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RESEARCH

Risk-adapted therapy in pediatric thyroid cancer: initial experience from a national reference program by the MET group

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Abstract

Background: Pediatric differentiated thyroid carcinoma (pedDTC) is rare but increasingly prevalent, requiring multidisciplinary care to ensure optimal outcomes. In 2021, the pediatric national reference program of the German Malignant Endocrine Tumor (MET) registry was established to standardize the management of pedDTC, with a particular focus on radioactive iodine (RAI) use and minimizing treatment variability.

Methods: This study evaluated the program's first 3.5 years, including 43 inquiries concerning 39 patients with confirmed or suspected pedDTC. A weekly national expert tumor board provided individualized recommendations based on multidisciplinary input and risk stratification. Data were analyzed for demographic trends, therapeutic decisions, and short-term outcomes.

Results: Among 34 patients with confirmed pedDTC, RAI use was reduced or omitted in 70.6% of cases, particularly among low-risk patients, in alignment with the American Thyroid Association 2015 guidelines. Surgical strategies were modified in 61.5% of cases to balance disease control with treatment-related morbidity. No systemic medical therapy was recommended during initial management. At a mean follow-up of 0.7 years, all patients were alive; persistent disease was observed in 15.4%.

Conclusions: The national reference program has successfully introduced a structured, individualized approach to the management of pedDTC in Germany. Ongoing data collection and longer follow-up will be essential to assess the long-term impact of this centralized, risk-adapted model.

Keywords: children and adolescents; differentiated thyroid carcinoma; radioactive iodine therapy; reference program

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Introduction

Pediatric differentiated thyroid carcinoma (pedDTC) is a rare but clinically significant malignancy, with an incidence of approximately 20–30 new cases annually in Germany (1). While it accounts for only a small fraction of pediatric cancers, it is the most common endocrine malignancy in children and has shown a rising global incidence (2, 3, 4). Pediatric cases often present at more advanced stages than adult thyroid carcinomas, with a higher prevalence of regional lymph node involvement and distant metastases (5, 6). Despite these aggressive features, the long-term prognosis is excellent, with survival rates exceeding 95% (6, 7).

The standard management of pedDTC has evolved from a uniform approach of total thyroidectomy, selective neck dissection, and radioiodine therapy (RAI) for thyroid remnant ablation to a more targeted strategy focusing on metastatic disease treatment (8, 9). The American Thyroid Association (ATA) advocates for empiric and dosimetry-guided RAI protocols in children to optimize therapeutic efficacy while minimizing toxicity (10).

The excellent survival outcomes have prompted a critical reevaluation of RAI use, particularly in low- and intermediate-risk disease. This shift is driven by concerns about both acute side effects (e.g. sialadenitis) and long-term risks (e.g. pulmonary fibrosis, secondary malignancies, or gonadal toxicity), alongside growing evidence of overtreatment in certain risk groups. These considerations have led to the development of more nuanced, pediatric-specific treatment guidelines (9, 11, 12).

In 2015, the ATA recommended against routine RAI for low-risk pedDTC patients, characterized by absent distant metastases and minimal residual disease (9). This position reflects efforts to balance favorable survival outcomes with minimization of treatment-related morbidity. The European Thyroid Association (ETA), however, has maintained a more conservative stance, citing insufficient consensus and the need for long-term outcome data to support these modified treatment strategies (13).

In Germany, the care of pedDTC is traditionally localized at the intersection of multiple disciplines, including surgery, nuclear medicine, pediatric endocrinology, and pediatric oncology. Unlike other pediatric malignancies, there are no established standardized protocols specifically developed for the management of pedDTC. This multidisciplinary but unstandardized approach underscores the need for harmonized treatment practices to ensure consistency and optimize outcomes. Recognizing these challenges, the German Malignant Endocrine Tumor (MET) group established a pediatric national reference program for RAI in 2021. This centralized initiative aims to reduce treatment variability, provide expert-driven oversight for RAI dosing, and minimize associated risks. Through standardized recommendations for nuclear medicine practices, the program aims to optimize outcomes while safeguarding the long-term health of children and adolescents with DTC.

