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Research Article

Compliance, Toxicity & Survival function analysis of Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck treated with definitive Radiotherapy Concurrent with weekly Cisplatin

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Abstract: Background: The standard of care for Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN) is Concurrent Chemo-Radio-Therapy (CCRT), with cisplatin at least 40 mg/m^2 per week being standard weekly schedule; so as to keep minimum cumulative dose to be 200 mg/m^2. **Methods:** The present retrospective study was carried out at department of Radiotherapy, SMS Medical College, Jaipur; on 174 patients with LASCCHN treated with definitive 3DCRT (70 Gy in 35 fractions) with concurrent weekly cisplatin; during July 2013 to December 2014. Results were analysed for compliance, toxicity, locoregional control (LRC), and progression free survival (PFS). **Results**: Compliance to RT & CT was seen in 90.8% & 76.4% patients, respectively. Treatment interruptions were seen in 76.4% of patients, 81.1% patients required hospitalisation at least once, 28.2% patients required feeding naso-gastric tube insertion, and 15.5% patients required tracheostomy. At three months, complete response was seen in 81.6% patients. Grade III or higher acute dermatitis was seen in 18.9% of patients, mucositis in 41.9%, dysphagia in 16.7%, xerostomia in 13.2%, vomiting in 10.9%, diarrhea in 2.3%, leucopenia in 1.7%, and anemia in 6.3% of patients. The median follow up was 40 months (range, 31- 48 months). At last follow up, LRC was 66.9%, distant metastases were seen in 12.1% patients, deaths were reported in 8% of patients, and PFS was 71.8%. **Conclusion**: The findings of present study match with most of the studies cited in literature. Compliance to both CT and RT was good; acute toxicities were within the accepted levels, and were manageable. Higher LRC was significantly associated with stage III (versus IV, $P < 0.001$), larynx (versus oral cavity, $P = 0.02$), and ≥5 CT cycles ($P = 0.01$);, whereas PFS with stage III (versus IV, $P < 0.001$), larynx (versus oral cavity, $P = 0.03$), and absence of treatment interruptions ($P = 0.03$).

INTRODUCTION

Head & neck cancer is one of the leading cancers among Indian population, with estimated incidence of about 14.3% (23.3% in males and 6.3% in females) and estimated mortality of about 15.4% (22.8% in males and 7.3% in females) for all cancer cases. [1, 2] At our centre, department of Radiotherapy, SMS Medical College, Jaipur; head and neck malignancies constitute approximately 25% of all cancers. Treatment for loco-regionally advanced head and neck cancers remains challenging because the disease is within an anatomic environment that contains several critical structures, such as spinal cord, salivary glands, mandible, major vessels and the organs of speech, swallowing, hearing and respiration. Attempts to cure such patients with aggressive multimodality treatment have not succeeded till date. Most of the diagnosed head and neck cancers are histologically squamous cell carcinomas (90-95%). More than two third cases require radiotherapy (RT), either as definitive or as adjuvant mode, concurrently with chemotherapy; or for palliation. The standard of care for Locoregionally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN) is Concurrent Chemo-Radio-Therapy (CCRT) with an absolute benefit of 6.5% in overall survival (OS) at 5 years when compared to radiotherapy alone [3].

The two dimensional radiotherapy techniques has been associated with higher incidences of adverse effects like dermatitis, mucositis, xerostomia and dysphagia, requiring enteral or parenteral nutrition support hampering quality of life. The reactions sometimes are severe enough warranting treatment interruptions ultimately affecting treatment outcome. With development of modern radiotherapy techniques, like Three Dimensional Conformal Radiation Therapy (3DCRT) and Intensity Modulated Radiation Therapy (IMRT); it is possible for us to precisely deliver radiation to the tumor while sparing organs at risk (OAR) leading to decreased adverse effects. The most common

chemotherapeutic (CT) agent used for Concurrent Chemo-Radio-Therapy CCRT is cisplatin (CDDP, cis-diamminedichloridoplatinum). The optimal regimen of CDDP is still unknown. The most widely accepted schedule of CDDP found in literature is 100 mg/m^2 given intravenously (IV) every three weeks. However, this has been associated with higher toxicities leading to undesired treatment interruptions. Alternatively, weekly schedule of CDDP at 40 mg/m^2 concurrently with radiotherapy has been the standard practice for LAHNSCC at our institute. It allows for treatment to be delivered on an out-patient basis and is well tolerated. This retrospective study aims at evaluating the compliance, toxicity profile, loco regional control (LRC), and progression free survival (PFS) of patients with LAHNSCC undergoing CCRT with weekly cisplatin at 40 mg/m^2 with main emphasis on the modality of radiotherapy used and schedule of cisplatin given.

