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Health Implications of Radioactive Iodine Therapy for Thyroid Related Diseases Patients: A systematic Review

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Abstract: After thyroid surgery, radioiodine therapy remains the main course of treatment; giving radioactive iodine is an essential component of the therapeutic regimen for persons with thyroid conditions. The rates of death, recurrence, and metastasis can be significantly decreased with the use of radioactive iodine as a therapy. Both sexes have experienced a noticeable rise in the incidence of thyroid cancer in almost all nations. The most typical kind of differentiated thyroid cancer, which includes papillary and follicular subtypes, is surgery followed by radioactive iodine when necessary. Thyroid hormone suppression medication after treatment can lower cancer-related mortality and recurrence. Iodine therapy has some possible drawbacks in addition to its benefits, including the risk of pulmonary fibrosis, radiation thyroiditis, bone marrow suppression, gastrointestinal problems, sialadenitis/xerostomia, gonadal damage, dry eye, genetic implications, and secondary malignancies. Additionally, the cumulative iodine intake is linked to these negative effects. Ionizing radiation has been shown to accelerate the development of atherosclerosis and other illnesses in the human body when internal organs are exposed to it. A study revealed that the cumulative radioactive iodine exposure marginally increased the incidence of atrial fibrillation in addition to the established negative consequences. It is believed that the direct and indirect effects of radiation on bodily cells caused by radioactive iodine delivered to the patient are the cause of the known risks. Despite this, it is clear from the literature that there is little information on whether RAI can directly harm the heart, blood vessels, or other organs, just that it can cause indirect harm by producing reactive oxygen species through the radiolysis of water. A systematic review of the literature from Google Scholar, Research Gate, and other sources was conducted to identify studies reporting the health implications (either long-term or short-term effects) of RAI treatment in patients with thyroid disorders like differentiated thyroid cancer (DTC), Grave Diseases (GD), and papillary thyroid cancer. The number of publications during a particular time period represents the research trends that have been developing in the field of iodine therapy. Formal dosimetry studies should be considered in patients with very low lesional uptake to

determine whether a therapeutic radiation dose can be given to the tumor with a very high RAI uptake. This will help to prevent excessive whole-body radiation exposure and associated bone marrow and pulmonary issues. Short- and long-term effects were examined in patients with small-volume, non-progressive, non-life-threatening residual malignant illnesses. RAI therapy's immediate and long-term side effects in these patients, who have a minimal risk of dying from DTC, might not be necessary.

Keywords: Radioactive iodine, therapy, thyroid cancer, thyroidism and Iodine health implication.

1. Introduction

The use of the radioisotope iodine-131 in medicine is referred to as "radioactive iodine" (RAI). It is a generally accepted treatment method for DTC and is typically used after thyroid-ablating surgery to provide sensitive follow-up and in circumstances with a higher relapse risk. Therapeutic effects of RAI may also be employed to suppress or eliminate malignancies in patients with advanced local, regional, or metastatic illnesses. RAI has been used to treat well-DTC since 1946, largely in the form of 131I. The benefits and drawbacks of 131I are constantly being investigated and discussed. This study explores the potential risks of RAI therapy over the short- and long-term, as well as the most recent recommendations for mitigating and treating these side effects. Complications from RAI therapy have increased in frequency along with the prevalence of thyroid cancer. Early detection of the illness has led to postoperative RAI therapy being standard practice in many centers. While 61% of individuals had long-term issues (> 3 months after treatment), 76.8% of patients suffered early side effects from RAI treatment (Stephanie, 2010). Sialadenitis was a side effect that affected about 33.0% of patients, while temporary loss of taste or smell affected 27.1%. To effectively manage side effects when they do occur and to adequately inform patients on the short- and long-term effects of this therapy, it is essential to understand the risk of RAI (Stephanie, 2010). Nneka et al. (2022) claim that radioactive iodine therapy successfully treated hyperthyroidism with just one dose. The outcomes are comparable to those of further trials carried out elsewhere utilizing a similar dosing approach. When patients are being discharged, steps should be taken to reduce the dose rates, according to Mubarak et al., 2021. Four distinct kinds of shielding materials were selected to form a neckline. With a decrease percentage of 38.48%, silicon-based rubber that has been infused with iodine was shown to be the best shielding material. According to Caio et al., 2022, internal dosimetry should be used to gather data on acceptable dose limits for use with DTC radioiodine therapy, especially in advanced cases of the condition when the use of more intensive activities is necessary. The most common applications of RAI therapy are for residual ablation, adjuvant therapy, and the treatment of metastatic illness. Remainder ablation uses RAI to destroy healthy residual functioning thyroid tissues in order to increase the sensitivity of long-term thyroglobulin level monitoring, staging with post-therapy whole-body scan to detect local and distant metastasis, and facilitating the effectiveness of subsequent 131I treatment if a significant amount of remnant is present. Based on first pathologic staging, RAI adjuvant therapy uses 131I to eliminate microscopic thyroid cancer that has not yet been identified. During RAI treatment, known locoregional or distant metastases are eliminated using 131I to reduce mortality and recurrence or for palliative purposes. For recurrence or persistent disease, a small percentage of patients with differentiated thyroid cancer need additional doses of RAI, with 28% of patients receiving 2 doses and 8.80% obtaining 3 doses, according to one study with a median follow-up of 19.30 months (Mendoza et al., 2004). During the radioactive decay of 131I, beta and gamma particles are emitted. To image and locate RAI avid tissue for

staging, a gamma camera can be used to detect the gamma rays. With the help of a gamma camera, the RAI avid tissue can be seen and located for staging using the gamma rays. Normally, gamma rays pass through tissues without affecting or destroying biological components. Biological components that beta particles contact with result in 94% of the radiation from 131I is composed of beta particles, which impact with biological components and cause nuclear damage.

Radioactive iodine therapy has moderate short-term adverse effects, although they can occasionally become significant, according to Armaghan and colleagues (2014). Adina et al. 2022 showed that the release of hematological inflammatory mediators such neutrophils and lymphocytes be related with the time period between 46 and 69 hours be associated with the elimination of tumor cells in response to iodine-131 therapy. The evaluation of human health risks includes determining the kind and severity of adverse health effects in those who may have gotten too much iodine as a result of treatment. The current investigation examined iodine exposure and its detrimental effects on health based on the various studies that were assessed. To calculate the carcinogenic risks of iodine therapy, the incremental lifetime risk of developing malignancy due to exposure to a potentially carcinogenic pollutant (iodine) was used. This review showed that the radionuclide (iodine) that was given to the patient, which gave off radiation, is what is responsible for the health burden after therapy.

2. Material and method

2.1. Search Technique

A literature search was conducted in July, 2022 in accordance with the Preferred Reporting Items for Systematic Reviews and Mata-analysis, and it was further not restricted to a particular time frame. The following search terms were entered in the title or abstract: "Radioactive iodine therapy," "Health implications," "Thyroid problems," and "Side effects of iodine therapy." The synonyms added for each primary phrase. The search was restricted to studies involving people who had radioactive iodine treatment. The "related article" feature of the databases and the references of pertinent articles were both used to look for further articles. Two researchers (B.S. and A.B.) improved the data extraction table before data extraction. These two researchers performed separate searches of citation databases, including Google Scholar, Research Gate, and other databases, and then used predefined tables to obtain data Table 1. Having a dialogue with a third investigator helped to clarify any discrepancies (D. D).

