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RESEARCH ARTICLE

EFFICACY AND TOLERANCE OF HYPOFRACTIONATED RADIOTHERAPY AFTER MASTECTOMY AND LYMPH NODE IRRADIATION IN BREAST CANCER

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Abstract

This retrospective study evaluates the efficacy and tolerance of hypofractionated radiotherapy (HFRT) in patients with locally advanced breast cancer following mastectomy and lymph node irradiation. Data from 607 patients treated between 2018 and 2022 were analyzed, comparing a hypofractionated regimen (40.05 Gy in 15 fractions) to a normofractionated regimen (50 Gy in 25 fractions). The results demonstrated comparable efficacy between the two regimens in terms of local control and survival, with a low rate of chronic toxicity, including a chronic lymphedema rate of 0.39% in the hypofractionated group. While acute toxicity (radiodermatitis) was more frequent in the hypofractionated group, it was primarily grade I II. The study confirms that HFRT is an effective and safe alternative to conventional radiotherapy for locally advanced breast cancer, with potential for further optimization through ultrafractionation.

Introduction:-

It is now well established that conventional radiotherapy after mastectomy or breast-conserving surgery significantly improves long-term outcomes by reducing local recurrence and breast cancer-related mortality [1],[2]. With advancements in radiotherapy technologies, techniques aimed at reducing treatment duration, costs, and toxicity have emerged, notably hypofractionated radiotherapy (HFRT). This approach, which involves delivering higher doses per fraction over a shorter period, has demonstrated equivalent local control rates and toxicity compared to conventional radiotherapy in early-stage breast cancer and is now widely accepted in clinical practice [14], [3].

However, the use of HFRT in locally advanced breast cancer with lymph node involvement remains limited due to the risks of late toxicity, such as brachial plexopathy or cardiopulmonary damage.

It is therefore essential to better understand the efficacy and safety of hypofractionated radiotherapy after mastectomy and lymph node irradiation to optimize the management of these patients.

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Objectives:

The objective of this study is to evaluate the efficacy and tolerance of hypofractionated radiotherapy applied to the chest wall and regional lymph node areas in patients with breast cancer.

The primary endpoints include the assessment of overall survival and recurrence-free survival (RFS) in groups treated with normofractionated and hypofractionated radiotherapy, as well as the comparative analysis of acute and chronic toxicity between these two approaches.

Methods:

Study Design: A retrospective cross-sectional study evaluating the clinical and therapeutic data of patients with locally advanced breast cancer treated with radiotherapy at Mohammed VI University Hospital in Marrakech between January 1, 2018, and December 31, 2022, over a five-year period.

Study Population: The study includes all patients with a confirmed histopathological diagnosis of locally advanced breast cancer (stages IIb to IIIc according to the AJCC 2017 classification). Inclusion criteria comprised adjuvant radiotherapy following radical mastectomy and/or lymph node irradiation. Patients with incomplete data or insufficient follow-up were excluded.

Collected Data: Epidemiological, clinical, histopathological, and therapeutic data were collected from medical records, the Hosix information system, the Mosaiq radiotherapy system, and the Xio radiotherapy treatment planning system.

Radiotherapy Protocol:

Patients received three-dimensional conformal radiotherapy (3D-CRT) using an ELEKTA Synergy Platform linear accelerator with a multileaf collimator. Two fractionation schedules were applied:

- Hypofractionation: 40.05 Gy in 15 fractions of 2.67 Gy (82.7% of cases).
- Normofractionation: 50 Gy in 25 fractions of 2 Gy (17.3% of cases).

Statistical Analysis: Data were entered into Microsoft Excel Office Professional 2016 and analyzed using IBM SPSS version 25. Descriptive statistics were used to characterize epidemiological, clinical, and therapeutic variables. Continuous variables were expressed as means (± standard deviation), and qualitative variables as percentages. Differences in toxicity rates and clinical outcomes between fractionation schedules were assessed using Fisher's exact test for qualitative variables and the Mann-Whitney test for quantitative variables. A p-value < 0.05 was considered statistically significant.