METHODS

The present study is retrospective in nature carried out at department of Radiotherapy, SMS Medical College, Jaipur; on patients with LASCCHN of oral cavity, oropharynx, hypopharynx and laryngopharynx who were treated with definitive radiotherapy with curative intent with three dimensional conformal radiation therapy (3DCRT) over linear accelerator, with concurrent weekly CDDP; during July 2013 to December 2014. Patients with early stage, previous history of surgery, other than squamous histology, location of primary other than cited above, who received less than 66 Gy of radiation, previous history of RT, RT other than 3DCRT, no history of CCRT, chemotherapy other than CDDP, or palliative intent of treatment, were excluded from the study. RT details and follow up record of patients treated over linear accelerator was extracted, and a total of one hundred and seventy four patients were found eligible for the present study. Being retrospective nature of the study, ethics committee approval was not required as the patients were treated according to standard institutional protocol.

Table 1 Baseline patient & tumour characteristics

Characteristics		Number (%)
Age (years)	(Median, Range)	56, 32-77
Gender	Male	148 (85.1)
	Female	26 (14.9)
Smoking	Yes, present	41 (23.6)
	Yes, quit	117 (67.2)
	No	16 (9.2)
Site	Oral cavity	24 (13.8)
	Oropharynx	82 (47.1)
	Hypopharynx	37 (21.3)
	Laryngopharynx	31 (17.8)
AJCC Stage	III	52 (29.9)
	IVA	103 (59.2)
	IVB	19 (10.9)

AJCC: American Joint Committee on Cancer

All patients had undergone basic laboratory investigations prior to administration of every CT cycle; and baseline clinical examination, radiological evaluation (either a contrast enhanced computed tomography or a magnetic resonance imaging of head and neck region), laryngoscopic evaluation and metastatic work-up prior to RT. Patients were treated on Seimens Oncor Expression dual energy linear accelerator machine with 6 megavoltage photon energy beam with immobilization in supine position using a thermoplastic device, with parallel opposed field for the primary and matched anterior field for the lower neck. Patients were planned to receive 70 Gy in 35 fractions with 2 Gy per fraction per day, for five days a week to the tumor and involved lymph nodes, and 50 Gy to uninvolved nodes. Planning computerized tomography (CT) scan of the area of interest was done followed by delineation of Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV) and organs at risk (OAR) volumes as per the RTOG atlas. All patients received injection cisplatin at 40 mg/m2 given intravenously concurrently with radiotherapy every week, with adequate hydration as per the institutional protocol. This was followed one to two hour later by delivery of RT.

Table 2 Treatment characteristics

Parameters		Number (%)
Treatment interruptions	Nil	41 (23.6)
	< 1 week	95 (54.6)
	≥ 1 week	38 (21.8)
Parenteral support required at least once during CCRT		141 (81.1)
Compliance to	RT	158 (90.8)
	CT, <5 cycles	41 (23.6)
	CT, ≥5 cycles	133 (76.4)
Nasogastric tube feeding required		49 (28.2)
Tracheostomy required		27 (15.5)
3 months follow up	CR	142 (81.6)
	Non CR	32 (18.4)

CCRT: Concurrent chemoradiation, CR: Complete Response, CT: Chemotherapy, RT: Radiotherapy

