

Radioiodine is not the Preferred Choice of Treatment for Pediatric Graves' Disease

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Abstract

Radioactive iodine (RAI) ablation for treatment of hyperthyroidism in Pediatric Graves' disease is effective but limited literature exists regarding its long-term safety. There is no long-term prospective randomized controlled study on long-term safety of pediatric Graves' disease receiving RAI ablation. There are concerns regarding development of both thyroid and non-thyroidal malignancy, and primary hyperparathyroidism in subjects receiving RAI. Current evidences do not support routine use of RAI ablation in such situation. Surgery is a safe option.

Keywords: Adrenal tumor, PET, incidentaloma.

Graves' disease (GD) is the most common cause of thyrotoxicosis in children and adolescents.¹ GD has profound impact on physical development, learning, school performance and quality of life in children.¹ Ideal treatment should be effective, safe, with minimal immediate and long-term adverse effects and without the need for long-term surveillance.

The options for treatment of GD in children and adolescents are antithyroid drugs (ATDs), radioactive iodine (RAI) therapy and surgery (total thyroidectomy). The ideal therapy remains controversial and varies in different countries.^{1,2} ATDs are often used as first line therapy in pediatric GD. ATDs are effective, but are associated with low remission rates, drug toxicity and compliance issues. The chance of long-term remission after ATDs as first line therapy in children and adolescents is only 20 to 30%.^{2,3} Hence, most of the children with GD will need definitive treatment with either RAI ablation or surgery. The choice of definitive treatment is based on consideration of the long-term adverse effects of RAI vs complications of thyroid surgery.

RAI ablation is presently the treatment of choice in adults with GD in some countries like United States of America (USA) as it is an effective, definitive and safe treatment. RAI ablation is effective in the ablative management of GD in children.⁴ However, there are safety concerns regarding the use of RAI in young children and adolescents. Traditionally, RAI has been avoided in children and

adolescents because of the inherent risk of radioactivity in inducing mutagenesis, gonadal exposure and teratogenicity.

¹³¹I is the most commonly used radioiodine isotope used for the definitive treatment of GD. RAI concentrates in the thyroid follicular cells and undergoes gradual radioactive decay with effective half-life in the thyroid of approximately 8 days. Up to 94% of total radiation dose from RAI is due to particulate radiation and is responsible for the biologic effects of RAI.⁵

There is risk of thyroid malignancy with the use of RAI. There is scant data of therapeutic use of RAI in children and hence the majority of information has been derived from radiation exposure of children to external radiation, accidental nuclear fallouts and from adult data on RAI use.

The thyroid gland is one of the most sensitive organs to the carcinogenic effects of radiation, especially during childhood. Younger children are more sensitive to radiation. In a pooled analysis of 7 studies, the risk of developing thyroid carcinoma after external irradiation below 5 years of age was 2 fold higher than in children treated with irradiation between 5 to 9 years of age, and 5 fold higher than in children treated between 10 to 14 years of age.⁶ The high susceptibility of young children to the carcinogenic effects of radiation to the thyroid thus contrasts with the very low susceptibility of adults. This is consistent with experimental studies on animals and suggests greater radiation effects during periods of rapid cell proliferation, as observed during the development of the thyroid gland.

The risk of thyroid cancer is not significant when individuals are over 15 or 20 years of age at exposure.

Follow-up data from the Chernobyl nuclear power plant accident (exposure to high doses of RAI due to accidental fallout) has shown significantly higher risk (odds ratio 5.5-8.4 at exposure of 1 Gy) of thyroid cancer in children and there is a dose—response relationship with thyroid cancer.⁷ The risk is highest in children below 5 years of age. There may be a long latency of up to more than 20 years in the development of thyroid cancer. There is inadequate dosimetry data regarding RAI in therapeutic doses in children, and hence data from Chernobyl accident is vital. In therapeutic doses in adults, RAI dose lesser than 75 $\mu\text{Ci/gm}$ of thyroid tissue increases the risk of thyroid cancer, whereas there is no increase in risk when the dose is greater than 150 $\mu\text{Ci/gm}$ indicating that low doses have more carcinogenic potential.² High dose radiation may lead to total ablation of thyroid tissue, leaving no residual thyroid tissue for later development of neoplasia.²

RAI use in adults with thyrotoxicosis has shown conflicting results in various studies on the standardized risk of cancer as shown in Table 1.⁸⁻¹² The relative risk of cancer of the thyroid and nonthyroidal tissues has been found to be increased following RAI therapy in some studies, but other studies show no increase (Table 1).

