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ORIGINAL RESEARCH ARTICLE

Dosimetric Analysis and Clinical Correlation of Brachial Plexus Toxicity in Head and Neck Cancer Patients Treated with Chemoradiotherapy by IMRT Technique

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ABSTRACT

Introduction: Radiation-induced brachial plexopathy (RIBP) is an uncommon but potentially disabling late complication of radiotherapy in head and neck cancer. Despite the increasing use of intensity-modulated radiotherapy (IMRT), the brachial plexus is not routinely contoured as an organ at risk (OAR), and its dose–toxicity relationship remains inadequately studied. The aim is to evaluate the dosimetric parameters of the brachial plexus in head and neck cancer patients treated with IMRT-based concurrent chemoradiotherapy and to correlate these parameters with clinical, radiological, and neurophysiological evidence of brachial plexus toxicity.

Materials and Methods: This prospective observational study included 38 patients with stage II–IVA histologically proven squamous cell carcinoma of the head and neck treated between November 2019 and April 2021. Patients received definitive radiotherapy (70 Gy/35 fractions) or adjuvant radiotherapy (60 Gy/30 fractions), with concurrent weekly cisplatin when indicated. The brachial plexus was retrospectively delineated according to RTOG guidelines, and dosimetric parameters including Dmax, Dmean, V40–V70, D50, and D80 were analyzed. Clinical assessment was performed using CTCAE v5.0, an 18-item brachial plexopathy questionnaire, neurological examination, MRI, and nerve conduction velocity (NCV) studies. The median follow-up was 39 months (range: 12–54 months).

Results: The mean maximum dose (Dmax) to the brachial plexus was 65.15 Gy, exceeding recommended tolerance limits in many patients. Clinically, 22 of 38 patients (57.9%) developed symptoms suggestive of brachial plexopathy, most commonly sensory disturbances (65.7%), proximal arm weakness (63.1%), impaired hand function (42.1%), and limitation of daily activities (42.1%). Over 20 patients underwent MRI and NCV evaluation; among them, 14 (70%) demonstrated clinical evidence of brachial plexopathy, while 10 (50%) showed concordant clinical, MRI, and NCV abnormalities. MRI findings included nerve root thickening, T1/T2 hyperintensity, edema, and contrast enhancement. Significant deterioration in NCV parameters was observed in the median, radial, axillary, musculocutaneous, and left ulnar nerves. Patients receiving 70 and 60 Gy had comparable brachial plexus Dmax values (66.9 vs. 66.5 Gy), with RIBP observed in 41 and 52.3% of patients, respectively.

Conclusion: The brachial plexus frequently receives doses exceeding recommended tolerance during IMRT for head and neck cancer when no specific dose constraints are applied. A substantial proportion of patients developed clinical, radiological, and neurophysiological features of RIBP during follow-up. Routine contouring of the brachial plexus as an OAR, implementation of dose constraints (maximum dose ≤60–66 Gy), and long-term surveillance are recommended to minimize the risk of radiation-induced brachial plexopathy and improve functional outcomes.

Keywords: Head and neck cancer, Brachial plexus, Radiation-induced brachial plexopathy, IMRT, Organ at risk, Dosimetry, MRI, Nerve conduction study.

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INTRODUCTION

Head and neck cancer consists of a multimodality treatment approach in terms of surgery, radiotherapy and chemotherapy, mostly in a concurrent setting.[1] Initial stages usually require only a single modality, either surgery or radiotherapy. Advance stages of head and neck cancer require a multimodality approach with a combination of different therapies. With the introduction of the concept of organ preservation, concurrent chemoradiation has become the standard of care in most of the head and neck cancers.[2]

The side effects of radiotherapy are classified into early and late reactions. The common early side effects include mucositis, odynophagia, fungal infection, dysphagia, skin changes and change in voice, which leads to poor nutrition, hydration, and weight loss. Common late side effect includes xerostomia and fibrosis, and less

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commonly osteoradionecrosis. The other side effects are hypothyroidism and brachial plexus toxicity, which are not routinely evaluated.

Brachial plexopathy is generally not evaluated at the time of follow-up visits. It presents clinically as neuropathic pain, sensory loss, or motor weakness of the upper extremities and can cause significant morbidity.[4] Radiation-induced brachial plexopathy (RIBP) is a late toxicity that can present months to years following a course of radiotherapy. Classically, the dose tolerance as defined by Emami for the brachial plexus is 62, 61 and 60 Gy to one third, two thirds, and the whole plexus volume, respectively, for a 5% risk of radiation-induced brachial plexus toxicity at 5 years.[5]

In Emami's recent update, the dose tolerance for the brachial plexus remained at 60 Gy, but is now stated as a maximum point dose to highlight the serial nature of the plexus as an organ.[5] Modern RTOG constraints vary between 60 and 66 Gy maximum point doses.[6] The supporting evidence for these recommendations is scarce, however and is derived from a small number of observational studies that comprise the basis of these widely accepted clinical guidelines.

In this study, we will assess the dosimetric parameters of the brachial plexus in head and neck cancer patients treated with concurrent chemoradiation by intensity modulated radiotherapy (IMRT) technique and clinically correlate the dosimetric parameters with brachial plexus toxicity.

MATERIAL AND METHODS

All patients who were treated in the Department of Radiation Oncology for head and neck malignancies from Nov 2019 to April 2021 by radiotherapy were included in this study.

Patient Selection

- Histologically proven squamous cell carcinoma of head and neck cancer (all subsites) stage II – IVA, receiving definitive or adjuvant chemoradiation.
- Age >18 years, Karnofsky performance scale more than 70; normal blood parameters and normal 2D-ECHO were included in the study.
- Patients with prior or synchronous malignancy, previously treated with radiotherapy or chemotherapy; stage IV b disease and comorbid conditions like diabetes mellitus, hypertension, thyroid disorders, and signs and symptoms of peripheral neuropathy were excluded.

