MANAGEMENT OF A PATIENT WITH AN AXILLARY LYMPH NODE METASTASIS BUT OCCULT PRIMARY

18TH UP CONTROVERSIES AND PROBLEMS IN SURGERY SYMPOSIUM

Ines Buccimazza

Breast Unit
Department of Surgery
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal
Durban

INTRODUCTION

Malignant cells in keeping with metastatic carcinoma

CONTENT

- Cancer of unknown primary: concept and challenges
- Diagnostic work-up
  - Isolated axillary adenopathy
  - Identification of putative primary site
- Sub-group: occult breast primary

DEFINITION AND INCIDENCE

- Occult primary/ cancer unknown primary (CUP)
  - Metastatic cancer with undetectable anatomical site of origin at presentation
- Incidence
  - 4% - 5% invasive cancers
- CUP
  - Heterogeneous group of cancers; many 1° sites
  - Varying biologic behaviour; shared biologic properties

CATEGORIES

Categories of CUP

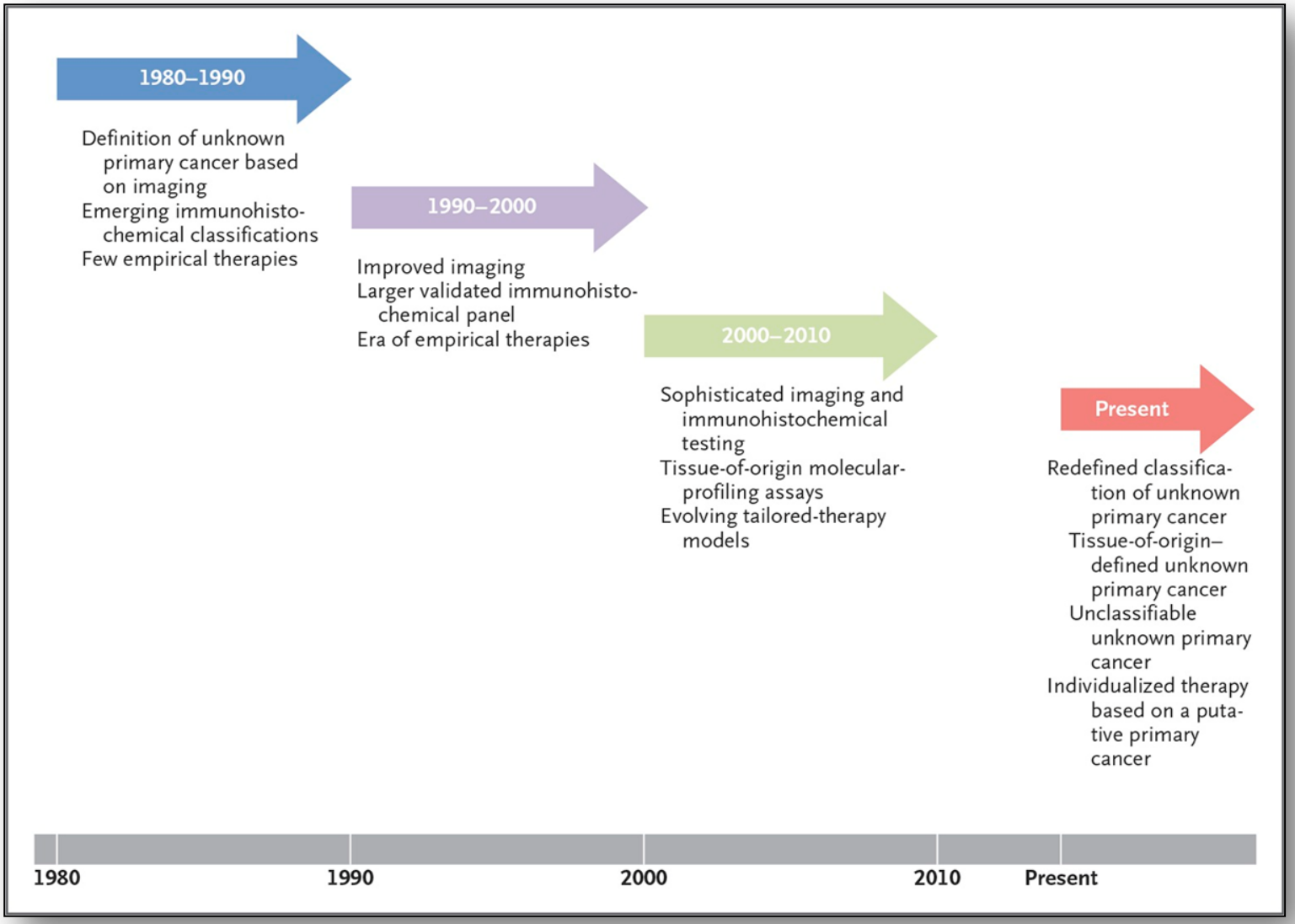
Adenocarcinomas	70%
Poorly differentiated neoplasms • Poorly differentiated carcinomas • Other o Poorly differentiated adenocarcinoma o Sarcoma o Melanoma o Lymphoma	20% - 25% 80% 20% 10% 10%
Squamous cell carcinoma	5%
Neuroendocrine carcinoma	1%

