



REVIEW ARTICLE

Health Risk from Radioactive Iodine (RAI) Therapy and Medical Imaging: A Short Review

Siti Umairah Nasir¹, *Siti Amira Othman¹, Nurul Izzah Mohamad Nordin¹

¹Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia, 84600, Pagoh, Johor, Malaysia

*Corresponding author: sitiamira@uthm.edu.my

Received: 14/02/2022, Accepted: 20/08/2022, Published: 31/10/2022

Abstract

Different role of radioactive iodine (RAI) has a different dosage. RAI is the effective treatment for cancer but has a short or long side effects such as xerostomia and loss of taste or smell. Ablation, adjuvant and therapeutic is the role of RAI and all of it has risk. RAI tend to increase the survival for the patient on progression-free survival and disease-free survival. Aside from that, computed tomography radiation has been associated to a small but significant increase in the chance of fatal cancer during a person's lifetime. This review aims to promote public awareness and lead initiatives to eliminate unneeded computed tomography scans. Despite evidence of recognized hazards of radiation-related computed tomography and cancer induction, the usage of pediatric computed tomography continues to rise. In the United States of America, more than 60 million computed tomography scans are projected to be conducted each year, with 7 million of those being performed on children. To decrease radiation exposure, pediatric radiologists employ the ALARA ('as low as reasonably achievable') concept. This idea is reinforced through education and lobbying directed towards recommending physicians. Clinical strategies that restrict computed tomography scanning and encourage non-radiation imaging modalities like ultrasound and magnetic resonance imaging might help decrease radiation exposure even further. Although individual risk estimates are tiny, the widespread use of computed tomography in the community may result in future public health concerns.

Keywords: Radioactive iodine; computed tomography; radiation; health effect

Introduction

The effective therapy for well-differentiated thyroid cancers such as papillary thyroid cancer (PTC) that demonstrate iodine uptake is known as radioactive iodine (RAI; ¹³¹I) (Gray et al., 2019). A nuclear medicine physician, Saul Hertz, the director of the Thyroid Clinic at MGH and a nuclear medicine physician was the first to use radioactive iodine for therapeutic use in humans (Sawin & Becker, 1997). Iodine isotopes were

act as agents that can cause thyroid and other types of cancer. Large epidemiologic investigations of survivors of the atomic bombings in Hiroshima and Nagasaki at the end of World War II firmly defined this association. For example, researchers from the United States and Japan discovered a 4.4-fold increased risk of thyroid cancer in atomic bomb survivors who were younger than ten years old at the time of exposure, with a well-defined linear relationship between levels of radioactive iodine exposure, age, and the risk of thyroid cancer (Pilli et al., 2007)

RAI has become one of the most common therapeutic services provided in Malaysia, with nuclear medicine facilities in various tertiary hospitals and institutions. The sole hospital that offers RAI along the Northeast Coast of Peninsular Malaysia is Hospital Universiti Sains Malaysia (HUSM), which is located in Kelantan and acts as a referral centre for the two neighbouring states of Terengganu and Kedah. The selection of cases for RAI, the preparation for RAI, the dosage of radioiodine, and the procedure for the use of anti-thyroid medications before and after RAI vary from centre to centre. Despite the fact that there are established international recommendations for RAI therapy, differing methods may result in varied RAI therapy outcomes from centre to centre, particularly in terms of the incidence of hypothyroidism after RAI therapy (Wan et al., 2018).

¹³¹Iodine is a beta-emitting radionuclide with an average energy of 0.192 MeV that have a tissue range of 0.8 mm, but it also causes cell death and mutation, causing all iodine isotopes to be swiftly absorbed into thyroid follicles. As a result, thyroid follicles can only go through the organification process. The thyroid follicles absorb and organise ¹³¹I beta radiation, resulting in extremely localised destruction of those follicles. Generally, the ¹³¹I isotope has a half-life of 8 days. Thyroid hormone production is disrupted by ¹³¹I, which causes blood vessel damage and follicular necrosis (Mumtaz et al., 2009). There are 3 categories oncologic rationale for RAI administration which are, adjuvant therapy, remnant ablation and definitive therapy. On a practical level, RAI improves the staging and monitoring of most patients after surgery. After a complete thyroidectomy in some patients, RAI ablates minor amounts of remaining normal thyroid tissue or microscopic malignancy. The purpose of ablating small amounts of tissue is to make it easier to monitor blood thyroglobulin levels by lowering them to zero and, if necessary, using diagnostic whole-body iodine scans for surveillance. The RAI scan after treatment can also be used as a staging tool to detect metastatic disease that was missed during the first workup (between 25 and 53 percent of cases in certain studies) and can provide a targeted approach to RAI-avid lesions. The greatest candidates for RAI therapy are patients who are allergic to antithyroid medications and do not have TMNG or thyroid cancer. RAI therapy kills thyroid tissue, resulting in either euthyroid or hypothyroid people. Hypothyroidism is a common long-term side effect of RAI, requiring lifelong thyroxine replacement. There are numerous aspects to consider.

