Assessment of Arm Lymphedema After Once-weekly Hypofractionated Radiotherapy for Breast Cancer Patients in Qena University Hospital

Alaa A. Hassan[a*], Mohammed Mostafa Wahman[a] , Ahmed A A Ali[b] ,Eisa Mohamed Hegazy[c], Mostafa Elsayed Abd Elwanis[d]

[a]Clinical Oncology Department, Faculty of Medicine, South Valley University, Qena, Egypt

[b]Plastic surgery Department, Faculty of Medicine, South Valley University, Qena, Egypt

[c]Dermatology,Venereology, and Andrology Department, Faculty of Medicine, South Valley University, Qena, Egypt

[d]Radiation Oncology Department, South Egypt Cancer Institute, Faculty of Medicine, Assuit University, Assiut, Egypt

Abstract

Background: The use of a hypofractionated 15–16 fraction radiotherapy course replaced the standard fractionated whole breast irradiation (SF–WBI) more than 10 years ago, resulting in shorter waiting lists, lighter machine loads, and more patient compliance.

Objectives: Assessment of Arm Lymphedema in breast cancer patients postmastectomy treated with adjuvant single-weekly hypofractionated radiotherapy to the whole breast. Aiming to improve the lifestyle and reduce the suffering of cancer patients.

Patients and ethods: Adjuvant RTH to the chest wall was given to 30 post-mastectomy women who had infiltrating duct carcinoma of the breast that was histologically confirmed. The dose was 30 or 28.5 Gy in 5 fractions given once a week at a dose of 6.0 or 5.7 Gy. All patients were assessed for ipsilateral arm lymphedema by monitoring the arm circumference on both sides before radiation treatment and at 3, 12, and 24 months after radiation treatment.

Results: The incidence of lymphedema grade 0 was (93.3%) in the study group before radiotherapy; at 12 and 24 months after the end of radiotherapy, it was (83.3%) and (80%), respectively (P = 0.044). Grade I was noted in 2 patients (6.66%) before RTH and in 4 patients (13.3%) at 24 months of follow-up (P = 0.682). One case (3.33%) showed grade 2 lymphedema at 3 months after radiation treatment, and 2 cases (6.66%) after 24 months of the end of RTH (P = 0.194).

Conclusion: Breast cancer patients can achieve satisfactory results in terms of dosimetric parameters and lymphedema grades by receiving once-weekly whole breast irradiation.

Keywords: Breast cancer ; Single Weekly hypofractionated ;Lymphedema ; BMI.

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***Correspondence**: aalaa.ahmed@med.suv.edu.eg

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Introduction

Breast cancer is still the most common cancer in women and the main reason for mortality from cancer globally. In 2020, there were over 2.3 million new cases of cancer (25 percent of all female malignancies) and 685,000 fatalities (15 percent of all female cancer deaths) **. (Sung et al., 2021)**

Standard fractionated whole breast irradiation (SF WBI) has long been advised as the treatment for breast cancer after lumpectomy. SF-WBI has some disadvantages, including the expense and pain of the patient needing to attend daily therapy sessions for 5 to 7 weeks. As a result, studies on hypofractionated whole breast irradiation (HF-WBI) have been carried out, offering the possibility of improving patient comfort, lowering healthcare costs, and expanding access to care without affecting treatment outcomes. **(Kim et al .,2016)**

Due to these challenges, the effectiveness of reducing the number of radiation fractions for adjuvant breast radiotherapy was questioned. Recruitment for the START pilot experiment began in 1986, followed by the START A&B trial and then the Canadian trial. The outcomes of these mildly hypofractionated 15–16 fraction regimens were equivalent to those of the SF–WBI in terms of local control and cosmetic outcome, and they were adopted as the norm in several nations beginning with the UK in 2009. **(Haviland et al .,2013)**

The justification for further hypofractionated schedules was created. The UK FAST study began giving whole breast radiation in five-weekly fractions in 2004 and implemented a weekly hypofractionated schedule. **(Yarnold et al .,2011)**

Following the positive outcome in the 28.5 Gy arm and the early 3-year findings in 2011, the UK FAST-FORWARD study initiated a hypofractionated schedule that provided adjuvant breast radiation in a single week. The 5-year findings in 2020 demonstrated that the 26 Gy arm was not inferior in terms of safety on normal tissue and local tumour management. **(Murray et al.,2020).**

Patients and methods

The purpose of the current prospective study was to assess arm lymphedema in breast cancer patients postmastectomy treated with adjuvant single-weekly hypofractionated radiotherapy to the whole breast from May 2021 to June 2023 at the Clinical Oncology Department of the Qena University Hospital in Qena, Egypt .

