Occult Primary
Clinical Practice Guidelines in Oncology

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Overview
Occult primary tumors, or cancers of unknown primary (CUPs), are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation.\(^1,2\) They have a wide variety of clinical presentations and a poor prognosis in most patients. Patients with occult primary tumors often present with general complaints, such as anorexia and weight loss. Clinical absence of primary tumor, early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors.\(^3\) Life expectancy is very short, with a median survival of 6 to 9 months.\(^4\)

In most patients, occult primary tumors are refractory to systemic treatments, and chemotherapy...
is only palliative and does not significantly improve long-term survival. However, certain clinical presentations of these tumors are associated with a better prognosis. Special pathologic studies can identify subsets of patients with tumor types that are more responsive to chemotherapy. Treatment options should be individualized for this selected group of patients to achieve improved response and survival rates.

**Epidemiology**

Occult primary tumors occur roughly equally in men and women, with an average age at diagnosis of 60. An estimated 30,500 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2011, accounting for approximately 2% of all cancers diagnosed in the United States. However, deaths from cancer of unspecified primary site are estimated to be 44,260 in 2011. This discrepancy is believed to be from the lack of specificity in recording the underlying cause of death on death certificates.

A recent analysis of the Swedish Family-Cancer Database revealed that occult primary tumors may have a genetic basis. The analysis showed that 2.8% of occult primary cases were familial (i.e., a parent and offspring were both diagnosed with occult primary cancer). In addition, occult primary tumors were associated with the occurrence of lung, kidney, and colorectal cancers in families, suggesting that these tumor types are often the primary site of the disease.

**NCCN Occult Primary Panel Members**

<table>
<thead>
<tr>
<th>Name</th>
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</tr>
</thead>
<tbody>
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<td>The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute</td>
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</tbody>
</table>

KEY:

*Writing Committee Member*

Specialties: †Medical Oncology; #Pathology; PInternal Medicine; ¶Surgery/Surgical Oncology; #Diagnosis/Interventional Radiology; †Hematology/Hematology Oncology; §Radiation Oncology/Radiotherapy
**Occult Primary Version 1.2012**

**Initial Evaluation**

- Complete H&P, including breast, genitourinary, pelvic, and rectal exam, with attention to and review of:
  - Past biopsies or malignancies
  - Removed lesions
  - Spontaneously regressing lesions
  - Existing imaging studies
  - CBC
  - Electrolytes
  - Liver function tests
  - Creatinine
  - Calcium
  - Chest/abdominal/pelvic CT scan
  - Symptom-directed endoscopy
  - PET/CT scan (category 2B)

**Workup**

- Biopsy:
  - Core needle biopsy (preferred) and/or FNA of most accessible site
  - Consult pathologist for adequacy of specimen and additional studies including immunohistochemical stains
  - Gene signature profiling for tissue of origin is not recommended for standard management at this time

**Pathologic Diagnosis**

- Epithelial; not site specific
- Lymphoma and other hematologic malignancies
- Thyroid carcinoma
- Melanoma
- Sarcoma
- Germ-cell tumor
- Nonmalignant diagnosis

**Further evaluation and appropriate follow-up**

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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**Notes:**

aFor many patients, the apparent uncertainties surrounding the diagnosis of an unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognosis, and the provision of support and counseling both by the primary oncology team and specialized services, may help alleviate this distress. See NCCN Guidelines for Distress Management.

bBased on clinical findings.

cMany patients are referred with PET/CT scans. Routine use is not recommended. PET/CT scans may be warranted in some situations, even in patients with unknown primary, especially when considering local/regional therapy.

dSee Immunohistochemistry Markers for Unknown Primary Cancers (pages 1376–1379).

**Clinical trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
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**PATHOLOGIC DIAGNOSIS**

- Epithelial; not site-specific
  - Adenocarcinoma or Carcinoma not otherwise specified
    - Squamous cell carcinoma
    - Neuroendocrine tumor

**CLINICAL PRESENTATION**

- Cervical nodes
- Supraclavicular nodes
- Axillary nodes
- Mediastinum
- Chest (multiple nodules)
- or pleural effusions
- or Peritoneal/ascites
- Retroperitoneal mass
- Inguinal nodes
- Liver
- Bone
- Brain
- Multiple, including skin

*See Clinical Presentation (page 1362)*
*See Clinical Presentation (page 1363)*
*See Clinical Presentation (page 1364)*
*See Clinical Presentation (page 1365)*
*See Clinical Presentation (page 1370)*
*See NCCN Guidelines for Neuroendocrine Tumors*

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**CLINICAL PRESENTATION**

- Adenocarcinoma or Carcinoma not otherwise specified
  - Mediastinum
  - Peritoneal/Ascites
  - Chest (multiple nodules) or Pleural effusion

**ADDITIONAL WORKUP**

- Men and women:
  - Chest/abdominal/pelvic CT
  - Beta-hCG, alpha-fetoprotein
- Women:
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
- Men:
  - > 40 y: PSA
  - Testicular ultrasound, if beta-hCG and alpha-fetoprotein markers elevated

- Men and women:
  - Chest/abdominal/pelvic CT
  - CA-125
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
  - Consider gynecologic oncologist consult if clinically indicated
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
- Men:
  - > 40 y: PSA

- Men and women:
  - Chest/abdominal/pelvic CT
  - Urine cytology; cystoscopy if suspicious
  - Serum CA19-9 level if pancreatic or biliary tract primary suspected
- Women:
  - CA-125
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
  - Gynecologic oncologist consult
- Men:
  - > 40 y: PSA

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*Symptom-directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers.

†An expanded panel of immunohistochemical markers may be used as appropriate. See Immunohistochemistry Markers for Unknown Primary Cancers (pages 1376–1379).
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ADDITIONAL WORKUP

- Men and women:
  - Bone scan (if PET/CT scan not previously done)
  - Radiographic studies for painful lesions and/or bone-scan–positive lesions and/or weight-bearing areas
  - Chest/abdominal/pelvic CT

- Women:
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
  - Men:
  - PSA

- Men and women:
  - See NCCN Guidelines for Central Nervous System Cancers* for Primary Treatment of CNS Metastatic Lesions
  - Chest/abdominal CT

- Women:
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated

- Men and women
  - Chest/abdominal/pelvic CT
  - Appropriate immunohistochemistry (e.g., ER/PR, HER2)
  - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
  - Men:
  - PSA

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CLINICAL PRESENTATION

Head and neck

Supraclavicular (unilateral or bilateral)

Localized adenocarcinoma or carcinoma not otherwise specified

Axillary

Mediastinum

MANAGEMENT BASED ON WORKUP FINDINGS

Treat per NCCN Guidelines for Head and Neck Cancers*

Treat per NCCN Guidelines for Head and Neck Cancers*

Women:
- Treat per NCCN Guidelines for Breast Cancer*

Men:
- Axillary node dissection, consider RT if clinically indicated ± chemotherapy (category 2B)

< 40 y

Treat as poor-risk germ cell tumor per NCCN Guidelines for Testicular Cancer or germ cell tumor per NCCN Guidelines for Ovarian Cancer*

40 to < 50 y

Treat as poor-risk germ cell tumor per NCCN Guidelines for Testicular Cancer* or germ cell tumor per NCCN Guidelines for Ovarian Cancer* or treat per NCCN Guidelines for Non-Small Cell Lung Cancer*

≥ 50 y

Treat per NCCN Guidelines for Non-Small Cell Lung Cancer*

Consider additional consultation with pathologist to determine if further analysis would be helpful

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For many patients, the apparent uncertainties surrounding the diagnosis of an unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognosis, and the provision of support and counseling both by the primary oncology team and specialized services, may help alleviate this distress. See NCCN Guidelines for Distress Management*.

