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RESEARCH

Hemoglobin patterns and anemia in forward-planned intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy among patients with breast cancer

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ABSTRACT

Background. Radiotherapy (RT) to the chest or other large areas of the body may cause bone marrow suppression, resulting in anemia and other changes in blood cell counts.

Objective. To compare the post-RT hemoglobin levels between patients who underwent forward- planned intensity-modulated radiotherapy (FPIMRT) and those who underwent three-dimensional conformal radiotherapy (3D-CRT).

Design. Retrospective cohort study.

Setting. Department of Radiological and Imaging Sciences, Southern Philippines Medical Center, Davao City, from October 2018 to March 2019.

Participants. 94 women with invasive ductal carcinoma, aged 29 to 75 years, who received at least 28 fractions (with or without boost dose) of either 3D-CRT or FPIMRT.

Main outcome measures. Mean hemoglobin counts and anemia within 4 weeks post-RT.

Main results. Of the 94 women, 62 (65.96%) underwent 3D-CRT, and 32 (34.04%) underwent FPIMRT. The proportion of patients with left-sided tumors was significantly higher in the FPIMRT group than in the 3D-CRT group. The baseline hemoglobin levels (12.60 ± 1.04 g/dL for 3D-CRT vs 12.49 ± 0.80 g/dL for FPIMRT; p=0.5994) and the mean changes in hemoglobin count from baseline (-0.11 ± 0.72 g/dL for 3D-CRT vs -0.18 ± 0.67 g/dL for FPIMRT; p=0.6707) were both comparable between the two groups. The proportions of patients with anemia within four weeks post-RT were also comparable between the two groups (13/62, 20.97% for 3D-CRT vs 8/32, 25.00% for FPIMRT; p=0.6565). Left-sided tumors were significantly associated with post-RT anemia (unadjusted OR 2.87; 95% CI 1.00 to 8.22; p=0.0498), even after controlling for type of RT technique (adjusted OR 3.15; 95% CI 1.01 to 9.87; p=0.0484).

Conclusion. After RT, the mean hemoglobin levels of patients with breast cancer who underwent 3D-CRT were comparable with those of patients who underwent IMRT. The type of RT technique was not significantly associated with the occurrence of post-RT anemia in these patients.

Keywords. post-mastectomy radiation therapy, invasive ductal carcinoma, anemia, hematological effects

INTRODUCTION

Radiation therapy (RT) to the pelvis, legs, chest, or abdomen can damage the bone marrow.[1] In adults, the greatest amount of active marrow is located in the spine (36%)—18% of which is found in the thoracic region—followed by the pelvis (23%), and ribs/scapulae/clavicles (15%).[2] Bone marrow suppression, which is a dose-limiting side effect of RT,[3] is characterized by acute and chronic changes in blood cell counts—i.e., decrease in hemoglobin, erythrocytes, leukocytes, and platelets, and increase in lymphocytes.[4] Anemia has been significantly associated with an increased risk of locoregional cancer recurrence and poor survival in patients undergoing adjuvant RT.[5]

In the past few decades, advanced RT techniques, such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), two types of external beam radiation therapy (EBRT),

IN ESSENCE

Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) are two types of external beam radiation therapy that are used to treat breast cancer.

In this retrospective cohort study among patients with breast cancer, the post-RT weekly mean hemoglobin levels of patients who underwent 3D-CRT were comparable with those of patients who underwent IMRT. The proportions of patients who had anemia within four weeks post-RT were also comparable between the two groups.

Left-sided breast cancer significantly increased the odds of having anemia post-RT.

are used to treat breast cancer. 3D-CRT uses multiple radiation fields to deliver radiation to the breast, but oftentimes may include the lymph nodes in irradiation. IMRT, on the other hand, is a form of high-precision 3D-CRT that further modifies the radiation beam by modulating the radiation beam intensity into multiple beamlets. This allows uniformity of dose delivery and reduces acute and late toxicities to nearby organs.[6,7] In patients with breast cancer, IMRT has been shown to improve treatment results, since it allows higher doses of radiation to be delivered, while sparing the surrounding healthy tissues.[7] Patients with anal canal carcinoma and prostate and bladder carcinoma who received IMRT had lesser decrease in hematologic indices compared to those who received 3D-CRT.[8,9] 3D-CRT, however, is less labor-intensive and time-consuming to administer than IMRT,[10] and in our institution, it costs less than IMRT.[11]

