

## Concurrent Radiotherapy and Cisplatin Administered Weekly versus Every Three Weeks for Definitive Treatment of Locally Advanced laryngeal Cancers

Alaa Maria M.D. and Mohamed Sheta M.D.

Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital, Egypt.

[alaamarial@hotmail.com](mailto:alaamarial@hotmail.com)

**Abstract: Objective:** This study aimed at comparing response rate and acute toxicities, in patients with locally advanced laryngeal squamous cell carcinomas (SCC) who received definitive radiotherapy (RT) concurrent with either of two cisplatin regimens (100 mg/m<sup>2</sup> administered every 3 weeks or 40 mg/m<sup>2</sup> administered weekly). **Methods:** Fifty previously untreated patients with stage III or IVA cancer larynx were enrolled throughout the period between June 2013 and June 2016. **Results:** Of all treated patients, 46% had clinical response. Patient treated with every 3 weeks sensitization had apparent insignificant better response than those treated with weekly sensitization ( $p=0.538$ ). Thirty-six (72%) patients had treatment interruption and 3 (6%) patients discontinued their planned treatment due to side effects. However, this interruption was not significant between the two arms ( $p=0.733$ ). Patients treated with weekly sensitization had significantly lower leukopenia, nausea and acute renal injury ( $p<0.05$ ). The median OS time was 37 vs. 29 months for every 3 weeks versus weekly treated patients with the 2-year OS rate was 72% and 64% respectively ( $p=0.153$ ). The median PFS was 29 vs. 27 months with the 2-year PFS rate was 68% and 60% respectively ( $p=0.592$ ). **Conclusions:** Concurrent chemoradiotherapy (CRT) with weekly low-dose cisplatin is a reasonable and less toxic alternative to high-dose cisplatin given every 3 weeks in the treatment of locally advanced laryngeal SCC. More studies comparing the two regimens are required, particularly in patients with cancer at specific sites who need definitive CRT.

[Alaa Maria and Mohamed Sheta. **Concurrent Radiotherapy and Cisplatin Administered Weekly versus Every Three Weeks for Definitive Treatment of Locally Advanced laryngeal Cancers.** *J Am Sci* 2017;13(12):7-13]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). <http://www.jofamericanscience.org>. 2. doi:[10.7537/marsjas131217.02](https://doi.org/10.7537/marsjas131217.02).

**Keywords:** Locally advanced laryngeal cancer, concurrent chemoradiotherapy, weekly cisplatin.

### 1. Introduction

Radiotherapy is an important therapeutic modality in the treatment of locally advanced head & neck squamous cell carcinoma (HNSCC) and is given as a definitive treatment or as adjuvant treatment after surgery. Also, concomitant chemotherapy improves overall survival as well as loco-regional control<sup>(1-3)</sup>. Concurrent chemoradiation (CRT) was superior to radiotherapy alone and sequential approaches for definitive treatment and became the standard modality for these patients<sup>(4-6)</sup>.

Cisplatin (100 mg/m<sup>2</sup> every three weeks) concurrent with radiation therapy is the most used regimen as a definitive chemoradiation in primary and postoperative settings<sup>(2, 3, 7-11)</sup>. However, increase in acute toxicities (i.e. mucositis, high emetic potential, neurotoxicity, ototoxicity, and nephrotoxicity) can induce early treatment termination or at least, decrease in treatment compliance<sup>(2,3,6,7,12)</sup>.

The main aim now is to decrease the toxicity associated with chemoradiation without altering its efficacy. Therefore, modifying the full dose of cisplatin aiming at decrease toxicities and increase compliance while maintaining dose intensity seem to be logical. Trials used other regimens; 40 mg/m<sup>2</sup>

weekly during radiotherapy<sup>(6, 13-15)</sup>, or 20 mg/m<sup>2</sup> for 4 days in week 1 and 5 of radiotherapy<sup>(16)</sup>.

