

Pediatric differentiated thyroid carcinoma leading to fatal lung fibrosis

Michaela Kuhlen, Marina Kunstreich, Friederike Eilsberger, Markus Luster, Antje Redlich

Angaben zur Veröffentlichung / Publication details:

Kuhlen, Michaela, Marina Kunstreich, Friederike Eilsberger, Markus Luster, and Antje Redlich. 2025. "Pediatric differentiated thyroid carcinoma leading to fatal lung fibrosis." *European Thyroid Journal* 14 (1): e240341. <https://doi.org/10.1530/etj-24-0341>.

CASE REPORT

Pediatric differentiated thyroid carcinoma leading to fatal lung fibrosis

Michaela Kuhlen¹, Marina Kunstreich^{1,2}, Friederike Eilsberger³, Markus Luster³ and Antje Redlich²¹Pediatrics and Adolescent Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany²Department of Pediatrics, Pediatric Hematology/Oncology, Otto-von-Guericke-University, Magdeburg, Germany³Department of Nuclear Medicine, University Hospital Marburg, Marburg, GermanyCorrespondence should be addressed to M Kuhlen: Michaela.Kuhlen@uk-augsburg.de

Abstract

Introduction: This case report aims to discuss the development of fatal lung fibrosis in a young boy following treatment of metastasized differentiated thyroid carcinoma (DTC).

Case presentation: A 3.6-year-old boy was diagnosed in year 1995 with papillary thyroid carcinoma with extensive metastases. He underwent total thyroidectomy and received multiple courses of radioactive iodine (RAI) therapy between September 1995 and February 1998. The patient received six courses of RAI therapy within 30 months, cumulatively amounting to 10 GBq ¹³¹I, in response to significantly elevated thyroglobulin levels and morphologically persistent miliary lung metastases. Despite the significant regression of his metastatic disease, the patient exhibited progressive lung fibrosis 2.75 years after the sixth RAI therapy. This condition ultimately led to respiratory failure and resulted in the patient's death 6.7 years following the initial diagnosis.

Discussion/conclusion: This case highlights the potential severe complications associated with several courses of RAI therapy in young children suffering from extensive lung metastases and underscores the need for careful treatment planning and long-term monitoring. Given the risks of RAI therapy, particularly the risk of fatal lung fibrosis, it is crucial to tailor RAI therapy carefully, especially in young patients. Notably, thyroglobulin levels can decrease even after cessation of RAI therapy, indicating that levels immediately post-therapy are not necessarily representing the development of the response over the following months.

Keywords: children and adolescents; differentiated thyroid carcinoma; pulmonary fibrosis; radioactive iodine therapy

Established facts

- Pediatric DTC typically has a good prognosis, but treatments such as RAI therapy can lead to significant long-term complications, including pulmonary fibrosis.
- Radiation-induced lung fibrosis has been well documented in adult patients with DTC treated with RAI, particularly after high cumulative activities.
- Pediatric cases of lung fibrosis after RAI therapy are rare but have been reported, especially in children with extensive pulmonary metastases and high cumulative RAI activities.
- Lung fibrosis often manifests years after treatment, with few cases reporting fatal outcomes in pediatric patients.

Novel insights

- This case represents the youngest reported patient who developed fatal lung fibrosis only 6 years after receiving high cumulative activities of RAI for pediatric DTC.
- Unlike most reported cases, where fibrosis appears after a prolonged latency, this patient developed severe respiratory failure relatively soon after treatment, highlighting the need for even more cautious RAI dosing in very young children.
- The case underscores the critical need for the implementation of dosimetry in pediatric RAI therapy to minimize the risk of radiation-induced complications while maintaining therapeutic efficacy.

Introduction

Differentiated thyroid carcinoma (DTC) in children, while rare, typically has an excellent prognosis. However, the treatment regimens, which include total thyroidectomy and radioactive iodine (RAI) therapy, can lead to significant long-term complications. This case report discusses a young boy who succumbed to fatal lung fibrosis 6 years after DTC diagnosis following multiple courses of RAI treatment, underscoring the need for careful consideration of treatment risks, especially in very young patients.

