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# Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence

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**Abstract** Axillary lymph node metastases from adenocarcinoma or poorly differentiated carcinoma of unknown primary (CUPAx) represent a rare clinical entity without consensus on its biology, management and outcome. We systematically reviewed published CUPAx series and identified 24 retrospective studies enrolling 689 patients from 1975 till 2006. CUPAx affected women at a mean age of 52 years, 66% of whom post-menopausal harbouring low-volume (N1, 48%) or high-volume (52%) nodal disease from ductal adenocarcinoma (83%). Among a total of 446 patients managed with mastectomy, a small breast primary was identified histologically in 321 (72% of cases). Hormone receptor protein expression was observed in 40–50% of cases, while HER2 overexpression in 31%. CUPAx patients were managed with axillary lymph node dissection coupled to mastectomy (59%), primary breast irradiation (26%) or observation (15%). Observation was associated with high locoregional relapse rates (42%) and risk of metastatic spread. Mastectomy or radiotherapy provided locoregional disease control in 75–85% of cases, while adjuvant systemic therapy was associated with a non-significant trend for improved survival in few series. Five-year survival ranged from 59.4 to 88% at a median follow-up of 62 months (mean 5-year survival 72%), with axillary tumour burden being the pivotal prognostic factor. CUPAx is associated with similar presentation, biology and

outcome to resected node-positive overt breast cancer and should be treated accordingly.

**Keywords** Axillary metastases · Cancer of unknown primary · Prognosis

## Introduction

The fundamental characteristics of cancer of unknown primary (CUP) are early dissemination and unpredictable metastatic pattern coupled to dormancy or regression of the primary tumour and aggressive biologic behaviour [1]. Among the most important advances in understanding CUP biology was the identification of favourable clinicopathologic subsets affecting 10–20% of patients with CUP. Appropriate diagnosis of such cases is of great importance as they warrant specific treatment, which is frequently effective. Adenocarcinoma or poorly differentiated carcinoma found in isolated unilateral axillary lymph nodes without an obvious primary tumour (CUPAx) is a clinical situation challenging for physician and patient alike. The standardized diagnostic approach for investigation of the primary and staging consists of bilateral mammography, CT of chest/abdomen/pelvis supplemented by sign- or symptom-directed additional radiologic or endoscopic studies [1, 2]. Malignant neoplasms known to metastasize to the axilla include lymphoma, melanoma and carcinomas of the breast, lung and gastrointestinal tract [3]. When the diagnosis is an adenocarcinoma or undifferentiated carcinoma, the most frequent culprit is breast cancer and a thorough investigation for a breast primary is warranted. Haematoxylin–eosin light microscopy examination supplemented by immunohistochemistry including oestrogen receptor (ER), progesterone receptor (PgR) protein expression may

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contribute to precise identification of the cellular origin of the malignancy. Still, no consensus exists on a common battery of immunohistochemical studies, on the sequence of imaging modalities to be used, nor on the management strategy of these patients. Areas of dubiety include the management of the axilla, the need for surgical or radiotherapeutic extirpation of the presumed primary in the breast, the impact on patient outcome of adjuvant systemic chemotherapy or hormonal therapy. Moreover, prognosis of patients with CUPAx has not been clearly defined or related to the outcome of patients with node-positive breast cancer.

Due to its relative rarity there are no published randomized trials regarding management and outcome of patients with CUPAx, the only evidence for this entity originating from small retrospective studies. We sought to systematically review and analyse published data from prospective or retrospective studies of CUPAx patients in order to present available evidence on epidemiology, diagnosis, management and outcome as well as reach appropriate recommendations.

## Patients and methods

We did a search of PubMed, MEDLINE and EMBASE using the following keywords for our literature search (cancer OR carcinom\* OR neoplas\* OR malignan\* OR tumour OR tumor) AND (unknown primary OR unknown origin OR occult primary) AND (breast OR axilla\* OR axillary lymph node metastases), restricting our search to English language. We also searched oral presentations at ESMO and ASCO conferences. Eligible patients were those with isolated axillary lymphadenopathy with adenocarcinomatous or carcinomatous deposits without evidence of primary tumour or distant metastatic deposits at initial diagnostic work-up. Histopathological identification of an occult breast tumour in subsequent mastectomy specimens or at autopsy did not exclude these patients from the CUPAx population. All patients had undergone bilateral mammographic imaging in order to be eligible for inclusion in the CUPAx cohort. All those in whom baseline imaging showed a breast lesion histologically confirmed as the primary tumour were not classified in the CUPAx population and were excluded from further analysis. A PRISMA flow diagram is presented in Supplementary figure [4].