The weekly schedule had lower toxicity with an expectation to have efficacy similar to that of the every 3 weeks schedule. Espeli et al, (2012)<sup>(17)</sup> reported that 100 mg/m<sup>2</sup> of cisplatin had better overall survival (OS) with similar progression-free survival (PFS) compared to weekly cisplatin while Fayette et al, (2015)<sup>(18)</sup> in their study had significantly better OS and PFS on univariate but not on multivariate analyses. On another hand, Tsan et al, (2012)<sup>(19)</sup> and Geiger et al, (2014)<sup>(20)</sup> found that the outcomes were not significantly different between the two regimens.

The primary purpose of this analysis was to compare response rate and acute toxicities, in patients with locally advanced laryngeal SCC receiving definitive chemoradiotherapy with either of two cisplatin regimens (100 mg/m<sup>2</sup> administered every 3 weeks or 40 mg/m<sup>2</sup> administered weekly) concurrent with radiotherapy. The secondary endpoints included OS, locoregional progression-free survival rates.

### 2. Patients and Methods

This phase II prospective study was conducted in clinical oncology department, Tanta University Hospital, throughout the period between June 2013

and June 2016. Fifty previously untreated patients with cancer larynx (stage III or IVA) according to the American Joint Committee of Cancer (AJCC) staging system 2010 were enrolled with a minimum follow-up period of 12 months.

All patients were informed of the nature of the study and had consented for admission into the study.

### **2.1. Inclusion criteria**

All patients aged between 18 to 70 years who had a histologically confirmed locally advanced unresectable squamous cell carcinoma of the larynx with a performance status (PS) of 0 to 2 according to an Eastern Cooperative Oncology Group (ECOG), adequate bone marrow, renal and liver function profile and had no prior surgery, chemotherapy or radiotherapy.

### **2.2. Exclusion criteria**

Patients presented with evidence of distant metastasis, previous head and neck irradiation, other malignancy or life-threatening comorbid illness, hepatic or renal impairment that interfere with either completion of therapy or follow-up and pregnant or lactating woman were excluded from the study.

### **2.3. Regimen design**

All patients received Cisplatin as a radio-sensitizing agent either at a weekly dose of 40 mg/m<sup>2</sup> or 100 mg/m<sup>2</sup> on day 1, 22, 42 administered as an I.V. infusion over 1 hour period during the course of radiotherapy.

All patients received prophylactic hydration and antiemetic agents and were monitored for potential toxicity through clinical examination and laboratory investigations weekly.

The radiation dose to the primary tumor and clinically positive nodes was 70 Gy/35 fractions, 2 Gy/fraction over a seven-week period. The entire neck, including the supraclavicular areas and the posterior neck, was irradiated with a minimum of 50 Gy. Clinically positive nodes was supplemented with the beams that covered the primary tumor, with electrons, or with tangential anteroposterior beams.

### **2.4. Assessment**

Patients were assessed by full personal, present, past and smoking history; full clinical examination including general and locoregional examinations with evaluation of performance status. Fiber-optic laryngopharyngoscopy and biopsy were done for all cases. A dental consultation was done to all patients before treatment.

Laboratory investigations included complete blood picture, liver & renal function.

Radiological investigations included baseline CT scan or MRI of the neck. Radiological investigations to the chest, abdomen, and pelvis to exclude metastasis included chest X-ray (or CT chest if there is

suspicious lesion); abdominopelvic sonar and bone scan if indicated.

Patients were advised to avoid spicy foods, very cold or hot drinks as well as solid and sour food, receive adequate nutrition by frequent meals with a high-calorie intake.

