Management of patients presenting with axillary metastases and unknown primary

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Take home messages

- Breast MRI will identify many of the breast primaries that were not detected by mammography or US

- Treatment of the breast with mastectomy or radiotherapy is required to avoid a high risk of local relapse

Introduction

- Axillary metastases with unknown breast primary account for 1% of all breast cancers
- First described by Halstead in 1907
- Staged as T0 N1 (Stage II)
- Characteristics of T0 N1 patients similar to those with stage II disease
- A primary breast cancer in the axillary tail may be confused for an axillary node
- Limited literature with small retrospective studies
- No randomised control trials
- Comparisons from previous studies difficult as better imaging has reduced the number of occult breast primaries

Axillary nodes

- Benign
  - Infections (viral, bacterial inc. TB), trauma, inflammation (RA, SLE)
- Malignant
  - Lymphomas
  - Breast
  - Lung
  - GI
  - Pancreas
  - Stomach
  - Ovarian
  - Thyroid

- Breast is the commonest primary for women presenting with axillary nodes with adenocarcinoma or undifferentiated morphology

NICE Clinical Guidance (CG104)

Metastatic malignant disease of unknown primary origin in adults: diagnosis and management

- Organisation of services and support
  - Every hospital with a cancer centre or unit should establish a CUP team

- Diagnosis
  - Phase 1: aim is to perform the most appropriate investigations efficiently to identify
    - a primary site, which will guide treatment decisions
    - non-epithelial malignancy, which can be treated regardless of primary site (eg lymphoma, melanoma, sarcoma, germ-cell tumours)
    - metastatic epithelial or neuroendocrine malignancy without an identifiable primary site (a diagnosis of provisional CUP)
  - Phase 2: special investigations for patients with provisional CUP diagnosis

NICE Clinical Guidance (CG104)

Metastatic malignant disease of unknown primary origin in adults: diagnosis and management

- Immunohistochemistry
  - Use a panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER and PSA in all patients with adenocarcinoma of unknown origin
  - Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies above and the clinical picture
- Gene-expression-based profiling
  - Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP

Diagnostic work-up of unknown primary: IHC and Molecular Profiling

- Identify broad cancer type
  - Carcinoma — Cytokeratins
  - Melanoma — S100
  - Lymphoma/leukaemia — CLA, CD20, CD3 etc
  - Sarcoma — Vimentin, actin, c-kit etc
- If carcinoma or related, then identify its subtype
  - Adenocarcinoma — CK7, CK20
  - Squamous carcinoma — CK5, p63
  - Neuroendocrine carcinoma — Chromogranin, CD56, synaptomysin
- If adenocarcinoma, then predict possible primary site
  - Breast — ER, PgR, HER2
  - lung — TTF1
  - Ovary — CA125
  - Colon — CDX2

Oien KA & Dennis JL. Ann Oncol 2012; 23: 271-77

Diagnostic work-up of unknown primary: Molecular Profiling

- A number of tests are commercially available
  - Oncofocus from Oncologica UK Ltd (costs £1,500)
  - Cancer type ID from bioTheranostics (costs $3,600)
  - Rosetta Cancer Origin Test, formerly miRview mets2 (costs $4,356)
  - Tissue of Origin from Cancer Genetics (costs $3,250)
  - Caris Molecular Intelligence from Caris Life Sciences (costs £3,480)
  - The FoundationOne test from Roche Foundation Medicine (costs £3,000)

- All use formalin-fixed, paraffin-embedded tissue and use small tumour samples

- Tumours difficult to distinguish in morphology and IHC also difficult for molecular profiling
- May contribute to the diagnosis of poorly differentiated tumours