## Results

We identified 30 studies dealing with CUPAx patients, but we did not include in our analysis six of them because three

had an update study and three had overlapping patients with series that were published over the following years from the same institutes [5–31]. Accordingly, a total of 689 patients presented with axillary carcinomatous metastases of unknown primary in 24 clinical series published from 1975 until 2006. All were small retrospective studies, making it difficult to draw solid conclusions based solely on low-level evidence. The last search update was performed in July 2009.

## Demographics—patient and tumour characteristics

The true incidence of CUPAx seems to range from 0.12 to 0.67% of all diagnosed malignancies. Patient and tumour characteristics are summarized in Table 1. Mean age at diagnosis was 52.4 years and in 66% of the cases it appeared in postmenopausal women. Following axillary clearance mean nodal size was 2.4 cm (0.5–10 cm) with 52% of patients harbouring N2-3 disease (four or more involved nodes), according to pathologic TNM staging. A positive family history of malignancy could be identified in 23.4% of the CUPAx patients. In CUPAx patients managed with ipsilateral mastectomy in whom an occult primary tumour was identified on histopathologic

**Table 1** Patient and tumour characteristics

Number of studies	24
Years (of publication)	1975–2007
Incidence (% of all malignancies)	0.12–0.67%
Total number of patients	689
Gender	All females
Mean age at diagnosis (range)	52.4 (32–79)
Median follow-up of patients	42 months (15 studies)
Laterality	Data from 9 studies ( <i>N</i> = 270) Left 146 (54%) Right 124 (46%)
Menopausal status	Data from 9 studies ( <i>N</i> = 203) Premenopausal = 64 (31.5%) Postmenopausal = 134 (66%) Perimenopausal = 5 (2.5%)
Mean axillary size (range)	Data from 7 studies 2.4 cm (0.5–10 cm)
Positive Family History for malignancy	Data from 7 studies ( <i>N</i> = 184) 43/184 (23.4%)
Nodal status (pN)	Data from 12 studies ( <i>N</i> = 384) N1 = 184/384 (48%) N2-3 = 200/384 (52%)

**Table 2** Occult breast primaries in mastectomy specimens

	All CUPAx patients	Invasive tumours found in breast	In situ carcinomas found in breast	Number and size of invasive tumours
Owens [5]	27	25		15 <1 cm 5 >1 cm
Feurman [6]	2	1		
Fitts [7]	11	7		
Haagensen [8]	13	12		
Ashikari [9]	34	20	3	7 <1 cm 7 1–2 cm 6 >2 cm
Feigenberg [10]	4	3		
Vezzoni [11]	44	33		11 <0.5 cm 12 0.5–1 cm 10 1–2 cm
Iglehart [31]	5	5		3 <1 cm 2 1–1.5 cm
Kemmeny [12]	11	3	2	2 <2 cm 1 >2 cm
Bhatia [13]	11	9	2	8 <2 cm 1 >2 cm
Rosen [16]	38	27	7	Median 1.5 cm (0.1–6.5) 18 <2 cm 4 >2 cm
Ellerbroek [17]	13	1		
Merson [18]	33	27		9 <1 cm 6 1–2 cm 5 >2 cm
Svastics [19]	29	11		
Van Ooijen [20]	1	0		
Kyokane [21]	92	72	9	Median 1 cm (1–10) 2 cm
Vlastos [24]	13	1		
Medina-Franco [25]	3	0		
Matsuoka [27]	10	5	2	7 <2 cm
Blanchard [28]	18	5	1	Mean 2.9 cm (1.5–6)
Chen [29]	16	16		Median 1 cm (0.5–1.5)
Total	446	321 (72%)	26 (5.8%)	

examination, the size of the primary lesion was less than 2 cm in 87% of cases (43.5% 0–1 cm, 43.5% 1–2 cm) (Table 2). Among a total of 446 patients managed with mastectomy, an occult breast primary was identified histologically in 321 (72%). Though the impact of removing an occult primary on survival is not clear, these data support mastectomy as an effective diagnostic modality. Ductal or lobular carcinomas in situ were detected in 5–10% of mastectomy CUPAx cases, in keeping with published incidence in the general population.