Clinical assessment was done weekly during CRT phases. At each visit, toxic effects from CT and RT were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

### **2.5. Response evaluation**

Tumor response was assessed at least 1 month after the end of the radiotherapy by ENT examination, CT scan of the neck, fiber-optic endoscopy and biopsy from the primary site. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria <sup>(21)</sup>. Complete remission (CR) was defined as complete disappearance of all target lesions without an occurrence of new lesions that was maintained for four weeks. Partial remission (PR) was defined as a decrease in the sum of the longest lengths of all baseline target lesions  $\geq 30\%$  which was maintained for four weeks. Stable disease (SD) was defined as a decrease in the sum of the longest lengths of all baseline target lesions less than PR, or enlargement of the lesions without progression. Progressive disease (PD) was defined as an increase in the sum of the longest lengths of the detected smallest target lesion  $\geq 20\%$ , or occurrence of one or more new lesion sites.

### **2.6. Follow-up**

Patients were followed monthly by clinical examination, laboratory investigation to evaluate the toxicity and response stability. Every 3 months by neck CT or MRI, fiber-optic endoscopy and biopsy if needed from the primary site for 2 years then every 6 months annually.

### **2.7. Statistical analysis**

The primary endpoints include assessment of treatment response and safety profile of the treatment protocol. The secondary endpoints include evaluation of the OS and the PFS rates. Overall survival was calculated from the date of diagnosis to the date of death, regardless of cause or the last visit. Progression-free survival was defined as the time from the start of treatment to the date of disease progression documentation or last visit. Overall survival and PFS rates were analyzed by the Kaplan-Meier method. Efficacy endpoints were analyzed according to the intention-to-treat principle-i.e. all patients who met the eligibility criteria were included in the analysis. The log-rank test was used to compare the 2 groups of patients. A *p*-value  $< 0.05$  was considered statistically significant. All statistical analysis was performed

using Statistical Package for Social Sciences software V.21.0 (SPSS, Inc. Chicago, IL).

### 3. Results

The median age of patients was 58 (range, 40-65) years with mean  $\pm$  SD age was  $55.9 \pm 6.8$  years. Eighty-Two percent had PS  $<2$  and 66% had pathological grade  $<3$ . All T & N stages were

presented with 62% of all patients had pathological stage III and 38% had stage IVa (Table 1).

#### 3.1. Response rate

Forty-Six percent of all treated patient had clinical response (CR + PR). Patient treated with every 3 weeks sensitization had an apparent better response to those treated with weekly sensitization, but the difference was not significant ( $p=0.538$ ) (Table 2).

**Table 1.** Patients and tumor characteristics.

Characteristics	Whole Group No. (%)	3 Weeks No (%)	Weekly No (%)	<i>p</i>
<b>Age</b> (Median: 58, Range: 40-65 years)				
$\leq 58$	24 (48%)	9 (37.5)	15 (62.5)	0.089
$> 58$	26 (52%)	16 (61.5)	10 (38.5)	
<b>Sex</b>				
Male	42 (84%)	21 (50)	21 (50)	1
Female	8 (16%)	4 (50)	4 (50)	
<b>Performance status</b>				
0	4 (8%)	0 (0)	4 (100)	0.113
1	37 (74%)	20 (54.1)	17 (45.9)	
2	9 (18%)	5 (55.6)	4 (44.4)	
<b>Tumor grade</b>				
Grade 1	6 (12%)	4 (66.7)	2 (33.3)	0.683
Grade 2	27 (54%)	13 (48.1)	14 (51.9)	
Grade 3	17 (34%)	8 (47.1)	9 (52.9)	
<b>T stage</b>				
1	3 (6%)	2 (66.7)	1 (33.3)	0.351
2	11 (22%)	3 (27.3)	8 (72.7)	
3	24 (48%)	14 (58.3)	10 (41.7)	
4	12 (24%)	6 (50)	6 (50)	
<b>N stage</b>				
0	16 (32%)	10 (62.5)	6 (37.5)	0.437
1	26 (52%)	12 (46.2)	14 (53.8)	
2	8 (16%)	3 (37.5)	5 (62.5)	
<b>Stage</b>				
T3	31 (62%)	16 (51.6)	15 (48.4)	0.771
T4a	19 (38%)	9 (47.4)	10 (52.6)	

