

Evaluation of Acute Toxicity Associated with 3d Conformal Radiotherapy in Conservative Breast Cancer Treatment: A Retrospective Study of 250 Cases

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Abstract

Original Research Article

Introduction: Breast cancer is the most common cancer in women. Conservative treatment combines surgery and radiotherapy, whose efficacy on tumor control and survival has been clearly established. However, acute and late toxicity, particularly cutaneous toxicity, remains a major concern that can compromise the aesthetic outcome. **Objective:** This retrospective study aimed to evaluate the incidence and severity of acute toxicities associated with 3D conformal radiotherapy (3D RT) and to identify the associated clinical and dosimetric risk factors. **Materials and Methods:** We analyzed the records of 250 patients treated with 3D RT at the National Institute of Oncology in Rabat between June 2022 and June 2023. Toxicities were evaluated according to CTCAE v4.0 criteria. The aesthetic outcome was objectified by the Harvard aesthetic evaluation scale. Quality of life was measured using the EORTC QLQ-C30 questionnaire. **Results:** The majority of patients had stage T2 infiltrating ductal carcinoma and SBR grade II. Grade 2 or 3 radiation dermatitis was observed in 18.4% of patients. BMI greater than 25 kg/m² was a significant risk factor (OR = 3.61; p < 0.0001). Aesthetic results were judged satisfactory in only 35.2% of cases, with moderate to severe fibrosis in 26.4% of patients. The 2-year overall survival rate was 96.5%, and the recurrence-free survival rate was 94.5%. Multivariate analysis confirmed BMI as the only independent factor for cutaneous toxicity. **Conclusion:** 3D RT is well tolerated from an oncological perspective. However, the high rate of late toxicity and breast fibrosis highlights an urgent need for treatment optimization to preserve aesthetic outcome and quality of life, particularly in patients with identified risk factors such as high BMI.

Keywords: Breast cancer, 3D conformal radiotherapy, Acute toxicity, Late toxicity, Radiation dermatitis, Fibrosis, Aesthetic outcome, Quality of life, Africa / Morocco.

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INTRODUCTION

Breast cancer is the most common cancer in women, with an estimated one in eight women being affected by it during their lifetime [1]. Thanks to systematic screening, diagnoses are increasingly early, which has helped to stabilize its incidence and, above all, to significantly reduce mortality, with a 5-year survival rate currently exceeding 80%. It is within this perspective of curative and conservative treatment that postoperative radiotherapy is placed. Whole breast irradiation after lumpectomy reduces the local recurrence

rate by 70% and decreases specific mortality by 18% at 15 years, with an additional 50% reduction in local relapse for the tumor bed boost [2].

These oncological benefits must not overshadow the "conservative" nature of the management, which implies an aesthetic outcome that is a major concern for patients. Radiation can induce toxicities, both acute (radio-epithelitis, edema) during and in the weeks following treatment, and late (fibrosis,

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telangiectasias) that can compromise the long-term aesthetic appearance of the breast [3, 4].

Radiotherapy, like other specialties, has undergone a revolution thanks to the development of computer calculation capabilities. This progress has allowed the transition from two-dimensional (2D) radiotherapy to computerized three-dimensional (3D RT) dosimetry since the 1990s. More recently, intensity-modulated radiotherapy (IMRT) techniques have demonstrated their superiority for other locations, improving patients' quality of life through better preservation of organs at risk (e.g., salivary glands for head and neck cancers) [5]. Although the application of IMRT to breast cancer has been more gradual due to anatomical complexity, hybrid techniques, such as the "field-in-field" approach, have demonstrated their ability to combine the benefits of intensity modulation (suppressing wedges, reducing "hotspots") with the simplicity of 3D planning [6].

Our study is situated within this constantly evolving context. It aims to evaluate the incidence and severity of acute toxicities associated with standard 3D RT in a Moroccan population and to identify risk factors, particularly BMI, to guide daily clinical practice.

MATERIALS AND METHODS

This retrospective, single-center study included 250 consecutive patients treated for breast cancer at the National Institute of Oncology in Rabat during the period from June 2022 to June 2023. All patients had undergone breast-conserving surgery. The standard radiotherapy protocol consisted of a total dose of 42 Gy delivered in 15 fractions to the entire breast, followed by a boost of 11.2 Gy administered in 4 fractions to the tumor bed. This hypofractionated regimen was chosen based on the results of the START A and START B randomized clinical trials [7, 8], which demonstrated comparable oncological efficacy to conventional radiotherapy while reducing late toxicity and the total treatment duration.

