Clinical and Translational Imaging (2023) 11:71–82
https://doi.org/10.1007/s40336-022-00529-1

SYSTEMATIC REVIEW

Pharmacological protection of the thyroid gland against radiation damage from radioactive iodine labeled compounds in children: a systematic review

Bas de Lijster[1] · Clara T. M. M. de Kanter[2] · Bart de Keizer[1,3] · Godelieve A. M. Tytgat[1] · Thomas Vulsma[4] · Martin Offringa[5,6,7] · Hanneke M. van Santen[1,8]

Received: 10 August 2022 / Accepted: 12 October 2022 / Published online: 27 October 2022

Abstract

Purpose There is currently no consensus on which protective strategy is most effective to prevent I-131 uptake in the thyroid during medical interventions in children. We aimed to collect the best available evidence to determine which pharmacological intervention is most effective in protecting the thyroid gland from damage by radioactive iodine (RAI).

Methods Literature searches were performed using PubMed, Embase, OLDMEDLINE, and the Cochrane Central Register of Controlled Trials. Only original studies were included (1950–2022). Studies comparing pharmacological prevention of the thyroid against RAI uptake or occurrence of hypothyroidism, thyroid nodule or thyroid cancer were included. Included studies were graded according to the Grading of Recommendations Assessment, Development and Evaluation considerations. Pharmacological interventions were compared for effectiveness on reduction of thyroidal intake or relevant clinical thyroidal outcomes.

Results Forty studies were included. Quality of included studies was low and many different outcome variables were used, making meta-analysis impossible. In 81% of studies, the pharmacological intervention could not prevent RAI uptake or thyroid damage. The administration of potassium iodide (KI) 1 h before exposure to RAI seemed most effective to reduce thyroidal uptake, however, hypothyroidism was reported in up to 64% as well as several cases of thyroid carcinoma. The combination of KI, thyroxine and thiamazole reduced RAI uptake and occurrence of hypothyroidism; yet, after follow-up of 9 years, still 50% of patients developed hypothyroidism. KI with potassium perchlorate showed hypothyroidism to occur in up to 12% of patients after short follow-up time.

Conclusions The lack of well-designed studies impairs making strong recommendations on the optimal way to prevent thyroid damage when using radioactive coupled ligands for medical interventions. To improve the protection of the thyroid against radiation damage by I-131, well-designed randomized clinical trials with sufficient follow-up time, comparing new protective strategies' effects on valid and well-defined thyroid outcomes are needed.

Keywords Thyroid damage · Thyroid cancer · Hypothyroidism · I-131 · I-123 · Radioactive iodine

✉ Hanneke M. van Santen
h.m.vansanten@umcutrecht.nl

1 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

2 Department of Pharmacy, Curaçao Medical Center, Willemstad, Curaçao

3 Department of Nuclear Medicine and Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

4 Department of Pediatrics and Neonatology, Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands

5 Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, Toronto, ON, Canada

6 Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

7 Division of Neonatology, The Hospital for Sick Children, Toronto, ON, Canada

8 Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center Utrecht, PO Box 85090, 3508 AB Utrecht, The Netherlands

Abbreviations

RAI	Radioactive iodine
KI	Potassium iodide
TSH	Thyroid stimulating hormone
T_4	Thyroxine
$KClO_4$	Potassium perchlorate
I-131	Iodine-131
MIBG	Meta-iodobenzylguanidine
NIS	Sodium-iodide symporter
CR	Clinical relevance
I-123	Iodine-123
GRADE	Grading of Recommendations Assessment, Development and Evaluation
T_3	Triiodothyronine
I-127	Iodine-127
NaI	Sodium iodide
SSKI	Saturated solution of potassium iodide
KIO_3	Potassium iodate
$t_{1/2}$	Effective half-life
CBZ	Carbimazole

Introduction

Radioactive iodine (RAI) liganded compounds, using beta-radiation emitting iodine-131 (I-131) are used in the treatment of childhood cancers, specifically neuroblastoma where iodine-131-metaiodobenzylguanidine ([^{131}I]MIBG)

