ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 6, Issue, 02, pp. 6838-6843, February, 2016

International Journal of
DEVELOPMENT RESEARCH

Full Length Research Article

INDUCTION CHEMOTHERAPY FOLLOWED BY CONCOMITANT CHEMO-RADIOTHERAPY IN ADVANCED HEAD AND NECK CANCER: CENTER EXPERIENCE

[1,*]Ehab Abdou, [2]Khaled Al-Shahhat and and [3]Mohamed Gaafar

[1]Department of Radiation Oncology, AL-Azhar University, Cairo, Egypt,
Consultant Oncology Bahrain oncology center SMC, Bahrain
[2]Department of Radiation Oncology, AL-Azhar University, Cairo, Egypt
[3]Department of Epidemiology, Shebeen Alkoom University, Almunofyia, Egypt

ARTICLE INFO

Article History:
Received 18th November, 2015
Received in revised form
19th December, 2015
Accepted 10th January, 2016
Published online 29th February, 2016

Key Words:
Advanced head and neck cancer,
Chemotherapy and radiotherapy.

ABSTRACT

Objective: Retrospective assessment of response rate, clinical outcome and toxicity in head and neck cancer patients treated with induction chemotherapy followed by concomitant chemo radiotherapy.

Patients and Methods: From April 2011 till March 2014, we collected the data for patients with locally advanced head and neck cancer who were treatment with 3 cycles of induction chemotherapy using cisplatin and fluorouracil (5-FU), (PF) followed by radiation therapy for a total radiation dose of 66 Gy and concomitant cisplatin at a dose of 100 mg/m2 on days 1, 22, and 43 of radiotherapy.

Results: Twenty patients were included more than 90% had stage III disease and only 20 % had laryngeal cancer. Eighty percent of patients had performance status 0 and 25% of patients had >5% weight loss at the start of treatment. The response to PF was complete response(CR) in three patients (15 %) while 40 % (8 patients) achieved partial response (PR). Nine patients (45%) had stable disease (SD) and no patients had progressive disease (PD). By the end of concurrent chemo-irradiation, seven patients (35%) had CR, 3 patients (15%) had PR. Four patients (20%) had stable disease (SD) and 6 patients (30%) had PD. At a median follow-up time of 12.5 months (range 1-23), nine patients (45%) were still alive and seven patients of living (35% of all patients and 77.77% of living) were progression-free. The median duration of response was 10 months (range 0-20), the median progression-free survival was 9.5 months (range 0-25), the median overall survival time was 10 months (range 1-23). The toxicity was significant and consisted mainly of mucositis and, to a lesser extent, neutropenia/thrombocytopenia.

Conclusion: In our center experience the induction chemotherapy and chemo-radiotherapy program has been found moderately active but with apparent significant toxic profile.

Copyright © 2016 Ehab Abdou et al. *This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

INTRODUCTION

Concomitant chemo radiotherapy can now be considered as one possible standard treatment option for unresectable head and neck cancer. In the past two decades, numerous randomized studies have demonstrated that chemotherapy given concomitantly with RT leads to a better outcome than RT alone (Hitt *et al.,* 2005). Two recent meta-analyses have confirmed these findings (Adelstein *et al.,* 2003; Haddad *et al.,* 2008). Concomitant chemo radiotherapy has resulted in increasing disease-free survival and/or overall survival in several randomized studies (Hitt *et al.,* 2002; Saunders *et al.,* 2011 Garden *et al.,* 2004; Monnerat *et al.,* 2002). These positive results reflect the ability of concomitant chemo radiotherapy to increase loco regional tumor control, the clinically most frequent site of first recurrence (Adelstein and Leblanc, 2006; Hitt *et al.,* 2002; Vokes *et al.,* 2003). However, the survival advantage obtained in randomized studies has been modest and no specific chemotherapy regimen or schedule has been identified as standard therapy. The goal of organ/function preservation has been the main purpose in the therapeutic approach to advanced stage head and neck cancer for a long time (Posner *et al.,* 2007; Cohen *et al.,* 2004; Brizel and Esclamado, 2006). We perfectly shared the rationale of the study of (Adelstein and Leblanc, 2006) that initial induction chemotherapy decreases

