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Review

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Nuclear medicine approaches in the field of oncologic pediatric surgery and review the risk factors for pediatric thyroid nodules

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ABSTRACT

Imaging methods used in nuclear medicine are non-invasive and can be applied to all pediatric age groups, including the neonatal period. F-18 FDG-PET/CT is used for staging, evaluation of treatment response, detection of metastases, and follow-up of various pediatric malignancies. In addition, the incidence of thyroid cancer in childhood has recently increased. In this review, we examined the F-18 FDG PET/CT imaging method that guide the management of the most common malignancies in children. We also discuss in detail the risk factors used in the diagnosis of thyroid cancer frequently encountered by pediatric surgeons.

Keywords: Pediatric surgery, nuclear medicine, PET/CT, thyroid cancer, risk factors

USE OF F-18 FDG PET/CT IN CHILDHOOD MALIGNANCIES

As the incidence of cancer in the childhood age group is lower than that in the adult age group, the incidence of childhood cancers is defined as per million. According to European data, it was reported to be 140 per million in the 0-15 age group and 157 per million in the 0-19 age group.[1] According to between 2014-2018 data from the Department of Cancer of the Public Health Institution of Turkey, the incidence of cancer in boys and girls aged 0-14 years is 10-50 per million, although it varies according to the type of cancer.[2]

Although the incidence of childhood cancers is low, it has serious clinical importance since it is the 2nd most common cause of death in this age group. The most common childhood malignancies are leukemias (30%), central nervous system and brain tumors (20%), lymphomas (14%), neuroblastoma (7%), soft tissue sarcomas (7%), Wilms' tumors (6%), bone tumors (5%), germ cell tumors (3%), retinoblastoma (3%), melanoma (3%), and hepatic tumors (1%).[3]

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) plays an important role in the diagnosis, staging, restaging, response to treatment, and evaluation of prognosis of childhood malignancies.[4] F-18 FDG PET/CT is a noninvasive molecular imaging method that reflects the metabolic properties of the tumor along with its structural status. F-18 FDG PET/CT is being used with increasing frequency in the diagnosis and follow-up of childhood tumors, but the imaging procedure, patient preparation, and calculation of radiation doses require greater care than in the adult age group. It is important to ensure sedation during imaging in pediatric patients. The practice guidelines of the American Academy of Pediatrics can be considered as a guiding example in this regard. In addition, to prevent harmful effects due to radiation, it is necessary to be more careful when calculating radiation doses compared to the adult group. In 2010, the North American Consensus Guideline was published, and the radiopharmaceutical doses to be applied were determined.[5]

CHILDHOOD LYMPHOMAS AND F-18 FDG PET/CT

F-18 FDG PET/CT is a functional and metabolic imaging method that plays a major role in the staging, treatment response evaluation, and residual/recurrence detection of HL and NHL.[6] The sensitivity, specificity, and accuracy (95.9%, 99.7%, and 99.6%, respectively) of 18F-FDG PET/CT were found to be higher (**Figure 1**) than those of other conventional imaging methods (70.1%, 99.0%, and 98.3%, respectively) for initial staging of lymphoma in children.[7]

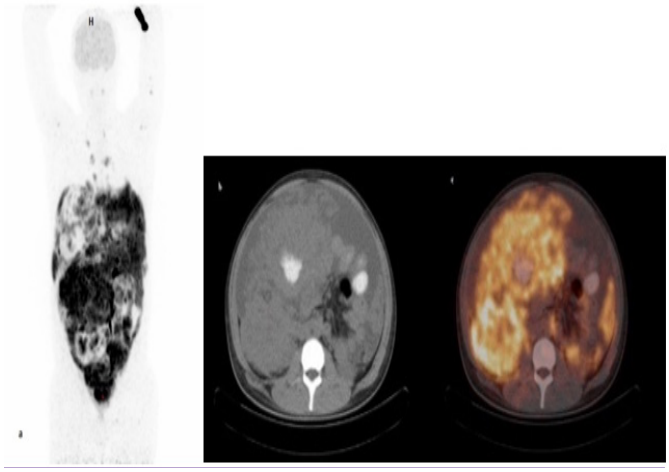

Figure 1. MIP (a), transaxial CT (b) and fusion (c) F-18 FDG PET/CT images of a 15 years-old male patient. Abdominal lymph node biopsy revealed high grade malign B cell lymphoma (Burkitt). On F-18 FDG PET/CT imaging, there were multipl hyper-metabolic mediastinal, abdominal, pelvic lymph nodes, massive abdominal fluid and bone marrow involvement
Figure 1 was obtained from Bıçakçı N, et al.[4]

