Occult Primary (Cancer of Unknown Primary [CUP])

Version 1.2015

NCCN.org

Continue
Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.
Updates in Version 1.2015 of the Guidelines for Occult Primary from Version 3.2014 include:

**MS-1**
- The discussion section was updated to reflect the changes to the algorithm.

**OCC-9**
- Under Management Based on Workup Findings, the 5th bullet, "stereotactic body radiotherapy (SBRT)" is new to the page.

**OCC-B (2 of 4 and 3 of 4)**
- The docetaxel and cisplatin regimen is new to adenocarcinoma. For squamous cell an additional dosing schema has been added for docetaxel and cisplatin.

**OCC-B (4 of 4)**
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

Routine use of PET/CT is not recommended. PET/CT scans may be warranted in some situations.

Based on clinical findings.

There may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Clinical Presentation

Adenocarcinoma or Carcinoma not otherwise specified

Cervical nodes

See NCCN Guidelines for Head and Neck Cancers/Occult Primary

Supraclavicular nodes

Men and women:
• Neck/chest/abdominal/pelvic CT (if not done)
• Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
• Appropriate immunohistochemistry
Men:
• >40 y: Prostate-specific antigen (PSA)

Axillary nodes

Men and women:
• Neck/chest/abdominal CT (if not done)
• Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
• Appropriate immunohistochemistry
Men:
• >40 y: PSA

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

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 (OCC-A).
Adenocarcinoma or Carcinoma not otherwise specified

CLINICAL PRESENTATION

Mediastinum

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 (OCC-A).

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

ADDITIONAL WORKUP

Men and women:
• Chest/abdominal/pelvic CT (if not done)
• Beta-hCG, alpha-fetoprotein

Women:
• Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
• Appropriate immunohistochemistry

Men:
• >40 y: PSA
• Testicular ultrasound, if beta-hCG and alpha-fetoprotein markers elevated

Men and women:
• Chest/abdominal/pelvic CT (if not done)
• CA-125
• Appropriate immunohistochemistry

• Consider gynecologic oncologist consult if clinically indicated
• Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
• PSA

Men and women:
• Chest/abdominal/pelvic CT (if not done)
• Urine cytology; cystoscopy if suspicious
• Serum CA19-9 level if pancreatic or biliary tract primary suspected

Women:
• CA-125
• Appropriate immunohistochemistry

• Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
• Gynecologic oncologist consult

Men:
• >40 y: PSA

*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 (OCC-A).
CLINICAL PRESENTATION

ADDITIONAL WORKUP

Men and women:
- Chest/abdominal/pelvic CT (if not done)
- Urine cytology; consider cystoscopy if suspicious

Women:
- CA-125
- Appropriate immunohistochemistry
- Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated
- Gynecologic oncologist consult if clinically indicated

Men:
- >40 y: PSA
- <65 y: Beta-hCG, alpha-fetoprotein, testicular ultrasound if markers elevated

Men and women:
- Abdominal/pelvic CT (if not done)
- Proctoscopy if clinically indicated

Women:
- CA-125
- Gynecologic oncologist consult

Men:
- >40 y: PSA

Men and women:
- Chest/abdominal/pelvic CT (if not done)
- Endoscopic evaluation
- Serum CA19-9 level if pancreatic or biliary tract primary suspected
- Alpha-fetoprotein

Women:
- Appropriate immunohistochemistry
- Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated

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

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 (OCC-A).
CLINICAL PRESENTATION

Bone

Brain

Multiple sites of involvement

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 (if not done)

Women:
- Appropriate immunohistochemistry
- Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated

Men:
- PSA

Men and women:
- See NCCN Guidelines for Central Nervous System Cancers for Primary Treatment of CNS Metastatic Lesions
- Chest/abdominal CT (if not done)

Women:
- Appropriate immunohistochemistry
- Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated

Men and women:
- Chest/abdominal/pelvic CT (if not done)

Women:
- Appropriate immunohistochemistry
- Mammogram; if non-diagnostic and histopathologic evidence for breast cancer, breast MRI and/or breast ultrasound indicated

Men:
- PSA

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 (OCC-A).

