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Retrospective Study Evaluating Efficacy and Toxicity of Concurrent Chemoradiotherapy in Head and Neck Cancer Patients

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ABSTRACT: Head and neck cancer is the most common cancer in developing countries. The concurrent chemoradiotherapy (CCRT) was a standard care for patients with locally advanced squamous cell carcinoma. So, the aim of the present retrospective study was to assess the efficacy and toxicity of the radical concurrent chemo-radiotherapy in head and neck cancer patients and to identify the prognostic and therapeutic factors affecting the outcome. This current study included 102 patients receiving radical radiotherapy concurrently with chemotherapy (Cisplatin, paclitaxel, and Docetaxel plus Cisplatin). These data were collected from the databases at South Egypt Cancer Institute and Assuit University Hospital.
In these patients, the sites of tumor were in the following descending order: larynx (65.7%), the oral cavity (16.7%), the hypopharynx (14.7%) and oropharynx (2.9%). The tumor stage IV was recorded in 83 patients (81.4%).
The loco-regional control after the treatment was 74.5%. The median follow up was 12 months. The 2-year overall survival (OS) and progression free survival (PFS) were 26.7% and 23% respectively. The prognostic factors that were significantly associated with the tumor response were the tumor stage, the histopathologic grade, the radiation dose and radiation treatment time. The primary tumor site was the only significant independent prognostic factor affecting both OS and PFS and the radiation technique significantly affected OS but not PFS. The hazard ratio was considered in the significant prognostic factors to determine the importance of factor levels. The most common treatment toxicities recorded were for mucositis (29.4%), dysphagia (28.4%) and skin reaction (21.6%).

KEYWORDS: Head and Neck, Cancer, Chemoradiotherapy, Retrospectives, Cisplatin, Cox regression.

1 INTRODUCTION

Head and neck cancer (HNC) is the most common cancer in developing countries and is responsible for many deaths worldwide [1]. Head and neck cancer is the sixth type of cancer [2],[3], representing about 6% of all cases and accounting for an estimated 650,000 new cancer cases and 350,000 cancer deaths worldwide every year [4].

Concurrent chemoradiotherapy (CCRT) is the current standard of care for patients with locally advanced squamous cell carcinoma of the head and neck [5],[6]**.** CCRT provides organ preservation that can affect the psychological status, performance status and quality of life of patients. [7].

Treatments used in the management of head and neck tumors may induce more mutilations and malfunctions, worsening the quality of life. Consequently, optimizing outcomes in terms of survival, tumor control, function, and quality of life is a challenge [2],[8].

Most randomized clinical trials exhibit the superiority of combined radiotherapy (RT) and chemotherapy to RT alone for the treatment of locally advanced, non-metastatic squamous carcinoma of the head and neck (HNC) [5],[6]. In Meta-Analysis

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of Chemotherapy on Head and Neck Cancer (MACH-NC), concurrent chemoradiotherapy was found to be the most effective approach with an absolute benefit of 6.5% in 5 years [9].

Chemotherapy is being combined with radiotherapy for improvement of locoregional control and organ preservation and to reduce the formation of distant metastasis [10],[11]. Medina [10] and NCCN [12] also stated that neoadjuvant therapy has yet to be conclusively proven to be beneficial.

The overall survival rate for this cancer depends on the primary site and disease stage with variability [13]. In the case of oral cavity cancer, the overall survival rate is 50% over five years [3]. For other sites (pharynx and larynx), the rate is greater than 50% for early stage disease and generally less than 50% at advanced stages [14].

Toxicity from concurrent chemoradiotherapy was tolerated in most of the patients [15],[16]. Acharya et al. [17] reported that the most common toxic effects of the CRT are oral mucositis, skin reactions and hematological toxicities. Acharya et al. [17] stated also that despite acute toxicities, most of the patient completed the intended treatment; this was facilitated by administration of aggressive supportive care.

According to the previous findings, the current study aimed at the evaluation of the efficacy and toxicity of the radical concurrent chemoradiotherapy in locally advanced head and neck cancer patients of the South Egypt Cancer Institute and Assiut University Hospital and the identification of the prognostic and therapeutic factors affecting the corresponding outcome.

2 PATIENTS AND METHODS

2.1 ELIGIBILITY AND EXCLUSION CRITERIA

The medical records of all patients with head and neck squamous cell carcinoma (HNSCC) treated with radical CRT in South Egypt cancer Institute (SECI) and Assiut University Hospital (AUH), Clinical oncology Department, Assiut, Egypt between 2008 and 2012 were reviewed and assessed retrospectively. The current study included patients with loco-regionally advanced American Joint Committee on Cancer (AJCC) Stage III & IV HNSCC excluding nasopharyngeal cancers which were histologically diagnosed and planned for definitive CCRT. Patients treated with induction chemotherapy prior to the CCRT were included. Patients who had distant metastatic disease or fatal co-morbidity at treatment initiation were excluded.

2.2 RADIOTHERAPY

All patients were irradiated with megavoltage beams either on a telecobalt or a Linear Accelerator, with conventional fractionation (200 cGy per fraction, one fraction per day, 5 days per week) using 2D (Fig. 1), conventional technique or 3D (Fig. 2), conformal radiotherapy with shrinking field technique. Most patients were treated with bilateral opposing portals to the face and neck as per the institutional policy. Three-field technique (bilateral opposing for primary and upper neck matched onto a low anterior neck field) was used sparingly at the discretion of the treating oncologist. The radiation portals were dictated by primary site and disease stage. Beam modifiers and posterior neck boosts with appropriate electron energy were used as and when indicated. Spinal cord shielding was applied after 46 Gy in 23 fractions.

