

REVIEW ARTICLE

Side Effects of High-dose Radioactive Iodine for Ablation or Treatment of Differentiated Thyroid Carcinoma

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ABSTRACT

Iodine-131 or radioactive iodine benefits patients with differentiated thyroid carcinoma by treating recurrences and in reducing relapses after operation. Postoperative ablation of thyroid remnants facilitates follow-up by serial monitoring of serum thyroglobulin. The clinical benefits of reducing recurrences are well documented in many retrospective studies. Recently, a systematic review and meta-analysis showed a positive role of radioactive iodine ablation in patients with postoperative adjuvant radioactive iodine ablation. A pooled reduction of 10-year locoregional recurrence risk to 0.31 and an absolute reduction in distant metastasis of 3% were documented. While the use of radioactive iodine is becoming more prevalent, information about side effects is important in patient management. Acute side effects are usually mild and well tolerated. Organ-specific side effects such as damage to salivary glands, bone marrow and gonads are usually mild and reversible. However, these dose-dependent side effects may become permanent with repeated doses. Radiation pneumonitis and lung fibrosis is rarely observed nowadays. Effects on fertility, secondary solid tumours and leukaemias are also reviewed. From the current literature, radioactive iodine is a safe treatment modality, provided that the precautions are well observed.

Key Words: Iodine radioisotopes, Review, Side effects, Thyroid neoplasms, Treatment outcome

INTRODUCTION

Radioactive iodine (RAI) is an isotope with emission of both beta and gamma energies during decay. Ninety percent of its energy is deposited with an effective range of 2 mm. A small portion of the energy is deposited as a mixture of photon emissions. The half-life of 'physical decay' is 8.02 days.¹ The median 'biological half-life' in the human body is around 14 hours, with substantial variations.² RAI is most commonly employed in thyrotoxicosis and thyroid cancer. It is administered by the oral route and excreted through the renal system. RAI will be concentrated in thyroid follicular cells or differentiated thyroid cancer cells.

In patients with no gross postoperative disease, RAI can be used to ablate thyroid remnant. Apart from eradicating microscopic foci of tumour cells in the thyroid

remnant, RAI ablation facilitates detection of early relapses by serum thyroglobulin (Tg) determination and RAI treatment of RAI-avid relapses. Early detection of relapses could be achieved by checking serum Tg or stimulated Tg (by endogenous thyroid-stimulating hormone [TSH] or recombinant human TSH [rhTSH]). In a meta-analysis of 9094 patients in 46 articles, the highest sensitivity of Tg in monitoring thyroid cancer recurrences was found in patients with RAI ablation and thyroid hormone withdrawal.³ The pooled sensitivity and specificity were 0.961 and 0.947, respectively. Without RAI ablation, the Tg sensitivity decreased to 0.759. Therefore, RAI ablation is important to improve the sensitivity of Tg monitoring.

RAI has been shown to reduce the likelihood of relapse⁴⁻¹³ and to improve survival.^{4-6,9,10,13} It is also effective for distant metastases.^{10,14-18} Sawka et al published a systematic review and meta-analysis after scrutinizing 1543 English language references.¹⁹ The pooled reduction in locoregional relapse was 0.31: the 10-year locoregional recurrence was reduced from 10% to 4%. An absolute reduction in distant metastasis of 3% was found. However, the impact on survival was not confirmed.

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Submitted: 5 January 2006; Accepted: 14 February 2006.

The indications for RAI ablation are inconsistent. Some routinely apply RAI ablation after surgery for all patients,²⁰ whereas others select the high-risk group for RAI treatment.^{6,13,21} The British Thyroid Association/Royal College of Physicians (2002) recommended RAI for tumours with ≥ 1 cm.²² The National Comprehensive Cancer Network guidelines (2005)²³ recommended RAI treatment for tumours with uptake in thyroid bed on scanning or in those with positive Tg of more than 10 ng/mL (off thyroid hormone) but negative uptake in scanning.

Radioisotope therapy is unfamiliar to the general public and even doctors of specialties other than oncology, nuclear medicine and endocrinology. This article reviews the clinical side effects of high-dose RAI in medical treatments.

