The incidence of differentiated thyroid cancer (DTC) has increased dramatically over the last several decades. Although the etiology and clinical impact of this increase are a matter of continuing debate, a greater number of pediatric patients present for DTC evaluation and care. To date, the approach to evaluation and care of DTC in pediatrics has followed the established adult guidelines, with striking low disease-specific mortality outcomes (1). However, for both families and providers there is a significant degree of angst in determining the best approach to care based on opposing observations between clinical presentation, disease characteristics, and the potential risks of therapy expressed over the child’s lifetime. Furthermore, limitations in pediatric-specific resources often place children and adolescents in a hybrid care team split between the adult and pediatric medical system. As we work to improve our approach to caring for pediatric patients with DTC, it is critically important to identify a means to stratify our approach to acute and long-term medical care as well as to identify factors related to the psychological impact of diagnosis and treatment on a patient population undergoing critical phases of physical, cognitive, and psychosocial development. To this end, the study by Oren et al. (2) in this month’s issue of the JCEM is a timely and welcome initial examination of health-related quality of life (QOL) and anxiety in adolescents with DTC.

Based on the data from the National Cancer Institute’s Surveillance, Epidemiology and End Results database, DTC accounts for less than 2% of all pediatric malignancies (3). However, over the last few decades, the incidence of DTC has increased dramatically, with a recent review reporting a 47.9% change in incidence between 1973 and 2007 (4). Caucasian, adolescent females 15–19 yr of age comprise the highest risk group, with DTC currently the second most common cancer diagnosis in this age group after Hodgkin’s lymphoma (5). For the majority of pediatric patients, DTC is diagnosed after an asymptomatic thyroid nodule is identified either on physical examination or as an incidental discovery during unrelated head and neck imaging. Similar to adults, papillary thyroid cancer (PTC) is the most common thyroid malignancy. Yet, despite similar histology, there are marked differences in clinical presentation and behavior of PTC in pediatric patients. Children and adolescents with PTC have a higher likelihood of both cervical lymph node and pulmonary metastasis, with an estimated incidence of 70–80 and 15–20%, respectively (6). Because of this invasive behavior, an aggressive approach to therapy is most frequently pursued, which includes total thyroidectomy followed by radioiodine remnant ablation (RAI) (7). Reoperative procedures (8) and repeat doses of RAI (9) are frequently needed in an effort to eradicate disease, defined by a negative RAI whole body scan and undetectable thyroglobulin. This treatment approach has been associated with very low disease-specific mortality and an estimated 10- and 20-yr survival of greater than 98% (1, 6, 9, 10).

Abbreviations: DTC, Differentiated thyroid cancer; LT4, levothyroxine; PTC, papillary thyroid cancer; QOL, quality of life; RAI, radiiodine remnant ablation.

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Unfortunately, despite an excellent overall prognosis for children with DTC, there are multiple challenges that impact disease morbidity. A higher rate of treatment-related complications results from reduced availability of centers that regularly treat children and adolescents with DTC due to the lower incidence of the disease relative to other malignancies. For example, there is significant evidence to demonstrate a strong correlation between a lower number of thyroid surgeries per year and an increased incidence of endocrine as well as non-endocrine complications, both associated with longer hospital stays and higher costs (11, 12). These risks of surgical complications also correlate with the extent of disease at presentation, patient age, and the surgeon’s experience. Although these associations are well known, over 50% of pediatric patients continue to have thyroid surgeries performed in centers reporting less than 12 thyroidectomies per year (13).

In addition to surgical complications, RAI has also received increased scrutiny over the last several years based on several reports suggesting an increased risk of nonthyroid, second, primary malignancies in patients that received RAI compared with those without RAI exposure (14–16). In adults, there have been multiple, prospective studies defining a low-risk population that does not appear to benefit from RAI remnant ablation (17). Unfortunately, such studies have not been carried out within the pediatric population; however, in an effort to reduce RAI exposure in children, there are increasing attempts to define similar, low-risk pediatric patients with DTC. Defining the most effective approach to care of patients with stable but persistent disease is also under discussion. For example, pediatric patients with pulmonary metastasis and detectable, persistent, yet nonprogressive pulmonary disease fail to demonstrate disease resolution despite repeated RAI (18). Even under the best circumstances, when care is provided in centers that regularly evaluate and treat pediatric patients with thyroid cancer, survival may not equate to cure. Remission is achievable for the majority of patients; however, the risk of recurrence is high—estimated at 30 to 40% over three to four decades of follow-up (14). Thus, although pediatric DTC is a disease with low disease-specific mortality, it is also a disease where families face enormous challenges in finding centers that care for pediatric patients with DTC on a regular basis and a disease with a high risk of short- and long-term complications. In addition, whereas a significant number of patients may achieve remission within the first few years after diagnosis, all patients require lifelong surveillance, given the high risk of recurrent disease.