Thirty postmastectomy women older than 30 years with previously untreated infiltrating duct cancer of the unilateral breast that has been histologically verified and who have normal cardiac, renal, and pulmonary function..

Eligibility criteria

A-Inclusion criteria:

-Age > 30 years.

-Breast cancer that is radiotherapy indicated and pathologically confirmed.

-At diagnosis, there was no macroscopic indication of distant metastases.

B. Exclusion criteria:

-Patients with contraindications to receiving adjuvant radiotherapy. (pregnancy, scleroderma, uncontrolled rheumatoid arthritis).

-Patients with bilateral synchronous breast or prior malignancy.

-Positive surgical margins.

-Tumor bed boost indication

Methods:. All patients enrolled underwent surgery (either a radical mastectomy or breast conserving surgery) and were submitted to a pre-treatment examination that included a history-taking and a full clinical assessment.

1-Patient positioning and CT Simulation: Patients performed a supine computed tomography (CT) simulation from the mandible to the diaphragm with a 3mm slice thickness. The patient was positioned on the supine breast board with their arms up. The medial marker was positioned in the midline above the sternum, the lateral marker in the mid axillary line, and the third marker was positioned around the curve of the breast. **(Guenzi et al .,2013)**

2- Dose prescriptions and radiotherapy technique: All patients received a dose of 28.5 Gy in 5 fractions of 5.7 Gy weekly dose over 5 weeks to treated volumes (equivalent to 25 fractions of 2.0 Gy over 5 weeks, assuming value for breast α/β of 3.0, 3D-CRT technique was used in all plans with energy of 6MV. **(Dragun et al .,2017)**

3-Assessement : All patients were assessed for ipsilateral arm lymphedema by monitoring the arm circumference on both sides at 3 points: 3 cm below rest joint, 5 cm below the elbow and 5 cm above the elbow before radiation treatment and at 3, 12, and 24 months after radiation treatment

Ethical considerations

1. Trial approval: The ethics committee gave the trial permission to proceed after the Committee of Clinical Oncology department gave it its seal of approval up. The approved code of ethics is MEDONM027-2-21-5-203 .

2. Patient Consent: Each patient in the present investigation gave their informed consent to participate in the research in writing and for publication after being told of the study's goals and contents

Statistical analysis

Data were examined using the SPSS software (version 26), which stands for Statistical Package for Social Sciences.By using the chi-square test, qualitative variables were compared and reported as frequencies and percentages. A student t-test was used to compare a quantitative measure that was provided as means standard deviation (SD). As shown, regression analysis and correlation between various variables were carried out. Significant results will have a P value <0•05.

Results

From May 2021 to June 2023 , 30 women were included and treated according to the protocol. (**Table .1)** summarizes the baseline demographic characteristics of the study population. The median age was 53 years. (**Fig.1).**

Table 1. Demographic characteristics of the study population

Variables	Hypofractionated Adjuvant Radiotherapy N:30
Age:	
Median(range)	53(30-69) years
Less than 40	4(13.33%)
40-60	19(63.33%)
More than 60	7 (23.33%)
Menopause state	
Pre-menopausal	10(33.33%)
Post menopausal	20(66.66%)

Family history **No** **Yes**	 22(73.33%) 8(26.66%)
Previous Radiation exposure **No**	 30 (100%)
Skin disease **No**	30 (100%)