#### Imaging of the breast

Data from 20 studies evaluating a total of 498 patients established a rate of radiologic identification of a primary lesion in 100 (20%). The impact of application of high-resolution digital mammography is currently unknown in this setting. Breast ultrasound performed in six studies of 84 CUPAx patients identified abnormalities in only 4% of cases and seems only to have a role for differentiation of cystic/solid lesions. Magnetic resonance imaging (MRI) of

the breast managed to reveal a primary in 96 out of 162 patients (59%), suggesting that it is a selected modality with high sensitivity for detection of occult breast tumours that may find a place in the diagnostic algorithm of CUPAx patients.

### Histology

Histopathologic data were reported for the carcinomatous deposits in either axillary lymph nodes or the occult mammary tumour in 385 cases. The carcinomatous deposit in 319 (83% of cases) was a ductal carcinoma, lobular in 50 (13%) and other types in 4%. Good to moderate differentiation was observed in 342 (89% of cases) while 43 (11%) were poorly differentiated. Among 184 CUPAx tumours with available data, positive staining for oestrogen receptor was seen in 76/175 (43%) and for progesterone receptor in 16/39 (41%). Only scarce data were available for immunohistochemical (IHC) HER2/neu protein overexpression (IHC 3+), though the 31% incidence observed (4/13 cases) is in the range reported for node-positive breast cancer.

### Axillary management

A level I and II axillary lymph node dissection (ALND) was routinely practiced by the vast majority of investigators in the published series (92% of CUPAx patients). In the minority of cases, in which axillary excisional biopsy was applied, irradiation of the axilla followed. It is unknown if resection of involved lymph nodes only is suboptimal, though this is likely to result in residual disease left in lymph nodes microscopically involved. In 1976 Feigenberg et al. [10] reported a 50% recurrence rate when the axilla is treated only with RT and recommended ALND as an essential component of the primary treatment of patients with CUPAx in view of the benefits in local control of the disease. In-axilla failure rates were generally lower after a level I/II ALND at less than 10% and higher (20–50%) when excisional biopsy and/or axillary irradiation were used. These data argue in favour of ALND as the preferred treatment that offers diagnostic and therapeutic benefit. Management and outcome data on analysed clinical series are shown in Tables 3, 4, 5 and 6.

### Management of the ipsilateral breast

Treatment of the ipsilateral breast in patients with CUPAx remains controversial. Treatment options that have been tested in the above mentioned studies include: mastectomy, breast conserving surgical excision of suspicious lesions and whole breast radiotherapy, external beam breast irradiation only and observation. In 59% primary treatment consisted of mastectomy with or without chest wall

**Table 3** Clinical series with breast observation only

	<i>N</i>	Breast failure	Latent period (months)
Haagensen [8]	5	3/5	Range 5–64
Feigenberg [10]	4	0/4	
Kemmeny [12]	7	0/7	
Bhatia [13]	2	2/2	Median 6.2
Campana [14]	1	1/1	Median 7
Rosen [16]	5	0/5	
Ellerbroek [17]	13	7/13	Median 27 Range 11–47
Merson [18]	17	9/17	Mean 13
Svastics [19]	14	2/14	Median 4.1
Van Ooijen [20]	14	2/14	Median 10.3
Jackson [22]	8	7/8	Mean 15 months Range 6–39
Foroudi [23]	6	5/6	Median 7
Shannon [26]	13	7/13	
Matsuoka [27]	1	1/1	Median 37
Total		46/110(42%)	

*N* sample size

**Table 4** Therapy of CUPAx patients

Treatment data available for <i>N</i> = 600 patients	<i>N</i> (%)
<i>Primary therapy</i>	
Axillary lymph node dissection only	61 (10)
Axillary excisional biopsy only	31 (5)
Mastectomy (with axillary local treatment)	240 (40)
Mastectomy + chest wall RT (with axillary local treatment)	111 (19)
Primary breast RT (with axillary local treatment)	157 (26)
<i>Adjuvant systemic therapy</i>	
Chemotherapy (with or without endocrine)	239 (40)
Hormonotherapy (with or without chemotherapy)	71 (12)
Combined chemohormonotherapy	57 (10)
Anthracycline-based	132/600 (21)
Anthracycline + taxane combinations	5/600 (1)
Alkylator-based	102/600 (18)

RT radiation therapy, *N* sample size

radiotherapy. Whole breast irradiation was the primary treatment in 26%, while observation of the breast was chosen in 15% of cases (Table 4).

