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RESEARCH ARTICLE

Approaches combining chemotherapy and radiation therapy in locally advanced head and neck cancers: Retrospective record-based study

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ABSTRACT

Background: Head and neck cancer is a locoregional disease. Radiotherapy and surgery are the treatment options, where radiotherapy is the preferred treatment. Several approaches for combining chemotherapy and radiation have been used to improve treatment outcomes. Nonetheless, the chemotherapy schedule consisting of induction chemotherapy (ICT) followed by concurrent chemo-radiotherapy (CCRT), CCRT alone, or CCRT + adjuvant chemotherapy (AC)) remains to be defined. **Aim:** Our goal is to compare the efficacy and toxicity of induction chemotherapy (ICT) followed by CCRT to standard CCRT alone in patients with locally advanced squamous cell carcinoma in the head and neck (LASCCHNC). **Material & Methods:** This is a retrospective record-based study that enrolled all patients attending to Clinical Oncology and Nuclear Medicine Department, Suez Canal University Hospital, Ismailia, Egypt, with a proven pathological diagnosis of head and neck cancer. The study included a total of 168 patients, including 84 in each group. Group A received CCRTH alone, while Group B received IC followed by CCRTH between January 2014 and December 2018, with a follow-up period ending in January 2024. **Results:** According to Kaplan Meier analysis with the Log-rank test, no statistically significant impact on progression-free survival (PFS) among both groups. Overall survival (OS) analysis showed that patients in Group B who received ICT followed by CCRTH had a higher OS than patients in Group A who received CCRTH only. **Conclusions:** Induction chemotherapy followed by concomitant chemoradiotherapy is a suitable option with improved outcomes for patients with LAHNSCC.

Keywords: Concurrent chemoradiotherapy, Head and neck cancer, Induction chemotherapy, locally advanced, Radiotherapy

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INTRODUCTION

Approximately 90% of head and neck cancers are squamous cell carcinomas, which develop from the epithelial lining of the oral cavity, pharynx, and larynx (Sung et al., 2021). Various types of malignancies that affect the head and neck are categorized according to their anatomical location. Because the presenting symptoms, treatment regimens, and prognosis vary per anatomical sub-site, they are addressed as separate entities (Thomas et al., 2018). Most of them have locoregional advanced head and neck squamous cell carcinoma (LAHNSCC) (Haddad et al., 2018). HNC is treated using a multimodal approach that involves surgery, chemotherapy, and radiation, depending on the location and stage of the disease. More than 75% of HNC patients require radiotherapy (RTH), which can be given alone or alongside chemotherapy. RTH was suggested for 74% of all patients with head and neck cancer (Santos et al., 2019, Ferrari et al., 2020).

A meta-analysis of chemotherapy in head and neck cancer (MACH-NC) determined that combined platinum-based chemotherapy radiation (CCRT) is the best treatment for LASCCHN (Haddad et al., 2018). SCCHN is a locoregional illness, where distant metastases are uncommon at the time of diagnosis. Radiotherapy and surgery are the preferred therapies, with radiotherapy taking precedence in terms of organ preservation. One of the most important biological elements influencing radiation outcomes in squamous cell carcinoma is the growth of tumor stem cells after treatment. A longer overall treatment period may diminish the possibility of tumor control (Haddad et al., 2008). Whereas a significant number of clinical data indicates that a shorter overall treatment time may increase tumor control. Concurrent chemoradiotherapy alone can result in a shorter treatment period for advanced HNC. Several randomized trials have been done to determine the efficacy of chemotherapy in locally advanced HNCs (LASCCHN) (Argiris et al., 2005, Therasse et al., 2000). Chemotherapy has been used as an induction treatment, alongside radiation, and as an adjuvant treatment after irradiation, surgery, or both (Zorat et al., 2004). Cisplatin-based combination chemotherapy has been demonstrated to provide 70-90% overall response rates and 20-50% complete response rates in patients with

previously untreated locally advanced head and neck cancer (Brockstein et al., 2004).

Induction or neoadjuvant chemotherapy occurs before radiation or surgery. The study aimed to improve treatment outcomes for individuals with locally advanced squamous cell carcinoma of the head and neck by including an active induction regimen before final radiation or surgery. Significant tumor reduction has the potential to reduce distant metastases while improving local and regional management and organ preservation (Posner et al., 2004). Early single-arm trials confirmed the efficacy of platinum-based induction regimens and showed that chemotherapy and radiation may be given sequentially without increasing radiation toxicity (Bourhis et al., 2007). Previously, induction chemotherapy was considered a promising approach for larynx preservation. The Veterans Affairs (VA) randomized trial found that implementing an induction strategy is effective. Chemotherapy followed by radiation for responders and surgery for non-responders resulted in laryngeal preservation with no significant difference in survival compared to the initial surgery (Pignon et al., 2009). EORTC observed similar outcomes in pyriform sinus cancers (Lefebvre et al., 1996).

Although these trials did not include a radiation-alone arm and there was no increase in survival, they concluded that larynx preservation was possible, but the role of induction chemotherapy was unclear. Induction chemotherapy was proposed as a method for predicting which patients would respond well to radiation and identifying candidates for larynx preservation. Our study aims to compare the efficacy and toxicity of induction chemotherapy (ICT) followed by CCRT to standard CCRT alone in patients with locally advanced squamous cell carcinoma of the head and neck.

PATIENTS AND METHODS

This is a retrospective record-based comparative study, enrolled all patients attending the Clinical Oncology and Nuclear Medicine Department, Suez Canal University Hospital, Ismailia, Egypt, with a proven pathological diagnosis of LASCCHNC, in the period between January 2014 and December 2018, with a follow-up period till January 2024. The sample size included 168 patients.

Study population

The study was conducted in two groups: Group A (CCRT alone): A total of 70 Gy in 35 fr (2Gy per fraction), was administered daily (5 days per week) for 7 weeks (conventionally fractionated radiotherapy) with weekly Cisplatin 40 mg/m2 or weekly carboplatin AUC 2. Group B (ICT followed by CTRT): Three cycles of induction chemotherapy each consisted of IV Docetaxel 75 mg/m^2 on day 1, Cisplatin 75 mg/m^2 divided into two doses on D1 and D2 and 5 FU 1 gm/m^2 on days 1-4; or 3 cycles of gemcitabine 1000 mg/m^2 day 1, 8, cisplatin 100 mg/m^2 divided into 2 doses day 1, 2 followed by 7 weeks of concurrent CCRT consist of standard RTOG regimen with weekly IV Cisplatin 40 mg/m^2 or weekly carboplatin AUC 2 Plus RT by conventional fractionation.

Inclusion criteria

For eligibility, patients aged from 18 to 80 years old.