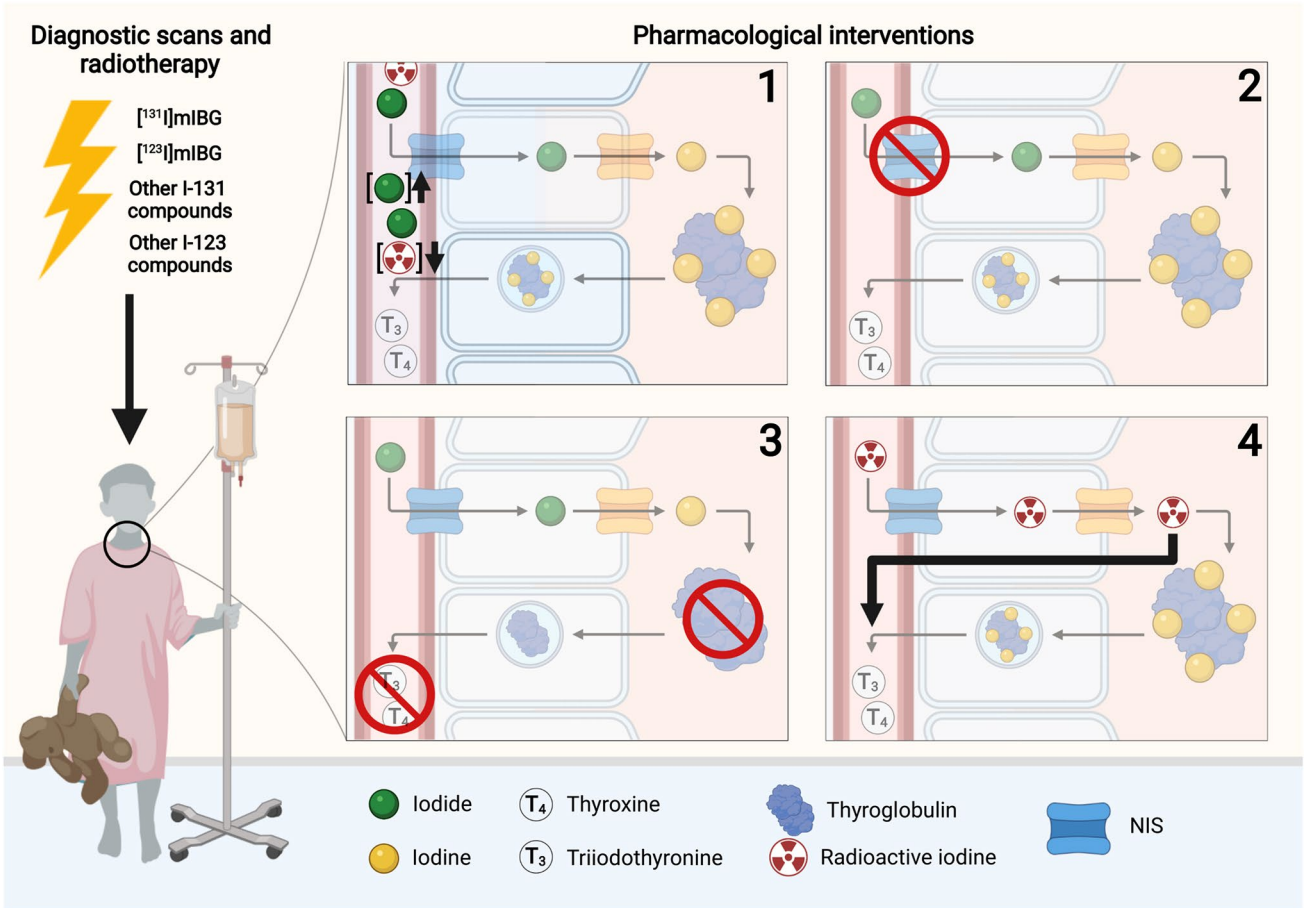

Fig. 1 Schematic figure for the iodine pathway in the thyroid follicle and the possible sites of radiation prevention. After stimulation of TSH (produced by the hypothalamus and pituitary gland), iodide is actively taken up by the sodium-iodide transporter (NIS). Subsequently, I^- is transported via the apical membrane into the follicular lumen, where it is enzymatically (thyroid peroxidase, TPO) oxidized and subsequently bound to thyroglobulin (Tg). After stimulation by TSH, Tg is endocytosed, hydrolyzed and mono- and diiodotyrosine (MIT and DIT) are deiodinated and T_4 and T_3 are secreted into the circulation. When the intra-thyroidal concentration of iodide is high, NIS activity is reduced. When I-131 is administered, I-127 as thyroid protection dilutes the I-131 concentration (#1), reduces the vascularization of the thyroid, and inhibits the organification of iodide. Perchlorate (ClO_4^-) salts inhibit the (radio)iodide uptake by the NIS (#2). Thiamazole (TMZ) inhibits the iodide organification (#3) and decreases the forming of free radicals. Thyroid hormone (T_4 and T_3) decreases (radio)iodide uptake by NIS by decreasing TSH plasma concentration (#4)

can be part of the treatment [1]. During such treatment, free I-131 entering the circulation can damage the thyroid gland. This may result in thyroid dysfunction (described in up to 64% of children) or structural abnormalities, either benign or malignant, which may have lifelong consequences for the developing child [2, 3]. Of note, I-123 is also used for medical diagnostics but does not damage the thyroid gland because I-123 has different physical characteristics and the amount of activity used for diagnostic purposes is much lower [4, 5].

Protection of the thyroid gland against exposure to I-131 focuses on diluting the circulating RAI (#1), reducing thyroidal uptake of RAI (#2), decreasing binding of RAI to thyroglobulin within the thyroid follicular cell (#3) or increasing discharge of RAI from the thyroid (#4), or a combination of one or more of these strategies (Fig. 1).

To date, the most commonly used protection of the thyroid gland from damage by RAI is by administration of potassium iodide (KI) [6]. KI as thyroid protection has internationally been acknowledged as most effective in blocking the thyroid from uptake of RAI, for instance, during nuclear accidents [7]. Despite these recommendations, hypothyroidism following administration of KI as thyroid protection was described. For this reason, other pharmacological interventions have been studied to reduce thyroid injury, such as potassium perchlorate ($KClO_4$), thiamazole, thyroxine (T_4) or combinations of aforementioned [8].

There are clear rationales for these interventions. KI prevents exposure of the thyroid gland to RAI by hindering uptake into the thyroid gland via the sodium-iodide symporter (NIS). This is firstly done by dilution (Fig. 1, #1) and thus decreasing the amount of circulating RAI. In addition to dilution, iodine excess will also result in down-regulation of the NIS by the Wolff-Chaikoff effect (Fig. 1, #2) [9]. A different way of blocking the NIS, is the administration of perchlorate salts.

In case RAI has accumulated in the thyroid gland, prevention of further radiation damage may be accomplished by shortening the time that RAI is captured within the thyroid cell; in other words, by accelerating the efflux of RAI. Antithyroid drugs will block the subsequent organification and thus limit binding of RAI to thyroglobulin in the follicular cell and thus stimulate elimination of iodine. Thyroid stimulating hormone (TSH) stimulates the iodine turnover with utilization of thyroglobulin and thereby increases the secretion of thyroid hormone and efflux of iodine. A drawback of administrating TSH aiming to increase the efflux of RAI, is the fact that TSH also stimulates uptake of iodine into the thyroid gland by the NIS (Fig. 1).

Despite the availability of several interventions that may reduce radiation injury to the thyroid gland during medical interventions using RAI in children, each with a clear rationale, there is currently no consensus on which protective strategy is the most effective to prevent uptake of RAI causing subsequent thyroid damage in children or adults given RAI for medical purposes. Protection of the thyroid gland in children may be even of greater importance than in adults as the thyroid gland in children has been shown to be more vulnerable to the effects of radiation and they have a longer life span [10]. This is especially relevant when considering the carcinogenic effect of RAI, taking into account that latency time to develop thyroid cancer after radiation exposure can be up to 10 years [11].

To appraise the available evidence on pharmacological preventive interventions and to identify knowledge gaps in this field, we undertook a systematic review of the published literature since 1950 on protective strategies that reduce radiation-induced thyroid damage from RAI in humans, with special interest in the evidence that has been produced in children. The primary objective of this systematic review was to determine which pharmacological preventive intervention is most effective in protecting the thyroid gland from damage when treated with I-131 containing radiopharmaceuticals. We aimed to answer the following questions:

1. Which pharmacological preventive interventions have been reported to reduce thyroid damage from I-131 in humans?
2. Which biomarkers and clinical outcomes have been used to evaluate the effects of these interventions?
3. Which of these interventions reduce uptake of RAI in the thyroid, prevalence of thyroid dysfunction, the occurrence of nodules or thyroid cancer after exposure to I-131?
4. What is the quality of the evidence for pharmacological preventive interventions in children?

Methods

Search strategies and information sources

This review comprises data of two literature searches (Online Resource Table 1a and 1b), one performed in 2004 and an updated search performed in 2020. During the first search that was performed in 2004, the following electronical databases were searched: PubMed (1966–2004, week 20), Embase (1980–2004, week 22), OLDMEDLINE, Cochrane Central Register of Controlled Trials. Additionally, relevant studies that were referred to in review articles or other articles that were not found by this search strategy were included until 1 September 2004. From the search in OLDMEDLINE, studies were selected by title since no abstracts were available (Online Resource Table 1a).

The second search was an update of the first search and was performed in PubMed, including all relevant papers

published between 2004, week 21 and 2020, week 39. Additionally, relevant studies that were referred to in review articles or other studies that were not found by this search were included (Online Resource Table 1b).

Eligibility criteria

Inclusion criteria were original studies, written or translated in the English language. Studies had to report outcome of thyroidal uptake or occurrence of hypothyroidism, thyroid nodule or thyroid cancer as late effect after exposure to RAI after providing a pharmacological intervention. Participants of all ages and genders treated with RAI for medical purposes other than thyroid disease were included.