SHORT-TERM SIDE EFFECTS

Preparation for RAI ablation includes thyroxine withdrawal for 4 to 6 weeks. Although not considered a side effect of RAI treatment, patients often attribute symptoms of 'hypothyroidism' to RAI. 'Hospitalization' and isolation for a few days according to radiation protection rules is also very inconvenient to some patients. In centres employing low-dose RAI or having less stringent rules, patients can be treated as outpatients.

It is rare to have immediate discomfort after oral administration of RAI. Table 1 summarizes the acute symptoms. Mild clinical effects are nausea, acute sialadenitis, transient neck pain related to thyroiditis (especially in patients with large thyroid remnant after surgery; e.g., lobectomy), and haematological depression.²⁴⁻²⁶

Immediately after RAI administration, a study showed that 65.2% of patients had gastrointestinal complaints, 50% had salivary gland swelling with pain, 9.8% had change in taste and 4.4% of patients had headache.²⁷ Dose per body weight and TSH values significantly

affected gastrointestinal symptoms. Endogenous TSH change is dependent on extent of surgery, time interval of thyroxine withdrawal, gender and age. The most common gastrointestinal symptoms were appetite loss (60.9%) and nausea (40.2%). For salivary gland swelling and pain, females had more frequent complaints. For taste changes and headache, no significant predictors could be identified.²⁷ It is difficult to differentiate whether symptoms of nausea are attributable to hypothyroidism or radiation sickness. Dose-independent transient alopecia was observed in 28.1% of patients in a cohort of patients after at least 100 mCi of RAI.²⁶

Acute swelling does occur in patients with bulky thyroid remnant and large metastasis. Transient pain was reported in bone metastasis with high uptake.²⁸ The most serious acute complications are acute oedema or haemorrhage in tumour or metastasis causing pressure effects. This is particularly important in cerebral metastasis²⁹ or those tumours situated near a major airway.

To avoid symptoms of hypothyroidism while achieving the minimal requirement of TSH level to 30 mIU/L, the thyroxine withdrawal period can be decreased to 3 weeks if the patient has had total thyroidectomy. Over 90% of patients can achieve this serum TSH level after 3 weeks of thyroxine withdrawal.^{30,31} A second method which completely avoids symptoms of hypothyroidism is the use of rhTSH.³² Studies proved that rhTSH can be equally effective for preparation before whole body scan and in stimulated Tg testing. More data are awaited regarding its use in ablation and treatment of metastasis.

LONG-TERM AND ORGAN-SPECIFIC SIDE EFFECTS

The most common chronic side effect after RAI treatment is decreased saliva production. Severe long-term side effects are rare. Organ-specific side effects are found in salivary glands, lacrimal glands, bone marrow, lungs and reproductive organs (ovary and testis).

Table 1. Acute side effects of radioactive iodine (RAI) in thyroid remnant ablation.

Acute side effects	Patients with symptoms (%)	Remarks
Loss of appetite	60.9% ²⁷	The most common gastrointestinal symptom
Change in taste	9.8%-10% ²⁶	Dependent on dose of RAI ²⁶
Nausea	40.2% ²⁷	Dependent on dose of RAI ²⁷ and thyroid-stimulating hormone values ²⁷
Sialadenitis	33% ²⁶ -50% ²⁷	Lemon candies should not be given until 24 hours after RAI therapy ³⁷
Neck swelling	-	In patients with large thyroid remnant or patients having lobectomy
Haematological depression	-	Usually reversible. Depends on dose of RAI, age of patients and interval of treatment
Headache	4.4% ²⁷	

Incidence of secondary malignancies and leukaemia might increase with higher RAI doses. The effects on salivary glands, bone marrow and lungs are dose-dependent. These are tabulated in Table 2.

Salivary Gland

Iodide is secreted into saliva with a concentration reported from 20 to 100 times that in serum.³³ Objective scintigraphic salivary gland dysfunction was found in

Table 2. Organ-specific side effects in radioactive iodine (RAI) treatment.