Ethical Approval: This study was approved by the ethics committee of Mohammed VI University Hospital in Marrakech. Patient confidentiality was strictly maintained throughout the study.

Results:

Between January 1, 2018, and December 31, 2022, 607 patients were treated in the Radiation Oncology Department at the Mohammed VI University Hospital in Marrakech. The mean age of the patients was 49.7 years, ranging from 19 to 84 years, with the majority being women (n=595, female-to-male sex ratio of 49.5). Among the patients, 73% were from urban areas, and 89.9% had health insurance coverage.

Only 30 female patients had no risk factors for breast cancer. Additionally, 85 patients experienced menarche before the age of 12, and 14.1% of postmenopausal women had late menopause (≥ 55 years). A total of 195 women (32.1%) used oral contraceptives, with an average usage duration of 7.2 years. Furthermore, 94 women (15.8%) were nulliparous, and 71 (16.3%) had never breastfed. A family history of breast cancer was reported in 89 patients (14.6%). The mean time before consultation was 7.6 months.

According to the 2017 AJCC classification, clinical stage IIb was the most common, accounting for 37.5% of cases, followed by stage IIIa (19%), stage IIIb (30%), and stage IIIc (13.5%) (Table 1). The most common molecular profiles were Luminal B (47.6%), followed by Luminal A (26.1%), HER2 (14.3%), and triple-negative (12%).

All patients underwent curative adjuvant radiotherapy following surgery, with 64.7% having a radical mastectomy and 35.3% undergoing conservative surgery. Additionally, 88.6% of the patients received chemotherapy, of whom 71.9% received adjuvant chemotherapy and 28.1% received neoadjuvant chemotherapy. Hormone therapy was prescribed to 407 patients (67%), and 111 patients (18.2%) received targeted therapy, including 14.3% HER2-positive patients and 3.9% with a Luminal B HER2-overexpressing profile.

All patients received three-dimensional conformal radiotherapy (3D-CRT) using the ELEKTA Synergy Platform linear accelerator with a multi-leaf collimator (Figure 1). A hypofractionated regimen (40.05 Gy in 15 fractions of 2.67 Gy) was applied in 82.7% of cases, including chest wall treatment in 328 cases (Figure 2), breast treatment in 174 cases, and supraclavicular and subclavicular areas in 401 cases (Figure 3), with axillary irradiation in 295 cases.

Conversely, 17.3% of patients received a standard fractionation regimen of 50 Gy in 25 fractions of 2 Gy, involving chest wall irradiation in 65 cases, breast irradiation in 40 cases, and treatment of the supraclavicular and subclavicular areas in 84 cases, with axillary irradiation in 77 cases.

Regarding complications, 35% of patients experienced acute toxicity in the form of grade I to II radiodermatitis (Figure 4). This toxicity was significantly more frequent in patients treated with the hypofractionated regimen (40%) compared to the normofractionated regimen (10.5%), with a highly significant difference ($p<0.0001$). In terms of chronic toxicity, three patients who received axillary radiotherapy developed chronic lymphedema (Figure 5), which was slightly less frequent with the hypofractionated regimen (0.39%) compared to the normofractionated regimen (0.95%). However, this difference was not statistically significant ($p=0.435$). No bone, pulmonary, or chronic cardiac toxicity was reported.

The rates of locoregional recurrence were similar between the two regimens (4.8% for normofractionated versus 4.2% for hypofractionated), as were the rates of metastatic recurrence (8.6% vs. 7.6%).

After a median follow-up of 42 months (ranging from 18 to 60 months), 468 patients had controlled disease, 73 had experienced a relapse (26 locoregional and 47 distant recurrences), 11 had died from their cancer, and 55 were lost to follow-up. The three-year overall survival rate, calculated using the Kaplan-Meier method, was 81% (Figure 6).

