Original Article

Prediction Factors of Radiation Esophagitis in Breast Cancer Patients Undergoing Supraclavicular Radiotherapy

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Abstract

Purpose: The aim of this study was to investigate demographic and dosimetric parameters which may link with esophagitis in patients with breast cancer receiving three-dimensional conformal radiotherapy to the supraclavicular fossa. **Materials and Methods:** We examined 27 breast cancer patients with supraclavicular metastases. All patients were treated with radiotherapy (RT) with a prescribed dose of 40.5 Gy in 15 fractions for 3 weeks. Esophagitis was recorded weekly and esophagus toxicity was evaluated and graded according to the tadiation therapy oncology group. The following factors were examined regarding their correlation with grade 1 or worse esophagitis by univariate and multivariate analyses: age, chemotherapy, smoking history, maximum dose (D_{max}), mean dose (D_{mean}), esophagus volume receiving 10 Gy (V10), esophagus volume receiving 20 Gy (V20), and length of esophagus in the treatment field. **Results:** Of 27, 11 (40.7%) patients developed no esophageal irritation throughout therapy. Approximately half of the patients 13/27 (48.1%) had maximum grade 1 esophagitis. 2/27 (7.4%) patients had grade 2 esophagitis. The incidence of grade 3 esophagitis was (3.7%). D_{mean}, D_{max}, V10, and V20 were 10.48 ± 5.10 Gy, 38.18 ± 5.12Gy, 29.83 ± 15.16, and 19.32 ± 10.01, respectively. Our results showed that D_{mean}, V10, and V20 were the significant factors for the development of esophagitis, whereas esophagitis was not significantly associated with the chemotherapy regimen, age, and smoking status. **Conclusions:** We found that D_{mean}, V10, and V20 correlated significantly with acute esophagitis. However, the chemotherapy regimen, age, and smoking status did not affect esophagitis development.

Keywords: Breast cancer, dosimetric parameters, esophagitis, radiotherapy

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Introduction

Radiotherapy (RT) is essential in the overall management of breast cancer patients, from early-stage disease toward locally advanced and metastatic cases. Moreover, RT to the lymph nodal area in node-positive women with breast cancer results in a reduction in overall mortality and breast cancer recurrence.[1] However, RT to supraclavicular fossa (SCF) nodal is suspected to result in esophagitis.[2] The esophagus is near the SCF node, mainly on the left side of the cervical spine and anatomically divided into three parts: cervical, thoracic, and abdominal, and it begins at the lower border of the cricoid cartilage. The general orientation of the esophagus is vertical, but there are two small bends in the esophagus. It is initially located at the midline, then tilts to the left to the root of the neck, then gradually returns to the midline at the level of the 5th thoracic vertebrae, eventually deflecting to the left. It moves forward with a rupture of the esophagus of the diaphragm and gastric joint.[3] Therefore, radiotherapy to the supraclavicular lymph nodes might expose a substantial part of the esophagus to radiation. This could result in an increase in acute radiation esophagitis (RE).

Patients with esophagitis are often assessed based on their clinical symptoms, such as dysphagia, odynophagia, chest pain, or any combination of these. In extremely rare situations, patients may develop acute or subacute esophageal bleeding or perforation which can negatively impact patient's quality of life.[4]

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Esophagitis has been more extensively investigated in areas of lung and head-and-neck RT. However, even in these studies, it was not possible to determine the dose at which esophagitis was likely to occur. Overall, studies have reported many dosimetric factors that are accounted for predicting esophagitis, such as mean esophageal dose, maximum esophageal dose, and various doses to esophageal volume.[5-11] Clinical factors have been widely described for lung cancer RT; including chemotherapy and fractionation. Chemotherapy may independently induce esophageal toxicity when it is used concurrently with radiotherapy.[6] In addition, hypofractionated radiotherapy regimen can result in increase in the risk of esophageal toxicity for lung cancer.[12]

Very few studies have documented the clinical factors affecting acute esophagitis due to RT to supraclavicular nodes, of the very limited number of studies available, West *et al*. evaluated some factors that associated with the development of acute esophageal toxicity, using conventional fractionation radiotherapy (50 Gy in 25 fractions).[2]

The purpose of this study was to investigate dosimetric parameters that linked with esophagitis in patients with breast cancer receiving three-dimensional conformal radiotherapy (3D-CRT) to the SCF, using with hypofractionated (total dose of 40.5 Gy in 15 fractions over 3 weeks), attempting to investigate whether factors such as age, chemotherapy, radiotherapy regimen, and smoking history, contributed to the development of esophagitis.

