ORIGINAL ARTICLE

Induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone for locally advanced laryngeal & nasopharyngeal cancers: A retrospective study

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Received: July 24, 2022 **Accepted:** August 19, 2022 **Online Published:** August 25, 2022
DOI: 10.5430/jst.v12n2p1 **URL:** https://doi.org/10.5430/jst.v12n2p1

ABSTRACT

Background: One of the most common cancers all over the world is Head and Neck cancers, with higher mortality rates among developing countries. Squamous cell carcinomas (SCCs) represent more than 90%. SCCs arise commonly from the mucosal lining of the upper aerodigestive tract.

Objective: To Compare between Concurrent Chemoradiation following Neoadjuvant Chemotherapy versus Concurrent Chemoradiation alone in Locally Advanced Larynx & Nasopharynx Cancer (stage III or IV$_{A,B}$) regarding efficacy, toxicity, progression free survival, disease free survival and organ preservation (in laryngeal cancer).

Methods: A Retrospective study was conducted to Compare between Concurrent Chemoradiation following Neoadjuvant Chemotherapy versus Concurrent Chemoradiation alone in Locally Advanced Larynx & Nasopharynx Cancer (stage III or IV A, B) in the Clinical Oncology Department, Suez Canal University Hospital, Ismailia, Egypt between 1/2017 & 12/2018, with follow up 2 years (from 1/2019 to 12/2020).

Results: Results of our study show a statistic significance in progression free survival in Concurrent chemoradiation following Neoadjuvant chemotherapy compared with concurrent chemoradiation alone.

Conclusions: Neoadjuvant chemotherapy by TPF or PF is a wise choice in the locally advanced squamous cell carcinoma of the nasopharynx and larynx (non-metastatic cases). Better results were detected in radiological assessment post radiation therapy in laryngeal cancer cases and progression free survival in both treatment groups.

Key Words: Squamous cell carcinomas, Concurrent chemoradiation, Laryngeal & nasopharyngeal cancers

1. INTRODUCTION

Head& neck cancers are aggressive disease in its biological nature. Cancer can result in cervical lymph node enlargement, airway obstruction and bone destruction. Disease can metastasize early despite effective local treatment.[1]

Risk factors for head and neck cancers include tobacco smoking, alcohol consumption and viral infection (Epstein Barr virus in nasopharynx carcinoma & human papilloma virus in head and neck cancers). Poor oral hygiene, chewing betel nut and diet with low fruits and vegetable intake increase the risk of disease development.[2]

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Incidence decrease, as well as morbidity, in case of good oral hygiene, cessation of smoking and vaccine administration.[3]

Larynx and oral cavity cancers represent most common affected head & neck cancer sites. Both sites of cancers are commonly affected in cancer registries. Incidence of Laryngeal cancer in the United States is 0.7% with males' predominance about 5 to 6 folds.[4]

Nasopharyngeal cancers are rare. South Asia, Middle East and North Africa are the most common regions of affection in cancer registries.

Nasopharyngeal cancer can affect any age group, including young age & children. In the United States, half of nasopharyngeal cases are less than 55 years old. Risk of nasopharyngeal cancer increases cumulative throughout life.[5]

Management depends on tumor site, staging, age and ECOG performance status. Management of Head & neck cancers include surgery, radiation therapy, chemotherapy, targeted therapy, or combined modality treatment.[6]

Recently, Definitive radiotherapy and Concurrent Chemoradiotherapy have proved marvelous efficacy over the last 30 years in the management of locally advanced head and neck cancers. In certain circumstances, they are preferred over surgery.[7]

Concurrent Chemoradiotherapy in locally advanced head and neck squamous cell carcinoma treatment has been widely used with better treatment outcome. Over the last years, chemotherapy has been administered in the adjuvant & neoadjuvant settings and concurrently with radiation.[8]

Concurrent chemoradiotherapy has proved efficacy in treatment as the most common pattern of recurrence is locoregional. This approach is preferred among Clinical Oncologists over years due to its high response rate.[9]

The meta-analysis of chemoradiation versus radiation alone included additional trials that were comparisons of induction, concurrent, or adjuvant chemoradiotherapy. The meta-analysis found that there was high response of locoregional control with concurrent chemoradiation compared with Neoadjuvant chemotherapy followed by radiation therapy.[6]

2. METHODS

2.1 Study design

A retrospective study was conducted to Compare between Concurrent Chemoradiation following Neoadjuvant Chemotherapy versus Concurrent Chemoradiation alone in Locally Advanced Larynx & Nasopharynx Cancer (stage III or IV A, B) regarding efficacy, toxicity, progression free survival, disease free survival and organ preservation (in laryngeal cancer).

