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甲状腺癌精准管理的范式转变

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摘　要

近年来，甲状腺癌发病率持续上升，而总体死亡率保持相对稳定，过度诊断与过度治疗问题逐渐凸显，促使其诊疗理念发生深刻转变。传统以手术和放射性碘为核心的“一刀切”模式，已难以同时满足惰性肿瘤精准降级管理与侵袭性、放射性碘难治性疾病强化治疗的双重需求。随着病理分类体系的更新、分子生物学研究的深入及系统治疗手段的发展，甲状腺癌正进入以分子特征和动态风险评估为导向的精准管理时代。本文系统综述了近年来甲状腺癌在病理分类与风险分层演进、诊断与初始管理策略转变，以及局部晚期和转移性疾病系统治疗方面的关键进展，重点讨论主动监测、分子诊断、再分化治疗、高选择性靶向治疗及免疫联合策略的临床价值与局限，并展望液体活检和多组学技术在未来管理中的潜在作用。总体而言，构建整合风险评估、治疗选择与随访调整的动态闭环管理模式，将是实现甲状腺癌精准全程管理的关键方向。

关键词

甲状腺癌，精准管理，风险分层，主动监测，靶向治疗

Paradigm Transformation of Precision Management of Thyroid Cancer

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Abstract

In recent years, the incidence of thyroid cancer has continued to rise, while overall mortality has remained relatively stable. This epidemiological paradox has highlighted the growing problem of overdiagnosis and overtreatment, driving a fundamental shift in diagnostic and therapeutic paradigms.

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Traditional “one-size-fits-all” strategies centered on surgery and radioactive iodine are increasingly inadequate to meet the dual clinical demands of de-escalated management for indolent tumors and intensified treatment for aggressive or radioactive iodine-refractory disease. With updates in pathological classification systems, advances in molecular biology, and the rapid development of systemic therapies, thyroid cancer management is entering an era of precision medicine guided by molecular features and dynamic risk assessment. This review systematically summarizes recent progress in pathological classification and risk stratification, evolving diagnostic and initial management strategies, and systemic treatment for locally advanced and metastatic thyroid cancer. Particular emphasis is placed on the clinical value and limitations of active surveillance, molecular diagnostics, redifferentiation therapy, highly selective targeted therapies, and immunotherapy-based combination strategies, as well as the emerging roles of liquid biopsy and multi-omics technologies. Overall, the development of a dynamic, closed-loop management model integrating risk assessment, treatment decision-making, and follow-up adjustment will represent the critical direction for achieving truly individualized and comprehensive precision management of thyroid cancer.

Keywords

Thyroid Cancer, Precision Management, Risk Stratification, Active Surveillance, Targeted Therapy

1. 引言

过去二十余年，甲状腺癌的全球发病率持续上升，已成为增长最快的实体肿瘤之一[1]。多国癌症登记数据显示，这一趋势在亚洲尤为显著，我国甲状腺癌发病率亦呈持续攀升态势[2]。然而，与发病率快速增长形成鲜明对比的是，其总体死亡率长期保持相对稳定，未出现同步上升[3]。进一步分析发现，新增病例主要集中于分化型甲状腺癌，尤其是乳头状甲状腺癌(Papillary Thyroid Carcinoma, PTC)，其中微小乳头状癌(≤1 cm)所占比例逐年提高[4]。这一“发病率上升–死亡率稳定”的流行病学悖论，被普遍认为与影像学技术进步、体检普及和筛查强度增加密切相关，而非真实肿瘤生物学行为的整体恶化[3] [4]。由此，“过度诊断”逐渐成为甲状腺癌领域无法回避的核心议题，即大量生物学惰性肿瘤被提前发现并纳入治疗路径，给患者带来潜在的过度干预与长期负担。

长期以来，甲状腺癌的临床管理主要围绕手术切除及放射性碘(Radioactive Iodine, RAI)治疗展开，形成了以病理分型和肿瘤分期为核心的相对标准化治疗模式[5]。这一策略在改善总体生存率方面发挥了重要作用，但其局限性亦日益显现。一方面，对于占多数的低风险分化型甲状腺癌患者，常规全切或近全切联合 RAI 治疗，可能导致不必要的甲状腺功能终身替代、并发症风险增加及生活质量下降[6]。另一方面，对于局部晚期、转移性或 RAI 难治性甲状腺癌，传统治疗手段往往疗效有限，缺乏有效的系统治疗选择，尤其在低分化癌和未分化癌中，预后仍然不理想[7]。由此，传统“一刀切”式诊疗模式在同时应对惰性肿瘤与高度侵袭性肿瘤时，逐渐暴露出适配性不足的问题。

在上述背景下，甲状腺癌的诊疗理念正经历深刻转变。近年来，随着病理分类体系的更新(如世界卫生组织 2022 年第五版分类) [8]、分子生物学研究的深入以及系统治疗手段的快速发展，单纯依赖术后病理与解剖分期的静态决策模式已难以满足临床需求[9]。新的管理框架逐步强调分子特征、治疗反应及随访过程中的动态风险评估，将患者置于一个持续调整的精准管理体系之中[10]。

这一转变不仅推动了低风险甲状腺癌主动监测策略的兴起[11]，也为 RAI 难治性疾病的再分化治疗、靶向治疗及免疫治疗探索奠定了基础[12]。美国甲状腺协会等专业组织提出的风险分层与随访理念，亦反映出从“标准化治疗”向“个体化全程管理”的方向演进[13]。基于此，本文将系统回顾近年来甲状腺癌在风险评估、诊断策略及系统治疗方面的关键进展，探讨诊疗新范式形成的内在逻辑，并对未来发展方向进行展望。

2. 病理分类与风险分层：精准管理的结构性基础

2.1. 世界卫生组织 2022 年第五版病理分类的关键更新

病理分类体系是甲状腺癌诊疗决策的基础。2022 年世界卫生组织发布的第五版甲状腺肿瘤分类，在延续传统组织学分型的同时，进一步强化了对肿瘤生物学侵袭性的识别[14]。其中最重要的变化之一，是对高级别分化型甲状腺癌(High-Grade Differentiated Thyroid Carcinoma)和低分化甲状腺癌(Poorly Differentiated Thyroid Carcinoma, PDTC)的界定更加明确[15]。

新版分类强调，部分形态学上仍保留分化特征的肿瘤，若伴随高核分裂指数、坏死或明显侵袭行为，其临床生物学特性已明显不同于经典分化型甲状腺癌[16]。这一调整有助于解释临床实践中观察到的“形态温和但预后不良”的病例差异[17]，也提示单纯依赖组织学类型已不足以准确评估风险。

2.2. 美国甲状腺协会风险分层体系的演进与局限

在临床管理层面，美国甲状腺协会于 2015 年发布的风险分层体系，系统整合了肿瘤大小、局部侵犯、淋巴结及远处转移等因素，将患者分为低、中、高复发风险等级。该体系的核心思想在于以复发风险而非单纯生存作为管理目标，并据此指导手术范围、RAI 应用及随访强度[13]。

这一分层模式显著推动了甲状腺癌治疗的规范化，尤其在避免部分低风险患者过度治疗方面发挥了积极作用[18]。然而，其局限性亦逐渐显现。首先，ATA 风险分层主要基于术后病理与初始临床信息，具有明显的静态特征，难以反映肿瘤生物学行为在治疗和随访过程中的动态变化[19] [20]。其次，传统分层对分子异质性的考虑有限，无法解释同一风险等级患者间复发和进展差异显著的现象[21]。

2.3. 分子标志物驱动的动态风险评估模式

随着分子病理学的发展，BRAF、TERT 等驱动基因突变被证实在甲状腺癌侵袭性和预后评估中具有重要价值[22]。其中，BRAF V600E 突变在乳头状甲状腺癌中发生率较高，单独存在时对预后的影响相对有限[23]，但在部分研究中与局部侵袭、淋巴结转移及 RAI 不敏感性相关[24] [25]。相比之下，TERT 启动子突变虽发生率较低，却与复发、远处转移及死亡风险显著相关[26]。

更为重要的是，BRAF 与 TERT 的协同突变被认为代表了一类生物学行为更为激进的亚型，其预后明显劣于单一突变或野生型患者[27]。这一发现为解释传统风险分层中的异质性提供了分子层面的依据，也推动分子特征逐步进入临床风险评估体系[28]。

在实践中，分子标志物的价值不仅体现在初始风险判断，还体现在随访策略的动态调整中[19]。结合术后生化指标、影像学反应及分子特征的动态风险评估(Dynamic Risk Stratification)模式，正在逐渐取代单次分层的静态决策思维，使风险管理从“分组判断”转向“持续校正”[29] [30]。这一转变为主动监测、个体化随访以及系统治疗时机的精准选择提供了理论基础。

