Induction Chemotherapy Versus Upfront Chemoradiation for Locoregionally Advanced of Head and Neck Cancer

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Abstract
Aim of the work: evaluatethe response rate , acute and late adverse effects of induction chemotherapy followed by concurrent chemoradiotherapy . secondary end points include overall survival and progression free survival in patients with locoregionally advanced of Squamous cell head and neck cancer (HNSCC) .
Patients and Method: A retrospective study of 48 patientswith pathologically proven Stage III-IVB ofSquamous cell head and neck cancer (HNSCC) who presented to the clinical oncology department, sohag University hospital fromJanuary 2010 to March 2017. Patients were treated with induction chemotherapy followed by concurrent chemoradiation therapy or initially concurrentchemoradiation therapy. This study was conducted by hand search in the files and radiotherapy sheetof these patients.
Results: Fourty_eight patients with locally advanced head and neck squamous cell carcinoma were included in this study. It was conducted at the Clinical Oncology and Nuclear Medicine Department, Sohag Faculty of Medicine .Of the 48 identified patients, 20 patients received IC followed with CCRT and 28 patients received only CCRT. Therewas no statistically significant difference between both groups as regards response at 24 , 36 and 45 months.In group of CCRT , 18 patients had CR to primary treatment , 7 Patients had PR and 7 Patients had Progressive disease . Ingroup of IC, 12 patients had CR ,6 patients had PR and one patient have Progressive disease . Acute skin reactions andacute mucositiswere experienced by all patients .There was no statistically significant difference between the two groups as regards xerostomia and Chronic skin and subcutaneous toxicity .
Conclusion: Our findings did not show that adding induction chemotherapy to chemoradiotherapy was better than concurrent chemoradiotherapy alone in locally advanced head and neck cancer , so the latter remains standard therapy in patients with LAHNC .

Introduction
The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year. **(Jemal A et al 2011)** About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide. Pathological diagnosis should be made according to the World Health Organization classification from a surgical biopsy Sample .

Routine staging includes physical examination, chest X-ray ,head and neck endoscopy, and head and neck computed tomography (CT) scan or magnetic resonance imaging (MRI) . Squamous cell head and neck cancer should be staged according to the TNM system.

A multidisciplinary treatment schedule should be established in all cases. Treatment depends on primary tumor location and extension. In early stage (I–II), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) gives similar loco-regional control.**(Gregoire V et al, 2010) .**

Standard options for locally advanced stage III and IV tumours are: surgery

including reconstruction plus postoperative radiotherapy and, for those patients found at surgery to have high-risk features (nodal extracapsular extension and/or R1 resection), post-operative chemoradiotherapy (CRT) with single-agent platinum(**Jay S,2012).** Chemoradiotherapy (CRT) has been the standard of care for patients with unresectable SCCHN and for organ preservation in North America and in many countries in Europe for the last decade**.(Marshall P, 2008) .**

Induction chemotherapy, the use of systemic chemotherapy before definitive surgery and/or radiation therapy, has been an intuitively attractive approach in the management of squamous cell head and neck cancer (HNSCC) for the last 25 years .**(David J , 2006)** .

The Aim Of Work:

The main objective of this study is to determine the response rate , acute and late adverse effects of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy . secondary end points include over all survival and progression free survival in patients with locoregionally advanced of Squamous cell head and neck cancer (HNSCC) .

.**Materials and Methods**:

From a retrospective database of 200 patients with HNSCC, we identified 48 patients with Stage III-IVB who were treated with induction chemotherapy followed by concurrent chemoradiation therapy or initially concurrent chemoradiation therapy. We included all available records of patients treated and received their routine follow-up at, Clinical Oncology and Nuclear Medicine Department, Sohag Faculty of Medicine ,during the period from January 2010 to March 2017 .

Ethical consideration:

The study was reviewed and accepted by the University Ethics Committee before enrollment .

Patients eligibility

Patients with pathologically proven non-metastatic, previously untreated, locally advanced HNSCC ,stage III or IV, were eligible. Patients were between 18 and 70 years of age, had a WHO performance status of 0&1. Exclusion criteria were Presence of any other comorbid disease .