	Side effects	Percent	High-risk patients	Remarks and precautions
Salivary gland	Acute swelling	27-33% ^{26,36}	In patients with repeated dose	Good hydration Amifostine (not widely applied) Pilocarpine (not tested) Avoid sour/lemon candies until 24 hours after RAI therapy
	Chronic sialadenitis	11.5-42.9% ^{24,26}	Dose dependent	
	Xerostomia	42.9% reduced salivary function 4.4% ²⁶ complete xerostomia		
	Taste changes		Usually associated with sialadenitis	
Lacrimal gland	Xerophthalmia	25.3% at first year, 13.9% at third year ³⁵		
Lung	Radiation pneumonitis	6.3% ⁴¹	Diffuse bilateral lung metastasis	Avoid giving single dose of RAI >125 mCi Interval of retreatment >6 months This complication is rarely reported in recent literature; difficult to differentiate from progressive lung metastasis
Bone marrow	Transient leukopenia and thrombocytopenia		Age >45 years Multiple bone metastasis RAI treatment in short intervals High cumulative dose of RAI	Dose-dependent Usually reversible
	Leukaemia		Age >50 years Short treatment intervals <12 months Dose >800 mCi	Rarely reported in dose <300 mCi Commonest type is acute myeloid leukaemia
Ovary	Temporary failure Menstrual disturbance Earlier onset of menopause ⁶⁹ Pregnancy outcome	17-27% ⁶⁷	Older age Higher cumulative dose	Pregnancy should be avoided in the first year post-RAI ^{75,76,84}
			No association of previous RAI exposure to unfavourable pregnancy outcome ^{75,76} Higher rate of miscarriage after surgery, irrespective of RAI treatment ⁷⁵ More miscarriage if RAI is administered within 1 year before conception or in older age group ⁷⁵ Higher rate of preterm delivery in female patients with RAI treatment ⁷⁶	
Testis	Oligospermia Fertility and offspring condition		Usually transient and reversible Dose-dependent fertility impairment Children fathered by patients having history of RAI administration had no major congenital malformation ⁸²	Sperm banking and counselling if high repeated doses are anticipated
Secondary solid tumour	Increased risk of tumours at bone and soft tissue, female genital organs, central nervous system		Dose dependent: increased risk after dose >7.4 GBq ⁶¹	Breast cancer risk is associated with thyroid cancer, not related to treatment by RAI or external radiotherapy ^{62,65}
Tumour metastasis	Acute swelling		Brain metastasis Bone metastasis at spine Metastasis near major airway	

69% of patients; the majority affecting the parotid glands.³⁴ Single-dose RAI of less than 5 GBq gave a lower than 10% rate of sialadenitis and taste changes.²⁶ A dose-dependent increase in frequency of sialadenitis and taste changes was observed.

Among those who received 18.5 to 37 GBq, 55% of patients experienced sialadenitis. Complete xerostomia occurred in 4.4% of patients; xerostomia was usually transient. Subjective xerostomia decreased from 32.9% in the first year to 15.2% after the third year, while objective xerostomia decreased similarly from 50.6% to 13.9%.³⁵ With repeated high-dose RAI treatments, 27% to 33% of patients had salivary swelling.^{26,36} Thirty percent of patients had dry mouth.³⁶ Secondary salivary gland damage includes xerostomia, taste changes, infection, increased caries and candidiasis.

Hastening the transit time of RAI through the salivary glands has been tried. Some centres use agents such as sour/lemon candies and pilocarpine, without any proven benefit. According to a randomized trial, empirical use of lemon candies is not justified.³⁷ An early start of sucking lemon candy within 1 hour after RAI therapy increased the incidences of sialadenitis, taste loss and dry mouth. Therefore, lemon candies should not be given until 24 hours after RAI therapy. Amifostine, acting as a radiation protector, was tried in a double-blind scintigraphic study with good preliminary protective effect.³⁸

Lacrimal Gland

Dry eyes or xerophthalmia occurred in 25.3% patients at the first year and 13.9% at the third year after RAI treatment.³⁵