A standard approach in several series was to perform a “blind” modified radical mastectomy at the time of ALND. In our review we observed that a breast malignancy was found upon histologic review of the breast specimen in 72% of the resected cases with an additional 5.8% of DCIS (Table 2). Radical whole-breast radiotherapy has been used as an alternative to mastectomy, though there are no

**Table 5** Outcome and prognosis

Mean 5-year overall survival	Available data from 14 studies $N = 559$ $OS = 72\%$ (Range 59.4–87.5%) Median follow-up 62 months (range 27–133)		
Prognostic/predictive factors ( $P < 0.05$ )	Investigators		
Number of involved axillary lymph nodes	Kemmeny [12], Svastics [19], Whillis [15], Merson [18], Kyokane [21], Vlastos [24]		
ALND	Ellerbroek [17]		
Absence of residual gross disease	Ellerbroek [17]		
Local treatment of breast (surgery or RT)	Vlastos [24], Foroudi [23], Shannon [26], Blanchard [28]		
Impact of adjuvant systemic therapy	5-year overall survival		
	Adjuvant therapy (%)	No adjuvant therapy (%)	2-sided $P$
Ellerbroek ( $n = 42$ ) [17]	92	67	0.15
Shannon ( $n = 29$ ) [26]	88	86	0.4
Merson ( $n = 56$ ) [18]	87	79	0.2
Blanchard ( $n = 35$ ) [28]	55	65	0.59
(mastectomised patients $n = 18$ )	97 (3-year OS)	75 (3-year OS)	

$N$  sample size,  $OS$  overall survival,  $ALND$  axillary lymph node dissection,  $RT$  radiation therapy

randomized trials directly comparing these two approaches. Published breast only control rate ranged from 75 to 100% (Table 6). The natural history of CUPAx when the ipsilateral breast is not treated is provided in Table 3. A breast primary subsequently developed in the untreated breast in 42% of cases (46/110 in our review) with a latent period from the initial diagnosis of 4–64 months.

#### Observation versus local treatment

Despite the high incidence of occult primary identification in breast pathology specimens, certain series came to question the need for a mastectomy. Though some small series suggested absence of a survival difference whether the breast was treated or not, their small sample size precluded identification of small or moderate differences in outcome. In fact, series with larger sample sizes identified superior survival of CUPAx patients who had the ipsilateral breast treated with mastectomy or irradiation at diagnosis rather than observed. Statistical significance of these survival differences was reached occasionally.

In 1990 Ellerbroek et al. [17] presented a series of 42 patients of whom 13 were treated with mastectomy, 16 with breast irradiation and 13 observed. They reported that breast cancer-free 5-year survival was 83% for patients who had their breasts conserved but treated with irradiation versus 43% for those who were managed with observation ( $P = 0.06$ ). In 1991 Merson et al. [18] reported 5-year survival rates of 80% for 39 CUPAx patients managed with

breast resection or irradiation versus 65% for 17 patients observed until disease relapse, a difference not statistically significant. In two other series by Rosen et al. and Jackson et al. [16, 22], among 17 patients who opted for breast observation 13 experienced disease relapse or death, prompting the authors to suggest that observation is not an acceptable treatment option for CUPAx patients. In 2000 Foroudi et al. [23] further confirmed these data as they reported local recurrence rates of 100% for the observation group versus 30% for the group receiving breast irradiation and 0% for the mastectomy group. Patients in the observation group had poorer RFS when compared to the groups on local treatment (median RFS 7 versus 182 months,  $P = 0.003$ ). Finally, in 2004 Blanchard et al. reported 5-year RFS and OS of 64 and 73% in resected patients versus only 19 and 36%, respectively in patients who retained their breasts ( $P < 0.05$ ). Overall, these data show the inferiority of breast observation versus mastectomy in terms of disease control and survival.