This study was done in the Clinical Oncology Department, Suez Canal University Hospital, Ismailia, Egypt from 1/2017 to 12/2018 with follow up two years after (from 1/2019 to 12/2020).

2.2 Study population

Study population included patients with measurable, previously untreated, histopathologically proven SCCs of Larynx & Nasopharynx (stage III and IV$_{A,B}$) and not candidate for surgery (either due to irresectable disease, advanced tumor stage or organ preservation protocol for laryngeal cancer cases).

2.2.1 *Inclusion criteria*

- Histologically proved squamous cell carcinoma of larynx and nasopharynx cases , presented to Clinical Oncology Department during the period from 1/2017 to 12/2018 & follow up period from 1/2019 to 12/2020.
- Patients with locally advanced larynx (who were candidates for organ preservation) and nasopharynx cancer (stage III or IV$_{A,B}$).
- Patients proved radiologically to be non-metastatic with a measurable disease.
- Patients with ECOG performance state ≥ 2.
- Patients of either sex, age group (20-60 years old) & previously untreated.
- Patients were not candidate for surgery (either due to irresectable disease, advanced tumor stage or organ preservation protocol for laryngeal cancer cases).

2.2.2 *Exclusion criteria*

- Patients with other pathological subtypes as lymphomas, blastomas, sarcomas and neuroendocrine tumors.
- Patients with other comorbidities or poor performance status ECOG > 2 who can't tolerate chemotherapy.
- Patients with serious cardiopulmonary disease and other serious chronic illnesses as unstable cardiac, renal & hepatic patients.

2.2.3 *Enrollment of participants*

A list of all eligible patients in the specified period (from 1/2017 to 12/2018 & follow up from 1/2019 to 12/2020) was retrieved from the patients' records and traced to record disease outcome and clinicopathological parameters.

The data required for this study was collected from the files recording system in Clinical Oncology Department.

In this system, personal, clinical, laboratory, radiological, pathological, treatment received, and follow up data for every patient are recorded in separate files.

The following information was obtained from files about each patient:

- Personal data: name, age at diagnosis (20-60 years old), sex (male or female), history of smoking.
- All patients underwent a complete clinical examination.
- Staging; TNM staging system at diagnosis.
- Performance status.
- Co-morbidities.
- Tumoral variables; tumor site (larynx, nasopharynx), histological type, differentiation, LVI, PNI, and LN involvement.
- Baseline examinations and investigations: Endoscopy, Laryngoscopy, Computerized tomography scan of head & neck, Magnetic resonance imaging or PET CT, abdominal & pelvic ultrasound, and dental assessment before starting radiotherapy.

2.2.4 *Clinical & pathological evaluation*

- Larynx and nasopharyngeal carcinoma were diagnosed after the onset of symptoms.
- Common clinical presentations include neck swelling, change in voice, nosebleed, difficult breathing and nasal discharge.
- Diagnosis of laryngeal & nasopharyngeal cancer warrants Physical examination, endoscopic examination for mucosal mapping, and biopsy for diagnostic confirmation of diagnosis and baseline radiological assessment.
- Laboratory studies were done with a goal of assessing patients' organ function (liver, kidneys) in anticipation of diagnostic and therapeutic procedures.

2.2.5 *Studies include the following*

- Full laboratory study (Complete blood count, liver and kidney functions)
- Ultrasound of the abdomen/liver.
- Chest radiograph or CT scan.
- PET CT scanning.

The TNM staging system was used for adequate staging. Patient prognosis was determined according to the clinical, radiological and pathological stage of laryngeal & nasopharyngeal cancer at diagnosis. Histologic grade, and evidence of lymph vascular and perineural invasion were also determined.