All patients had undergone weekly assessment while CCRT was going on for development of any acute toxicity. Toxicities like mucositis, dermatitis, xerostomia, dysphagia, nephrotoxicity and gastrointestinal toxicity were assessed according to Radiation Therapy Oncology Group (RTOG) Acute and Late Radiation Morbidity Scoring Criteria; whereas haematological toxicities like leucopenia, anemia and thrombocytopenia; nausea and vomiting were assessed as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.03). In all toxicities, the worst grade was reported. All patients underwent clinical evaluation at six weeks post CCRT followed by both clinical and radiological evaluation every three months for the first two years, thereafter every six months till the last follow up. Response was assessed as per the WHO Criteria. A complete response (CR) was defined as no evidence of disease 3 months after the completion of CCRT, evaluated by clinical and radiological examinations; persistence or progression of disease at that time was determined as non-CR. Disease after achieving of CR was defined as recurrence. A diagnosis of residual disease, progression or recurrence was based on clinical or radiological examinations or pathological confirmation.

Locoregional control (LRC) was defined as no reappearance of disease at local or regional site after a complete response (CR) was achieved. Progression free survival (PFS) was defined as the time between start of CCRT and either systemic progression (development of distant metastasis or second primary), death from any cause, or the last follow-up date.

For statistical analysis, all data were prepared and processed on Microsoft Excel 2007 using XLSTAT software version 2017 for windows (Addinsoft, New York, USA). Multivariate analysis was performed using Cox proportional hazard methodology. To identify predictors of LRC and PFS; hazard ratio, 95% confidence interval and P value were calculated. P-value reports were two tailed and an alpha level of 0.05 was used to assess statistical significance. Age was analysed as a continuous variable, whereas gender, stage, site of primary, number of CT cycles and treatment interruptions were analysed as discrete variables. Survival curves were calculated using the Kaplan-Meier method.

Table 3 Treatment related acute and late toxicities

Toxicity		Number (%)
Acute dermatitis	Grade I/II	85 (48.9)
	Grade III/IV	33 (18.9)
Acute mucositis	Grade I/II	98 (98.3)
	Grade III/IV	73 (41.9)
Dysphagia	Grade I/II	88 (50.6)
	Grade III/IV	29 (16.7)
Acute xerostomia	Grade I/II	119(68.4)
	Grade III/IV	23 (13.2)
Nausea	Grade I/II	76 (43.7)
	Grade III/IV	19 (10.9)
Vomiting	Grade I/II	78 (44.8)
	Grade III/IV	19 (10.9)
Acute gastrointestinal toxicity	Grade I/II	34 (19.5)
	Grade III/IV	4 (2.3)
Acute nephrotoxicity	Grade I/II	22 (12.6)
	Grade III/IV	0
Leucopenia	Grade I/II	37 (21.2)
	Grade III/IV	3 (1.7)
Anemia	Grade I/II	39 (22.4)
	Grade III/IV	11 (6.3)
Thrombocytopenia	Grade I/II	23 (13.2)
	Grade III/IV	0

RESULTS

The baseline patient and tumor characteristics are shown in Table 1. Median age of patients was 56 years, with male outweighing females by a ratio of 5.5:1. Most common site of primary was oropharynx and the least common was oral cavity. The most common stage was IVA and the least common was III. Treatment related parameters are shown in Table 2. Treatment interruptions were seen in 76.4% of patients, 81.1% patients required hospitalisation at least once, 28.2% patients required feeding naso-gastric tube insertion, and 15.5% patients required tracheostomy. Compliance to RT (completing 70 Gy of radiation) was seen in 90.8% patients, whereas compliance to CT (receiving cumulative 200mg/m2, i.e. a minimum of 5 cycles) was seen in 76.4% of patients. A CR was seen in 81.6% of patients at three months follow up. The treatment related acute toxicities are shown in Table 3. Grade III or higher acute dermatitis was seen in 18.9% of patients, mucositis in 41.9%, dysphagia in 16.7%, xerostomia in 13.2%, vomiting in 10.9%, diarrhea in 2.3%, leucopenia in 1.7%, and anemia in 6.3% of patients.