The success of centralized quality control in other pediatric oncology contexts, such as the German radiotherapy quality control program's role in the SIOP PNET5 MB trial for medulloblastoma, underscores the potential of this model to reduce variability and improve outcomes (14, 15).

Here, we report our initial experience with the pediatric national reference program.

Methods

This study analyzed the first 3.5 years of experience within the pediatric national reference program, established in March 2021, to standardize care for children and adolescents with pedDTC in Germany. The initiative is embedded within the national STEP (Seltene Tumor-Erkrankungen in der Pädiatrie)-MET tumor board, a virtual, interdisciplinary platform convened weekly to discuss rare pediatric malignancies. The (GPOH-) MET registry was approved by the ethics committees of the Otto-von-Guericke-University Magdeburg (IRB 174/12 and 52/22), Germany.

The tumor board includes pediatric oncologists, nuclear medicine specialists, and endocrine and pediatric surgeons. Referring physicians submit each case using a standardized registration form that captures key clinical data, including patient demographics, imaging findings, histopathological results, laboratory values, and prior treatments (Supplemental File (see section on Supplementary materials given at the end of the article)). Treating providers are encouraged to attend the tumor board and present their patient's case directly. If participation is not feasible, the board reviews the submitted data and may request additional information or original reports. This process supports shared decision-making and ensures individualized recommendations. To promote consistency across centers, the MET group developed several standardized tools. A detailed case report form (CRF) was implemented to guide data collection, including tumor staging, surgical and histopathological findings, RAI therapy data, and follow-up status (Supplemental File).

A standard operating procedure outlines the submission and review process, including timelines, case presentation, and documentation (Supplemental File). All data protection procedures adhere to national regulations for clinical data management.

Case discussions focus on comprehensive review of the submitted clinical materials. Treatment recommendations, including those related to RAI

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therapy, were individualized based on ATA risk stratification, patient age, extent of surgery, presence of lymph node or distant metastases, postoperative thyroglobulin levels, and, when applicable, prior RAI treatment and activity. For patients with low-risk disease and limited surgery (e.g. hemithyroidectomy), a watch-and-wait approach was sometimes advised over completion thyroidectomy and RAI.

All recommendations were documented and communicated to the referring physicians.

The collected data were subsequently analyzed for demographic trends, types of inquiries, treatment recommendations, and short-term outcomes.

Results

The pediatric national reference program evaluated 43 inquiries concerning 39 patients during its first 3.5 years of operation (March 2021–September 2024). These included 34 inquiries for confirmed pedDTC and nine with suspected disease. The patients were discussed multiple times: two were discussed twice, and one was reviewed on three separate occasions. The cohort comprised 27 females (69.2%) and 12 males (30.8%), with a median age at presentation of 13.0 years (range: 3.2–17.5 years). For patients with confirmed pedDTC, the mean follow-up duration was 0.7 years (range: 0–7.0 years), and the mean time since tumor board discussion was 0.1 years (range: 0–0.8 years).

Detailed clinical and demographic characteristics are summarized in Table 1.

Tumor board inquiries were classified into four main categories: RAI therapy recommendations (n = 17), surgical considerations (n = 13), diagnostic and follow-up strategies (n = 9), and systemic therapy decisions (n = 4). Five patients had not achieved complete remission, as defined by Tuttle *et al.* (16). These patients were significantly younger than those in remission (mean age: 8.1 vs 12.8 years; P < 0.001).

Table 1 Patient demographics and clinical characteristics of confirmed and suspected pedDTC cases.

	pedDTC		
Characteristics	**Confirmed**	**Suspected**	**Total**
Total, *n*	30	9	39
Female, *n* (%)	21 (70.0)	6 (66.7)	12 (30.8)
Male, *n* (%)	9 (30.0)	3 (33.3)	27 (69.2)
Age (years) at presentation*	12.0	14.0	13.0
Other interventions			
RAI	16	1	17
(Additional) surgery	10	3	13
Diagnostics and follow-up	4	5	9
Systemic medical therapy	4	0	4

*Median values.

