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Acute Pharyngo-Oesophagitis During Three-Dimensional Conformal Radiotherapy [3-D CRT] of Chestwall/Breast is Predictable Using Dose Volume Histogram parameters V3, V4, V5 and Mean Dose of Oesophagous: A Retrospective Clinico-Dosimetric Study

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Abstract

Background: *Acute Pharyngo-oesophagitis though a known complication of chestwall/breast irradiation for carcinoma breast is less described in literature. A retrospective study was carried out to identify acute pharyngo-oesophagitis in breast cancer patients receiving adjuvant radiotherapy and to correlate it with probable patient, tumor and dosimetric [treatment] variables.*

Methods and Materials: *Seventy-two patients of carcinoma breast who received adjuvant radiotherapy to chestwall/breast, axilla and supraclavicular lymphnode region by 3-D CRT in conventional fractionation consecutively were identified. Oesophagous was contoured on individual planning computed tomography images and different dosimetric parameters were calculated from dose volume histogram retrospectively. Variables of patient, tumor and treatment related attributes were analyzed with respect to acute pharyngo-oesophageal [PE] toxicity by suitable statistical tests using Statistical Package for Social Sciences [SPSS] version 20.*

Results and Statistics: *Acute pharyngo-oesophagitis of any grade was found in 44 patients [61%]. Age of patient, laterality of tumor, hormone/human epidermal growth factor receptor 2 status, target volume [chestwall versus whole breast], chemotherapy [Anthracycline/taxane], position of neck [midline versus rotated], total delivered dose, volume of oesophagous, duration of radiotherapy were not found to be related to appearance of acute pharyngo-oesophageal [PE] toxicity with statistical significance. Binary logistic regression analysis suggested maximum dose, mean dose to oesophagous,V3/V4/V5 oesophagous to be related to appearance of acute PE toxicity. Receiver Operating Characteristics[ROC] curve plotting revealed mean dose to oesophagous [when 9Gy,sensitivity for appearance of toxicity 57%], V3oesophagous[when 27%, sensitivity for appearance of toxicity 59%],V5oesophagous[when 19.5%, sensitivity for appearance of toxicity 84%],V4oesophagous[when 20%, sensitivity for appearance of toxicity 86%] are credible predictors of toxicity.*

Conclusion: *Acute PE toxicity is not uncommonly encountered during irradiation of chest wall/breast as part of adjuvant management of breast cancer. Mean dose to oesophagous, V3/V4/V5 oesophagous can be useful in estimating acute PE toxicity in chest wall / breast irradiation and can add to optimization of conformal radiotherapy planning.*

Key Words: *Adjuvant breast radiotherapy,3-D CRT, Conventional fractionation, acute pharyngooesophagitis, oesophagous dosimetric parameters*

Introduction

Breast cancer is the most common cancer among women worldwide both as per incidence as well as mortality (1). As per GLOBOCAN report breast cancer constituted 11.7% of total incidence of malignancies across globe in 2020 (1).In India Breast cancer tops the chart as the most commonly diagnosed cancer by incidence as well as mortality in contemporary times (2). Scores of scientific studies have evaluated the utility and benefit of adjuvant radiotherapy either to whole breast[post conservation surgery] or to chestwall [post radical mastectomy] with or without inclusion of axilla, internal mammary chain[IMC] lymph nodes and supraclavicular fossa [SCF] in treatment fields. Most of these studies have found radiotherapy benefitting patient outcomes in terms of loco-regional control [LRC] as well as overall survival [OS] (3-5).Early Breast Cancer Trialist's Collaborative Group meta-analysis of adjuvant radiotherapy in breast malignancy has matured the evidence level with which radiotherapy can be prescribed to improve outcome6.Over the years with optimum utilization of EBRT in loco-regional management of breast cancer, experiences about resulting morbidities arising thereof have also accumulated. Toxicity involving skin is perhaps the most common acute side effect of radiotherapy in carcinoma breast but long term toxicities arising from unintended irradiation of lungs/heart poses definite challenge in preparing a balanced radiotherapy plan (7,8). While morbidities resulting from inadvertent irradiation of Organs at Risk [OAR] especially heart and lungs during loco-regional irradiation of breast cancer have been examined in many studies; assessment of acute radiation induced toxicities such as pharyngo-oesophagitis has far fewer details. The available literature regarding acute pharyngo-oesophagitis has mostly been restricted to acute and chronic oesophagitis encountered during and after irradiation of intrathoracic malignancies (9,10,11).

