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Radiation Induced Dermatitis In Patients Receiving Neoadjuvant Chemoradiation. A Phase II Prospective Feasibility Study

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Abstract

Background: *Locally advanced breast cancer patients represent nearly half of newly diagnosed breast cancer patients in developing countries and despite the different systemic treatment options in neoadjuvant settings they still represent a challenging situation. Applying radiation therapy concurrently with systemic therapy may improve pathological response in such patients and therefore facilitate surgery and improve survival outcomes.*

Materials and Methods: *Eighty female breast cancer patients were enrolled, all received neoadjuvant systemic therapy in the form of Adriamycin and cyclophosphamides followed by Taxanes concurrently with Radiation Therapy. Surgery was performed 6-8 weeks post Radiation- therapy. Radiation Therapy Details: All patients received whole breast as well as regional lymphatics irradiation 4005 cGy in 15 fractions. Boost was given to patients younger than 50 years old or pathological Grade 3. Treatment plans were done using Monaco planning system and patients were treated using Elekta Versa HD machine.*

Results: *ninety percent of the patients had stage III disease.*
Luminal disease represented 49% of the patients, while Her2 represented 45% of the patients. Grade (G) 1: dermatitis represented the majority of events, G2 and G3
represented 15% only with no G 4 toxicity.
Postoperative complications were observed in 16% of the patients.

Conclusion: *Applying concurrent chemoradiation in preoperative settings is safe and feasible with acceptable complications rate.*

Keywords: *Neoadjuvant Chemoradiation, breast cancer, Radiation Induced Dermatitis.*

1. BACKGROUND

Breast cancer remains the most common malignancy worldwide.1 Despite extensive national efforts toward early detection and screening—such as the Presidential Initiatives for Women's Health—a significant proportion of patients continue to present with locally advanced breast cancer (LABC). (This clinical scenario remains particularly challenging and requires a multidisciplinary approach, typically involving systemic therapy, surgery, and radiation therapy (RT). In conventional treatment sequences, RT is usually administered as the final component. Neoadjuvant chemotherapy (NACT) has become the standard initial treatment for LABC, aiming to downstage tumors, enable breast conserving surgery, and improve long-term survival outcomes. A favorable response to NACT, especially the achievement of a pathologic complete response (pCR), is associated with improved disease-free survival (DFS) and overall survival (OS). However, NACT alone may not be sufficient to achieve operability or negative surgical margins in all patients with inoperable LABC. 2

Radiotherapy (RT) may be utilized to induce further tumor regression. Yet, this sequential approach often results in delays to definitive surgery, and in some instances, patients remain inoperable even after radiotherapy (RT) 3. Moreover, although concurrent chemoradiation (NACCRT) is widely practiced in

the treatment of other malignancies such as head and neck, cervical, esophageal, and rectal cancers, it has not been routinely adopted in breast cancer due to concerns regarding treatment-related toxicity. Nonetheless, there is growing interest in NACCRT for breast cancer, as it offers several potential benefits over NACT alone. These include enhanced local control through the radiosensitizing effects of chemotherapy and the simultaneous management of systemic disease. Studies have shown that concurrent chemoradiation can yield higher pCR rates than chemotherapy alone in patients with LABC 4Additionally, neoadjuvant radiation therapy has been associated with a shorter overall treatment duration, better cosmetic outcomes, and at least equivalent oncologic safety compared to adjuvant radiation delivered postoperatively5.

Crucially, evidence also suggests that delaying radiotherapy beyond six months from the initiation of chemotherapy may negatively impact survival, further supporting the rationale for early integration of RT into the treatment sequence. Delivering radiation preoperatively may also reduce radiation-related complications in patients undergoing breast reconstruction by sparing the reconstructed breast from radiation exposure6. A retrospective analysis using the SEER7 database reported a 12% absolute improvement in 20-year disease-free survival among breast cancer patients receiving preoperative RT following NACT compared to those treated with surgery followed by postoperative radiation therapy. The rationale for applying NACCRT in breast cancer is underpinned by the moderate radiosensitivity of breast tumors and the success of this approach in other solid tumors such as gastric, rectal, and lung cancers. Improved local control and potential survival benefits observed in these cancers support its investigation in breast cancer treatment.