Interventions using sex steroids or prolactin were excluded as these ways of pharmacological interventions were not considered to be suitable for thyroid protection in children. Studies on the effects of RAI given to treat thyroid nodules or cancer, Graves' disease, with less than five persons, in vitro, that described radiation effects only on other organs than the thyroid (e.g., salivary gland), review articles and studies published before 1950 were excluded.

Selection process

All included studies were critically appraised by two or three reviewers (HvS and TV (initial literature search) and by HvS, CdK, BdL (second literature search)). During this appraisal, first the research question and methods of the studies were discussed. Subsequently, consensus was reached on the clinical relevance (CR), i.e., whether a protective intervention could be relevant and has the potential to be implemented in current pediatric clinical practice. A score was given ranging from one to ten denoting 'totally irrelevant' and 'highly relevant', respectively. Criteria for high CR were studies in children versus adults, strength of data (i.e., number of patients, length of follow-up) and feasibility of the intervention (i.e., whether practical, free of side effects and/or at low financial costs).

Data extraction

From each included study, the following data set was extracted (HvS and BdL): Article: first author name, year of publication; study: characteristics of the subjects or patients, type of study; type of RAI given (gamma radiation emitting iodine-123 (I-123) as diagnostic agent or beta-radiation emitting I-131 as therapeutic agent) total activity and fractions; Prevention strategy: nature and duration of the thyroid protection strategy given, time to follow-up; Thyroid outcome: thyroid outcome measures and follow-up; results: summary of the relevant results, side effects induced by the pharmacological interventions; authors' conclusions.

Table 1 Thyroid outcomes used in the included studies after exposure to RAI

Outcomes	#
Thyroid function	**52**
TSH	17
T_4	12
T_3	9
Free T_4	5
Free T_3	2
Thyroglobulin	2
TRH test	1
rT_3	1
Thyroid function, not further defined	3
Concentration iodine	**17**
Urine [I]	8
Protein bound iodine	5
Serum [I]	3
Feces [I]	1
Antibodies	**9**
Anti-TPO	5
Anti-Tg	4
Other	**36**
Thyroid uptake of RAI	24
Total body counts	3
Ultrasound thyroid	3
Absorbed dose in other organs than thyroid	1
Adrenal scintigraphy	1
Clinical examination thyroid	1
Height	1
Questionnaires	1
Not defined	1
Total	**114**

TSH, thyroid stimulating hormone, T_4, levothyroxine, T_3, triiodothyronine, *TRH*, thyrotropin-releasing hormone, rT_3, reverse T_3, *TPO*, thyroperoxidase, *Tg*, thyroglobulin, *RAI*, radioactive iodine

Effect measures

Effect measures used in the individual studies were summarized in Tables 1 and 2.

Synthesis methods

Meta-analysis could not be undertaken due to the heterogeneity of the interventions, outcome measures and study designs. Therefore, summaries of findings tables on outcomes and interventions were developed. These tables comprise summaries of the different outcome measure categories, interventions used per type of RAI and the effectiveness of the pharmacological interventions against uptake of RAI. Subsequently, the results of the studies were discussed within the author group and conclusions were drawn.

Table 2 Effectiveness of pharmacological interventions against uptake of I-131

	I-127	TSH + other	ClO_4^-	Diuretics[c]	Priodax	T_4 + TMZ + KI	T_3 + Lugol's	ACTH
Thyroidal uptake	Reduction of uptake: 1.8 mg: 33% and 48%; 4.2 mg: 69% and 62% [45]; 40% [23]; 1999: 42%; 2000: 42%; 2001: 38% [46]; 10–50 mg: 80–84%, 100 mg: 90%, 200–500 mg: 97.5% [47] Highest reduction: 30 mg, continuous 35 mg [16]; 200 mg [17]; 130 mg [48] Uptake: 5% [18]; 62.7% [30]	–	Reduction of uptake: 99%[b] (+ KI) [24] Uptake: [41]	Uptake: no significant change [33]	Uptake: reduced to < 10%[d] [22]	Uptake: In 5.3% of scans [8]; 2% (weak) [6] No uptake: 88.4% of scans [6]	Uptake: 29% minimal, 33% moderate/intense [30]	–
$t_{1/2}$ elim	6.5 ± 0.6 d (KI), 6.9 ± 0.7d (control) [31] Lower [32]	2.5 ± 0.7d (TSH + KI), 6.9 ± 0.7d (control) [31] Lowest for TSH + CBZ + KI & TSH + CBZ + $KClO_4$ [32]	–	–	–	–	–	–
Excretion	Higher [18, 32] Massive overload [49]	Highest increase with TSH + CBZ + $KClO_4$ [32]	–	No significant change [33]	–	–	–	Increased[e] [50]
Thyroidal dysfunction (TE + HT)	TE: 8.4% [51]; 29% [14]; 42% [13]; 0.3%, transient [23] HT: 40% [49]; 42.9% [3]; 85.7% [52]; 10% asymptomatic (+ $KClO_4$) [25]; 56% [53]; 12 ± 4% (+ $KClO_4$) [27] No HT: [54], KI + $KClO_4$ [26] Decreased incidence with KI + $KClO_4$ [27]	–	HT: 10% (+ KI) [25], 12 ± 4% (+ $KClO_4$) [27] Thyroid toxicity: 1.3% [28] Decreased incidence with KI + $KClO_4$ (20)	–	–	HT: 17.4% [8] TE: 12.9% [6]	HT: 63% [30]	–
Other	Side effects: extrathyroidal[a] [23]; no side effects [55]	PBI: significant increase after TSH + CBZ + $KClO_4$ [32]	Thyroidal activity: lower than T_3 + Lugol's [29]	–	–	–	Thyroidal activity: higher than $KClO_4$ [29]	–

KI, potassium iodide; *TE*, TSH elevation; *HT*, hypothyroidism; *TSH*, thyroid stimulation hormone; *CBZ*, carbimazole; *KClO4*, potassium perchlorate; *PBI*, protein bound iodine; T_3, triiodothyronine; T_4, thyroxine; *TMZ*, thiamazole; *ACTH*, adrenocorticotropic hormone

[a]Headache, stomachache, diarrhea, vomiting, shortness of breath, skin rashes

[b]No arguments given

[c]Meralluride, hydrochlorothiazide, acetazolamide

[d]Research performed on cholecystography

[e]Unclear if it is a change in thyroid state or renal clearance

Certainty and bias assessment

Thirty-three studies were graded by two reviewers (HvS and TV performed the grading of evidence in 2004, which was reevaluated in 2020 by three reviewers (HvS, CdK, BdL). Seven studies were graded and evaluated by three reviewers (HvS, CdK, BdL). All studies were graded according the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias). The certainty of evidence were assessed as high, moderate, low or very low [12]. Disagreements about grading were resolved through discussion.

