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NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION FOR LOCALLY ADVANCED HEAD AND NECK CANCERS

By

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ABSTRACT

Background: The administration of chemotherapy with radiotherapy in the treatment of patients with locally advanced head and neck carcinoma has been broadly used. For many years, chemotherapy has been administered in the adjuvant or neoadjuvant settings and concurrently with radiotherapy.

Objective: To evaluate the role of neoadjuvant chemotherapy before concurrent chemoradiotherapy in treatment of locally advanced head and neck cancers regarding overall survival, progression free survival, toxicity and organ preservation.

Patients and Methods: A 40 patients (all of whom had stage III or IVA disease with no distant metastases and tumors considered to be unresectable or were candidates for organ preservation) received 3 cycles of **TPF** (docetaxel plus cisplatin and fluorouracil) induction chemotherapy, followed by chemoradiotherapy with weekly carboplatin and radiotherapy (70 Gy over 7 weeks) for 5 days per week.

Results: With a minimum of 6 months of follow-up (median follow up period 14.3 months), over all response rate was 95% with complete remission in 30 patients (75%), partial response in 3 patients (7.5%), stationary disease in 5 patients (12.5%) and progressive disease in 2 patients (5%). The median overall survival was not reached and 3 years survival was 62.8%. The toxicity associated with this protocol was controlled and no chemotherapy associated deaths recorded.

Conclusion: Induction chemotherapy by TPF is a reasonable approach for unresectable locally advanced head and neck squamous cell carcinoma and organ preservation for laryngeal and hypopharyngeal cancer patients. Also, it is of benefit in large tumor volume to decrease the volume of radiotherapy and subsequently its toxicity.TPF induction must be considered as one of the standards for larynx preservation.

INTRODUCTION

The concurrent administration of chemotherapy and radiotherapy has been the most promising approach, given that the dominant pattern of failure with radiotherapy is local and regional relapse. However, the high response rates seen with induction chemotherapy have historically made this approach attractive as well **(Pointreau et al., 2011)**.

Adding chemotherapy to loco-regional treatment was associated with an absolute survival benefit of 4% at both 2 years and 5 years, compared with loco-regional treatment alone **(Pignon et al., 2000*).***

During the last 30-40 years, there has been a gradual shift from surgery to definitive radiotherapy or chemoradiotherapy as effective approaches to treatment of locoregionally advanced head and neck cancers. Head and neck tumors often affect the structures associated with speech and swallowing and therapeutic intervention may damage these structures (**Machiels et al., 2014**).

The meta-analysis of chemoradiotherapy versus radiotherapy alone included additional trials that were comparisons of induction, concurrent, or adjuvant chemoradiotherapy. The meta-analysis found that there was a benefit of loco-regional control for concurrent chemoradiotherapy compared with induction chemotherapy followed by radiotherapy, but the comparisons should be viewed with caution considering the recent successes with the use of taxane-based induction regimens that were not included in the meta-analysis **(Pignon et al., 2009)**.

The induction regimen of docetaxel, cisplatin, and 5-fluorouracil has shown a survival advantage over cisplatin/5-fluorouracil, in the context of subsequent radiation treatment alone or subsequent radiation treatment and low-dose weekly carboplatin **(Posner et al., 2007*).***

The present work aimed to evaluate the neoadjuvant chemotherapy followed by concurrent chemoradiation for locally advanced head and neck cancers.

PATIENTS AND METHODS

Patients with previously untreated, measurable, nonmetastatic, histologically proven squamous cell carcinoma of the oral cavity, larynx, nasopharynx, oropharynx, hypopharynx, paranasal sinuses and nose who were operable (technically resectable) and candidates for organ preservation, or with a poor chance of cure, or inoperable were eligible. Patients received three cycles of TPF (docetaxel: 60 mg/m2 administered as a 1-hour i.v. infusion, i.v.cisplatin:75mg/m2 administered during a period of 2–3 hours, plus fluorouracil 1000 mg/m2/d as a continuous 24-hours infusion for 4 days).Induction chemotherapy was given every 3 weeks for three cycles. Assessment of the disease response by computed tomography (CT) of the head and neck and ENT assessment after finishing neoadjuvant chemotherapy. Responders then received 7 weeks of chemoradiotherapy with weekly carboplatin (area under the curve 1.5) and daily radiotherapy, starting 3–8 weeks after the start of the third cycle of induction chemotherapy. Dental assessment was a must and any dental procedure was done before starting radiation therapy by at least 7-10 days. All patients were given prophylactic granulocyte-colony stimulating factor (G-CSF) after 48 hours of administering chemotherapy by subcutaneous injection daily for five days. In case of residual disease after finishing concurrent chemoradiotherapy either in the primary site or neck lymph nodes a biopsy was considered and surgical intervention if possible, otherwise salvage chemotherapy was considered.

