Evaluation of Interleukin-8 (IL-8) Levels before and after Radiotherapy in Thyroid Carcinoma Patients

Zahraa A.G. Al Ghuraibawi*

Iraqi National Cancer Research Center/ University of Baghdad, Baghdad, Iraq

Abstract: *Background*: Thyroid cancer is a health concern and the most common endocrine tumor in adults with a significant increase in incidence in recent years.

Objective: This study investigates the role of interleukin-8 in thyroid cancer patients before and after treatment with radiotherapy and study association of it with tumor progression and inflammatory response as part of the tumor microenvironment.

Subjects and Methods: A total of 45 thyroid cancer patients (21 male and 24 female) in the educational laboratories/Medical City Hospital/Baghdad from February to April 2025. participated based on the recommendations of the specialist physician after the results of clinical examination, X-ray imaging, and laboratory tests, and 18 healthy controls participated in the study. IL-8 levels were measured before and after treatment with radiotherapy using an ELISA kit, and statistical analyses were performed to assess differences between groups while taking into account demographic characteristics

Result: Thyroid cancer patients showed significantly elevated levels of interleukin-8 compared to controls; IL-8 levels increased significantly after radiotherapy, indicating an enhanced inflammatory response.

Conclusion: The results emphasize the potential role of interleukin-8 as a biomarker for assessing thyroid cancer progression and response to radiotherapy, highlighting its role in the tumor microenvironment and its implications for patient management.

Keywords: IL-8, Thyroid carcinoma, Cancer, Inflammatory cytokines, Radiotherapy.

INTRODUCTION

Thyroid carcinoma is a major public health concern and the most common of all endocrine tumors in adults, accounting for approximately 95% of endocrine cancers and 2.5% of all malignancies and the incidence has increased dramatically in recent years, increasing by approximately 4% per year [1]. Consequently, thyroid cancer is the fastest-growing malignancy, for example in the United States, its incidence has nearly tripled in the past three decades, perhaps due to increased awareness of the disease and improved diagnostic capabilities [1,2]. The diagnosis of thyroid cancer has improved with ultrasound, as small thyroid nodules are better detected than before the use of ultrasound, which is attributed to the significantly increased detection rates of thyroid cancer [3].

Thyroid cancers can be classified into several types, as a high percentage (about 79%) of most thyroid cancers are follicular thyroid carcinoma (FTC) or papillary thyroid carcinoma (PTC) and arise from follicular cells and are considered well-differentiated tumors [4]. Another type of thyroid tumor, known as Hürthle cell carcinoma (HCC), constitutes about 5% of cancers from follicular cells in the thyroid gland, and medullary thyroid carcinoma (MTC) represents 4 % of all thyroid cancers, as this type arises from the C cells that are adjacent to the follicle, and other types fall within the rare thyroid cancers, such as anaplastic thyroid carcinoma (ATC) and poorly differentiated thyroid carcinoma (PDTC) [5].

The cellular and structural tumor microenvironment (TME) components play a pivotal role in cancer development and metastasis and regulate essential tumor survival functions. TME allows cancer cells to invade and spread from the primary site to relatively distant sites, using a complex, multi-step metastasis sequence [6].

Interleukin-8 (IL-8) is a component of the tumor microenvironment and is a chemokine produced by several cell types, including epithelial cells and macrophages, and it has important roles, primarily as a chemoattractant for immune cells [7]. It also plays a role in promoting angiogenesis, which provides assistance for tumor growth and metastasis and the studies have shown that elevated levels of IL-8 in the serum of patients with several malignancies, including lung, breast, and colorectal cancer, are associated with disease progression, dissemination, and poor prognosis [7,8].

*Address correspondence to this author at the Iraqi National Cancer Research Center/ University of Baghdad, Baghdad, Iraq;
E-mail: zahraa.a.315@bccru.uobaghdad.edu.iq

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One of the standard methods of treating thyroid cancer is radiotherapy, especially for patients at risk of recurrence or those with localized disease [9]. Radiation therapy works to destroy the DNA of cancer cells, resulting in the death of cancer cells through programmed death or necrosis [10]. Although radiation therapy is effective for treating malignant tumors, its effectiveness depends on individual patient factors and the tumor microenvironment [11].

Assuming that changes in the tumor microenvironment are affected by radiotherapy, this study aims to investigate the levels of IL-8 in thyroid cancer patients before and after exposure to radiotherapy.

SUBJECTS AND METHODS

This study was conducted in the educational laboratories/Medical City Hospital/Baghdad from February to April 2025, where 45 patients with thyroid cancer (21 male and 24 female) were studied. 18 healthy individuals were included as a control group, excluding those with chronic diseases, autoimmune disorders, recent antibiotic or steroid treatment, and smokers.

