



· 专家述评与论著 ·



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儿童青少年甲状腺癌诊治指南解读及其进展——核医学部分

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【摘要】 儿童分化型甲状腺癌（children differentiated thyroid cancer, cDTC）的病理生理、临床特征及远期预后与成人DTC（adult DTC, aDTC）均存在较大差异，以往的指南及其证据多基于aDTC证据的推荐，2015年美国甲状腺协会（American Thyroid Association, ATA）发布的cDTC诊治指南在一定程度上填补了目前cDTC临床决策指导的空白。就cDTC的病理及预后特征、风险分层、术后评估、¹³¹I治疗决策及随访对该儿童指南进行解读，并纳入近年来有关cDTC的研究证据对指南部分内容加以补充说明。

【关键词】 儿童甲状腺癌指南；分化型甲状腺癌；¹³¹I治疗；研究进展

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The interpretation of management guidelines for children with thyroid nodules and differentiated thyroid cancer: radioactive iodine therapy and new progress YANG Ke¹, ZHENG Rong¹, LIN Yansong² (1. Department of Nuclear Medicine, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, 100021, China; 2. Department of Nuclear Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China)

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【Abstract】 Compared with adults differentiated thyroid cancer (aDTC), children differentiated thyroid cancer (cDTC) exhibit differences in pathophysiology, clinical presentation, and long-term outcomes. However, previous guidelines for the management of thyroid nodules and cancers were based on the evidence of aDTC. The American Thyroid Association (ATA) children guidelines provide recommendations for the evaluation and management of cDTC to help guide the clinical decisions. This article interprets the pathology and clinical outcomes of cDTC, risk stratification, postoperative assessments, decisions regarding ¹³¹I therapy and follow-

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up in ATA children guidelines as well as updated literature about cDTC in recent years.

[Key words] Management guidelines for children with thyroid cancer; Differentiated thyroid cancer; Radioactive iodine therapy; Research progress

核医学以其独特的放射性核素示踪及靶向特征在甲状腺癌诊治中具有其独特的地位及意义。甲状腺癌尤其是分化型甲状腺癌(differentiated thyroid carcinoma, DTC)保留了部分甲状腺组织的摄碘等碘代谢功能,为核医学在其治疗中的应用提供了分子生物学依据。自1946年第一次将¹³¹I应用于DTC的治疗以来,核医学已成为术后降低中高危DTC患者复发及死亡风险的重要手段。之前有关DTC的诊治指南及其证据多侧重于成人DTC(adult DTC, aDTC)的指导,但儿童DTC(children DTC, cDTC)的病理生理、临床特征及远期预后与成人均存在较大差异。用于指导成人的指南及治疗策略可能会造成过度治疗并增加长期不良反应的风险,因此其可能并不适用于指导死亡风险较低的cDTC的诊治。有鉴于此,2014年由来自美国弗吉尼亚联邦大学Richmond儿童医院的Francis教授牵头的美国甲状腺协会(American Thyroid Association, ATA)儿童甲状腺指南编写工作组启动了cDTC指南的编写,历时1年余成文并发表于*Thyroid*杂志。虽然该指南中有关cDTC的研究涵盖多个年龄段,其中最大年龄为21岁,但考虑到大多数儿童患者在18岁前已发育完全,因此,为了更准确地评估发育过程中生理学的改变对肿瘤生物学行为的影响,该指南将儿童的年龄界定为≤18周岁。文中广泛纳入现有cDTC的研究证据,针对儿童DTC的病理及分子学特征、术后危险分层及术后评估、¹³¹I治疗的指征、剂量选择及不良反应、cDTC的随访等形成29条推荐意见,为cDTC的诊治提供了指导依据。本文仅就cDTC的病理特征及核医学诊治加以解读。

1 病理分类及病理分子特征

儿童甲状腺癌的病理学分类与成年人同样基于世界卫生组织(World Health Organization, WHO)标准。与成年人相比,儿童DTC以儿童甲状腺乳头状癌(children papillary thyroid cancer, cPTC)所占比例更高(90%以