- Squamous cell carcinoma
  - Uncommon in absence of obvious 1° lesion; exception neck mass

PRESENTATION

- Presentation
  - Determined by site(s) of metastatic involvement
  - Multiple
  - Liver, lung, **lymph nodes**, bone
- Common primary sites
  - Lung, pancreas, hepatobiliary system, kidney → 60% cases
  - Breast ; prostate
- Primary site
  - Not identified 20% - 30% cases

Classification of Unknown Primary Cancer through the Decades



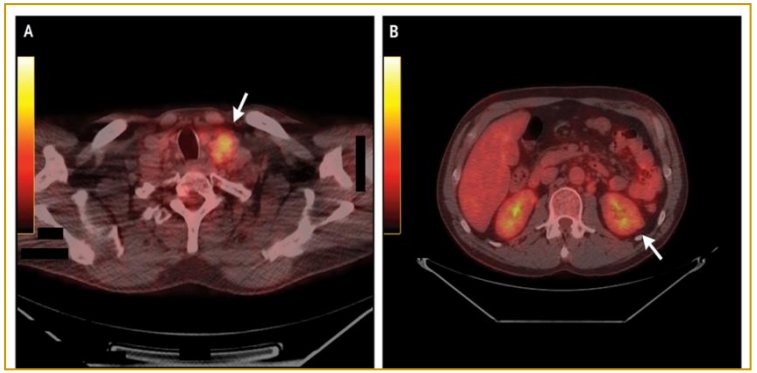
Varadhachary GR, Raber MN. *N Engl J Med* 2014;371:757-765

DIFFERENTIAL DIAGNOSIS

- Palpable axillary nodes
  - Benign > malignant diseases
- Malignancy
  - Most common primary: breast
    - ≥ 50% several series; mixed populations
  - Other neoplasms:
    - Lymphomas, melanomas, sarcomas, other carcinomas
      - Thyroid, skin, lung, uterine, ovarian, sweat gland, gastric
- Metastatic axillary adenopathy
  - Primary site not identified 30% cases

INITIAL CLINICAL EVALUATION

- Thorough clinical assessment
- Laboratory tests
  - Tumour markers?
    - CEA; CA 19-9; CA 15-3; CA 125
- CT or MRI: chest, abdomen, pelvis
  - Women: pelvic examination; MMG
  - Men: prostate examination; PSA
- PET-CT
  - Renal insufficiency; cervical CUP
  - Otherwise role unclear: 1° site 40%



- No exhaustive imaging and endoscopic testing
  - Rarely detect 1° site; confusion if false positive results

DIAGNOSTIC WORK-UP

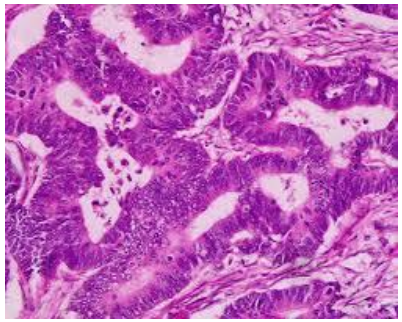
Biopsy

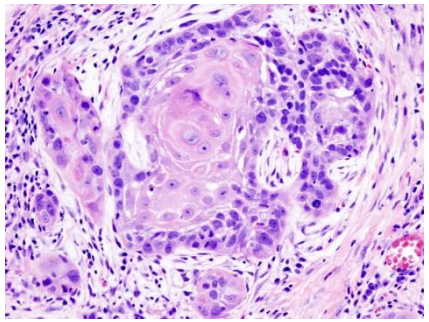
- Pathological findings supersede radiology
- Adequate tissue sampling
  - Core biopsy or excision
  - Communication

DIAGNOSTIC WORK-UP

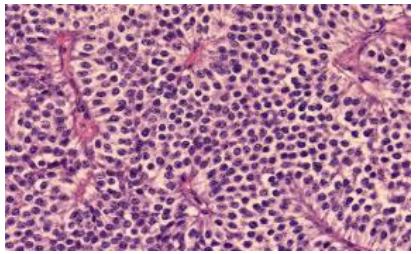
Biopsy

- Light microscopy
  - Hematoxylin and eosin
    - Adenocarcinoma
    - Squamous cell carcinoma
    - Neuroendocrine carcinoma





