Original paper

Early transient radiation-induced brachial plexopathy in locally advanced head and neck cancer

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Aim of the study: Early transient brachial plexopathy following radiotherapy (RT) in patients with head and neck cancer may be underreported and associated with a dose-response. Our purpose was to determine the incidence of early transient radiation-ınduced brachial plexopathy (RIBP) in patients receiving primary RT (± chemotherapy) for locally advanced head and neck cancer (HNC).

Material and methods: Twenty-seven locally advanced HNC patients who have no finding of brachial plexopathy at the diagnosis were evaluated 3 times by a specifically developed 13-item questionnaire for determining early transient RIBP. The 54 brachial plexus in 27 patients were delineated and dose volume histograms were calculated.

Results: Median follow-up period was 28 (range: 15–40) months. The mean BP volume was 7.9 ±3.6 cm^3, and the mean and maximum doses to the BP were 45.3 (range: 32.3–59.3) Gy, and 59.4 (range: 41.4–70.3) Gy, respectively. Maximum dose to the BP was ≥ 70 Gy only in 2 nasopharyngeal cancer patients. Two (7%) early transient RIBP were reported at 7^{th} and 8^{th} month after RT under maximum 67.17 and 55.37 Gy, and mean 52.95 and 38.60 Gy RT doses.

Conclusions: Two (7%) early RIBP were seen in the patient group, although brachial plexus maximum doses were ≥ 66 Gy in 75% of patients.

Key words: head and neck cancer, brachial plexus, radiotherapy, early transient radiation-induced brachial plexopathy (RIBP).

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Introduction

The use of radical radiotherapy (RT) is a standard of care for organ preserving strategies and for unresectable disease in locally advanced head and neck cancer (HNC) [1]. With the advent of advanced highly conformal RT techniques and the ability to spare organ at risk (OAR), understanding the relationship between dose parameters and both acute and late side effects is increasingly important.

Historically, the brachial plexus (BP) has not been routinely contoured as an OAR for three-dimensional conformal RT (3DCRT). Due to concerns regarding the consequences of high doses delivered using modern radiotherapy techniques, there has been increasing focus on the brachial plexus as an OAR [2]. Recommended dose constraints to minimize the risk of brachial plexopathies are differed from 60 Gy (RTOG 0435, 0522, and 1008) to 66 Gy (RTOG 0615, 0619, and 0912) in the Radiation Therapy Oncology Group (RTOG) guidelines (Table 1) [3–6].

Early transient radiation induced brachial plexopathy (RIBP) occurring within year following RT is uncommon toxicity [7]. There are few case reports of an early transient RIBP that occurs during or within weeks to months of RT with symptoms of paraesthesia, sensory changes, numbness, and weakness at relatively low dose and may resolve spontaneously [8]. In retrospective studies, the incidence of early transient RIBP has been variably estimated as 1% to 20%; clinical experience suggests that lower estimates are more accurate [9].

The frequency of early RIBP remains unclear in head and neck patients treated with RT in the literature. The dose at which it occurs and incidence are uncertain eventhough using with modern RT techniques. Radiation related early onset plexopathy can be ignored in head and neck cancer patients during the treatment because of the other severe acute toxicities such as mucositis, esophagitis, and dermatitis. In this respect, our purpose was to determine whether these brachial plexus constraints impacted early RIBP. We recently reviewed the treatment plans of patients with local advanced head and neck carcinoma who underwent radical 3DCRT at our center, and also administered questionnaires to determine whether these brachial plexus constraints led to early onset plexopathy.