Included Criteria

The inclusion criteria included patients aged ≥ 18 years old diagnosed with thyroid carcinoma. They were included before and after commencing radiotherapy to evaluate baseline immunological profiles effectively. Also, participated based on the recommendations of the specialist physician after the results of clinical examination, X-ray imaging, and laboratory tests. taking into account ethical considerations and patient privacy, with initial consent from the participating patients.

Excluded Criteria

Patients with autoimmune diseases, current infections, or pre-existing hematological problems were excluded from the study; additionally, to maintain the accuracy and dependability of the data, we also excluded pregnant women and those with incomplete medical records.

5 ml blood samples were collected from all participants in gel separation tubes and centrifuged at 3000 rpm for 20 minutes to separate serum for IL-8 analysis. IL-8 levels (ng/ml) were measured in the sera of patient (before and after radiotherapy) and control groups using an ELISA kit from CLOUD CLONE Company/American (SEA080HU), with readings taken on a HumaReader HS device/GERMAN. Ethical approval for the study was obtained from the Ethics Committee of Iraqi National Cancer Research Center/University of Baghdad.

Statistical Analysis

The Statistical Analysis System—SAS (2018)—program was used to detect the effect of different groups (before and after) on study parameters. The t-test was used to significantly compare between means. The chi-square test was used to significantly compare between percentages (0.05 and 0.01 probability) in this study.

RESULTS

This study included 45 patients with thyroid carcinoma, 21 male patients (46.67%), and 24 female patients (53.33%). The p-value = 0.654 indicates that the distribution of participating patients of both sexes is not statistically significant, as shown in Table **1**.

Table 1: Distribution of the Thyroid Carcinoma Patients Group according to Gender

Factor		No	Percentage (%)
Sex: No (%)	Male	21	46.67
	Female	24	53.33
	Total	45	100%
P-value		---	0.654 NS

NS: Non-Significant.

The patients were distributed according to age groups into two groups (≤25 and >25 yr), where the age group (>25 yr) 27 (60%) out of a total of 45 patients was the most among those afflicted with thyroid cancer, but the statistical analysis did not show significant differences (P-value = 0.179) (Table **2**).

Table 2: Distribution of the Thyroid Carcinoma Patients Group according to Age Groups

Factor		No	Percentage (%)
Age group: No (%)	≤25 yr.	18	40.00
	>25	27	60.00
	Total	45	100%
P-value		---	0.179 NS

NS: Non-Significant.

The data in Table **3** show the distribution of patients under study according to the severity of the disease,

where the samples were distributed between moderate 25 (55.56%) and severe 20 (44.44%), with no significant difference (p-value = 0.456) when comparing the percentage of the two groups.

Table 3: Distribution of the Thyroid Carcinoma Patients Group according to Status

Factor		No	Percentage (%)
Status: No (%)	Moderate	25	55.56
	Severe	20	44.44
	Total	45	100%
P-value		---	0.456 NS

NS: Non-Significant.

The results data in Table **4** show the differences in IL-8 levels in the sera of females and males participating in the thyroid cancer patients group and the control group. In the patient group, the mean ± SE ng/ml of IL-8 level was 400.17 ± 43.78 in males, while it was 346.96 ± 44.24 in females, with no significant difference (P = 0.199) when comparing them. As for IL-8 levels in the control group, it was 90.75 ± 8.14 in males and 91.57 ± 6.29 in females, with no significant difference (P = 0.465) between males and females. When comparing IL-8 levels between the patient and control groups, the results show a noticeable increase in the patient group, with a highly significant difference in both males (p < 0.001**) and females (p = 0.002**).

Table 4: The Differences in IL-8 Level between Male and Female in Study Groups

Groups	IL-8(Mean±SE) ng/ml				P-*value*	T-test
	Male	N	Female	N		
Patient	400.17±43.78	21	346.96±44.24	24	0.199 NS	0.840
Control	90.75±8.14	11	91.57±6.29	7	0.465 NS	0.087
P-*value*	>0.001**		0.002**		----	----
T-test	5.051		3.075		----	----

Table **5** shows the personal correlation between serum IL-8 levels and body mass index (BMI) of thyroid cancer patients. The correlation coefficient (R) is 0.601, indicating a strong positive association between IL-8 levels and BMI among thyroid carcinoma patients. The p-value> 0.001 suggests that the correlation is highly statistically significant.

