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A Comparison of the Adverse Effects of Radiotherapy and Chemotherapy in the Treatment of Non-Small Cell Lung Cancer

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Abstract: **Background:** Concurrent chemoradiotherapy (CCRT) involves the administration of chemotherapy alongside radiation therapy, while radiation therapy (RT) involves the use of high-energy radiation to kill cancer cells. Late toxicities refer to the long-term side effects that may occur months or even years after the completion of treatment. **Method:** A retrospective study conducted in central and southern Iraq designed to assess the risk of acute and late toxicities in patients with grade ≥ 3 non-small cell lung cancer (NSCLC), which was related to CCRT and RT alone. Information was gathered from a number of both governmental and private hospitals and clinics. The CCRT group of patients in the trial received a variety of medication types, whereas the radiation group received a recommended dose that typically ranged from 60 to 70 Gy. Dermatitis, a dry cough, mucositis, dysphagia, leukopenia, liver and renal failure, nausea and vomiting, neutropenia, and peripheral neuropathy were among the acute toxicities. **Results:** In cases of Acute Toxicity, there were significantly higher rates of dry cough, Mucositis, nausea and vomiting, dermatitis, and neutropenia in the CCRT group compared to RT. Additionally, in terms of late toxicities, the CCRT group experienced significantly more instances of dry cough, mucositis, and neutropenia. Both late CCRT and late RT toxicities showed significantly higher occurrences of dry cough, mucositis, neutropenia, and nausea and vomiting compared to acute CCRT and acute RT toxicities. **Conclusion:** Our research indicates that CCRT is more likely to result in late-stage severe toxicities than radiation therapy. Furthermore, for both CCRT and RT, the importance of late toxicities particularly late severe toxicities is emphasized. These results are in line with the given assertion.

Key Words: NSCLC, CCRT, radiotherapy, acute and late toxicities, neutropenia

I. INTRODUCTION

NSCLC is a term used to describe a group of lung cancers, including adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Adenocarcinoma is associated with half of all NSCLC cases, making it the most common type. Previously, squamous cell carcinoma was the most frequently diagnosed type of carcinoma, often originating in the tracheo-bronchial tree, but is now more commonly found in the outer parts of the lung [1]. Radiation therapy (RT) involves the use of high-energy ionizing radiation to specifically target and destroy cancer cells [2]. To enhance treatment effectiveness, chemotherapy and radiation therapy can be combined for a more aggressive approach to cancer treatment. However, this combination can lead to significant adverse effects on normal tissues, impacting the patient's quality of life. Therefore, accurately predicting and managing these adverse effects before or during the early stages of treatment is a crucial aspect of personalized medicine [3].

Radiotherapy and CCRT can lead to different levels of acute dry cough [4], mucositis [5], dysphagia [6], leukopenia [7], liver and kidney dysfunction [8], nausea and vomiting [9] in NSCLC patients, which can increase the risk of infection and potentially delay treatment [10]. Additionally, the use of anti-cancer medications in combination with radiation can damage the mucosal lining and lead to the death of epithelial cells [11]. These significant side effects have the potential to affect treatment adherence, diminish patients' quality of life, and pose life-threatening risks [12].

A. AIM

The purpose of this study was evaluated and contrast the immediate and long-term side effects of radiation treatment with chemotherapy and radiation therapy (CCRT).

II. MATERIALS AND METHODS

A. METHOD

Between January 11, 2023, to February 1, 2024, the data was collected from different government and private hospitals or centers in center and south of Iraq. A retrospective study was investigated the risk of acute and late toxicities of concurrent chemoradiotherapy (CCRT) and radiotherapy alone in patients with grade $\geq$ 3 of Non-Small Cell Lung Cancer (NSCLC). Patients' treatment by the CCRT group involved varying dosages and durations of cisplatin, cisplatin complexes, 5-fluorouracil, oxaliplatin, and carboplatin. For patients in the radiation group, the recommended dose typically ranged between 60 and 70 Gy. Each week, patients received clinical evaluations, computed tomography scans, chest x-rays, and abdominal ultrasounds. In all patients, treatment failures were classified as locoregional or distant, and side effects were assessed and scored. Patients whom already on chemotherapy or radiation, they have chronic diseases or other types of malignancy, and weight loss of over 20%, were excluded from the study.

