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Research Article

Hypofractionated Radiotherapy in Young Women with Early-Stage Breast Cancer: Impact on Recurrence-Free Survival and Skin Toxicity

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ABSTRACT

Background: Breast cancer in young women (<40 years) is associated with delayed diagnosis, aggressive tumor biology, and poorer outcomes compared to older patients. Hypofractionated radiotherapy (HF-WBI) has emerged as an effective alternative to conventional fractionation, but its use in younger populations remains debated due to concerns about long-term toxicity.

Methods: This retrospective study analyzed 231 young breast cancer patients treated at Hassan II University Hospital, Fès, Morocco (2012–2023). Patients received HF-WBI (42 Gy in 15 fractions) following surgery. Outcomes included recurrence-free survival, skin toxicity, and overall survival.

Results: The mean age at diagnosis was 31.9 years, with a mean tumor size of 4.6 cm. Most tumors were invasive ductal carcinomas (80%) and hormone receptor-positive (65.8%). Acute skin toxicities occurred in 21.6% of patients (Grade 1: 38 cases; Grade 2: 10 cases), with no late toxicities reported. After a median follow-up of 6 years, the 5-year overall survival rate was 63%, and 151 patients experienced disease progression, primarily bone metastases.

Conclusion: HF-WBI demonstrated comparable efficacy and acceptable acute toxicity in young women with early-stage breast cancer. Further research is needed to assess long-term effects and optimize personalized treatment strategies for this high-risk group.

Keywords

Radiotherapy, Breast Cancer, Skin Toxicity, Aggressive tumor.

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide, with its incidence continuing to rise despite significant advancements in early detection and treatment. While the disease primarily affects older women, it also occurs in younger populations, typically defined as those under 40 years of age [1]. Breast cancer in young women poses distinct challenges, as it is often diagnosed at more advanced stages and is associated with more aggressive tumor biology, leading to poorer prognoses compared to older patients. Several factors contribute to these disparities, including denser breast tissue that limits the sensitivity of mammographic screening, a higher prevalence of

hormone receptor-negative tumors, and an increased likelihood of hereditary mutations such as BRCA1 and BRCA2 [2,3].

Radiotherapy is a fundamental component of breast cancer management, particularly following breast-conserving surgery, where it significantly reduces local recurrence rates. In recent years, hypofractionated radiotherapy delivering higher doses per session over a shorter overall treatment duration has become an attractive alternative to conventional fractionation. Clinical trials have demonstrated its comparable oncological outcomes, reduced treatment burden, and improved patient convenience [4-6]. However, the use of hypofractionation in young women remains a subject of debate due to concerns about long-term toxicity, including heightened risks of skin reactions, fibrosis, and potential secondary malignancies. Given that younger patients have longer life expectancies and distinct physiological responses to radiation, assessing the balance between efficacy and safety in this population is crucial [7].

Our study aims to evaluate the impact of hypofractionated radiotherapy on recurrence-free survival and skin toxicity in young women with early-stage breast cancer. By analyzing clinical outcomes and treatment-related adverse effects, we seek to contribute to the growing body of evidence supporting tailored radiotherapy approaches that optimize both disease control and quality of life for this high-risk group.

Methods

Breast cancer is the most common reason for consultation in our department. The primary objective of this study is to investigate the various epidemiological, clinical, pathological, therapeutic, and prognostic aspects of breast cancer in women under 40 years of age. The secondary objective is to evaluate the impact of hypofractionated radiotherapy in the management of this cancer, specifically focusing on recurrence-free survival and cutaneous toxicity.

Study Design and Setting

We performed a retrospective descriptive analysis on female patients diagnosed with breast cancer over a 40-year period, from January 2012 to December 2023. The study was conducted at the Radiotherapy Department of Hassan II University Hospital in Fes, which serves a large central region of Morocco. All patients diagnosed with breast cancer under 40 during this period were included, and their medical records were reviewed. Follow-up records were used to assess the outcomes and survival of these patients.

Study Population

This study included women aged 40 years or younger at the time of diagnosis with histologically confirmed non-metastatic breast cancer. Patients with metastatic disease at diagnosis, those admitted outside the study period, and those lost to follow-up before histological confirmation were excluded.

