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DOSIMETRIC ANALYSIS AND CLINICAL OUTCOME OF BRACHIAL PLEXUS AS AN ORGAN-AT-RISK IN BREAST CANCER PATIENTS TREATED WITH CONFORMAL RADIOTHERAPY

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ABSTRACT **INTRODUCTION:** Radiotherapy is an integral component of management of breast cancer as adjuvant post mastectomy irradiation. Post mastectomy radiotherapy improve loco regional control. Brachial plexus (BP) consider as organ – at-risk for irradiation of ipsilateral supraclavicular area irradiation in post mastectomy radiotherapy. The purpose of this study was to evaluate the dose on brachial plexus in breast cancer patients treated with conformal radiotherapy and report incidence of radiation induced brachial plexopathy. **METHODS:** A prospective study was done at ATRCTRI Bikaner, total 30 patients were included. Post mastectomy 3D-conformal radiotherapy was given. Total dose was 40.06 Gy, 2.67Gy/fraction, 5 days in a week for 3 week. Brachial plexus were contoured ipsilaterally in breast cancer and bilaterally in HNSCC patients. 16 months follow-up done for plexopathy sign and symptoms. **RESULTS:** In post mastectomy breast cancer cases mean of BP Dmax.was 42.10±2.76 Gy. The mean of brachial plexus volume 9.4cc.Patients received dose >40Gy was 18.33% and >45Gy was 8.3%. The dose constraints for BP is Dmax 66 Gy. On follow-up of 16 months no patients reported with sign and symptoms of brachial plexopathy. **CONCLUSION** Patients with higher nodal category, N2+ received higher dose than N0/N1. All the patients were followed up for assessment of features associated with brachial plexopathy. Overall, pain, requirement of analgesics and pain associated with movement numbness, movement restrictions, complaint that interfere with daily activity and edema were observed in few of cases , however all the features were transient and none were permanent. However on 16 month follow-up no patients had brachial plexopathy.

KEYWORDS : Post-mastectomy radiotherapy, 3dimensional conformal radiotherapy, locoregional control rate, radiation induced brachial plexus neuropathy

INTRODUCTION:

Cancer is the rapid uncontrolled growth of abnormal cells beyond their usual boundaries. Cancer is one of the leading cause of mortality around world. In women world widely breast cancer is most common cancer. As per GLOBOCAN 2020, nearly 2 million (11.7%) breast cancer was identified and 0.68 million (6.9%) deaths. Globally, in women, 24.5% of all cancer are breast cancer. According to GLOBOCON 2020 data, in India incidence of breast cancer is 0.178 million (13.5%) and amongst women is 26.3%[1].Risk of breast cancer associated with BRCA1 and BRCA2 gene mutations, family history and genetic mutations which are not inherited. Besides these various other known factors like age, lifestyle, sex hormone exposure & obesity are considered as risk factors for breast cancer. Ductal (85%) is the most frequent than lobular (10-15%) carcinoma. In invasive carcinoma, invasive ductal carcinoma is the most common (85%). In breast cancer, adjuvant post mastectomy radiotherapy (PMRT) can improve the loco regional control rate (LCR) and survival rate of patients with locally advanced breast cancer, especially with axillary lymph node metastasis[2-3] Conformal radiotherapy shapes the radiation beam to closely fit the area of tumor[4]. The 3D- CRT is better than conventional radiotherapy as it uses 3D images. 3D-CRT involves imaging, precise radiation dose calculation, computer-optimized treatment planning, and computer-controlled treatment delivery. Treatment plans for each patient are individually designed. With 3D-CRT, the amount of radiation received by the surrounding healthy tissues can be significantly reduced.

Structures such as brachial plexus (BP) and cochlea which were not considered critical, have now bought in attention, as radiation induced brachial plexopathy is potentially debilitating. Brachial plexus is organ-at-risk (OAR) in head-and-neck cancer, breast cancer and lung cancer. The brachial plexus (BP) is network of nerves which originating from C5 to T1 nerve root[5], forms three lower trunks (upper, middle, and lower). These trunks divide beneath clavicle to form three cords (medial, lateral and posterior) in close approximation to axillary artery and pectorals major. These cords give terminal branches median, radial, ulnar, and musculocutaneous nerve, which innervate musculature and skin of chest, shoulder and upper limb[6]. The brachial plexus on both side present near to lymph nodes so inevitably covered in the radiation portals. BP is adjacent to elective nodal groups in the upper neck, and in the supraclavicular fossa as it traverses lower nodal volumes.