This is an attempt to produce credible scientific report regarding acute pharyngo-oesophagitis observed in breast cancer patients undergoing adjuvant loco-regional irradiation with possible co-relation of dosimetric parameters.

Methods and Materials

For the retrospective study

Inclusion criteria consisted of

1) Histopathologically proven case of breast cancer
2) Age≥18 years
3) External Beam Radiotherapy in adjuvant setting following definitive resection
4) Conventionally fractionated EBRT
5) 3-D CRT technique.

Exclusion criteria comprised of

1) Chest wall or breast irradiation with palliative intent
2) EBRT fractionation other than conventional
3) EBRT technique other than 3-D conformal
4) Brachytherapy either alone or in combination with EBRT
5) Inadequate acute oesophagitis toxicity data record.

Patients who fulfilled above inclusion criteria and did not fall into exclusion class were taken up as study subjects. Consent for analysis of patient related data for research and training purposes were obtained preemptively at the time of registration at department and was according to institutional protocol.

Seventy two subjects had received adjuvant 3-D CRT to chestwall [post MRM two-third of total patients] or whole breast [post BCS one-third of total patients] along with Axilla level-III and Supraclavicular Fossa[SCF] in High Energy Linear Accelarator [HELA] Elekta Versa HDTM [Elekta AB Sweden] during 2019-20.Subjects had undergone Computed Tomography [CT] simulation at 2.5-5mm slice interval with or without intravenous contrast followed by contouring of target volumes and Organs at Risk [OAR] using Monaco Treatment Planning System[TPS,version 5.51]. The treatment target included chestwall post Modified radical Mastectomy [MRM] or whole breast post Breast Conservation Surgery [BCS] and level

III axillary lymphnode space, supraclavicular fossa[SCF] in all subjects and a boost dose was employed to tumor bed post Whole Breast radiotherapy [WBRT] in conserved breast patients. EBRT treatment plans were prepared using 6MV tangential beams with or without wedge pair covering chestwall/breast and 10MV mono-isocentric antero-posterior beam to supraclavicular area to a dose that ranged from 44Gy to 50Gy. The boost dose [range 10-14 Gy] to tumor bed were planned using tangential photon beams of energy 6MV with or without wedge pairs in conserved breast cases so that the overall total dose to Planning Target Volume [PTV] ranged 44Gy to 64Gy [Median dose 50Gy]. All the selected patients had undergone weekly evaluation and acute morbidities were recorded as per Radiotherapy Oncology Group[RTOG]/European Organization For Research and Treatment Of Cancer[EORTC] acute toxicity criteria (12).

On the CT simulation images of selected subjects who already had undergone EBRT; oesophagous was contoured retrospectively using mediastinal window beginning at the cricoid cartilage superiorly and included gastro-oesophageal junction till it ended in stomach inferiorly. The contour was placed over adventitia and was inclusive of mucosa, submucosa and muscular layers. Multiple oesophageal dosimetric parameters were obtained by retrospective calculation from the executed plan. Statistical calculation and data analysis were performed using Statistical Package for Social Sciences [SPSS] version 20.

Results and Statistical Analysis

Patient and tumor characteristics are categorized and recorded in table1.Study subjects included 71 females and one male [total 72] diagnosed and operated cases of breast carcinoma [age ranged from 20 to74 years, median age 45.5 years, Standard Deviation (SD) 11] who received multimodality management for breast cancer such as surgery, combination chemotherapy [either in neoadjuvant or in adjuvant setting], EBRT, anti-HER2neu therapy, hormonal therapy in definitive intent. Majority of patients had right sided breast [55.6%] primary. Histopathologically Infiltrating Ductal Carcinoma Not Otherwise Specified [IDC NOS] was found in almost all [97.2%] tumors. Approximately 62.5% of the resected malignancy harbored Estrogen Receptor [ER] and 47.2% possessed Progesterone Receptor [PR]. Human Epidermal Growth Factor Receptor 2[HER2neu] status in the study was negative in majority[70.8%].