Data Collection

Patient identification was accomplished via the radiation therapy department's hospitalization register, with data collected from HOSIX electronic data capture tools hosted at Hassan II University Hospital of Fez, individual patient paper records, and ARIA software treatment records. An exploitation form was developed through bibliographic research to obtain epidemiological, clinical, histological, therapeutic, and prognostic data. Variables collected included patient history, demographic information, diagnostic parameters, FIGO stage, therapeutic protocols, and disease progression. Data entry and preliminary analysis were performed using Excel 2016. All data were collected with strict adherence to patient anonymity and confidentiality.

Statistical Analysis

Statistical analyses were conducted using SPSS software v.27, with data processed as percentages, means, or medians. The frequency of breast cancer in young women was calculated relative to all women hospitalized for breast cancer during the same period. Tumor classification was based on the 8th edition of the TNM classification (2017). Survival analysis was performed using the Kaplan-Meier method to estimate patient outcomes.

Ethical Considerations

given that the study was a retrospective observational non-interventional analysis, written consent was not deemed necessary. The work was conducted with due regard for the principles of anonymity. The ethical committee of CHU Hassan II in Fes granted ethical approval for the study.

Results

General Characteristics

Over a 12-year period from January 2012 to December 2023, breast cancer was the leading cause of consultation at the Radiotherapy Department of Hassan II University Hospital in Fez, Morocco. In our series, 231 young patients under the age of 40 were identified, with an average of 19.2 cases per year, ranging from a minimum of 4 to a maximum of 42 (Figure 1). The mean age at diagnosis was 31.9 years, with extremes of 16 and 40 years. The most affected age group was 31–35 years, accounting for 46.3% of cases. Parity data were available for 166 patients, showing a predominance of pauciparity (46.3%), followed by primiparity (10.8%), while multiparity and nulliparity accounted for 7.4%. Among the remaining 65 cases, 55 were single women, and 10 had unspecified parity status. Personal history of fibrocystic mastopathy was noted in 4 patients (1.7%), and fibroadenoma in 2 patients (0.8%).

Regarding family history, 47 patients (20.3%) had a family history of cancer, with 34 cases (14.7%) specifically related to breast cancer. These included 15 maternal aunts (2 deceased), 7 mothers (4 deceased), 7 sisters (1 deceased), and 5 cousins (2 maternal, 3 paternal). Other familial malignancies included endometrial, cervical, prostate, and brain cancers.

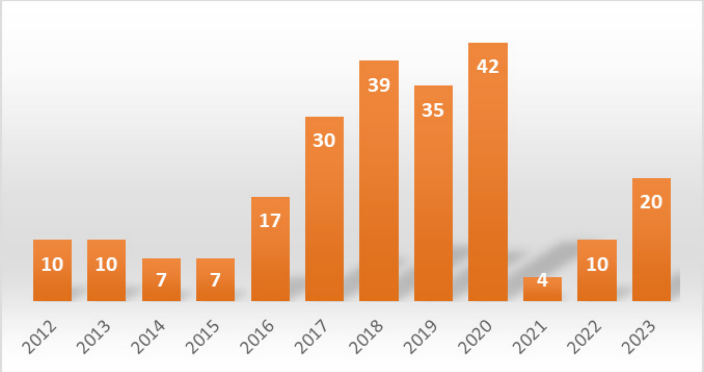

Figure 1: Annual incidence of breast cancer in young women.

Clinical and Paraclinical Presentations

The diagnostic delay, defined as the time between symptom onset and the first medical consultation, had a mean duration of 8.63 months. While 16% of patients sought medical attention within ≤3 months, 7.8% experienced a delay exceeding 12 months. Breast cancer was self-detected in nearly 98% of cases based on warning signs, with self-palpation of a lump being the most common mode of discovery (91.8%). Only 2.2% of cases were identified during routine medical examination.

Clinical breast examination revealed right breast involvement in 50.6% of cases and left breast involvement in 49.4%. The upper outer quadrant was the most frequent tumor location, observed in 37.7% of cases. The mean clinical tumor size was 4.6 cm, with a range from 1 to 10 cm. Palpable lymphadenopathy was present in 17.7% of patients, with 14.2% having mobile nodes and 3.5% presenting with fixed nodes. Notably, one patient exhibited both axillary and supraclavicular lymphadenopathy.

