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Review

# Follicular-cell derived thyroid cancer in children

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**Abstract**

Thyroid carcinoma is a rare disease in children, and is mostly of the papillary histological type. It is often extended at presentation with frequent lymph node metastases. Treatment includes surgery (total thyroidectomy and lymph node dissection) and radioiodine therapy in case of extensive disease. Life long thyroxine treatment is given to all patients and when carefully controled is devoided of adverse effects. Long term prognosis is favorable, but a few deaths have been reported some decades after initial treatment. Adverse prognostic indicators are younger age at discovery and presence of distant metastases.


## 1. Introduction

In children, most thyroid carcinomas are derived from follicular cells [1–3]. Medullary thyroid carcinomas derived from parafollicular cells (or C cells) are rare and beyond the scope of this review.

## 2. Incidence

Thyroid cancer is a rare disease in children, accounting for 1.5–3% of all childhood cancers in North America and Europe, with an annual incidence of 0.5–1 cases per million children [4]. Its incidence is similar among series. It is exceptional before the age of 10 years, after which its incidence increases with age. The sex ratio (F/M) is close to unity before puberty, and reaches 2.5–6.0:1 after puberty.

## 3. Pathology

In children, the great majority (>90%) of follicular cell-derived thyroid carcinomas are papillary (PTC). PTC variants, such as diffuse sclerosing and follicular, develop more frequently, and a solid/follicular growth pattern is frequently observed in very young children.

As compared to adult PTC, a large thyroid tumour, multifocality and bilaterality, extension beyond the thyroid capsule, neck lymph-node metastases (present in up to 80% of cases, frequently large with extension beyond the capsule) and lung metastases (present in 10–20% of cases) are more frequently found in children [5–9]. This large extent of disease, particularly in young children, may be related to a late diagnosis or to an aggressive course.

## 4. Aetiology

Epidemiological studies have shown that the thyroid gland is one of the most sensitive organs to the tumorigenic effects of external radiation during childhood [10]. This was confirmed by the increased incidence of thyroid carcinoma in highly contaminated children in Belarus and Ukraine after the Chernobyl nuclear disaster [7,8]. Among nodules occurring in persons with a history of radiation exposure during childhood, about 20–30% are malignant, the large majority being PTC and the others benign adenomas. The sensitivity of the thyroid gland to the carcinogenetic effects of radiation is maximal during the first years of life and then decreases with increasing age at exposure. The risk is not significant for exposure

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in those older than 15–20 years. The risk is significant for radiation doses to the thyroid as low as 100 mGy; for higher doses it increases linearly with the dose. The excess relative risk is high. For 1 Gy delivered during the first years of life it is equal to 7.7, and more than 80% of thyroid carcinomas occurring in these individuals can be attributed to radiation exposure. There is a 5- to 10-year period after radiation exposure before nodules start to appear. Their incidence peaks at 15–19 years after exposure and then declines but remains elevated for at least 20 years. The prognosis and response to therapy are similar in spontaneously occurring and in radiation-induced PTC, and, in general, are favourable [11,12]. The aggressiveness of thyroid carcinomas observed in highly contaminated children a few years following the Chernobyl accident may be related to the type of radiation exposure, to late diagnosis or incorrect treatment, to young age at occurrence or to other, as yet undetermined, factors. In Western countries, there has been no significant increase in the incidence of thyroid carcinoma in children since the Chernobyl accident.

In approximately 5% of children there is a familial history of PTC. This may occur in families with adenomatous polyposis or Cowden's disease. In other families, there are no associated lesions and linkage studies have permitted chromosomal mapping of at least three syndromes [13].

## 5. Genetics

Several genetic defects have been shown in childhood PCT, including *RET*/*PTC* rearrangements and activating point mutations in the signal-transduction pathway (in *RAS* and *B-RAF* genes) [14].

Of particular interest is the finding of *RET*/*PTC* rearrangement in 10–30% of childhood PTC occurring in the absence of radiation exposure and in 50–80% of PTC occurring after exposure to external radiation or after internal contamination following the Chernobyl accident. Also, *RET*/*PTC3* is associated with aggressive tumours and *RET*/*PTC1* with classical PTC.

## 6. Prognosis

Age at diagnosis and extent of disease are the most significant prognostic factors for thyroid cancer. In the TNM classification, childhood thyroid cancer without distant metastases is defined as stage I; when distant metastases are present it is defined as stage II [15]. This classification indicates that young patients are at a low risk for cancer-related death, despite frequently extensive disease at diagnosis, but underscores their risk for recurrence, which is much higher than in adults. It should be noted than even if survival rates at 10 and 20 years are optimal, cancer-related deaths have been reported in adulthood, mostly in those who had been treated initially before the age of 10 years.