Material and methods

Patients treated between June 2010 and July 2012 for locally advanced disease, were included for this prospective study based on the following inclusion critieria: Stage III/IV head and neck carcinoma, treatment with curative intent, absence of documented brachial plexus symptoms at presentation. Patients treated with primary surgery were excluded. Any patient who underwent a neck dissection prior to radiotherapy were also excluded. Staging was performed according to the 2010 TNM classification system of the

Table 1. Brachial plexus constraints on Radiation Therapy Oncology Group (RTOG) head and neck cancer protocols

Name of protocol	Brachial plexus dose constraint and Dmax
RTOG 0435	$D_{max} \leq 60$ Gy
RTOG 0522	$D_{max} \leq 60$ Gy
RTOG 0615	$D_{max} \leq 66$ Gy
RTOG 0619	$D_{max} \leq 66$ Gy, D05 ≤ 60 Gy
RTOG 0912	$D_{max} \leq 66$ Gy to point source at least 0.03 cm^3
RTOG 1008	$D_{max} < 60$ Gy if no involved low neck nodes; < 66 Gy if low neck involved

American Joint Committee on Cancer (AJCC) at the time of diagnosis [10].

All patients were treated with three-dimensional conformal radiotherapy. Patients were simulated supine with a using with individual thermoplastic masks and shoulder retractors for immobilization. Using the Toshiba Aquilion 64 slice computerized tomography device, image sections with 5 millimeters intervals were taken, and data were loaded into the XiO treatment planning system (CMS, Elekta). Prechemotherapy imaging was used to define target volumes. The clinical target volume included primary site and bilateral Level Ib, II, III, IV, and V lymph nodes. Retropharyngeal lymph nodes were variably included, depending on tumor site and stage. Treatment was routinely planned with a two-phase conformal technique of two lateral parallel opposed 6-MV photon fields, with a matched anterior neck field. The posterior border of the lateral photon fields was brought anterior to spinal cord to avoid cord toxicity after 40–44 Gy in 20–22 fractions. Matched electron fields were applied to the posterior neck. Standard doses were 70 Gy in 35 fractions over 7 weeks, with 50 Gy in 25 fractions over 5 weeks to the matched anterior neck. The median dose to low neck was 50 Gy in patients with N0 disease, although boost dose was added in extension of the lymph nodes in node positive neck.

Concurrent cisplatin 100 mg/m^2 IV on days 1, 22, and 43 or 40–50 mg/m^2 IV weekly for 6–7 week chemotherapy was also administered in 25 (92.6%) of patients. Tumour response was assessed 3–4 months after the completion of the treatment. Response assessment routinely included clinical examination, panendoscopy, and imaging (CT, MRI and/or PET-CT). Biopsy was considered in the event of clinical or radiological suspicion. Subsequently, patients were followed up with physical examination every 6–8 weeks in the first year after treatment, every 3 months for an additional 2 years, and every 6 monthly until discharge at 5 years.

Delineation of brachial plexus

Tumor and OAR volumes were contoured in accordance with the RTOG atlas for head and neck contouring and the relevant literature (Fig. 1) [3–6].

