

Prospective Observational Study on Esophagitis in Breast Cancer Patients with Supraclavicular Nodal Irradiation - A Common Predicament

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Background: The present study aimed to assess the dosimetric parameters that may be associated with oesophagitis in patients with breast cancer undergoing three-dimensional radiotherapy.

Methods: A single-arm study was conducted on 25 breast cancer patients. Enrolled patients received 40.05Gy in 15 fractions to the chest wall and supraclavicular nodes with 3DCRT. Toxicity grading was examined once a week to assess the onset of grade 2 esophagitis in respective patients. Analyzed parameters incorporate mean oesophageal dose and maximum doses to the esophagus, esophagus volume, and oesophageal length within the supraclavicular nodal PTV treatment area.

Results: The mean age was 43.48 years and Grade 2 oesophagitis was noted in 13 of the 25 patients (52%). The onset of oesophagitis was significantly associated with the oesophageal length associated with the treating area ($p=0.04$). The laterality of disease did not show a significant relation ($p=0.93$). For the commencement of grade 2 oesophagitis, odds ratios were 2.33 (95% CI=1.1-3.89, $p=0.02$) for a mean esophageal dose ≥ 12 Gy and 2.5 (95% CI=1.2-5.18, $p=0.04$) for ≥ 4.5 cm of esophagus length within supraclavicular nodal PTV area.

Conclusion: In patients receiving radiation to the supraclavicular area, the mean oesophageal radiation dose and oesophageal length included in the treatment area correlate with the development of acute oesophagitis, which can be minimized by reducing those two parameters.

Introduction

Radiotherapy (RT) is an essential treatment modality in the overall management of breast cancer patients, from early-stage disease to locally advanced and metastatic cases which effectively reduces breast cancer recurrence and mortality [1]. Since the publication of guidelines on delineating the supraclavicular fossa (SCF) nodes in the treatment position for radiotherapy to the breast which includes SCF and become more personalized. As anatomically, the oesophagus is situated adjacent to the regional nodes, so there is potential to expose greater volumes of the oesophagus when implementing these guidelines. Therefore, regional nodal irradiation may increase the risk of greater frequency and increased severity of acute oesophagitis during treatment [2, 3].

Radiation oesophagitis causes a various clinical symptom i.e. odynophagia or substernal pain and dysphagia and having to modify their diet which adversely affects the quality of life. According to updated clinical guidelines formatted by an expert panel from the American Society for Radiation Oncology and the society of Surgical Oncology, recommended the use of SCF radiotherapy for patients with one to three positive lymph nodes [4]. MA20 randomised trial follows these guidelines, analysed that patients with early breast cancer and involving one to three axillary nodes, received radiation to the SCF and internal mammary chain with breast observed significant benefits. Results demonstrated an increase in 10-year disease-free survival in the group who received regional node irradiation as compared to the control group [5]. This finding is likely to increase the number of patients who receive RT to the SCF and experience oesophagitis. In the area of radical lung, head and neck RT, oesophagitis has been more widely researched. However, these studies not able to define an exact dose at which oesophagitis is likely to occur due to difficulty in defining the oesophagus on CT scans. Studies have reported a wide range of dose and volume parameters that may correlate with oesophagitis. Very few studies have documented the clinical factors affecting acute oesophagitis due to RT to supraclavicular nodes. So present study is formulated to assess the dosimetric parameters such as mean dose and oesophageal length which may influence the incidence and severity of oesophagitis in breast cancer receiving three-dimensional conformal radiotherapy (3D-CRT) to the SCF. Made an attempt to investigate whether factors such as chemotherapy regimen and laterality of disease may influence the onset of oesophagitis.

Materials and Methods

Patient selection- consecutive patients diagnosed with early breast cancer treated with RT at ATCRI, Bikaner, to the SCF after breast-conserving surgery or mastectomy were included in this single-arm prospective observational study. Inclusion criteria incorporate the patient's age ≥ 18 years, willingness to participate in study and availability for once in weekly review for the duration of RT. Patients must receive a planned dose of 40 Gy in 15 fractions to the breast or chest wall and SCF (IMC and axillary nodal irradiation are also allowed). Exclusion criteria include suspected or confirmed pregnancy, previous RT to the ipsilateral breast, a history of collagen vascular disease or any other condition in which RT is contraindicated. Before treatment, written informed consent was taken from all patients. Oesophagitis was graded by using a modified Radiation Therapy Oncology Group (RTOG) acute morbidity scoring scale [6], once in week throughout treatment and until all symptoms of oesophagitis had subsided after treatment completion. (Table 1).

