Review article

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# Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma

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**Use of radioactive iodine is an essential adjuvant treatment strategy after thyroidectomy in patients with differentiated thyroid carcinoma. Although generally safe, radioiodine therapy has some potential side effects, classified as early and late complications, which we have reviewed in this paper. Early complications include gastrointestinal symptoms, radiation thyroiditis, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eye, and nasolacrimal duct obstruction. The late complications include secondary cancers, pulmonary fibrosis, permanent bone marrow suppression, and genetic effects. As $^{131}$I is an efficacious form of treatment that can significantly decrease the rate of mortality, recurrence, and metastasis, and as the side effects are often minor and well tolerated, radioiodine therapy remains the principal mode of treatment for patients with differentiated thyroid carcinoma.** *Nucl Med Commun* **35:808–817 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Radioactive iodine (RAI) ablation following thyroidectomy is recommended for most patients diagnosed with papillary and follicular thyroid carcinoma [1,2]. The objectives of radioiodine treatment include eliminating residual normal or tumoral thyroid cells, improving the sensitivity of serum thyroglobulin assays, increasing the sensitivity of detection of locoregional and/or metastatic disease on follow-up RAI whole-body scans, and allowing a post-treatment scan to reveal additional foci of disease that were not previously identified [2–8].

Radioactive iodine therapy (RAIT) is generally well tolerated but may be associated with complications such as transient neck pain and edema, dysfunction of body organs including pulmonary, gastrointestinal, and hematopoietic systems, salivary glands, nasolacrimal apparatus and gonads, as well as second primary malignancies [3,8–10]. These complications are rarely life threatening, but they can negatively affect the patient's quality of life. Knowledge about the side effects of RAIT is essential both in considering precautionary measures before treatment and in the management of complications after therapy. Radioiodine therapy is usually carried out with high doses of iodine-131 ($^{131}$I), and in many occasions treatment is repeated to get a favorable response in cases of recurrent or progressive iodine-avid metastatic disease; hence, special concern persists regarding its potential hazards. To avoid unnecessary radiation exposure in cases of non-iodine-avid thyroid tumors in which repeated $^{131}$I treatments are not beneficial but only increase the total body radiation exposure and the risk of significant side effects, adequate management with alternative treatments such as surgical resection, external beam radiotherapy, chemotherapy, radio-frequency ablation, chemoembolization, or monitoring without additional therapy if stable should be considered [1,2,5]. In view of the importance of RAIT complications in patients with differentiated thyroid carcinoma (DTC), we decided to prepare a comprehensive article on this subject.

## Materials and methods

We performed a literature search on MEDLINE and EMBASE, using keywords such as differentiated thyroid carcinoma, radioiodine therapy, I-131, complications, adverse effects, and side effects, and chose the most relevant studies until February 2014 to prepare this review on the side effects of RAIT for thyroid cancer. We contacted authors of published studies, where appropriate, for further information. To organize the information, RAIT complications have been divided into early and late effects. However, these effects can be overlapping, as some of the effects classified as early effects may well be seen later in life.

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## Early effects

### *Gastritis-nausea and vomiting*

Nausea is estimated to occur in about 30% of adults [11]. Nausea and vomiting are clearly more frequent in children than in adults, and in the study by Jarzab *et al.* [9] nausea is mentioned as a rule in very young children. In the study by Van Nostrand *et al.* [12], nausea with occasional emesis from gastrointestinal irradiation is common; it begins about 4–12 h after $^{131}$I administration, has a prevalence of 50–70%, and generally resolves by 36 h. However, the incidence rate reported after a low dose of radioiodine [1.48 GBq (40 mCi)] is much lower (about 5%) and resolves completely in most patients within a week [13].

It is shown that common gastrointestinal side effects occur with $^{131}$I doses of 5.55 GBq (150 mCi) or greater, which are doses prescribed for the treatment of regional metastatic disease [2,14,15]. It is suggested that most of these complaints can be prevented with proper medication [14]. Laxatives will reduce the gastrointestinal and whole-body dose. Antiemetic therapy with selective serotonin 5-HT3 receptor blockers, such as ondansetron, granisetron, and dolasetron (efficacy being potentiated by dexamethasone), has been effective in preventing emesis and in reducing the prevalence of nausea after RAIT [15].

