Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201963131-135

Management of Carcinoma of Unknown Primary Involving Axillary Lymph Node (CUPAx)

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ARTICLE INFO

Received:
28 July 2019
Revised:
08 August 2019
Accepted:
18 August 2019

Key words:
Unknown primary tumors, lymph nodes, axilla.

ABSTRACT

Background: Cancer of unknown primary involving axillary lymph nodes (CUPAx) is a very rare type of cancer. There are still many challenges about the management and outcome of the disease. This retrospective study is an attempt to assess the overall survival and the outcome of CUPAx in Iranian women.

Methods: Based on inclusion and exclusion criteria, 20 patients primarily diagnosed with CUPAx referred to our breast multidisciplinary team (MDT) sessions between July 2010 and December 2016 were evaluated. The patients were categorized into three groups based on the types of treatment: mastectomy and radiation therapy, radiation therapy, and observation group.

Results: The mean age of the subjects was 52 ± 7.91 years (range: 42-74). The results manifested significant differences between the outcomes of three types of treatments. The patients who received both mastectomy and radiotherapy had a higher survival rate and no sign of the disease compared with other groups (P= 0.03). The median survival time in the mastectomy group was 78 months and 23 months for the group with no mastectomy (95% CI: 7.64-38.36) (P <0.001).

Conclusion: The result suggested that mastectomy was effective in lowering the risk of disease progression in Iranian women diagnosed with CUPAx and highly suspicious breast origin. More studies on larger sample groups are needed.

Introduction

Cancers of unknown primary (CUPs) are a group of histologically confirmed metastatic cancer of which the primary site is undetectable even after a complete and standard diagnostic and pathologic workups. The incidence rate of CUPs is 3-5% of all solid malignant tumors.[1] The most affected sites were the bones, liver, lungs, and lymph nodes. The CUP involving axillary lymph nodes (CUPAx) is a very rare case and the incidence rate is reported between 0.12 to 0.67 % of all diagnosed cancers.[2, 3] Some evidences manifest the incidence of CUP involving axillary lymph nodes is between 0.1 and 1 % of all patients with breast cancer.[4-7] The primary site of CUPAx is most often hidden in the breasts; however lung, ovary, thyroid, pancreas, urogenital tract, or intestines are the other possible primary sites.[8] The CUPAx affects women in the 6th decade of life with a mean age of 52 and the most frequent histology is ductal adenocarcinoma.[9] About 23.4% of the CUPAx patients had a history of malignancy in their family.[2]

Finding the primary source of CUPAx is a diagnostic challenge and requires extensive investigations. Magnetic Resonance Imaging (MRI) is widely utilized to this end,[10,11] and it seems MRI is

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one of the modalities with high sensitivity to detect occult breast cancer in CUPAx patients. Some studies on CUPs have reported that accuracy of fluorodeoxyglucose (FDG) PET ranges from 25% to 43%.[9]

The CUPAx belongs to favorable subsets of CUP which respond to local or systematic treatments with a longer survival term. Some studies have compared the prognosis of patients with CUPAx to early breast cancer patients. Montagna *et al.* did not find any significant difference in disease-free survival (DFS) and overall survival (OS) between occult breast cancer and early invasive cancer.[8] Pentheherodakis *et al.* reviewed 14 studies (a total of 559 CUPAx patients) and concluded that the mean 5-year OS rate was higher or similar to stage II-III patients with breast cancer.[2] The literature review by Lee *et al.* suggested that, with a 10-year survival ranging from 50% to 71%, prognosis resulted in better outcomes comparing with the cases diagnosed at stage II.[7] Another report indicated that patients of CUPAx had 10-year overall survival of 96.8% in N1 feature and 82.6% and 80.8% in N2 and N3 cases respectively.[6] There is no consensus on the management of CUPAx with suspected breast origin. Local therapy of the breast varies from observation to quadrantectomy, mastectomy, or whole breast irradiation.[2, 7] Many researchers have investigated the role of local breast treatment on the survival of the patients. Walker *et al.* reported that 10-year Cause Specific Survival (CSS) rate was 75.7% for patients who experienced breast conservative therapy (BCT) versus 73.9% for patients who experienced mastectomy. They concluded that, comparing with BCT, mastectomy had no effect on CSS.[12]

The management of the axilla in CUPAx is less controversial. In a review by Pentheherodakis *et al.*, the vast majority of practitioners routinely practiced axillary lymph node dissection (ALND) (level I and II); however, in smaller groups of cases, axillary excisional biopsy and irradiation of the axilla were applied. They reported that in-axilla failure rate after a level I/II ALND (<10%) was lower than excisional biopsy and/or axillary irradiation (20% to 50%).[2]

The present study was an attempt to examine the long-term outcome of CUPAxin patients at Cancer Institute of Imam Khomeini hospital based on patients' characteristics and treatment plans.