2.3 Sample size

The sample size was determined using the following equation:[10] see Equation 1.

$$n = 2\left[\frac{(Z_{\alpha/2}+Z_{\beta})*\sigma}{\mu_1-\mu_2}\right]^2 \quad (1)$$

n: The required sample size
$Z_{\alpha/2}$: The critical value that divides the central 95% of the Z distribution from the 5% in the tail = 1.96
Z_beta: The critical value that separates the lower 20% of the Z distribution from the upper 80% = 0.80
σ: The estimate of standard deviation of survival lifetime among induction chemotherapy group in patients with locally advanced larynx and nasopharyngeal cancer = 0.19 years[11]
μ_1: Mean survival lifetime among Neoadjuvant chemotherapy group in patients with locally advanced larynx and nasopharyngeal cancer = 4.59 years[11]
μ_2: Mean survival lifetime among concurrent chemoradiation group in patients with locally advanced larynx and nasopharyngeal cancer = 4.46 years[11]

Therefore, the calculated sample size was 32 participants in each group; however, after adding the expected (drop-out) rate (10%), the final sample size was 35 participants in each group.

2.4 Procedure

For Group A receiving neoadjuvant chemotherapy, patients receive either TPF or PF treatment protocol according to patient tolerability. TPF was given as docetaxel 75 mg/m^2 intravenously on day 1, cisplatin 100 mg/mm^2 intravenously on day 1, and 5FU 1 gm/mm^2 on days 1–4 as continuous infusion. PF was given as cisplatin 100 mg/mm^2 intravenously on day 1, and 5FU 1 gm/mm^2 on days 1–4 as continuous infusion Patient should perform echocardiography first before receiving 5FU to evaluate cardiac condition. Patients received 3 cycles every 21 days. Patients in group A undergo radiological assessment after the neoadjuvant chemotherapy and before going on to concurrent chemoradiotherapy with cisplatin (weekly 40 mg/mm^2).

For group A and Group B receiving concurrent chemoradiation, Conformal radiotherapy was given once daily over 6 to 7 weeks. The total dose was 66 to 70 Gy, in 2 Gy fractions. In both groups, radiotherapy was given 5 days a week (i.e., excluding weekends). For Group A, chemoradiotherapy after TPF/PF protocol of chemotherapy started within a minimum interval of 3 weeks and no later than 6 weeks after the start of the last cycle of chemotherapy.

Chemoradiotherapy was expected to start as soon as possible after chemotherapy allowing for patient's recovery and radiation planning to occur. Radiological assessment was done after concurrent chemoradiotherapy among both treatment groups. Response was evaluated according to Recist criteria and Adverse events were assessed according to the National Cancer Institute CTCAE.

The primary end point was progression free survival, disease free survival (among patients achieving complete response only) and toxicity profile.

2.5 Data management & statistical analysis

All analyses were performed using statistical package for social sciences (SPSS) for windows version 22.0 (SPSS, Chicago, IL, USA). Descriptive data was presented as mean ± *SD* or percentages. Fisher's exact test and chi-square test were used for statistical analysis of categorical variables. Analysis of continuous variables were performed by independent *t*-test or non-parametric Mann-Whitney *U*-test according to the normality of the distributions. Correlation between numerical variables was assessed using Pearson's correlation coefficient or non-parametric Spearman's correlation coefficient according to the normality of the distributions. For all tests a probability value of less than 0.05 was considered statistically significant.

3. RESULTS

Between January 1, 2017, to December 31, 2018, 70 patients were enrolled. 35 patients were assigned to receive neoadjuvant chemotherapy followed by concurrent chemoradiotherapy (group A) and 35 patients assigned to receive concurrent chemoradiotherapy alone (group B). Patient's characteristics were matched between both groups (se Table 1). Median follow up period in (months) were 29.28 with a range (24.0-46.0).

Table 1. Patients characteristics

	Induction chemotherapy Group A (n = 35)		**Concurrent chemoradiation alone Group B (n = 35)**		**Test of Sig.**	***p***
	No.	**%**	**No.**	**%**		
Sex						
Male	30	85.7	31	88.6	$\chi^2 = 0.128$	$^{FE}p = 1.000$
Female	5	14.3	4	11.4		
Age (years)						
Min – Max	39.0 – 60.0		38.0 – 60.0			
Mean ± *SD*	51.69 ± 7.09		53.51 ± 5.93		$t = 1.170$	.246
Median (IQR)	53.0 (45.0 – 58.0)		55.0 (52.0 – 56.5)			
Chronic illness						
No	25	71.4	21	60.0	1.014	.314
Yes						
IHD	0	0.0	2	5.7	2.059	$^{FE}p = .493$
DM	6	17.1	7	20.0	0.094	.759
HTN	6	17.1	10	28.6	1.296	.255
HCV	1	2.9	2	5.7	0.348	$^{FE}p = 1.000$
CKD	0	0.0	2	5.7	2.059	$^{FE}p = .493$
History of stroke	0	0.0	1	2.9	1.014	$^{FE}p = 1.000$
Smoking						
Non-smoker	11	31.4	7	20.0	1.197	.274
Smoker	24	68.6	28	80.0		
Performance status						
0	21	60.0	18	51.4	1.213	
1	12	34.3	16	45.7		
2	2	5.7	1	2.9		
Follow up period (months)						
Min – Max	24.0 – 46.0					
Median	29.28					