3. 诊断与初始管理策略的转变

3.1. 超声与 AI 辅助诊断：从经验判断到数据驱动

高分辨率超声长期以来是甲状腺结节评估的核心工具，但其诊断准确性在很大程度上依赖操作者经

验，尤其在滤泡性病变及侵袭性预测方面存在明显局限[31] [32]。近年来，深度学习与影像组学技术的引入，为甲状腺结节的客观化评估提供了新的可能[33]。基于大规模超声图像训练的卷积神经网络模型，已在结节良恶性鉴别中展现出与资深超声医师相当甚至更高的诊断性能[34]。

除良恶性判断外，AI 模型进一步拓展至侵袭性特征预测，如包膜外侵犯、淋巴结转移及高危分子亚型的间接识别[35] [36]。部分研究显示，将影像组学特征与临床参数相结合，可显著提高对中央区淋巴结转移的预测能力，从而优化术前决策[37]。然而，当前 AI 应用仍面临模型泛化能力不足、训练数据异质性大及真实世界验证有限等问题[38]。此外，不同中心设备差异和数据标准化不足，也限制了其广泛推广[39]。

在上述技术局限的背景下，AI 辅助诊断结果对临床决策的潜在影响亦需谨慎评估。假阳性判断可能导致生物学惰性的低风险结节被误判为高危，从而加剧过度诊断和不必要的手术干预；而假阴性结果则可能延误侵袭性病变的及时识别，影响初始治疗策略的制定。因此，在缺乏高质量前瞻性研究和真实世界循证证据支持的情况下，人工智能输出结果不宜作为独立决策依据，而应与超声医师的综合评估相结合。

3.2. Bethesda III/IV 结节的分子诊断突破

细针穿刺细胞学(FNA)不确定结节，尤其是 Bethesda III/IV 类结节，一直是甲状腺诊疗中的难点[40]。这类结节恶性风险中等但不确定[41]，传统处理策略往往倾向于诊断性手术，导致相当比例患者接受了事后证实为良性的切除[42]。近年来，多基因分子检测的应用为这一困境提供了新的解决方案。以 ThyroSeq、Afirma 为代表的分子检测平台，通过分析多基因突变、融合及表达特征，提高了对不确定结节良恶性的判别能力[43] [44]。多项前瞻性及真实世界研究表明，在特定人群中应用分子检测，可显著降低不必要的诊断性手术比例，同时维持较高的阴性预测值[45]。

然而，分子检测并非适用于所有患者。其高昂成本、检测可及性以及不同人群中预测性能差异，仍是临床实践中需要权衡的问题[46] [47]。此外，分子检测结果更多反映的是恶性风险概率，而非明确诊断，因此其价值应被视为风险评估工具，而非替代病理诊断的“金标准”[48]。如何在循证证据、经济负担与患者期望之间取得平衡，是分子诊断进一步推广所面临的现实挑战。

3.3. 低风险甲状腺癌的主动监测：理念与实践的转向

在过度诊断背景下，低风险分化型甲状腺癌的管理策略发生了最具代表性的转变——主动监测(Active Surveillance) [49]。大量来自日本及其他国家的长期随访研究显示，对于符合严格标准的低风险微小乳头状癌患者，选择密切观察而非即刻手术，其肿瘤进展率和远期结局均可接受，且不影响肿瘤相关生存[50] [51]。

主动监测的核心在于精准的人群选择与规范化随访。一般认为，肿瘤局限于甲状腺内、无淋巴结或远处转移、未累及重要结构的患者，更适合该策略[52]。随访过程中，超声检查是主要评估手段，肿瘤直径增长及新发淋巴结转移是触发干预的重要依据[50] [53]。

然而，主动监测的实施不仅是医学问题，更涉及患者心理接受度与医患共同决策[54]。部分患者对“带瘤生存”存在焦虑，可能影响长期依从性[55]。此外，随着分子病理研究的深入，是否应将高危分子特征作为主动监测的排除条件，仍存在争议[56]。目前证据尚不足以支持单纯依据分子突变否定主动监测，但其在风险再评估中的潜在价值值得进一步探索[57]。

4. 局部晚期与转移性甲状腺癌的系统治疗进展

4.1. 放射性碘难治性分化型甲状腺癌的再分化治疗

分化型甲状腺癌(DTC)之所以总体预后良好，关键在于其保留了甲状腺特异性功能基因表达，尤其是钠/碘同向转运体(NIS)介导的碘摄取能力[58]。然而，部分患者在复发或转移过程中出现去分化，表现为

NIS 及相关碘代谢基因下调、RAI 摄取减少甚至消失，形成放射性碘难治(RAIR-DTC) [13] [59]。去分化过程与 MAPK 通路持续异常激活密切相关，例如 BRAF V600E 或上游/下游信号重编程可抑制甲状腺分化程序并降低 RAI 相关基因转录[60]；同时，PI3K/AKT/mTOR、表观遗传调控及肿瘤微环境亦可共同促成“功能缺失”的稳定状态[61] [62]。

再分化治疗的策略基于“解除 MAPK 过度激活–恢复分化基因表达–再给予 RAI”的逻辑，代表性探索包括 MEK 抑制剂或 BRAFi/MEKi 组合后进行碘显像与治疗。临床研究提示，部分患者在靶向短程干预后 RAI 摄取可恢复并获得肿瘤控制，尤其在具有特定通路依赖性的病例中更为明显。需要强调的是，再分化并非对所有 RAIR-DTC 有效：其获益与突变谱(如 BRAF、RAS 及融合基因)、既往 RAI 累积剂量、肿瘤负荷及代谢活跃程度相关[63] [64]；此外，恢复摄碘并不必然带来长期缓解，仍可能出现再次去分化或耐药克隆选择[65]。

4.2. 靶向治疗的迭代：从多靶点到高选择性

4.2.1. 多靶点 TKI：从“可用”到“更会用”

在 RAIR-DTC 的系统治疗中，多靶点 TKI 仍是临床最常用的基础方案[13]。索拉非尼与仑伐替尼通过抑制 VEGFR、PDGFR、RET 等多靶点，发挥抗血管生成与抑制肿瘤增殖作用，能显著延长无进展生存并改善疾病控制率[66]；国内也有安罗替尼等药物在真实世界或研究中用于相似人群管理[67]。此类药物的关键价值在于：当患者出现进行性病灶、症状负担或威胁器官功能时，能够提供相对稳定的“降速”效果，为后续序贯治疗争取时间[68]。

但多靶点 TKI 的核心矛盾在于“有效但不轻松”。高血压、蛋白尿、乏力、腹泻、体重下降、手足综合征等不良反应常见，且长期治疗的耐受性直接决定疗效能否兑现[66] [69]。近年来临床共识更强调剂量管理与毒性预防前置：例如治疗前评估心血管风险并优化降压方案，随访中动态调整剂量，必要时短暂停药再恢复；对皮肤/黏膜毒性与营养问题尽早干预，以减少因不良反应导致的非计划停药[70] [71]。

此外，序贯治疗的策略逐渐受到重视：并非所有影像学进展都需立即换药，更应结合进展速度、病灶部位(如骨/脑)、症状与生活质量综合判断[72] [73]；局部进展可考虑局部消融、放疗或手术与 TKI 联合，以延长同一线治疗的获益窗口[74] [75]。

4.2.2. 高选择性抑制剂：分子分型驱动的范式级改变

随着分子检测普及，高选择性抑制剂正在重塑进展期甲状腺癌的治疗逻辑。RET 改变在甲状腺髓样癌(MTC)中以突变为主，在部分 PTC 中以融合为主[76]；高选择性 RET 抑制剂(如塞普替尼、普拉替尼)在相应人群中可获得更深、更持久的缓解，并通常具有更好的靶向特异性与耐受性，使“以突变选药”在甲状腺癌中真正落地[77] [78]。

NTRK 融合虽在甲状腺癌中比例不高，却是典型的“组织无关靶点”[79]。拉罗替尼与恩曲替尼等 NTRK 抑制剂在融合阳性患者中常可实现快速而显著的肿瘤缩小，提示对罕见驱动事件的识别能带来极高的治疗回报[80] [81]。