2.2. Study Selection and Articles Quality Assessment

Studies that fit the following criteria were considered in this review: sample size, injected iodine activity, thyroid disorders, and potential health implications (early and late side effects of RAI). B.S and A.B independently and blindly screened the titles and abstracts. B.S conducted the full-text screening and discussed it with D.D & B.U; in the event of a dispute, A.I & A.A a third reviewer was consulted. Included were original researches describing the short and long term negative effects of RAI treatment on thyroid problem patients' health. The final criteria for inclusion were full-text accessibility. Exclusion standards included publications published in languages other than English language, Dutch, German, Spanish, French and Italian, articles having only abstracts, non-original articles, and articles on animal studies, and studies with insufficient information on the outcome of undesirable side effects. Using the Critical Appraisal Skills Program Checklist, a small portion of the full- text screening was a serious evaluation to determine the quality of each study. The employed checklist is applicable to all of the included

publications because it was created for the health implications research of radioactive iodine therapy.

2.3. Data Extraction

Data was extracted by B.S., and results were verified by A.B. Information was acquired regarding the treatment's goal, sample size, radioactive Iodine activity used, and side effects. The implications for health were found to have both immediate and long-term detrimental impacts. Studies on the side effects of RAI that focused on either euthyroidism or ablation were evaluated and reviewed. Long term side effects were defined as those that persisted for more than three months after RAI treatment, whereas short-term side effects occurred within three months of RAI treatment.

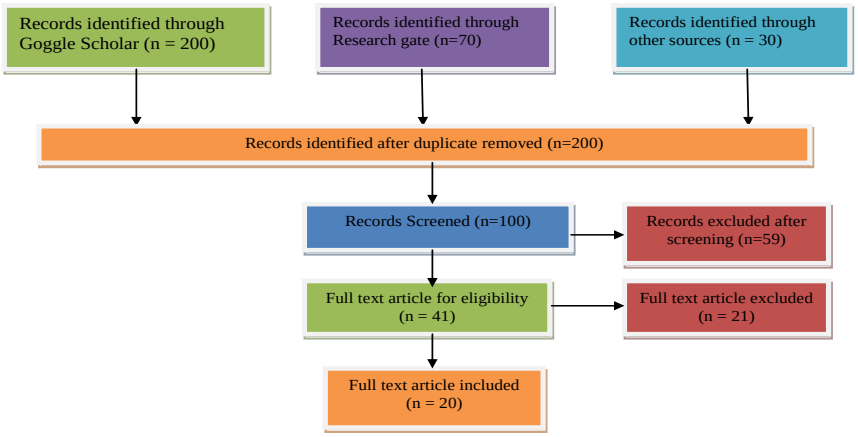

Figure 1. Scheme of strategic search term.

3. Results and Discussion

In July 2022, searches on Google Scholar, Research Gate, and other websites produced 300 different papers. A literature search on Google Scholar turned up 200 of the 300 studies, Research Gate provided 70, and other sources provided 10. There were 260 papers left after title, abstract, and full-text screening. After duplicate studies were eliminated, a total of 20 papers were added to the meta-analysis. Research with insufficient data and studies that didn't meet the requirements for inclusion had been removed Figure 1. According to the quality evaluation, two of the included studies got a good quality rating, sixteen received a medium quality rating, and two had a moderate quality rating out of the twenty (20) retrospective, observational, cohort, and national studies that were assessed for this review Figure 1. An overview of the features of each study is given in Table 1.

Table 1. Overview of Administered Activities and its associated health implications

S/N	Medical Conditions	No. of patients	Administered Activity	Health Implications	References
1	PTC	NA	30-850 (331 mCi)	Secondary leukemia	Hailan and Yassin, 2021
2	DTC	NA	51-450 mCi [187 MBq -16.65GBq]	nasal problems, neck pain, edema, gastrointestinal,	Douglas *et al.*, 1986

				non-salivary, and bone marrow suppression symptoms	
3	DTC	NA	50 mCi & ≥100 mCi (1850 MBq)	excessive tearing, nausea, dry mouth, taste disturbances, periorbital edema, and problems with the salivary glands	Pablo at al., 2016
4	DTC	117	100–250 mCi (3.7 - 9.25 GBq)	Neck pain, stomach discomfort, slivary gland swelling, headache, dizziness, insomnia, paralysis of the vocal cords, and overall malaise	Liyan et al., 2016
5	DTC	127	1.1–93.4 GBq (16.2 ± 5.4 GBq)	Early adverse effects include nausea, radiation thyroiditis, sialadenitis, dry mouth, and suppression of the bone marrow (BM). Recent negative impacts Permanent BM suppression, infertility, pulmonary fibrosis, and second malignancy. Permanent malfunction of the salivary glands.	Domenico et al. 2017
6	DTC	42	16 mCi (592 MBq)	At 48 hours (2 days), histological changes (enamel surface with multifocal and irregular patches), and at 8 days, several, very deep,	Mester et al., 2021

				delimited cavities were observed.	
7	DTC	33	75-150 mCi	Ovarian Reserve Reduction	Evranos et al., 2018
8	DTC	20	5.5 GBq	xerostomia at 12 months	Hyer *et al.,* 2006
9	DTC	7,000	100 mCi (3.7 GBq)	Solid malignant tumors and leukemia	Rubino et al., 2003
10	DTC	30	30 to 150 mCi	Effect on ovarian reserve	Iris et al., 2018
11	DTC	36	3700 MBq (1,110 - 40,700 MBq)	younger age at menopause, irregular periods, amenorrhea,	Marceline et al., 2020
12	DTC	40	50 mCi greater than or equal to100 mCi	Infertility and short reproductive life in women	Pino *et al.,* 2021
13	GD	48	356.5 ± 64.5 MBq	Leukopenia	Kaoru *et al.,* 2021
14	TC	13,310	>3.7 GBq >5.55 GBq	Cardiovascular Diseases CVD CVD-specific mortalities	Kao *et al.*, 2021
14	DTC	542	3700 for remnant ablative therapy 5550 - 7400 MBq for cervical lymph node metastasis	Change in White & Red Blood Cells	Zhongying *et al.,* 2021
15	DTC	139	1.1 GBq - 3.7 GBq	Salivary dysfunctions	Clémence et al., 2022
16	HT	479 452	370 MBq	Breast and solid cancer mortality	Shim *et al.,* 2021
17	DTC	NA	>175 mCi	thrombocytopenia and lymphopenia	Bircan et al., 2021
18	DTC	62	1850 MBq	DNA damage Inductions	Alberto et al.,2022
19	DTC	NA	>100 mCi (3.7 GBq)	Xerostomia (Parenchymal damage &Chronic salivary	Sunavala-Dossabhoy, 2018

				dysfunction)	
20	DTC	458	30–150 mCi (2.96 - 5.55 GBq)	Impairment of salivary gland function	Xiaolan et al., 2022

3.1. Discussions

Patients who had radioactive iodine therapy experienced both immediate and long-term health impacts. Vomiting, nausea, radiation thyroiditis, sialadenitis, dry mouth, and transient bone marrow suppression are some of the early adverse effects. Lung fibrosis, second cancers, prolonged BM suppression, permanent salivary gland dysfunction, and reproductive problems are late side effects. The discussion was divided into the following subsections based on Table 1 above**:**

Gastrointestinal disorder, Salivary gland dysfunctions, neck pain, bone marrow suppression and Nasolacrimal duct obstruction

About 30% of adults experienced nausea after iodine treatment. Children definitely experience nausea and vomiting more frequently than adults do, and in the previous study, nausea was noted as a general phenomenon in very young children. Nausea with occasional emesis caused by gastrointestinal irradiation is widespread; it usually starts 4-12 hours after iodine-131 injection, has a frequency of fifty to seventy percent and goes away in most cases by 36 hours. The occurrence rate, which is recorded following a low dosage of ^{131}I (40.0 mCi)] is, however, significantly lower (roughly 5%) and resolves entirely in the majority of patients within a week. It has been demonstrated that iodine-131 dosages of 150mCi or higher, which are doses recommended for the treatment of regional metastatic illiness, cause typical gastrointestinal adverse effects. According to some reports, the majority of these symptoms can be avoided with the right treatment. Laxatives will lessen the dose to the gastrointestinal and entire body. Preventing emesis and lowering the prevalence of nausea during radioactive iodine therapy have been successefully accomplished with antiemetic medication using selective serotonin receptor blockers, such as ondansetron, granisetron, and dolasetron (effectiveness being potentiated by dexamethasone).