Note. IQR: Inter quartile range; *SD*: Standard deviation; *t*: Student *t*-test; χ^2: Chi square test; FE: Fisher Exact; *p*: *p*-value for comparing between the studied groups

In group A, age range were between 39.0-60.0 years old with a mean age of 51.69 ± 7.09 years, while in group B, the age range were 38.0 – 60.0 years with a mean age 53.51 ± 5.93 years. Patients were mostly males. There was no statistically significant difference between both groups regarding age, gender, chronic illness, and smoking status. All patients enrolled had ECOG performance status less than or equal 2.

Our study included 39 patients with laryngeal cancer and 31 patients with nasopharyngeal cancer. Pathological grading and TNM staging were well balanced between both study groups (see Table 2).

The most common clinical presentation was hoarseness of voice [12 patients (66%) in group A and 12 patients (57.1%) in group B] noticed mostly among laryngeal cancer patients, and neck swelling [12 patients (70.6%) in group A and 9 patients (64.3%) in group B] noticed among nasopharyngeal cancer patients.

Table 2. Pathological characteristics

Pathology	Larynx (n = 39)				NPC (n = 31)			
	Induction chemotherapy (n = 18)		Concurrent chemoradiation alone (n = 21)		Induction chemotherapy (n = 17)		Concurrent chemoradiation alone (n = 14)	
	No.	%	No.	%	No.	%	No.	%
Grade I	0	0.0	1	4.8	0	0.0	0	0.0
II	13	72.2	13	61.9	11	64.7	10	71.4
III	5	27.8	7	33.3	6	35.3	4	28.6
Staging III	9	50	4	19	7	41.2	4	28.6
IVa	5	27.8	10	47.6	10	58.8	10	71.4
IVb	4	22.2	7	33.3	0	0	0	0

Table 3. Toxic effects in group (A) post neoadjuvant chemotherapy

Induction chemotherapy induced toxicity	TPF (n = 24)		PF (n = 11)		χ^2	*p*
	No.	%	No.	%		
Hepatotoxicity	8	33.3	8	72.7	4.717*	.030*
Grade 1	8	100.0	8	100.0	–	–
Grade 2	0	0.0	0	0.0		
Grade 3	0	0.0	0	0.0		
Vomiting	8	33.3	7	63.6	2.828	^{FE}p = .144
Mild	4	50.0	4	57.1	0.511	^{MC}p = 1.000
Moderate	2	25.0	2	28.6		
Severe	2	25.0	1	14.3		
Diarrhea	5	20.8	2	18.2	0.033	^{FE}p = 1.000
Grade 1	3	60.0	0	0.0	3.143	^{MC}p = .577
Grade 2	1	20.0	2	100.0		
Grade 3	1	20.0	0	0.0		
Neuropathy	15	62.5	3	27.3	3.747	.053
Mild	0	0.0	0	0.0	2.880	^{FE}p = .216
Moderate	8	53.3	0	0.0		
Severe	7	46.7	3	100.0		
Febrile neutropenia	11	45.8	5	45.5	0.000	.983
Grade 1	3	27.3	0	0.0	1.493	^{MC}p = .616
Grade 2	5	45.5	3	60.0		
Grade 3	3	27.3	2	40.0		

Note. IQR: Inter quartile range; *SD*: Standard deviation; *t*: Student *t*-test; χ^2: Chi square test; FE: Fisher Exact; **p*: *p*-value for comparing between the studied groups

In group A receiving neoadjuvant chemotherapy, 24 patients receive TPF protocol, and 11 patients receive PF protocol, according to patient tolerability. We noticed that hepatotoxicity was more common among patients receiving PF protocol, with statistically significant results (see Table 3). No significant difference was noticed between both treatment protocols according to post chemotherapy assessment.