Results

Study selection

The initial search conducted in 2004 using PubMed, Embase, OLDMEDLINE and Cochrane, yielded a total of 1693 records. Of these, 33 studies met the inclusion criteria. In the updated search in 2021, another 226 studies were found using PubMed and five studies were found through other resources (Online Resource Tables 1a and 1b), of which seven in total could be included. In total, forty studies were included for data extraction and critical appraisal (Fig. 2). Online Resource Table 3 shows the characteristics of the included studies. Of these forty studies, $n = 11$ (27.5%) reported on children (age < 18 years), $n = 11$ (27.5%) reported on adults (age > 18 years), $n = 6$ (15.0%) reported on children and adults and $n = 12$ (30.0%) did not report any age.

Risk of bias

Risk of bias assessment was done by grading according the five GRADE considerations (Online Resource Table 3). As shown in Table 1, many different thyroid outcomes were used. In studies using I-123, effectiveness of thyroid protection was measured as percentage of uptake or elimination of RAI, instead of thyroid function during follow-up due to the fact that I-123 does not affect thyroid function. Due to the many heterogenous outcomes used in these studies, results are presented using descriptive analysis.

Results of individual studies

As shown in Table 1, twenty-four different parameters were used to evaluate the effectivity of the pharmacological intervention(s) against thyroidal uptake or damage of RAI in the thyroid gland. In many studies, more than one outcome was reported. Yet, in 10% of studies the thyroid outcome was not well-defined: in one study, thyroid function biomarkers were not defined at all, and in three the intent was stated 'to evaluate thyroid function' without further detail. Plasma concentration of TSH was most frequently reported as thyroid function test (42.5%), followed by plasma concentrations of T_4 (30.0%) and triiodothyronine (T_3; in 22.5%). The effectiveness of the interventions on uptake of I-131 and I-123 are stated in Tables 2 and 3, respectively.

In the below, we review the findings on the interventions' effectiveness by protective mechanism.

Protection against uptake of RAI in the thyroid by dilution (#1) and decreasing uptake of I-131 by NIS (#2)

Stable iodine The most frequent used intervention strategy was the administration of stable (not radioactive) iodine-127 (I-127) (in 53.8% of included studies, Online Resource Table 2), which was administered in a variety of preparations: orally as solid KI or sodium iodide (NaI), Lugol's solution (a solution of potassium iodide with iodine in water), saturated solution of KI (SSKI) and as dermal tincture (2% solution (2 g per 100 ml)). In several studies, the exact administered dose could not be retrieved. Moreover, in two studies, Lugol's solution and SSKI were considered the same; however, Lugol's solution contains about 8.4 mg iodine and SSKI about 38 mg iodine per drop [13, 14]. The administered doses of stable iodine varied from 0.1 to 2000 mg/day (Online Resource Table 3).

In 81.3% of studies in which KI was used for thyroid protection, the intervention strategy proved to be insufficient, expressed as visible uptake of RAI in the thyroid despite KI administration or the development of hypothyroidism (TSH elevation). In one study performed in adults, it was observed that despite the administration of 100 mg KI, uptake of RAI in the thyroid gland was visible in 74% of subjects, [15]. In children, given 100 mg KI (divided in 3 doses/day), the thyroid gland was reported to be visible in 21.5% [3]. Overall, in 35.3% of the studies and in up to 64% of patients in which KI was given as thyroid protection during a medical intervention with RAI coupled to a compound, the development of hypothyroidism was reported.

The dose and timing of KI administration differed widely between the studies. At higher doses of KI, the efficacy in reduction of uptake seemed to diminish, although reduction of RAI uptake was found until doses of 200 mg in adults. In one study, uptake of RAI was reduced to 0.0% after 247 mg KI orally [16], but in all other studies iodine excess led to a maximum reduction of uptake of 95–97%.

Blocking of RAI uptake in the thyroid occurred within 30 min after the administration of 100–200 mg KI. After the oral administration of 30 mg KI, inhibition of uptake was reported after 2 h. The most optimal reduction in RAI

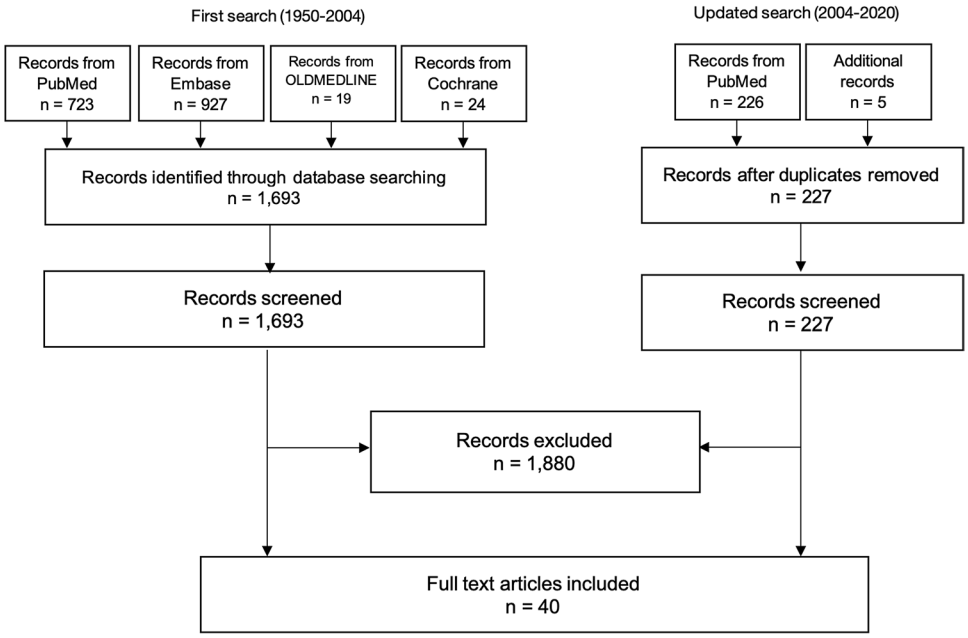

Fig. 2 Flow diagram showing study selection. The initial search conducted in 2004 using PubMed, Embase, OLDMEDLINE and Cochrane, yielded a total of 1693 records. Of these, 33 studies met the inclusion criteria. In the updated search in 2021, another 226 studies were found using PubMed and five studies were found through other resources of which in total seven could be included. In total, forty studies were included for data extraction and critical appraisal

Table 3 Effectiveness of pharmacological interventions against uptake of I-123

Intervention	References	Thyroidal uptake
I-127 (stable iodine)	Sternthal [56]	10 mg: 12.5% uptake > 30 mg: 1.5% uptake
	Weber [57]	Low iodine supply: 80% Adequate iodine supply: 44–50%
	Friedman [58]	Significant difference in uptake between late and early image
T_4 + thiamazole + KI	Clement [6]	4.2% (7 images) showed uptake
KIO_3	Thurlow [20]	No uptake: 91.9% (159 images) Low-level uptake: 6.9% (12 images) Moderate uptake: 1.2% (2 images)
$KClO_4$	Thurlow [20]	No uptake: 45.3% (24 images) Low level uptake: 26.4% (14 images) Moderate uptake: 22.6% (12 images) High-level uptake: 5.7% (3 images)
Iohexol + KIO_3	Thurlow [20]	No uptake: 80% (4 images) Low-level uptake: 20% (1 image)

T4, thyroxine, *KI*, potassium iodide, *KIO_3*, potassium iodate, *$KClO_4$*, potassium perchlorate

uptake was achieved by the administration of KI 1 h before exposure to RAI. The protective ability of KI diminished rapidly when given after exposure to RAI; when KI was administered 3 h after exposure, the uptake was reduced with 50.0% [17]. When continuously exposed to RAI, repeated administration of KI was shown to be necessary for an optimal blockade of uptake of RAI by the thyroid gland [16–18]. The administration of iodized compounds, originally used for radiologic examinations, decreased RAI uptake to less than 10.0% [19].

