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RADIATION INDUCED HYPOTHYROIDISM AN UNDERESTIMATED ENTITY-OBSERVATIONAL STUDY

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ABSTRACT

This observational study highlights the specific symptoms as well as the aetiology related to radiation induced hypothyroidism after radiotherapy thereby it facilitates the prevention of radiation induced hypothyroidism and reduce its incidence. Hypothyroidism is a known complication after radiotherapy of regional cancers and radio iodine ablation of thyroid gland. Where the higher the radiation dose is proportional to the incidence of hypothyroidism. The incidence of hypothyroidism gradually increases with time so regular follow up is required. Intensity modulated radiotherapy should limit the dose to the thyroid, which would reduce the incidence of hypothyroidism. The incidence of radiation induced hypothyroidism in head and neck cancer is also related to the radiation dose, radiotherapy technique, thyroid volume, female sex, and age. As the incidence of cancers are increasing we need larger and long term follow up studies for better understanding of radiation induced hypothyroidism thereby timely action.

Introduction.

One of the imputable side effects of therapeutic medical radiation exposure [external beam radiotherapy (EBRT) and radioactive iodine ablation therapy (RAI)], is hypothyroidism (HT). Other radiation exposures such as CT scans of the head and neck region may expose the thyroid to 10–20 mGy in adults, and 30–50 mGy in children and in both paediatric and adult patients the use of iodinated contrast media (I-131) may increase doses by up to 35%. However, these doses are these are 3-4-fold lower than EBRT or RAI. In this article we focussed our discussion mainly on external beam radiotherapy induced hypothyroidism (RIHT).

Materials and observations.

This observational study was done at Saptagiri institute of medical sciences Bangalore, a total of 15 patients of radiation induced hypothyroidism secondary to various cancers were studied. Though RIHT can cause both primary as well as secondary hypothyroidism, our case series had only primary hypothyroidism. The age group ranged from 24years to 70 years, Female to male ratio was 11 to 4. Most of these patients had come for the follow up management of hypothyroidism, so a detailed history is important for the diagnosis of this entity. RIHT can be Overt or Subclinical hypothyroidism, with time those with subclinical hypothyroidism progress to overt hypothyroidism. Though onset of RIHT occurs within 5 years after receiving of radiation it varies from months to years for its development, so annual thyroid function should be assessed in at risk individuals. The aetiology of RIHT includes vascular damage, parenchymal damage & autoimmune reaction. Majority of these patients had a presenting complaint of dysphagia and swelling of face. On examination they had no goitre, darkening of neck because of past radiation. Unlike autoimmune hypothyroidism where thyroid function varies with time most of the RIHT once sets in, had a stable thyroid function with appropriate dosage of levothyroxine. Owing to their dysphagia, they prefer to have small sized tablets or they take levothyroxine after dissolving it in water.

Discussion.

External Beam Radiotherapy.

HT may occur during post-curative treatment of head and neck cancers (HNC) which include otolaryngological cancer, oral and maxillofacial cancer, and neck cancer and central nervous system tumours. Globally, it has been reported that approximately 19% to 53% of the patients with HNC develop hypothyroidism after radiotherapy. [1,2] In India the incidence of radiation induced hypothyroidism (RIHT) lies between 17% to 55 primarily clinical hypothyroidism, and subclinical was reported in 22% to 40% patients undergoing radiotherapy for HNC.[3,4,5] The risk of RIHT was found to be greater in those with carcinoma larynx followed by hypopharynx compared to other sites. The increased risk is attributed to RT totally encircling the neck, including thyroid region, thus exposing the gland to high dose. RIHT leads to additional morbidity and subsequent decline in quality of life in patients with HNC. HNCs are the second most common cancers in the Indian population with 30-40% of all cancers being HNCs while CNS tumours account for 2% of all malignancies. These cancers require routine radiotherapy, and the pituitary or thyroid is involved in the radiation field, ensuing in a high frequency of hypothyroidism in India as well as globally. ,[7,8]

The common clinical symptoms of HT are fatigue, drowsiness, intolerance to cold, weight gain, constipation, aural changes, and dry skin with no conspicuous symptoms in mild or subclinical HT. Severe cases are associated with an increased incidence of cardiovascular diseases (CVD) with increased risk of fatal outcomes depending age, gender, and duration of untreated diseases.

The RIHT may occur due to thyroid cell fibrosis, vascular proliferation, autoimmune response and thyroid atrophy. Elevated expression of anti-thyroid peroxidase and ant thyroglobulin antibodies in patient's post-RT indicate that an immune response could be an underlying mechanism of RIHT. [9]

The survival of patients with malignant diseases has largely improved in recent years. It is therefore essential to provide them a good quality of life, which involves reduction in post-treatment burden of adverse effects like RIHT. This suggests that it is vital to understand the factors associated with RIHT.