在侵袭性最强的未分化甲状腺癌(ATC)中，BRAF V600E 是最具可操作性的靶点之一[82]。BRAFi/MEKi 联合(如达拉非尼 + 曲美替尼)在 BRAF 突变 ATC 中显示出快速起效的特点，部分患者可在短期内改善压迫症状、获得手术或放疗窗口，从而改变传统 ATC“无药可用、进展迅速”的被动局面[83]。在部分进展期 PTC 中，BRAF/MEK 抑制亦可作为序贯或桥接方案探索[84]。

需要注意的是，高选择性靶向药并非“一劳永逸”。耐药机制(旁路激活、二次突变、表型转化等)仍会导致复发[85]；因此，治疗前的分子分型应尽可能完整(突变 + 融合)，治疗过程中需关注耐药线索并

考虑再次活检或液体活检以指导后续序贯[86]。

4.3. 免疫治疗及联合策略的探索

与黑色素瘤或肺癌相比，分化型甲状腺癌总体免疫原性较低，肿瘤突变负荷通常不高，免疫浸润与抗原呈递能力差异较大，这些因素共同导致 PD-1/PD-L1 抑制剂在多数 DTC 中单药响应有限[87] [88]。即便在更具侵袭性的 PDTC/ATC 中，免疫治疗单药也常呈现“少数获益、总体不稳”的特征，其背后与免疫抑制性微环境(Treg、TAM、免疫排斥型浸润)及促血管生成状态密切相关[89] [90]。

因此，联合策略成为研究重点，最典型的是“靶向 + 免疫”。多靶点 TKI 通过抑制 VEGF 轴可改善异常血管、降低免疫抑制细胞募集并提升 T 细胞进入肿瘤的机会，为免疫治疗提供“进入场地”的条件；免疫检查点抑制剂则可能将这种微环境改善转化为真实抗肿瘤效应[91] [92]。一些研究探索了仑伐替尼联合帕博利珠单抗等方案在进展期患者中的潜在活性，但其毒性管理更为复杂[93]：免疫相关不良事件与 TKI 不良反应可能叠加，需更严格的监测与分级处理[94]。

未来免疫治疗能否在甲状腺癌中找到稳定定位，关键在于三点：其一，明确最可能获益的亚群(如 ATC、特定分子亚型或免疫炎症表型)；其二，建立可复现的生物标志物组合，而非仅依赖 PD-L1 单一指标；其三，优化联合序贯与剂量策略，在保证安全性的前提下提高反应深度与持续性。

Table 1. Summary of systemic treatment agents for advanced thyroid cancer
表 1. 晚期甲状腺癌系统治疗药物汇总表

药物类别	药物名称	试验名称	研究类型	研究对象	实验组/对照组(例)	ORR (%)	实验组中位 PFS (月)	主要不良反应
多靶点 TKI	索拉非尼	DECISION [66]	随机对照研究	RAI 难治 DTC	207/210	12.2	10.8	手足皮肤反应、腹泻、脱发、皮疹/脱屑、高血压
多靶点 TKI	仑伐替尼	SELECT [100]	随机对照研究	RAI 难治 DTC	261/133	64.8	18.3	高血压、腹泻、乏力/乏力样症状、食欲下降、体重下降、蛋白尿
高选择性 RET 抑制剂	塞普替尼	LIBRETTO-001 [101]	单臂研究	RET 突变/融合甲状腺癌	360	77.6~95.8	NR-41.4	高血压、转氨酶升高、QT 间期延长、腹泻
高选择性 RET 抑制剂	普拉替尼	ARROW [102]	单臂研究	RET 突变的甲状腺癌	175	55.7~90.9	NR-25.8	高血压、肝功能异常、血液学毒性、QT 间期延长、肺炎/肺炎样反应
高选择性靶向治疗	达拉非尼 + 曲美替尼	ROAR [82]	单臂、篮式研究	BRAF V600E 突变 ATC	36	56	6.7	发热、贫血、肺炎、低钠血症、乏力、食欲下降、皮疹
高选择性靶向治疗	拉罗替尼	NAVIGATE/SCOUT /NCT02122913 [103]	多中心单臂研究	TRK 融合阳性的甲状腺癌	29	71	NR	肌痛、乏力、头晕、ALT/AST 升高、贫血、淋巴细胞减少
多靶点 TKI + 免疫检查点抑制剂	仑伐替尼 + 帕博利珠单抗	[93]	回顾性单中心队列研究	局部晚期或转移性 ATC/PDTC 患者	8	75	17.6	高血压、乏力、体重下降/厌食、腹泻、口腔黏膜炎、蛋白尿、手足综合征、关节/肌肉疼痛

注：ORR 指客观缓解率；PFS 指无进展生存期；NR 指在既定随访时间内尚未达到中位无进展生存期；TKI 指酪氨酸激酶抑制剂；RAI 指放射性碘；DTC 指分化型甲状腺癌；ATC 指未分化甲状腺癌；PDTC 指低分化甲状腺癌。

4.4. 新兴治疗靶点与早期探索

除 RET、NTRK、BRAF 等成熟靶点外，进展期甲状腺癌仍存在显著未满足需求，尤其是缺乏可操作驱动事件或发生多线耐药的患者[95]。近年来，围绕表观遗传调控、PI3K/AKT/mTOR 轴、MET/ALK 等旁路信号的组合抑制，被用于解释与对抗耐药演化[96] [97]。另有靶向膜蛋白(如 CLDN18.2 等)或抗体偶联药物、细胞治疗等策略在部分实体瘤中快速推进，为甲状腺癌提供了可借鉴的研发路径[98] [99]，但目前多处于早期探索阶段，证据有限且适用亚群尚不清晰。为便于系统梳理目前晚期甲状腺癌中已获得关键临床证据的系统治疗方案，并为新兴治疗策略的探索提供参照，本研究对代表性多靶点 TKI、高选择性分子靶向药物及部分联合治疗方案进行了汇总(表 1)。

5. 新技术与未来方向：迈向动态、闭环的精准管理

5.1. 液体活检与 ctDNA：从结果评估到过程监测

液体活检，尤其是循环肿瘤 DNA (Circulating Tumor DNA, ctDNA)的发展，为甲状腺癌的动态监测提供了新的技术路径[104]。相较于传统影像学与血清学指标，ctDNA 能够更直接反映肿瘤分子层面的变化，为疗效评估与耐药识别提供潜在的前瞻性信号[105]。在局部晚期或转移性甲状腺癌中，ctDNA 水平的变化与肿瘤负荷、治疗反应之间呈一定相关性，其动态下降往往提示治疗有效，而持续升高或再次出现则可能预示疾病进展[106] [107]。

更重要的是，ctDNA 使耐药突变的早期发现成为可能[108]。对于接受靶向治疗的患者，二次突变或旁路激活常先于影像学进展出现，液体活检有望在临床症状或影像改变之前捕捉分子演化线索，从而为治疗调整争取时间[106] [109]。然而，ctDNA 在分化型甲状腺癌中的灵敏度仍受肿瘤负荷及生物学特性限制，其临床应用亟需标准化检测流程与阈值界定[110]。

尽管 ctDNA 为甲状腺癌的动态监测和耐药识别提供了新的技术路径，但其临床应用仍存在明显局限。分化型甲状腺癌通常具有肿瘤负荷较低、DNA 释放量有限等生物学特征，使 ctDNA 的检测灵敏度在部分患者中受到制约，阴性结果并不能可靠排除疾病活动[111]。此外，不同检测平台在基因覆盖范围、分析阈值及结果解读标准方面尚未实现统一，限制了 ctDNA 数据在多中心及真实世界环境中的可比性[112]。在缺乏明确阈值界定和前瞻性验证的情况下，单纯依据 ctDNA 变化调整治疗方案，可能导致过早换药或延误必要干预。因此，当前 ctDNA 更适合与影像学评估、血清学指标及临床表现相结合，用于风险再评估和治疗反应监测，而非作为独立指导系统治疗决策的依据[112] [113]。

5.2. 单细胞与空间多组学：重新认识异质性与去分化

单细胞测序与空间多组学技术的引入，使甲状腺癌研究从“平均信号”迈向“细胞层级解析”[114]。相关研究揭示，即便在同一病理类型中，肿瘤细胞亦呈现显著的转录和功能异质性，不同亚群在分化状态、代谢特征及免疫调控能力上存在差异[115] [116]。这一发现为解释临床上观察到的治疗反应不均与耐药演化提供了新的生物学基础。

在去分化与 RAI 难治过程中，单细胞分析显示部分细胞群逐渐丧失甲状腺特异性基因表达，同时获得更强的侵袭性和存活优势[115] [117]；而空间多组学进一步揭示，肿瘤细胞与免疫细胞、成纤维细胞之间的空间关系，可能决定局部免疫抑制与治疗敏感性[118] [119]。这些技术不仅拓展了对疾病机制的理解，也为未来精准靶点的发现提供了重要线索。