This study is a feasibility study, assessing the safety of combining radiation therapy and chemotherapy in locally advanced breast cancer patients.

2. PATIENTS AND METHODS:

This is a prospective single arm feasibility study done at the National Cancer Institute of Egypt between July 2021 and September 2022. This study was approved by the institutional review board and all patients provided an informed consent before being enrolled in the study. The study aimed to prospectively assess the radiation induced toxicity in the settings of Neoadjuvant Chemoradiation in breast cancer patients with a locally advanced disease.

The primary objective was to assess the rates of radiation induced toxicity. The secondary outcome was the wound complications and feasibility of surgery.

All female patients were18 years old or older with suspicious breast masses and presented to NCI clinics were eligible for proper diagnosis and staging that starts with:

- Full history and examination by specialized oncology physicians.
- 2 Pregnancy Test.
- 3.Radiologically using the appropriate imaging modality (Bilateral Sono-mammography, Contrast enhanced SPECTRAL mammography or Breast MRI).
- **Routine labs:** CBC, liver and kidney functions as well as tumor markers — CEA - CA15.3 5. Echocardiography.
- **Metastatic Work-up:** Contrast enhanced CT chest, abdomen and pelvis, Bone Scan, PET-CT if indicated.

Breast cancer diagnosis was made by core needle biopsies that were taken from the primary breast tumor by a specialized breast radiologist under radiographic guidance whether sonographically or stereotactically and sent for histopathological evaluation of the tumor. Lymph node staging was done only by clinical examination and radiological evaluation. Clinically suspicious lymph nodes associated with suspicious sonographic criteria or pathological lymph nodes that were detected on imaging studies only were considered positive. Biopsy specimens from the tumor were assessed for the histological type, grade, and its biological subtype. To determine the biological subtype, all specimens were subjected to

immunohistochemical analysis to determine the hormone receptor status for estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor receptor 2 (HER2) status. The proliferative index Ki-67 was not routinely performed.

All patients were then reviewed by a multidisciplinary tumor board specialized in breast cancer in the breast unit of our institution. The tumor board included a surgical oncologist, a medical oncologist, and a radiation oncologist. All patients were staged in light of the results of the examination8 (Recht et al., 1996) and imaging studies priorly performed according to the 7th edition of the AJCC TNM staging system.9

Inclusion criteria: 1. Female patients. 2. Age: 18 years or older. 3. ECOG performance status (PS) score 0 to 2 4. Locally advanced tumors (stage IIIA or above) of any subtype. 5. Early breast cancer of the HER2+ or TNBC subtype when: a. Node-negative, T2 or T3. b. Node-positive, any T stage.

Exclusion Criteria: 1. Patients initially presenting with metastatic breast cancer. 2. Patients unfit to receive planned regimen of treatment that had a poor PS (i.e.: PS 3 and 4). 3. Inflammatory breast cancer (T4d) patients. 4. Patients having contraindications to radiotherapy (e.g.: Pregnancy, history of previous chest wall, breast, or axillary irradiation) 5. History of previous ipsilateral breast cancer surgery. 6. Comorbidities that would affect skin healing or integrity, like uncontrolled diabetes mellitus or active autoimmune collagen or vascular diseases.

Eighty patients were enrolled in this study. Neoadjuvant Treatment plan started with Neoadjuvant Anthracycline and Cyclophosphamide (AC) as four cycles. Following the AC the patients started (Weekly) Taxanes (+/- Carboplatin in some cases). AntiHer2 was prescribed in Her2+ patients (either Herceptin only or Herceptin/Perjeta).

Radiation Therapy was given concurrently with 4th or 5th week of Taxanes (+/- AntiHer2 agents) in a hypofractionated course (4005cGy in 15 fractions over 3 weeks with Boost in patients younger than 50 years old or having Grade III tumors) to the whole breast and lymphatics. Internal mammary chain was irradiated only whenever positive by Computed Tomography or PET CT. Before radiation therapy the patients were provided with a health education session where they learnt about radiation therapy in details with the common side effects and how to prevent. Also, all the patients were informed that this is a study and not standard of care with an informed consent provided by each patient before joining the protocol. CT simulation was performed using SOMATOM CT simulator using a breast board and deep inspiratory breast hold technique (DIBH) whenever possible. Contouring was done according to the RTOG contouring guidelines.