Pre-treatment Evaluation

Complete medical and physical examination; baseline haematological tests (Hemogram, renal function tests, liver function tests); chest radiography (PA view); CECT Neck (Radiotherapy planning); MRI- Neck; 2D ECHO; Baseline EMG/NCV were done.

All patients were planned and delivered either definitive radiotherapy (dose of 70 Gy in 35 fractions over 7 weeks) or adjuvant radiotherapy (dose of 60 Gy in 30 fractions over 6 weeks) along with concurrent cisplatin at 35 mg/m^2 weekly (If indicated).

Radiotherapy Planning

The patients who were planned for radiotherapy were immobilized using a 5-point thermoplastic cast system. The patients underwent thermoplastic cast preparation followed by radiotherapy planning. Computed tomography of neck (CT-RTP) with 3 mm slice thickness was taken. These images were transferred to the treatment planning system (TPS).

Delineation of Structures

In accordance with the radiation therapy oncology group, the IMRT volumes were delineated: *GTV:* gross disease, including the primary tumour and enlarged lymph nodes as seen on imaging modalities, *CTV* (clinical target volume): A margin of 1-cm around the GTV was taken. Areas of local-regional drainage for the nodal region, PTV (The planning target volume): A margin of 5 mm around CTVs, to account for patient setup error.

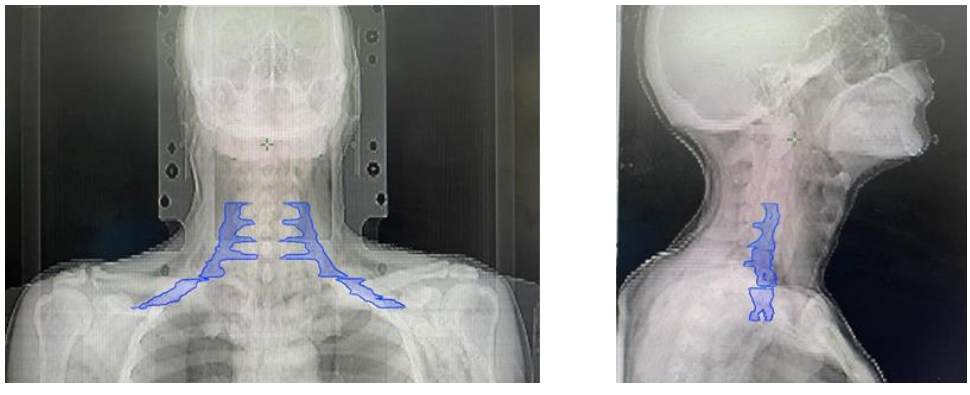

Figure 1: Contouring of brachial plexus in coronal and saggital view

OARS delineation

Brainstem, spinal cord, eyes, lens, optic nerve, optic chiasma, cochlea, parotids, mandible, and lips were delineated as per DAHANCA guidelines.

Brachial Plexus Delineation

- The brachial plexus was delineated by using an H&N CT scan window width of 350 HU and a centre scan level at 35 HU.
- The brachial plexes was delineated according to guidelines given by Hall *et al* & Domenico *et al*.[7]
  - Cranial – Neural foramina C4–C5,
  - Caudal – First half of clavicular head
  - Lateral – Sternocleidomastoid muscle, subclavian and axillary neurovascular bundle
  - Medial – C4–T1 neural foramina; C4–T1 vertebral peduncle
  - Anterior – Neck vascular bundle (C4–C6), anterior scalenus muscle (C6–T1)
  - Posterior - Middle scalene muscle first rib, subclavian vein.

Dose Prescription

PTV-70 Gy in 35 fractions or 60 Gy in 30 fractions in postoperative cases. OARS-PRV brainstem (Dmax≤54 Gy), PRV spinal cord (Dmax≤ 50 Gy), eye (Dmax≤ 55 Gy), lens (Dmax≤ 7 Gy), optic nerve (Dmax ≤55 Gy), optic chiasma (Dmax ≤ 55 Gy), cochlea (Dmean ≤ 45 Gy), lips (Dmean ≤ 30 Gy), parotid (Dmean ≤ 26 Gy). mandible (Dmax ≤ 70 Gy)

Brachial plexus: No dose constraint was prescribed to the brachial plexus. The dose received by the brachial plexus was evaluated after the plan evaluation.

IMRT Planning

- Coplanar multiple fields around the isocentre using isotropic gantry angles will be used and may be adjusted slightly to avoid the beam entry through OAR's.
- In the next step of fluence optimization, the dose coverage minimum and maximum required for PTV and dose tolerance to OAR's were defined.
- Optimization of fluence was calculated for the LINAC specification.
- The plan was evaluated by two methods: isodose coverage of PTV and DVH.
- The plan was compared with the alternate plan to improve treatment quality, and treatment was then delivered
- To normalize the plan, the planning goal had a homogeneity between - 5 and +7% (95–107%).