上)^[1-6],而儿童甲状腺滤泡癌(children follicular thyroid cancer, cFTC)并不常见,儿童髓样甲状腺癌(children medullary thyroid cancer, cMTC)及低分化甲状腺癌和未分化癌则较为罕见。有文献报道^[7]对于0~4岁的儿童,cMTC为主要的病理类型,但随着年龄增加,cPTC及cFTC所占比例逐渐增高并占据主要病理类型。

cPTC包括以下亚型:经典型、实体型、滤泡亚型、弥漫硬化型。与成年人相比,弥漫硬化亚型所占比例较高^[8]。对于<10岁的cPTC患者,并未呈现典型的乳头状形态学特征,肿瘤可表现为无包膜并且腺体内外的广泛侵犯,还会有滤泡状和实体状的结构、独特的核型及伴随大量砂粒体^[9-10]。对于cPTC患者尤其是年龄<5岁者,其诱发主要危险因素是甲状腺的放射性暴露^[11-12]。

cPTC与cFTC的临床病理学特征存在较大差异。cPTC常表现为多灶及双侧分布,并且易出现区域性颈部淋巴结转移^[1, 5, 10, 13-21];经血液循环转移至肺的发生率可达25%^[10, 16, 19, 22-30],通常仅发生于广泛的淋巴结转移之后^[1, 31]。典型的cFTC则多呈单一灶分布,初期就容易经血液循环转移至肺和骨,而区域淋巴结转移并不常见。cFTC的组织学变异包括Hurthle细胞亚型、透明细胞型和孤立型(低分化)。

与aPTC相比,cPTC分子病理学特征呈更高的基因重排率以及更低的原癌基因点突变率。*BRAF*基因突变为aPTC最常见的基因事件,其突变率为36.0%~83.0%^[32]。该指南中引用的文献发现在cPTC尤其是年龄较小的患者,*BRAF*基因突变较为罕见(0.0%~3.2%)^[33-34]。然而近期多篇研究发现,*BRAF*基因突变在cPTC并不少见,最高可达40.0%,尤其在经典型PTC中更为常见^[35-37]。这种差异可能与不同研究纳入的样本量不同有关。*RAS*基因突变为aDTC常见的基因事件,其在FTC、滤泡型甲状腺乳头状癌(follicular variant of papillary thyroid

carcinoma, FVPTC) 和 PTC 的发生率分别为 30.0%~55.0%、25.0%~45.0% 及 10.0%~15.0%^[38-41], 但在 cDTC 中较为少见(文献报道为 2.5%~13.0%)^[35, 42]。由于 *RAS* 和 *BRAF* 的点突变可导致基因的不稳定状态及失分化, 并表现为 NIS 的表达降低^[43-44], 因此, cPTC 较低的 *BRAF* 突变率从另一个角度解释了¹³¹I 治疗 cDTC 有效及预后良好的机制, 及其相对较低的疾病死亡率及罕见失分化特征。其他 aDTC 出现的基因点突变事件如 *TERT*、*PIK3CA*、*PTEN* 突变, 在 cDTC 中则更为少见^[42]。此外, 尽管在该指南中未提及 cPTC 中 *NTRK* 基因融合的发生率及其对疾病预后的影响, 但近期多项研究显示 *NTRK* 基因融合在 cPTC 中的发生率较 aPTC 更高(5.0%~25.0%), 并且在发生于辐射暴露导致的 cPTC 中更为常见, 其与淋巴结转移及更具侵犯性的临床病理特征相关^[45-47]。近期美国食品药品监督管理局(Food and Drug Administration, FDA) 批准了拉洛替尼用于治疗携带 *NTRK* 基因融合的局部晚期或转移性实体瘤的成人及儿童实体瘤患者, 这将为部分碘难治性或局部晚期并存在 *NTRK* 基因融合 cPTC 患者提供新的治疗靶点。

2 cDTC 危险分层系统及术后评估

目前最广泛应用于描述成人的疾病侵犯性程度及判断预后的分期系统是美国癌症联合会(American Joint Committee on Cancer, AJCC) 的 TNM 分期。但是由于 cPTC 极低的疾病特异性死亡率, 以及所有 <45 岁(AJCC 第 8 版 <55 岁) 患者仅以远处转移界定的过于简单的 I、II 期分期特征, 使得 TNM 分期在预测 cPTC 预后方面存在局限性。但 TNM 分期系统在描述疾病侵犯情况及分层评价, 特别是有关淋巴结累及情况方面, 仍对儿童甲状腺癌的风险分层有指导作用。有研究发现, 与不伴可触及的淋巴结患者相比, 在诊断时伴有可触及的肿大淋巴结的 cPTC 更易呈多灶性(89.0% vs 16.0%), 同时呈现更高概率的肺转移(20.0% vs 0.0%)、疾病持续状态(30.0% vs 0.0%) 和(或)复发率(53.0% vs 0.0%)^[31, 48]。

该指南参照 aDTC 术后复发危险评估系统, 并基于 TNM 分期系统, 特别是针对区域淋巴结转移和远处转移的分期, 制定了儿童版 cDTC 危险分层系统, 与 aDTC 相近, 该分层更侧重于识别出患者存在的持续淋巴结病灶风险而非死亡风险, 以协助制定长期随访方案。该分层将 cDTC 进行低中高危分层(表 1)。