### Radiation thyroiditis

Radiation thyroiditis with mild, transient neck pain and edema is not uncommon (10–20%). Symptoms of swelling and discomfort are more frequent in patients with large thyroid remnants and can be limited by the use of nonsteroidal anti-inflammatory agents and/or corticosteroids for a few days [9,16].

Symptoms start 1–10 days after ablation. Pain on swallowing is frequent, and may radiate into the ear or chest. Severe or persistent pain is uncommon, and rarely will the swelling be severe enough to induce airway obstruction. Radiation thyroiditis is usually accompanied by a temporary increase in thyroid hormone levels resulting from release of thyroid hormones from the remnant. Mild discomfort can be treated with routine analgesics, but severe pain or swelling requires administration of corticosteroids. Prednisolone at a dose of 30 mg daily is usually effective and can be tapered rapidly over 7 days. It may be necessary to repeat the course of prednisolone once or twice before the symptoms totally resolve [10]. The incidence of this complication is related to the amount of residual thyroid tissue after thyroidectomy. Patients with more limited surgery before RAIT have a higher rate of local complications than do patients treated with more extensive surgery before radioiodine ablation [17,18]. It is recommended that in these situations, in patients likely to receive $^{131}$I therapy, contralateral thyroid resection be performed [17]. If the remaining thyroid mass is large and a high dose of $^{131}$I is given, the pain can be significant and a thyroid storm may occur within 2 weeks. In this circumstance, the radiolabeled iodoprotein released from the irradiated thyroid gland may give considerable radiation dose to the marrow. Hence, in such rare cases that the patient is thyrotoxic from an excessively functioning tumor mass, euthyroid status should be achieved before the cancer treatment [15].

### Sialadenitis/xerostomia

Sialadenitis is a relatively common complication with an approximate incidence of 30% in adults [16] and less than 5% in children, which may result in subsequent xerostomia [9]. Malpani *et al.* [19] reported the incidence of salivary gland dysfunction (represented by abnormal uptake or excretion) to be as high as 72.73%. An evaluation of the volume in the salivary glands using sonography showed a significant increased volume in the parotid glands after RAIT depending on the received activity and the time from irradiation [20].

The salivary glands concentrate iodide by a factor of 30–40 compared to blood. The salivary gland dose during the first 12 h after the therapeutic dose could be as high as 6 Gy [15,21]. Acute or chronic sialoadenitis has been observed in 12–30% of patients receiving about 7.4 GBq (200 mCi) of $^{131}$I, with the time of onset being 2 days to 6 months after the dose, characterized by pain, tenderness, swelling, xerostomia, and bitter taste [15,22].

For salivary gland swelling with pain, female patients displayed a significantly higher incidence compared with male patients [14]. In a study by Nabaa *et al.* [23], which assessed the volume of salivary glands after $^{131}$I therapy by means of a CT scan, and salivary dysfunction by means of salivary gland scintigraphy, significant decrease in salivary gland volume with an increase in dysfunction for both the parotid and submandibular glands was noted.

Our study on the effect of $^{131}$I therapy on salivary gland function by semiquantitative assessment showed that high dose of radioiodine in DTC patients induced a significant effect on salivary gland function, which was dose related and more prominent in the parotid glands [24]. The finding of the parotid gland being more susceptible to the radiation effect of $^{131}$I was supported by some other studies [25–28]. Salivary damage seems to be less serious on using rhTSH, compared with of levothyroxine withdrawal [29].