Methods

The records of patients filed in the Breast multidisciplinary team (MDT) sessions (Cancer Institute of Imam Khomeini Hospital) between July 2010 and December 2016 were retrospectively reviewed. The participants signed an informed letter of consent at the time of final follow up. In addition, the ethics committee of the hospital approved this study. Patients with CUPAx entered the study and their hospital charts were reviewed. Different types of data were retrieved including: history, physical examination, demographic characteristic, imaging studies (Mammography, Ultrasonography, MRI, and metastatic work up), pathology, IHC results (ER, PR, HER-2, TTF1, CK7, GCDFP15, CK AE1/AE3, and HMB45), and local and systemic therapies.

Breast MDT recommendation to all patients was ALND with systemic therapy before ALND. Either mastectomy and chest wall radiation or whole breast irradiation was recommended as local treatment of the breast. The final treatment would differ depending on patients' priorities and principal physician's decision.

The patients were categorized according to the local treatment of the breast into three groups: 1- mastectomy and radiation therapy, 2- radiation therapy, 3- no local therapy of the breast (observation group). In addition, all patients received chemotherapy.

Patients with incomplete data, primary lesion in the breast imaging, history of breast cancer in contralateral breast, evidence of distant metastasis, other cancers based on histologic results, and IHC of axillary lymph node were excluded. Standard followed up procedure was implemented and the outcome was categorized according to the last follow up. The final outcomes were no evidence of disease (NED), alive with disease (AWD), and dead of disease (DOD).

The collected data was analyzed in SPSS (version 13, Chicago, IL, USA). Categorical variables were expressed in number (%) and continuous variables were represented as mean ± standard deviation. Chi-squared test or Fisher's exact test was used to compare categorical variables ($P< 0.05$). Kaplan-Meier approach was used to estimate the median survival from the time of diagnosis to the time of event (death or alive with disease) and overall survival was compared between treatment groups with a log-rank test.

Results

Between July 2010 and December 2016, 20patients with primary diagnosis of CUPAx referred to our breast MDT sessions were selected based on the exclusion and inclusion criteria (n= 20). Four patients had a suspicious lesion in mammography or US. Biopsy of these lesions revealed three fibroadenomas and one cases of usual ductal hyperplasia. Five patients had suspicious lesion on breast MRI, which was detectable on targeted US. The biopsy of these lesions proved to be benign. Lymph node IHC results such as TTF1, CK7, CK 20, GCDFP15, CK AE1/AE3, and HMB45 were in line with breast cancer origin. Table 1 lists the patients' characteristics. The mean age of the affected women was 52 ±7.91 years (range: 42-74) and 55% of them were in postmenopausal status.

Figure 1 illustrates the overall survival of all

Table 1. Patient's characteristics (N=20)

Variables		N (Range-%)
Mean age at diagnosis (range)		52 (42-74)
Median follow-up (range)		38 (14-78)
Laterality	Right Left	11 (55%) 9 (45%)
Menopausal status	Premenopausal Postmenopausal	9 (45%) 11 (55%)
Positive family history of malignancy		4 (20%)
IHC results of lymph nodes	Luminal A, B Her2-enriched Basal-Like	12 (60%) 2 (10%) 6 (30%)
Chemotherapy	Adjuvant Neoadjuvant	16 (80%) 4 (20%)
Nodal Status	N1 (1 to 3 involved lymph nodes) N2 (4-9 involved lymph nodes)	7 (35%) 13 (65%)
Lymph node pathology, n (%)	IDC Metastatic carcinoma Undifferentiated carcinoma Poorly differentiated carcinoma	3 (15%) 10 (50%) 5 (25%) 2(10%)

Data are presented as number and percentage in parenthesis.

Table 2. Patients' information considering treatment and outcomes

	Follow up Median (Min-Max)	Status of patients			P
Treatment Type		NED N=12	AWD N=7	DOD N=1	
Mastectomy + Radiotherapy	51 (22-78)	10 (76.9%)	3 (23.1%)	0 (0.0%)	0.03*
Radiotherapy alone	29 (14-44)	2 (50%)	1 (25%)	1 (25%)	
No local therapy	19 (16-23)	0 (0.0%)	3 (100%)	0 (0.0%)	

Min: minimum, Max: maximum, NED: No evidence of disease, AWD: Alive with disease, DOD: Dead of disease.
** P refers to Fisher's exact test.*

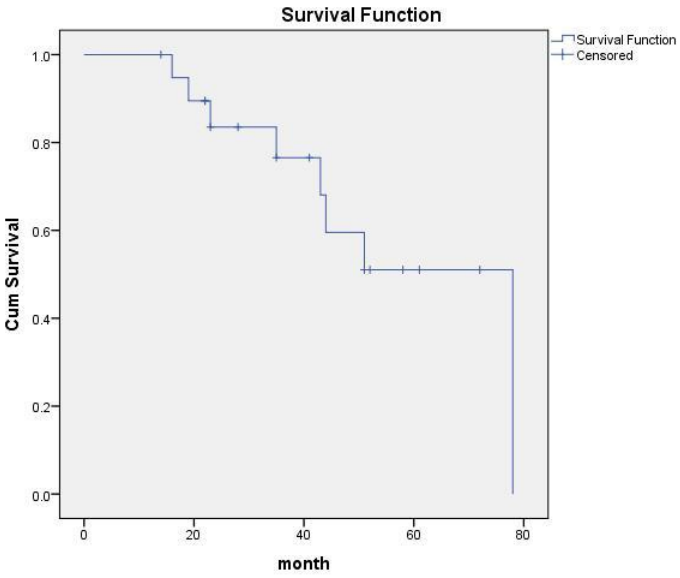

Figure 1. Overall survival of CUPAx in the present study sample.

patients who participated in this study. The mean survival time was 57.19 months (95% CI: 44.75-69.64).