According to Mandell (2003), sialadenitis was caused by radioactive iodine (^{123}I) uptake into the gland 20 to 100 times greater than that of plasma on diagnostic whole-body scan. Mendoza et al., (2004) identified acute radiation sialadenitis and chronic sialadenitis with or without signs of dry mouth as the two categories of consequences induced by RAI. Dose-dependent declines in salivary gland function following RAI therapy in a prospective quantitative research, and the research hypothesized that exposures of more than 500 mCi are linked to total salivary gland failure. Technetium-99 uptakes by the salivary glands at 10 minutes and the percentage of technetium 99 excretion from the glands in response to a sialogogue can be used to measure salivary gland damage. These experiments demonstrated that the parotid glands functioned less than the submandibular glands function. Caglar *et al.* (2002) noted that after patients receiving RAI treatment, between 12% and 67% of patients have been observed to get acute radiation sialadenitis with swelling and pain. The patient's age, co morbid conditions, current administered dose, and total dose of ^{131}I are likely to vary depending on the problems. According to one study, sialadenitis affected 11.5% of patients receiving a mean dose of 100 mCi of 131I, and 90% of the symptomatic

patients had previously undergone ^{131}I treatments (Allweiss et al., 1984). A recent retrospective investigation by Grewal et al. (2009) reported that 39% of patients experience sialadenitis in the first year with a median dose of 141 mCi, higher dosages of ^{131}I showed a dose response, which increased the incidence of swollen salivary glands but not dry mouth. Most symptoms were away within a few weeks; however 5% of patients continued to have issues 7 years following treatment. Patients should be made aware before starting RAI therapy for thyroid cancer that salivary gland damage may occur and can be either acute or chronic. This damage can cause pain, swelling, and xerostomia in the salivary glands, which calls for strict oral hygiene, the avoidance of anticholinergic medications, and dehydration. It was reported that in three to seven days after receiving RAI therapy, radiation thyroiditis with swelling and thyroid discomfort develops. After a total or almost total thyroidectomy without significant neck metastases, this risk is often quite low. Within 48 hours following the RAI therapy, a painless neck swelling has been reported too. This edema is thought to represent a hypersensitive reaction in the thyroid's peritoneal tissues. Corticosteroids can be used to treat neck swelling, whether it is painful or not (Stephanie, 2010). About 3% (10/390) of patients experienced watery eyes and tear overflow in 13 to 23 months after receiving repeated doses of ^{131}I, with a mean cumulative ^{131}I dose of 467 mCi, according to a retrospective review conducted by Stephanie, (2010). The tear ducts include the sodium iodide symporter, and following RAI therapy, the radioactive tears cause ductal stricture. Epiphora is brought on by a tightening and obstruction of the tear duct, which can be treated with stent or dilatation implantation but requires surgical diversion of the tear duct for complete occlusion. In order to choose a more sensible maximum safe dose of radioiodine (dosimetry) to treat metastatic functional well-differentiated thyroid cancer, Douglas et al. (1986) have advised estimating radiation exposure to the blood. Benua, Leper, and others have supported this method (BEL). The immediate (during hospitalization) and intermediate (from discharge up to 3 month) side effects following the initial 15 medications in ten patients were assessed after adopting the BEL dosimetry approach. From 51 mCi (1, 87 MBq) to 450 mCi, the doses were administered (16.65 GBq). Almost 80% of patients experienced immediate side symptoms, which are fully described as follows: digestive problems (10/15), salivary (9/15), non-salivary (2/15), neck ache, edema, etc., and pulmonary (0/15). About 67% of people reported experiencing intermediate side effects, which are fully explained as follows: stomach pain (0/15), saliva (3/15), nonsalivary, neck ache, edema, etc. (3/15), (2/15) for nasal symptoms, (9/10) for temporary bone marrow suppression, and (0/15) for pulmonary. No patient needed blood transfusions, and no complications due to low blood counts occurred. All patient complaints were cured, although one year following therapy, some patients may have had lower baseline blood counts. Although the average follow-up has only been 15 months, no other long-term negative effects have been reported. In other perspective, the researchers have not yet noticed any negative effects that would prevent from using and evaluating the BEL dosimetry approach going forward.

Na and Wanchun (2022) examined characteristics of differentiated thyroid cancer patients with nasolacrimal duct obstruction following iodine-131 therapy and provided recommendations for clinical decision-making with reference to nasolacrimal duct obstruction. Thirty one participants underwent logistic multifactor regression and chi-square analyses. A higher risk of nasolacrimal duct obstruction was observed in patients who were older than 50, had metastatic iodine uptake, received iodine doses larger than 5.55 GBq, and inhaled iodine-131 nasally. The study's findings suggested that medical professionals should consider a wide range of variables when determining iodine-131 therapeutic doses. Iodine-131 therapy, however, might make nasolacrimal drainage system obstruction more common. Thyroid cancer was identified by Sunavala-Dossabhoy (2018)

as an endocrine malignancy with a rising frequency in the United States. In 2017, around 57,000 new cases of thyroid cancer were discovered. Thyroidectomy followed by high-dose radioactive iodine ablation of thyroid remains the mainstay of ^{131}I therapy for differentiated thyroid carcinoma. In addition to thyroid glands, ^{131}I builds up in salivary gland cells and impairs their functionality. Therefore, xerostomia is a common and frequently ongoing issue among patients. By demonstrating a dose-response relationship between activity (>100 mCi; 3.7 GBq) and symptoms of salivary morbidity, it was demonstrated that xerostomia following ^{131}I treatment was dose-related. Parenchymal injury and persistent salivary dysfunction are seen in a significant number of individuals despite the use of typical preventative strategies. Saliva plays a crucial role in maintaining oral homeostasis; hence its reduction raises the danger of oral morbidity. Maintaining salivary gland function is especially important because differentiated thyroid carcinoma patients have a very good prognosis. The quality of life for thyroid cancer survivors can be considerably enhanced by concentrating on therapies that maintain or restore long-term salivary flow. It was noted that after receiving therapy with iodine-131 (^{131}I), patients with differentiated thyroid carcinoma (DTC) had their salivary gland function assessed by Xiaolan et al. in 2022. There were 458 DTC patients in all, divided by sex and age. To assess salivary gland function before and after ^{131}I treatment, salivary gland scintigraphy was carried out. Two pairs of parotid glands and submandibular glands had their uptake fraction (UF), uptake index (UI), and excretion fraction (EF) measured and compared. The Chi-square test was performed based on the number of functional impairments. Diverse age groups and sexes had substantially different salivary gland functions, particularly in women under the age of 55 who had decreased UF, UI, and EF of all four glands without basal damage. Some salivary glands with basic function impairment prior to ^{131}I treatment had increased secretion or uptake function after iodine treatment. After multiple treatments, only a tiny percentage of men displayed decreased functional metrics. The first and third examinations showed the greatest variation in the number of impaired salivary glands, which was more pronounced in females.) The submandibular gland experienced the greatest uptake drop. Young females receiving DTC treatment are more likely to see changes in salivary gland function. The number of treatments and total ^{131}I dose are connected to impaired salivary gland function. The early treatment improved some salivary gland functions that were compromised prior to the ^{131}I treatment. Rarely, acute stomatitis is observed, and it is believed that the mucosal radiation from the ^{131}I released into saliva is the cause of this condition. Many professionals have observed this problem 5–7 days following iodine therapy, despite the fact that it has not been reported in the literature. An elixir mouthwash comprising dexamethasone, viscous lidocaine, diphenhydramine, aluminum, and magnesium hydroxide can control symptoms (Mandel, 2003).