  - Infrequently lineage unclear



DIAGNOSTIC WORK-UP

- Immunohistochemistry
  - Peroxidase-labelled antibodies against specific tumour antigens → establish lineage

CHARACTERISTIC IMMUNOHISTOCHEMICAL STAINING PATTERNS

NEOPLASM	CYTOKERATIN	EMA	LCA	S-100	DESMIN/ VIMENTIN	HCG AFP PLAP	CHROMOGRANIN SYNAPTOPHYSIN
CARCINOMA	+	+	-	S	-	S	S
MELANOMA	-; R	-	-	+	+	-	-
SARCOMA	-	S	-	-	+	-	-
LYMPHOMA	-	-;R	+	-	-	-	-
NEURO ENDOCRINE CARCINOMA	+	+	-	-	-	-	+
GERM CELL TUMOUR	-; R	-	-	-	-	+	-

EMA: Epithelial membrane antigen

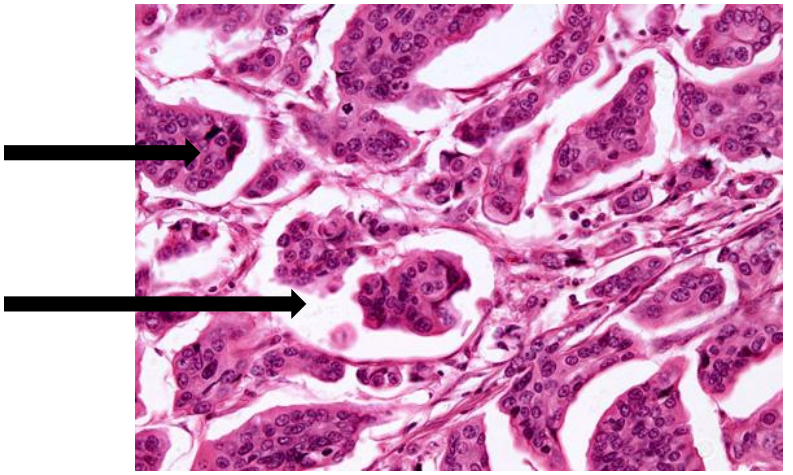
LCA: Leucocyte common antigen

PLAP: Placental leucocyte alkaline phosphatase

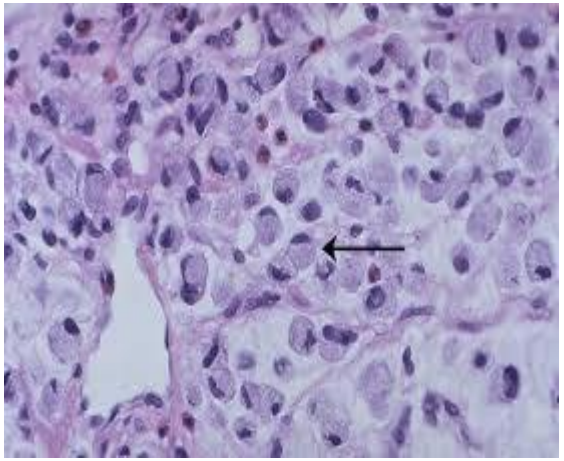
JD Hainsworth, FA Greco
www.uptodate.com 2014

DIAGNOSTIC WORK-UP

Biopsy



- Light microscopy
  - All adenocarcinomas
    - Similar features
  - Characteristic morphologic features
    - Not sufficiently specific
  - Unable to determine site of primary tumour



DIAGNOSTIC WORK-UP

Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

CK7+ CK20+	CK7+ CK20-	CK7- CK20+	CK7- CK20-
Urothelial tumors	Non-small cell lung cancer	Colorectal cancer	Hepatocellular cancer
Mucinous ovarian cancer	Small cell lung cancer	Merkel cell cancer	Renal cell cancer
Pancreatic or biliary cancer	Breast cancer		Prostate cancer
	Endometrial cancer		Squamous cell lung cancer
	Nonmucinous ovarian cancer		Head and neck cancer
	Mesothelioma		
	Squamous cancer of cervix		

Modified from: Dabbs D. Diagnostic Immunohistochemistry, 2nd ed, Churchill Livingstone, 2006.