Radiation induced brachial plexus neuropathy (RIBPN) is characterized by sensory and motor function loss which gradually progress to total function loss of arm[7].Acute and long term squeal of radiotherapy are highly prevalent which affect quality of life[8]. Acute RIBPN occurs from several days to 6 months, which is characterized by inflammatory edema due to the direct neurotoxicity of radiation. Delayed RIPBN occurs 6 months later. Risk factors associated with radiation induced Brachial plexopathy are dose of radiation to brachial plexus and fraction size.[9]

The QUANTEC studies, did not specify guidelines for brachial plexus dose tolerance .Modern RTOG constraints vary between 60 Gy and 66 Gy maximum point doses. It has been reported 14%-20% breast cancer patients developed radiation-induced brachial plexus neuropathy (RIBPN) after radiotherapy in recent years.

The purpose of this study was to contour brachial plexus of the radiation in CT based planning ,document the dosimetric parameters of the BP and follow –up for features of brachial plexopathy .

MATERIAL AND METHODS

A prospective study done at tertiary cancer center, from November 2019 to January 2021. 30 breast cancer patients who undergone modified radical mastectomy and completed chemotherapy were selected. The study included patients aged between 29 and 61 years, ECOG performance status 0–2 with no history of diabetes mellitus. All patients were immobilized in supine position using custom fitted thermoplastic mold. In all patients computed tomography contrast enhanced simulation done in supine position with ipsilateral arm abducted (90degree or more) & neck rotated to opposite side. 5mm thickness slices were taken. The data was transferred to Eclipse Treatment Planning System (Varian medical system USA) version 13.8 panning software. Radiation therapy was delivered using megavoltage linear accelerator (Varian medical system, USA) with 6MV photons.

All patients were treated with 3D- conformal radiotherapy to chest wall and ipsilateral supraclavicular area. The single observer based BP contouring done (figure 1) using the guidelines developed by Hall et al. [10] .The planning objectives were to cover at least 95% of the volume of the PTV with 95% of the prescription isodose with not more than 1% receiving more than 110% of the planned dose. The follow-up protocol was 2-monthly for the 16 months. At each follow-up, the patient was examined for brachial plexopathy related questionarre.

Statistical analysis

SPSS 19.0 software was used for data analysis. The correlation between the radiation dose to the BP and its volume was analyzed. The independent effects of the clinical and dosimetric parameters

associated with RIBPN development were determined by univariate regression analysis.

RESULTS

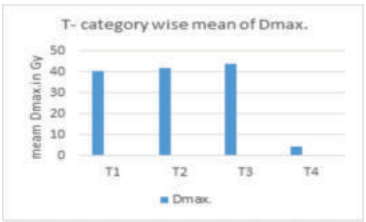
Table1 shows the stage wise distribution of patients. In pathological T-category, T1, T2, %T3, are 16.7%, 63.3%, and 20% respectively. In nodal category N0, N1a, N1b, N1c, N2a, N2b&N3a are 16.7%, 36.7%, 13.3%, 3.3%, 16.7%, 3.3%, 10% respectively.

Table 1- Distribution of patients according to pTNM staging.

TNM staging		Breast cancer (n=30)	
pT	n	%	
	x	0	0.0
	1	5	16.7
	2	19	63.3
	3	6	20.0
	4	0	0.0
pN	0	5	16.7
	1a	11	36.7
	1b	4	13.3
	1c	1	3.3
	2a	5	16.7
	2b	1	3.3
	3a	3	10
	3b	0	0
	3c	0	0

(Figure 1& 2)shows that higher T- category and N- category patients receive more dose at brachial plexus.

Figure 1: Mean Of Maximum Dose On Brachial Plexus Stagewise



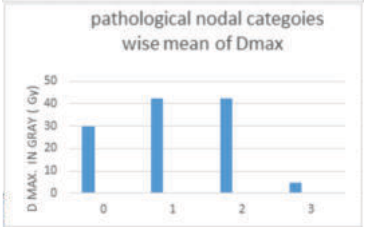


Figure2: Mean Of Maximum Dose At Brachial Plexus According To Nodal Category.

BMI of patients were 21.45±1.87 kg/m2. Volume of brachial plexus was 9.83±2.21 cc.

Mean dose received on brachial plexus was 34.53± 2.37Gy and maximum dose was 42.10 ±2.76Gy. Dose received by 5% and 10% volumes (D5%, D10%) were 39.12±3.39Gy and 37.44±3.54Gy respectively. Volumetric parameters were V40, V45 were 2.55±2.26 cc and 0.16±0.36 cc respectively (Table 2). Table. 2

PARAMETER		MEAN	SD
BMI (kg/m^2)		21.45	1.87
BP volume (cc)		9.83	2.21
Volumetric analysis (cc)	V40	2.55	2.26
	V45	0.16	0.36
Dosimetric volume (Gy)	D5%	39.12	3.39
	D10%	37.44	3.54
	D mean	34.53	2.37
	Dmax.	42.10	2.76

All the patients were examined for plexopathy related features pain, edema, numbness, requirement of analgesic, movement's restriction and pain on movement.