RAI has been widely used in the management of thyroid cancer and a recent meta-analysis has shown slight increased standardized incidence rate of second primary malignancy with increased risk of cancers of GIT, breast, prostate, CNS, soft tissue and leukemia.¹³ The factors determining the possibility of second primary malignancy is age (younger age being more susceptible) and total radioactivity used.¹³

There are concerns of development of primary hyperparathyroidism (PHPT) in subjects exposed to external radiation and RAI. A higher incidence of PHPT has been documented in subjects with prior external radiation exposure.¹⁴ Prior radioiodine exposure has also been documented to increase the incidence of PHPT, although not confirmed in other studies (Table 2).¹⁴⁻¹⁸ The development of PHPT is dose related, occurs after a long latency and young and elderly subjects are more likely to be affected. Experimental studies in rats have also shown high incidence of PHPT.^{19,20} It is imperative that subjects exposed to RAI in childhood require life-long surveillance for PHPT. PHPT is usually due to parathyroid adenoma or hyperplasia and the surgery in post RAI setting is difficult due to local cicatrization.

Another potential risk of RAI therapy observed in adults with GD is worsening of ophthalmopathy. However, data from RAI therapy in the pediatric age group do not

Table 1: Risk of malignancy in adult thyrotoxic patients treated with radioiodine

Study, year	Patients	Follow-up	Overall cancer risk/ SIR	Thyroid cancer risk	Relative risk (RR)/ SIR of nonthyroidal cancers
Hoffman DA, 1982 ⁸	1005 patients treated with RAI. Controls treated with surgery, n = 2141	> 1 year	RR 1 No increase in risk	No increase	Breast 0.8 Leukemia 0.6 Salivary glands, digestive tract, kidney, bladder 1.8
Holm LE, 1991 ⁹	10,552 Swedish patients (100% treated with RAI)	Mean 15 years	Overall cancer SIR 1.06	No increase	Stomach 1.33 Kidney 1.51 Brain 1.63
Ron E, 1998 ¹⁰	35,593 hyperthyroid patients, 65% treated with RAI	Mean 21 years	Total cancer SMR 1.02	SMR due to thyroid cancer 3.94	No increase in SMR of other cancers
Franklyn JA, 1999 ¹¹	7417 patients (100% treated with RAI)	72,073 person years	SIR 0.83	SIR for thyroid cancer 3.25	Small bowel cancer 4.8
Metso S, 2007 ¹²	n = 2793, controls, n = 2793	10 years	RR 1.25	No increase in risk	Stomach cancer 1.75 Kidney cancer 2.32 Breast cancer 1.53

RR—Relative risk

SIR—Standardized incidence rate

SMR—Standardized mortality rate

Table 2: Radiation exposure and development of primary hyperparathyroidism

Author, year	Type of radiation exposure	Number exposed	Follow-up, years	Incidence of primary hyperparathyroidism
Schneider AB, 1995 ¹⁴	External beam radiotherapy to the head and neck for benign conditions	2555	Mean 36.6 years	36 confirmed cases
Esselstyn CB, 1982 ¹⁵	RAI for Graves' disease	159	–	10 cases
Tsuchiya T, 1996 ¹⁶	RAI for Graves' disease	2954-RAI 530-ATDs	–	2.5% in RAI group 1.19% in ATD group
Rasmuson T, 2006 ¹⁷	Adults patients with thyrotoxicosis treated with RAI	6082 patients with thyrotoxicosis	1-19 years	SIR 1.14 as compared to reference population
Colaco, 2007 ¹⁸	RAI for benign thyroid disease and thyroid cancer	Clinic based study of 11 cases + Literature search of 36 reported cases	2-30 years	47 cases
Triggs and William, ¹⁹ 1997	Rats treated with RAI within 2 days of life	–	–	61% incidence of parathyroid tumors in adult rats
Wynford–Thomas V, 1983 ²⁰	Rats treated with RAI within 24 hours after birth	67 rats—5 μ Ci 67 rats—10 μ Ci 67 rats—Unirradiated	2 years	Unirradiated controls—0% RAI treated rats 5 μ Ci—33% 10 μ Ci—40%

RAI—Radioiodine

ATD—Antithyroid drugs

SIR—Standardized incidence rate

demonstrate development of new ophthalmopathy or worsening of pre-existing ophthalmopathy.²¹

