疗前及每 3 个月进行心脏彩超和 NT-proBNP 检测，左室射血分数下降 > 10%时应启动心功能保护方案[74]。

2.3. 细胞毒性药物

细胞毒性化疗药物是 NENs 治疗的重要药物，常用方案包括 CAPTEM 方案、FOLFOX 方案、EP 方案等(表 2) [19]。

Table 2. Common chemotherapy regimens and their usage and dosage [19]
表 2. NENs 常用化疗方案及其用法用量[19]

方案	药物	具体用法用量
CAPTEM	卡培他滨、替莫唑胺	卡培他滨：750 mg/m^2，口服，bid，d1-14； 替莫唑胺：200 mg/m^2，口服，qd，d10-14；q4w
FOLFOX	奥沙利铂、亚叶酸钙、5-FU	奥沙利铂：85 mg/m^2，静滴，d1； 亚叶酸钙：400 mg/m^2，静滴，d1； 5-FU：400 mg/m^2，静注，d1； 5-FU：2400 mg/m^2，输液泵持续静注 46h；q2w
XELOX	奥沙利铂、卡培他滨	奥沙利铂 130 mg/m^2，静滴，d1； 卡培他滨 1000 mg/m^2，口服，bid，d1-14；q3w
S-1/TMZ	替吉奥、替莫唑胺	替吉奥：40~60 mg，口服，bid，d1-14； 替莫唑胺：200 mg，口服，qd，d1-14；q3w

续表

EP	依托泊苷、顺铂	依托泊苷：100 mg/m^2，静滴，d1-3； 顺铂：75 mg/m^2，分 3 天静滴，d1-3；q3w
EC	依托泊苷、卡铂	依托泊苷：100 mg/m^2，静滴，d1-3； 卡铂：AUC 4~6，静滴，d1；q3w
IP	伊立替康、顺铂	伊立替康：60 mg/m^2，静滴，d1、d8、d15； 顺铂：60 mg/m^2，静滴，d1；q4w
FOLFIRI	伊立替康、亚叶酸钙、 5-氟尿嘧啶	伊立替康：180 mg/m^2，静滴，d1； 亚叶酸钙：400 mg/m^2，静滴，d1； 5-FU：400 mg/m^2，静注，d1； 5-FU：2400 mg/m^2，输液泵持续静注 46 h；q2w

Qd：每日一次，Bid：每日两次；5-FU：5-氟尿嘧啶；AUC：曲线下面积(Area Under Curve)。

2.3.1. G1/G2 级胃肠胰神经内分泌肿瘤的化疗应用

对于分化良好(G1/G2 级)的胃肠胰神经内分泌肿瘤(GEP-NETs)，临床常用的全身化疗方案包括卡培他滨联合替莫唑胺(CAPTEM)、FOLFOX、替莫唑胺联合 S-1 (TMZ/S-1)以及链脲霉素(STZ)联合 5-氟尿嘧啶(5-FU)或蒽环类药物等。E2211 III 期随机对照试验[75]表明，与替莫唑胺单药相比，CAPTEM 方案可显著延长患者无进展生存期(中位 PFS：22.7 个月 vs 14.4 个月)，这一结果在后续一项纳入 151 例患者的回顾性队列研究[76]中进一步得到验证。然而，FOLFOX 方案在神经内分泌肿瘤(NENs)中的疗效证据主要来源于回顾性数据[77] [78]，其治疗晚期胰腺神经内分泌肿瘤(pNETs)及胃肠神经内分泌肿瘤(GI-NETs)的中位 PFS 分别为 6~9 个月和 3~14 个月，而直肠神经内分泌肿瘤的疗效相对有限。值得注意的是，以链脲霉素为基础的联合化疗方案虽在国际指南中占有一席之地，但受限于药物可及性和毒性管理问题，其在国内临床实践中应用甚少。基于现有证据，化疗的推荐适用人群需严格筛选，通常建议用于肿瘤负荷较高、疾病进展迅速、Ki-67 指数 > 10%且对生物治疗(如生长抑素类似物)、靶向药物(如依维莫司)或肽受体放射性核素治疗(PRRT)耐药的患者，优先选择 CAPTEM 或 FOLFOX 等循证支持方案[79]。