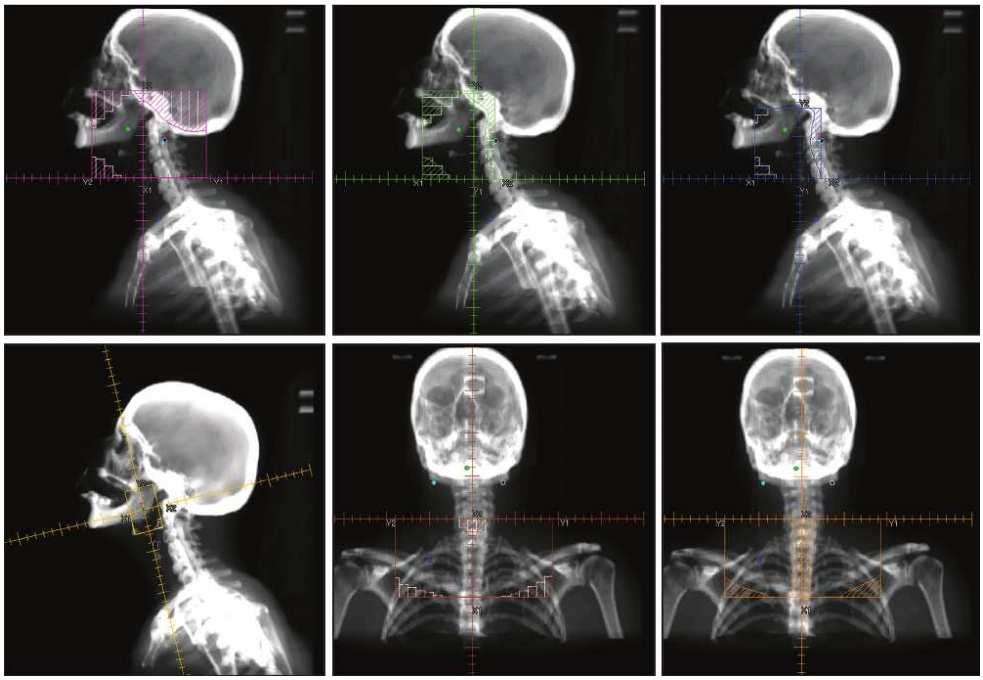


Fig. 1. A typical example of the conventional three-field technique. (A) The beam's eye view (BEV) of one of the bilateral fields for the initial 21 fractions. (B) The BEV of one of the off-cord lateral fields for the subsequent 6 fractions. (C) The BEV of the first cone-down to the primary tumor and the high-risk clinical tumor region for the next 6 fractions. (D) The BEV of the second cone-down for 3 more fractions. (E) The BEV of the anterior supraclavicular field for 22 fractions with a larynx block in the middle. (F) The BEV of the anterior field with the spinal cord block for additional 3 fractions [18]

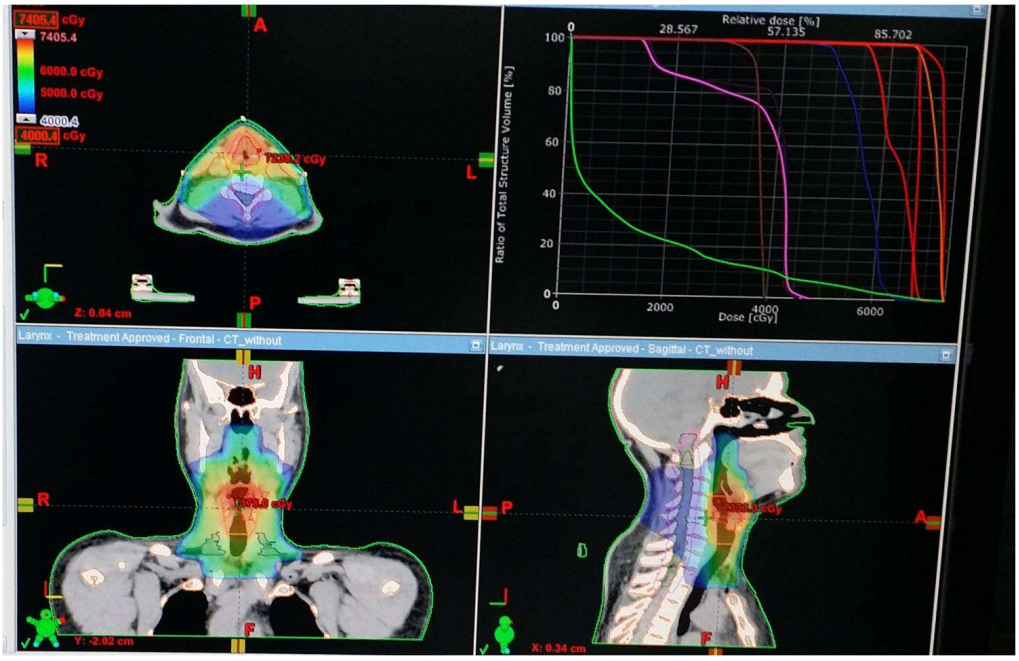


Fig. 2. Example of the 3D conformal radiotherapy planning technique showing dose distribution for axial, coronal and sagittal views and dose volume histogram

2.3 CHEMOTHERAPY

Three regimen of concurrent chemotherapy were included in the present study; weekly cisplatin 30-40 mg/m2, weekly paclitaxel 40 mg/m2 and weekly docetaxel 20-25mg/m2 plus cisplatin 20-25 mg/m2. Two or three cycles of induction chemotherapy that includes docetaxel, cisplatin, and 5-fluorouracil (TPF) were given prior to the CCRT. TPF regimen given in

21-day cycles (Docetaxel, 75 mg/m2, Intravenous (I.V.) on day 1; Cisplatin, 75 mg/m2, I.V. on day 1; 5-fluorouracil, 1000 mg/m2/day by continous I.V. infusion over 24 hours on days 1 through 4).

2.4 FOLLOW UP

All patients were monitored closely weekly during the course of CCRT for assessing the toxicity of therapy. Toxicity grading was done according to the Radiation Therapy Oncology Group (RTOG) [19],[20] and Common Toxicity Criteria (CTC) grading systems [21] for radiation-related and chemotherapy-related toxicities respectively. The patients were followed up at 4–6 weeks from completion of therapy to assess response, toxicity and disease status. Post treatment evaluations included physical examination, fiberopticnasolaryngoscopy and contrast-enhanced neck Computerized Tomography (CT) scan. Subsequent follow-up visits were scheduled at 3–6 monthly intervals for the first 2 years and annually thereafter. Patients who dropped out or did not complete planned course of treatment were included as events for all the outcome measures. The disease status of patients who had completed the planned course of therapy, but not actively following-up was updated by telephonic contact. Non-responding patients were considered lost to follow-up and censored for statistical consideration.

2.5 STATISTICAL ANALYSIS

The survival is defined as the time for registration to death regardless of the cause. The overall survival (OS) and progression free survival (PFS) were calculated using the method of Kaplan-Meier. All estimates were calculated from the date of diagnosis till the defined event if any or until last contact or death. The data was compared using the log-rank test and Cox regression model for multivariate analyses. The statistical analysis for comparing the percentages in different groups was performed using Chi-square test. All analysis was done by IBM SPSS statistical package version 20 [22]. Descriptive statistics were estimated in terms of mean, number (No), and percentages (%).The hazard ratio (HR) was considered in the significant prognostic factors to determine the importance of factor levels.

3 RESULTS

A total of 102 patients with AJCC Stage III and IV HNSCC (excluding nasopharynx) who were treated with definitive concurrent CRT at a period from 2008 to 2012 at SECI and AUH, Clinical Oncology Department were included in the dataset. Patients with progressive disease or dropouts after a few fractions of RT without completing the planned radical course either due to toxicity or socio-personal reasons were also included in the analysis.