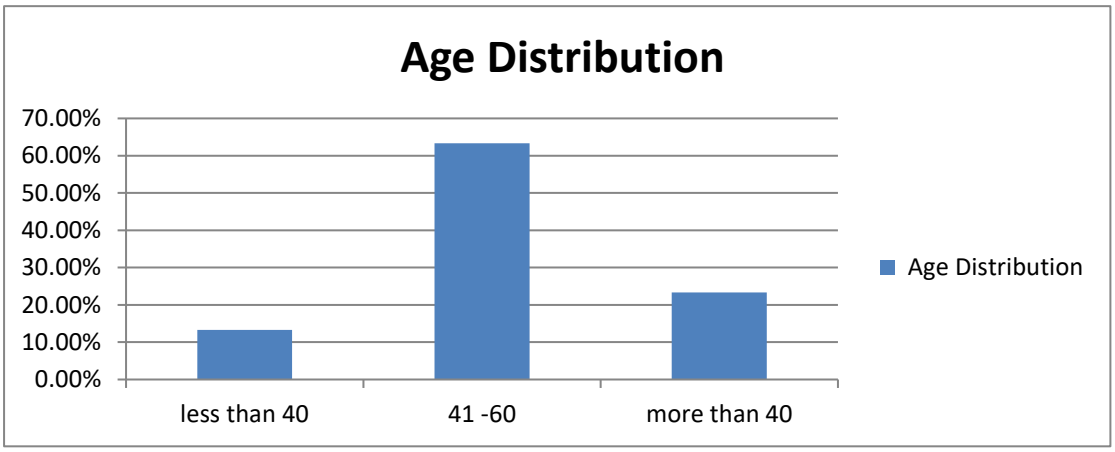

Fig.1. Age distribution in study group

Ten (33.33%) patients were premenopausal, whereas 20 (66.66%) had undergone their menopause. As regard family history 73.33% of patients have a positive family history and 26.66% have no family history. All patients were assessed for ipsilateral arm lymphedema by monitoring the arm circumference on both sides before radiation treatment and at 3, 12, and 24 months after radiation treatment. As regard lymphedema. The incidence of grade 0 was (93.3%) in the study group before radiotherapy; at 12 and 24 months after the end of radiotherapy, it was (83.3%) and (80%), respectively (P = 0.044). **(Table .2, Fig.2).**

Table 2. Grades and incidence of lymphedema

Lymphedema	**Before RTH**	**At 3 months follow up**	**At 12 months follow up**	**At 24 months follow up**	**P value**
	No (%)	**No (%)**	**No (%)**	**No (%)**	
Grade 0	28 (93.3%)	26 (86.7%)	25 (83.3%)	24 (80%)	**0.044***
Grade 1	2 (6.67%)	3 (10%)	3 (10%)	4 (13.3%)	**0.682**
Grade 2	0 (0%)	1 (3.33%)	2 (6.66%)	2 (6.66%)	**0.194**

*Cochran's Q test

Grade I lymphedema was noted in 2 patients (6.66%) before RTH and in 4 patients (13.3%) at 24 months of follow-up (P = 0.682). One case (3.33%) showed grade 2 lymphedema at 3 months after radiation treatment, and 2 cases (6.66%) after 24 months of the end of RTH (P = 0.194). **(Table.2, Fig.3)**

