Review of: "Strategies for Management and Long-term Surveillance of Pediatric Differentiated Thyroid Cancer: Balancing Efficacy and Quality of Life"

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Potential competing interests: No potential competing interests to declare.

Overall, this is a well-written review article on pediatric thyroid carcinomas, covering both follicular- and C-cell-derived thyroid carcinomas. It summarizes disease characteristics, diagnosis, treatment, and current challenges of pediatric thyroid cancer to guide the standardized diagnosis and treatment of pediatric thyroid cancer. The review also highlights the importance of considering the psychological burden on this specific age group of pediatric patients.

This reviewer agrees with the author’s conclusions:

1) The management and follow-up of pediatric differentiated thyroid carcinoma (DTC) necessitates a nuanced and individualized approach, reflecting an evolving understanding of the disease's distinct behavior in children compared to adults.

2) While surgery remains the cornerstone of treatment, the decision-making process around the extent of thyroidectomy and the use of radioactive iodine (RAI) therapy must be judicious and guided by a comprehensive risk assessment strategy that balances the potential benefits against the risks of long-term adverse effects.

3) Postoperative management should emphasize the importance of tailored thyrotropin suppression therapy and vigilant surveillance to detect recurrence, which requires a lifelong commitment due to the extended risk period.

4) The psychosocial aspects and quality of life of pediatric patients must be integrated into the therapeutic equation, addressing the challenges of adherence to therapy and the potential psychological impacts of the disease and its treatment.

5) Ultimately, the goal is to optimize long-term health outcomes for children with DTC by ensuring effective tumor control while minimizing unnecessary interventions and their associated toxicities, thereby fostering a better quality of life.

Major criticisms:

1. Although descriptions and recommendations from Western guidelines, particularly the American Thyroid Association (ATA) clinical guidelines, offer valuable insights that enhance our understanding of the disease and aid in establishing domestic management guidelines adapted to each country's unique characteristics, this reviewer feels that the author's interpretation leans heavily towards North American viewpoints. As the author is a Chinese researcher practicing in

China, where the emphasis is not primarily on avoiding malpractice litigation, this reviewer recommends that the author present a more scientific basis to mitigate overdiagnosis and overtreatment of pediatric thyroid carcinoma, which are often driven by defensive medicine practices prevalent in North America. Especially considering that the profit-seeking nature of thyroid nodule practice in North America contributes to overtreatment. It is crucial to recognize that healthcare policies in many other countries, including China, are based on socialistic principles rather than the profit-driven models of North America. Therefore, this reviewer advises avoiding interpretations and recommendations related to defensive medicine and profit-seeking practices in this review. The reviewer stresses that overtreatment, such as total thyroidectomy (TTX) and/or RAI treatment, is mostly unnecessary for low-risk DTC. These procedures are recommended more for the safety of physicians rather than for the benefit of the patients.

2. In North America, tumor recurrence after lobectomy is often the target of malpractice litigation due to ATA management guidelines recommending TTX for pediatric PTC patients. More than 90% of patients undergo TTX in Western thyroid nodule practice. As the author emphasizes, treatment-related complications, such as vocal cord paralysis and hypoparathyroidism, can create life-long problems for the patient. Hypothyroidism inevitably occurs in 100% of patients treated with TTX, and more than 30% of patients with lobectomy. Furthermore, while many physicians regard hypothyroidism as treatable with hormone supplements, this is not always the case. Research indicates that many patients continue to experience hypothyroid-related symptoms even with normal serum TSH levels (PMID: 38357535). This reviewer suspects that this is one of the reasons why thyroid cancer patients in the USA are more likely to become bankrupt than patients with other types of cancer (PMID: 31862171, PMID: 35511135). Another concern is that as patients age and struggle to manage their hormone supplements independently, hypothyroidism can pose serious health risks such as coronary heart disease and reduced social activities (PMID: 37981725). Therefore, preserving thyroid function is crucial for pediatric patients in most countries. Lobectomy offers a viable alternative that preserves thyroid function in a significant number of patients. In contrast, thyroid cancer has a mortality risk of only 6% in the next 40 years.
3. One of the reasons why TTX is recommended in most Western guidelines is the high incidence of multifocality of PTCs in the thyroid gland (PMID: 32933805). To make the patient disease-free, most Western surgeons strongly believe TTX is oncologically the most appropriate intervention. However, this is not true; the small PTCs in the opposite lobe are indolent lesions that can be observed clinically (so-called active surveillance) as long as they remain asymptomatic.
4. The ATA clinical guidelines address three important recommendations/suggestions on how to handle low-risk small PTCs in adult patients: (1) do not perform thyroid FNA on nodules < 1 cm unless there is evidence of extrathyroidal extension or of lymph node or distant metastases; (2) restrict surgery (currently the Standard of Care) to lobectomy and avoid RAI in those with low-risk features; and (3) conduct further research to define the role of active surveillance instead of surgery for patients with low-risk tumors. Medical imaging enables the identification of small nodules well below the limits of clinical detection. Second, when these small nodules are subjected to ultrasound-guided FNA, about 5% reveal cancer cells. The usual next step is surgical removal, often followed by radioactive iodine and life-long thyroid hormone therapy. This approach is costly, creates risks from the treatments, and offers little or no benefit to most patients. The reviewer encourages the author to consider the cost effectiveness of thyroid cancer treatment for

pediatric patients, with the aim of saving significant social expenses.

5. Even in family members of MEN2 syndrome, patients can be effectively treated once early-stage MTCs develop. Some researchers have emphasized that it may be possible to delay treatment without causing significant harm until the patient reaches an age where they can make informed decisions about their treatment options (PMID: 22162466).

Minor comments:

There seem to be significant mistakes in the reference list. Please review your references thoroughly for relevance:

1. Reference #1 is “A novel SOS1-ALK fusion variant in a patient with metastatic lung adenocarcinoma and a remarkable response to crizotinib” by Dr. Chen et al. This study discusses lung cancer; however, in the review, it was cited after the following sentence: “The diagnosis and treatment of thyroid cancer can adversely affect their physical, psychological, and social development.”

2. Reference #5 is “Circulating tumor DNA as an emerging liquid biopsy biomarker for early diagnosis and therapeutic monitoring in hepatocellular carcinoma” by Dr. Wu et al. This study is about hepatocellular carcinoma; however, in the review, it was cited after the following sentence: “It is necessary to fully understand the differences between pediatric and adult thyroid cancers in terms of clinical pathological characteristics and disease prognosis, and to develop individualized management strategies.”