Characteristics		Frequency	Percent	Statistical Significance
Tumour Laterality	Left	27	37.5	
	Right	40	55.6	P=0.000
	Bilateral	5	6.9	
Histopathology	IDC NOS	70	97.2	
	IDC Papillary	1	1.4	P=0.000
	Sarcoma	1	1.4	
Estrogen Receptor	Positive	45	62.5	P=.045
	Negative	27	37.5	
Progesterone Receptor	Positive	34	47.2	P=0.724
	Negative	38	52.8	
HER2neu	Positive	19	26.4	P=0.000
	Negative	51	70.8	
	Equivocal	2	2.8	

Table-1 Patient and Tumor Characteristics [n=72]

Treatment characteristics of the selected subjects are presented in table-2. Nearly 67% patients had undergone Modified Radical Mastectomy [MRM] as part of definitive surgical procedure, breast was conserved in one-fourth of the patients and bilateral mastectomy/MRM were conducted in 5 patients[7%]. Correspondingly radiotherapy was delivered to chestwall in 67% patients, whole breast radiotherapy+tumor bed boost in 26% patients and b/l chestwall were irradiated in approximately 7% patients. Axillary lymph node level-III/SCF were included in treatment portal of all patients except one. Inclusion of chemotherapy combining all scenarios was found in nearly 97% of the cohort and anti-HER2neu drug [Trastuzumab/Lapatinib] was used in 21% patients. The proportion of patient who received EBRT with neck in midline were nearly equal [52.8%] to the proportion of patients who received treatment [47.2%] with neck rotated to contralateral side; the difference being statistically not significant. Among the selected 72 subjects acute pharyngo-oesophagous [PE] toxicity during the course of irradiation was observed in nearly 61% patients. While grade1 toxicity was noted in nearly 51% patients, grade 2 PE was found in about 10% patients. Grade 3 or higher acute PE toxicity was not observed. Sixty one percent of patients experienced any grade of pharyngo-oesophagitis [Grade 1 or grade 2] during the course of

irradiation which was higher than patients not experiencing [39%] it; the difference being statistically significant.

Characteristics		Frequency	Percent	Statistical significance
Surgery	MRM	48	66.7	P=0.000
	BCS	19	26.4	
	B/l Mastectomy	1	1.4	
	B/l MRM	4	5.6	
EBRT	Chestwall+Axilla level III+SCF	51	66.7	P=0.000
	Whole Breast+Axilla level III+SCF+Boost	19	26.4	
	B/l Chestwall+Axilla level III+SCF	2	5.6	
	B/l Chestwall	1	1.4	
Chemotherapy	Yes	70	96.6	P=0.000
	No	2	3.4	
Anthracycline	Yes	55	77.6	P=0.000
	No	17	22.4	
Taxane	Yes	63	86.2	P=0.000
	No	9	13.8	
Anti-HER2Neu	Yes	12	20.7	P=0.000
	No	46	79.3	
Neck position during treatment	Midline	38	51.7	P=0.896
	Rotated	34	48.3	
Acute Pharyngo-oesophagitis	No	28	38.9	Between No Toxicity or any toxicity P=0.059
	Grade 1	37	51.4	
	Grade 2	7	9.7	
	Grade 1+Grade 2	44	61.1	

Table-2 Treatment Characteristics [n=72]

None of the parameters such as tumor laterality, type of surgery, receptor status [ER/PR/HER2neu], use of Anthracycline/ taxane, position of neck was found to be associated with occurrence of acute PE toxicity in terms of statistical significance.

Dose and related entities are analyzed and enlisted in table 3. Total Dose planned and delivered to target volume varied [Median Dose 50Gy, Mean dose 52.6Gy, Standard Deviation (SD) 5.4] from a minimum of 44Gy to maximum of 65Gy among the subjects. Median duration of treatment was 37.5 days [mean 40 days, SD 6.6, median 37.5, range 31-64 days]. Volume of oesophagous differed from a minimum recorded 16 cc to maximum value of 89 cc [median 27.2, mean 28.4, [SD 9.9]. Maximum and mean dose to oesophagous varied from 51.3Gy to 1.6Gy[Mean 41.6,SD14.8,Median 46.7Gy] and 15.7Gy to 0.9Gy[Mean 7.3,SD14.8,Median 7.7Gy] respectively. None of these parameters were found to have statistically significant correlation with acute PE toxicity.