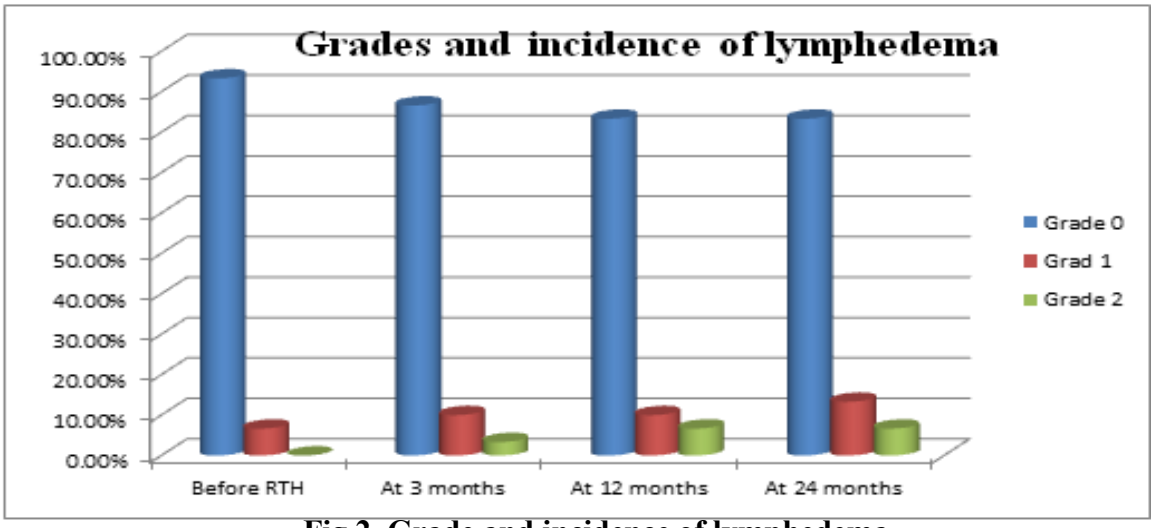

Fig.2. Grade and incidence of lymphedema

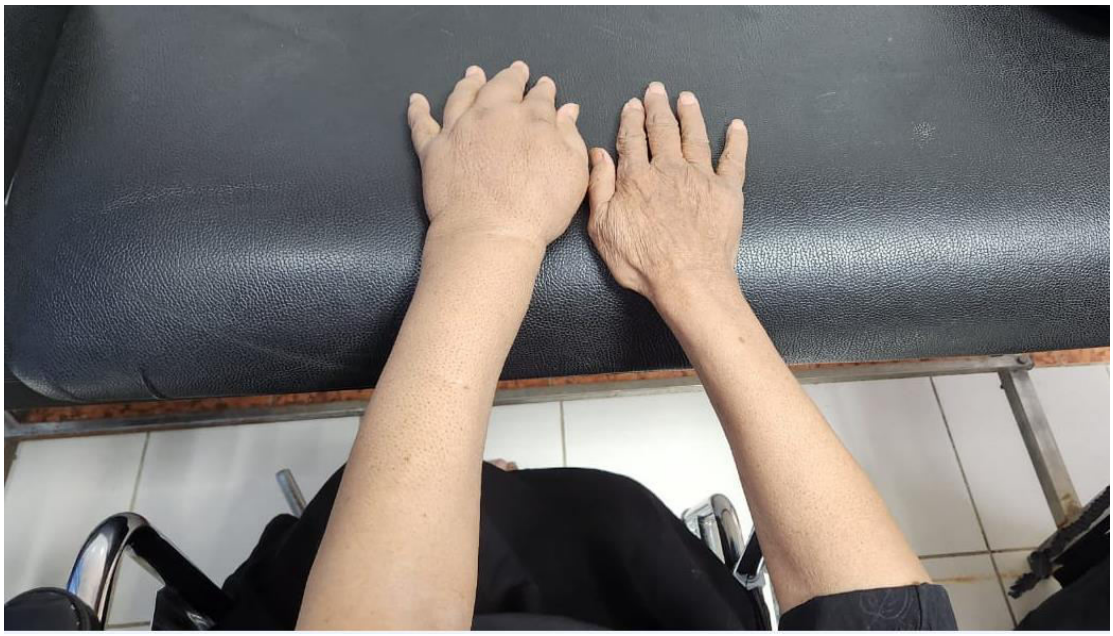

Fig.3 . Patient with grade 2 lymphedema at 24 months follow up

The majority of cases (73.1%) had a BMI ≥30 kg/m2, and 7 cases (23%) had a BMI ≥ 35. Out of the included patients, 6 patients (20%) suffered from D.M. (**Table.3, Fig.4).** Most of the patients submit to breast-conservative surgery with axillary dissection (80%). Six patients (20%) underwent a modified radical mastectomy. **(Table.3)**

Table 3.Analysis of factors associated with lymphedema

Variable	Hypofractionated Adjuvant Radiotherapy N:30
Body Mass Index (Kg/m2)	
≤ 25 kg/m2	2(6.66%)
25-30 Kg/m2	6(20%)
30-35 Kg/m2	15(50%)
≥ 35 Kg/ m2 6	7 (23%)
Comorbidities disease (DM)	
No	24 (80%)

Yes	6 (20%)
Type of surgery **MRM** **Breast conservative**	 6(20%) 24(80%)
Type of axillary surgery **SLNB** **ALND**	 4 (13%) 15 (50%)

