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FREQUENCY OF RADIATION-INDUCED HYPOTHYROIDISM IN HODGKIN LYMPHOMA

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Abstract

Objective: *The study aimed to calculate the rate of radiation-induced hypothyroidism (RIHT) and its connection with various patient and treatment factors in the case of Hodgkin lymphoma (HL) patients undergoing radiotherapy.*
Study Design: *Case series study.*
Place and Duration of the Study: *Department of Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from May 2025 till 15 July 2025.*
Methodology: *Continuous non-probability sampling was utilized to enroll one hundred HL patients of both sexes and up to 45 years who were receiving external beam radiotherapy. Demographic and treatment variables like age, duration of the disease, radiation dose, and treatment duration were recorded. Serum thyroid-stimulating hormone (TSH) levels were measured three months after the radiotherapy. The data were then analyzed using SPSS version 27; the chi-square test was done for evaluators, with p<0.05 set as significant.*
Results: *Out of 100 patients (57% males, 43% females; mean age 32.25 ± 8.27 years), RIHT was present in 70 (70%) cases. There were significantly older hypothyroid patients (33.33 ± 8.05 vs 29.73 ± 8.36 years; p=0.050), longer disease duration (22.41 ± 9.67 vs 17.50 ± 10.64 months; p=0.034), higher radiation dose (36.84 ± 7.11 vs 32.23 ± 7.67 Gy; p=0.005), and longer treatment duration (40.04 ± 13.19 vs 30.03 ± 11.08 days; p=0.001). Gender and stage of disease showed no significant association with RIHT.*
Conclusion: *Radiation therapy caused hypothyroidism due to radiation in 70% of patients with Hodgkin lymphoma. Its occurrence was notably greater in patients above the age of 30 years with long disease duration, high radiation doses, and prolonged treatment periods.*

Introductions:

Radiation-induced hypothyroidism (RIHT) is one of the most frequent and serious complications that develop over time in patients who have been treated for Hodgkin lymphoma (HL), and it is mainly because of the radioactive exposure of the thyroid gland during the therapy. The thyroid gland gets destroyed from radiation, and therefore the patient needs to be treated with thyroid hormones, which can be diagnosed by high TSH levels and/or low thyroid hormones. The worldwide incidence of RIHT in HL patients is estimated to be between 20% and 50% depending on various factors, including the dose, the technique, and the time of follow-up(1). The treatment of HL usually involves lower doses of radiation (20–30 Gy) compared to other malignant tumors in the head and neck region; nevertheless, the rates of thyroid dysfunction remain considerable(2). The modern radiotherapy technique, such as intensity-modulated radiation therapy (IMRT), may differ in the risk compared to 3-dimensional conformal radiation therapy (3D-CRT), and in some cases, the former may have a higher rate of hypothyroidism because of the new way of dose distribution(3).

In the region, the evidence from Pakistan and other countries with low to middle incomes suggests that RIHT is a significant problem among survivors of HL, though local incidence rates are less frequently reported. A study in Pakistan showed that the frequency of hypothyroidism in children treated with radiation for HL and other head and neck cancers was about 13.6%(4). Besides, international studies have recognized thyroid volume, radiation dose-volume parameters, and the use of thyroid avoidance structures as significant predictors of RIHT during radiation planning aimed at risk mitigation(5). To illustrate, any dose that results in the exposure of more than 25 Gy to the thyroid area is associated with a high risk. These dosimetric insights are pivotal for the optimization of therapies that can simultaneously achieve effective HL treatment and lessen endocrine toxicity(6).

The justification for the study of RIHT frequency in HL patients is twofold: through the reduction of endocrine complications that are not unavoidable, the quality of survivorship will be improved, and also the radiation planning will be tailored to the patient demographics and the healthcare capacities of the region. With HL survival rates getting better, knowing the international and local figures supports the making of clinical decisions based on evidence, monitoring of the patient's health over a long period of time, and strategies that are essential for patient care.

Methodology:

This descriptive case series was performed at the Department of Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from May 2025 till 15 July 2025 following the approval of the institutional ethical review committee.

Inclusion criteria: The study enrolled both males and females with a diagnosis of Hodgkin lymphoma confirmed by histopathology and immunohistochemistry, and receiving external beam radiotherapy, aged 45 years or less.

Exclusion criteria: The patients who died before the follow-up, those who emigrated or were not reachable for any other reason, and those who were considered clinically unfit for assessment were excluded. After thoroughly explaining to the participants the purpose of the study, written informed consent was obtained from everyone taking part.