Corresponding author: Ehab Abdou,
Department of Radiation Oncology, AL-Azhar University, Cairo, Egypt, Consultant Oncology Bahrain oncology center SMC, Bahrain

local tumor burden and allows for subsequent organ-preserving surgery and/or killing of distant micro metastases. The additional concomitant chemo-radiotherapy may increase the loco regional control and eliminate residual disease following induction chemotherapy leaving organ-preserving surgery as a final local approach in case of residual disease. Cachexia is among the most debilitating and life-threatening aspects of head and neck cancer (Posner *et al.,* 2004). The purpose of the study was to assess response rate, clinical outcome, organ/function preservation and toxicity in head and neck cancer patients treated with induction chemotherapy followed by concomitant chemo-radiotherapy.

PATIENTS AND METHODS

Data for the patients who were treated in our center between April 2011 till March 2014 were collected. Twenty patients with locally advanced, non-metastatic squamous cell carcinoma of head and neck (SCCHN) were enrolled in the study.

Eligible patients should have

- Histological or cytological diagnosis of SCCHN,
- Stage III (A-B) according to TNM staging.
- 18 and up to 65 years of age.
- Eastern cooperative oncology group (ECOG) performance status of 0-2,
- Life expectancy of more than 12 weeks.
- Normal renal, liver, and hematological profile.
- No prior radiation therapy or chemotherapy.

Pretreatment evaluation included patient history, clinical examination, laboratory investigations (blood count, liver function tests, renal function tests) radiological studies (chest x-ray, computerized tomography of the chest, pelvi-abdominal ultrasound, MRI of the head and neck) Bone scan and CT of the brain when indicated as well as triple endoscopy.

Treatment methods

The treatment plan consisted of 3 cycles of induction chemotherapy with cisplatin and 5-FU (PF) followed by response evaluation and concomitant chemo radiotherapy. Organ-preserving or no surgery at the primary site and/or surgery at involved nodes (N2-N3) was performed when appropriate.

Induction chemotherapy

The PF consisted of cisplatin, 100 mg/m^2, on day 1, followed by a continuous infusion of 5-FU at 1000 mg/m^2 per day for 5 days. Severe malnutrition or continuous weight loss during therapy was an indication for intravenous or nasogastric hyper alimentation. Forced hydration was used with 2,000 mL 5% dextrose in 2 normal saline plus 40 mEq potassium chloride infused over 24 hours before and 24 hours after administration of cisplatin and the second mannitol infusion. Mannitol 12.5 g by intravenous bolus was administered just before cisplatin, and mannitol 25 g in 1,000 mL D5 **2** normal saline plus 30 mEq potassium chloride to run over 4 hours was administered immediately after cisplatin. Patients were treated every 3 weeks. The evaluation of clinical response was performed during the second week after the third cycle of induction chemotherapy and, given that one study objective was to eliminate radical surgery procedures and allow for organ preservation, therefore, in patients who had a partial response (PR) or complete response (CR) to induction chemotherapy, chemo-radiotherapy was initiated 28 days after the third cycle of induction chemotherapy.

Radiotherapy and concomitant chemotherapy

Time: Irradiation was started 4-6 weeks after induction chemo-therapy using 18 MV LINAC machine. The primary tumor and draining lymphatic system were treated isocentrically with parallel opposed lateral portals with a source-to-isocenter distance of 80 to 100 cm.

Position: All patients were treated in supine position with fixation device.

Localization: CT-based treatment planning was done in the same position as simulation.

Fields arrangements: We used of complex; multiple field arrangement utilizing wedges filters, tissue compensators, field weighting, and bolus to achieve an adequate coverage of the target volume.