表 1 ATA 甲状腺癌儿童危险分层

Tab. 1 ATA pediatric thyroid cancer risk level

	Definition	Explanation
Low	Disease grossly confined to the thyroid with N ₀ /N _x disease or patients with incidental N _{1a} disease (microscopic metastasis to a small number of central neck lymph nodes)	These patients have the lowest risk for distant metastasis but may still be at risk for residual cervical disease, especially if the initial surgery did not include a central neck dissection (CNS)
Intermediate	Extensive N _{1a} or minimal N _{1b} disease	These patients appear to be at low risk for distant metastasis but are at an increased risk for incomplete lymph node resection and persistent cervical disease. The impact of the pathologic identification of microscopic (extrathyroidal extension) (T ₃ disease) on management and outcomes has not been well studied in cPTC
High	Regionally extensive disease (extensive N _{1b}) or locally invasive disease (T ₄ tumors), with or without distant metastasis	Patients are at the highest risk for incomplete resection, persistent disease, and distant metastasis

可以看出, cDTC 复发危险分层和 aDTC (ATA 指南 2015 版) 存在较大差别, 淋巴结转移以及病灶局部侵犯程度是其分层的主要依据, 这可能与 cDTC 病例数量本身较少导致研究数据不足有关。另外从 cDTC 分层可以看出, 颈侧区淋

巴结转移对患者复发风险有着较大影响, 这方面亦与 aDTC 存在较大差异。其他影响 cDTC 复发危险分层的因素尚有待进一步研究。

关于术后的再评估, 该指南推荐大多数患者在术后 12 周内进行初步分期及风险评估, 旨在评

价其是否仍存在病灶及能否从后续 ^{131}I 治疗中获益。虽然目前在cPTC中基于危险分层制定诊疗策略及治疗前评估的前瞻性研究较少,但指南仍推荐根据患者的复发危险分层来选择合适的手段进行评估。

对于cDTC低危分层患者,可仅监测其抑制性甲状腺球蛋白(thyroglobulin, Tg)并定期随访。而对cDTC中高危患者,则推荐行促甲状腺激素(thyroid-stimulating hormone, TSH)刺激性Tg及诊断性 ^{131}I (或 ^{123}I)全身显像(diagnostic whole body scan, DxWBS)等影像学检查,以决策后续治疗。指南推荐针对cDTC患者尽可能使用 ^{123}I 进行DxWBS显像,以减少患者的辐射

剂量。针对DxWBS所示甲状腺床无摄碘或少量摄碘者,进一步采取刺激性Tg量化分层来决策 ^{131}I (图1)。针对甲状腺床外的颈部摄碘灶,其他影像学检查包括颈部超声和单光子发射计算机断层成像术(single-photon emission computed tomography, SPECT)/电子计算机断层扫描(computed tomography, CT)等有助于其更准确的定位,如经外科会诊对其可行手术切除者,建议手术。针对无需再次局部手术干预的远处转移患者,指南推荐行 ^{131}I 治疗及治疗性全身显像(post-treatment whole body scan, RxWBS),这部分患者的后续治疗及随访见后文及图3。