#### Whole breast irradiation

The use of whole breast irradiation was first reported by Vilcoq in 1982 [32] and was reinforced by subsequent data. In 1989 Campana et al. [14] reported 5- and 10-year survival rates of 76 and 71% in 31 CUPAx patients managed with conservative breast radiotherapy (RT), while Whillis et al. [15] similarly published a 5-year actuarial survival of 66% in 18 patients treated with breast radiotherapy. In

**Table 6** Detailed management and outcome data of CUPAx patients in published series

Author	Median FU (months)	N	Nodal disease	Treatment	Adjuvant systemic therapy	Site of first relapse	Outcome
Ashikari 1976		42		36 Mastectomy 3 RT 1 ALND			5-year OS 79% for the whole group Mastectomy NED 26/36 RT NED 2/3 ALND NED 1/1
Feigenberg 1976	60	8		4 Sector mastectomy+ RT 2 Mastectomy + RT 2 RT	No	2 LR, 1 distant None 2 LR	5-year OS 87.5%
Vezzoni 1979		49		44 Mastectomy (+10 chemo, 26 RT.) 3 RT	Alkylator-based in 12		5-year OS 87% Outcome better than stage II breast cancer patients
Kemmeny 1986		20	N1 6 N2 3 N3 6	1 chemo/RT 1 observation 11 Mastectomy		4 distant 1 LR, 1 distant	
Bhatia 1987	Mean 38	11	N1 3 N2 4 N3 3	7 ALND (2 with RT) 9 Mastectomy 1 chemo 1 observation	Adj chemotherapy in 8 pts	1 LR 1 distant 1 LR	
Campana 1989	108	31		RT	Alkylator-based in 8, chemo+TAM in 1, TAM in 1	4 LR, 10 distant 3 LR+ 5 distant	5-year OS 76%
Whillis 1990	39	18	N1 14 N2-3 4	RT	TAM in 4, oophorectomy in 1	5-year OS 66%	Similar to stage II breast cancer
Rosen 1990	60	48	N1 24 N2-3 24	35 Mastectomy 3 Mastectomy+RT 9 Observation	Adj chemotherapy in 25 pts	All patients 5-year OS 79% Not mastectomised pts 5-year OS 45%.	Outcome similar to stage II breast cancer
Ellerbroek 1990 [17]	133	42	N1 32 N2-3 8	1 Chemotherapy 16 RT 13 Observation	Anthracycline-based in 9, alkylator in 5	3 LR 7 LR none	5-year OS 72% for the whole group. No difference between mastectomy and no mastectomy. 5-year DFS 83% for breast conservation+RT vs 43% observation ( $P = 0.06$ )
Merson 1991 [18]	123	56	N1 23 N2-3 23	6 RT 33 Mastectomy 17 observation	Alkylator in 29, TAM in 8	2 LR, 3 distant none 9 LR, 2 distant	5-year OS 76.6% Better than stage II breast cancer. Mastectomy or RT 5-year OS 80% vs observation 5-year OS 65% ( $P = NS$ )
Svastics 1993 [19]		43		20 mastectomy 9 ALND+ quadrantectomy 14 observation		2 distant 3 LR 2 LR	5-year OS 47% Worse than stage II breast cancer



**Table 6** continued

Author	Median FU (months)	N	Nodal disease	Treatment	Adjuvant systemic therapy	Site of first relapse	Outcome
Van Ooijen 1993 [20]	95	15		1 Mastectomy 1 RT	Alkylator-based in 1, TAM in 1	Among all patients, 4 LR and 3 distant	Median OS 92 months
Kyokane 1995 [21]		97	N1 25 N2 18 N3 19 Unknown 30	13 observation 82 Mastectomy 5 RT	Adj chemotherapy in 25, chemoendocrine in 15, TAM in 1		5-year OS 59.4% Similar to node-positive breast cancer
Jackson 1995 [22]		8		Observation	Alkylator in 6	7 LR	Mean survival 42 months Worse than N+ breast cancer
Foroudi 2000 [23]	73	20		6 Observation 2 Mastectomy 12 RT	Adj chemotherapy in 5, chemoendocrine in 1, TAM in 11	6 LR None	Median OS 56 months for observation versus not reached for mastectomy, RT ( $P < 0.05$ )
Vlastos 2001 [24]	84	45	N1 35 N2-3 10	13 Mastectomy 32 RT	Anthracycline-based in 23, chemoendocrine in 8, TAM in 2	4 LR, 2 distant 2 LR, 4 distant 4 LR, 8 distant	5- y OS 75% for mastectomy patients vs 79% for RT patients ( $P = NS$ )
Medina-Franco 2002 [25]	27	10	N1 2 N2 3 N3 5	3 Mastectomy 6 RT 1 chemotherapy	Adj chemotherapy in all patients		Median OS of all patients 31 months
Shannon 2002 [26]	44	29		16 RT 13 No local treatment	Chemoendocrine in 19 (anthracycline 14, alkylator 5), TAM in 2	2 LR, 2 distant 9 LR	5-year OS 88% for all patients. 5-year OS 71% for RT patients versus 65% for no local treatment patients ( $p = NS$ )
Matsuoka 2003 [27]	54	11	N1 5 N2 2 N3 4	9 Mastectomy 2 ALND	Alkylator 2, Anthracycline 3, chemo+TAM 1	4/11 (2 LR and 2 distant)	5-year DFS 62.5%
Blanchard 2004 [28]	41	35		18 Mastectomy 16 No mastectomy	Adj chemotherapy in 22	None 9 LR	5-year OS 72.7% for mastectomy patients vs 35.7% for no surgery pts ( $P = 0.047$ )
Chen 2004 [29]	60	16	N1 9 N2 4 N3 3	10 Mastectomy 6 RT	Chemoendocrine in 6, chemotherapy in 10 (anthracycline+taxane)	1 LR, 3 distant among all pts	5-year OS 87%
Varadarajan 2006 [30]	57	10	N1 6 N2 2 N3 2	2 Mastectomy+RT 8 RT	Chemoendocrine in 6, anthracycline-based chemotherapy in 2	None	NED 100% at last follow-up