2.3.2. G3 级 NET 的化疗应用

针对高增殖活性(G3 级)神经内分泌肿瘤的全身化疗策略尚未形成统一标准。回顾性研究显示，替莫唑胺为基础的治疗方案在晚期 G3 级 NET 中表现出一定潜力，客观缓解率(ORR)可达 41%，中位 PFS 介于 5.7~20.7 个月，且联合卡培他滨、胰腺原发灶以及一线使用时疗效更为显著[80]。国内多中心回顾性数据[76]同样支持 CAPTEM 方案对 G3 级 GEP-NENs 患者的生存获益。此外，FOLFOX 方案在部分临床实践中被尝试用于 G3 级 NET，一项多中心回顾性分析[80]报道其一线治疗的 ORR 为 56.4%，中位 PFS 为 6.4 个月，但相较于 CAPTEM 方案其生存优势稍逊。NORDIC NEC 研究[81]进一步揭示了 Ki-67 指数的预测价值：当 Ki-67 ≥ 55%时，患者对依托泊苷联合铂类(EP/EC)方案的反应率显著提高(42% vs 15%)，因此推荐对此类患者优先选择铂类化疗；而对于 Ki-67 < 55%者，则建议采用 CAPTEM 或 FOLFOX 等非铂方案以平衡疗效与毒性风险。

2.3.3. 肺及胸腺 NET 的化疗应用

临床实践证据显示，肺及胸腺神经内分泌肿瘤(NETs)的全身化疗选择主要基于回顾性研究数据。多项回顾性分析表明，替莫唑胺(TMZ)单药或联合卡培他滨在肺及胸腺神经内分泌肿瘤中显示出适度抗肿瘤活性，客观缓解率(ORR)介于 10%至 30%之间，中位无进展生存期(PFS)为 5 至 13 个月[44]。以奥沙利铂为基础的联合化疗方案(如 FOLFOX)亦表现出潜在疗效，部分研究报道其 ORR 可达 20%，中位 PFS 范

围为 8 至 15 个月[44]。基于现有证据，临床指南推荐对晚期或进展期肺及胸腺神经内分泌肿瘤患者采用以 TMZ (联合或不联合卡培他滨)或奥沙利铂为核心的化疗方案。

2.3.4. 其他罕见神经内分泌肿瘤的化疗应用

对于侵袭性或晚期垂体神经内分泌肿瘤(PitNETs)、甲状腺髓样癌(MTC)、嗜铬细胞瘤/副神经节瘤(PPGLs)及默克尔细胞癌(MCC)，化疗通常作为后线治疗选择。临床研究数据证实，在 PitNETs 中，替莫唑胺单药治疗被证实具有显著临床获益，尤其适用于生长激素腺瘤等特定亚型[82]。MTC 患者经酪氨酸激酶抑制剂(TKIs)治疗进展后，可考虑转换至传统细胞毒药物治疗，包括阿霉素单药或联合顺铂方案，以及 5-FU 与达卡巴嗪的联合方案，尽管此类治疗应答率普遍偏低[8]。对于嗜铬细胞瘤/副神经节瘤(PPGLs)，环磷酰胺联合长春新碱及达卡巴嗪(CVD 方案)或替莫唑胺为基础的联合方案可能提供疾病控制。MCC 的化疗策略通常保留于 PD-1/PD-L1 抑制剂治疗失败或存在免疫治疗禁忌证的患者，可选方案包括 EP 或 EC 方案，以及环磷酰胺、阿霉素与长春新碱(CAV)的联合方案，但需警惕此类方案较高的血液学毒性风险[83]。

2.3.5. 化疗在 NEC 中的应用

1) 肺大细胞神经内分泌癌(LCNEC)

肺 LCNEC 的标准治疗仍存在争议[84]。针对肺 LCNEC 的一线治疗，指南推荐 EP 或 EC 的标准化疗方案[85]。疾病进展后，二线治疗可选择伊立替康、拓扑替康、紫杉类或培美曲塞等细胞毒药物。