SYMPATHETIC NERVOUS SYSTEM TUMOURS AND F-18 FDG PET/CT

Neuroblastoma (NB) is the most common tumor in this group, with 90% of cases diagnosed by the age of 5 years. The use of F-18 FDG PET/CT in the diagnosis, staging, and evaluation of response to treatment is limited. In a study, it was reported that F-18 FDG showed moderate uptake in the metaiodobenzylguanidine (MIBG) (-) and (+) groups and was not as successful as MIBG in showing bone and bone marrow metastases.[8]

Treatment modalities for NB usually include 4-6 cycles of induction therapy followed by surgical resection and radiotherapy to the primary site and other active residual disease sites. A recent study evaluated the benefit of surgical resection in a subgroup of patients with poor response to induction therapy (tumor volume >50% of the initial volume after six cycles of induction therapy). The results showed a statistically significant improvement in the 3-year overall survival of patients who responded poorly to induction therapy and underwent tumor resection compared with those who did not undergo surgery.[9] The promising MIBG-labelled PET radiopharmaceuticals, F-18 DOPA (18-F-L 3,4-dihydroxyphenylalanine), Ga-68 DOTA peptids in NB are important for guiding high-dose therapy with I-131 MIBG and Lu-177 DOTA peptids.[10]

WILMS' TUMOR AND F-18 FDG PET/CT

Wilms' tumor (nephroblastoma) is the 4th most common tumor in childhood. Although its etiology is unknown, genetic diseases are associated with 5% of the cases. The overall 5-year survival rate exceeds 90%.[11] Tumor staging, such as tumor location, size, local extension, vascular compression or invasion, and local lymph node metastases, are best assessed by CT, MR imaging, and ultrasonography.[12] The most common site for metastases is the lungs, which are typically assessed by chest CT.[12]

Therefore, the use of F-18 FDG PET/CT for diagnosis and staging has been limited. Wilms tumors show strong 18F-FDG uptake.[13,14] The mean SUV has been reported to be 6.8.[14] Anaplastic Wilms tumors showed particularly high 18F-FDG uptake, and the SUVmax value greater than 5 was due to the highly expressed glucose transporter 1.[13] Apart from this, no significant correlation was found between 18F-FDG uptake and tumour histopathology.[12] F-18 FDG PET/CT appears useful for assessing the response to treatment.[15]

RHABDOMYOSARCOMA AND F-18 FDG PET/CT

Rhabdomyosarcoma (RMS), arising from embryonic mesenchymal cells differentiating into skeletal muscle, accounts for 20% of all solid tumors in children.[16] Although the cases are sporadic, some congenital and genetic diseases increase the risk of RMS (Li Fraumeni syndrome, Beckwith Wiedemann syndrome, Neurofibromatosis type 1, Costilla syndrome, Nooan syndrome). There are embryonal and alveolar histological types of RMS, and the incidence in boys is slightly higher than that in girls (male/female ratio of 1.51).[17]

In the past, aggressive surgical methods such as amputation and pelvic and orbital exenteration had an important role in the treatment of RMS, but in the current treatment of RMS, organ-preserving surgery with chemotherapy and radiotherapy is at the forefront. The survival rate, which was 25% with radical surgical treatment, increased to 70% with the addition of radiotherapy and chemotherapy to the surgical treatment.

F-18 FDG PET/CT is used in RMS to determine the malignancy potential of the lesion, biopsy site selection, staging, and evaluation of response to treatment. This group of tumors showed high FDG accumulation, which increased as the tumor grade increased.

Although F-18 FDG PET/CT is not routinely used for initial staging in pediatric RMS, it is specifically used for the detection of nodal involvement and distant metastatic spread. For nodal involvement, F-18 FDG PET/CT showed a sensitivity of 80%[18] or 100%[19-21] and specificity of 89-100%. F-18 FDG PET/CT has a higher chance of detecting lung metastases larger than 1 cm (**Figure 2**) and bone, and bone marrow metastases than conventional methods. For the detection of distant metastatic sites, PET-CT has a sensitivity of 95%[19] or 100%[18-21] and specificity of 80-100%.