Lung

RAI is effective in patients with lung metastasis. Its effectiveness depends on the functional uptake of RAI and the morphological appearance of metastasis in imaging. Use of RAI in lung metastasis is safe. Studies on the capillary diffusion capacity did not show any adverse effects of RAI.³⁹ Radiation pneumonitis fatality reports were found in patients with multiple fine diffuse lung lesions.⁴⁰ Rall et al suggested that the amount of RAI delivered to patients with multiple diffuse lung metastases should not exceed 125 mCi in any single dose.⁴⁰ The retreatment interval should be scheduled at more than 6 months. In a review by Maxon and Smith, RAI-induced pneumonitis was found in 6.3% (9/143) of patients with lung metastasis.⁴¹

These findings should be interpreted with caution. Clinically, differentiation of RAI-induced pneumonitis from progressive pulmonary metastases is difficult.⁴² Sometimes, RAI uptake in inflammatory lung disease can mimic diffuse lung metastasis.⁴³ In lung metastasis, pathological examination of lung biopsies showed that small lung metastases were found more extensively than expected.⁴⁴ However, clinical reports of RAI-induced pneumonitis are rare in the literature, especially in the recent decade. In our hospital, we did not document a single case of RAI-induced pneumonitis. After considering the pros and cons, RAI is still the most effective and appropriate treatment in lung metastasis.

Bone Marrow and Secondary Leukaemia

Transient leukopenia and thrombocytopenia were observed after RAI administration,^{26,45,46} the marrow toxicity being dose-dependent.^{45,46} Severe leukopenia and thrombocytopenia is only seen after high-dose therapy (>22.2 GBq). The frequency of micronuclei in peripheral lymphocytes increased, indicating that RAI therapy induces chromosome damage in these lymphocytes.⁴⁷ The sensitivity of lymphocytes to the effects of RAI depends on lymphocyte phenotype and RAI activity. NK cells are most sensitive, followed by B lymphocytes and then T-helper lymphocytes. However, these do not result in clinical immunosuppression.⁴⁸

Bone marrow recovery after RAI treatment is less in age >45 years.²⁸ Bone marrow suppression after RAI treatment according to the World Health Organization classification was studied in a German cohort. Most of the blood count alterations were mild and reversible (grade I or II). Grade III (persistent severe blood count suppression) and grade IV (bone marrow aplasia or acute myeloid leukaemia) were less commonly observed. In this cohort of 107 patients with bone metastasis, blood count alterations in those aged ≤45 were mild, usually grade I or II. However, in patients with high uptake in bone metastasis, it was observed that 8 out of 107 patients died of bone marrow problems. Four patients had bone marrow aplasia (mean RAI dose, 69.93 GBq). Four had acute myeloid leukaemia (mean RAI dose, 87.4 Gbq); all of them were older than age 45.²⁸ It should be noted that these patients were treated with a total of 11.1 GBq of RAI when metastasis was detected (3.7 GBq followed by 7.4 GBq immediately after the scan was positive for metastasis); i.e., a high dose of RAI within a very short interval.

There is a threat of sublethal radiation damage to marrow cells resulting in leukaemia. Some cases of acute

leukaemia were reported, especially in those with bone metastasis.^{28,42,49} Almost all cases of leukaemia after RAI treatment received more than 800 mCi, were >45 years and treated within short intervals.^{28,42,50} Only very rarely is acute leukaemia found in patients receiving a small RAI dose of <300 mCi.^{51,52} Acute myeloid leukaemia is the commonest observed type of leukaemia after RAI treatment. Only a few cases of chronic myeloid leukaemia are reported.^{53,54}

Studies of low-dose RAI treatment in large patient populations are very reassuring. A French report by de Vathaire et al revealed no instances of leukaemia, at a mean follow-up of 10 years, in 1497 patients who received an average of 7.2 GBq of RAI.⁵⁵ In our cohort of 1348 patients (the majority Chinese) in Queen Elizabeth Hospital, we did not observe a single case of acute leukaemia after a mean dose of 3.4 GBq in papillary thyroid carcinoma and 4.14 GBq in follicular thyroid carcinoma. RAI appears to be safe in young patients. We observed no single case of second malignancy in 36 young patients <21 years of age who received a mean dose of 117 mCi (4.3 GBq), after a mean follow-up of 14 years.¹⁸ Menzel et al also observed no case of leukaemia in nearly 2000 patients treated in a single institution.⁴⁵ The risk of leukaemia was not elevated in several large studies including patients with RAI treatment for thyrotoxicosis or diagnostic scans.⁵⁶ Wong et al estimated that the risk of leukaemia is so small that it does not outweigh the benefit of RAI treatment: the loss of life caused by recurrence of thyroid cancer exceeds that from leukaemia by 4- to 40-fold.⁵⁷