For groups A (Neoadjuvant chemotherapy followed by chemoradiotherapy with cisplatin) and B (chemoradiotherapy with cisplatin only): radiotherapy was given once daily over 6 to 7 weeks. The total dose was 66 to 70 Gy, in 2 Gy fractions. In both groups, radiotherapy was given 5 days a week (ie, excluding weekends). For Group A, chemoradiotherapy after TPF/PF protocol of chemotherapy started within a minimum interval of 3 weeks and no later than 8 weeks after the start of the last cycle of chemotherapy. Chemoradiotherapy was expected to start as soon as possible after chemotherapy allowing for patient recovery and radiation planning to occur. Radiation breaks were present our study. 19 patients (13 In group A and 6 in group B) had a radiation break of 5 days or more. We noted a statistically significant difference between two studied groups as regard duration of Interruption of treatment due to toxicity, with more prolonged duration of interruption in group A.

On comparison between the two studied groups regarding post radiotherapy assessment, there were a statistically significant difference noted mostly in Group A receiving neoadjuvant chemotherapy followed by concurrent chemoradiotherapy more among laryngeal cancer patients (see Table 4).

We noticed a statistically significant difference between both treatment groups regarding mucositis (p = .041) & poor oral feeding (p = .027), with more toxicity noted among Group A receiving neoadjuvant chemotherapy. No serious adverse events occur among both study groups (see Table 5).

Table 4. Comparison between the studied groups according to post radiotherapy assessment

Post radiotherapy assessment (Nasopharyngeal cases)	Group A				Group B				χ^2	^{MC}p
	TNM3 (n = 7)		TNM4a (n = 10)		TNM3 (n = 4)		TNM4a (n = 10)			
	No.	%	No.	%	No.	%	No.	%		
Stationary	1	14.3	1	10.0	0	0.0	2	20.0	8.892	.128
Partial response (regression)	1	14.3	7	70.0	1	25.0	6	60.0		
Complete response	5	71.4	2	20.0	3	75.0	2	20.0		
Progression	0	0.0	0	0.0	0	0.0	0	0.0		

Post radiotherapy assessment (Laryngeal cases)	Group A						Group B						χ^2	^{MC}p
	TNM3 (n = 9)		TNM4a (n = 5)		TNM4b (n = 4)		TNM3 (n = 4)		TNM4a (n = 10)		TNM4b (n = 7)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Stationary	0	0.0	0	0.0	1	25.0	0	0.0	2	20.0	3	42.9	22.247*	.028*
Partial response (regression)	2	22.2	3	60.0	2	50.0	1	25.0	6	60.0	4	57.1		
Complete response	7	77.8	2	40.0	1	25.0	3	75.0	1	10.0	0	0.0		
Progression	0	0.0	0	0.0	0	0.0	0	0.0	1	10.0	0	0.0		

Note. χ^2: Chi square test; MC: Monte Carlo; *p: p-value for comparing between the studied groups

Median follow up period in (months) were 29.28 with a range (24.0-46.0). Both treatment groups show nearly same incidence of treatment progression and relapse. Kaplan-Meier survival curve were used to analyze whether Groups influenced the prognostic value of progression free survival among all study population. In group A, PFS mean was 22.06, median was 20.0. In group B, PFS mean was 16.30, median was 12. 6-month Progression free survival rate was 100% for group A and 69.2% for group B. 1 year Progression free survival rate was 88.9% for group A and 34.6% for group B. 2 years PFS was 33.3% for group A and 22% for group B. Kaplan–Meier survival curve show statistically significant difference between both groups regarding progression free survival with more favorable outcomes among Group A (p =.039) (see Figure 1).

Kaplan-Meier survival curve were used to analyze whether Groups influenced the prognostic value of disease-free survival among patients achieved complete response only according to Recist criteria. In group A, DFS mean was 18.99 & median was 24.0. In group B, DFS mean was 20.0 and

median was 18. 6 months DFS for group A & B was 94.1% and 100%, respectively. 1 year and 2 years DFS was 76.5%, 32.2% for group A and 88.9%, 22.2% for group B respectively, showing statistically significant between both treatment groups (p = .897)(see Figure 2).

