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Radiation induced brachial plexopathy in head and neck cancer patients treated with definitive radiotherapy and correlation with disease characteristics and dosimetric parameters

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ABSTRACT

Background: Definitive concurrent chemoradiotherapy (CRT) is the standard of care in advanced stages of head and neck cancer (HNC). With evident increase in survival rate there is also simultaneous increase in toxicity affecting the quality of life. One of the less researched late toxicity is radiation induced brachial plexopathy (RIBP). In this dosimetric study we intent to contour the brachial plexus (BP) as an organ at risk (OAR) and determine the factors that contribute to dose variations to BP, and clinically evaluate the patients for RIBP during follow-up using a questionnaire.

Materials and methods: 30 patients with HNC planned for CRT from September 2020 to June 2022 were accrued. Patients were treated to a dose of 6600 cGy with intensity modulated radiotherapy using the simultaneous integrated boost technique. From the dose-volume histogram (DVH) statistics the BP volume, Dmax and other parameters like V66, V60 were assessed and was correlated with respect to primary tumour and nodal stage.

Results: On corelation, more than the T stage, the N stage and the primary location had a significant impact on the Dmax. With a median follow-up of 17.9 months, the incidence of RIBP was 6.67%. The 2-year disease free survival and the 2-year overall survival were 53.7% and 59.4%, respectively.

Conclusions: In oropharyngeal/hypopharyngeal primaries and in advanced nodal disease, BP receives higher doses contributing to RIBP. Primary tumor and nodal stage also impacted V60 and V66 of BP. Hence, contouring of BP as an OAR becomes imperative, and respecting the DVH parameters is essential.

Key words: head and neck neoplasms; radiation induced brachial plexopathy; chemoradiotherapy; quality of life; radiation tolerance; organs at risk

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Introduction

Head and neck cancers (HNC) comprise nearly one-third (29.3%) of all cancers across various anatomic sites in India [1]. A majority of HNC patients (60–70%) present with locoregionally advanced disease (stage III, IVA and IVB), which carry a poor overall survival of less than 40% [2].

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So, to optimize the chances for long term disease control, the modern standard of care is chemo-radiotherapy (CRT) [3]. CRT has shown a significant increase in the survival rate. However, this approach goes with increased toxicity. Therefore, both the disease and its treatment affect the quality of life (QoL) [4]. As a result, considering the QoL of long-term survivors is crucial during the treatment of HNC patients [5]. The common acute toxicities that worsen QoL include xerostomia, mucositis, dysphagia, dysgeusia, dermatitis, and aspiration [6]. The conformal radiotherapy techniques such as Intensity-Modulated Radiotherapy (IMRT), has shown promising outcomes in managing these toxicities [7]. For instance, parotid sparing IMRT has significantly reduced xerostomia, which is the most common late toxicity [8]. Additionally, there are less researched late toxicities that may manifest months to years after treatment completion like subcutaneous fibrosis, thyroid function impairment, hearing impairment, and brachial plexopathy.

One of the known late toxicities in HNC is radiation-induced brachial plexopathy (RIBP), where RT can lead to direct axonal injury or damage the vasa nervorum, resulting in axonal ischemia and multifocal denervation. RIBP typically manifests with hypoesthesia, paraesthesia, and weakness in the affected limb and shoulder [9]. Due to these vague symptoms, RIBP diagnosis is often challenging during follow-up. Moreover, there is a paucity of literature on RIBP, and the reported incidence varies due to the lack of routine contouring of the brachial plexus (BP) as an organ at risk (OAR). Since RIBP is a late toxicity, the follow-up period required for symptom manifestation remains uncertain. Therefore, this study aims to report the dose received by the BP in patients with HNC receiving radical radiotherapy, the factors contributing to the dose variations in the BP and the evaluation of patients developing RIBP after CRT.