Case report/case presentation

In 1995, a 3.0-year-old boy presented with cervical lymphadenopathy, bilateral nodular goiter II, and slightly elevated thyroid-stimulating hormone (TSH) levels with low-normal T4 levels. Under the suspicion of an infectious cause of lymphadenopathy, antibiotic treatment was administered several times and levothyroxine therapy (50 µg per day) was initiated. Six months later, both lymphadenopathy and thyroid enlargement remained unchanged while thyroid hormone levels were euthyroid under levothyroxine intake. At the age of 3.6 years, diagnostic evaluations, including fine-needle aspiration biopsy and thyroglobulin testing (6790 ng/mL), determined the diagnosis of papillary thyroid carcinoma (PTC). The patient underwent a total thyroidectomy with central neck dissection, followed by lateral neck dissection to address the metastatic lymph nodes. Histopathological evaluation confirmed PTC with multifocal disease and extensive cervical lymph node metastases (pT4N2bM1 according to Union for International Cancer Control 1987 TNM classification).

Postoperatively, further diagnostics during the first RAI therapy demonstrated a stimulated thyroglobulin level of 43,200 ng/mL and military lung metastases. The patient subsequently received six courses of RAI therapy over 30 months due to persistently elevated thyroglobulin levels, which showed a gradual decline during treatment. Details on thyroglobulin levels and RAI therapy are shown in Fig. 1.

The six RAI therapy cycles included administered activities of 1500, 2000, 1000, 1500, 2000 and 2000 MBq, respectively, cumulatively amounting to a lifetime activity of 10 GBq ^{131}I . While we lack details on the planning method for therapy (e.g. dosimetry or fixed activity), the administered activities in relation to body weight are depicted in Fig. 1. Over time, the patient developed progressive lung fibrosis, likely exacerbated by repeated high-activity RAI treatments. At the time of the second, third and fourth RAI treatments, his peak flow was normal for his age. However, 2.75 years after the sixth RAI therapy, he exhibited severe respiratory compromise with a forced expiratory volume in 1 s (FEV1) of 20%, a forced vital capacity (FVC) of 17%, and an oxygen requirement of 4 liters per minute. A therapeutic attempt was made with prednisone, pentoxifylline and tocopherol, following the protocol described by Delanian *et al.* (1). During the 6.7-year follow-up period post-diagnosis, the patient experienced recurrent pneumonia, chronic respiratory failure, pulmonary hypertension (mean pulmonary artery pressure of 75–85 mm Hg), pulmonary heart disease and progressive lung fibrosis. Unfortunately, at the age of 10.3 years, the patient succumbed to respiratory failure due to extensive lung fibrosis. Six months before his death, his unstimulated thyroglobulin level was 6 ng/mL.

The patient's case was retrospectively registered with the German Malignant Endocrine Tumors (GPOH-MET) Registry (IRB 97-125 University of Luebeck, Germany).

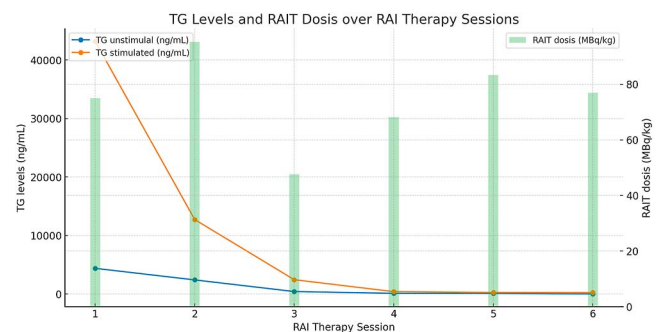


Figure 1

Thyroglobulin levels and RAI therapy activities over RAI therapy sessions.

Discussion

This case underscores the nature of pediatric DTC and the potential severe consequences of its treatment if performed aggressively. While RAI therapy is effective in managing metastatic thyroid carcinoma, it poses a potential risk of long-term complications, particularly in very young patients with developing tissues. The occurrence of fatal lung fibrosis in this patient demonstrates the need for a balanced approach in managing high-risk pediatric DTC, weighing the benefits of aggressive treatment against the potential for very rare but serious life-threatening complications.

