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Research Article

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

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Pediatric differentiated thyroid cancer (DTC) presents unique challenges distinct from its adult counterparts, including higher rates of multifocality, regional lymph node involvement, and distant metastases. This article reviews the latest advancements and controversies in the surgical management, postoperative care, and long-term surveillance of pediatric DTC, emphasizing the importance of a tailored approach based on individual risk assessments. The evolving landscape of treatment strategies aims to balance the imperative of effective cancer control with the need to mitigate long-term adverse effects and ensure quality of life. The review also highlights the critical need for ongoing research and multidisciplinary collaboration to refine and optimize management protocols for this vulnerable population.

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1. Introduction

Thyroid cancer is a common malignancy of the endocrine system in children and adolescents (hereinafter referred to as "children"), accounting for 5% to 7% of all malignant tumors in children. Since the children are in a critical period of growth and development, the diagnosis and treatment of thyroid cancer can adversely affect their physical, psychological, and social development [1][2][3][4]. Therefore, 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 [5][6][7][8][9]. This article reviews the disease characteristics, diagnostic and treatment protocols, and existing issues of pediatric thyroid cancer, combining recent clinical studies and management guidelines/consensus from China and the United States, to guide the standardized diagnosis and treatment of pediatric thyroid cancer.

2. Epidemiology of Pediatric Thyroid Cancer

Pediatric thyroid cancer is relatively rare. According to the World Health Organization's survey of cancer data from 49 countries worldwide, the age-standardized incidence rate of thyroid cancer in children (0-18 years) is 0.5-14.9 cases per million person-years; the incidence rate increases with age, and the rate is higher in females than in males. Consistent with the trend in adult thyroid cancer incidence, the incidence of pediatric thyroid cancer has been increasing in

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recent years, primarily in differentiated thyroid cancer (DTC). Data from the United States show that the incidence rate of pediatric DTC increased by an average of 1.11% per year from 1973 to 2006, and by an average of 9.56% per year from 2006 to 2013, indicating a significant upward trend. However, in discussing the reasons for this phenomenon, two points should be noted: on the one hand, not all new cases are early-stage or micro-cancers detected through imaging studies, but also include thyroid cancers larger than 25mm in diameter and cases with lymph node metastasis; on the other hand, the United States does not conduct routine screening for thyroid nodules and thyroid cancer [10][11][12][13][14]. Therefore, the increase in the incidence rate of pediatric thyroid cancer cannot be entirely explained by advances and widespread use of imaging studies.

In recent years, an important set of epidemiological data on pediatric thyroid cancer comes from a screening project in Japan. The screened population was children under 18 years old, and the study found no difference in incidence rates between areas with high, medium, and low radiation levels, with most cases concentrated among 12-18 year olds. The incidence of thyroid cancer in older children does not have the same characteristics. Therefore, some scholars suggest that the incidence of pediatric thyroid cancer is strongly related to age and less so to other factors.

3. Clinical Characteristics of Pediatric Thyroid Cancer

3.1. Risk Factors

The exact cause of pediatric thyroid cancer is not yet clear, but the recognized risk factors mainly include radiation and certain genetic factors. The thyroid in children is the only organ where a radiation dose of less than 0.01 Gy can lead to cancer, and the thyroid of children under five years old is most sensitive to radiation [15][16][17][18][19][20]. Compared to high-dose radiation exposure, moderate and low doses are more likely to cause thyroid abnormalities and even thyroid cancer, possibly because high doses usually kill all cells, whereas lower doses can damage cell DNA, leading to structural abnormalities in thyroid genes [21][22][23][24]. Before 1990, many children received radiation therapy to the head and neck for conditions such as facial acne, thymic hyperplasia, and blood malignancies, leading to a significant increase in the incidence of pediatric thyroid cancer. Such treatments have now been abandoned.

Having a family history of hereditary tumor syndromes is a risk factor for pediatric thyroid cancer [22][23][24][25][26]. These hereditary tumor syndromes include familial adenomatous polyposis (where papillary thyroid cancer of the cribriform-morular variant is common), PTEN hamartoma tumor syndrome, and DICER1 syndrome (caused by germline mutations in DICER1) [27][28][29][30][31]. Additionally, children with a family history of medullary thyroid cancer (MTC) should be vigilant for hereditary MTC. Hereditary MTC accounts for 20% to 25% of all MTC cases and is caused by germline mutations in the RET gene, including multiple endocrine neoplasia (MEN) types 2A and 2B and familial MTC without MEN.

