Dosimetric Evaluation of Oesophagus in Hypofractionated Supraclavicular Nodal Irradiation in Breast Cancer - A Retrospective Observational Study in a Tertiary Care Cancer Centre in Alappuzha, Kerala

Sajeev George Pulickal[1], Reshma Bhaskaran[2], Aparna Perumangat[3], Harikrishnan Reghu[4], Girish Babu Moolath[5]

[1, 4] Department of Radiation Oncology, Government T.D. Medical College, Alappuzha, Kerala, India.
[2, 3] Department of Radiation Physics, Government T.D. Medical College, Alappuzha, Kerala, India.
[5] Department of Statistics, Government Arts and Science College, Kozhikode, Kerala, India.

ABSTRACT

BACKGROUND

Acute esophagitis (AE) is a common toxicity seen in patients undergoing radiotherapy (RT) for breast cancer, which can affect their quality of life. Thus, majority of our patients receiving hypo fractionated dose of 40 Gy in 15 fractions were having AE. We conducted this study to evaluate the dosimetric parameters of oesophagus and correlate with published literature.

METHODS

Treatment plans of 80 post mastectomy patients who underwent radiotherapy for carcinoma of breast (Ca breast) with a dose of 40 Gy in 15 fractions to the chest wall along with supra clavicular fossa (SCF) were selected. Out of these, 44 patients (22 each in right and left side) were simulated in neck straight position and 36 in neck tilted position (18 each in right and left side). The oesophageal volume was contoured in already executed plans from the inferior border of cricoid cartilage to the inferior border of the SCF planning target volume (PTV). No plan modification was done after contouring the oesophagus. Dosimetric parameters like the maximum dose (D_{max}) and mean dose (D_{mean}) to oesophagus, volume of oesophagus receiving ≥ 5 Gy (V5), ≥ 10 Gy (V10), ≥ 15 Gy (V15), ≥ 20 Gy (V20), ≥ 25 Gy (V25), ≥ 30 Gy (V30) were derived from dose volume histogram (DVH) data and analysed.

RESULTS

D_{mean} in straight neck group irrespective of side was 18.57 (± 7.30) Gy and in tilted neck 22.94 (± 9.53,) Gy, P = 0.023. Subgroup analysis shows D_{mean} was significantly high in patients with left sided disease than those with right sided disease (24.10 vs. 13.03, P = 0.00) in the straight neck cases. In the neck tilted group there was a nonsignificant increase in D_{mean} in left sided cases (25.36 vs. 20.53, P = 0.13).

CONCLUSIONS

Evaluation of oesophageal dosimetric parameters in hypofractionated dose showed that D_{mean}EQD2 was within the values of published studies in conventional fractionation.

KEYWORDS

Oesophageal Dosimetric Parameters, Breast Cancer

Corresponding Author:
Dr. Sajeev George Pulickal,
 # 41, Ginger County,
Vadayambady Post,
Puthenkurish, Ernakulam,
Kerala, India.
E-mail: pulickan7@gmail.com

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BACKGROUND

The oesophagus is composed of rapidly proliferating squamous epithelium and courses longitudinally through the entire extent of the mediastinum. As a result, in patients with centrally located tumours or with nodal metastases, the oesophagus can receive clinically significant radiation dose and become inflamed during treatment. Acute esophagitis (AE) (occurring ≤ 90 days after treatment initiation) is a common toxicity seen in patients undergoing radiotherapy (RT) for thoracic or breast malignancy. Radiotherapy is an integral part in the treatment of breast cancer which includes irradiation of post mastectomy chest wall or conserved breast, and regional nodes (RN).There are various guidelines for contouring chest wall, conserved breast, axillary and supraclavicular fossa nodes (SCF).[1,2] Medial border of SCF is related to midline structures and excludes thyroid gland and trachea. Oesophagus begins in the neck at the lower border of the cricoid cartilage. The general direction of the oesophagus is vertical, but it presents two slight curves in its course. At its commencement, it is placed in the middle line, but it inclines to the left side as far as the root of the neck, gradually passes to the middle line again at the level of the fifth thoracic vertebra, and finally deviates to the left as it passes forward to the oesophageal hiatus in the diaphragm and joints with stomach.[3] As such, there is potential to expose greater volumes of the oesophagus to radiation when following these guidelines. This may result in increased frequency and severity of acute radiation oesophagitis during treatment.