According to a study by Clémence et al. (2022), patients' nutritional health and quality of life may suffer as a result of salivary gland inflammation following radioiodine (131I) therapy for differentiated thyroid cancer. Little is known about the frequency of these dysfunctions after 131I-therapy, and no clinical or genetic criteria have been identified to date to identify patients who are at-risk, allowing the provided activity to be changed to account for the potential risk of salivary dysfunctions. The goals of this study are to characterize at-risk patients, estimate the prevalence of salivary dysfunctions, identify patients at risk of developing post-treatment dysfunctions using clinical, bimolecular, and biochemical factors, and identify the effects of 131I therapy on patients' quality of life and nutritional status. The dose that was given to the salivary glands in order to investigate the relationship between absorbed doses and dysfunctions in those glands. Patients in a Paris hospital who are prescribed 131I-therapy as part of treatment for differentiated thyroid cancer will be enrolled in this prospective trial (40 and 80 patients in the 1.1 GBq and 3.7 GBq groups,

respectively). Three preset visits serve as the basis for the follow-up: inclusion (T0, right before 131I-therapy), six months (T6), and 18 months (T18) after treatment. For each visit, a certified clinical research associate gives questionnaires on nutritional status (visual analog scale), salivary dysfunctions, and quality of life (Hospital Anxiety and Depression Scale, Medical Outcomes Study 36-Item Short Form Survey). Each person's salivary flow is assessed with and without activating the salivary glands at T0 and T6, when saliva samples are collected. External thermal luminescence dosimeters are positioned on the skin at the sternal fork and across from the salivary glands prior to the administration of 131I. Five days later, they are eliminated. The radiation received at the salivary glands was calculated from the doses recorded by the dosimeters using physical and computational phantoms. Genetic and epigenetic studies were conducted between September 2020 and April 2021 on 139 patients (99 women, 71.2%; mean age 47.4, SD 14.3 years; 45 and 94 patients in each group) to explore for potential indicators of the susceptibility to develop salivary dysfunctions after 131I-therapy. 139 patients were included in the study between September 2020 and April 2021 (99 women, or 71.2%; mean age, 47.4, SD 14.3 years) (45 and 94 patients in the 1.1 GBq and 3.7G Bq groups, respectively). In statistical research, the correlations between salivary dysfunctions and absorbed dosages to the salivary glands were assessed by taking into account relevant characteristics. The impact on patients' quality of life was also looked at. The study was the first to investigate the risk of salivary dysfunctions (using both objective and subjective markers) in connection to organ (salivary glands) doses using individual dosimeter data and dose reconstructions. It was now able to recognize patients who were in risk thanks to the results. The results allowed doctors to identify patients who are at risk for salivary dysfunctions and to advise a more individualized follow-up and/or countermeasures to deleterious effects. In patients with thyroid carcinoma (DTC), radioiodine (RAI) administration produces negative effects, according to Pablo et al. (2016), although there is little information on how severe and long-lasting these effects are. Nearly 80% of the patients accepted the RAI. Early signs of RAI were periorbital edema, excessive crying, issues with the salivary glands, dry mouth, taste changes, and nausea. Regarding late symptoms, RAI patients had more frequent and severe dry mouth, periorbital edema, and pain and swelling in the salivary glands. The frequency or severity of side effects did not differ between low and high RAI dosages (50 versus 100 mCi). RAI-related symptoms are frequently still present six months after delivery, even at low doses. This information must be taken into account when deciding whether to administer RAI, particularly in low risk patients where the advantages are in question. After the start of treatment, responses to the initial survey were gathered on average 2.5 months later. The following RAI-related symptoms were more prevalent in patients who developed RAI: periorbital edema, excessive tearing, salivary gland swelling, pain, dry mouth, hypogeusia, impaired sense of smell, dysgeusia, and nausea. Additionally, compared to those who did not receive RAI treatment, those receiving it had significantly more severe symptoms. The incidence of excessive tears, painful and swollen salivary glands, dry mouth, and peculiar taste and smell was higher in patients who received low RAI dosages (50 mCi) (1850 MBq) than in those who did not. The frequency or severity of any of the RAI-related symptoms investigated did not change between low and high RAI dosages, though. Six months after starting treatment, symptoms such excessive tearing, discomfort in the salivary glands, and dry mouth worsened but became less severe. Even though side effects frequently diminish over a longer period of time, we must take into account this knowledge while evaluating RAI usage in low risk DTC patients due to the higher frequency and severity of symptoms during the first year after RAI treatment.

According to Liyan et al., (2016) adverse effects are possible with iodine-131 treatment for differentiated thyroid cancer (DTC) (2016). This study's objectives included reporting and analyzing symptoms that occurred after receiving IODINE-131 treatment while being hospitalized, as well as demonstrating pertinent medical action. For the removal of thyroid remains or the treatment of DTC metastases, doses of IODINE-131 ranging from 3.7 to 9.25 GBq (100–250 mCi) were used. The majority of the time, symptoms did not demand emergency medical attention, despite the fact that they were not unusual. Radioiodine-131 (I131) therapy for differentiated thyroid carcinoma (DTC) is generally a safe and efficient treatment, according to Domenico et al (2017). despite the possibility of some side effects. Though well-documented in studies of adults, these impacts on children have received less focus. Our objective was to describe radioactive I131's damaging effects on patients under the age of 18 both immediately and later. All patients who were 18 years of age and treated for DTC between the years of 1980 and 2015 underwent retrospective evaluations of both the early and late radioiodine side effects. Some of the initial side effects include nausea/emesis, radiation thyroiditis, sialadenitis, dry mouth, and transient bone marrow (BM) suppression. Examples of late effects include permanent BM suppression, lung fibrosis, secondary malignancies, and reproductive problems. In our division, 302 radioiodine treatments for DTC were administered to 155 children patients under the age of 18. There were 127 early issues total, including 44 episodes of vomiting and nausea, 30 cases of sialoadenitis, 24 cases of thyroiditis, 18 cases of dry mouth, and 11 occurrences of short BM suppression. Any treatment's initial side effects were correlated with the radioactivity dose employed. Twelve kids experienced the development of twenty issues, including four persistent BM suppression, five pulmonary fibrosis, four secondary malignancies, and five changes in fertility. With the exception of reproductive alterations, the quantity of therapies and overall activities of I131 were associated with late occurrences. In contrast to late effects, which are connected with the total amount of radioiodine delivered throughout all treatments, early unfavorable effects of I131, with the exception of fertility difficulties, are correlated with the amount of radioiodine supplied during each treatment. Salivary gland toxicity is a frequent but unappreciated adverse effect of high-dose radioiodine, according to a research by Hyer et al. (2006). (131I). This study investigated how frequently differentiated thyroid cancer patients experienced signs of salivary gland injury after receiving 131I treatment. 76 thyroid cancer patients who consistently treated themselves were included in this prospective study. At follow-up appointments and during hospital admission, the symptoms of salivary gland injury, dry mouth, pain, and swelling were assessed. Additionally, a retrospective analysis of patients recorded in our database who developed chronic salivary gland swelling after 131I ablation was carried out. Twenty people (26%) had salivary gland toxicity; 11 (15%) of these individuals had symptoms in the first 48 hours, and seven of these patients had symptoms that persisted for a full year. Nine more (12%) patients with persistent symptoms didn't start experiencing toxicity until three months after taking their medicine. At 12 months, 16 (21%) of the patients exhibited persisting toxicities, frequently characterized by xerostomia. After being exposed to 131I numerous times, more patients developed toxicity. After examining our thyroid cancer database, we identified an additional five patients who had chronic sialadenitis (chronic sialadenitis or pleomorphic adenoma) 20 months to 23 years after 131I. Pain, swelling, and dry mouth were typical side effects following 131I; but, for other persons, symptoms did not manifest for months or even years. If abnormalities with the salivary glands were detected sooner, the morbidity in these people might be reduced.