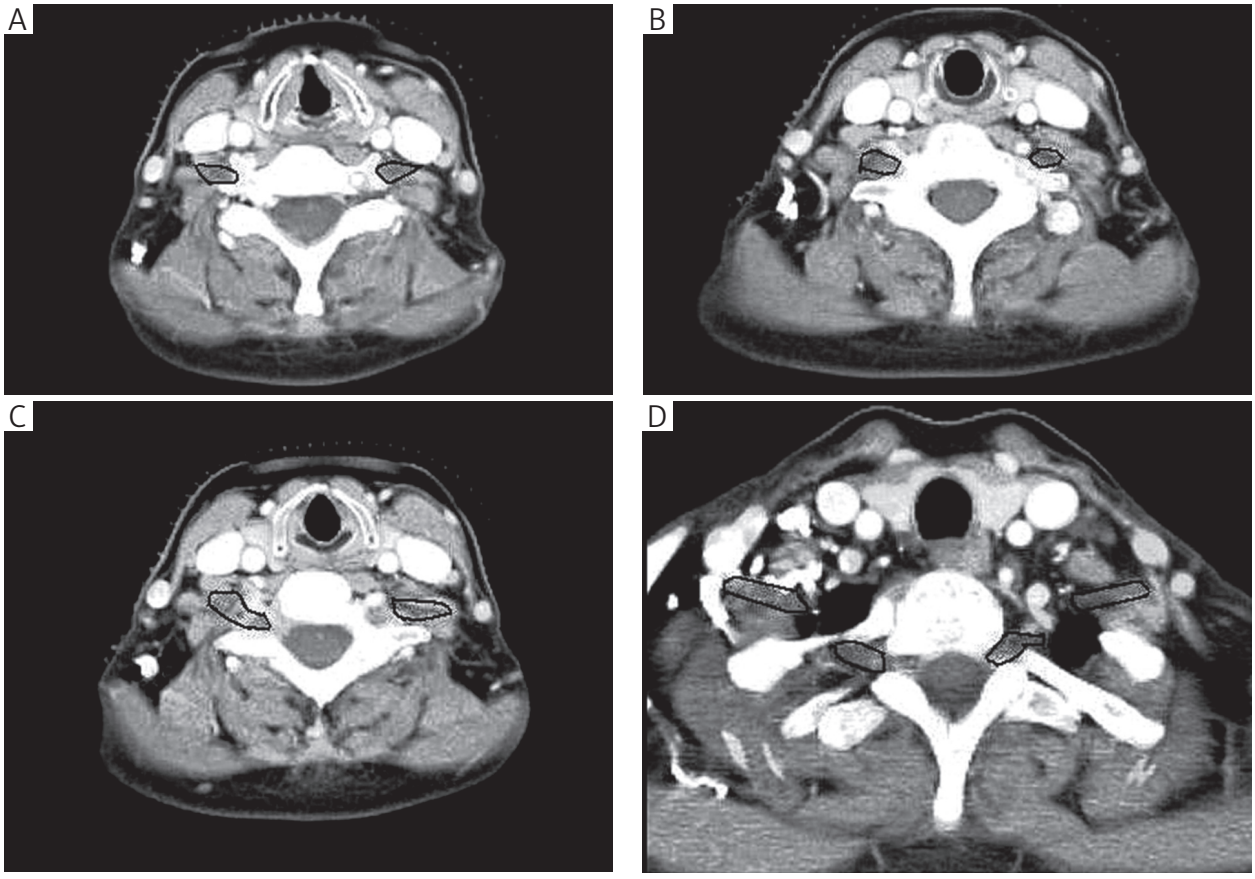

Fig. 1. A,B,C, and **D** passing through level of C5, C6, C7, and T1, respectively, shows contouring the brachial plexus (BP) (patient no. 4)

At the time of treatment, the BP was not considered an OAR, and, as a consequence, there was not delineated nor included in the treatment-planning process in any of the patients. The right and left brachial plexus (BP) retrospectively contoured as separate OARs in all patients (total 54 BPs) to evaluate BP doses. The mean and maximum doses and volumes of BPs were calculated. The BP was delineated beginning of the neural foramina from C5 superiorly to T1 inferiorly. A neuroradiologist assisted with contouring the BP.

Evaluation of RIBP

Patients were assessed at the outpatient clinic for evaluation of brachial plexopathy. During the treatment and in their visit at the follow-up, patients independently completed specifically developed 13-item questionnaire, probing for early RIBP. The questionnaire to determine the early RIBP was adapted from a validated questionnaire for identification of RIBP in breast cancer patients, modifications were based on prior work by Platteaux *et al*., which used questionnaires to evaluate RIBP in HNC patients treated with chemoradiotherapy [11]. Questions were included to assess sensory and motor functions of both upper extremities (Appendix 1).

First questionnaire was adminstered at the middle of the radiation therapy, second and third questionnaire were given at the following median of 3 (range: 2–5) and 8 (range: 6–12) months after the completion of 3DCRT. Detailed neurological examination was performed, and all findings were recorded to assess duration of symptoms, pain, swelling, analgesic requirements.