DISCUSSION

On analysis it showed that the dose to the BP was related to irradiation to the ISCL area. This finding is consistent with that of Stanic et al[11]. There have been few studies on the occurrence of RIBPN symptoms, including worsening chronic pain and decreased sensory and motor function, among the patients with breast cancer, head and neck cancer, and lung cancer after irradiation to the BP. In this study, mean age of patients was 45.13±9.22 years. Median age of patients with breast cancer was 47 years and all the cases were females in a study of Goyal S et al (2019).[12]Median age of patients with breast cancer ranged from 47 to 57 years in a study of Mutter RW et al (2020).[13]Lundstedt et al[14], reported that the incidence of RIBPN is 20% after conventional fractionation radiotherapy when the prescribed dose to ISCL is 50 Gy [11]. In this study 40.06 Gy dose was given with 2.67 Gy per fraction . Olson et al.and Lundstedt et al. have reported that the incidence of RIBPN was higher in young patients. However, in this study no significant relation were observed between age, BMI, and maximum dose to brachial plexus. Conformal radiotherapy is a form of therapy which helps in delivering the radiation dose closely in the area of tumor, without much damage to surrounding tissues. Delineation of BP is challenging task in CT based planning due to poor visibility and its complex anatomy [3]The present study was therefore an attempt to contour brachial plexus using guidelines given by Hall et al. and analyses dosimetric parameters of BP. In 2019Goyal S ,attempted to adapt Radiation Therapy Oncology Group (RTOG) guidelines on brachial plexus (BP) contouring (head and neck cancer) to breast cancer patients receiving post-mastectomy loco regional radiotherapy , to determine (I) feasibility of identifying BP in the treatment position for breast cancer, and (II) radiation dose received by BP with respect to the planned dose. In this study, mean dose received on brachial plexus was 34.53± 2.37Gy and maximum dose was 42.10 ±2.76Gy and volume of brachial plexus was 9.83±2.21 cc. In Goyal S study Mean ipsilateral BP volume was 13.8 cc. Medians of maximum and mean BP doses were 54.65 and 36.62 Gy, respectively.. Mean BP volume receiving >50 Gy was 27.81% (range, 13.01–51.80%). The maximum BP doses always exceeded prescribed dose, and although lower than tolerance dose (66 Gy) should be evaluated to reduce adverse events' risk. Albeit safe in conventional terms, the risk of high doses leading to increased risk of plexopathy warrants consideration especially with regard to relation to tumor boost volumes as well as when using hypofractionated regimens which may be less forgiving for late effect. In our study , V40, V45 were 2.55±2.26 cc and 0.16±0.36 cc. Brachial plexopathy may be either transient or permanent, and is characterized by pain, weakness, paresthesia and motor dysfunction of upper extremity or chest.[15] Brian C. Bowen divided RIBP into acute plexopathy and classic delayed injury. Acute injury develops several days to 6 months after the completion of radiotherapy. The main pathological of acute injury is inflammatory edema due to the direct neurotoxicity of radiation. Delayed injury occurs 6 months or later, it may be caused by the late toxicity of accumulated rays within neighboring tissues.[16] Risk factors associated with radiation induced Brachial plexopathy are dose of radiation to brachial plexus and fraction size[17] In this study ,numbness and hyperalgesia found in none patients . Movement restriction analgesic requirement, edema & interference in routine work found, pain was observed in 16.7% cases 13.3% & 13.3% cases presented with pain at 2 month, 4 months and 6 month respectively. Movement restriction found at 2, 4, 8 & 10 month in 10 %, 6.7%, 3.4% & 3.4% cases respectively. Analgesic requirement occurred at 2 month and 12 month in 13.3% and 3.4 % cases.Edema was reported in 1 case of breast cancer at 2 month. Complaint that interfere with daily activity were observed in 13.3% cases. In contrast to present study, **Wu SG et al[18] (2014)** in their case report documented the features of radiation induced brachial plexopathy after 36 months of radiation therapy, these features were numbness, pain and motor disturbance.**Truong MT et al [19](2012)** reported brachial plexopathy in none of the patients of head and neck cancer after IMRT.**Thomas TO et al[20] (2015)** also suggested BP contouring in IMRT to minimize the risk of brachial plexopathy. They reported no incidence of acute or late brachial plexopathy up to 24 months.There are several limitations to this study that should be considered. First, the sample size was relatively small, second was IN CT- based planning it was difficult to identify brachial plexus. In addition, the follow-up duration was relatively short. Therefore, the results cannot represent the majority of population.

CONCLUSION

In our analyses of the 3DCRT plans of 30 patients who received PMRT to the ISCL area and CW showed that the dose to BP was related to irradiation to the ISCL area. Patients with higher nodal category received higher dose. Based on the results of this study, none of patient

have brachial plexopathy .It appears safe to prioritize PTV over to BP, even if the fraction size was more than 2Gy.

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