Dosimetry studies and comparative studies on radiation-induced adverse effects of 3D-CRT and IMRT have been extensively discussed in literature, but the hematological effects—particularly on hemoglobin levels—of these two types of radiation therapy in patients with breast cancer, have not been well-documented. We did this study to compare the post-RT hemoglobin levels of patients who underwent forward-planned IMRT (FPIMRT) with those who underwent 3D-CRT.

METHODOLOGY

Setting

We did a retrospective cohort study among patients who had undergone EBRT at the Radiation Oncology Section of the Department of Radiological and Imaging Sciences of Southern Philippines Medical Center from October 2018 to March 2019. This section caters to an average of 180 new patients with breast cancer annually. In this section, the standard RT protocol for patients with breast cancer consists of a total RT dose of 6,040 cGy in 33 fractions (28 fractions of conventional dose of 5,040 cGy and additional 5 fractions of 1,000 cGy boost dose to the tumor bed). All dose fractions are given daily for 33 consecutive days, excluding weekends and holidays.

Participants

All patients with biopsy-proven invasive ductal carcinoma, presenting with solitary lesions, who had undergone a full course of RT of at least 28 fractions (with or without the boost dose) of EBRT (3D-CRT or FPIMRT), and with hemoglobin count of ≥10 g/dL, the lower limit of the acceptable baseline hemoglobin levels (or grade 1 anemia)[12] prior to radiation therapy, were eligible to participate in the study. We excluded patients with known blood dyscrasias, with distant metastases, and those with breast tumor recurrence, with or without metastatic disease. FPIMRT is defined in this study as a field-in-field radiotherapy technique that uses multileaf collimators (MLC) to reduce the radiation dose absorbed by tissues outside the irradiated target organ and improve dose homogeneity within the tumor volume. The weight of the MLC segment is preselected at fixed values.[13]

To determine the minimum sample size for this study, we assumed that the proportion of patients who had anemia during RT was 44.4%.[14] Calculation was done in order for the study to detect a 30% difference in proportion of patients who had anemia between two groups of patients receiving different RT procedures as statistically significant. In a test for comparison between two independent proportions carried out at 95% level of confidence, a sample size of at least 33 patients per group will have 80% power to reject the null hypothesis if the alternative holds.

Data collection

From the patients' medical records, we collected data on age, diagnosis, tumor laterality, stage of breast cancer [early stage for tumor-node-metastasis (TNM) stage I or II; late stage for TNM stage III], number of chemotherapy cycles, surgical procedure (modified radical mastectomy) for breast cancer, hematocrit, baseline hemoglobin count taken within two weeks prior to start of RT, and post-RT hemoglobin counts taken weekly for four weeks after the full course of RT.

From the records, we also classified the patients into either of the two exposure groups—those treated with 3D-CRT and those treated with FPIMRT—and collected the number of RT fractions per patient.

The main outcome measures for this study were mean hemoglobin count, presence of anemia (hemoglobin count <11.5g/dL), and mean change in hemoglobin count from baseline (hemoglobin count on the fourth week post-RT minus baseline hemoglobin count). For each patient, we computed the change in hemoglobin count by subtracting the hemoglobin count at baseline from that at week 4 post-RT.

Statistical analysis

We summarized continuous variables as means and standard deviations, and compared means using t-test. We summarized categorical variables as frequencies and percentages, and compared proportions using the chi-square test or Fisher's exact test. We also performed univariate logistic regression to determine the unadjusted and adjusted associations of the type of RT technique and tumor laterality with the occurrence of anemia. We expressed associations of the variables as odds ratios (OR) and their 95% confidence intervals. We used Epi Info™ 7.2.2.6 for all our statistical tests.