- Life expectancy exceeds 6 months.
- Have an Eastern Cooperative Oncology Group (ECOG) score of 0-2,
- Have no prior experience with cancer-related therapy.
- Have adequate baseline hematological, cardiac, renal, or liver function tests.
- Newly diagnosed individuals with pathologically proven malignant squamous cell carcinoma in the head and neck.
- Patients with locally advanced head and neck cancer (stages 3 and 4 according to the UICC TNM cancer staging manual, eighth edition).
- Patients who have completed their data, files, and medical records.
- Adequate bone marrow and organ functions; no nerve affection.
- For unrespectable tumors, inoperability criteria include tumor fixation, invasion to either the skull base, vertebrae, nasopharynx, or fixed amalgamated lymph nodes) or tumor stage (T3–4, N2–3, excluding T1N2 based on the UICC TNM cancer staging manual, 8th edition). Patients who were inoperable owing to medical issues were ineligible.

Exclusive criteria

- Distant metastasis.
- Recurrent lesions.
- Concurrent malignancies.
- Severe comorbidities.
- Prior treatment with one of the following techniques for another diagnosis: surgery, radiation, or chemotherapy. Breastfeeding and pregnant women.

Sample size and technique

The study sample was drawn from the cancer patients' registry using a rigorous sampling technique. Patients diagnosed with head and neck cancer by pathology who met the inclusion and exclusion criteria were enrolled. Patients who had a histopathologically confirmed diagnosis of head and neck cancer at Suez Canal University Hospital

between January 2014 and December 2018 were included.

Sample size

The sample size was calculated using the equation of Wang et al. (2007):

$$n = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1(1-p_1)+p_2(1-p_2)) / (p_1-p_2)$$

Where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p_1 and p_2 are the expected sample proportions of the two groups.

Where P1 = 42.5% and P2 = 28% (M. G. Ghi et al., 2017).

According to the previous equation: The calculated sample size was 167 participants. Based on the above data, the sample size was 168 participants (84 patients in each group). The sample was collected from January 2014 to December 2018 according to data completely fulfilled from medical records, with a follow-up period till January 2024).

Methods of data collection

This Retrospective record-based study contained two groups (proven from patients' files and retrospective medical records according to the patient's treatment line), and the following data was acquired from the records: Group A: participants received a total of 70 Gy in 35 fr (2 Gy each fraction), administered daily (5 days per week) for 7 weeks (conventional fractionated radiotherapy), with weekly injections. Cisplatin 40 mg/m2 or carboplatin AUC 2.

Group B patients got three cycles of induction chemotherapy, each comprising of injections. On day one, administer 75 mg/m2 of docetaxel via injection. Cisplatin 75 mg/m2 divided into two doses on D1 and D2, and IV 5FU 1 g/m2 on days 1-4; or gemcitabine 1000 mg/m2 on days 1, 8, cisplatin 1, 8, and Cisplatin 75 mg/m2 divided into two doses on day 1, 2, followed by 7 weeks of concurrent CTRT consisting of a normal RTOG regimen with weekly injection. Cisplatin 40 mg/m2, or carboplatin AUC 2 plus RT by conventional fractionation. Each group was evaluated for disease response using RECIST criteria and efficacy by examining the patient clinically and radiologically before and after treatment, as well as comparing the acute toxicity of each regimen during cycles of radiation therapy.

- Detailed medical history, including age, gender, chronic illness, ECOG-PS score, and smoking history. Disease data included main symptoms, pathology, staging, and co-morbidities.
- The information above was obtained from patients' medical records at the Clinical Oncology Department.
- Periodic clinical exams to assess the patient clinically (cervical lymph node examinations, cranial nerve tests, swallowing and speech assessments, nutritional status, and a thorough physical examination of the chest and abdomen to rule out distant metastases).
- Treatment-related toxicity.
- To determine treatment response, perform an MRI head and neck with contrast prior to induction chemotherapy and concomitant chemoradiotherapy. PET/CT or conventional CTs are used for staging distant metastases.

Endpoints

The primary effectiveness endpoint was the difference in OS between groups A and B (from diagnosis to death from any cause or the January 2024 cutoff date). Secondary efficacy goals included overall response rate (ORR) based on RECIST criteria, and PFS was estimated from first-line treatment to disease progression. Toxicity was assessed using the November 2017 Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

The statistical analysis was performed using SPSS software for Windows, version 28 (IBM Co., Armonk, NY, USA). Normality was tested and then numerical data were reported as mean with standard deviation and examined using an independent t-test or median and interquartile range (IQR), which were analyzed using the Mann-Whitney test. Categorical data were provided as frequency and percentage and evaluated with the Chi-square test. To analyze the many factors related to survival over time, a Kaplan-Meier curve was used in conjunction with Cox regression.

RESULTS

Patients were randomly assigned to two therapy groups, with 84 patients in each:

- Patients in Group A (CCRTH alone) received a total of 70 Gy in 35 fractions (2 Gy each fraction), delivered daily (5 days per week) for 7 weeks (conventionally fractionated radiotherapy), with weekly IV Cisplatin 40 mg/m2 or carboplatin AUC 2.
- Group B (ICTH followed by CCRTH): patients received three cycles of induction chemotherapy (either three cycles of the TPF protocol or gemcitabine cisplatin), followed by seven weeks of concurrent CCRTH (RT by

conventional fractionation consisting of a standard RTOG regimen with weekly IV. Cisplatin 40 mg/m2 or carboplatin AUC 2), as shown in Figure 1.

Patient characteristics

Regarding patient demographic data, groups A & B showed significantly (P<0.001) different patterns of age, with the age group between 50 and 59 years as the predominant one (47.6% of group B and 40.5% of group A). Also, group B elicited a significantly lower mean BMI than group A (P = 0.034). The prevalence of chronic illness was significantly lower in group B compared to group A (27.4% vs. 54.8%, P<0.001), with a smaller proportion of diabetic (13.1% vs. 28.6%, P = 0.014) and hypertensive patients (13.1% vs. 33.3%, P = 0.002). However, both groups were similar in terms of sex, smoking history, and other comorbidities. The percentage of patients with ECOG PS 1 was significantly higher in group B as compared to group A (94% vs. 69% respectively P<0.001), which indicates a better functioning level. Numerical data are presented as Mean (SD) or median and interquartile range (IQR) based on normality. Categorical data are presented as frequency (%), Statistical significance was set at P value<0.05, BMI: Body mass index, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease. ECOG: Eastern Cooperative Oncology Group.

Numerical data were examined using an independent T-test or Mann-Whitney test. Categorical data were evaluated with the Chi-square test.