FU follow-up, RT: radiation therapy, ALND axillary lymph node dissection, Chemo chemotherapy, TAM tamoxifen, Adj adjuvant, LR locoregional relapse, OS overall survival, NED no evidence of disease, DFS disease-free Survival, NS not significant



2002 Shannon et al. [26] published data on 16 CUPAx patients treated with breast RT and 13 who were observed. Convincingly, patients who received radiotherapy had better relapse-free survival ( $HR = 0.31$ ,  $P = 0.04$ ), though there was no significant difference in overall survival ( $HR = 1.04$ ; 95% CI 0.2–5). In 2001, Vlastos et al. [24] presented a retrospective series of 45 patients with CUPAx and reported no significant difference between mastectomy versus breast conserving surgery and irradiation in terms of locoregional recurrence (15% versus 13%,  $P = 0.9$ ), distant metastases (31% versus 22%,  $P = 0.53$ ) and 10-year survival (66% versus 64%,  $P = 0.9$ ). This study was further supported by similar efficacy of mastectomy versus breast irradiation reported by Medina-Franco et al. [25]. In contrast to data presented by Foroudi et al., cumulative experience from all those series suggested that in the absence of gross breast abnormalities, breast irradiation coupled to surgical extirpation of axillary disease, is feasible and effective in achieving favourable local control rates and survival.

#### Adjuvant systemic therapy

Adjuvant systemic therapy was commonly administered according to clinical guidelines used for patients with resected node-positive breast cancer. This was more often the case for clinical series published after 1990, when the utility of adjuvant therapy had been firmly established in early breast cancer. Among 600 patients with available data, chemotherapy was administered in 239 (40%), with or without endocrine therapy. Seventy-one patients (12%) received endocrine therapy, almost exclusively tamoxifen, alone or combined with chemotherapy. Fifty-seven patients (10%) were managed with combined chemoendocrine therapy. Administered adjuvant chemotherapy consisted of anthracycline-based regimens in 132/600 (21%), anthracycline–taxane combinations in five (1%) and alkylating regimes (CMF variants) in 102/600 (18%).

As most series were retrospective and small, the impact of systemic adjuvant therapy on patient outcome could not be assessed. However, in four studies data on outcome of patients managed with and without adjuvant therapy were provided. Outcome seems to be superior for patients managed with adjuvant chemotherapy in the series published by Ellerbroek et al. (5-year OS 92% versus 67%,  $P = 0.15$ ) [17] and Merson et al. (5-year OS 87% versus 79%,  $P = 0.2$ ) [18], while no difference is seen in the Shannon series (5-year OS 88% versus 86%,  $P = 0.4$ ) [26]. Finally, in the series by Blanchard et al. [28], survival may be positively influenced by adjuvant chemotherapy only in patients managed with mastectomy (3-year OS 97% versus 75%,  $P > 0.05$ ), the ones most likely not harbouring gross

tumour burden. Data on adjuvant chemotherapy are summarized in Tables 4 and 5.

