

# Efficacy and Safety of Radioiodine in the Treatment of Disseminated Differentiated Thyroid Cancer in Children

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## Abstract

Paediatric thyroid cancer is a rare disease, with well under 15% of all differentiated thyroid cancers (DTC) being diagnosed in childhood. Although DTC in paediatric patients frequently presents with metastases (60–80% nodal and 10–20% distant), the presence of metastases does not seem to negatively affect overall survival. The indolent nature of this disease together with its low incidence makes it difficult to determine optimum treatment strategies, which usually include surgery, radioiodine and thyroid hormone therapy. Although there is almost unequivocal agreement that total or near-total thyroidectomy should be the initial treatment in childhood DTC, there are still many controversies about radioiodine application. This article discusses the key aspects of radioiodine treatment in DTC in children, with the emphasis on its benefits.

## Keywords

Children, differentiated thyroid cancer (DTC), radioiodine treatment

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Paediatric thyroid cancer is a rare disease, with well under 15% of all differentiated thyroid cancers (DTCs) being diagnosed in childhood. However, as in adults DTC is the most common endocrine malignancy. DTCs account for ~10% of malignant tumours and ~35% of carcinomas in children.<sup>1</sup> In the US, ~350 people <20 years of age are diagnosed with thyroid carcinoma each year.<sup>1</sup>

Although DTC in paediatric patients frequently presents with metastases (60–80% nodal and 10–20% distant), the presence of metastases does not seem to have a negative impact on overall survival. Five-year survival is about 99% (95% confidence interval [CI] 95–100%) and more than 90% of patients survive for 20 years after diagnosis.<sup>2</sup> The indolent nature of this disease, together with its low incidence, makes it difficult to determine optimum treatment strategies, which usually include surgery, radioiodine and thyroid hormone therapy. Although there is almost unequivocal agreement that total or near-total thyroidectomy should be the initial treatment in childhood DTC,<sup>3–5</sup> there are still many controversies about radioiodine application. This article discusses key aspects of radioiodine treatment in paediatric DTC, with the emphasis on its benefits and risks and the recent use of recombinant human thyrotropin-stimulating hormone (rhTSH) in this group.

## Use of Radioactive Iodine in Differentiated Thyroid Cancer

Radioiodine remains the mainstay of post-operative treatment of DTC and has been used for more than 60 years.<sup>6</sup> It is used both in patients without any signs of persistent disease as an adjunct to surgical treatment and to treat patients with disseminated or locally inoperable disease. In the first case, radioiodine treatment has to ablate any residual normal thyroid tissue in order to facilitate the follow-up and

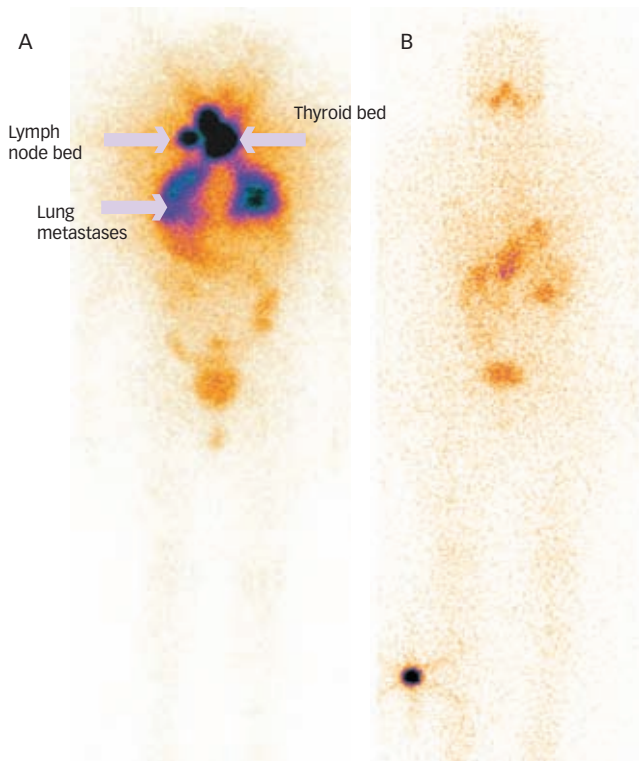
early detection of persistent or recurrent disease by measurement of serum thyroglobulin (with or without TSH stimulation) or radioactive iodine scanning. Traditionally, this kind of radioiodine treatment has been called 'thyroid ablation.' Another goal of ablation is to destroy any residual microscopic thyroid cancer foci in an effort to decrease the risk of recurrence and disease-specific mortality. In these settings it is a typical adjuvant cancer treatment. Radioiodine is also an effective treatment for persistent and metastatic DTC.