SLNB; sentinel lymph node biopsy, ALND; axillary lymph node dissection

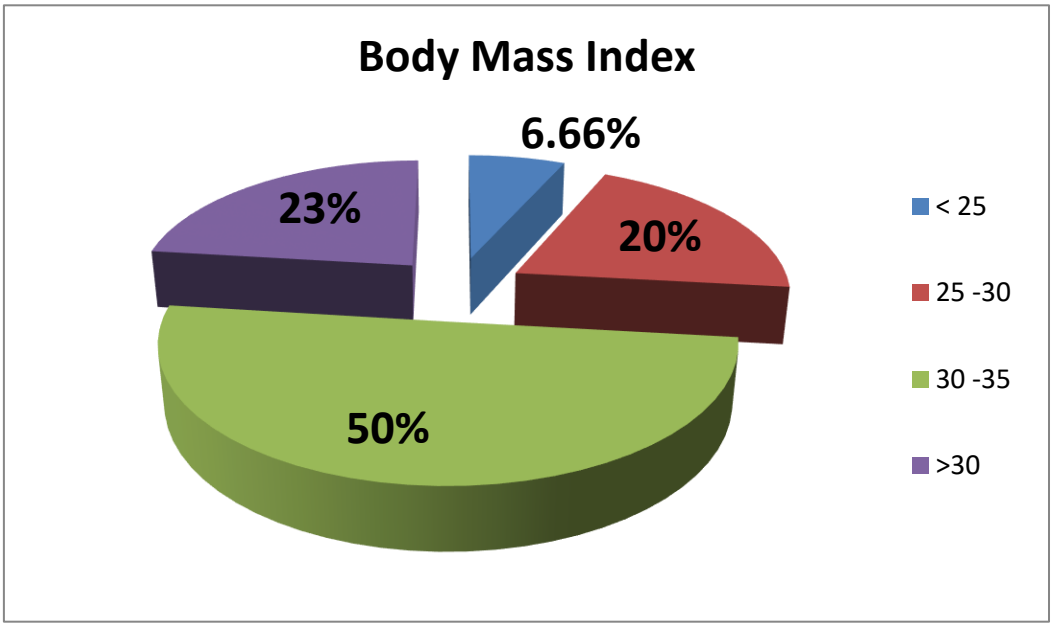

Fig. 4. BMI in study group

With the exception of mobility impairment, chi-squared tests showed that all of the lymphedema-related symptoms outlined in **(Table.4)** coexisted in a highly significant way. In 30 patients in our study, 6 (30%) reported having developed arm lymphedema after their treatment, and about 10% of them complained of chronic skin damage. P=0.033. **(Fig.5).**

Table 4. Lymphedema-related symptoms and coincidence with secondary arm lymphedema

Symptoms	**Y/N**	**Number of patients (%)**	**Secondary arm lymphedema**		**P value**
			Yes (6)	**No (24)**	
			No. (%)	**No. (%)**	
Chronic skin damage	**Yes**	3 (10%)	2 (66.7%)	1 (33.3%)	**0.033***
	No	27 (90%)	4 (14.8%)	23 (85.2%)	
Pain	**Yes**	5 (16.7%)	3 (60%)	2 (40%)	**0.014***
	No	25 (83.3%)	3 (12%)	22 (88%)	
Peripheral neurologic symptoms	**Yes**	6 (20%)	4 (66.7%)	2 (33.3%)	**0.001***
	No	24 (80%)	2 (8.3%)	22 (91.7%)	
Impairment of shoulder/arm movement	**Yes**	2 (6.67%)	1 (50%)	1 (50%)	**0.272**
	No	28 (93.3%)	5 (17.9%)	23 (82.1%)	