Patients with acute radiation esophagitis typically experience dysphagia, odynophagia, or acid reflux like symptoms or all of these. Patients can also experience sternal and epigastric chest pain.[4] Patients with pre-existing oesophageal diseases, such as chronic or poorly controlled gastroesophageal reflux or hiatal hernias, may be more susceptible to developing radiation esophagitis or may experience more severe symptoms of esophagitis. Less commonly, patients can develop intermittent oesophageal spasms that can be more intensely symptomatic when present. These symptoms can directly influence patient quality of life. Moreover, these patients would have already completed adjuvant chemotherapy which may have already affected their quality of life adversely. This infers that acute radiation esophagitis and dose received by oesophagus are a concern in radiation treatment of breast cancer.

Dose escalation of standard fractionated RT and hypo fractionated RT regimens can increase the risk of esophagealtoxicity.[5] Chemotherapy can independently cause oesophageal toxicity, and when delivered concurrently with radiotherapy, it can synergistically and detrimentally affect the esophagus.[6] In the study "Radiation therapy oncology group" (RTOG) 94 - 10, grade ≥ 3 esophagitis was seen in only 4 % of patients in the sequential chemotherapy and radiation arm, but it was experienced by 22 % of patients in the concurrent arm.[7] Furthermore, the risk of esophagitis can be potentiated by hyper fractionation.[8] Radiation dose received by the oesophagus has consistently been shown to influence the risk of developing esophagitis, either as a dose delivered or as a function of the volume of oesophagus that receives a clinically significant dose. Multivariate analysis showed the mean dose (D_{mean}) had a better correlation with esophagealtoxicity.[9] Another study by Wijsman et al. also demonstrated that the mean dose was a good predictor of AE.[10]

Most of the studies about acute esophagitis and oesophageal dosimetric parameters were related to lung cancer treatment and very few related to breast cancer. In a recent study by Katrina west et al.[11] using intensity modulated radiotherapy (IMRT), in conventional fractionation schedule of 50 Gy in 25 fractions, found that keeping oesophageal mean dose ($D_{mean)}$ < 31 Gy can reduce oesophageal toxicity. Hypo fractionated dose in breast cancer radiation is well accepted and commonly practiced.[12] Most of the studies evaluating the oesophageal toxicity in hypo fractionated schedule is in lung cancer.[13,14] In our center we are practicing hypo fractionated dose (40 Gy / 15 fractions) delivered by three-dimensional conformal radiotherapy technique (3DCRT) for the treatment of breast cancer. Odynophagia and dysphagia were common complaints among our patients undergoing breast radiation. So, we decided to conduct this study.

Objectives

The primary objective is to evaluate dosimetric parameters such as mean dose ($D_{mean)}$ maximum dose (D_{max}), and volume of oesophagus receiving doses, which may influence the incidence and severity of oesophagitis in breast cancer patients receiving hypo fractionated 3DCRT to the chest wall and SCF and secondary objective is to do subgroup analysis based on affected side right vs. left and to correlate results with published studies prescribing conventional fractionation dose of 50 Gy in 25 fractions delivered by IMRT / 3DCRT techniques. This will help us to take measures to modify our treatment planning so as to decrease the dose received by oesophagus and thereby reduce the incidence of acute esophagitis and improve quality of life of the patients.

METHODS

This is a retrospective observational study conducted in a tertiary care cancer centre attached to Government T.D Medical College, Alappuzha, Kerala, from March 2019 to April 2020.