Materials and Methods

Patient selection

We prospectively observed breast cancer patients treated with radiotherapy at the Zhianaw Cancer Center from November 2021 to May 2022. Patients eligible for this study included those: willingness to participate in the study, age >18 years, and breast cancer patients who needed radiotherapy to the supraclavicular region, RT dose 40.5 Gy in 15 fractions over 3 weeks, and completed questionnaire of RE. Cases with only chest wall were excluded from the study. Finally, 27 patients were eligible.

Follow-up and toxicity evaluation

Patients were evaluated weekly during radiotherapy, and the assessment of esophagitis was recorded on the 1st day of admission to the center before receiving radiotherapy, at the end of the 1st-week radiotherapy treatment, and at the end of the 2nd and 3rd week radiotherapy, and 1 week after radiotherapy with each follow-up, taking history and physical examination were performed. Radiation-induced acute esophagus toxicity was evaluated and graded according to the radiotherapy oncology group. The severity was graded on a scale of 0–3, with 0 representing no effect and 3 being the worst possible outcome [Table 1]. The clinical parameters studied in the univariate analysis included patient age, smoking status, and use of chemotherapy.

Table 1: Criteria for acute esophagitis according to the radiotherapy oncology group

Grade	Description
0	No dysphagia or odynophagia observed
1	Mild dysphagia or odynophagia. Normal diet
2	Moderate dysphagia or odynophagia; change diet
3	Severe dysphagia or odynophagia change totally, require feeding tube, IV fluids

IV: Intravenous

Radiotherapy

All patients were treated with RT. Radiation was delivered using 3D-CRT, with prescribed doses of 40.5 Gy in 15 fractions, for 3 weeks. All 3D-CRT plans were delivered using 6MV or 10 MV photon beams to the chest wall and 6MV or 10 MV to SCF generated by the Elekta Synergy® linac (Elekta Ltd, Crawley, United Kingdom). Planning was completed using the CMS XIO. We contoured the esophagus from the caudal edge of the cricoid cartilage. Dose-volume histograms were generated to assess the dose received by the organs at risk. As the patients in this study were treated with hypofractionation (2.7 Gy/fraction), the biologically equivalent dose in 2 Gy per fraction for D_{max} and D_{mean} was generated to compare the results to the published studies.

Ethics approval

Ethical approval was obtained by the local ethics committee (College of Health and Medical Technology). All patients provided oral informed permission for study participation.

Statistical analysis

Basic descriptive variables are used to present the patient characteristics. Data were statistically analyzed using Statistical Package for Social Sciences stands for (SPSS). Version 21. P <0.05 were considered significant. The correlation between mean dose, V10, and V20 associated with the risk of grade 1 or greater esophagitis was found through logistic regression analysis and adjusted for the maximum dose, administration of chemotherapy, age, smoking status, and treatment sites.

Results

Patient characteristics and dosemetric data

A total of 27 patients were evaluated. The enrolled patients vary in age from 40 to 69 years. All 27/27 (100%) received chemotherapy before RT either (4 cycles of Adriamycin and cyclophosphamide (AC) or 4 cycles of AC followed by 4 cycles of Taxol) depending on the stages of disease. Only 2/27 (5%) are ex-smoker. Five (16.7%) had diabetes mellites, clinical features, and demographic data are shown in Table 2. The transverse slice showing the isodose lines crossing esophagus with treatment fields overlaid for a patient with left breast cancer is shown in Figure 1a. The same slice for a patient with right breast cancer is shown in Figure 1b.

The D_{mean} and D_{max} of the esophagus were 10.48 ± 5.10 Gy and 38.18 ± 5.12 Gy, respectively, and the length of esophagus