To limit this complication or reduce its severity, several methods including liberal hydration and use of lemon juice, chewing gum, amifostine, sour candies, and cholinergic agents as discussed below have been used [15]. The effect of sialogogues like sour liquids on radiation-induced sialoadenitis and/or xerostomia after therapeutic administration of $^{131}$I is controversial. There are some studies supporting their use in reducing radiation dose to the salivary glands and the resultant sialoadenitis

[15,30–34]. However, this effectiveness is not backed up by all studies. In the study by Liu *et al.*, consumption of vitamin C as a sour stimulant by thyroid cancer patients had only a limited effect on the salivary absorbed dose [35]. Another study, performed using salivary gland dosimetry, indicated that lemon juice stimulation shortly after $^{131}$I administration increases the absorbed dose in the salivary glands [36]. In the study by Bohuslavizki *et al.* [37], despite the use of a protective regimen of ascorbic acid as a sialogogue, loss of salivary gland parenchymal function was noted. One study has suggested that an early start of sucking lemon candy may induce a significant increase in salivary gland damage and recommended that lemon candy not be given until 24 h after RAIT [38].

Amifostine is thought to be a radioprotector of salivary glands, used in conjunction with RAIT. This intravenously administered medication may reduce salivary gland radiation damage [39–41]. However, there are some studies against its effectiveness [42,43]. To assess the effects of amifostine on salivary glands in radioiodine-treated DTC patients, Ma *et al.* [43] performed a meta-analysis that showed that amifostine has no significant radioprotective effects on salivary glands. This study suggests that the use of acid-stimulating agents to increase salivation should remain the first choice during RAI treatment of DTC and the patients should also be well informed of the importance of hydration [43].

Pilocarpine is a cholinergic drug that can increase the secretion of exocrine glands, including lacrimal and salivary glands, improving saliva flow, and has been used both for prevention and for treatment of radiation-induced xerostomia [44–47]. Silberstein used pilocarpine for the prevention of radiation-induced sialoadenitis with a dose of 5 mg orally every 8 h for 1 week, which was started after $^{131}$I administration. However, in that study pilocarpine did not reduce radiation sialadenitis [44], whereas in some other studies with the same dose of pilocarpine, but with a longer duration of administration (3 months after the radiation therapy), it proved effective in the treatment of radiation-induced xerostomia [45,46]. Aframian *et al.* [47] used a single dose of pilocarpine hydrochloride (5 mg) in DTC patients treated with RAIT and concluded that a significant elevation in saliva flow rate occurred at 1, 2, and 3 h after administration in patients with impaired salivary gland function.

The study performed at our center showed that vitamin E consumption at a dose of 800 IU/day for a duration of 1 week before to 4 weeks after a single dose of RAI uptake [3.7–5.55 GBq (100–150 mCi)] had a significant protective effect against radiation-induced dysfunction in salivary glands in patients with DTC [48].

Dental caries: radiation effects on salivary glands can result in xerostomia and these patients are at increased risk for dental caries [49–52]. Salivary gland dysfunction [24,53], and hence dental caries, occurs mainly after receiving higher cumulative radioiodine activity [median dose 7.4 GBq (200 mCi) (range, 1.9–35.0 GBq)]. This emphasizes the need for taking preventive measures after RAIT, especially in patients with high cumulative radioiodine activities and postradioiodine xerostomia [49]. These measures include preserving oral hygiene and a wet mouth [54], avoiding dehydration, taking anticholinergic drugs, and maintaining salivary gland flow with glandular massage [34].

Abnormalities of taste and smell: abnormalities of taste and smell are frequent but transient [10] and are usually associated with sialoadenitis [38]. The reported incidence rate for change in taste is from 9.8% [14] to 39% [38].

Dysphagia: clinical dysphagia could be due to difficulty in draining saliva, resulting from salivary gland dysfunction [27].

### Bone marrow suppression

Bone marrow (BM) suppression is mostly transient and results in a decrease in white blood cell and platelet count for up to 6–10 weeks and occasionally results in increased susceptibility to infection or bleeding if the marrow dose exceeds about 2 Sv (200 rem) [1]. The total incidence is about 25%, with leukocyte and platelet count nadirs 1–2 months after radioiodine administration [9,11,34]. However, its incidence depends on the administered activity; severe BM suppression increases with multiple bone metastases and large cumulative radioiodine activity [$>$18.5 to 22.2 GBq (500–600 mCi)] [2,16].