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

Primary found

- Head and Neck
- Supraclavicular
- Axillary
- Mediastinum

Localized adenocarcinoma or carcinoma not otherwise specified

- Lung nodules
- Pleural effusion
- Peritoneal
- Retroperitoneal mass

- Inguinal node
- Liver
- Bone
- Brain

Disseminated metastases

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

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

See Follow-up (OCC-16)
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines Version 1.2015**

**Occult Primary**

---

**CLINICAL PRESENTATION**

- **Lung nodules**
  - Management based on workup findings:
    - If resectable, consider surgery
    - Clinical trial preferred
    - Consider chemotherapy
    - Symptom control
    - Stereotactic body radiotherapy (SBRT)
    - Treat per NCCN Guidelines for Breast Cancer
  - If histology consistent with germ cell tumor in both men and women:
    - Surgery and/or RT
    - Consider chemotherapy for selected patients (category 2B)

- **Pleural effusion**
  - Consider local management
  - Breast marker positive:
    - Other
  - Breast marker negative:
    - Other

- **Peritoneal/Ascites**
  - If histology consistent with germ cell tumor:
    - Treatment as poor-risk germ cell tumor per NCCN Guidelines for Testicular Cancer or germ cell tumor per NCCN Guidelines for Ovarian Cancer
  - Non-germ cell histology:
    - Other

- **Retroperitoneal mass**
  - Other

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

---

*a* 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 to alleviate this distress. See NCCN Guidelines for Distress Management.

*See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).*

---

See Follow-up (OCC-16)
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

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

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

hSee Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

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

MANAGEMENT BASED ON WORKUP FINDINGS

Mediastinum

Treat per NCCN Guidelines for Non-Small Cell Lung Cancer

Site-specific squamous cell carcinoma

Multiple lung nodules

• Clinical trial preferred
• Chemotherapy
• Symptom control

Pleural effusion

• Clinical trial preferred
• Chemotherapy
• Symptom control

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

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 to alleviate this distress. See NCCN Guidelines for Distress Management.

hSee Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).
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 to alleviate this distress. See NCCN Guidelines for Distress Management.

See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
FOLLOW-UP FOR ALL OCCULT PRIMARIES
(NO ACTIVE TREATMENT)

• For patients with either active disease, or localized disease in remission, follow-up frequency should be determined by clinical need
  ‣ H&P
  ‣ Diagnostic tests based on symptomatology

• For patients with active and incurable disease, psychosocial support, symptom management, end-of-life discussions, palliative care interventions, and hospice care should all be considered and utilized as appropriate.

• See NCCN Guidelines for Palliative Care and NCCN Guidelines for Distress Management.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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></th>
<th>CAM5.2(^1)</th>
<th>Epithelial Membrane Antigen (EMA)</th>
<th>S-100</th>
<th>CD-45 (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>
<td>NEG/POS</td>
</tr>
<tr>
<td>Melanoma</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
</tr>
<tr>
<td>Lymphoma/Leukemia</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>NEG</td>
</tr>
<tr>
<td>Nonseminoma</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
</tr>
<tr>
<td>Germ Cell Neoplasm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ Cell Seminoma</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
</tr>
</tbody>
</table>

This figure was published in Diagnostic Immunohistochemistry, Dabbs DJ, Copyright Elsevier (2010).

\(^1\)Other pan-cytokeratin markers are available and may be more appropriate.

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

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

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.