Induction Chemotherapy: Patients received 3 cycles of TPF, docetaxel (at a dose of 60 mg/m^2) was administered as a 1-hour intravenous infusion, followed by intravenous cisplatin (75 mg/m^2), administered during a period of 0.5 to 3

hours. After completion of the cisplatin infusion, fluorouracil (1000 mg/m^2/ day) was administered as a continuous 24-hour infusion for 4 days. Patients were given dexamethasone to prevent docetaxel-related hypersensitivity reactions, skin toxic effects, and fluid retention. Primary prophylaxis with recombinant granulocyte colony-stimulating factor was permitted.

Chemoradiotherapy: All patients received chemoradiotherapy starting by a mean period of 40.6 days after the start of the third cycle of induction chemotherapy by 3 dimensional conformal radiotherapy (3 D-CRT). Weekly carboplatin at an area under the curve of 1.5 was given as an intravenous infusion during a 1-hour period for a maximum of seven weekly doses during the course of radiotherapy. The definitive curative radiation dose administered to the primary tumor was 70 Gy administered as fractions of 2 Gy per day 5 days per week. The dose administered to uninvolved lymph nodes was at least 50 Gy. Involved lymph nodes were to receive 60 to 70 Gy.

Surgery: In case of residual disease after finishing concurrent chemoradiotherapy either in the primary site or neck lymph nodes a biopsy was considered and surgical intervention if possible, otherwise salvage chemotherapy was considered.

Assessments and Outcomes: A complete medical history was obtained and tumor assessment was performed at baseline. Tumor responses were assessed by clinical evaluation and imaging studies and were characterized according to modified WHO criteria after 3th cycle of induction chemotherapy, 6 to 12 weeks after the completion of chemoradio-therapy, and during follow-up visits until disease progression. Overall survival was calculated from the date of starting the study to the date of death; progression free survival was calculated from the date of starting the study to progression or death from any cause, whichever occurred first. Patients were monitored every three months in the first year, and every six months thereafter, Toxic effects were assessed weekly during induction chemotherapy, during and on completion of chemoradiotherapy, and at subsequent predefined intervals. We used the Common Toxicity Criteria (1994 version) of the Clinical Trials Group of the National Cancer Institute of Canada and the criteria of the Radiation Therapy Oncology Group of the EORTC for acute and late toxic effects of radiation.

Statistical Analysis: The analysis of survival was conducted in the intention-to-treat population with the use of the Kaplan–Meier method. Confidence intervals were calculated for median survival according to the method of Brookmeyer and Crowley. Hazard ratios were calculated with the use of the Cox proportional-hazards model. Study groups were compared by means of the log-rank test. All treated patients were included in the analysis of adverse events. All other hypothesis testing was two-sided at a significance level of 0.05.

RESULTS

During the period between November, 2011 and May, 2015, a total number of 40 patients were included at our study at Clinical Oncology and Nuclear Medicine Department, Al-Hussein University Hospital with a provisional diagnosis of head and neck squamous cell carcinoma. The cutoff date for the analysis of overall

survival was 31th July 2016 corresponding to 6 months of follow-up for the last patient enrolled in the study. Out of these patients, 19 patients (47.5%) were laryngeal squamous cell carcinoma, 7 patients (17.5%) were nasopharyngeal squamous cell carcinoma, 4 patients (10%) were squamous cell carcinoma of the oral cavity , 3 patients (7.5%) were squamous cell carcinoma of the Hypopharynx, 3 patients (7.5%) were squamous cell carcinoma of the oropharynx, 3 patients (7.5%) were squamous cell carcinoma of Paranasal sinuses and 1 patient (2.5%) was squamous cell carcinoma of the nasal cavity.

Patient's characteristics: The whole study group had mean age of 54.5 years (SD:± 8.8), 29 patients (72.5%) were males and 11 patients (27.5%) were females, Twenty eight patients (70%) were smokers and 8 patients (20%) still smoking along the course of treatment. The mean weight for patients was 71 kg with its range (55-98 kg - Table 1)**.**

Tumor characteristics: The whole study group showed squamous cell carcinoma in all patients (100%), grade II in 24 patients (60%), grade III was found in 10 patients (25%), and grade IV (Undifferentiated) in 6 patients (15%). Nineteen patients (47.5%) presented with T4 staging, while T3 staging was found in 13 patients (32.5%), and only 8 patient (20%) had T2 staging. Regional lymph node involvement was observed in 26 patients (65%),7 patients (17.5%)were N1disease,19 patients (47.5%) were N2 disease and 1 patient (2.5%) were N3 disease,13patients (32.5%) had negative nodal disease,17 patient(42.5%) were stage III and 23 patients(57.5%) were stage IVA disease (Table 2).

Table (1): Patients Characteristics.

Count / Characteristics		Number(40)	Percent
Age(years)	Mean ± standard deviation	54.5±8.8	
Gender	Male	29	72.5%
	Female	11	27.5%
Duration of symptoms before diagnosis (months)	Mean	5	
	range	1-12	
Smokers	No	12	30**%**
	Yes	28	70%
Role of surgery(Operability, number=33)	Non	17	51.5%
	Operable	16	48.5%
No role for surgery(number=7)	No role for surgery (nasopharynx)	7	17.5%
Weight (kg)	Mean	71	
	Range	55-98	

Table (2): Tumor characteristics.