Gross target volume (GTV): Accurate delineation of gross tumor volume of primary cancer depends on positive findings obtained from all diagnostic modalities used in pretreatment evaluation, including computed tomography whichever was positive or magnetic resonance imaging (MRI) scans.

Planned target volume (PTV): The treatment volume encompasses the primary tumor with a 2cm safety margin around and draining lymphatic system.

Dose: Patients were treated with 18 MV LINAC machine. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of up to 54 Gy in 27 fractions over a period of 5.5 weeks. Regions that were at high risk for malignant dissemination received a 12-Gy boost (total, 66 Gy) in 33 fractions over a period of 6.5 weeks. The dose to the spinal cord was limited to 45 Gy.

Dosimetric evaluation: the 3-D computer planning system was used to have the best dose homogenicity to cover the target volume into the 95 % isodose curve. Doses to the spinal cord, heart, lungs, liver, and kidneys were kept within the tolerance limits to reduce sequelae and morbidity. Weekly verification of the target volume was done. Patients were assessed on daily bases for proper repositioning and tolerance to radiation therapy. Also weekly CBC was done for any hematological toxicity detection.

Concurrent chemotherapy: Intravenous cisplatin at a dose of 100 mg/m^2 on days 1, 22, and 43 was administered concomitantly with radiotherapy.

Evaluation of response and Toxicity: Response evaluation was performed at the end of induction chemotherapy, plus concomitant chemo radiotherapy, and at completion of all therapy. Response assessment included a repeat clinical and

endoscopic examinations plus CT or MRI scans. Response and toxicity were evaluated according to WHO criteria as follows

- Complete response (CR): was defined as complete disappearance of all measurable lesions for a minimum of 4 weeks.
- Partial response (PR): was defined as a 50% or more decrease in the sum of the products of perpendicular diameters of all measurable lesions for a minimum of 4 weeks.
- Stable disease (SD): was defined as a less than 25% decrease in the sum of products of measurable lesions or a less than 25% increase.
- Progressive disease (PD): was defined as a 25% or more increase in the size of measurable lesions or the appearance of new lesions.
- All toxic reactions are graded 0-5 implying: none (0), mild (1), moderate (2), sever (3), life threatening (4); and fatal (5) (Adelstein and Leblanc, 2006).

Statistical Analysis

Statistical package for social sciences (SPSS) version 16 was used for data base construction and analysis. Quantitative variables were summarized using mean and SD, median minimum and maximum values. Qualitative data were summarized using frequencies and percentage. The starting point was the date of diagnosis for survival and response while it was the end of treatment for the time to relapse. Immediate local failure was counted whenever residual tumor is detected. Survival analysis was done using Kaplan- Meier, comparisons between survival curves was done using Log-rank test. Differences were considered significant when p was <0.05 and highly significant when p<0.01. (17).

RESULTS

Patient characteristics

Twenty patients were enrolled. Patient characteristics are listed in Table 1. All patients had squamous cancer, more than 90% of them had stage III disease and only 20% had laryngeal cancer. Eighty percent of patients had performance status 0 and 25% of patients had >5% weight loss at the start of treatment.

Response

The response to PF was complete response (CR) in three patients (15 %) while 40 % (8 patients) achieved partial response (PR). Nine patients (45%) had stable disease (SD) and no patients had progressive disease (PD) (Table 2). By the end of treatment and on first follow up there were 7 patients (35%) who had CR, only 3 patients (15%) had PR and 4 patients (20%) had stable disease (SD). There were 6 patients (30%) who had PD (Table 3).

Outcome of all patients

At a median follow-up time of 12.5 months (range 1-23), nine patients (45%) were still alive and seven patients of living (35% of all patients and 77.77% of living) were progression-free. The median duration of response (Figure 1) was 10 months (range 0-20), the median progression-free survival was 9.5 months (range 0-25), the median overall survival time (Figure 2) was 10 months (range 1-23).