Cardiovascular Diseases and Radioactive Iodine Therapy

Kao et al. (2021). have investigated how radioactive iodine (RAI) affects thyroid cancer patients' long-term cardiovascular disease (CVD) morbidity and death. The study was conducted using information from the Taiwan National Health Insurance Database during the years of 2000 and 2015. Two groups of patients under 20 with thyroid cancer were created: RAI (thyroidectomy with RAI) and non-RAI (thyroidectomy only). The Kaplan-Meier method and the Cox proportional hazard regression model were both used in the analysis. The study had about 310 patients in total. The Kaplan-Meier analysis revealed that the cumulative risks of CVD (log-rank p = 0.72) and CVD-specific mortality (log-rank p = 0.62) were similar in both groups. The cumulative dosage >3.7 GBq showed a higher risk of CVD, according to Cox regression analysis of various RAI dosages (hazard ratio = 1.69, 95% confidence interval = 1.24-2.40, p 0.001). According to the results, patients with thyroid cancer did not have a higher incidence of CVD when they had RAI. Patients who get cumulative RAI doses beyond 3.7 GBq should be watched for CVD, nevertheless. Kyeong et al. (2020) confirmed, in 4,845 thyroid cancer patients treated with and without Iodine-131 therapy, the impact of radioactive iodine treatment on cardiovascular disease. 2,533 patients received a total median cumulative dosage of 103 mCi of radioactive iodine-131. The incidence of the primary CVD outcome in patients who got radioactive iodine-131 therapy and those who did not was 17.32 and 13.96 per 1,000 person-years, respectively, after multivariate adjustments for variable confounding variables. The risks of ischemic stroke, hemorrhagic stroke, and heart failure were comparable in patients who received RAI therapy compared to those who did not. There was no cumulative dose-dependent risk of cardiovascular disease associated with radioactive iodine-131 therapy for thyroid cancer. According to Adina et al. (2022) research, differentiated thyroid cancer patients who get high cumulative doses of iodine-131 experience a variety of cardiovascular side effects. by Cari et al. in 2019 When radioactive iodine-131 is used to treat hyperthyroidism, higher organ-absorbed doses find out to be modestly positively correlated with the chance of mortality from solid tumors, including breast cancer. To completely comprehend the risks and advantages of the main hyperthyroidism treatment options, however, more research is required. Kyeong et al., 2020 claim that there was no cumulative dose-dependent risk of cardiovascular disease associated with radioactive iodine-131 treatment for thyroid cancer.

Iodine therapy's effects on renal dysfunction and histology

Liang et al. (2022) examined the effects of high-activity iodine-131 therapy on the clinical metrics of renal function in patients with differentiated thyroid carcinoma. It was calculated using the Equation for Automated Analysis and Dietary Modification in Renal Disease. A total of 524 volunteers had iodine therapy as a way to examine the effects of elevated iodine activity. Three groups of patients were separated. A total of 5, 2, and 2 patients, in sub-categories 1, 2, and 3, respectively, showed signs of renal impairment following iodine-131 therapy. There were no statistically significant differences in the incidence of renal dysfunction in the third subcategory (p = 0.423). In DTC patients with normal renal function, regardless of gender, high-activity Iodine-131 therapy has remarkably little nephrotoxicity. High-activity Iodine-131 therapy, however, may hasten the loss of renal function in patients with renal failure. The damage to renal function, however, gets worse as iodine-131's total activity rises. Similar to this, Mester et alresearch .'s from the year 2021 discovered that radioiodine-131 is an essential treatment for those with differentiated thyroid carcinomas (DTC). However, some patients may develop early or late issues in the oral and maxillofacial regions. Iodine-131 is generally well tolerated and safe. This work used histological analysis, scanning electron microscopy (SEM), and atomic force microscopy to explore in-vitro the change of enamel and dentin after exposure to Iodine-131 (AFM). Iodine-131 irradiation is

performed using an in-vitro methodology that mimics the irradiation therapy process used on patients with DTCs. On average, 42 teeth were divided into 7 groups (n = 6) and subjected to radiation in the following ways: control, irradiation groups (3, 6, 12, 36, 48 h, 8 days). Histological changes were seen at 48 hours (multifocal and irregular spots on the enamel surface) and at 8 days (enamel surface with multiple, very deep, delimited cavities). SEM imaging shows that enamel deterioration increases with treatment time. The amount of dislodged hydroxyapatite debris is excessive, and the alterations penetrate deep into the enamel. After six hours, the enamel-dentine interface has very small gaps and after twelve hours, a very well-developed valley; after eight days, the microstructure of the interface has undergone significant change. According to AFM imaging, the protein connection between hydroxyapatite nanocrystals is impacted by iodine-131, leading to a loss of cohesion, which causes a significant rise in nanoparticle diameter after 6 hours. Both the enamel and the dentin appear to have changed between 12 and 48 hours, as well as eight days after starting treatment.

Change in White/Red Blood Cell, Chromosomal and DNA damages

Permanent BM suppression as a late consequence is unusual, but persistent modest reductions in platelet and/or white blood cell counts are prevalent in individuals who have undergone numerous radioactive iodine therapy treatments. Alberto *et al.* (2022) found that oxidative stress plays a significant role in the development of DNA damage caused by ionizing radiation. By analyzing the Comet assay, micronuclei, and chromosome abnormalities with multicolor fluorescence in situ hybridization, their research sought to determine if thyroid residual ablation with modest activity of 131I (1850 MBq) is linked with DNA damage (M-FISH). The research looked at 62 patients who had either thyroid hormone withdrawal or rhTSH preparation (THW). Stable and unstable genomic were examined which lead to changes in both groups prior to ^{131}I therapy as well as one week and three months following ^{131}I administration. Additionally, correlation found between the genetic damage and a number of factors, such as the level of radiation-induced oxidative stress, genetic polymorphisms of DNA-repair enzymes, and anti-oxidative stress. Comparable numbers of DNA breaks were detected using the Comet assay and the micronuclei test in both patient groups at various time points, but patients who had undergone THW preparation had a significantly higher number of stable chromosome aberrations (breaks and translocations) detected using M-FISH. Overall, increased retained body radioactivity and adverse gene polymorphism were linked to high chromosome damage. At any given time, all patients had high levels of free oxygen radicals and low levels of antioxidants. At 3 months, free oxygen radical levels were especially greater in patients treated with THW than in those prepared with rhTSH. In patients prepared with THW but not in patients prepared with rhTSH, an increase in stable chromosome aberrations relative to baseline is observed after administration of low doses of 131I. It is still unknown how these chromosomal changes may affect patients' clinical outcomes. Patients with differentiated thyroid carcinoma were investigated by Zhongying et al. (2021) to determine how 131I therapy affected their complete blood count (CBC) (DTC). In 542 patients with DTC, the total blood count was examined. The patients were separated into groups based on treatment cycles and cumulative dose, and then by sex and age. Analysis was done on how the various groups and subgroups responded to the 131I therapy. Patients were grouped by treatment cycles and doses, and it was discovered that the effects of 131I therapy on CBC varied by patient sex and age. While increases in hemoglobin (Hb) were more significant in men, the effect on white blood cell (WBC) counts maintained longer in women. In patients aged 45 to 54, the impact on red blood cell (RBC) levels was transient. Only those patients who were 55 years of age or older and had received three or four