### CYTOKERATIN/KERATIN DISTRIBUTION

<table>
<thead>
<tr>
<th>CK 7+ 20+</th>
<th>CK 7- 20+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary mucinous</td>
<td>Colorectal adeno</td>
</tr>
<tr>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>Merkel cell</td>
</tr>
<tr>
<td>65%</td>
<td>70%</td>
</tr>
<tr>
<td>Pancreas adeno</td>
<td>Gastric adeno</td>
</tr>
<tr>
<td>65%</td>
<td>35%</td>
</tr>
<tr>
<td>Cholangio</td>
<td>Excluded tumors</td>
</tr>
<tr>
<td>65%</td>
<td>≤5%</td>
</tr>
<tr>
<td>Gastric adeno</td>
<td>Breast; Carcinoid lung; Cholangio;</td>
</tr>
<tr>
<td>40%</td>
<td>Esoph squam; Germ cell;</td>
</tr>
<tr>
<td>Excluded tumors</td>
<td>Lung all types; Hepatocellular;</td>
</tr>
<tr>
<td>≤5%</td>
<td>Ovary; Pancreas adeno; Renal</td>
</tr>
<tr>
<td>Carcinoid; Germ cell; Esoph squam;</td>
<td>adeno; Transitional cell; Uterus</td>
</tr>
<tr>
<td>Head/neck squam; Hepatocellular;</td>
<td>endometrioid</td>
</tr>
<tr>
<td>Lung small cell &amp; squam; Ovary-non mucinous; Renal adeno</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CK 7+ 20-</th>
<th>CK 7- 20-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary non mucinous</td>
<td>Adrenal</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Thyroid (all three types)</td>
<td>Seminoma &amp; YST</td>
</tr>
<tr>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Breast</td>
<td>Prostate</td>
</tr>
<tr>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Lung adeno</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Uterus endometrioid</td>
<td>Renal adeno</td>
</tr>
<tr>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td>Embryonal</td>
<td>Carcinoid GI &amp; lung</td>
</tr>
<tr>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Lung small cell &amp; squam</td>
</tr>
<tr>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>Esoph squam</td>
</tr>
<tr>
<td>35%</td>
<td>70%</td>
</tr>
<tr>
<td>Pancreas adeno</td>
<td>Head/neck squam</td>
</tr>
<tr>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>Cholangio</td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>Excluded tumors</td>
<td>Excluded tumors</td>
</tr>
<tr>
<td>≤5%</td>
<td>≤5%</td>
</tr>
<tr>
<td>Colorectal adeno; ovary mucinous;</td>
<td>Breast; Cholangio; Lung adeno;</td>
</tr>
<tr>
<td>seminoma; yolk sac tumor (YST)</td>
<td>Ovary; Pancreas adeno</td>
</tr>
</tbody>
</table>

Adapted from “Applications of immunohistology to non-heme tumor differential diagnosis” by Rouse RV (http://surgpathcriteria.stanford.edu).

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

Carcinomatous tumors → Broad-spectrum CKs+, S100-, HMB45-, CD45-

<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><code> uroplakin +</code> <code>thrombomodulin +</code> <code>p63 +</code> <code>CK5/6 (~½+)</code></td>
<td><strong>Breast CA</strong> <code>ER/PR +</code> <code>GCDFP +</code> <code>mammoglobin +</code> <code>CEA +</code> <code>Endometrioid adeno CA</code> <code>vimentin +</code> <code>ER/PR +</code> <code>CEA -</code></td>
<td><strong>Cholangio CA</strong> <code>CEA+</code> <code>CK19 +</code> <code>MOC31+</code> <code>CA19-9 +</code> <code>CDX2 +/-</code> <code>HepPar1-</code></td>
<td><strong>Thyroid CA</strong> <code>TTF-1 +ψ</code> <code>thyroglobulin +ψ</code> <code>CEA - (expect medullary CA)</code></td>
</tr>
<tr>
<td><strong>Pancreatic adeno CA</strong> (~2/3) <code>CEA +</code> <code>CA19-9 +</code> <code>MUC5-AC +</code> <code>MUC-2 -</code></td>
<td>**CDX2 +/-`</td>
<td><strong>DPC4-</strong></td>
<td><strong>Ovarian mucinous CA</strong> <code>MUC5-AC +</code> <code>MUC-2 -</code></td>
</tr>
<tr>
<td><strong>Ovarian serous CA</strong> <code>WT1 +</code> <code>ER/PR +</code> <code>mesothelin +</code> <code>CEA -</code></td>
<td><strong>Lung adeno CA</strong> <code>TTF-1 +</code> <code>NapsinA</code> <code>CK5/6 -</code> <code>p63 -</code></td>
<td>**Mesothelioma (~2/3)<code> </code>calretinin +<code> </code>WT1 +`</td>
<td><strong>Pancreatic adeno CA</strong> (subset) <code>CDX2 +/-</code> <code>DPC4-</code></td>
</tr>
<tr>
<td><strong>AdenoCA of bladder</strong> <code>thrombomodulin +</code> <code>CDX2 +/-</code></td>
<td><strong>Gastric adeno CA</strong> (subset) <code>CDX2 +/-</code></td>
<td><strong>Cholangio CA</strong> (minor subset) <code>CDX2 +/-</code></td>
<td><strong>ScC</strong> <code>p16 +</code></td>
</tr>
</tbody>
</table>

CA, carcinoma; adenoCA, adenocarcinoma; SmCC, small cell carcinoma; SCC, squamous cell carcinoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; ¶, seminoma is keratin negative, OCT3/4 positive; * NE markers, neuroendocrine markers, including synaptophysin, chromogranin, and CD56; ψ undifferentiated anaplastic thyroid carcinoma is often negative for thyroid transcription factor 1 (TTF-1); and ξ characteristic canalicular pattern.