See Principles of Chemotherapy (pages 1380–1381).
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See Principles of Chemotherapy (pages 1380–1381).
CLINICAL PRESENTATION

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MANAGEMENT BASED ON WORKUP FINDINGS

Localised adenocarcinoma or carcinoma not otherwise specified

Unilateral

Bilateral

Unresectable

Resectable

Liver

Bone

Brain

Inguinal node

If surgery is medically contraindicated, then treat as unresectable (see above pathway)

Surgical resection ± chemotherapy

Isolated lesion or painful lesion or lesion with potential for fracture in weight-bearing area

Lymph node dissection, consider RT if clinically indicated ± chemotherapy

Bilateral lymph node dissection, consider RT if clinically indicated ± chemotherapy (category 2B for RT alone)

Treat as disseminated disease and/or consider locoregional therapeutic options (see NCCN Guidelines for Hepatobiliary Cancers for locoregional therapy options)

If surgery is medically contraindicated, then treat as unresectable

Surgery for impending fracture (in patients with good performance status) and/or RT

See NCCN Guidelines for Central Nervous System Cancers for management of CNS Metastatic Lesions

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See Principles of Chemotherapy (pages 1380–1381).
**CLINICAL PRESENTATION**

- Head and neck nodes
  - Head and neck workup
    - See NCCN Guidelines for Head and Neck Cancers*

- Supraclavicular nodes
  - Head and neck workup
    - See NCCN Guidelines for Head and Neck Cancers*
  - Chest CT

- Axillary nodes
  - Chest CT

- Squamous cell carcinoma
  - Abdominal/pelvic CT
  - Careful perineal and lower-extremity exam, including:
    - Penis
    - Scrotum
    - Gynecologic areas
    - Anus
  - Gynecologic oncologist consult
  - Anal endoscopy
  - Cystoscopy, if clinically indicated

- Inguinal nodes
  - Bone scan (if PET/CT scan not previously done)
  - Radiographic studies for painful lesions and/or bone scan–positive lesions and/or weight-bearing areas

- Bone

**ADDITIONAL WORKUP**

- **Head and neck workup**
  - See NCCN Guidelines for Head and Neck Cancers*
- **Supraclavicular nodes**
  - Chest CT
- **Axillary nodes**
- **Squamous cell carcinoma**
  - Abdominal/pelvic CT
  - Careful perineal and lower-extremity exam, including:
    - Penis
    - Scrotum
    - Gynecologic areas
    - Anus
  - Gynecologic oncologist consult
  - Anal endoscopy
  - Cystoscopy, if clinically indicated
- **Inguinal nodes**
- **Bone**

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Symptom-directed endoscopy based on clinical findings and immunohistochemical markers can be considered for individual patients.
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**WORKUP FINDINGS**

Primary found

- Head and neck
- Supraclavicular
- Axillary

Site-specific squamous cell carcinoma

- Mediastinum
- Multiple lung nodules
- Pleural effusion

- Inguinal
- Bone
- Brain

Disseminated metastases

- Symptom control
- Clinical trial preferred
- Consider chemotherapy on an individual basis

**MANAGEMENT BASED ON WORKUP FINDINGS**

Treat per NCCN disease-specific guidelines (see list of NCCN Guidelines, available online, at www.NCCN.org)

See Management of Site-Specific Disease (page 1372)

See Management of Site-Specific Thoracic Disease (page 1373)

See Management of Site-Specific Disease (page 1374)

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CLINICAL PRESENTATION

MANAGEMENT BASED ON WORKUP FINDINGS

Site-specific squamous cell carcinoma

- Mediastinum
  - Treat per NCCN Guidelines for Non-Small Cell Lung Cancer*

- Multiple lung nodules
  - • Clinical trial preferred
  - • Chemotherapy
  - • Symptom control

- Pleural effusion
  - • Clinical trial preferred
  - • Chemotherapy
  - • Symptom control

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FOLLOW-UP FOR ALL OCCULT PRIMARIES
(NO ACTIVE TREATMENT)

• H&P every 3-6 mo for first 3 y, then as indicated
• Diagnostic tests based on symptomatology
• Psychosocial support
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### IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS

Immunohistochemistry markers for unknown primary cancers are provided as a resource to assist in localizing a primary but are not uniformly specific or sensitive. Avoid a large series of immunohistochemistry markers. Communication with the pathologist is essential to workup.

### KEY SCREENING ANTIBODIES FOR UNDIFFERENTIATED MALIGNANCY

<table>
<thead>
<tr>
<th>CAM5.2</th>
<th>Epithelial Membrane Antigen (EMA)</th>
<th>S-100</th>
<th>Leukocyte Common Antigen (LCA)</th>
<th>Placenta-Like Alkaline Phosphatase (PLAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>POS</td>
<td>POS</td>
<td>NEG/POS</td>
<td>NEG</td>
</tr>
<tr>
<td>Melanoma</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>NEG</td>
</tr>
<tr>
<td>Lymphoma/Leukemia</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
</tr>
<tr>
<td>Nonseminoma Germ Cell Neoplasm</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
</tr>
<tr>
<td>Germ Cell Seminoma</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
</tr>
</tbody>
</table>

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1 Other pan-cytokeratin markers may be used.
IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS

Immunohistochemistry markers for unknown primary cancers are provided as a resource to assist in localizing a primary but are not uniformly specific or sensitive. Avoid a large series of immunohistochemistry markers. Communication with the pathologist is essential to workup.

TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tumor</th>
<th>Staining Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF-1</td>
<td>Lung, thyroid</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Thyroid</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>HepPar-1</td>
<td>Hepatocellular</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>CDX2</td>
<td>Colorectal/duodenal</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Villin</td>
<td>Gastrointestinal (epithelia with brush border)</td>
<td>Apical</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Breast, ovary, endometrium</td>
<td>Nuclear</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>Breast</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>Breast</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>RCC marker</td>
<td>Renal</td>
<td>Membranous</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>PAP</td>
<td>Prostate</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Uroplakin III</td>
<td>Urothelial</td>
<td>Membranous</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Sex cord–stromal, adrenocortical</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Melan-A</td>
<td>Adrenocortical, melanoma</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Calretinin</td>
<td>Mesothelioma, sex cord–stromal, adrenocortical</td>
<td>Nuclear/cytoplasmic</td>
</tr>
<tr>
<td>WT1</td>
<td>Ovarian serous, mesothelioma, Wilms, desmoplastic small round cell</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Mesothelioma</td>
<td>Cytoplasmic/membranous</td>
</tr>
<tr>
<td>D2-40</td>
<td>Mesothelioma, lymphatic endothelial cell marker</td>
<td>Membranous</td>
</tr>
</tbody>
</table>

Abbreviations: ER/PR, estrogen receptor/progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15; HepPar-1, hepatocyte parafin 1; PAP prostate acid phosphatase; PSA, prostate-specific antigen; RCC, renal cell carcinoma; TTF-1, thyroid transcription factor 1.

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Carcinomatous tumors

<table>
<thead>
<tr>
<th>CK7+/CK20+</th>
<th>CK7+/CK20-</th>
<th>CK7-/CK20+</th>
<th>CK7-/CK20-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urothelial CA</strong></td>
<td>Breast CA</td>
<td>CholangioCA</td>
<td>Thyroid CA</td>
</tr>
</tbody>
</table>
| uroplakin + thrombomodulin + p63 + CK5/6 (~1/2+) | ER/PR + GCDFP + mammoglobin + CEA + | CEA + CK19 + MOC31 + CA19-9 + CDX2 +/- HepPar1 - | TTF-1 +
| Endometrioid adenocA | Lung SmCC (majority) NE markers* + p63 - | Lung SmCC (majority) NE markers* + p63 - | TTF-1 +
| | (minor subset) | | |
| Ovarian mucinous CA | Ovarian serous CA | AdenoCA of bladder | AdenoCA of bladder |
| MUC5-AC + MUC-2 - CDX2 +/- | WT1 + ER/PR + mesothelin + CEA - | Thrombomodulin + CK5/6 - p63 - | Mesothelioma (~1/3) |
| | | | |
| **Gastric adenoCA** (subset) CDX2 +/- | **CholangioCA** (minor subset) CDX2 +/- | **Colorectal adenoCA** | **Prostate adenoCA** |
| | | Lung SmCC (majority) NE markers* + p63 - | Lung SmCC (majority) NE markers* + p63 - |
| | | | |
| | | | |
| **Pancreatic adenoCA** (~2/3) | Breast CA | Adenocortical CA | Adenocortical CA |
| CEA + CA19-9 + MUC5-AC + MUC-2 - CDX2 +/- DPC4- | | | |
| | | | |
| **Ovarian mucinous CA** | **Gastric adenoCA** (subset) CDX2 +/- | **Pancreatic adenoCA** (subset) CDX2 +/- DPC4- | **Gastric adenoCA** (subset) CDX2 +/- |
| MUC5-AC + MUC-2 - CDX2 +/- | | | |
| | | | |
| **AdenoCA of bladder** thrombomodulin + CDX2 +/- | | | |
| | | | |
| **Gastric adenoCA** (subset) CDX2 +/- | | | |
| | | | |
| **CholangioCA** (minor subset) CDX2 +/- | | | |

Abbreviations: AdenoCA, adenocarcinoma; CA, carcinoma; CEA, carcinoembryonic antigen; cholangioCA, cholangiocarcinoma; ER/PR, estrogen receptor/progesterone receptor; GCT, germ cell tumor; HCC, hepatocellular carcinoma; NE, neuroendocrine; PAP, prostate specific antigen; SCC, squamous cell carcinoma; SmCC, small cell carcinoma; TTF-1, thyroid transcription factor 1. 

*Neuroendocrine tumor is keratin-negative, OCT3/4-positive.

*Including synaptophysin, chromogranin, and CD56.

†Undifferentiated anaplastic thyroid carcinoma is often negative for thyroid transcription factor 1 (TTF-1).

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PRINCIPLES OF CHEMOTHERAPY

- Consider chemotherapy in symptomatic patients PS 1-2 or asymptomatic patients (PS 0) with an aggressive cancer.
- Base the chemotherapy regimen (list below and others) to be used on the histologic type of cancer.

SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Neuroendocrine Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel(^1)</td>
<td>Paclitaxel(^6) 175 mg/m(^2) over 3 h IV day 1</td>
<td>For poorly differentiated (high-grade or anaplastic) or small cell subtype other than lung neuroendocrine tumors, see NCCN Guidelines for Small Cell Lung Cancer*</td>
</tr>
<tr>
<td>Carboplatin(^1)</td>
<td>Cisplatin(^6) 100 mg/m(^2) IV day 2</td>
<td>For moderate and well-differentiated neuroendocrine tumors, see NCCN Guidelines for Neuroendocrine Tumors for Carcinoid Tumors*</td>
</tr>
<tr>
<td></td>
<td>5-FU(^6) 500 mg/m(^2)/d continuous infusion over 120 h, repeat cycle every 3 wk</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel(^2)</td>
<td>Docetaxel(^7) 75 mg/m(^2) IV day 1</td>
<td></td>
</tr>
<tr>
<td>Carboplatin(^2)</td>
<td>Cisplatin(^7) 75 mg/m(^2) IV day 1</td>
<td></td>
</tr>
<tr>
<td>Etoposide(^2)</td>
<td>5-FU(^7) 750 mg/m(^2)/d continuous infusion days 1-5, repeat cycle every 3 wk</td>
<td></td>
</tr>
<tr>
<td>Docetaxel(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine(^4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin(^4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1250 mg/m(^2) IV days 1 and 8</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine(^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel(^5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 mg/m(^2) IV days 1 and 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 mg/m(^2) IV day 8, repeat cycle every 3 wk</td>
<td></td>
</tr>
</tbody>
</table>

ECOG PERFORMANCE STATUS (PS)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>


See references on facing page.
Occult Primary Version 1.2012

REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES


*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.
A primary tumor site is found in fewer than 30% of patients who present initially with an occult primary tumor. In 20% to 50% of patients, the primary tumor is not identified even after postmortem examination.\textsuperscript{6,9,10}

**Pathology**

Occult primary tumors often have multiple chromosomal abnormalities and overexpression of several genes, including Ras, BCL2, HER2, and p53.\textsuperscript{11,12} BCL2 and p53 genes are overexpressed in 40% and 53% of occult primary tumors, respectively.\textsuperscript{13} BRD4-NUT oncogene resulting from the chromosomal translocation t(15;19) has been identified in children and young adults with carcinoma of midline structures and unclear primary sites.\textsuperscript{14,15}

Occult primary cancers can be classified into 5 major subtypes after routine evaluation with light microscopy. The most frequently occurring subtype is well- or moderately differentiated adenocarcinoma (60%), followed by poorly differentiated adenocarcinoma or undifferentiated carcinoma (29%), squamous cell carcinoma (SCC; 5%), and poorly differentiated malignant neoplasm (5%).\textsuperscript{1,16} Additionally, because of improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary have been recognized (1%).\textsuperscript{17,18}

Multiple sites of involvement are observed in more than 50% of patients with occult primary tumors.\textsuperscript{19} The common sites of involvement are the liver, lungs, bones, and lymph nodes.\textsuperscript{16,20} Although certain patterns of metastases suggest possible primaries, occult primaries can metastasize to any site. Therefore, one should not rely on patterns of metastases to determine the primary site.