Dosimetric Parameters	**Mean**	**Median**	**Standard Deviation**	**Minimum**	**Maximum**
Age	46.8	45.5	11.0	20	74
Total Dose (Gy)	52.6	50.0	5.4	44	65
Duration of Treatment	40.0	38.5	6.2	31	64
Oesophagous Volume	27.8	27.0	9.1	16.1	89.4
Oesophagous Maximum Dose	41.2	46.6	14.9	1.5	51.3
Oesophagous Mean Dose	7.5	8.2	3.4	0.9	15.7
V3	25.0	26.5	12.5	0.0	85.0
V4	22.7	24.2	11.2	0.0	79.6
V5	20.9	22.8	8.8	0.0	38.3

Table-3 Age and Dosimetric parameters [n=72]

Several dosimetric parameters computed from Dose Volume Histogram [DVH] were statistically analyzed for possible co-relation with acute pharyngo-oesophagitis recorded during treatment. Oesophagous volume receiving doses of 3Gy,4Gy, 5Gy, 10Gy, 15Gy, 20Gy, 25Gy, 30Gy, 35Gy, 40Gy Maximum and mean doses respectively were analyzed using binomial logistic regression analysis for possible correlation

with occurrence of acute PE toxicity. V3,V4,V5, maximum dose, mean dose of oesophagous [table 4] were found to be associated with appearance of acute PE toxicity in the analysed subjects.

Parameters	Chi-square	-2 Log Likelihood	Cox&Snell R Square	Nagelkerke R Square	P value	ROC Area	Asymptotic Significance
V3	6.922	82.996	0.092	0.124	0.009	0.764	0.000
V4	7.258	88.970	0.096	0.130	0.007	0.770	0.000
V5	15.373	80.855	0.192	0.261	0.000	0.758	0.000
Mean Dose Oesophagous	13.232	82.996	0.168	0.228	0.000	0.746	0.000
Maximum Dose Oesophagous	5.917	90.311	0.79	0.107	0.015	0.601	0.149

Table 4 Binary Logistic Regression and ROC Analysis

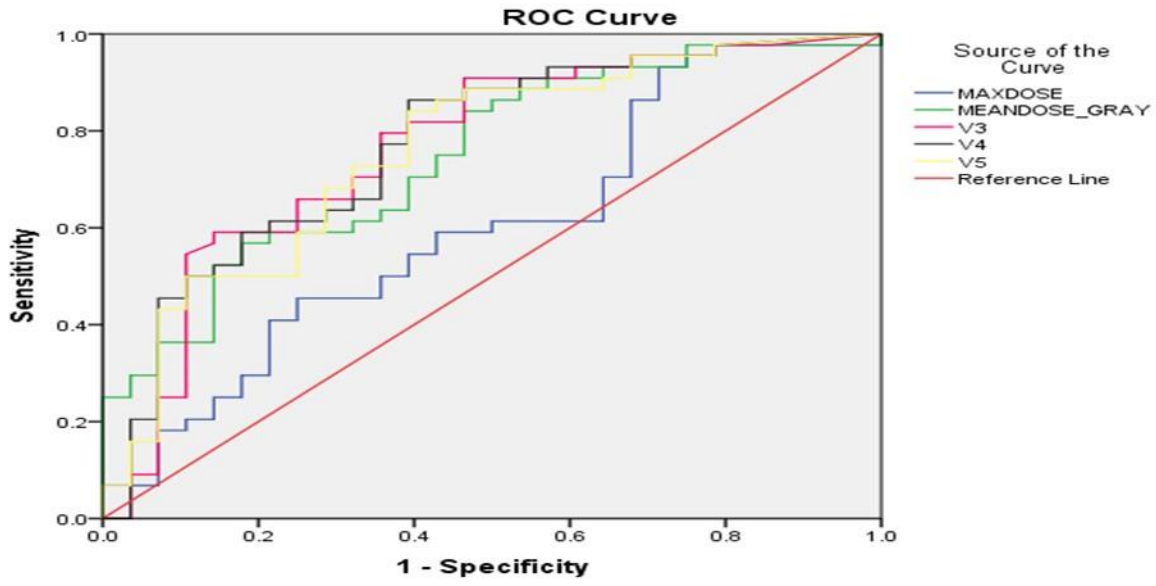

Figure-1 Receiver Operating Characteristics [ROC] of Dosimetric Parameters V3, V4, V5, Mean Dose, Maximum Dose