Parameters / Pathological character	Pathological type	Number=40	Percent
	Squamous cell carcinoma	40	100%
Grade	II	24	60%
	III	10	25%
	IV	6	15%
T stage	T2	8	20%
	T3	13	32.5%
	T4	19	47.5%
N stage	N0	13	32.5%
	N1	7	17.5%
	N2	19	47.5%
	N3	1	2.5%
T.N.M. Stage	III	17	42.5%
	IVA	23	57.5%

Efficacy: At the time of the last analysis, patients had been followed for a minimum of 6 months and a median of 14.3 months. Median overall survival was not reached because of a relative short period of follow up. Estimated survival was at one year, two years and three years were, 81.8%, 68% and 62.8% respectively (Figure 1). The statistical difference in overall survival was in the age group (≤55 years and >55 years) with a significant p value (p=0.040) and with the early response to induction chemotherapy with the best overall survival in patients who achieved early C.R. than no early C.R. with a significant p value (**P=0.043** - Table 5).

Tumor progression was the most common cause of death occurred in 14 patients (35%) from the 40 included in the study, 12 patients (30%) had local relapse and 2 patients (5%) had local and distant metastasis in the lungs (1 patient was paranasal sinus cancer and 1 patient was nasal cancer), 2 patients (5%) died due to disease non related cause, one of them was due to sudden active hematemesis at home and the other one was due to sudden death at home.

Among patients with resectable tumors who were candidates for organ preservation, the median survival was not reached and 3 years overall survival was 74.6%. In patients with unresectable tumors, median survival was 30 months (**95% confidence interval; 12 -47.9) P =0.159)** and 3 years overall survival was 34.8%.

The median progression-free survival was not reached with the one year, two years and three years progression free survival were 76.7%, 65.2% and 65.2% respectively (Table 4 and Figure 2).

Assessment after induction chemotherapy revealed overall response rate 100% with complete remission in 10 patients (25%), partial response in 27 patients (67.5%) and stationary disease in 3 patients (7.5% - Table 3).

Assessment after finishing the course of treatment revealed over all response rate 95% with complete remission in 30 patients (75%), partial response in 3 patients (7.5%), stationary disease in 5 patients (12.5%) and progressive disease in 2 patients (5% - Table 3).

Complete response rate to induction chemotherapy is affected by the site of the primary tumor with the early response rate in the larynx and hypopharynx then the nasopharynx, paranasal sinuses and nasal cavity followed by the oropharynx and oral cavity with a significant P-value (**P=0.031**), Patients who achieved early C.R. have a higher O.S. than others with a significant P-value (**P=0.043**).

A subgroup analysis of the patients with cancer of the larynx and hypopharynx to assess the rate of laryngeal preservation after induction chemotherapy followed by concurrent chemoradiotherapy revealed that the laryngeal preservation rate was 65.8% in all cases and 96% in alive patients with the median LPFS 20 months for all patients and not reached in alive cases (Figures 6 & 7)

Table (3): Response rate.

Response rate \ Count		Number=40	Percent
Overall response rate after induction chemotherapy	C.R.	10	25%
	P.R.	27	67.5%
	S.D.	3	7.5%
Overall response rate after concurrent chemoradiotherapy	C.R.	30	75%
	P.D.	2	5%
	P.R.	3	7.5%
	S.D.	5	12.5%

C.R: complete response, P.R: partial response, S.D: stationary disease, P.D: progressive disease.

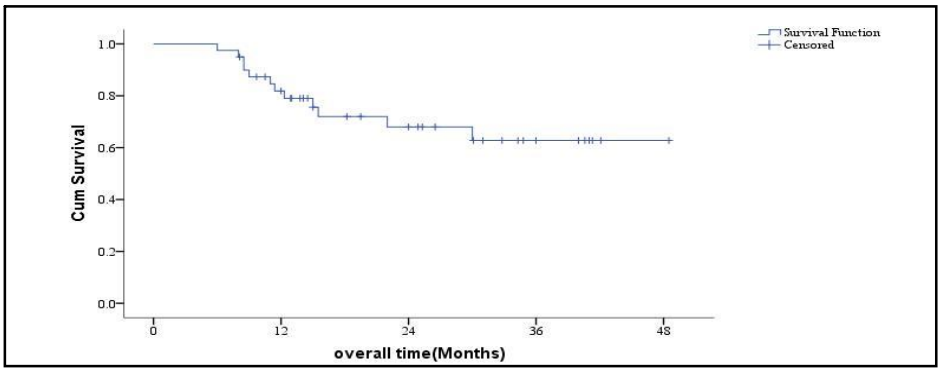

Figure (1): Overall survival curve.