Patients with occult primary tumors may present with favorable or unfavorable sets of prognostic signs.\textsuperscript{1,21–23} Favorable prognostic factors include poorly differentiated carcinoma with midline distribution, women with papillary adenocarcinoma of the peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, SCC involving cervical lymph nodes, isolated inguinal adenopathy (SCC), poorly differentiated neuroendocrine carcinomas, men with blastic bone metastases and elevated prostate-specific antigen (PSA; adenocarcinoma), and patients with a single, small, and potentially resectable tumor.\textsuperscript{22,24,25} Cervical lymph node metastases of SCC constitute 2% to 5% of all cases of occult primary cancers.\textsuperscript{26}

Unfavorable features include male gender, pathologic diagnosis of adenocarcinoma with multiple metastases involving multiple organs (liver, lung, or bone), nonpapillary malignant ascites (adenocarcinoma), multiple cerebral metastases (adenocarcinoma or SCC), and adenocarcinoma with multiple lung/pleural or bone lesions.\textsuperscript{22}

**Immunohistochemistry**

Immunohistochemical studies are useful for the characterization of poorly differentiated or undifferentiated tumors.\textsuperscript{27,28} In patients with occult primary tumors, immunohistochemical markers are useful for cell-type determination and pathologic diagnosis.\textsuperscript{29,30} Because immunohistochemistry markers for unknown primary cancers are not uniformly specific or sensitive, a large series of marker studies should be avoided. Communication with the pathologist is essential to workup. Immunohistochemical studies should be used in conjunction with imaging studies to select the best possible treatment options for patients with occult primary tumors.

Carcinomas are usually positive for anticytokeratin antibody CAM5.2 and epithelial membrane antigen. S-100 is usually expressed in melanoma, clear cell sarcoma, glioma, and malignant peripheral nerve sheath tumors. Leucocyte common antigen (LCA or CD45) is expressed in virtually all hematolymphoid malignancies and is highly specific for non-Hodgkin lymphoma. Placental alkaline phosphatase is mainly found in seminomas but is also expressed in some nonseminoma germ cell tumors, genitourinary, gastrointestinal, and pulmonary carcinomas. Carcinoembryonic antigen can be useful for the differential diagnosis of gastrointestinal adenocarcinomas, endocervical cancer, and some lung tumors from other sites of origin.\textsuperscript{31}

Cytokeratins are useful for cell-type determination in primary and metastatic carcinomas. Low-molecular-weight cytokeratins (CK7 and CK20) are the 2 most common immunostains used in occult primary tumors to define subsets of carcinomas.\textsuperscript{12–14} CK7 is mainly found in tumors of the lung, ovary, endometrium, thyroid, and breast. CK20 is usually expressed in gastrointestinal, urothelial, and Merkel cell carcinomas. CK7-positive/CK20-negative staining narrows the diagnosis to lung, breast, thyroid, pancreatic, ovarian, endometrioid, gastric, urothelial, or endocervical carcinomas. CK7-negative/CK20-positive cells are indicative of colorectal, gastric, and Merkel...
cell carcinomas. CK7/CK20 phenotype is also useful for differentiating between prostate (CK7-negative/CK20-negative) and urothelial (CK7-positive/CK20-positive or negative) carcinoma.

CK5 and CK6 can be useful for the differential diagnosis of poorly differentiated metastatic SCC. Most poorly differentiated SCCs (84%) show CK5/6 positivity, whereas only 21% of non-SCCs are positive for CK5/6. In addition to poorly differentiated SCC, urothelial carcinomas (35%) and all mesotheliomas express CK5 and CK6.

In addition to the above-mentioned cytokeratins, some of the other immunohistochemistry markers that are used to distinguish occult primary tumors include thyroid transcription factor (TTF-1), thyroglobulin, gross cystic disease fluid protein-15 (GCDFP-15), uroplakin III, and WT1. The use of TTF-1 staining further distinguishes lung primary tumors from other CK7-positive tumors, because most lung and thyroid carcinomas are positive for TTF-1. Thyroglobulin is a very specific marker for thyroid carcinoma (papillary and follicular). GCDFP-15 and uroplakin III are highly specific markers for breast and urothelial cancer, respectively; however, neither is very sensitive for the deduction of breast and urothelial carcinomas. In a study involving 690 neoplasms, GCDFP-15 was able to identify breast carcinomas with a sensitivity of 74% and a specificity of 95%. Uroplakin III is expressed in approximately 60% and 50% of primary and metastatic urothelial carcinomas, respectively. WT1 is a sensitive marker for epithelioid mesothelioma, and it is also positive in almost all cases of ovarian serous carcinoma, including high-grade forms. The p53 homologue nuclear transcription factor p63 can also be useful for identifying carcinomas with squamous cell, urothelial, and myoepithelial differentiation. Most poorly differentiated SCCs (86%) show immunoreactivity for p63, whereas only 14% of non-SCCs are positive for p63. Malignant mesotheliomas are consistently negative for p63, whereas p63 is expressed in 70% to 95% of urothelial carcinomas.

**Molecular Profiling**

Molecular profiling is an emerging diagnostic tool to help identify tissue of origin. Recently, several gene expression profiling (GEP) assays have been developed to identify the tissue of origin in patients with occult primary cancers. Talantov et al. developed a molecular assay that is designed to detect tumors originating from lung, breast, colon, ovary, pancreas, and prostate through evaluating the expression of 10 specific genes using real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR). This assay identified the tissue of origin of metastatic carcinomas in 204 of 260 tested samples with an overall accuracy of 78%. Varadhachary et al. assessed the feasibility of this assay retrospectively in 104 patients with CUP. The tissue of origin was identified in 61% of patients, and the results were compatible with clinicopathological features and response to therapy in most cases. Similarly, Ma et al. developed a 92-gene–based qRT-PCR assay to identify the site of origin for metastatic tumors, especially in patients with CUP. In a retrospective, multicenter study, this assay identified primary sites in 75% of patients after the initial diagnosis of CUP.

These GEP tests are now commercially available and are being evaluated in prospective clinical studies. Preliminary data from a prospective study in which treatments were based on the identification of primary sites by the 92-gene assay showed that clinical features and response to treatment were generally consistent with assay results. Similarly, 32 patients whose tumors were classified as being of colorectal origin by both of these GEP assays (the 10-gene assay of Talantov et al. and the 92-gene assay of Ma et al.) showed a response to colorectal chemotherapy regimens, as would be expected for patients with stage IV colorectal.