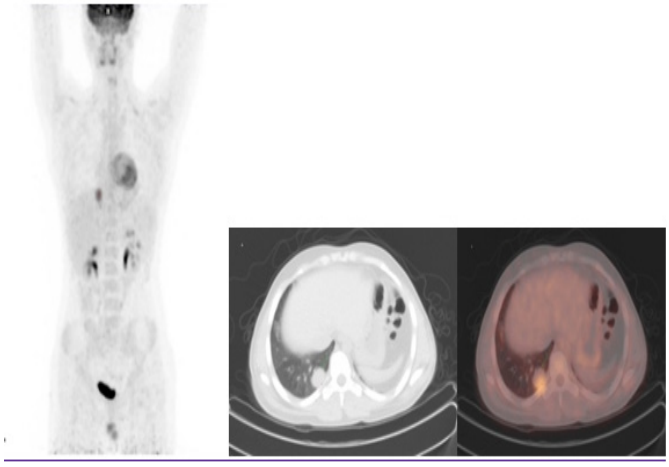

Figure 2. MIP (a), transaxial CT (b) and fusion (c) F-18 FDG PET/CT images of a 16 years-old male patient. Histopathologically diagnosis was rhabdomyosarcoma. On F-18 FDG PET/CT imaging, there were hyper-metabolic metastatic nodule in right lung posterobasal segment
Figure 2 was obtained from Bıçakçı N, et al.[4]

REVIEW OF RISK FACTORS FOR AT THE MANAGEMENT OF PEDIATRIC THYROID NODULES

Clinical Risk Factors for Pediatric Thyroid Nodules

The incidence of childhood thyroid cancer is increasing recently.[22] Despite the rapid increasing incidence, pediatric thyroid cancers constitute less than 2 % of all thyroid cancers.[23] Owing to the high prevalence of thyroid cancer in adults, the main diagnostic and prognostic criteria for thyroid cancer have been developed for adults and were adapted to secondarily applied to children. The American Thyroid Association (ATA) and American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) for reporting sonographic findings and The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) were both developed the management of adult thyroid nodules but are widely used the classification of thyroid nodules in children.[24-26]

Differences in the underlying biology of thyroid tumors between adults and children may affect the risk of malignancy (ROM) predicted by various sonographic and cytopathological findings.

Although thyroid nodules are detected at a much higher rate in adults than in children, they are five times more likely to be malignant in children (26.4%) than in adults (5%).[27] Radiation exposure, autoimmune thyroid disease, and chronic iodine deficiency are well-established risk factors for the development of thyroid malignancies in both adults and children.[28-30]

Childhood thyroid cancer is often diagnosed at a more advanced stage compared to adults, and is more likely to develop regional lymph node and lung involvement and higher recurrence rate. Distant metastases almost always occur in the lungs. These are diffuse and are usually identified by I-131 whole-body imaging (**Figure 3**).[31]

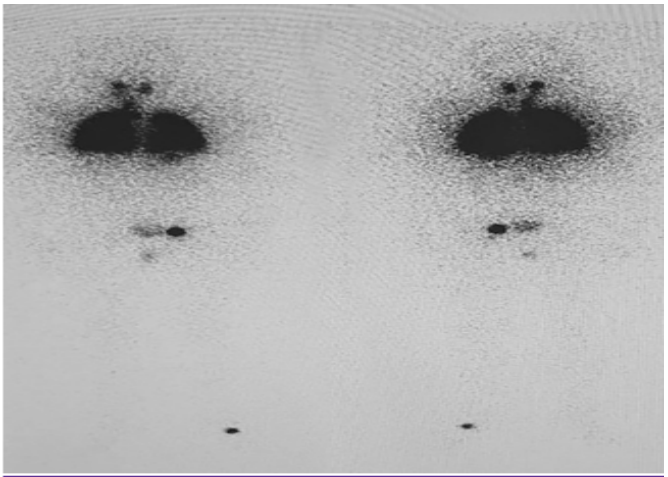

Figure 3. A 12-year-old girl who underwent total thyroidectomy for papillary thyroid cancer. Tg:22.62 µg/L, whole-body scan with 5 mCi I-131 shows diffuse metastatic foci in the lungs, left sacrum and heel of the left
Figure 3 was obtained from Aslı Ayan, MD.