Tumor characteristics

As shown in Table 1, the most prevalent diagnosis was laryngeal carcinoma, which affected 56% of patients in group A and 44% of those in group B. Nasopharyngeal cancer followed laryngeal cancer with 20.2% and 29.8% of cases among groups A and B, respectively. The most common presentation was horsiness of voice, which accounted for 36.9% of group A and 31% of group B. Another common presentation was neck swelling, with 15.5% and 23.8% of cases among Groups A and B, respectively. According to pathology, all tumors were SCCs. Furthermore, 54.8% of group A vs. 67.9% of group B were verified to have grade 2 (moderately differentiated squamous cell carcinoma), whereas 34.5% vs. 20.2% had grade 3 (poorly differentiated squamous cell carcinoma), with no statistically significant difference in tumor grading across groups. As for the TNM staging system, T3 and N1 were the predominant stages, with rates of 28.6% of group A vs. 45.2% of group B for T3 and 67.9% vs. 52.4% for N1. It is worth noting that stage 3 was recorded in more than half of the patients in each group (64.3%). The comparison revealed no statistically significant differences between both groups in the TNM staging system.

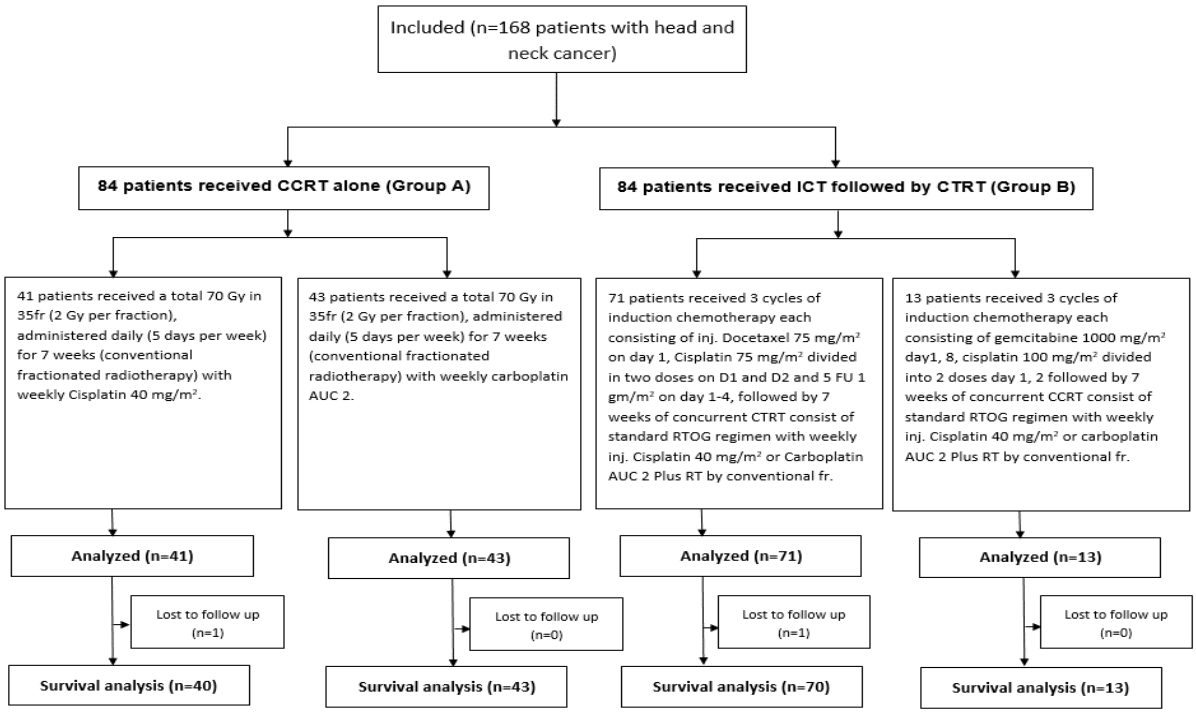

Figure 1. STROBE flow chart showing patient enrollment and randomization.

Table 1. Demographic data of patient and tumor characteristics.

Item		Group A (n=84)	Group B (n=84)	P value
Age	20 - 39	4 (4.8%)	9 (10.7%)	<0.001*
	40 - 49	7 (8.3%)	20 (23.8%)	
	50 - 59	34 (40.5%)	40 (47.6%)	
	60 - 69	28 (33.3%)	14 (16.7%)	
	70 - 79	11 (13.1%)	1 (1.2%)	
BMI (kg/m^2)	Mean (SD)	27.83 (6.26)	25.8 (6.08)	0.034*
Sex	Male	65 (77.4%)	62 (73.8%)	0.59
	Female	19 (22.6%)	22 (26.2%)	
Comorbidities	No chronic illness	38 (45.2%)	61 (72.6%)	<0.001*
	Cardiac disease	6 (7.1%)	1 (1.2%)	0.117
	DM	24 (28.6%)	11 (13.1%)	0.014*
	Hypertension	28 (33.3%)	11 (13.1%)	0.002*
	Chronic liver disease	5 (6%)	3 (3.6%)	0.72
	Chronic kidney disease	2 (2.4%)	0 (0%)	0.497
	Thyroid disease	2 (2.4%)	0 (0%)	0.497
	COPD	1 (1.2%)	1 (1.2%)	>0.999
Smoking		50 (59.5%)	52 (61.9%)	0.752
Performance	ECOG PS 1	58 (69%)	79 (94%)	<0.001*
	ECOG PS 2	26 (31%)	5 (6%)	
Diagnosis	Laryngeal cancer	47 (56%)	37 (44%)	0.182
	Oral cavity cancers	14 (16.7%)	10 (11.9%)	
	Cancer of the oropharynx	3 (3.6%)	5 (6%)	
	Cancer of the nasopharynx	17 (20.2%)	25 (29.8%)	
	Cancer of the hypopharynx	2 (2.4%)	4 (4.8%)	
	Maxillary sinus tumours	0 (0%)	3 (3.6%)	
	Ethmoid sinus tumours	1 (1.2%)	0 (0%)	
Presentation	Hoarseness of voice	31 (36.9%)	26 (31%)	0.415
	Progressive tongue mass	1 (1.2%)	0 (0%)	>0.999
	Mouth ulcer	6 (7.1%)	8 (9.5%)	0.577
	Neck swelling	13 (15.5%)	20 (23.8%)	0.174
	Dyspnoea/Stridor	6 (7.1%)	3 (3.6%)	0.496
	Facial pain and swelling	4 (4.8%)	4 (4.8%)	>0.999
	Submandibular mass	1 (1.2%)	0 (0%)	>0.999
	Lip ulcer	1 (1.2%)	2 (2.4%)	>0.999
	Dysphagia	5 (6%)	7 (8.3%)	0.549
	Nasal congestion and hearing problem	0 (0%)	1 (1.2%)	>0.999
	Alveolar mass	3 (3.6%)	2 (2.4%)	>0.999
	Eye ptosis	0 (0%)	1 (1.2%)	>0.999
	Ear pain (otalgia)	3 (3.6%)	5 (6%)	0.72
	Decrease of voice tone	5 (6%)	7 (8.3%)	0.549
	Nasal obstruction	2 (2.4%)	1 (1.2%)	>0.999
	Epistaxis	1 (1.2%)	1 (1.2%)	>0.999
	Vertigo	0 (0%)	1 (1.2%)	>0.999
	Odynophagia	0 (0%)	1 (1.2%)	>0.999
	Aphonic	4 (4.8%)	0 (0%)	0.121
Grade	Grade 1	2 (2.4%)	3 (3.6%)	0.211
	Grade 2	46 (54.8%)	57 (67.9%)	
	Grade 3	29 (34.5%)	17 (20.2%)	
	Grade 4	7 (8.3%)	7 (8.3%)	
T stage	T1	20 (23.8%)	12 (14.3%)	0.101
	T2	20 (23.8%)	20 (23.8%)	
	T3	24 (28.6%)	38 (45.2%)	
	T4	20 (23.8%)	14 (16.7%)	
N stage	N0	6 (7.1%)	10 (11.9%)	0.152
	N1	57 (67.9%)	44 (52.4%)	
	N2	11 (13.1%)	20 (23.8%)	
	N3	10 (11.9%)	10 (11.9%)	
M stage	M0	84 (100%)	84 (100%)	---
TNM stage	Stage 3	54 (64.3%)	54 (64.3%)	0.873
	Stage 4a	16 (19%)	18 (21.4%)	
	Stage 4b	14 (16.7%)	12 (14.3%)	