therapy cycles had significantly lower monocyte numbers. CBC was significantly impacted by cumulative dosage in men. Only patients 55 years of age or older saw a change in platelet and monocyte counts after receiving ^{131}I therapy, in the high- and low-dose groups, Hb dramatically dropped and increased, respectively. During follow-up, no notable issues were noticed. While changes in RBC counts and Hb were more noticeable in men, ^{131}I treatment had a bigger effect on WBC levels in women. Depending on the sex and age of the patient, physicians should monitor various CBC indications during 131I therapy, but the hazards of a changed CBC are unlikely to outweigh the advantages of 131I. The present study's findings may alleviate the worries of many DTC patients and their families regarding how ^{131}I therapy affected their CBC levels. A researcher Carmela et al. (2021) examined the risk of primary breast cancer in patients receiving radioactive iodine-131 therapy for differentiated thyroid carcinoma. Out of 14 separate researches, almost 200,247 were evaluated. The study employed the PRISMA statement methodology. In patients with DTC who received radioactive iodine-131 treatment compared to those who did not receive radioactive iodine-131 treatment, the relative risk of primary breast cancer ranged from 0.45 to 2.55, the pooled relative risk was 0.83 (95% confidence interval, 0.70-0.99), and the heterogeneity was 71.5%. According to the results, DTC patients who receive RAI treatment do not have a higher chance of developing primary breast cancer than DTC patients who do not receive RAI treatment. According to these results, breast cancer risk is not raised by radioactive iodine-131 therapy.

Ovarian problems, hypospermia and Infertility

Permanent BM suppression as a late complication is uncommon, however people who have received several treatments with radioactive iodine therapy frequently experience persistent, mild declines in their platelet and/or white blood cell counts. According to Alberto et al. (2022), oxidative stress is a major factor in the progression of DNA damage brought on by ionizing radiation. Their study examined the Comet assay, micronuclei, and chromosome abnormalities in order to ascertain whether thyroid residual ablation with low activity of 131I (1850 MBq) is associated with DNA damage (M-FISH). The study included 62 patients who had rhTSH preparation or thyroid hormone withdrawal (THW). Prior to 131I therapy, as well as one week and three months later, both groups' stable and unstable genomes were analyzed, which resulted in modifications. The degree of radiation-induced oxidative stress, genetic polymorphisms of DNA-repair enzymes, and anti-oxidative stress were all found to be associated with the genetic damage. At various time points, comparable numbers of DNA breaks were found in both patient groups using the Comet assay and the micronuclei test, but M-FISH results showed that patients who had undergone THW preparation had a significantly higher number of stable chromosome aberrations (breaks and translocations). Overall, higher levels of chromosome damage were associated with increased retained body radioactivity and unfavorable gene polymorphism. All patients had high amounts of free oxygen radicals and low levels of antioxidants at any given period. At three months, patients receiving THW treatment had significantly higher free oxygen radical levels than those receiving rhTSH preparations. After the injection of low doses of 131I, an increase in stable chromosome aberrations relative to baseline is seen in individuals prepared with THW but not in patients prepared with rhTSH. How these chromosomal abnormalities might impact patients' clinical results is still a mystery. Zhongying et al. (2021) examined patients with differentiated thyroid cancer to see if 131I therapy influenced their complete blood count (CBC) (DTC). The complete blood count in 542 DTC patients was investigated. The patients were divided into groups first by sex and age, then by treatment cycles and cumulative dose. The responses of the various

groups and subgroups to the 131I therapy were examined. The effects of 131I therapy on CBC were shown to vary by patient sex and age when patients were classified according to treatment cycles and doses. Men experienced more significant increases in hemoglobin (Hb), whereas women experienced a longer-lasting effect on white blood cell counts. The effect on red blood cell (RBC) counts was very temporary in patients aged 45 to 54. Only patients who had completed three or four therapy cycles and were 55 years or older had significantly decreased monocyte counts. Cumulative dosage in men had a considerable effect on CBC. After undergoing 131I therapy, platelet and monocyte counts only changed in patients 55 years of age or older. Hb drastically changed in the high- and low-dose groups, respectively. Follow-up revealed no significant problems. Men were more likely to observe changes in RBC counts and Hb, whereas women were more likely to notice changes in WBC levels after receiving 131I treatment. During 131I therapy, doctors should keep an eye on a variety of CBC indicators depending on the patient's age and sex, but it's unlikely that the risks of an altered CBC will outweigh the benefits of 131I. The conclusions of the present study may allay the concerns of many DTC patients and their families regarding the impact of 131I therapy on their CBC levels. The risk of primary breast cancer in patients undergoing radioactive iodine-131 therapy for differentiated thyroid carcinoma was studied by researchers Carmela et al. in 2021. Nearly 200,247 studies from 14 different researches were analyzed. The PRISMA statement methodology was used in the study. The relative risk of primary breast cancer ranged from 0.45 to 2.55 in DTC patients who underwent radioactive iodine-131 treatment compared to those who did not, the pooled relative risk was 0.83 (95% confidence interval, 0.70-0.99), and the heterogeneity was 71.5%. The findings show that DTC patients who undergo RAI treatment do not increase their risk of getting primary breast cancer compared to DTC individuals who do not. These findings show that radioactive iodine-131 therapy does not increase the chance of developing breast cancer.

Leukopenia, thrombocytopenia and lymphopenia

According to Kaoru et al. (2021), RAI treatment for Graves' disease may suppress bone marrow, but this is questionable. RAI treatment for differentiated thyroid cancer is known to produce bone marrow suppression, which occurs roughly a month after treatment. The aim of this study was to evaluate the short- and long-term impacts of RAI therapy on bone marrow function in individuals with Graves disease. In this retrospective cohort research, patients with Graves' disease who received RAI therapy just once at Tokyo Women's Medical University between 2003 and 2019 were included. Blood cell counts were evaluated before starting RAI therapy to values at 1, 2, 4, 12, 24, 48, and 240 weeks afterwards. White blood cell (WBC) count and leukopenia variations after 1 week of RAI treatment were also examined using baseline patient data. The signing included up to 48 patients. One week after starting RAI treatment, six patients had leukopenia, and the total WBC count significantly decreased at that time. Even so, after two weeks, there was little difference in the outcomes. The red blood cell count did not significantly alter, nor did the platelet count. Additionally, regardless of other factors, the baseline neutrophil count was highly inversely linked with changes in WBC count or the onset of leukopenia 1 week after the RAI therapy. These results showed that WBC levels briefly fell following RAI treatment one week later, but later rebounded. Following multiple dosage treatment, significantly elevated levels of lymphopenia and thrombocytopenia were observed. The prevalence of anemia, thrombocytopenia, leukopenia, neutropenia, and lymphopenia was higher in patients with advanced-stage disease. Individuals with advanced cancer received higher doses and more frequent doses than those with early-stage cancer. It was shown that hematologic malignancies were more common than they were in the overall

population. We advise treating cytopenia more seriously in persons above the age of 60. The main cause of lower platelets after RAI therapy is male gender. The most important clinical predictor for cytopenia is advanced illness stage, which is linked to the combined effects of applied high dose activity, various dosing regimens.