While, CT scans are an essential and beneficial supplement to a variety of imaging modalities for children. CT scans in babies and children employ X-rays to offer rapid, consistent, and thorough information on practically all organ systems. Due to the importance of X-rays in the generation of images with CT, radiation exposure is required throughout the test. Individuals exposed to significant doses of ionizing radiation have been demonstrated to have an increased risk of cancer. Generally, most of the increased exposure in the United States is due to CT scanning and nuclear imaging, which require larger radiation doses than traditional X-rays. A chest X-ray, for example, delivers 0.1 mSv, while a chest CT delivers 7 mSv. Furthermore, recent papers have examined the cancer risk associated with lesser radiation exposure than CT scans. Pediatricians, patients, and families have expressed worry about this publication. However, this assessment of the literature reveals a broad range of views on the cancer risk of diagnostic imaging examinations. Although there are many different statements about the risk of ionizing radiation in the literature, the authors of the article to which this report refers have consistently supported one principle: any estimate of the risk of a CT scan is far less than the possible benefit to the patient to demonstrate.

Computed tomography is immensely popular because of its low radiation dosage and extensive use. According to the consensus statement on radiation risk, it is fair to operate on the presumption that low doses of radiation provide a modest risk of cancer. The medical community should look for ways to decrease radiation exposure by employing the lowest possible dose and only doing these investigations when absolutely required. The advantages of computed tomography scans are widely acknowledged to greatly exceed the hazards. Pediatric healthcare providers' responsibilities in the use of computed tomography in children include determining whether scans are necessary and addressing hazards with patients and their families.

Results and Discussion

Radioactive Iodine Therapy and Follow-up

Patients were administered adjuvant RAI therapy after thyroidectomy at the discretion of the treating clinicians. Patients were typically prepared in the United States by following a low-iodine diet and taking levothyroxine or recombinant thyroid-stimulating hormone. In France, patients must cease using levothyroxine on their own. The patients were given a 100 mCi RAI dose. The RAI dose in the American cohort ranged from 50 mCi to over 400 mCi. Patients were divided into intermediate-dose RAI (median 100 mCi, IQR 100–100 mCi) and high-dose RAI (median 150 mCi, IQR 149–158 mCi) for analysis. Only the initial postoperative dose of RAI was considered in the primary analysis. After treatment, patients were evaluated with ultrasound and blood thyroglobulin levels every 6 to 12 months, with further imaging as clinically necessary (Gray et al., 2019).

The administered activity of ^{131}I can be low, typically at 20–30 mCi (740–1110 MBq), 30 mCi being more widely used, or high, typically at 100 mCi (3.7GBq) or more. Preparation can use endogenous TSH stimulation (following thyroid hormone withdrawal) or exogenous TSH (after injection of recombinant human TSH [rhTSH] (Mallick et al. 2012; Schlumberger et al., 2012; Verburg et al., 2014; Marti et al., 2018). Post operative RAI therapy has three objectives:

- Ablation: Used to remove postoperative physiological thyroid remains in order to obtain an undetected serum Tg level and allowing for easier follow-up and early recurrence identification. It also allows for high-sensitivity whole-body imaging to detect and locate any residual disease; post-ablation scintigraphy can also be utilised as a prognosticator using the "dynamic reclassification" method, allowing for more personalised follow-up.
- Adjuvant: ^{131}I therapy enables irradiation and destruction of occult infra-radiologic residual disease in the neck or other occult micrometastases, improving recurrence-free survival;
- Therapeutic: in patients with known residual or metastatic disease, ^{131}I therapy aims to treat iodine-avid metastases in order to achieve cure or remission, reduce persistent or recurrent disease, and improve overall prognosis.

Table 1. shows the role of radioactive iodine (RAI) with recommended dosages (Clement et al, 2015).