Included criteria for acute toxicities, such as at least one of the following: dermatitis, dry cough, mucositis, dysphagia, leukopenia, liver and kidney dysfunction, nausea and vomiting, neutropenia, and peripheral neuropathy, while the dry cough, dysphagia, mucositis, peripheral neuropathy, neutropenia, and nausea and vomiting.

B. STATISTICAL ANALYSIS

For this study, all analyses were performed using Statistical Package for the Social Sciences version 26.0 (SPSS Inc.; Chicago, IL, USA). Graphs were generated using GraphPad Prism 8.1 (GraphPad software, San Diego, CA). To compare differences between the RT and CCRT groups, a one-way ANOVA test for dependent samples with correction for multiple testing was conducted. Pairwise comparisons between acute and late for both CCRT and RT groups were calculated using the Wilcoxon pairwise test corrected for multiple testing.

III. RESULTS

A. PATIENTS' DEMOGRAPHICS PROPERTIES

200 patients assigned to radiotherapy alone and 200 patients in the group that received combined treatment. Furthermore, the combined-treatment group received the three cycles of chemotherapy concurrently with radiation therapy. The average age of patients in the radiation therapy group was 34-45 years, while those in the CCRT group ranged from 30 to 45 years old.

B. ACUTE TOXICITY INCIDENCE

The incidences of dry cough (46.2% vs. 32.3%), Mucositis (36.6 vs 29.0%), nausea and vomiting (34.6% vs. 11.2%), dermatitis (15.3% vs. 11.7%), and neutropenia (22.8% vs. 0.3%) were high significantly CCRT when compared with RT. There was a significant increase in the risk of acute dry cough, mucositis, and dermatitis with CCRT, whether assessed by event frequency (OR=1.43, 1.26, 1.30, respectively. Additionally, CCRT significantly increased the risk of acute nausea/vomiting (OR=23, P<0.001), leukopenia (OR=21, P<0.001) and neutropenia (OR=17.5, P<0.001). Table 1 and Figure 1.

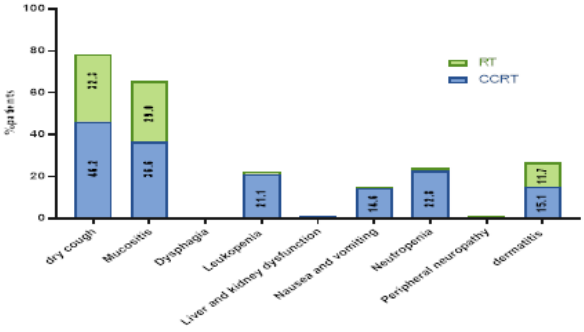

FIGURE 1: Percentage of patients with Acute toxicity

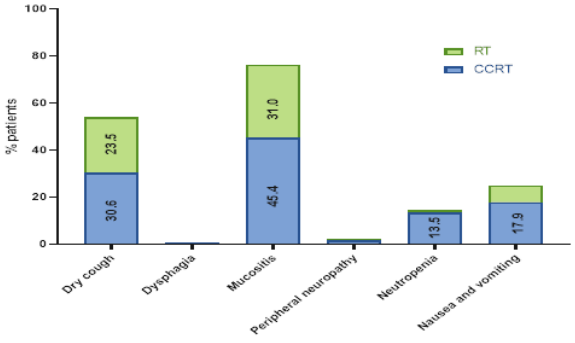

FIGURE 2: Percentage of patients with late toxicities

C. LATE TOXICITY INCIDENCE

For late toxicities, the CCRT group exhibited significantly higher events of dry cough (30.6% as compared to 23.5%), mucositis (55.4% as compared to 31%), and neutropenia (23.5% as compared to 1%). The results of our study showed that CCRT led to an increased risk of late severe dry cough (OR=1.30, P=0.044) as compared to radiotherapy. There was a significant increase in the risk of acute dry cough and mucositis with CCRT, whether assessed by event frequency (OR=1.30, and 1.79). Additionally, both the CCRT and radiotherapy alone groups had a similar incidence of xerostomia, with a slight difference between the two groups. Table 2 and Figure 2.