## Benefits of Radioactive Iodine in Children Adjuvant Radioiodine Treatment Decreases the Risk of Differentiated Thyroid Cancer Recurrence in Children

The recurrence rate of DTC in children ranges from 7 to 35%<sup>7–13</sup> and is highest in studies with the longest observation times.<sup>7,9,13</sup> In a large retrospective study including more than 1,528 patients with 16.6 years of follow-up, Mazzaferri and Massoll<sup>14</sup> reported a recurrence rate approaching almost 40% in patients with PTC diagnosed <20 years old; this is almost twice the recurrence rate in patients diagnosed between 20 and 50 years of age. This high recurrence rate is underscored by the report that the risk of death in paediatric DTC is almost 10 times higher in cases of recurrent disease.<sup>15</sup>

It was recently demonstrated that post-operative radioiodine therapy can decrease this high number of locoregional recurrences.<sup>16</sup> In a multivariate analysis of 235 patients with thyroid cancer diagnosed <18 years of age, it was shown that radioiodine therapy decreased the risk of thyroid-bed recurrence by a factor of 11 and in lymph nodes by a factor of three. Similarly, in a univariate analysis Chow and colleagues<sup>12</sup> demonstrated that local DTC relapse was reduced in children from 42.0 to 6.3% when <sup>131</sup>I was administered

**Figure 1: Fifteen-year-old Girl Diagnosed with T2mN1bM0 Papillary Thyroid Carcinoma**



After near-total thyroidectomy and modified lymphadenectomy, <sup>131</sup>I treatment was administered. In post-therapy total body scan (A), <sup>131</sup>I uptake was visible in lung metastases, thyroid and the lymph node bed. Clinical staging was changed to M1. Lung computed tomography was negative. After four cycles of <sup>131</sup>I therapy (cumulative activity 14.5GBq), complete scyntigraphic and biochemical remission was achieved (B).

post-operatively (p=0.001). Ten-year locoregional failure-free survival in children without distant metastases at diagnosis was 86.5% compared with 71.9% for those not treated with radioiodine (p=0.04).

It was recently demonstrated that although pre-pubertal children often suffer from advanced disease (e.g. extrathyroid extension, lymph node and distant metastases) compared with pubertal adolescents, disease outcome is similar in both groups if adequate treatment consisting of thyroid surgery and radioiodine is applied.<sup>17</sup> These results are in agreement with a meta-analysis of remnant ablation outcomes in DTC patients of all ages, which determined that radioiodine reduced the risk of locoregional and distant recurrence.<sup>18</sup>

Nevertheless, it should be stressed that not all authors agree on the beneficial role of radioiodine in the post-surgical management of childhood DTC as there are studies in which radioiodine did not affect the outcome in children with DTC.<sup>13,19</sup> In a recent large retrospective study of 215 DTC patients <21 years of age at DTC diagnosis, Hay and colleagues<sup>13</sup> did not find any difference in incidence of recurrence in children regardless of whether they had been treated with adjuvant radioiodine treatment after total or near-total thyroidectomy.

**Adjuvant Radioiodine Treatment Increases the Accuracy of Disease Staging**

Another issue is that a substantial number of paediatric patients can only be properly staged on the basis of a radioiodine scan, preferably after high radioiodine activity. In about 20–50% of paediatric DTC patients affected with distant metastases, only a post-ablation

total-body scan enables the detection of lung metastases.<sup>20-24</sup> These lung ‘micrometastases’ are not visible on chest X-ray or computed tomography; they are only evident on a <sup>131</sup>I scan performed after total thyroidectomy and thyroid ablation. Unless detected in a <sup>131</sup>I scan, such metastases remain silent for years. However, sooner or later they will emerge with a greater tumour burden.