Evaluation during and post-treatment

All patients were clinically evaluated twice a week during Treatment .Toxicity was evaluated weekly according to the RTOG Toxicity Criteria. After completion of simultaneous treatment, 4 to 8 weeks were allowed for mucosal recovery before response assessment .Patients underwent routine follow-up starting one month after radiotherapy and followed every 2 months for 2 years, every 4–6 months during years 3–5 and yearly there after.

Induction Chemotherapy ;

Induction chemotherapy consisted of either TPF docetaxel (75 mg/m2) on day 1, cisplatin(75 mg/m2) on day 1, and 5-fluorouracil (750 mg/m2/d) on days1-5 for 2–3 cycles every 21 daysor PF ICT which consisted of cisplatin(80 mg/m2) on day 1 and 5-FU (1000 mg/m2)on days 1-5 as a continuous peripheral infusion,everythree weeks.

Concurrent Chemotherapy

Concurrent chemotherapy consisted of cisplatin 100 mg/m2 days 1, 22 and 43,orCisplatin, 35 mg/m2/week, throughout the duration of radiotherapy. Carboplatin AUC 4 was substituted for cisplatin if creatinine clearance was <55 ml/min Cisplatin was administered as an overnight in-patient stay.

Radiotherapy

All patients were treated with a 6-MV photon beam .Parallel opposed lateral

fields, withpatients immobilized in a supine position were used. The borders of the fields were determined according to the location of the primary tumor and known extension by CT findings and endoscopy. Radiotherapy was delivered oncedaily, five days a week as a single 2 Gy fraction The lower neck was irradiated by the anterior single portal. The dose to the primary site was 66.6 to 72 Gy (median, 70.2 Gy). The posterior and inferior limits of lateral ports were reduced when a dose of 45 Gy reached them to exclude the spinal cord. Posterior cervical lymphatics were treated with up to 50 Gy by electron beam. A total of 50 Gy was given for management of the clinically negative neck. The dose to the lower neck was 50 Gy. Palpable neck nodes were boosted with electron beam.

Statistical analysis

Data was analyzed using STATA intercooled version 12.1. Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed Mann-Whitney test was used. Qualitative data was presented as number and percentage and compared using either Chi square test. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. Graphs were produced by using Excel or STATA program. P value was considered significant if it was less than 0.05.

Results

Fourty_eight patients with locally advanced head and neck squamous cell carcinoma were included in this study , patients were treated with induction chemotherapy followed by concurrent chemoradiation therapy or initially concurrent chemoradiation therapy. It was conducted at the Clinical Oncology and Nuclear Medicine Department, Sohag Faculty of Medicine .

Patient Population and characteristics data Analysis

Of the 48 identified patients, 20 patients received IC followed with CCRT and 28 patients received only CCRT. The median age was 60 years (range 18 -77) and 33 (68.75%) were male. Smoking history was positive in 29 (60.42%) of the patients and 19 (39.58 %) never smoked. All patients included had an Eastern Cooperative Oncology Group PS 1 or less.

Analysis of Disease characteristics

Characteristic of the tumors in studied populations are listed in (Table 1 & 2) .

The most common presentation was Hoarseness of voice 23 patients (47.92%) , followed by Dysphagia 8patients (16.67%) , Nasal obstruction 6 patients (12.50%) ,Neck mass 5 patients (10.42%) and less common Dyspnea ,Epistaxis , Facial swelling ,Lt. Facial pain , Rt. check mass and Stomatitis .

The location of the primary disease was the larynx 26 patients (54.17%) , followed by the Nasopharynx 9 patients (18.75%) ,Hypopharynx 5 patients (10.42%)and Oral cavity andTongue each of them 3 patients (6.25%) .

(68.75%) of the pathology were Undifferentiated Carcinoma followed by SCC (31.25%) .

