RESEARCH ARTICLE

Progression free survival in Iraqi breast cancer patients treated with adjuvant 3D conformal radiotherapy: A cross-sectional study [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Breast cancer is a common malignancy in Iraq, accounting for one-third of female cancers in the Iraqi Cancer Registry. Radiotherapy confers benefits for local control and progression free survival (PFS) in patients with breast cancer. This study aimed to assess PFS in patients treated by hypofractionated three-dimensional conformal radiotherapy (3DCRT) and correlate PFS with patients' clinical and pathological profiles.

Methods: We retrospectively reviewed 299 women with breast cancer treated at Baghdad Radiation Oncology Center between October 2017 and May 2018. Regarding radiotherapy, 4005 cGy in 15 fractions over 3 weeks was adopted as standard practice for patients undergoing mastectomy and 4005 cG in 15 fractions + 1000 cG in 5 fractions as a booster dose for women undergoing breast-conserving surgery.

Results: Age ranged from 25 to 75 years, and the mean age was 49.9±10.99 years. The most common stage was T2 (156, 53.9%), which mostly comprised luminal A (105, 36.3%). The results showed a high frequency of N1 (109, 37.2%), with luminal A (69, 23.4%). Relapse occurred in 35/299 (11.7%) patients, and the chest wall was a common relapse site in 9 of these patients (25.9%).

Conclusions: We conclude that adjuvant radiotherapy reduces locoregional recurrence, distant metastasis and mortality rate.

Keywords

3D conformal radiotherapy, Breast cancer, Progression free survival, Luminal subtypes, HER2 neu receptors

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Introduction

Breast cancer is a common cancer in women, and it is estimated that one in eight women in the US will develop it in their life¹. It is the leading cancer among women in both Europe and the US and has become an emerging disease in developing countries^{2,3}. In Iraq, 3845 patients were estimated to have breast cancer in 2011⁴. Therapy requires a multidisciplinary team involving surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, and supportive care personnel¹. Adjuvant radiotherapy decreases locoregional relapse, increases survival and palliates symptoms; after breast-conserving surgery (BCS), it is an essential component of treatment¹. In oncology, progression free survival (PFS) referred to the length of time during and after the treatment of a cancer, that a patient lives with it but it does not get worse and refers to situations in which a tumor is present, as demonstrated by laboratory, radiology, and/or clinical evidence⁵. In developing countries, survival rates are poorer than those in developed countries⁶. Approximately 30% patients with early-stage cancer develop metastases, whereas metastatic breast cancer occurs in 6 – 7% of newly diagnosed patients⁷. The 5-year survival rate with metastasis is 25%, and the overall survival (OS) is reported to be 24 months⁸. Adjuvant radiotherapy reduces the incidence of locoregional recurrence from 30% to 10.5% at 20 years and decreases deaths by 5.4% at 20 years⁹.

This study aimed to assess PFS in patients treated by hypofractionated three-dimensional conformal radiotherapy (3DCRT) and correlate PFS with patients' clinical and pathological profiles.

Methods

Study design and setting

We retrospectively reviewed 299 women who were consecutively treated at Baghdad Radiation Oncology Center between October 2017 and May 2018. Patients were included if they planned to undergo adjuvant 3DCRT. Medical records were reviewed in detail after approval was obtained from our institution. All women were treated after completing chemotherapy cycles in a period not less than 13 weeks from the last cycle.

Inclusion criteria

1. T3, T4 stages.
2. All patients with node positive status.
3. All patients after breast conservative surgery.
4. Multifocal breast tumors, extensive DCIS, central tumors in a small breast and incomplete excision.

Exclusion criteria

1. Significant pre-existing cardiac or lung disease.
2. Scleroderma.
3. Limited shoulder mobility.
4. M1 breast cancer (metastasis).

Data collection

Individual data and information on primary and advanced disease were collected. The following variables were studied as possible

prognostic factors for specific clinical outcomes: age, tumor-node-metastasis staging, lymph nodes (LN), histopathology, grades, estrogen receptors, progesterone receptors, human epidermal growth factor receptor 2 (HER2) neu, surgery types, body mass index (BMI), period between the last cycle of chemotherapy and radiotherapy, date of radiotherapy, follow-up time, and metastatic or recurrent events (brain, supraclavicular LN, axillary LN, liver, chest wall scars and bones).

Radiotherapy doses

1. 4005 cGy in 15 fractions over 3 weeks adopted in **mastectomy, the indications are**^{10–13}:
 - a. Involvement of one or more axillary lymph nodes.
 - b. T3 (>5 cm tumor), T4 (skin/chest wall invasion) or stage III tumor.
 - c. Positive surgical margin.
 - d. Gross residual disease.
 - e. Multiple primary tumors (multi-centricity).
2. 4005 cGy / 15 fractions / 3 weeks performed for **breast conserving surgery** BCS plus 1000 cGy / 5 fractions / 1 week as booster^{10,11,13}.

