Management of Unknow Primary Breast Cancer in the Axilla

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Introduction:

- Axillary primary breast cancer, also known as occult breast cancer, occurs with identification of metastatic breast cancer to the axilla with no evidence of primary tumor in the breast.

- Occult primary breast cancer has been described since the Halsted era of surgery. William Halsted described a case series of 3 patients with axillary metastatic disease and no appreciable primary breast mass, who were ultimately diagnosed as breast cancers.

- Even in the modern era, data is limited to small case series, and large retrospective database series.

- The incidence is low, with modern retrospective database series identifying occult breast cancer in less than 1% of all breast cancers

- National Cancer Database (NCDB)-based study identified occult breast cancer as less than 0.1% of all breast cancers.

Diagnosis:

- Appropriate diagnostic pathology confirmation
  - The most common tumor subtype of cancers of unknown primary are adenocarcinomas (70%), followed by poorly differentiated carcinomas (15–20%).

- Thorough imaging to identify any primary
  - Historically, up to a third of patients had unidentified primary neoplasms; however, improved imaging and pathologic techniques have altered the diagnostic work up

Work up:

- thorough pathologic evaluation:
  - ➢ multiple techniques to characterize the tumor and identify the organ site of origin.
  - ➢ There is no single pathologic marker expression pattern that is diagnostic of breast cancer
  - ➢ Patterns consistent with breast carcinomas are characterized by a combination of positive staining for estrogen and progesterone receptors
  - ➢ mammaglobin, CA 125, CEA, CK7, and BRST2 and negative staining for CK20 and TTF-1. Her2 and S-100 staining is nonspecific as diagnostic criteria, but necessary as a part of therapeutic decision-making

Differential diagnosis:

- Other cancers which may present as axillary nodal metastases include:
  - ➢ lymphoma
  - ➢ melanoma, non-melanoma skin cancers
  - ➢ Thyroid
  - ➢ rarely lung or gastrointestinal cancers.

- If pathologic evaluation remains non-diagnostic, consideration of these other pathologies should be considered and pursued with appropriate physical examination and imaging.

Work up of Unknown Primary:

- Once pathologic evaluation has identified the breast as the likely primary site:
  - appropriate imaging work up should be pursued to identify the primary breast cancer.
    - physical exam
    - diagnostic mammography
    - ultrasound of both breasts and axilla

- If no mass or imaging abnormality is identified on exam or routine breast diagnostic imaging, then breast MRI is indicated.

MRI:

- MRI is a highly sensitive imaging modality and should be considered standard in the evaluation of occult breast cancer in particular.

- A review of eight retrospective studies, evaluating the role of MRI in occult breast cancer identified:
  - Pooled sensitivity of 90%
  - Specificity of 31
  - Pooled detection rate of 72%

- Non-histopathologically confirmed imaging findings on MRI are associated with a high false-positive rate

- If all imaging, including MRI, is negative for primary breast tumor, whole body staging is appropriate:
  - PET/CT
  - CT chest, abdomen, and pelvis in combination with a bone scan if indicated

Clinical diagnosis of axillary metastases
(palpable lymphadenopathy, incidental
finding)

Thorough history and physical
Bilateral Diagnostic Mammogram
Breast and Axillary Ultrasound
Biopsy of Axillary Mass

Breast MRI

+/- PET CT or CT with Bone Scan per NCCN
staging guidelines

Pathologic Evaluation of Biopsy

Cytokeratin
EMA
LCA
S-100
Desmin/vimentin
OCT4/HCG/AFP/PLAP
Chromogranin/synaptophysin
ER/PR/Her2 (can be positive or negative)