Using a microarray approach, Monzon et al. developed a 1550-GEP test, which had an 88% sensitivity and a 99% specificity in diagnosing uncertain primary tumors in a blinded multicenter validation study. This test is also commercially available.

Another form of molecular profiling has recently generated some interest for its potential to identify the tissue of origin of CUPs. This assay is based on the presence of microRNAs (miRNAs), which are noncoding RNAs that regulate gene expression and show high tissue specificity. Using a panel of 48 miRNAs, blinded sets of samples were identified with an accuracy of 85% to 89%. When this assay was prospectively studied in patients with occult primary tumors, the tissue of origin diagnosed was consistent with clinical and/or pathologic features of the disease in 62 of 74 patients (84%).

Currently, the panel feels that data are insufficient to confirm whether molecular profiling can be used for choosing treatment options that would im-
prove the prognosis of patients with occult primary cancers. Hence, the panel does not recommend molecular profiling as part of routine evaluation.

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Psychosocial Distress

For many patients, the apparent uncertainties surrounding the diagnosis of a CUP may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognoses, and the provision of support and counseling both by the primary oncology team and specialized services, may help alleviate this distress. Please also see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Distress Management (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Treatment Options

Chemotherapy

Many chemotherapeutic regimens have been evaluated in patients with occult primary tumors in an attempt to prolong survival and provide relief of symptoms when present. Studies conducted in the 1980s used 5-flourouracil–based or cisplatin-based chemotherapeutic regimens.51–57 Most of the patients in these studies had adenocarcinoma, with only 5% to 10% having poorly differentiated carcinoma. Overall response rates to these regimens were 20% to 35%, with median survival times of 5 to 10 months, although some of the studies reported longer median survival duration. These older regimens are not used as standard treatment for adenocarcinoma, because complete response is rarely observed.

In recent years, newer regimens containing taxanes and/or gemcitabine have shown efficacy in phase II studies in the treatment of patients with occult primary tumors.58–62 In one study, taxane-based chemotherapy was associated with long-term survival in some patients with CUP, with 1-, 2-, 3-, and 4-year survival rates of 42%, 22%, 17%, and 17%, respectively.62 The median survival was 10 months. Schneider et al.58 reported that the combination of carboplatin, gemcitabine, and capecitabine was active in occult primary tumors in patients with good performance status. Median progression-free survival was 6.2 months, and 1- and 2-year survival rates were 35.6% and 14.2%, respectively. In another phase II study conducted by the Minnie Pearl Cancer Research Network, the combination of carboplatin, gemcitabine, and paclitaxel followed by weekly paclitaxel was active and tolerable for patients with occult primary tumors and poor prognostic features.39

Recently, Hainsworth et al.63,64 reported that the combination of bevacizumab and erlotinib (alone or combined with paclitaxel and carboplatin) had substantial activity as first- or second-line therapy in patients with occult primary tumors. In a phase II trial, the combination of bevacizumab and erlotinib induced partial responses in 10% of patients, and stable disease in 61%.63 Median survival was 7.4 months (1-year survival, 33%), which, in retrospective comparison, was superior to that observed by the same group with gemcitabine alone and gemcitabine and irinotecan (3 and 4.5 months, respectively). In a recent multicenter phase II study, the combination paclitaxel and carboplatin with bevacizumab and erlotinib was active and well tolerated as first-line therapy in patients with CUP.64 After a median follow-up of 19 months, the median progression-free survival time and 2-year overall survival rates were 8 months (38% progression-free survival at 1 year) and 27%, respectively.

In general, chemotherapy shows limited efficacy and considerable toxicities in patients with occult primary tumors. Therefore, these guidelines recommend that chemotherapy for patients with disseminated disease should be limited to symptomatic patients with a performance status (PS) of 1 to 2 or asymptomatic patients with a PS of 0 and aggressive cancer. The choice of the regimen should be based on the histologic type of cancer. Regimens in addition to those listed in the guidelines can be considered.

Adenocarcinoma: Poorly differentiated carcinomas and adenocarcinomas or undifferentiated CUPs respond differently from well- to moderately differentiated CUPs. Tumors in the former group seem to be highly responsive to cisplatin-based combination chemotherapy.65,66 Objective response rates reported in 2 studies were 53% (van der Gaast et al.63) and 63% (Hainsworth et al.66), with complete response rates of 12% and 26%, respectively. In one study, patients who had tumors with extragonadal germ cell features showed a high response rate.65 In the other,
In phase II studies, the combination of paclitaxel and carboplatin with or without etoposide was found to be effective for the treatment of adenocarcinoma of occult primary tumors. In the Hellenic Cooperative Oncology Group study, the combination of paclitaxel and carboplatin produced an overall response rate of 38.7% according to intent-to-treat (ITT) analysis; no difference was seen in the response rates for adenocarcinomas and undifferentiated carcinomas. In another phase II trial, long-term follow-up of patients treated with the triple-drug combination of paclitaxel, carboplatin, and oral etoposide showed 1-, 2-, and 3-year survival rates of 48%, 20%, and 14%, respectively. In a recent phase III randomized study, the triple-drug regimen had comparable efficacy to gemcitabine and irinotecan in the first-line treatment of patients with CUP. In a randomized prospective phase II study conducted by the German CUP Study Group, the paclitaxel and carboplatin combination showed better clinical activity than the gemcitabine and vinorelbine combination. The median overall survival, 1-year survival rate, and response rate were 11.0 months, 38%, and 23.8%, respectively, for patients treated with paclitaxel and carboplatin, compared with 7.0 months, 29%, and 20%, respectively, for those treated with gemcitabine and vinorelbine. Sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan was also found to be active in patients with occult primary tumors. Although survival was similar to that observed in previous phase II trials, the overall toxicity of sequential treatment was found to be greater than that observed with other regimens.

Greco et al. reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated adenocarcinoma. Major response to therapy was observed in 26% of patients receiving docetaxel and cisplatin, with a median survival of 8 months and a 1-year survival of 42%. In patients receiving docetaxel and carboplatin, the corresponding response rate was 22%, with a median survival of 8 months and 1-year survival of 29%. Docetaxel in combination with carboplatin was better tolerated than docetaxel with cisplatin in this study.

In a recent report of the Hellenic Cooperative Oncology Group phase II study, a 1-hour treatment with docetaxel and carboplatin every 3 weeks was found to be safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated carcinoma with performance status of 0 to 2. Median time to progression was 5.5 months, whereas overall survival was 16.2 months. Survival was better in favorable-risk patients (23 vs. 5 months for those with visceral metastases). Predictors of superior outcome included good performance status and low volume disease.