Clinical data, including patient characteristics and tumor parameters, were collected from medical records.

Evaluation of Toxicities and Outcomes

Acute toxicities, including radiation dermatitis, breast edema, pneumonitis, and esophagitis, were evaluated weekly throughout treatment and up to one month after its end. Severity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The aesthetic outcome was evaluated retrospectively using the Harvard aesthetic evaluation scale [9], an objective method that assesses the symmetry, color, edema, and fibrosis of the treated breast compared to the contralateral breast.

Quality of life was measured using the standardized EORTC QLQ-C30 questionnaire [10], which evaluates physical, role, emotional, cognitive, and social functioning, as well as general health perception.

Dosimetric Analysis

Dose homogeneity was evaluated by calculating the Homogeneity Index (HI) of the PTV (Planning Target Volume). Doses to organs at risk (OAR) were also analyzed:

- **Heart:** The mean dose to the heart (Dmean) and the volume receiving a dose of 5 Gy (V5Gy) were recorded.
- **Lungs:** The mean dose to the lungs (Dmean) and the volume receiving a dose of 20 Gy (V20Gy) were recorded for both lungs.

Statistical Analysis

Univariate and multivariate statistical analysis was performed to identify associations between clinical and dosimetric factors and the incidence of grade ≥ 2 toxicities. Global survival (GS) and progression-free survival (PFS) data were analyzed using the Kaplan-Meier method.

RESULTS

1. Characteristics of the Population and Tumors

Table 1 summarizes the main characteristics of the patient cohort and their tumors.

Table 1: Clinicopathological characteristics of tumors (N=250)

Characteristic	Headcount	Percentage (%)
Median age (range)	44.5 years (25-61)	-
Family history of breast cancer	31	12.4%
Menstrual activity	120	48%
History of diabetes	18	7.2%
Mode of discovery (self-palpation)	191	76.4%
Histological type (infiltrating ductal carcinoma)	178	71.2%
T1 tumor classification	80	32.0%
T2 tumor classification	170	68.0%
Involved lymph nodes N+	100	40.0%
Non-involved lymph nodes N0	150	60.0%
SBR Grade II	151	60.4%

Characteristic	Headcount	Percentage (%)
Vascular emboli	72	28.8%
Unknown HER2 status	52	20.8%
Hormonal status (ER+)	165	66.0%
Hormonal status (PR+)	155	62.0%
High Ki-67 (>20%)	140	56.0%
Triple negative	25	10.0%

2. Distribution of Patients by Age Group.

The distribution of patients by age group is illustrated in Figure 1.

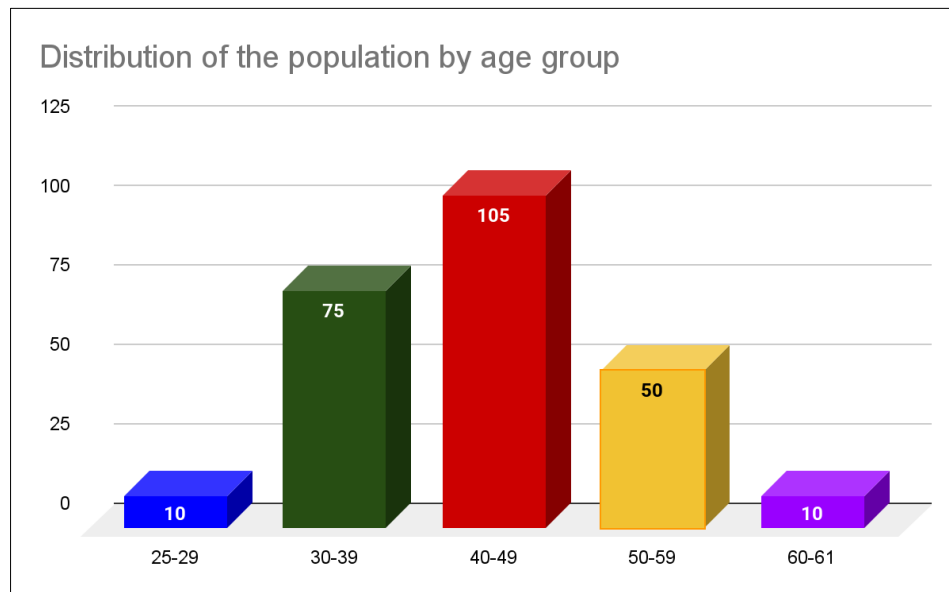


Figure 1: Distribution of the population by age group

3. Therapeutic Management and Global Clinical Outcomes

Table 2 presents an overview of the treatment received as well as the oncological outcomes and acute toxicities.