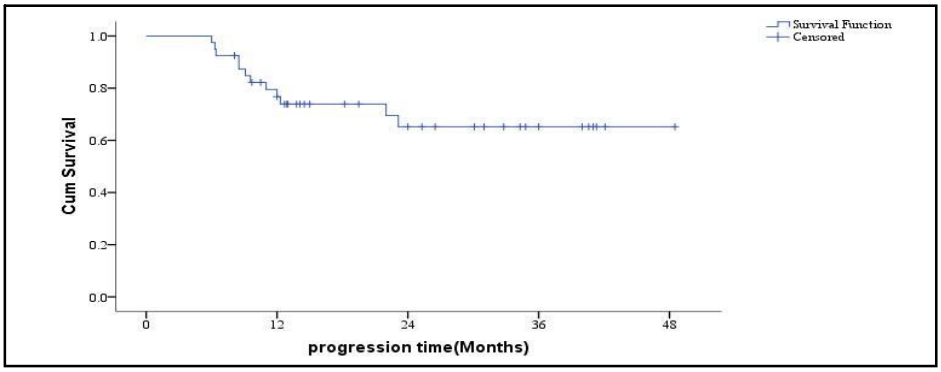

Figure (2): Progression free survival curve.

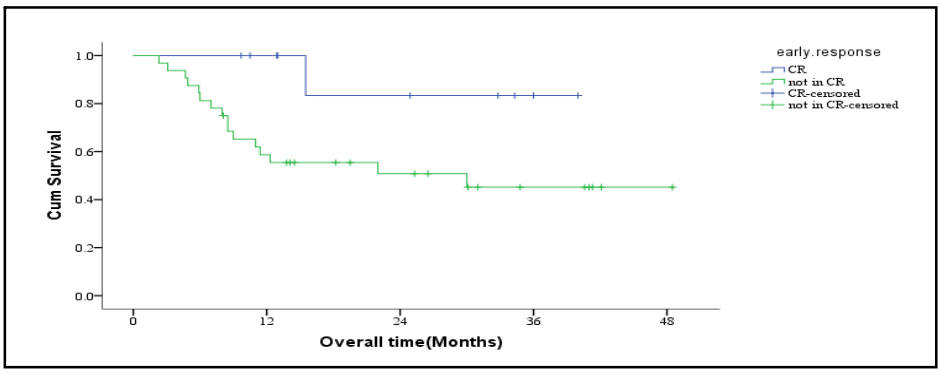

Figure (3): Effect of early complete response on overall survival.

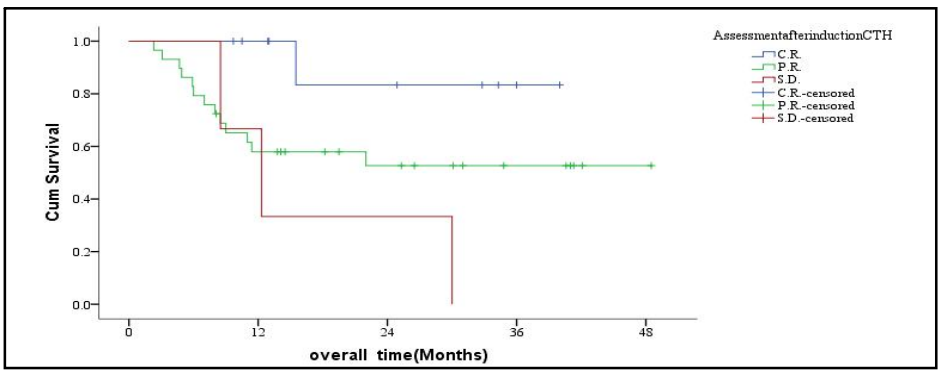

Figure (4): Effect of response to induction chemotherapy on overall survival.

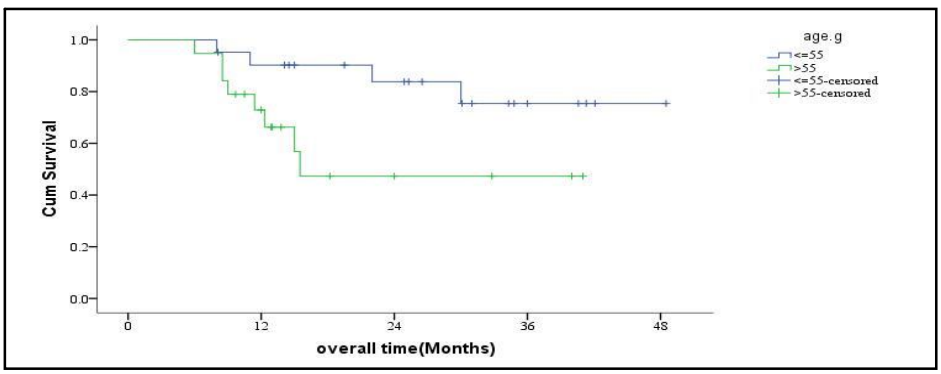

Figure (5): Effect of age on O.S.