Plan Evaluation

- Dose–volume histograms (DVHs) corresponding to the delivered IMRT plan were generated for each contoured region.
- The planning technique was evaluated using a dose-volume histogram (DVH).
- PTV dosimetric parameters for evaluation were as follows: PTV receiving 95% dose will be designated as PTV (V95%), dose given to 95% PTV will be designated as PTV (D95), maximum dose to the PTV (Dmax), mean dose to the PTV (Dmean), conformity index (CI), and homogeneity index (HI).
- The CI is defined as CI = TV/PTV, where TV is the volume of the reference dose (95%) inside the PTV. CI value closer to 1indicates a conformal plan.
- The HI is defined as HI= (D2%–D98%)/D50%, where D2%, D98%, and 50% of the PTV volume. HI value closer to 0 indicates a homogeneous plan.
- The dose received by all the structures was evaluated.
- The volume of other OARs receiving dose was quantified, and these dosimetric parameters were designated as follows: Brainstem: D-max; Spinal cord: D-max; PRV Spine: D-max; Optic chiasma: D-max; Mandible: D-max; Optic nerve: D-max; Parotid gland: D-mean; Cochlea bone: D-mean; Eye: D-max; Lens: D-max; Lips: D-mean
- The mean dose and maximum dose to the brachial plexes, was tabulated. Other dosimetric parameters to evaluate dose to the brachial plexes will include V40, V45, V50, V54, V60, V66, V70, V75, D50, D80

Patient Assessment During Treatment

- Hemogram (Hb/ TLC/DLC/PLT), KFT, LFT was repeated in all patients before every chemotherapy cycle and haematological toxicities were graded according to CTCAE V.5. During treatment assessment was done every week. Skin/mucosal/ pharyngeal radiation toxicity were assessed by RTOG Acute and Late morbidity scoring criteria and brachial plexopathy based on CTCAE version 5.0 (RTOG guidelines do not define brachial plexopathy)
- Patients were assessed every week during chemoradiotherapy for assessment of acute radiation reaction and monthly for late radiation reactions.
- Early radiation induced brachial plexopathy were assessed with a specifically developed point questionnaire. Included questions assess sensory and motor functions of both upper extremities. Questionnaire based assessment was done pre and post treatment.

Assessment of Toxicity

- Skin, mucosal and hematologic toxicities, brachial plexopathy were assessed by radiation therapy oncology group (RTOG) acute and late morbidity scoring criteria.
- Acute RTOG morbidity criteria are applicable from the day of commencement of radiotherapy till 90 days post-treatment. Patients were assessed weekly during chemoradiation for assessment of acute radiation reactions.
- Late radiation reactions were assessed using RTOG late morbidity criteria that will be applicable from 90 days onwards. Haematological toxicities were assessed by CTCAE guidelines.
- During treatment, assessment was done on a weekly basis and thereafter on a monthly basis by the Common Terminology Criteria for Adverse Events, CTCAE (Version 5).
- The brachial plexes toxicity was assessed by the 18-item questionnaire.

Clinical Response Assessment

The patients were assessed for objective tumor response according to WHO criterion: Complete response (CR)- Total tumor regression for at least four weeks; Partial response (PR)- 50% or more reduction in product of two major perpendiculars of the measurable tumor for at least four weeks; Stable disease (SD)- Less than 50% or more reduction to less than 25% increase in cross product; Progressive disease (PD)- Growth of measurable tumor by 25% or more or appearance of new lesion.

Brachial plexus toxicity assessment questionnaire

Brachial plexus toxicity was assessed with the help of a questionnaire, which is broadly based on the clinical symptoms of the patient in terms of grade and duration was done in all patients. The brachial plexus toxicity was assessed by the 18-item questionnaire (Platteaux *et al*).
The following were assessed –
Proximal arm weakness: problems raising the arm above the head; Problems carrying heavy objects such as a shopping bag; Problems lifting objects from a high shelf

Impaired hand functions: Problems cutting vegetables or unscrewing a bottle top.

Sensory scale (four items) EORTC CIPN20 Tingling; Numbness; Stinging or burning sensation; Distinguishing temperature

Complaints that interfere with daily activities: hair brushing, sweater pullover; back zipper

Others-Pain arm/shoulder; Swelling arm/shoulder; Stiffness in arm/shoulder; Involuntary movements; Fasciculations; Movement restrictions; Analgesics requirement

Neuro-physical examination

The following muscles were assessed with the appropriate clinical test. Tone and power were assessed in both arms separately. The examination was done before treatment, in follow-up 3 monthly and at least 12 months after completion of treatment for all patients.

Shoulder Muscles

Supraspinatus - Jacobs Test; Infraspinatus - external rotation of the shoulder joint; Serratus Anterior - Wall Press Test; Deltoid - Swall Tail Sign; Pectoralis Major & Minor - To Touch The C/L Shoulder; Rhomboidus Major & Minor - Pushing Shoulder Blade back Together.

Upper ARM Muscles

Biceps - Yergason Test; Triceps - Triceps reflex

Lower ARM Muscles

Supinator - Supination of arm; Pronator Teres - Flexion & pronation of arm; Brachioradialis – Flexion of forearm in mid pronation; Extensor Carpi Radialis Longus & Brevis – Extension & abduction of hand; Flexor Carpi Radialis - Flexion & abduction of hand; Extensor Digitorum - Extension at MCP; Flexor Carpi Ulnaris - Flexion & adduction of hand; Extensor Digiti Minimi - Extension of little finger at MCP; Extensor Carpi Ulnaris - Extension & adduction of hand; Extensor Policis Longus - Extension of thumb at CP, MCP & IP; Extensor Policis Brevis - Extension of thumb at CP & MCP; Abductor Policis Longus - Extension & Abduction of thumb at C- MCP; Extensor Indicis - Extension of middle finger; Flexor Digitorum Superficialis – Flexion of proximal phalanges at MCP; Flexor Digitorum Profundus – Flexion of distal phalanges at DIP; Pronator Quadratus – Pronation; Flexor Policis Longus - Flexion of phalanges of thumb

Intrinsic Hand Muscles

Adductor Policis – Adduction; Opponens Policis - Touch thumb to little finger; Flexor Policis Brevis - Touch the palm with thumb; Interossei - Adduction, abduction of fingers; Abductor Policis Brevis - Palm towards the ceiling; Lumbricals - Extension of MCP, Flexion of IP