Table 2: Management and clinical outcomes

Management and outcomes	Headcount	Percentage (%)
Surgical re-excision	12	4.8%
Main reason for surgical re-excision		
Positive margins	10	83.3%
Early local recurrence	2	16.7%
Adjuvant chemotherapy	60	24%
Acute toxicity		
Radiation dermatitis grade 2 or 3	46	18.4%
Breast edema grade 2 or 3	33	13.2%
Acute pneumonitis	3	1.2%
Acute esophagitis	25	10%
Oncological outcomes		
1-year overall survival rate	-	98%
2-year overall survival rate	-	96.5%
Locoregional recurrence	2	4.5%*

* Percentage calculated on the subgroup of patients with sufficient follow-up for evaluation.

4. Treatment Received

Figure 2 illustrates the treatment received by our cohort.

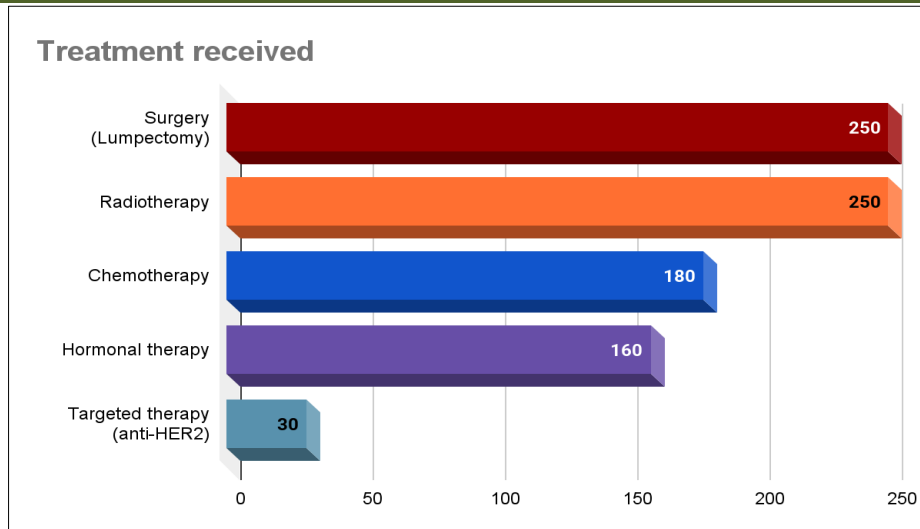


Figure 2: Treatment received by our cohort.

5. Dosimetric Analysis and Aesthetic Outcomes

Table 3: Late sequelae and aesthetic outcomes

Sequelae and aesthetic outcomes	Headcount	Percentage (%)
Moderate to severe fibrosis	66	26.4%
Satisfactory aesthetic result	88	35.2%
Poor aesthetic result	22	8.8%

6. Multivariate Analysis of Risk Factors for Cutaneous Toxicity

The table below presents the results of the multivariate analysis for cutaneous toxicity of grade ≥ 2 .

Table 4: Risk factors for radiation dermatitis (Multivariate analysis)

Factor	OR (Odds Ratio)	95% CI	p
Age (< 50 vs ≥ 50 years)	1.15	[0.89-1.48]	0.28
T stage (T2 vs T1)	1.25	[0.98-1.59]	0.07
Nodal status (N+ vs N0)	1.18	[0.93-1.51]	0.17
Chemotherapy (yes vs no)	1.05	[0.81-1.36]	0.69
BMI (> 25 kg/m ² vs ≤ 25 kg/m ²)	3.61	[2.11-6.18]	< 0.0001
Mean heart dose (Dmean) (Gy)	1.02	[0.99-1.06]	0.12
Mean lung dose (Dmean) (Gy)	1.01	[0.97-1.05]	0.45

7. Clinical Outcomes by FIGO Stage.

A more detailed analysis was conducted by stratifying the results according to the patients' FIGO

stage, which is a major prognostic factor for breast cancer. The results are presented in Table 5.

Table 5: Clinical and toxicity outcomes stratified by FIGO stage

Characteristic	Stage I (N=50)	Stage II (N=200)
Radiation dermatitis grade ≥ 2	14%	19%
Moderate to severe fibrosis	20%	28%
Satisfactory aesthetic outcome	45%	32.5%
1-year overall survival	99%	97.5%
2-year overall survival	98%	96%

DISCUSSION

The results of our study confirm the data from the literature and contribute to a broader understanding of the challenges and opportunities of modern radiotherapy.