These dosimetric parameters [V3, V4, V5, Mean dose, Maximum dose] whose association with appearance of acute PE toxicity were found to be statistically significant by binary logistic regression have

been further analyzed using Receiver's Operating Characteristics [ROC] curve[Figure-1].The curve representing maximum dose received by oesophagous has dented beyond the diagonal having area under curve of 0.601 with asymptotic p value of 0.149[Table-4]. These parameters suggest that maximum dose received by oesophagous is not an ideal predictor of observed acute PE toxicity. From the ROC curve analysis cut-off value for relevant dosimetric parameters [mean,V3,V4,V5oesophagous]were obtained[table-5] and plotted[figure-1].It was observed that at mean dose oesophagous of 8.8Gy the chance of acute PE toxicity came 57% with chance of false positivity 18%.By keeping the cut-off value of V3 at around 27% the sensitivity of predicting acute PE toxicity is 59% with chance of false positivity 14%.When sensitivity of prediction increased chance of false positivity too increased[Figure-2] as evidenced by V4 and V5 cut-off values. Limiting the false positive value at 39%, V4oesophagous was more sensitive in predicting acute PE toxicity [86.4% at cut-off 20.3%] than V5oesophagous [84.1% at cut-off 19.5%].

Parameters	Cut-off Value	Sensitivity	False Positive
Mean dose [Gy]	8.8	57	18
V3	27.1	59.1	14
V4	20.3	86.4	39.3
V5	19.5	84.1	39.3

Table-5 Dosimetric parameters oesophagous with cut-off value for acute Pharyngo-oesophagitis

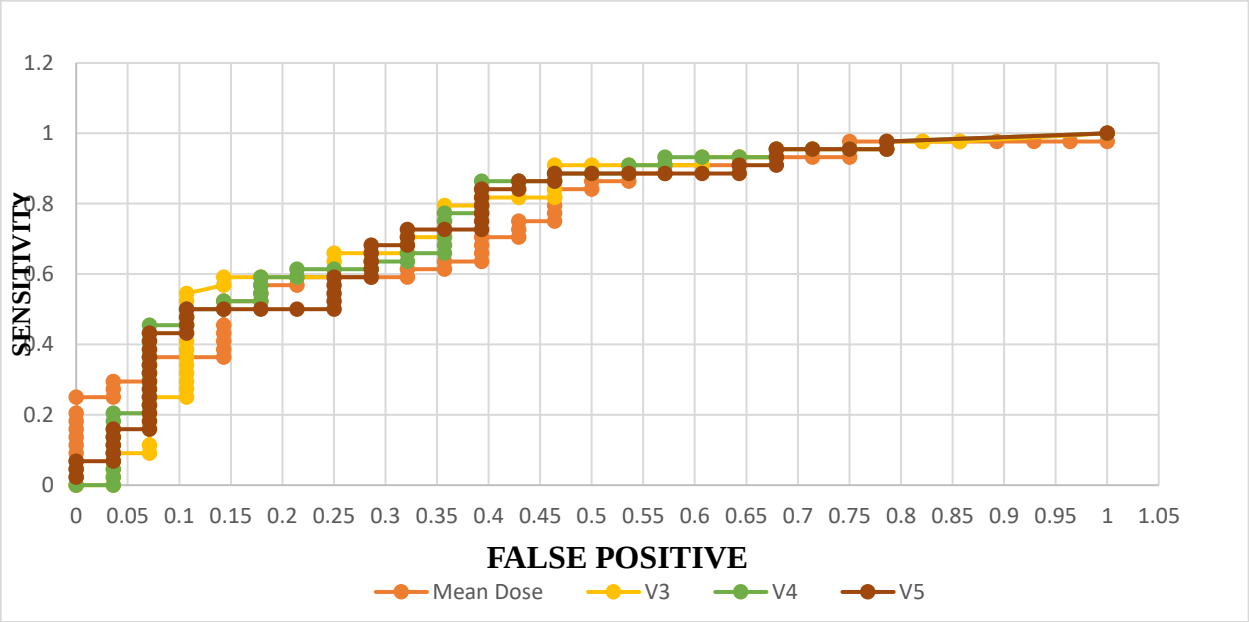

Figure-2 Plot of sensitivity of Mean dose, V3, V4, V5 as predictor of acute PE toxicity against false positive