5.3. “整合式展望”迈向动态闭环的甲状腺癌管理模式

综合来看，新技术的真正价值不在于替代既有工具，而在于推动甲状腺癌管理模式的整体升级。未

来的精准管理将不再是基于单次病理或初始分层的静态决策，而是整合分子特征、治疗反应与随访数据的动态闭环过程。在这一框架下，风险评估、治疗选择与随访策略彼此联动，可根据疾病演化不断调整管理路径。

从阶段性治疗转向全程管理，意味着对过度治疗与治疗不足的双重规避：低风险患者可在安全前提下减少干预，而高风险或进展性患者则能更早获得合适的系统治疗。如何将液体活检、多组学数据与临床决策有效融合，并在真实世界中验证其可行性，将是未来甲状腺癌研究与实践面临的关键任务。

6. 结论

总体而言，甲状腺癌的诊疗已从以手术和放射性碘为核心的标准化模式，迈入以分子特征和动态风险评估为导向的精准管理时代。随着病理分类体系的更新、风险分层理念的演进以及系统治疗手段的丰富，临床决策正逐步摆脱“一刀切”的思维，转向更符合肿瘤生物学本质的个体化路径。

当前已形成若干共识性进展：其一，低风险分化型甲状腺癌并非均需即刻干预，主动监测在严格筛选人群中具有安全性与可行性；其二，分子分型在指导系统治疗选择方面的价值日益凸显，高选择性靶向抑制剂正在重塑局部晚期和转移性疾病的治疗格局；其三，系统治疗的目标已从单纯延缓进展，逐步扩展至长期疾病控制与生活质量优化。

然而，甲状腺癌管理仍面临诸多挑战，包括去分化与耐药机制尚未完全阐明、免疫治疗获益人群有限以及新技术在真实世界中的转化障碍等。未来研究需聚焦于整合分子标志物、治疗反应与随访数据，构建动态、闭环的管理体系，以在降低过度治疗的同时，提升高风险患者的长期获益，最终实现真正意义上的精准全程管理。

参考文献

[1] Davies, L., Morris, L.G.T., Haymart, M., Chen, A.Y., Goldenberg, D., Morris, J., *et al*. (2015) American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: The Increasing Incidence of Thyroid Cancer. *Endocrine Practice*, **21**, 686-696. https://doi.org/10.4158/ep14466.dscr

[2] Gong, Y., Jiang, Q., Zhai, M., Tang, T. and Liu, S. (2024) Thyroid Cancer Trends in China and Its Comparative Analysis with G20 Countries: Projections for 2020-2040. *Journal of Global Health*, **14**, Article 04131. https://doi.org/10.7189/jogh.14.04131

[3] Vaccarella, S., Franceschi, S., Bray, F., Wild, C.P., Plummer, M. and Dal Maso, L. (2016) Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. *New England Journal of Medicine*, **375**, 614-617. https://doi.org/10.1056/nejmp1604412

[4] Li, M., Maso, L.D. and Vaccarella, S. (2020) Global Trends in Thyroid Cancer Incidence and the Impact of Overdiagnosis. *The Lancet Diabetes & Endocrinology*, **8**, 468-470. https://doi.org/10.1016/s2213-8587(20)30115-7

[5] Mihailović, J. (2025) Evolving Paradigm in Radioactive Iodine Therapy for Differentiated Thyroid Cancer: Historical Perspectives, Current Practices and Future Directions. *Diagnostics*, **15**, Article 1438. https://doi.org/10.3390/diagnostics15111438

[6] Ullmann, T.M., Papaleontiou, M. and Sosa, J.A. (2022) Current Controversies in Low-Risk Differentiated Thyroid Cancer: Reducing Over-Treatment in an Era of Overdiagnosis. *The Journal of Clinical Endocrinology & Metabolism*, **108**, 271-280. https://doi.org/10.1210/clinem/dgac646

[7] Chen, D.W., Lang, B.H.H., McLeod, D.S.A., Newbold, K. and Haymart, M.R. (2023) Thyroid Cancer. *The Lancet*, **401**, 1531-1544. https://doi.org/10.1016/s0140-6736(23)00020-x

[8] Basolo, F., Macerola, E., Poma, A.M. and Torregrossa, L. (2023) The 5th Edition of WHO Classification of Tumors of Endocrine Organs: Changes in the Diagnosis of Follicular-Derived Thyroid Carcinoma. *Endocrine*, **80**, 470-476. https://doi.org/10.1007/s12020-023-03336-4

[9] Tuttle, R.M. and Alzahrani, A.S. (2019) Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-Up. *The Journal of Clinical Endocrinology & Metabolism*, **104**, 4087-4100. https://doi.org/10.1210/jc.2019-00177

[10] Giannoula, E., Melidis, C., Papadopoulos, N., Bamidis, P., Raftopoulos, V. and Iakovou, I. (2020) Dynamic Risk Stratification for Predicting Treatment Response in Differentiated Thyroid Cancer. *Journal of Clinical Medicine*, **9**, Article 2708. https://doi.org/10.3390/jcm9092708

[11] Sugitani, I. (2023) Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma. *Best Practice & Research Clinical Endocrinology & Metabolism*, **37**, Article 101630. https://doi.org/10.1016/j.beem.2022.101630

[12] Ho, A.L., Grewal, R.K., Leboeuf, R., Sherman, E.J., Pfister, D.G., Deandreis, D., *et al*. (2013) Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer. *New England Journal of Medicine*, **368**, 623-632. https://doi.org/10.1056/nejmoa1209288

[13] Haugen, B.R., Alexander, E.K., Bible, K.C., Doherty, G.M., Mandel, S.J., Nikiforov, Y.E., *et al*. (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*, **26**, 1-133. https://doi.org/10.1089/thy.2015.0020

[14] Christofer Juhlin, C., Mete, O. and Baloch, Z.W. (2023) The 2022 WHO Classification of Thyroid Tumors: Novel Concepts in Nomenclature and Grading. *Endocrine-Related Cancer*, **30**, e220293. https://doi.org/10.1530/erc-22-0293

[15] Jung, C.K., Bychkov, A. and Kakudo, K. (2022) Update from the 2022 World Health Organization Classification of Thyroid Tumors: A Standardized Diagnostic Approach. *Endocrinology and Metabolism*, **37**, 703-718. https://doi.org/10.3803/enm.2022.1553

[16] Harahap, A.S., Roren, R.S. and Imtiyaz, S. (2024) A Comprehensive Review and Insights into the New Entity of Differentiated High-Grade Thyroid Carcinoma. *Current Oncology*, **31**, 3311-3328. https://doi.org/10.3390/curroncol31060252

[17] Chatterjee, S., Mair, M., Shaha, A.R., Paleri, V., Sawhney, S., Mishra, A., *et al*. (2024) Current Evidences in Poorly Differentiated Thyroid Carcinoma: A Systematic Review and Subsection Meta-Analysis for Clinical Decision Making. *Endocrine*, **85**, 509-519. https://doi.org/10.1007/s12020-024-03771-x

[18] Wu, J., Hu, X.Y., Ghaznavi, S., Kinnear, S., Symonds, C.J., Grundy, P., *et al*. (2022) The Prospective Implementation of the 2015 ATA Guidelines and Modified ATA Recurrence Risk Stratification System for Treatment of Differentiated Thyroid Cancer in a Canadian Tertiary Care Referral Setting. *Thyroid*, **32**, 1509-1518. https://doi.org/10.1089/thy.2022.0055

[19] Pitoia, F. and Jerkovich, F. (2019) Dynamic Risk Assessment in Patients with Differentiated Thyroid Cancer. *Endocrine-Related Cancer*, **26**, R553-R566. https://doi.org/10.1530/erc-19-0213

[20] Tuttle, R.M., Tala, H., Shah, J., Leboeuf, R., Ghossein, R., Gonen, M., *et al*. (2010) Estimating Risk of Recurrence in Differentiated Thyroid Cancer after Total Thyroidectomy and Radioactive Iodine Remnant Ablation: Using Response to Therapy Variables to Modify the Initial Risk Estimates Predicted by the New American Thyroid Association Staging System. *Thyroid*, **20**, 1341-1349. https://doi.org/10.1089/thy.2010.0178