2) 局限期小细胞肺癌(SCLC)

局限期 SCLC 的一线治疗采用 EP/EC 方案化疗 4 周期，并同步联合胸部放疗以增强局部控制[86][87]。术后辅助化疗推荐相同方案以降低复发风险。近年来，免疫治疗在局限期 SCLC 中的探索取得突破，ADRIATIC III 期临床试验证实，放化疗后使用度伐利尤单抗巩固治疗可显著延长无进展生存期(PFS)和总生存期(OS) [88]。疾病进展后的二线治疗可选择拓扑异构酶抑制剂(伊立替康/拓扑替康)、吉西他滨或长春瑞滨等药物，或优先纳入新型疗法的临床试验。

3) 广泛期小细胞肺癌(SCLC)

广泛期 SCLC 的一线治疗标准已从传统化疗转向免疫联合治疗，EC 方案联合 PD-L1 抑制剂(如斯鲁利单抗、阿得贝利单抗等)显著改善患者生存[89]-[92]。完成 4 周期联合治疗后未进展者需继续免疫维持治疗至疾病进展。替代方案包括 EP/EC 方案或伊立替康联合铂类(IP/IC 方案) [93]-[96]。二线治疗策略与局限期进展后方案相似，但对停药超过 6 个月复发的患者可尝试重启原治疗方案。安罗替尼作为多靶点抗血管生成药物，已在国内获批用于三线及以上治疗[97]。

4) 晚期/转移性肺外神经内分泌癌(NEC)

肺外转移性高级别 NEC (包括 SCNEC 和 LCNEC)的一线治疗推荐 EP/EC 方案，或基于 Ki-67 指数分层选择：Ki-67 ≥ 55%者优先采用铂类方案，Ki-67 < 55%者则考虑替莫唑胺(TMZ)为基础的方案[98]-[101]。一线治疗进展后，二线可选 CAPTEM、伊立替康或奥沙利铂联合方案(如 FOLFOX/XELOX)，联合贝伐珠单抗可能增强疗效[102]-[104]。特殊分子特征患者(如 dMMR/MSI-H)可从免疫检查点抑制剂(ICIs)单药治疗中获益[105]。对于多线治疗失败的难治性病例，可尝试 ICIs 联合治疗(如纳武利尤单抗 + 伊匹木单抗)或联合抗血管生成酪氨酸激酶抑制剂(TKIs) [38] [106]-[109]。需强调，所有晚期 NEC 患者初始治疗前应经多学科团队(MDT)评估局部干预的必要性。

2.4. 放射性核素治疗

基于分子靶向的放射性配体疗法(PRRT)与常规核素治疗构成神经内分泌肿瘤(NENs)的重要治疗体

系。PRRT 通过将放射性同位素与生长抑素类似物(SSAs)共价结合，利用肿瘤细胞表面过表达的生长抑素受体(SSTR)实现精准辐射传递，通过电离辐射诱导 DNA 双链断裂发挥抗肿瘤效应[110]-[112]。该疗法尤其适用于高分化神经内分泌肿瘤(NETs)，因其普遍呈现 SSTR 高表达特征。临床实践中，177Lu 标记的 DOTATATE 因具备更优的辐射能量分布及较低的肾脏辐射吸收剂量，已逐步取代 90Y 成为主流治疗核素[111]。

经 FDA 及 EMA 批准，177Lu-DOTATATE 目前被确立为 SSTR 阳性胃肠胰神经内分泌肿瘤(GEP-NETs)的标准治疗方案。关键性 NETTER-1 研究证实，在转移性高分化(G1/G2)中肠 NET 患者中，联合标准剂量奥曲肽(30 mg/4 周)可使中位无进展生存期(PFS)显著延长至 28.4 个月(对照组 8.5 个月)，但总生存期(OS)未达统计学差异(48 vs 36 个月，P = 0.3) [113]。