PTC is more aggressive when diagnosed before the age of 10 years [9]. In these younger children, a solid/follicular growth pattern, large tumour size, multifocality and extension beyond the capsule are frequent at presentation, as well as lymph-node involvement and lung metastases [16]. The recurrence rate was indeed higher than in older children and the cancer-related mortality was significantly increased, with death occurring at an adult age. In contrast, in older children and adolescents the initial extent of disease and outcome are similar to those observed in young adults [1,5–9,17–23]. This is consistent with the high degree of tumour-cell differentiation: $^{131}$I uptake is found in more than 80% of children with metastatic disease and $^{131}$I concentration is frequently high in tumour tissue. Thus, $^{131}$I treatment will deliver high radiation doses and will yield a high cure rate. Among patients with distant metastases, younger age at their discovery is a significant independent prognostic factor for cure [16]. In some series no cancer-related deaths are reported, but in series with the longest follow up, up to 15% of patients died from their thyroid carcinoma [17–23].

## 7. Clinical presentation

The clinical presentation of childhood thyroid cancer is mainly a thyroid nodule that is frequently large, either isolated or associated with neck lymph nodes. Palpable thyroid nodules are more frequently malignant in children than in adults. Fine-needle aspiration biopsy of either a thyroid nodule or an enlarged neck lymph node, with cytological analysis, should confirm the diagnosis. Lung metastases are more frequently present than in adults. They are diffuse and micronodular, and may be not detected on standard chest radiographs or even on spiral computed tomographic (CT) scans.

The clinical presentation of childhood thyroid cancer has been changing over the past decades [20]. The incidence of local tumour extension, palpable neck lymph nodes and lung metastases has decreased. This probably reflects a greater attention by paediatricians to routine examination of the thyroid gland.

## 8. Treatment

Treatment is based on surgery, radioiodine and thyroid hormone therapy. There is no role for external radiation therapy or chemotherapy.

## 9. Surgery and radioiodine therapy

The initial treatment for all thyroid cancers is surgery. As PTC in children are frequently multifocal and

bilateral, a total thyroidectomy is warranted. However, as most PTC have a favourable outcome, some advocate less aggressive treatment in order to decrease the risk of morbidity [21], but there is then a major risk of under-treatment. Similarly, as lymph-node metastases are frequently present and may be large, routine lymph-node dissection is justified. '*En bloc dissection*' is the only recommended procedure. Dissection of the central neck compartment (level VI) is routinely performed and may be extended to the supraclavicular area. When involved, the anterosuperior mediastinum should also be carefully dissected. When a jugulocarotid metastasis is present, a modified jugulocarotid lymph-node dissection preserving the sternocleidomastoid muscle, the spinal accessory nerve and the internal jugular vein is carried out.

Moreover, in children and adolescents, most lung metastases are not visible on chest radiographs or on CT scans, and are only found on $^{131}$I total-body scans performed after thyroid ablation. In patients who were not submitted to radical initial surgery, measurement of serum thyroglobulin (Tg) is less specific and $^{131}$I imaging is less sensitive. In consequence, metastases may remain silent for years and emerge with a greater tumour burden. For these reasons, most clinicians favour a total thyroidectomy and lymph-node dissection, and $^{131}$I therapy in patients with extensive disease.

The ablative dose of $^{131}$I in children is approximately 37 MBq/kg body wt. When only a lobectomy or a partial thyroidectomy has been performed, a completion thyroidectomy may be indicated, according to the size of the remnants and the risk of persistent disease. When performed, it should be done with a lymph-node dissection, according to the protocol of the initial operation.

This combined treatment is probably the only currently available method that may decrease the risk of local and regional recurrence and achieve a cure [1].

## 10. Hormonal therapy

Following thyroidectomy, the treatment of choice is L-thyroxine (L-T4). Compared to adults, children require higher doses per kg body wt to decrease the concentration of thyroid-stimulating hormone (TSH) to below 0.1 μU/ml (which is considered adequate for suppressing TSH-dependent tumour growth), with a normal FT3 (which will avoid iatrogenic thyrotoxicosis). Thus a child below the age of 10 years may require an L-T4 dose of 3–4 μg/kg a day; at the age of 16–18 years a daily dose of 2.4–2.8 μg/kg may be sufficient.

Serum TSH and FT3 are measured 3 months after beginning therapy and then at least every 6 months. Growth rate is normal, with the expected height reached at an adult age, puberty occurs normally, and no permanent side-effects on the heart or the skeleton have been observed in adulthood.

Of course, TSH-suppressive therapy is not mandatory for all children. In the majority of patients who appear to be in complete remission, the daily dose of L-T4 may be decreased to achieve a TSH in the normal range (around 0.5 μU/ml).

## 11. Diagnosis and treatment of persistent and recurrent disease

The search for persistent disease includes a $^{131}$I total-body scan performed 3–5 days after the administration of the large dose given to ablate thyroid remnants. Any uptake focus outside the thyroid bed, in lymph-node areas or in lungs is related to metastatic spread and should be treated. Then, L-T4 treatment is begun and the serum Tg is measured 3 months later, without discontinuing L-T4. Serum Tg is obtained again 6–9 months later, following TSH stimulation, and neck ultrasonography is performed [24]. Prolonged withdrawal of thyroid hormone treatment is often poorly tolerated by children, and for this reason the use of recombinant human TSH may be particularly beneficial. When no abnormalities are found (undetectable serum Tg following TSH stimulation and normal neck ultrasonography), the L-T4 dose can be decreased, and the serum Tg estimation during L-T4 treatment and neck ultrasonography repeated every year [2,25].