Treatment Plan Selection

Treatment plans of post mastectomy patients who had already received adjuvant RT of dose 40 Gy in 15 fractions to the SCF along with chest wall and contoured based on RTOG breast contouring atlas were selected. Treatment plans of patients having an enlarged thyroid were excluded. Clearance for the study was obtained from the institutional review board and ethical committee. Our department had changed the planning computed tomography (CT) simulation position of breast cancer patients with head and neck in the straight position instead of head and neck turned to contralateral side by the year 2019.

22 treatment plans were selected in each group of patients having right and left sided breast cancer, simulated in straight neck position. 18 plans were selected from patients simulated in neck turned to contralateral side each in right and left sided disease. A total of 80 patients treatment plans were selected for this study.

Simulation and Treatment Planning

All patients were simulated and planned as per department protocol for breast cancer radiation. 44 patients were simulated in straight neck position and 36 patients were in neck turned to contralateral side. The acquisition of axial CT images was done using 16 slice Philips big bore CT with slice thickness of 2.5 mm. Eclipse soma vision version 11 (Varian Medical Systems, Inc., Palo Alto, CA, USA) was used for contouring and Eclipse Ver 11 treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA) was used to generate the 3DCRT treatment plans for the patients. RTOG breast contouring atlas was followed for delineation of clinical target volume (CTV) and planning target volume. (PTV) (1).

All PTVs and OARs were delineated by the treating radiation oncologist (RO). The organs at risk (OAR) routinely contoured were bilateral (B/L) lungs, heart, contralateral breast and spinal cord. Before this study we did not contour oesophagus routinely as OAR. Mono isocentric 3DCRT was used to treat both chest wall and the SCF together. A dose of 40 Gy in 15 fractions was delivered with the aim to deliver 95 % of the prescribed dose to minimum 95 % of the PTV. Dose constraints as prescribed in for hypofractionation were considered while planning. In this study, using the transverse plane of the planning CT, the oesophageal volume was contoured in already treated plans from the inferior border of cricoid cartilage to the inferior border of the SCF PTV by the same radiation oncologist. No plan modification was done.

Dosimetric parameters like the mean dose (D_{mean}) maximum dose (D_{max}) received by oesophagus, volume of oesophagus receiving ≥ 5 Gy (V5), ⩾10 Gy (V10), ≥ 15 Gy (V15), ≥ 20 Gy (V20), ≥ 25 Gy (V25), ≥ 30 Gy (V30) were estimated from dose volume histogram (DVH) data. Doses were converted to EQD2 for comparing with conventional fractionation. Patient related data including treatment site, side, neck position was recorded.

Statistical Analysis

Collected data was analysed using statistical package for social studies (SPSS ver. 21). Oesophageal dose-volume parameters like D_{max}, D_{mean}, volume of oesophagus receiving ≥ 5 Gy (V5), ≥ 10 Gy (V10), ≥ 15 Gy (V15), ≥ 20 Gy (V20), ≥ 25 Gy (V25), ≥ 30 Gy (V30), ≥ 35 Gy (V35) were compared between neck straight vs neck tilted to opposite side. Subgroup analysis based on affected side right vs left was also done using independent sample t-test. Results were interpreted using P value of ≤ 0.05 as statistically significant. Difference between two groups were shown in bar plot.

RESULTS

On analysis all dosimetric parameters except D_{max} and V_5 were significantly high in neck tilted plans compared to neck straight. (Table 1) fig. 1. D mean was higher in tilted neck 22.94 Gy vs. 18.57 Gy in straight neck. (P - 0.023). D max was slightly higher in straight neck plans (41.95 Gy vs. 41.37 Gy in tilted neck) and non-significant (P - 0.357). In the low dose region V5 also higher in neck tilted plan but the difference was non-significant (76.26 vs 71.29, P - 0.31)