RESULTS

A total of 94 participants, 62 (65.96%) in the 3D-CRT group and 32 (34.04%) in the for FPIMRT group, were included in the analysis of this study. The baseline and clinical characteristics of patients in the two exposure groups are shown in Table 1. For the 3D-CRT group, 39/62 (62.90%) patients had right-sided tumor and 23/62 (37.10%) had left-sided tumor, while for the FPIMRT group, 6/32 (18.75%) had right-sided tumor, and 26/32 (81.25%) left-sided tumor, and the distribution difference of tumor laterality between the two groups was statistically significant ($p<0.0001$). Other demographic and clinical characteristics were comparable between the two groups at baseline.

Table 2 shows the comparison of mean hemoglobin counts and proportions of patients with anemia at baseline (pre-RT) and weekly for four weeks after the full course of RT, and the mean changes in hemoglobin count between patients treated with 3D-CRT and those treated with FPIMRT. The two exposure groups were comparable in terms of baseline and post-RT mean hemoglobin counts and proportions of patients with anemia. The rest of the outcome measures were also comparable between the two groups.

Table 3 shows the comparative tumor stage distribution between patients with left-sided tumors and those with right-sided tumors. There was no significant difference in tumor stage distribution between patients with left-sided tumors and those with right-sided tumors.

The associations of type of RT technique and tumor laterality with the presence of anemia among patients with breast cancer in this study are shown in

Table 1 Baseline demographic and clinical characteristics

Characteristics	3D-CRT n=62	IMRT n=32	p-value
Mean age ± SD, *years*	52.90 ± 9.61	49.66 ± 10.32	0.1336
Laterality, *frequency (%)*			
Right	39 (62.90)	6 (18.75)	
Left	23 (37.10)	26 (81.25)	
TNM stage of breast cancer, *frequency (%)*			0.7029
IA/B	1 (1.61)	2 (6.25)	
IIA/B	9 (14.52)	6 (18.75)	
IIIA	12 (19.35)	7 (21.88)	
IIIB	28 (45.16)	12 (37.50)	
IIIC	12 (19.35)	5 (15.63)	
Mean number of chemotherapy cycles ± SD	7 ± 1	6 ± 1	0.1872
Modified radical mastectomy, *frequency (%)*	61 (98.39)	32 (100.00)	1.0000†
Mean number of radiotherapy fractions ± SD	33 ± 0	33 ± 0	
Mean baseline hematocrit ± SD	0.37 ± 0.04	0.38 ± 0.07	0.5746

3D-CRT=three-dimensional conformal radiotherapy; IMRT=intensity-modulated radiotherapy; TNM=tumor, node, metastasis
*significant at p<0.05
†Fisher's exact test

Table 2 Comparison of outcomes

Outcomes	3D-CRT n=62	IMRT n=32	p-value
Mean hemoglobin count ± SD, x10 g/dL			
Baseline (pre-RT)	12.60 ± 1.04	12.49 ± 0.80	0.5994
Week 1 post-RT	12.50 ± 1.07	12.37 ± 0.99	0.5410
Week 2 post-RT	12.47 ± 1.17	12.28 ± 0.81	0.4291
Week 3 post-RT	12.53 ± 1.13	12.37 ± 1.01	0.5053
Week 4 post-RT	12.50 ± 1.23	12.32 ± 0.87	0.4723
Mean change in hemoglobin count ± SD, x10 g/dL	-0.11 ± 0.72	-0.18 ± 0.67	0.6707
Anemia, *frequency (%)*			
Baseline (pre-RT)	7 (11.29)	3 (9.38)	1.0000*
Week 1 post-RT	8 (12.90)	6 (18.75)	0.4506
Week 2 post-RT	8 (12.90)	3 (9.38)	0.7439*
Week 3 post-RT	8 (12.90)	6 (18.75)	0.4506
Week 4 post-RT	11 (17.74)	5 (15.63)	0.7958
Within four weeks post-RT	13 (20.97)	8 (25.00)	0.6565

*Fisher's exact test

Table 3 Stages of breast cancer according to tumor laterality

TNM stage of breast cancer	Left-sided tumor n=49	Right-sided tumor n=45	p-value
IA/B	1 (2.04)	2 (4.44)	0.6914
IIA/B	6 (12.24)	9 (20.00)	0.6914
IIIA	12 (24.49)	7 (15.56)	0.6914
IIIB	21 (42.86)	19 (42.22)	0.6914
IIIC	9 (18.37)	8 (17.78)	0.6914

TNM=tumor, node, metastasis

Table 4 Logistic regression analysis on the associations of anemia with type of RT technique and tumor laterality

Characteristics	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
3DCRT	0.80 (0.29 to 2.18)	0.6569	1.27 (0.42 to 3.86)	0.6712
Left-sided tumor	2.87 (1.00 to 8.22)	0.0498*	3.15 (1.01 to 9.87)	0.0484*

*significant at p<0.05.