D. ACUTE TOXICITY VS LATE TOXICITY INCIDENCE

The incidence of dry cough, mucositis, neutropenia, and nausea and vomiting was significantly higher in late CCRT and RT toxicities compared to acute CCRT and RT toxicities (Table 3 and Figure 3). Our study results indicate that CCRT

	Treatment group		P value	Odd ratio
	CCRT %	RT alone %		
Dry cough	46.2	32.3	0.0289	1.43
Mucositis	36.6	29	0.0047	1.26
Dysphagia	0.6	0	>0.9999	
Leukopenia	21.2	1	<0.0001	21
Liver and kidney dysfunction	1.4	0	0.1238	
Nausea and vomiting	14.6	0.2	<0.0001	23
Neutropenia	22.8	1.3	<0.0001	17.5
Peripheral neuropathy	0	1.1	0.4974	
Skin reaction	15.1	11.7	0.1473	1.30

TABLE 1: Summary of acute toxicities

	Treatment group		P value	Odd ratio
	CCRT %	RT alone %		
Dry cough	30.6	23.5	0.044	1.3
Dysphagia	0.7	1	0.2467	
Mucositis	55.4	31.0	0.0006	1.79
Peripheral neuropathy	1.6	0.5	0.1065	
Neutropenia	13.5	1	<0.0001	14
Nausea and vomiting	17.9	7.2	0.0536	2.5

TABLE 2: Summary of late toxicities

and RT toxicities are associated with a significantly increased risk of dry cough, mucositis, neutropenia, and nausea and vomiting. The odds ratios for acute toxicities are 2.3, 1.2, 0.8, and 1.3, respectively, with a p-value of less than 0.0001. For late toxicities, the odds ratios are 117.5, 1.1, 3.3, and 36, also with a p-value of less than 0.0001, compared to acute toxicities.

IV. DISCUSSION

In our study, we compared the incidence and risk of severe acute and late toxicities associated with CCRT versus RT alone in patients with NSCLC. The toxicities included acute effects such as dry cough, mucositis, nausea and vomiting, neutropenia, dermatitis, and hepato-renal function, as well as late effects like Dry cough, dysphagia, mucositis, peripheral neuropathy, neutropenia, nausea and vomiting. Our findings showed that CCRT was associated with higher incidence of dry cough, mucositis, nausea and vomiting, dermatitis, and neutropenia compared to radiotherapy alone.

We found that CCRT is associated with a higher risk of acute toxicities, such as nausea/vomiting (OR=23), leukopenia (OR=21), and neutropenia (OR=17.5) compared to radiotherapy. It has been shown that accumulated dose, radioactive source, target volume, dose intensity, and xerostomia are strongly correlated with side effects caused by radiation therapy [13]. Repeated use of cytotoxic agents can damage endothelial tissues [14], connective tissue epithelium [15], and bone marrow [16] as a result of chemotherapy. Thus, concurrent chemoradiotherapy (CCRT) appears to be associated with a greater risk of oral mucositis and bone marrow damage than radiotherapy alone. An anti-neoplastic drug is usually administered one week after the start of radiotherapy in clinical practice.