3.1 PATIENTS' CHARACTERISTICS (TABLE 1)

The median age of the patients was 59 years (range 28–87 years). The males were 82 patients (80.4%) while the females were 20 patients (19.6%) with sex ratio 4.1:1 in favor of males. The most common tumor site was larynx in 67 patients (65.7%) followed by the oral cavity in 17 patients (16.7%) then the hypopharynx and oropharynx in 15 patients (14.7%) and 3 patients(2.9%) respectively. According to TNM staging system, stage III was recorded in 19 patients (18.6%) while stage IV was represented by 83 patients (81.4%). The histopathology was identified to be squamous cell carcinoma in all patients, with grades I (GI), II (GII) and III (GIII) represented by 26 (25.5%), 48 (47%) and 28 (27.5%) patients respectively. Smokers were 37 patients (36.3%) and non-smokers were 65 patients (63.7%); all females in the current study were non-smokers.

3.2 TREATMENT CHARACTERISTICS (TABLE 1)

All 102 patients received radical concurrent chemoradiotherapy (CCRT) and 20 patients (19.6%) of them received induction chemotherapy followed by the CCRT. The patients received three different types of concurrent chemotherapy including; weekly cisplatin in 81 patients (79.4%), weekly paclitaxel in 12 patients (11.8%), and weekly docetaxel plus cisplatin in 9 patients (8.8%). The median total dose of radiation for the entire study was 60Gy. Most of the patients received 66-70 Gy. The median radiation treatment time (RTT) was 50 days. The radiation planning technique used 2D, conventional technique in 81 patients (76.4%) and 3D, conformal radiotherapy in 21 patients(20.6%).

Table 1. Patients and treatment characteristics

Variable	No.(n=102)	%
Age		
≤59	51	50
>59	51	50
Sex		
Male	82	80.4
Female	20	19.6
Tumor site		
Larynx	67	65.7
Oral cavity	17	16.7
Hypopharynx	15	14.7
Oropharynx	3	2.9
Stage		
III	19	18.6
IV	83	81.4
Pathologic grade		
GI	26	25.5
G II	48	47
G III	28	27.5
Smoking		
-	65	63.7
+	37	36.3
Treatment modalities		
Radical CRT	82	80.4
Induction CT+ radical CRT	20	19.6
Chemotherapy type		
Cisplatin	81	79.4
Paclitaxel	12	11.8
Docetaxel + Cisplatin	9	8.8
Radiation dose (Gy)		
<60	20	19.6
≥60	82	80.4
Radiation technique		
2D	81	76.4
3D	21	20.6
Radiation treatment time	52	51
≤50	50	49
>50		

3.3 EFFICACY ANALYSIS

3.3.1 LOCAL CONTROL AND TREATMENT RESPONSE:

Local control after the treatment occurred in 74.5% of the patients. Tumor response was evaluated 4-6 weeks after completion of the treatment. Complete response (CR), partial response (PR), Stable disease (SD) and progression of disease were recorded in 20 (19.6%), 44 (43.1%), 12 (11.8%) and 7 (6.9%) patients respectively. 19 patients (18.6%) did not complete the planned radiation regimen due to toxicity or socio-personal reasons (Fig. 3). Most of the patients with PR, SD or progressed disease continued their treatment with chemotherapy or salvage surgery.

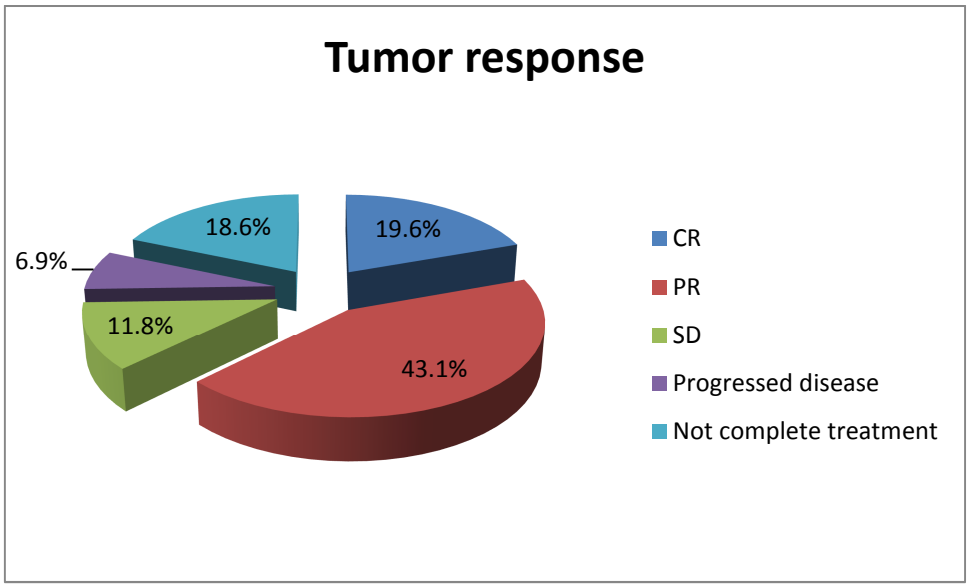


Fig. 3. Tumor response to the treatment

The influence of age, sex, tumor site, stage, histopathologic grade, smoking, treatment modalities, chemotherapy type, radiation dose, RTT and planning technique were studied by Chi-square test in association with tumor response. The prognostic factors that significantly affected the tumor response (P< 0.05) were the tumor stage, the histopathologic grade, radiation dose and RTT.

3.3.2 THE SURVIVAL

With a mean follow-up of 12 months (range 0–92 months) for all patients, the 2-year overall survival and PFS were 26.7% and 23% respectively (Figs. 4 & 5). Three patients (2.9%) developed distant metastases, three patients (2.9%) developed local recurrence after CR and four patients (3.9%) showed progression of their disease was detected on follow up.