Discussion:

Context and Justification

Although the radiosensitivity of tissues—whether skin, chest wall, or adjacent organs at risk (OARs)—is comparable after breast-conserving surgery or radical mastectomy, hypofractionated radiotherapy (HFRT) for the chest wall and lymph node areas still raises concerns. These concerns are primarily related to the fear of late toxicities such as brachial plexopathy, arm lymphedema, or cardiopulmonary damage, as well as the initial lack of robust evidence in this specific setting. However, accumulating data from clinical trials and practical experience in recent years support the growing use of HFRT as an effective and safe alternative.

The START trials represent the main long-term evidence supporting hypofractionation in patients with locally advanced breast cancer. While these trials were not specifically designed to analyze this subgroup and lacked the statistical power to draw definitive conclusions for this population, they demonstrated that hypofractionation was as effective as conventional fractionation in terms of tumor control and late toxicity [5,6,7]. In these studies, 12% of mastectomized patients received hypofractionated radiotherapy to the chest wall and lymphatic drainage stations. The 10-year results of these trials showed no significant difference between conventional and hypofractionated radiotherapy in terms of efficacy and late toxicity. The incidence of symptomatic pneumonia or brachial plexopathy was also rare (<1%) [5].

Based on these findings, as well as the experience of numerous British and Dutch centers using hypofractionated radiotherapy outside clinical trials for over 10 years, UK guidelines have stated since 2016 that more than 15 fractions are not needed for breast, chest wall, or nodal irradiation. The hypofractionated regimen delivering 40 Gy in 15 fractions has become the standard of care for all local or locoregional adjuvant radiotherapy in breast cancer in the UK [8].

The first randomized phase III non-inferiority trial comparing post-mastectomy hypofractionated radiotherapy (43.5 Gy in 15 fractions) to conventional fractionation was published by Wang et al. in 2019. This Chinese study included 820 patients with T3/T4 breast cancer or at least 4 positive lymph nodes. At a median follow-up of 5 years, Wang et al. found no statistically significant difference in locoregional recurrence rates between the two groups (8.3% in the hypofractionated group vs. 8.1% in the conventional group). Additionally, there was a lower rate of grade 3 acute skin toxicity in the hypofractionated regimen compared to the conventional one; no cases of brachial plexopathy were observed, and the incidence of lymphedema was low (≤19% for grade 2 or higher) [9].

Our results demonstrate a low locoregional recurrence rate (4.8% in normofractionated vs. 4.2% in hypofractionated) and a chronic lymphedema rate of 0.39% in the hypofractionated group. No severe toxicity was observed, in line with Wang et al.'s findings, which also report rare and manageable late toxicity.

Analysis of Toxicities:

The major clinical trials evaluating hypofractionation in breast radiotherapy have shown reassuring results regarding both short-term and long-term toxicity. In the START-A trial, significant differences in favor of the 39 Gy regimen, compared to 50 Gy, were reported, with a reduced rate of grade 2 or 3 breast induration, telangiectasia, and breast edema. However, no difference was observed between the 41.6 Gy regimen and the 50 Gy regimen for these items [5].

In the START-B trial, fewer long-term side effects were reported in the hypofractionated arm compared to the control arms. This reduction was significant for the rates of breast retraction (31.2% vs. 26.2%), telangiectasia (5.8% vs. 4.2%), and breast edema (9% vs. 5.1%). No significant difference was observed for the rate of breast induration (17.4% vs. 14.3%). Similar to the results of the START-A trial, costal, pulmonary, and cardiac toxicity were minimal [5].

When analyzing patients who received lymph node irradiation in both START-A and START-B trials, no significant difference in lymph node-related toxicity was found between the experimental and control arms [4].

In the Canadian trial, no significant difference was found between the groups regarding late cosmetic outcomes (71.3% of good or excellent cosmetic results after 42.5 Gy in 16 fractions vs. 69.8% after 50 Gy in 25 fractions). Only 4% of the patients included in this trial experienced grade 3 skin or subcutaneous lesions [14].