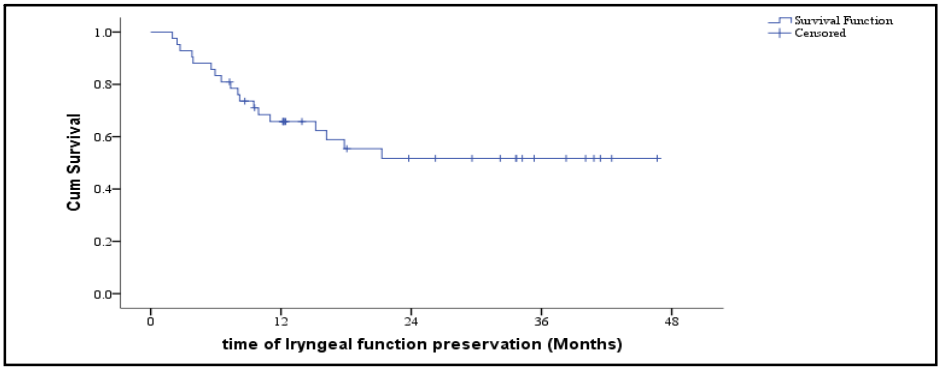

Figure (6): Laryngeal preservation free survival in all cases.

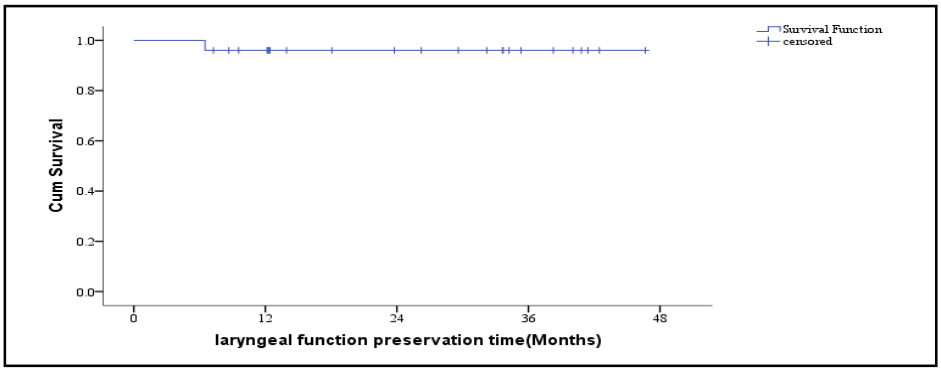

Figure (7): Laryngeal preservation free survival in alive case.

Adverse Events

Induction chemotherapy induced toxicity: Hematological toxicity including 1 patient (2.5%) developed grade III afebrile neutropenia , 1 patient (2.5%) developed grade IV afebrile neutropenia, while 2 patients (5%) developed grade IV febrile neutropenia and they were admitted in the hospital, received medical treatment with improvement then discharged and continued the protocol (Table 6).

Non hematological toxicity including 1 patients (2.5%) developed grade III vomiting. Two patients (5%) developed grade III diarrhea, they received medical treatment and improved, grade III hepatic toxicity was developed only in 1 patient (2.5%)who accidentally discovered to be HCV positive patient, hospital admission and hepatology cooperation, toxicity relieved and continued treatment. Grade III alopecia was developed in all patients (100%), grade III renal toxicity was developed in only one patient (2.5%) after the third cycle of induction CTH mostly due to dehydration at home, the patient was hospitalized and nephrology follow up was done till improvement and continued the protocol (Table 6).

Concurrent chemoradiation induced toxicity: Twenty two patients (55%) developed grade III oral mucositis. Seven patients (17.5%) developed grade III xerostomia, grade III dysphagia was developed in only 5 patient (12.5%), 3 patients (7.5%) developed grade III acute skin toxicity and 1 patient (2.5%) developed grade III thrombocytopenia, grade III afebrile neutropenia was developed only in 1 patient (2.5 %).and 1 patient developed grade III acute laryngeal toxicity (Table 7)**.**

Table (4): Progression free rate.

Rate / Factors	n	Progression free rate			Median(m) (95% CI)	P value
		1 yr.	2 yrs.	3 yrs.		
All	40	76.7	65.2	65.2	NA	NA
Age (yrs)						
≤55	21	90.2	76.3	76.3	NA	0.054
>55	19	62.2	55.3	55.3	NA	
Site						
Oropharynx and Oral Cavity	7	57.1	42.9	NA	22.0(0.0-55.1)	0.286
Larynx and Hypopharynx	22	81.3	75.5	75.5	NA	
Nasopharynx, Nasal Cavity and Paranasal Sinuses	11	81.8	70.1	70.1	NA	
T stage						
T2	8	75.0	75.0	75.0	NA	0.662
T3	13	76.9	76.9	76.9	NA	
T4	19	77.6	47.8	47.8	23.1	
N stage						
N0-N1	20	78.8	63.0	63.0	NA	0.575
N2-N3	20	74.4	63.3	63.3	NA	
Operability						
No	17	70.1	42.5	42.5	23.1 (8.5-27.7)	0.165
Yes	16	80.4	80.4	80.4	NA	
Stage						
III	17	81.6	81.6	81.6	NA	0.109
IVA	23	68.3	51.3	51.3	NA	

Table (5): Overall survival rate.