Discussion

Acute pharyngo-oesophagitis occurs during the course of irradiation of thoracic/chestwall target volumes notably in the management of lung, breast malignancies and mediastinal lymphoma due to unavoidable irradiation of adjacent structure particularly oesophagous. True incidence of acute PE toxicity due to irradiation of chestwall/breast with or without inclusion of axilla, IMC, SCF in treatment portals as part of adjuvant radiotherapy in breast cancer is less known. However it's not unusual to meet patient complaining of acute onset throat discomfort/difficulty in swallowing during the course of EBRT and the incidence is not uncommon contrary to certain reports (13). Radiation induced damage to mucosal cells incite pro-inflammatory mediators concentration in local milieu compounding inflammatory damages predisposing epithelial cells to death leading to mucosal ulcerations. Clinical symptoms of throat discomfort, difficulty in swallowing follows mucosal ulceration which improves when mucosa heals and worsens if mucosal healing is delayed. Ionizing radiation beam energy, characteristics of dose deposition, different doses received by different volumes of oesophagous, oesophageal movement are the physical and anatomical factors that influence occurrence and severity of acute PE toxicity during breast/chestwall irradiation. According to researches single nucleotide polymorphism [SNP] of transformation growth

factor beta[TGF-ß] is one of the genetical reason behind severe radiation induced oesophagitis (14,15).The diagnosis of radiation induced acute pharyngo-oesophageal toxicity is predominantly done by clinical symptoms and from history. RTOG/EORTC takes in to account the features such as dysphagia, odynophagia, need for topical anaesthetic, soft diet etc to assign grade to acute pharyngo-oesophagitis during and up to 3 months post start of radiotherapy. While grade1 and 2 acute PE toxicities are largely innocuous and improve with dietary changes and minimal symptomatic care, toxicities of higher-grade demand interruption of radiotherapy, naso-gastric tube feeding and sometimes intervention too if complete obstruction, perforation or fistula occurs.

Definitive management of breast cancer in the institute includes surgery, adjuvant EBRT, systemic therapy in the form of chemotherapy, anti-HER2neu agent, hormonal therapy in appropriate sequence as per standard guidelines and institutional protocol. In accordance to departmental consensus adjuvant EBRT in breast cancer is approved when the tumor stage is T3 or higher[as per Tumor Node Metastasis (TNM) staging 2018] ,clinical presence of involved loco-regional lymph node in patient who has undergone neoadjuvant chemotherapy regardless of post chemotherapy lymphnodal pathological status, histopathologically involved lymphnode [even if one lymph node is positive], resection margin is positive[without scope of re-excision] or when breast conservation surgery has taken place. Irradiation of chestwall/breast with inclusion of axillary lymphnode level III and SCF lymphnode area is conducted in all patients in alignment with principle of comprehensive radiotherapy for breast cancer.

In the chosen study cohort of 72 breast cancer patients who received adjuvant EBRT to chestwall/breast, ipsilateral level-III axilla and SCF lymphnodal area by 3-D CRT using photon beam of energy 6MV and/or 10MV; the incidence of acute PE toxicity of any grade was 61 percent. Grade-1 PE toxicity occurred in 51% patients while grade-2 PE toxicity was noted in approximate 10% of patients. Toxicity of interest higher than grade-2 was not observed in any of the patients. Highest grade of acute PE toxicity in respective subjects occurred between 2nd to 4th week of irradiation with peak frequency in 3rd week [36%]. In literature the reported incidence of grade-3 or higher acute PE toxicity during EBRT[±chemotherapy] of thoracic primary has been found at a frequency of 8-12 percent (16,17) which is at par with the observed frequency of grade 2 toxicity in this cohort. According to a retrospective analysis of 623 Non-Small Cell Lung Cancer [NSCLC] patients from MD Andersen Cancer Center [MDACC] who received 3-DCRT and concurrent chemotherapy the acute PE toxicity reached maximum grade in 3rd week and in that aspect our finding is coherent (18).