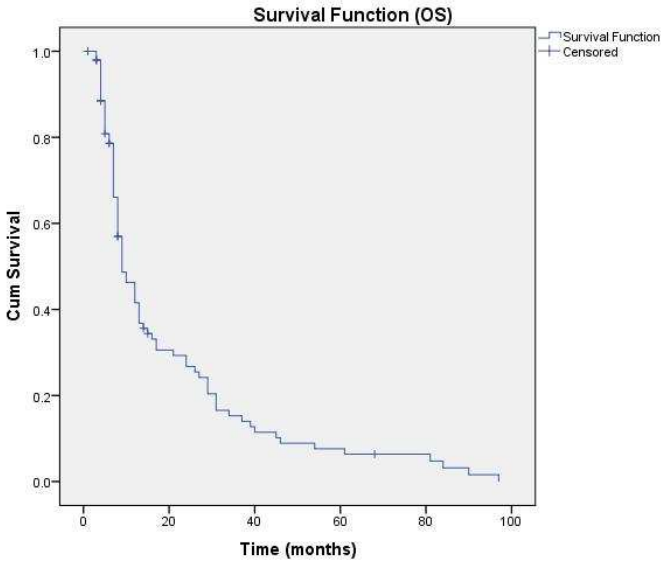


Fig. 4. Kaplan-Meier plots of overall survival (OS) for all patients

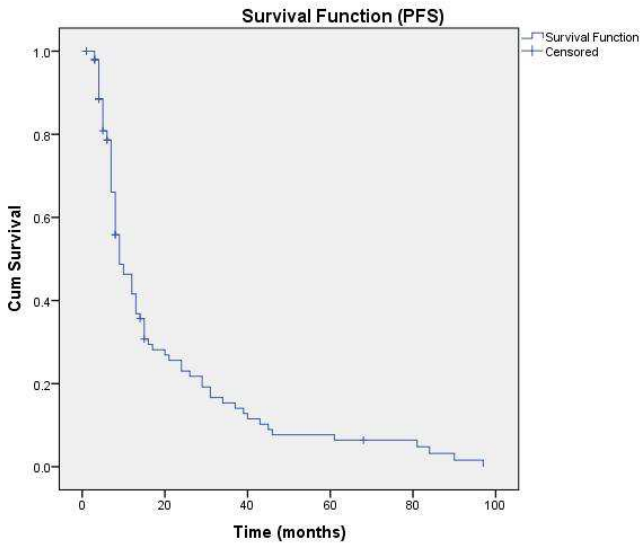
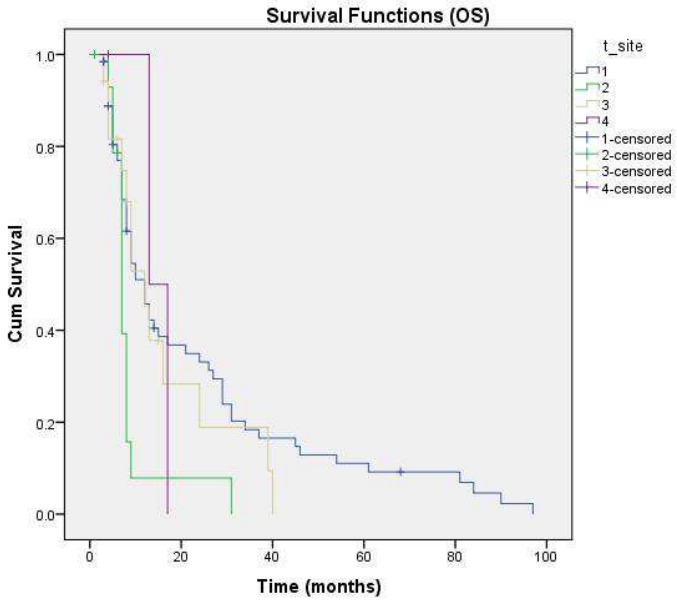


Fig. 5. Kaplan-Meier plots of progression free survival (PFS) for all patients

The impact of different prognostic factors on OS and PFS was studied (Table 2). The primary tumor site was highly significant for both OS and PFS (P= 0.04 for both) (Fig. 6). Patients with oropharyngeal cancer showed the worst outcome, with a 2-year OS and PFS of 0% for each may be due to less number of the patients enrolled in the study. In contrast patients with laryngeal and oral cavity cancers had the best 2-year outcomes. Their 2-year OS and PFS was 33.1% & 27.6% and 18.9% & 15.9% respectively. Hypopharyngeal cancer fared intermediately with 2-year outcomes of 2.5% and 2.4% for OS and progression free survival respectively.



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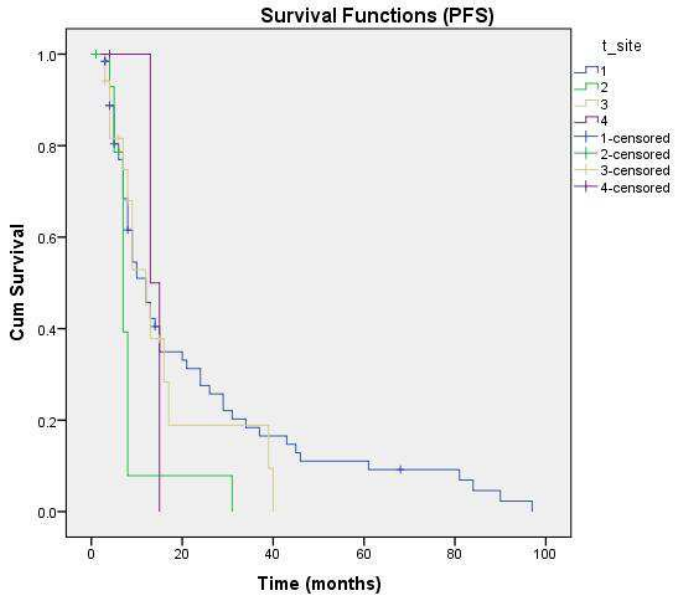
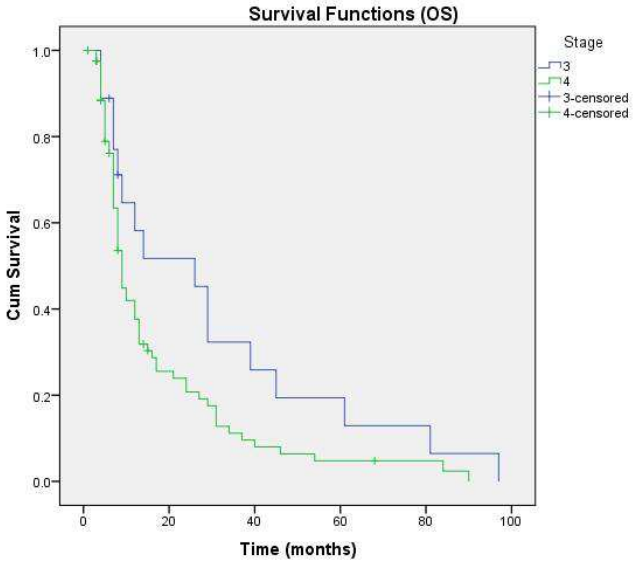


(b)

Fig. 6. Kaplan-Meier plots of overall survival (a) and progression free survival (b) for the primary tumor site

The AJCC stage grouping was highly significant for both OS and PFS (Fig. 7). The 2-year OS and PFS was 46.4% and 41% respectively for stage III disease as compared to 20.8%and 17.7% for stage IV with significant p-values (p =0.05).