Secondary Primary Malignancy

Risk of secondary primary malignancy (SPM) is a real concern in RAI treatment. A small excess of bladder cancer and leukaemia was observed by Edmonds and Smith.⁴² Some studies reported a small excess risk of cancers in those organs that concentrate RAI, such as salivary gland, colon and bladder.^{42,51,58} Most of these patients received very high RAI doses (more than 40.7 GBq or 1100 mCi).⁴²

A study of 7417 patients receiving RAI treatment for thyrotoxicosis in the United Kingdom showed that the relative risk (RR) of cancer mortality was decreased after RAI treatment.⁵⁹ Lower incidence of cancers of the pancreas, bronchus, trachea, bladder, and lymphatic and haemopoietic systems was found. Mortality from cancers at all of these sites was also reduced but

findings were significant only for bronchus and trachea. There were significant increases in incidence and mortality for cancers of the small bowel and thyroid, although absolute risk of these cancers was small.

A Swedish report by Hall et al found that organs that were estimated to have received more than 1 Gy had a significantly increased risk of a subsequent malignancy.⁵⁶ They studied the cancer risks in 834 patients with average dose of 4551 MBq. A dose-related increased risk of cancer was observed. For patients receiving dose of <1850 MBq, there was no significantly elevated risk of subsequent malignancy.⁵⁶

An Italian study by Dottorini et al found an elevated standardized incidence for salivary gland tumours and melanoma in 814 female patients.⁶⁰

A French study by de Vathaire et al found that the risk of solid tumours, excluding digestive tract cancers, was not increased after RAI treatment.⁵⁵ The risk of colorectal cancer was increased, and was related to the total activity of RAI administered 5 years or more before its diagnosis (excess RR = 0.5 per GBq, $p = 0.02$). A possible explanation is the accumulation of RAI in the colon lumen.

As elucidated above, the sites of secondary malignancy from different reports are not consistent.^{55,56,60} Rubino et al combined data from 3 European countries.⁶¹ This study has high statistical power by combining data from large populations of Sweden,⁵⁶ Italy⁶⁰ and France.⁵⁵ They studied the risk of SPM in 6841 2-year survivors of thyroid cancer.⁶¹ Compared to the general population of each of the 3 countries, there was an increased risk of cancer of 27%. The RRs of cancers of bone and soft tissue (RR = 4), female genital organs (RR = 2.2), central nervous system (RR = 2.2) and leukaemia (RR = 2.5) were increased after RAI exposure, after adjusting for external radiotherapy (EXT). A strong relationship was found between cumulative dose of RAI and risk of cancers of bone and soft tissue, colon-rectum and salivary gland. Only the dose range of 7.4 to 14.7 GBq was associated with increased RR of solid cancers but not leukaemia. No significant association was found between EXT and risk of SPM, except for bone and soft tissue cancers.

Thyroid cancer and breast cancer are associated.⁶¹⁻⁶⁴ This relationship is not related to treatment by RAI nor EXT.^{62,65} Women aged <45 years with primary thyroid

cancer have greater risk of developing secondary breast cancer.^{62,65}

While diagnostic doses of RAI do not increase risk of thyroid cancers,⁶⁶ caution should be exercised in the use of RAI ablation in low-risk patients and in therapy of patients whose disease did not take up RAI. The principle of “as low as reasonably achievable” or ALARA should be followed.