Role of RAI	2009 ATA* recommended dosage	2015 ATA* recommended dosage
Remnant ablation	30-100mCi	30 mCi
Adjuvant therapy	100-200mCi	30-150 mCi
Therapy	100-200 mCi (empiric dosing) Repeat RAI therapy every 6- 12 months as long as disease concentrate RAI and respond clinically.	100-200 mCi (empiric dosing) Repeat RAI therapy every 6-12 months as long as disease concentrate RAI and responds clinically.

*ATA, American Thyroid Association; Cumulative RAI doses above 600 mCi are associated with a significantly increased risk of second primary cancers

Risks of Radioactive Iodine (RAI) Treatment

Overall RAI is safe and is well tolerated, with side effects. Many of the side effects occur early and are transient, however some may appear late and become permanent. The most common acute side effects include salivary gland dysfunction, occurring in 16-54% of patients, leading to sialadenitis, epiphora, and dysgeusia. The mechanism of salivary gland dysfunction involves the sodium-iodine cotransporter, where the salivary glands concentrate I-131. Transient loss of smell is also reported (Alexander et al., 1998). Temporary gonadal dysfunction may also occur, with oligospermia reported in 20-73% of male patients and amenorrhea in 20-27% of female patients.

Xerostomia, diminished taste, and lacrimal gland malfunction leading to dry eyes are some of the long-term consequences (reported in 11 percent of patients). Furthermore, the majority (60 percent) of patients who get high dose RAI (100-200 mci, some patients receiving repeated treatments) develop long-term symptoms such as loss of taste or smell that last more than a year (Alexander et al. 1998). Aplastic anaemia and myelosuppression have also been described.

The most concerning long-term risk of RAI therapy is an increased risk of developing second primary malignancies (SPMs), which is caused by radioactive iodine concentrating in other bodily tissues. Rubino et al. (2003) studied the occurrence of SPM in 6841 thyroid cancer patients, 62% of whom had had radioactive iodine treatment. Patients treated with radioactive iodine had a 27 percent greater chance of developing an SPM as a result of RAI therapy (stated as the increased risk above the baseline risk of developing a second malignancy). Soft tissue tumours (RR [relative risk] 4.0), ovarian or endometrial cancers (RR 2.2), central nervous system malignancies (RR 2.2), leukemias (RR 2.5), colorectal cancer, and salivary gland cancer all had the strongest link. Rubino et al. calculated that if 100 mCi of RAI were given, the rate would be.

As a result, the risks of RAI, including the potential of SPM development, must be balanced against the benefits for each patient individually. This is especially important when RAI is being considered for a patient whose benefits are likely to be low or non-existent. Iyer et al. (2011) investigated into this exact issue. For example, a patient with a small, intrathyroidal, node-negative (T1N0) well differentiated thyroid cancer would not benefit from postoperative RAI. Under any of the current thyroid cancer recommendations, RAI is not indicated. Despite this, the use of RAI treating patients with these tumours has expanded considerably since the 1970s, with RAI being used by 38 percent of T1N0 well-differentiated thyroid cancer patients under 45 years of age in the United States in 2006.

The development of SPM was then monitored in these very low-risk patients. In the end, the use of RAI was linked to an extra 46 malignancies per 10,000 patients tracked for ten years. According to the authors, this corresponds to a risk of 1 more malignancy for every 200 very-low-risk individuals who receive RAI. Salivary gland cancer was shown to be 11-fold more common in one study, and leukaemia was found to be approximately 6-fold more common. While these concerns may be tolerated in patients who may benefit from RAI therapy, they were especially found in patients who were unlikely to benefit from RAI therapy.

Younger RAI patients have been shown to have similar SPM risks. The increased risk of SPM (particularly salivary gland cancers) in paediatric and young adult RAI patients was shown to be comparable to the risk in adult patients. Over the course of a decade, one out of every 227 RAI-treated paediatric and young adult patients acquired an SPM. RAI therapy was connected to the development of salivary gland cancer in one out of every 588 patients.

RAI Efficacy and Outcomes

Given the indolent nature of many thyroid cancers, the advantages of RAI for remnant ablation and therapy may best be measured by its ability to increase disease-specific survival and decrease recurrence risk. Parameters such as progression-free survival and disease-free survival are similarly informative. As described above, routine use of RAI conclusively improves both outcome measures in older patients (>45 years old) with larger thyroid cancers (>4 cm), in patients with gross extrathyroidal extension, and in patients with distant metastases. Specifically for remnant ablation intent, the current ATA recommended dosage has decreased from 30-100 mCi to only 30 mCi. For adjuvant therapy intent, current recommended dosages have similarly dropped from 100-200 mCi down to 30-150 mCi are shown in Table 2.