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF CHEMOTHERAPY

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

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, eg, 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>


Neuroendocrine Tumors

For poorly differentiated (high grade or anaplastic) or small cell subtype other than lung neuroendocrine tumors, see NCCN Guidelines for Small Cell Lung Cancer

For well-differentiated neuroendocrine tumors, see NCCN Guidelines for Neuroendocrine Tumors-Carcinoid Tumors

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

#### ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel, Carboplatin</td>
<td>200 mg/m²/3 h IV Day 1, AUC = 6 IV Day 1, Repeat cycle every 3 weeks¹</td>
</tr>
<tr>
<td>Paclitaxel, Carboplatin, Etoposide</td>
<td>200 mg/m²/1 h IV Day 1, AUC = 6 IV Day 1, 50 mg/d PO alternating with 100 mg/d PO Days 1–10, Repeat cycle every 3 weeks²</td>
</tr>
<tr>
<td>Docetaxel, Carboplatin</td>
<td>65 mg/m² IV Day 1, AUC = 6 IV Day 1, Repeat cycle every 3 weeks³</td>
</tr>
<tr>
<td>Gemcitabine, Cisplatin</td>
<td>1250 mg/m² IV Day 1 and 8, 100 mg/m² IV Day 1, Repeat cycle every 3 weeks⁴</td>
</tr>
<tr>
<td>Docetaxel, Cisplatin</td>
<td>75 mg/m² IV Day 1 and 8, 75 mg/m² IV Day 8, Repeat cycle every 3 weeks⁵</td>
</tr>
<tr>
<td>Gemcitabine, Docetaxel</td>
<td>1000 mg/m² IV Day 1 and 8, 75 mg/m² IV Day 8, Repeat cycle every 3 weeks⁵</td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, Day 1, Leucovorin 400 mg/m² IV over 2 hours, Day 1, 5-FU 400 mg/m² IV bolus on Day 1, then 1200 mg/m²/d x 2 Days (total 2400 mg/m² over 46–48 hours) IV continuous infusion, Repeat cycle every 2 weeks⁶,⁷</td>
</tr>
<tr>
<td>CapeOX</td>
<td>Oxaliplatin 130 mg/m² IV over 2 hours, Day 1, Capecitabine 850–1000 mg/m² PO twice daily Days 1–14, Repeat cycle every 3 weeks⁶</td>
</tr>
</tbody>
</table>

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### Selected Chemotherapy Regimens for Occult Primaries

#### Squamous Cell

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel &amp; Carboplatin</td>
<td>200 mg/m²/3 h IV Day 1</td>
</tr>
<tr>
<td>Cisplatin &amp; Gemcitabine</td>
<td>100 mg/m² IV Day 1</td>
</tr>
<tr>
<td>mFOLFOX6</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, Day 1</td>
</tr>
<tr>
<td>Docetaxel &amp; Cisplatin &amp; 5-FU</td>
<td>75 mg/m² IV Day 1</td>
</tr>
<tr>
<td>Paclitaxel &amp; Cisplatin</td>
<td>175 mg/m² IV Day 1</td>
</tr>
<tr>
<td>Docetaxel &amp; Carboplatin</td>
<td>75 mg/m² IV Day 1</td>
</tr>
<tr>
<td>Docetaxel &amp; Cisplatin</td>
<td>60 mg/m² IV Day 1</td>
</tr>
<tr>
<td>Docetaxel &amp; Cisplatin</td>
<td>75 mg/m² IV Day 1</td>
</tr>
<tr>
<td>Cisplatin &amp; Fluorouracil</td>
<td>20 mg/m² IV Days 1–5</td>
</tr>
</tbody>
</table>