100 patients were recruited through non-probability sampling, which was consecutive. The WHO sample size calculator was used to determine the sample size by assuming a 95% confidence level, 30% anticipated proportion, and a 9% margin of error(7).

Demographic data, the length of the illness, the level at which the disease was diagnosed, the radiation dose, and the length of the radiation treatment were documented in a pre-made form. The protocols of the hospital were followed for radiation treatment of all patients, and they were monitored for three months after the treatment was done. Blood samples were taken and analyzed to measure serum levels of thyroid-stimulating hormone (TSH) in the hospital laboratory, which showed whether or not the patients developed hypothyroidism.

The data were processed and interpreted with the help of the Statistical Package for the Social Sciences SPSS version 27.0. For quantitative variables like age, disease duration, radiotherapy dose, and treatment duration, mean ± standard deviation was used for presentation, whereas frequencies and percentages were used for qualitative variables like gender, disease stage, and radiation-induced hypothyroidism. The poststratification chi-square test was performed to check the impact of age, gender, disease duration, disease stage, and radiation dose as modifiers on the occurrence of hypothyroidism, with a p-value of less than 0.05 being considered statistically significant.

Results:

The average age of the patient group that participated in the research was 32.25 ± 8.27 years; the ages were between 18 and 45 years. The period of the disease was from 3 to 35 months, with an average of 20.94 ± 10.18 months. The average dose of radiation therapy given was 35.46 ± 7.55 Gy, with a minimum of 9.1 Gy and a maximum of 52.1 Gy. The period of radiation treatment varied from 15 to 59 days, and the average time period was 37.04 ± 13.36 days.

Variable	Minimum	Maximum	Mean	SD
Age (years)	18	45	32.25	8.27
Duration of Disease (months)	3	35	20.94	10.18
Radiotherapy Dose (Gy)	9.1	52.1	35.46	7.55
Duration of Radiotherapy (days)	15	59	37.04	13.36

From the total of 100 patients taking part in the research, there were 43 (43.0%) females and 57 (57.0%) males. When it comes to the diagnosis stage, 18 (18.0%) were found to have Stage I, 31 (31.0%) Stage II, 23 (23.0%) Stage III, and 28 (28.0%) Stage IV cancer. In all, radiation-induced hypothyroidism was seen in 70 (70.0%) patients, whereas 30 (30.0%) patients remained euthyroid post-radiotherapy.

Variable	Frequency (n)	Percentage (%)
Gender		
Female	43	43.0
Male	57	57.0
Stage at Diagnosis		
Stage I	18	18.0
Stage II	31	31.0
Stage III	23	23.0
Stage IV	28	28.0
Radiation-Induced Hypothyroidism		
Yes	70	70.0
No	30	30.0

The age of the patients who experienced radiation-induced hypothyroidism was higher on average (33.33 ± 8.05 years) than that of the patients without hypothyroidism (29.73 ± 8.36 years), and the difference was significant from the statistical point of view (p = 0.050). The mean time of disease was also longer for patients with hypothyroidism (22.41 ± 9.67 months) than for non-hypothyroid patients (17.50 ± 10.64 months; p = 0.034). The mean radiation therapy dose given was also substantially greater among the hypothyroid patients (36.84 ± 7.11 Gy) than the non-hypothyroid (32.23 ± 7.67 Gy; p = 0.005). Additionally, the time of radiation treatment was strikingly extended for those developing hypothyroidism (40.04 ± 13.19 days) as compared to the non-hypothyroid (30.03 ± 11.08 days; p = 0.001). The data imply that higher age, longer disease duration, larger radiotherapy dose, and prolonged treatment time are the factors significantly linked with the occurrence of radiation-induced hypothyroidism.

Variable	Yes Hypothyroidism (n = 70) Mean ± SD	No Hypothyroidism (n = 30) Mean ± SD	*p*-value (Asymp. Sig., 2-tailed)
Age (years)	33.33 ± 8.05	29.73 ± 8.36	0.050
Duration of Disease (months)	22.41 ± 9.67	17.50 ± 10.64	0.034
Radiotherapy Dose (Gy)	36.84 ± 7.11	32.23 ± 7.67	0.005
Duration of Radiotherapy (days)	40.04 ± 13.19	30.03 ± 11.08	0.001

Discussion:

The data obtained through the studies on radiation-induced hypothyroidism (RIH) in Hodgkin lymphoma (HL) patients make it possible to perform a critical comparison with the current study, where a 70% rate of hypothyroidism after radiotherapy was reported. The incidence rate is, in fact, a lot higher than that of most of the recent papers which have reported a range of approximately up to 50% with the lowest being around 30; the reason for this difference is mainly the variability in the different studies which are due to factors such as the radiation dose, treatment duration, diagnostic definitions, and follow-up timings(8).