[21] Wang, B., Cen, X., Zhang, B. and Zhang, W. (2025) The Effect of BRAFV600E Mutation on Radioiodine Therapy in Patients with Papillary Thyroid Carcinoma: A Meta-Analysis and Systematic Review. *Frontiers in Endocrinology*, **16**, Article ID: 1665545. https://doi.org/10.3389/fendo.2025.1665545

[22] Vuong, H.G., Duong, U.N.P., Altibi, A.M.A., Ngo, H.T.T., Pham, T.Q., Tran, H.M., *et al*. (2017) A Meta-Analysis of Prognostic Roles of Molecular Markers in Papillary Thyroid Carcinoma. *Endocrine Connections*, **6**, R8-R17. https://doi.org/10.1530/ec-17-0010

[23] Czarniecka, A., Oczko-Wojciechowska, M. and Barczyński, M. (2016) BRAF V600E Mutation in Prognostication of Papillary Thyroid Cancer (PTC) Recurrence. *Gland Surgery*, **5**, 495-505. https://doi.org/10.21037/gs.2016.09.09

[24] Anekpuritanang, T., Uataya, M., Claimon, A., Laokulrath, N., Pongsapich, W. and Pithuksurachai, P. (2021) The Association between Radioiodine Refractory in Papillary Thyroid Carcinoma, Sodium/Iodide Symporter Expression, and BRAFV600E Mutation. *OncoTargets and Therapy*, **14**, 3959-3969. https://doi.org/10.2147/ott.s308910

[25] Sun, D., Zhang, X., Jin, X., Shi, C., Sun, Y., Zhang, Y., *et al*. (2025) BRAFV600E Mutation Is Associated with Better Prognoses in Radioactive Iodine Refractory Thyroid Cancer Patients Treated with Multi-Kinase Inhibitors: A Retrospective Analysis of Registered Clinical Trials. *Thyroid Research*, **18**, Article No. 5. https://doi.org/10.1186/s13044-025-00223-0

[26] Liu, C., Liu, Z., Chen, T., Zeng, W., Guo, Y. and Huang, T. (2016) TERT Promoter Mutation and Its Association with Clinicopathological Features and Prognosis of Papillary Thyroid Cancer: A Meta-Analysis. *Scientific Reports*, **6**, Article No. 36990. https://doi.org/10.1038/srep36990

[27] Xing, M., Liu, R., Liu, X., Murugan, A.K., Zhu, G., Zeiger, M.A., *et al*. (2014) *BRAF* V600E and *TERT* Promoter Mutations Cooperatively Identify the Most Aggressive Papillary Thyroid Cancer with Highest Recurrence. *Journal of Clinical Oncology*, **32**, 2718-2726. https://doi.org/10.1200/jco.2014.55.5094

[28] Nylén, C., Mechera, R., Maréchal-Ross, I., Tsang, V., Chou, A., Gill, A.J., *et al*. (2020) Molecular Markers Guiding Thyroid Cancer Management. *Cancers*, **12**, Article 2164. https://doi.org/10.3390/cancers12082164

[29] Cano-Palomares, A., Castells, I., Capel, I., Bella, M.R., Barcons, S., Serrano, A., *et al*. (2014) Response to Initial Therapy of Differentiated Thyroid Cancer Predicts the Long-Term Outcome Better than Classical Risk Stratification Systems. *International Journal of Endocrinology*, **2014**, Article ID: 591285. https://doi.org/10.1155/2014/591285

[30] van Velsen, E.F.S., Stegenga, M.T., van Kemenade, F.J., Kam, B.L.R., van Ginhoven, T.M., Visser, W.E., *et al*. (2019) Evaluating the 2015 American Thyroid Association Risk Stratification System in High-Risk Papillary and Follicular Thyroid Cancer Patients. *Thyroid*, **29**, 1073-1079. https://doi.org/10.1089/thy.2019.0053

[31] Brito, J.P., Gionfriddo, M.R., Al Nofal, A., Boehmer, K.R., Leppin, A.L., Reading, C., *et al*. (2014) The Accuracy of Thyroid Nodule Ultrasound to Predict Thyroid Cancer: Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology & Metabolism*, **99**, 1253-1263. https://doi.org/10.1210/jc.2013-2928

[32] Yang, J., Luo, Z., Wen, Y. and Zhang, J. (2025) Artificial Intelligence-Enhanced Ultrasound Imaging for Thyroid Nodule Detection and Malignancy Classification: A Study on YOLOv11. *Quantitative Imaging in Medicine and Surgery*, **15**, 7964-7976. https://doi.org/10.21037/qims-2025-257

[33] Liang, J., Huang, X., Hu, H., Liu, Y., Zhou, Q., Cao, Q., *et al*. (2018) Predicting Malignancy in Thyroid Nodules: Radiomics Score versus 2017 American College of Radiology Thyroid Imaging, Reporting and Data System. *Thyroid*, **28**, 1024-1033. https://doi.org/10.1089/thy.2017.0525

[34] Park, V.Y., Han, K., Seong, Y.K., Park, M.H., Kim, E., Moon, H.J., *et al*. (2019) Diagnosis of Thyroid Nodules: Performance of a Deep Learning Convolutional Neural Network Model Vs. Radiologists. *Scientific Reports*, **9**, Article No. 17843. https://doi.org/10.1038/s41598-019-54434-1

[35] Qi, Q., Huang, X., Zhang, Y., Cai, S., Liu, Z., Qiu, T., *et al*. (2023) Ultrasound Image-Based Deep Learning to Assist in Diagnosing Gross Extrathyroidal Extension Thyroid Cancer: A Retrospective Multicenter Study. *eClinicalMedicine*, **58**, Article 101905. https://doi.org/10.1016/j.eclinm.2023.101905

[36] Shi, Y., Zou, Y., Liu, J., Wang, Y., Chen, Y., Sun, F., *et al*. (2022) Ultrasound-Based Radiomics XGBoost Model to Assess the Risk of Central Cervical Lymph Node Metastasis in Patients with Papillary Thyroid Carcinoma: Individual Application of SHAP. *Frontiers in Oncology*, **12**, Article ID: 897596. https://doi.org/10.3389/fonc.2022.897596

[37] Zhang, M., Zhang, S., Wang, Y., Yu, Z., Yang, Z., Ma, H., *et al*. (2025) Prediction of Contralateral Central Lymph Node Metastasis in Unilateral Papillary Thyroid Carcinoma Based on Radiomics. *Scientific Reports*, **15**, Article No. 21948. https://doi.org/10.1038/s41598-025-04588-y

[38] Toro-Tobon, D., Loor-Torres, R., Duran, M., Fan, J.W., Singh Ospina, N., Wu, Y., *et al*. (2023) Artificial Intelligence in Thyroidology: A Narrative Review of the Current Applications, Associated Challenges, and Future Directions. *Thyroid*®, **33**, 903-917. https://doi.org/10.1089/thy.2023.0132

[39] Yu, J., Deng, Y., Liu, T., Zhou, J., Jia, X., Xiao, T., *et al*. (2020) Lymph Node Metastasis Prediction of Papillary Thyroid Carcinoma Based on Transfer Learning Radiomics. *Nature Communications*, **11**, Article No. 4807. https://doi.org/10.1038/s41467-020-18497-3

[40] Bongiovanni, M., Spitale, A., Faquin, W.C., Mazzucchelli, L. and Baloch, Z.W. (2012) The Bethesda System for Reporting Thyroid Cytopathology: A Meta-Analysis. *Acta Cytologica*, **56**, 333-339. https://doi.org/10.1159/000339959

[41] Hassan, I., Hassan, L., Balalaa, N., Askar, M., Alshehhi, H. and Almarzooqi, M. (2024) The Incidence of Thyroid Cancer in Bethesda III Thyroid Nodules: A Retrospective Analysis at a Single Endocrine Surgery Center. *Diagnostics*, **14**, Article 1026. https://doi.org/10.3390/diagnostics14101026

[42] Roy, M., Ghander, C., Bigorgne, C., Brière, M., Deniziaut, G., Ansart, F., *et al*. (2025) An Update on Management of Cytologically Indeterminate Thyroid Nodules. *Annales d'Endocrinologie*, **86**, Article 101711. https://doi.org/10.1016/j.ando.2025.101711

[43] Steward, D.L., Carty, S.E., Sippel, R.S., Yang, S.P., Sosa, J.A., Sipos, J.A., *et al*. (2019) Performance of a Multigene Genomic Classifier in Thyroid Nodules with Indeterminate Cytology: A Prospective Blinded Multicenter Study. *JAMA Oncology*, **5**, 204-212. https://doi.org/10.1001/jamaoncol.2018.4616