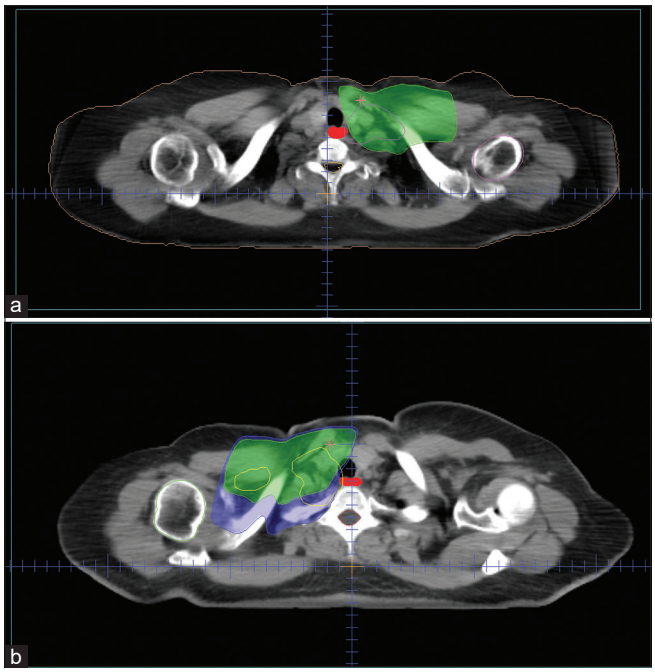

Figure 1: (a) The transverse slice showing the isodose lines crossing esophagus with treatment fields overlaid for a patient with left breast cancer. It can be seen that the esophagus is in red color and isodose line in (green color) is 38.04 Gy. Prescription dose was 40.5 Gy in 15 fractions. (b) The transverse slice showing the isodose lines crossing esophagus with treatment fields overlaid for a patient with right breast cancer. It can be seen that the esophagus is in red color and isodose line in (green color) is 38.04 Gy and in (blue color) is 36.04Gy. Prescription dose was 40.5 Gy in 15 fractions

inside the field (cm) was 3.56 ± 1.39 cm [Table 3]. D_{mean} and D_{max} were 14.14 ± 2.70 Gy and 39.21 ± 3.11 Gy, respectively, when the tumor was on the left side. However, the D_{mean} on right-sided breast cancer was 8.70 ± 3.05 and the D_{max} was 36.13 ± 5.19 [Table 4]. In addition, the volume of esophagus that received a dose 10 and 20 Gy were 29.83 ± 15.16 and 19.32 ± 10.01, respecetively. V_{10} and V_{20} of esophagus were higher in patients with left breast cancer with $P < 0.05$. V10 for right-sided breast cancer and left-sided breast cancer was 20.42 ± 5.02 and 44.57 ± 8.32, respectively. V20 was 13.72 ± 5.05 and 28.08 ± 5.36 for right-sided and left-sided breast cancer, respectively.

As detailed in Figure 2, 11 (40.7%) patients developed no esophageal irritation throughout therapy. Approximately half of the patients 13 (48.1%) had maximum grade 1 esophagitis. Two (7.4%) patients had grade 2 esophagitis. The incidence of grade 3 esophagitis was (3.7%).

Grade 1 toxicity was developed within 1st week of treatment, whereas grade 2 and 3 were presented and peaked in the 2nd and 3rd week of radiotherapy, respectively. Grade 2 reached maximum in the 2nd week of treatment, whereas grade 3 was maximum in the 3rd week of treatment. However, both grade 2 and 3 toxicity were completely disappeared 1 week after treatment ended, are shown in Figure 3.

Table 2: Patient characteristics

Variable	Content	*n* (%)
Age	Mean (minimum–maximum)	49 (40-69)
Laterality of treatment area	Right	12 (44.4)
	Left	15 (55.5)
Marital status	Single	22 (83.3)
	Married	5 (16.7)
	Divorced/widowed	0
Family history of cancer	Yes	8 (27.8)
	No	19 (72.2)
Patient history of cancer	Yes	5 (16.7)
	No	22 (83.3)
administration of Chemotherapy	Yes, prior to radiotherapy	27 (100.0)
	Yes, with radiotherapy	0
	No	0
Smoking status	Yes	0
	Yes, years/months ago	2 (5.6)
	No	25 (94.4)
Exercises	Daily	2 (5.6)
	Sometimes	10 (38.9)
	Never	15 (55.6)
History of diseases	Cerebrovascular disease	0
	coronary disease	0
	Diabetes mellitus	5 (16.7)
	hypertension	0
	Others	18 (66.7)
Stage of disease	Stage II	15 (55.6)
	Stage III	12 (44.4)

Table 3: Dosimetric parameters; mean dose (D_{mean}) Gy, maximum dose (D_{max}) Gy, volume receive a dose of 10 Gy (V_{10}), volume receive a dose of 20 Gy (V_{20}) and length of esophagus