Radiation-induced lung fibrosis occurs through a cascade of biochemical and inflammatory processes (2). The initial radiation exposure causes direct and indirect damage to cellular macromolecules, generating reactive oxygen species such as superoxide and hydrogen peroxide. This oxidative stress leads to DNA damage, particularly double-strand breaks, which trigger a series of cellular responses, including the release of damage-associated molecular patterns and activation of toll-like receptors (3, 4). The inflammatory response involves the activation of inflammasomes and the release of pro-inflammatory cytokines such as IL-1 β and IL-18, further promoting lung tissue damage and fibrosis. The persistent inflammation and fibrosis result in impaired lung function, which can be severe and progressive (4, 5).

A historical study from the 1950s first identified radiation pneumonitis and fibrosis as complications of RAI therapy in adults with metastatic thyroid cancer (6). More recent studies have reaffirmed these findings, noting that adults who receive high cumulative activities of RAI, especially those with extensive pulmonary involvement, are at increased risk of developing lung fibrosis (7, 8, 9, 10, 11). A case report described an adult patient who required lung transplantation due to severe fibrosis following extensive RAI therapy for metastatic DTC (12).

A few studies and case reports have documented cases of pediatric patients developing lung fibrosis following multiple RAI treatments (13, 14, 15). One study reviewed outcomes of children treated with RAI post-Chernobyl, where 5 of 69 (7.2%) patients developed lung fibrosis (5). Among these five patients, two had additionally received bleomycin, a lung-toxic antineoplastic drug. One of those patients died of lung fibrosis 17.5 years after therapy, including five courses of RAI therapy in addition to the previous treatment with bleomycin. In addition, two patients in this study showed transient evidence of lung fibrosis on computed tomography. Another study reported that 5 of 20 (25%) patients with pulmonary metastases developed lung fibrosis (14). All five patients had miliary pulmonary metastases and had received high cumulative activities of ^{131}I (more than 3 GBq), resulting in subsequent permanent complete remission. One report highlighted

a pediatric patient who developed severe pulmonary complications 3 months after one RAI therapy, leading to significant fibrotic changes and chronic respiratory distress despite anti-inflammatory treatments (15). While lung fibrosis has been reported, especially in children diagnosed with DTC at young ages, it is typically diagnosed following a latency of many years. Our case, however, represents the youngest patient reported to date who succumbed to lung fibrosis only 6 years after RAI therapy.

Given the potential risks of RAI therapy, particularly the risk of fatal lung fibrosis, it is crucial to tailor RAI therapy carefully, especially in young patients (16). Reiners *et al.* observed a continuous 35% yearly decline in median thyroglobulin concentrations during the 10 years after RAI therapy cessation in children with disseminated pulmonary metastases and no progression of lung metastases (17). Similarly, Biko *et al.* reported that pediatric patients from the Chernobyl collective with ^{131}I -refractory disease exhibited further declines in thyroglobulin levels and ^{131}I uptake on diagnostic whole-body scans over time, despite the absence of additional RAI therapy (18). Importantly, TSH-suppressive levothyroxine therapy was the primary treatment after the refractory state was established, emphasizing its role as a cornerstone in the management of metastasized pediatric DTC. In addition to optimizing treatment strategies to minimize the cumulative risks of RAI therapy, careful monitoring for adverse effects is equally important. Regular pulmonary function monitoring between RAI therapy cycles is essential to detect early signs of fibrosis. Early identification of pulmonary impairment provides an opportunity to adjust treatment and reduce the risk of severe, irreversible damage. In our case, pulmonary function was normal until the fourth RAI therapy, but assessments were not conducted before the fifth and sixth RAI therapies. Pulmonary function testing 2.3 years after the sixth RAI therapy revealed significant deterioration, with FEV1 at 20% and FVC at 17%. These findings highlight the importance of consistent pulmonary function monitoring between therapy cycles to catch early signs of fibrosis, allowing for timely modification of treatment strategies and potentially preventing life-threatening complications.