Stable iodine not given as KI or Lugol were only examined in one single study. Potassium iodate (KIO_3) demonstrated a significant lower absorbed dose of RAI in the thyroid when compared to $KClO_4$ (median absorbed dose 2.18, 1.96 and 1.98 mGy versus 10.7 mGy, respectively) [20]. Amiodarone, containing 75 mg iodine per 200 mg tablet, was shown to induce hypo- and hyperthyroidism. Uptake of RAI was decreased in the euthyroid and hyperthyroid patients but preserved in hypothyroid patients with an elevated TSH. This is presumably caused by a failure of the escape mechanism of the inhibitory effects of iodide (persistent Wolff-Chaikoff effect) [21]. The administration of Priodax (an iodine-containing preparation) with or without TSH administration, showed a reduction of more than 90.0% in RAI uptake in the thyroid gland [22].

Side effects of stable iodine were reported, mainly hyperthyroidism in the elderly (up to 35.0%) and transient TSH elevation and vomiting in the young [23].

KI combined with potassium perchlorate ($KClO_4$) The combination of $KClO_4$ (dose ranging from 400 to 600 mg/day and 8 mg/kg) and KI (dose ranging from 120 mg/day, 6 mg/kg and 3dd 2 drops) was administered in five studies [24–28]. In these cohorts, hypothyroidism was found in 0–12.0% of the patients. In one study, 800 mg of $KClO_4$ alone was administered which showed a reduction of RAI uptake in the thyroid gland, although radioactivity in the thyroid was still seen (5.7 mGy/MBq administered [^{131}I]MIBG and 0.3–0.76 mGy/MBq when coupled to [^{131}I]iodocholesterol [29]).

T_3 in combination with Lugol's solution The administration of T_3 with Lugol's solution did not prove to be effective. One study showed the development of hypothyroidism in 62.7% of subjects and thyroidal uptake in more than 60.0% of subjects [24]. Another study showed that the combination of T_3 with Lugol's solution was less effective than the administration of $KClO_4$ alone [22].

Protection of the thyroid from I-131 damage by decreasing binding of RAI to thyroglobulin (#3)

Thiamazole in combination with KI and T_4 In one study in which [^{131}I]MIBG (median dose 9975 Mbq) was administered to children with neuroblastoma, thiamazole (0.5 mg/kg/day for 4 weeks) was combined with KI (3 dd 30 mg for 2 weeks) and T_4 (100 mcg/m^2 for 4 weeks). A reduction of uptake in the thyroid was seen when compared to a historic control group given only KI (thyroid visible in 2.0% vs. in 28%, respectively). Prolonged follow-up after 9 years of 24 children given this combined (thiamazole, KI and T_4) protection, however, showed thyroid disorders in 50.0% ($n=12$) of patients, of which nine developed thyroid dysfunction, five thyroid nodules and one thyroid carcinoma [6].

Protection of the thyroid by increasing the elimination of RAI (#4)

TSH in combination with KI and other pharmacological interventions The administration of TSH in addition to KI, after exposure to RAI diminished the effective half-life ($t_{1/2}$) of RAI in the thyroid gland with 60% compared to KI alone (2.5 ± 0.7 days and 6.5 ± 0.6 days, respectively) [31]. Lividas et al. experimented with various combinations of pharmacological interventions (KI, carbimazole (CBZ), $KClO_4$ and TSH) and found that the combination of TSH, CBZ and $KClO_4$ was most effective to reduce RAI uptake (reduction of $t_{1/2}$ from 76.0 to 7.8 days, $p<0.005$), when given 7 days after exposure to RAI [32]. The administration of TSH as monotherapy, which was applied in two studies, also reduced $t_{1/2}$ (from 94 to 16 days) [31, 32].

Other pharmacological interventions The administration of diuretics had no effect on uptake of RAI in the thyroid gland or on its elimination [33].

Discussion

With improved survival rates in childhood cancers [34], it is becoming increasingly important to prevent damage to healthy organs during cancer treatment. For children, the hormones produced by the thyroid gland are essential for a normal mental, motor and pubertal development and growth into adolescence and adulthood [35]. Prevention of damage to endocrine organs such as the thyroid must, however, not only focus on protecting its function (required to maintain optimal circulating concentrations of hormones) but must also aim to prevent the development of secondary malignancies, such as differentiated thyroid cancer. Thyroid damage in childhood cancer survivors may be caused by multiple factors such as external cervical irradiation, anti-neoplastic drugs or immunotherapy. In children with neuroblastoma, a high prevalence of hypothyroidism, thyroid nodules and several cases of thyroid cancer have been reported after the use of [^{131}I]MIBG [6, 36].

Although the damaging effects of exposure to I-131 on the thyroid gland are very well known, among others due to the follow-up studies after the Chernobyl nuclear disaster, the current state of evidence for thyroid protection strategies during exposure to RAI in the medical setting in childhood is concerning [37, 38]. To know how to protect the thyroid gland of young children against radiation damage is of special importance, as the younger thyroid has been shown to be more vulnerable to radiation damage [10]. We reviewed and summarized all existing studies since the 1950's and found a low number of studies, in which only a few patients were studied using many different intervention strategies, and more than twenty different outcome measures. The wide variety of preventive measures and endpoints makes it complicated to draw definite conclusions. In addition, biochemical endpoints have been used in many studies, whereby patient relevant outcomes such as fear for (secondary) thyroid cancer, fatigue or quality of life have not been studied. We found it neither possible nor sensible to try and statistically combine numerical results into overall estimates of the interventions' effectiveness. However, several important lessons can be learned from our review, and several implications for practice and for research can be identified.

All current reported protective interventions are aimed at reducing uptake of RAI in the thyroid gland (by dilution or

decreasing uptake by NIS) or at increasing its elimination (such as by decreasing the binding of RAI to thyroglobulin). It must be considered, however, that radiation exposure to thyroid follicle cells may also occur by RAI passing through the blood vessels through and around the thyroid gland. Considering the great vulnerability of the thyroid gland, this exposure may potentially cause radiation damage to the thyroid which cannot be overcome by reducing its uptake into the thyroidal follicle cells but may be influenced by decreasing its vascularization (which can be done for instance by decreasing the concentration of circulating TSH).