Variable	Mean±SD	95% CI	Minimum-maximum
Mean dose (D_{mean}) Gy	10.48±5.10	7.99-13.02	4.36-24.03
Maximum dose (D_{max}) Gy	38.18±5.12	33.93-39.51	22.73-44.07
Volume receive a dose of 10 Gy (V_{10})	29.83±15.16	21.84-37.88	10.33-60.80
Volume receive a dose of 20 Gy (V_{20})	19.32±10.01	14.42-24.47	4.71-35.72
Length of esophagus inside the field (cm)	3.56±1.39	2.86-4.25	1.5-7.0

CI: Confidence interval, SD: Standard deviation

Esophagitis analysis

Among the dosimetric values investigated, the maximum esophagus dose, mean dose, the volumes received a dose of 10 and 20 Gy and the length esophagus in the treatment field. All dosemetric parameters associated with the risk of grade 1 or greater esophagitis through logistic regression analysis as shown in Table 5. However, we found that esophagitis was not significantly associated with the administration of chemotherapy, age, and smoking status. The mean dose to the esophagus of ≥11.5 Gy was linked to an increased rate

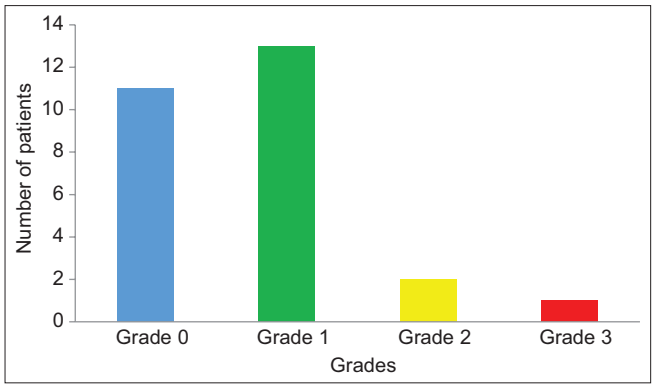

Figure 2: Esophagitis in breast cancer patients starting from grade 0 to grade 3

Table 4: Dosimetric parameters; mean dose (D_{mean}) Gy, maximum dose (D_{max}) Gy, volume receive a dose of 10 Gy (V_{10}) and volume receive a dose of 20 Gy (V_{20}) among patients according to laterality of breast treated

	Laterality of breast treated	Mean±SD	95% CI	*P*
Mean dose (D_{mean}) Gy	Left	14.14±2.70	10.81-17.99	0.07
	Right	8.70±3.05	6.54-10.90	
Maximum dose (D_{max}) Gy	Left	39.21±3.11	36.12-40.83	0.25
	Right	36.13±5.19	31.10-40.10	
Volume receive a dose of 10 Gy (V_{10})	Left	44.57±8.32	32.52-57.47	0.027
	Right	20.42±5.02	14.92-27.87	
Volume receive a dose of 20 Gy (V_{20})	Left	28.08±5.36	20.36-36.63	0.034
	Right	13.72±5.05	9.54-18.25	

CI: Confidence interval, SD: Standard deviation

Table 5: The mean dose and laterality of breast treated in relation with frequency of grade 1 and grade 2 esophagitis

	Grade		Total	*P*
	≤1	≥2		
Mean dose (Gy), *n* (%)				
<11.5	11 (45.8)	0	15 (55.5)	0.048
≥11.5	13 (54.2)	3 (100.0)	12 (44.4)	
Laterality of breast treated, *n* (%)				
Left	14 (58.3)	2 (66.6)	16 (59.2)	0.055
Right	10 (41.1)	1 (33.3)	11 (40.7)	

of grade 1 and grade 2; 13/24 (54.2)%) ≥11.5 Gy versus 11/24 (45.8) <11.5 Gy for grade ≤1, and 3/3 (100%) ≥11.5 Gy versus 0/3 (0.00%) <11.5 Gy for grade ≥2, (P = 0.023).

In comparing the laterally of treatment, the study showed occurring a higher rate of grade ≥1 esophagitis on the left side of treatment 14/24 (58.3%) versus 10/24 (41.1%) on the right side. Similarly, the incidence of grade ≥2 esophagitis was higher in patients with left-sided breast cancer 2/3 (66.6%) versus 1/3 (33.3%) for the right side, (P = 0.055) [Table 5].