The present investigation indicated 70% of subjects had hypothyroidism as a consequence of radiotherapy, which supports some high incidence reports from the literature, while being above the median range. For instance, the rates of hypothyroidism among HL patients treated with IMRT or 3D-CRT obtaining involved-site radiotherapy were around 40-41% according to Pinnix et al. (2018)(9,10). Another study mentioned a 38.6% occurrence of hypothyroidism within three years after radiation, with the average time to onset being about 21 months(10,11). The slightly higher rate in this study may be due to the radiation dose and duration of treatment, since our patients got an average dose of 35.46 Gy over about 37 days, both parameters being higher than the historic averages of 20-30 Gy.

The strong statistical significance observed with higher radiation doses in patients with underactive thyroid (mean 36.84 Gy vs 32.23 Gy, p=0.005) supports the literature of recent times. The risk of hypothyroidism due to thyroid radiation is on the increase as the dose is on the increase consistently increasing in the studies, and doses like V25 and V30 (volumes of the thyroid getting 25 or 30 Gy, respectively) are emphasized as the main predictors(12,13). The dose-response relationship is such that it gives support to the finding that a larger dose is the chief contributor to the risk, which is in line with the current view of radiation oncology that the careful sparing of the thyroid gland from irradiation or the application of dose constraints there reduces the frequency of hypothyroidism(14).

Longer disease duration (22.41 months vs 17.50 months, p=0.034) and older age (33.33 years vs 29.73 years, p=0.050) are the ones that have been associated with hypothyroidism. Prior research has, however, corroborated this. According to the research, those who were older at diagnosis had a higher risk of developing the disease, which was potentially due to less thyroid dispersal capacity with aging, and up to this point, he/she had received treatment that lasted for a longer duration, thus more intense(15). For example, a study singled out aging as a risk factor, while in some groups, female sex was a contributory factor, although in the case of the current study, sex was not found to be significant(16).

In hypothyroid patients, the average radiation treatment time was significantly longer (40.04 days vs. 30.03 days, p=0.001). Whereas there are not many studies that assess treatment time effects directly, it could be argued that prolonged radiation courses might lead to exceeding the thyroid's cumulative exposure limits and/or mirror intensified treatment regimens, which in turn cause endocrine toxicity(17). All these factors open up a new chapter in terms of defining the

standards of care in clinical practice and diametric planning through further research.
Although the current research included 43% of females and 57% of males without a clear correlation by sex, previous studies have reported various results regarding the female gender as a risk factor in RIH with some studies confirming it while others exhibiting no such effect at all and the reason for this could be the combined effect of thyroid volume and radiations dose(18,19).
Among the strengths of the study are a large patient sample of 100, excellent documentation of clinical and treatment parameters, and proper statistical analyses that resulted in proving the associations to be significant. The approach taken in studying different aspects, such as radiation dose, treatment length, and patient age, provides a thorough insight into the risk of RIH.
One of the limitations is that no long-term follow-up data is available, and only immediate post-radiotherapy data exists; hypothyroidism may appear years later, so later incidence could be underestimated. The study fails to describe the exact radiation field techniques or thyroid volume dosimetry data, which the recent literature has pointed out as important predictors. Also, the potential confounders like baseline thyroid function, autoimmunity, or chemotherapy effects were not examined deeply.
The factors that are considered to be the main ones causing thyroid dysfunction by radiotherapy and that are according to the agreement of recent studies the greater doses of radiation, the longer time of treatment and the older patient age, and the longer duration of the disease. This highlights the importance of the use of radiation methods that spare the thyroid, regular monitoring by endocrinologists, and timely hormone replacement therapy so that H.L. patients can receive the best possible care during their lifetime. Moreover, more research should take into account detailed dosimetric analysis and follow-up over a longer period in order to improve the prediction of risk and the development of preventive strategies.

Conclusion:
The current study has strong support for the idea that radiation treatments can lead to hypothyroidism and that this condition is a frequent and important late consequence, with a rate of 70% among Hodgkin lymphoma patients receiving radiotherapy.

Contribution
Conception and Design
Acquisition of Data
Article Writing
Statistical Analysis
Proofreading

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