Table 1. Clinical characteristics of the patients

	No. (20)	%
Sex (male/female)	14/6	
Age mean (median)	53.2 (50.4)	
Range	35-62	
Site		
Oral cavity	2	10
Oropharynx	8	40
Hypopharynx	6	30
Larynx	4	20
Tumor grade		
Well differentiated	4	20
Moderately differentiated	9	45
Poorly differentiated	7	35
ECOG Performance status		
0	16	80
1	4	20
Tumor size		
T1	2	10
T2	5	25
T3	8	40
T3	3	15
T4	2	10
Nodal status		
N0	1	5
N1	7	35
N2	7	35
N3	5	25
Weight loss (%)		
None	12	60
0-5	4	20
5-10	2	10
>10	2	10

Table 2. Clinical response after 3 cycles of induction chemotherapy

	No.	%
Complete response (CR)	3	15.8
Partial response (PR)	8	36.8
≥70%	3	10.5
<70%	5	26.3
Overall response (OR)	11	55
Stable disease (SD)	9	45

None of our patients had progressive disease.

Table 3. Clinical response after end of whole treatment plan

	No.	%
Complete response (CR)	7	35
Partial response (PR)	3	15
≥70%	1	5
<70%	2	10
Overall response (OR)	3	1
Stable disease (SD)	4	20
Progressive disease (PD)	6	30

Toxicity

Both induction chemotherapy (PF) and concomitant chemo-radiotherapy resulted in significant toxicity, which consisted mainly of mucositis (grade 3/4 in 40% of patients during PF and 65% during concomitant chemo-radiotherapy) and neutropenia /thrombocytopenia (grade 3/4 in 35% for both during PF, 50 and 40%, respectively, during concomitant chemo-radiotherapy).

Table 4. Hematologic and non-hematologic toxicities during induction chemotherapy

Toxicity	Grade 0		Grade I		Grade II		Grade III		Grade IV	
	No.	%	No.	%	No.	%	No.	%	No.	%
Anemia	4	20	8	40	5	25	3	15	0	0.0
Neutropenia	2	10	7	35	4	20	3	15	4	20
Platelets	6	30	1	5	6	30	3	15	4	20
Creatinine	15	75	2	10	2	10	1	5	0	0.0
Nausea/vomiting	15	75	1	5	2	10	2	10	0	0.0
Diarrhea	14	70	1	5	1	5	3	15	1	5
Mucositis	5	25	4	20	3	15	6	30	2	10
Neurotoxicity	18	90	1	5	1	5	0	0.0	0	0.0

Table 5. Hematologic and non-hematologic toxicities during concomitant chemo-radiotherapy

Toxicity	Grade 0		Grade I		Grade II		Grade III		Grade IV	
	No.	%	No.	%	No.	%	No.	%	No.	%
Anemia	2	10	8	40	7	35	3	15	0	0.0
Neutropenia	1	5	4	20	5	25	6	30	4	20
Platelets	4	20	1	5	7	35	4	20	4	20
Creatinine	14	70	3	15	2	10	1	5	0	0.0
Nausea/vomiting	12	60	3	15	3	15	2	10	0	0.0
Diarrhea	11	55	4	20	1	5	3	15	1	5
Mucositis	0	0	4	20	3	15	10	50	3	15
Neurotoxicity	17	85	2	10	1	5	0	0.0	0	0.0