Results

In total 34 patients were enrolled who met the inclusion criteria for this study, and finally 27 of this 34 patients were evaluated who completed the all 3 questionnaires during and after treatment. The median follow-up time was 28 (range: 15–40) months. The follow-up time of all patients were ≥ 18 months, except 2 patients. One of these 2 patients was still in 17th follow-up after his treatment, other patient is under follow-up at 15th month in different city which he moved. There were 22 (81.5%) male and 5 (18.5%) female patients, with a median age of 60 years (range: 37–76 years) at the time of diagnosis. The primary tumor was localized in the nasopharynx (40%), oropharynx (22%), larynx (22%), and hypopharynx (15%). 19 (70%) of patients had T3/4 disease and 22 (82%) had clinically and/or radiologically node positive disease. Table 2 outlines patient and disease characteristics.

Twenty (74%) of patients completed 70 Gy RT. Median RT dose was 66 Gy in other 7 patients. Concurrent Cisplatin 100 mg/m^2 IV on days 1, 22, and 43 in 10 (37%) patients, and 40–50 mg/m^2 IV weekly in 15 (55%) patients.

The mean BP volume was 7.9 ±3.6 cm^3 (right (R), 8.1 ±3.5 cm^3; left (L), 7.9 ±3.7 cm^3). Mean and maximum doses to the BP were 45.3 Gy (range: 32.3–59.3 Gy; R, 35.5–59.3; L, 32.3–59.3 Gy), and 59.4 Gy (range: 41.4–70.3; R, 41.4–70.3; L, 41.4–67.1 Gy), respectively. Twenty-three (42%) of 54 BPs received a maximum dose of ≥ 60 Gy. BP doses were ≥ 70 Gy in only two (7%) patients, both of whom had nasopharyngeal cancer. Any BP dose > 55 Gy were 40% vs. 76% respectively in the negative vs positive nodal status. More than 5% weight loss were observed in 20%, and 43% of patients at the end of the treatment with BP doses ≤ 66 Gy, and > 66 Gy, respectively. Table 3 outlines tumor and treatment characteristics in total 23 (42%) of 54 BPs in 12 patients who received a maximum dose of ≥ 60 Gy.

Analysis of the questionnaires suggested the development of two (7%) cases of early transient RIBP in these 27 patients. One patient was a 44 year old male, who had completed concurrent cisplatin-radiotherapy 70 Gy including with maximum and mean BP doses in 55.37 and 38.60 Gy for T4N2M0 oropharyngeal cancer reported tolerable pain and numbness in his left arm on the second questionnaire returned 7 months following the completion of treatment. This patient was heavy smoker prior to RT, and continued to smoke during chemo-RT. An EMG performed following specialist neurology review was normal, although the neurological findings suggested that the brachial plexopathy. The symptoms resolved after a 3 month

Table 2. Patient and disease characteristics of 27 locally advanced head and neck cancer patients treated with primary radiotherapy

Characteristic	*n* (%)
Sex	
Male	22 (81.5)
Female	5 (18.5)
Age	
≤ 60	14 (51.9)
> 60	13 (48.1)
KPS	
90–100	20 (74)
60–80	7 (26)
Primary site	
Nasopharynx	11 (40.8)
Larynx	6 (22.2)
Oropharynx	6 (22.2)
Hypopharynx	4 (14.8)
AJCC stage	
III	11 (40.7)
IV	16 (59.3)
T-stage	
T1	0 (0)
T2	8 (29.6)
T3	9 (33.3)
T4	10 (37)
N-stage	
N0	5 (18.5)
N1	5 (18.5)
N2	13 (48.1)
N3	4 (14.8)

	N-stage				
T-stage	**N0**	**N1**	**N2**	**N3**	**Total**
T2	0	0	4	4	8
T3	4	2	3	0	9
T4	1	3	6	0	10
Total	5	5	13	4	27

AJCC – American Joint Committee on Cancer; RT – radiation therapy; n – number of patients

interval with no suggestion of long term RIBP injury on long term follow up (current). He's alive with lung metastases which diagnosed 21 months after his RIBP, and he continues the 2nd line chemotherapy without any plexopathy sign and symptoms at 34th months follow-up.