Despite more advanced disease at presentation, children with thyroid cancer have a much lower death rate, with overall cumulative survival rates as high as 97-99%.[32]

The majority of thyroid cancers in children are papillary thyroid carcinoma (PTC) (80-90%), followed by follicular thyroid carcinoma (FTC) (10%), medullary thyroid carcinoma (MTC) (3-5%). Anaplastic thyroid carcinoma (ATC), and poorly differentiated thyroid carcinoma (PDTC) are rarely encountered.[33,34]

ATC is a dedifferentiated thyroid cancer via transformation of differentiated thyroid cancer.[35] It is extremely rare in children. Poor outcomes in children are largely due to regional and distant metastases, rather than the local spread of dedifferentiated tumors as seen in adults.[33]

Genetic Risk Factors for Pediatric Thyroid Cancer

Recent molecular profiling studies have suggested that thyroid cancer in adults and children has different developmental origins, which may explain their different clinical characteristics. PTC is the most common histological type of thyroid cancer in both adult and pediatric populations, although the histological subtype frequencies are different between children and adults.[34,36]

Notably, BRAF V600E, RAS (mostly HRAS and NRAS) point mutations, and gene fusions are mutually exclusive causes of DTC.[37]

Unlike the adult thyroid cancer profile, there is a high prevalence of gene fusion in pediatric PTC. RET, NTRK1, NTRK3, ALK, BRAF, AKAP9, and MET gene fusions are among the most common in pediatric PTC.[38] However, there is a lower frequency of point mutations in the RAS, BRAF and, GNAS genes in children with PTC than in adults.[39] Specific fusions tend to be associated with different histological subtypes of pediatric thyroid cancer. For example, AKAP9-BRAF is a less frequent BRAF alteration associated with classic papillary histology, whereas PAX8-PPARG has a follicular histology.[33]

Pediatric PTCs associated with fusion mutations have a higher frequency of aggressive subtypes, including diffuse sclerosing, tall cell, and solid variant.[36] RET-PTC rearrangements are associated with solid PTC variants. Rearrangements are typical in pediatric patients with radiation-induced PTC.[40]

Between 15-19 years of age, fusion mutations decrease and point mutations potentially lead to dedifferentiation, and radioactive iodine resistance begins to increase as in adults.[41]

Genetic syndromes are also known risk factors for pediatric thyroid cancer, accounting for approximately 5% of all pediatric DTC cases. Some of the more common syndromes affecting the thyroid include PTEN hamartoma tumor syndrome, APC-associated polyposis (e.g., familial adenomatous polyposis), Carney complex, DICER1 syndrome, and Werner syndrome.[33] Medullary thyroid cancer (MTC) is frequently associated with mutations in the RET proto-oncogene and accounts for 5% of all pediatric thyroid cancer cases.[37] Most MTC cases in the pediatric population are hereditary, with germline RET mutations resulting in multiple endocrine neoplasia (MEN) type 2A syndrome (90-95% of childhood MTC), MEN type 2B, or familial medullary thyroid carcinoma (FMTC).[42]

Adult tumors caused by gene fusion do not usually progress to more aggressive diseases. Rather, progression of adult thyroid cancer involves the accumulation of additional point mutations associated with local disease spread, metastasis, and transformation to aggressive dedifferentiated anaplastic and poorly differentiated subtypes. PTC progression is associated with the inclusion of other secondary gene mutations such

as TP53, PIK3CA, and AKT1. These secondary mutations are extremely rare in children and have not been detected in several recent large-scale sequencing studies on pediatric thyroid cancer.[42,43]

Ultrasonographic Risk Classification

Ultrasonography (US) is the most commonly used imaging modality for detecting thyroid nodules, measuring nodule size, and determining nodule shape, borders, location and number, echogenicity, content, and assessment of associated changes in the thyroid gland.[44]

Multiple risk classification systems based on US features of thyroid nodules have been developed to provide general terminology for the identification and classification of nodules at the greatest risk of morbidity and avoiding biopsies of benign nodules.[45]

The ability of the ACR TI-RADS[46] to accurately predict the risk of malignancy in pediatric thyroid nodules is currently unclear, as it was predominantly validated using adult data. However, recommendations for the evaluation and management of pediatric thyroid nodules have historically been based on the adult guidelines.[33]

One of the two most widely used systems in clinical practice is the ACR TI-RADS, which is used by many radiologists, and the other is the ATA guidelines, which is used by many endocrinologists. ACR TI-RADS summarizes this by scoring each of the five ultrasound findings (composition, echogenicity, shape, border features, and echogenic foci of the nodule) and defines the risk levels from TR1 to TR5. Fine-needle aspiration biopsy (FNAB) is recommended for TR3 nodules ≥2.5 cm, TR4 nodules ≥1.5 cm and TR5 nodules ≥1 cm. The biopsy and follow-up criteria according to ACR TI-RADS are summarized in **Table 1**.[45]