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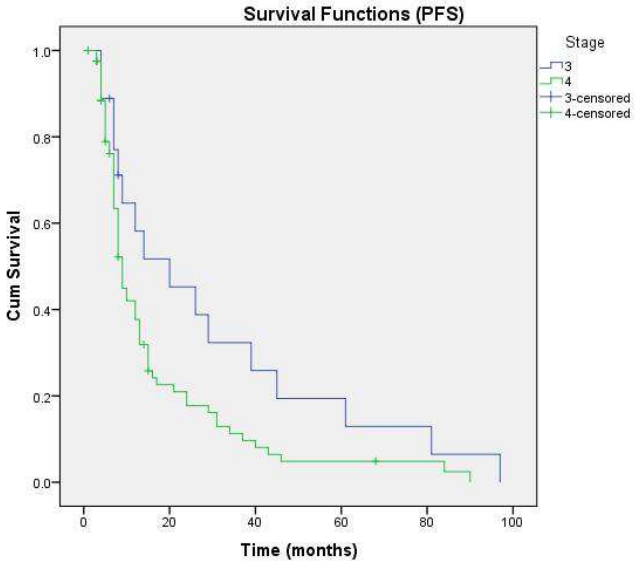
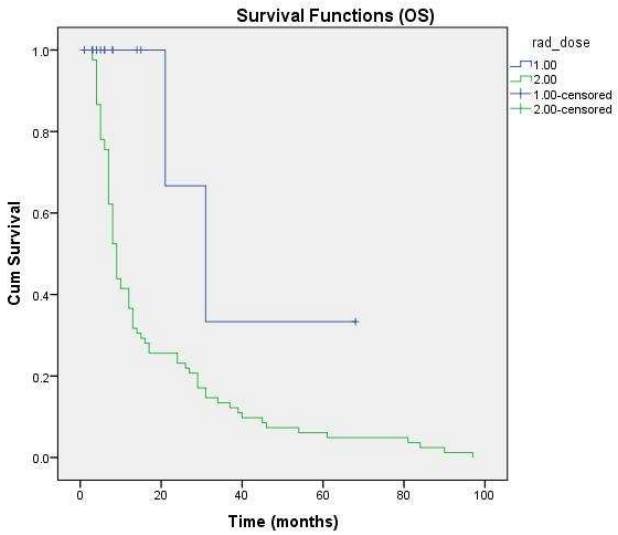


(b)

Fig. 7. Kaplan-Meier plots of overall survival (a) and progression free survival (b) according to the tumor stage

The intensity of treatment affected all the outcome measures significantly. On the basis of total dose of RT delivered, the patients were categorized into two dose groups, <60 Gy; and ≥60 Gy. The 2-year OS in patients receiving <60 Gy was 23.2% as compared to 56.7% in patients receiving ≥60 Gy (p = <0.001). Similarly patients receiving higher total doses had better 2-year PFS (19.5% vs 56.7%, p = <0.001) (Fig. 8).



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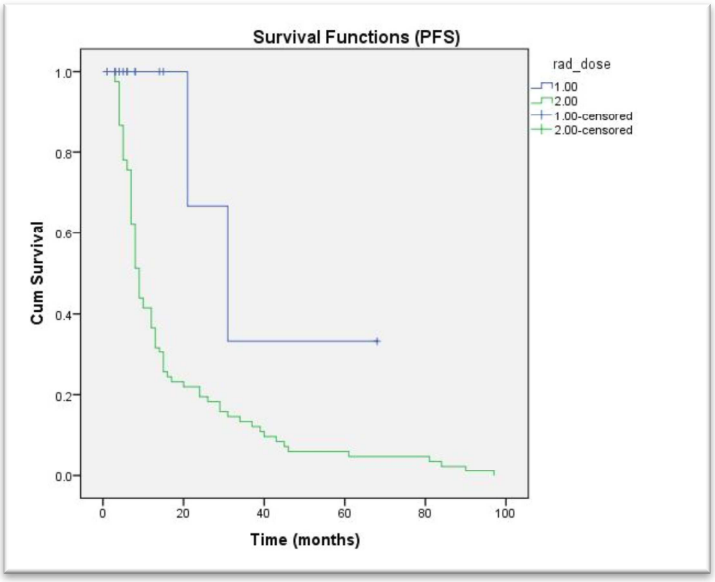
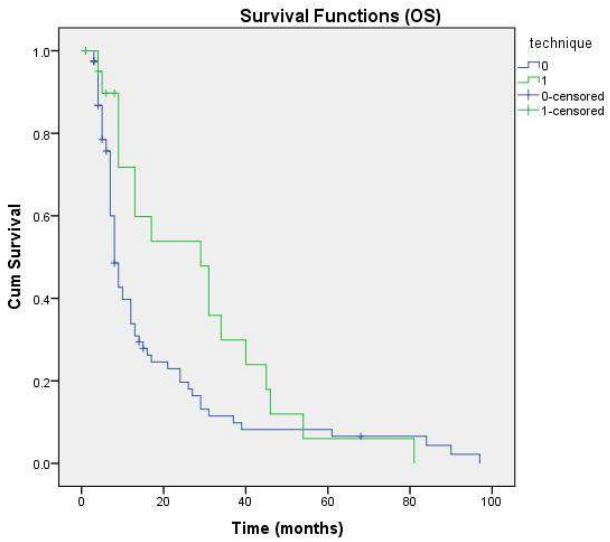


(b)

Fig. 8. Kaplan-Meier plots of overall survival (a) and progression free survival (b) according to the radiation dose (rad_dose)

In the current study, radiation technique was a significant predictor of outcome with patients treated with 3D planning showing better survival than patients treated with 2D. The 2-year OS and 2-year PFS were 50.4% vs 19.7% (P= 0.05) and 50.3% vs 14.9% (P= 0.05) for 3D and 2D respectively emphasizing on the more efficacy of 3D planning in comparison with 2D planning (Fig. 9).



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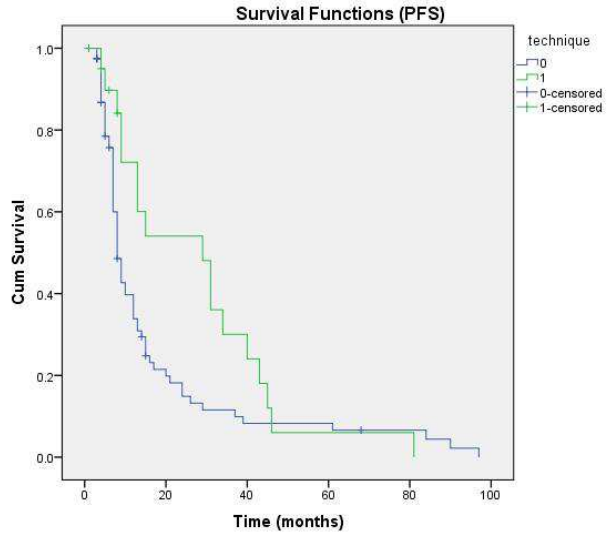
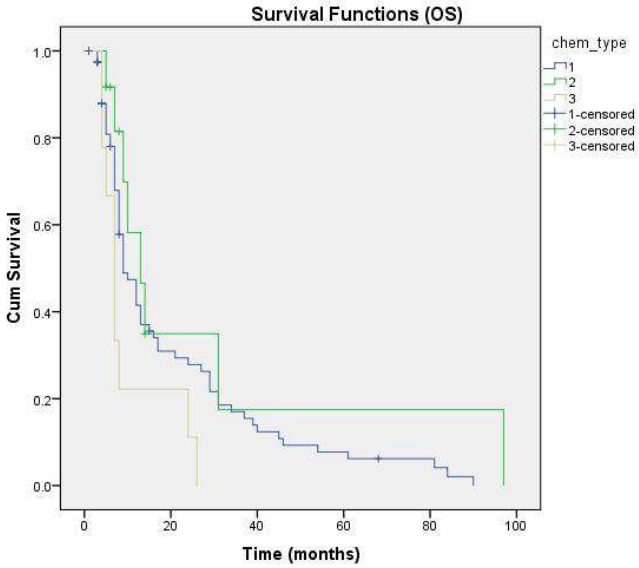


(b)

Fig. 9. Kaplan-Meier plots of overall survival (a) and progression free survival (b) according to the radiation technique

The type of chemotherapy used concurrently with radiotherapy affected significantly the OS but not the PFS. The 2-year OS for cisplatin, paclitaxel and docetaxel plus cisplatin were 27.8%, 24.7% and 11.1% (P=0.05) whereas, the 2-year PFS were 23.7%, 17.5% and 11.1% respectively (P=0.07) (Fig. 10).