Materials and methods

Study design and setting

After obtaining Institutional Ethical Clearance, a prospective descriptive study was planned to analyse HNC patients who were scheduled for definitive CRT using the IMRT technique at the Department of Radiation Oncology, St. John's Medical College and Hospital from September 2020 to June 2022. A sample size of 30 was obtained using convenience sampling for the pilot study [10] and a written informed consent was obtained from all the study patients. All HNC patients aged from 18–70 years with histo-pathologically proven cancer receiving radical radiotherapy with concurrent chemotherapy were included in the study. Patients who had undergone previous HNC surgery were excluded from the study. Post-operative patients were excluded from the study due to the challenges in contouring the BP in post-operative necks, which can undergo anatomical disfiguration. Additionally, nerve-related issues such as pain in these patients may hinder the accurate assessment of RIBP.

Radiation therapy

All patients were treated with the IMRT technique on the Elekta Synergy linear accelerator. All OAR (except BP) were contoured following the Consensus Guidelines in the head and neck region [11]. BP was contoured as an OAR, as per the Hall et al. guidelines [12]. Contouring begins with identification of C4 and T2 vertebrae in the sagittal section (Fig. 1A). Bilateral anterior and middle scalene muscles from the level of C4 vertebra to its insertion on the first rib were marked (Fig. 1B). BP was contoured using a 2.5 mm brush tool from the neural foramina of C4 vertebra. Laterally, the contours were extended into the narrow space between the anterior and middle scalene muscles (Fig. 1B and 1C) till T2 vertebra. The volumes of interest include the gross disease and the gross lymph nodes. For well-lateralized tumours of buccal mucosa only the ipsilateral neck nodes was included in the treatment field. In central lesions (tumours of soft palate, base of tongue, tip of tongue, larynx, hypopharynx, nasopharynx) and in all other cases, bilateral neck nodes were encompassed in the treatment field, following the consensus guidelines by Gregoire et al. [13]. As per our institutional protocol, a 3 mm planning target volume (PTV) margin was given for all cases [14]. Patients were treated using the simultaneous integrated boost (SIB) technique with a two-volume approach. The gross disease and neck nodes were treated to a total dose of 66 Gy in 30 fractions (2.2 Gy per fraction), while the clinical target volume (CTV) received a total dose of 54 Gy in 30 fractions (1.8 Gy per fraction). All patients received 5 fractions per week over 6

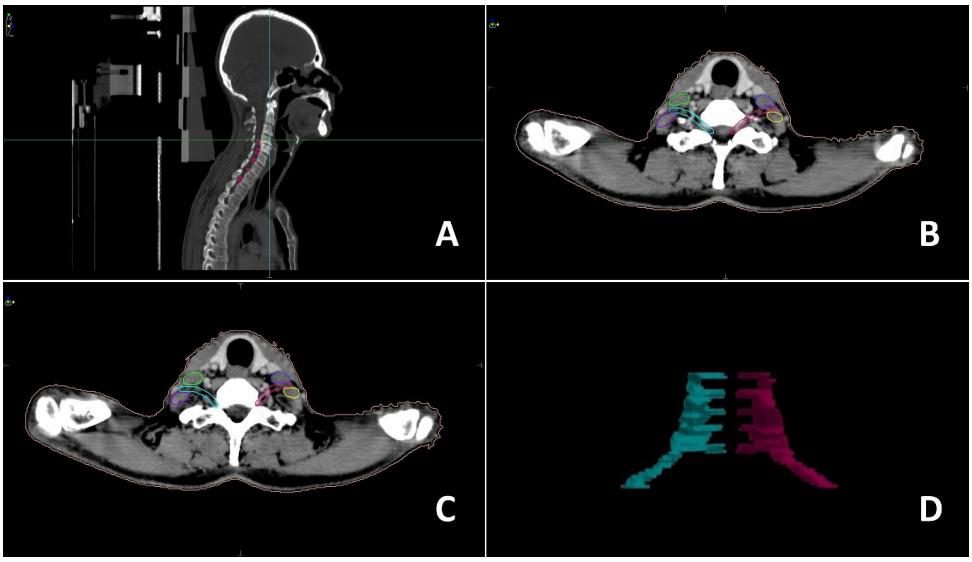

Figure 1. Delineation of brachial plexus (BP). **A.** Identification of C4, T1, and T2 vertebral levels in sagittal section; **B.** Axial section at the level of neural foramina; **C.** Axial section where there is no neural foramina. (*Green* — right anterior scalene muscles, *Violet* — right middle scalene muscles, *Blue* — left anterior scalene muscles, *Yellow* — left middle scalene muscles, *Cyan* — right BP, *Pink* — Left BP); **D.** Three dimensional reconstruction of BPKaplan Meier survival curve of overall survival