Graphic 58475 Version 2.0

DIAGNOSTIC WORK-UP

Biopsy

- Immunohistochemistry
  - Specific markers
    - Estrogen (ER) and progesterone (PR) receptors
      - Positive staining breast cancer; ovarian, uterine, lung, stomach, thyroid, hepatobiliary cancers
    - Gross cystic disease fluid protein-15 (GCDFP)
      - Positive in 65% - 80% breast cancers; skin adnexal, uterine
    - Mammaglobin
      - Less specific for breast; positive for gynecological, lung, thyroid
    - Thyroid transcription factor 1 (TTF-1)
      - Rarely positive in breast; 70% - 80% positive in non-squamous lung cancers

IMMUNOPEROXIDASE TUMOUR STAINING PATTERNS USEFUL IN THE DIFFERENTIAL DIAGNOSIS OF POORLY DIFFERENTIATED CARCINOMA

TUMOUR TYPE	IMMUNOPEROXIDASE STAINING
Colorectal carcinoma	CK7 (-); CK20 (+); CDX-2 (+)
Lung carcinoma	
• Adenocarcinoma	TTF-1 (+); Surf-A and Surf-B (+)
• Other non-small cell carcinoma	CK7 (+); CK20 (-); TTF-1 (-)
• Small cell carcinoma	TTF-1 (+); chromogranin (+); NSE (+)
Neuroendocrine carcinoma	Chromogranin (+); synaptophysin (+); epithelial stains (+)
Germ cell tumour	HCG (+); AFP(+); placental alkaline phosphatase (+); epithelial stains (+)
Prostate carcinoma	PSA (+); CK7(-); CK20 (-); epithelial stains (+)
Pancreas carcinoma	CA $^{19-9}$ (+); CK7 (+); mesothelin (+); trifoil factor (+)
Breast carcinoma	ER (+); PR (+); Her-2 neu (+); CK7 (+); CK20 (-); GCDFP-15 (+); epithelial stains (+)

CDX-2: Homeobox protein
NSE: neuron-specific enolase

JD Hainsworth, FA Greco
www.uptodate.com 2014

OCCULT BREAST PRIMARY

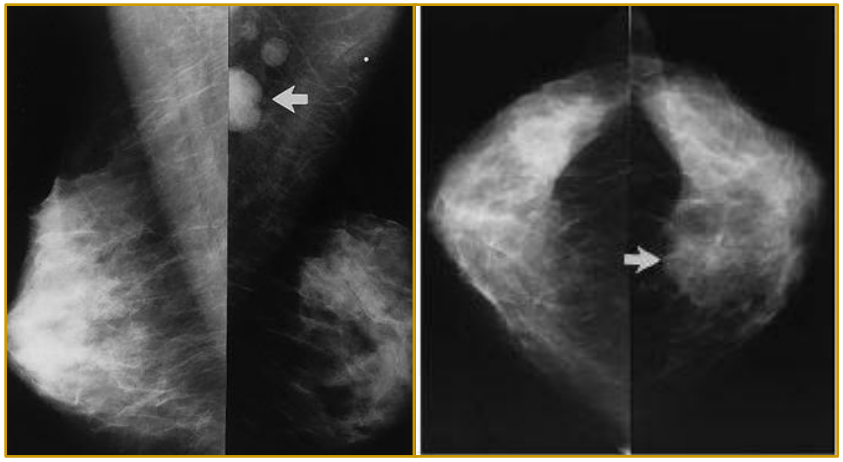
- Axillary node
  - Adenocarcinoma/ poorly differentiated carcinoma histology → suggesting breast 1°
  - IHC → breast cancer specific markers

  → finding breast primary

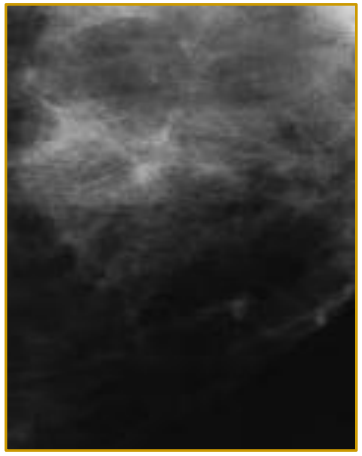
- Occult breast cancers
  - 0.1% - 0.8%
  - Incidence not deceased