Therapeutic recommendations

A primary objective of the reference program was to optimize treatment through individualized, risk-adapted strategies. In more than half of the confirmed pedDTC cases, this led to recommendations for reduced therapeutic intensity.

Of the 17 RAI-related inquiries, the tumor board advised against RAI in 12 cases (70.6%), confirmed the original plan in four cases (23.5%), and recommended RAI in one case (5.9%) despite the referring team initially opting against it. A subset of patients with available data on RAI dosing is summarized in Supplemental Table 1, including age, weight, and administered activity.

Among 13 surgical inquiries, the planned approach was confirmed in five cases (38.5%). A more extensive surgical strategy was recommended in five cases (38.5%) to optimize disease control, while a less aggressive approach was advised in three cases (23.0%) to minimize procedural morbidity. More extensive surgery typically involved upgrading from hemithyroidectomy to total thyroidectomy with central or lateral neck dissection based on imaging or histopathological findings, while less aggressive recommendations included deferring completion thyroidectomy in low-risk patients with no evidence of residual disease.

In all four cases evaluated for systemic medical therapy, the board advised against initiating treatment and instead recommended close clinical monitoring with scheduled reassessment. Of the nine diagnostic/follow-up inquiries, five (55.6%) concerned thyroid nodule management, and four (44.4%) focused on follow-up in patients with confirmed pedDTC. In one case, the proposed follow-up plan was endorsed; in the remaining three, the board recommended a less intensive approach, such as extending follow-up intervals or tapering TSH suppression. A summary of recommendation types is shown in Fig. 1.

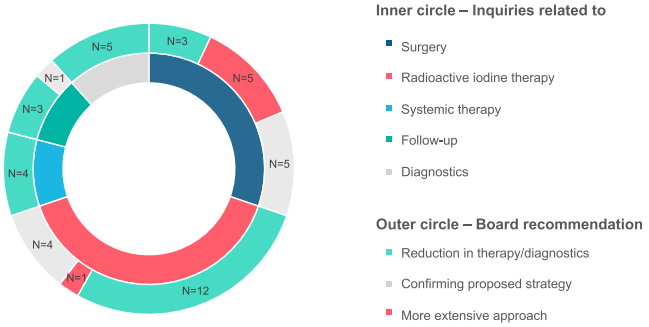

Figure 1

Recommendations for RAI therapy, surgical strategies, systemic therapies, and diagnostics (outer circle) in comparison to the approach initially suggested by the referring physician (inner circle).

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Therapeutic recommendations by risk stratification

Treatment recommendations were stratified according to ATA risk categories. Among the 16 evaluable patients with confirmed pedDTC, seven (43.8%) were classified as low-risk, five (31.3%) as intermediate-risk, and four (25.0%) as high-risk. RAI was omitted in three low-risk patients, aligning with the board´s strategy to avoid unnecessary exposure in this group. For intermediate-risk patients, recommendations included dose reduction in one case and confirmation of the proposed activity in another.

Surgical recommendations followed a similar pattern. In the low-risk group, surgery was confirmed in three reviewed cases, and a more extensive approach was recommended in another. For the single intermediate-risk patient requiring surgical review, a more extensive approach was advised. Systemic medical therapy was considered for four patients – one intermediate-risk and three high-risk – but was not recommended in any case. Instead, the board advised careful monitoring based on dynamic response and clinical evaluation. A full summary by risk category is presented in Table 2.

Outcome analysis

All 39 patients were alive at the time of analysis, including six with persistent disease. Among these, two had locoregional lymph node involvement with persistent iodine uptake in nodal metastases, and four had pulmonary metastases – either with elevated TG levels or structural persistence on imaging. All six patients received, before or following tumor board recommendation, one to three courses of RAI therapy, with administered activities ranging from 1.1 to 3.7 GBq, tailored to individual risk profile and treatment history. In two patients, the tumor board advised close monitoring due to stable disease and the potential for delayed TG decline over time.

Due to the short follow-up period (mean: 0.7 years), long-term outcome assessment and remission analysis remain limited. Ongoing data collection will enable future evaluation of treatment efficacy, late effects, and relapse risk.