Treatment planning was done either as 3DCRT or forward IMRT using Monaco planning system. Treatment verification using either EPID or CBCT on the first treatment day and weekly thereafter was done.

Follow up: weekly follow up was done at radiation therapy department's floor clinic during radiation therapy and weekly after that till surgery.

Radiation induced dermatitis was assessed using RTOG acute morbidity scoring system. Dermatitis was managed according to the grade.

Surgery was done 6-8 weeks post the end of radiation therapy (3 weeks post systemic treatment) by specialized surgical oncologists. Mastectomy (with or without reconstruction) or Breast Conservation surgery were done as indicated. Feasibility of surgical dissection was assessed by the surgeons also surgical complications were assessed at 7 and 15 days postoperatively and monthly after that till 6 months.

Adjuvant Systemic Treatment was prescribed as indicated either adjuvant endocrine therapy, AntiHer2 or Chemotherapy (Capecitabine) according to the molecular subtype and response to therapy.

Statistical methods:

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 27. Numerical data were summarized using means and standard deviations or medians and/or ranges, as appropriate. Categorical data were summarized as numbers and percentages. Estimates of the frequency were done using the numbers and percentages. Numerical data were explored for normality

using Kolmogrov-Smirnov test and Shapiro-Wilk test.

3. RESULTS:

This is a prospective phase II feasibility study conducted at NCI from July 2021 to September 2022. The trial enrolled 80 female patients with locally advanced breast cancer The median age was 50 years (range, 27-64). Fifty seven percent of the patients were premenopausal. (Table:1)

Table (1): Clinico- epidemiological data

	Median (range)
Age	50 (27-64)
No of offsprings	2 (1-7)
	n=80 (%)
Age	
<50	39 (48.8)
≥50	41 (51.2)
Marital status	
Single	7 (8.8)
Married	73 (91.3)
Offsprings	
Yes	72 (90)
No	8 (10)
Family history	
Positive	9 (11.3)
Negative	71 (88.8)
Menopause	
Premenopausal	46 (57.5)
Postmenopausal	34 (42.5)

The disease related data of the whole population is summarized in table (2).

Table (2): Disease related data

Disease related Data	**Median (range)**
T Stage	
T1	1 (1.3)
T2	14 (17.5)
T3	23 (28.7)
T4a	1 (1.3)
T4b	41 (51.2)
N Stage	
N0	0 (0)
N1	55 (68.8)
N2	13 (16.3)
N3	12 (15)

Stage	
2B	9 (11.3)
3A	24 (30)
3B	35 (43.8)
3C	12 (15)
Pathology	
IDC	69 (86.3)
ILC	8 (10)
Mucinous	2 (2.5)
Mixed	1 (1.3)
Grade	
Grade 1	2 (2.5)
Grade 2	62 (77.5)
Grade 3	16 (20)
ER	
Positive	59 (73.8)
Negative	21 (26.3)
PR	
Positive	60 (75)
Negative	20 (25)
Her-2	
Positive	36 (45)
Negative	44 (55)
Molecular subtype	
Her2	9 (11.3)
Luminal	39 (48.8)
Luminal her2	27 (33.7)
TNBC	5 (6.3)
Side	
Left	41 (51.2)
Right	39 (48.8)

Treatment related data of the enrolled patients is summarized in table (3).

Table (3): Treatment related data

	Experimental n=80 (%)
Type of surgery	
CBS	10 (12.5)
Mastectomy	70 (87.5)
Type of mastectomy	
MRM	66 (82.5.3)
NSM	1 (1.25)
SSM	3 (3.7)
Breast reconstruction	

Implant	1 (1.25)
Latissimus dorsi flap	2 (2.5)
Oncoplastic surgery	2 (2.5)
Axillary surgery	
Axillary evacuation	73 (91.3)
SLNB	7 (8.8)
Type of anti-Her2	
Not received	4 (11)
HP	19 (52.7)
Herceptin	13 (36.1)
Number of neoadjuvant AntiHer2 cycles	Median (range)
No of cycles	5 ±1