**Radioiodine Treatment Is Effective in Children with Disseminated Differentiated Thyroid Cancer**

The prevalence of distant metastases is high in children, with an incidence of 20–30%.<sup>25-27</sup> Dissemination outside the lungs is very rare. Unlike adult lesions, paediatric pulmonary DTC metastases are overwhelmingly miliary, seldom nodular and almost always functional.<sup>9,24,28,29</sup> Among 95 Byelorussian children with radiation-induced DTC with lung metastases, 92 (96.8%) had miliary, disseminated-type pulmonary radioiodine uptake and only three (3.15%) had nodular uptake.<sup>24</sup> This type of lung metastasis – miliary with disseminated lung radioiodine uptake – was also typical in other studies.<sup>22,30</sup>

The high prevalence of functional metastases in pediatric DTC results in very effective radioiodine treatment. In publications to date, this modality achieved complete remission in the majority of children with lung metastases (see Figure 1).<sup>7,30</sup> Even patients with partial response rarely subsequently progressed<sup>31</sup> and over a 20-year follow-up, only a few cause-specific deaths in pediatric patients with lung metastases were observed.<sup>9</sup>

**Use of Recombinant Human Thyrotropin-stimulating Hormone in Radioiodine Treatment of Childhood Differentiated Thyroid Cancer**

To maximise radioiodine uptake, serum TSH should be above 30mIU/ml. The only approved method by which to stimulate TSH in children is endogenous TSH stimulation after L-thyroxin (L-T4) withdrawal. L-T4 is usually withdrawn for four to five weeks, often with a mixed regimen including triiodothyronine for the first two to three weeks. It has been demonstrated that in children a shorter two-week withdrawal time may be sufficient for adequate endogenous TSH stimulation.<sup>32</sup> Whichever protocol is applied, it often leads to symptomatic hypothyroidism – a very unfavourable condition in a young individual who is still developing.

In cases of non-compliance with the preparation regimen or if there is a substantial thyroid remnant still producing thyroid hormones, TSH can be insufficiently stimulated. The use of rhTSH avoids many of these drawbacks; however, its use in children is not approved in Europe or the US and it can only be used ‘off-label’.

There are limited data on the use of rhTSH for radioiodine treatment in this age group.<sup>33-35</sup> Ten children were evaluated for the success rate of thyroid remnant ablation with rhTSH-aided radioiodine treatment. In five cases treatment resulted in complete loss of radioiodine uptake and low thyroglobulin levels. In two patients there was some persistent, minimal (<1%) uptake in the thyroid bed with low thyroglobulin level without indications for repeated radioiodine therapy. In one patient, thyroid remnant ablation was successful but led to an increasing thyroglobulin level. In two patients (20%) ablation was unsuccessful and repeated radioiodine therapy was necessary. The largest group of children and adolescents diagnosed or treated with rhTSH was described recently by Luster and colleagues<sup>36</sup> in a multicentre, retrospective study. In 40 patients, rhTSH preparation

was used for radioiodine thyroid remnant ablation (in eight patients with advanced disease). In the other cases, rhTSH was used for diagnostic purposes. As the report focused on the tolerability of the drug and its serum TSH effect, the results of ablation are unfortunately unknown. After the standard schedule of rhTSH administration in most rhTSH courses, peak TSH concentration on the third day after the first rhTSH injection was  $\geq 25$  mU/l in 144 (98%) of 147 patients and was inversely correlated with the body mass index of patients. Clinical adverse effects related to rhTSH were reported in 12% of cases. The most commonly reported adverse effects in descending frequency were nausea, vomiting, headache, rash, fatigue and breathing difficulties, none of which had an incidence  $>5\%$ . There was no relationship between rhTSH dosing or peak serum TSH levels and the occurrence of adverse effects.

The main advantage of rhTSH-aided radioiodine therapy in children is the reduced total-body irradiation. Compared with hypothyroidism, the euthyroid state at the time of  $^{131}\text{I}$  administration increases renal radioiodine clearance and decreases both whole-body and blood radiation dose, which is a surrogate measure of bone marrow radiation.<sup>37,38</sup> This should, at least theoretically, decrease the risk of radiation-related side-effects in children – mainly the risk of secondary neoplasm. The results of a recent study<sup>39</sup> in which the frequency of lymphocyte chromosomal rearrangements after radioiodine treatment was significantly lower after preparation with rhTSH than in the withdrawal group favours this hypothesis. This indicates that rhTSH reduces the potential risk of chromosomal aberration associated with blood irradiation. Of note is the fact that rhTSH preparation also allows avoidance of the adverse physical and neuropsychological side effects connected with hypothyroidism – a very important issue in a young, developing person.