Presentation of studied population Table (1) :

Presentation	Number (%)
Hoarseness	23 (47.92%)
Dysphagia	8 (16.67%)
Nasal obstruction	6 (12.50%)
Neck mass	5 (10.42%)
Dyspnea	1 (2.08%)
Epistaxis	1 (2.08%)
Facial swelling	1 (2.08%)
Lt. Facial pain\dysphagia	1 (2.08%)
Rt. check mass	1 (2.08%)
Stomatitis	1 (2.08%)

Characteristic of the tumors in studied populations Table (2) ;

Variable	Summary statistics
Site	
Larynx	26 (54.17%)
Nasopharynx	9 (18.75%)
Hypopharynx	5 (10.42%)
Oral cavity	3 (6.25%)
Tongue	3 (6.25%)
Oropharynx	1 (2.08%)
Cheek	1 (2.08%)
Pathology	
SCC	15 (31.25%)
Undifferentiated Carcinoma	33 (68.75%)
NK SCC	2 (4.17%)
Anaplastic	1 (2.08%)
Grade	
G1	4 (8.33%)
G2	27 (56.25%)
G2-3	4 (8.33%)
G3	11 (22.92%)
HG	2 (4.17%)
Stage	
III	20 (41.67%)
IVA	27 (56.25%)
IVB	1 (2.08%)
T classification	
T1	2 (4.17%)
T2	9 (18.75%)
T3	23 (47.92%)
T4	14 (29.17%)
N classification	
N0	8 (16.67%)
N1	14 (29.17%)
N2	25 (52.08%)
N3	1 (2.08%)

Most patients 27 patients (56.25%) had stage IVA cancer; 20 patients (41.67%) had stage III HNSCC and only one patient (2.08%) had stage IVB.T stage of the primary tumor was balanced between both groups.
8 out of 48 patients (16.67%) had N0 disease, 14 patients (29.17%) had N1, 25 patients (52.08%) had N2, and one patient (2.08%) had N3.

Treatment Response

All patients (48) were evaluated two months after the end of treatment. All patients showed an objective response،either complete or partial response. There was no statistically significant difference between both groups as regards objective response rates. The median duration of response in both group(CCRT&IC) it was 12 months (range 2- 45 months). Therewas no statistically significant difference between both groups as regards response at 24 , 36 and 45 months.In group of CCRT , 18 patients had CR to primary treatment , 7 Patients had PR and 7 Patients had Progressive disease . Ingroup of IC, 12 patients had CR ,6 patients had PR and one patient have Progressive disease table (3) .

Characteristics related to response Table (3)

Variable	Summary statistics
Initial response	
Complete response	34 (70.83%)
Partial response	8 (16.67%)
Progressive disease	1 (2.08%)
Stationary disease	1 (2.08%)
Died	1 (2.08%)
Missed	3 (6.25%)
Time to initial response	
Mean ± SD	2.97±1.05
Median (range)	3.00 (2.00-6.00)
Duration to achieved response	
Mean ± SD	16.33±13.53
Median (range)	12.00 (1.00-45.00)
Further outcome	
Complete response	30 (68.18%)
Partial response	1 (2.77%)
Progressive disease	13 (29.55%)
Site of progression if present	
Local	9 (69.23%)
Lung	3 (23.08%)
Both	1 (7.69%)
Over all response	
Progressive	12 (27.27%)
Responsive	32 (72.73%)

The Effect of Different Prognostic Factors onResponse

No statistically significant effect of sex, age and performance status on response. No statistically significant effect of primary tumor site, stage and pathological grade on response .No statistically significant difference between the two groups (IC & CCRT)

as regards response by sex, age, primary tumor site, stage, nodal status،pathological grade and performance status table (4) .

Comparison between patients using / not using induction chemotherapy according to patients' characteristics Table (4) :

Variables	Induction chemotherapy		P value
	No	Yes	
Age			
Mean± SD	58.29±13.84	54.7±16.92	0.42
Median (range)	60.5 (18-77)	60 (20-70)	
Gender			
Females	5 (17.86%)	10 (50.00%)	0.02
Males	23 (82.14%)	10 (50.00%)	
Smoking			
Non-smoker	9 (32.14%)	10 (50.00%)	0.21
Smoker	19 (67.86%)	10 (50.00%)	

Survival

At a median follow-up of 12 months (range 1-45 months) , there was no statistically significant effect of the smoking , primary tumor site, disease stage, nodal status or response on survival in both group (IC &CCRT) . But there was a statistically significant effect of gender (P- value 0.03)on over all survival . and T stage of thetumor (P-value 0.03) on over all survival and progression free survivaland there was a statistically significant effect of age on disease free survival After correlation between the response and other prognostic factors, response had an insignificant effect on survival (Table 5& 6) .