MRI assessment of brachial plexus toxicity

- The brachial plexus toxicity was done by MRI under the following headings on both sides, as per feasibility.
- U/L thickening of nerve roots; symmetrical & B/L Thickening of nerve roots; hyperintensity on T2 W imaging; hyperintensity on stir sequence; mild

Table 1: Dosimetric parameters of PTV

	D-2	D-50	D-95	D-98	D-100	D-max	D-mean
Mean	66.94	65.68	64.46	62.61	46.36	68.48	64.51

Table 2A: Table showing dosimetric parameters of neurogenic OARS

	PRV Brain stem	PRV Spine	Optic Chiasma	Optic Nerve (R)	Optic Nerve (L)	Eye (L)	Eye (R)
Mean	33.12	41.89	4.49	6.51	5.73	6.22	6.25

Table 2B: Table showing dosimetric parameters of other OARS

	Parotid (L)	Parotid (R)	Cochlea (R)	Cochlea (L)	Lips	Mandible
Mean	34.81	34.66	20.90	18.60	26.95	62.73

Table 3: Table showing dosimetric parameters of brachial plexus (Left, Right and Combined)

Parameters	*Right brachial plexes*			*Left brachial plexes*			*Combined brachial plexus*		
	Mean	*Max*	*Minimum*	*Mean*	*Max*	*Minimum*	*Mean*	*Max*	*Minimum*
V-40	4.88	7.9	2.8	81.85	100	0.00	79.05	99.7	0.00
V-45	63.81	74.8	2.19	75.09	99.91	0.00	72.39	98.83	0.00
V-50	50.04	67.03	1.38	65.20	98.94	0.00	63.03	96.9	0.00
V-54	20.52	36.28	0.31	54.20	98.04	0.00	53.57	94.5	0.00
V-60	52.13	70.36	52.13	36.96	92.31	0.00	34.9	87.8	0.00
V-66	40.62	49.69	2.4	18.76	74.91	0.00	18.59	74.0	0.00
V-70	4.88	5.90	1.8	7.44	47.51	0.00	6.79	50.0	0.00
Volume	9.88	6.9	4.8	4.54	7.7	2.40	65.15	74.84	3.22
D-max	62.81	74.8	7.19	64.52	73.73	3.22	51.12	67.50	1.45
D-mean	57.04	65.03	1.38	51.26	67.94	1.54	18.32	46.96	0.00
D-min	21.52	37.28	0.31	20.14	43.71	0.00	9.47	15.60	5.30
D-50	52.13	68.36	52.13	54.17	69.88	0.00	52.28	70.94	0
D-80	60.81	49.69	1.4	43.7	80.04	0.00	39.44	64.04	0

contrast enhancement; oedema; inflammation (Acute/Chronic) neovascularization; diffusion study

Nerve Conduction Velocity (NCV) Test

- The brachial plexus toxicity was done by nerve conduction velocity study post treatment *as per feasibility* under the headings of Lat 1 (mS), Dur (mS), amplitude, NCV(m/S). It was done in both arms to assess the brachial plexus toxicity bilaterally. The following nerves were assessed and documented –
- Ulnar nerve; median nerve; radial nerve; axillary nerve; long thoracic nerve, thoraco-dorsal nerve; musculocutaneous nerve

Follow up

- Patients were assessed weekly during radiotherapy, at the end of radiotherapy, and thereafter monthly.
- As per our institutional practice, regular follow-up for HNSCC patients included evaluation of treatment - induced adverse events that were graded according to CTCAE v 5.0 and reported in patients.

Table 4: Table showing parameters of brachial plexopathy

Brachial plexus toxicity parameters	*Percentage (%)*
Proximal arm weakness	24 (63.1%)
Impaired hand function	16 (42.1%)
Sensory scaling	25 (65.7%)
Daily activities	16 (42.1%)
Others	18 (47.3%)

- NCV and MRI of the neck were done every 6 months, after completion of treatment and were compared with the pre-treatment MRI and NCV

All patients were followed up for a period minimum of 12 months and a maximum of 5 years, with a median follow-up of 39 months.

Statistical Analysis

Results were tabulated or graphically reported to draw conclusions.

Collected data will be analyzed using standard statistical methods and software to calculate the level of significance using the "*p*" value.

Table 5: NCV parameters of different nerves pre and post-treatment

S.No.	Nerve	p-value			
		Lat 1 (mS)	Dur (mS)	Amp	NCV (m/S)
1	Left ulnar nerve	0.56	0.43	0.31	0.02
2	Right ulnar nerve	0.12	0.20	0.09	0.07
3	Left median nerve	0.40	0.35	0.14	0.04
4	Right median nerve	0.37	0.33	0.12	0.02
5	Left radial nerve	0.11	0.01	0.35	0.49
6	Right radial nerve	0.05	0.01	0.44	0.01
7	Left axillary nerve	0.16	0.05	0.14	0.10
8	Right axillary nerve	0.15	0.00	0.21	0.18
9	Left musculocutaneous nerve	0.25	0.02	0.00	0.45
10	Right musculocutaneous nerve	0.01	0.19	0.29	0.08

RESULTS

A total of 38 patients with head and neck malignancies were enrolled from November 2019 to April 2021 in this study. All the patients have received radiotherapy to a total dose of 70 GY in 35 fractions at the rate of 2 Gy per fraction over a period of 5 weeks. On follow up clinical assessment was done in all 38 patients, whereas MRI and EMG testing was done in 20 patients, as some patients expired due to covid and some did not turn up for follow-up due to restrictions of movements in different zones.

The median follow-up of patients is 39 months (Range 12 to 54 months).

Patient Characteristics

In this study, the mean age of the patients was 53.84 years, the median age of the patient were 56 years and the age range of the patients was between 28 years and 80 years. Less than half of the patients belonged to the 6^{th} decade, with 29% of patients. About 87% of cases were male. Male: Female ratio 6.6:1.0.