Leukemia and Secondary malignancy (cancers)

It has been demonstrated that patients with differentiated thyroid carcinoma getting radioactive iodine therapy have a slightly increased chance of developing leukemia and subsequent malignancies. Leukemia is a rare side effect of iodine-131 treatment, and it usually appears after a high cumulative dose of more than 18.5-22.2 GBq (500-600 mCi). Despite this, there have been cases of this malignancy occurring even with iodine-131 doses as low as 5.5 GBq (150 mCi) and 11.1 GBq (300 mCi) in other studies. It is advised to consider delaying treatments by a year because it is believed to reduce the risk of leukemia. On the other hand, if there is convincing evidence that the patient's condition is worsening (an increase even if it has been less than three months after the last therapy as a result of changes in thyroglobulin or the size of the metastases), the patient should start receiving fresh medication. Many patients have received more than 74 GBq (2 Ci) of iodine-131 since, in the opinion of some doctors, the total radioiodine dose required to treat severe metastatic cancer has no established top limit. Along with leukemia, the prevalence of solid second malignant neoplasms (SMN) may increase following radioactive iodine therapy. In another study, patients with radioiodine-treated differentiated thyroid carcinoma who received cumulative iodine-131 doses greater than 40 GBq (1.08 Ci) had an increased probability of developing solid second malignancy. Another article claims that following treatment with iodine-131, the prevalence of subsequent malignancies—most notably leukemia and bladder cancer—has increased. While bladder cancer and leukemia were not present at total activity of less than 37 GBq (1 Ci) iodine-131, these side effects were observed with high radiation doses. In the study of 1771 differentiated thyroid cancer patients, about 13 of the 80 patients who developed SMNs went on to develop colorectal cancer, which was associated with the accumulation of iodine-131 in the colon lumen. Female differentiated thyroid carcinoma patients receiving radioactive iodine therapy appeared to be more susceptible to developing a nonsynchronous second primary tumor than the general population. However, according to some research, people with differentiated thyroid cancer do not significantly increase their risk of getting a second primary tumor after receiving radioactive iodine therapy compared to the general population. Iodine-131 should only be administered when benefits are predicted, and the bare minimum therapeutic activity should be offered, according to studies that usually suggest people exposed to high cumulative doses of the radioactive isotope are more likely to acquire cancer. It should be noted that uncertainties exist as to whether the development of these malignancies following thyroid cancer is the result of difficulties caused by radioactive iodine therapy, a coincidence, or a heightened risk of secondary malignancies brought on by the malignant process itself. Radioactive iodine (RAI) using I131 has a well-established role in the treatment of differentiated thyroid carcinoma, particularly papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. On the other hand, concerns have been expressed about its potential to induce cancer. This paper was created to raise attention to the CML, which has been the subject of several reports. All articles from the 1960s to the present that discussed CML after RAI treatments were searched in Google Scholar and PubMed. Different search terms were used. Ten articles detailing twelve cases were discovered. We found that the bulk of the reports were for men under the age of 60. I131 was administered at doses between 30 and 850 millicuries (mCi), with a mean dose of 331 mCi. The onset of t-CML also occurred in the

first ten years (9/12), typically four to seven years after exposure therapy. A few studies following RAI therapy showed a statistically significant rise in leukemia incidence; other research showed a relative risk of 2.5 for I131 vs. no I131. These studies demonstrated a linear relationship between cumulative I131 dose and the probability of developing leukemia; doses greater than 100 mCi were associated with a higher risk of later leukemia development, and the majority of leukemia cases manifested during the first ten years of exposure.

According to Shim et al. in 2021 to examine the incidence and mortality of cancer specific to a given place and to evaluate the radiation dose-response relationship following RAI treatment for hyperthyroidism, it is still unclear whether radioactive iodine (RAI) therapy for hyperthyroidism can increase cancer risk. The Medline, Cochrane Library, and Embase electronic databases were screened up to October 2020 using the Medical Subject Headings phrases and text keywords. The following criteria were employed for study inclusion: including at least 1 comparison group made up of individuals who were not exposed to RAI treatment; (1) include patients treated for hyperthyroidism with RAI and followed until cancer diagnosis or death (such as the general public or patients treated for hyperthyroidism with thyroidectomy or antithyroid drugs); or (3) Including effect size measures (i. e, standardized incidence ratio [SIR], risk ratio [RR], hazard ratio [HR], or standard mortality ratio [SMR]). Two separate researchers gathered the information in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE). The overall quality assessment complied with the guidelines of the United Nations Scientific Committee on the Effects of Atomic Radiation. The random-effects meta-analysis, the SIR and SMRs, and the RRs and HRs were all pooled. Cancer incidence and mortality are dependent on the amount of RAI given activity as well as whether or not a patient receives RAI therapy. Based on data from 12 studies with 479 452 participants, the overall pooled cancer incidence ratio was 1.02 (95% CI, 0.95-1.09) and the pooled cancer mortality ratio was 0.98 (95% CI, 0.92-1.04) for exposure vs. non-exposure to RAI therapy. There were no statistically significant increases in risk for any specific malignancies, with the exception of thyroid cancer incidence (SIR, 1.86; 95% CI, 1.19-2.92) and mortality (SMR, 2.22; 95% CI, 1.37-3.59). However, the inability to account for confounding by indication and other types of bias constituted a significant disadvantage of studies contrasting RAI exposure with nonexposure. A substantial correlation between RAI and breast and solid cancer mortality was shown by dose-response analysis based on two studies (mortality due to breast cancer per 370 MBq: 1.35; P =.03; mortality owing to solid cancer per 370 MBq: 1.14; P =.01). The total pooled cancer risk following exposure to RAI therapy compared to non-exposure was not statistically significant, despite the linear dose-response connection between RAI therapy and solid cancer mortality in this meta-analysis. The chances of radiation-induced cancer following RAI therapy for hyperthyroidism are negligible, and they may only be detectable in observational studies at higher administered dosage levels, per these findings. In order to attain an intrathyroidal activity absorbed of between 110 and 350 MBq for the 24-hour radioactive iodine-131 absorption value, Je'nine, 2019, claims that the computation of an administered activity was essential. People with DTC who get RAI do not have a higher risk of developing primary breast cancer than those who do not, claim Carmela et al. in their 2021 study. These findings show that radioactive iodine-131 therapy does not increase the chance of developing breast cancer.

Radioactive iodine-131-induced lung fibrosis

Patients with differentiated thyroid carcinoma who received recurrent radioiodine therapy over short intervals of time were at risk for developing pulmonary fibrosis. The presence of pulmonary dysfunction is not immediately apparent, though. Fibroses were associated with radioiodine as a

result of certain children receiving bleomycin. It is difficult to adequately distinguish between restrictive lung illness brought on by differentiated thyroid carcinoma and radiation-induced consequences. The only known risk factors for pulmonary fibrosis appear to have been high lung uptake of iodine-131 and extremely advanced lung illness. The little pulmonary alveolar capillary membrane injury associated with radioactive iodine therapy for differentiated thyroid cancer lung metastases was predicted to occur, but is shown to have occurred due to the normal pulmonary clearance of 99mTc-DTPA aerosols. If pulmonary fibrosis is suspected, the appropriate periodic pulmonary function testing and consultation should be performed. The possibility of ongoing radioactive iodine therapy for metastatic disease may be made possible by the presence of pulmonary fibrosis. To treat pulmonary micro metastases, however, in accordance with ATA guidelines, radioactive iodine therapy should be repeated every 6 to 12 months as long as the sickness is concentrated and responds clinically, as this subgroup has the highest rates of complete remission. In order to avoid radiation pneumonitis and eventual pulmonary fibrosis, dosimetry with a limit of 2.96 GBq (80 mCi) whole-body retention at 48 h and 200 cGy to the red BM should be taken into consideration in patients with diffuse iodine-131 pulmonary metastases.

Persistent Dry eye and sialadenitis

Some patients may continue to have lacrimal gland dysfunction, which can lead to chronic dry eyes. As the lacrimal sac and nasolacrimal duct express sodium iodide symporter, which transports radioiodine in the targeted tissues, and as there is evidence that iodine-131 is released in the tears, dry eye can result from lacrimal gland injury after treatment with iodine-131. Sialadenitis, which was extensively described in this study, is one of the early complications of radioactive iodine therapy that is typically temporary; nevertheless, it can develop chronic and cause xerostomia, which has been reported to occur in anywhere between 4.4 and 20% of cases in various studies.