Table 5: The Correlation between IL-8 and BMI in Thyroid Carcinoma Patient

Parameters		R	P-*value*
IL-8 ng/ml	BMI	0.601	>0.001

Table **6** and Figure **1** show the serum IL-8 levels (mean ± SE) ng/ml in the patient group pre and post-radiotherapy compared with the control group. The mean IL-8 level in the control group was 91.14 ± 5.42 ng/mL. Before radiotherapy, the patient group showed a mean IL-8 level of 371.79 ± 31.11 ng/mL. After radiotherapy, the mean IL-8 level in the patient group increased significantly to 1001.94 ± 29.36 ng/mL. The T-test value was 91.478, indicating a highly significant difference (p ≤ 0.001) in IL-8 levels before and after treatment. These results indicate a significant increase in IL-8 levels in thyroid cancer patients post-radiotherapy compared with the control group and their levels pre-radiotherapy treatment.

DISCUSSION

The results of the current study showed a slightly higher prevalence of thyroid cancer in females. Although the difference was not statistically significant, which may be due to the small sample size, most studies are consistent with these results. Gender affects the incidence and mortality rate of thyroid cancer, as differences are observed between the sexes in clinical characteristics such as tumor size and metastases [12]. Many studies indicate that thyroid cancer is more common in women, with a female-to-male ratio ranging from 2:1 to 3:1. For example, Du *et al*. in their research conducted in China, indicate that the prevalence of well-differentiated thyroid cancer is

Table 6: IL-8 Levels Pre and Post-Radiotherapy of the Patient Group Compared to the Control Group

Group	Mean ± SE of IL-8 Conc. (ng/mL)
Control	91.14 ±5.42 c
Before treatment	371.79 ±31.11 b
After treatment	1001.94 ±29.36 a
T-test	91.478 **
P-value	0.0001

** (P≤0.01).

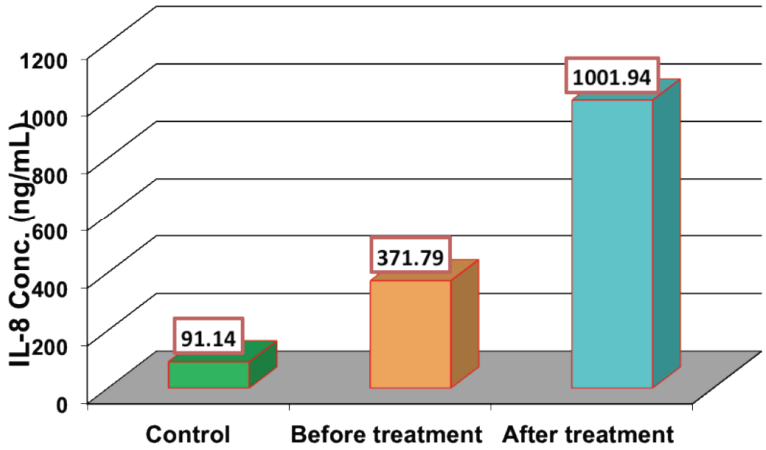

Figure 1: Comparison between different groups in IL-8 conc.

three times higher in females, while the incidence of poorly differentiated thyroid cancer was similar in both sexes [13]. Female hormones appear to play a role in the higher incidence of thyroid cancer in women [14], and early screening may contribute to this difference [15]. The prevalence of thyroid cancer between the sexes is more evident during the reproductive period in females aged 15 to 50 years [16]. The data presented in Table **2** reveal that 40% of thyroid cancer patients are aged 25 years or younger, while 60% are aged over 25 years. The p-value of 0.179 indicates that this age distribution is not statistically significant, suggesting that age may not play a decisive role in thyroid cancer incidence. Previous studies have shown that thyroid cancer incidence increases with age. According to the literature, it rises from adolescence to middle age, peaking at age 65 for males and about 55 for females before beginning to decline [17, 18]. Research has also documented the spread of thyroid cancer among younger patients in recent years [19, 20].