Table 2 Therapeutic recommendations stratified by American Thyroid Association risk category (9).

	Risk category		
Recommendations	**Low**	**Intermediate**	**High**
RAI not recommended	3	0	0
RAI confirmed	2	2†	0
Surgery confirmed	3	0	0
Surgery more aggressive*	1	1	0
Systemic therapy not recommended	0	0	4

*The surgical strategy 'more aggressive' refers to upgrading from hemithyroidectomy to total thyroidectomy with central or lateral neck dissection based on imaging or histopathological findings. †Including dose reduction in one case and confirmation of the proposed activity in another.

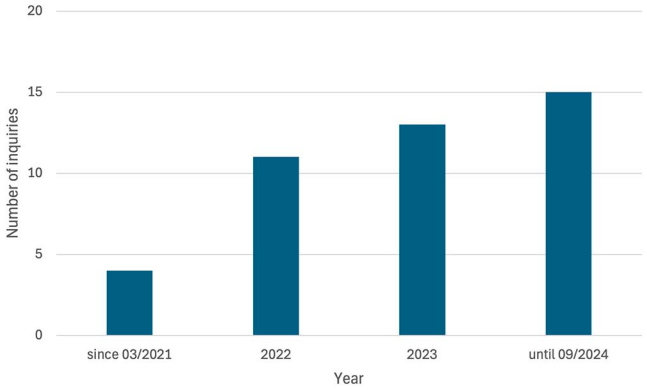

Figure 2

Increase in inquiries over time.

Growing acceptance of the national reference program

Since its launch in March 2021, the pediatric national reference program has seen a steady increase in utilization (Fig. 2). Based on current projections, the expected number of inquiries in 2024 (n = 19) represents a substantial proportion of the estimated 25–35 annual pedDTC cases in Germany (4, 6). This growing referral pattern reflects increasing national recognition and acceptance of the program.

Discussion

This study presents the first analysis of the pediatric national reference program within the MET registry, established to standardize care for children and adolescents with pedDTC in Germany. The program facilitates interdisciplinary, case-specific recommendations with the goal of reducing variability in therapeutic approaches – particularly in RAI use – while supporting individualized, risk-adapted decision-making. The feasibility and benefit of a centralized, countrywide consultation model are highlighted by growing engagement and alignment with contemporary treatment principles. A similar initiative was recently launched in the Netherlands to support national consensus-building in pedDTC care (17).

The role of RAI therapy in pedDTC – especially for low- and intermediate-risk patients – remains controversial, as long-term outcome data have yielded inconsistent results (9, 13, 18, 19, 20, 21, 22). In alignment with this, our tumor board recommended against RAI in the

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majority of low-risk cases, supporting a growing international trend to minimize radiation exposure in patients with favorable prognosis (9, 21, 23, 24, 25). This approach is supported by a SEER database analysis showing that RAI therapy, while frequently used in pediatric patients with advanced disease features, was not associated with reduced recurrence or mortality (25). In contrast, some data support the benefit of RAI therapy in higher-risk patients; for example, Toraih *et al.* reported a 53.1% reduction in recurrence risk following RAI in pediatric cohorts (22). Our program's guidance – favoring RAI for high-risk disease and individualized assessment for intermediate-risk patients reflects this risk-stratified strategy.

Dynamic risk stratification, as described by Tuttle *et al.* was employed to guide follow-up and treatment planning (16). This framework was especially useful in patients who had undergone total thyroidectomy followed by RAI, allowing classification into excellent, indeterminate, biochemical incomplete, or structural incomplete response. In patients treated with hemithyroidectomy or without RAI, response assessment was adapted to TG trends, imaging findings, and clinical judgment.