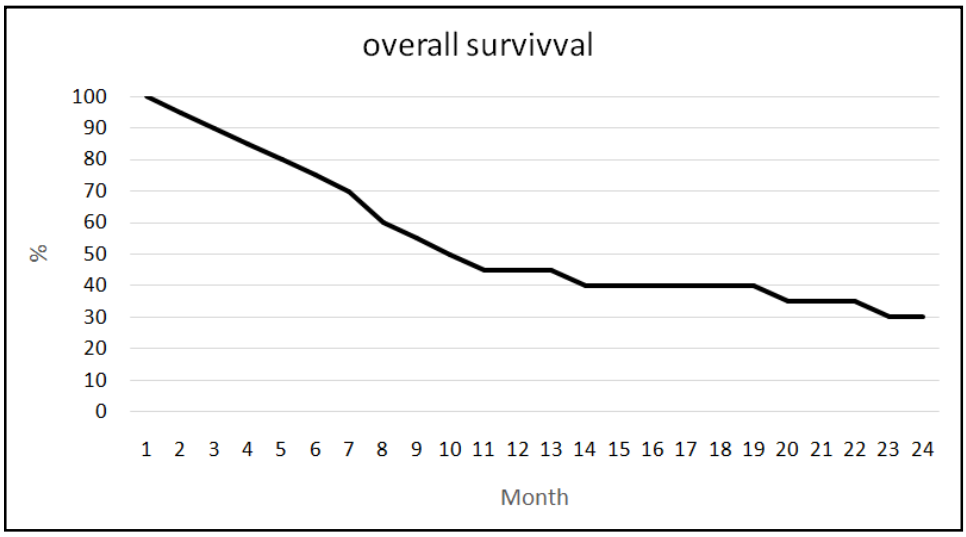

Figure 1. progression free survival curve

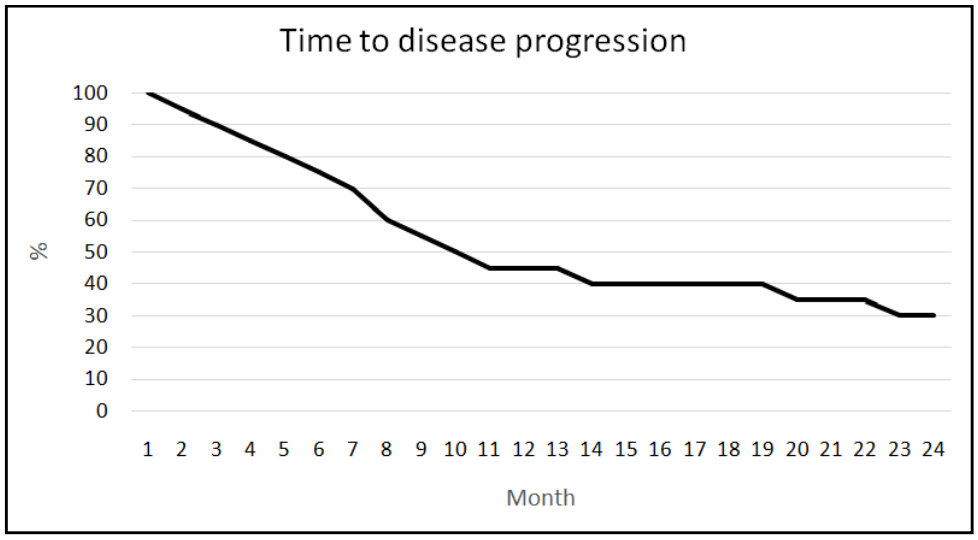

Figure 2. The overall survival

Grade 3/4 diarrhea occurred in 20% of patients during PF. The evaluation of the single symptoms showed that ten patients (50%) had an increase of the pain in the mouth with eleven (55%) patients had experienced an increase of the mouth dryness during treatment. Seven patients (35%) had a reduction of the painful throat and nine patients (45%) reported to be less bothered by their appearance during treatment. Five patients (25%) had much less problems with their teeth during treatment. Three patients (15%) did not gain weight, whereas four patients (20%) gained weight during treatment.