*Chi-square test

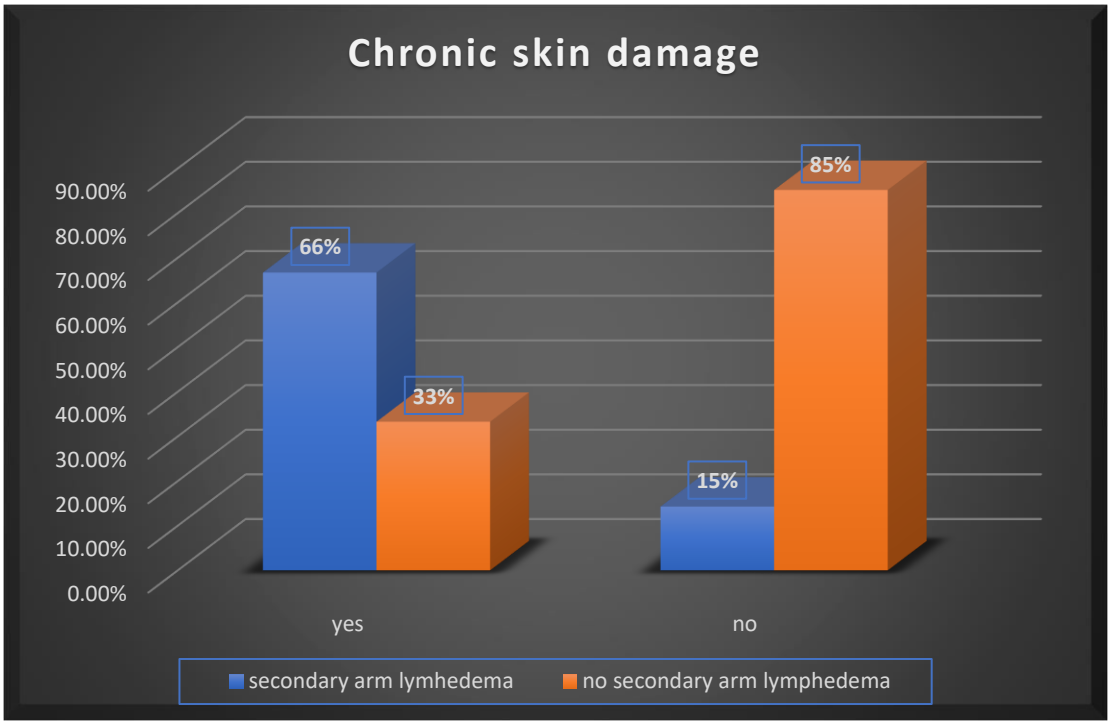

Fig.5. Chronic skin damage among patients with and without secondary lymphedema

The rates of other symptoms such as pain **(Fig.6)**, peripheral neuropathy, and impairment of arm movement were 60%, 66%, 13.3%, and 50%, respectively, **(Table.4, Fig.7).**