扩展适应症研究显示，PRRT 在肺 NET 及多部位转移性 NET 中同样具有应用价值。回顾性队列分析(n = 443)表明，177Lu-DOTATATE 治疗可实现 39%的客观缓解率(ORR)及 82%的疾病控制率，中位 PFS 达 29 个月[114]。对于 SSTR 阳性的转移性副神经节瘤/嗜铬细胞瘤(PPGLs)，尽管 ORR 相对较低(7%~28%)，但疾病控制率可达 42%~100%，提示其在姑息治疗中的重要地位[115]。

安全性评估显示，PRRT 相关 3/4 级血液学毒性发生率较低(血小板减少 2%、淋巴细胞减少 9%)，在规范氨基酸肾保护方案下未观察到显著肾功能损害[111]。常规核素治疗中，131I-MIBG 通过模拟去甲肾上腺素转运机制靶向神经内分泌组织，在 MIBG 显像阳性的不可切除 PPGLs 中实现 30% ORR 及 82%疾病控制率，成为重要替代治疗方案[115]。

2.5. 免疫治疗

2.5.1. 免疫调节剂

对于难治性类癌综合征，可用干扰素(Interferon, IFN)作为免疫治疗联合 SSAs 作为二线治疗方案[49] [116]，一项经典临床研究 PROMID [117]证明联用干扰素及奥曲肽治疗组的无进展生存期显著优于对照组，但总生存期无显著差距。但由于其副作用显著，包括流感样症状、骨髓抑制、甲状腺功能异常。目前，依维莫司/舒尼替尼等靶向药物已取代 IFN 成为主流二线方案[45]。

2.5.2. 免疫检查点抑制剂

近年来，免疫检查点抑制剂(ICIs)作为靶向 PD-1/PD-L1 通路的创新疗法，已在多种实体瘤治疗中展现出差异化临床响应特征[118] [119]。然而在神经内分泌肿瘤(NENs)领域，除 Merkel 细胞癌(MCC)及小细胞肺癌(SCLC)外，其他亚型的免疫治疗仍处于探索阶段。现有临床研究数据显示，PD-1/PD-L1 抑制剂在多数 NENs 中总体有效率偏低[120] [121]，因此目前仅推荐用于经多线系统治疗失败且存在特定分子特征(如微卫星高度不稳定/MSI-H、错配修复缺陷/dMMR 或高肿瘤突变负荷)的晚期病例。

MCC 的免疫治疗机制具有独特生物学基础：紫外线暴露相关亚型呈现高肿瘤突变负荷及显著 CD8+ T 细胞浸润特征，而 MCPyV 病毒相关亚型则表现为 PD-L1 高表达伴免疫细胞浸润增强[122]。这种“免疫热肿瘤”特性使其成为 ICIs 的理想治疗靶点。临床研究数据显示，纳武利尤单抗与帕博利珠单抗等 PD-1 抑制剂在转移性 MCC 中展现出 33%~68%的 ORR，其中完全缓解率可达 11.4%~30.0% [123]-[125]。基于当前证据，虽缺乏III期临床试验数据支持，NCCN 指南仍将 ICIs 列为晚期 MCC 的一线治疗方案。此外，术后辅助治疗领域的研究表明，根治性切除后应用纳武利尤单抗可显著改善无病生存(DFS)，较观察组复发风险降低[37]。

在垂体神经内分泌肿瘤(PitNETs)治疗领域，小样本回顾性研究提示替莫唑胺(TMZ)耐药后，库欣病及泌乳素瘤患者接受 ICIs 治疗可能获得 50%的疾病控制率，推测与 TMZ 诱导的基因组不稳定性增加相关[82]。鉴于该病种罕见性导致的临床研究局限性，目前推荐 ICIs 作为挽救治疗方案用于经 TMZ 治疗失

败的进展期病例。值得注意的是，上述结论仍需通过多中心协作研究进一步验证。

2.5.3. 免疫治疗困境

现有证据显示 PD-1 单抗在 G3 神经内分泌癌中的客观缓解率仅约 3.7%，免疫相关不良事件达 75.5% [126]，且存在超进展风险。在一项双免疗法前瞻研究中，研究结果提示度伐利尤单抗联合曲美木单抗在神经内分泌肿瘤一线治疗失败患者中获益有限[121]。