The most common complaints of head and neck patients were weight loss (17%), swelling (31.5%), ulcer (31.5%), and difficulty in chewing. The most common addiction of patients in our study was tobacco chewing (31.84%), followed by smoking (39.47%) and alcohol intake (18.42%).

Among all the patients, the most common site was the oral cavity, 19 (50%), followed by oropharynx 13 (34%), the larynx, 4 (10%) & PNS and nasopharynx with 1 (3%) each. Maximum lesions were T2 (2–4 cm) and T4a (more than 4 cm); 13 (34.2%), 3 (34.2%), respectively. The majority of the cases were N2 stage (42.1%), N0 (26%), N1, N3 (15.7%). The majority of the cases were locoregionally advanced stage III & IV, 34 (89.4%).

Table 6: Brachial plexopathy summary- clinical/MRI/NCV on follow-up of 12 months

S.No.	Clinical manifestations	MRI parameters	NCV parameters
1	Present	Present	Present
2	Present	Present	Present
3	Absent	Absent	Absent
4	Present	Present	Present
5	Present	Absent	Absent
6	Present	Present	Present
7	Present	Present	Present
8	Present	Absent	Absent
9	Absent	Absent	Present
10	Present	Present	Present
11	Absent	Present	Absent
12	Present	Present	Present
13	Present	Absent	Absent
14	Absent	Absent	Absent
15	Absent	Absent	Absent
16	Present	Present	Present
17	Present	Present	Absent
18	Present	Present	Absent
19	Present	Present	Present
20	Absent	Present	Present

Table 7: Table showing the mean of Dmax to the brachial plexus to PTV 70 and PTV 60

Dose to PTV	Mean of D max of BP	No patients assessed	RIBP
70 Gy	66.9 Gy	17	7 (41%)
60 Gy	66.5 Gy	21	11 (52.3%)

Table 8: Table showing the neurological and radiological assessment of patients for brachial plexopathy (12 months to 5 years with a median follow-up of 39 months)

SNO.	Clinical manifestation		MRI findings		NCV findings	
	At 12 months	At last follow-up (median 39 months)	At 12 months	At last follow-up (median 39 months)	At 12 months	At last follow-up (median 39 months)
1	Present	Present	Present	Present	Present	Progressed
2	Present	Progressed	Present	Progressed	Present	Progressed
3	Present	Progressed	Present	Progressed	Present	Progressed
4	Present	Present	Present	Progressed	Present	Progressed
5	Present	Progressed	Present	Progressed	Present	Progressed
6	Present	Present	Present	Present	Present	Progressed
7	Present	Progressed	Present	Progressed	Present	Progressed
8	Present	Progressed	Present	Progressed	Present	Progressed
9	Present	Present	Present	Progressed	Present	Progressed
10	Present	Progressed	Present	Progressed	Present	Progressed

Dosimetric Parameters

Table 1 shows dosimetric parameters of PTV (D2, D50, D95, D-98, D100, Dmax, Dmean). All the parameters were achieved according to the institutional protocol.

Table 2a shows dosimetric assessment of neurogenic organs at risk: PRV brainstem, PRV spine, optic chiasma, optic nerve and eye.

Table 2b shows the dosimetric assessment of other organs at risk: Mandible, parotid, cochlea and, lips. All the constraints were achieved as per the RTOG and QUANTEC Guidelines.

Table 3 shows the dosimetric parameters of the brachial plexus (left, right and combined). In the majority of cases, it is shown that the brachial plexus was receiving more than the prescribed doses. (Dmax < 60 -66 GY).

Clinical Assessment for Brachial Plexopathy

In the present study of 38 patients, 57.89% (n=22) developed brachial plexopathy within the first year. Among 22 patients who developed brachial plexopathy, the most common symptom was sensory disturbance in the form of tingling and numbness (65.7%), followed by proximal arm weakness (63.1%), followed by impaired hand function (42.1%) and activities interfering with daily activities (42.1%), such as difficulty in hair combing. Other toxicity includes pain and stiffness (Table 4).

MRI Findings of Brachial Plexopathy at 1 year

Thickening of nerve root pre and post treatment – unilateral thickening and bilateral thickening

50% of patients (n=10) developed left-sided thickening of nerve roots, 45% of patients (n=9) developed right-sided thickening, 35% of patients (n=7) developed B/L thickening of nerve.

Hyperintensity on T2-weighted image pre and post treatment

Left-sided brachial plexus showed contrast enhancement in 55% of patients (n = 11), whereas right-sided brachial plexus showed contrast enhancement in 70% of patients (n = 14) and B/L brachial plexus was enhanced in 60% of patients (n = 12).

Hyperintensity on T1-weighted image pre and post treatment

Left-sided brachial plexus showed contrast enhancement in 60% of patients (n = 12). In contrast, right-sided brachial plexus showed contrast enhancement in 55% of patients (n = 11) and B/L brachial plexus was enhanced in 50% of patients (n = 10).

Edema pre and post treatment

left-sided brachial plexus showed oedematous changes in 20% of patients (n = 4), whereas right-sided brachial plexus showed oedematous changes in 25% of patients (n = 5) and B/L brachial plexus showed oedematous changes in 20% of patients (n = 4).

MRI findings of mild contrast enhancement pre and post treatment

Left-sided brachial plexus showed contrast enhancement in 30% of patients (n = 6), whereas right-sided brachial plexus showed contrast enhancement in 25% (n = 5) patients and B/L brachial plexus was enhanced in 25% of patients (n = 5).

NCV Findings of Brachial Plexopathy at 1 year

Table 5 shows the comparison of NCV findings pre and post-treatment. The *p-value* was significant for left ulnar, left and right median, left and right radial, left and right

axillary and musculocutaneous nerve indication the damage post 12 months after treatment.