Induction Chemotherapy Group (Group B)

In the study population, 84 patients underwent induction chemotherapy. 71 patients (84.5%) received 3 cycles of TPF (Taxotere, Cisplatin, and 5 FU), and 13 patients (15.5%) received 3 cycles of Gemcitabine, Cisplatin. Tumor response was assessed using RECIST criteria, and 21.4% had a complete response, while 59.5% obtained a partial response, with an ORR of 81%. Patients were evaluated for toxicity. As a result, 88.1% developed toxicity manifested as grade 2 febrile neutropenia in 21.4%, mild vomiting in 19%, mild neurotoxicity in 17.9%, and grade 1 diarrhea in 15.5%, as shown in Table 2.

Post concomitant chemo-radiotherapy

In terms of concurrent chemotherapy, 48.8% of group A (CCRT alone) and 85.7% of group B (ICT followed by CCRTH) received weekly cisplatin, while 51.2% and 14.3%, respectively, received weekly carboplatin. Regarding patient compliance, 89 individuals had their treatment halted. Radiotherapy was postponed to 46.4% of group A (with a median duration of 6 consecutive days) and 59.5% of group B (with a median duration of 7 consecutive days). Moreover, the onset of radiotoxicity was significantly earlier in group B at a median of 13^{th} sessions vs. 15^{th} sessions in group A, with a statistically significant difference (P = 0.008), as demonstrated in Table 3. As shown in Figure 2, Group B (ICTH followed by CCRTH) had a considerably greater overall response rate following concurrent chemo-radiotherapy than group A (CCRTH alone) (82.1% vs. 69%, P=0.048). In groups A and B, the rate of complete response was 23.8% compared to 51.2%, the rate of partial response was 45.2% compared to 31%, the rate of stable disease was 25% compared to 11.9%, and the rate of progressive disease was 6% in both groups. Interestingly, Group B had a greater complete response rate (51.2%) than Group A (23.8%). All patients experienced concomitant chemo-radiotherapy-induced toxicity, with varying degrees of severity. Oral fungal infection occurred in both groups, with group B having a considerably (P = 0.001) lower severity grade than group A (22.6% vs. 15.5% mild grades and 6% vs. 29.8% intermediate grades).

Table 2. Induction chemotherapy data for Group B.

Item		N	%
Induction chemotherapy	Induction with 3 cycles TPF	71	84.5
	Induction with 3 cycles Gemzar, cisplatin	13	15.5
Induction chemotherapy-induced toxicity		74	88.1
Oral fungal infection	Moderate grade 3	1	1.2
	Severe grade 4	1	1.2
Skin toxicity	Mild grade 1 – 2	1	1.2
Poor oral feeding		4	4.8
Hepatotoxicity elevated liver enzymes	Grade 1	3	3.6
	Grade 2	8	9.5
	Grade 3	1	1.2
Neurotoxicity	Mild	15	17.9
	Moderate	12	14.3
Febrile neutropenia	Grade 1	9	10.7
	Grade 2	18	21.4
	Grade 3	6	7.1
Vomiting	Mild	16	19
	Moderate	7	8.3
	Severe	2	2.4
Diarrhea	Grade 1	13	15.5
	Grade 2	8	9.5
	Grade 3	2	2.4
Anaemia	Grade 1	1	1.2
Hypo cellular bone marrow	Grade 1	5	6.0
	Grade 2	3	3.6
Easy fatigability		7	8.3
Vocal cord paralysis (laryngitis)		1	1.2
Acute kidney injury		6	7.1
Post CTH assessment	Complete response	18	21.4
	Partial response	50	59.5
	Stable disease	14	16.7
	Progressive disease	2	2.4
Overall response rate		68	81

In addition, the level of skin toxicity differed considerably between groups (P = 0.047), with group B having fewer light grades (39.3% vs. 20.2%) and moderate grades (8.3% vs. 11.9%) as illustrated in Table 3.

Progression-free survival and overall survival analysis

Patients were enrolled from January 2014 to December 2018 based on data totally obtained from medical records, with a follow-up period ending in January 2024. The Kaplan-Meier curve and log-rank test analysis showed no significant difference in progression-free survival between the two therapy groups, as demonstrated in Figure 3a. Overall survival analysis revealed that patients who received ICTH followed by CCRTH had a significantly better OS than those who received CCRT alone (P=0.022), with a median of 50 months (95%CI: 49 to 52) vs. 42 months (95%CI: 40 to 45) and HR of 0.68 (95%CI: 0.49 to 0.95), as demonstrated in Table 5 & Figure 3b.

