

# Acute and Late Skin Toxicities of Hypofractionated Radiotherapy in Breast Cancer Among Young and Elderly Women

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## Abstract :

**Objective:** The aim of this study is to determine predictive factors and compare the acute and late skin toxicities of hypofractionated radiotherapy on breast cancer patients, focusing on differences between young and elderly women.

**Materials and Methods:** Our study is a retrospective analysis that included 208 patients (142 young patients aged 40 years or younger, and 66 elderly patients aged 65 years or older) out of a total of 1442, treated between January 2019 and January 2021, with invasive breast cancer. All our patients were treated with hypofractionated RT doses ranging from 42 to 53.2 Gy, 2.8 Gy per fraction, 5 fractions per week. Acute radiotherapy skin toxicities were assessed on the last day of treatment, and late skin toxicities after three months during the follow-up consultation after radiation treatment compliance and every 3 months thereafter. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 21. The significance level for all statistical analyses was set at  $p < 0.05$ .

## Results :

- In the group of elderly women, the age ranges from 68 to 88 with a mean of 74.72 +/- 4.18. The BMI of the patients was less than 18.5 in 2 patients, between 18.5 and 25 in 22 patients, between 25 and 30 in 23 patients, and above 30 in 19 patients. Regarding medical history, 39.4% have hypertension followed by diabetes in 28.8% and thyroid disorders in 9.1%. All patients underwent surgery, with mastectomy in 40.90% and lumpectomy in 59.09%, with axillary lymph node dissection or sentinel lymph node biopsy. Chemotherapy was received by 71.2% of patients. Acute toxicities were represented by radiodermatitis, which was observed in all patients (Grade 1 78.8% and Grade 2 21.2%). Local edema was observed in 53% of cases. Regarding late toxicities, hyperpigmentation was observed in 56.1% and fibrosis in 31.8%
- In the group of young women, the age ranged from 25 to 40 with a mean of 34.83 +/- 3.60. The BMI of the patients was less than 18.5 in 2 patients, between 18.5 and 25 in 58 patients, between 25 and 30 in 43 patients, and above 30 in 24 patients. Regarding medical history, hypertension was present in 7.7% of cases, diabetes in 7.7%, and thyroid disorders in 7%. All patients underwent surgery, with mastectomy in 56.3% and lumpectomy in 43.6%, with axillary lymph node dissection or

sentinel lymph node biopsy. The most frequent TNM stage was T2 in 64.1% and N0 in 55.6%. Chemotherapy was received by 71.2% of patients.

Acute toxicities were represented by radiodermatitis, observed in 79.6% of patients (G1 67.6% and G2 12%). Local edema was observed in 24.6% of cases. Regarding late toxicities, hyperpigmentation was observed in 60.6% and fibrosis in 36.6%.

- In univariate analysis, we notice that both elderly and young women show similar results regarding radiodermatitis, especially grade 2, which is more frequent in women with a BMI higher than 25, diabetic women, and those with thyroid disorders, with a p-value <0.048. Local edema was frequent in elderly and young patients who underwent lumpectomy with a p-value of 0.000, as well as in young patients with a BMI over 30 with a p-value of 0.037, with no significant value among elderly women. As for hyperpigmentation, it is more frequent in elderly and young women who underwent mastectomy, whereas fibrosis is more common in cases of lumpectomy, with a p-value of 0.000.

**Conclusion:** These results underline the importance of considering comorbidities and surgical interventions in managing toxicities associated with breast cancer radiation. Future studies could further explore these associations and investigate other potential risk factors to better understand and optimize patient management.

**Keywords :** Breast Cancer, Radiotherapy, Hypofractionated Radiation, Skin Toxicities

### 1. Introduction :

Adjuvant radiation therapy (RT) is crucial for local control and contributes to overall survival in early-stage and locally advanced breast cancers, following breast-conserving lumpectomy or mastectomy.[1, 2]

The conventional normo-fractionated RT regimen typically consists of 50 Gy delivered in 25 daily fractions of 2 Gy over 5 weeks, with an additional boost of 10 to 16 Gy to the tumor bed in case of breast-conserving surgery (BCS). In recent years, hypofractionated radiation therapy (HFRT) schedules have emerged to shorten the treatment duration and reduce costs. Long-term randomized trials have demonstrated that HFRT yields comparable outcomes in terms of local control and cosmetic results when compared to conventional fractionation, while also leading to reduced acute toxicities.[3]

Adjuvant radiation therapy to the breast or chest wall following surgery for breast cancer is usually well tolerated. However, acute skin toxicity is a common side effect that can impact the quality of life.