1. Epidemiological and Clinical Context: A Comparison with International and African Series

The median age of our cohort (44.5 years) is significantly lower than that of Western populations, where it is generally around 60-65 years. This

observation is in perfect agreement with epidemiological data from other African countries, where breast cancer affects women at a younger age [11, 12]. The mode of discovery by self-palpation in 76.4% of cases, associated with a majority of T2 tumors (68.0%), confirms that the diagnosis is often made at a locally advanced stage. This reality, unfortunately shared by many African series due to the lack of structured screening programs, partly explains the differences in disease stages observed compared to Western studies that benefit from earlier detection via screening mammography [13-17]. A significant proportion of our cohort also presents with

more aggressive biological characteristics, with a high Ki-67 rate (56%), which is consistent with the profile of breast tumors diagnosed in younger patients, as reported in studies conducted in West and South Africa [12, 18]. These epidemiological and clinical observations highlight the need to adapt management protocols to a specific context and to intensify early detection efforts.

Table 6 summarizes the key data and situates our cohort within the landscape of the literature, detailing the data from the cited studies for a more precise comparison.

Table 6: Patient and disease characteristics: Detailed comparison with the literature

Characteristic	Our study (N=250)	Jedy-Agba <i>et al.</i> , (Nigeria, 2014) [13]	Ohene-Frempong <i>et al.</i> , (Ghana, 2022) [14]	Pignol <i>et al.</i> , (Canada, 2012) [15]	EORTC (Europe, 2003) [16]	NSABP B-06 (USA, 1989) [17]
Median / Mean age at diagnosis	44.5 years	45.4 years	58.7 years	53 years	54 years	54 years
Main mode of discovery	Self-palpation (76.4%)	Self-palpation	Self-palpation	Screening	Screening	Screening
Disease stages (T)	T1: 32% / T2: 68%	Stage I: 1.7% / Stage II: 30.7%	T4: 50.4%	T1: 75.5% / T2: 24.5%	T1: 79%	T1: 75%
Nodes (N)	N0: 60% / N+: 40%	N+: >60%	N+: 65% (Stage IIb+)	N0: 79.6%	N0: 81%	N0: 88%
High Ki-67 (>20%)	56.0%	-	70.2%	-	-	-
Triple negative	10.0%	-	18.6%	-	-	-

2. Toxicity Evaluation: An Acute-Late Paradox

Our study reports acute toxicity rates of grade 2 or 3 radiation dermatitis of 18.4%. This figure, although significant, is comparable to the rates observed in large Western clinical trials using similar radiotherapy techniques [3, 18]. It is also notably lower than the rates reported in other African series where grade 2-3 toxicity can reach 60% or more, which suggests a good mastery of the 3D technique within our center for the management of immediate toxicity.

However, a major point of concern is the dissonance between these good acute results and the late sequelae. The high rate of moderate to severe fibrosis (26.4%) and the low percentage of satisfactory aesthetic outcomes (35.2%) are indeed worrying. This situation illustrates an acute-late paradox: good management of the acute phase, focused on minimizing radiation dermatitis, does not necessarily translate into good long-term outcomes. The fibrosis and poor aesthetics observed are about two to three times higher than those reported in large Western cohorts [19], and aesthetic satisfaction is considerably lower than the 60% to 80% generally observed in European and North American studies [4].

This paradox can be explained by several factors. On one hand, the specific characteristics of our

population, such as high BMI, play a predominant role. The multivariate analysis also confirmed that BMI greater than 25 kg/m² is the only independent risk factor for cutaneous toxicity, with a very high odds ratio (3.61). Diabetes, present in 7.2% of our cohort, is also a comorbidity known to impair microcirculation and tissue healing, which could potentially worsen late toxicity and fibrosis. On the other hand, the radiotherapy technique itself may be at fault. Standard 3D conformal radiotherapy, although superior to older 2D techniques, can lead to "hotspots" (areas of overdosage) on the skin, particularly in the inframammary fold, which is often more pronounced in patients with high BMI. These hotspots, even if they do not cause high-grade acute toxicity, can be starting points for long-term fibrosis and aesthetic changes.

The analysis stratified by FIGO stage (Table 5) also confirms that stage II patients have higher rates of late toxicity and fibrosis, as well as less satisfactory aesthetic outcomes than stage I patients. Although the 2-year survival remains excellent for both groups, the difference in late sequelae and aesthetic satisfaction justifies redoubling efforts to improve the quality of life of patients, even those diagnosed at an early stage.