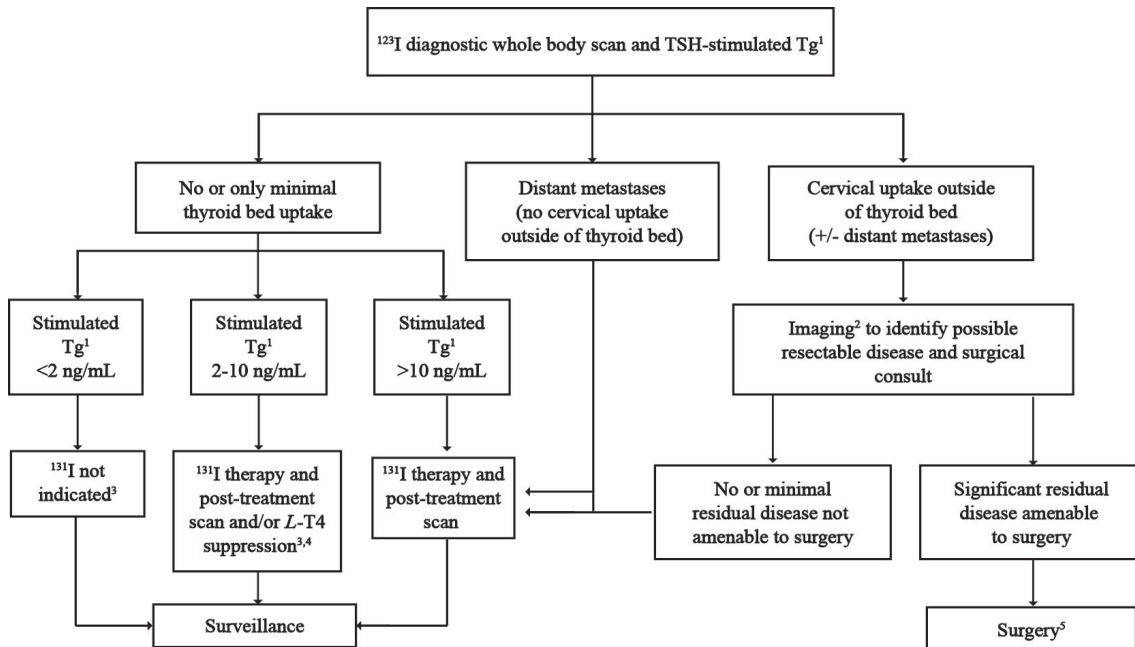


图1 cDTC中、高危分层患者的术后评估

Fig. 1 Initial postoperative staging for American Thyroid Association intermediate- and high-risk pediatric thyroid carcinoma

TSH: Thyroid-stimulating hormone; Tg: Thyroglobulin; TgAb: Thyroglobulin antibody. ¹: Assumes a negative TgAb and a TSH >30 mU/L, in TgAb-positive patients, consideration can be given (except in patients with T₄ tumors or clinical M₁ disease) to deferred evaluation to allow time for TgAb clearance ("delayed" staging). ²: Imaging includes neck ultrasonography-SPECT/CT at the time of the diagnostic thyroid scan. ³: Consider ^{131}I in patients with thyroid bed uptake and T₄ tumors or known residual microscopic cervical disease. ⁴: While there are no prospective studies in patients younger than 18 years of age, the use of ^{131}I remnant ablation may not decrease the risk for persistent or recurrent disease. Consider surveillance rather than ^{131}I with further therapy determined by surveillance data. ⁵: Repeat postoperative staging 3-6 months after surgery; L-T4: Levo-thyroxine

针对术后刺激性Tg预测疾病预后的研究在cDTC中仍较少。一项小样本单中心研究发现,经过5年随访后无病生存(disease-free survival, DFS)患者的术后刺激性Tg中位数为8.5 ng/mL,预测DFS的最佳cut-off值则为31.5 ng/mL,其灵敏度及特异度均为100%^[49]。另一项研究则发

现预测远处转移的术后刺激性Tg的cut-off值为154.0 ng/mL,灵敏度及特异度分别为87.5%及91.7%^[50]。可以看出,上述cDTC的Tg界值点均高于aDTC的相应数据。

3 ^{131}I 治疗目标

自1946年首例伴有转移灶的成年甲状腺癌

患者接受¹³¹I治疗并证实有效后,¹³¹I被提议作为DTC特异性的治疗方法,并被广泛应用于aDTC的治疗。尽管从文献可知早在1947年就已尝试用¹³¹I治疗cDTC^[51],但相比aDTC,探索cDTC的¹³¹I治疗潜在获益的研究证据仍相对较少,这可能与cDTC样本量较少,以及不论是否进行辅助¹³¹I治疗其预后较好有关。目前多数研究显示,具有摄碘功能的肺转移cDTC患者可从¹³¹I治疗中获益,其中约47%的患者可达完全缓解,38%达到部分缓解,特别是那些微小和较小肺转移患者^[22, 52-55],不难看出,相较于肺转移性aDTC患者,¹³¹I在肺转移性cDTC的治疗效果更佳,因此,对于肺转移的cDTC¹³¹I具有其治疗意义。而对于有残留病灶的患者,部分研究发现¹³¹I治疗可以降低疾病的复发风险^[19, 22, 27, 54]。¹³¹I可用于手术不可切除的摄碘性局部病灶、淋巴结或远处转移灶的治疗。

对于¹³¹I治疗后仍存在持续病灶的cDTC患者,需结合临床特征及前次治疗后疗效进行利弊权衡及个体化¹³¹I治疗决策。

由于cDTC本身预后好于aDTC,加之近年来有关¹³¹I治疗引起继发肿瘤的相关报道,该指南对cDTC的¹³¹I治疗指征把握也较前更为严格,例如,指南中并不推荐以清除残余甲状腺为目的的¹³¹I治疗,这也与最新成人ATA指南的思路相近。