MAMMOGRAPHY

- Identification clinically occult lesion: 10% - 20% cases



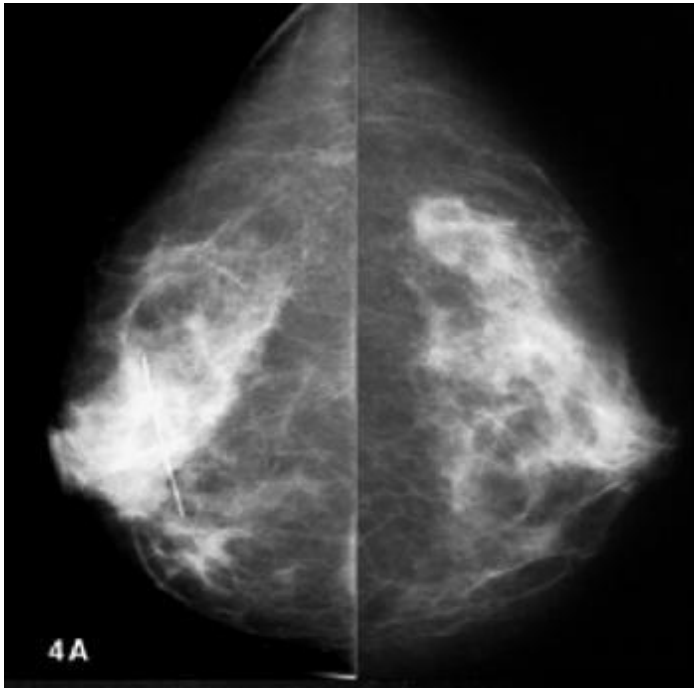
- Missed
  - Small size (≤ 5mm)
  - Dense fibroglandular tissue
- Abnormal MMG findings
  - Biopsy

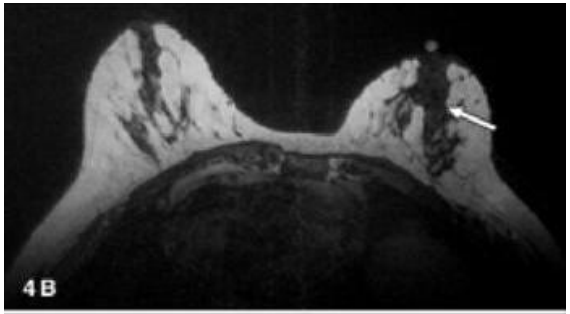


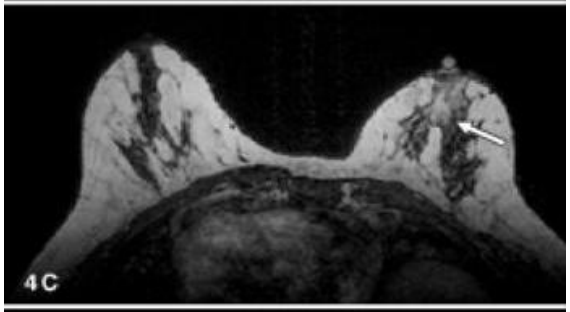
- Negative MMG → further imaging evaluation

MAGNETIC RESONANCE IMAGING

- Standard approach for suspected occult breast 1°
- SEN MRI > MMG and US







Utility of breast MRI for mammographically-occult breast cancer in patients presenting with metastatic axillary lymphadenopathy

Author, year	n	MRI-positive, percent	Histologic diagnosis of breast cancer
Morris, E; 1997	12	9 (75)	8
Brenner, R; 1997	4	4 (100)	4
Tilanus-Linthorst, M; 1997	4	4 (100)	4
Schorn, C; 1999	14•	9 (64)	6/9
Henry-Tillman, R; 1999	10	8 (80)	8
Olson, J; 2000	40	28 (70)	21/22*
Obdeijn, I; 2000	20	8 (40)	8
Fourquet, A; 2004	15	14 (93)	9/11
Buchanan, C; 2005	69	42 (76)	26/42 MRI+
			4/12 MRI-

Identification rate ~ 77 %

Average true positive rate ~ 89%

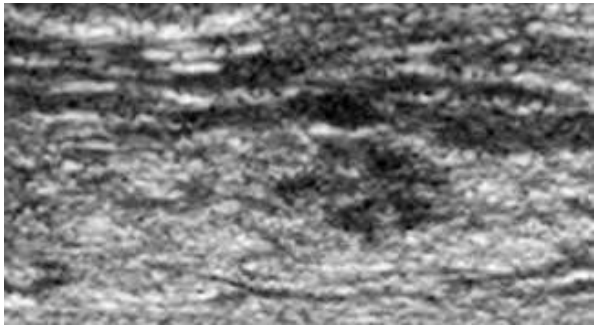
V. Kaklamani, W. Gradishar
www.uptodate.com 2014

* Number of patients with confirmed MRI findings at the time of surgery.