The radiation dose to the BM is typically the limiting factor. To avoid severe cytopenia, several studies showed that the estimated radiation dose to the BM should be less than 2 Sv (200 rem) [1,2,55,56]. For treatment of distant metastases, an activity of 7.4 GBq (200 mCi) or more is often given.

Single doses greater than 7.4 GBq (200 mCi) have not been shown to be more effective than 7.4 GBq (200 mCi) of $^{131}$I [57]. Some patients will have mild pancytopenia at this dose, with a nadir between 5 and 8 weeks, resolving in 6–12 months. One dosimetry study suggested that 7.4 GBq of $^{131}$I gave about 94 rad to the blood and 60 rad to the marrow [58], but it should be noted that the range from this dosage is wide and can exceed 200 rad, a myelosuppressive dose. Blood and whole-body dosimetry may be indicated when a high activity of $^{131}$I is planned to treat metastatic disease [1,59,60]. Permanent BM suppression is rare [16], and usually the suppression resolves without therapy or clinical consequence [9]. Radiation to the BM is impacted by renal function. It is recommended that patients receiving therapeutic doses of RAI should undergo baseline CBC and assessment of renal function [2].

### Hypospermia

In men, RAIT for thyroid cancer may be associated with a reduction in sperm counts and elevated serum follicle-stimulating hormone (FSH) levels, which is usually transient [2,9,16,61–65]. The testicular radiation dose in a patient with hypothyroidism ranges from 0.5 to 1.5 rad/mCi; hence, therapeutic doses as low as 1.85 GBq (50 mCi) can cause testicular damage with elevated FSH levels [15]. Higher cumulative activities of 18.5–29.6 GBq (500–800 mCi) in men are associated with an increased risk for persistent elevation of serum FSH levels, but fertility and risk of miscarriage or congenital abnormalities in subsequent pregnancies are not changed with moderate RAI activities of 7.4 GBq (200 mCi) [2,66,67].

Permanent male infertility is unlikely with a single ablative activity of RAI, but theoretically there could be cumulative damage with multiple treatments [2,63].

Clinically important oligospermia occurs in men receiving gonadal doses in excess of 50–100 rad.

Spermatogenesis may recover in 20–48 months, but it is not always reversible [9,15,68–70]. The study by Smith *et al.* [71] on the long-term probability of infertility from doses up to 9.25 GBq (250 mCi) showed that the risks for infertility or birth defects were not different from those of the general population. To reduce gonadal complications, especially in male patients, treatment should be performed with the lowest possible doses and all necessary measures to reduce this radiation, including good hydration, frequent micturition to empty the bladder, and avoidance of constipation, should be taken. Pretreatment sperm banking should be offered to male patients if multiple activities of $^{131}$I are planned [16,61,63].

Conception should be avoided for at least 6 months after RAIT, an interval that allows the replacement of irradiated with nonirradiated spermatozoa and decreases the risk of fetal abnormalities [16,69,72,73].

### Pregnancy and ovarian complications

Pregnancy must be excluded with a β-hCG test, ideally within 24 h before RAIT [1]. Adjunctive use of ultrasonography to rule out pregnancy may also be considered [2,16]. It should be noted that the beta-hCG assay can detect pregnancy much earlier than ultrasonography, and is usually positive at about 1 week of gestation [74], whereas the gestational sac of pregnancy first becomes visible on a transvaginal ultrasound by the fourth week and on a transabdominal ultrasound by the fifth week of pregnancy [75]. Thus, in general practice, beta-hCG is almost always applied for this purpose.

Physicians caring for women of childbearing age (premenopausal state) who are candidates for RAIT need to be aware of the risks of fetal exposure to radioiodine and take all measures to avoid inadvertent exposure during pregnancy. Before implantation, the major concern is miscarriage and death of the embryo above a radiation threshold of 100 mGy (10 rad). Exposure to $^{131}$I at a very early stage of pregnancy, before implantation, is unlikely to result in major malformations or thyroid dysfunction in surviving embryos. It is believed that radiation injury during early gestation is an 'all-or-nothing' effect [76,77]. Although exposure later in pregnancy – that is, during thyroidogenesis (from 10 weeks' gestation) and organogenesis (from 2 weeks' gestation) – at similar radiation thresholds may result in fetal thyroid ablation, birth defects and, in later life, growth retardation and a reduction in IQ, studies on patients receiving a high dose of $^{131}$I therapy show that post-RAIT congenital abnormalities are not different from those seen in the general population [15,68,71,78]. However, to reduce the risk of congenital abnormalities, it is recommended that conception be avoided for 6–12 months after RAIT [2,16,72].