4 cDTC ¹³¹I剂量选择

目前尚无标准化的cDTC¹³¹I治疗剂量公式,以及有关cDTC给予不同剂量¹³¹I时的有效性、安全性和长期预后的研究。经验性治疗剂量具有简便易行的优点,另外就是根据体质量或体表面积折算[如儿童体质量(kg)/70 kg]¹³¹I的剂量,这是基于治疗相似病情成人的标准剂量来确定的^[56-58]。总的来说,在病情相似的情况下,15岁的cDTC患者需给予成人剂量的5/6,10岁者给予成人剂量的1/2,5岁者则需要给与成人剂量的1/3^[59]。

对于存在摄碘性弥漫性肺转移灶或其他远处转移灶需要多次¹³¹I治疗的cDTC患者,或经过之前化疗、放射性治疗已经达到骨髓剂量上限者,应使用全身剂量学计算最大可给

予的¹³¹I剂量,以确保血液的吸收剂量不超过200 cGy^[60-62]。在广泛肺转移或存在其他远处(例如骨)转移瘤等肿瘤负荷较重时,也可以通过病灶的吸收剂量来确定¹³¹I有效的给予剂量^[61, 63-66]。由于儿童相比成人质量和碘清除率差异较大,指南建议由经验丰富的医师来确定¹³¹I剂量。

5 cDTC的监视与随访

该指南中对Tg、超声、DxWBS在儿童PTC随访中的作用,以及Tg阳性DxWBS、颈部持续/复发疾病、肺转移患者的诊疗分别进行了阐述。

5.1 Tg及甲状腺球蛋白抗体(thyroglobulin antibody, TgAb)检测

Tg在儿童DTC的评估、治疗、长期随访中可视为敏感的肿瘤标志物,应同时进行TgAb水平的检测,随访过程中最好在同一实验室用相同试剂检测,相较单次的检测结果,Tg和TgAb的变化趋势对判断疾病状态更有价值。对于不同水平Tg的解读,cDTC与aDTC较为相似,并强调动态观察Tg或TgAb的变化比单次检测结果更有利于评估疾病的状态。刺激性Tg低至不可检测水平(TgAb阴性)提示其更接近疾病缓解及无病状态生存,相应可逐渐降低随访强度及TSH的抑制程度;经手术及¹³¹I治疗后低水平刺激性Tg(Tg为2~10 ng/mL)提示可能为持续疾病状态;而高刺激性Tg(>10 ng/mL)水平则需要进一步评估来探查可能存在的病灶,并及时权衡手术和(或)¹³¹I治疗的获益^[67-72]。值得注意的是,有研究发现,部分接受甲状腺全切除术及清甲治疗患者的Tg水平可能会在治疗后数年内逐渐降低^[67, 69, 73],需通过持续监测抑制性Tg和TgAb的变化及影像学评估继续对患者进行随访,而不必急于再次¹³¹I治疗。针对TgAb阳性患者,因其会干扰Tg的检测并使结果被高估或低估影响其准确解读,建议应用同一检测条件下动态观察TgAb的变化趋势,如果TgAb呈明显上升趋势,则需要进一步的评估。

此外,有研究发现,cDTC患者的Tg水平也许会稍高于病情程度类似的aDTC患者^[53, 74]。其原因尚不清楚,推测其部分可能源于cDTC的

生物学行为及临床病理特征与aDTC存在较大差异,因此,是否可将aDTC的有关Tg对疾病状态预测的相关界值直接应用于cDTC仍有待进一步研究。

5.2 超声诊断

指南推荐对cPTC采用颈部超声进行随访,初次手术后治疗至少6个月后进行颈部超声检查,此后进行分层随访,低危者每12个月、中高危者每6~12个月行颈部超声检查。5年后则根据患者的复发风险进行个体化随访。

5.3 DxWBS

① 与在aDTC的应用相似,DxWBS可用于探测cDTC残留病灶,并为再次¹³¹I治疗及剂量决策提供依据。对于已行¹³¹I治疗并经评估提示无病的患者,DxWBS是证实已无摄碘灶、无需再次治疗的重要证据。② 推荐已经接受过¹³¹I治疗的高危患者,或前次RxWBS提示存在摄碘转移灶的患者行DxWBS,并且至少随访12个月后再行DxWBS检查。③ 若DxWBS结果为阴性且患者无持续疾病的临床证据,在之后的随访中不建议继续常规采用DxWBS探查是否存在疾病复发。