It is within this context that we need to consider, investigate, and identify risks and resiliencies in psychosocial adaptation for children and adolescents with DTC. Surprisingly, the study by Oren et al. (2) of QOL and anxiety is the first published report on this topic. A strength of this exploratory, cross-sectional study is the use of validated measures of QOL and anxiety. Measures were administered to 16 patients (nine females) with DTC and their parents; four patients were surveyed within 12 months of diagnosis, two patients within 12–24 months, and 10 patients at more than 24 months after diagnosis (2). Eleven of the 16 patients were in remission at the time of the assessment. Treatment varied across patients; 10 had undergone one surgery, and six had undergone two; 10 patients had received one dose of RAI, five received two, and one received three doses; all patients were receiving levothyroxine (LT4) suppressive therapy at the time of evaluation. Scores were compared with published norms for a healthy pediatric population as well as to a control group of patients with Hashimoto’s thyroiditis (selected based on similar need for repeat clinic visits and daily LT4 therapy). Contrary to study hypotheses of lower QOL and higher anxiety for patients with DTC, findings revealed no significant differences in QOL or anxiety across the three groups. Furthermore, the time since diagnosis, replacement vs. suppressive LT4 therapy, and whether patients were in remission were not associated with QOL and anxiety. Acknowledging limitations of this exploratory study, including small sample size and the cross-sectional study design, Oren et al. (2) conclude that findings are promising and highlight the resilience of children and adolescents with cancer (i.e. high adaptability and a tendency to focus on positive aspects of life may outweigh potential negative impacts of being diagnosed with DTC and its treatment) (19).

While this is the first study to examine QOL in pediatric patients with DTC, there are comparative data for adult patients with DTC as well as for pediatric patients with nonthyroid cancers. In the adult literature, mixed results from studies examining QOL in thyroid cancer patients have been reported (20), and in contrast to Oren et al. (2), the majority of these studies highlight more frequent complaints of sleep disturbance, fatigue, cognitive, and impaired social functioning in adult DTC patients compared with healthy controls. Differences in gender, staging, time since diagnosis, remission vs. persistent or recurrent disease, and use of recombinant human TSH instead of thyroid hormone withdrawal for RAI evaluation and therapy have been identified as confounding variables that clearly impact on QOL. In addition, when analysis includes a larger cohort of patients, less frequent complications specific to DTC treatment are identified to include difficulties with speech secondary to RAI-induced salivary gland damage (21).
Review of the published QOL reports in childhood cancer survivors reveals multiple potential areas of similarity and concern. The acuity and intensity of therapy between thyroid cancer and other forms of childhood malignancies are clearly different; however, the studies provide a foundation from which future studies on QOL in pediatric patients with DTC should be based. A systematic review of the literature by Klassen et al. (22) identified 58 articles using nine cancer-specific and nine generic QOL questionnaires: 14 studies limited to children receiving treatment, 22 to survivors, and 22 to a combination of both. Treatment variables associated with poorer QOL included active cancer treatment phase; treatment-related complications, both acute and long-term; cancer recurrence; and older age at the time of diagnosis (due to the deleterious influence of cancer and treatment on developmental areas of emerging autonomy, self-image, and social functioning). In addition, underscoring the importance of family-centered care, a higher degree of anxiety, depression, psychological distress, and chronic health condition in parents was associated with lower QOL in patients (22). Our own research suggests that adolescents and young adults with cancer are at risk for poorer physical and emotional QOL, with parent-child relationships and general functioning contributing significantly to adaptation (23). Although studies have generally not supported psychopathology (depression, anxiety, externalizing symptoms) among children and adolescents with other forms of pediatric malignancies, symptoms of posttraumatic stress have been identified, indicating that cancer and treatment are traumatic in nature with subsequent negative and positive trauma responses (24).

Studies of QOL among children and adolescents with cancer and pediatric cancer survivors suggest that the study of Oren et al. (2) of QOL and anxiety is a long overdue initial assessment of adaptation among adolescents on and off treatment for DTC. There is much to learn as we make efforts to outline the best approach to care for children and adolescents with DTC. Redefining survivorship to account for treatment late effects, demands of lifelong surveillance, impacts on health-related QOL, and possible negative and positive trauma responses for patients and families must be included in these efforts. Future studies should apply stronger methods (e.g. adequate sample size and increased power; reduced heterogeneity of populations studied, including postpubertal status, treatment phase, extent of disease, length of follow-up, and presence or absence of remission status; inclusion of a range of sociodemographic and family predictors of outcome; and prospective designs) to more clearly elucidate the impact of DTC on psychosocial outcomes and to better understand the impact of these essential variables on QOL. Furthermore, the use of QOL measures specific to pediatric cancer that account for physical and psychosocial functioning (including school, social, and emotional functioning) and prospective studies are imperative to not only identify factors predictive or associated with QOL but also to establish treatment and outcome causality (22). In the end, as the authors suggest, there may be a significant number of pediatric patients with DTC that have the skills, support, and resiliency to successfully navigate the acute and lifelong challenges associated with the diagnosis of DTC. The only definite conclusion and most significant contribution from this pilot study is, however, the obvious need for additional future studies that will allow for the eventual development of medical and psychosocial treatments that result in improved rates of cure while minimizing medical and psychosocial late effects.

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References

ated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr Relat Cancer 12:773–803


16. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD 2008 The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab 93:504–515