Investigations of patient presenting with axillary nodes

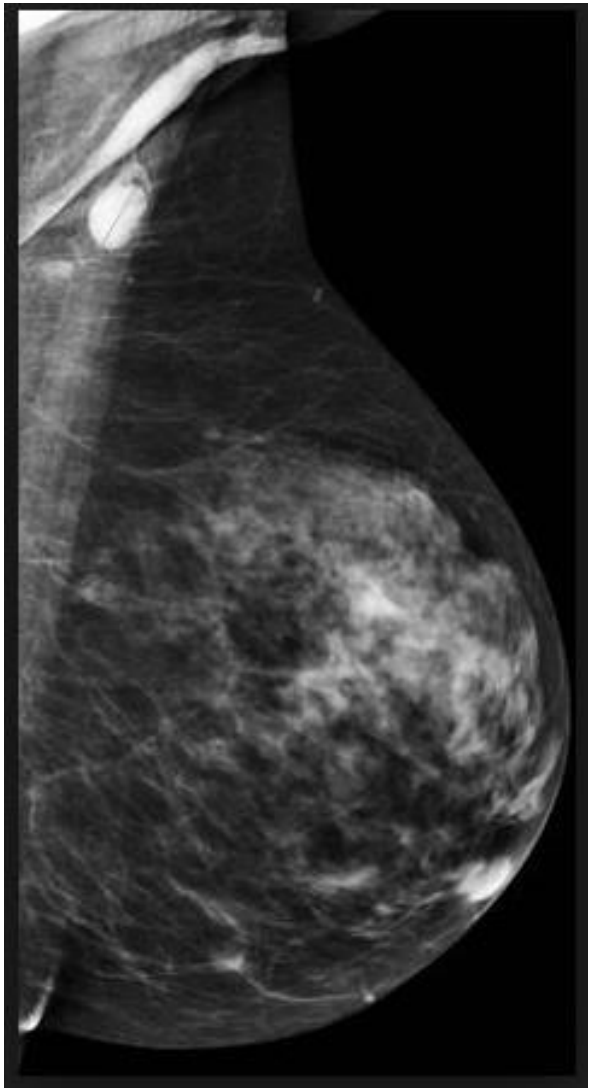
- Confirmation of malignancy
  - Axillary node biopsy or excision
- Search for Breast Primary
  - Mammography
  - US
  - Breast MRI
- Search for primary and staging
  - CT scan
  - PET Scan

NICE Clinical Guidance (CG104)

Metastatic malignant disease of unknown primary origin in adults: diagnosis and management

- Breast MRI
  - Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider MRI to identify lesions suitable for targetted biopsy