[44] Patel, K.N., Angell, T.E., Babiarz, J., Barth, N.M., Blevins, T., Duh, Q., *et al*. (2018) Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. *JAMA Surgery*, **153**, 817-824. https://doi.org/10.1001/jamasurg.2018.1153

[45] Kim, N.E., Raghunathan, R.S., Hughes, E.G., Longstaff, X.R., Tseng, C., Li, S., *et al*. (2023) Bethesda III and IV Thyroid Nodules Managed Nonoperatively after Molecular Testing with Afirma GSC or Thyroseq V3. *The Journal of Clinical Endocrinology & Metabolism*, **108**, e698-e703. https://doi.org/10.1210/clinem/dgad181

[46] Dharampal, N., Smith, K., Harvey, A., Paschke, R., Rudmik, L. and Chandarana, S. (2022) Cost-Effectiveness Analysis of Molecular Testing for Cytologically Indeterminate Thyroid Nodules. *Journal of Otolaryngology-Head & Neck Surgery*, **51**, Article No. 46. https://doi.org/10.1186/s40463-022-00604-7

[47] Lévesque, F., Payne, R.J., Beaudoin, D., Boucher, A., Fortier, P., Massicotte, M., *et al*. (2024) Publicly Funded Molecular Testing of Indeterminate Thyroid Nodules: Canada's Experience. *The Journal of Clinical Endocrinology & Metabolism*,

110, e1031-e1037. https://doi.org/10.1210/clinem/dgae355

[48] Patel, J., Klopper, J. and Cottrill, E.E. (2023) Molecular Diagnostics in the Evaluation of Thyroid Nodules: Current Use and Prospective Opportunities. *Frontiers in Endocrinology*, **14**, Article ID: 1101410. https://doi.org/10.3389/fendo.2023.1101410

[49] Ito, Y., Miyauchi, A., Fujishima, M., Yamamoto, M. and Sasaki, T. (2024) Active Surveillance for Adult Low-Risk Papillary Thyroid Microcarcinoma—A Review Focused on the 30-Year Experience of Kuma Hospital. *Endocrine Journal*, **71**, 7-21. https://doi.org/10.1507/endocrj.ej23-0395

[50] Miyauchi, A., Ito, Y., Fujishima, M., Miya, A., Onoda, N., Kihara, M., *et al*. (2023) Long-Term Outcomes of Active Surveillance and Immediate Surgery for Adult Patients with Low-Risk Papillary Thyroid Microcarcinoma: 30-Year Experience. *Thyroid*®, **33**, 817-825. https://doi.org/10.1089/thy.2023.0076

[51] Lee, E.K., Moon, J.H., Hwangbo, Y., Ryu, C.H., Cho, S.W., Choi, J.Y., *et al*. (2022) Progression of Low-Risk Papillary Thyroid Microcarcinoma during Active Surveillance: Interim Analysis of a Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma in Korea. *Thyroid*, **32**, 1328-1336. https://doi.org/10.1089/thy.2021.0614

[52] Miyauchi, A. (2016) Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. *World Journal of Surgery*, **40**, 516-522. https://doi.org/10.1007/s00268-015-3392-y

[53] Yamamoto, M., Miyauchi, A., Ito, Y., Fujishima, M., Sasaki, T. and Kudo, T. (2023) Active Surveillance Outcomes of Patients with Low-Risk Papillary Thyroid Microcarcinoma According to Levothyroxine Treatment Status. *Thyroid*®, **33**, 1182-1189. https://doi.org/10.1089/thy.2023.0046

[54] Sawka, A.M., Ghai, S., Rotstein, L., Irish, J.C., Pasternak, J.D., Gullane, P.J., *et al*. (2022) A Quantitative Analysis Examining Patients' Choice of Active Surveillance or Surgery for Managing Low-Risk Papillary Thyroid Cancer. *Thyroid*, **32**, 255-262. https://doi.org/10.1089/thy.2021.0485

[55] Nakamura, T., Miyauchi, A., Ito, Y., Ito, M., Kudo, T., Tanaka, M., *et al*. (2020) Quality of Life in Patients with Low-Risk Papillary Thyroid Microcarcinoma: Active Surveillance versus Immediate Surgery. *Endocrine Practice*, **26**, 1451-1457. https://doi.org/10.4158/ep-2020-0201

[56] Kim, K.J., Kim, S.G., Tan, J., Shen, X., Viola, D., Elisei, R., *et al*. (2020) BRAF V600E Status May Facilitate Decision-Making on Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma. *European Journal of Cancer*, **124**, 161-169. https://doi.org/10.1016/j.ejca.2019.10.017

[57] Xue, S., Wang, P., Hurst, Z.A., Chang, Y.S. and Chen, G. (2018) Active Surveillance for Papillary Thyroid Microcarcinoma: Challenges and Prospects. *Frontiers in Endocrinology*, **9**, Article ID: 736. https://doi.org/10.3389/fendo.2018.00736

[58] Chung, J., Youn, H.W., Kang, J.H., Lee, H.Y. and Kang, K.W. (2010) Sodium Iodide Symporter and the Radioiodine Treatment of Thyroid Carcinoma. *Nuclear Medicine and Molecular Imaging*, **44**, 4-14. https://doi.org/10.1007/s13139-009-0016-1

[59] Oh, J.M. and Ahn, B. (2021) Molecular Mechanisms of Radioactive Iodine Refractoriness in Differentiated Thyroid Cancer: Impaired Sodium Iodide Symporter (NIS) Expression Owing to Altered Signaling Pathway Activity and Intracellular Localization of Nis. *Theranostics*, **11**, 6251-6277. https://doi.org/10.7150/thno.57689

[60] Romei, C., Ciampi, R., Faviana, P., Agate, L., Molinaro, E., Bottici, V., *et al*. (2008) BRAFV600E Mutation, but Not RET/PTC Rearrangements, Is Correlated with a Lower Expression of Both Thyroperoxidase and Sodium Iodide Symporter Genes in Papillary Thyroid Cancer. *Endocrine Related Cancer*, **15**, 511-520. https://doi.org/10.1677/erc-07-0130

[61] Liu, J., Liu, Y., Lin, Y. and Liang, J. (2019) Radioactive Iodine-Refractory Differentiated Thyroid Cancer and Redifferentiation Therapy. *Endocrinology and Metabolism*, **34**, 215-225. https://doi.org/10.3803/enm.2019.34.3.215

[62] Zhang, Z., Liu, D., Murugan, A.K., Liu, Z. and Xing, M. (2013) Histone Deacetylation of NIS Promoter Underlies BRAF V600e-Promoted NIS Silencing in Thyroid Cancer. *Endocrine-Related Cancer*, **21**, 161-173. https://doi.org/10.1530/erc-13-0399

[63] Weber, M., Kersting, D., Riemann, B., Brandenburg, T., Führer-Sakel, D., Grünwald, F., *et al*. (2022) Enhancing Radioiodine Incorporation into Radioiodine-Refractory Thyroid Cancer with MAPK Inhibition (ERRITI): A Single-Center Prospective Two-Arm Study. *Clinical Cancer Research*, **28**, 4194-4202. https://doi.org/10.1158/1078-0432.ccr-22-0437

[64] Toro-Tobon, D., Morris, J.C., Hilger, C., Peskey, C., Durski, J.M. and Ryder, M. (2024) Clinical Outcomes of Radioactive Iodine Redifferentiation Therapy in Previously Iodine Refractory Differentiated Thyroid Cancers. *Thyroid*®, **34**, 70-81. https://doi.org/10.1089/thy.2023.0456

[65] Buffet, C., Wassermann, J., Hecht, F., Leenhardt, L., Dupuy, C., Groussin, L., *et al*. (2020) Redifferentiation of Radioiodine-Refractory Thyroid Cancers. *Endocrine-Related Cancer*, **27**, R113-R132. https://doi.org/10.1530/erc-19-0491

[66] Brose, M.S., Nutting, C.M., Jarzab, B., Elisei, R., Siena, S., Bastholt, L., *et al*. (2014) Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 3 Trial.