3.2. Clinical Pathological and Molecular Characteristics

In pediatric thyroid cancer, papillary thyroid cancer (PTC) is the most common, with a higher proportion of diffuse sclerosing and tall cell subtypes compared to adults; follicular thyroid cancer (FTC) accounts for 5% to 10%; while medullary thyroid cancer (MTC), poorly-differentiated thyroid cancer (PDTC), and anaplastic thyroid cancer (ATC) are relatively rare. Pediatric MTC may appear as part of multiple endocrine neoplasia type 2 (MEN2).

Compared to adults, pediatric thyroid cancers are more often multifocal and more likely to have distant metastases at diagnosis. Studies have reported that a high proportion of pediatric thyroid cancers have lymph node metastases at diagnosis, with pulmonary metastases occurring in 8% to 29% of cases, potentially related to age, tumor size and number, and extrathyroidal invasion.

In pediatric thyroid cancer, gene fusions are more common than point mutations, with a higher occurrence rate of RET/PTC than in adults, while the BRAF mutations common in adult thyroid cancers are less frequent in children. Recent studies show that in pediatric thyroid cancers with distant metastases, the most common genetic alterations are RET gene fusions and NTRK1/3 gene fusions, while BRAF mutations account for only 19%. These molecular characteristics suggest that pediatric thyroid cancers may have a different molecular basis.

3.3. Tumor Prognosis

Metastasis is generally a significant marker of poor prognosis. However, in pediatric thyroid cancer, despite the majority of patients having lymph node or distant metastases at diagnosis, most have a good prognosis [32][33][34][35][36]. The 10-year survival rate for children with DTC is as high as 95%, and the thyroid cancer-related mortality rate after 40 years of follow-up is only 6%. A follow-up study on pediatric thyroid cancer patients reported an overall 15-year survival rate of 99%, with no statistical difference in overall survival rates among different histological types of tumors.

Although the mortality rate of pediatric thyroid cancer is low, the potential impact of this disease on children should not be underestimated. The risk of recurrence in pediatric thyroid cancer is higher than in adults, with literature reporting high 5-year and 10-year recurrence rates. Thyroid cancer can recur even 30 to 40 years after the initial diagnosis, so patients may require lifelong monitoring and follow-up.

4. Assessment of Pediatric Thyroid Cancer

Current guidelines/consensus do not provide clear recommendations for or against screening for pediatric thyroid cancer [37][38][39][40]. However, in clinical practice, it is recommended to inquire whether children have high-risk factors for thyroid cancer (such as radiation exposure, genetic factors); those with high-risk factors should consider undergoing thyroid cancer screening, primarily through ultrasound examination, and those with a family history of MTC should have calcitonin (Ctn) testing.

Most pediatric thyroid cancers have no obvious clinical symptoms and are often diagnosed due to the child or parents noticing a painless neck mass, which may be accompanied by breathing difficulties and/or thyroid function abnormalities, rarely resulting in hoarseness or coughing when drinking water. Nineteen percent of pediatric PTCs may present as diffuse infiltrative changes, appearing as unilateral or entire thyroid gland diffuse enlargement. Therefore, further ultrasound examination is needed once a pre-neck nodule or mass, asymmetrical thyroid lobes, or lymph node lesions are detected.