Table 4. 3D-CRT did not significantly increase the odds of anemia within four weeks post-RT (OR 0.80; 95% CI 0.29 to 2.18; p value=0.6569). This odds ratio did not significantly change after controlling for tumor laterality (adjusted OR 1.27; 95% CI 0.42 to 3.86; p value=0.6712). On the other hand, having a left-sided tumor significantly increased the odds ratio of having anemia (OR 2.87; 95% CI 1.00 to 8.22; p=0.0498). When controlled for RT technique, the odds ratio remained significantly high (adjusted OR 3.15; 95% CI 1.01 to 9.87; p=0.0484).

DISCUSSION

Key results

In this study, the post-RT weekly mean hemoglobin levels of patients who underwent 3D-CRT were comparable to those of patients who underwent FPIMRT. The proportions of patients who had anemia within four weeks post-RT were also comparable between the two groups, and the type of RT had no significant association with the occurrence of anemia post-RT. Having left-sided breast cancer significantly increased the odds ratio of having anemia post-RT.

Strengths and limitations

We were able to determine the effects of 3D-CRT and FPIMRT on the post-RT hemoglobin levels of patients with breast cancer. We were also able to establish that 3D-CRT is comparable to FPIMRT in terms of proportions of patients with anemia within four weeks post-RT.

There were some limitations in the study. We did not obtain data on comorbidities—especially the presence of cardiac diseases or menstrual disorders prior to RT—or the occurrence of cardiovascular events during the course of RT, which could somehow influence the occurrence of post-RT anemia in our patients. We also did not obtain dosimetry data used during contouring at the planning phase of radiation therapy. As reflected in dosimetry, the radiation doses delivered during therapy can potentially affect bone marrow production via irradiation of organs at risk, and subsequently induce changes in blood cell counts. Incorporating data on dosimetry and damage to organs at risk in the regression analysis can make the estimated association of anemia with radiation type or tumor laterality more accurate.

Interpretation

Post-mastectomy radiation therapy plays a vital role in breast cancer management. Radiation that is delivered to the chest wall and the regional lymph nodes after mastectomy has been shown to improve local control and overall survival in select patients.[15 16]

In patients receiving RT, the hemoglobin level post-treatment has been shown to be more important than the pretreatment levels in predicting disease outcomes.[17] The hemoglobin level (<12g/dL or ≥12g/dL) during RT is a significant prognostic factor for patient survival. Among patients with carcinoma of the cervix, the rates of overall relapse, local recurrence, and distant metastases have inverse associations with the average weekly nadir hemoglobin.[18]

Despite the high amount of active marrow found in the chest—i.e., the ribs, scapulae, clavicles, humeral head, and the thoracic spine[2]—that may become irradiated during therapy, both 3D-CRT and FPIMRT did not demonstrate a substantial decrease in hemoglobin levels post-RT among patients with breast cancer, as shown in our study. In a previous study among patients with early-stage breast cancer, radiation therapy did not contribute significantly to a reduction in hemoglobin levels. There was also no difference in the incidence of post-RT anemia among these patients regardless of anemia status at baseline.[19] In another study among patients with cervical cancer, no significant difference was found between IMRT and 3D-CRT treatment groups in terms of hemoglobin, white blood cell, platelet, and absolute neutrophil counts after chemoradiotherapy.[20 21]