Diluting RAI in the circulation and reducing NIS uptake by stable iodine (#1 and #2)

As described in the results, various preparations of stable iodine were used caused by the fact that high doses of stable iodide may be found in various solutions, such as NaI or Lugol's solution (KI, SSKI).

Summarizing the results of our review, a maximum reduction of RAI uptake in the thyroid of 97.5% may be achieved if the optimal timing (preferably 1 h before exposure) and optimal dosage (up to 200 mg in adults) are given. Because the risk of developing a radiation-induced thyroid malignancy is increased already at low radiation doses, reduction of RAI uptake must be aimed up to 100% [39, 40]. As was shown, KI as thyroid protection in children given [^{131}I] MIBG resulted in a high percentage of children with hypothyroidism (ranging from 12.0 to 85.7%) and three cases of differentiated thyroid cancer [2, 3]. With these reports, KI alone (using 100 mg/day) cannot be considered sufficient in children in the clinical setting and additional protective interventions must be outweighed. For children almost no side effects were reported after the administration of iodide excess. Perhaps increasing the dose of KI to the adult dose of 200 mg may improve thyroid blockade, however, studies on efficacy or side effects of using KI doses higher than 100 mg are lacking in children.

The effectiveness of administrating KI after exposure to RAI was shown to decrease rapidly in time. For this reason, it seems of no benefit to start the administration of KI (or other forms of stable iodine) 24 h after exposure to RAI in the medical setting. In such cases (e.g., when KI was forgotten) it may be considered to administer the combination of TSH, CBZ and $KClO_4$ [30]. In situations where there is continuous exposure to RAI, it may be considered to continue its use.

Reducing NIS uptake by perchlorate (#2)

Blocking the uptake of RAI through the NIS can be done by stable iodine but also by administration of perchlorate salts. Three studies reported high effectivity against thyroidal uptake in combination with stable iodine resulting in a lower percentage of patients with hypothyroidism as late effect [25, 27, 41]. Perchlorate was shown to be more effective than when compared to the administration of T_3 in combination with stable iodine [29]. However, it must be pointed out that the follow-up time of the perchlorate studies was short. Long term follow-up studies are lacking in children given perchlorate protection of the thyroid gland. Considering the positive short-term results that have been reported, the use of perchlorate as effective protective measure should be further investigated. None of the studies reported side effects after treatment with perchlorate. However, side effects as agranulocytosis, aplastic anemia and leukopenia have been reported after administration of perchlorate in adults [42, 43].

Reducing NIS uptake by thyroid hormones (#2)

The addition of T_4 to pharmacological thyroid protection procedures may serve three purposes. Firstly, by decreasing the plasma concentration of TSH which will subsequently lower the thyroid's cell metabolism and vascularization, which theoretically reduces its radio-susceptibility. Secondly, decreasing the plasma concentration of TSH will lower the uptake of (radio)iodine by NIS, and thirdly the administration of thyroid hormone ensures euthyroidism during the administration of, for example, thiamazole. Two studies have reported upon the use of T_4 in combination with thiamazole and KI. This pharmacological combination resulted in a decreased RAI uptake (5.3% compared to 21.5%) as well as a diminished occurrence of permanent hypothyroidism compared to children that were only given KI for thyroid protection (60.0% compared to 78.6%). The fact that still 17.4% of all patients in one study developed hypothyroidism, expressed as permanent thyrotropin elevation and additionally some uptake in the thyroid gland could be detected, necessitates the exploration of alternative or additional actions [6]. Also one patient with thyroid carcinoma was reported after the use of this combined thyroid protection [2].

Considering the studies included in this review, the evidence suggests that the addition of T_4 (and thiamazole) improve the thyroid protection when compared to the administration of KI alone.

Eliminating RAI from the thyroid gland by TSH and anti-thyroid drugs (#3 and #4)

Combined administration of TSH and anti-thyroid drugs (i.e., CBZ) may increase the efflux of RAI. However, an increase in plasma concentration of TSH will also increase the uptake of RAI by NIS, indicating that these compounds should only be administered hours after exposure, when the greater fraction of RAI is already removed by the kidneys.

In the medical situation, these interventions might be considered when RAI uptake is detected in the thyroid gland at first scanning. The addition of anti-thyroid drugs that block organification to thyroid protection with KI and T_4 was shown to improve thyroid protection. In this situation T_4 is administered to prevent a rise of plasma concentrations of TSH and to ensure euthyroidism [8].

Outcomes

Heterogeneity in outcome measures and interventions made it difficult to draw definite conclusions and to make suggestions on the most effective way of protecting the thyroid gland against damage from RAI as used in the medical setting. The included studies were too heterogeneous with regards to patients, indications and age groups, as well as regarding intervention and outcome measures used.

Children have a different thyroid cell metabolism than adults, including different TSH and free T_4 reference values, different iodine metabolism with reaction to the Wolff-Chaikoff mechanism (higher % that escapes for this mechanism) and different cell biology (e.g., radiation vulnerability). In addition, children have a longer life span, increasing the need for thyroid protection especially with regard to the development of thyroid cancer after RAI exposure. Therefore, children may need different pharmacological interventions when compared to adults to protect their thyroid from RAI uptake and other effectiveness outcomes need to be defined. To overcome ongoing research waste caused by this wide heterogeneity of outcomes, we recommend a core outcome set be developed for studies in this field including consensus-definitions for the presence of thyroid dysfunction, nodules, thyroid cancer and more standardized follow-up time.

Primary study limitations

Most included studies had major limitations in the design, conduct and reporting. Many of the included studies had small sample sizes, and age of patients was often not reported. To not report the patient's age may be considered an important limitation because thyroid cell metabolism, uptake of iodide by NIS, Wolff–Chaikoff effect as well as vulnerability of the thyroid cells for RAI differ with age. Various studies did not primarily focus on the effects of the pharmacological intervention on the thyroid function, which resulted in missing information on dosage and dosage schemes.

Strengths and weaknesses of this review

Strengths of our review include the completeness of the literature search and the grading of the literature by an expert multidisciplinary team including a pediatric endocrinologist with expertise in thyroid cell metabolism, a pediatric oncologist with expertise on MIBG and neuroblastoma, a nuclear physicist with expertise on the RAI metabolism and half-life and MIBG treatment, a pediatrician-methodologist with expertise in systematic literature reviews and a hospital pharmacist. The limited data sources and associated risk of publication bias (e.g., no abstracts and restriction to English literature) may be considered a weakness of this review.

Implications for practice, policy, and future research

While administration of high doses of stable iodide still seems to be "best practice", for thyroid protection in case of nuclear emergency, stable iodide alone appears to be insufficient when used for children in the medical setting [44]. Adding perchlorate or thiamazole to T_4 may reduce the uptake or increase elimination of RAI in the thyroid gland and protect the thyroid's integrity, although even after adding these drugs still hypothyroidism and thyroid cancer were reported.