Recent studies, including those by Castellanos *et al.* and Bojarksy *et al.* have demonstrated that select pediatric patients with early-stage disease – even those with limited lymph node involvement – can achieve excellent outcomes without RAI (21, 26). These findings underscore the importance of vigilant surveillance and risk-adapted management, both of which are core to the recommendations provided by our program. Correspondingly, over half of the patients with confirmed pedDTC in our cohort were managed with reduced therapeutic intensity, including omission or dose reduction of RAI. Treatment recommendations across ATA risk strata further illustrate the program's precision-driven philosophy. For low-risk patients, RAI was omitted in 60%, while intermediate-risk cases were handled conservatively when appropriate. In younger children, where event-free survival is generally lower, caution was applied to avoid overtreatment and long-term toxicity (27). Persistent TG elevation alone was not considered sufficient to prompt immediate RAI, acknowledging the known delayed decline in TG levels after prior treatment.

The tumor board also contributed to harmonizing surgical management across institutions. Recommendations included more extensive procedures for high-risk disease or less aggressive interventions for low-risk cases, such as avoiding completion thyroidectomy after hemithyroidectomy. In this context, centralized review may have provided both clinical clarity and broader expert consensus – especially helpful in scenarios where responsibility for aggressive or conservative strategies must be carefully balanced.

Some of the most challenging cases involved patients with mildly elevated TG levels but no structural disease, incomplete surgical data, or uncertain RAI response. These discussions demonstrated the value of structured, multidisciplinary review in navigating clinical ambiguity and tailoring care.

The program's collaborative framework is inherently aligned with the principles of precision medicine and mirrors evolving international guidelines (9, 21, 23, 24, 25). Importantly, the advisory role of the tumor board respects the autonomy of treating physicians while offering expert guidance that is evidence-informed and individualized.

The main limitation of this analysis is the relatively short follow-up period, which prevents robust evaluation of recurrence or long-term survival (20). Preliminary data are promising in terms of treatment de-escalation and disease control, but extended follow-up is essential to validate these trends. In addition, data on the RAI activity initially planned by referring centers were incomplete, limiting the ability to quantify dose reductions. Future efforts should focus on standardized collection of treatment intent, delivered doses, and patient-reported outcomes.

Although surgical practices remain heterogeneous across institutions, the board's structured recommendations increasingly serve to align treatment approaches, particularly with respect to lymph node management and extent of resection. As the program matures, greater standardization in pre- and postoperative assessment, including recurrent nerve monitoring, is anticipated.

Another challenge is the potential underrepresentation of patients from centers less engaged in centralized tumor board participation. Ongoing outreach and integration into national protocols may help to increase awareness and accessibility. Encouragingly, growing inquiry volume suggests wider acceptance and integration into clinical workflows.

Efforts to increase awareness and accessibility of the program are ongoing, with projected growth in inquiries indicating broader acceptance among pediatric oncology centers.

The key lessons from program implementation include the importance of structured documentation, interdisciplinary collaboration, and adaptability to institutional variability. As adoption increases, these elements continue to support harmonization of care for pedDTC. The findings from this initial evaluation align with broader shifts toward individualized, risk-based management in pedDTC. The MET registry´s national reference program offers a feasible and

scalable model for centralized expert consultation. It integrates contemporary evidence with clinical pragmatism, addressing a critical gap in the management of pediatric thyroid cancer patients.

Implementation of similar tumor boards in other countries would require adaptation to local systems, including legal frameworks for medical responsibility, data protection regulations, and funding mechanisms. Our program defines a clear advisory role, with final treatment decisions remaining with the referring teams – an approach that supports legal clarity while fostering trust and collaboration.

Conclusion

The pediatric national reference program represents a significant step forward in the harmonized management of pedDTC in Germany. By standardizing care and reducing variability – particularly in the use and dosing of RAI – the program promotes individualized, evidence-based recommendations tailored to each patient´s risk profile. As follow-up data continue to mature, future analyses will be essential to assess the long-term outcomes and broader impact of this centralized, risk-adapted approach.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-25-0035.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

MiKu and AR were responsible for the conceptualization. AR developed the methodology and performed the formal analysis. All authors participated in the investigation. MK and AR provided the necessary resources. MK prepared the original draft. All authors contributed to writing, review and editing. AR was responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript.

Patient consent

Written informed consent for enrollment in the MET Registry and publication was obtained from patients and/or legal guardians, as appropriate.

Statement of ethics

The study was conducted in accordance with the ethical standards of the institution and the Declaration of Helsinki.

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