**Table (2): Response rate.**

Response Rate	Whole Group No. (%)	3 Weeks No (%)	Weekly No (%)	<i>p</i>
<b>CR</b>	8 (16%)	5 (62.5%)	3 (37.5%)	0.538
<b>PR</b>	15 (30%)	9 (60%)	6 (40%)	
<b>SD</b>	16 (32%)	7 (43.8%)	9 (56.3%)	
<b>PD</b>	11 (22%)	4 (36.4%)	7 (63.6%)	

#### 3.2. Toxicity of treatment

All patients received CRT with median RT dose 72 (range, 44-72; mean  $\pm$  SD,  $67.5 \pm 7.9$ ) Gy given over median time of 54 (range, 30-62) days. Thirty-six (72%) patients had treatment interruption and 3 (6%) patients discontinue their planned treatment due to side effects. However, this interruption was not significant between the two arms ( $p=0.733$ ). Patients treated with weekly sensitization had significantly lower leukopenia, nausea and acute renal injury

( $p<0.05$ ) than those treated with every 3 weeks sensitization. (Table 3).

#### 3.3. Survival outcome

The median follow-up time from treatment start was 34 (range 7-51) months. At the end of the follow-up period, 18 (36%) patients were alive. The median OS time was 32 (range, 5-49; 95% CI, 27.7-36.3) months in the whole group of patients, while it was 37 (range, 6-49; 95% CI, 31.3-42.7) months and 29 (range, 5-47; 95% CI, 24.9-33.1) months for every 3

weeks versus weekly treated patients respectively. The 2-year OS rate was 68% in the whole group of patients while it was 72% and 64% for the 2 groups respectively ( $p=0.153$ ) (Table 4, Fig. 1).

The median PFS was 28 (range, 1-49; 95% CI, 24.7-31.3) months in the whole group of patients, while it was 29 (range, 1-49; 95% CI, 26.6-31.4)

months and 27 (range, 1-47; 95% CI, 22.2-31.8) months for every 3 weeks versus weekly treated patients respectively. The 2-year PFS rate was 64% in the whole group of patients while it was 68% and 60% for the 2 groups respectively ( $p=0.592$ ) (Table 4, Fig. 2).

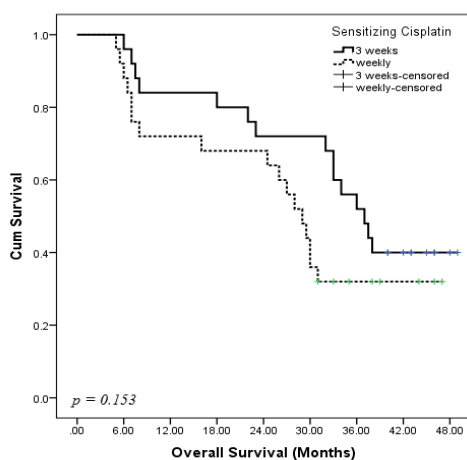
**Table (3): Toxicity of treatment.**

Toxicity	3 Weeks (no, %)			Weekly (no, %)			<i>p</i>
	0	I/II	III/IV	0	I/II	III/IV	
<b>Hematological</b>							
Anemia	8 (32)	15 (60)	2 (8)	13 (52)	11 (44)	1 (4)	0.343
Leukopenia	9 (36)	11 (44)	5 (20)	17 (68)	7 (28)	1 (4)	0.049*
Thrombocytopenia	14 (56)	10 (40)	1 (4)	19 (76)	6 (24)	0 (0)	0.252
<b>Non-hematological</b>							
Mucositis	3 (12)	17 (68)	5 (20)	4 (16)	17 (68)	4 (16)	0.881
Anorexia	5 (20)	19 (76)	1 (4)	3 (12)	22 (88)	0 (0)	0.423
Nausea	6 (24)	18 (72)	1 (4)	15 (60)	10 (40)	0 (0)	0.028*
Vomiting	7 (28)	16 (64)	2 (8)	15 (60)	9 (36)	1 (4)	0.074
Dysphagia	4 (16)	20 (80)	1 (4)	3 (12)	22 (88)	0 (0)	0.538
Diarrhea	14 (56)	10 (40)	1 (4)	17 (68)	8 (32)	0 (0)	0.469
Acute Renal Injury	13 (52)	9 (36)	3 (12)	21 (84)	4 (16)	0 (0)	0.033*
Neuropathy	13 (52)	11 (44)	1 (4)	16 (64)	9 (36)	0 (0)	0.470