weeks. An optimal IMRT plan was generated using Monaco software version 6. The planned objective was to ensure that 95% of the PTV would receive more than 95% of the prescribed dose. Additionally, it was aimed that not more than 10% and 1% of the volume should receive 107% and 110% of the planned dose, respectively. No dose constraints were imposed on BP and even if the PTV overlapped with the BP contour, priority was given to cover the target volume.

Chemotherapy

All patients received concurrent weekly Cisplatin chemotherapy. Cisplatin was administered at a dose of 40 mg per square meter of body surface area per week. The number of chemotherapy cycles were titrated based on patient tolerance. Hydration, anti-emetics, and dose modifications were done according to the department protocol. Chemotherapy was not given after the completion of RT.

Study outcome

The primary objective of the study was to assess the radiation dose received by BP in patients with HNC treated with IMRT, and to correlate the dose received by BP with factors like location of primary, T and N categories. Using Dose-Volume Histograms (DVH), the BP volume in cc, Dmax, Dmean and D0.03 received by the BP were obtained. Similarly, the BP volume receiving 66 Gy (V66) and 60 Gy (V60) were obtained. The secondary outcome was to clinically evaluate for symptoms of RIBP, and to report the overall survival (OS) and disease free survival (DFS). The RIBP was evaluated with a questionnaire during the follow-up visits. The study patients were evaluated once every three months for symptoms of RIBP using the symptomatic questionnaire which was modified by Chen at al. (15) from a previously validated instrument [16]. The questionnaire comprised the following 5 basic questions, requiring a "yes" or "no" answer:

1. Do you have any pain in your arm or hand?
2. Do you have any numbness or tingling of the hand or fingers?
3. Do you have any problems carrying and lifting objects with your arm?
4. Do you have any problems with your fingers, such as with writing or unscrewing a bottle?
5. Are there any contributory factors for the above-mentioned complaints?

In the event of a patient developing symptoms of RIBP, the corresponding doses to the BP were correlated. OS was defined as the period from the time of diagnosis to death due to any cause. DFS was defined as the period from the time of diagnosis to any disease event such as recurrence (locoregional or distant), progression, or death due to any cause.

Statistical analysis

Data was analysed using SPSS v.24. All categorical data was summarized using frequency and percentages, all continuous data was described using mean and standard deviation or median and inter quartile range based on the distribution. ANOVA or Kruskal Wallis test was applied to study the correlation of dose (Dmax, V66 and V60) with tumour and nodal factors. P-value was considered significant at 5% level of significance for all comparisons. Both OS and DFS were analysed with Kaplan-Meier survival methods.

Results

A total of 30 histologically proven HNC patients consecutively treated with definitive radiation using IMRT with concurrent chemotherapy from September 2020 to June 2022 in Department of Radiation Oncology of our institute were prospectively analysed. The median follow-up time was 17.9 months. Baseline characteristics of the patients are summarised in Table 1. The median age group of our patients is 58 years [interquartile range (IQR): 44.25–62]. Among the study population, 70% of the patients were diagnosed with Stage IV disease. The location of the primary tumor was predominantly in the oral cavity (33.33%), followed by the larynx (30%) and oropharynx (26.67%). Twelve patients had bilateral gross lymph nodes and more than 70% of the patients had received at least 4 cycles of concurrent chemotherapy with weekly cisplatin. All patients received the prescribed dose of 66 Gy.