Grade	Description
Grade 0	No dysphagia or odynophagia
Grade 1	Mild dysphagia or odynophagia
Grade 2	Moderate dysphagia or odynophagia
Grade 3	Severe dysphagia or odynophagia with dehydration or weight loss of greater than 15% from pre-treatment baseline requiring NG tube feeding, IV fluids or hyper alimentation
Grade 4	Complete obstruction, ulceration, perforation or fistula

Table 1. Adaptation of the Radiation Therapy and Oncology Group (RTOG) Scoring Criteria for Acute Oesophagitis.

Treatment planning

As per departmental guideline for breast cancer treatment, all patients were simulated and planned. Patients were positioned supine on an elevated breast board, with arms positioned above the head and supported by a customised vacuum-form cushion, with the head turned away from the ipsilateral side. Intravenous iodine contrast was administered to patients immediately before

scanning, unless contraindicated, for enhanced delineation of the regional lymph nodes. The acquisition of 2.5 mm axial CT images using the GE Lightspeed scanner was taken using the local breast protocol, with the length of the CT to cover superiorly to the level of the chin and inferiorly to include all breast tissue plus markers. A total dose of 40 Gy in 15 fractions was planned using the 3D-CRT technique with the aim of delivering 95% of the prescribed dose to the planning target volume (PTV). All PTVs were delineated by the treating radiation oncologist (RO) and OARs were delineated by the radiation therapist. Using the transverse plane of the planning CT, the oesophageal volume was contoured from the superior to the inferior border of the SCF PTV. Due to the consistent location of SCF nodes and the difficulty delineating the oesophagus in the mid-thoracic region, only the oesophagus at the level of the SCF PTV was contoured for this study. A previous study also confirmed in-field oesophagus to be more predictive of toxicity than the whole oesophageal length [7].

Statistical Analysis

Collected data were analysed by using variables i.e. mean oesophageal dose, oesophagus in field length, side of treatment and involvement of IMC nodes for treatment were compared between grade 0-1 and grade 2. Fisher's exact test was used to analysed these variables with 0.05 significance level ($p < 0.05$), considered as statistically significant. Correlation between mean dose and oesophagus length and grade 2 oesophagitis were examined using multivariate logistic regression.

Results

The study was conducted on 25 consecutive patients, the average age of the patients was 44 ± 9.19 years (Table 2) with left versus right side breast (14/25 versus 11/25, respectively) (Table 3).

Variable	Mean	SD	Min	Max	Median
Age in years	43.48	9.19	31	62	44
Total Length of Oesophagus in PTV SCF (CM)	3.55	1.78	0	6.09	3.73
Mean Dose (GY)	10.65	2.69	4	15.6	10.87
Max Dose (GY)	41.22	2.62	30.3	44.76	41.47
Total Volume of Oesophagus (CC)	18.42	6.34	11.3	34.4	16.7
Volume of Oesophagus in PTV SCF (CC)	1.30	0.97	0.00	3.40	1.10

Table 2. Clinical Data of Breast Cancer Patients Undergoing Radiation Therapy in Prescribed Dose of 40 Gy to SCF (Total n=25).

SIDE of Breast	N	%
Left	14	56.00
Right	11	44.00

Table 3. Laterality of Disease.

Almost all patients (21/25, 96 %) had chemotherapy before radiotherapy. Half of the patients (13/25, 55%) received radiotherapy to the breast or chest wall and SCF only with an average mean dose to the oesophagus of 10.65 ± 2.69 Gy as mentioned in Table 4.

	Oesophagitis (N)		Total (N)	P-Value
	≤ Grade 1	Grade 2		
Oesophagus Mean Dose (Gy)				
< 12	8	6	14	0.024
≥12	4	7	11	
Length of Oesophagus in PTV SCF (CM)				
< 4.5 cm	9	7	16	0.049
≥ 4.5 cm	3	6	9	
Laterality				
Left	7	7	14	0.9345
Right	5	6	11	

Table 4. Comparison of Mean Dose, Length of Oesophagus and Treatment Side.

Toxicity

Twelve patients (48%) patients showed grade 1 toxicity (mild oesophagitis) and thirteen patients (52 %) showed grade 2 toxicity (moderate oesophagitis), no patients were observed for grade 3 toxicity (severe oesophagitis). Commencement of grade 2 toxicity was in second week of treatment and reached its peak in the week after completion of treatment. It was observed that 10-14 Gy, by 1 Gy increment and an overall mean dose to oesophagus of ≥12 Gy was associated with increased frequency of grade 2 oesophagitis in (7/11 (63.63%) versus <12 Gy 6/14 (42.85%) as mentioned in Table 4.