#### Outcome and prognosis

5-year survival in the series analysed ranged from 59.4 to 88% at a median follow-up of 62 months (Table 5). Five year survival data were quoted in 14 studies for a total of 559 CUPAx patients, the mean 5-year OS rate being 72%. When compared to the survival of node-positive (pN1–3, stage II–III) breast cancer patients, CUPAx seemed to have a favourable or similar prognosis. In particular, three series [11, 16, 28] reported favourable outcome of CUPAx patients in comparison to patients with resected node-positive overt breast cancer, while two found similar outcomes for these two patient cohorts [15, 21]. These comparisons were only matched for stage and involved historical controls, thereby constituting a low level of evidence. On the contrary, Svastics et al. [19] and Jackson et al. [22] argued that patients with CUPAx fared worse than matched patients with stage II breast cancer. Regarding clinicopathologic prognosticators nodal burden was recognized as the sole factor of prognostic significance [12, 15, 18, 19, 21, 24], with patients with N1 disease (1–3 involved axillary lymph nodes) experiencing better locoregional disease control, fewer distant failures as well as superior overall survival when compared to patients with N2–3 disease. Other parameters with reported favourable prognostic or predictive significance were performance of axillary nodal dissection and absence of gross disease after surgery [17], local treatment of the ipsilateral breast by means of mastectomy or irradiation [23, 24, 26, 28]. Data on outcome of patients with CUPAx are shown in Tables 5 and 6.

#### Discussion

Women with adenocarcinoma or carcinoma involving only axillary lymph nodes represent such a relatively rare CUP cohort of patients who may enjoy long-term survival [33]. In our review, we analysed clinicopathologic, management and outcome data on 689 patients with CUPAx in order to shed light in one pivotal query: is this entity a variant of node-positive breast cancer or are there significant biologic differences between the two? A second objective was to distill even low-level evidence from published CUPAx series in order to formulate recommendations that may contribute to standardisation of the management of these patients.

Although a non-palpable lesion is identified mammographically in 10–20% of breast cancer cases, many occult non-palpable tumours are missed because of their small size (up to 30% of occult tumours being  $< 5$  mm) or are

obscured by dense fibroglandular tissue [4, 34]. A negative mammogram should prompt imaging of the breast with ultrasound and/or breast magnetic resonance imaging (MRI), which is more sensitive than either mammography or breast ultrasound [35]. In our review of CUPAx patients, breast MRI identified a primary in 59% of 162 cases, data that confirm accuracy rates published previously [35, 36]. The identification of a primary breast cancer by MRI may facilitate breast conserving surgery instead of mastectomy. However, breast MRI is also characterized by high false-positive rates (29% in one study), therefore biopsy of suspicious lesions is advisable [37].

Basic clinicopathologic data of CUPAx patients are not dissimilar to those of patients affected by overt stage II or III breast cancer. It is known that axillary nodal metastases may stem from primaries < 1 cm: in fact, in a report of 953 breast cancer patients, axillary metastases were detected in 20% of those with tumours smaller than 1 cm [38, 39]. In our CUPAx review, a definition bias may be responsible for the high percentage of well differentiated tumours, as in several series adequate tissue differentiation towards glandular morphology was a prerequisite for inclusion in the CUPAx cohort. The incidence of CUPAx hormone-receptor positivity (40–50%) or HER2 overexpression (30%) is in agreement with accumulated experience from overt breast cancer [40]. In surgical series, blind mastectomy resulted in histologic detection of a small primary in 72% of cases, a finding further supporting the absence of biologic differences between CUPAx and early breast cancer. However, it is striking that despite a 72% rate of histologic identification of an occult breast tumour in mastectomy specimens, 60% among those managed with breast observation remained free from locoregional progression at follow-up times of 1–2 years. This finding suggests that the occult breast primary indeed grows more indolently than overt breast primaries.

Regarding management, ALND seems to be a necessary component of treatment because it offers superior staging, prognostic information as well as local control of disease, while associated with fewer side-effects (lymphedema) [41]. On the other hand, observation of the untreated axilla or breast is contra-indicated for several reasons: the rate of locoregional relapse in observed patients was 42% in our review and may be underestimated since several series had a short follow-up time of only 2–3 years, thus missing late relapses. Even considering the alternative of delayed treatment of the breast upon progression, the latter strategy provides plenty of time for expansion/divergence of the malignant clone, accumulation of further genetic damage and dissemination to distant sites [42]. Although all studies were retrospective and underpowered to show a statistically significant survival advantage for immediate versus

delayed locoregional therapy, such a trend was present in six series published [16–18, 22, 23, 28].