4. Less frequent consequences of high-dose iodine-131 therapy

After radioactive iodine therapy for thyroid cancer, both permanent and temporary hyperparathyroidism and the ensuing hypocalcaemia have been documented. Radioiodine therapy for radioactive iodine treatment of metastases may cause cerebral edema. If there are one or more foci of a brain tumor, neurosurgical resection or stereotactic radio surgery is recommended and may improve survival. The cornerstones of therapy historically have been surgical excision and external beam radiotherapy, and there are few studies demonstrating radioactive iodine therapy effectiveness. To reduce the consequences of a probable TSH-induced increase in tumor size and the following inflammatory effects of radioactive iodine therapy, prior external beam radiation and concurrent glucocorticoid therapy are strongly advised. Secondary cord compressive symptoms and vertebral metastatic lesions are infrequent but dangerous, requiring radioactive iodine therapy. After radioactive iodine therapy, corticosteroids should be given for a few days. If the bones are metastasis sites, it is critical that the vertebral column and weight-bearing regions be evaluated on a regular basis. If a patient has a tumor that has spread to the spinal cords epidural space, the bone scan enables an early diagnosis and the implementation of suitable preventive actions. With the exception of cases where there is bone instability, radiation appears to be as effective as decompressive surgery for neurologic problems including spinal cord compression or nerve root compression. A rare side effect of thyroid gland iodine-131 ablation is vocal cord paralysis caused by damage to the recurrent laryngeal nerve. When there is already some kind of lesion in the recurrent laryngeal nerves, this consequence happens more commonly. After iodine ablation, a

patient whose 5.5 GBq (150 mCi) iodine-131 capsule unexpectedly lodged in the mid cervical esophagus for around 2.5 hours on the day of therapy was diagnosed with esophageal stricture. This issue might be brought on by the radiation dose that the proximal esophagus received as a result. According to a research on kidney and liver function, radioactive iodine therapy decreased absorptive and secretary hepatocytic function as well as overall renal function. The changes were mild, consistent, and connected to both a radiation component and hypothyroidism. Cystitis is a rarely described side effect of radioiodine. As the kidneys and bladder serve as the primary organs for iodine-131 clearance, an accumulation of radioiodine in the urine may result in irritation of this organ. To lessen the radiation exposure to the bladder, patients are instructed to urinate once every 1-2 hours for several days. The renal clearance of iodine-131 will be accelerated by a diuretic. With a smaller cumulative dose of radioiodine, adverse radioactive therapy effects are less frequent. Although it has been argued that utilizing a low dosage of radioiodine for ablation such as 1110 MBq (30 mCi), rather than a high dose of 3700 MBq (100 mCi) can reduces the success rate of ablation and necessitates more treatments, some studies back the use of low-dose radioactive therapy. Especially in the low to intermediate risk group of differentiated thyroid cancer patients, with equivalent efficacy, were resulting in a lower cumulative dose and fewer problems.

4.1. Changes in Taste and Smell

While emesis is sporadic with RAI therapy, nausea is the most common gastrointestinal side effect. Studies show that between 50% and 67% of patients feel nausea, which may begin two hours after taking a drug and extend for up to two days. One study found a relationship between a high dose of 131I (100 mCi) and more nausea than a low dose (30 mCi). 37 It was found in a prospective study that 50% of the patients who received 150 mCi of 131I felt sick. Antiemetics can be administered intravenously to patients with severe symptoms to halt emesis and facilitate oral hydration. Acute radiation sickness, which includes emesis, headaches, nausea, and tiredness, is very rare when radiation exposure to the blood is kept to levels of less than 200 mCi and 200 cGy (Lassmann et al., 2010). Although there hasn't been any prospective research on preventive antinausea drugs, experts assert that they work whether they are given prior to, during, or after RAI delivery. Moderate nausea may be treated with a highly effective antiemetic, such as ondansetron, 8 mg by mouth every 8 hours for two doses, then 8 mg by mouth every 12 hours. Severe nausea with some emesis can be treated with ondansetron, 8 mg or 0.15 mg/kg intravenously twice daily, as well as fluid hydration to enhance the renal clearance of the medication. Dysgeusia, or altered taste, is thought to be caused by radiation from the RAI that enters the saliva and kills the lingual taste buds (Mendoza et al., 2004). In studies comparing low and high doses of 131I (30 vs. 100 mCi), a larger dose was associated with a higher prevalence of taste disturbance. Nevertheless, there is little data to back up this common clinical observation. The taste loss and any accompanying metallic or chemical taste often fade away between 4 to 8 weeks. No incidents have been reported.

4.2. Thyroid Cancer Patients' experience during radioactive iodine-131 therapy

Jeong and Shin-Young (2022) have lucidly described the nature of thyroid cancer patients' experiences during radioactive iodine treatment after complete thyroidectomy by a thorough examination in Korea. 22 patients took part in their investigation. The study employed the phenomenological analysis technique suggested by Colaizzi. Three groups of participants, six topic clusters, and thirteen study-related themes were created. The three groups were found to have

experienced the following things: a broken life, loneliness in a throng, and a shift in positive ideals. The six theme clusters were identified as death anxiety, social isolation, self-struggle, life support, an active attitude toward life, and imperfect being. Physical and psychological struggles were the subjects that came up most frequently. Family culture and values were mentioned in four of the thirteen themes. The study detailed the experiences of Korean thyroid cancer patients. The study found that the physical and psychological symptoms of patients, as well as their unpleasant experiences, were significantly reduced by medical nurse interventions. Family support systems must be built, nevertheless. The radiation dose absorbed during iodine therapy was primarily determined by radioiodine avidity and the total amount of decay, according to research by Joachim et al. (2022), whereas small target size and spheroid eccentric received significantly lower absorbed doses from the same amount of radioiodine. The report made no mention of the potential effects on radiological health. Jeong & Shin-study Young's from 2022 on thyroid cancer patients in Korea detailed similar experiences. Medical nurse treatments, particularly those for physical and psychological symptoms, are critical for lowering patients' unpleasant experiences, according to the research. Family support systems must be built, nevertheless. The 48-hour retention method was proven by Touqir et al., 2022, to have overstated the maximum tolerated activity of iodine-131. According to Cheng et al. 2022, impairment can happen for any duration longer than six months. Doctors should make acceptable preparations for their patients within a time frame of no more than six months, based on the resources at their disposal.

5. Conclusion

Based on the administered activity, radioactive iodine therapy for differentiated thyroid cancer and other thyroid illnesses typically results in sporadic severe side effects and very minor short-term harm. The risks and benefits of radioactive iodine therapy must be balanced for each individual patient and should continue to be the most important aspect of patient management given the clearly demonstrated benefits of this treatment modality, including increased survival, decreased recurrence rate, and effective palliative outcomes. The short- and long-term adverse effects of RAI therapy can interfere with and disturb patients' lifestyles, according to a review of the acute and long-term side effects. Clinicians should exercise greater caution when giving 131I to all patients, but particularly to low-risk individuals who might not even need it, as well as to patients with non-iodine-avid diseases or bulky illnesses who are not likely to benefit from 131I therapy. Low risk patients who require 131I residual ablation should have the radioisotope in the smallest doses possible while staying well-hydrated. They should also get rhTSH stimulation, which due to faster renal clearance than hypothyroidism decreases whole-body radiation. Practitioners must also be mindful of the higher danger brought on by repeated 131I treatments for progressing or fatal conditions with excessive iodine intake. Recurrent sialadenitis, xerostomia, and an elevated risk of second primary malignancies are all part of this risk. Formal dosimetry studies should be taken into account in individuals with very low lesional uptake to prevent excessive whole-body radiation exposure and associated lung and bone marrow problems. These acute and long-term effects of RAI should be thoroughly explored in patients with non-life-threatening, non-progressive, small-volume residual malignant disease. These patients may not be justified in experiencing the short- and long-term side effects of RAI therapy due to the low likelihood that they will pass away from thyroid disease. It will be possible to administer a therapeutic radiation dose to a tumor with a very high RAI absorption using the results of this systematic review.

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