Temporary amenorrhea/oligomenorrhea lasting 4–10 months occurs in 20–27% of menstruating women after RAIT for thyroid cancer. It is shown that long-term rates of infertility, miscarriage, and fetal malformation are not elevated in women after RAI therapy; in addition, subsequent pregnancies are safe without any significant consequences to offspring [15,68,78–87].

Breastfeeding should be discontinued for two reasons: first, to prevent $^{131}$I in the milk from reaching the infant and particularly the infant's thyroid gland; and second, to limit radiation of the breast tissue, which, through the increased expression of sodium iodide symporter that occurs during lactation, promotes $^{131}$Iconcentration [74]. Patients should be advised to discontinue breastfeeding for at least 6–8 weeks before radioiodine administration, and a delay of 3 months will more reliably ensure that a lactation-associated increase in breast sodium iodide symporter activity has returned to normal [2,15,16,33,74]. If the RAIT is urgent after lactation cessation, breast uptake can be assessed on a preablation scan ($^{123}$I or $^{99m}$Tc-pertechnetate), and, if significant breast uptake is observed, therapy is postponed to allow for mammary tissue involution [1,74].

### Dry eye

Dry eye and disturbed lacrimal gland function is another reported complication of RAIT, which is mostly transient [53,88]. A study carried out at our institution showed that patients treated with radioiodine had a lower Schirmer test value compared with the control group, indicating a higher rate of dry eye in these patients [89]. Patient preparation with rhTSH is reported to result in less lacrimal dysfunction compared with T4 withdrawal [29].

### Nasolacrimal obstruction

Nasolacrimal obstruction (NLDO) after RAIT has been reported by several studies [90–94]. RAI uptake by

nasolacrimal duct mucosa with subsequent inflammation, edema, and fibrosis may be responsible for lacrimal duct obstruction [93]. Local toxicity from $^{131}$I may be caused either by the passive flow of RAI containing tears through these tissues or by the active uptake and concentration of $^{131}$I in lacrimal drainage system tissues through the sodium/iodide symporter [91]. The study by Fonseca *et al.* [93] showed that the cumulative high dose of radioiodine [mean cumulative dose 21.12 GBq (571 mCi) (range: 200–1200 mCi)] is associated with this complication, and also a great percentage of younger patients present with dacryocystitis after RAIT when compared with idiopathic dacryostenosis. In the study by Burns *et al.* [91], the incidence of documented NLDO was reported to be 3.4%. However, our study on the possible hazard of $^{131}$I on the lacrimal drainage system, performed using dacryoscintigraphy, which has been proved to be a valuable method for this purpose [95], showed that 18% of exposed eyes had evidence of NLDO on scintigraphic images. The frequency of complete NLDO significantly increases when the cumulative dose of radioiodine exceeds 11.1 GBq (300 mCi) [90].

## Late effects

### *Leukemia and secondary cancers*

A slight increased risk for leukemia and secondary cancers has been reported in DTC patients treated with RAIT [96–105]. Leukemia is a rare complication of $^{131}$I therapy [2,96–100], usually developing after a high cumulative dose of more than 18.5–22.2 GBq (500–600 mCi) [2,5]. However, there are reports on the occurrence of this malignancy even after lower doses of $^{131}$I [total dose of 11.1 GBq (300 mCi) in the study by Bitton *et al.* [96] and 5.5 GBq (150 mCi) in the study by Jeong *et al.* [97]].