To improve health outcomes of children exposed to RAI for medical purposes we propose a multicenter randomized clinical trial comparing different protective strategies including the combination of KI and $KClO_4$ and the combination KI, T_4, and thiamazole in comparison to the administration of stable iodide alone. In such a controlled trial, the observers and patients should be blinded to the pharmacological intervention, using standardized outcomes such as yearly TSH, free T_4, thyroid ultrasound for presence of thyroid nodules or cancer, percentage of RAI uptake in the thyroid gland, and have a minimal follow-up time of 5 years to evaluate late adverse effects on growth, development, and well-being. In addition, for current medical practice, it may be useful to image the patient after therapy administration for dosimetric purposes and to forecast any thyroid side effects.

Conclusion

The evidence on pharmacological protection of the thyroid gland against RAI in the medical setting in childhood is poor. Recommendations for best clinical practice cannot be based on the current evidence. Well-designed randomized clinical trials with sufficient follow-up time, comparing new protective strategies' effects on valid and well-defined thyroid outcomes are needed. A comparative effectiveness trial evaluating the three current used strategies is recommended.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40336-022-00529-1.

Acknowledgements The authors thank Professor Jan de Vijlder for contributing to the initial literature search, and the fruitful discussions on the included studies.

Author's contribution BdL: formal analysis, investigation, writing—original draft, review and editing, visualization. CdK: writing—review and editing. BdK: writing—review and editing. GT: writing—review and editing. TV: conceptualization, methodology, investigation, writing—review and editing, supervision. MO: writing—review and editing. HvS: conceptualization, methodology, formal analysis, investigation, writing—review and editing, supervision.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sharp SE, Trout AT, Weiss BD, Gelfand MJ (2016) MIBG in neuroblastoma diagnostic imaging and therapy. Radiographics 36(1):258–278
2. Van Santen HM, Tytgat GAM, Van De Wetering MD, Van Eck-Smit BLF, Hopman SMJ, Van Der Steeg AF et al (2012) Differentiated thyroid carcinoma after 131I-MIBG treatment for neuroblastoma during childhood: description of the first two cases. Thyroid 22(6):643–646
3. Van Santen HM, De Kraker J, Van Eck BLF, De Vijlder JJM, Vulsma T (2002) High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during 131I-meta-iodobenzylguanidine treatment in children with neuroblastoma. Cancer 94(7):2081–2089
4. Clement SC, Tytgat GAM, van Trotsenburg ASP, Kremer LCM, van Santen HM (2022) Thyroid function after diagnostic 123I-metaiodobenzylguanidine in children with neuroblastic tumors. Ann Nucl Med 36(6):579–585
5. Giovanella L, Avram AM, Ovčariček PP, Clerc J (2022) Thyroid functional and molecular imaging. Press Medicale. https://doi.org/10.1016/j.lpm.2022.104116
6. Clement SC, van Rijn RR, van Eck-Smit BLF, van Trotsenburg ASP, Caron HN, Tytgat GAM et al (2015) Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during 131I-metaiodobenzylguanidine treatment in children with neuroblastoma. Eur J Nucl Med Mol Imaging 42(5):706–715
7. Leung AM, Bauer AJ, Benvenga S, Brenner AV, Hennessey JV, Hurley JR et al (2017) American thyroid association scientific statement on the use of potassium iodide ingestion in a nuclear emergency. Thyroid 27(7):865–877
8. Van Santen HM, De Kraker J, Van Eck BLF, De Vijlder JJM, Vulsma T (2003) Improved radiation protection of the thyroid gland with thyroxine, methimazole, and potassium iodide during diagnostic and therapeutic use of radiolabeled meta-iodobenzylguanidine in children with neuroblastoma. Cancer 98(2):389–396
9. Bürgi H (2010) Iodine excess. Best Pract Res Clin Endocrinol Metab 24(1):107–115
10. Sinnott B, Schneider AB (2010) Exposing the thyroid to radiation: a review of its current extent, risks, and implications. Endocr Rev 31(5):756–773
11. Iglesias ML, Schmidt A, Al Ghuzlan A, Lacroix L, de Vathaire F, Chevillard S et al (2017) Radiation exposure and thyroid cancer: A review. Arch Endocrinol Metab. 61(2):180–7
12. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64(4):401–6
13. Press OW, Eary JF, Appelbaum FR, Martin P, Badger C, Nelp W (1993) Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. N Engl J Med 329(17):1219–1224
14. Press OW, Appelbaum F, Martin PJ, Matthews DC, Bernstein ID, Eary JF et al (1995) Phase II trial of 131I–B1 (anti-CD20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. Lancet 346(8971):336–340
15. Bacher K, Brans B, Monsieurs M, De Winter F, Dierckx R, Thierens H (2002) Thyroid uptake and radiation dose after 131I-lipiodol treatment: is thyroid blocking by potassium iodide necessary? Eur J Nucl Med 29(10):1311–1316
16. Ramsden D, Passant F, Peabody C, Speight RG (1967) Radioiodine uptakes in the thyroid. Studies of the blocking and subsequent recovery of the gland following the administration of stable iodine. Health Phys. 13(6):633–46
17. Blum M, Eisenbud M (1967) Reduction of thyroid irradiation from 131-I by potassium iodide. JAMA 200(12):1036–1040
18. Saxena K, Chapman E, Pryles C (1962) Minimal dosage of iodide required to suppress uptake of iodine-131 by normal thyroid. Science 138(3538):430–1
19. Thoren A (1960) The influence of iodide and iodized compounds on the PBI and the 131-I tracer test with special reference to various biologic states of the thyroid. Acta Endocrinol 35:351–358
20. Thurlow B, Morris E, Price L, Melhuish T, Michopoulou S, King S et al (2020) A comparison of thyroid blockade strategies in paediatric 123I-meta-iodobenzylguanidine scanning: a dual centre study. Nucl Med Commun 41:436–42
21. Wiersinga W, Touber J, Trip M, Van Royen E (1986) Uninhibited thyroidal uptake of radioiodine despite iodine excess in amiodarone-induced hypothyroidism. J Clin Endocrinol Metab 63(2):485–491
22. Cupp C, Newman S (1960) Influence of iodoalphionic acid priodax, with and without thyrotropin, on thyroidal I 131 uptake in euthyroid patients. J Clin Endocrinol Metab 17(1):94–98
23. Nauman J, Wolff J (1993) Iodide prophylaxis in Poland after the chernobyl reactor accident: benefits and risks. Am J Med 94(5):524–532
24. Behr T, Juweid M, Sharkey R, Dunn R, Ying Z, Becker W (1996) Thyroid radiation doses during radioimmunotherapy of CEA-expressing tumours with 131I-labelled monoclonal antibodies. Nucl Med Commun 17(9):767–780
25. Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A et al (1998) Phase I dose escalation of