而免疫联合化疗则有所获益，2022 年的一项 III 期临床研究探索了 PD-1 抗体斯鲁利单抗联合 EC 方案一线治疗进展期 SCLC 的疗效，结果中位 OS (15.4 月 vs 10.9 月)与 PFS (5.7 月 vs 4.3 月)有统计学差异[91]。提示联合治疗策略优化对于 NENs 的治疗有获益。

3. 放射治疗

3.1. 头颈部肿瘤的放疗

头颈部小细胞神经内分泌癌(SCNEC)作为头颈部恶性肿瘤的特殊亚型，其发病率较低，但具有显著侵袭性生物学特征。流行病学数据显示超过 80%的病例在初诊时已进展至局部晚期(III~IV期)，相较于头颈部鳞状细胞癌，该病种表现出更差的临床转归[127] [128]。针对局部进展期病例的多中心研究指出，多模式治疗策略(手术结合放化疗)相较于单纯化放疗方案未能显著改善患者预后指标，这一发现提示同步放化疗可能构成此类患者的标准治疗选择[129]。对于已发生远处转移的晚期病例，系统性化疗仍为治疗基石，现有证据表明增加局部放射治疗并未能有效提升 OS 获益[129]。

头颈部副神经节瘤(PGLs)的放射治疗主要适用于解剖结构复杂(如颈动脉体瘤)或存在手术禁忌(如颅内延伸病灶)的特殊病例[130]。临床数据显示常规分割放疗的客观缓解率维持在 20%~30%区间，而立体定向消融放疗(SABR)通过精准剂量投照(20~25 Gy/3~5 次或单次 12~15 Gy)可显著提升局部控制率至 90%~100%，同时使 80%患者的肿瘤相关临床症状获得显著改善[131] [132]。

3.2. 垂体神经内分泌肿瘤(PitNETs)的放疗

垂体神经内分泌肿瘤(PitNETs)的放疗策略需建立在多学科诊疗基础上。当患者对药物干预及外科干预产生抵抗时，放射治疗可作为有效干预手段[133]。近年来立体定向放射外科技术(SRS)的临床应用显示，与传统分割放疗相比，SRS 在激素活性肿瘤的控制效率方面具有优势，同时能显著降低放射性视神经病变等并发症发生率[134]。长期随访数据显示放疗后 4 年病灶控制率可维持在 88%~97%区间[135]，但需关注其导致的迟发性内分泌功能障碍，特别是 5 年内继发性垂体功能不全发生率可达 20% [136]。对于术后影像学评估存在明确肿瘤残留的病例，辅助性放疗可显著降低局部复发风险，因此被推荐为标准化辅助治疗方案[137]。

3.3. 胸部神经内分泌肿瘤的放疗

小细胞肺癌(SCLC)作为高级别神经内分泌癌的代表性病种，其放射治疗方案需依据疾病分期进行分层管理。局限期病例接受胸部放疗联合预防性脑照射(PCI)可获得显著生存获益，5 年生存率提升具有临床意义[42]。剂量优化研究指出，采用大分割模式(60 Gy/40 次)可进一步提升局部控制效率[138]。对于化疗敏感的广泛期病例，原发灶巩固放疗联合 PCI 可改善 OS [139]。在肺大细胞神经内分泌癌(LCNEC)治疗领域，I~II期病例根治术后辅助放疗的生存获益证据不足，而III期病例实施手术联合放疗可显著改善预后[140]。针对支气管肺及胸腺类癌(AC)术后管理，NCDB 队列分析显示完整切除术后辅助治疗(放化疗)未能提高生存指标[141]，但对于切缘阳性或存在纵隔淋巴结转移的高危病例，推荐采用多模式辅助治疗[142] [143]。

3.4. 泌尿生殖系统神经内分泌癌的放疗

膀胱小细胞神经内分泌癌具有高度恶性特征，临床实践指南强调需采用手术切除联合放化疗的综合治疗方案以提高生存获益[144]-[146]。宫颈小细胞神经内分泌癌的生物学行为显著区别于鳞癌，早期病例推荐根治性手术联合术后辅助化疗或同步放化疗，晚期病例则需通过同步放化疗实现OS延长[147]-[150]。值得注意的是，该病种不同分期的治疗反应差异提示需建立基于分子分型的个体化放疗方案。