Our data shows a significant association between concurrent chemoradiotherapy (CCRT) and late toxicities, including dry cough (OR=1.30) and mucositis (OR=1.79). Previous research has also demonstrated a link between the use of chemotherapeutic regimens and these toxicities. Previous studies showed that up to 95% of NSCLC patients had different degrees of dosage-dependent radiation side effects, which raised their risk of infection and prolonged their course of treatment. Furthermore, endothelial tissue cells and connective tissue epithelium cells may experience apoptosis and mucosal damage as a result of the combined effects of anti-neoplastic medications and radiography radiation [**?**].

The incidence of dry cough, mucositis, neutropenia, and nausea and vomiting was found to be significantly higher in late CCRT and RT toxicities compared to acute CCRT and RT toxicities. Patients undergoing CCRT and RT should be aware of the potential side effects and work closely with their healthcare provider to manage them effectively. The studies mention that RT-induced cardiopulmonary toxicities, such as lung inflammation, radiation-induced lung damage (RILD), and late lung fibrosis, can be significant concerns for patients receiving radiation for lung cancer. These side effects can be influenced by various factors, including the immune system, cytokine expressions, and radiation dosage [20], [21]. While the specific comparison of side effects between acute and late RT toxicities is not addressed in the provided search results, it is important to note that the incidence and severity of side effects can vary depending on the individual patient, the specific treatment regimen, and other clinical factors [22], [23].

V. CONCLUSIONS

The primary objective of the current study is to assess and compare the acute and late toxicities of radiation therapy alone versus CCRT. According to the results, CCRT is a greater danger than radiation therapy to cause late severe toxicities. On the other hand, late toxicities are more significant

	CCRT Acute	CCRT Late	P value	OR	RT Acute	RT Late	P value	OR
Dry cough	13.5	30.6	<0.0001	2.3	0.2	23.5	<0.0001	117.5
Mucositis	45.4	55.4	<0.0001	1.2	29	31	<0.0001	1.1
Neutropenia	17.9	13.5	<0.0001	0.8	0.3	1	<0.0001	3.3
Nausea and vomiting	13.5	17.9	<0.0001	1.3	0.2	7.2	<0.0001	36

TABLE 3: Compared the risk factor between acute and late toxicities of the CCRT and RT

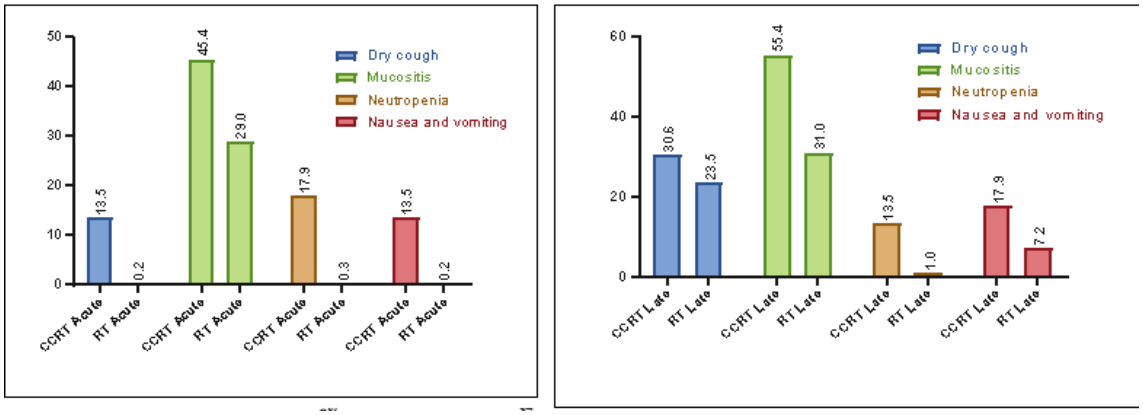

FIGURE 3: Compared between acute and late toxicities

than acute toxicities for both CCRT and RT.

VI. RECOMMENDATION

To minimize the immediate and long-term side effects of concurrent chemoradiotherapy (CCRT), we suggest either starting with chemotherapy before radiation or vice versa.

FUNDING

None.

CONFLICTS OF INTEREST

No conflicts of interest have been declared by the authors.

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