		Neck Straight	SD	Neck Tilted	SD	P
Dose Gy	D max	41.95	2.21	41.37	3.38	0.357
EQD2	D mean	18.57	7.3	22.94	9.53	0.023
% volume	V5	71.29	17.92	76.26	25.41	0.310
	V10	53.30	21.38	65.52	26.53	0.022
	V15	45.94	21.98	61.37	25.27	0.005
	V20	40.32	21.89	56.51	25.92	0.003
	V25	34.85	21.38	51.58	26.10	0.002
	V30	28.43	20.19	45.03	25.64	0.002
	V35	17.37	15.65	29.21	21.59	0.006

Table 1. Comparison of Dosimetric Parameters in Neck Positions Straight vs. Tilted SD - Standard Deviation

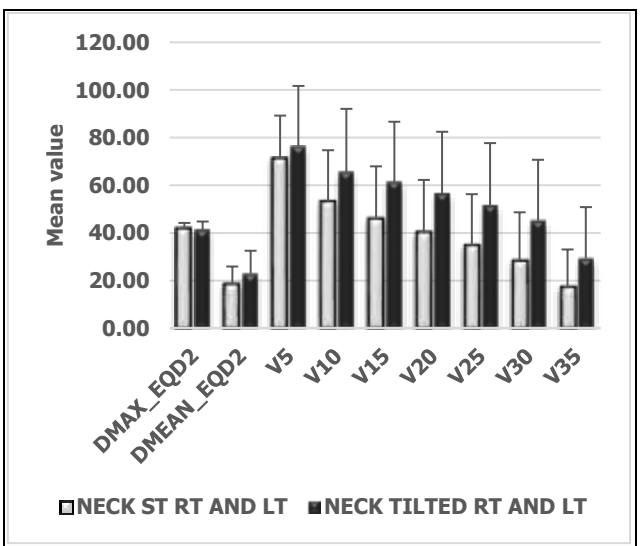

Figure 1. Comparison of Dosimetric Parameters in Neck Positions Straight vs Tilted

Neck Straight Plans

Sub group analysis of straight neck plans showed all dosimetric parameters were significantly higher in left sided treatment plans (Table 2). Fig. 2 D mean was 13.03 Gy in right sided plan vs 24.1 Gy in left side. (P - 0.00) D max was 41.22 Gy vs. 42.68 Gy right vs. left, (P - 0.02)

Neck Straight		Right	SD	Left	SD	P
Dose Gy	D max	41.22	2.05	42.68	2.16	0.02
(EQD2)	D mean	13.03	3.88	24.10	5.46	0.00
% volume	V5	57.38	12.09	85.20	10.30	0.00
	V10	36.22	11.30	70.38	14.05	0.00
	V15	28.64	10.85	63.24	15.63	0.00
	V20	23.38	10.48	57.27	16.43	0.00
	V25	18.53	9.78	51.17	16.79	0.00
	V30	13.24	8.81	43.63	16.55	0.00
	V35	6.55	6.48	28.19	14.65	0.00

Table 2. Comparison of Dosimetric Parameters in Straight Neck Position Right vs. Left SD - Standard Deviation

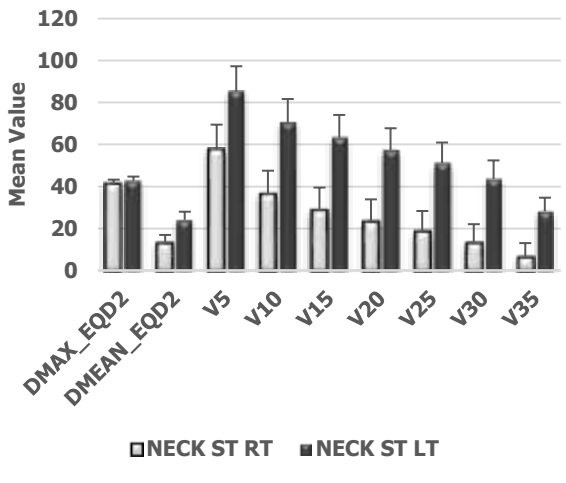

Figure 2. Comparison of Dosimetric Parameters in Straight Neck Position Right vs Left

Neck Tilted Plans

While in neck tilted position even though the dosimetric parameters were higher in left sided disease plans the difference was not significant. (Table 3) (Fig 3) D mean in right side is 20.53 vs. 25.36 in left and is nonsignificant P = 0.13.