Although the prevalence of thyroid nodules in children is lower compared to adults, the risk of malignancy in pediatric thyroid nodules (3% to 70%) is significantly higher than in adults. Therefore, once a thyroid nodule is discovered in a child, it is essential to differentiate between benign and malignant nodules. The assessment of benign and malignant pediatric thyroid nodules is generally the same as in adults, but several points need attention: First, decreased thyrotropin (TSH) levels suggest the nodule may be a hyperfunctioning nodule, further diagnosed by thyroid scintigraphy; scintigraphically hot nodules are mostly benign in adults, but up to 30% of pediatric thyroid hot nodules may be malignant, hence the need for fine needle aspiration (FNA) examination or direct surgical treatment (lobectomy). Second, nodule size should not be the sole criterion for deciding whether to perform FNA on pediatric thyroid nodules; a comprehensive assessment should combine ultrasound characteristics and clinical risk factors, and FNA should be conducted under ultrasound guidance. Third, for most nodules that cannot be definitively diagnosed through cytology, surgical removal (lobe + isthmus) is preferable to repeated FNA. Fourth, if molecular testing is performed on FNA samples, attention should not be limited to mutations like BRAF but should also consider monitoring for multiple gene mutations and rearrangements; mutations positive cases are highly likely to be associated with malignancy, but mutation-negative cases are not sufficient to rule out malignancy. Fifth, to minimize the negative impact of medical radiation exposure on children, the use of computed tomography (CT) and positron emission computed tomography (PET-CT) should not be indiscriminately expanded; for thyroid tumors with larger invasive ranges, magnetic resonance imaging (MRI) may be considered as an auxiliary examination in devising surgical plans.

5. Management of Pediatric Thyroid Cancer

5.1. Surgery

Surgery is the preferred treatment option for pediatric differentiated thyroid cancer (DTC). One current controversy regarding surgical treatment is whether total thyroidectomy should be performed on all pediatric thyroid cancer patients. Studies have shown that the incidence of bilateral or multifocal PTC is high, and those who undergo total thyroidectomy have a lower probability of tumor residue, recurrence, and reoperation, and it is helpful for postoperative monitoring by measuring Tg levels. Therefore, both

Chinese and American guidelines recommend prioritizing total thyroidectomy. Considering the short-term and long-term risks that total thyroidectomy may bring to children, some scholars suggest that lobectomy may also be chosen for tumors confined to one lobe without lymph node metastasis. In clinical practice, the proportion of total thyroidectomy exceeds 90% in Western countries, but in two single-center studies in Southeast Asia, the proportion of total thyroidectomy is less than one-fourth. Such a significant difference reflects the relative conservatism in the choice of surgical methods for pediatric thyroid cancer in Southeast Asia, and the impact on the prognosis of pediatric thyroid cancer is worth exploring.

For children with DTC who have extrathyroidal invasion and/or central lymph node dissection, central lymph node dissection (CND) is widely accepted in the industry because this approach can increase the disease-free survival rate (DFS). Unilateral CND is performed for single foci, and whether contralateral CND is needed is judged based on intraoperative conditions. However, whether to perform prophylactic CND for children without extrathyroidal invasion and local metastasis is another point of controversy, mainly because the impact of prophylactic CND on DTC-specific survival rates and recurrence rates is inconclusive. In the United States, given the uncertainty of the benefits and the increased risk of surgical complications, the ATA does not recommend routine prophylactic CND; while in China, considering the higher postoperative recurrence rate of pediatric thyroid cancer and the significantly increased difficulty of reoperation after recurrence, routine prophylactic ipsilateral CND is recommended.

In pediatric thyroid cancer, another surgical topic worth paying attention to is the prophylactic thyroidectomy in children with MEN2 carrying high-risk (C634 and A883F) or very high-risk (M918) RET mutation genotypes. Global multicenter retrospective studies have indicated significant benefits from prophylactic removal, hence foreign guidelines recommend that the aforementioned children should undergo prophylactic thyroidectomy as early as possible within 1 year and 5 years, respectively. However, there are very few related reports in my country, and both doctors and patients lack adequate awareness of this situation, finding it difficult to accept total thyroidectomy for thyroid glands with no abnormal appearance. Therefore, domestic guidelines emphasize decision-making after full communication with the guardians of the child. Clearly, more clinical experience needs to be accumulated.

The current optimal surgical approach for pediatric thyroid cancer should involve comprehensive consideration of disease factors (including tumor type, size, and number, lymph node metastasis confirmed preoperatively and intraoperatively, etc.), surgeon factors (mainly surgical experience), and patient and family factors (such as physiological and psychological development status, level of concern about the disease itself, acceptance of surgical complications, etc.), after which the decision should be made jointly by the doctor and patient.