It is advisable to consider a 1-year interval between treatments because it is believed to reduce the risk for leukemia. However, if there is convincing evidence of disease progression (an increase in thyroglobulin or size of the metastases) the patient should be retreated even if the interval from the previous treatment is as short as 3 months [10]. Some scholars believe that there is no fixed upper limit for the cumulative amount of radioiodine required to treat aggressive metastatic disease and have given several patients over 74 GBq (2 Ci) of $^{131}$I [10]. In addition to leukemia, the incidence of solid second malignant neoplasms (SMN) may increase after RAI [101–103]. In our study on radioiodine-treated DTC patients, the chance of developing SMN increased in patients who had received a cumulative activity of $^{131}$I exceeding 40 GBq (1.08 Ci) [101]. Glanzmann [102] showed an increase in the incidence of subsequent malignancies, mainly leukemia and bladder cancer, after $^{131}$I treatment. These complications were observed after high radiation doses, and at a total activity of less than 37 GBq (1 Ci) $^{131}$I no cases of bladder cancer or leukemia were observed [102]. In the study by de Vathaire *et al.* [103] on 1771 DTC patients, a total of 80 patients developed an SMN, among whom 13 developed colorectal cancer, which was attributed to the accumulation of $^{131}$I in the colon lumen. According to the study by Lang *et al.* [104], female DTC patients treated with RAIT appeared to be at elevated risk for nonsynchronous second primary malignancy when compared with the general population. However, some studies show that there is no significant risk for second primary malignancy after RAIT in patients with DTC, compared with the general population [105,106].

In general, studies show that the small increased rate of malignancy is mainly found in patients exposed to high cumulative activities of $^{131}$I; hence, $^{131}$I should be given only when benefits are expected, and the minimum appropriate activity should be administered. It should be noted that there are still concerns about whether the development of these malignancies after thyroid carcinoma represents a RAIT-induced complication, a coincidence, or an increased susceptibility to secondary malignancies due to the malignant process itself [97–104,107].

### Radiation pulmonary fibrosis

Patients with DTC with diffuse pulmonary metastases who received repeated activities of radioiodine over short intervals of time may develop pulmonary fibrosis [1,9,15,55,108–114]. However, in the study by Reiners *et al.* [112], it is unclear whether pulmonary fibroses were attributable to radioiodine, because some children had been given bleomycin. Samuel *et al.* [109] also could not entirely distinguish between DTC-induced restrictive lung disease and radiation-induced effects. In general, pulmonary fibrosis seems to have essentially affected only patients with very advanced lung disease and high $^{131}$I lung uptake [9,114]. Pulmonary alveolar capillary membrane damage, which was suggested to result from RAIT for lung metastases of DTC, was negligible, as supported by the normal pulmonary clearance of $^{99m}$Tc-DTPA aerosols [109]. If pulmonary fibrosis is suspected, appropriate periodic pulmonary function testing and consultation should be obtained. The presence of pulmonary fibrosis may limit the ability to further treat metastatic disease with RAI. However, according to ATA guidelines [2], pulmonary micrometastases should be treated with RAIT and repeated every 6–12 months as long as disease continues to concentrate RAI and responds clinically, because the highest rates of complete remission are reported in this subgroup [2,115–119]. To prevent radiation pneumonitis with subsequent pulmonary fibrosis, it is recommended that dosimetry with a limit of 2.96 GBq (80 mCi) whole-body retention at 48 h and 200 cGy to the red BM be considered in patients with diffuse $^{131}$I pulmonary metastases [1,15,55,118–121].

#### Permanent bone marrow suppression

Permanent BM suppression as a late complication is rare [16]; however, persistent mild decrease in white blood cell count and/or platelets is not uncommon in patients who have received multiple RAI therapies [2,9].

#### *Genetic effects*

No adverse effect on fetal outcome following RAI treatment is noted as discussed in the section on hypospermia and ovarian complications [10,15,68,78–87].

#### Chronic dry eye

The impaired function of lacrimal glands may persist in some patients and result in a chronic dry eye state [50,88]. As sodium iodide symporter, which transports radioiodine in the targeted tissues, is expressed in the lacrimal sac and in the nasolacrimal duct [122], and there is evidence of secreted $^{131}$I in the tears [123,124], dry eye can develop secondary to lacrimal gland damage on treatment with $^{131}$I [53,88].