Factors related to PFS and OS in participants from both groups

In univariate Cox regression analysis, the TNM stage was statistically significant; patients with stages 4A and 4B had a significantly higher risk of disease progression than those with stage 3, with HR (95%CI) of 1.59 (1.07 to 2.36, P = 0.023) and 1.66 (1.07 to 2.58, P = 0.024), respectively. This is shown in Table 6. In multivariable analysis, patients with chronic diseases had a lower hazard of disease progression as compared to those with no chronic diseases, (HR=0.68, 95%CI: 0.47 to 0.98, P=0.039). In comparison to patients who received CCRT alone, those who received ICT followed by CCRT showed a significantly lower hazard of having disease progression (HR=0.59, 95%CI: 0.40 to 0.85, P=0.005), as demonstrated in Table 4**.** In univariate Cox regression analysis, patients with chronic diseases had better survival as compared to those with no chronic diseases (HR = 0.72, 95% CI: 0.47 to 0.98, P = 0.039). As regards TNM stage, patients with stage 4b had significantly shorter survival than those with stage 3 (HR = 1.67, 95% CI: 1.07 to 2.59, P = 0.023). In comparison to patients receiving CCRT alone, those receiving ICT followed by CTRT had significantly better survival (HR = 0.71, 95% CI: 0.52 to 0.97, P = 0.03). In multivariate analysis, the line of treatment and having chronic illness were substantially linked with OS among patients as follows: Patients who received ICT followed by CTRT showed significantly better survival than those who received CCRT alone (HR=0.47, 95%CI: 0.32 to 0.69, P<0.001). Patients with chronic diseases had better survival as compared to those with no chronic diseases (HR = 0.64, 95% CI: 0.43 to 0.95, P = 0.026), as illustrated in Table 5.

Chemotherapeutic regimens in the ICTH Group

Patients undergoing ICT followed by CCRT were separated into two subgroups: Group IB: Included 71 patients subjected to induction by 3 cycles of TPF. Group IIB: Included 13 patients subjected to induction by 3 cycles (Gemcitabine & cisplatin/carboplatin). Group IB had significantly lower rates of hepatotoxicity (5.6% vs 30.8% had grade 2 and 0% vs 7.7% had grade 3), as well as hypo-cellular bone marrow (4.2% vs 15.4% had grade 1 and 0% vs 23.1% had grade 2) as shown in Table 6 & Figure 4. Among patients who received induction chemotherapy, there was no statistically significant difference in PFS & OS between patients who received 3 cycles (Docetaxel /cisplatin/5fu) and those who received 3 cycles (Gemcitabine & cisplatin/carboplatin) as in Figure 5a, b.

DISCUSSION

Surgery, chemotherapy, and radiation therapy are all part of the multimodal strategy used to treat HNC, depending on the disease's location and stage. More than 75% of HNC patients require radiotherapy, which can be given alone or in combination with chemotherapy (Santos et al., 2019; Ferrari et al., 2020). RT was suggested at some time in 74% of all patients with head and neck cancer (Delaney et al., 2005).

The goal of this retrospective record-based study was to better evaluate the efficacy and safety of induction chemotherapy (ICT) followed by CCRT versus standard CCRT alone in patients with LASCCHNC. In our study, the mean age of patients ranged from 50 to 59 years old, with a male predominance, and the most common stage was performance ECOG 1 with T3 and N1. This is consistent with the Paradigm study, which found that patients were relatively young (median age 54 years) with a male predominance, and that all patients had a WHO performance status of 0-1 (Haddad et al., 2018). The present results are consistent with Dhaka et al. (2022) who deals with the fact that most of the patients had ECOG performance 1 and 2, median age 59 years, male gender, and stage 3 and 4 in both arms.

Tumor response was assessed in our study using RECIST criteria, and the total response rate was considerably greater in the induction group than in the CCRTH alone group (82.1% vs. 69%, with a P value of 0.048). The complete response rate was higher in Group B (51.2%) than in Group A (23.8%).

Table 3. Concurrent chemo-radiotherapy results of the analyzed groups.

		Group A (n=84)	Group B (n=84)	P value
Concurrent chemotherapy	Weekly Cisplatin	41 (48.8%)	72 (85.7%)	<0.001*
	Weekly Carboplatin	43 (51.2%)	12 (14.3%)	
Radiotherapy delay	No	45 (53.6%)	34 (40.5%)	0.089
	Yes	39 (46.4%)	50 (59.5%)	
Duration of delay (days)		6 (4 – 8)	7 (3.75 – 14)	0.358
Onset of radiotoxicity (sessions)		15 (12 - 20)	13 (9 - 18)	0.008*
CCRTH induced toxicity		84 (100%)	84 (100%)	---
Oral fungal infection	Mild grade 1 - 2	13 (15.5%)	19 (22.6%)	0.001*
	Moderate grade 3	25 (29.8%)	5 (6%)	
	Severe grade 4	5 (6%)	6 (7.1%)	
Dysphagia	Mild grade 1 - 2	19 (22.6%)	15 (17.9%)	0.837
	Moderate grade 3	30 (35.7%)	30 (35.7%)	
	Severe grade 4	19 (22.6%)	23 (27.4%)	
Mucositis	Mild grade 1 - 2	13 (15.5%)	8 (9.5%)	0.499
	Moderate grade 3	22 (26.2%)	19 (22.6%)	
	Severe grade 4	5 (6%)	8 (9.5%)	
Skin toxicity	Mild grade 1 - 2	17 (20.2%)	33 (39.3%)	0.047*
	Moderate grade 3	10 (11.9%)	7 (8.3%)	
	Severe grade 4	1 (1.2%)	1 (1.2%)	
Poor oral feeding		16 (19%)	22 (26.2%)	0.269
Xerostomia		6 (7.1%)	6 (7.1%)	>0.999
Taste disorder		9 (10.7%)	7 (8.3%)	0.599
Febrile neutropenia	Grade 1	1 (1.2%)	0 (0%)	>0.999
	Grade 2	1 (1.2%)	1 (1.2%)	
Vomiting	Mild	1 (1.2%)	0 (0%)	>0.999
Hypo cellular bone marrow	Grade 1	0 (0%)	1 (1.2%)	>0.999
Easy fatigability		0 (0%)	3 (3.6%)	0.246
Hoarseness of voice		0 (0%)	1 (1.2%)	>0.999
Acute kidney injury		0 (0%)	2 (2.4%)	0.497
Post RTH assessment	Complete response	20 (23.8%)	43 (51.2%)	0.002*
	Partial response	38 (45.2%)	26 (31%)	
	Stable disease	21 (25%)	10 (11.9%)	
	Progressive disease	5 (6%)	5 (6%)	
Overall response rate		58 (69%)	69 (82.1%)	0.048*

Numerical data are presented as median (IQR) and categorical data are presented as frequency (%), Statistical significance at P value<0.05.