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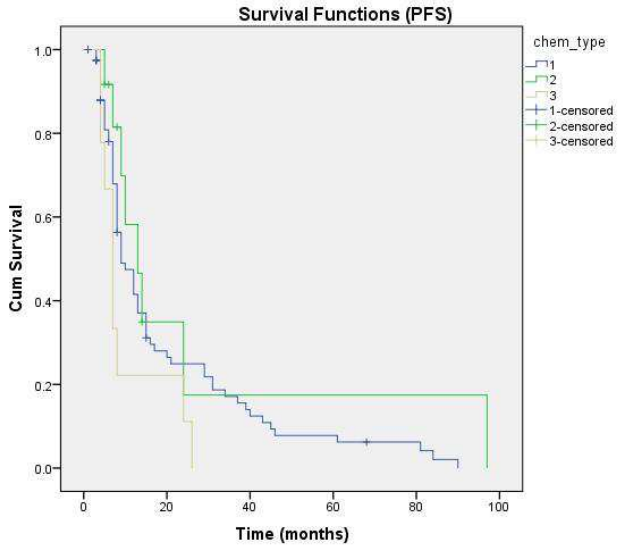

(b)

Fig. 10. Kaplan-Meier plots of overall survival (a) and progression free survival (b) according to the chemotherapy type (chem_type)

Younger age as a prognostic factor did show a trend towards improved outcome which did not reach statistical significance. It is well-accepted that older patients tend to have worse outcomes with aggressive schedules due to lower compliance and higher toxicity rates. Histological grade, sex and smoking were not found to affect outcome significantly (P>0.05). The therapeutic factors as the treatment modalities and radiation treatment time also were not significantly affect the OS and PFS.

All the significant prognostic factors recorded by the Kaplan-meire univariate analysis were subjected for further multivariate analysis. Multivariate analysis using Cox proportional hazards model confirmed the importance of the primary tumor site as significant and independent prognostic factors for both OS and PFS (P=0.04) and the importance of radiation technique as a significant prognostic factor for OS (P=0.04) but not for PFS (P=0.06). The value of hazard ratio (HR) for tumor site showing that the affection on OS for hypopharynx, oral cavity and oropharynx is 2.0 times, 1.2 times, and 1.7 times respectively higher compared to the larynx whereas the affection on PFS is 2.1 times, 1.2 times and 1.6 times respectively

higher compared to the larynx. The 2D technique reflects a risk of 2.1 times over that of 3 D technique on the OS (Tables 3 & Figs. 11-13).

Table 2. Prognostic factors affecting both the overall (OS) and progression-free (PFS) survivals (Kaplan-Meire analysis- log rank test)

Prognostic factor	2-year OS		2-year PFS	
	%	P value	%	P value
Age				
≤59	34.7	0.90	29.8	0.86
>59	18.4		15.6	
Sex				
Male	28.9	0.08	24.2	0.08
Female	18.2		15.1	
Tumor site				
Larynx	33.1		27.6	
Oral cavity	18.9	0.04	15.9	0.04
Hypopharynx	2.5		2.4	
Oropharynx	0		0	
Stage				
III	46.4	0.05	41	0.05
IV	20.8		17.7	
Pathologic grade				
GI	30.4		25.6	
G II	26.7	0.96	21	0.96
G III	21.2		17.3	
Smoking				
-	26.5	0.66	20.1	0.60
+	27.4		27.4	
Treatment modalities				
Radical CRT	28.9		24.3	
Induction CT+ radical CRT	18.1	0.13	18.1	0.17
Chemotherapy type				
Cisplatin	27.8		23.7	
Paclitaxel	24.7	0.04	17.5	0.07
Docetaxel + Cisplatin	11.1		11.1	
Radiation dose(Gy)				
<60	23.2	<0.001	19.5	<0.001
≥60	56.7		56.7	
Radiation technique				
2D	19.7	0.05	14.9	0.05
3D	50.4		50.3	
Radiation treatment time				
≤50				
>50	25.4	0.84	25.9	0.84
	26		20	
Tumor response				
CR	45.8		45	
PR	15.9	<0.001	11.4	<0.001
SD	13.6		13.6	
Progressed disease	0		0	
Not complete treat.	-		-	

Table 3. Significant factors in multivariate analysis (Cox-regression) for overall survival (OS) and profression free survival (PFS)-based outcome measures (Hazard ratio, HR and 95% confidence limits, CL)

Multivariate Cox-regression results					
		OS		PFS	
Variable	No.	HR (95%CL)	P-value	HR (95%CL)	P-value
Tumor response					
Not complete treatment	19	(reference, ref)		(reference, ref)	
CR	20	4.2 (0.2-76.3)	0.33	3.8 (0.2-70.2)	0.36
PR	44	4.4 (0.2-80.6)	0.32	4.3 (0.2-78.6)	0.32
SD	12	6.3 (0.4-102.6)	0.19	5.7 (0.4-94.2)	0.22
Progression	7	6.8 (0.3-136.8)	0.20	6.6 (0.3-131.2)	0.21
Chemotherapy type					
Cisplatin	81	(ref)		(ref)	
Paclitaxel	12	0.7 (0.3-1.8)	0.48	0.8 (0.3-1.9)	0.60
Docetaxel +Cisplatin	9	1.5 (0.7-3.3)	0.29	1.4 (0.7-3.0)	0.38
Radiation dose					
<60	20	(ref)		(ref)	
≥60	82	2.0 (0.2-16.0)	0.52	2.1 (0.3-17.4)	0.47
Tumor site					
Larynx	67	(ref)		(ref)	
Hypopharynx	15	2.0 (1.0-4.1)	0.04	2.1 (1.0-4.1)	0.04
Oral cavity	17	1.2 (0.6-2.3)	0.53	1.2 (0.6-2.3)	0.56
Oropharynx	3	1.7 (0.4-8.8)	0.49	1.6 (0.3-8.1)	0.55
Radiation technique					
3D	21	(ref)		(ref)	
2D	81	2.1 (1.0-4.4)	0.04	2.0 (0.9-4.1)	0.06
Stage					
III	19	(ref)		(ref)	
IV	83	1.7 (0.9-3.2)	0.11	1.7 (0.9-3.2)	0.11