Since 1962, there has been an approach to dosimetric activity determination for RAI therapy, which is now firmly established into everyday clinical practice, but at the time of our case report, it was not performed on such a regular basis (17). This dosimetric approach to estimate the radiation exposure of organs at risk (bone marrow and lungs in the case of disseminated metastases) is fundamentally intended to minimize the risks of RAI therapy while at the same time ensuring treatment efficacy (17). The generally applicable threshold values for this approach are an absorbed dose to red bone marrow of 2 Gy (using blood as a surrogate), a whole-body retention of less than 4.4 GBq at 48 h, and lung

uptake in the presence of diffuse pulmonary metastases of less than 3 GBq at 24 h to minimize the risk of damage to bone marrow and pulmonary fibrosis (17). Meanwhile, various protocols have been published on the standardized procedure of dosimetry before RAI therapy, for example, by the European Association of Nuclear Medicine, as well as other reports, for example on the performance of dosimetry using ^{124}I -PET/CT in children (17).

In addition, advances in radioprotective agents and anti-fibrotic therapies offer hope for mitigating the risk and severity of radiation-induced lung damage (4, 19, 20).

To address these challenges, we recently established a national reference center for RAI therapy in children and adolescents with DTC. This center aims to optimize treatment protocols, provide specialized care and offer comprehensive follow-up for young patients, thereby aiming to minimize the risk of severe complications such as pulmonary fibrosis. Through this initiative, we aim to improve long-term outcomes and quality of life for pediatric patients with thyroid carcinoma.

Conclusion

This case report highlights the critical need for a balanced approach in the treatment of pediatric DTC, recognizing the potential very rare but severe complications of RAI therapy, such as pulmonary fibrosis. In response to these challenges, a national reference center for RAI therapy in children and adolescents with DTC has been established.

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.

Funding

The German MET studies were funded by Deutsche Kinderkrebsstiftung, grant numbers DKS 2014.06, DKS 2017.16, DKS 2021.11, Mitteldeutsche Kinderkrebsforschung and Magdeburger Förderkreis krebskranker Kinder e.V.

Author contribution statement

MK contributed to conceptualization. MK, ML and AR contributed to methodology. MK and AR conducted formal analysis. MK, MK, FE, ML, and AR carried out the investigation. MK and AR provided resources. MK prepared and wrote the original draft. All authors contributed to writing, reviewing and editing. MK and AR acquired funding. All authors have read and agreed to the published version of the manuscript.

Patient consent

The patient was retrospectively enrolled in the GPOH-MET 97 protocol with informed consent of the parents/legal guardians, including the permission for publication.

Ethics statement

The GPOH-MET 97 protocol was approved by the ethics committee of the University of Luebeck, Germany (IRB 97125) and was performed in accordance with the Declaration of Helsinki.