Efficacy and toxicity of combination regimens, including cisplatin with either gemcitabine or irinotecan, were evaluated in a randomized phase II study conducted by the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). Well-differentiated adenocarcinoma was the most common histology, with one-fourth of patients having a single metastatic site. Objective response rates were 55% for the gemcitabine and cisplatin arm and 38% for the irinotecan and cisplatin arm. Median survival rates were 8 and 6 months, respectively, for these 2 combination regimens, which were both associated with significant toxicities.

Finally, a non–cisplatin-based regimen containing gemcitabine and docetaxel was found to be well tolerated and active as first-line therapy in patients with occult primary tumors. The overall response rate was 40%, with a median survival of 10 months. SCC: Platinum-based regimens are used to treat disseminated SCC. Historically, the combination of cisplatin and 5-fluorouracil was the most frequently used regimen for patients with SCC of unknown primary. More recently, however, studies have shown that adding paclitaxel or docetaxel to this regimen is beneficial to patients with SCC. In a randomized phase III study, cisplatin and 5-fluorouracil was compared with the combination of paclitaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. Induction chemotherapy with paclitaxel, cisplatin, and 5-fluorouracil produced a higher complete response rate (33% vs. 14%) and was better tolerated than the cisplatin and 5-fluorouracil regimen.

In a randomized phase III trial, induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil was compared with cisplatin and 5-fluorouracil in patients with locally advanced larynx and hypopharynx cancer. The 3-drug regi-
men produced significantly superior overall response rate (80% vs. 59%) compared with the 2-drug regimen.\textsuperscript{79}

**Neuroendocrine Tumors:** Neuroendocrine carcinomas of unknown primary site are uncommon and their clinical behavior is dependent on the tumor grade and differentiation.\textsuperscript{80} Neuroendocrine tumors, regardless of grade, represent a favorable prognostic subset of occult primary tumors that are responsive to combination chemotherapy, and long-term survival is possible in a minority of patients.\textsuperscript{17}

Hainsworth et al.\textsuperscript{81} evaluated the efficacy of a combination regimen containing paclitaxel, carboplatin, and etoposide in metastatic poorly differentiated neuroendocrine (PDNE) carcinomas in patients who had received no prior treatment. Of these patients, 62% had PDNE carcinoma of unknown primary site; patients with known primary sites were also eligible for the study. Major responses were observed in 53% of the patients, and the median survival was 14.5 months; 2- and 3-year survival rates were 33%, and 24%, respectively. The results of this trial showed that PDNE carcinomas are chemosensitive, with a high overall response rate to combination chemotherapy and a minority of complete responses.

In 2 small series of patients, temozolomide, as a single agent or in combination with thalidomide, was found to be effective in the treatment of advanced or metastatic neuroendocrine tumors.\textsuperscript{82,83}

Poorly differentiated neuroendocrine tumors can be treated following small cell lung cancer regimens. In a randomized phase III trial (JCOG 9702), the combination of carboplatin plus etoposide was equally efficient as cisplatin plus etoposide in elderly or poor-risk patients with extensive small cell lung cancer who were not previously treated.\textsuperscript{84} No significant differences were seen in response rate (73% for both regimens) and median overall survival (10.6 months for carboplatin and etoposide vs. 9.9 months for cisplatin and etoposide).

In one study, the combination of cisplatin and etoposide produced significant responses in patients with poorly differentiated, rapidly progressing neuroendocrine tumors (carcinoids and pancreatic neuroendocrine tumors of known primaries) when used as a second- or third-line treatment.\textsuperscript{85}

**Radiation Therapy**

Radiation therapy is a treatment option for a variety of localized tumors, particularly as follow-up treatment after lymph node dissection for the involvement of axillary or inguinal nodes if more than 2 nodes are involved or extracapsular extension is present. Radiation therapy alone may also be considered for bone lesions, a retroperitoneal mass with a non-germ cell histology, or supraclavicular nodal involvement in site-specific SCC.

**Locoregional Therapeutic Options**

In patients with unresectable localized liver lesions (either adenocarcinoma or neuroendocrine), locoregional therapeutic options may be considered. Locoregional therapeutic options include hepatic artery infusion, chemoembolization, hepatic cryosurgery, radiofrequency ablation of hepatic lesions, or percutaneous ethanol injections.

**Specialized Approaches**

Specialized approaches are suggested as a treatment option in all patients with disseminated metastases. The term emphasizes the importance of an individual approach. Specialized approaches may include palliative treatment options, such as thoracentesis and paracentesis; novel forms of drug delivery; targeted therapies, such as radioimmunotherapy; and novel forms of radiation therapy, such as intraoperative radiation therapy, intensity-modulated radiation therapy, image-guided radiation therapy, or proton therapy.\textsuperscript{86}

**NCCN Recommendations**

These guidelines focus on 3 pathologic diagnoses in patients with epithelial occult primary cancer:

- Adenocarcinoma, or carcinoma not otherwise specified
- SCC
- Neuroendocrine tumors

The guidelines suggest diagnostic tests based on the location of disease and the patient’s gender, where appropriate. For example, for SCC the guidelines focus on the most common sites of clinical presentation, namely, the head and neck nodes, supraclavicular nodes, inguinal nodes, and bone. For adenocarcinoma, 12 different clinical presentations are addressed, with suggested diagnostic tests for each location.

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma and site-specific SCC. The panel endorses enrollment of patients in appropriate
clinical trials when possible. For each of the 3 pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on recommendations in the NCCN Guidelines for the cancer site corresponding to the primary (see list of NCCN Guidelines for Treatment of Cancer by Site, available online, at www.NCCN.org). In patients with disseminated disease for all of the pathologic diagnoses listed earlier, the treatment goals are directed toward symptom control and providing the best quality of life possible.

Initial Evaluation

These guidelines recommend that patients undergo an initial evaluation, including a detailed review of biopsy findings. At this point, a specific pathologic diagnosis may be made (e.g., epithelial occult primary [not site-specific], thyroid, lymphoma or other hematological malignancy, melanoma, sarcoma, or germ cell tumor).

Initial evaluation of a patient with a suspected metastatic malignancy should include a complete history and physical examination, including breast, genitourinary, pelvic, and rectal examinations, with attention to and review of past biopsies or malignancies, removed lesions, spontaneously regressing lesions, and existing imaging studies; routine laboratory studies (CBC, electrolytes, liver function tests, creatinine, calcium); occult blood stool testing; and symptom-directed endoscopy. Other diagnostic studies should be based on the clinical presentation and subsequent histopathologic findings. CT scan of the chest, abdomen, and pelvis is also recommended; it is important to determine if the initially identified malignancy is localized or disseminated, because the treatment for localized and disseminated disease may be different.