Neck tilted		Right	SD	Left	SD	P
Dose Gy (EQD2)	D max	41.03	4.53	41.70	1.67	0.56
	D mean	20.53	11.14	25.36	7.12	0.13
% Vol	V5	68.72	30.96	83.80	15.84	0.07
	V10	57.31	30.44	73.73	19.41	0.06
	V15	54.40	28.12	68.33	20.53	0.09
	V20	49.63	28.76	63.38	21.36	0.11
	V25	45.10	28.94	58.05	21.82	0.13
	V30	39.48	28.55	50.59	21.74	0.19
	V35	28.35	26.22	30.08	16.45	0.81

Table 3. Comparison of Dosimetric Parameters in Tilted Neck Position Right vs. Left SD - Standard Deviation

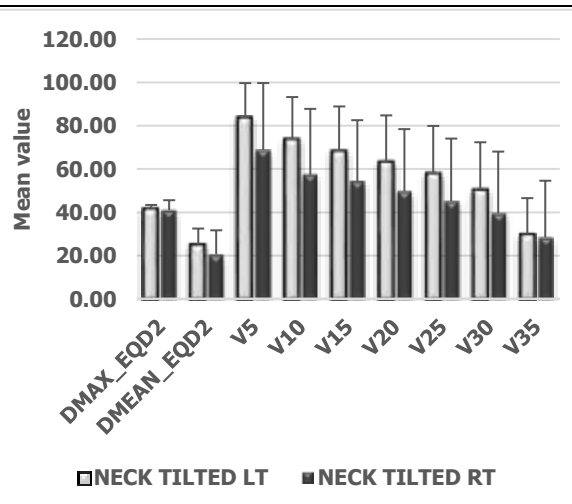

Figure 3. Comparison of Dosimetric Parameters in Tilted Neck Position Left vs. Right

DISCUSSION

80 patients treatment plan were included in this study of which 44 plans were simulated in straight neck position and 36 were of neck tilted to contralateral side. To the best of our knowledge this may be the first study to date to investigate the oesophageal dosimetric parameters in breast cancer patients undergoing hypo fractionated RT. On analysis of data, we found out that a mean dose (D_{mean}) of 18.57 ± 7.30 Gy in straight neck position and 22.94 ± 9.53 Gy in tilted neck position was received by the oesophagus and the difference was statistically significant. (P = 0.023) (table 1). Sub group analysis show that D_{mean} was significantly high in neck straight left side than right. (24.10 vs. 13.03), P = 0.00) (table 2). In neck tilted left sided disease group D_{mean} was higher but P value as non-significant. (25.36 vs 20.53) P = 0.13). (table 3). Other dosimetric parameters like D_{max}, V5, V10, V15, V20, V25, V30, V35 where significantly higher in left sided straight neck group when compared with right sided straight neck group (Table 2). Since the down ward course of oesophagus is slightly away from midline towards left as far as root of neck, SCF PTV on the left side is closer and even may overlap oesophagus, leading to higher radiation doses delivered to the oesophagus than the right-sided SCF PTVs.

In the study by Katrina west et al.[11] 77 patients were treated with IMRT technique and treatment position was neck tilted opposite to affected side. Mean dose ($D_{mean)}$ to oesophagus was 32.87 (± 7.4) Gy and maximum dose was 50.32 (± 2.2) Gy. The mean dose to the oesophagus in left side was higher as compared to right side 38 (± 6.03 Gy) vs. 28.9 (± 6.59 Gy). But it was not mentioned whether the difference was significant or not. When comparing treatment of the left versus right breast, there was a trend towards left-sided treatment reporting a higher frequency of grade 2 oesophagitis (16/24 (67 %) versus 8/24 (33 %), respectively); however, this did not reach significance (P = 0.0512).