Data analysis

Data were first entered into an Excel file, then transferred for statistical analysis into SPSS v22. For categorical variables, such as age, histo type, ER, PR, HER2, the frequency distribution calculated and analyzed with Fisher's test and chi-squared. Correlation coefficient (r) was used to detect significance relations. Kaplan-Meier survival curves for PFS were used, which is a way of graphically displaying the time until the study developed an endpoint, often death, or an event such as recurrence of cancer, which was obtained during follow-up.

Ethical considerations

Written informed consent was obtained from the patients, for the use of their data in this study, and the study was conducted according to the ethical standards established by the 1964 Declaration of Helsinki. The Medical Ethical Committee of College of Medicine, Baghdad University approved this study (code: 6/2018), which covers the Baghdad Radiation Oncology Center.

Results

Patient characteristics

The majority of patients were in the age group 46–55 years (115, 38.5%). BMI revealed that the majority of the patients were either overweight (60, 27.2%) or had moderate obesity (73, 33%) (Table 1).

Luminal A breast cancer type present in 197 patients (67.2%), while non-luminal A phenotypes were recorded as luminal B subtype (34, 11.6%), triple negative (33, 11.3%) and HER2 enriched (29, 9.9%) (Table 1).

Table 1. Iraqi breast cancer patient characteristics.

Variables		N (%)	Mean ± SD
Age (years) Range: 25–27	25–35	36 (12)	49.9±11
	36–45	70 (23.4)	
	46–55	115 (38.5)	
	56–65	61 (20.4)	
	66–75	17 (5.7)	
	Total	299	
BMI (m²/Kg) Range: 18–43	Underweight (<18.5)	2 (0.9)	29±5.2
	Normal (18.6–24.9)	51 (23.1)	
	Overweight (25–29.9)	60 (27.2)	
	Moderate obesity (30–34.9)	73 (33)	
	Severe obesity (35–39.9)	29 (13.1)	
	Morbid obesity (>40)	6 (2.7)	
	Total	221 (78 missing)*	
Molecular subtypes (n=293)			
HER2 enriched		29 (9.9)	
Triple negative		33 (11.3)	
Luminal B		34 (11.6)	
Luminal A		197 (67.2)	
Total		293 (6 missing)*	
Events			
Non-relapse		264 (88.3)	
Relapse**		35 (11.7)	
Total		299 (100)	

*Total sample sizes and numbers missing may differ due to missing values for selected variables.

**Relapsing include: chest wall relapse, liver metastasis, bone secondaries, axillary LN relapse, lung metastasis and supraclavicular LN relapsed.

Staging and molecular subtypes

The T2 stage was predominant (156, 53.9%), which mostly comprised luminal A (105, 36.3%). Other stages and subtypes presented in different proportions (Table 2). The results showed a high frequency of N1 in 109 patients (37.2%), related to molecular luminal A (69, 23.4%) (Table 2).

ER, PR and HER2 neu receptors

A significant result was obtained between age, BMI, and T stage when correlated to molecular subtypes, ER and HER2 neu receptors. Age correlated to molecular subtypes ($r = +1$); there was good correlation (2-tailed = 0.46 and $P = 0.043$). BMI was significantly correlated to estrogen receptors (ER) ($r = +1$, 2-tailed = 0.5 and $P = 0.046$). Furthermore the correlation between T stages and HER2 neu receptors showed a significant value ($r = +1$, 2-tailed = 0.99 and $P = 0.001$).

Relapse patterns

Relapse occurred in 35 (11.7%) women, while the reminder (264, 88.3%) were non-relapsed (Table 1). The waiting period from last cycle of chemotherapy to the date of starting radiotherapy in weeks of this study had median 17 weeks

and mode about 9 weeks, which ranged from 4 to 30 weeks (Figure 1).

PFS in this study presented in 264 women, while relapsing was evident in 35 cases. Chest wall relapse occurred in 9 patients (25.7%). Other relapses included liver metastasis, bone secondaries, axillary LN relapse, lung metastasis and supraclavicular LN in 8 (22.9%), 6 (17.1%), 5 (14.3%), 4 (11.4%), 3 (8.6%) patients, respectively (Figure 2).

The luminal A subtype relapsed in 69% of patients which represented major subtypes reliable for relapse, while HER2 enriched and triple negative subtypes occurred in 14% patients for both and 3% for luminal B (Figure 3).

Progression free survival

Kaplan Meier survival curve estimation of PFS is shown in Figure 4. The PFS rates for relapse were 35 (11.7%) versus 264 (88.3%) for non-relapse, estimated using this curve, which indicated that when a woman received adjuvant radiotherapy, she was about nine times more likely to survive beyond the time than someone who did not receive adjuvant radiotherapy.