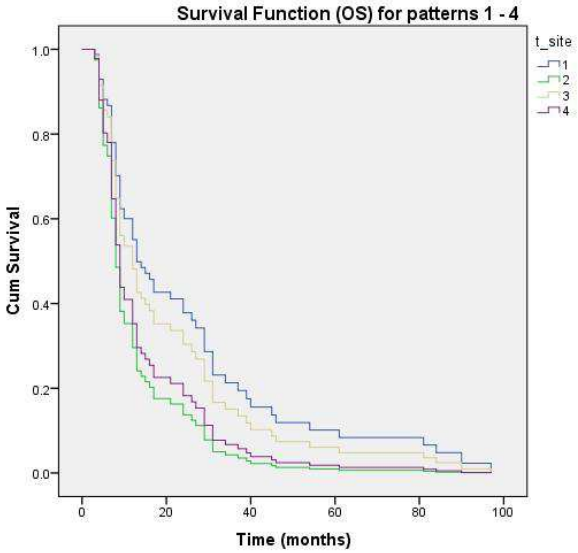

Fig. 11. The cumulative overall survival according to tumor site (t_site) patterns

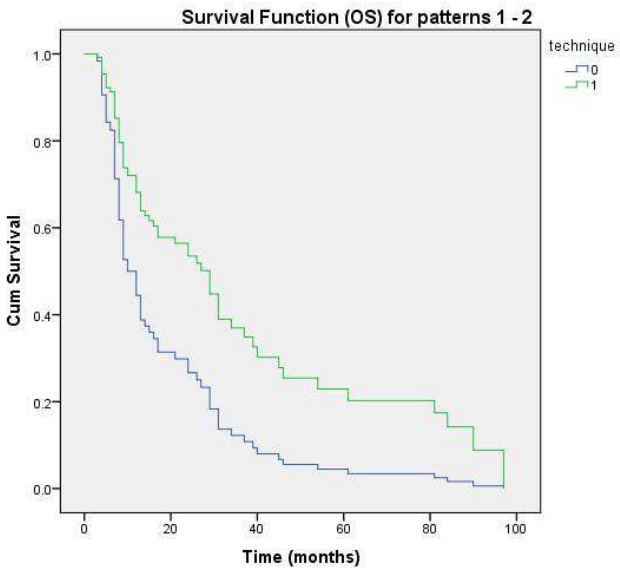

Fig. 12. The cumulative overall survival according to radiation technique patterns

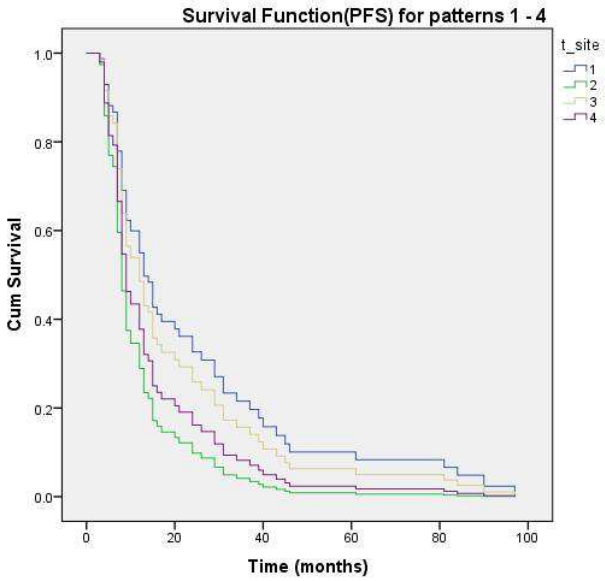

Fig. 13. The cumulative progression free survival according to tumor site (t_site) patterns.

3.4 TOXICITY ANALYSIS

Toxicity from concurrent chemoradiotherapy was tolerated in most of the patients considered. The present results (Fig. 14) exhibited that mucositis was the most common toxicities occurring in 30 patients (29.4%) followed by dysphagia occurring in 29 patients (28.4%) whereas the skin reaction was represented by 22 patients (21.6%). The RTOG acute grade III toxicity included mucositis, dysphagia and dermatitis occurring in 6 (5.9%), 5 (4.9%) and 9 (8.8%) patients respectively. Such grade of toxicity was recorded in most of the time in patients receiving more intense treatment i.e. doses ≥66 Gy and planning with 2D radiation technique.

In other toxicities recorded, only one patient developed grade III laryngeal edema and this patient underwent urgent tracheostomy. Grade I and III xerostomia occurred in 7 patients (6.9%) and 5 patients (4.9%) respectively. Grade I/II nausea and vomiting occurred in 7 (6.9%) patients. Acute hematologic toxicity in the form of neutropenia occurred in 4 (3.9%) patients. The incidence of CTC grade III neutropenia was 1.9% and no episodes of febrile neutropenia were recorded. There was minimal acute kidney dysfunction recorded in 3 (2.9%) patients. One patient developed ototoxicity and one patient

developed cardiac toxicity. Other radiation-enhanced complications were reported such as infection flaring by accumulation of pus behind the ear recorded in one patient and development of trachea-esophageal fistula in two other patients who did not complete their treatment and salvage surgery done.

Toxicity of the treatment may lead to patient interruption in receiving the planned dose of radiotherapy. This situation was recorded in 19 (18.6%) patients who dropped out of treatment and did not complete RT. The overall treatment regimen was well tolerated with acceptable acute toxicity. An analysis of late effects of the regimen was not attempted due to the lack of proper documentation of late toxicity.

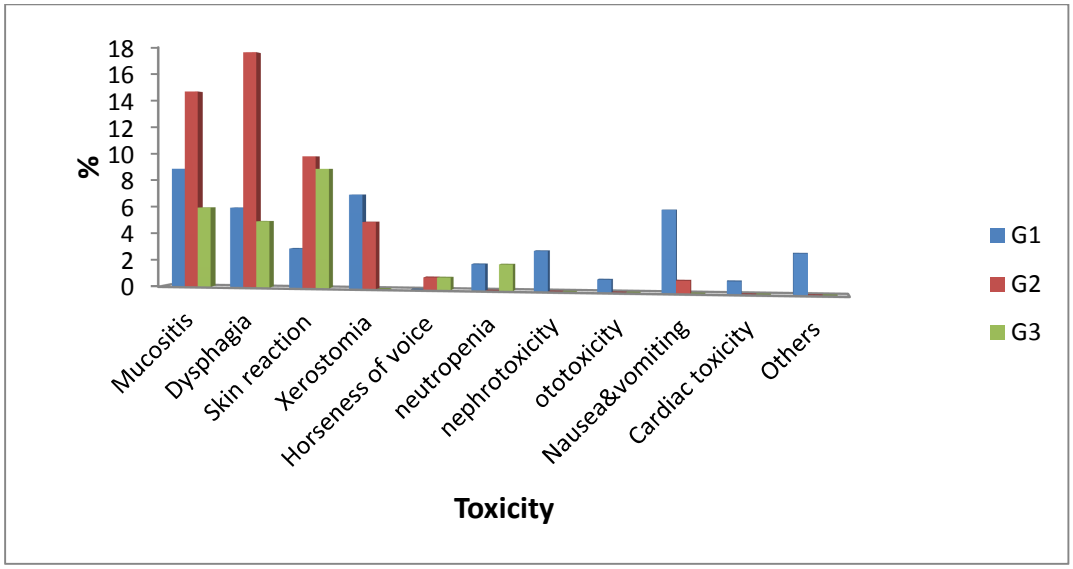

Fig. 14. Distribution of treatment-related toxicities according to the RTOG and CTC grading systems

4 DISCUSSION

Concurrent chemoradiotherapy is considered the standard treatment for locally advanced head and neck cancer patients [1],[5],[6],[11]. These authors referred to the efficacy of this regimen in improving the outcomes. However, the concurrent chemoradiotherapy was found to be associated with some types of toxicities [5],[11],[17],[23]. So, the present work assessed the efficacy and the toxicity of such treatment.