The aim of our study is to determine predictive factors and compare the acute and late skin toxicities of hypofractionated radiotherapy on breast cancer patients, focusing on differences between young and elderly women.

### 2. Aim of the study :

The aim of this study is to determine predictive factors and compare the acute and late skin toxicities of hypofractionated radiotherapy on breast cancer patients, focusing on differences between young and elderly women.

### 3. Materials and methods :

Our study is a retrospective analysis conducted over a period of 3 years, from January 2019 and January 2021, at the National Institute of Oncology in Rabat. This institute is the largest national

oncology center in Morocco and is a collaborator of the International Atomic Energy Agency (IAEA). It recruits the largest number of patients.

A total of 208 patients were included in this study out of a total of 1442, Treated with invasive breast cancer.

- 142 young patients aged 40 years or younger,
- 66 elderly patients aged 65 years or older

All our patients were treated with hypofractionated radiotherapy doses ranging from 42 to 53.2 Gy, 2.8 Gy per fraction ( depending on receiving a boost ), 5 fractions per week with conventionnelle radiotherapy 3D .

During the treatment , our patients were under a weekly surveillance looking for acute skin toxicities , and all the toxicities were assessed on the last day of treatment.

For late skin toxicities after three months during the follow-up consultation after radiation treatment compliance and every 3 months thereafter.

All data was collected from the patients medical records or directly through clinical examination for patients still under follow-up.

The toxicities being monitored were radiodermatitis and local oedema for acute skin toxicities, hyperpigmentation and fibrosis for late skin toxicities . They were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 21. The significance level for all statistical analyses was set at  $p < 0.05$ .

The inclusion criteria were as follows:

- Patients aged 40 years or younger,
- Patients aged 65 years or older
- Patients who received an adjuvant radiotherapy
- Patients with complete medical records

The exclusion criteria were as follows:

- Patients aged over 40 years
- Patients aged under 65 years
- Patient who didn't receive an adjuvant radiotherapy
- Patients with missing data

#### 4. Results :

- The number of our patients was two hundred eight ( $n=208$ ), with 142 young patients and 66 elderly patients.
- In the group of elderly women, the age ranges from 68 to 88 with a mean of  $74.72 \pm 4.18$ .
- The weight ranged from 35 to 96 kg, with an average of 67.5 kg. The BMI of the patients was less than 18.5 in 2 patients , between 18.5 and 25 in 22 patients , between 25 and 30 in 23 patients , and above 30 in 19 patients .

Regarding medical history, 39.4% have hypertension followed by diabetes in 28.8% and thyroid disorders in 9.1%.

All patients underwent surgery, with mastectomy in 40.90% and lumpectomy in 59.09%, with axillary lymph node dissection or sentinel lymph node biopsy. The most frequent TNM stage was T2 in 66.7% and N0 in 59.1%.

Chemotherapy was received by 71.2% of patients. Of course all our patient received an adjuvant radiation.

Acute toxicities were represented by radiodermatitis, which was observed in all patients (Grade 1 78.8% and Grade 2 21.2%). Local edema was observed in 53% of cases. Regarding late toxicities, hyperpigmentation was observed in 56.1% and fibrosis in 31.8%.

- In the group of young women, the age ranged from 25 to 40 with a mean of 34.83 +/- 3.60. The weight of our patients ranged from 45 to 111 kg, with an average of 68.28 kg. The BMI of the patients was less than 18.5 in 2 patients, between 18.5 and 25 in 58 patients, between 25 and 30 in 43 patients, and above 30 in 24 patients. Regarding medical history, hypertension was present in 7.7% of cases, diabetes in 7.7%, and thyroid disorders in 7%. . All patients underwent surgery, with mastectomy in 56.3% and lumpectomy in 43.6%, with axillary lymph node dissection or sentinel lymph node biopsy. The most frequent TNM stage was T2 in 64.1% and N0 in 55.6%. Chemotherapy was received by 63.4% of patients and all our patients underwent an adjuvant radiation. Acute toxicities were represented by radiodermatitis, observed in 79.6% of patients (G1 67.6% and G2 12%). Local edema was observed in 24.6% of cases. Regarding late toxicities, hyperpigmentation was observed in 60.6% and induration in 36.6%.
- All the descriptive results have been grouped in Tables 1 and 2.