Brachial Plexopathy

Out of the total 38 patients, 57.8% (n = 22) had clinical manifestations of brachial plexopathy.

Twenty patients underwent MRI and NCV in follow-up of more than one year (median follow-up 39 months). Of these 20 patients of long-term follow-up, 70% (n=14) developed clinical signs of brachial plexes toxicity, where 50% of patients (n = 10) had correlation with both MRI and NCV findings. (Table 6)

Seventeen patients received a dose of 70 Gy, out of which 41% (n = 7) had brachial plexopathy with a mean dose of DMax being 66.9 Gy. About 21 patients received 60 Gy, out of which 52.3% (n = 11) had brachial plexopathy with a mean dose of DMax being 66.5 Gy (Table 7)

Table 8 shows the neurological and radiological assessment of patients for brachial plexopathy in the follow-up after one year. Ten patients among the total cohort were followed for the median period of 39 months (range 12 months to 5 years). Six patients showed progression in clinical manifestations, eight patients showed progression in the MRI finding and all patients had progression in NCV findings.

DISCUSSION

Concomitant chemoradiotherapy (CRT) is the current standard of care for local-regional advanced head and neck squamous cell carcinoma (HNSCC). Intensity modulated radiation therapy (IMRT) is the commonly utilized radiation therapy technique in this setting. The incidence of brachial plexus–associated neuropathies after radiation therapy for head-and-neck cancer may be underreported. In view of the dose–response relationship identified, limiting radiation dose to the brachial plexus should be considered whenever possible.

Dose to the brachial plexus

In a study by Milender *et al.* regarding the evaluation of dose to the brachial plexus by IMRT in head and neck cancer stated that the mean of the D-max received by the brachial plexus was 69.6 Gy. Maximum point doses to the plexus ranged from 61.7 to 78.5 Gy (median 68.5, mean 69.6). Median volume of the brachial plexus receiving greater than 60 Gy was 1.71 cc (range 0.22–9.45, mean 2.38).[8]

Prakash *et al.*[9] in their study of Dosimetric analysis and clinical outcomes of the brachial plexus as an organ at risk in head and neck cancer patients treated with intensity-modulated radiotherapy, stated that the mean BP maximum dose (BPmax) was 62.4 Gy (+6.9), while the mean BP volume was 28.1 cc (+4.1). Proportion of patients receiving BPmax >66 and >70 Gy were 34.7% and 14.2%. The median follow-up was 28 months (interquartile range 16–42) and no patient had signs and features of brachial plexopathy. In a study by Alexander F *et al* with an intent to determine the dose variations to brachial plexes and clinically evaluate the patients for RIBP in Head and neck cancer, concluded that in oropharyngeal/ hypopharyngeal primaries and in advance nodal disease, brachial plexes are higher dose contributing to RIBP.

In a study by Dibbs *et al.*[10], aiming to identify factors associated with the development of RIBP in patients undergoing reirradiation for recurrent or second primary HNC, showed that RIBP incidence was significantly associated with all cumulative volumetric BP endpoints from V80-V120, with higher RIBP rates for V80 ≥ 1.94 cc, V100 ≥ 1.35 cc, V120 ≥ 0.89 cc, and EQD2 Dmax ≥ 103 Gy_2. This is the largest to date investigating rates of RIBP in patients with HNC treated with conventionally fractionated reirradiation.

Since 2008, RTOG has released contouring atlases for using structures of interest for head and neck cancer RT planning. Permeable dose for RIBP was reported as 60 Gy in RTOG studies 0435, 0522 and 0412, while in RTOG studies 0615 and 0617, the tolerated dose was reported as 66 Gy. At present, the RTOG guideline defines the maximum dose tolerated by the brachial plexus as 60 to 66 Gy.[11,12] In our study, the mean of the maximum dose received by the brachial plexus was 65.15 Gy. The main reason for his increased dose to the brachial plexus was that in our study, there was an increased incidence of lower neck lymph nodes, for which level IV and V group of lymph nodes were treated with doses equal to 66 Gy; thereby, the brachial plexuses in these patients received higher doses of radiation.

Neuro-Physical Examination

The majority of patients who have musculocutaneous nerve injuries present with difficulty in flexion at the elbow, brisk or absent biceps reflex, and sensory disruption in the entire distribution of the lateral cutaneous nerve of the forearm, whereas in patients with a localized lateral cutaneous nerve of the forearm neuropathy, it most commonly displays sensory disruption, but it is associated with normal muscle strength and biceps reflex. Patients having lateral cutaneous nerve of forearm impingement at the elbow most commonly developed pain with in the anterolateral aspect of the elbow region, which was worsened by pronation of the arm and extension at the elbow,[13] in contrary one patient of our study had difficulty in moving the elbow in all the directions, sensory disruptions in the forearm and decreased muscle strength, this is because of the advanced stage in the patient for which neck node

levels IV and V were treated and on dosimetric analysis higher doses (Dmax 67.35) was being received by the brachial plexus.

Axillary nerve lesions resulted in partial weakness of shoulder abduction and external rotation, motions that are partially maintained by the supraspinatus and infraspinatus muscles, respectively. Wasting of the deltoid region of the upper arm may lead to sensory loss over the lateral aspect of the upper arm.[14] In our study, the patient could not properly abduct the ipsilateral arm and was also experiencing pain and stiffness in the ipsilateral shoulder joint. This was because a very high dose (Dmax- 71GY) was received by the brachial plexus.