The main concern in rhTSH-aided radioiodine therapy is the risk of an insufficient radiation dose to target tissues, particularly in a group of patients where up to 20% can suffer from distant metastases at diagnosis. Indeed, in dosimetric evaluation of thyroid remnant ablation, radioiodine uptake at 48 hours was lower in patients treated with rhTSH than with TSH withdrawal; however, this was compensated for by a longer radioiodine effective half-time in remnants and resulted in similar remnant residence times in both groups.<sup>37</sup> Recent clinical data have showed that in the short term the recurrence rate is similar between patients with endogenous and exogenous rhTSH stimulation.<sup>40</sup>

The application of rhTSH for radioiodine treatment has also raised concerns about decreased activity due to the iodine content of L-T4 preparations. Despite this, a recent study indicates that the body iodine content is not an important determinant of thyroid ablation when preparing patients with either thyroid hormone withdrawal or rhTSH.<sup>41</sup>

### Radioactive Iodine Activities

No consensus has been reached regarding the  $^{131}\text{I}$  activities that provide maximum efficacy with minimum toxicity for adjuvant radioiodine treatment in children and adolescents with DTC. Some centres<sup>37</sup> give 3.7 MBq/kg (1 mCi/kg) bodyweight. However, bodyweight-based formulas seem to produce rather low activities, and body-surface-area-based formulas may be more appropriate.

Extensively analysing variable dosing issues in paediatric patients, Reynolds<sup>42</sup> noted that red bone marrow absorbs a greater dose of  $^{131}\text{I}$

in children than in adults, since the same activity is distributed to smaller organs and shorter distances between the organs increase the cross-radiation. According to his diagrams for calculating appropriate activity, a 15-year-old should receive about five-sixths of the adult activity. Younger children need further reductions, e.g. half of the adult activity for a 10-year-old and one-third of the activity for a five-year-old.

Another approach<sup>43</sup> is to adjust the ablation activity according to the 24-hour thyroid-bed uptake as well as administering it according to bodyweight:  $<5\%$  uptake would warrant an activity of 50 MBq/kg, whereas a 5–10% uptake would warrant an activity of 25 MBq/kg and a 10–20% uptake would warrant an activity of 15 MBq/kg.

None of these strategies has proved to be superior to the others. Flexible ablation dosing according to one or more individual patient body characteristic, i.e. weight, surface area and thyroid bed radioiodine uptake, appears to be a preferable strategy to fixed or flexible dosing based on age alone. It may be tempting to use the same strategy in children based on positive experiences in adult patients with single and fractionated low radioiodine activity to ablate thyroid remnants.<sup>44,45</sup> However, after adjusting for age or bodyweight such activities would be much lower than 1.1 GBq. It is highly improbable that such low activities would be efficient in the detection and treatment of previously unknown micrometastases or in reducing recurrence rate.

The current availability of accurately aligned, whole-body anatomic (computed tomography) and functional (positron emission tomography or gamma-camera scintigraphy) images has enabled the ongoing development of 3D imaging-based dosimetry.<sup>46</sup> Although time-consuming and still under development, this approach can be the most accurate way to calculate the  $^{131}\text{I}$  activities necessary to eradicate disease in metastatic childhood DTC while still being within the safety limits of radiation dose to normal organs.<sup>47</sup>

### Side Effects of Radioiodine Activity

There are two main concerns about the use of (internal or external) radiation therapy in children: the induction of secondary cancers and fertility disorders.

### Secondary Malignancies

To the authors' knowledge there have been 21 reports of secondary malignancies after therapeutic radioiodine use in children and adolescents.<sup>13,16,30,48</sup> Rubino and colleagues<sup>49</sup> detected 13 cases of secondary cancers among 344 patients diagnosed with thyroid cancer  $<20$  years of age. The overall risk of secondary cancers and of breast cancer in young patients with DTC was significantly increased compared with the general population. However, comparing the subgroups of patients with (61%) and without (39%) radioiodine treatment no carcinogenic  $^{131}\text{I}$  treatment effects were found. There are two possible explanations for these observations. First, the number of cases was too low to have reached statistical power when comparing children with or without  $^{131}\text{I}$  therapy. The second explanation is that in patients with thyroid cancer (including children) there can be increased susceptibility to malignant diseases compared with the healthy population. The CHEK2 polymorphism has been indicated as predisposing people to PTC and other cancers (e.g. breast or prostate).<sup>50</sup> This study serves as an example to support this hypothesis.