Breast irradiation may be an alternative to mastectomy, resulting in locoregional recurrence rates of 15–25%. Still, mastectomy is the only modality that provides unequivocal surgical extirpation of disease, data on presence of an occult primary, additional malignant tissue for testing, locoregional relapse rates of 5–15% and obviates the need for radiologic follow-up of the conserved breast. Moreover, it is well known from breast cancer that irradiation does not make up for inadequate surgical excision of the primary with involved resection margins [43]. Therefore, despite the low level of evidence, we suggest that fit patients accepting mutilating surgery should undergo mastectomy of the ipsilateral breast.

Adjuvant chemotherapy was given in only 40% and hormonal therapy in 12% of CUPAx patients, probably due to inclusion of seven papers published in the seventies/eighties, co-morbidity of some patients, failure to report related data and inherent belief of distinct biology. However, in view of lack of evidence for any biologic or outcome differences, CUPAx patients should receive adjuvant systemic therapy according to the indications for node-positive early breast cancer (similarly, trastuzumab for HER2-overexpressing tumours) [44]. It should be reminded that seven of 10 CUPAx patients would be found to harbour a small breast primary on mastectomy. Moreover, in three series a trend for survival advantage in CUPAx patients receiving adjuvant therapy was suspected [17, 18, 28] despite frequent lack of adequate management of the breast/axilla fully eradicating gross disease. No series provide information on use of neoadjuvant chemotherapy in patients with CUPAx: most patients undergo axillary nodal clearance immediately after fine needle aspiration/excisional biopsy or in the presence of unresectable lymph nodes, axillary irradiation. However, in the case of fixed axillary nodal masses administration of neoadjuvant chemotherapy followed by nodal clearance in case of response could be a valid option.

The outcome of CUPAx patients compares favourably to that of patients with stage II or III overt breast cancer, as 5-year survival in CUPAx series ranged from 59.4 to 88% [45]. Most clinical series reported that survival of CUPAx patients is not inferior to stage-matched patients with node-positive resected breast cancer [11, 16, 18, 21, 28], with only two showing inferior prognosis (Jackson et al.; Svastics et al) [19, 22]. However, in the latter series a significant proportion of patients were managed with observation or blind quadrantectomy. Failure to treat the ipsilateral breast harbouring the occult primary probably resulted in the reported poorer outcome than patients with stage II breast cancer. The similar prognosis further establishes the biological similarity of CUPAx with overt

early breast cancer, the two entities sharing the same pivotal prognosticator, axillary nodal status [46].

Overall, no molecular aberrations responsible for regression of the primary, early and atypical metastatic dissemination have been consistently identified in patients with CUP [33]. This observation reinforces what clinicians are already aware of, the heterogeneity of the group of tumours making up the CUP cohort. Deficits in angiogenesis of the primary tumour, early emergence of cellular clones with migratory phenotype, differential profile of the microenvironment/stroma in the primary organ and metastatic sites have been incriminated, but not proven to be the culprit. CUPAx seems to behave similarly to node-positive breast cancer, although in cases where no tumour is found in mastectomy, presence of subtle molecular differences responsible for regression of the primary should be hypothesized and sought for.

### Conclusions–recommendations

- The epidemiology, biology and outcome of CUPAx patients are similar to that of patients with resected node-positive overt breast cancer.
- This is in contrast to cases of CUP with several visceral metastases which are biologically classified by microarrays as “breast cancer”. Accordingly, there may exist two different clinical entities: (a) CUPAx which is the biologic equivalent of node-positive breast cancer, (b) poor risk visceral CUP “breast-like” which retains a molecular signature similar to breast cancer but harbours additional genetic aberrations.
- Bilateral mammography is needed, supplemented by bilateral breast MRI in negative cases, with biopsy of suspicious findings.
- ER, PR, HER2 status should be assessed in malignant tissue for diagnostic, prognostic and therapeutic purposes.
- Axillary lymph node dissection should be carried out as it offers optimal staging, prognostic information and local control. Breast/axilla observation is contraindicated.
- Mastectomy is preferable in a fit patient accepting mutilating surgery, as it provides breast screening for the primary, surgical extirpation of disease and obviates the need for follow-up of the breast. Breast irradiation is an alternative with acceptable locoregional failure of 15–25%.
- Adjuvant systemic therapy (chemotherapy, hormone-therapy, trastuzumab) should be administered in fit patients without medical comorbidities, according to indications for node-positive breast cancer.
- Prognosis is similar to stage II–III overt breast cancer.

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