References

- 1 Delanian S, Balla-Mekias S & Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J Clin Oncol* 1999 **17** 3283–3290. (<https://doi.org/10.1200/jco.1999.17.10.3283>)
- 2 Zheng M, Liu Z & He Y. Radiation-induced fibrosis: Mechanisms and therapeutic strategies from an immune microenvironment perspective. *Immunology* 2024 **172** 533–546. (<https://doi.org/10.1111/imm.13788>)
- 3 Ozasa K, Shimizu Y, Suyama A, *et al.* Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res* 2012 **177** 229–243. (<https://doi.org/10.1667/rr2629.1>)
- 4 Jarzebska N, Karetnikova ES, Markov AG, *et al.* Scarred lung. An update on radiation-induced pulmonary fibrosis. *Front Med* 2020 **7** 585756. (<https://doi.org/10.3389/fmed.2020.585756>)
- 5 Arango ML & Waguespack SG. A child with papillary thyroid cancer and metastatic pulmonary disease: Role of radioactive iodine therapy. In *Thyroid Cancer: A Case-Based Approach*, pp 209–219. Eds G Grani, DS Cooper & C Durante. Cham: Springer International Publishing. (https://doi.org/10.1007/978-3-030-61919-0_24)
- 6 Rall JE, Alpers JB, Lewallen CG, *et al.* Radiation pneumonitis and fibrosis: a complication of radioiodine treatment of pulmonary metastases from cancer of the thyroid. *J Clin Endocrinol Metab* 1957 **17** 1263–1276. (<https://doi.org/10.1210/jcem-17-11-1263>)
- 7 Zhu RS, Yu YL, Lu HK, *et al.* Clinical study of 312 cases with metastatic differentiated thyroid cancer treated with large doses of ^{131}I . *Chin Med J* 2005 **118** 425–428.
- 8 Fard-Esfahani A, Emami-Ardekani A, Fallahi B, *et al.* Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun* 2014 **35** 808–817. (<https://doi.org/10.1097/mnm.000000000000132>)
- 9 Jang EK, Kim WG, Kim HC, *et al.* Changes in the pulmonary function test after radioactive iodine treatment in patients with pulmonary metastases of differentiated thyroid cancer. *PLoS One* 2015 **10** e0125114. (<https://doi.org/10.1371/journal.pone.0125114>)
- 10 Verburg FA, Hanscheid H & Luster M. Radioactive iodine (RAI) therapy for metastatic differentiated thyroid cancer. *Best Pract Res Clin Endocrinol Metab* 2017 **31** 279–290. (<https://doi.org/10.1016/j.beem.2017.04.010>)
- 11 Yang J, Zheng R, Liang M, *et al.* Association of the cumulative dose of radioactive iodine therapy with overall survival in patients with differentiated thyroid cancer and pulmonary metastases. *Front Oncol* 2019 **9** 558. (<https://doi.org/10.3389/fonc.2019.00558>)
- 12 Lee J, Sogutlu G, Leard L, *et al.* Lung transplantation for pulmonary metastases and radiation-induced pulmonary fibrosis after radioactive iodine ablation of extensive lung metastases from papillary thyroid carcinoma. *Thyroid* 2007 **17** 367–369. (<https://doi.org/10.1089/thy.2006.0234>)
- 13 Chen L, Shen Y, Luo Q, *et al.* Pulmonary fibrosis following radioiodine therapy of pulmonary metastases from differentiated thyroid

- carcinoma. *Thyroid* 2010 **20** 337–340. (<https://doi.org/10.1089/thy.2009.0266>)
- 14 Albano D, Bertagna F, Panarotto MB, *et al.* Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. *Pediatr Blood Cancer* 2017 **64**. (<https://doi.org/10.1002/pbc.26595>)
- 15 Halada S, Leftin Dobkin S, Baran JA, *et al.* Pulmonary injury after radioactive iodine therapy in pediatric papillary thyroid cancer: a case report. *Horm Res Paediatr* 2023 **97** 477–482. (<https://doi.org/10.1159/000534190>)
- 16 Luster M, Lassmann M, Freudenberg LS, *et al.* Thyroid cancer in childhood: management strategy, including dosimetry and long-term results. *Hormones* 2007 **6** 269–278. (<https://doi.org/10.14310/horm.2002.1111023>)
- 17 Reiners C, Biko J, Haenscheid H, *et al.* Twenty-five years after Chernobyl: outcome of radioiodine treatment in children and adolescents with very high-risk radiation-induced differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2013 **98** 3039–3048. (<https://doi.org/10.1210/jc.2013-1059>)
- 18 Biko J, Reiners C, Kreissl MC, *et al.* Favourable course of disease after incomplete remission on (131)I therapy in children with pulmonary metastases of papillary thyroid carcinoma: 10 years follow-up. *Eur J Nucl Med Mol Imaging* 2011 **38** 651–655. (<https://doi.org/10.1007/s00259-010-1669-9>)
- 19 Smith T, Kirkpatrick D, Smith S, *et al.* Radioprotective agents to prevent cellular damage due to ionizing radiation. *J Transl Med* 2017 **15** 232. (<https://doi.org/10.1186/s12967-017-1338-x>)
- 20 Tu J, Chen X, Li C, *et al.* Nintedanib mitigates radiation-induced pulmonary fibrosis by suppressing epithelial cell inflammatory response and inhibiting fibroblast-to-myofibroblast transition. *Int J Biol Sci* 2024 **20** 3353–3371. (<https://doi.org/10.7150/ijbs.92620>)