Table 2. Tumor-node stages in relation to molecular subtypes.

T stages	Molecular subtypes				Total
	Luminal A (%)	Luminal B (%)	HER2 enriched (%)	Triple negative (%)	
T1	36 (12.4)	10 (3.4)	6 (2.0)	2 (0.7)	54 (18.6)
T2	105 (36.3)	18 (6.2)	15 (5.1)	18 (6.2)	156 (53.9)
T3	40 (13.8)	5 (1.7)	6 (2.0)	7 (2.4)	58 (20.0)
T4	13 (4.5)	1 (0.3)	2 (0.7)	5 (1.7)	21 (7.2)
Total	194 (67.1)	34 (11.7)	29 (10.0)	32 (11.0)	289 (10 missing)*
Fisher's Exact test=9.15, Chi-square=9.5, P = 0.031					
N stages					
N0	43 (14.6)	6 (2.0)	7 (2.3)	5 (1.7)	61 (20.8)
N1	69 (23.5)	16 (5.4)	12 (4.1)	12 (4.1)	109 (37.2)
N2	56 (19.1)	10 (3.4)	5 (1.7)	12 (4.1)	83 (28.3)
N3	29 (9.9)	2 (0.6)	5 (1.7)	4 (1.3)	40 (13.6)
Total	197 (67.2)	34 (11.6)	29 (9.9)	33 (11.2)	293 (6 missing)*
Fisher's Exact Test=6.2, Chi-square=6.23, P = 0.004					

*Total sample sizes and numbers missing may differ due to missing values for selected variables.

Figure 1. Waiting period (weeks) between last cycle of chemotherapy and date of radiotherapy.

The follow-up period was 12 months; the Kaplan Meier estimates of PFS for all the patients was censored at 9 months and the last was at 35 months. There was a trend for better PFS in patients receiving adjuvant radiotherapy, so radiotherapy was significantly associated with prolonged PFS.

Discussion

In the present study, the age of patients was 25–75 years with a mean± standard deviation of 49.9±10.99 years, with the majority

of patients in the group of 46–55 years (115, 38.5%). This is similar to the results of previous studies conducted in Iraq: Al-Rawaq *et al.*, 2016¹⁴, Al-Khafaji *et al.*, 2010¹⁵, and Al-Naqqash *et al.*, 2009¹⁶. Age represents an important factor both for occurrence and management of breast cancer¹⁷. In our study, the median age of onset was > 10 years younger than that shown in studies in Europe and North America¹⁸. It has been proposed that these differences are due to differences in exposure to hormones, diet, physical activities, and other risk factors¹⁷.

Figure 2. Relapsing pattern presented in the study participants (n=299).

Figure 3. Molecular subtypes in relation to relapsing status (n=293).

In most Arabian countries, breast cancer is commonly diagnosed in women younger than 50 years, which is consistent with the findings of our study, unlike in the US, where women aged 50 years and older are most commonly affected¹⁸.

The molecular subtype plays an important role in follow-up survival and prognosis in breast cancer. Luminal A (67.2%), luminal B (11.6%), triple-negative (11.3%), and HER2-enriched (9.9%) subtypes were observed in the present study. These results are similar to those found in Cheang's study¹⁸ and unlike those of other studies, such as Al-Naqqash *et al.*, 2009¹⁶, Al-Sarraf *et al.*, 2015¹⁹, and El-Fatemi and Chahbounil, 2012²⁰. In the present study, luminal A relapse was recorded in 69% of patients, while the remainder were non-luminal A; HER2-enriched, triple-negative and luminal B occurred in 14%, 14%, and 3% of patients, respectively. These results were inconsistent with the results of Fitzgibbons *et al.*, 2000²¹ and Al-Sarraf *et al.*, 2015¹⁹. Luminal A has the most favorable prognosis, with locoregional relapse rates of only 3–8% at 10 years²⁰. HER2-

enriched groups exhibit the highest rates of local recurrence and regional relapse²¹.

Tumor size (T stage) was directly correlated with survival and metastasis in the present study. Size rank is among the strongest predictors of metastasis, disease-free survival (DFS), and OS. Although tumor size correlates strongly with the presence of axillary LNs, this is clearly an independent prognostic factor^{5,21}. Among those with documented negative nodes, tumor size remained a strong and independent predictor⁵. Many studies showed a 20 year DFS of 79% for those with tumors smaller than 2 cm, compared with 64% for those with tumors larger than 2 cm⁵. This study demonstrated T2 stage was the most common (53.9%), followed by T3, T1 and T4; regarding the T stage related to molecular subtype, T2/luminal A was most common (36.3%). These results were similar to those of Al-Rawaq *et al.*, 2016¹⁴, Al-Khafaji *et al.*, 2010¹⁵, and Al-Naqqash *et al.*, 2009¹⁶, but different than those of Goldhirsch *et al.*, 2013²² and Cheang *et al.*, 2009¹⁸.