The distribution of disease severity in thyroid cancer can have a significant impact on prognosis and treatment strategy [21]. Studies show a difference in the distribution of thyroid cancer patients according to the severity and stages of the disease [21]. Confirmed that a large percentage of thyroid cancer patients suffer from the disease in its early (moderate) stages, where these are associated with higher survival rates. On the other hand, thyroid cancer in its advanced (severe) stages is often associated with worse results in treatment and poor prognosis. They are more susceptible to metastases, and the degree of treatment varies for them [22]. The results of the analysis of IL-8 levels in the group of thyroid cancer patients in the current study and comparing its levels with the healthy control group reveal insights into the extent of the inflammatory response to this type of cancer, as interleukin-8 is one of the types of pro-inflammatory cytokines, and its high levels are often associated with tumor progression [23]. When studying the differences in interleukin-8 levels between male and female thyroid cancer patients and study controls, it was noted that its levels did not reach statistical significance in both males and females in both study groups (patients and study controls), despite its levels being significantly higher in the patient group and in both sexes. The results of several studies are consistent with the results of this study. [24] reported in their study on different types of thyroid cancer that IL-8 levels were significantly higher in them compared to the control group, while a study found that IL-8 levels were higher in thyroid cancer patients compared to those with benign thyroid diseases [25]. In contrast, the results of a study indicated a lower level of IL-8 in the serum of thyroid cancer patients compared to healthy controls [26]. Where one study reported that IL-8 levels were significantly higher in the malignant thyroid nodule group compared to the benign thyroid nodule group and the control group [27]. The tumor microenvironment plays an important role in the development of the tumor. One of the factors in this microenvironment is IL-8, which plays multiple roles in stimulating the development of the tumor within the tumor microenvironment, as it promotes the proliferation of cancer cells or the possibility of converting them to a migratory or mesenchymal pattern, and it can also recruit large numbers of cells to the tumor site, which work to suppress immunity and also increase the formation of blood vessels in the tumor (angiogenesis) [28, 29].

According to the results of the current study, high body mass index is highly associated with high levels of IL-8. Obesity is implicated in increasing evidence as

a risk factor for various types of cancer, including thyroid cancer, by creating a microenvironment conducive to the growth and development of tumors by being associated with increased levels of inflammatory cytokines, including interleukin 8 [30, 31]. Studies have shown that higher BMI is associated with more aggressive forms of thyroid cancer, including lymph node metastasis, extrathyroidal extension, multifocality, and lymph node metastasis, which may be mediated by inflammatory pathways [32]. The results data in Table **6** provide a relatively convincing overview of the changes in IL-8 levels before and after radiotherapy of thyroid cancer patients compared to the control group. The results reveal significant differences in IL-8 levels that illustrate changes in the inflammatory response associated with radiotherapy of thyroid cancer patients. Patients show elevated levels of IL-8 compared to controls, indicating an increased inflammatory state before radiotherapy, and after radiotherapy, IL-8 levels are significantly elevated, indicating a greater and more intense inflammatory response than before treatment. The significant elevation in IL-8 levels after radiotherapy in thyroid cancer patients is particularly noteworthy and may be indicative of a larger radiation-induced inflammatory response, as radiation therapy primarily causes DNA damage in cancer cells, leading to apoptosis or necrosis (uncontrolled death), and this damage may extend to healthy cells and tissues adjacent to the tumor, leading to a stress response. Cells that survive radiation damage may also respond to a series of stress response pathways; ultimately, these events lead to increased activation of the pro-inflammatory signaling cascade [33, 34]. As an immune response, this tissue and cell damage leads to the release of several pro-inflammatory cytokines, including IL-8, and this occurs through several mechanisms, including activation of immune cells and enhanced secretion of pro-inflammatory cytokines in response to damage-associated molecular patterns (DAMPs) [35]. Radiation can also activate the inflammasome in immune cells, a multiprotein complex that stimulates the maturation and release of pro-inflammatory cytokines, contributing to elevated IL-8 levels [36].

IL-8 acts as a potent chemokine that attracts immune cells such as monocytes and neutrophils to the site of radiation-damaged cells, and this recruitment is critical to participate in the initiation of the healing process, but on the other hand, it can also create a tumor-friendly environment [37]. While interleukin-8 is part of the tumor healing environment, its excessive elevation also raises concerns about tumor recurrence and resistance to treatment, as high levels are associated with a more aggressive disease course and a poorer prognosis in many types of cancer, including high levels in advanced stages of thyroid cancer [38]. The most significant limitations of this study are the small sample size and short timeframe. Strict criteria and the rarity of disease conditions can hinder the recruitment process for clinical studies. Many studies face difficulties in recruiting sufficient participants due to factors such as the rarity of the disease under study, logistical issues, and limited communication capabilities. This is particularly true in specialized areas such as thyroid cancer. Studies are often constrained by predetermined data collection timelines, and researchers face pressure to complete studies within a specific timeframe. This can lead to underrecruitment and, consequently, small sample sizes.

CONCLUSION

IL-8 levels were significantly higher in thyroid patients compared to healthy controls. In addition, IL-8 levels increased further after radiotherapy, indicating a greater inflammatory response. These results suggest that IL-8 could be considered as a biomarker for assessing disease progression and response to treatment in thyroid cancer patients.

RECOMMENDATIONS

1 Further research on larger samples is needed to discover the mechanisms underlying the role of IL-8 in thyroid cancer.

2 Further research should focus on the role of IL-8 in thyroid cancer patients by targeting it for therapeutic strategies.

CONFLICTS OF INTEREST

No Conflicts of interest.

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