The efficacy of any curative approach is measured by its ability to achieve locoregional control and improve the survival [24],[25],[26]. In present work, the tumor response (locoregional control) after the treatment, OS, and PFS were considered as measures of efficacy.

As regards the patient response to the treatment, only 19.6% of the patients achieved CR. Mesía, et al. [25] concluded that 24% of their patients had complete response (CR). However, Adelstein, et al. [24] reported that 40.2% of their patients had CR. Such higher percentage may be due to inclusion of all the patients in their study with treatment of a total radiation dose of 70 Gy given in single, daily, 2 Gy fractions but the patients in current study were treated with different radiation dose with median dose of 60 Gy. In addition, the other prognostic factors considered in the present work could affect adversely the tumor response.

The present study revealed that the most significant factor affect the tumor response after treatment were the stage, the tumor grade, the total radiation dose and radiation treatment time (RTT) ($P < 0.05$). This was partially in agreement with Gupta, et al. [27] who stated that the stage grouping, primary site and intensity of treatment were significant predictor of the treatment outcome. As regarding the histological grading, van Weert, et al. [28] concluded in their study that histopathological grade proved to be an independent prognosticator. A situation emphasized by de Visscher, et al. [29] who reported the correlation of aggressive invasion pattern with poor local-regional control. Cannon, et al. [30] concluded that prolonged radiation treatment time is associated with inferior outcome and compromise tumor control in patients with head and neck cancer.

The current study reveals that 2-year OS and 2-year PFS were 26.7% and 23% respectively. This was comparable with the results of Peddi, et al. [31] revealed that the patients received concurrent cisplatin with RT showed the 2-year overall survival and progression free survival of 70% and 67% respectively. This difference may be due to receiving only single agent, concurrent chemotherapy, cisplatin for all patients included in their study since the cisplatin showed higher survival benefit. The findings of Forastiere, et al. [32] revealed better 2-year overall survival of 74%. Such higher value may be due to that all patients included in their study has only one tumor site, laryngeal carcinoma receiving total dose of 70 Gy with concurrent cisplatin. However, the current study included different tumor sites, different radiation doses and chemotherapy regimens that affected the outcome.

Statistical analysis of different prognostic factor in the present study showed that the tumor site independent significantly affect both OS and PFS (P=0.04) but the radiation technique significantly affect OS (P=0.04) but not for PFS (P=0.06). This result is in agreement with Gupta, et al. [27] who reported that the primary site was one of the significant and independent predictors of the outcomes. Moreover, Overgaard, et al. [33] referred to tumor site as a good prognostic value.

As regarding the radiation technique, Billan, et al. [34] concluded in their study that 3DCRT in head and neck cancer permits good coverage of the PTV than 2DRT. Clavel, et al. [35] reported superior outcomes (OS, DFS, and LRC) for IMRT patients compared to those treated with conventional radiation therapy techniques for locally advanced oropharyngeal cancer. However, Kouloulias, et al. [36] stated that there are no significant differences in terms of locoreginal control and overall survival between IMRT and 2-3D RT. These authors also mentioned that there are significant variations in tumor control and survival outcomes due to differences in patient sample, tumor stage, and follow up among several studies. In the current work, 2D technique reflects a risk of 2.1 times over that of 3D techniques on the overall survival in terms of hazard ratio (2.1, 95% CL of 1.0-4.4).

The current study included patients treated with concurrent chemoradiotherapy only who were 82 patients (80.4%) with 2-year OS and PFS of 28.9% and 24.3% respectively. The remaining 20 patients (19.6%) received induction chemotherapy followed by concurrent chemoradiotherapy with 2-year OS and PFS (18.1% for each). This result is different from the results reported by Lorch, et al. [37] and Wang, et al. [11] for phase III trial in which the induction chemotherapy lead to moderate benefit in clinical response and survival rate. However, NCCN [12] stated that an improvement in OS with incorporation of induction chemotherapy has not been established compared to receiving directly concurrent chemotherapy.

Among the three different regimens of chemotherapy concurrently used with radiotherapy in the present work, the first regimen; single agent cisplatin exhibited the highest survival benefits. In general, all types of chemotherapy have significant effects on OS (P=0.04). Similarly, Rades, et al. [38] reported that cisplatin alone was significantly associated with improved OS. Many other studies preferred cisplatin as a concurrent chemotherapy with radiotherapy [5],[9],[24],[39].

Most of the patients in the present study were treated up to doses of 66-70 Gy (median dose of 60 Gy) on a median radiation treatment time of 50 days (7 weeks). The patients received higher total dose with shorter treatment time showed better outcome. NCCN [12] reported that when using conventional definitive fractionation, the primary tumor and involved lymph nodes generally require a total of 66 Gy (2.2 Gy/ fraction) to 70 Gy (2.0 Gy/ fraction).

Trotti [40] stated that the addition of chemotherapy has introduced systemic toxicity as well as exacerbating local tissue reactions when used concurrent with radiotherapy. Tobias, et al. [23] mentioned mucositis to be the most common toxicity during treatment. In addition, Acharya, et al. [17] reported that the most common toxic effects of the CRT were mucositis, skin reactions and hematological toxicities. Among different CCRT-associated toxicities recorded in the current work, mucositis, dysphagia and skin reaction were the most common toxicities. So, it is recommended that the treatment of toxicities should be managed aggressively to limit treatment interruptions that lead to prolongation of the overall treatment time and affect the efficacy and treatment outcome.

5 CONCLUSION

In conclusion, induction chemotherapy followed by the radical chemoradiotherapy shows no improvement in the treatment outcome. The types Concurrent chemotherapy plays a significant role in the variation of the outcome and cisplatin as a mono-chemotherapy showed superior survival. It is concluded that the assessment of prognostic factors such as the tumor stage, the histopathologic grade, the radiation dose, radiation techniques, tumor site and radiation treatment time is a cornerstone in these therapies. Treatment toxicity was tolerable and was highly recorded in patients with high radiation dose and 2DRT.

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