5.4 Tg阳性但DxWBS或超声阴性的cDTC处理

对于抑制性Tg阳性但颈部超声和DxWBS阴性的cDTC患者,应当考虑行颈胸增强CT检查。由于¹⁸FDG-PET/CT在cDTC应用较少,指南不常规推荐将¹⁸FDG-PET/CT用于持续疾病cDTC患者的随访。临床处置方面亦不推荐对这类患者采用常规经验性¹³¹I治疗及将RxWBS用于探查病灶,除非存在临床疾病进展(如Tg升高等)和前次¹³¹I治疗有效的证据[血清学如Tg/TgAb和(或)CT等影像学],与aDTC相比,对cDTC的经验性治疗指征显然把握更加严格。

5.5 颈部持续/复发疾病的处理

对于已探查到的患者颈部病灶的处置,指南推荐根据患者年龄、初始的cDTC危险分层、是否存在远处转移灶、之前的诊疗史(包括之前治疗的并发症)等行个体化处理,同时将病灶大小、侵犯范围、解剖位置及摄碘情况纳入考虑(图2)。由经验丰富的外科医师对病灶>1 cm的

患者评估手术的可行性。对于存在摄碘性颈部病灶应根据患者的个体风险和是否存在远处转移灶进行个体化治疗决策,若病灶在颈部,尤其是位于之前未行清扫的淋巴结区,则手术更为推荐。再次施行手术后的患者,应进行术后再分期来决定是否行¹³¹I治疗。可以看出,儿童指南对于局部复发或疾病持续患者的处置原则与成人版也是大体一致的,即优先根据患者的临床特点评估是否可行手术,并建议术后再次评估能否从¹³¹I治疗中获益。

5.6 cDTC伴有肺转移的治疗

儿童发生DTC肺转移的风险高于成人,但其长期预后(尤其在接受¹³¹I治疗后)明显好于成人。根据cDTC肺转移的特点,该指南列举了6个推荐条目:① 经DxWBS证实的摄碘性肺转移患者推荐行¹³¹I治疗。② 针对不摄碘(DxWBS阴性)及对前次¹³¹I治疗无反应者不推荐¹³¹I治疗,这与aDTC的治疗策略相近。③ 针对¹³¹I治疗大于12个月且抑制性Tg呈上升趋势者,以及¹³¹I治疗后病情一度稳定后抑制性Tg上升者或12个月内出现疾病进展者,需进一步行DxWBS和刺激性Tg检查,依据病灶摄碘情况及对前次¹³¹I治疗反应进行后续个体化¹³¹I治疗决策(图3)。④ 而对于摄碘但疾病仍持续进展的患者,由于需将其远期不良反应等因素纳入考虑,因此需多方面综合判断其获益情况之后再决定是否继续行¹³¹I治疗。⑤ 该指南特别强调,需持续动态监测Tg的变化(每3~6个月)直至其对前次治疗达到完全的治疗响应再考虑是否进行下一步治疗。⑥ 对所有存在肺转移的患者,尤其是计划或接受多次¹³¹I治疗者,应对其肺功能进行监视及检测。

5.7 对于不再摄取¹³¹I或¹³¹I治疗无效的进展型甲状腺癌儿童患者的处置原则

指南推荐大多数无症状及非进展型¹³¹I难治性cDTC患者,在TSH抑制治疗下可安全地进行监控及随访。关于儿童进展型¹³¹I难治性甲状腺癌系统治疗的相关研究较少,在一些无法进行系统治疗的特殊病例,可选择临床试验或考虑口服激酶抑制剂。