---

**Note:** All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES


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

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

---

### Table of Contents

- **Overview** ................................. MS-2
- **Literature Search Criteria and Guidelines Update Methodology** ........................ MS-2
- **Epidemiology** ............................... MS-3
- **Presentation and Prognosis** ........................ MS-3
- **Pathology** ................................. MS-4
  - Immunohistochemistry ........................ MS-5
  - Key Screening Markers for Undifferentiated Malignancy ........................ MS-5
  - Cytokeratins 7 and 20 ........................ MS-5
  - Additional Markers for Carcinomatous Tumors .................. MS-6
- **Molecular Profiling** ........................ MS-6
  - Assessing the Clinical Benefit of Molecular Profiling ........................ MS-7
- **Initial Evaluation** .......................... MS-8
- **Diagnostic Imaging** ........................ MS-8
- **Workup** ................................. MS-9
  - Workup for Possible Breast Primary ........................ MS-9
  - Workup for Possible Germ Cell Primary ........................ MS-10
  - Workup for Possible Ovarian Primary .................. MS-10
  - Workup for Possible Prostate Primary ................ MS-10
  - Additional Workup for Adenocarcinoma or Carcinoma Not Otherwise Specified ................................ MS-10
  - Workup for SCC .......................... MS-11
  - Workup for Neuroendocrine Tumors ........................ MS-11
- **Management** .......................... MS-11
  - Psychosocial Distress ........................ MS-11
  - Supportive Care .......................... MS-11
  - Treatment Based on Workup Findings ........................ MS-11
    - Adenocarcinoma .......................... MS-11
    - SCC ................................ MS-13
    - Neuroendocrine Tumors ........................ MS-13
  - Chemotherapy .......................... MS-13
    - Adenocarcinoma .......................... MS-14
    - SCC ................................ MS-16
    - Neuroendocrine Tumors ........................ MS-18
  - Radiation Therapy ........................ MS-18
  - Locoregional Therapeutic Options ........................ MS-19
  - Specialized Approaches ........................ MS-19
- **Follow-up** .......................... MS-19
- **References** ........................ MS-20

Version 1.2015, 09/15/14 © National Comprehensive Cancer Network, Inc. 2014. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.
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.\textsuperscript{1,2} These heterogeneous tumors 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. Early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors.\textsuperscript{3} Life expectancy is generally very short. Patients with lymph node-confined metastases have a median survival of approximately 6 to 9 months, while patients with extranodal disease have a median survival of about 2 to 4 months.\textsuperscript{4-9} Select patients with favorable subsets of CUPs have median overall survival (OS) times in the range of 12 to 36 months.\textsuperscript{5}

These guidelines provide recommendations for evaluation, workup, management, and follow-up of 2 pathologic diagnoses in patients with epithelial occult primary cancer:
- Adenocarcinoma, or carcinoma not otherwise specified (NOS)
- Squamous cell carcinoma (SCC)

Recommendations for neuroendocrine tumors of unknown primary origin can be found in the NCCN Guidelines for Neuroendocrine Tumors (available at www.NCCN.org).

The NCCN Guidelines for Occult Primary suggest diagnostic tests based on the location of disease and the patient’s gender. 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. For each of the pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on recommendations in the NCCN Clinical Practice Guidelines for the cancer site corresponding to the primary tumor (see list of NCCN Guidelines for Treatment of Cancer by Site, available at www.NCCN.org).

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. In most patients, occult primary tumors are refractory to systemic treatments, and chemotherapy is only palliative and does not significantly improve long-term survival. In patients with disseminated disease in particular, the treatment goals are directed toward symptom control and providing the best quality of life possible. However, certain clinical presentations of these tumors are associated with a better prognosis.\textsuperscript{10} 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 optimal response and survival rates.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Occult Primary (Cancer of Unknown Primary), an electronic search of the PubMed database was performed to obtain key literature in cancers of unknown primary published between 06/01/2013 and 06/24/2014, using the following search terms: occult primary, unknown primary, or cancer of unknown origin. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.
Occult primary tumors occur roughly equally in men and women, with an average age at diagnosis of 60 years. An estimated 31,430 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2014, accounting for approximately 2% of all cancers diagnosed in the United States. However, deaths from cancer of unspecified primary site are estimated to be 44,680 in 2014. 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 SEER database from 1973 to 2008 found that the percentage of cancers diagnosed as occult primary has been decreasing over time. Unfortunately, no improvement in median survival was seen over this time period.

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 (ie, 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 sites of the disease.

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.

Presentation and Prognosis

Multiple sites of involvement are observed in more than 50% of patients with occult primary tumors. Common sites of involvement are the liver, lungs, bones, and lymph nodes. Although certain patterns of metastases suggest possible primaries, occult primaries can metastasize to any site. Therefore, physicians should not rely on patterns of metastases to determine the primary site.