Table 5. Comparison between the different studied groups according to toxicity during CCRTh

Toxicity	Larynx (n = 39)				NPC (n = 31)				χ^2	p
	Induction chemotherapy (n = 18)		Concurrent chemoradiation alone (n = 21)		Induction chemotherapy (n = 17)		Concurrent chemoradiation alone (n = 14)			
	No.	%	No.	%	No.	%	No.	%		
Oral fungal INF	10	55.6	16	76.2	7	41.2	9	64.3	5.059	.168
Mild	0	0.0	4	25.0	1	14.3	3	33.3	8.067	^{MC}p = .204
Moderate	6	60.0	8	50.0	3	42.9	6	66.7		
Severe	4	40.0	4	25.0	3	42.9	0	0.0		
Dysphagia	18	100.0	20	95.2	17	100.0	14	100.0	2.524	^{MC}p = 1.000
Mild	0	0.0	3	15.0	0	0.0	2	14.3	7.274	^{MC}p = .249
Moderate	12	66.7	13	65.0	9	52.9	9	64.3		
Severe	6	33.3	4	20.0	8	47.1	3	21.4		
Mucositis	14	77.8	18	85.7	14	82.4	13	92.9	1.438	^{MC}p = .740
Mild	0	0.0	7	38.9	2	14.3	3	23.1	12.311*	^{MC}p = .041*
Moderate	9	64.3	9	50.0	9	64.3	10	76.9		
Severe	5	35.7	2	11.1	3	21.4	0	0.0		
Skin toxicity	15	83.3	13	61.9	14	82.4	10	71.4	2.942	^{MC}p = .425
Grade I	4	26.7	1	7.7	1	7.1	1	10.0	8.130	^{MC}p = .530
Grade II	5	33.3	6	46.2	9	64.3	7	70.0		
Grade III	5	33.3	6	46.2	4	28.6	2	20.0		
Grade IV	1	6.7	0	0.0	0	0.0	0	0.0		
Poor oral feeding										
No	6	33.3	13	61.9	6	35.3	11	78.6	9.183*	.027*
Yes	12	66.7	8	38.1	11	64.7	3	21.4		
Xerostomia										
No	14	77.8	14	66.7	14	82.4	7	50.0	4.532	.209
Yes	4	22.2	7	33.3	3	17.6	7	50.0		
Taste disorder										
No	9	50.0	14	66.7	8	47.1	10	71.4	2.994	.392
Yes	9	50.0	7	33.3	9	52.9	4	28.6		

Note. χ^2: Chi square test; MC: Monte Carlo; *p: Statistically significant at $p \leq .05$

4. DISCUSSION

Management of LA-SCCHN has evolved over the last several years. Nowadays based on international guidelines, it's highly recommended for irresectable SCCHN to start concomitant chemoradiotherapy based on level I evidence. (12) The main role of neoadjuvant chemotherapy followed by radiotherapy or CCRT alone is to improve loco regional control and decrease the possibility of distant micro metastasis.[14, 15]

Effective treatment for irresectable disease and in organ preservation protocol, consists of the combination of chemotherapy and radiotherapy (RTX), either in a combined modality or sequential pattern.[15] In 2007, TAX 323 and TAX 324 trials examined a core question about the best neoadjuvant chemotherapy regimen in SCCHN.[16–18] Later on the GORTEC laryngeal study demonstrated the same results that TPF was considerably better than PF protocol for SCCHN in term of survival, local control, and organ preservation.[19]

Results of our study show a statistically significant differ-

ence between both study groups in progression free survival, which was better in group A receiving Neoadjuvant chemotherapy followed by concurrent chemoradiation compared with concurrent chemoradiation alone.

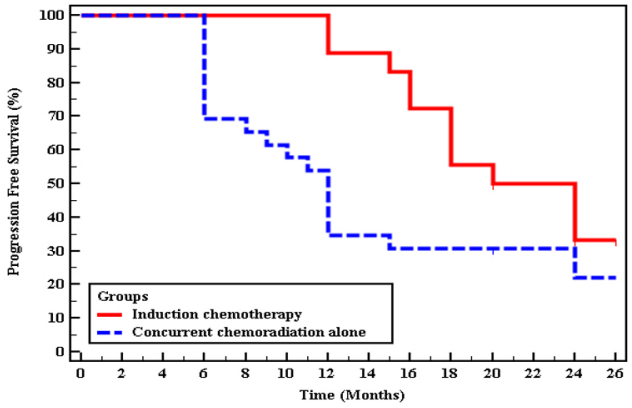

Figure 1. Kaplan-Meier survival curve for progression free survival among both treatment groups