DISCUSSION

The standard management of advanced head and neck cancer has been controversial. There were proponents of combined surgery and RT, while others preferred RT with surgery reserved as salvage treatment [30]. Actually, it is well established that standard therapy with RT, surgery, or the combination yields cure rates of less than 40% in patients with locoregionally advanced head and neck cancer [3], while randomized studies of concomitant chemo-radiotherapy have demonstrated the superiority of this modality over RT alone [5]. Though the acute, and perhaps chronic, toxicities may be greater with chemo-radiation than with RT alone, survival seems to be increased and organ preservation is made possible. Concomitant chemo-radiotherapy with multiagent chemotherapy may obtain even better outcomes, although toxicity may be increased (Pignon *et al.,* 2005; Kies *et al.,* 2010; Psyrri *et al.,* 2004; Adelstein *et al.,* 2006). Many phase III randomized trials plus a meta-analysis indisputably demonstrated that concomitant chemo-radiotherapy improves overall survival and local disease control compared to RT alone (Langerman *et al.,* 2007). The goal of our study was to assess our center experience using Sequential induction chemotherapy and chemo radiotherapy program. The distribution of our patients according to clinical characteristics and site of disease is similar to that of the study of Kies *et al*., 2010. The significant differences were only: better ECOG-PS (81%: 0) and more patients with weight loss (10% had lost >10% of bodyweight) in our study. The clinical response of our study was different from that of Kies *et al.,* 2010, the induction chemotherapy gave an ORR of 55% (with 15.8% CR) in our study vs. 66% CR in theirs. Thus, the results of the present study were inferior to those of Kies *et al* and are in the range of those reported in the literature using combined modality therapy (Langerman *et al.,* 2007; Garden *et al.,* 2004; Hitt *et al.,* 2005). Both induction chemotherapy (PF) and concomitant chemo-radiotherapy resulted in significant toxicity, which consisted mainly of mucositis (grade 3/4 in 40% of patients during PF and 65% during concomitant chemo-radiotherapy) and neutropenia /thrombocytopenia (grade 3/4 in 35% for both during PF, 50 and 40%, respectively, during concomitant chemo-radiotherapy). Grade 3/4 diarrhea occurred in 20% of patients during PF. The toxicity was significant although not severe: 40% of patients had grade 3/4 mucositis during induction chemotherapy and 65% during concomitant chemo radiotherapy; 35% of patients had grade 3/4 neutropenia and thrombocytopenia during induction chemotherapy, 50% and 40% of patients had grade 3/4 neutropenia and thrombocytopenia, respectively, during concomitant chemo radiotherapy. Overall, the toxicity was inferior to that experienced in the study of Kies *et al.,* 2010.

Conclusion

Sequential induction chemotherapy and chemo radiotherapy program has been found moderately active and significantly toxic.

Recommendations

The efficacy, drug availability and relative low cost might support the use of such protocol of treatment in locally advanced SCCHN with proper toxicity monitor in a group of selected patients with good performance status.

REFERENCES

Adelstein, D. J., Leblanc, M. Doesinductionchemotherapy have a role in the management of locoregionallyadvanced squamous cell head and neck cancer? *J Clin Oncol* 24:2624-2628, 2006

Adelstein, D.J. and Leblanc M.: Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer? *J Clin Oncol*., 10; 24(17): 2624-8, 2006.

Adelstein, D.J., Li Y., Adams, G.L., Wagner, H. Jr., Kish, J.A., Ensley, J.F., Schulle,r D.E. and Forastiere, A.A. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemo radiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 1; 21(1): 92-8, 2003.

Brizel, D.M. and Esclamado R. Concurrent chemo radiotherapy for locally advanced, non metastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. *J Clin Oncol*., 10; 24(17): 2612-7, 2006.

Cohen, E. E., Lingen, M. W., Vokes, E. E. The expanding role of systemic therapy in head and neck cancer. *J Clin Oncol.,* 22:1743-1752, 2004

Forastiere, A.A., Goepfert, H., Maor, M., Pajak, T.F., Weber, R., Morrison, W., Glisson, B., Trotti, A., Ridge, J.A., Chao, C., Peters, G., Lee, D.J., Leaf, A., Ensley, J. and Cooper, J. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 27; 349(22): 2091-8, 2003.