2015年针对aDTC的ATA指南正式引入动态

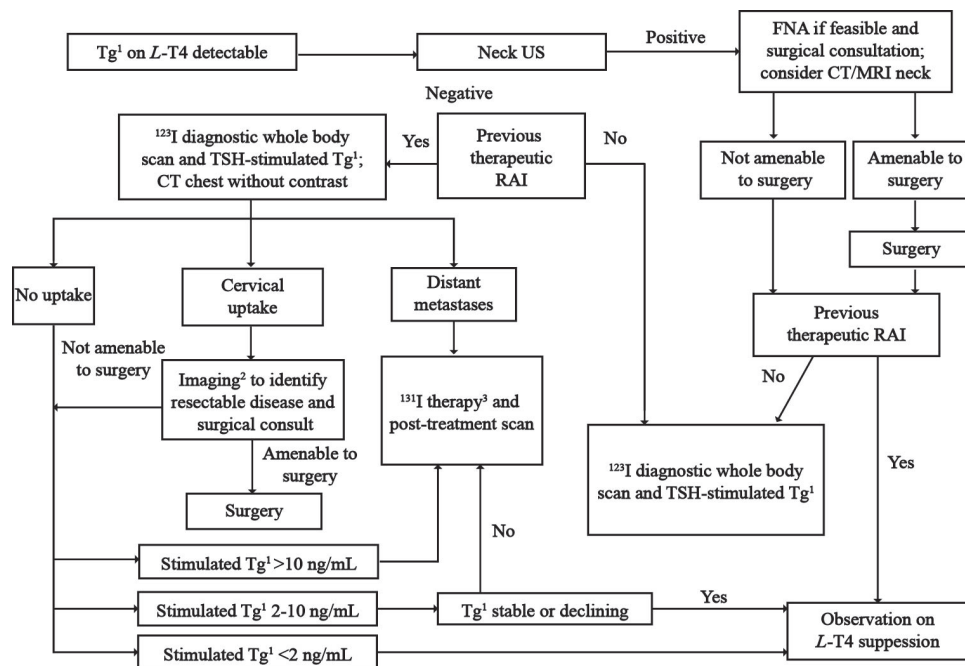


图2 存在已知或可疑残留或复发疾病患者的处置 (无确定的远处转移)

Fig. 2 Management of pediatric patient with known or suspected residual/recurrent disease (no known distant metastases)

This algorithm is intended to be used in children who are known or suspected to have residual or recurrent disease based upon the suppressed Tg level and knowledge of previous disease extent 6–12 months after all primary therapies have been completed. ¹: Assumes a negative TgAb, in TgAb-positive patients, the presence of TgAb alone cannot be interpreted as a sign of disease unless the titer is clearly rising. ²: Imaging includes SPECT/CT at the time of the diagnostic thyroid scan and/or contrast-enhanced CT/MRI neck. ³: Repeat ¹³¹I therapy in patients previously treated with high-dose ¹³¹I should generally be undertaken only if iodine-avid disease is suspected and a response to previous ¹³¹I therapy is observed. RAI: Radioactive iodine; FNA: Fine needle aspiration

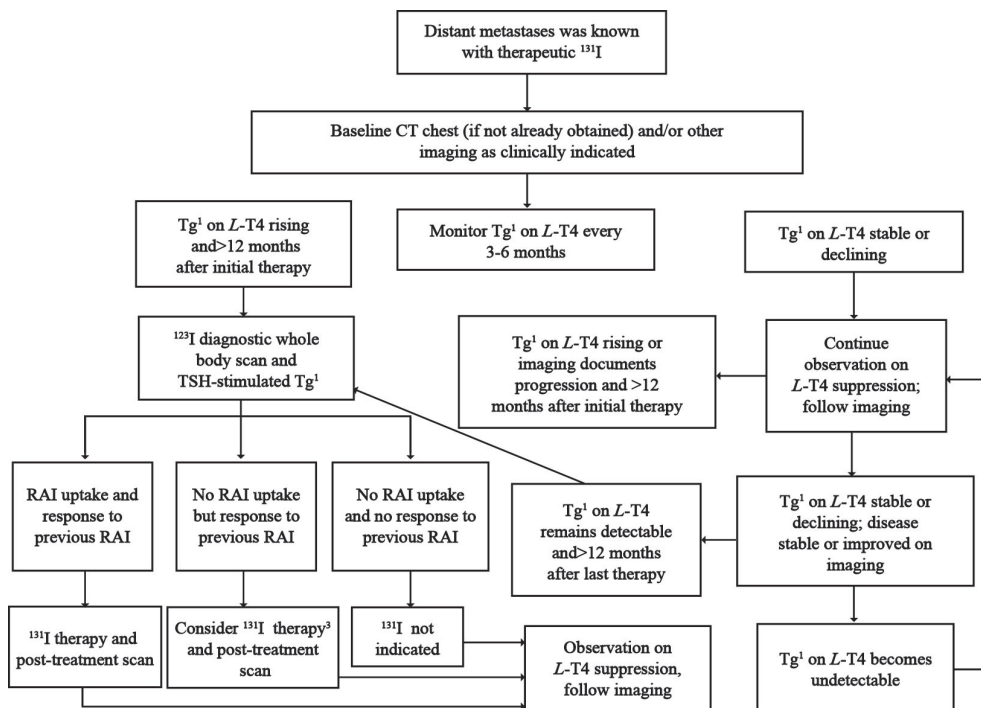


图3 伴有已知远处转移患儿的处置

Fig. 3 Management of pediatric patient with known distant metastases

¹: Assumes a negative TgAb; in TgAb-positive patients, the presence of TgAb alone cannot be interpreted as a sign of disease unless the titer is clearly rising; a declining TgAb titer would suggest continued response to treatment. ²: Tg can transiently rise after ¹³¹I therapy and should not be misinterpreted as evidence for progression. ³: Repeat ¹³¹I therapy in patients previously treated with high-dose ¹³¹I should be undertaken only if iodine-avid disease is suspected and if there is a previous response to therapy. RAI: Radioactive iodine