A recent phase II prospective study conducted in China by Jiang et al. compared 85 patients treated with 36.5 Gy in 10 fractions to 72 patients treated retrospectively with 42.5 Gy in 16 fractions. Late toxicities were mostly grade 1 and similar between the two treatment groups. Grade 1 pulmonary fibrosis was observed in 29.4% of patients receiving 36.5 Gy, compared to 23.6% of those receiving 42.5 Gy. Grade 1 lymphedema affected 21.2% of patients treated with 36.5 Gy, compared to 13.9% of those treated with 42.5 Gy [10].

In this context, recent studies like HypoG1andSKAGEN 1 have provided stronger evidence supporting the non-inferiority of hypofractionated radiotherapy for locoregional breast cancers. These two parallel phase III randomized trials compared the hypofractionated regimen delivering 40 Gy in 15 fractions with the conventional fractionation scheme. These studies aimed to address concerns about the increased exposure of normal tissues, such as the lungs and heart, when lymph nodes are included in the radiation field.

The results of the SKAGEN 1 Trial showed that the lymphedema rate in the hypofractionated group was 11.9%, compared to 10.2% in the conventional fractionation group. Similarly, in the HypoG-01 study, these rates were 24.1% in the hypofractionated group and 22.6% in the conventional group. These findings suggest that hypofractionation is just as safe as conventional fractionation in terms of lymphedema-related toxicity [11].

Thus, the HypoG1 and SKAGEN 1 studies confirmed the non-inferiority of hypofractionation, with similar rates of lymphedema between the two treatment groups. This further supports the effectiveness and safety of this approach, particularly in terms of reducing long-term side effects.

Integration of the Boost in Hypofractionated Radiotherapy: Efficacy and Safety

The addition of a dose boost is also possible within the framework of hypofractionated radiotherapy. This boost could be administered in a moderately hypofractionated manner or integrated into the treatment sessions (simultaneous integrated boost) [12], an approach that may provide additional benefits in terms of efficacy without compromising safety. This approach could be applied to all patients, regardless of age, and even to ductal carcinoma in situ (DCIS), particularly when the therapeutic sequences are adapted [13].

Limitations:

This study on hypofractionated radiotherapy in breast cancer is limited by its retrospective nature and lack of randomization, which may introduce selection and information biases. Furthermore, the small sample size reduces the statistical power and the generalization of the results.

Conclusion:

This retrospective study confirms the benefit of hypofractionated radiotherapy for the treatment of locally advanced breast cancer with regional lymph node irradiation. Our results, consistent with international data, suggest comparable efficacy and tolerance to conventional radiotherapy, with a low rate of chronic toxicity. The experience gained with HFRT opens exciting prospects toward ultrafractionation, which could further optimize patient comfort. Prospective studies with longer follow-up are needed to confirm these results and fully assess the potential of ultrafractionation.

Competing interests

No potential conflict of interest relevant to this article was reported.

Authors' contributions

IT was responsible for designing the study, supervising data collection, analyzing the data, and writing the manuscript. All the other authors contributed at each stage of the development, reviewed and approved the current version of this manuscript.

Tables and Figures :

Table 1: Distribution of patients according to AJCC 2017 clinical stage.

Stage	Percentage
IIb	37,5 %
IIIa	19 %
IIIb	30 %
IIIc	13.5 %

Table 2: Comparison of toxicities between the two fractionation schemes.

Toxicity	Hypofractionated RT	Conventional RT
Radiodermatitis grade I to II.	40 %	10,5 %
Chronic lymphoedema.	0,39 %	0,95 %
Chronic bone, pulmonary, or cardiopathy toxicity.	0 %	0 %