Consider alternative diagnoses and work up
symptoms, exam, or pathology suggestive:
Lymphoma (focused or whole body imaging)
GI Tract (CT A/P, upper or lower endoscopy)
Thyroid (Neck US)
Sarcoma (per exam and history)
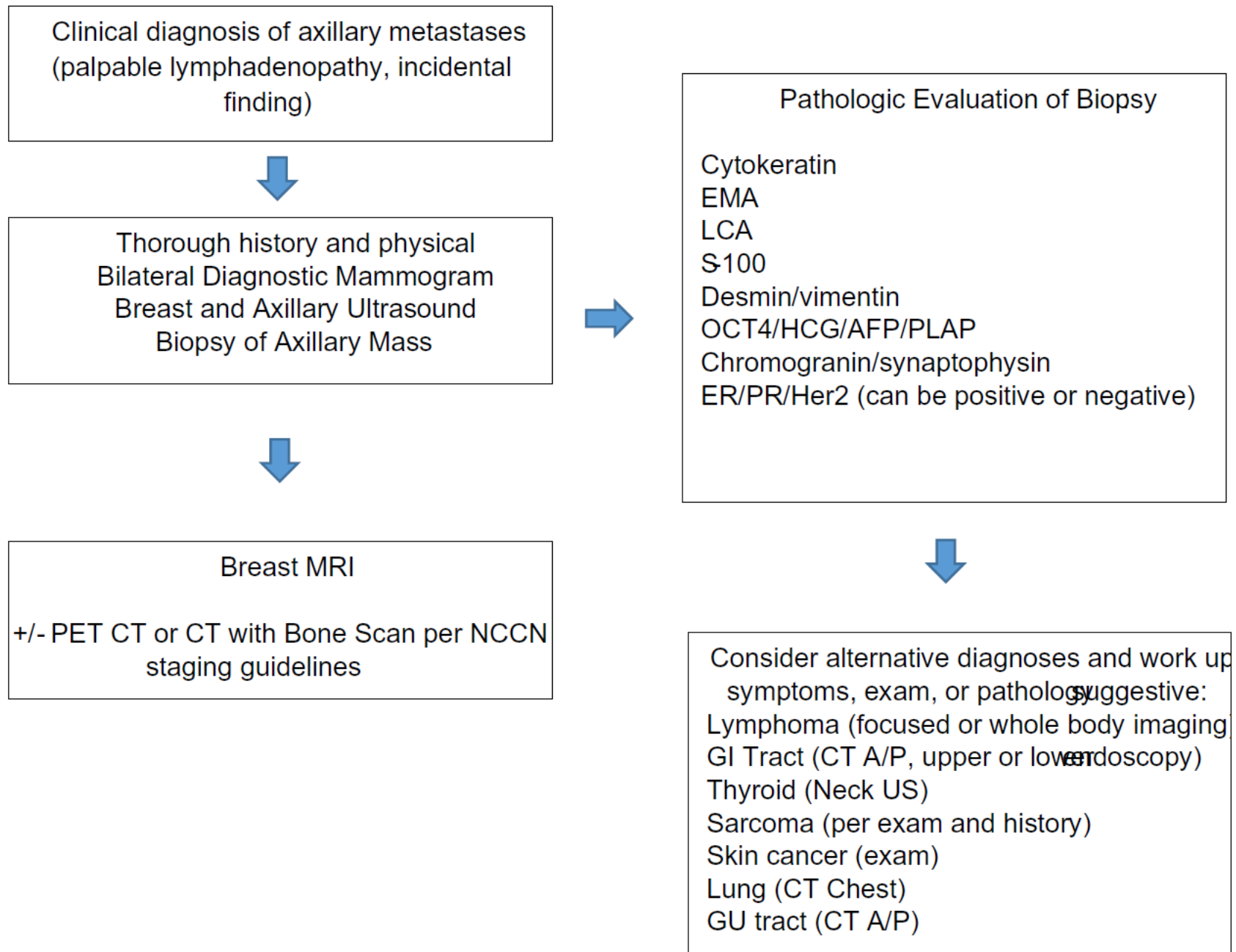Skin cancer (exam)
Lung (CT Chest)
GU tract (CT A/P)

Fig. 1 Algorithm for work up of axillary metastases with unknown primary