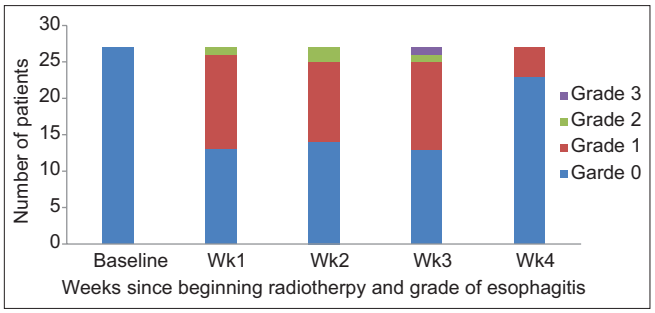

Figure 3: Esophagitis based on the number weeks spent on treatment. Week 1-week 3 indicates treatment period. Week 4 indicates post treatment-period

Discussion

While few studies have focused on the topic of RE in breast cancer patients, radiation-induced esophagitis has been discussed in many lung cancer studies. Previous lung cancer studies have indicated that dosemetric parameters are predictors of acute esophageal toxicity.[6,13,14] Similarly, the present study showed that dosemetric parameteres were associated with the development of esophagitis.

On the other hand, our results showed that a mean dose to esophagus was the most significant factor for the development of esophagitis. Similarly, previous breast cancer studies reported on dosimetric parameters predictive of grade 1 or worse esophagitis. Among them, West *et al*. reported 24 (31%) patients with grade 2 esophagitis and 53 (69%) patients with grade 1 esophageal toxicity in a population of 77 patients. This study reported a mean dose is a predictive of grade 2 RE and it was 32.87 (±7.4) while prescribing 50 Gy, Of 2 Gy per fraction.[2] The mean dose was higher than what has been reported by,[15] they reported esophageal mean dose, V10, and V20 were 11 Gy, 30%, and 15%; respectively, and 16.2% of patients had grade 2 esophagitis. Our study confirms the conclusions of the above study by that they presented an association between mean dose, V10, and V20 with RE. In our study, the majority of patients (48.1%) experienced grade 1 esophagitis, 7.4% developed grade 2, with only one patient had grade 3. These results are higher than those previously published study by Wang *et al*., which showed that acute toxicity grade 1 occurred in 18 (9%) and grade 2 in 3 (1.5%) of 200 patients and D_{mean} of the esophagus was 10.65 ± 2.43 Gy.[16] Grade 2 esophagitis in our study was less than in the previous studies.[2,15] This may have been because our prescription dose was lower than those in other studies, and the difference in the radiation delivery method (3D-CRT versus IMRT).

The incidence of grade 1 was maximum after the 1st week of RT which corresponds to nearly 14 Gy. Grade 2 esophagitis was most commonly observed after week 2 of RT or (10 fractions). These findings are consistent with previous studies in the lung

cancer RE often peaks in the 1st few weeks of a course of radiotherapy.[17] Almost all grades of acute esophagitis resolved within 1–2 weeks' posttreatment completion.

Most previous authors have noted that a combination of chemotherapy and radiotherapy results in more severe esophagitis that induced by RT alone.[4,18,19] We found no significant correlations between esophagitis and chemotherapy, most possibly because all patients in the present study had chemotherapy before RT. As a result, it was not possible to report on the association between chemotherapy and esophagitis in the current study.

The incidence of grade 2 esophagitis 11/20 (55%) was higher in left-sided breast cancer patients than the right-sided 9/20 (45%). This could be explained by that the location of esophagus very close to the SCF PTV on the left side. This could result in more dose received to the esophagus compared to the right side, this was in accordance with the result of a study carried out by Bhaskaran *et al*., which reported that the dose delivered to esophagus is higher in the left-sided breast cancer.[20]

This study also had some limitations and was restricted to women who had undergone chemotherapy before RT since the RT with chemotherapy result in increased esophagitis.[4] Although esophagitis data were recorded prospectively, they are not accurately determined due to patients' recollection bias on their onset of esophagitis and subsequently may lack some details. Furthermore, a greater number of patients can allow to provide more accurate data.

Conclusions

In this analysis of the various demographic and dosimetric parameters, we found that D_{mean}, V10, and V20 significantly correlated with grade 1 or worse esophagitis. However, we did not find associated with the chemotherapy regimen, age, and smoking status. Investigation of additional clinical, biologic, or other factors could further improve prediction, possibly resulting in reduced toxicity which may improve the quality of life for women undergoing RT for breast cancer.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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