In the past several years, PET scans and a combination PET/CT scan have become 2 of the most frequently used imaging modalities in the management of patients with occult primary cancers. PET scan has been shown to be a useful method for the diagnosis, staging, and restaging of many malignancies, and it might be warranted in some situations (e.g., presence of supraclavicular nodes). PET scan has shown intermediate specificity and high sensitivity in a few small studies, but larger studies are warranted to determine the clinical utility and role of PET scan in patients with occult primary tumors. In a comprehensive review of 10 published studies, Seve et al. concluded that PET is a valuable imaging modality for patients with occult primary tumors with a single site of metastasis and when therapy with a curative intent is planned.

One of the limitations of PET scans has been the limited accuracy of anatomic localization of functional abnormalities because of very little accumulation of F-fluorodeoxyglucose tracer in some neoplastic tissues. In these cases, the combination of PET scan with either CT scan or MRI can be more useful. Studies on the use of PET/CT scans for detecting occult primary tumors have reported that the combination of PET/CT identified the primary site in 25% to 57% of patients. A recent meta-analysis and systemic review on the use of PET/CT in patients with occult primaries found that primary tumors were detected in 37% of 433 patients from 11 studies, with pooled sensitivity and specificity both at 84%. These results indicate that combined modality scanning could play an important role in the diagnosis of occult primary tumors. However, these results must be confirmed in larger clinical studies with long-term follow-up.

Although PET or PET/CT scans detect more primary sites (24%–40%) than conventional imaging techniques (20%–27%), their exact role remains undefined because of the lack of prospective clinical trials comparing PET/CT scans with conventional imaging modalities. Therefore, the panel does not recommend using PET/CT scan for routine screening. However, PET/CT scans may be warranted in some situations, especially when considering local or regional therapy. In the guidelines, PET/CT scan is included for initial evaluation with a category 2B recommendation.

Workup

Patients with a suspected occult primary will typically present to the oncologist after undergoing an initial core needle biopsy (preferred) and/or fine needle aspiration. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether additional biopsy material is necessary (e.g., core needle, incisional, or excisional biopsy). Light microscopic examination of the biopsy material is usually performed first. Other techniques include electron microscopy and flow cytometry. Although immunohistochemical stains can be informative, large panels of immunohistochemical markers should be avoided.
Occult Primary

This initial evaluation will identify a primary site in approximately 30% of patients presenting with occult metastases. These patients should be treated according to the appropriate NCCN Guidelines for Treatment of Cancer by Site (see list of NCCN Guidelines for Treatment of Cancer by Site, available online, at www.NCCN.org).

For the remaining patients, a great deal of controversy remains regarding whether an exhaustive, time-consuming, costly evaluation should be conducted to search for the primary beyond these initial tests, as opposed to a more directed evaluation based on the complete history and physical examination, clinical presentation, histopathologic diagnosis, and metastatic sites of involvement. Suggested diagnostic tests for each pathologic subtype, location, and gender (where appropriate) are indicated in the guidelines and are discussed later. Additional studies can be important in determining whether the occult primary cancer is potentially curable, or in diagnosing a possible treatable disease associated with long-term survival. Effective therapies are available for lymphoma, breast, ovarian, thyroid, prostate, and germ cell tumors.

Workup for Possible Breast Primary: Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. These guidelines suggest the use of a mammogram and breast ultrasound for these patients. Appropriate testing for immunohistochemical markers, such as estrogen receptor/progesterone receptor (ER/PR) and HER2, is also recommended. Elevated ER/PR levels provide strong evidence for a breast cancer diagnosis. MRI of the breast should be considered for a patient with histopathologic evidence of breast cancer only when mammography and ultrasound are not adequate to assess the extent of the disease, especially in women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor, or to evaluate the chest wall. Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer, and may also facilitate breast conservation in selected women through allowing for lumpectomy instead of mastectomy. In one report, the primary site was identified using MRI in approximately half of the women presenting with axillary metastases, irrespective of the breast density.

For a woman with involvement of the mediastinum whose workup does not indicate primary breast cancer, additional consultation with a pathologist to determine whether further analysis would help differentiate between breast and non–small cell lung cancer should be considered.

Workup for Possible Germ Cell Primary: Involvement of mediastinal nodes in patients with adenocarcinoma suggests a possible germ cell tumor, as does a retroperitoneal mass in men younger than 65 years. Thus, these guidelines suggest β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) measurements. CT scans of the chest, abdomen, and pelvis are recommended in both men and women for mediastinal and retroperitoneal adenocarcinoma. Testicular ultrasound should also be considered if β-hCG and AFP levels are elevated in a man with a mediastinal or retroperitoneal mass.

For patients with involvement of the mediastinum whose workup does not indicate a primary germ cell tumor, additional consultation with a pathologist to determine whether further analysis would help differentiate between testicular or ovarian cancer and non–small cell lung cancer should be considered.

Workup for Possible Prostate Primary: All men older than 40 years with an adenocarcinoma or carcinoma not otherwise specified, except those with metastases limited to liver or brain, should undergo a PSA test. In addition, men presenting with bone metastases or multiple sites of involvement should have PSA levels assessed regardless of age.

Workup for Possible Ovarian Primary: An occult ovarian primary tumor is suspected for mediastinal, inguinal, chest, peritoneal, or retroperitoneal malignancies. Testing for the ovarian cancer marker CA-125 is recommended in these cases, as is a gynecologic oncologic consultation, if clinically indicated. CT scans of abdomen, pelvis, and sometimes chest (depending on site of involvement) are also recommended for these women.

Additional Workup for Adenocarcinoma or Carcinoma Not Otherwise Specified: In patients with peritoneal disease or liver involvement, serum CA 19-9 level can be considered if pancreatic or biliary tract primary is suspected. In patients with inguinal
lymph node involvement, the guidelines include proctoscopy for men and women, if clinically indicated, to assess for rectal or anal cancer. Bone scan (if PET/CT scan was not previously performed) and radiographic studies are recommended for adenocarcinoma involving painful or bone scan–positive bone lesions. Urine cytology is recommended for patients presenting with a retroperitoneal mass, followed by cytoscopy for suspicious findings.

Colonoscopy is recommended for patients presenting with malignancy in the liver, but is not routinely recommended in patients presenting with malignant ascites (i.e., peritoneal presentation). In the absence of a positive fecal occult blood test or other clinical factors suggesting a tumor in the colon, the diagnostic yield of colonoscopy is less than 5%. The use of AFP as a marker for hepatocellular carcinoma as part of the additional workup in adenocarcinoma or carcinoma not otherwise specified in the liver has been changed from a category 2B to a category 2A recommendation in the 2012 guidelines. Workup for SCCs: SCC can be present in the nodes of the head and neck region, supraclavicular, axillary, and inguinal nodes. CT scans of the abdomen and pelvis; perineal and lower-extremity examination; gynecologic oncologic consult; and anal endoscopy are recommended for patients with SCC with inguinal node involvement. For adenocarcinoma in the bone, bone scan (if PET/CT was not previously performed) and radiographic studies are recommended for SCC involving painful or bone scan–positive bone lesions.

