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Evaluation of Axillary Clearance and Whole Breast Radiotherapy for Occult Primary Breast Carcinoma Presented with Axillary Metastases Not Detected by MRI

Mohamed H. Zaid[1*], Ayman A. Talaat[1], Mostafa A. Amin[1], Diaa Eldin M. Sherif[2], Ahmed Khalil[1]

[1]Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2]Department of Medical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

***Corresponding author:**
Mohamed H. Zaid, MD
Department of General Surgery
Faculty of Medicine
Ain Shams University Cairo, Egypt
Mobile: +201223809457
E-mail: hamdymhz@gmail.com

ABSTRACT

Background: This study aimed to assess the overall survival and disease-free survival after axillary lymph node dissection (ALND) and whole breast radiotherapy (WBRT).
Methods: This was a prospective cohort study. Twenty female patients with enlarged ALN metastasis of breast origin with occult primary tumor not detected by MRI were recruited for ALND and WBRT with or without neoadjuvant chemotherapy.
Results: Twenty of 1823 patients (1%) were diagnosed with axillary metastasis of breast origin with occult primary breast carcinoma (OBC) not detected by MRI. Sixteen patients (80%) have N1 disease, sixteen (80%) were estrogen receptor–positive, four (20%) were HERII-positive and two (10%) were triple negative. Eighteen patients (90%) underwent ALND with WBRT and two (10%) underwent sentinel lymph node biopsy with WBRT. Five patients (25%) received neoadjuvant chemotherapy and two of them (40%) gave complete pathological response. No local recurrence in the follow-up period was detected. All patients will be followed after 3 years and 5 years as regard disease free survival & overall survival.
Conclusions: Due to limited experience in OBC, the optimal treatment is not yet established. There was no difference between modified radical mastectomy and ALND with WBRT as regard overall survival and disease-free survival.
Key words: occult primary breast cancer, axillary metastases, whole breast radiotherapy

Abbreviations:
ALND - axillary lymph node dissection,
WBRT - whole breast radiotherapy,
OBC - occult breast carcinoma,
MRM - modified radical mastectomy,
MRI - magnetic resonance imaging,
HR - hazard ratio,
ET - endocrine treatment,
ER - estrogen receptor,
NAC - neoadjuvant chemotherapy,
pCR - pathological complete response,
FNA - fine-needle aspiration,

INTRODUCTION

Breast cancer is the commonest carcinoma in women as it accounts for 29% of cancers in women & the commonest cause of mortality after lung cancer (1). This provided hope for breast cancer patients considering the importance of the breast as asexual organ hence having a good psychological impact on the female (2). Occult primary breast carcinoma (OBC)(pT0N+) presented with axillary lymph nodes metastases with non-detectable primary breast tumor either clinically or by imaging is considered a rare entity. The incidence rate of OCB is 0.3 to 1% among breast cancer (3). Modified radical mastectomy (MRM) is considered treatment of choice in OBC historically (4). Differential diagnosis of axillary lymph node metastases may be from adeno-

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carcinoma of uterus, ovary, stomach, lung or thyroid, tru-cut biopsy and pathological evaluation of ER, PR, HERII neu, GATA3 facilitate diagnosis of breast origin of the tumor (5,6). Magnetic resonance imaging (MRI) is a standard in patient presented with axillary lymph node metastases with OBC not detected clinically or by sono-mammography (7). MRI detect breast lesion in 72% of patients with normal ultrasound and mammography, 85% of these proved malignant on biopsy (8). ALND followed by whole-breast radiotherapy is an excellent option in treating patients who presented with axillary lymph node metastasis of breast origin with occult primary not detected by MRI (9-11). Macedo et al. analyzed 7 studies and found that no difference between modified radical mastectomy versus ALND and whole breast radiotherapy as regard oncological outcome and survival (12). Other retrospective studies reported that ALND combined with WBRT and chemotherapy has similar outcome of MRM (13-15). Shannon and colleagues, reported that a higher local recurrence rate in patients not receive WBRT than in patients who received (69%vs 12.5%, p=0.021)(16). In a review of 1,231 cases of OBC, the patients treated with WBRT and ALND reported that significantly better overall survival than those managed with mastectomy [hazard ratio (HR) 0.475](17). Axillary lymph node dissection provides the number of affected LNs, allowing accurate tumor staging, prognosis and assessment of the expression of tumor receptors for accurate molecular classification (18). Patients with OBC should be treated systematically as any other patient with Stage II or III breast cancer. There are currently no specific prospective data on the survival benefit of systemic therapy for OBC. The current practice is administration of adjuvant chemotherapy, targeted therapies for HER2 positive disease and endocrine treatment (ET) for estrogen receptor (ER) positive BC (19). Gene expression signatures in pathologically node-positive breast cancer patients is now an option in helping to guide decision regarding chemotherapy when it is less clear as to benefit. In cases of OBC tissue for testing would need to be nodal in origin (20). There is evidence that the use of neoadjuvant chemotherapy (NAC) in patients with clinical and radiological OBC; however, data suggested NAC is a reasonable option for OBC patients, for high grade HER2+ and triple negative disease where a pathological complete response (pCR) is more likely (21). Neoadjuvant chemotherapy can give complete pathological response, that offer sentinel lymph node biopsy of the affected lymph nodes instead of ALND that give the same results as regard overall survival and disease-free survival with less co-morbidities compared to ALND (22).