Disease free survival its relation to different factorsTable(5) ;

Factors	No.	Cum survival at 24 ms %	Cum survival at 36 ms %	Cum survival at end of study (max 45 ms) %	P-value
Whole group	34	73.79	67.08	67.08	
Age					
≤60	17	93.33	93.33	93.33	0.03
>60	17	52.73	42.19	42.19	
Gender					
Females	7	75.00	75.00	75.00	0.58
Males	27	72.64	65.37	65.37	
Smoking					
Non-smoker	11	87.50	65.63	65.63	0.43
Smoker	23	64.12	64.12	64.12	
Pathology					
SCC	26	66.86	59.43	59.43	0.39
Others	8	87.50	87.50	87.50	
Grade					
G1/G2	22	65.63	56.25	56.25	0.57
More than G2	12	82.50	82.50	82.50	
Stage					
III	16	80.81	80.81	80.81	0.15
IVA/IVB	18	67.46	53.97	53.97	
T classification					
T1/T2	10	83.33	83.33	83.33	0.29
T3/T4	24	69.01	57.51	57.51	
N classification					
N0/ N1	17	70.75	53.06	53.06	0.61
N2/N3	17	75.29	75.29	75.29	
Induction chemotherapy					
Yes	13	70.00	70.00	70.00	0.69
No		74.51	65.20	65.20	

Overall survival its relation to different factorsTable (6)

Factors	No.	Cum survival at 24 ms %	Cum survival at 36 ms %	Cum survival at end of study (max 62ms) %	P-value
Whole group	48	62.52	59.39	59.39	
Age					
≤60	25	59.95	59.95	59.95	0.91
>60	23	64.67	58.21	58.21	
Gender					
Females	15	41.90	41.90	41.90	0.03
Males	33	71.73	67.24	67.24	
Smoking					
Non-smoker	19	55.83	55.83	55.83	0.34
Smoker	29	66.42	60.89	60.89	
Pathology					
SCC	38	60.22	56.20	56.20	0.76
Others	10	70.00	70.00	70.00	
Grade					
G1/G2	31	62.44	57.24	57.24	0.92
More than G2	17	61.94	61.94	61.94	
Stage					
III	20	62.33	62.33	62.33	0.68
IVA/IVB	28	63.31	56.98	56.98	
T classification					
T1/T2	11	90.00	90.00	90.00	0.03
T3/T4	37	54.00	50.16	50.16	
N classification	22	53.79	53.79	53.79	0.56
N0/ N1		70.36	64.50	64.50	
N2/N3					
Induction chemotherapy					
Yes	20	58.85	58.85	58.85	0.84
No	28	64.71	60.39	60.39	

Treatment Related Toxicity

Acute and late toxicities were recorded according to RTOG scoring system .Toxicities were summarized in table (7) .

Acute skin reactions: Acute skin reactions were experienced by all patients. The maximum grade of toxicity was grade 4 which was experienced in one patient only of CCRT group (3.57 %) and four patients (20.00%) of IC groups . There was no statistically significant difference between the acute skin toxicities in the two groups.
Acute mucositis: Acute mucositis was experienced by all patients of both arms .The high grades of acute mucositis (grade 3 and 4) were frequently experienced in patients of CCRT group (39.28 of patients) and IC group (40.00% of patients) . There was no statistically significant difference between acute mucositis in the two groups .
There is no statistically significant difference between the two groups as regards acute dysphagia which was equal in both groups (75.00 % of patients) .
Chronic toxicities:
Xerostomia; There was no statistically significant difference between the two groups as regards xerostomia which experienced in (10.71%), (15.00%) of CCRT and IC respectively .
Chronic skin and subcutaneous toxicity:although Chronic skin and subcutaneous toxicity were experienced in patients of CCRT group only (25.00% of patients), no statistically significant difference between the two groups as regard chronic skin and subcutaneous toxicity. We found inOur study that the tested regimen showed a nearly equal tumor response rate and survival results in comparison with the control regimen.
Comparison between patients using / not using induction chemotherapy according to toxicity Table (7) :