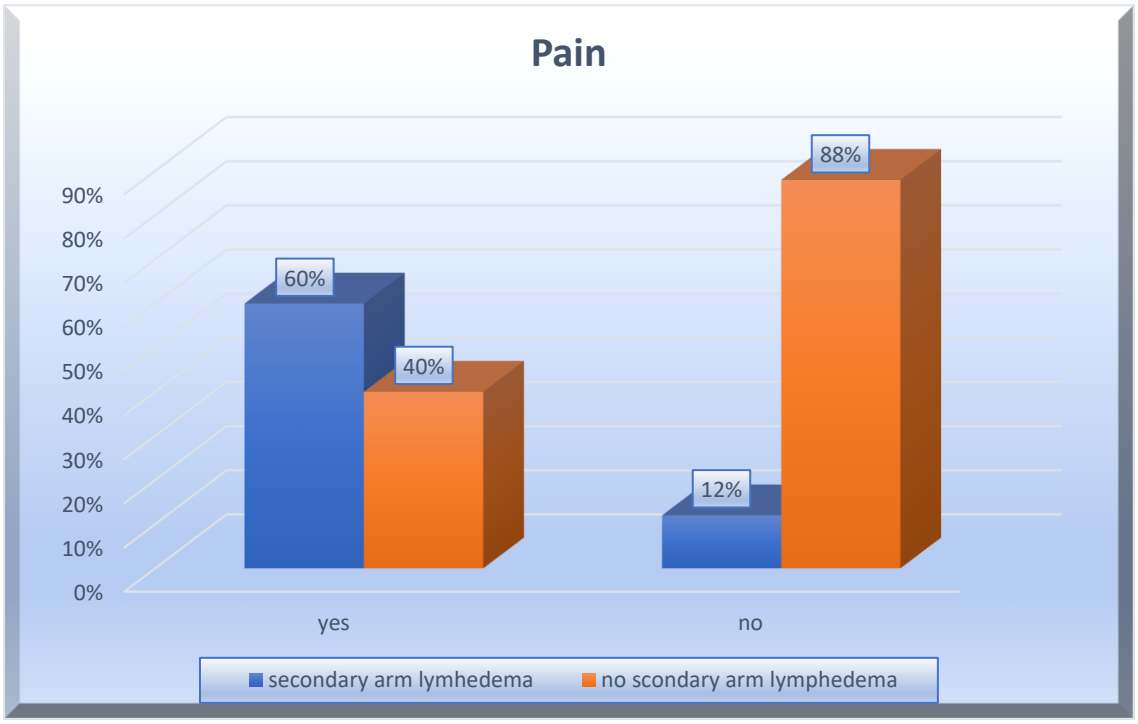

Fig.6. Pain among patients with and without secondary lymphedema

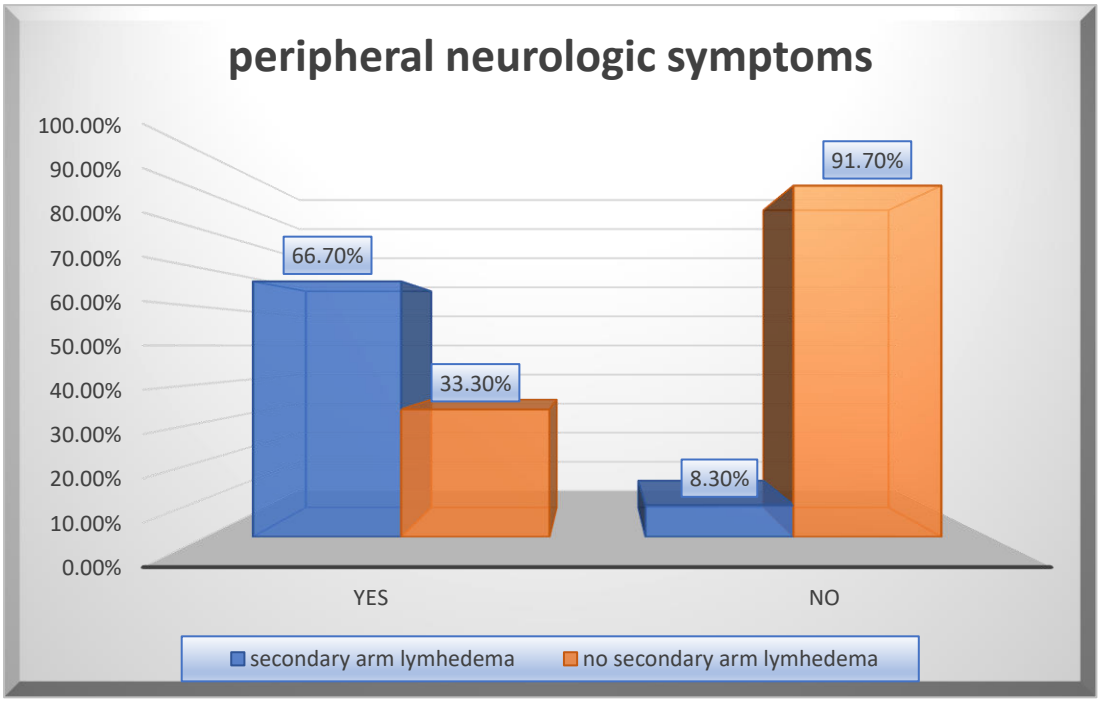

Fig.7. Peripheral neurologic symptoms among patients with and without secondary lymphedema

Discussion

With 33% of our patients being breast cancer patients, the radiation load on the treatment machines in our department is significant. In order to treat all patients quickly without sacrificing the oncological or cosmetic outcome and to make therapy more convenient for the patients, which would increase compliance, it was necessary to reduce the number of fractions . This study can serve as an alternative for patients with inability to commit to daily regimens especially during the circumstances we faced with the COVID-19 pandemic. As with the majority of research, the current study's design has limitations, such as the small number of patients involved .This was due to the fact that the majority of our older patients elected radical mastectomy, and there is no evidence of adjuvant radiation in early breast cancer. Most of the previous studies that go through once weekly adjuvant Breast radiotherapy included elderly patients as the median age in Fast Forward study was **61 years (Murray et al.,2020),** thus elderly patients often present other comorbidities so it may affect the final outcomes. A common criticism of these studies regards their limited applicability in that they include mainly lymph-node negative, postmenopausal patients with biologically favorable early stage invasive disease thus against our study which include lymph node positive patient which received either supraclvicular or axillary LN irradiation which eventually may affect lymphedema occurrence.

Despite the current study's limitations, we notice that patients with lymphedema come back to the follow-up visits more frequently when compared to the patients without lymphedema ; since they did not return, supposedly, they did not exhibit any worse condition, improving the general results Consequently, a longer follow-up in our cohort could be useful for a comparative analysis. From May 2021 to June 2023, we performed our prospective phase II study in order to adapt new radiation hypofractionated schedules. 30 eligible patients in all

got weekly adjuvant radiation sessions at a dose of 28.5 Gy divided across 5 fractions over the course of 5 weeks. At a median follow-up of 16.5 months (with a range of 12–24 months), the results were reported.