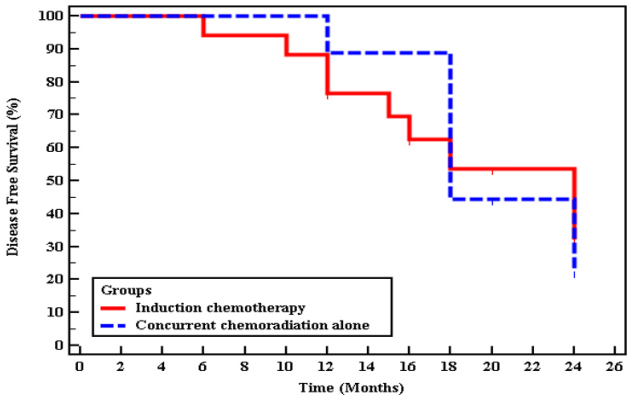

Figure 2. Kaplan-Meier survival curve for disease free survival among both treatment groups

In 2016, Wilfried et al. concluded that induction treatment with TPF before concurrent RT-CHX does not result in a statistical significant improvement of OS or PFS(20). Those results were in line with another meta-analysis by Zhang et al. that also detected no significant benefit for neoadjuvant TPF before concurrent chemoradiotherapy.[21]

Cohen et al. randomly assigned 285 patients with locally advanced SCCHN to receive either concurrent chemoradiotherapy with docetaxel or to neoadjuvant chemotherapy followed by concurrent chemoradiation. Neoadjuvant chemotherapy consisted of 2 cycles of TPF. Radiotherapy was administrated twice daily with 1.5 Gy to total doses of 74–75 Gy. Results of this study showed that neoadjuvant chemotherapy resulted in non-significant improvement of OS and PFS.[11]

Hitt et al. randomized 439 patients to receive either neoadjuvant chemotherapy (3 cycles TPF or PF protocol) followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in SCCHN. Chemoradiation was given as 70 Gy in 7 weeks of RT with cisplatin 100 mg/m^2 every 21 days. The primary endpoints were PFS and time-to-treatment failure (TTF). Neoadjuvant chemotherapy before concurrent RT-CHX resulted in no benefit in OS and PFS.[22]

Haddad et al. randomized 145 patients with locally advanced HNSCC to receive either 3 cycles neoadjuvant chemotherapy followed by concurrent chemoradiotherapy with weekly carboplatin or weekly docetaxel, or to concurrent chemoradiotherapy with cisplatin. Accelerated radiotherapy (72 Gy) was given within 6 weeks with a concomitant boost technique in both treatment groups. Concurrent chemoradiotherapy resulted in a better OS and PFS but not reaching statistical significance.[23]

The DeCIDE trial evaluated the role of neoadjuvant chemotherapy (2 cycles TPF) followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone (hyper fractionated regimen delivering 0.15 Gray twice per day every other week, potentiated with docetaxel, 5-FU, and hydroxyurea). The Study included high risk patients with N2 – N3 disease, and OS benefit was higher than expected but similar in both arms (HR = 0.91; 95% CI 0.59–1.41).[11]

Paccagnella et al. enrolled 101 patients with locally advanced SCCHN. patients were randomized into two groups, group A received neoadjuvant chemotherapy (with 3 cycles TPF) followed by concurrent chemoradiotherapy (70 Gy/35 fractions/7 weeks + cisplatin 20 mg/m2 and 5-FU 800 mg/m^2 continuous infusion days 1–4 + 43–46) and group B received concomitant chemoradiotherapy alone.

Results of this randomized phase II trial showed a statistically significant difference in complete response rate between both study groups, with high response rate noticed in group A (50% vs. 21%), with improvement observed in OS and PFS. These results are in line with the results of our study which demonstrate statistically significant improvement in PFS in group A receiving concomitant chemoradiotherapy.[24]

Posner et al. randomly allocated 501 patients in a phase III trial to receive neoadjuvant chemotherapy with TPF or PF followed by concurrent chemoradiotherapy with weekly carboplatin and radiation therapy 5 days per week. A radical dose with range between 70 to 74 Gy, administered with conventional dose (2 Gy per fractions in 5 days per week) was delivered.[25]

Vermorken et al. randomized patients with age of 18 and 70 years with locally advanced SCCHN to receive neoadju-

vant chemotherapy for 4 cycles. Assessment was done post neoadjuvant chemotherapy & patients without evidence of disease progression received radiotherapy. Patients received either conventional fractionation, accelerated or hyper fractionated regimens. In the conventional radiotherapy group, patients receive a total dose of 66–70 Gy, while a dose of 70 and 74 Gy in accelerated and hyper fractionated regimens respectively.[15]

In the TREMPLIN trial, patients received conventional EBRTH with a total dose of 70 Gy delivered in 2 Gy per fraction.[26] In RTOG trial, published in 2003 and followed by updated results in 2013, patients received a conventional dose of 70 Gy in 35 fractions,[27,28] which were in line with the dose of radiotherapy delivered in our study.