Variables	Induction chemotherapy		P value
	No	Yes	
Acute toxicity			
Mucositis grade 0 1 2 3 4	 1 (3.57%) 11 (39.29%) 5 (17.86%) 10 (35.71%) 1 (3.57%)	 0 6 (30.00%) 6 (30.00%) 4 (20.00%) 4 (20.00%)	0.22
Acute skin toxicity grade 0 1 2 3 4	 2 (7.14%) 9 (32.14%) 11 (39.29%) 5 (17.86%) 1 (3.57%)	 0 10 (50.00%) 3 (15.00%) 4 (20.00%) 3 (15.00%)	0.16
Dysphagia No Yes	 7 (25.00%) 21 (75.00%)	 5 (25.00%) 15 (75.00%)	1.00
Chronic toxicity			
No chronic toxicity Pigmentation Skin Xerostomia	18 (64.29%) 1 (3.57%) 6 (21.43%) 3 (10.71%)	17 (85.00%) 0 0 3 (15.00%)	0.12

Discussion

Although concurrent chemoradiation has become the standard of care for advanced and/or unresectable head and neck carcinoma patients, Induction chemotherapy is an issue of outstanding interest in LASCCHN treatment .

This retrospective analysis was designed to determind the efficacy and toxicity of induction chemotherapy followed by concurrent chemoradiotherapy compared with concurrent chemoradiotherapy alone in patients with advanced HNSCC.

Our findings show no advantage with induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone as regard overall survival , Progression free survival and disease free survival.

The TAX 323 **(Vermorken JB,2007)** and TAX 324 **(Posner MR,2007)** studies, published in 2007, investigated the important question of identifying the optimal induction chemotherapy regimen to use in head and neck cancer. These two studies and later the GORTEC laryngeal study 11 showed that TPF was significantly better than PF for survival, local control, and organ preservation. These studies defined a new standard of care for induction chemotherapy in the USA and Europe, and also led to regulatory approval of TPF for patients with resectable and unresectable disease.

The addition of induction chemotherapy to concurrent chemoradiotherapy was examined by a randomized phase 2 Italian study. Two groups were compared: TPF followed by chemoradiotherapy versus chemoradiotherapy alone. During chemoradiotherapy, PF was used as the chemotherapy backbone in both groups. The primary endpoint was complete radiographic response. The study showed the sequential chemoradiotherapy group to be better than the concurrent group, with higher complete response rates: 21. 2% for concurrent versus 50% for sequential**(Paccagnella A,2010)**.

The preliminary results of the DeCIDE trial have also been presented. In this phase 3 study, TPF followed by chemoradiotherapy was compared with chemoradiotherapyalone. Only patients with N2 and N3 stages were included in this study. This study was terminated early because of slow accrual and, did not show a survival improvement with the addition of induction chemotherapy**, (Cohen E,2012)**

Assumptions were made for the DeCIDE trial. Since then, advances in our understanding of the epidemiology and subsequent changes in prognosis and survival of patients with head and neck cancer have been striking. The reason for this is multifactorial. Oropharyngeal cancer that is related to HPV infection is a clear factorand, as we now know, these patients have a favourable prognosis and have survival rates well into the 70–90% ,**(Cohen E,2012)** .

We have effectively entered a new era in head and neck cancer where in, for the first time, we have an important prognostic marker such that, significant differences in outcome and different biology exist with different potential therapeutic pathways , so The absence of HPV data is a weakness in our study.