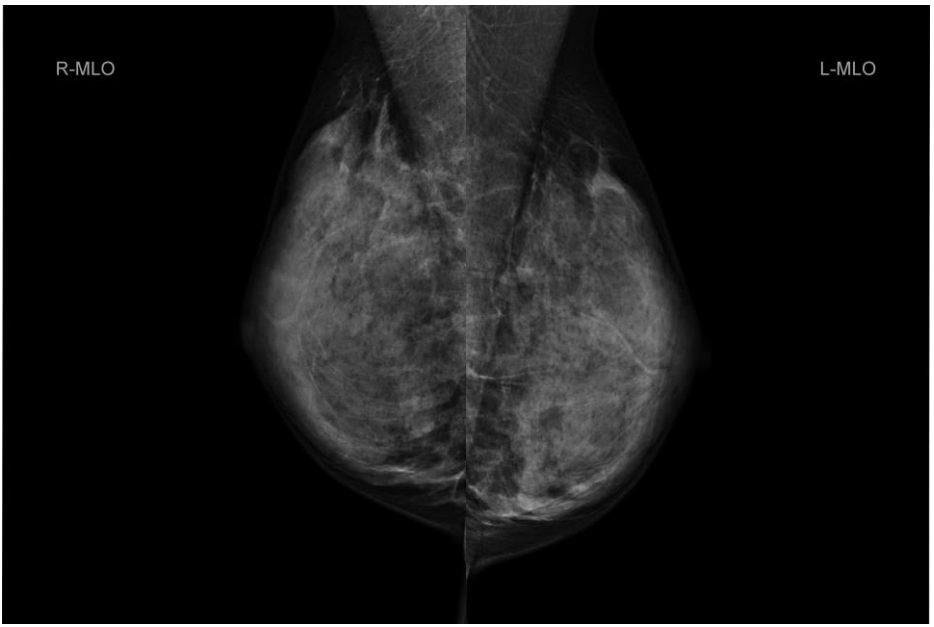
Mammography

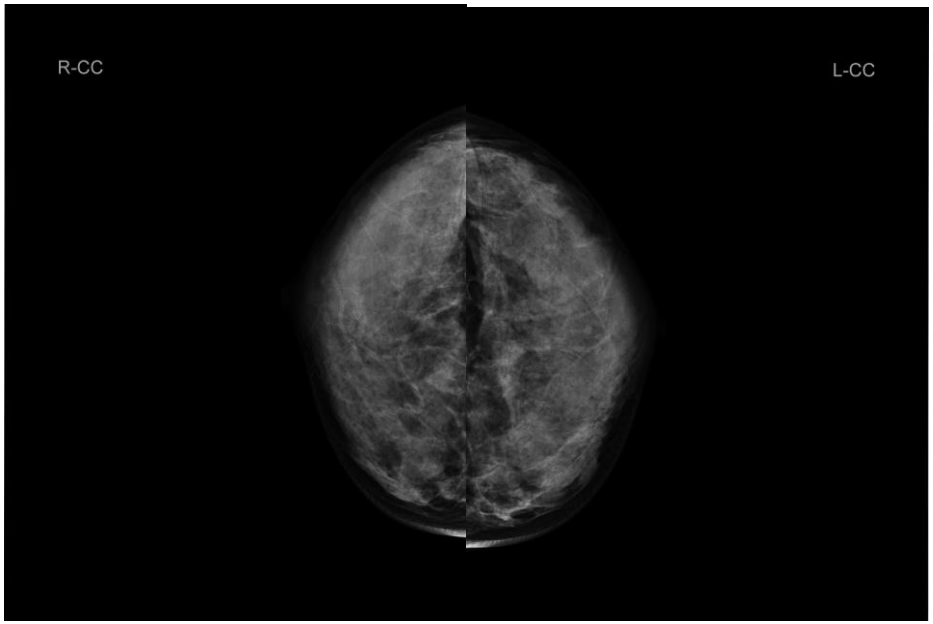


Case Study 1

- 33 year old presenting with enlarged right axillary nodes.
- US shows large abnormal nodes. Core biopsy shows metastatic adenocarcinoma probably of breast origin
- Mammograms normal