131I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol 16(1):229–236
26. Kaminski MS, Zasadny K, Francis IR (1993) Radioimmunotherapy of B-cell lymphoma with [131I]anti-B1 (anti-CD20) antibody. N Engl J Med 329:459–465
27. Quach A, Ji L, Mishra V, Sznewajs A, Veatch J, Huberty J et al (2011) Thyroid and hepatic function after high-dose 131I-metaiodobenzylguanidine (131I-MIBG) therapy for neuroblastoma. Pediatr Blood Cancer 56(2):191–201
28. Johnson K, McGlynn B, Saggio J, Baniewicz D, Zhuang H, Maris J (2011) Safety and efficacy of tandem 131I-metaiodobenzylguanidine infusions in relapsed/refractory neuroblastoma. Pediatr Blood Cancer 57(7):1124–1129
29. Barbarino A, Troncone L, Salvo D, Pasargiklian E (1975) Thyroidal accumulation of 131I during adrenal gland scintigraphy with 131I-19-iodocholesterol: effects of thyroid blocking agents. J Clin Endocrinol Metab 41(2):405–407
30. Bhandari S, Cheung N, Kushner B, Kramer K, Modak S, Larson S et al (2010) Hypothyroidism after 131I-monoclonal antibody treatment of neuroblastoma. Pediatr Blood Cancer 55:76–80
31. Blum M, Eisenbud M (1968) Therapeutic reduction of thyroidal irradiation from 131I by the use of potassium iodide and thyroid stimulating hormone. In: Proceedings of the first international congress of radiation protection. Elsevier, Amsterdam, pp 1309–1315
32. Lividas D (1975) Comparison of various treatment schedules for accelerating the elimination of radioiodine from the thyroid and the human body. Nucl Med (Stuttg) 14(3):219–227
33. Schteingart D, Perlmutter M, Numeroff M (1960) Effect of diuretics upon the serum protein bound iodine and the thyroidal uptake of radioactive iodine. Am J Med Sci 239:571–577
34. Zahnreich S, Schmidberger H (2021) Childhood cancer: occurrence, treatment and risk of second primary malignancies. Cancers 13(11):2607
35. Murray PG, Clayton PE (2013) Endocrine control of growth. Am J Med Genet Part C Semin Med Genet 163(2):76–85
36. Lebbink C, Waguespack S, van Santen HM (2021) Thyroid dysfunction and thyroid cancer in childhood cancer survivors: prevalence, surveillance and management. Front Horm Res 54:140–153
37. Reiners C, Drozd V, Yamashita S (2020) Hypothyroidism after radiation exposure: brief narrative review. J Neural Transm 127(11):1455–1466
38. Drozd V, Saenko V, Branovan DI, Brown K, Yamashita S, Reiners C (2021) A search for causes of rising incidence of differentiated thyroid cancer in children and adolescents after chernobyl and fukushima: comparison of the clinical features and their relevance for treatment and prognosis. Int J Environ Res Public Health 18(7):3444
39. Bhatti P, Veiga LHS, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA et al (2020) Radiation-related new primary solid cancers in the childhood cancer survivor study: comparative radiation dose response and modification of treatment effects. Int J Radiat Oncol Biol Phys 174(9):224–233
40. Milano MT, Vargo JA, Yorke ED, Ronckers CM, Kremer LC, Chafe SMJ et al (2021) Primary hypothyroidism in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. Int J Radiat Oncol. https://doi.org/10.1016/j.ijrobp.2021.02.001
41. Ertl S, Deckart H, Blottner A, Tautz M (1987) Radiopharmacokinetics and radiation absorbed dose calculations from 131I-meta-iodobenzylguanidine (131I-MIBG). Nucl Med Commun 8(8):643–653
42. Niziński P, Błażewicz A, Kończyk J, Michalski R (2021) Perchlorate—properties, toxicity and human health effects: an updated review. Rev Environ Health 36(2):199–222
43. Bogazzi F, Bartalena L, Tomisti L, Dell'Unto E, Cosci C, Sardella C et al (2008) Potassium perchlorate only temporarily restores euthyroidism in patients with amiodarone-induced hypothyroidism who continue amiodarone therapy. J Endocrinol Invest 31(6):515–519
44. World Health Organization (2017) Iodine thyroid blocking: guidelines for use in planning for and responding to radiological and nuclear emergencies. World Health Organization, Geneva
45. Cuddihy R (1966) Thyroidal iodine-131 uptake, turnover and blocking in adults and adolescents. Heal Phys 12(8):1021–1025
46. Huszno B, Hubalewska-Hola A, Baldys-Waligorska A, Sowa-Staszczak A, Szybinski Z (2003) The impact of iodine prophylaxis on thyroid 131-iodine uptake in the region of Krakow, Poland. J Endocrin Invest 26(2):7–10
47. Il'in L, Arkhangel'skaya G, Konstantinov Y, Likhtarev I (1972) Radioactive iodine in the problem of radiation safety. Virginia
48. Miller KL, Coen P, White W, Hurst W, Achey B, Lang C (1989) Effectiveness of skin absorption of tincture of I in blocking radioiodine from the human thyroid gland. Health Phys 56(6):911–4
49. Brans B, Monsieurs M, Laureys G, Kaufman J, Thierens H, Dierckx R (2000) Thyroidal uptake and radiation dose after repetitive I-131-MIBG treatments: Influence of potassium iodide for thyroid blocking. Blood 96(4):1259–1266
50. Kuhl W, Ziff M (1952) Alteration of thyroid function by ACTH and cortisone. J Clin Endocrinol Metab 12(5):554–559
51. Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M et al (2000) Radioimmunotherapy with iodine 131I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 96(4):1259–1266
52. Picco P, Garaventa A, Claudiani F, Gattorno M, De Bernardi B, Borrone C (1995) Primary hypothyroidism as a consequence of 131-I-metaiodobenzylguanidine treatment for children with neuroblastoma. Cancer 76(9):1662–1664
53. Magaña EG, Estrada JAS, Meguro EN, de Hernández A (2020) Thyroid dysfunction due to 131I-metaiodobenzylguanidine in patients with neuroblastoma. Rev Chil Pediatr 91(3):379–84
54. Klingebiel T, Treuner J, Ehninger G, Keller K, Dopfer R, Feine U (1989) [131I]-metaiodobenzylguanidine in the treatment of metastatic neuroblastoma. Clinical, pharmacological and dosimetric aspects. Cancer Chemother Pharmacol 25(2):143–8
55. Treuner J, Klingebiel T, Bruchelt G, Feine U, Niethammer D (1987) Treatment of neuroblastoma with metaiodobenzylguanidine: results and side effect. Med Pediatr Oncol 15(4):199–202
56. Sternthal E, Lipworht L, Stanley B, Abreau C, Fang S, Braverman L (1980) Suppression of thyroid radioiodine uptake by various doses of stable iodide. N Engl J Med 303(19):1083–1088
57. Weber K, Wellner U, Voth E, Schicha H (2001) Influence of stable iodine on the uptake of the thyroid–model versus experiment. Nuklearmedizin 40(1):31–37
58. Friedman NC, Hassan A, Grady E, Matsuoka DT, Jacobson AF (2014) Efficacy of thyroid blockade on thyroid radioiodine uptake in 123I-mIBG imaging. J Nucl Med 55(2):211–215