METHODS

Patients

This was a prospective cohort study conducted at Ain Shams University Hospitals, during January 2018 to February 2020. Twenty female patients with enlarged axillary lymph nodes metastasis of breast origin with occult primary tumor not detected by MRI (T0N+ breast cancer.) were recruited for this study.

Inclusion criteria

- Occult primary breast cancer detected by axillary metastasis not detected by MRI (T0N+ breast cancer).
- Cooperative and psychologically stable patients.

Exclusion criteria

- Clinically or radiologically identifiable breast tumor.
- Presence of distant metastasis.
- Presence of contraindications for irradiation.
- Patients with history of contralateral breast cancer.
- Axillary lymph node biopsy not proven of breast origin.
- Mass in breast tail.
- Male gender.

All patients were subjected to clinical assessment including history (past medical, surgical, family history and history of hormone replacement or oral contraceptive pills intake) taking and clinical examination of both breasts and axilla as well as the following investigations:

- Routine laboratory investigations: CBC, INR, urea and creatinine, liver enzymes.
- Imaging: Bilateral breast US, mammography, magnetic resonance imaging (MRI).
- Biopsy: ultrasound-guided fine-needle aspiration (FNA) or ultrasound-guided core biopsy.
- Receptor profile: ER, PR, Ki76, and Her2Neu.
- Metastatic work-up: abdominal US, Bone scan, chest X-ry or PET CT.

All patients with proven axillary lymph node biopsy of breast origin with occult primary breast cancer with negative imaging evaluation by MRI of

both breasts subjected to upfront surgery (ALND or SLNB + WBRT) or neo-adjuvant chemotherapy then surgery.

Whole breast irradiation

All patients received adjuvant ipsilateral whole breast irradiation with a hypo-fractionated schedule 270 cGy x 15 fractions, no sequential boost was given. Patients were treated using external beam 3-D conformal radiotherapy technique. They were treated in the supine position with the arm abducted (≥90 degrees) utilizing breast tilt boards with the chest wall slope parallel to the table. The planning target volume has been defined according to the Radiation Therapy Oncology Group (RTOG) breast cancer atlas consensus for whole breast irradiation. All patients received Supra/infra-clavicular nodal irradiation together with the whole breast irradiation, and being all patients underwent complete ALND, Axillary irradiation was not given, no patients received the internal mammary chain irradiation. Clinical target volume included the whole breast and the fascia of pectoralis major, and margin for planning target volume (PTV) was recommended as 1 cm superior-inferiorly and 0.5-0.7 cm in the other directions.

Systemic chemotherapy

Chemotherapy was administered to all except patients with major co-morbidities who received hormonal treatment only. Hormonal therapy was used in patients with ER and/or PR positive patients. Patients with HER2 positive cancer had received anti-HER2 therapy with adjuvant trastuzumab for 1 year.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy was administered to patients presented with N2 lymph nodes, HER2 positive patients or triple negative patients.

RESULTS

During our study period twenty of 1823 patients (1%) diagnosed with axillary metastasis of breast origin with OBC not detected clinically and by MRI. The median age was 51.3 years old. Eleven patients (55%) diagnosed by core needle biopsy, six patients (30%) diagnosed with FNAC and three patients (15%) diagnosed with excisional biopsy. The average size of lymph node detected radiologically 32.1 mm (range from 11 – 52 mm). Thirteen patients (65%) had right axillary lymph node metastasis. sixteen patients (80%) were ER positive, fifteen patients (75%) were PR positive, four patients (20%) were HER2neu positive, and two patients (10%) were triple negative (*table 1*).