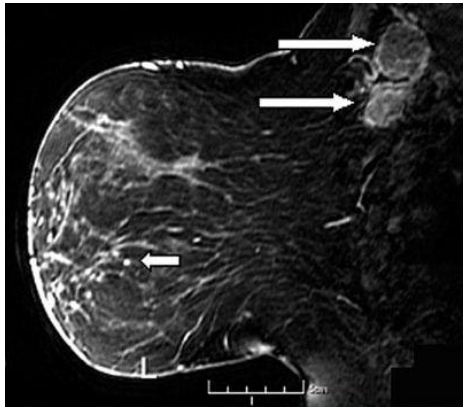
• Included six axillary nodal metastases, one supraclavicular nodal metastases, three bone metastases, three liver metastases, and one lung metastases with an unknown primary.

MAGNETIC RESONANCE IMAGING

- Disadvantages
  - False positive rate (~30%)
    - All suspicious findings → biopsied
    - "Second-look" US – USG biopsy
    - MRI-guided biopsy
  - Difficulty localising small contrast-enhancing foci



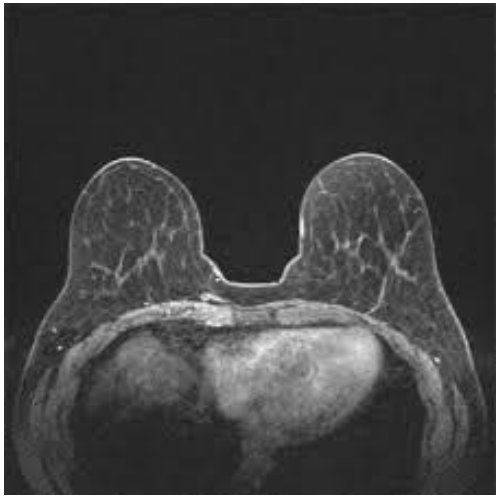
- Performed with breast coil
  - Expert radiologists
  - Specialised institutions
    - MRI-guided needle biopsy
    - MRI wire localization



- Focal lesion identified: standard BC guidelines

DILEMMA





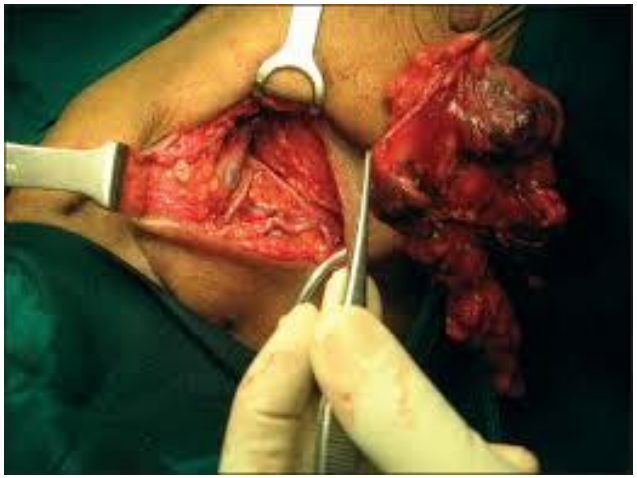
→ Mammary origin of metastatic nodes not established with absolute certainty

Histologic and IHC analysis compatible → treatment according to guidelines for Stage II breast cancer

NCCN guidelines: CT Chest, abdomen
Bone scan: symptomatic patients; ↑ ALP

LOCOREGIONAL TREATMENT

Axilla



- All: level II axillary dissection
- Rationale
  - Prognostic information → guide further treatment
  - Aids local control
- ~ 50%: 4 or more positive nodes
  - Post-mastectomy and supraclavicular radiation

LOCOREGIONAL TREATMENT

Ipsilateral breast

- Optimal treatment controversial
- Options:
  - Mastectomy
  - Breast conserving treatment with whole breast RT

(Mastectomy + ALND and whole breast RT + ALND similar outcomes)

  - Observation

LOCOREGIONAL TREATMENT

Ipsilateral breast: Mastectomy

Pathologic findings at mastectomy in patients with occult primary breast cancer

Author, year	Years	Mastectomy, n	In situ, n	Invasive, n	Cancer, percent
Owens H; 1954	1907-50	27	0	25	92
Feuerman L; 1962	1949-61	2	0	1	50
Fitts W; 1963	1948-63	11	0	7	70
Haagensen C; 1974	1916-66	13	0	12	92
Ashikari R; 1976	1946-75	34	3	20	67
Patel J; 1981	1952-79	29	0	16	60
Kemeny M; 1986	1973-85	11	2	3	45
Bhatia S; 1987	1977-85	11	2	9	100
Baron P; 1990	1975-78	28	4	16	71
Ellerbroek N; 1990	1944-87	13	0	1	8
Merson M; 1992	1945-87	33	0	27	82
Feigenberg S; 2003	1971-74	4	0	3	80
Blanchard D; 2004	1975-98	18	1	5	33
He M; 2012	1998-2010	64	16	4	31
Total	–	298	28	149	59