The concomitant use of chemotherapy and radiation proved considerably more successful. Multiple phase III studies of both single-agent and combination chemotherapy given concurrently with radiation have demonstrated clear improvements in both locoregional control and survival. The large, well-conducted Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC),

reported first in 2002 and then updated in 2009, by the InstitutGustave-Roussy group headed by Pignon, confirmed these observations. In their updated individual patient analysis of 17,346 patients from 93 randomized trials that were conducted between 1965 and 2000, 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. No overall survival benefit was identified from the induction chemotherapy schedules, although a marginal improvement was seen in those trials using the fluorouracil and cisplatin combination. Patterns of failure differed between the two treatment schedules.

Induction chemotherapy significantly improved the rate of distant metastases (HR, 0.73; 95% CI, 0.61 to 0.88; *P* _ .001) but did not influence locoregional failure. The concomitant schedules markedly improved the locoregional control (HR, 0.74; 95% CI, 0.70 to 0.79; *P*_.001) with a significant but less impressive improvement in distant control (HR, 0.88; 95% CI, 0.77 to 1.00; *P* _ .04). These 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 .

In our study we observed no statistically significant of acute and late toxicities of both arm , Acute mucositis was experienced by all patients of both arm, The high grades of acute mucositis (grade 3 and 4) were frequently experienced in patients of CCRT group (39.28 ofpatients) and IC group (40.00% of patients) which in general less than in CONDOR study **(C.M.L. Driessen ,2016) .**

There is no statistically significant difference between the two groups as regards acute dysphagia and Xerostomia

Retrospective studies are less solid for these types of conclusions, especially in patients with SCCHN. This is due to the presence of heterogeneous type of tumors sites, stages, patient populations (resectable and an unresectable populations), schedule of chemotherapy and radical treatments(radiotherapy, surgery/ radiotherapy and chemoradiotherapy) . For all these reasons, the real benefit of ICT is still controversial, so A cost-benefit and quality-of-life analysis might prove beneficial in addressing the true value of induction chemotherapy.

Finally , The question of whether the addition of induction chemotherapy to concurrent chemoradiotherapy improved survival over concurrent chemoradiotherapy alone remains unfortunately unanswered and it might not be answered soon .

Conclusions ; Our findings did not show that adding induction chemotherapy to chemoradiotherapy was better than concurrent chemoradiotherapy alone in locally advanced head and neck cancer , so the latter remains standard therapy in patients with LAHNC .

References

1- Cohen EE, Karrison T, Kocherginsky M, Huang CH, Agulnik M, Mittal BB, Yunus F, Samant S, Brockstein B, Raez LE, Mehra R, Kumar P, Ondrey FG, Seiwert TY, Villaflor VM, Haraf DJ, EE V (2012) DeCIDE: a phase III randomized trial of docetaxel (D), cisplatin (P), 5- fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advancedsquamous cell carcinoma of the head and neck (SCCHN). J ClinOncol, 2012 ASCO annual

meeting abstracts, vol 30, No 15_suppl (May 20 Suppl), 5500

2- C.M.L. Driessen , J.P. de Boer et al (2016) . Induction chemotherapy with docetaxel/cisplatin/ 5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study) (Dutch Head and Neck Society 08-01): A randomized phase II study

3- David J, Adelstein and Michael Le Blanc ; (2006) Does Induction Chemotherapy Have a Role in the Management of Locoregionally Advanced Squamous Cell Head and Neck Cancer? , JCO ; 24 (17) 2624 - 2627 **.**

4- -Gregoire V, Lefebvre JL, Licitra L, Felip E, Group E-E-EGW (2010) Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):v184–v186.

5- Jemal A, Bray F, Center MM; et al , (2011),. Global cancer statistics CA Cancer J Clin; 61(2):69-90.

6- Marshall Posnera and Jan B. Vermorken ; (2008) , Induction Therapy in the Modern Era of Combined-Modality Therapy for Locally Advanced Head and Neck Cancer , SeminOncol 35:221-228 .

7- Paccagnella A, Ghi MG, Loreggian L, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: phase II randomizedstudy. Ann Oncol 2010; 21: 1515–22.

8- Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, ViroglioRdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr, Haddad RI, Group TAXS (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357(17):1705–1715.

9- Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, van den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J, Lefebvre JL, Group ETS (2007) Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 357(17):1695–1704.