The histological type was specified for all patients. Invasive ductal carcinoma (IDC), or non-specific invasive carcinoma, was the most predominant, accounting for 80% of cases. This was followed by high-grade ductal carcinoma in situ (DCIS) and invasive lobular carcinoma (ILC), each representing 3%, and phyllodes sarcoma, which accounted for 2.2%. Other histological types were found at lower rates. Regarding tumor grading, the most common grade was SBR II, found in 106 patients (45.9%), followed by SBR III in 100 patients (43.2%), and SBR I in 25 patients (10.9%). Estrogen and progesterone receptors were positive in 152 patients (65.8%). Additionally, 137 patients (59.3%) had HER2-negative tumors.

Management and Outcome

The management plan for all our patients was determined during a multidisciplinary tumor board (MTB), which involved radiologists, pathologists, gynecological surgeons, oncologists, and radiation oncologists. Of the patients, 78.4% underwent total mastectomy, while 21.6% had tumor resection (lumpectomy). Sentinel lymph node biopsy was performed in 2 patients. Breast reconstruction was done using a flap technique in 5 patients. A total of 222 patients (96.1%) underwent lymph node dissection, and 2 patients underwent sentinel lymph node biopsy. All patients received sequential chemotherapy, which included anthracycline-based cyclophosphamide followed by taxane, in addition to anti-HER2 treatment for HER2-positive patients. In our series, 71 patients (30.7%) received neoadjuvant chemotherapy for locally advanced tumors, while 157 (68%) received adjuvant chemotherapy. Hormone therapy was prescribed to 155 patients (67.1%) with hormonal receptor expression, including Tamoxifen administered to 153 patients, and Fulvestrant to 1 patient. The mean duration of treatment was 5.8 years, with a range of 1 to 10 years. A total of 59 patients (25.5%) received targeted therapy, with 57 receiving Trastuzumab and 2 receiving Pertuzumab. Furthermore, 47 patients (20.3%) underwent chemical castration using monthly Goserelin injections. In our series, all patients received curative radiotherapy. The time intervals between surgery and radiotherapy ranged from 2 to 36 weeks, with a mean interval of 9.2 weeks. Radiotherapy was administered using a hypofractionated regimen of 42 Gy in 15 fractions, with each session delivering 2.8 Gy to the target volumes. The radiotherapy course was evenly distributed over 3 weeks for all patients. A total of 51 patients (21.6%) received a boost on the tumor bed, with doses ranging from 10 to 16 Gy; 43 patients (18.6%) received 11.2 Gy. Of these 51, 46 patients (19.9%) received external radiotherapy (RTE), while 5 patients received brachytherapy.

All patients underwent weekly follow-up consultations to assess treatment compliance, monitor tolerance, and diagnose acute toxicities for appropriate management. Toxicities were classified according to the CTCAE V.4, with grades corresponding to the severity of the adverse events. The clinical manifestations of acute radiodermatitis include progressive erythema often developing after 10 to 20 Gy (standard fractionation and spreading), edema of skin and subcutaneous tissues, dry desquamation followed by exudative desquamation, and, in rare cases, skin ulceration that can lead to skin necrosis. These effects generally resolve within one to four weeks after the completion of radiotherapy, although complete healing may take one to three months. In our series, 50 patients experienced acute complications: 38 cases of stage 1 radiodermatitis and 10 cases of stage 2 radiodermatitis (Figure 2).

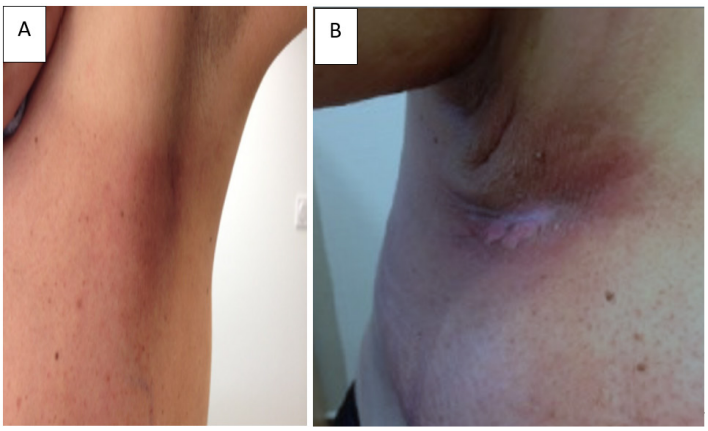

Figure 2: Radiodermatitis grade 1(A), grade II (B).