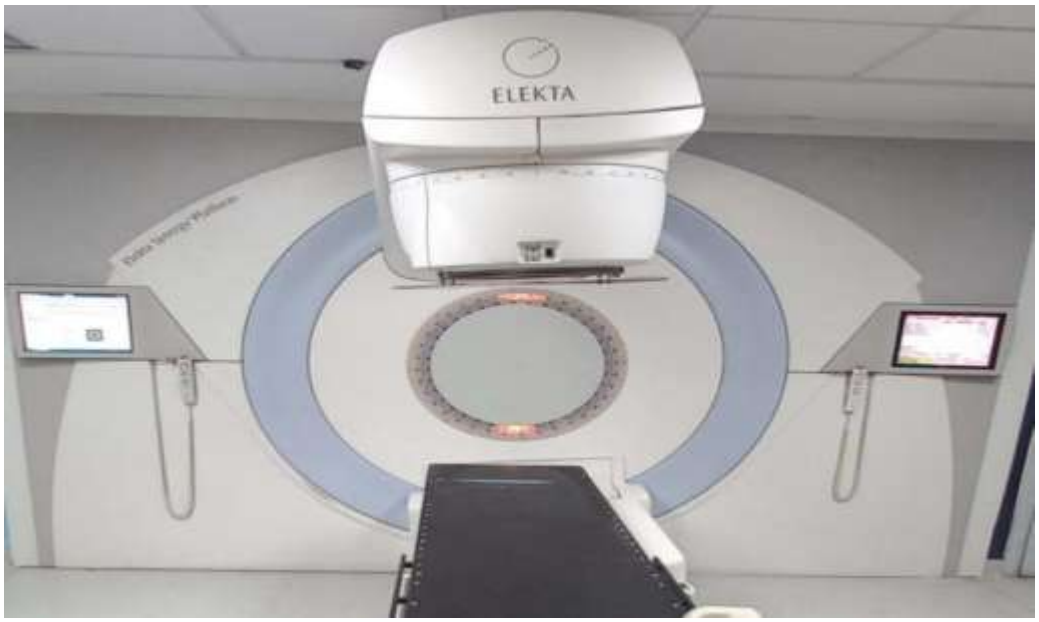

Figure 1: The ELEKTA Synergy Platform Linear Accelerator

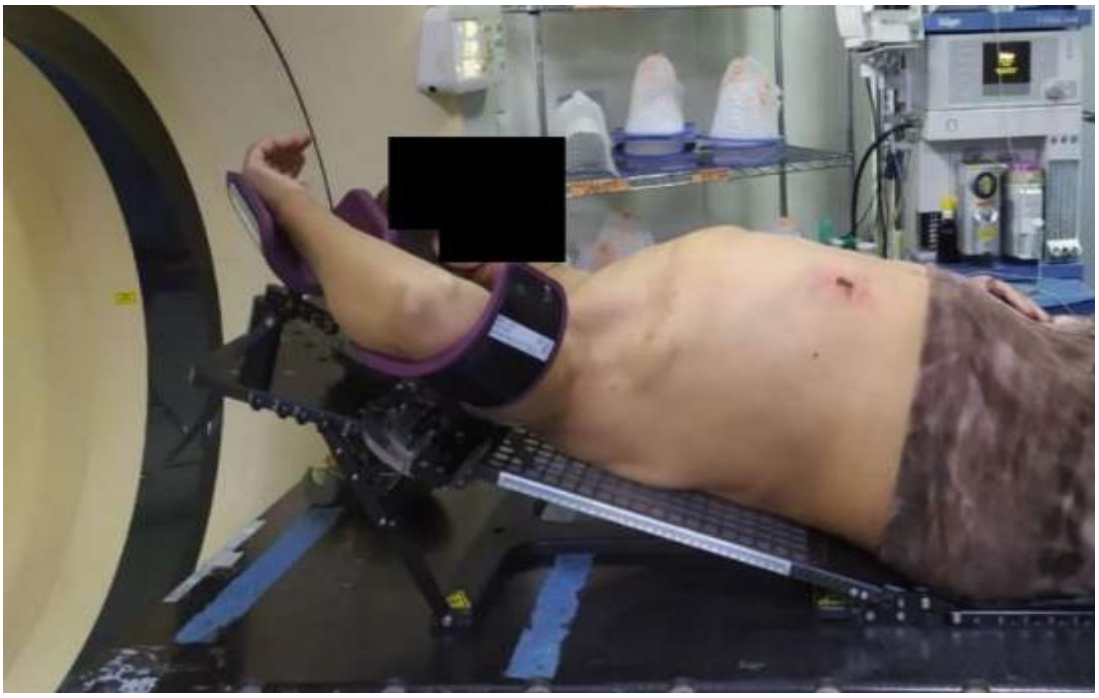

Figure 2: Positioning of a Patient Planned for Right-Sided Chest Wall Irradiation