Patients with occult primary tumors may present with favorable or unfavorable prognostic signs and patterns of presentation. A series of population-based analyses have been performed based on patient data from the Swedish Cancer Registry. Hemminki et al conducted an initial population-based survival analysis of >18,000 patients with occult primary tumors to elucidate 12-month survival rates and median survival times for each combination of histology and location. The data revealed that patients with metastases limited to lymph nodes had better prognoses than those with extranodal disease (median survival of 8 months vs. 3 months). In 2013, this group examined data from 9306 patients with occult primary tumors and extranodal metastases, examining survival rates based on the location of metastases. The
study suggested that location of metastasis may predict site-specific cancer deaths and provide insight into the location of primary tumors.\(^7\)

Most patients have an unfavorable prognosis. Unfavorable features include male gender, poor performance status (PS), pathologic diagnosis of adenocarcinoma with metastases involving multiple organs (eg, liver, lung, bone), nonpapillary malignant ascites (adenocarcinoma), peritoneal metastases, multiple cerebral metastases (adenocarcinoma or SCC), and adenocarcinoma with multiple lung/pleural or bone lesions.\(^22,25\) For these patients, an empiric approach to therapy is recommended, although the likelihood of benefit is questionable.

Patients with a favorable prognosis include those with poorly differentiated carcinoma with midline distribution; women with papillary adenocarcinoma of the peritoneal cavity; women with adenocarcinoma involving only axillary lymph nodes; patients with SCC involving cervical lymph nodes (constituting 2%–5% of all cases of occult primary cancers\(^26\)); patients with isolated inguinal adenopathy (SCC); patients with poorly differentiated neuroendocrine (PDNE) carcinomas; men with blastic bone metastases and elevated prostate-specific antigen (PSA; adenocarcinoma); and patients with a single, small, and potentially resectable tumor.\(^22,27,28\) For patients with favorable prognostic features, tailored approaches to treatment, such as locoregional treatments or specific chemotherapy regimens (eg, 5-FU–based therapy for suspected colon primary or cisplatin-based chemotherapy for possible germ cell tumor), are likely to provide clinical benefit and may prolong survival. However, little data exist to support this idea. In addition, results from a recent retrospective review of 179 patients with occult primary tumors suggested that patients with better PS, higher serum albumin, and lower serum lactate dehydrogenase (LDH) were more likely to benefit from chemotherapy.\(^29\)

Using data from 20,523 patients represented in the Swedish Cancer Registry, Riihimäki et al compared survival trends for occult primary cancers across 3 time periods (1987–1993, 1994–2000, and 2001–2008) to reveal slight improvements in survival across time for patients with adenocarcinomatous histology. Improvements were primarily observed among patients with occult primary cancers located in the pelvis, peritoneum, and nervous system.\(^8\) The group also compared a subset of patients with occult primary tumors with a cohort presenting with metastatic disease of known primary. Overall, metastatic disease from a known primary was associated with a lower hazard of death versus patients with occult primary tumors (HR= 0.69 [95% CI = 0.66–0.72]).\(^9\)

**Pathology**

Occult primary tumors often have multiple chromosomal abnormalities and overexpression of several genes, including $EGFR$, $c\text{-}kit/PDGFR$, Ras, BCL2, HER2, and p53.\(^30-32\) BCL2 and p53 are overexpressed in 40% and 53% of occult primary tumors, respectively.\(^33\) The $BRD4\text{-}NUT$ 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.\(^1,34,35\)

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%), SCC (5%), and poorly differentiated malignant neoplasm (5%).\(^1,20\) Additionally, because of improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary have been recognized (1%).\(^36,37\)
In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC).\textsuperscript{38-41} In addition, gene expression profiling (GEP) assays have been developed to attempt to identify the tissue of origin in patients with occult primary cancers.\textsuperscript{42,43} It is noteworthy that thus far the literature on this approach, as with the literature on IHC application in the workup of CUP, has focused far more on establishing a tissue of origin than on establishing whether such identification leads to better outcomes in patients. Thus, while there is diagnostic benefit of GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend molecular profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with CUP (category 2B).