The second patient identified by the questionnaire, was a 41 years old female, who received 70 Gy chemo-RT including with maximum and mean BP doses in 67.17 and 52.95 Gy for T3N0M0 hypopharynx cancer. She developed pain of the left shoulder and numbness 8 months following completion of radiotherapy. Oblique sagittal T1-weighted and axial fat-saturated gadolinium-enhanced T1-weighted images showed soft-tissue stranding about the brachial plexus with diffuse gadolinium enhancement and suggested that RIBP in MR imaging. The symptoms resolved after 2 months, following the use of diclofenac and vitamin B; she is disease free, and she has no ongoing symptoms of BP injury after 31 months of follow-up. On review of case notes, there are no cases of long term and late RIBP.

Discussion

Early transient RIBP is a symptom complex described in the literature following completion of RT [9, 11]. The onset period of symptoms are described in the literature as occurring early between 3–10 months post-RT [12–14]. Initial signs and symptoms include distal paresthesia sometimes associated with proximal pain. The pathogenesis is not known, but an autoimmune mechanism has been assumed [13–15]. The direct and transient effect on Schwann cells, which causes reversible demyelination, may be causal, as advocated by some experimental data [16]. Another hypothesis concerns the role of compression caused by reversible postradiation edema. Treatment is generally not required, the neurological deficit and symptoms improve spontaneously, often completely within weeks or months; corticosteroids and antiinflamatuary drugs may hasten resolution of symptoms.

We have done this study to evaluate incidence of the early transient RIBP, and investigate the relation with late toxicity. As we know, there was no certain data about incidence and dose tolerances for early transient RIBP that it predicts late RIBP. Early transient and late RIBP often not distinguished from each other in literature. Neck dissection can produce similar symptoms which confuses interpretation of current reports. Therefore we have excluded any patients with neck dissection from this study.

Since 2008, RTOG has provided contouring atlases for using structures of interest for HNC RT planning. Tolerated 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 [3–6]. The current RTOG guideline for BP maximum dose is 60 to 66 Gy (Table 1) [3]. Before we designed this study, BP was not considered an OAR for planning 3DCRT in HNC patients in our clinic, therefore the right and left BP (total $n = 54$) contoured retrospectively. We found 23 (42%) of 54 BPs received a maximum dose of ≥ 60 Gy to at least one of the two BPs.

Combined treatment-related factors concomitant or previous chemotherapy (cisplatin, taxanes); and patient-related factors such as young or advanced age, obesity, diabetes mellitus, collagen vascular diseases, radiosensitivity, alcohol consumption, and smoking are related with the incidence of the RIBP [7, 14, 17]. In Chen *et al.*'s study, 12% of patients reported neuropathic symptoms [18]. They also concluded that, concurrent chemotherapy, and radiation maximum dose ($p < 0.001$) were significant factors associated with RIBP [18]. In some studies shown that, BP doses are significantly different in patients with clinical/pathological nodal status (N3 > N0-2 disease), and T stage (T4 > T0-3) [16, 17]. Radiotherapy fields are larger in

Table 3. Tumor and treatment characteristics in total 23 (42%) of 54 BPs in 12 patients who received a maximum dose of ≥ 60 Gy