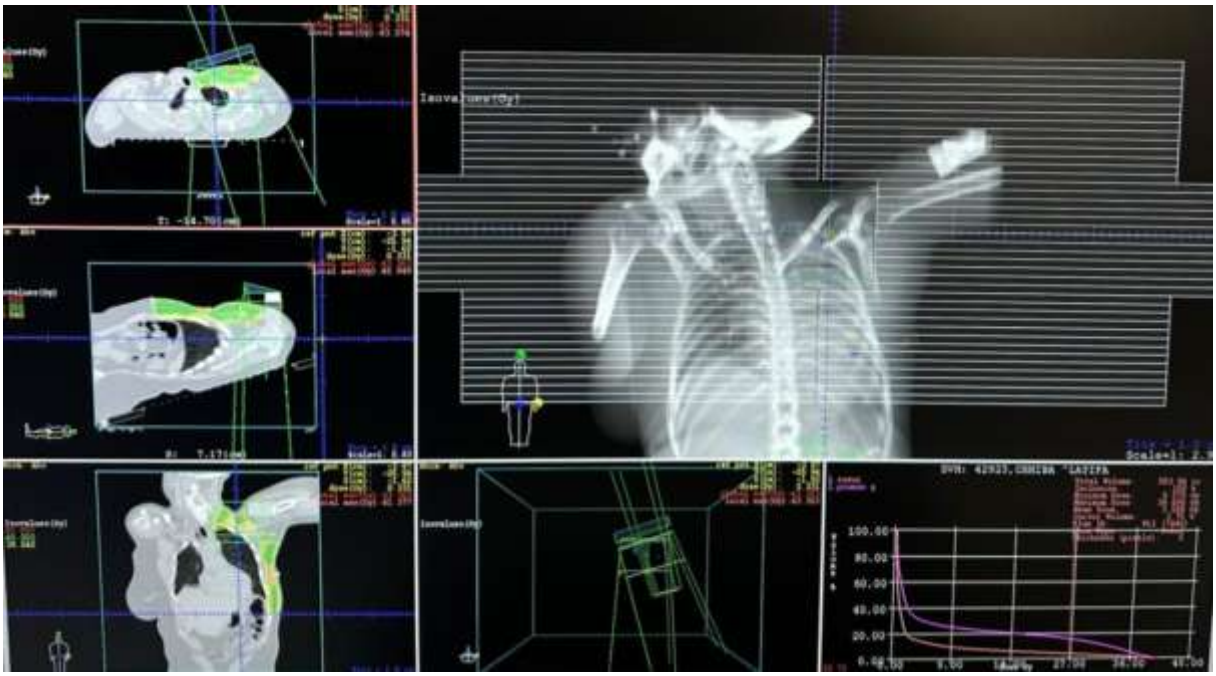

Figure 3: Dosimetry in a Patient Treated with Left Chest Wall Radiotherapy, Including Supraclavicular and Subclavicular Areas.