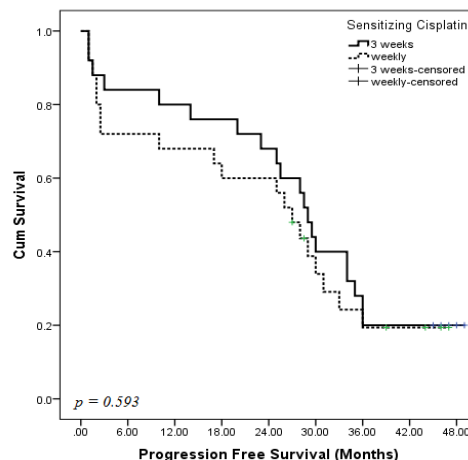
\* Significant,  $p<0.05$

**Table (4): Survival Outcome**

Overall Survival (OS)	Whole group	3 Weekly group	Weekly group	<i>p</i>
Median	32	37	29	
Range	5-49	6-49	5-47	
2-year OS	68%	72%	64%	0.153
95% CI	27.7-36.3	31.3-42.7	24.9-33.1	
<b>Progression Free Survival (PFS)</b>				
Median	28	29	27	
Range	1-49	1-49	1-47	
2-year PFS	64%	68%	60%	0.592
95% CI	24.7-31.3	26.6-31.4	22.2-31.8	



**Figure 1: Overall survival**



**Figure 2: Progression free survival**

#### 4. Discussion

The addition of chemotherapy to radiotherapy improves the locoregional control rates with demonstrated increased survival rates, however, the toxicities can be life-threatening<sup>(4-6)</sup>. The most important agent for definitive chemoradiotherapy of SCCHN is cisplatin. It is not yet clear whether concurrent weekly administration of 30–40 mg/m<sup>2</sup> cisplatin is as effective as the “standard” regimen 100 mg/m<sup>2</sup> of cisplatin given every 3 weeks with RT. The aim of this study is to contribute to the question whether weekly cisplatin is a reasonable and less toxic alternative to 100 mg/m<sup>2</sup> of cisplatin given every 3 weeks.

To avoid a potential selection bias caused by different anatomical sites that may affect prognosis and survival outcome, our study included patients with locally advanced laryngeal SCC, who had received definitive chemoradiotherapy.

As regard toxicity, patients in the present study treated with higher dose of cisplatin given every 3 weeks had more toxic side effect compared with patients treated with weekly dose, mainly in the form of leucopenia ( $p=0.049$ ), nausea ( $p=0.028$ ) and acute renal toxicity ( $P=0.033$ ).

Ho et al<sup>(13)</sup> retrospectively analyzed the results of the treatment of 51 patients with stage IVa HNSCC who were treated with radiotherapy (66-70 Gy/33-35 fractions) concurrent with cisplatin given every 3 weeks vs. weekly. Scheduled cisplatin cycles were delayed and cisplatin dose reduction was reported more frequently in the 3-week arm. Concerning the acute toxicities, they were comparable between the two arms.

Espeli et al,<sup>(17)</sup> analyzed the treatment outcome of cisplatin given every 3 weeks vs. weekly concurrent with intensity-modulated radiation therapy (IMRT) in 94 HNSCC patients presented with stage III/IV retrospectively. They reported significantly higher chronic renal failure rate with the 3-weekly regimen ( $p=0.04$ ) with less nephrotoxicity in the weekly arm.