Case Study 1

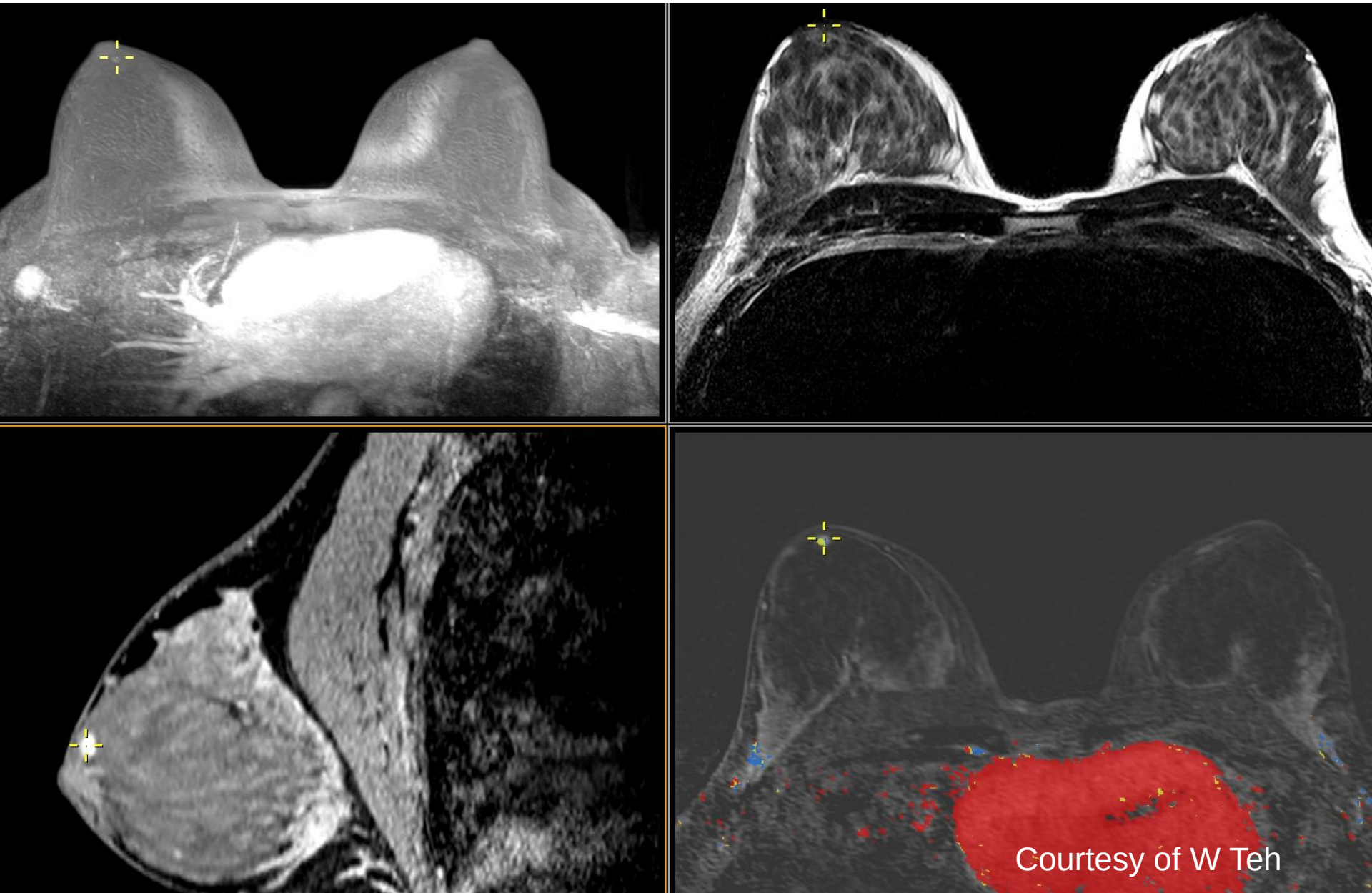




Mammograms of patient with right axillary nodes

Courtesy of W Teh

Case Study 1



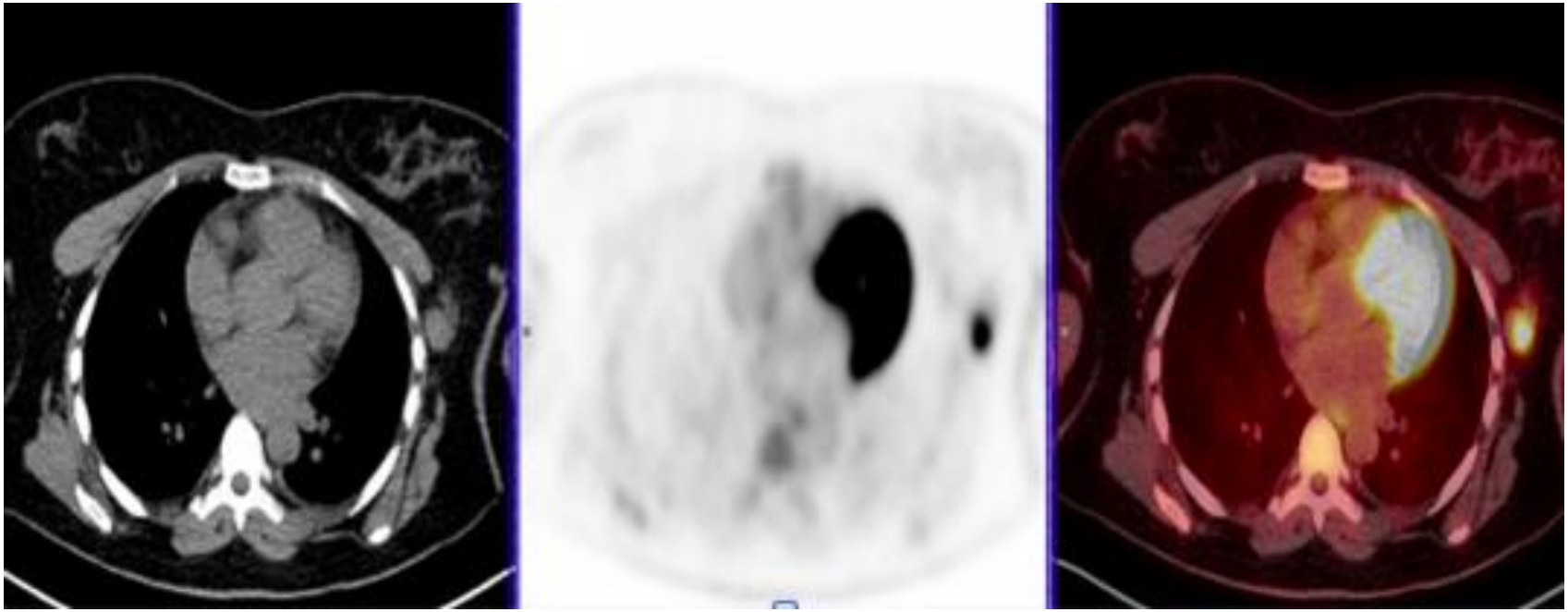
Case Study 1

- MRI shows solitary indeterminate mass lesion in right retroareolar area occult on second look ultrasound
- Referred for MRI biopsy
- MRI biopsy – IDC grade 2 ER8 PR8 Her-2 negative

Case Study 1

- MRI can detect primary breast cancer disease site in up to 70%
- MRI has high sensitivity but low specificity
- MRI biopsy can confirm primary site of disease
- This can guide appropriate surgical management