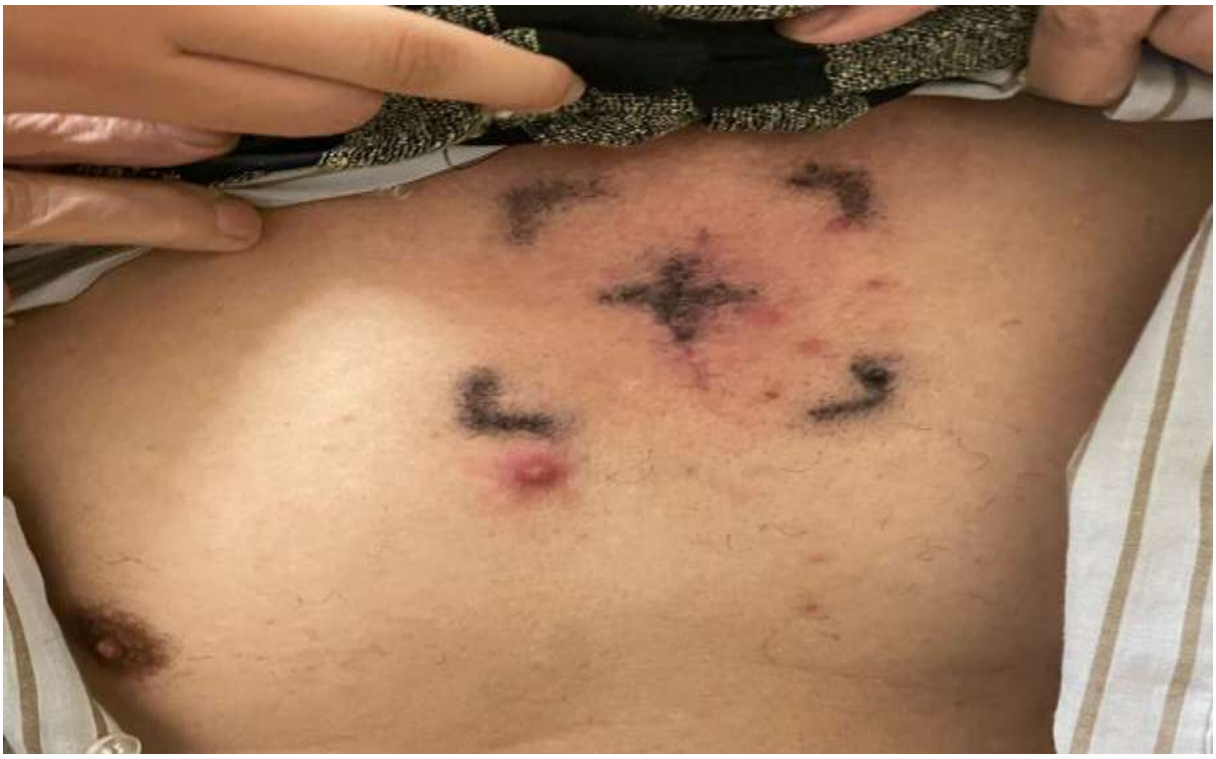

Figure 4: Grade I Radiodermatitis in a Patient Irradiated Post-Mastectomy, Including the Supraclavicular Region.