The workup recommendations for Occult Primary in the NCCN Guidelines for Head and Neck Cancers should be followed for unknown primary lesions in the head and neck and supraclavicular nodes (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [OCC-1]). Workup for Neuroendocrine Tumors: Neuroendocrine tumors can metastasize to several sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal nodes, liver, bone, brain, and skin. The workup recommendations for Neuroendocrine Unknown Primary in the NCCN Guidelines for Neuroendocrine Tumors should be followed (available at www.NCCN.org [NUP-1]).

Management Based on Workup Findings

Adenocarcinoma: Localized adenocarcinoma or carcinoma not otherwise specified is treated according to the most likely primary site. For example, patients with localized adenocarcinoma involving supraclavicular nodes (unilateral or bilateral) or in the head and neck should be treated according to the Occult Primary pathway described in the NCCN Guidelines for Head and Neck Cancers (available at www.NCCN.org [OCC-1]). However, those presenting with localized adenocarcinoma with a peritoneal mass or ascites consistent with ovarian histology should be treated according to the NCCN Guidelines for Ovarian Cancer. Localized adenocarcinoma with a retroperitoneal mass consistent with germ cell histology should be treated according to the NCCN Guidelines for Testicular Cancer or NCCN Guidelines for Ovarian Cancer. For women with localized adenocarcinoma involving axillary nodes and those who are hormone receptor–positive who have pleural effusion, these guidelines recommend treatment according to the NCCN Guidelines for Breast Cancer. To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

Localized adenocarcinoma occurring in the mediastinum most likely derives from either a germ cell tumor or a non–small cell lung tumor. Additional consultation with a pathologist should be considered to determine if further analysis would help determine the origin of the primary tumor. In the absence of additional diagnostic information, the recommended treatment depends on the age of the patient at diagnosis. Patients younger than 40 years and those between 40 and 50 years of age should be treated for poor-risk germ cell tumors according to the NCCN Guidelines for Testicular Cancer or the NCCN Guidelines for Ovarian Cancer. Alternatively, patients aged 40 to 50 years could be treated according to the NCCN Guidelines for Non–Small Cell Lung Cancer. Patients aged 50 years or older should be treated according to the NCCN Guidelines for Non–Small Cell Lung Cancer. To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

Other locations of unknown primary adenocarcinomas are not associated with a common primary site. Treatment recommendations in these cases are thus general and involve local and systemic therapies. For example, axillary node dissection and radiation therapy to axilla for gross extracapsular extension with or without chemotherapy is recommended.
for men with localized adenocarcinoma or carcinoma not otherwise specified with involvement of axillary nodes (category 2B). Surgery can be considered for resectable lung nodules, and chemotherapy can be considered with or without resection. Lymph node dissection is recommended for inguinal nodal involvement; radiation therapy with or without chemotherapy can also be considered if clinically indicated (category 2B recommendation for the use of radiation therapy alone in the case of bilateral inguinal node involvement).

Surgical resection with or without chemotherapy is recommended for patients with localized adenocarcinoma in the liver. If surgery is medically contraindicated or if the tumor is unresectable, these guidelines recommend chemotherapy and/or locoregional treatment options as described in the NCCN Guidelines for Hepatobiliary Cancers (available at www.NCCN.org).

For patients with good performance status and bone lesions with potential for fracture in a weight-bearing area, surgery and/or radiation therapy are options. In the case of patients with poor performance status or those with isolated or painful bone lesions, radiation therapy is recommended. Patients with brain metastases should be managed according to the recommendations for treating metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers (available at www.NCCN.org). Chemotherapy can be considered for patients presenting with hormone-negative pleural effusion or ascites/peritoneal mass of nonovarian origin. In the case of a retroperitoneal mass of non–germ cell histology, surgery and/or radiation therapy is recommended, with chemotherapy considered in select patients (category 2B).

Young men with disseminated metastases should be treated according to the NCCN Guidelines for Testicular Cancer (available at www.NCCN.org). For all other patients with disseminated carcinoma of unknown primary, a clinical trial is preferred with the additional recommendations of symptom control and the consideration of chemotherapy on an individual basis.

The following regimens are included in the guidelines for treating adenocarcinoma of unknown primary, based on the results of the phase II studies 67,68,72,74,75: Regimens other than those listed can also be considered.

- Paclitaxel and carboplatin with or without etoposide
- Docetaxel and carboplatin
- Gemcitabine and cisplatin
- Gemcitabine and docetaxel

SCC: Patients with site-specific SCC with localized axillary or inguinal involvement of lymph nodes may benefit from lymph node dissection with or without subsequent chemotherapy. Radiation therapy can be considered if clinically indicated (category 2B recommendation in the case of bilateral inguinal node involvement for the use of radiation therapy alone). Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin.

Patients with unilateral and bilateral involvement of the supraclavicular lymph nodes or with SCC involvement in the head and neck should be treated according to the recommendations for treatment of Occult Primary tumors described in the NCCN Guidelines for Head and Neck Cancers (available at www.NCCN.org [OCC-1]). Patients with site-specific SCC in the mediastinum should be treated according to the NCCN Guidelines for Non–Small Cell Lung Cancer. Participation in a clinical trial is the preferred treatment option for patients with multiple lung nodules or pleural effusion. Alternatively, chemotherapy can also be considered for this group of patients.

Surgery and/or radiation therapy for impending fracture are options for patients with an isolated bone lesion and good performance status. Patients with brain metastases should be managed according to the recommendations for metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers (available at www.NCCN.org).

For patients with disseminated SCC of unknown primary, a clinical trial is preferred with the additional recommendations of symptom control and the consideration of chemotherapy on an individual basis.

The following regimens are included in the guidelines for the treatment of SCC of unknown primary, based on randomized phase III studies 78,79: Regimens other than those listed can also be considered.

- Cisplatin, 5-FU, and paclitaxel
- Cisplatin, 5-FU, and docetaxel

Neuroendocrine Tumors: Management of neuroendocrine tumors should be follow the Neuroendocrine
Unknown Primary pathway in the NCCN Guidelines for Neuroendocrine Tumors (available at www.NCCN.org [NUP-1]).

Follow-Up
For all patients with occult primary tumors undergoing no active treatment, follow-up consists of a history and physical every 3 to 6 months for the first 3 years, and as clinically indicated thereafter. Diagnostic tests should be performed for symptomatic patients.

The apparent uncertainties surrounding the diagnosis of occult primary tumors may result in significant psychosocial distress in many patients. Psychological support should be ongoing. Psychological distress can be managed as described in the NCCN Guidelines for Distress Management (available at www.NCCN.org). Empathetic discussion about the natural history of this type of cancer and the prognosis, and provision of support and counseling by both the primary oncology team and specialized services, may help alleviate distress.

References
Occult Primary


Occult Primary


## Individual Disclosures of the NCCN Occult Primary Panel

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The NCCN guidelines staff have no conflicts to disclose.