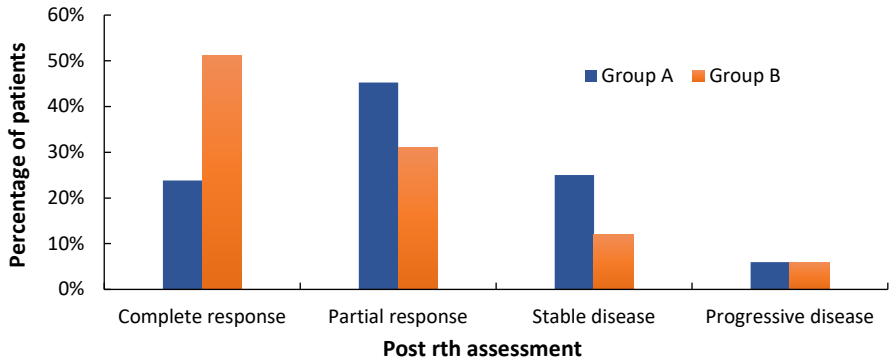

Figure 2. Post-radiotherapy assessment of the examined groups (P value=0.002*). Total number of patients=168, 84 patients in each group. Categorical data are presented as frequency (%). Categorical data were evaluated with the Chi-square test.

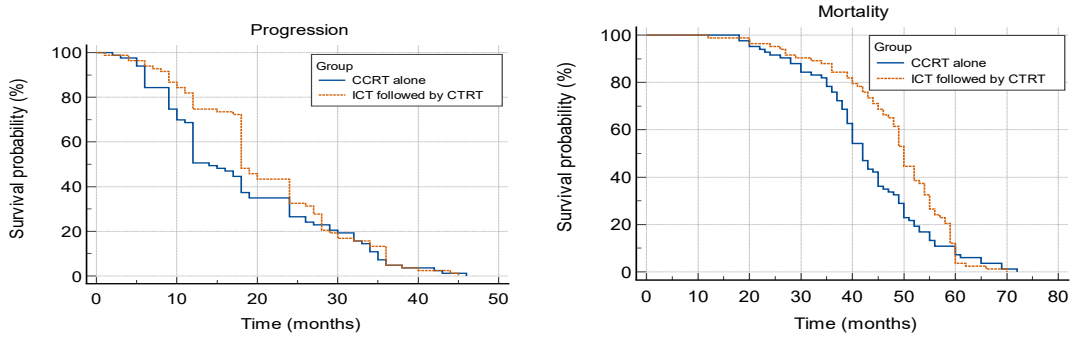

Figure 3. Kaplan-Meier curve for progression-free survival (a) and overall survival (b) of patients by treatment strategy. Group A and B (Number of events=83 patients in each group, Median (95%CI) was 14 and 18 respectively, HR (95%CI) was Ref and 0.79 respectively with P-value =0.159 in (A). Median (95%CI) was 42 and 50 respectively, HR (95%CI) was Ref and 0.68 respectively with P-value =0.022 in (b).

Table 4. Cox-regression analysis for covariates linked with patients' PFS.

Item		Univariate analysis			Multivariable analysis		
		HR	95%CI	P value	HR	95%CI	P value
Age (years)	20 - 39	Ref			Ref		
	40 - 49	1.60	0.82 to 3.10	0.169	1.72	0.81 to 3.61	0.156
	50 - 59	1.54	0.85 to 2.79	0.152	1.46	0.73 to 2.89	0.283
	60 - 69	0.88	0.47 to 1.67	0.704	0.70	0.31 to 1.57	0.389
	70 - 79	1.40	0.64 to 3.06	0.404	1.05	0.40 to 2.79	0.920
Sex	Male	Ref			Ref		
	Female	0.76	0.53 to 1.08	0.129	0.86	0.56 to 1.32	0.487
Having Chronic disease		0.78	0.57 to 1.07	0.126	0.68	0.47 to 0.98	0.039*
Smoking (+ve)		1.10	0.81 to 1.51	0.538	1.08	0.76 to 1.55	0.657
BMI		1.00	0.98 to 1.03	0.940	1.00	0.97 to 1.03	0.951
Performance	ECOG PS 1	Ref			Ref		
	ECOG PS 2	1.01	0.67 to 1.51	0.964	1.53	0.90 to 2.60	0.117
Diagnosis	Laryngeal cancer	Ref			Ref		
	Oral cavity cancers	0.62	0.39 to 1	0.051	0.67	0.38 to 1.16	0.154
	Cancer of the oropharynx	1.06	0.51 to 2.2	0.880	1.31	0.53 to 3.26	0.556
	Cancer of the nasopharynx	1	0.69 to 1.45	0.987	0.85	0.52 to 1.41	0.537
	Cancer of the hypopharynx	0.96	0.42 to 2.21	0.924	0.92	0.36 to 2.40	0.871
	Maxillary or ethmoid sinus tumors	0.71	0.26 to 1.95	0.508	0.77	0.25 to 2.35	0.644
TNM stage	Stage 3	Ref			Ref		
	Stage 4a	1.59	1.07 to 2.36	0.023	1.61	0.99 to 2.60	0.054
	Stage 4b	1.66	1.07 to 2.58	0.024	1.66	0.97 to 2.84	0.063
Line of treatment	CCRT alone	Ref			Ref		
	ICT followed by CTRT	0.82	0.6 to 1.11	0.193	0.59	0.40 to 0.85	0.005*
Duration of radiotherapy delay (days)		1.01	0.99 to 1.04	0.334	1.03	1.00 to 1.06	0.066
Onset of radiotoxicity (sessions)		1.01	0.98 to 1.04	0.64	0.99	0.96 to 1.03	0.749

Ref: Reference category, HR: Hazard ratio, CI: Confidence interval, Statistical significance at P value<0.05.

Table 5. Cox-regression analysis for characteristics associated with patients' overall survival.

Item		Univariate analysis			Multivariable analysis		
		HR	95%CI	P value	HR	95%CI	P value
Age (years)	20 - 39	Ref			Ref		
	40 - 49	1.43	0.73 to 2.77	0.293	1.48	0.71 to 3.10	0.298
	50 - 59	1.51	0.84 to 2.73	0.169	1.40	0.71 to 2.76	0.333
	60 - 69	0.92	0.48 to 1.74	0.788	0.74	0.32 to 1.69	0.468
	70 - 79	0.96	0.43 to 2.13	0.921	0.76	0.28 to 2.03	0.581
Sex	Male	Ref			Ref		
	Female	0.91	0.63 to 1.3	0.589	1.05	0.67 to 1.62	0.842
Having Chronic disease		0.72	0.52 to 0.99	0.049	0.64	0.43 to 0.95	0.026*
Smoking (+ve)		1.07	0.78 to 1.47	0.656	1.09	0.77 to 1.56	0.622
BMI		1.00	0.98 to 1.03	0.985	1.00	0.97 to 1.03	0.976
Performance	ECOG PS 1	Ref			Ref		
	ECOG PS 2	0.88	0.59 to 1.32	0.539	1.23	0.71 to 2.15	0.457
Diagnosis	Laryngeal cancer	Ref			Ref		
	Oral cavity cancers	0.68	0.42 to 1.09	0.110	0.67	0.38 to 1.16	0.154
	Cancer of the oropharynx	0.98	0.47 to 2.03	0.952	1.08	0.44 to 2.68	0.867
	Cancer of the nasopharynx	1.00	0.69 to 1.45	0.999	0.84	0.52 to 1.37	0.486
	Cancer of the hypopharynx	1.34	0.58 to 3.09	0.494	1.24	0.48 to 2.21	0.658
	Maxillary or ethmoid sinus tumors	0.74	0.27 to 2.03	0.743	0.78	0.26 to 2.37	0.663
TNM stage	Stage 3	Ref			Ref		
	Stage 4A	1.32	0.89 to 1.95	0.167	1.31	0.82 to 2.09	0.260
	Stage 4B	1.67	1.07 to 2.59	0.023	1.62	0.96 to 2.75	0.073
Line of treatment	CCRT alone	Ref			Ref		
	ICT followed by CTRT	0.71	0.52 to 0.97	0.030	0.47	0.32 to 0.69	<0.001*
Duration of radiotherapy delay (days)		0.99	0.97 to 1.02	0.569	1.01	0.98 to 1.04	0.386
Onset of radiotoxicity (sessions)		1.01	0.98 to 1.04	0.48	1.00	0.97 to 1.03	0.962