Female Fertility and Pregnancy Outcome

Temporary ovarian failure was reported in 17% to 27% of women within 10 months to 1 year after RAI therapy.⁶⁷ There was no case of permanent ovarian failure in a series of 322 patients in the United Kingdom.⁶⁸ Menstrual disturbance was related to higher cumulative dose of RAI⁶⁸ and older age.^{67,68} An earlier onset of menopause was also reported.⁶⁹

The possibility of genetic or physical damage to the offspring, in terms of congenital malformation and childhood malignancies, is a grave concern. Potential factors that might affect pregnancy outcome after thyroidectomy are adequacy and fluctuation of thyroid hormone replacement, radiation dose to ovaries, age at conception, socioeconomic class, alcohol intake and smoking. It is reassuring that there are no observed associations of previous RAI exposure to unfavourable pregnancy outcome.^{60,68,70-76} Schlumberger et al, in their largest reported series of 2113 pregnancies in a French population, revealed that the miscarriage rate increased from 11% to 20% after surgery, irrespective of RAI treatment.⁷⁵ Higher miscarriage rate was observed (40%) if RAI treatment was administered within 1 year before conception or in older age groups.

In Hong Kong, we studied the gestational history of 104 patients with pregnancy after diagnosis of DTC.⁷⁶ After a mean dose of 96.6 mCi of RAI, pregnancy outcome was not adversely affected by history of RAI treatment. There was no case of stillbirth. The rate of miscarriage, percentage of live births, condition of neonates (gender ratio, birth weight, congenital malformation) was not different from those patients without RAI. Development in children whose mothers had RAI administration was normal. However, the incidence of preterm delivery was higher in patients with history of RAI administration. Comparing the clinical data of pregnancies after RAI administration (>5 mCi) with that of a territory-wide hospital audit of 95,074 pregnancies in Hong Kong,⁷⁷ the demographic data were comparable.

A rapid washout of whole body RAI after administration is expected because of its short biological half-life. Observing a higher miscarriage rate⁷⁵ and some untoward pregnancy outcomes like birth defects,⁷² Edward syndrome⁷¹ and aplastic anaemia⁷¹ found in conceptions in the first post-RAI year, a recommendation to avoid pregnancy in the first year post-RAI treatment seems reasonable. In addition, this approach allows time for confirmation of disease remission⁷⁴ and control of thyroid hormonal status.⁷⁵ Some guidelines recommend avoidance of pregnancy for 4 months²² to 6 months⁷⁸ after RAI treatment or scanning, while others recommended 1 year.^{71,72,74,75,79}

RAI doses employed for ablation and treatment in female patients are safe. There is no definite evidence of an increased risk of permanent infertility or teratogenicity.^{60,68,70,75,76} It is important to educate patients and provide information on procedural instructions. Pregnancy testing before RAI administration and deferral of RAI administration (in case of doubt) can avoid inadvertent RAI in a pregnant patient. During pregnancy, thyroid function needs to be closely monitored. With these preventive measures and precautions, RAI should be a safe treatment method in women of child-bearing age.

Male Fertility

Reversible transient oligospermia occurs after RAI treatment. The damage to spermatogenesis is dose-dependent.⁸⁰ Serum follicle-stimulating hormone will increase⁸⁰⁻⁸³ and subsequently fall to normal at 12 months. Testosterone level did not change significantly following iodine treatment.⁸² Caution should be exercised with repeated high doses of RAI in young adult males, because of the risk of permanent infertility.⁸¹ Counselling and sperm banking should be considered in young males when high-dose RAI treatment is indicated.

A British study by Hyer et al studied 122 men <40 years at the time of treatment with a median follow-up of 21 years.⁸² Fertility was not impaired and children fathered by male patients with a history of RAI administration had no major congenital malformations. After a single ablative dose, the median estimated dose to each testis was low: 6.4 cGy following 3 GBq, 14.1 cGy following 5.5 GBq and 21.1 cGy following 9.2 GBq.

CONCLUSION

RAI treatment appears to be safe and effective in reducing the risk of relapse and probably in improving

survival. The issue of RAI ablation in low-risk patients is still unresolved. Prompt reporting of side effects and complications should be encouraged. Pooling of data should be encouraged in order to clarify the issues of secondary malignancy and leukaemia. With increasing use of RAI (almost 90% in Queen Elizabeth Hospital in recent years), practicing doctors should familiarise themselves with its role, indications and potential side effects.

Safe practice of RAI treatment should balance the risk of side effects with benefits. It is now a common practice to space RAI treatments by at least 6-month intervals, observe the total cumulative dose, and exercise caution in administration to elderly patients and those with diffuse lung metastasis. More studies or audits on the side effects based on large populations are awaited.

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