In the majority of cases, which were associated with pain, there was an involvement of the suprascapular nerve at the suprascapular notch, which is most prominently present along the upper & medial border of the scapula and finally radiates to the posterior and lateral shoulder. The pain may be referred to the arm, neck, or upper anterior chest wall and may be exacerbated by shoulder movements. The suprascapular notch becomes tender on palpation. When the suprascapular nerve is damaged or when it is encased at the suprascapular notch, it manifests primarily as weakness of the shoulder muscle, external rotation (infraspinatus muscle weakness). Shoulder abduction (supraspinatus muscle) is slightly enervated because of preservation of the deltoid muscle.

If injury occurs at the spino-glenoid ligament, then only infraspinatus weakness results, resulting in weakness of shoulder external rotation but no weakness of shoulder abduction. There is no alteration in the sensory supply of the skin.[15] Similar findings were noted in one patient in our study, where he had pain during the backward movement of the shoulder blades, which denotes damage to the musculocutaneous and suprascapular nerves and was also confirmed by EMG testing.

NCV Parameters

Electrodiagnostic testing of brachial plexus nerve damage is generally cumbersome, as it involves the study of multiple nerves and muscles to permit accurate localization. In the upper trunk plexopathies, electrodiagnostic sensory studies might reveal abnormalities in the following nerves: lateral cutaneous nerve of the forearm, median sensory (particularly at the thumb), and radial sensory (particularly to the thumb) nerves. In middle trunk plexopathies, the median sensory response is expected to be abnormal when recording from the middle finger. Routine studies of the median and ulnar motor nerves are within the normal range. In lower trunk damage, several sensory studies will be deranged, including the studies of the MAC nerve, the median sensory to the ring finger, the ulnar sensory to the little finger, and the dorsal ulnar cutaneous sensory nerve.

In examining the motor nerves, if there is enough axon damage, then the median and ulnar motor studies could also be abnormal, with the degree of abnormality being reported by the degree of axon loss. Partial axon loss leads to low compound muscle action potential (CMAP) amplitudes, mildly to moderately prolonged distal motor latencies, and mildly to moderately slowed conduction velocities. Severe axon loss may lead to nil responses.[16] Similarly, in our study, the nerve conduction parameters demonstrated a patchy asymmetric drop in sensory action potentials in the left upper limb. In addition, there was myokymia in the left brachial plexus, which is highly characteristic of radiation-induced neuropathy.

MRI Findings

Zhang *et al* in their study of the use of MRI in brachial plexopathy, stated that MRI could be used in all cases of brachial plexopathy, which are either due to traumatic, compressive, or non-traumatic causes. In cases of trauma, MRI is an alternative investigation modality to CT myelography for assessment of preganglionic nerve root avulsions and also has a sensitivity and specificity of up to 93 and 72%,[17] respectively, which was similar to our study where contrast-enhanced MRI was used to assess the incidence of radiation-induced brachial plexopathy. He also reported that the major difficulty in the procedure of MRI of the brachial plexus is getting high-spatial-resolution images of small target structures on the order of millimeters scale in the head and neck area, where air-tissue planes result in significant magnetic susceptibility. A customized brachial plexus MRI typically involves a mixture of two-dimensional and three-dimensional (3D) acquisitions. The two- dimensional sequences result in better in-plane spatial resolution and quicker acquisition time. Ideally, coronal and sagittal acquisition planes are oriented 90 degrees to the neurovascular bundles to profile the plexus; similarly, in our study two dimensional along with 3 dimensional imaging sequences were used to identify the radiation-induced brachial plexopathy (RIBP).

Skolka *et al*., in their study of pathological mechanisms of brachial plexopathy, stated that there are two main clinical syndromes of RIBP, corresponding to distinct pathophysiologic mechanisms, which are described: early transient radiation-induced plexopathy and classic progressive radiation plexopathy, whereas in our study, we found that there was an incidence of early transient radiation-induced plexopathy when treated by

conventional fractionation of radiation.[18] He also stated that radiation exposure leads to immediate lethal and sub-lethal oxidative molecular damage of connective tissues, setting off a complex biochemical cascade of events.

Early transient radiation-induced plexopathy manifests at an interval of 3 to 10 months following radiation therapy and is thought to be a sequela of an acute inflammatory response and small-vessel ischemia related to endothelial cell damage. In our study and the mean incidence of brachial plexopathy was reported at the time interval of 6 months post-radiotherapy.

Schierle *et al.*[19] in his study of radiation induced plexopathy review stated that classic progressive radiation plexopathy has a widely reported latency period for symptom onset of between 6 months and 30 years following radiation treatment, whereas in our study we had a follow up period post radiotherapy of 6 months, in which 65% of the patients showed signs and symptoms of brachial plexopathy and if long term follow up of these patients would have been done the incidence of classical progressive RIBP would have been increased.

Classical radiation-induced brachial plexes toxicity is caused by progressive fibrosis of the perineural connective tissues, with or without associated acute inflammation, which results in entrapment of nerve fibers, thickening of the endoneurium, demyelination, and damage to small vessels of the epineurial plexus,[20] these findings were properly correlated by MRI in our study.