5.2. Postoperative Management of Pediatric DTC

Previously, it was believed that pediatric DTC often presents as multifocal and is more likely to have regional lymph node and distant metastases, thus radioactive iodine (RAI) treatment and long-term intensive TSH suppression therapy (TSH well below the normal lower limit or undetectable) almost became the "standard" after surgery. Increasingly, it is recognized that patients with pediatric DTC can live for a long time, so postoperative management strategies should consider both short-term and long-term benefits and risks. The 2015 ATA guidelines clearly proposed a postoperative management model based on risk assessment, and the 2021 consensus in China also acknowledges and recommends this approach.

For postoperative risk assessment of pediatric DTC, it mainly includes the assessment of tumor-specific mortality risk and tumor recurrence risk. The division of mortality risk is still based on the TNM staging of the American Joint Committee on Cancer (AJCC), but in this staging, all patients under 55 years of age are classified as stage I (without distant metastases) or II (with distant metastases), and this assessment method focused only on distant metastases is inadequate to predict the recurrence risk of pediatric DTC and to guide treatment. In 2015, ATA first proposed the recurrence risk stratification for pediatric DTC — low risk refers to tumors confined within the thyroid with no lymph node metastasis (N0/Nx) or with incidental central lymph node metastasis (microscopic foci or few numbers of transferred N1a); intermediate risk refers to extensive central lymph node metastasis (N1a) or minor lateral cervical lymph node metastasis (N1b); high risk refers to extensive regional invasion (widespread lateral

cervical lymph node metastasis N1b) or extrathyroidal extension (T4), with or without distant metastases. This risk stratification should be done within 12 weeks postoperatively to guide subsequent treatment and follow-up of the patient.

Currently, recurrence risk stratification is the main basis for deciding on postoperative RAI treatment, targets for TSH suppression therapy, and the items and frequency of follow-up monitoring. For low-risk children, RAI treatment is not recommended, and the target of TSH suppression therapy can be set at the lower end of the normal range (0.5-1.0 mIU/L), with follow-up focusing on neck ultrasound and detection of thyroglobulin (Tg) under L-T4 medication. For medium and high-risk children, RAI ablation treatment is considered, and the TSH suppression targets are set at 0.1-0.5 mIU/L and <0.1 mIU/L respectively, with Tg testing and whole-body iodine imaging every 1-2 years during follow-up to help determine whether the tumor persists.

Compared to the past, current recommendations are more cautious about postoperative RAI treatment for children with DTC. The reasons are mainly threefold: (1) Large retrospective studies on the effectiveness of RAI treatment for children with DTC have inconclusive results and the benefits are not clear. (2) Short-term adverse reactions of RAI treatment (sialadenitis, xerostomia, dental caries, nasolacrimal duct blockage, etc.) and long-term adverse reactions (permanent xerostomia, gonadal damage, suppression of the bone marrow hematopoietic system, pulmonary fibrosis, etc.) can have a negative impact on physical and mental health and quality of life. (3) Studies analyzing all-cause mortality rates of pediatric thyroid cancer patients after long-term follow-up of 30-50 years found that about two-thirds of the cases died of a second cancer not originating from the thyroid, and three-quarters of these patients had received postoperative RAI treatment. Although evidence of RAI-induced secondary cancer risk is still insufficient, it is noteworthy. Therefore, overtreatment should be avoided when children are unlikely to benefit from RAI treatment. Besides, for those who have previously shown no significant response to RAI treatment, empirical repeated RAI treatment should also be avoided.

Childhood and adolescence are critical periods for growth and development, hence the risks of hypothyroidism and hypocalcemia after thyroidectomy should be monitored. In addition to regular medication and routine monitoring, it's also important to consider that the psychological state of children with thyroid cancer may not be stable. Additionally, suffering from the disease might lead to negative psychological effects, further impacting medication adherence and resulting in inadequate treatment. Therefore, if drug therapy is found to be substandard during postoperative follow-up, confirming compliance and providing psychological support are indispensable steps.

Since children with DTC can live for a long time and the disease can recur decades after the initial diagnosis, their follow-up should continue for life. For those without evidence of recurrence, the frequency of follow-up can be gradually reduced.

6. Conclusion

The management and follow-up of pediatric DTC necessitate a nuanced and individualized approach, reflecting an evolving understanding of the disease's distinct behavior in children compared to adults. 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, guided by a comprehensive risk assessment strategy that balances the potential benefits against the risks of long-term adverse effects. Moreover, 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. Additionally, 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. 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.

Statements and Declarations

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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