Hematological and renal toxicity are the main adverse events of neoadjuvant TPF. In our study, we noticed that hepatotoxicity was more common among patients receiving PF neoadjuvant treatment protocol, with statistically significant results. Neuropathy were more common among patients in group A receiving TPF, with statistically significant difference.

After receiving concurrent chemoradiotherapy, we noticed a statistically significant difference between both treatment groups regarding mucositis (p = .041) & poor oral feeding (p = .027), with more toxicity noted among Group A receiving neoadjuvant chemotherapy. No serious adverse events occur among both study groups.

In phase III trials evaluating neoadjuvant chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone, the proportion of patients not receiving radiotherapy due to various reasons (progression, death, toxicity, refusal of treatment) ranged from 8.8% to 10% in DeCIDE,[11] PARADIGM,[23] and GSTTC (26) trials. A high proportion was noticed also in the GORTEC 2007.02 study[14] (16.5%) and TTCC[18] trials (26%: 30.7% in the TPF arm and 22.4% in the PF arm).

In DeCIDE trial, adverse events noted during concomitant treatment include high grade stomatitis and radiation dermatitis. Those adverse events were similar in both study groups regardless the neoadjuvant chemotherapy regimen, but hematological toxicity was more frequently noticed in patient receiving neoadjuvant TPF.[11]

IN The TTCC trial, Grade 3–4 stomatitis and grade 3-4 renal dysfunction were more frequently reported in the neoadjuvant chemotherapy group (possibly due to high dose of cisplatin).[22] The best compliance to concomitant chemoradiotherapy were noticed in the Italian trial[24] and the Spanish trial.[22]

5. Conclusions

In conclusion, induction chemotherapy by TPF or PF is a reasonable approach for locally advanced non-metastatic nasopharyngeal and laryngeal squamous cell carcinoma as it gives better results in post radiotherapy assessment for laryngeal cancers and progression free survival for both laryngeal and nasopharyngeal cancer patients.

Study limitations

Some limitations of our study must be considered, due to its retrospective design, a selection bias cannot be fully excluded. We also took into consideration that it was a single center-based study with a small number of patients, with a relatively small sample size, that precluded the accurate matching of both groups, in term of comparable staging, hence their proper comparison.

A major limitation in the current study was the incompliance of some patients to regular follow ups and unavailability of some information. So, we recommend later research with a larger number of patients and longer period of follow up.

List of abbreviations

CCRTH: Concurrent chemoradiotherapy; CKD: Chronic Kidney disease; CT: computed tomography; DM: Diabetes Miletus; EBV: Epstien Barr virus; FOMSCU: Faculty of Medicine Suez Canal University; HCV: Hepatitis C virus; HPV: Human Papilloma virus; HTN: Hypertension; ICT: Induction chemotherapy; IHD: Ischemic heart disease; LA SCCHN: Locally advanced squamous cell carcinoma head and neck; LN: Lymph node; LVI: Lymphovascular invasion; MRI: Magnetic resonance imaging; NPC: Nasopharyngeal carcinoma; PET: Positron emission tomography; PF: Cisplatin 5FU; PNI :Perineural invasion; SCCs: Squamous cell carcinomas; TPF: Taxotere Cisplatin 5FU.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Suez canal University Department of Clinical Oncology & Nuclear medicine, Suez Canal University, and informed consent was waived being a retrospective medical record review study.

- Approval of the research ethics committee of FOMSCU to the final protocol.
- Clinical data will be collected after approval of the research ethics committee of (FOMSCU).
- The research data was collected from the patients' files. Confidentiality of the information and patient privacy, no personal data was published. Data will be used

only in that research, this is beside that patients' contact was required in order to minimize the problems of inaccurate recording and follow up.

- Analysis of data was demonstrated in a secret way without mentioning patients' names.

ACKNOWLEDGEMENTS

I would like to thank all authors for their contribution in the design of the work. Any opinions, findings, and conclusions expressed in this material are those of the authors.

AUTHORS' CONTRIBUTIONS

SHS, WSA contributed to the conception and design of the work. SHS, WSA contributed to the acquisition, analysis, and interpretation of the data. SHS, WSA, MLZ, EMH revised and supervised the work. SHS wrote the initial draft of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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