The Lancet, **384**, 319-328. https://doi.org/10.1016/s0140-6736(14)60421-9

[67] Chi, Y., Zheng, X., Zhang, Y., Shi, F., Cheng, Y., Guo, Z., *et al*. (2023) Anlotinib in Locally Advanced or Metastatic Radioiodine-Refractory Differentiated Thyroid Carcinoma: A Randomized, Double-Blind, Multicenter Phase II Trial. *Clinical Cancer Research*, **29**, 4047-4056. https://doi.org/10.1158/1078-0432.ccr-22-3406

[68] Gild, M.L., Topliss, D.J., Learoyd, D., Parnis, F., Tie, J., Hughes, B., *et al*. (2017) Clinical Guidance for Radioiodine Refractory Differentiated Thyroid Cancer. *Clinical Endocrinology*, **88**, 529-537. https://doi.org/10.1111/cen.13508

[69] Rendl, G., Sipos, B., Becherer, A., Sorko, S., Trummer, C., Raderer, M., *et al*. (2020) Real-World Data for Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer (RELEVANT): A Retrospective Multicentric Analysis of Clinical Practice in Austria. *International Journal of Endocrinology*, **2020**, Article ID: 8834148. https://doi.org/10.1155/2020/8834148

[70] Reed, N., Glen, H., Gerrard, G., Good, J., Lei, M., Lyon, A.R., *et al*. (2020) Expert Consensus on the Management of Adverse Events during Treatment with Lenvatinib for Thyroid Cancer. *Clinical Oncology*, **32**, e145-e153. https://doi.org/10.1016/j.clon.2019.11.010

[71] Colombo, C., Ceruti, D., De Leo, S., Bilo, G., Trevisan, M., Giancola, N., *et al*. (2023) Management of Hypertension during Lenvatinib for Advanced Thyroid Cancer: A Suggested Diagnostic and Therapeutic Algorithm. *European Thyroid Journal*, **12**, e230047. https://doi.org/10.1530/etj-23-0047

[72] Tahara, M. (2018) Management of Recurrent or Metastatic Thyroid Cancer. *ESMO Open*, **3**, e000359. https://doi.org/10.1136/esmoopen-2018-000359

[73] Fugazzola, L., Elisei, R., Fuhrer, D., Jarzab, B., Leboulleux, S., Newbold, K., *et al*. (2019) 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *European Thyroid Journal*, **8**, 227-245. https://doi.org/10.1159/000502229

[74] Porcelli, T., Luongo, C., Sessa, F., Klain, M., Masone, S., Troncone, G., *et al*. (2021) Long-Term Management of Lenvatinib-Treated Thyroid Cancer Patients: A Real-Life Experience at a Single Institution. *Endocrine*, **73**, 358-366. https://doi.org/10.1007/s12020-021-02634-z

[75] Porcelli, T., Sessa, F., Gambale, C., Luongo, C. and Salvatore, D. (2019) Management of One Patient with Oligoprogressive Thyroid Cancer during Treatment with Lenvatinib. *Future Oncology*, **15**, 21-25. https://doi.org/10.2217/fon-2019-0110

[76] Agrawal, N., Akbani, R., Aksoy, B.A., Ally, A., Arachchi, H., Asa, S.L., *et al*. (2014) Integrated Genomic Characterization of Papillary Thyroid Carcinoma. *Cell*, **159**, 676-690. https://doi.org/10.1016/j.cell.2014.09.050

[77] Wirth, L.J., Sherman, E., Robinson, B., Solomon, B., Kang, H., Lorch, J., *et al*. (2020) Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers. *New England Journal of Medicine*, **383**, 825-835. https://doi.org/10.1056/nejmoa2005651

[78] Subbiah, V., Hu, M.I., Wirth, L.J., Schuler, M., Mansfield, A.S., Curigliano, G., *et al*. (2021) Pralsetinib for Patients with Advanced or Metastatic Ret-Altered Thyroid Cancer (ARROW): A Multi-Cohort, Open-Label, Registrational, Phase 1/2 Study. *The Lancet Diabetes & Endocrinology*, **9**, 491-501. https://doi.org/10.1016/s2213-8587(21)00120-0

[79] Pekova, B., Sykorova, V., Mastnikova, K., Vaclavikova, E., Moravcova, J., Vlcek, P., *et al*. (2021) NTRK Fusion Genes in Thyroid Carcinomas: Clinicopathological Characteristics and Their Impacts on Prognosis. *Cancers*, **13**, Article 1932. https://doi.org/10.3390/cancers13081932

[80] Drilon, A., Laetsch, T.W., Kummar, S., DuBois, S.G., Lassen, U.N., Demetri, G.D., *et al*. (2018) Efficacy of Larotrectinib in *TRK* Fusion-Positive Cancers in Adults and Children. *New England Journal of Medicine*, **378**, 731-739. https://doi.org/10.1056/nejmoa1714448

[81] Doebele, R.C., Drilon, A., Paz-Ares, L., *et al*. (2020) Entrectinib in Patients with Advanced or Metastatic NTRK Fusion-Positive Solid Tumours: Integrated Analysis of Three Phase 1-2 Trials. *The Lancet. Oncology*, **21**, 271-282.

[82] Subbiah, V., Kreitman, R.J., Wainberg, Z.A., Cho, J.Y., Schellens, J.H.M., Soria, J.C., *et al*. (2022) Dabrafenib Plus Trametinib in Patients with BRAF V600e-Mutant Anaplastic Thyroid Cancer: Updated Analysis from the Phase II ROAR Basket Study. *Annals of Oncology*, **33**, 406-415. https://doi.org/10.1016/j.annonc.2021.12.014

[83] Subbiah, V., Kreitman, R.J., Wainberg, Z.A., Cho, J.Y., Schellens, J.H.M., Soria, J.C., *et al*. (2018) Dabrafenib and Trametinib Treatment in Patients with Locally Advanced or Metastatic *BRAF* V600-Mutant Anaplastic Thyroid Cancer. *Journal of Clinical Oncology*, **36**, 7-13. https://doi.org/10.1200/jco.2017.73.6785

[84] Ando, T., Oya, Y., Tomiie, Y., Ogawa, K., Kuki, T., Tanabe, Y., *et al*. (2025) A Single-Center Retrospective Study of Dabrafenib Plus Trametinib Combination Therapy in Patients with BRAF V600e-Positive Thyroid Cancer. *International Journal of Clinical Oncology*, **30**, 2257-2265. https://doi.org/10.1007/s10147-025-02861-8

[85] Clifton-Bligh, R.J. (2024) Mechanisms of Resistance to Ret-Directed Therapies. *Endocrine-Related Cancer*, **32**, e240224. https://doi.org/10.1530/erc-24-0224

[86] Vodopivec, D.M. and Hu, M.I. (2022) RET Kinase Inhibitors for *RET*-Altered Thyroid Cancers. *Therapeutic Advances*

in Medical Oncology, **14**, 1-18. https://doi.org/10.1177/17588359221101691

[87] Song, Y.S. and Park, Y.J. (2019) Genomic Characterization of Differentiated Thyroid Carcinoma. *Endocrinology and Metabolism*, **34**, 1-10. https://doi.org/10.3803/enm.2019.34.1.1

[88] Sun, J., Shi, R., Zhang, X., Fang, D., Rauch, J., Lu, S., *et al*. (2021) Characterization of Immune Landscape in Papillary Thyroid Cancer Reveals Distinct Tumor Immunogenicity and Implications for Immunotherapy. *OncoImmunology*, **10**, e1964189. https://doi.org/10.1080/2162402x.2021.1964189

[89] Capdevila, J., Wirth, L.J., Ernst, T., Ponce Aix, S., Lin, C., Ramlau, R., *et al*. (2020) PD-1 Blockade in Anaplastic Thyroid Carcinoma. *Journal of Clinical Oncology*, **38**, 2620-2627. https://doi.org/10.1200/jco.19.02727

[90] Yin, H., Tang, Y., Guo, Y. and Wen, S. (2020) Immune Microenvironment of Thyroid Cancer. *Journal of Cancer*, **11**, 4884-4896. https://doi.org/10.7150/jca.44506

[91] Huang, Y., Goel, S., Duda, D.G., Fukumura, D. and Jain, R.K. (2013) Vascular Normalization as an Emerging Strategy to Enhance Cancer Immunotherapy. *Cancer Research*, **73**, 2943-2948. https://doi.org/10.1158/0008-5472.can-12-4354

[92] Lanitis, E., Irving, M. and Coukos, G. (2015) Targeting the Tumor Vasculature to Enhance T Cell Activity. *Current Opinion in Immunology*, **33**, 55-63. https://doi.org/10.1016/j.coi.2015.01.011

[93] Dierks, C., Seufert, J., Aumann, K., Ruf, J., Klein, C., Kiefer, S., *et al*. (2021) Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma. *Thyroid*, **31**, 1076-1085. https://doi.org/10.1089/thy.2020.0322

[94] Boudin, L., Morvan, J., Thariat, J., Métivier, D., Marcy, P. and Delarbre, D. (2022) Rationale Efficacy and Safety Evidence of Lenvatinib and Pembrolizumab Association in Anaplastic Thyroid Carcinoma. *Current Oncology*, **29**, 7718-7731. https://doi.org/10.3390/curroncol29100610