Of note is the fact that the increased risk of secondary cancers was demonstrated in patients treated with high radioiodine activity. At up to 7.4GBq, no increase in secondary cancers was observed.<sup>49</sup> This could suggest that the risk of secondary malignancies is highest in advanced disease (e.g. distant metastases) as these are the only cases where high radioiodine activities are used. However, this group of patients benefited the most from radioiodine therapy. Additionally, in a recent study of chromosome damage in children and adolescents treated with ablative activities (1.1–4.4GBq) of radioiodine it was demonstrated that in peripheral T lymphocytes, early genome toxicity (expressed as a stable level of micronuclei formation) was not induced.<sup>51</sup>

Although the above-cited data are reassuring, the recent study by Hay and colleagues<sup>13</sup> in which increased mortality rate from secondary malignancies among paediatric DTC patients was demonstrated is alarming. Of the 15 patients who died from secondary malignancies, 11 (73%) had received post-operative therapeutic irradiation. All of the deaths occurred 30–50 years after initial diagnosis of DTC. However, if one looks closely at the results, only four cases were diagnosed after surgery and adjuvant radioiodine treatment. In seven cases, the patients were treated before 1950 and there was history of radium-seed or X-ray therapy. Among the patients who died from secondary malignancies and were treated after 1950, only four had received radioactive iodine (two with activity  $\leq 7.4$ GBq) and three were treated with surgery alone. The difference in mortality from secondary malignancies between these two groups is statistically insignificant ( $\chi^2$  test  $p=0.2$ . Data extracted from original manuscript: radioiodine group 4/63 events; surgery group 3/125 events). Based on these results, one cannot unequivocally say that radioiodine treatment increases the risk of secondary malignancies, but the general risk of radiation-induced cancer must be considered in this group of patients.

## Fertility Disorders

To date, no study has found a statistically significant association between <sup>131</sup>I exposure and unfavourable pregnancy outcome or increased infertility in women and in men. Nevertheless, transient gonadal effects of radioiodine therapy – i.e. oligospermia, increased follicle-stimulating hormone (FSH) levels, etc. – have been reported.<sup>52</sup> All of these observations are derived from studies on adults of childbearing potential where the dose after an estimated 3.7GBq radiation to the testis was 0.09cGy.

Long-term adverse events were recently evaluated in adults who had thyroid cancer diagnosed <18 years of age (manuscript in preparation). FSH level was increased in 26% of men investigated and its elevation correlated with higher levels of radioiodine but not with age at exposure. FSH results from DTC patients were then compared with healthy controls. Here, the frequency of abnormal FSH values was only borderline significant ( $p=0.052$ ). One cannot discount the fact that if the number of patients was higher, statistical significance

could have been found. Semen specimens were not evaluated, so conclusions about the functional consequences of increased FSH level cannot be made. Nevertheless, if a boy is post-puberty and there are no psychological contraindications, semen collection and banking should be considered before referral for <sup>131</sup>I treatment.

## Conclusions

Treating children with DTC is a challenge, given that children frequently present with advanced disease yet very rarely die from it. All of the available data on radioactive iodine in the management of paediatric DTC are retrospective and are usually based on a small number of patients. The two largest studies – one from the US<sup>13</sup> and the other from Europe<sup>16</sup> – have found contradictory results on recurrence free-survival. One can only speculate about the reasons for such results. In the US study, disease was less advanced at diagnosis, as only 6% of patients suffered from distant metastases at this time (which is much less than in other studies). Patient follow-up was based on physician examinations or on correspondence from patients and relatives, so some of the unfavourable events could have been missed. Of note is the fact that in the study by Hay and colleagues there was a tendency towards better recurrence-free survival in regional lymph nodes.

Based on the results of these two studies, it is hard to unequivocally recommend whether radioactive iodine should be used or not in the post-operative management of childhood DTC. However, the authors believe that, currently, when most children present with advanced disease radioiodine should be used to decrease the risk of disease recurrence. When referring children and adolescents for radioiodine therapy one should remember the possible side effects of radiation. However, there is no clear evidence that radioiodine can actually induce secondary neoplasms. ■



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