In patients who are diagnosed with features of newly onset brachial plexopathy and a history of malignancy treated with local radiation therapy, an MRI scan is useful in differentiating RIBP from recurrent or metastatic cancer. RIBP is visualized at MRI as a hyperechoic thickening of the brachial plexus and surrounding fat.[21] In our study, when the findings of MRI were consistent, which showed similar hyperechoic thickening of the roots along with loss of fat planes in about 40% of patients during follow-up because of inflammation of the brachial plexus. MRI findings suggestive of radiation neuritis consist of uniform longitudinal thickening of the nerves, often with increased T2 signal intensity and longitudinal thin enhancement.[22] Perineural fibrosis is seen as an ill-defined tissue that encases the normal perineural fat planes on T1-weighted MR images and has a varying T2 appearance, hypointense or hyperintense, with the latter thought to represent vascularized scar tissue. In contrast, tumor or perineural metastasis might have the same signal characteristics, T1 hypointense and T2 hyperintense, but is more likely to appear as a nodular, discretely enhancing lesion.[22] In our study, we found out that there were both unilateral and bilateral thickening of the nerve roots of the brachial plexus, along with hyperintensity on T1-weighted images and contrast enhancement on T2-weighted images. Shetty *et al.* in their study, stated that Radiation plexopathy typically manifests as T2 hypointense thickening of the brachial plexus components without focal mass[23,] which was similar to our study. He also quoted that in the cases of prior malignancy and local radiation to the brachial plexus, it is very important for the clinician to attempt to differentiate tumor progression/recurrence from benign radiation-induced plexopathy changes. In our study, we found significant changes in symmetrical & bilateral thickening of nerve roots in which the p value was significant when compared to pre RT MRI & post RT MRI. There were also significant changes in the presence of hyperintensity on T2-weighted imaging, along with hyperintensity on the STIR sequence. Mild contrast enhancement along with edema and inflammation was also clinically significantly seen in the post RT MRI images.

Radiation-Induced Brachial Plexopathy

In a study by Karin *et al.* on the incidence of radiation-induced brachial plexus toxicity after radiotherapy, the follow-up from the first sign of symptoms in the patient until the last follow-up ranged from 8–57 months, making it possible to identify the dynamics and characteristics of symptoms for a long time. The most common symptoms started with either pain or numbness, and over time progressed to pain in combination with numbness and eventually pain, numbness and motor weakness developed, whereas in our study, after a follow-up period of 6 months, the most common presenting symptom was tingling, pain, and numbness. A longer follow-up is needed to see further progression of the symptoms.[24] Time course is key to discerning these entities, as radiation induced plexopathy occurs between 5 and 30 months post radiation therapy (peak incidence 10 to 20 months post radiation)[25] Similarly in our study most of the signs and symptoms of brachial plexopathy was seen at 6 months post treatment approximately 50% of the patients experienced the symptoms, further long term follow up is needed to confirm the duration of brachial plexopathy.

Clinical correlation of RIBP with Radiological & Neurological Assessment

In a study by Prakash *et al.*[9] on dosimetric analysis and clinical outcomes of brachial plexus as an organ at risk in head and neck cancer patients treated with intensity modulated radiotherapy, The patients were planned for IMRT in the definitive setting received either one of the two dosing schedules-66 Gy, 60 Gy, and 54 Gy in 30

fractions over 6 weeks or 70 Gy, 63 Gy, and 56 Gy in 35 fractions over 7 weeks to the high-, intermediate-, and low-risk PTV, respectively. The follow-up protocol was 2-monthly for the first 2 years, followed by 6-monthly from the 3rd year onward. At each follow-up, the patient was asked for symptoms suggestive of brachial plexopathy. If suggestive of brachial plexopathy, clinical examination and nerve conduction study were performed and dose–volume analysis of BP was performed, whereas in our study, all the patients received either 60 Gy in 30 fractions over 6 weeks or 70 Gy in 35 fractions over 7 weeks.

In a study by Besbes *et al*.[26], which aimed to evaluate late brachial plexopathy after primary chemoradiotherapy for locally advanced nasopharyngeal carcinoma with IMRT and determine the maximum tolerated dose. A cohort of 50 patients was selected. Clinical and treatment-related characteristics were collected and all cases were reviewed for RIBP. They observed that all patients received a minimum dose of more than 60 GY. All patients were followed up for 2 years with a median follow-up duration of 36 months. Only 5 patients in their cohort developed symptoms of brachial plexopathy. In our study, the follow-up protocol followed was monthly for the first 3 months, followed by six-monthly for 2 years. MRI and NCV were done pre-treatment and 6 months post-treatment and thereafter annually. Clinical examination for brachial plexopathy was done pre-treatment and 3 months post-treatment. Out of the 38 patients recruited in our study, only 20 patients were able to complete all three parameters to assess the brachial plexopathy. Out of those patients, 14 (70%) developed clinical signs of brachial plexus toxicity, and in 10 (50%) patients, clinical symptoms were also correlated with MRI and EMG findings. In 3 (15%) patients, clinical signs of brachial plexopathy were absent, whereas MRI and EMG parameters were indicative of brachial plexopathy, which indicates the presence of subclinical disease that needs a longer follow-up to manifest. In the rest, 18 patients who were only clinically assessed for brachial plexopathy, 8 patients developed positive clinical findings of brachial plexopathy. These patients could have shown positive MRI and NCV findings on 6-monthly follow-up, but because of the lockdown, they deferred follow-up. The mean of Dmax going to the brachial plexus in PTV70Gy and PTV 60 Gy was 66.9 and 66.5 Gy respectively, with an incidence of radiation-induced brachial plexus toxicity of 41.4% in patients with PTV 70 Gy and 35.4% in patients with PTV 60 Gy. This is because the brachial plexus was not prescribed any dose constraint before planning and also not evaluated during plan evaluation; hence, it became a site for dose dumping and there was no difference seen in the dose received by the plexus in both the PTV's.

CONCLUSION

The brachial plexus is neither delineated nor prescribed any dose constraint during the planning of head and neck cancer patients. In our study, we found a high dose being received by the brachial plexus, i.e mean of Dmax – 65.6 Gy, and there was not much difference in the dose received by the brachial plexus in *post-op* and *de novo* cases. Therefore, the brachial plexus should be considered as a potent organ at risk and optimal dose constraints should be prescribed to the brachial plexus and also the dose going to the brachial plexus should be evaluated during plan evaluation. Usually, patients presenting with complaints of numbness, tingling, paresthesia and pain are correlated with cervical inflammation (cervical spondylitis) and the diagnosis of RIBP is missed; therefore, patients presenting with these symptoms should be adequately screened.

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