Fayette et al<sup>(18)</sup> studied 262 patients presented with HNSCC retrospectively. All the patients received IMRT associated with cisplatin as sensitizing agents either every 3 week so weekly. They reported more toxicity in the 3-week arm in the form of loss of weight, mucositis, dermatitis, treatment interruption and renal failure.

Tsan et al<sup>(19)</sup> randomly treated 55 patients with high-risk oral SCC post-operatively with adjuvant RT (66 Gy/33 fractions) concurrent with cisplatin every 3 weeks or weekly. Significantly grade  $\geq 3$  mucositis was reported in the weekly arm, ( $p=0.012$ ) with nearly comparable other acute toxicities.

Rades et al<sup>(22)</sup> studied 75 patients presented with locally advanced HNSCC and treated with RT

concurrently with cisplatin given either every 3 weeks or weekly and reported significantly higher toxicity in the 3-week arm, grade  $\geq 3$  hematotoxicity ( $p=0.004$ ), grade  $\geq 2$  renal failure ( $p=0.004$ ).

Melotek et al<sup>(23)</sup> studied 212 patients with HNSCC treated with RT concurrent with platinum-based regimens given either every 3 weeks or weekly, retrospectively. Patients in the 3-week arm had significant acute kidney injury (50.0% vs. 22.1%;  $p<0.001$ ) with increased hospitalization days ( $p=0.03$ ).

In the present study, with 34 (range 7-51) months median follow-up, the 2-year OS rate was 72% for the 3-week arm vs. 64% for the weekly arm ( $p=0.153$ ). The 2-year PFS rate was 68% and 60% for the 2 groups respectively ( $p=0.592$ ). This non-significant difference between the two arms was also reported in many trials on patients with locally advanced HNSCC.

Tsan et al<sup>(19)</sup> reported that after 12 months median follow-up, the 1-year OS rate was 79.3% vs. 71.6%, respectively ( $p=0.978$ ), and the 1-year locoregional recurrence free survival was 71.1% vs. 60.0%, respectively ( $p=0.806$ ).

Geiger et al<sup>(20)</sup> studied the results of postoperative treatment of 104 patients with locally-advanced oropharyngeal SCC who received adjuvant RT concurrent with cisplatin either every 3 weeks or weekly. The reported 3-year OS rate was 84% vs. 75%, respectively ( $p=0.30$ ) and the 3-year recurrence-free survival was 71% vs. 74%, respectively ( $p=0.95$ ).

Melotek et al<sup>(23)</sup> reported that with 23.7 months median follow-up, both arms of treatment had non-significant survival differences with 2-year OS rate was 75.7% vs. 69.9% ( $p=0.71$ ) and 2-year PFS rate was 53.1% vs. 50.7% ( $p=0.55$ ), respectively.

Other trials showed a significant advantage in either OS or PFS or both favoring the 3-week regimen. Espeli et al,<sup>(17)</sup> reported longer OS with every 3-weeks regimen ( $p=0.041$ ) but the PFS was nearly equal in both arms ( $p=0.47$ ). Fayette et al<sup>(18)</sup> reported that with 73 months median follow-up, the 5-year OS rate was 62.3% vs. 52.6% ( $p=0.014$ ) and the 5-year PFS rate was 55.8% vs. 43.6% ( $p=0.016$ ) in the 3-week vs. weekly regimens respectively. Rades et al<sup>(22)</sup> showed improved OS rate with 3-week arm ( $p=0.023$ ) on multivariate analysis. Ho et al<sup>(13)</sup> reported that with 49 months follow-up in the 3-week arm, the OS rate was 52% & the local control was 63% vs. 71% & 79% respectively in the weekly arm after 26 months median follow-up.

#### Conclusions

In definitive concurrent CRT, weekly low-dose cisplatin is a reasonable and less toxic alternative to high-dose cisplatin given every 3 weeks in the treatment of locally advanced laryngeal SCC. More studies comparing the two regimens are required,

particularly in patients with cancer at specific sites who need definitive CRT.