Regarding the clinical characteristics, the mean age of our patients was 53 (range, 30-69 years), and around 33.33% of them were premenopausal. As the lower limit for the UK FAST study was 50 years of age, this was younger than the mean age there, which was 62.9 years (range, 50-88 years). **(Murray et al.,2020)**. Additionally, our findings are at odds with international data; for example SEER data show that the median age at diagnosis for breast cancer is 62 years of age .**(DeSantis et al.,2016)**. In our study the mean BMI was 33.2 (range, 23-48.3) and this is compatible with the study conducted by Alebshehy et al., which showed that the prevalence of overweight and obesity in the Mediterranean Region, including Egypt, ranges from 74% to 86% among females **(Alebshehy et al.,2016)** .

Eighty percent of the patients had axillary dissection along with conservative breast surgery. In ten patients (20%), a modified radical mastectomy was performed.

While 93.5% of participants in the FAST-Forward trial had conservative breast surgery with axillary dissection, while 6.5% had a radical mastectomy. **(Murray et al.,2020)**.

Regarding axillary surgery 13% did sentinel lymph node biopsy and 50% had axillary evacuation. This was unlike WHBI US trial which reported SLNB in 72.8% of the total population **(Dragun et al. 2017).** This is due to the fact that our patients were mostly node positive diseases(56%) .

Seventy percent of the cases were T2; the remaining instances were T1 (26.6%) and T3 (3.33%). This agrees with a study by MA Zerella et al. in 2022, which revealed that the majority of BC were pT1 (77%), with the remaining percentages being T2 (22.2%) and T3 (0.4%). **(Zerella et al .,2022)**. Unlike the UK FAST study, which omitted the patient with a positive node, axillary status was negative in 43% of the participants and N1 in 36.66%. **(Murray et al.,2020)**.

As a regard to lymphedema the incidence of grade 0 was (93.3%) in the study group before radiotherapy; at 12 and 24 months after the end of radiotherapy, it was (83.3%) and (80%), respectively (P = 0.044). Grade I lymphedema was noted in 2 patients (6.66%) before RTH and in 4 patients (13.3%) at 24 months of follow-up (P = 0.682). One case (3.33%) showed grade 2 lymphedema at 3 months after radiation treatment, and 2 cases (6.66%) after 24 months of the end of RTH (P = 0.194).

It is somewhat comparable to the findings of the Rais F et al study, which revealed that nine (18%) individuals had ipsilateral arm lymphedema. This was classified as Grade 1 in 5 patients (10%) and Grade 2 in 4 patients (8%), with no occurrence of Grade 3 lymphedema. **(Rais et al.,2021)**

Conclusion

Our weekly hypofractionated radiation treatment for early breast cancer met all of the requirements for feasibility. These side effects were determined to be minor and manageable. To properly understand the effects at different organ sites, however, more research and longer follow-ups are needed; this is also supported by published data. More women will be able to finish adjuvant radiotherapy in a shorter amount of time once its safety and effectiveness are proven.

Abbreviations

3D: Three Dimensional

SF-WBI: Standard fractionated whole breast irradiation
RTH: Radiotherapy
Gy: Gray
BMI: Body Mass Index
DM: Diabetes Mellitus
HF-WBI: Hypo fractionated whole breast irradiation
CT :Computed tomography CT
CRT :Conformal Radiation Therapy
MV : Megavoltage
SPSS :Statistical Package for Social Sciences
SD :Standard deviation

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Author contributions: In producing this manuscript, each author contributed equally.
The submitted version of the work was reviewed and approved by all authors.

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Availability of data and materials : The corresponding author will provide the datasets applied or assessed during the current work upon reasonable request.

Ethics approval and consent to participate : The ethical review board of South Valley University's faculty of medicine gave the study its blessing. SVU-MEDONM027-2-21-5-203 is the ethical approval code. After acquiring each case's informed written consent, data were gathered.

Consent for publication: Written informed permission was provided by each patient to participate in the study.

Competing interests : The authors claim to have no conflicts of interest.

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