**Table 1 : Socio-Demographic, Medical, and Therapeutic Characteristics of the Patients .**

	<b>Older Patients</b>	<b>Young Patients</b>
<b>Age</b>	68 to 88 years old	25 to 40
<b>IMC</b>		
Less than 18.5	2%	2
Between 18.5-25	22%	58
Between 25 and 30	23%	43
Above 30	19%	24
<b>Comorbidities</b>		
HTA	39.4%	7.7%
Diabetes	28.8%	7.7%
Thyroid Disorder	9.1%	7%
<b>Surgical treatment</b>		
Mastectomy	40.90%	56.3%
Lumpectomy	59.09%	43.6%
<b>TNM Stage</b>		
T1	18.1%	11.2%
T2	66.7%	64.1%
T3	10.6%	19%
T4	4.5%	4.6%

N0	59.1%	45.1%
N1	30.3%	54.9%
N2	7.6%	0%
N3	3%	0%
<b>Adjuvant Chemotherapy</b>	71.2%	63.4%
<b>Adjuvant Radiation</b>	100%	100%
Boost	34.6%	56.3%
No Boost	65.4%	43.6%

**Table 2 : Acute and late toxicities in the oldery and young patients**

	Acute Toxicities			Late Toxicities	
	Radiodermatisi s		Local Oedema	Hyperpigmentaitio n	Fibrosis
	G1	G2			
<b>Older Patient</b>	78.8%	21.2%	53%	56.1%	31.8%
<b>Young Patient</b>	67.6%	12%	24.6%	60.6%	36.6%

- In univariate analysis, we notice that both elderly and young women show similar results regarding radiodermatitis, especially grade 2, which is more frequent in women with a BMI higher than 25.

Local edema was also frequent in young patients with a BMI over 30 with a p-value of 0.03 , with no significant value among elderly women. There was no signification between BMI and hyperpigmentation and fibrosis

Diabetic women, and those with thyroid disorders may also present radiodermatitis with a p-value <0.048.

Surgery had an important role for toxicities : Local edema was frequent in eledery and young patients who underwent lumpectomy with a p-value of 0.000,. As for hyperpigmentation, it is more frequent in elderly and young women who underwent mastectomy, whereas induration is more common in cases of lumpectomy, with a p-value of 0.000.

Patients who underwent a boost radiation had more radiodermatitis G2 with a p- value 0.000 , and induration with a p value 0.04.

### 5. Discussion :

Breast cancer ranks as the most prevalent malignant tumor in women and can occur at any age. Despite its high incidence, breast cancer mortality rates have steadily decreased over the past few decades due to earlier detection from improved screening as well as therapeutic advancements.[4]

Radiotherapy represents an important element in the therapeutic process. Randomized controlled trials have demonstrated that adjuvant radiation therapy (RT) reduces breast cancer recurrence. As a result, RT has become a standard-of-care treatment modality for breast cancer. [5, 6]

Large randomized trials with more than 10-years follow-up have shown that adjuvant hypofractionated radiation therapy (HFRT) of the breast, achieves equivalent rates of local control and toxicity to healthy tissue compared to conventional radiotherapy. Therefore, HFRT for early breast cancer has become widely accepted in clinical practice [7]

Our patients were treated by HFRT with a dose of 42 Gy 2.8gy per fraction and for the boost 11.8 2.8gy per fraction. This regimen has shown its efficacy in a retrospective study. [8]

Patient-reported symptoms of late toxicity are relatively common in patients treated with hypofractionated radiation therapy for early breast cancer. The 10 year results of these trials showed no significant differences between conventional and hypofractionated radiotherapy in terms of late toxicity. [9]

Several skin manifestations can occur during or long after radiation, such as radiodermatitis, local edema, hyperpigmentation, or fibrosis.

Radiation dermatitis is the most common adverse effect of RT, observed in 90% of patients with breast cancer who receive RT, with 30% experiencing moderate to severe presentations. Several risk factors have been identified such as smoking, darker skin, higher radiation dose, larger breast size, and higher body mass index.

Several studies report a high BMI is associated with radiation-related skin toxicity, with the rate of grade  $\geq 2$  skin toxicity being reported to occur in up to 30%. When adjusted for age, comorbidity and radiation field, patients with obesity were over 3 times more likely to have skin toxicity. [10]

In our study, BMI has been a major risk factor for either radiodermatitis or local edema for both population.