Rate / Factors	n	Overall survival rate			Median (months) (95% CI)	P value
		1 yr.	2 yrs.	3 yrs.		
All	40	81.8	68.0	62.8	NA	NA
Age (yrs)						
≤55	21	90.2	83.8	75.4	NA	0.040
>55	19	72.9	47.3	47.3	15.5	
Site						
Oropharynx and Oral Cavity	7	57.1	42.9	42.9	22 (0.0-49.2)	
Larynx and hypopharynx	22	86.1	70.3	70.3	NA	0.300
Nasopharynx, nasal Cavity and Paranasal Sinuses	11	90.9	81.8	68.2	NA	
T stage						
T2	8	75.0	75.0	75.0	NA	
T3	13	76.2	76.2	76.2	NA	0.650
T4	19	88.9	55.9	41.9	30 (11.7-48.3)	
N stage						
N0-N1	20	88.9	70,0	52.5	NA	0.682
N2-N3	20	74.1	63.5	63.5	NA	
Stage						
III	17	87.5	81.6	81.6	NA	0.125
IV	23	72.8	59.3	51.3	NA	
Operability						
No	17	76.0	52.3	34.8	30.0 (12 -47.9)	0.159
Yes	16	87.1	74.6	74.6	NA	
Early response to induction chemotherapy						
Early C.R.	10	100	83.3	83.3	NA	0.043
No early C.R.	30	54.4	49.8	44.2	30	

Table (6): Induction chemotherapy induced toxicity.

Count / Toxicity of induction CTH	Number = 40	Percent
Neutropenia		
- **Grade 3**	1	2.5%
- **Grade 4**	3	7.5%
Vomiting		
- **Grade III**	1	2.5%
Diarrhea		
- **Grade III**	2	5%
Liver toxicity		
- **Grade III**	1	2.5%
Alopecia		
Grade III	40	100%

Table (7): Concurrent chemoradiation induced toxicity.

Count / Toxicity of CCRTH	Number = 40	Percent
Mucositis		
Grade III	22	55%
Xerostomia		
Grade III	7	17.5%
Acute laryngeal toxicity		
Grade III	1	2.5%
Acute skin toxicity		
Grade III	3	7.5%
Dysphagia		
Grade III	5	12.5%
Thrombocytopenia		
Grade III	1	2.5%
Afebrile neutropenia		
Grade III	1	2.5%

DISCUSSION

The rationale for using induction chemotherapy prior to radiotherapy or chemoradiotherapy in the treatment of locally advanced SCCHN is to reduce the local tumor volume and also to minimize the risk for developing distant metastases. Cisplatin-based induction chemotherapy doublets have been generally used as induction chemotherapy and PF, has become a common treatment standard. The addition of a taxane to induction chemotherapy, in the form of a cisplatin–taxane doublet, or, more frequently, a taxane, cisplatin, and 5-flurouracil (5-FU) triplet, has improved the activity of induction chemotherapy. TAX 324 trial have confirmed the superiority of the triplet docetaxel, cisplatin, and 5-FU (TPF) regimen over PF, followed by chemoradiotherapy, in terms of progression-free and overall survival, and TPF is now a standard choice for use in induction chemotherapy. The results of this study of induction chemotherapy by docetaxel/cisplatin/5FU, followed by concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of the head and neck, was designed to show the efficacy of induction chemotherapy by TPF followed by CCRT using weekly carboplatin (area under the curve =1.5) regarding survival and organ preservation in comparison to its toxicity.

The tested regimen was found effective with manageable acute toxicity when appropriate supportive care was employed. After TPF induction, 100% of our patients achieved an overall response rate. This was comparable to the TPF arm in the TAX 324 trial (72%), and the rate of complete response was also higher in our patients (25%) in comparison to the TAX 324 (17%) or TAX 323 (8.5%).

In comparison to the study by **Paccagnella et al. (2010)** the radiologic ORR was 69.5% (95% CI 49.2% to 77.1%) and the CR was 6.5% in the 46 assessable patients. Following CT/RT, the radiologic CR rate was 21.3% (95% CI 10.7% to 35.7%) in concurrent chemoradiation arm and 50% (95% CI 34.9% to 65.1%) in TPF induction arm followed by chemoradiation compared to our study where ORR after chemoradiation was 95% and CR rate was 75%.

Few years ago, the results of the **PARADIGM** and **DeCIDE** trials failed to confirm any survival advantage associated with adding TPF induction chemotherapy to concomitant chemoradiation over concomitant chemoradiotherapy alone **(Haddad et al., 2013 and Cohen et al., 2014)**.

In unresectable cancers (patients with very low probability of being cured), it could be used as a tool to choose between an aggressive curative or a less intensive palliative treatment program **(Strojan et al., 2013).**

In our study population which had initially unresectable cancers the occurrence of early CR after induction chemotherapy was an indicator of statistically longer overall survival. The response rates to induction CTH in our study was affected by the site of the primary tumor with the highest CR was seen in the larynx and hypopharynx (40.9 %) followed by the nasopharynx, paranasal sinuses and nose (9.1%) and no oral cavity or oropharyngeal cases achieved early CR and this early CR was

associated with a significant long OS.This indicates that induction chemotherapy by TPF had a good results in laryngeal and hypopharyngeal SCC regarding OS and organ preservation in those patients so it is a good option in those patients to preserve their larynx and improve their survival.