BP was contoured as an OAR in all 30 patients bilaterally, resulting in a total of 60 BP contours. The BP volume, Dmax, BP mean, D0.03, V66, and V60 dose received by the right and left BP are shown in Table 2. The Dmax dose received by the right and left BP was 62.594 Gy ± 4.65 Gy and 60.97 Gy ± 10.95 Gy, respectively. The proportion of patients receiving Dmax doses of ≤ 60 Gy, 61–65 Gy, and > 65 Gy are 43.33%, 26.67% and 30%, respectively, to the right BP and 36.67%, 30% and 33.33%, respectively, to the left BP.

Table 1. Baseline characteristics

Characteristics	No (%)
Total No of patients	30 (100)
Sex	
Female	4 (13.33)
Male	26 (86.67)
Primary location	
Oral cavity	10 (33.33)
Oropharynx	8 (26.67)
Larynx	9 (30)
Others	3 (10)
T Stage	
T1	2 (6.67)
T2	2 (6.67)
T3	15 (50)
T4a	6 (20)
T4b	5 (16.67)
N Stage	
N0	7 (23.33)
N1	4 (13.33)
N2a	0 (0)
N2b	1 (3.33)
N2c	6 (20)
N3a	0 (0)
N3b	12 (40)
Stage grouping	
III	9 (30)
IVA/IVB	21 (70)

Table 2: Dose received by brachial plexus (BP)

Parameter	Right BP				Left BP			
	Mean	SD	Min	Max	Mean	SD	Min	Max
BP volume [cc]	12.90	1.81	9.09	15.66	12.35	1.79	8.70	16.48
Dmax [Gy]	62.59	4.65	57.07	72.41	60.97	10.95	29.08	73.68
Dmean [Gy]	45.13	4.90	37.65	55.99	43.21	9.78	15.63	54.36
D0.03 [Gy]	61.47	4.53	56.35	71.92	59.86	10.90	28.47	72.33
	Median	IQR	Min	Max	Median	IQR	Min	Max
V66	0	0	0	30.54	0	0–0.4	0	37.22
V60	10	0–2.86	0	46.02	0.435	0–9.58	0	48.45

SD — standard deviation; IQR — interquartile range

Table 3. Factors affecting dose to brachial plexus (BP)

Category	N	Dmax			V66 (%)			V60 (%)		
		Mean [Gy]	SD [Gy]	p	Median (%)	IQR (p25–75)	P	Median (%)	IQR (p25-75)	P
T Stage										
T1	4	69.20	5.61		11.6	3.87–26.40		21.46	8.01–37.74	
T2	4	66.47	5.22		0.2	0–10.05		3.07	1.43–16.26	
T3	30	61.27	3.29	0.0007	–	–	0.05	0.02	0–0.71	0.01
T4a	12	65.90	5.27		0.13	0–8.43		4.41	0.05–19.82	
T4b	10	53.49	15.42		–	–		0	0–0.3	
N Stage										
N0	14	59.79	1.65		–	–		0	0–0.01	
N1	8	58.11	9.47		–	–		0.34	0–1.09	
N2b	2	59.36	0.007	0.35	–	–	0.16	–	–	0.0008
N2c	12	62.14	3.49		–	–		0.14	0–0.94	
N3b	24	64.18	11.48		0.29	0–11.6		8.87	0.12–21.82	
Primary location										
Nasopharynx/ Oral cavity	24	59.58	11.70		0	0–0.33		0.05	0–3.90	
Oropharynx/ Hypopharynx	18	66.24	4.995	0.02	0.01	0–11.02	0.02	9.13	0.49–23.06	0.0007
Larynx	18	60.24	1.70		–	–		0	0–0.09	

SD — standard edviation; IQR — interquartile range

Factors affecting dose to BP

The Dmax, V66 and V60 were analysed in relation to the T-category, N-category and primary tumor location (Tab. 3). The initial analysis revealed a significant difference in the mean Dmax dose received by the different T categories. The mean dose was higher in the lower T stage when compared to the higher T stage. When the mean Dmax dose was correlated with the location of the primary tumor using ANOVA analysis, a significant difference ($p = 0.02$) was observed. The BP received a higher dose in patients with N3b disease when compared to those with lower nodal stages; however, the difference was not statistically significant. BP in patients with oropharyngeal/hypopharyngeal cancers had received a higher dose (66.24 Gy) when compared to other primary tumours. Correlation analysis using the Kruskal-Wallis test, as shown in Table 3, revealed that the primary location, the tumour and the nodal stage has a significant impact on both V60 and V66.