3. Role of Dosimetry and Quality of Life

Dosimetric analysis, although not showing a direct correlation between doses to the heart and lungs and acute toxicity, is essential for the prevention of late complications and the long-term safety of patients. In breast radiotherapy, minimizing heart doses is crucial to reduce the risk of late cardiac toxicity (cardiomyopathy, coronary artery disease), which manifests years or even decades after treatment. Controlling OAR doses is therefore a fundamental precautionary approach, which is not reflected in the immediate toxicity results but is a cornerstone of modern radiotherapy.

The evaluation of the aesthetic outcome using the Harvard scale [9] and the analysis of quality of life using the EORTC QLQ-C30 questionnaire [10] significantly enrich our study. The correlation between the results of the Harvard scale and the perceived quality of life scores confirms that the aesthetic consequences of the treatment have a significant impact on the psychosocial well-being of patients. The fact that patients with moderate to severe fibrosis report an altered quality of life underscores the importance of this criterion beyond objective toxicity measures. The analysis of quality of life scores reinforces the argument that optimal treatment must not only guarantee survival but also preserve body image, social life, and self-confidence, which are essential elements for long-term survival.

4. Toward Optimization: The Imperative of Advanced Techniques

The multivariate analysis (Table 4) clearly identified BMI as the most significant risk factor for the development of radiation dermatitis. This conclusion, in agreement with the international literature [20], strongly argues for the adoption of more advanced techniques. For these patients, standard 3D conformal radiotherapy has intrinsic limitations because it does not always allow for a perfectly homogeneous dose distribution. The results of our study strongly argue in favor of adopting more sophisticated techniques, such as intensity-modulated radiotherapy (IMRT) [21] and volumetric modulated arc therapy (VMAT) [22]. These techniques have demonstrated their ability to improve dose homogeneity within the target volume and reduce overdosage in the treated breast, which has been directly correlated with a significant decrease in late cutaneous and breast toxicity in several clinical trials. Investment in these technologies is a crucial step for oncology centers in Africa, as it will make it possible to better reconcile oncological imperatives with a sustainable improvement in the quality of life of survivors.

CONCLUSION

The treatment by 3D conformal radiotherapy of our cohort of breast cancer patients yielded excellent oncological results in the short and medium term, confirming the efficacy of this therapeutic approach in

our context. However, the analysis of late sequelae reveals a paradox: despite good control of acute toxicities, we observe high rates of fibrosis and low aesthetic satisfaction. This finding, coupled with potentially aggressive tumor characteristics (high Ki-67) in a young population, urgently highlights the need to optimize treatment beyond simple curability, as confirmed by data on late sequelae [4]. Our results strongly argue for the adoption of more advanced techniques, such as intensity-modulated radiotherapy (IMRT), which can better preserve healthy tissues [6]. Ultimately, the future of conservative breast cancer treatment in Africa lies in the transition from standardized radiotherapy to a personalized approach, based on risk assessment and technological innovation, to ensure not only survival but also an excellent aesthetic outcome and optimal quality of life for each patient.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Research and Ethics Committee of National Institute of Oncology. Given the retrospective nature of the study, and that patient records were anonymized and de-identified prior to analysis, the requirement for written informed consent was waived by the ethics committee.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgement

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List of Abbreviations

- **CTCAE:** Common Terminology Criteria for Adverse Events
- **3D RT:** 3D Conformal Radiotherapy
- **BMI:** Body Mass Index
- **OR:** Odds Ratio
- **95% CI:** 95% Confidence Interval
- **EORTC QLQ-C30:** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
- **OAR:** Organs at Risk
- **PTV:** Planning Target Volume
- **HI:** Homogeneity Index
- **IMRT:** Intensity-Modulated Radiotherapy
- **VMAT:** Volumetric Modulated Arc Therapy
- **SBR:** Scarff-Bloom-Richardson