V. Kaklamani, W. Gradishar
www.uptodate.com 2014

RESULTS OF WHOLE BREAST RADIATION FOR NODE-POSITIVE OCCULT PRIMARY BREAST CANCER

Author, year	Number of patients	Median follow-up	Breast treatment	Breast-only control, (%)	Survival (%)
Vilcoq J; 1982	11	>5 yr	XRT	73%	10/11 (5 year)
Ellerbroek N; 1990	16 13 13	133 mo	XRT None Mastectomy	83% 43% N/A	-* -* -*
Foroudi F; 2000	12	73 mo	XRT	75%	11/12 (5 year)
Vlastos G; 2001	25 13	7 yr	XRT Mastectomy	92% 85%	79% (5 year) 75% (5 year)
Medina-Franco H; 2002	6	48 mo	XRT	100%	100%
Varadarajan R; 2006	8	57 mo	XRT	100%	100%
He D; 2012	95	38.2 mo	MRM+ALND XRT+ALND ALND	89% 92% 72%	85% (3 year) 81% 71%

Average 5 year survival 87%

XRT: whole breast radiation therapy; N/A: not available; ALND: axillary lymph node dissection

*survival described as "no different" when patients undergoing mastectomy were compared to those who did not undergo mastectomy. Actuarial survival for entire group was 72% at five years and 65% at 10 years

Local recurrence of breast cancer in patients with occult primary breast cancer not undergoing local therapy

Author, year	Breast failures (percent)	Delay in months
Atkins H; 1960	5/9 (56)	9 to 17
Feuerman L; 1962	0/1 (0)	-
Haagensen C; 1974	3/5 (60)	5 to 64
Kemeny M; 1986	0/7 (0)	-
Campana F; 1989	2/2 (100)	9 to 67
Ellerbroek N; 1990	7/13 (54)	11 to 47
Merson M; 1992	9/17 (53)	2 to 34
Van Ooijen B; 1993	3/14 (21)	16 to 56
Fouroudi F; 2000	5/6 (83)	7 (median)
Feigenberg S; 2003	0/4 (0)	-
Blanchard D; 2004	12/16 (75)	-
Total	**46/94 (49)**	-

V. Kaklamani, W. Gradishar
www.uptodate.com 2014

ADJUVANT THERAPY

Systemic therapy

- Benefit not studied
  - Retrospective report: higher 5 year survival with chemotherapy (93% vs. 64%)
- Extrapolate as for clinically apparent breast cancer
  - NCCN and other guidelines:
    - Chemotherapy for all node positive breast cancer
    - Trastuzumab for Her-2 over-expressing tumours
    - Hormone therapy for hormone-responsive tumours

ADJUVANT THERAPY

Radiotherapy

- Post-mastectomy RT in high-risk women
  - ↓ risk locoregional recurrence
  - ↑ disease-free survival
  - ↓ mortality from breast cancer
- Supraclavicular radiation
  - 4 or more axillary nodes

PROGNOSIS

Studies addressing prognosis of occult breast cancer

Study	Place	Year	Number of patients	5 year OS, percent
Ashikari, R; 1976	Memorial Hospital, NYC	1946-75	42	79
Campana, F; 1989	Institute Curie	1960-85	31	76
Baron, P; 1990	MSKCC	1975-88	35	75
Ellerbroek, N; 1990	MD Anderson	1944-87	42	72
Rosen, P; 1990	MSKCC	1966-85	48	60
Kyokane, T; 1995	Japan	NR	97	59
Foroudi, F; 2000	Australia	1979-96	20	93 (mastectomy or XRT) 41 (no local treatment)
Matsuoka, K; 2003	Japan	1985-98	11	63
Blanchard, D; 2004	Mayo	1975-98	35	73 (mastectomy) 36 (no mastectomy)

NR: Not reported; OS: Overall survival; MSKCC: Memorial Sloan Kettering Cancer Center; NYC: New York City.