Radiation induced brachial plexopathy — clinical outcome

With a minimum follow-up of 16 months and a maximum follow-up of 32 months, only 2 patients reported symptoms related to RIBP based on the questionnaire administered during the 3-monthly follow-up after completion of the treatment. One patient had right shoulder pain 25 months after completing treatment, with a Dmax dose to the right BP of 60.43 Gy. The pain persisted for 3 months. Another patient developed right upper limb weakness and tingling sensation 21 months after treatment, with a Dmax dose to the right BP of 58.63Gy. These symptoms persisted for 8 months. Both patients were treated conservatively.

Survival outcome

After a median follow-up of 17.9 months, 19 patients were alive, 10 patients had locoregional progression and 1 patient was diagnosed with secondary malignancy. The 2-year DFS was 53.7% [35.3–81.59%, 95% confidence interval (CI)] (Fig. 2). Among the 11 deaths, 7 were attributed to cancer progression, 1 to heart failure, 1 to secondary cancer and the cause of death was unknown for 2 patients. The median survival was not achieved for the study cohort, and the 2-year OS was 59.4% (43–81.3%, 95% CI) (Fig. 3).

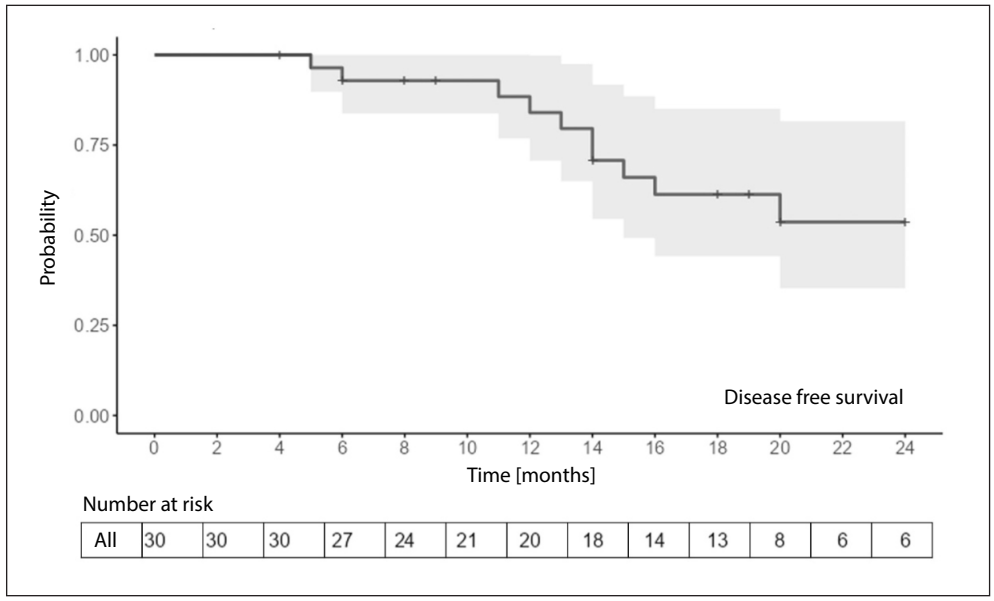

Figure 2. Kaplan Meier Survival curve of disease free survival

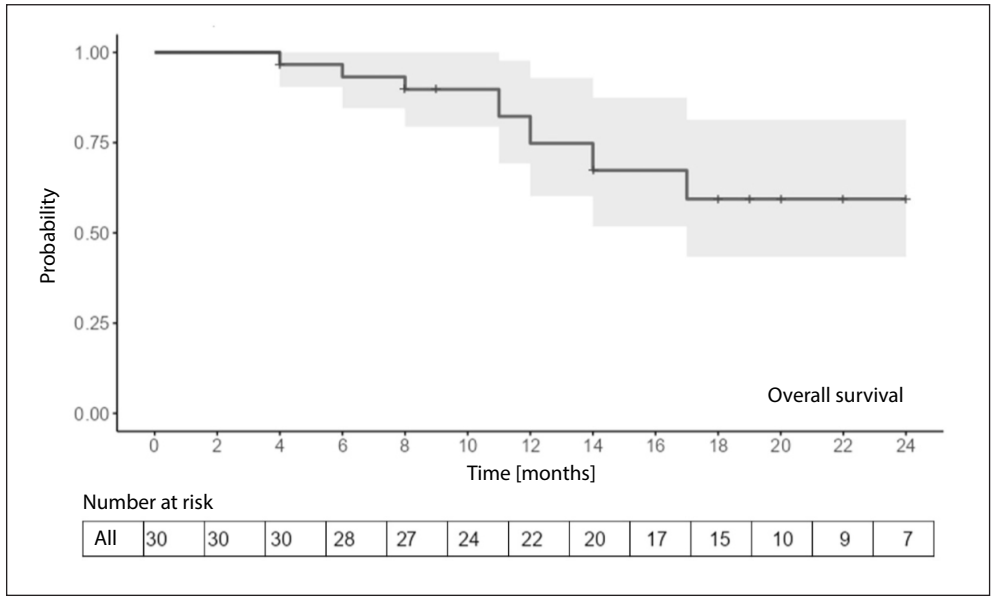

Figure 3. Kaplan Meier survival curve of overall survival

Discussion

In our study the mean brachial plexus volume was 12.62 cc. After a median follow-up of 17.9 months, 2 year DFS and 2 year OS were 53.7% and 59.4%, respectively. Recent systematic review and meta-analysis by Yan et al. suggested that the current BP constraints of 60–66 Gy are safe [17]. In 60% of our patients, BP received doses higher than 60 Gy, which was influenced significantly by the N category and the primary tumor location rather than the T staging. Similar studies with the incidence and dose to BP along with the instrument used to determine the RIBP are presented in Table 4.

