Axillary Metastasis of Unknown Primary

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Axillary Metastasis of Occult Primary

- In 1907, William Halsted first described three patients

- Proper clinical and mammographic evaluation confirms the absence of a small breast tumor

- Incidence varies from 0.35% (35 in 10014) at MSKCC to 0.5% (60 in 12000) at NCI in Milan
Axillary Metastasis of Occult Primary

- The commonest cause in females is ipsilateral breast cancer

- Lymphoma, melanoma, lung, thyroid, ovary, liver, kidney, gastric, colorectal, and pancreatic malignancy
Evaluation

- A careful history and physical examination

- This may detect a benign etiology, which is more common

- A fine-needle aspiration biopsy or core biopsy can be performed as the initial diagnostic test

- A negative result does not exclude a malignancy and an excisional biopsy may be necessary
Investigations

- Histopathological diagnosis and appropriate immunohistochemistry

- **Hormone receptors** is helpful in confirming the diagnosis as it is positive in 50–60% of the cases
  - Negative result does not exclude breast primary
  - Positive result can be seen in other malignancies like melanoma, renal cell, and colorectal carcinoma
Immunohistochemistry

- CK7 + CK20 +
  - Urothelial tumors
  - Ovarian mucinous adenocarcinoma
  - Pancreatic adenocarcinoma
  - Cholangiocarcinoma
- CK7 + CK20 -
  - Breast carcinoma
  - Lung adenocarcinoma
  - Thyroid carcinoma
  - Endometrial carcinoma
  - Cervical carcinoma
  - Salivary gland carcinoma
  - Cholangiocarcinoma
  - Pancreatic carcinoma
- CK7 - CK20 +
  - Colorectal Carcinoma
  - Merkel cell carcinoma
- CK7 - CK20 -
  - Hepatocellular carcinoma
  - Renal cell carcinoma
  - Prostate carcinoma
  - Squamous cell and small cell lung carcinoma
  - Head and neck carcinoma
Investigations

- Routine haematological and biochemical tests
- Bilateral mammography
- Breast ultrasonography
- Chest radiography
- Abdominal ultrasonography
- Bone scan

- Extensive work-up for a primary source other than breast is not recommended

- Molecular markers and gene expression profiles
Molecular Markers of Adenocarcinoma Characteristic of the Site of Origin

Gene Expression Profiling by Gene Expression Profiling by Microarray Analysis

Biological Sample → Isolate Sample RNA → Test Sample → Fluorescent Labeling

ARRAY Hybridization (Single Color) → Oligonucleotide Synthesis (25 to 60-mer)

ARRAY Hybridization (Two Color) → cDNA Clone (LIBRARY) → PCR Products (1 to 2 Kb)

Oligonucleotide Microarrays → PE

cDNA Spotted Array
Identifying Tumor Origin Using a Gene Expression-based Classification Map

Cancer Res 2003;63:4144–9
Mammography is usually the first investigation.

Sensitivity of mammography in the identification of the occult lesion ranges from 0% to 56%.

Ultrasonography and colour-doppler sonography may be helpful.
Magnetic resonance imaging (MRI) is the imaging diagnostic of choice.

Absence of abnormality on mammography and MRI does not exclude the diagnosis of primary breast cancer.

Radionuclide scan: PET/CT, 111In-pentetreotide scan.
### Sensitivity, Specificity, and Positive Predictive Value of Three Screening Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
<th>PPV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical exam</td>
<td>17.9</td>
<td>98.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Mammography</td>
<td>33.3</td>
<td>95.0</td>
<td>8.0</td>
</tr>
<tr>
<td>MRI</td>
<td>79.5</td>
<td>89.8</td>
<td>7.1</td>
</tr>
</tbody>
</table>

- The proportion of small invasive tumors ($\leq 10$ mm) was significantly greater in surveillance group (43.2%) than in control group (14.0%).

False-negative Mammograms in MRI-detected Carcinoma

Mammography

Gad-Enhanced MRI

Breast MRI in Patients with Axillary Node Metastases and Unknown Primary

- 22 women with axillary adenopathy and negative mammogram and physical examination findings

- MRI detected primary breast carcinoma in 19 patients (86%)

- Tumour size 4-30 mm (mean, 17 mm)

- MRI offers potential not only for cancer detection but also for staging cancer within the breast, which maybe useful for local treatment planning

Radiology 1999; 212:543-9
## MRI of the Breast and Occult Carcinoma

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of Patients</th>
<th>Diagnostic Accuracy</th>
<th>MRI Localization</th>
<th>Local Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris(^2)</td>
<td>12</td>
<td>9/12 (75%)</td>
<td>8 Focal</td>
<td>8 MRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Multifocal</td>
<td>4PM/AND</td>
</tr>
<tr>
<td>Porter(^3)</td>
<td>6</td>
<td>4/6 (66%)</td>
<td>3 Focal</td>
<td>3 Focal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Multifocal</td>
<td>1 MRM</td>
</tr>
<tr>
<td>Tilanus-Linthorst(^4)</td>
<td>4</td>
<td>4/4 (100%)</td>
<td>3 Focal</td>
<td>1 MRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Multifocal</td>
<td>2 PM/AND</td>
</tr>
<tr>
<td>Davis(^5)</td>
<td>1</td>
<td>1/1 (100%)</td>
<td>1 Focal</td>
<td>1 PM</td>
</tr>
<tr>
<td>Present study</td>
<td>10</td>
<td>8/8 (100%)</td>
<td>3 Focal</td>
<td>4 Chemo/MRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 Multicentric</td>
<td>4 MRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Bilateral</td>
<td></td>
</tr>
</tbody>
</table>