As regard the survival analysis, the median progression free survival rate was not reached and PFS was 76.7% at 1 year, and 65.2% at 2 and 3 years. These results are comparable to the TPF arm of the TAX 324 trial which had a median PFS of 36 months and not reached at 3 years and a 2 years PFS of 53% and 3 years PFS of 49% **(Posner et al., 2007).** This mild superiority at 3 years in our results is mostly due to inclusion of nasopharyngeal cancer patients in our study while they were not included in TAX-324 trial.

Concerning overall survival analysis, the median overall survival in our study was not reached due to a relatively short follow up period. Survival rate at 1 year was 81.8%,at 2 years was 68.0% and 62.8% at 3 years.In contrast, the TAX 324 patients in the TPF arm had a median OS of 71 months, a 2 years overall survival of 67% and 62% at 3 years, our results seems to be equal to the TAX 324 trial.

Hypopharyngeal cancer was the most common non-operated primary site of locally advanced head and neck cancer. This observation is mostly related to the technical difficulties related to surgical resection of such patients and the lack of appropriate supportive care for this kind of patients after surgery, with high rate of long term complications. Report from a French university hospital which is a referral center for such surgeries showed that significant complications occurred in 80 patients (38.3%). Several patients had more than one complication (**Triboulet et al., 2001)**.So, organ preservation for those patients is a good alternative to these mutilating surgeries.

Regarding nasopharyngeal cancer patients only, our results showing an OS at 3 years was 85.7% and it was comparable to the results obtained by a phase III trial of induction chemotherapy in nasopharyngeal cancer patients revealing OS at 4 years was 87.5% and proved that taxanes-based induction chemotherapy (IC) did not improve any survival except among patients with T4N1-2M0 and stage IVb, taxanes-based IC significantly prolonged the 4-year distant metastasis free survival by 11.2% (86.1% vs 74.9%, P = 0.034), and marginally improved PFS (P = 0.133) and OS (P = 0.215) **(Blanchard et al., 2015)**.

In the subgroup analysis of our laryngeal and hypopharyngeal cancer patients (22 patients), the 3 year laryngeal preservation rate was 65.8 % in all cases, this seemed to be inferior to that reported in the laryngeal preservation trial (GORTEC) 2000-01 that showed the 3-year larynx preservation rate was significantly higher in the TPF arm than in the PF arm (70% versus 58%).In the TAX-324 the 3 years laryngeal preservation rate was 55% which seems inferior to our results. The inferiority of our results to the (GORTEC) 2000-01 is mostly because all patients in the (GORTEC) 2000-01 were operable and tested for organ preservation while in the TAX-324 there were many patients inoperable like our patients **(Pointreau et al.,2009).**

Despite several decades of intensive investigation, the optimal sequencing of chemotherapy, radiation, and surgery in the management of locoregionally advanced head and neck squamous cell cancer (HNSCC) remains a subject of intense debate. Multiple phase III trials have failed to demonstrate a consistent survival or locoregional control benefit from the induction approach over concomitant chemoradiation. The concomitant use of chemotherapy and radiation proved considerably more successful. The large, well-conducted Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACHNC), reported first in 2000 (**Pignon et al., 2000**) and then updated in 2009 (**Pignon et al., 2009)** and 2011 by the Institut Gustave-Roussy group (**Blanchard et al., 2011**), confirmed these observations. In their updated individual patient analysis of 17,346 patients, a 6.5% 5-year absolute survival benefit (hazard ratio [HR], 0.81; 95% CI, 0.78 to 0.86; $P < .001$) was demonstrated for concomitant treatment. Many reports solidified concomitant chemoradiotherapy as a treatment standard in the definitive management of locoregionally advanced HNSCC. Induction chemotherapy remained investigational except in the larynx preservation setting.

Nevertheless, with the modest proven effect of ICT in locally advanced head and neck cancers, **our study suggested that** induction chemotherapy by TPF was a reasonable approach for unresectable locally advanced head and neck SCC and organ preservation for laryngeal and hypopharyngeal cancer patients. Also, it was of benefit in large tumor volume to decrease the volume of radiotherapy and subsequently its toxicity. TPF induction must be considered as one of the standards for larynx preservation. Also this question needs further phase III clinical trials with direct comparison between the standard CRT and induction chemotherapy by TPF.

REFERENCES

1. **Blanchard P, Baujat B and Holostenco V (2011):** Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol., 100: 33-40.

2. **Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT and Ma J (2015):** Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta analysis. Lancet Oncol., 16: 645-655.