Tumor laterality, histopathology, hormone/HER2 neu receptor status, type of surgery, chemotherapy, use of anthracycline/taxane, or position of neck were not significantly related to occurrence of acute PE toxicity by chi-square evaluation. Quantitative variables such as age, total dose, duration of treatment, volume of oesophagous were not found to be associated with occurrence of acute PE toxicity either. On binary logistic regression analysis five chosen dosimetric parameters namely the maximum as well as mean dose received by oesophagous, V3/V4/V5 oesohagous were found to have statistically significant association [Table 4] with appearance of acute PE toxicity. Receiver Operating Characteristics[ROC] analysis was performed next to identify the cut-off value at which individual dosimetric parameter can be predictive about appearance of acute PE toxicity. The ROC of maximum dose to oesophagous not only ingressed into and beyond the diagonal but also had least area under curve and p value of 0.149. Hence it's scope of being a significant predictor of acute PE toxicity was questionable. The remaining four dosimetric parameters Mean dose to oesophagous,V5,V3,V4 oesophagous were found to have asymptotic significance value<0.05 and AUC value in increasing order. It was found that keeping the cut-off value of mean dose at approximate 9 Gy the chance of truly predicting appearance of acute PE toxicity during the course of loco-regional EBRT will be 57%. Similarly using V3 cut-off value of 27%; the correct chance of predicting acute PE toxicity will be nearly 60%. Between V4 and V5 since both the curves almost overlapped each other the cut-off value were found to be pretty similar with nearly same sensitivity in identifying the chance of toxicity. Keeping the V5 oesophagous at 19.5% the sensitivity of identifying acute PE toxicity was 84%[false positive 39.3%] whereas by keeping the value of V4 at nearly 20% the sensitivity of predicting acute PE toxicity was 86%[false positive 39.3%].V4 turns out to be slightly better predictor of acute PE toxicity as compared to V5 since for the same value of false positive prediction it had better sensitivity. The retrospective experience from MDACC identified relative V20 to be significantly associated with occurrence of grade-3 oesophagitis in multivariate analysis of NSCLC cohort17.But in our study after analyzing dose bins at an increment of 5Gy from V5 to V40 only the lowest dose bin i.e V5 and further lower dose bins were found to be significantly associated with acute PE toxicity up to grade 2. It has been evident from a study that analyzed 414 breast cancer patients who received adjuvant loco-regional EBRT; dose to oesophagous was contributed maximum from field treating SCF/Internal Mammary Chain[IMC] (19).Since almost all the patients in our study cohort received SCF area irradiation hence this study suggests the frequency ,grade and appearance of acute pharyngo-oesophagitis during adjuvant loco-regional irradiation of breast cancer. All of the experienced acute PE toxicities were managed with appropriate symptomatic care such as soft diet, luke warm water

intake, frequent gurgling with lukewarm water to which the patients responded favorably. None of the patient needed interruption of treatment to recuperate from this toxicity.

Strength of this study is the selection of cohort who have undergone adjuvant comprehensive irradiation of chestwall/breast,axilla level III,SCF using uniform technique, total dose, dose per fraction, beam energies, TPS and linear accelerator.The probable fallacies of this study includes assignment of acute PE toxicity depending upon the subjective symptoms which might happen due to pharyngo-oesophageal infection, pre-existing gastro-oesophageal reflux and incidental irradiation of stomach (20). Being retrospective in nature the study inherently is incapable of eliminating the confounding factors such as described above. Study design with higher number of patients could further clarify and quantify the observations.

Conclusion

Acute pharyngo-oesophageal toxicity is not an uncommon toxicity encountered during adjuvant irradiation of chestwall/breast/axilla/SCF as part of definite breast cancer management. The toxicity is mostly of low grade when 3-DCRT technique is employed and can be well managed with supportive advices without interruption of treatment. Dosimetric parameters such as mean dose to oesophagous, V3/V4/V5 oesophagous are well suited to predict chance of this toxicity while undergoing radiotherapy. These criteria can prove to be useful in anticipating this less described toxicity for better information of treating radiation oncologist as well as appropriate counseling of patient. Dose limit criteria derived from this study can act as founding stone for further research in this context.

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