All the patients completed their planned neoadjuvant systemic treatment either AC followed by taxanes (+/- carboplatin which was administered in 6 patients: 4 TNBC and 2 Her2+ patients)
Most of the patients received dual HER2 blockade (more than 50 percent). More than ninety percent of patients with Her2 positive disease received antiHer2 agents in the neoadjuvant settings.
Regarding radiation therapy, all the patients received radiotherapy to the whole breast and regional lymphatics (axilla, supraclavicular fossa and internal mammary nodes (when indicated) using hypo fractionated course (4005 cGy over 15 fractions over 3 weeks) with boost given to patients with either grade 3 disease and/or younger than 50 years old (in 50% of the patients). Radiation therapy was delivered in 4th or 5th week of Taxanes in 94% of the patients, the remaining patients started radiation therapy in 6th week.
The incidence of radiation induced dermatitis observed in the study: is summarized in table (4).

Table (4): Radiation Induced Dermatitis

	Experimental n=80 (%)
Dermatitis	
Yes	56 (70)
No	24 (30)
Dermatitis grade	
0	24 (30)
1	41 (51.2)
2	12 (15)
3	3 (3.8)

When assessing the impact of Boost dose on the incidence of dermatitis there was insignificant difference in dermatitis between Boost or no boost patients (p=0.187), however Boost had a statistically significant impact on Grades 2 and 3 dermatitis.
All patients were managed by conservative measures, no treatment interruption due to the radiation induced toxicity was observed.
Surgery could be safely done in all the patients. Feasibility of axillary dissection was assessed by different surgeons who reported only 3 cases of difficulty in dissection. However, this difficulty didn't cause an increase in axillary morbidity or inadequate dissection (least number of dissected Lymph nodes was 10 lymph nodes).

The total incidence of postoperative complications was 16 % in the whole population. Four patients (5%) had surgical site infections, three patients (4%) experienced skin necrosis (managed conservatively with the exception of only one patient who required surgical debridment) and 6 patients (7%) had seroma.

4. DISCUSSION:

Locally advanced breast cancer (LABC) was initially defined as a heterogeneous group of tumors deemed inoperable either by size or by extension. Traditionally the use of preoperative systemic treatment was limited to inoperable cases aiming at achieving complete resection. With better understanding of tumor biology and the wide adoption of personalized medicine approach the use of neoadjuvant systemic treatment shifted towards more operable cases. In such cases the preoperative approach has many advantages rather than operability including: in vivo therapeutic test, early tackling subclinical disease and
higher conservative surgery rates10

Several trials assessing the neoadjuvant approach showed strong correlation between pathologic complete response (pCR) and prognosis. So, it has been believed that pCR is a surrogate endpoint and predictive of higher disease-free survival.11

Unfortunately, there is still a cohort of locally advanced breast cancer patients who achieve unsatisfactory pathologic response which in turn has a negative impact of disease-free survival. NCCN guidelines suggest the use of preoperative radiation therapy after neoadjuvant systemic treatment in case of refractory or progressive disease2.

The use of radiation therapy in preoperative settings is revisited aiming at achieving higher pathological response, facilitating conservative surgical approaches and immediate reconstruction surgeries in a shortened overall treatment duration without affecting the oncological outcomes.

Our study is a prospective single arm phase II study assessing the safety of neoadjuvant chemoradiation as well as the feasibility of surgery following this neoadjuvant treatment plan.

The patient population in our study was composed mainly of locally advanced breast cancer patients (88.8%), of which 41 patients (51.2%) were T4b. Mastectomy was performed in 87% of the patients. Two studies done in India 3and Canada12 studied only patients (more than 200 patients in both studies) with locally advanced inoperable tumors who received their neoadjuvant chemoradiotherapy protocol and was followed by only modified radical mastectomy. Ciérvide and co-workers13 of Spain studied a population of only patients that presented with HER2 positive tumors or TNBC and received preoperative concurrent chemoradiation, where out of 56 patients included 37 underwent breast-conserving surgery and 19 patients had a modified radical mastectomy. 13

All the patients in our study received the standard systemic treatment as indicated. Radiation was given concurrently with taxanes (+/- antiHer2 whenever indicated) This approach is accepted by other researchers, Iyer et al3 applied preoperative radiation therapy concurrently with taxanes as well did Brackstone et al.12. Other researchers such as Zinzindohoue et al 14preferred the sequential approach.