Radiography, fluoroscopy, angiography, and CT all use X-rays. Patient characteristics (such as age and size), technical characteristics (equipment settings and procedure length), and equipment model all influence dosage. However, it is beneficial to get familiar with some of the example dosages for routine imaging tests, as given in Table 3 below.

Table 2. Risk Category (Haugen et al., 2016)

Risk Category	2009 ATA Guidelines	2015 ATA Guidelines additions	2015 RAI recommendation	% NED after TT/RAI
Low risk	<ul style="list-style-type: none"> No local No macroscopic tumor remaining No ETE No vascular invasion Nonaggressive histology If RAI given, no RAI-avid metastatic foci outside the thyroid bed on the post-treatment whole body RAI scan. 	<ul style="list-style-type: none"> Clinical no Less than or equal with 5 pathologic NI micrometastases (<2mm in size) Intrathyroidal; FTC with capsular invasion and minimal vascular invasion (<4 foci) Intrathyroidal papillary microcarcinoma, unifocal or multifocal, including BRAF mutation. 	Not routinely recommended	78-86%
Intermediate risk	<ul style="list-style-type: none"> Minimal ETE RAI-avid metastatic foci in neck on first post-treatment whole body RAI scan Aggressive histology (tall cell, columnar) PTC with vascular invasion 	<ul style="list-style-type: none"> Clinical NI >5 pathologic NI (all involved LN <3 cm in size) Multifocal papillary microcarcinoma with ETE and BRAF mutation 	Can be considered	52-63%
High risk	<ul style="list-style-type: none"> Gross ETE Incomplete tumor resection Distant metastases Postoperative TG suggesting distant metastases 	<ul style="list-style-type: none"> Pathologic NI with LN greater or equal 3 cm in size FTC with extensive vascular invasion (>4 foci) 	Routinely recommend	14-31%

*ATA, American Thyroid Association; ETE, extrathyroidal extension; TT, total thyroidectomy; RAI, radioactive iodine; NED, no evidence of disease; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

Table 3. Doses of common radiological procedures

Examination	Average effective dose (mSv)	Values reported in the literature
Posterior anterior study of chest	0.02	0.007-0.05
Head CT	2	0.9-4.0
Thorax CT	7	4.0-18.0
CT Pulmonary angiogram	15	13.0-40.0
Abdomen CT	8	3.5-25
Pelvic CT	6	3.3-10
Coronary angiography	16	5.0-32

CT scanning, rather than diagnostic imaging, has become the focus of modern research in ionizing radiation exposure due to three considerations. For starters, CT scanning exposes patients to far more radiation than diagnostic imaging. CT scans accounted for 11 percent of ionizing radiation treatments in big university radiology departments in 2000, but 67 percent of radiation exposures, according to Mettler et al. Second, the number of CT scans and the indications for them both grew quickly. CT scanning accounted for 15% of the procedure and 75% of the dosage in a more recent trial at the same institution (Wiest et al., 2002). Third, CT scanning may be done using a number of procedures that yield virtually comparable image quality while exposing the patient to varying levels of radiation. When the radiation dosage is increased in typical ("plain") radiographs, the picture becomes darker, and most people will detect that the film is overexposed.

Changing the quantity of radiation used in CT scans, on the other hand, impacts the amount of mottle (or picture noise) while having no influence on image appearance. Mottle decline with greater radiation will not impair the diagnostic accuracy of CT examinations and may not be appreciated beyond the threshold of diagnostic quality, although the exposure may not be excessive, especially in youngsters (Ravenel et al., 2001). Children and adults were previously subjected to the same CT testing conditions.

Computed Tomography (CT) Scan: Radiation Exposure and Cancer Risk

Given that some experimental and epidemiological evidence has associated low-dose radiation exposure with solid organ development, the fast expansion in the use of CT has raised major public concern about the dosage of ionizing radiation supplied during scanning leukemia and cancer (Freudenberg and Beyer, 2011; Royal HD, 2008). Large doses of ionizing radiation are commonly regarded as increasing the probability of a person developing cancer later in life, however the relationship between low-dose radiation (from the arrangement used in conventional diagnostic screening) and oncogenesis is questionable.