The median follow up was 40 months (range, 31- 48 months). At last follow up, LRC rate of entire cohort was 66.9%. Distant metastases were seen in 12.1% patients, metachronous second primary in 2.3%, and deaths were reported in 8% of patients; 5.7% patients lost to follow up. The PFS of entire cohort was 71.8% at last follow-up. The Kaplan Meier plot for LRC and PFS is shown in Figure 1. Table 4 and 5 represents the association of LRC and PFS with stage and site of tumor. Both LRC and PFS were higher in stage III compared to stage IV; worst with oral cavity being primary and highest with larynx being the primary. LRC was significantly associated with site of primary (best with larynx, and worst with oral cavity, P = 0.02), AJCC stage (higher with stage III, P < 0.001), and number of chemotherapy cycles taken (higher with ≥5 CT, P = 0.01); whereas PFS was significantly associated with site of primary (best with larynx, and worst with oral cavity, P = 0.03), AJCC stage (higher with stage III, P < 0.001), and treatment interruptions (higher with no treatment interruptions, P = 0.03).

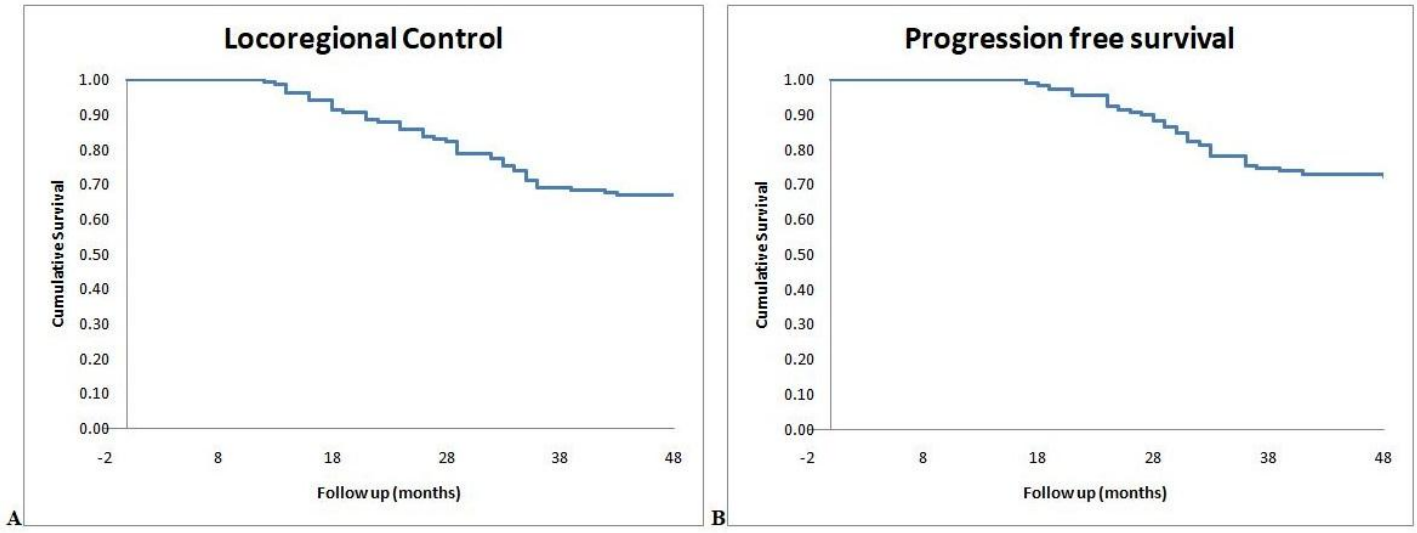

Fig. 1 (A) Locoregional control, & (B) Progression free survival; in patients of locoreginonally advanced squamous cell carcinoma head and neck treated with definitive 3-dimensional conformal radiotherapy concurrent with weekly cisplatin.