风险评估系统以实时评估疾病的转归,而在该指南中由于缺乏相关研究的证据支持仍未纳入该系统。在该指南发布后,近期有多项研究利用成人版动态风险评估系统来评价cDTC的疗效,并认为该系统同样可用于预测cDTC的疾病状态并调整后续随访及治疗方案^[75-78]。其中一项研究预测治疗满意(excellent response, ER)的术后刺激性Tg的cut-off值为37.8 ng/mL,其灵敏度及特异度分别可达81%及100%^[77]。因此相信在未来该指南的更新中,整合更多的研究数据后将会纳入动态风险评估系统以更有效地指导cDTC的随访及治疗。

6 cDTC ¹³¹I治疗的急性和长期不良反应

针对¹³¹I治疗可出现的急性和长期不良反应,该指南进行了阐述。大多数的作用机制与给药方式以及药物的吸收、分布、排泄途径等有关。

急性不良反应主要包括一些可以摄取¹³¹I组织的辐射损伤,造成唾液腺炎、口干、龋齿、胃炎、眼干、鼻泪管堵塞^[79-80]。由于专门针对儿童的研究数据较少,因此急性不良反应的预防措施主要参考成人的指南,如¹³¹I治疗后24 h给予酸性糖果或柠檬汁,并在3~5 d内充分饮水。生殖系统的不良反应主要为性腺损伤^[81-82],女性还可出现一过性闭经及月经失调。儿童不涉及短期内的生育问题,但需要注意的是对于¹³¹I累积剂量大于等于14.8 GBq的青春后期男性,应考虑预先储存精子等问题^[83]。

部分cDTC患者可出现急性的骨髓抑制,但一般¹³¹I治疗后60 d内血常规检查一般会恢复至正常值。长期骨髓抑制较为罕见。指南推荐多次¹³¹I治疗期间需留出一定时间待骨髓恢复至正常。对于存在肺转移的cPTC患者,当滞留的¹³¹I剂量超过3.0 GBq时,¹³¹I引起肺纤维化的风险显著增高^[84-85]。因此,指南建议对于DxWBS观察到转移灶摄碘明显的儿童患者,应根据剂量学确定¹³¹I剂量或相应地减少¹³¹I剂量。

关于¹³¹I治疗与继发肿瘤风险增高以及总死亡率升高的研究近年来已引起广泛关注,尤其是2017年发表于*Leukemia*及2018年发表于*Journal of Clinical Oncology*上的两篇重磅文章^[86-87],

指出¹³¹I治疗与血液系统肿瘤风险增加存在一定关系,因此引起了不少的议论。然而这两篇文章并未将儿童单独进行分组并加以分析,因此¹³¹I是否增加儿童血液系统肿瘤风险仍需进一步的研究。由于cDTC患者相对较少、儿童患者生存期较长等因素,目前有关其长期安全性研究的证据很少,因此,该指南未推荐出¹³¹I治疗累积剂量限值,亦未明确¹³¹I治疗与继发肿瘤风险之间的联系。由于儿童身体各部位及器官仍处于发育阶段,相比成人器官的体积更小,细胞增殖潜能更大,这些因素使cDTC ¹³¹I治疗的安全性问题会被过度关注甚至引发恐慌,因此对于cDTC来说,面临的挑战是识别出哪些儿童患者可以从¹³¹I治疗中获益,哪些即使终止¹³¹I治疗也不会影响其生存或疾病特异性死亡率。

综上,该指南首次针对cDTC提出诊疗推荐。指南基于现有的研究证据及临床经验,并根据儿童较为特殊的病理生理及临床特征提出一系列建议及推荐,在¹³¹I治疗评估及诊治体系中,提出了cDTC术后风险分层及¹³¹I个体化治疗理念;强调¹³¹I治疗后动态评估在随诊中的作用和意义;强调¹³¹I治疗效果的充分发挥,严格把握再次治疗指征以避免过度治疗,以达到cDTC ¹³¹I治疗获益最大化为目的的治疗原则。这些理念的更新将有助于核医学科医师针对cDTC的¹³¹I治疗决策及其规范化。应当指出的是,循证医学证据相对较少、级别较低是该指南的不足。但可以看到,继该指南发布后,后续的研究进展正不断地填补着之前的不足及空白。

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