Table 2 lists the number of patients with different treatments and outcomes. The significant differences between the outcome of three types of treatments are evident. The patients who received both mastectomy and radiotherapy have a higher survival rate and no evidence of disease compared with other groups (P= 0.03). Categorizing the patients into two groups based on mastectomy revealed that 76.9% (10/13) of patients who received mastectomy had no evidence of disease and the complication occurred only in three patients (23.1%). However, 29% (2/7) of patients who did not receive mastectomy were alive without disease and the complication occurred in five patients (71%). This difference is also statistically significant (P= 0.06) (Data not shown in the table). Survival time period comparison with Log Rank test manifested the median survival time of the mastectomy group was 78 months and 23 months for the other group (no mastectomy) (95% CI: 7.64-38.36); the difference is statistically significant (P <0.001).

There was a patient in the mastectomy and irradiation group with follow up of 42 months (total of 13 patients) with regional relapse in axillary

lymph node and another patient with liver metastasis. In the irradiation group with follow up of 25 months (total of 4 patients), one patient developed multiple bone metastasis and the other patient died from widespread visceral (ovary & lung) and bone metastasis at 44th month from her first presentation. Finally, in the group without any local treatment with follow up period of 22 months (totally 4 patients), one patient demonstrated local recurrence on the chest wall with ulceration, another one developed cervical lymph node metastasis, and the third patient developed multiple bone metastasis.

Discussion

The CUPAx is a rare clinical entity and it has been reported in case reports.[13-16] There are also a few studies with large sample size.[5, 6] Breast is the most likely origin of CUPAx and ER or PR positive in IHC assay of axillary lymph node could support the origin of breast; still, negative results do not exclude the breast origin.[14]

Twenty cases of CUPAx who referred to our cancer institute with the median follow-up of 38 months (range: 14-78) were studied. Interestingly, the mean age of subjects (52 years old) was similar to a large systematic review.[2] The result suggested that mastectomy was effective in lowering the risk of disease progression and as a best modality, it should be recommend to all patients with CUPAx with highly suspicious breast origin

Consistent to the present study, Sohn *et al.*'s investigation showed the overall survival in patients undergoing ALND only, breast conserving surgery, and mastectomy with ALND was not significantly different (P= 0.061).[6] The authors believe that the statistical uncertainty of our result is due to the small sample size. However, Sohn *et al.* evaluated 142 cases and they reported the same results. Another study with 48 CUPAx cases revealed that the patients with ipsilateral radiotherapy and breast conservation therapy (BCT) or mastectomy had better 5-year local recurrence free survival compared with observation group.[5] They did not evaluate the survival time for mastectomy and BCT separately. They recommended a standard radiotherapy to improve local control in patient with occult primary breast cancer. However, in the present study only one patient died from the disease and she only received radiation therapy. Therefore, we suggest only radiation therapy without considering surgery may be a threat to the patient's health.

Another study in 2010 systematically reviewed published CUPAx case series and 24 retrospective studies enrolling 689 patients. Among the total of 446 patients managed with mastectomy, 72% of them histologically showed that the breast was the primary origin. The authors concluded that mastectomy or radiotherapy provided loco-regional disease control in 75% to 85% of cases. The effect of removing an occult primary on survival was unclear; however, these data supported mastectomy as an effective diagnostic modality.[2] Our result was consistent with this systematic review so that mastectomy provided disease control in 77% of our cases.

A mini-review in 2015 recommended radiotherapy and adjuvant chemotherapy afterwards and/or hormone therapy depending on the risk factors for patients with CUPAx. The authors did not suggest mastectomy as an effective treatment. [9] However, according to a survey by the American Society of Breast Surgeons (ASBS) in 2005, 43% of the experts preferred mastectomy, while 37% opted for whole breast radiation, and 20% selected other treatments (including 6% that chose observation).[17]

Finally, although there is a consensus about the necessity of ALND and chemotherapy in treatment of CUPAx patients, still the recommendations regarding the local management of the breast are controversial.

As shown by the results here and in the other studies, in CUPAx patients, local therapy of breast by mastectomy or radiation therapy is associated with better results in local control, distant metastasis, and overall survival. Larger prospective studies are required to address this question with more certainty.

Acknowledgement

We would like to show our gratitude to the breast multidisciplinary team of Cancer Institute of Imam Khomeini hospital.

Conflict of Interest

The authors declare that there is no conflict of interest.

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