Neck lymph-node metastases may be present in patients with undetectable serum Tg during L-T4 treatment. Neck palpation is not sensitive enough and lymph nodes are often discovered on routine neck ultrasonography and diagnosed at fine-needle biopsy with cytology and Tg measurement in the fluid aspirate. The discovery of lymph-node metastases should lead to a complete examination and treatment, starting with the administration of a large activity of $^{131}$I, with a total-body scan 3 days later that will localize lymph-node metastases and search for distant metastases. Surgery is then undertaken, using an intraoperative probe. The extent of excision will depend on the extent of recurrent disease and on the protocol of the primary operation. With this practice, complete resection of neoplastic foci was obtained in more than 90% of patients [26].

In patients with lung metastases, treatment is based on $^{131}$I (37 MBq/kg body wt) with a total-body scan performed 3–5 days after the dose. This is repeated every 6 months until the disappearance of any uptake on the scan. Cure is obtained after four to six courses of $^{131}$I treatment in more than 80% of children with $^{131}$I uptake. The other rare children with lung metastases do not achieve a cure, and this can be related to the incorrect use of $^{131}$I or insufficient $^{131}$I uptake in the metastases. The growth rate of metastases is usually very slow on

L-T4 suppressive therapy, but, due to the long life expectancy, persistent disease may cause death several decades after initial treatment.

Children with lung metastases often show large mediastinal lymph nodes: lung metastases can be treated with $^{131}I$ and cure is frequently achieved, but large lymph nodes may require surgical resection following several treatments; this may decrease their size and facilitate their resection.

Finally, a few children with lung metastases may develop bone or brain metastases that may require surgery, external radiation therapy and $^{131}I$ treatment when uptake is present.

## 12. Treatment-related morbidity

Treatment-related morbidity is particularly relevant for the developing body of a child whose life expectancy is long.

In expert hands, the risk of laryngeal nerve palsy, and of permanent hypoparathyroidism after total thyroidectomy with lymph-node dissection, is minimal and similar to that reported in adult patients. The likelihood of surgical complications is increased during central neck dissection and at reoperation, but should not tip the balance towards conservative surgery but should rather underscore the absolute need to refer the young patient to a surgeon who has expertise in the field.

The risk of laryngeal nerve palsy is transient in the majority of cases. However, nerve resection may be necessary when the nerve is involved in a tumour mass.

The risk of permanent hypoparathyroidism may be decreased by localizing the parathyroid glands with methylene blue staining and autotransplanting them into a muscle. The clinical features of hypocalcaemia are severe in children and include anxiety, paraesthesia, carpopedal spasm and, in extreme cases, laryngospasm and convulsions. It should be promptly treated. Measuring the serum ionized calcium and circulating parathyroid hormone (PTH 1–84) is the simplest way of monitoring the recovery of parathyroid gland function or documenting permanent hypoparathyroidism. The goal of medical therapy is to render the patient asymptomatic and to stabilize the serum calcium in the lower part of the normal range. A serum calcium in the upper part of the normal range exposes the patient to chronic hypercalciuria, with the risk of renal complications. Both calcium (1.5–2.5 g per day) and vitamin D analogues are needed. Vitamin D analogues to be administered are calcitriol (1,25-$(OH)_2D_3$), at a daily dose of 0.5–2.0 μg, or alfacalcidol (1-OH $D_3$) at a daily dose of 1.0–3.0 μg. Blood calcium is monitored once a week at the beginning of therapy, and once every 3–4 months thereafter, with determination of 24-h calciuria.

The risk of pulmonary fibrosis can be avoided when $^{131}I$ activity is limited to about 37 MBq/kg body wt per treatment and with at least 6-month intervals between two courses.

The occurrence of second malignancies has never been addressed specifically in childhood thyroid cancer. In adult series, a significant increased incidence of second cancers and leukaemias is observed in patients treated with high cumulative doses of $^{131}I$. As the relation between the cumulative activity administered and the risk of second tumours is linear, an excess risk per GBq of 39% for leukaemia and of 4% for solid cancers has been calculated [27]. This risk underlines that $^{131}I$ should be used only in children in whom it may be beneficial.

Decreased fertility or infertility have been reported in male patients after high cumulative doses of $^{131}I$ [28]. This complication is particularly important in young patients who have an otherwise excellent life expectancy and sperm preservation may be recommended. This is particularly true in patients with lung metastases after puberty, as they may require several treatments with $^{131}I$. Conversely, the outcome of pregnancies was not altered in women previously exposed to radioiodine [29].

## 13. Conclusion

Despite favorable long-term survival, childhood PTC should be considered as a potentially lethal disease to be treated with radical surgery (total thyroidectomy and lymph-node dissection) and by radioiodine in cases with extensive disease, followed by L-thyroxine therapy. This will ensure definitive cure and a normal quality of life for most young patients with PTC.

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