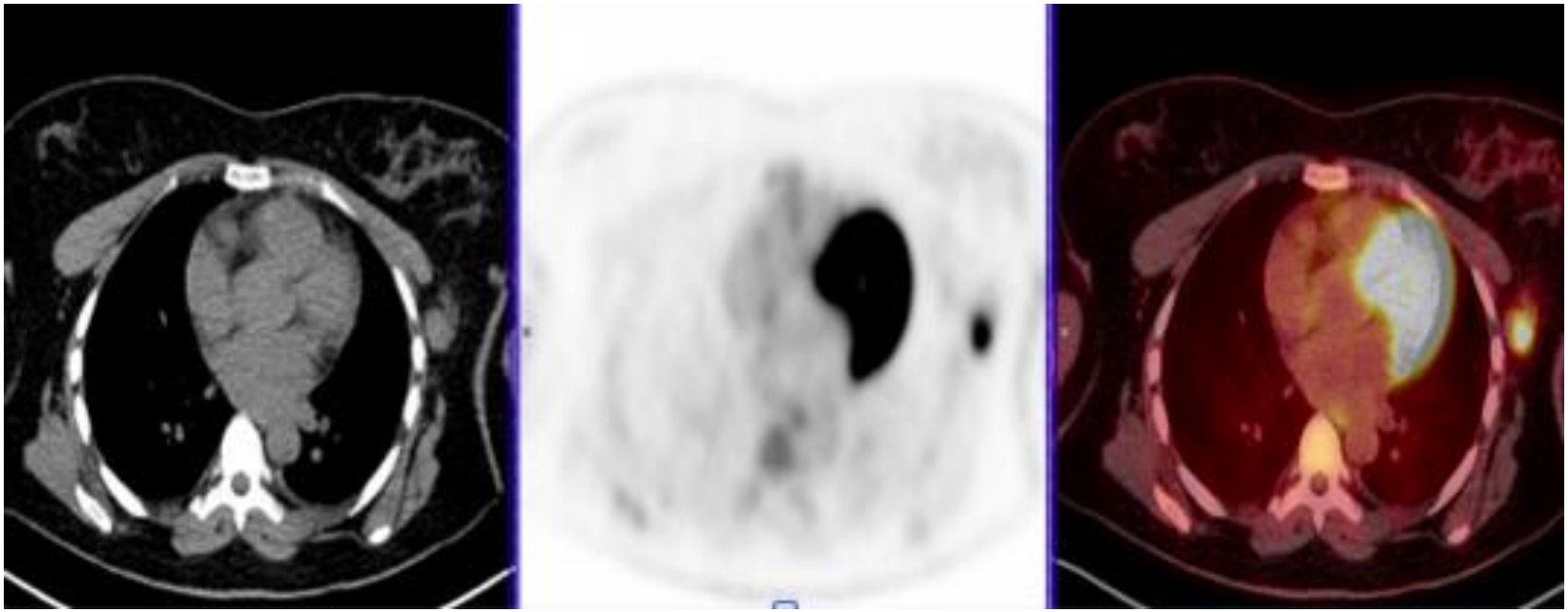
Role of PET

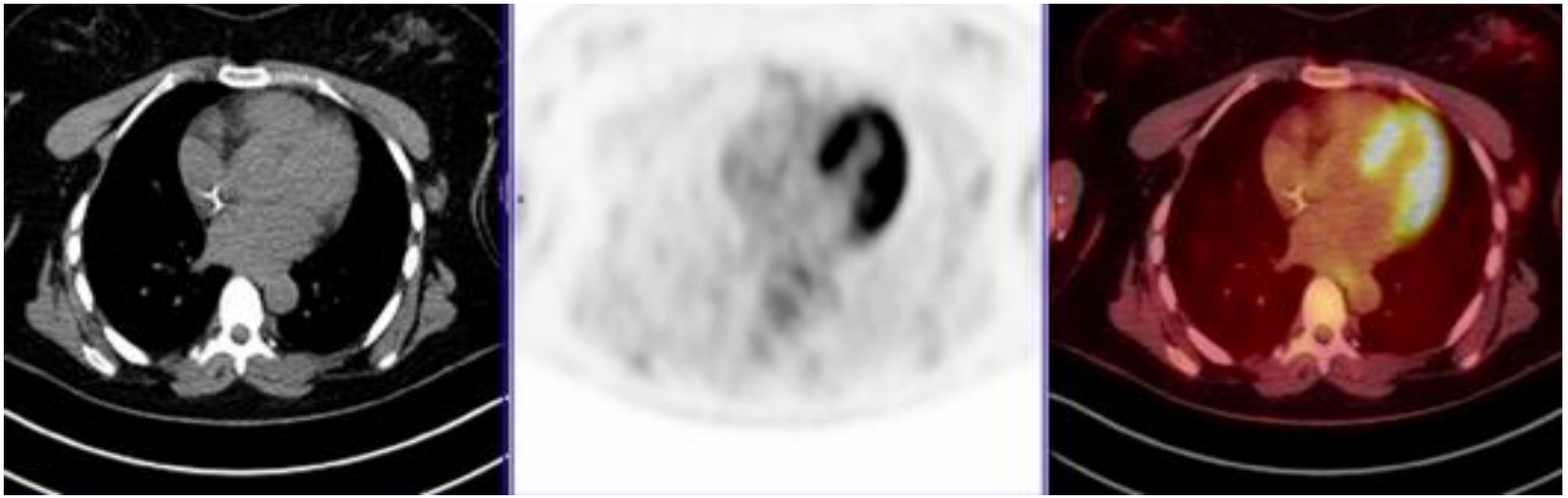


PET has low sensitivity but high specificity

May be used to monitor response to treatment

Role of PET- Monitoring response





Treatment of patients presenting with axillary metastases and presumed breast primary

Treatment of malignant axillary nodes (presumed breast primary)

- Patients can present with operable nodes or fixed inoperable nodes

- Operable nodes can be treated with initial surgery of axillary node dissection or neoadjuvant therapy followed by axillary surgery. Neoadjuvant therapy can be chemotherapy +/- anti-HER2 treatment or endocrine therapy (in older patients with ER+ disease)

- Inoperable nodes are treated with primary chemotherapy +/- anti-HER2 treatment and surgery if sufficiently downstaged

Systemic treatment

- Systemic treatment is used based on ER, PR and HER2 according to clinical guidelines as would be used for patients with resected primary and node positive disease
  - Endocrine therapy
  - Chemotherapy
  - Anti-HER2 treatment (Trastuzumab, Pertuzumab)