Ref: Reference category, HR: Hazard ratio, CI: Confidence interval, Statistical significance at P value<0.05.

Table 6. Induction chemotherapy-induced toxicity and response of group B according to induction type.

Item		Group IB (n=71)	Group IIB (n=13)	P value
Induction chemotherapy-induced toxicity		62 (87.3%)	12 (92.3%)	>0.999
Oral fungal infection	Moderate grade 3	1 (1.4%)	0 (0%)	>0.999
	Severe grade 4	1 (1.4%)	0 (0%)	
Skin toxicity	Mild grade 1 - 2	0 (0%)	1 (7.7%)	0.155
Poor oral feeding		3 (4.2%)	1 (7.7%)	0.496
Hepatotoxicity elevated liver enzymes	Grade 1	3 (4.2%)	0 (0%)	0.008*
	Grade 2	4 (5.6%)	4 (30.8%)	
	Grade 3	0 (0%)	1 (7.7%)	
Neurotoxicity	Mild	15 (21.1%)	0 (0%)	0.097
	Moderate	11 (15.5%)	1 (7.7%)	
Febrile neutropenia	Grade 1	7 (9.9%)	2 (15.4%)	0.713
	Grade 2	16 (22.5%)	2 (15.4%)	
	Grade 3	6 (8.5%)	0 (0%)	
Vomiting	Mild	14 (19.7%)	2 (15.4%)	0.532
	Moderate	7 (9.9%)	0 (0%)	
	Severe	2 (2.8%)	0 (0%)	
Diarrhea	Grade 1	12 (16.9%)	1 (7.7%)	0.178
	Grade 2	8 (11.3%)	0 (0%)	
	Grade 3	1 (1.4%)	1 (7.7%)	
Anaemia	Grade 1	1 (1.4%)	0 (0%)	>0.999
Hypo cellular bone marrow	Grade 1	3 (4.2%)	2 (15.4%)	<0.001*
	Grade 2	0 (0%)	3 (23.1%)	
Easy fatigability		7 (9.9%)	0 (0%)	0.589
Vocal cord paralysis (laryngitis)		1 (1.4%)	0 (0%)	>0.999
Acute kidney injury		5 (7%)	1 (7.7%)	>0.999
Post CTH assessment	Complete response	18 (25.4%)	0 (0%)	0.113
	Partial response	41 (57.7%)	9 (69.2%)	
	Stable disease	11 (15.5%)	3 (23.1%)	
	Progressive disease	1 (1.4%)	1 (7.7%)	

Categorical data are presented as frequency (%), Statistical significance at P value<0.05.

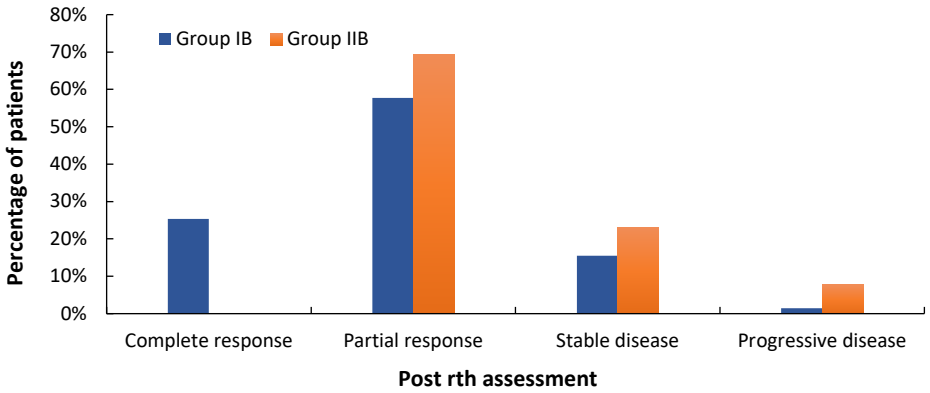

Figure 4. Post-induction chemotherapy assessment of group B based on type (P-value =0.113). Number of patients= 84. Data are presented as frequency (%) and were evaluated with the Chi-square test.

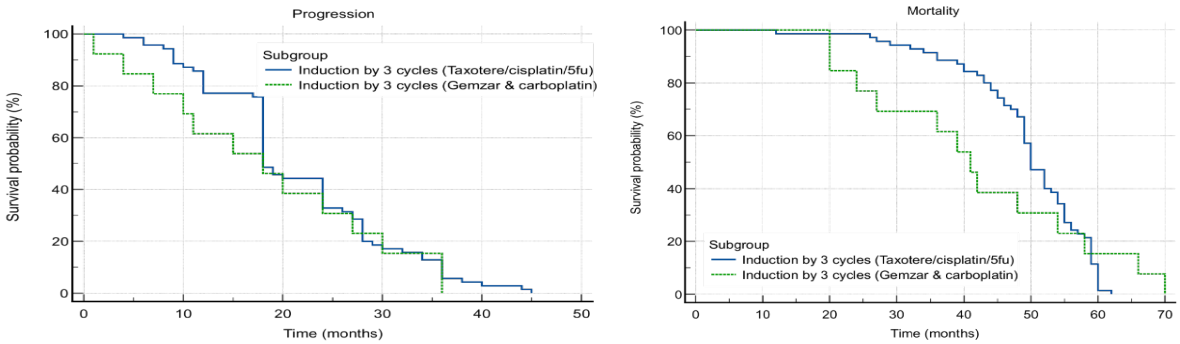

Figure 5. Kaplan-Meier curve for progression-free survival (a) and overall survival (b) of group B by induction chemotherapy type. Number of patients= 84. Median PFS was 18 months in group IB and 18 months in group IIB with insignificant P value (P value= 0.437). Median OS was 50 months in group IB and 41 months in group IIB with insignificant P value (P value= 0.716).