#### Chronic sialadenitis and xerostomia

Sialadenitis, which was discussed at length in this paper, is usually transient and among the early complications of RAIT; however, it may become chronic and lead to xerostomia with a range from 4.4 to 20% in different studies [27,28,125].

#### Less common adverse effects of high-dose iodine-131 treatment

#### *Hypocalcemia*

Both persistent and transient hypoparathyroidism and resultant hypocalcemia have been reported after RAIT for thyroid cancer [126–128].

#### *Brain edema*

Treatment of brain metastasis with radioiodine may induce cerebral edema. Neurosurgical resection or stereotactic radiosurgery is preferred in case of one or more brain tumor foci and may increase survival [129,130]. Surgical resection and external beam radiotherapy traditionally have been the mainstays of therapy and there are few data showing the efficacy of RAI [2]. However, if RAI is being considered, prior external beam radiotherapy and concomitant glucocorticoid therapy are strongly recommended to minimize the effects of a potential TSH-induced increase in tumor size and the subsequent inflammatory effects of RAI [2,131].

#### *Cord compression*

Cord compressive symptoms secondary to RAIT for vertebral metastatic lesions are uncommon, but serious [10]. Corticosteroids should be administered for several days after RAIT [16]. It is important that the vertebral column and the weight-bearing areas be assessed periodically if the bones are sites of metastases. The bone scan allows the early diagnosis and application of appropriate preventive interventions if a patient has epidural involvement of the spinal cord by tumor [15]. For neurologic complications such as spinal cord compression or nerve root compression, radiotherapy appears to be as beneficial as decompressive surgery in most situations, except in the presence of bony instability [2,132].

#### *Recurrent laryngeal nerve paralysis*

Vocal cord paralysis from injury to the recurrent laryngeal nerve is a rare complication of $^{131}$I ablation of the thyroid gland [133]. This complication occurs more frequently when there is already some type of lesion in the recurrent laryngeal nerves [134].

#### *Esophageal stricture*

A case of esophageal stricture after iodine ablation was reported in the patient in whom the 5.5 GBq (150 mCi) $^{131}$I capsule lodged accidentally in the midcervical esophagus for approximately 2.5 h on the day of therapy. The resulting radiation dose to the proximal esophagus could be the cause of this condition [135].

#### *Impaired liver and kidney function*

The study by Vasil'ev *et al.* on liver and kidney function showed a decrease in absorptive and secretory hepatocytic function, and a decrease in total renal function after RAIT. The changes were of moderate nature, stable, and related both to hypothyroidism and to a radiation factor [136].

#### *Cystitis*

A rare reported complication of radioiodine is cystitis [137]. As the main route of $^{131}$I clearance is through the kidneys and bladder, accumulation of urine containing radioiodine can potentially cause inflammation in this organ. Patients are asked to void every 1–2 h for several days to reduce the radiation dose to the bladder. A diuretic will accelerate the $^{131}$I renal clearance [15,137,138].

Adverse effects of RAIT are seen less commonly with lower cumulative dose of radioiodine [1,2,10,15]. Although it is suggested that using a low dose [1110 MBq (30 mCi)] of radioiodine for ablation versus a high dose [$\geq$3700 MBq (100 mCi)] reduces the rate of successful ablation and increases the need for repeated therapies [139,140], several studies support the use of low-dose RAIT with comparable efficacy, especially in the low to intermediate risk group of DTC patients, which in turn results in reduced cumulative dose and hence fewer complications [141–150].

## Conclusion

RAIT for DTC generally causes relatively mild short-term toxicity and, infrequently, serious complications. Considering the strongly proven benefits of this

treatment modality, especially increased survival [2,5,9,10], decreased recurrence rate [1,2,5,10], and effective palliative results [2,10,16], the risks and benefits of RAIT must be balanced for each individual patient and should continue to remain the most essential part of patient management.

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### Conflicts of interest

There are no conflicts of interest.

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