**MRM**, modified radical mastectomy; **PM**, partial mastectomy; **AND**, axillary node dissection; **Chemo**, chemotherapy.

MRI-detected Carcinoma in Negative Mammograms
MRI-detected Carcinoma in Negative Mammograms
PET detected Breast Carcinoma

A

B

C

Left

Left

Left
Detection of primary breast cancer presenting as metastatic carcinoma of unknown primary origin by $^{111}$In-pentetreotide scan

Annals of Oncology 1998;9: 213-6
Unknown Primary with Greatest Potential for Long-term Survival

- Axillary nodal adenocarcinoma
- Peritoneal carcinomatosis
- Unrecognized extragonadal germ cell tumours
- Squamous cell carcinoma of cervical nodes
- Poorly differentiated neuroendocrine carcinoma
Treatment

- Follows the same guidelines for breast cancer treatment as in stage II/III disease
- Local control of disease in the axilla and breast, and adjuvant systemic treatment
- All available data are retrospective
Axillary lymph node dissection (ALND) either as part of breast conservation therapy (BCT) or in conjunction with mastectomy

Benefits of ALND over axillary radiation include better local control, prognostic evaluation by examining the number of positive nodes, and provision of tissue for hormone receptor analysis.
Overall Survival Depends on Numbers of Positive Nodes

Ann Surg Oncol 2001;8:425–31
Controversy with 2 distinct options: mastectomy or breast conservation therapy (BCT)

- Total mastectomy originally described by Halsted in 1907

- Pathologist should be alerted as more sections may be required to locate the tumour
## Mastectomy Specimen

- A primary tumour is identified only in 64%–93%.

- Infiltrating duct carcinoma is the commonest tumour, while carcinoma in situ is seen in 8-20% of cases.

- Median tumour size of 1.5 cm (0.1–6.6 cm).

- 45% of cases can be multifocal.
Negative MRI Predicts Low Tumour Yield in Surgical Specimen

<table>
<thead>
<tr>
<th></th>
<th>MRM</th>
<th>BCT*</th>
<th>Tumor yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI positive</td>
<td>13</td>
<td>9</td>
<td>21/22 (95%)</td>
</tr>
<tr>
<td>N = 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI negative</td>
<td>5</td>
<td>0</td>
<td>1/5 (20%)</td>
</tr>
<tr>
<td>N = 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>9</td>
<td>22/27 (81%)</td>
</tr>
</tbody>
</table>

* Lumpectomy + ALND.

Breast Conservation Therapy

- BCT can be divided into surgical (blind upper outer quadrantectomy) and nonsurgical (radiation or observation)

- A blind upper outer quadrantectomy was first described by Feigenberg et al in 1976

- Fail to produce a better outcome and a significant number of cancers would be missed
Observation of the breast was initially proposed by Van Ooijen et al in 1993.

Subsequent identification of breast cancer in patients who are observed is 14% to 83% compared to 12% to 33% in patients receiving breast radiotherapy.

Survival of 50% vs 83% between patients who were observed and those receiving radiotherapy.
Observation vs Breast Treatment

![Graph showing survival rates for different treatment options over time. The graph indicates a significant difference in survival rates between local treatments and observation or no local treatment, with a p-value of 0.003.]( graphtable.png)
Breast Conservation

- Breast conservation can be facilitated by:
  1. by improved identification of small tumors amenable to lumpectomy
  2. by identifying women without detectable tumors who may be treated adequately by XRT alone

- Between mastectomy and breast irradiation, there was no significant difference in locoregional recurrence, distant recurrence, disease-free or overall survival
Overall Survival in Breast Irradiation vs Total Mastectomy

Ann Surg Oncol 2001;8:425–31
Based on the results of retrospective studies:

- Observation is not a viable option as the benefits from either radiation therapy or mastectomy are clearly seen.

- With whole breast radiation, the breast is preserved and the survival rates support its use as an alternative to mastectomy.

- All available imaging modalities must be used to search for a malignancy in the breast and allow BCT in a more conventional sense.
Axillary adenopathy

Excisional/needle biopsy

Adenocarcinoma – consistent with breast primary

Repeat physical exam
Reassess mammography/US

Abnormal mammogram/US or palpable mass

Breast conserving therapy or mastectomy

Normal exam/mammogram/US

Additional imaging (MRI, NM, PET)

Positive

BCT vs mastectomy

Negative

Mastectomy vs radiotherapy/chemotherapy