Garden, A. S., Asper, J. A., Morrison, W. H., *et al*. Is concurrent chemoradiation the treatment of choice for all patients with Stage III or IV head and neck carcinoma? Cancer 100:1171-1178, 2004.

Haddad, R. I., Shin, D. M. Recent advances in head and neck cancer. *N Engl J Med*., 359:1143- 1154, 2008.

Hitt, R., López-Pousa, A., Martínez-Trufero, J., Escrig, V., Carles, J., Rizo, A., Isla, D., Vega, M.E., Martí, J.L., Lobo, F., Pastor, P., Valentí, V., Belón, J., Sánchez, M.A., Chaib, C., Pallarés, C., Antón, A., Cervantes, A., Paz-Ares, L. and Cortés-Funes, H. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemo radiotherapy in locally advanced head and neck cancer. *J Clin Oncol*., 1; 23(34): 8636-45, 2005.

Hitt, R., Lopez-Pousa, A., Martinez-Trufero, J., *et al*. Phase III

study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol*., 23:8636-8645, 2005

Hitt, R., Paz-Ares, L., Brandáriz, A., Castellano, D., Peña, C., Millán, J.M., Calvo, F., Ortiz de Urbina, D., López, E., Alvarez-Vicent J.J. and Cortés-Funes H.: Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long-term results of a phase II trial. *Ann Oncol.* 13 (10): 1665-73, 2002.

Kies, M. S., Holsinger, F. C., Lee, J. J., *et al*. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol,* 28: 8-14, 2010.

Langerman, A., Maccracken, E., Kasza, K. *et al*. Aspiration in chemoradiated patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*., 133:1289-1295, 2007

Monnerat, C., Faivre, S., Temam, S., *et al*. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. *Ann Oncol.,* 13:995-1006, 2002

Olmi, P., Crispino, S., Fallai, C., Torri, V., Rossi, F., Bolner, A., Amichetti, M., Signor, M., Taino, R., Squadrelli, M., Colombo, A., Ardizzoia, A., Ponticelli, P., Franchin, G., Minatel, E., Gobitti, C., Atzeni, G., Gava, A., Flann, M. and Marsoni, S. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy--a multicenter randomized trial. *Int. J. Radiat Oncol Biol Phys*. 1; 55(1): 78-92, 2003.

Pignon, J.P., Baujat, B. and Bourhis, J. Individual patient data meta-analyses in head and neck carcinoma: what have we learnt? *Cancer Radiother*. 9 (1):31-6, 2005.

Posner, M. R., Hershock, D. M., Blajman, C. R., *et al*. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*., 357:1705- 1715, 2007

Posner, M.R., Haddad, R.I., Wirth, L., Norris, C.M., Goguen, L.A., Mahadevan, A., Sullivan, C. and Tishler, R.B. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. *Semin Oncol*., 31(6):778-85, 2004.

Psyrri, A., Kwong, M., DiStasio, S., Lekakis, L., Kassar, M., Sasaki, C., Wilson, L.D., Haffty, B.G., Son, Y.H., Ross D.A., Weinberger, P.M., Chung, G.G., Zelterman, D., Burtness, B.A. and Cooper, D.L. Cisplatin, fluorouracil, and leucovorin induction chemotherapy followed by concurrent cisplatin chemo radiotherapy for organ preservation and cure in patients with advanced head and neck cancer: long-term follow-up. *J Clin Oncol*. 22(15): 3061-9, 2004.

Saunders, D. B. and Trapp, G. R., *et al*. Basic and clinical biostatistics, 5th edition, Connecticut, *Appleton & Lang*., 2011.

Vokes, E. E., Stenson, K., Rosen, F. R., *et al*. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: Curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol.,* 21:320-326, 2003

****