DISCUSSION

Treatment of head and neck malignancy is a multimodality approach, requiring surgery, chemotherapy and radiotherapy according to site and stage of the tumor. More than two third of head and neck cancer patients require radiotherapy, which can be given either alone or concurrently with chemotherapy. Radiotherapy can be given either as definitive or adjuvant form, sometimes even for palliation. Delaney and his colleagues have described the utilisation rate of radiotherapy in head and neck carcinoma. [4] According to their study, radiotherapy was indicated at some point in 74% of all patients with head and neck carcinoma. The optimal radiotherapy utilization rates by subsite were 74% for oral cavity; 20% for lip; 87% for salivary glands; 100% for larynx, oropharynx, hypopharynx, nasopharynx, and paranasal sinuses; and 90% for unknown squamous cell carcinoma of the head and neck. The widely used conventional radiotherapy has been associated with significant acute and late toxicities. To overcome this, newer techniques like 3DCRT and IMRT have evolved with the aim of delivering radiation precisely to the tumor while delivering minimum dose to surrounding normal tissues. The development of newer radiotherapy techniques have been described in detail by Bucci, and Ling et al. [5, 6] These sophisticated techniques have advantage of adjusting radiation beam to irregularly shaped target volumes reducing the radiation to the surrounding healthy critical structures like spinal cord, brain stem, parotid glands, larynx etc. in case of head and neck cancer malignancy.

Table 4 Multivariate analysis for factors associated with locoregional recurrence and overall survival

Factors	Locoregional control		Progression free survival	
	Hazard ratio (95% CI)	***P*- value**	**Hazard ratio (95% CI)**	***P*- value**
Age[*]	0.999 (0.978-1.021)	0.92	0.994 (0.965-1.024)	0.69
Gender (male vs. female)	1.153 (0.341-3.895)	0.82	0.647 (0.176-2.372)	0.51
Site (oral cavity vs. others)	0.809 (0.682-0.960)	0.02	0.824 (0.713-0.984)	0.03
Treatment interruptions (absent vs. present)	1.291 (0.724-2.300)	0.39	2.113 (1.803-4.123)	0.03
AJCC Stage (IV vs. III)	0.083 (0.038-0.182)	<0.001	0.058 (0.028-0.118)	<0.001
Chemotherapy cycles (≥5 vs. <5)	1.973 (1.186-3.283)	0.01	1.102 (0.431-2.985)	0.81

[*]Continuous variable; CI: Confidence Interval, AJCC: American Joint Committee on Cancer

The role of CCRT in LAHNSCC has been studied in MACH-NC Collaborative Group Meta-Analysis. [7, 8] The main meta-analysis of 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy yielded a pooled hazard ratio of death of 0.90 (95% CI 0.85-0.94, P < 0.001), corresponding to an absolute survival benefit of 4% at 2 and 5 years in favour of chemotherapy. There was no significant benefit associated with adjuvant or neoadjuvant chemotherapy. Chemotherapy given concomitantly to radiotherapy gave significant benefits, but heterogeneity of the results prohibits firm conclusions. Later on, the updated meta-analysis included trials comparing loco-regional treatment to loco-regional treatment along with chemotherapy in HNSCC patients and conducted between 1965 and 2000. Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 (P < 0.001) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction (P < 0.001) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 (P < 0.001) and the absolute benefit 6.5% at 5 years.

Head and Neck Disease Site Group has concluded that CCRT with cisplatin at least 40 mg/m2 per week given as radical or postoperative adjuvant remains a standard treatment approach for LASCCHN that improves overall survival but increases toxicity; 5-FU plus platinum is supported by less data but may be a reasonable alternative for patients unsuitable for cisplatin. [9] Cetuximab-RT is suggested only for patients not candidates for CDDP-RT. Taxane-based triplet induction chemotherapy is superior to doublets for rapid tumour downsizing and for larynx preservation, but does not improve overall survival and should be used with primary G-CSF prophylaxis.

Table 5 Locoregional control and progression free survival as a function of site and stage of tumor

		Locoregional control, n (%)	**Progression free survival, n (%)**
AJCC Stage	III	11 (21.2)	11 (21.2)
	IVA	26 (25.2)	31 (30.1)
	IVB	10 (52.6)	7 (36.8)
Primary site of cancer	Oral cavity	11 (45.8)	9 (37.5)
	Oropharynx	22 (26.9)	27 (32.9)
	Hypopharynx	8 (21.6)	9 (24.3)
	Laryngopharynx	6 (19.4)	4 (12.9)

AJCC: American Joint Committee on Cancer

Sautois et al. conducted a single centre retrospective study to evaluate efficacy and acute toxicity of definitive CCRT with 40 mg/m2 weekly cisplatin in 112 patients with LAHNSC (with a median cumulative dose of 200 mg/m2). [10] Overall CR was 81.3%, which is matched with the present study (81.6%). With a median follow up of 38.4 months, median OS was 75 months, not influenced by RT type or cisplatin dose received. In our study also, PFS was not significantly associated with