Patients who had at least 4.5 cm of the oesophagus included in SCF fields were more likely to develop grade 2 oesophagitis compared with those who had < 4.5cm of oesophagus in treatment field (6/9 (66.66%) versus 7/16 (43.75%), respectively, $p=0.04$). In the multivariate analysis, the odd ratio of developing grade 2 oesophagitis with a mean dose to the oesophagus ≥ 12 Gy compared to <12 Gy was 2.33(95 % C.I.=1.1-3.89, $p=0.02$). The odd ratio for developing grade 2 oesophagitis with ≥ 4.5 cm of oesophagus in comparison to <4.5 cm involved was 2.57 (95% C.I.=1.23-5.18, $p=0.04$). Both of these factors were observed to be independent predictors of grade 2 oesophagitis.

On comparing side of treatment, left versus right breast, more patients reported left-sided treatment but results were not statistically significant ($p=0.93$). The mean volume of oesophagus for patients was 18.42 ± 6.34 cc and mean volume of oesophagus in PTV SCF was 1.30 ± 0.97 cc. Internal mammary chain was included in the treatment volume of all patients.

Discussion

It was analysed that mean threshold of ≥ 12 Gy to the oesophagus lead to significantly higher frequency of oesophagitis in breast cancer patients undergoing radiotherapy. Also observed that if length of oesophagus involved in treatment field was ≥4.5 cm, it increases the risk of onset of grade 2 oesophagitis.

There are limited studies conducted on radiation induced oesophagitis in breast cancer patients however many studies conducted on lung cancer patients which analysed that dosimetric parameters are predictors of acute oesophageal toxicity.

According to the Common Toxicity Criteria for Adverse Events definition, symptomatic oesophagitis is at least grade 2 in severity. Literature regarding incidence of symptomatic grade 2 oesophagitis from previous studies in patients ranging from 6.2 % to 44.8 %. This variation may be due to study

type and the oesophagitis grading scale. Prospective studies tend to capture more radiation oesophagitis. The incidence of grade 2 oesophagitis was 52 % in present prospective study which was supported by results of study conducted by Wang et al [8] and Vijayaraghavan et al. [9]. While a retrospective study by Dzul et al [10] reported 19 % patients who experienced grade 2 oesophagitis and defined oesophagitis treated with Mylanta- lidocaine as analgesics. Similarly, Yaney et al [11] in their retrospective study observed 16.2 % of patients with grade 2 oesophagitis which was diagnosed with use of mucosal protective agents. In present study, oesophagitis commenced at second week, peaked in last week of radiotherapy and symptoms lasted for 3 weeks after completion of radiotherapy. These findings were supported by West et al [12] study which concluded that earliest onset of grade 2 oesophagitis was at week 2 of treatment and peaked in the week after treatment was completed and completely resolved within 2 to 3 weeks after treatment.

Various clinical and treatment factors were associated with oesophagitis risk. In present study, left sided treatment increases the incidence of grade 2 toxicity but on comparison with grade 1, result was statistically insignificant which is supported by West et al [12] and Wang et al [8]. These findings can be illustrated by oesophageal anatomy, as the oesophagus runs on the left of the midline, this organ will receive more irradiation with left-sided than with right-sided treatment. Lamart et al [13] found that the supraclavicular and internal mammary node fields contributed the highest dose to oesophagus.

Previous breast cancer studies observed that dosimetric parameters were predictive of radiation oesophagitis. West et al [12] reported predictive mean dose for grade 2 oesophagitis and it was 32.87 ± 7.4 during prescribing dose of 50 Gy in 25 fractions where as Yaney et al [11] concluded 11 Gy as mean oesophageal dose, Wang et al [7] reported 10.65 ± 2.43 Gy as mean oesophageal dose and Amin et al [14] observed mean dose of 10.48 ± 5.10 Gy. In present study mean dose to oesophagus recorded was 10.65 ± 2.69 and which was similar to results provide by above all studies except West et al [12] which may be because of low prescription dose than this study and the difference in radiation delivery method (3D-CRT versus IMRT).

It was concluded in present study that mean dose > 12 Gy increases the incidence of grade 2 oesophagitis which is supported by study of Yaney et al [11] and Amin et al [13] who reported >11 Gy and ≥ 11.5 Gy mean oesophageal dose. While West et al [12] analysed mean dose > 31 Gy as independent indicator of grade 2 oesophagitis, it might be due to fact that grade 2 oesophagitis was defined as moderate dysphagia or odyphagia requiring narcotic analgesia. Many previous studies proved that combination of chemotherapy and radiotherapy leads to severe oesophagitis than induced by radiotherapy alone. In present study significant association not found between chemotherapy and oesophagitis because almost all recruited patients had chemotherapy before radiotherapy.

In conclusion, the oesophageal dosimetric parameters were evaluated in this study with hypofractionated dose and mean dose was within the values of most published studies. Prospective clinical studies with large sample size were required to evaluate mean oesophageal dose and grade acute oesophagitis. Routine contouring of oesophagus and planning accordingly may decreases incidence of acute oesophageal toxicity and oesophageal dose.

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Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.

- All authors have contributed to implementation of this research.

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