3.5. 皮肤 Merkel 细胞癌(MCC)的放疗

该高侵袭性皮肤神经内分泌癌具有显著的局部复发倾向，文献报道术后局部复发风险可达 40% [151]。放射敏感性分析显示，MCC 对放射线具有良好的生物学响应特征。临床实践指南建议，对于接受局部扩大切除术(切缘 ≥ 1 cm)的患者，联合辅助放疗可显著改善总体生存预后[152]。针对淋巴结转移风险(约 33%病例)，区域性淋巴结放射治疗(包括淋巴引流区清扫术后补充放疗)可有效降低复发相关死亡风险，尤其在存在多发性淋巴结转移或大体积转移灶(直径 > 3 cm)的高危群体中具有重要治疗价值[153]。

3.6. 其他神经内分泌肿瘤的放疗

在晚期神经内分泌肿瘤综合治疗体系中，放射治疗主要发挥局部病灶控制和症状缓解的双重作用。临床决策需基于多维度评估，包括肿瘤负荷分布、组织学分级及分子特征等生物学指标。

4. 心理干预

心理社会因素在肿瘤发生演进及预后调控中具有明确的病理生理学意义，有一项纳入了 198 项研究的荟萃分析指出心理干预对情绪困扰的肿瘤患者的生活质量有显著的、小到中等的影响[154]。也有研究提出心理社会干预通过神经内分泌–免疫通路(如下调皮质醇、提升 NK 细胞活性)影响肿瘤生物学行为的机制[155]。临床观察显示，肿瘤患者在诊断、治疗及康复各阶段均可出现多维度的心理应激反应，这要求临床工作者建立覆盖全病程的动态筛查体系，精准识别患者特异的心理社会需求并实施分层干预策略。国际权威指南(如 NCCN 痛苦管理指南)强调[156]，应在初诊时建立基线心理评估，并在治疗节点转换、疾病进展等关键阶段进行周期性再评估。值得注意的是，临床实践中需严格鉴别适应性心理反应(如情境性焦虑、预期性悲伤)与符合诊断标准的精神障碍(如广泛性焦虑症、重度抑郁发作)，后者常伴随治疗依从性下降、症状感知放大及不良预后风险增加，ESMO 指南明确指出此类患者群体需优先获得精神心理专科介入[157]。

肿瘤心理干预体系包含多层级支持方案：基础层面通过疾病认知重构及适应性技能训练增强患者的自我管理能力；中层级干预采用认知行为疗法修正负性自动化思维，结合正念减压训练改善情绪调节功能；针对终末期等特殊情境，可实施意义中心疗法或尊严治疗等人本主义干预模式。社会支持网络的构建亦不可或缺，包括建立病友互助联盟、完善照护者教育体系、整合社区慈善资源等系统性工程。现代肿瘤诊疗强调将心理社会肿瘤学专家纳入多学科团队(MDT) [158]，通过生物–心理–社会–灵性多维评估模型，制定个体化整合照护方案，这不仅能优化患者生存质量，更有望通过心身交互机制影响疾病生物学进程，形成更具循证依据的精准医疗范式。

5. 结论

神经内分泌肿瘤(NENs)的临床管理因生物学异质性、诊断复杂性及治疗选择多样性面临严峻挑战。传统治疗模式以手术、化疗及生长抑素类似物为基础，但随着分子机制研究的深入，治疗策略已逐步转向靶向药物、核素治疗及多学科协作的个体化精准模式。未来需进一步解析驱动突变与肿瘤微环境特征，

推动新型生物标志物与跨机制联合疗法的开发，同时整合人工智能、液体活检等技术优化早期诊断与动态监测体系。尽管在免疫耐药性、长期毒性管理等方面仍存瓶颈，通过全球协作网络与创新临床试验设计，NENs 诊疗有望实现从“疾病控制”到“个体化治愈”的跨越，为患者提供更高效、安全的全程管理方案。

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