[95] Kim, W.B., Jeon, M.J., Kim, W.G., Kim, T.Y. and Shong, Y.K. (2020) Unmet Clinical Needs in the Treatment of Patients with Thyroid Cancer. *Endocrinology and Metabolism*, **35**, 14-25. https://doi.org/10.3803/enm.2020.35.1.14

[96] Zhang, K., Wang, J., He, Z., Qiu, X., Sa, R. and Chen, L. (2023) Epigenetic Targets and Their Inhibitors in Thyroid Cancer Treatment. *Pharmaceuticals*, **16**, Article 559. https://doi.org/10.3390/ph16040559

[97] Petrulea, M.S., Plantinga, T.S., Smit, J.W., Georgescu, C.E. and Netea-Maier, R.T. (2015) PI3K/AKT/mTOR: A Promising Therapeutic Target for Non-Medullary Thyroid Carcinoma. *Cancer Treatment Reviews*, **41**, 707-713. https://doi.org/10.1016/j.ctrv.2015.06.005

[98] Liu, J., Yang, J., Sun, Y., Gong, J., Yue, J., Pan, Y., *et al*. (2025) CLDN18.2—Targeting Antibody-Drug Conjugate IBI343 in Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: A Phase 1 Trial. *Nature Medicine*, **31**, 3028-3036. https://doi.org/10.1038/s41591-025-03783-8

[99] Takakura, T., Shimizu, T. and Yamamoto, N. (2024) Antibody-Drug Conjugates in Solid Tumors; New Strategy for Cancer Therapy. *Japanese Journal of Clinical Oncology*, **54**, 837-846. https://doi.org/10.1093/jjco/hyae054

[100] Schlumberger, M., Tahara, M., Wirth, L.J., Robinson, B., Brose, M.S., Elisei, R., *et al*. (2015) Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *New England Journal of Medicine*, **372**, 621-630. https://doi.org/10.1056/nejmoa1406470

[101] Wirth, L.J., Brose, M.S., Subbiah, V., Worden, F., Solomon, B., Robinson, B., *et al*. (2024) Durability of Response with Selpercatinib in Patients with *RET*-Activated Thyroid Cancer: Long-Term Safety and Efficacy from Libretto-001. *Journal of Clinical Oncology*, **42**, 3187-3195. https://doi.org/10.1200/jco.23.02503

[102] Subbiah, V., Hu, M.I., Mansfield, A.S., Taylor, M.H., Schuler, M., Zhu, V.W., *et al*. (2024) Pralsetinib in Patients with Advanced/Metastatic Rearranged during Transfection (RET)-Altered Thyroid Cancer: Updated Efficacy and Safety Data from the ARROW Study. *Thyroid®*, **34**, 26-40. https://doi.org/10.1089/thy.2023.0363

[103] Waguespack, S.G., Drilon, A., Lin, J.J., Brose, M.S., McDermott, R., Almubarak, M., *et al*. (2022) Efficacy and Safety of Larotrectinib in Patients with TRK Fusion-Positive Thyroid Carcinoma. *European Journal of Endocrinology*, **186**, 631-643. https://doi.org/10.1530/eje-21-1259

[104] Romano, C., Martorana, F., Pennisi, M.S., Stella, S., Massimino, M., Tirrò, E., *et al*. (2021) Opportunities and Challenges of Liquid Biopsy in Thyroid Cancer. *International Journal of Molecular Sciences*, **22**, Article 7707. https://doi.org/10.3390/ijms22147707

[105] Duffy, M.J. and Crown, J. (2022) Circulating Tumor DNA as a Biomarker for Monitoring Patients with Solid Cancers: Comparison with Standard Protein Biomarkers. *Clinical Chemistry*, **68**, 1381-1390. https://doi.org/10.1093/clinchem/hvac121

[106] Allin, D.M., Shaikh, R., Carter, P., Thway, K., Sharabiani, M.T.A., Gonzales-de-Castro, D., *et al*. (2018) Circulating Tumour DNA Is a Potential Biomarker for Disease Progression and Response to Targeted Therapy in Advanced Thyroid Cancer. *European Journal of Cancer*, **103**, 165-175. https://doi.org/10.1016/j.ejca.2018.08.013

[107] Iyer, P.C., Cote, G.J., Hai, T., Gule-Monroe, M., Bui-Griffith, J., Williams, M.D., *et al*. (2018) Circulating *BRAF*V 600e

Cell-Free DNA as a Biomarker in the Management of Anaplastic Thyroid Carcinoma. *JCO Precision Oncology*, **2**, 1-11. https://doi.org/10.1200/po.18.00173

[108] Qin, Y., Wang, J.R., Wang, Y., Iyer, P., Cote, G.J., Busaidy, N.L., *et al*. (2021) Clinical Utility of Circulating Cell-Free DNA Mutations in Anaplastic Thyroid Carcinoma. *Thyroid*, **31**, 1235-1243. https://doi.org/10.1089/thy.2020.0296

[109] Bettegowda, C., Sausen, M., Leary, R.J., *et al*. (2014) Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies. *Science Translational Medicine*, **6**, 224ra24.

[110] Zeyghami, W., Hansen, M.U., Jakobsen, K.K., Groenhøj, C., Feldt-Rasmussen, U., von Buchwald, C., *et al*. (2023) Liquid Biopsies in Thyroid Cancers: A Systematic Review and Meta-Analysis. *Endocrine-Related Cancer*, **30**, e230002. https://doi.org/10.1530/erc-23-0002

[111] Marotta, V., Cennamo, M., La Civita, E., Vitale, M. and Terracciano, D. (2022) Cell-Free DNA Analysis within the Challenges of Thyroid Cancer Management. *Cancers*, **14**, Article 5370. https://doi.org/10.3390/cancers14215370

[112] Merker, J.D., Oxnard, G.R., Compton, C., Diehn, M., Hurley, P., Lazar, A.J., *et al*. (2018) Circulating Tumor DNA Analysis in Patients with Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *Journal of Clinical Oncology*, **36**, 1631-1641. https://doi.org/10.1200/jco.2017.76.8671

[113] Dang, D.K. and Park, B.H. (2022) Circulating Tumor DNA: Current Challenges for Clinical Utility. *Journal of Clinical Investigation*, **132**, e154941. https://doi.org/10.1172/jci154941

[114] Tan, J.K., Awuah, W.A., Roy, S., Ferreira, T., Ahluwalia, A., Guggilapu, S., *et al*. (2023) Exploring the Advances of Single-Cell RNA Sequencing in Thyroid Cancer: A Narrative Review. *Medical Oncology*, **41**, Article No. 27. https://doi.org/10.1007/s12032-023-02260-x

[115] Pu, W., Shi, X., Yu, P., Zhang, M., Liu, Z., Tan, L., *et al*. (2021) Single-Cell Transcriptomic Analysis of the Tumor Ecosystems Underlying Initiation and Progression of Papillary Thyroid Carcinoma. *Nature Communications*, **12**, Article No. 6058. https://doi.org/10.1038/s41467-021-26343-3

[116] Wang, T., Shi, J., Li, L., Zhou, X., Zhang, H., Zhang, X., *et al*. (2022) Single-Cell Transcriptome Analysis Reveals Inter-Tumor Heterogeneity in Bilateral Papillary Thyroid Carcinoma. *Frontiers in Immunology*, **13**, Article ID: 840811. https://doi.org/10.3389/fimmu.2022.840811

[117] Lu, L., Wang, J.R., Henderson, Y.C., Bai, S., Yang, J., Hu, M., *et al*. (2023) Anaplastic Transformation in Thyroid Cancer Revealed by Single-Cell Transcriptomics. *Journal of Clinical Investigation*, **133**, e169653. https://doi.org/10.1172/jci169653

[118] Liao, T., Zeng, Y., Xu, W., Shi, X., Shen, C., Du, Y., *et al*. (2025) A Spatially Resolved Transcriptome Landscape during Thyroid Cancer Progression. *Cell Reports Medicine*, **6**, Article 102043. https://doi.org/10.1016/j.xcrm.2025.102043

[119] Ning, K., Zou, B., Yu, Y., Cai, T., Luo, Z., Guo, Y., *et al*. (2025) Spatial Transcriptomics Reveals Transcriptomic and Immune Microenvironment Reprogramming during Thyroid Carcinoma Dedifferentiation. *Advanced Science*, **12**, e06925. https://doi.org/10.1002/advs.202506925