The 2009 ATA adult guidelines indicate that the evaluation and treatment of thyroid nodules in children should be the same as those adults.[47] The 2009 ATA adult guideline states that FNAB is not necessary for nodules smaller than 1 cm, unless they are high-risk, has a history of ionizing radiation, or have a pathological regional lymph node. However, the size criterion in children is more problematic because thyroid volume changes with age and nodule size alone does not predict malignant histology. Therefore, US features of malignant lesions, such as hypoechogenicity, irregular borders, microcalcifications, increased intranodular blood flow, and clinical signs, should be given more importance in defining nodules requiring FNAB. US evaluation of cervical lymph nodes should be performed in all children with suspicious nodules.[48,49]

It should also be noted that in the, the diffuse sclerosing subtype which is invasive form of PTC, the tumor shows diffuse microcalcifications without nodules or macroscopic metastases in the cervical lymph nodes.

Evaluation of Pediatric Thyroid FNAB Cytopathology with the Bethesda Classification System

US is often the first step in imaging thyroid nodules. ACR TI-RADS is a well-established tool for evaluating the risk of malignancy in adult thyroid nodules, but its application to pediatric thyroid nodules is still in progress.[50]

Thyroid nodules that are suspicious on US underwent FNAB for differential diagnosis to guide further management decisions. As cytomorphology does not always provide a clear difference between benign and malignant lesions, it is important to have specific diagnostic criteria to stratify the ROM of thyroid nodules based on FNAB results. TBSRTC had been developed and published in 2010.[26] Among the TBSRTC categories, atypia of undetermined significance (AUS), follicular neoplasm (FN), and suspected malignancy (SM) were considered indeterminate. TBSRTC was first updated in 2017 to include non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) as a new histological entity, which may alter the ROM of adult thyroid nodules.[51]

Table 1. ACR-TIRADS classifications and recommendations

Composition (choose one) Spongioform 0 point Cystic 0 point Mixed 1 point Solid 2 point Cannot be determined	**Echogenity (choose one)** Anechoic 0 point Iso/hyperechoic 1 point Hypoechoic 2 point Very hypoechoic 3 point	**Shape diameter (choose one)** Wider than tall 0 point Taller than wide 3 point	**Margin (choose one)** Smooth 0 point Ill-defined 0 point Lobulated 2 point irregular 2 point ETE 3 point	**Echogenic foci choose all that apply** None 0 point Comet like artifact 0 point Macrocalcification 1 point Rim calcification 2 point Small echogenic foci 3 point (microcalcification)
Add points from all categories to determine TI-RADS level				
0 points	1 points	2 points	4-6 points	7 points or more
TR1 benign no FNAB	TR2 not suspicious no FNAB	TR3 mildly suspicious FNAB if ≥2.5 cm follow if ≥1.5cm	TR4 Moderately suspicious FNAB if ≥1.5 cm follow if ≥1 cm	TR5 Highly suspicious FNAB if ≥1 cm follow if ≥0.5 cm
Composition	**Echogenicity**	**Shape**	**Margin**	**Echogenic foci**
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. Mixed cystic and solid: Assign points for predominant Solid component. Assign 2 points if composition cannot be determined because of calcification.	Anechoic: Applies to cystic or almost completely cystic nodules. Hyperechoic/isoechoic/ hypoechoic: Compared to adjacent parenchyma. Very hypoechoic: More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	Taller-than-wide: Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	Lobulated: Protrusions into adjacent tissue. Irregular: Jagged, spiculated, or sharp angles. Extrathyroidal extension: Obvious invasion=malignancy. Assign 0 points if margin cannot be determined.	Large comet-tail artifacts: V-shaped, >1 mm, in cystic components. Macrocalcifications: Cause acoustic shadowing. Peripheral: Complete or incomplete along margin. Punctate echogenic foci: May have small comet-tail artifacts.