Read et al²² have shown relative long-term safety of RAI in children with GD. In this retrospective study, 98 children (3.6-19.8 years) were administered RAI in doses ranging from 5.3 to 7 mCi and a questionnaire based assessment was performed after 26 to 36 years by their family physicians. The assessment was done for reproductive history, malignancy (thyroidal and nonthyroidal) and occurrence of primary hyperparathyroidism. This study demonstrated the long-term safety of RAI in children and adolescents. Though this study has been hailed as a strong evidence of safety of RAI, this study had significant limitations in that it was retrospective, observational and questionnaire based and involved only a small number of subjects. The dose of RAI used was only 32 μ Ci/gm of thyroid tissue as against the current standard practice of 100 to 150 μ Ci/gm. Furthermore, only 6 subjects were less than 6 years of age and there was no control group. Hence, the true carcinogenic potential in children remains unclear.

In a recent cochrane database review on RAI treatment in pediatric GD, paucity of data was observed. There were

no randomized controlled trials comparing RAI with surgery and available studies were of low quality.⁴ The limited data showed that RAI is potentially effective for pediatric Graves' disease, but at a higher risk for hypothyroidism as compared to ATDs. No studies addressed issues of other long-term adverse effects of RAI.

There are cultural issues and physician preferences involved with the use of RAI in children. The stigma of Nagasaki and Hiroshima is still considered as hallmark of the effect of radioactivity and hence RAI is generally not preferred in Japan. Various surveys of use of RAI use in adults have revealed widespread acceptance of RAI in the management of adult GD. However, in children, none of the physicians in European thyroid association (ETA) and European society of pediatric endocrinologists (ESPE) chose RAI as the first option in a child with GD, while only 23% chose RAI in recurrent thyrotoxicosis after surgery or ATD (Table 3).^{23,24} Similar trends in physician preferences for avoiding RAI in children are also observed in similar surveys from Asia and Europe, Table 3.²³⁻²⁵ As opposed to physicians in Europe and Asia, physicians in USA more often advocate RAI as a initial and definitive treatment for

Table 3: Questionnaire studies on physician preferences for treatment of Graves' disease in children and adolescents

Study	Number of physicians who responded to questionnaire	Case	ATD	Surgery	RAI
Perrild H, 1994 ²³	99 physicians from ETA and ESPE	Child with uncomplicated GD	99%	1%	Nil
		Recurrent thyrotoxicosis after surgery or ATDs	–	30%	23%
Krassas GE, 2003 ²⁴	61 physicians from Europe	7-year-old, GD, first time	100%	Nil	Nil
		7-year-old, GD, relapse	5%	74%	21%
		15-year-old, GD, first time	77%	10%	13%
		15 years, GD, relapse	47%	33%	20%
Sato H, 2007 ²⁵	125 physicians from Japan	Primary treatment for childhood-onset GD	100%	Nil	Nil
		Relapse of childhood onset GD	97%	4%	1%

ETA—European thyroid association

ESPE—European society of pediatric endocrinology

GD—Graves' disease

ATDs—Antithyroid drugs

RAI—Radioiodine

GD in children.² However, even physicians in the USA still avoid RAI in children < 5 years of age with GD due to the high susceptibility of the developing thyroid for development of malignancy.²

There are advantages of surgery as definitive treatment for GD in children: Currently, thyroid surgery in pediatric GD is safe and effective, when performed by an experienced surgeon. In an experience of 78 such surgeries at the Mayo Clinic, 65% subjects were subjected to near-total thyroidectomy and rest to subtotal thyroidectomy.²⁶ The incidence of permanent recurrent laryngeal nerve palsy and permanent hypoparathyroidism was nil. Though the incidence of ophthalmopathy in pediatric GD is low, there was improvement in eye signs in up to 85% of cases. Similar rates of efficacy and safety are observed in other cases series of thyroid surgery for GD treatment.²⁷⁻²⁹ Hence, total thyroidectomy is a safe option, if performed by an experienced surgeon with low risk of complications and proven long-term efficacy and safety without any risk of thyroid malignancy.

CONCLUSION

RAI therapy is effective as definitive treatment of GD in children and adolescents. But, there is paucity of data on long-term safety of RAI therapy in children. The main concern is possible carcinogenesis of the thyroid from RAI, as children less than 5 to 10 years of age with a developing thyroid are more prone for carcinogenesis from radiation

exposure. In the absence of conclusive data on long-term safety of RAI in children and adolescents, RAI ablation should not be the preferred choice of treatment in pediatric GD.

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