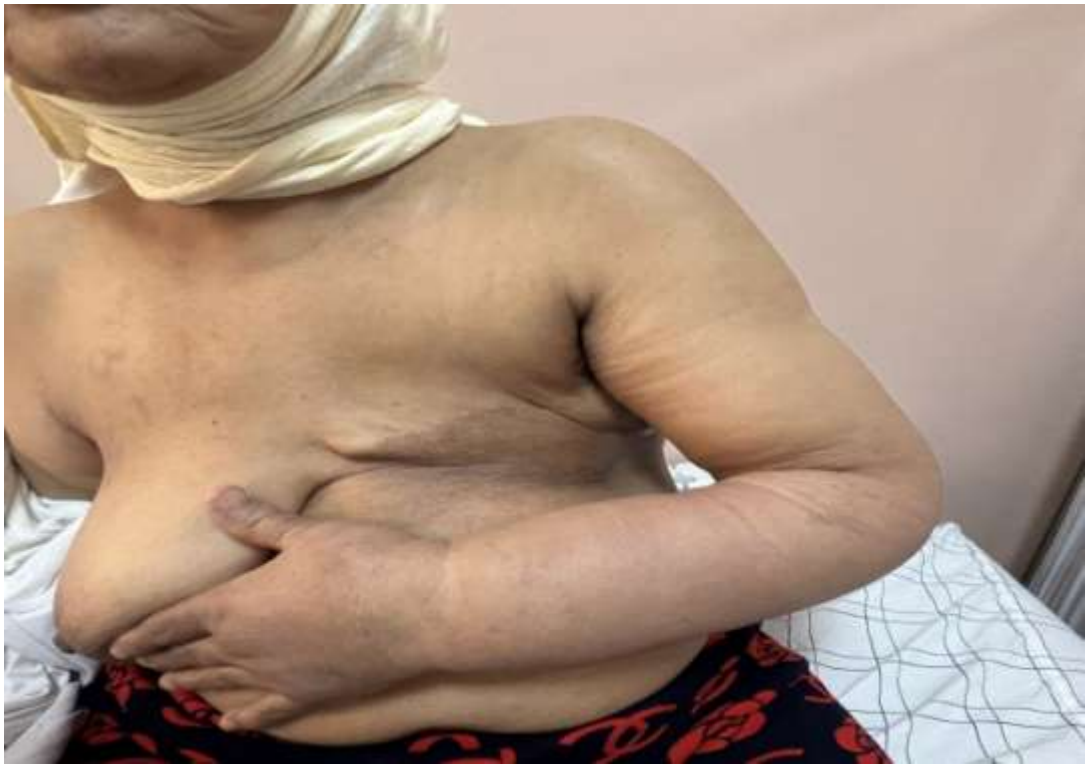

Figure 5: Left Upper Limb Lymphedema in a Patient Treated with Radiotherapy to the Chest Wall and Supraclavicular, Subclavicular, and Axillary Lymph Node Areas.

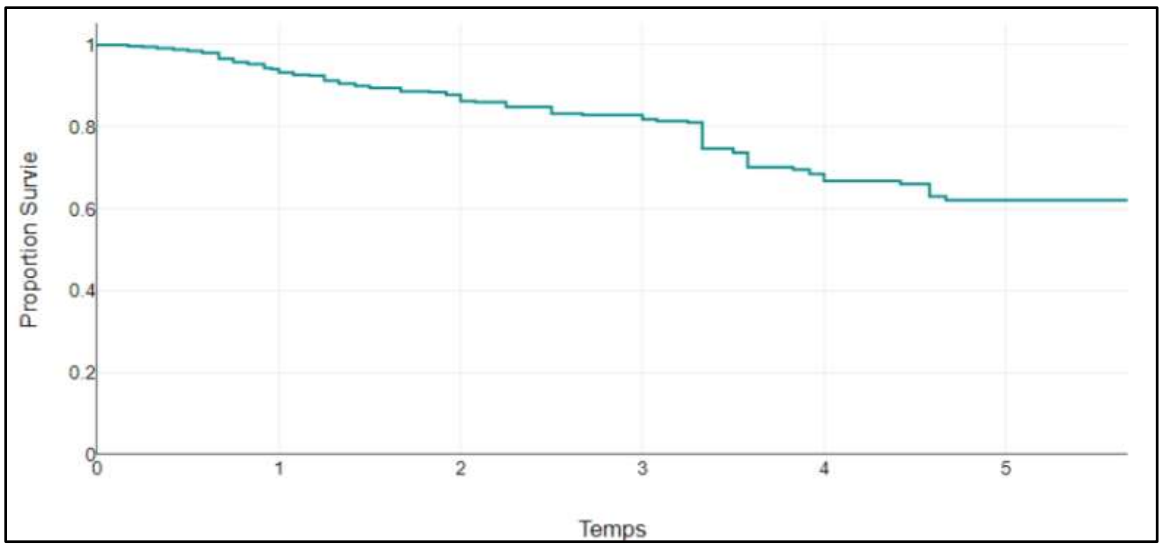

Figure 6: Overall Survival Curve According to Kaplan-Meier

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