In contrast, in a study done among patients with prostate and bladder cancer, IMRT was associated with lesser absolute and relative decrease in hematologic indices, including hemoglobin, when compared to 3D-CRT.[9] In patients with cervical cancer, concurrent chemoradiotherapy using 3D-CRT to the pelvis and lower spine—where majority of the hematopoietically-active bone marrow is located—has resulted in anemia and neutropenia. On the other hand, IMRT had a distinctive advantage on pelvic bone marrow sparing, with a notable decrease in radiation doses to the bone marrow.[22 23] Because of its highly conformed dose distribution, IMRT use in breast cancer produces reduced acute toxicity to the skin, heart, and ipsilateral lung.[24 25]

Compared to the 3D-CRT group, the FPIMRT group had a higher proportion of patients with left-sided tumors in our study. The radiation team may have preferred FPIMRT to 3D-CRT for the treatment of left-sided tumors since FPIMRT has been shown to significantly decrease the mean radiation dose that goes to the ipsilateral lung and the heart during irradiation of left-sided breast cancer tumors.[26] Among the patients in our study, anemia was significantly associated with left-sided tumors. Theoretically, left-sided breast cancer has been associated with shorter time to first metastasis, increased risk of distant metastasis, and higher rate of axial bone metastases.[27] This may be attributed to the anatomical difference in lymphatic drainage of the right and the left breasts. The left lymphatic duct—which drains the left breast—drains an area of the body that is approximately three times larger than the area drained by the right lymphatic duct.[28] Therefore, it may be hypothesized that, if cancer cells from the breast tumor pass through the left lymphatic flow, there is a greater likelihood for these cells to move more rapidly into the systemic circulation and increase the risk of earlier metastasis.[27] Metastases from breast cancer can invade the bone marrow, and anemia is its most frequent symptom at presentation.[29 30] Looking at the baseline tumor stage distributions of the patients in our study, however, we found no significant indication that patients with left-sided breast tumors had more advanced malignancies than those with right-sided breast tumors when the study began. By the end of therapy, complications leading to anemia could have possibly occurred in a subset of patients with left-sided tumors.

Moreover, we did not include data on radiation dosimetry and damage to organs at risk—especially bones with active marrow—in the analysis. These data can potentially elucidate the nuances of the significant statistical association that we found between left-sided breast cancer and post-RT anemia. IMRT characteristically delivers non-uniform radiation doses with wide dosimetric variations to target tumors, while 3D-CRT delivers a more uniform radiation flow.[31 32] Dosimetric consequences in IMRT may be attributable to intrafraction geometric uncertainties or misalignments that occur when the patient and/or the target organ moves during therapy. Hence, the delivered dose to tumors and organs at risk can sometimes be higher or lower than the prescribed dose.[33 34] Had this study collected data on dosimetry, calculations on the association of RT technique with post-RT anemia would have been more precise.

Generalizability

The results of the study are applicable to most patients with breast cancer who were diagnosed to have invasive ductal carcinoma, who underwent either 3D-CRT or FPIMRT after chemotherapy, and who share similar demographic and clinical characteristics with the patients in our study.

Due to its high conformality, FPIMRT is considered more precise in delivering radiation to its target tissue. It is, however, more expensive and time-consuming. In this study, the post-RT hemoglobin levels and occurence of post-RT anemia among patients who underwent 3D-CRT were comparable with those of patients who underwent the more precise FPIMRT. In making a decision to pick one of these two RT techniques, and if hemoglobin levels and anemia are the only important safety concerns, 3D-CRT may be considered as a cheaper alternative to FPIMRT for post-mastectomy, post-chemotherapy radiation of patients with invasive ductal carcinoma. To refine our conclusions in this study, we also recommend doing further studies on the effects of radiotherapy on hemoglobin counts and incidence of post-RT anemia among patients with breast cancer, with dosimetry-related parameters included in the analysis.

CONCLUSION

In this retrospective cohort study among patients with invasive ductal carcinoma, the post-RT hemoglobin levels of patients who underwent 3D-CRT were comparable with those of patients who underwent FPIMRT. The proportion of patients with anemia within four weeks post-RT were also comparable between the two groups.

Contributors

SRLA and MLBL had substantial contributions to the study design, and to the acquisition, analysis and interpretation of data. SRLA wrote the original draft and subsequent revisions, and reviewed, edited, and approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work.

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Ethics approval

This study was reviewed and approved by the Department of Health XI Cluster Ethics Review Committee (DOH XI CERC reference P19022601).

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