Even though the D_{max} and D_{mean} oesophagus were higher than our results D_{mean} 32. 87 (± 7.4) Gy vs 22.94 (± 9.53) Gy in tilted neck position) our study also confirms a higher D max and D mean oesophagus in left side. The higher dose in their study may be due to fixing a set of constraints for target volumes and organs at risk (OAR) and efforts to achieve it in IMRT planning. The difference in contouring guidelines followed may also cause the higher value.

In the observational study by Qiong wang, Wuyun Jie et al.[15] 50 Gy to chest wall and supra clavicular regional nodes in 25 fractions delivered as IMRT with neck positioned opposite to affected side and reported that only 3 / 200 (1.5 %) patients who were treated developed grade 2 esophagitis during treatment. This study reported a Dmean and Dmax of the oesophagus of 10.65 (± 2.43) Gy and 40.61 (± 4.45) Gy respectively. This study used RTOG guidelines for PTV delineation.

Dmean oesophagus in our study was more than that in this study. 22.94 (± 9.53) Gy in tilted neck position vs 10.65 (± 2.43) Gy. This difference may be due to the radiation delivery techniques (3DCRT vs. IMRT) and constraints set for OARs. Our study was retrospective and there was no re planning after contouring of oesophagus. Re-planning accordingly to minimise the oesophageal dose could have reduced the mean oesophageal dose.

Alexander Yaney et al.[16] retrospectively compared oesophageal dose volume parameters and oesophageal toxicity in radiation treatment of breast cancer treated with IMRT vs 3DCRT (Prescribed dose was 50 Gy in 25 fractions). Their results showed that > 15 % of patients receiving regional nodal irradiation (RNI) with IMRT develop G2E. Using normal tissue complication probability (NTCP) modelling, they found that the most robust constraints related to acute radiation esophagitis were oesophageal mean dose < 11 Gy, V_{10} < 30 % and V_{20} < 15 %. In contrast to the 31 % G2E rate by West et al. this study showed 16 % G2E rate. The oesophageal constraints set was < 15 - 20 Gy in IMRT planning and this is near to finding of our study D_{mean} 18.57 ± 7.30 in straight neck and 22.94 ± 9.53 in tilted neck position, treated with 3DCRT.

In this study, it was not mentioned about the neck position whether straight or tilted. Our study was also retrospective but was not correlated with incidence and grading of esophagitis. Since most of our patients complain of esophagitis, we assume that the mean oesophageal dose < 11 Gy found by Yaney et al. to limit G2 esophagitis were relevant in our patients also. Hence prospective studies and modification of treatment plan accordingly to decrease oesophageal dose is required to generate clinical correlation with development of AE. Findings of above-mentioned studies were compared with present study and summarised in table 4.

Study	Dose Gy/fr	Technique	D_{mean} Gy ±SD	G2E %	Neck Position	Type	SCF Contouring
Katrina West et al.	50 / 25	IMRT	32.87 (± 7.4)	31	Tilted	Prospective	NR
Qiong wang et al.	50 / 25	IMRT	10.65 (± 2.43)	1.5	Tilted	Retrospective	RTOG
Alexander Yaney et al.	50 / 25	IMRT vs 3DCRT	< 11*< 15 - 20 Gy**	16.2	NR	Retrospective	RTOG
Present study	40 / 15	3DCRT	22.94 (± 9.53) Tilted 18.57 (± 7.30) Straight EQD2	NR	Tilted and straight	Retrospective	RTOG

Table 4

*calculated for G2E using NTCP model**constraints set in IMRT planning, NR not reported

CONCLUSIONS

We had evaluated the oesophageal dosimetric parameters in this study with hypofractionated dose and found that D_{mean} EQD2 was within the values of most of the published studies in conventional fractionation. Prospective clinical correlative studies with a greater number of patients were required to assess D_{mean} oesophagus and grade acute esophagitis. Routine contouring of oesophagus and planning accordingly may reduce oesophageal dose and acute oesophageal toxicity.

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