### 5. Corresponding author

Alaa Mohamed Maria, MD.

Clinical Oncology Department, Faculty of Medicine, Tanta University, Al Gaish St., Tanta, Gharbia 11312, Egypt.

[alaamaria1@hotmail.com](mailto:alaamaria1@hotmail.com)

### 6. References

1. Saunders MI, Rojas AM. Management of cancer of the head and neck – a cocktail with your PORT? *N Engl J Med*, 2004; 350: 1997-9.
2. Bernier J, Dornge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*, 2004; 350(19): 1945-52.
3. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*, 2004; 350(19): 1937-44.
4. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*, 2004; 22(1): 69-76.
5. Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*, 2009; 92(1): 4-14.
6. Traynor AM, Richards GM, Hartig GK, Khuntia D, Cleary JF, Wiederholt PA, et al. Comprehensive IMRT plus weekly cisplatin for advanced and neck cancer: the university of Wisconsin experience. *Head Neck*, 2010; 32(5): 599-606.
7. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*, 2003; 21(1): 92-8.
8. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*, 2003; 349(22): 2091-8.
9. de Castro Jr G, Snitcovsky IM, Gebrim EM, Leitão GM, Nadalin W, Ferraz AR, et al. High-dose cisplatin concurrent to conventionally delivered radiotherapy is associated with unacceptable toxicity in unresectable, nonmetastatic stage IV head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol*, 2007; 264(12): 1475-82.
10. Rades D, Fehlaue F, Sheikh-Sarraf M, Kazic N, Basic H, Poorter R, et al. Toxicity of two cisplatin-based radiochemotherapy regimes for the treatment of patients with stage III/IV head and neck cancer. *Head Neck*, 2008; 30(2): 235-41.
11. Bourhis J, Sire C, Graff P, Grégoire V, Maingon P, Calais G, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol*, 2012; 13(2): 145-53.
12. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Radiat Oncol Biol Phys*, 2003; 55(1): 93-8.
13. Ho KF, Swindell R, Brammer CV. Dose intensity comparison between weekly and 3-weekly Cisplatin delivered concurrently with radical radiotherapy for head and neck cancer: a retrospective comparison from New Cross Hospital, Wolverhampton, UK. *Acta Oncol*, 2008; 47(8): 1513-8.
14. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single institution experience. *Head Neck Oncol*, 2009; 1: 17.
15. Loimu V, Collan J, Vaalavirta L, Back L, Kapanen M, Makitie A, et al. Patterns of relapse following definitive treatment of head and neck squamous cell cancer by intensity modulated radiotherapy and weekly cisplatin. *Radiother Oncol*, 2011; 98(1): 34-7.
16. Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for

- locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. *Head Neck*, 2006; 28(3): 189-96.
17. Espeli V, Zucca E, Ghielmini M, Giannini O, Salatino A, Martucci F, et al. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. *Oral Oncol*, 2012; 48(3): 266-71.
  18. Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupard M, et al. Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. *Drug Des Devel Ther*, 2015; 9: 6203-10.
  19. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, et al. The comparison between weekly and three-weekly Cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. *Radiat Oncol*, 2012; 7: 215.
  20. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, et al. Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. *Oral Oncol*, 2014; 50(4): 311-8.
  21. Therasse P, Arbutk SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*, 2000; 92(3): 205-16.
  22. Rades D, Seidl D, Janssen S, Bajrovic A, Karner K, Strojjan P, et al. Comparison of weekly administration of cisplatin versus three courses of cisplatin 100 mg/m<sup>2</sup> for definitive radiochemotherapy of locally advanced head-and-neck cancers. *BMC Cancer*, 2016; 16: 437.
  23. Melotek JM, Cooper BT, Koshy M, Silverman JS, Spiotto MT. Weekly versus every-three-weeks platinum-based chemoradiation regimens for head and neck cancer. *J Otolaryngol Head Neck Surg*. 2016; 45(1): 62.

12/4/2017