3. **Cohen E.W., Karrison G., Masha Kocherginsky and Jeffrey Mueller (2014):** Docetaxel Based Chemoradiotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer (DeCIDE). Journal of Clinical Oncology, 32: 2735-2743.

4. **Haddad R, O'Neill A and Rabinowitz G (2013):** Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemo-radiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomized phase 3 trial. Lancet Oncol., 14: 257-264.

5. **Machiels JP, Lambrecht M, Hanin FX, Duprez T, and Gregoire V (2014):** Advances in the management of squamous cell carcinoma of the head and neck. F1000 Prime Rep., 6: 6-44.

6. **Monnerat C, Faivre S, Temam S, Bourhis J and Raymond E (2002):** End points for new agents in induction chemotherapy for locally advanced head and neck cancers. Ann. Of Oncol., 13: 995-1006.

7. **Paccagnella A, Ghi MG and Loreggian L (2010):** Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. Ann Oncol., 21: 1515-1522.

8. **Pignon JP, Bourhis J, Domenge C and Designé L (2000):** Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet, 355: 949- 955.

9. **Pignon JP, le Maître A, Maillard E and Bourhis J (2009):** Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother. Oncol., 92: 4-14.

10. **Pointreau Y, Garaud P and Chapet S (2009):** Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst., 101: 498-506.

11. **Pointreau Y, Atean I, Fayette J, Calais G and Lefebvre JL (2011):** Induction chemotherapy in head and neck cancer: a new paradigm. Anticancer Drugs., 22: 613-620.

12. **Posner MR, Hershock DM `and Blajman CR (2007):** Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med., 357:1705-1715.

13. **Strojan, P., Haigentz, M., Bradford, C.R., Wolf, G.T., Hartl, D.M., Langendijk, J.A., Rinaldo, A., Eisbruch, A., Mendenhall, W.M., Forastiere, A.A., Takes, R.P. and Ferlito, A (2013):** Chemoradiotherapy vs. total laryngectomy for primary treatment of advanced laryngeal squamous cell carcinoma. Oral Oncol., 49: 283-286.

14. **Triboulet JP, Mariette C, Chevalier D and Amrouni H (2001):** Surgical Management of Carcinoma of the Hypopharynx and Cervical Esophagus. Arch Surg., 136: 1164-1170.

العلاج التحفظى لسرطان الرأس والرقبة المتقدم موضعياً عن طريق استخدام العلاج الكيميائي متبوعا بالعلاج الاشعاعى المتزامن مع العلاج الكيميائي

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خلفية البحث: أصبح إستخدام العلاج الكيميائي مع العلاج الاشعاعى علي نطاق كبير في علاج المرضى المصابين بسرطان الراس والرقبة المتقدم موضعيا، ولسنوات عديدة تم إعطاء العلاج الكيميائي في اوضاع متعددة منها التكميلي أو المبدئي أو المتزامن مع العلاج الإشعاعي.

الهدف من البحث: تقييم دور العلاج الكيميائي المبدئي ما قبل العلاج الاشعاعى المتزامن مع العلاج الكيميائي في علاج سرطان الراس والرقبة المتقدم موضعيا في معدل البقاء علي قيد الحياة ،معدل البقاء بدون زيادة المرض ، معدل المحافظة علي العضو مع تقييم الاعراض الجانبية.

المرضى وطرق البحث : تم علاج اربعين مريضا مصابين بسرطان الرأس والرقبة بالمرحلة الثالثة والرابعة الغير منتشر والغير قابل للاستئصال الجراحي او المحول للحفاظ علي الأعضاء عن طريق ثلاث جرعات من العلاج الكيميائي المبدئي المكون من الدوسيتاكسيل والسيسبلاتين والفلورويوراسيل متبوعا بالعلاج الإشعاعى (سبعون جراي) المتزامن مع العلاج الكيميائي الأسبوعي كاربوبلاتين.

النتائج: تمت المتابعة للمرضى بحد ادني ستة اشهر (متوسط المتابعة اربعة عشر شهرا ونصف) وكان معدل الاستجابة الكلي خمس وتسعون بالمائة منها خمس وسبعون بالمائة استجابة كاملة ،سبع ونصف بالمائة استجابة جزئية ،اثني عشر ونصف بالمائة استقرار للمرض و خمس بالمائة زيادة للمرض. متوسط البقاء علي قيد الحياة لم يتم الوصول إليه وكانت نسبته في ثلاث سنوات في حدود ثلاث وستون بالمائة. المضاعفات المتسببة من البروتوكول المستخدم كانت في الحدود المتحكم فيها ولم يسجل حالات وفاة بسببها.

الاستنتاج : العلاج الكيميائي المبدئى يمكن إستخدامه للمرضى المصابين بسرطان الرأس والرقبة المتقدم موضعيا والغير قابل للاستئصال الجراحي او للحفاظ علي الأعضاء وتجنب عمل الجراحة لحالات سرطان الحنجرة والبلعوم الحنجري، كما انه له فاعلية في حالات الأورام الكبيرة حجما لتصغيرها و ذلك لتصغير الحقل الإشعاعي وتقليل مضاعفات الإشعاع.