This pattern of results is like prior research conducted by Jakhar et al. who found 37.5% versus 53.3% CR rate and 79.1% versus 82.1% total response rate (CR + PR) at 6-8 weeks of treatment completion in CTRT versus ICT-CTRT groups, which was consistent with Hitt et al. work (Hitt et al., 2014; Jakhar et al., 2017).

The present study results support the hypothesis that therapy techniques showed no statistically significant influence on progression-free survival. The overall survival demonstrated that patients who had ICTH followed by CCRTH had a significantly higher median OS than those who received CCRT alone, with a median of 50 months versus 42 months. These findings are congruent with the claims made in a randomized phase 2 Italian trial. The study found that the sequential chemo-radiotherapy group performed better than the concurrent group, with greater completion rates. Response rates were 21.2% for concurrent and 50% for sequential. The findings prompted an Italian phase 3 trial to compare the two therapies (Paccagnella et al., 2010).

Furthermore, the DeCIDE study has been introduced. Induction chemotherapy followed by chemo-radiotherapy was compared with chemo-radiotherapy in this phase 3 trial treatment. In this study, only patients with N2 and N3 stages were included, this one was also stopped early due to slow accrual. Induction chemotherapy did not improve survival when added, but it did seem to lower the cumulative incidence of distant metastasis when compared to chemo-radiotherapy alone (Cohen et al., 2012).

The results of this research provide supporting evidence that both groups had an oral fungal infection; however, group B's grade was noticeably less severe than group A's (6% vs. 29.8% exhibited moderate grades, and 22.6% vs. 15.5% showed mild grades). Additionally, there was a significant difference in the degree of skin toxicity across groups ($P = 0.047$), with group B showing less skin toxicity than group A (39.3% vs. 20.2% exhibited mild grades and 8.3% vs. 11.9% showed moderate grades). This pattern of results is consistent with the previous literature showing that no patient exhibited toxicity in Grade 4. Anemia and neutropenia were the most frequently reported Grade 2–3 hematologic toxicities, while stomatitis, skin responses, dysphagia, nausea, and vomiting were the most frequently reported non-hematologic toxicities. The ICT-CTRT arm's toxicities were noticeably higher (Dhaka et al., 2022). The expected greater proportion of febrile neutropenia (ICT-CTRT) was managed with prophylactic G-CSF. There were no toxicity-related deaths in either arm. The GP regimen for induction chemotherapy was effective, acceptable, and had mild toxicity.

In the present work, we assess the efficacy of GP as an IC regimen to the TPF regimen, including treatment response, toxicity, and survival outcomes (Zhang et al., 2022; Zhu et al., 2024). In our study, the complete response rate after concurrent chemo-radiotherapy was significantly higher in group B (ICTH followed by CCRTH) than in group A (CCRTH alone) (82.1% vs. 69%). Group B received a larger percentage of complete responses (51.2%) than Group A (23.8%) and this match with YAU and colleagues that found three cycles of GP as induction treatment for loco regionally NPC improved overall clinical outcomes response rates exceeded 90% (Yau et al., 2006). We found that Group IB exhibited markedly reduced rates of hepatotoxicity (5.6% compared to 30.8% for grade 2 and 0% compared to 7.7% for grade 3), alongside lower instances of hypo-cellular bone marrow (4.2% versus 15.4% for grade 1 and 0% versus 23.1% for grade 2).

Among patients who received induction chemotherapy, there were no statistical differences in PFS and OS between patients who received 3 cycles (Docetaxel /cisplatin/5fu) and those who received 3 cycles (Gemcitabine & cisplatin/carboplatin). This matches the results gained by Zhang et al. who showed that induction GP combined with concurrent chemoradiation significantly improved failure-free survival and OS in loco regionally progressed NPC compared to concurrent chemoradiation alone. 97% of the recipients successfully finished all three cycles of GP treatment, demonstrating their high level of tolerance to the regimen (Zhang et al., 2019). A study done by Gharib et al. showed that the 3-year OS was 90.8% in the GP group and 81% in the TPF group, while the 3-year PFS rate was 88.6% in the GP group and 81.7% in the TPF group. Although there was no discernible difference, the 3-year survival rates were higher than the GP regimen. The findings were in line with those of Zeng et al.; the OS was 94.4% against 81.6% and the 3-year DFS was 83.1% versus 92.0% in the TPF and GP groups, respectively (Zeng et al., 2018; Gharib et al., 2024).

CONCLUSION

We concluded that IC followed by concomitant chemoradiotherapy is a sensible option with improved outcomes for patients with LAHNSCC. Our investigation was limited by the fact that it was carried out utilizing data from a cancer registry in the past. All patients passed away on the deadline, and some data was overlooked. The small number of patients overall in both groups was another

drawback, and we suggest more patients be included in future studies.

LIST OF ABBREVIATION

AC: adjuvant chemotherapy, AUC: Area under the curve, BMI: body mass index, CCRTH: concomitant chemo-radiotherapy, CI: confidence interval, CT: computed tomography, ECOG: Eastern Cooperative Oncology Group, EORTC: European Organization for Research and Treatment of Cancer, 5 FU: 5 fluorouracil, Gy: gray, HNC: head and neck cancer, HR: hazard ratio, ICT: induction chemotherapy, IQR: interquartile range, LASCCHN: locally advanced squamous cell carcinoma in head and neck cancers, MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer, ORR: overall response rate, OS: overall survival, PET: Positron emission tomography, PFS: progression-free survival, RECIST: Response evaluation criteria in solid tumors, RTH: radiotherapy, RTOG: Radiation therapy oncology group, SCC: squamous cell carcinoma, SCCHN: squamous cell carcinoma head and neck, TPF: Taxotere cisplatin 5FU; UICC: Union for International Cancer Control; VA: Veterans Affairs.

AUTHORS' CONTRIBUTIONS

SHS and MMA conceptualized and designed the work. SHS and MMA collected, analyzed, and interpreted the data. SHS and MMA reviewed and supervised the work. SHS and MMA wrote the first draft of the manuscript. All writers agreed on the final version of the manuscript.

FUNDING

None

THE AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this investigation are accessible from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Research Ethics Committee of the Suez Canal University Department of Clinical Oncology & Nuclear Medicine approved the study, and informed consent was waived because it was a retrospective medical record review. FOMSCU's research ethics committee approved the final protocol. Clinical data were collected upon approval by FOMSCU's research ethics committee. The research data was gathered from the patient's records. The material was kept confidential and patient privacy was protected; no personal data was disclosed. The data was only utilized for research. In addition, patient interaction was necessary to reduce the problems of faulty recording and follow-up. Data analysis was demonstrated in a secretive manner, with no mention of patients' names.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

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