Pertuzumab for patients with axillary nodes and occult primary

- NHS England
  - Pertuzumab for the neoadjuvant treatment of **locally advanced**, inflammatory or early breast cancer at high risk of recurrence (TA 424)

- CDF
  - Pertuzumab for 1st line treatment of **locally advanced** or metastatic breast cancer (PER1_ver3.2)

Axillary nodal metastases from carcinoma of unknown primary: a systematic review of published evidence

- Based on 26 retrospective studies, published between 1975 and 2006, with total of 689 patients
  - Incidence of 0.12-0.67%
  - Mean age 52.4yrs (66% postmenopausal)
  - After AND, 48% N1 and 52% N2/3
  - Among 446 patients who had mastectomy, an occult breast primary was identified histologically in 321 (72%)
  - MRI revealed primary in 96/162 patients (59%)

- Prognosis based
  - Nodal status
  - Treatment of axilla
  - Treatment of breast

Pentheroudakis G et a. Breast cancer Res Treat 2010; 119:1-11

Axillary nodal metastases from carcinoma of unknown primary: a systematic review of published evidence

- Outcome
  - 5-year survival ranged from 59-88% (median follow-up of 62 months)
  - Some studies compared survival with stage-matched patients with node-positive resected breast cancer and outcome reported as similar

Pentheroudakis G et a. Breast cancer Res Treat 2010; 119:1-11

Systemic treatment

In the systematic review by Pentheroudakis

- Chemotherapy used in only 40% of women
- Only 5 women (1%) received an anthracycline-taxane combination
- No information on use of neoadjuvant chemotherapy from individual studies
- As studies were small the impact on outcomes could not be determined
- Preceded the introduction of trastuzumab

Pentheroudakis G et a. Breast Cancer Res Treat 2010; 119:1-11

Management of the axilla

- Axillary dissection provides prognostic information and local control
- Level I and II axillary node dissection has been used in the majority of published studies
- Axillary excisional biopsy and subsequent radiotherapy is an alternative
- Axillary relapse rates were higher when axillary dissection was not used and excision +/- radiotherapy used, but this is from an era when systemic treatment was less effective than what is currently used

Pentheroudakis G et a. Breast cancer Res Treat 2010; 119:1-11

Management of the breast

- Treatment options:
  - Mastectomy 59%
  - Whole breast radiotherapy 26%
  - Observation 15%

- When mastectomy was used breast malignancy was found in 72% of cases (with an additional 6% having DCIS)

- When the breast was not treated, a primary subsequently developed in the untreated breast in 42% of cases (46/110)

- Breast cancers developed in the untreated breast 4-64 months from diagnosis

Pentheroudakis G et a. Breast Cancer Res Treat 2010; 119:1-11

Radiotherapy

- Whole breast radiotherapy as an alternative to mastectomy was first reported by Vilcoq et al in 1982
- Subsequent studies suggested similar local control and survival to mastectomies
- Doses of 40Gy 15# and 50Gy 25# can be used

- Chest wall radiotherapy after mastectomy is consistent with benefits from the EBCTCG overview in patients with breast primary and involved nodes

- Radiotherapy may also be needed to the upper axilla and/or SCF depending on the extent of nodal involvement. If axillary dissection has not been used the whole axilla should be treated

Vilcoq JE et al. Arch Surg 1982; 117: 1136-1138
Vlastos G et al. Ann Surg Oncol 2001; 8: 425-431
Medina-Franco H et al. Rev Invest Clin 2002; 54: 204-208

Conclusion

- Axillary metastases with unknown breast primary is an uncommon presentation of breast cancer
- Characteristics of T0 N1 patients similar to those with stage II disease
- **Breast MRI will identify many of the breast primaries that were not detected by mammography or US**
- Axillary dissection provides prognostic information and local control
- Chemotherapy may be used before or after surgery
- Chemotherapy before surgery is the treatment of choice in patients with large volume axillary disease
- For HER2 positive disease anti-HER2 therapy with trastuzumab and pertuzumab is used
- **Treatment of the breast with mastectomy or radiotherapy is required to avoid a high risk of local relapse**