Table 1 - Patient demographics and tumor characteristics

	n	%
age	Median = 51.3	Range 37-67
Menopausal status		
Postmenopausal	11	55%
Premenopausal	9	45%
Family history		
Yes	6	30%
No	14	70%
Side of axillary LN		
Right	13	65%
Left	7	35%
Size of axillary LN	Median = 32.1 mm	Range 11- 52 mm
Estrogen receptor–positive	16	80%
Progesterone receptor–positive	15	75%
HER-2–positive	4	20%
Molecular subtype		
Luminal A	5	25%
Luminal B	9	45%
Luminal B/HER2 positive	2	10%
HER 2 overexpression	2	10%
Triple-negative	2	10%
N1	16	80%
N2	3	15%
N3	1	5%

Nine patients (45%) presented with ultrasound, eleven patients (55%) presented with sono-mammography, all patients underwent bilateral breast dynamic MRI. Five patients (25%) underwent PET CT while other fifteen patients (75%) underwent CT and bone scan. Chemotherapy was administered to all except two patients (90%) with major co-morbidities who received hormonal treatment only. All patients received whole breast radiotherapy. Five patients (25%) received neoadjuvant chemotherapy, two patients (10%) received Trastuzumab, two patients (10%) had complete pathological response to neo-adjuvant systemic therapy, one of them was triple negative (received neoadjuvant Anthracycline + Taxane) and the other patient was HERIIneu positive (received neoadjuvant Anthracycline + Taxane + Trastuzumab), two patients of five patients (40%) who received neoadjuvant chemotherapy give complete pathological response.sixteen patients (80%) received hormonal therapy and fifteen patients (75%) underwent upfront surgery, eighteen patients (90%) underwent ALND (*figure 1*) and two

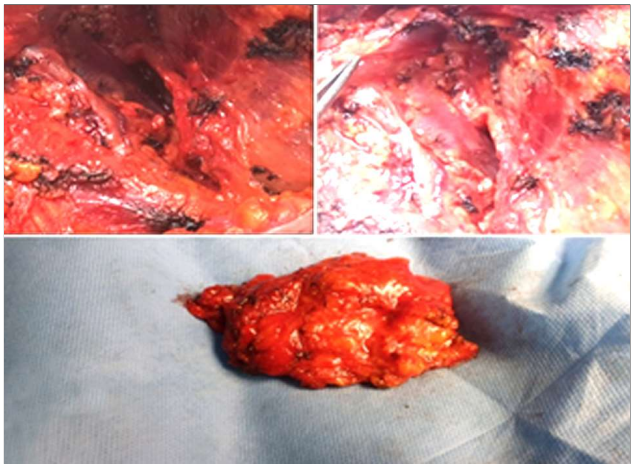

Figure 1 - Axillary lymph node dissection

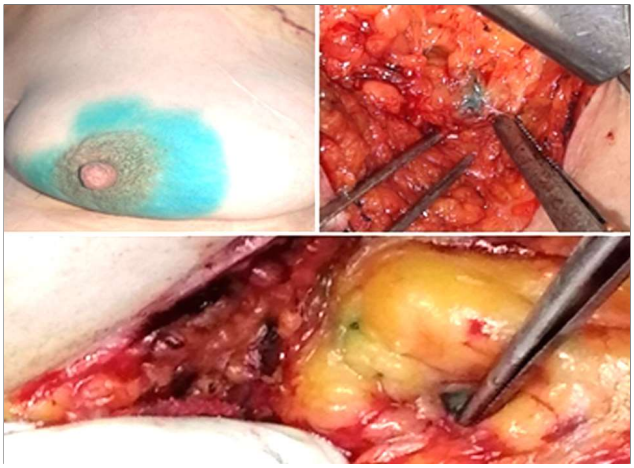

Figure 2 - Sentinel lymph node biopsy using patent blue dye

patients (10%) underwent sentinel lymph node biopsy (SLNB) (*figure 2*, *table 2*).

All patients received adjuvant ipsilateral whole breast irradiation with a hypo-fractionated schedule 270 cGy x 15 fractions, no sequential boost was given. Patients were treated using external beam 3-D conformal radiotherapy technique. All patients received Supra/infra-clavicular nodal irradiation together with the whole breast irradiation. Two patients (10%) developed lymphedema, six patients (30%) developed breast edema in the first six months after surgery (mainly three months after radiotherapy), one patient (5%) developed numbness at the distribution of intra-costo-brachial nerve and one patient (5%) developed wound seroma. The overall complications were 20%. Seventeen patients (85%) developed radiation dermatitis that healed eventually. Three patients (15%) developed radiation pneumonitis which presented with fever and cough and treated with prednisone (40 mg/day) resulted in rapid clinical and radiological improvement (*table 3*).