Average 75%

V. Kaklamani, W. Gradishar www.uptodate.com 2014

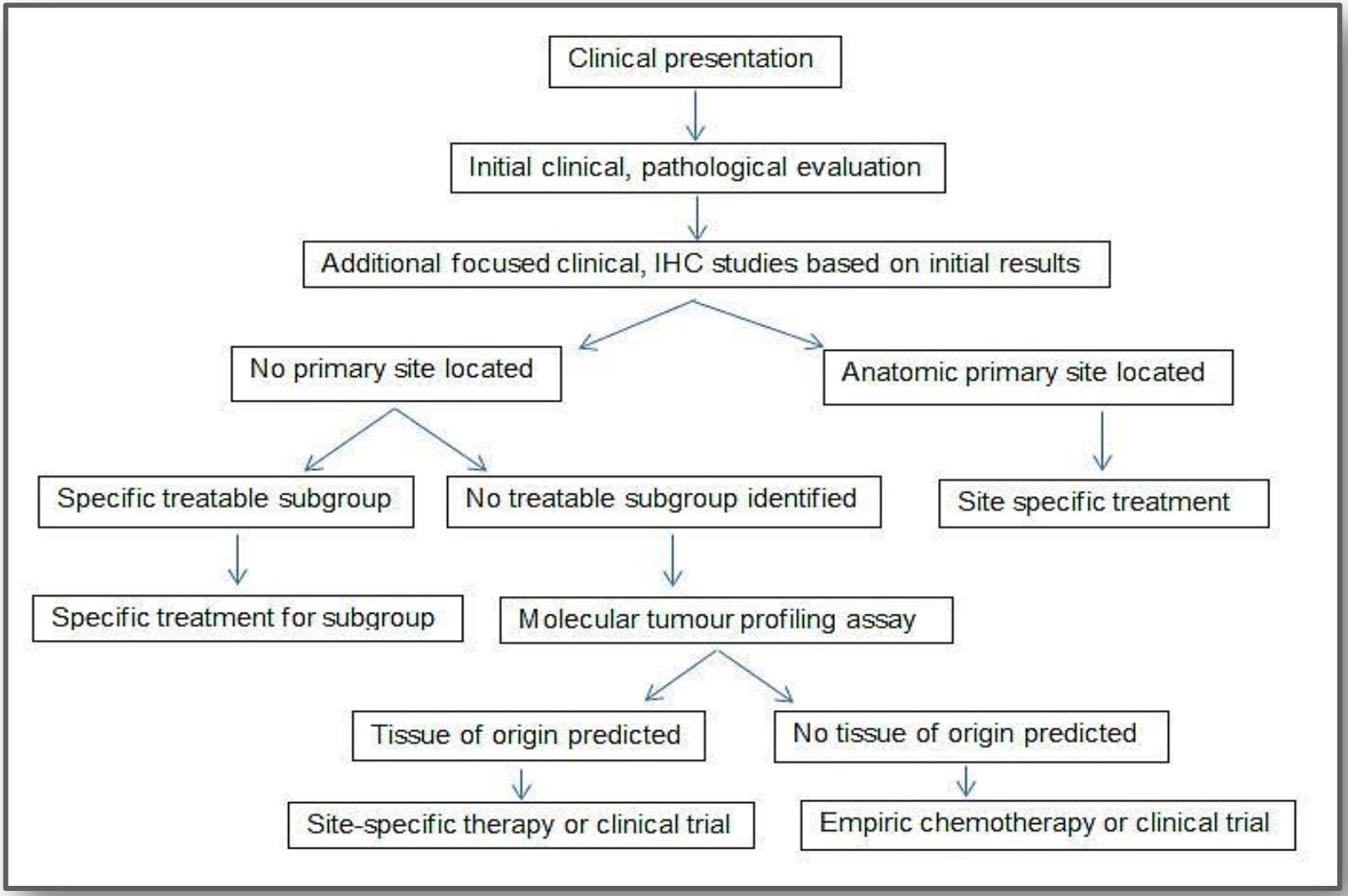
CONCLUSION

- Metastatic axillary disease with unknown primary poses a diagnostic challenge
- Improved imaging and IHC stains identify primary site in ⅔ cases
- Occult breast primary: favourable prognosis if treated according to stage II BC guidelines
- All require level II ALND

CONCLUSION

- Optimal treatment of ipsilateral breast ranges from mastectomy to whole breast RT
- Observation alone not recommended
- Adjuvant systemic therapy as per Stage II BC guidelines
- Post-mastectomy RT required depending on number of involved nodes

ALGORITHM


Clinical presentation
Initial clinical, pathological evaluation
Additional focused clinical, IHC studies based on initial results
No primary site located
Anatomic primary site located
Specific treatable subgroup
No treatable subgroup identified
Site specific treatment
Specific treatment for subgroup
Molecular tumour profiling assay
Tissue of origin predicted
No tissue of origin predicted
Site-specific therapy or clinical trial
Empiric chemotherapy or clinical trial