No patients presented with late skin toxicity. At the conclusion of their treatment, all patients received regular follow-up. The follow-up schedule consisted of visits every 3 months for the first 2 years, every 6 months for the following 3 years, and annually after the 5th year. After an average follow-up of 6 years, 54 of our patients had passed away. Additionally, 151 patients experienced disease progression or relapse, manifesting as locoregional recurrence, metastatic dissemination primarily to the bones, or both simultaneously (Figure 3). Overall survival (OS) was calculated from the date of breast cancer diagnosis to the date of death or the last consultation. The 5-year OS rate was 63% (Figure 4).

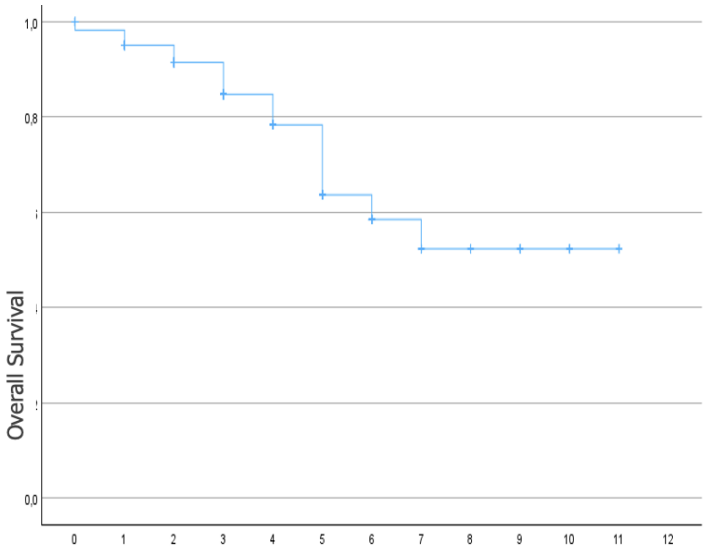

Figure 3: Kaplan-Meier Curves for Recurrence-Free Survival.

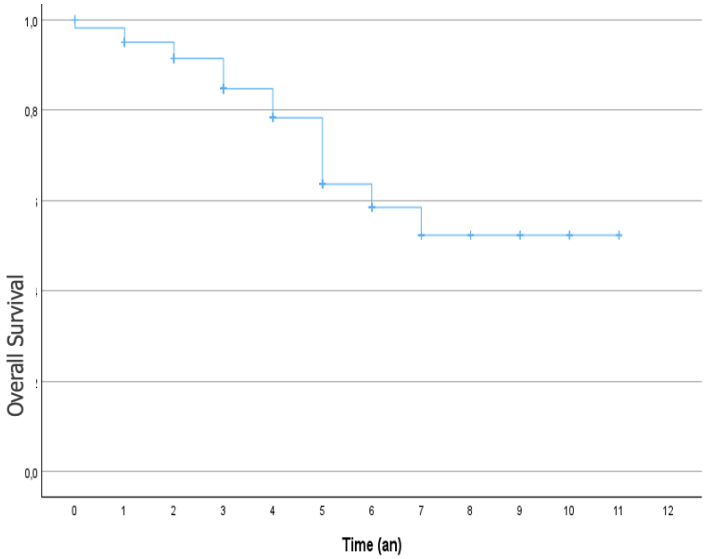

Figure 4: Kaplan-Meier Curves for Recurrence-Free Survival.