No	Tumor localisation	T stage	N stage	Total RT dose (Gy)	Mean BP dose (Gy)	Max BP dose (Gy)	BP ≥ 66 Gy	BP ≥ 70 Gy
1	nasopharynx	2	2	70	52.96	62.78	no	no
2	larynx	3	0	60	45.27	60.62	no	no
3	nasopharynx	2	2	70	47.29	63.54	no	no
4	larynx	3	1	70	44.04	69.85	yes	no
5	nasopharynx	4	2	70	50.62	70.37	yes	yes
6	hypopharynx	4	1	70	53.17	70.06	yes	yes
7	nasopharynx	2	3	70	59.30	66.04	yes	no
8	nasopharynx	2	3	70	50.39	66.88	yes	no
9	larynx	4	2	70	35.81	66.59	yes	no
10	hypopharynx	3	0	70	52.95	67.17	yes	no
11	hypopharynx	4	0	70	53.10	66.55	yes	no
12	larynx	3	1	70	45.98	68.76	yes	no

local advanced stage HNC patients related with the stage, even using with new technology.

The incidence of RIBP is < 1–2% in patients receiving usual plexus total doses < 55 Gy [9]. Although only two patients have developed early transient RIBP symptoms who received mean BP doses < 55 Gy; suggesting again that the development of RIBP is a multifactorial process. One of the patients was heavy smoker (mean right and left BP doses were 35.05 and 38.6 Gy), and the second patient has occured grade 3 mucositis, grade 2 dermatitis, and > 15% loss in weight during the chemo-RT which considered a sensitivity (mean right and left BP doses were 52.9 and 48.3 Gy). Due to weight loss doses delivered to BP may not be as on pre-treatment CT.

We have seen brachial plexopathy in low doses of brachial plexus in only two (7%) patients without any late toxicity during the median follow-up period of 28 months, and our data suggests early transient RIBP has a much low dose relationship than late RIBP.

Objective neurological follow-up of patients starting from the early period following the completion of RT, might clinically contribute to the management of early transient RIBP in HNC patients. Regardless of the underlying some causes, early transient RIBP are likely an underreported complication of chemo-RT of HNC.

Limitations of our study are evaluation of non-IMRT data, few number of patients with heterogeneous tumor location, and relatively limited follow-up time to show relation between early and late toxicity. The development of a questionnaire form for objective early assessment and reporting, and prospective evaluation in months post-RT and due to the currently limited number of studies in literature on early transient RIBP, our study may serve as a guide for future studies and endeavours. Our study provides a good baseline for comparison with IMRT experience for further studies in future.

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A part of this study was presented at the National Radiation Oncology Congress, Turkey, April 23–27, 2014.

The authors declare no conflict of interest.

Appendix 1. Questionnaire form for evaluation of early-onset RIBP following RT [Symptom questionnaire prospectively administered to all patients returning for follow-up after completing radiation therapy for head and neck cancer]

A) Early period inquiry of neurological symptoms/complaints following RT (Will be marked separately for each one of the two upper extremities; localization will be indicated)
I Pain: (0) none (1) minimal (2) moderate (3) severe
II Numbness: (0) none (1) minimal (2) moderate (3) severe
III Movement restriction: (0) none (1) minimal (2) moderate (3) severe
IV Analgesic requirement: (0) none (1) minimal (2) moderate (3) severe
V Complaints that interfere with daily activity: (0) none (1) minimal (2) moderate (3) severe
VI Duration of complaints: (0)no complaints (1) less than 1 month (2) 1–3 months (3) more than 3 months
B) Early period neurological physical examination following RT (Will be marked separately for each one of the two upper extremities; localization will be indicated)
I Active movement dysfunction: (0) none (1) minimal (2) moderate (3) severe
II Passive movement dysfunction: (0) none (1) minimal (2) moderate (3) severe
III Hyperalgesia with palpation of nerve tracts: (0) none (1) minimal (2) moderate (3) severe
IV Hyperalgesia with palpation of associated cutaneous tissue: (0) none (1) minimal (2) moderate (3) severe
V Pathology in anatomical appearance: (0) none (1) minimal (2) moderate (3) severe
VI Hyperesthesia: (0) none (1) minimal (2) moderate (3) severe
VII Pain caused by movement: (0) none (1) minimal (2) moderate (3) severe

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