ANOVA analysis showed that patients with N3b disease had a higher mean Dmax (64.18 Gy) compared to those with N0 disease (59.79 Gy), but this difference was not statistically significant ($p = 0.35$). Similar findings were reported by Prakash et al. [18] who observed a statistically significant differ-

Table 4. Reported Incidence of radiation-induced brachial plexopathy (RIBP)

Literature	Study	Sample size	Mean Dmax [Gy]	Follow up [months]	Incidence of RIBP	Instrument used
Chen et al.	Retrospective	352	65	40	14%	Self administered standardised symptom questionnaire
Truong et al.	Retrospective	114	58.1 ± 12.2	20.9	0%	(Not mentioned)
Thomas et al.	Retrospective	68	72.96	24	0%	CTCAE 3.0 Scale
Prakash et al.	Retrospective	67	62.4	28	0%	Nerve Conduction Study
Platteaux et al.	Retrospective	43	64.20	24	0%	13 item questionnaire
Metcalfe et al.	Retrospective	27	59.4	28	14%	13 item questionnaire
Present Study	Prospective	30	61.78	17.9	6.6%	Self administered standardised symptom questionnaire (used in Chen at al.)

CTCAE — Common Terminology Criteria for Adverse Events

ence in BP dose with N category, with an average of 4.2 Gy higher doses in patients with advanced nodal stage. Truong et al. [19] also reported an increased dose of 8.1 Gy to the BP in advanced stage nodal disease.

In the study by Prakash et al. [18], patients with T4 tumours received a significantly higher dose to the BP compared to the patients with T1 disease. In our study, when Dmax was correlated to the T category, a significant difference ($p = 0.0007$) was also observed. However, on subgroup analysis, the mean Dmax dose in patients with T4b tumours was found to be lower than in patients with T1 disease. This disparity can be attributed to the prevalence of T3 and T4 lesions primarily affecting the oral cavity/nasopharynx, while laryngeal/hypopharyngeal lesions, often in proximity to the BP, are mainly T1 or T2 diseases. This factor might have influenced the relationship between the T stage and the Dmax dose. In addition, the N stage might also have influenced the observed inverse relationship as the analysis was only a univariate analysis.