Patients were followed-up after 6 months, 12 months, 3 years and 5 years as regard disease-free survival, nodal recurrence and distant metastasis. No local recurrence occurred. One patient (diagnosed triple negative adenocarcinoma) developed liver metastasis after 21 months from original diagnosis. The patient who developed liver metastasis died after 3 months from developed metastasis.

DISCUSSION

Occult primary breast carcinoma (OBC)(pT0N+) presented with axillary lymph nodes metastases with non-detectable primary breast tumor either clinically or by imaging is considered a rare entity. The incidence

Table 2 - Diagnostic imaging evaluation and oncologic treatment

	n	%
Ultrasound	9	45%
Mammography	11	55%
Bilateral breast MRI	20	100%
CT and bone scan	15	75%
PET CT	5	25%
Neo-adjuvant chemotherapy	5	25%
Anthracycline + Taxane	4	20%
Anthracycline + Taxane + Trastuzumab	1	5%
Adjuvant chemotherapy	13	65%
Adjuvant trastuzumab for 1 year	2	10%
Hormonal therapy	16	80%
ALND	18	90%
SLNB	2	10%

Table 3 - Surgical complications, complication of irradiation and disease-free survival

	n	%
Wound seroma	1	5%
Wound hematoma	0	
Lymphedema	2	10%
Grade 1	1	5%
Grade 2	1	5%
Radiation dermatitis	17	85%
Grade 1	14	70%
Grade 2	3	15%
Grade 3	0	0%
Radiation pneumonitis	3	15%
Grade 1	2	10%
Grade 2	1	5%
Nodal recurrence	0	
Distant metastasis	1	5%
Mortality	1	5%

rate of OCB is 0.3 to 1% among breast cancer (3).

Bilateral breast mammography detects only 10% to 20% of primary breast tumor in clinically occult primary (23, 24).

Bilateral dynamic breast MRI has high sensitivity up to 86% in detection of primary breast tumor in clinically and mammographically occult primary (7, 25).

ALND with WBRT in patients with occult primary breast cancer give an equivalent result to mastectomy (26, 27).

Meta-analysis shows no difference between MRM and ALND with WBRT as regard locoregional recurrence, distant metastasis and mortality (14).

Despite of the same outcomes of MRM and WBRT with ALND but 43% of the American society breast surgeon prefer MRM in occult primary breast cancer and 37% underwent ALND with WBRT (28).

Neoadjuvant chemotherapy play a role in nodal disease and its effect differ according to hormonal receptor, HERII expression or triple negative (29-31).

In our study 40% of patients who received neo-aduvant chemotherapy give pathological complete response (pCR) that similar to same results that published by authors (29-31) that report that Neoadjuvant chemotherapy can achieve complete pathological response in nodal disease in 20% to 40% of patients.

Yang et al. (15) evaluated pCR in 5 patients with OBC received neoadjuvant chemotherapy followed by mastectomy, ALND and RT. One patient lost in follow up and the other four patients give pCR. Rueth et al. (14) achieved a pCR in 80% of patients (15/25) after neo-adjuvant chemotherapy. In our study 40% of patients who received neoadjuvant chemotherapy give pCR, which is comparable to most series.

In our study two patients underwent SLNB after neoadjuvant chemotherapy that achieved the same results of ALND as regard overall survival. Mamtani et al. (32) reported that SLNB replaced ALND in 48% of node-positive patients who achieved a nodal pCR following neoadjuvant chemotherapy.

SLNB decrease complications (lymphedema, numb-ness and pain), hospital stay and cost when compared to ALND (33, 34).

Multiple studies reported the accuracy of SLNB after neoadjuvant chemotherapy (29, 31).

In our study all patients received WBRT. Radio-therapy is a golden standard in management of OBC with positive axillary lymph nodes as it improves overall survival and local recurrence (12, 35).

Patients follow up after 6 months and 12 months all patients will be followed after 3 years and 5 years as regard disease free survival, nodal recurrence and distant metastasis.

CONCLUSIONS

Due to limited experience in OBC, as OBC is a rare entity, the optimal treatment is not yet established, but there is no difference between MRM and ALND with WBRT with or without nodal RT as regard local recurrence and disease-free survival. More patients and longer follow-up are needed to establish safe management of OBC. ALND with WBRT has less morbidity, blood loss and less hospital stay than MRM.

Conflicts of interest and source of funding

None declared.

Ethical approval

Ethical approval was obtained from the Ethical Committee of Ain Shams University Hospitals, and informed written consents were obtained from all patients.

All authors confirm that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

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