Clinical Elements Associated with RIHT incidence

Dose of RT and Thyroid gland Volume

Decades ago, the predicted 5-year risk of thyroid dysfunction was 5% with a 45-Gy dose and 50% with an 80-Gy dose. Several studies found that the incidence of hypothyroidism increased with the decrease in thyroid volume and the increase in the mean radiation dose; nevertheless, the optimal threshold dose for the thyroid remained undetermined. Some thyroid dosimetric studies with three-dimensional conformal radiation therapy (3D-CRT) in the last decade did suggest mean dose of ≤ 30-50 Gy as protective of thyroid and ≥ 50% as an independent predictor of HT.[10,11,12] Studies with intensity modulated radiotherapy (IMRT) stated that the relative risk of hypothyroidism for patients with D mean > 45 Gy was nearly five-fold greater than that for patients receiving a lower dose. [13] A recent study with IMRT stated that V25 > 95%, V35 > 90%, and V45 > 75% are risk factors for HT and need to be averted. VSx (volume of thyroid spared X Gy) or higher VSx parameters may be more appropriate than Vx (percent of thyroid receiving at least X Gy) parameters to guess the incidence of RIHT. This is due to the fact that the thyroid is a parallel organ, and the proportion of thyroid follicular cells unexposed to high dose radiation is a significant element in retaining its capacity to synthesize and secrete hormones necessary for preserving usual

metabolism. Several studies have suggested that the risk of HT is directly linked to the volume of the gland. Studies have found that for every cm3 reduction of the gland the risk of HT increases by 5-7%.[15, 16] A dosimetric study found that thyroid gland volume threshold of 8cm3 could be useful. For these volumes setting the thyroid dose to D3CC < 45Gy could minimize the incidence of HT, while for smaller thyroid volumes more stringent limits have been proposed.[17]

Pituitary Gland

The RT field of the HNCs also includes hypothalamus and pituitary. Studies have shown that patients whose thyroid and pituitary were exposed to high doses had highest incidence (83.3%) of HT followed by those whose thyroid was exposed to high doses confirming the susceptibility of thyroid to radiation damage. Though central HT risk is seldom in question, it should not be overlooked.

RT type

There have been considerable advances in RT technology with IMRT offering non-affected parts better protection than 3D-CRT. However, the outcomes in studies comparing these two methods have been ambiguous with some in favour of either and vice-versa.12, Therefore, limited thyroid radiation dose use to restrict unwarranted exposure and thus reduce the incidence of HT has been advocated.

Adjunctive cancer Treatment modalities

The correlation of chemotherapy and surgery in increasing the risk for RIHT is obscure due to limited evidence.

Gender and Age

Similarly, though females have smaller volume of thyroid gland, there is no robust data to suggest that they are at increased risk of RIHT. However, most researchers believe that female are at increased risk and should be periodically monitored. While most studies suggest an association of HT with age with greater susceptibility to HT in those < 18 years of age, some disagree. Some studies suggested 0.9-4% decrease with every increase in age. Studies in elderly with HNC found that RT in comparison to surgery alone doubled the risk of HT and risk enduring for almost a decade post-RT. Therefore, based on currently available evidence, it could be argued that the thyroid profile should be periodically monitored in younger and older patient groups for longer durations.[19, 21]

Stage of malignancy

The extent of RT field depends on the tumour-node-metastases (TNM) stage of the tumours, and hypothetically may affect hypothalamus and pituitary with ensuing central HT. However, evidence related to the tumour stage and RIHT is ambivalent. The incidence of HT has been found to be significantly higher positive lymph nodes since these increase the tumour mass and thus magnitude of irradiation required.12 Therefore patients with advanced node involvement should be followed for thyroid profile investigations post RT.

Factors increasing risk of RIHT
RT factors
1. Higher Thyroid and Pitutary dose volume
2. Radiotherapy technique
Clinical factors
1. Female gender
2. Young age
3. Advanced clinical stage of cancer

Radioiodine (I-131) (RAI) Therapy.

Another medical irradiation therapy involves use of radioactive iodine (I-131) for the treatment of Graves' disease which generally results in permanent HT within 3-6 months of therapy. Within one year nearly 33% and by 10- and 25-year post RAI, 59%-82% developed HT.[22]While in non-immunogenic hyperthyroidism (nodules, goitre) RAI results in lower incidence of RIHT 4% after 1 year, 15% after 10 years, and 32% after 25 years. Unlike RIHT for HNC treatment in which females were at higher risk, women treated with I-131 were less likely to develop HT. Further the usage of antithyroid drug post RAI was significantly associated with a HT. Patients treated with I-131 should be monitored for clinical and biochemical evidence of hypothyroidism.

External versus Internal RT: Risk of RIHT.

Lower thyroid doses of EBRT induce HT with comparable frequency as do 4-5-fold higher doses of "internal radiotherapy" with I-131. The reason being cumulative direct and indirect effect of RT on thyroid and pituitary respectively. Further, ß-particles of I-131 which enter the thyroid cells have a short range of only 0.4 mm in tissue.[23] Therefore, vasculature supplying the thyroid remain unaffected. On the contrary, in EBRT, structures adjacent to the thyroid are not spared.[23]

Conclusion.

Though current evidence does not robustly define the high-risk groups for RIHT, monitoring and treatment post EBRT and RAI is imperative. Moreover, further data needs to be generated to resolve certain questions regarding impact of RT on foetus, mechanism of RIHT and differences in impact of EBRT and RAI on HT.

This information is pertinent to improve the quality of life in RIHT by early detection and timely treatment.

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