ETE: Extra thyroidal extention, ACR TI-RADS: American College of radiology thyroid imaging reporting and data system, FNAB: Fine-needle aspiration biopsy
Table 1 was established using the ACR TI-RADS guidelines.[24]

Table 2. The 2023 Bethesda system for reporting thyroid cytopathology. This table was established using the 2023 Bethesda system for reporting thyroid cytopathology guideline.[32]

	Adult		Pediatric	
Diagnostic category	ROM mean % (min-max)	Usual management	ROM mean % (min-max)	Usual management
Nondiagnostic (Bethesda I)	13% (5-20)	Repeat FNAB with ultrasound guidance	14% (0-33)	Repeat FNAB with ultrasound guidance
Benign (Bethesda II)	4% (2-7)	Clinical and ultrasound follow-up	6% (0-27)	Clinical and ultrasound follow-up
Atypia of undetermined significance Bethesda III	22% (13-30)	Repeat FNAB Molecular testing Lobectomy Surveillance	28% (11-54)	Repeat FNAB lobectomy
Follicular neoplasm (Bethesda IV)	30% (23-34)	Molecular testing Diagnostic lobectomy	50% (58-100)	Surgical resection
Suspicious for malignancy (Bethesda V)	74% (67-83)	Molecular testing Lobectomy or near-total thyroidectomy	81% (40-100)	Surgical resection
Malignant (Bethesda VI)	97% (97-100)	Lobectomy or near-total thyroidectomy	98% (86-100)	Surgical resection

ROM: Risk of malignancy, FNAB: Fine-needle aspiration biopsy, min-max: Minimum-maximum

A pediatric cohort study reported that the performance of TBSRTC in pediatric populations is unlikely to be affected by the addition of NIFTP.[52] The third edition of the TBSRTC was released in 2023 with updated ROMs (**Table 2**).[53] The new TBSRTC includes two subclassifications of AUS: AUS nuclear atypia and AUS other. In addition, for the first time, the new TBSRTC includes information on its application to pediatric thyroid nodules.

Differences between guidelines have highlighted the need for new methodologies to classify the risk of indeterminate thyroid nodules in pediatric populations. In the third TBSRTC, AUS is divided into two main groups: AUS with nuclear atypia and AUS with any other form of atypia (AUS other).[56] In a retrospective cohort study of 68 pediatric AUS thyroid nodules, there was an increased ROM when there was nuclear atypia (59% for nuclear atypia vs. 6.5% for architectural atypia). The highest ROM was observed in the nodules with both nuclear and architectural atypia (75%). The results of this study demonstrate that risk stratification of AUS pediatric thyroid nodules by atypia type may identify a subset of nodules that require surgical management and reduce overtreatment of nodules that do not have nuclear atypia.[54]

Molecular Techniques for Risk Stratification of Indeterminate Thyroid Nodules

Recently, there have been rapid developments in cytomolecular testing to reduce the need for Bethesda III and IV diagnostic surgery. The Afirma Genomic Sequencing Classifier (Afirma GSC) and Thyroseqv3 (TSv3) performed well, similar to undiagnosed FNAB results (Bethesda III and IV). TSv3 was found to have a relatively high sensitivity and negative predictive value of 90% and 96%, respectively. However, their diagnostic confirmatory performance for malignancy remains limited.[57] Although the use of molecular techniques is increasing, the cost of molecular testing remains the most important problem.

The rate of structural malignancy in BRAFV600E positivity alone in intrathyroidal micropapillary cancer was approximately 1-2%. Bilateral thyroidectomy, lymph node dissection, and RAI treatment are recommended for BRAF-positive intrathyroidal tumors. Active follow-up may be considered for BRAF-negative micropapillary cancers, and lobectomy may be considered for BRAF-negative or BRAF-positive micropapillary cancers. In patients with BRAF V600E+TERT or RAS+TERT promoter mutations, aggressive treatment approaches are selected, even if micropapillary cancer is present.[58]

CONCLUSION

There are many risk stratification systems according to the US characteristics of thyroid nodules, and the most widely used in clinics are the ATA guidelines and ACR TI-RADS. FNAB is the gold standard for evaluating nodules according to US risk stratification. TBSRTC is the most widely used cytomorphological classification for FNAB. The last TBSRTC reporting system covering the adult and pediatric populations was updated in 2023. Recently, there has been a trend towards the use of molecular testing of FNAB specimens, especially those diagnosed as Bethesda III and IV, to reduce the need for diagnostic surgery and to guide treatment.

In conclusion, an excellent prognosis for pediatric DTC may be possible with a review of diagnostic processes and management guidelines for pediatric thyroid cancer.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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