Extrapolation data from studies of atomic bomb survivors dropped in Japan in 1945 and evaluations of the relative elevated risk of neoplasia in people exposed to radiation in the nuclear industry are used to make the link between radiation and later neoplasia development (E. Cardis et al., 2007). Brenner and Hall, (2007) estimated that 1%–2% of all cancers in the United States will occur in the future as a result of the effects of ionizing radiation transmitted by medical imaging, while Berrington de González et al, (2007) predicted that 29000 additional cancers and 14500 additional deaths could be expected each year using this method of extrapolation where a small hypothetical risk is multiplied by a large number of patients.

CT Scanning: Recommendations for the Future

The link between radiation exposure and oncogenesis, on the other hand, has yet to be thoroughly understood. Despite this, the objective should always be to employ a dosage that is "as low as reasonably practicable" during patient imaging. Imaging can only be utilized when the possible clinical benefit surpasses the potential danger, regardless of risk. The International Radiological Protection Commission outlines three essential concepts of radiation: (1) rationale, (2) dosage optimization, and (3) dose limitations. Radiation optimization in the future will incorporate physician and patient education. The Image Gently and Image Wisely campaigns are examples of such attempts. Image Gently informs parents and clinicians about the radiation safety of the pediatric population and promotes dose optimization (Strauss et al., 2010).

The Image Carefully campaign promotes adult radiation safety and has created a list of accolades for establishments and associations who have promised to "draw wisely" in their practices (Brink et al., 2010). Under the name Step Lightly, the Image Gently campaign has been expanded to provide particular recommendations on pediatric intervention techniques (Sidhu, 2010), The Food and Drug Administration has initiated a national program to limit needless radiation exposure to patients in response to the Cedar-Sinai scandal in the United States. It is obvious that doctors do not adequately share the hazards of radiation exposure with their patients, even if the risks are minor. When there is a high danger of radiation dosage exposure, such as during an intervention surgery, radiation risk should be a part of the consent process. With the rising prevalence of radiological studies, the medical profession must address patient education regarding the hazards of radiation exposure in order to appropriately explain possible concerns.

The Interventional Radiology Patient Safety Program, among others, has published guidelines that have resulted in changes to procedures when excessive intra-procedure radiation doses are provided (Steele et al., 2012). Auditing as a standard in the radiology department can assist lower the amount of radiation provided to each patient (Miglioretti et al., 2014), and it will be useful when discussing these scans with our patients. The creation of a national reference level for various CT tests will allow audits to be conducted at the local, national, and worldwide levels (McCullough et al., 2011). While there is still debate

over the specific oncogenic hazards associated with CT scanning, ignoring the problem is untenable; auditing, education, and re-evaluation are essential for greater knowledge and safer practice.

Conclusion

Radioactive iodine therapy is the effective treatment for thyroid cancer but the side effect may occur such as salivary gland dysfunction, dysgeusia and epiphora. The side effect may appear early or late and sometimes become permanent for the patient. After the treatment, the patient need to follow up the adjuvant RAI therapy at the discretion of the treating clinicians. There is also a different role for RAI based on American Thyroid Association (ATA) which are remnant ablation, adjuvant therapy and therapy which represent the different function for RAI and different recommended dosage. High dose tend to develop long term of symptoms such as lose a taste or smell over a year and aplastic anaemia.

The risk of cancer caused by ionizing radiation actually depends on factors such as the amount of radiation received, by the organs exposed to radiation, the age and gender of the patient. Although the risk of cancer is higher for younger patients, the overall risk of cancer is low for exposure to medical imaging regardless of the age of the patient. If an X-ray procedure is medically necessary, the medical benefits will always outweigh the cancer risk in a justification concept. Therefore, radiation risk estimates should not be taken into account in deciding whether or not an examination should be performed on a particular patient. Therefore, the appropriateness of performing Diagnostic Imaging depends on the doctor who treats the child based on the medical needs and the ability of the examination to provide information. If there is a medical need for a particular X-ray procedure and other examinations that do not use ionizing radiation such as ultrasound and MRI, or low-dose radiation are not appropriate. Radiation risk considerations and the patient's decision to perform the procedure should not influence the physician's decision to perform the procedure.

Acknowledgement

The authors would like to thank the faculty of applied sciences and technology for facilities provided that make the research possible.

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How to cite this paper:

Siti Umairah Nasir, Siti Amira Othman and Nurul Izzah Mohamad Nordin (2022). Health Risk from Radioactive Iodine (RAI) Therapy and Medical Imaging: A Short Review. *Malaysian Journal of Applied Sciences*, 7(2), 44-52.