CDDP dose received. The clinically significant grade 3/4 acute toxicities were higher than the present study; stomatitis (35.7%), neutropenia (25%), anemia (12.5%) and acute kidney injury (5.4%). Sharma et al. have demonstrated the superiority of weekly cisplatin 40 mg/m^2 added to RT versus RT alone (70 Gy/35 fractions over 7 weeks) in 153 patients of stage II-IV oropharynx and nasopharynx carcinoma. [11] CR was 67.1% versus 80.5% in RT and CCRT arms (P = 0.04), which is similar to the present study (81.6%). There were frequent treatment interruptions (9.3% versus 28.9%; P = 0.003) and hospitalization (20% versus 40.8%) in the CCRT group, which is less than half of present study (76.2% and 81.1%, respectively). OS was superior in the CCRT arm (P = 0.02); 27 months for RT versus not reached for CCRT. Three-year OS was 42% for RT and 62% for CCRT group.

Gupta et al. have studied the effects of CCRT in 264 LASCCHN patients, excluding nasopharynx, planned for radical radiotherapy (66-70 Gy) with concurrent weekly cisplatin (30 mg/m2) treated in a single unit between 1996-2004. [12] Two-thirds of patients received ≥ 85% of planned cisplatin dose (versus 76.4% in present study). With a mean follow-up of 19 months, the 5-year local control; loco-regional control; and disease free survival was 57%; 46%; and 43% respectively. Acute grade 3 or worse mucositis and dermatitis was seen in 29% and 35% patients respectively (41.9% and 18.9% in present study, respectively). Gupta, Baxi & Hoyne have studied assess feasibility, compliance and toxicity of CCRT in 26 patients of LAHNSC in remote Australia between January 2010 and September 2012. [13] Most common acute (grade 3/4) toxicities were mucositis, dysphagia and dermatological in 54%, 31% and 23% respectively (41.9%, 16.7% and 18.9% in present study, respectively). Hospitalisation occurred in 23% patients and treatment break of >2 days in 38% patients. At median follow-up of 16 months, overall survival was 58% with progression-free survival of 50%. Iqbal et al. have retrospectively analysed the compliance, toxicity and survival in 122 patients with histologically proven squamous cell carcinoma of head and neck (nasopharynx, oropharynx, larynx, hypopharynx, and oral cavity) treated with definitive CCRT; 63 Gy in 30 daily fractions with concomitant weekly cisplatin 40mg/m2, during January 2007 to December 2009. [14] They concluded that 68% of patients managed to complete all six cycles of CT (76.4% in present study). Incidence of grade 3/4 toxicity was 33% for mucositis, 41% for dermatitis, 15% for dysphagia, 17% for mouth/neck pain, 2% for neutropenia, and 3% for renal impairment (41.9%, 18.9%, 16.7%, not calculated, 1.7%, and nil in present study respectively). 53% patients required at least one hospital admission for symptom control. The 5-year overall survival rate was 60%.

CONCLUSION

The present study highlights on clinical profile, treatment related toxicities, compliance to treatment, and survival function analysis in terms of LRC and PFS of LASCCHN patients treated with modern radiotherapy techniques i.e. 3DCRT at a tertiary cancer center of SMS Medical College, Jaipur. Compliance to both CT and RT was good and comparable with most of the studies done earlier (90.8% and 76.4% respectively). Acute toxicities were within the accepted levels, and were manageable. At median follow up of 40 months, LRC rate and PFS rate was 66.9% and 71.8% respectively, which is higher than most of the previous studies. Higher LRC was significantly associated with stage III (versus IV), larynx (versus oral cavity), and ≥5 CT cycles, whereas PFS with stage III (versus IV), larynx (versus oral cavity), and absence of treatment interruptions. The findings of present study match with most of the studies cited in literature. Retrospective nature is one of the biggest limitations of the present study. Also, for better study of LRC and PFS, longer follow up is needed.

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CONFLICTS OF INTEREST

The authors have reported no conflict of interest.

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