Older age has been considered as a risk factor for the chronic radiodermatitis [5]. The skin's response of young women to radiation may differ due to factors such as skin elasticity, hormone levels, and overall health status [11]. In contrast, elderly women may experience different degrees of toxicity due to aging skin, comorbidities, and potentially slower healing processes. [12]

In a retrospective study, patients who underwent either mastectomy or breast conservation all received adjuvant hypofractionated. Although acute toxicity was not detailed, late toxicity was limited to grade  $\geq 2$  hyperpigmentation and grade 3 fibrosis [8]

A boost dose is frequently administered for patients who underwent lumpectomy to reduce local recurrence. This boost is responsible for an increase in the occurrence of post-radiation fibrosis and late sequelae [7]: severe fibrosis was significantly more frequent in the group treated with the dose boost, with a ten-year rate of 4.4% compared to 1.6% [13]. The prospective randomized EORTC trial of boost versus no boost did not show a significant difference in long-term cosmetic outcomes between a boost delivered by photons and a boost delivered by electrons. However, there was a lower incidence of late subcutaneous fibrosis with a boost delivered by electrons. [14]

It has been shown that diabetes and hypertension increase the radiosensitivity of the patient, which leads to an increased production of co-factors responsible for the alteration of the skin barrier and the appearance of skin toxicities, particularly radiation-induced fibrosis [15]. The main risk factors for fibrosis are the administered radiation dose, the volume of irradiated tissue, an accelerated radiation schedule, and concurrent chemotherapy treatment. [16-18].

## 6. Conclusion :

In conclusion, our study highlights that hypofractionated radiotherapy in breast cancer treatment exhibits similar patterns of acute and late skin toxicities in both young and elderly women. Factors such as higher BMI, comorbidities, type of surgery and the addition of the boost were significantly associated with increased skin toxicities.

These findings underscore the necessity of considering patient comorbidities and specific surgical histories when managing skin toxicities from breast cancer radiotherapy. Future research should delve deeper into these associations and explore additional risk factors to enhance patient management and optimize treatment outcomes in order to provide a better quality of life.

## References

1. PS, O.M.H., et al., Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*, 1997. **337**(14): p. 949-55.
2. Group, E.B.C.T.C., Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *The Lancet*, 2011. **378**(9804): p. 1707-1716.
3. Haviland, J.S., et al., The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *The lancet oncology*, 2013. **14**(11): p. 1086-1094.
4. Montero, A., et al., Acute skin toxicity of ultra-hypofractionated whole breast radiotherapy with simultaneous integrated boost for early breast cancer. *Clinical and Translational Radiation Oncology*, 2023. **41**: p. 100651.
5. Ramseier, J.Y., M.N. Ferreira, and J.S. Leventhal, Dermatologic toxicities associated with radiation therapy in women with breast cancer. *International Journal of Women's Dermatology*, 2020. **6**(5): p. 349-356.
6. Taylor, C., et al., Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. *The Lancet*, 2023. **402**(10416): p. 1991-2003.
7. De Matteis, S., et al., Hypofractionated radiation therapy (HFRT) of breast/chest wall and regional nodes in locally advanced breast cancer: toxicity profile and survival outcomes in retrospective monoinstitutional study. *Clinical Breast Cancer*, 2022. **22**(3): p. e332-e340.
8. Bellefqih, S., et al., Hypofractionated regional nodal irradiation for women with node-positive breast cancer. *International Journal of Radiation Oncology\* Biology\* Physics*, 2017. **97**(3): p. 563-570.
9. De Felice, F., et al., Relation between hypofractionated radiotherapy, toxicity and outcome in early breast cancer. *The Breast Journal*, 2017. **23**(5): p. 563-568.
10. Lomma, C., H. Chih, and A. Chan, Adjuvant Dose Dense Chemotherapy in Patients With Obesity: Short-Term Toxicities and Breast Cancer Outcome. *Clinical Breast Cancer*, 2023. **23**(5): p. 491-499.
11. Porock, D., Predicting the severity of radiation skin reactions in women with breast cancer. 1998.
12. Mohiuddin, A.K., Skin aging & modern age anti-aging strategies. *Int. J. Clin. Dermatol. Res*, 2019. **7**: p. 209-240.
13. Bartelink, H., et al., Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *Journal of Clinical Oncology*, 2007. **25**(22): p. 3259-3265.

14. Vrieling, C., et al., The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC ‘boost vs. no boost’ trial. *Radiotherapy and Oncology*, 2000. **55**(3): p. 219-232.
15. Delanian, S. and J.-L. Lefaix, The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. *Radiotherapy and oncology*, 2004. **73**(2): p. 119-131.
16. Edwards, M.J., et al., Squamous cell carcinoma arising in previously burned or irradiated skin. *Archives of surgery*, 1989. **124**(1): p. 115-117.
17. Straub, J.M., et al., Radiation-induced fibrosis: mechanisms and implications for therapy. *Journal of cancer research and clinical oncology*, 2015. **141**: p. 1985-1994.
18. Parekh, A., et al., Predictors of radiation-induced acute skin toxicity in breast cancer at a single institution: Role of fractionation and treatment volume. *Advances in radiation oncology*, 2018. **3**(1): p. 8-15.