Figure 4. Kaplan Meier survival curve of progression free survival in the study.

The status of LNs is an important prognostic factor related to survival and predictors of systemic micro-metastases²², disease recurrence, and poor prognosis²³. In the present study, the N1 frequency was 37.2% followed by N2, N0, and N4. The N1/luminal A frequency was 23.5%, which was recorded commonly, whereas the N3/luminal B frequency was the lowest (0.6%). These agree with the results of Al-Rawaq *et al.*, 2016¹⁴ and Al-Khafaji *et al.*, 2010¹⁵, while they disagree with those of Goldhirsch *et al.*, 2013²² and Cheang *et al.*, 2009¹⁸.

In the present study, the PFS, which was obtained using Kaplan Meier survival curves, estimated an association between receiving adjuvant radiotherapy and/or locoregional or recurrence rates and/or distant metastasis and/or the end point (death). The estimated resampling study findings in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 2011, found that after BCS, radiotherapy halved the rate of recurrence and reduce the death rate by about a sixth²⁴, which was similar to that reported in the EBCTCG study in 2014, which found that radiotherapy beyond mastectomy and axillary dissection reduced both recurrence and mortality²⁵.

In the present study, non-relapse represented a large group (88.3%), whereas relapse was recorded in 11.7%, after a follow-up period from 6 to 12 months. Both proportional and absolute reductions in the recurrence rate are large in the first year, whereas the reduction in death becomes definite after the first few years⁵.

Conclusions

The fifth decade of life is the most common age of presentation for breast cancer in this Iraqi population, and the luminal A phenotype is the most common molecular subtypes. The commonest stage is T2 and N1, while the least common is T4 and N3. There was a strong correlation between age, BMI, and staging for molecular subtypes and hormonal status. Adjuvant radiotherapy treatment reduced locoregional recurrence, distant metastasis and death rates, and the period of waiting from last chemotherapy cycle to the date of radiotherapy represented a risk factor that affected the survival curve. Chest wall recurrence is most common site of disease progression.

Data availability

Underlying data

Zenodo: Progression free survival in Iraqi breast cancer patients treated with adjuvant 3D conformal radiotherapy: A cross-sectional study, <http://doi.org/10.5281/zenodo.2528529>²⁶.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Grant information

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Julie A. Bradley

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Outcomes of women with breast cancer in Iraq is an important, and the authors have done substantial work collecting and analysing the data.

The primary area that is unclear is whether all patients in this cohort had radiation, or some did not. If all had radiation, then it cannot be concluded from this data that radiation improves disease outcomes, as there is no control group for comparison. The outcomes of this series can be compared to historical published series of no radiation. This statement is not substantiated by the data presented: "The PFS for relapse were 35 vs 264 with non-relapse... which indicated that when a woman received radiation therapy, she was 9 times more likely to survive... than someone who did not receive adjuvant radiotherapy." If all patients received radiation, then this comparison cannot be performed. If some did not receive radiation, then the numbers for those who received and did not receive radiation need to be provided.

Were recurrences more common in those with positive lymph nodes? What percent of patients had recurrence after having undergone lumpectomy versus mastectomy?

Did patients receive adjuvant endocrine therapy if they were estrogen/progesterone receptor positive?

Specifics of the radiation techniques would be very helpful. Was CT simulation used? Were contours drawn? What energy photons? Was bolus used for the chest wall? What nodal levels were treated (ie were internal mammary nodes included)? What were the indications for nodal radiation?

What type of chemotherapy was used? What % of patients received chemotherapy?
How was the axilla addressed – what % of patients had sentinel lymph node biopsy versus axillary lymph node dissection?

This data is interesting and important, and can be strengthened by consideration of the above

points.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 12 March 2019

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Angel Montero-Luis

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It is a very interesting job. The authors have conceived a serious and exhaustive analysis of their own data. The study is well justified, and the characteristics of the patients and the intervention are clear and concise, both in the text and in the tables. The results are in agreement with the existing data in the current scientific literature.

However, the authors state that the observed progression-free survival data allows them to argue that adjuvant radiotherapy reduces the risk of recurrence and significantly increases PFS, which is a gratuitous statement since it has not been compared to any control arm without radiotherapy and, therefore, the conclusion is only an extrapolation of the data of a particular series.

It would be much more correct for the authors to limit their conclusions to presenting their own data, very satisfactory and consistent with the evidence, rather than maintaining statements that cannot be substantiated scientifically in the analyzed data. Finally, the article is well structured and written and the bibliography is consistent and updated.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical oncology, radiation oncology, brachytherapy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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