As mentioned earlier, the dose to the neck region is relatively small in cases of oral cavity and nasopharynx primary lesions, as the gross disease was located away from the BP. However, in patients with oropharyngeal or laryngeal disease, the primary tumor itself received a dose of 6600 cGy and was in close proximity to the BP. So, on correlating the primary tumor with Dmax using ANOVA analysis, a statistically significant difference with higher dose deposition in patients with oropharyngeal and hypopharyngeal cancers was observed.

The highest recorded Dmax dose was 73.68 Gy (0.001 cc) in a patient with oropharyngeal malignancy, with a T stage of T1 and a N stage of N3b. This suggests that besides the T category and the primary location of the tumor, the N staging and its location also influence the dose to the BP.

Thomas et al. [20], in a retrospective analysis of 68 head and neck squamous cell carcinoma (HNSCC) patients who received definitive or adjuvant RT observed that tumour and nodal stage had significantly influenced both V50 and V60 values. In our study, we correlated the median values of V60 and V66 parameters and found a statistically significant difference with the primary tumour, T stage, and N stage. However, to determine the correlation of V60 and V66 parameters with the incidence of RIBP, a longer follow-up is needed.

In the present study, only two patients (6.67%) developed symptoms of RIBP during the median follow-up of 17.9 months. Despite a modest 7% incidence rate of RIBP, contouring the BP in HNC cases was essential because its impact on QoL remains less explored, unlike the common late side effects like xerostomia, mucositis and dysphagia. By implementing BP contouring with imposed constraints, we have the opportunity to mitigate the 7% toxicity associated with RIBP, which may significantly improve the patient outcomes and overall QoL. Treatment-related factors such as post-surgery and chemotherapy, have been known to contribute to the incidence of RIBP according to the previous studies [20, 21]. However, in our study, we have only included patients receiving definitive radiation with concurrent chemotherapy. Therefore, these factors will not be considered as confounders in our analysis. As this is a prospective study, we could administer the questionnaire

at 3-monthly intervals during the follow-up period to assess the development of the symptoms of RIBP.

Limitations of the present study

Our study has its own limitations. Firstly, the RIBP incidence rate of 6.67% is based on a median follow-up of only 17.9 months. So there is a need for a longer follow-up, as long term studies have demonstrated higher incidence rates. Secondly, inherent bias might be associated with our study design; but we have tried to overcome this by including all the consecutive patients treated at our institution. Lastly, the sample size of 30, while deemed sufficient for a pilot study, may warrant consideration for a larger scale study in the future.

Conclusion

The primary tumor and nodal stage also impacted V60 and V66 of the brachial plexus. Oropharyngeal and hypopharyngeal primaries and advanced nodal disease led to higher doses to the brachial plexus, potentially contributing to radiation-induced brachial plexopathy. Contouring the brachial plexus as an OAR and respecting dose volume parameters like Dmax, V60, and V66 becomes essential. During our study with a median follow-up of 17.9 months, the incidence of RIBP was only 6.67%, indicating the need for a longer follow-up to determine RIBP incidence accurately.

Statement of ethics

The study was approved by the Institutional Ethics Committee of St. Johns Medical College, Bangalore, with an IEC reference No: 336/2020 and informed consent was obtained from all study participants.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

Study concepts: H.N.A.F., N.S., S.M.; study design: H.N.A.F., N.S., S.M.; data acquisition: H.N.A.F., D.C.T., S.M., J.S.MG, N.S., R.P.K.; quality control of data and algorithms: H.N.A.F., N.S., S.M.; data analysis and interpretation: H.N.A.F., N.S., S.M., J.S.MG; statistical analysis: J.M.R.; manuscript preparation: H.N.A.F., S.M., N.S., A.H.U.; manuscript editing: H.N.A.F., S.M., N.S., A.H.U.; manuscript review: H.N.A.F., S.M., N.S., A.H.U.

Data availability

The data that support the findings of the current study are available from the corresponding author upon reasonable request.

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