Discussion

Age is a significant risk factor for breast cancer, with incidence rates increasing as women age. The incidence of breast cancer increases with age, doubling approximately every ten years until menopause, after which the rate of increase slows down [8]. The average age of onset for breast cancer in young women is typically after 30 years. The definition of 'young age' in women with breast cancer is not uniform. Various studies have defined a 'young' woman as being under 30, 35, 40, or 45 years old, or simply premenopausal [3,9,10]. In our study, we defined young patients as those who were 40 years old or younger at the time of diagnosis.

Despite progress in breast cancer management, young women with breast cancer continue to face specific challenges, including diagnostic delays and a lack of awareness in many countries. In addition, young women with early-stage breast cancer are known to have a higher risk of local recurrence and greater absolute benefit for adjuvant breast irradiation. However, it should be emphasized that young patients are often underrepresented in clinical trials, including those evaluating local treatments. As a result, there is a potential risk of overtreatment based solely on age considerations rather than individualized risk assessments. This underscores the need for more robust evidence to guide treatment decisions in this population [11].

Hypofractionation is a radiation therapy regimen that delivers higher doses per session over fewer treatments compared to conventional schedules. Its increasing interest is due to the potential enhancement of the therapeutic ratio with larger fraction sizes. The effectiveness and safety of hypofractionated whole breast irradiation (HF-WBI) have been assessed in several randomized clinical trials [4-6]. In terms of toxicity, late adverse effects on normal tissues were similar between both groups, while early skin reactions were either more moderate or at least comparable to those observed with the hypofractionated scheme.

In key randomized trials of HF-WBI, only 21%–30% of patients were under 50, with even fewer aged ≤40. However, younger age did not compromise local control [12]. The 10-year follow-up of the START trials suggested better local-regional relapse control with HF-WBI in younger patients, though not statistically significant. Notably, disease-free survival was significantly higher in the HF-WBI group. Despite comparable tumor control and side effects, HF-WBI remains underutilized for young patients in many countries. Reflecting strong clinical evidence, the 2018 ASTRO guidelines and UK consensus statements now recommend HF-WBI as the standard approach, regardless of age, tumor stage, or prior chemotherapy.

Regarding radiation-induced skin toxicity in breast cancer treatment, available data indicate that HF-WBI is associated with lower toxicity compared to CF-WBI. These findings align with results from a single prior randomized trial and a limited number of prospective studies assessing acute skin reactions. However, specific data on the impact of HF-WBI in younger women remain scarce [13].

Breast cancer remains a serious disease with a rising incidence among young women. This study on breast cancer in women

under 40 allowed us to highlight its distinct epidemiological, clinical, therapeutic, and prognostic characteristics. Our findings align with international data, emphasizing the more aggressive nature and poorer prognosis of breast cancer in young patients compared to older women. This is attributed to delayed diagnosis, larger tumor size, frequent lymph node involvement, higher histological grade, hormone receptor negativity, increased genetic predisposition, higher rates of locoregional and distant recurrences, and lower overall survival. A multidisciplinary approach is essential to improve outcomes, including earlier diagnosis, oncogenetic consultations for high-risk women, and treatment strategies tailored to prognostic factors. Since young women are not included in standard screening programs, promoting self-examination and identifying high-risk individuals for specialized follow-up is crucial, given the rising incidence and unfavorable prognosis in this population. With advances in precision medicine, imaging (MRI, PET scan), pathology, high-throughput sequencing (NGS), surgery, breast reconstruction, systemic therapies (immunotherapy, hormone therapy, chemotherapy, targeted therapies, PARP inhibitors), and modern radiotherapy techniques, the management of breast cancer in young women exemplifies a multidisciplinary approach. Hypofractionated radiotherapy emerges as a promising option, offering comparable efficacy, improved quality of life, logistical advantages, and reduced side effects. Finally, receiving a breast cancer diagnosis at a young age is a profound psychological trauma, highlighting the need for psychological support and awareness campaigns.

Conclusion

Managing breast cancer in young women requires a multidisciplinary approach that integrates advances in precision medicine, imaging, pathology, systemic therapies, and modern radiotherapy techniques. Psychological support and awareness campaigns also play a vital role in addressing the profound emotional impact of a breast cancer diagnosis at a young age. By fostering collaboration across disciplines and prioritizing patient-centered care, we can strive toward improving survival rates and enhancing the quality of life for young women affected by this disease.

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