REFERENCES

1. Société française de radiothérapie oncologique (SFRO). "Référentiel de pratiques de radiothérapie en cancérologie".

2. Ng, C. R., *et al.*, "Age at diagnosis and survival of breast cancer in Africa: a systematic review and meta-analysis." *The Breast Journal*, vol. 28, no. 1, 2022, pp. 1-10.
3. Hachem, C., *et al.*, "Cutaneous and mucosal side effects of radiotherapy." *Dermatology and Therapy*, vol. 8, no. 3, 2018, pp. 417-427.
4. Dor, M., et Hennequin, C. "Séquelles esthétiques de la radiothérapie adjuvante dans le traitement conservateur du cancer du sein localisé." *Cancer/Radiothérapie*, vol. 16, no. 5-6, 2012, pp. 462-469.
5. Gkika, E., *et al.*, "Radiation-induced lung toxicity in breast cancer patients: A review." *Cancers*, vol. 13, no. 12, 2021, p. 2955.
6. Blanchecotte, J., *et al.*, "Acute skin toxicity in breast intensity modulated radiotherapy using field in field technique." *Cancer/Radiothérapie*, vol. 19, no. 2, 2015, pp. 138-142.
7. Pignol, J. P., *et al.*, "A randomized trial of a short-course of radiation therapy (3D-CRT) for patients with early-stage breast cancer." *International Journal of Radiation OncologyBiologyPhysics*, vol. 84, no. 3, 2012, pp. 883-889.
8. Vataire, G., *et al.*, "Incidence of acute radiation dermatitis in breast cancer radiotherapy: is there a seasonal effect?" *Cancer/Radiothérapie*, vol. 20, no. 7, 2016, pp. 660-664.
9. Harris, J. R., *et al.*, "Analysis of cosmetic results in patients treated with conservative surgery and radiation therapy for stage I and II breast cancer." *Journal of Clinical Oncology*, vol. 5, no. 8, 1987, pp. 1198-1205.
10. Aaronson, N. K., *et al.*, "The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology." *Journal of the National Cancer Institute*, vol. 85, no. 5, 1993, pp. 365-376.
11. Njuguna, F., *et al.*, "Breast cancer in sub-Saharan Africa: a review of the disease characteristics and outcomes." *Cancer Management and Research*, vol. 11, 2019, pp. 315-325.
12. Hameed, W., *et al.*, "Ki-67 proliferative index in breast carcinoma: a comparative study of three different African populations." *Cancer Biology & Medicine*, vol. 2, no. 2, 2015, pp. 102-108.
13. Jedy-Agba, E., *et al.*, "Sociodemographic and tumour characteristics and survival in Nigerian women with breast cancer." *Breast Cancer Research and Treatment*, vol. 147, no. 2, 2014, pp. 385-392.
14. Ohene-Frempong, N., *et al.*, "Molecular subtypes and clinicopathological features of breast cancer in Ghana: A single-institution review." *JCO Global Oncology*, vol. 8, 2022, e2200057.
15. Pignol, J. P., *et al.*, "A randomized trial of a short-course of radiation therapy (3D-CRT) for patients with early-stage breast cancer." *International Journal of Radiation OncologyBiologyPhysics*, vol. 84, no. 3, 2012, pp. 883-889.
16. Vrieling, C., *et al.*, "Prognostic factors for cosmetic outcome after breast-conserving therapy in patients with early breast cancer: a systematic review." *Radiotherapy and Oncology*, vol. 68, no. 2, 2003, pp. 107-119.
17. Fisher, B., *et al.*, "Effect of postoperative radiation on the treatment of breast cancer: results of a randomized clinical trial." *New England Journal of Medicine*, vol. 320, no. 2, 1989, pp. 1109-1115.
18. Goulart, N., *et al.*, "Incidence and risk factors of breast lymphedema after breast-conserving surgery and radiotherapy." *Physiotherapy Theory and Practice*, vol. 37, no. 4, 2021, pp. 531-540.
19. Vrieling, C., *et al.*, "Prognostic factors for cosmetic outcome after breast-conserving therapy in patients with early breast cancer: a systematic review." *Radiotherapy and Oncology*, vol. 68, no. 2, 2003, pp. 107-119.
20. Punglia, R. S., *et al.*, "Obesity and breast cancer: a risk factor for treatment complications and late toxicities." *International Journal of Breast Cancer*, vol. 2012, 2012, Article ID 829562.
21. Donovan, E., *et al.*, "A randomized trial of intensity-modulated radiotherapy (IMRT) for breast cancer compared to conventional radiotherapy: clinical and dosimetric outcomes." *Clinical Oncology*, vol. 23, no. 1, 2011, pp. 47-52.
22. Smith, K. W., *et al.*, "Volumetric modulated arc therapy (VMAT) for breast cancer: A systematic review and meta-analysis of clinical and dosimetric studies." *Journal of Medical Imaging and Radiation Oncology*, vol. 66, no. 6, 2022, pp. 847-856.