Radiation therapy in our study was delivered in a hypofractionated approach (4005cGy in 15 fractions in 3 weeks and boost- given in grade 3 tumors and females younger than 50 years old- sequential 1000cGy in 5 fractions). Like us, the hypofractionated schedule in neoadjuvant settings was applied in other studies.13

Other researchers preferred the conventional fractionation due to the fear of radiation induced toxicity. Iyer 3 et al delivered radiation therapy as 46 Gy in 23 fractions and reported 19% radiation dermatitis with a majority of mild cases. Another study used 50 Gy in 25 Fractions and observed mild radiation induced toxicity. 14

When it comes to the radiation induced dermatitis, which is considered the most surgically dreaded side effect of neoadjuvant radiation therapy as it raises the risk of surgical complications which in turn delays the adjuvant treatment and impairs oncological outcomes.

Seventy percent of the patients developed dermatitis. No grade 4 dermatitis was observed in the study, Grade (G) 1 was observed in 50% of the patients, G 2 in 15% and G 3 in 3.8% of the patients.
In the previously mentioned studies applying preoperative chemoradiation therapy, the reported rates of dermatitis were higher than ours. Brackstone12 and Iyer et al.3 reported a rate of 25% and 19.3% of grade 3 radiation dermatitis, respectively. Ciérvide et al13; reported a high incidence of grade 1 radio-induced skin toxicity in 77.6% (n=45) of their patients, and 13.8% and 8.6% for grades 2 and 3 toxicity, respectively (all the patients received hypofractionated schedule.
In the PRADA trial15 97% of the patients developed dermatitis (67% G1, 27% G2 and 3% G3).
The use of boost dose to the tumor increased the rates of G2 and 3 dermatitis without a statistically significant impact on the overall rates of dermatitis in the whole cohort.
Postoperative complications being one of our main concerns were assessed. The total rate was 16 % in the whole population. Four patients (5%) had surgical site infections, three patients (4%) experienced skin necrosis (managed conservatively with the exception of only one patient who required surgical debridment) and 6 patients (7%) had seroma. In the study by Iyer et al3 (Iyer et al., 2023) reported 10.6% rate of surgical morbidity (19 patients out of 202, 14 of them had infections and the remaining had necrosis). The French pilot study 14 studied the safety of immediate breast reconstruction after preoperative systemic treatment and radiation therapy reported the incidence of 6% necrosis (5 patients out of 82, 3 with prosthesis and 2 without) which is slightly higher than our observed rates.
The median interval between the end of radiation therapy and surgery was 8 weeks (range 5- 14 weeks) this wide range is attributed to a number of patients (n=10) whose interval between neoadjuvant treatment and surgery was longer than 8 weeks. Of those 10 patients, only 1 was delayed in part due to prolonged grade 2 radiation dermatitis (10.1 weeks) which was initially due to a delay in starting her radiotherapy beyond week 5 of Taxanes for logistic reasons (however the interval from the neoadjuvant systemic treatment to surgery didn't exceed 5 weeks), another one due to suffering from community-acquired pneumonia. The rest were only delayed as a result of improper patient compliance.
The interval between the end of neoadjuvant treatment and surgery was variable in different studies, with most of the studies3,13,16 having radiotherapy as the last modality before surgery being given sequentially. When given sequentially, the average interval was about 6 weeks between the end of neoadjuvant treatment and surgery, with one group extending up to 8 weeks and another having a mean of only approximately 3 weeks. On the other hand, when concurrent chemoradiation was administered, this interval was of an average duration of 8 weeks in most of the reported studies. However, when Ciérvide et al13 applied neoadjuvant chemoradiation approach radiotherapy ended on the 3rd week of neoadjuvant systemic treatment and surgery was done on the 27th week, with an interval of 24 weeks from the end of radiation therapy to syrgery .
One of the major limitations of our study, is the small number of patients in each molecular subtype. Limiting the use of Boost to a certain group not exceeding 40 patients didn't allow proper assessment of dose escalation on radiation induced toxicity and surgical complications.

RECOMMENDATION:

Based on our results, applying radiation therapy in neoadjuvant settings concurrently with systemic treatment didn't significantly impact the patients' toxicity profile. Wound complication rates were acceptable despite the different surgical procedures following this approach.

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