In a recent blinded, multicenter study by Handorf et al, the diagnostic accuracy of one GEP assay (discussed in more detail below) was compared to that of IHC staining in a set of metastases from known primaries.\textsuperscript{44} The results indicated that the accuracies were similar, with 89% accuracy for GEP and 83% accuracy for IHC ($P = .013$). A similarly designed study by Weiss and colleagues\textsuperscript{45} compared a different GEP assay with IHC and found similar results (79% accuracy for GEP vs. 69% for IHC; $P = .019$). The Handorf study\textsuperscript{44} also demonstrated that performing additional rounds of IHC testing after a first round generally failed to provide additional diagnostic information. The panel thus recommends that only one round of staining (8–10 stains) should be performed when IHC is used.

Overall, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately. Both of these techniques are discussed in more detail below.

**Immunohistochemistry**

In patients with occult primary tumors, immunohistochemical studies are useful for the characterization of poorly differentiated or undifferentiated tumors and for cell-type determination and pathologic diagnosis.\textsuperscript{38-41} However, because IHC markers for unknown primary cancers are not uniformly specific or sensitive and because immunohistochemical analysis has not been shown to improve patient outcomes, 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.

**Key Screening Markers for Undifferentiated Malignancy**

Carcinomas are usually positive for wide-spectrum cytokeratins and epithelial membrane antigen. S-100 is usually expressed in melanoma, clear cell sarcoma, glioma, and malignant peripheral nerve sheath tumors. HMB45 is also highly specific for melanoma.\textsuperscript{46} CD45, also known as leukocyte common antigen or LCA, 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, and genitourinary, gastrointestinal, and pulmonary carcinomas.

**Cytokeratins 7 and 20**

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{47-49} 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. The CK7/CK20 phenotype is also useful for differentiating between prostate (CK7-negative/CK20-negative) and urothelial (CK7-positive/CK20-positive or -negative) carcinomas.

**Additional Markers for Carcinomatous Tumors**

For carcinomatous tumors that stain positively for broad-spectrum cytokeratins, but negatively for S100, HMB45, and CD45, additional markers can be assessed to help identify the tissue of origin. Markers can be chosen based on CK7 and CK20 staining results (see *Immunohistochemistry Markers for Unknown Primary Cancers [OCC-A page 4 of 4] in these guidelines*). However, a large series of IHC markers should be avoided.

The use of TTF-1 staining distinguishes lung and thyroid 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. Uroplakin III is expressed in approximately 60% and 50% of primary and metastatic urothelial carcinomas, respectively. In a study involving 690 neoplasms, GCDFP-15 was able to identify breast carcinomas with a sensitivity of 74% and a specificity of 95%.

WT1 is a sensitive marker for epithelioid mesothelioma and 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.

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 SCCs, urothelial carcinomas (35%) and all mesotheliomas express CK5 and CK6. Carcinoembryonic antigen (CEA) can be useful for the differential diagnosis of gastrointestinal adenocarcinomas and endocervical cancer from cancers from other sites of origin.

**Molecular Profiling**

Over the past decade, studies have examined various molecular assays designed to identify the tissue of origin in occult primary tumors (recently reviewed by Varadhachary and Hainsworth and Greco). Talantov et al developed a GEP assay that is designed to detect tumors originating from the lung, breast, colon, ovary, pancreas, and prostate by evaluating the expression of 10 specific genes using real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR). In a blinded study, this assay identified the tissue of origin of metastatic carcinomas for which the primary was known 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. A presumed tissue of origin was identified in 61% of patients, and the results were believed to be compatible with clinicopathologic 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 of 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. A more recent validation study of 149 archival tumor specimens found similar rates (74%–77%) of diagnostic accuracy compared to identified primary tumors, IHC diagnoses, and clinical/histologic findings. This test is commercially available.

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

Another microarray GEP assay has been developed that assesses the expression of 495 genes to identify tissue of origin of occult primary tumors. This assay has also been validated, but is not currently commercially available in the United States. A recent feasibility study by GEFCAP found that use of this test changed clinical management in as many as 50% of cases. This group is planning a randomized phase III trial to assess changes in progression-free survival (PFS) between patients with CUP treated empirically and those treated based on results of GEP.

A third microarray GEP assay of 2000 genes has been validated to help determine tissue of origin of occult primary tumors. A multicenter study recently compared the diagnostic accuracy of this test with IHC for identification of the primary site of metastatic tumors. The GEP approach was found to be more accurate than IHC, particularly for poorly differentiated/undifferentiated carcinomas and specimens that required a second round of immunostaining. This test is commercially available.

MicroRNA (miRNA)-based assays have recently generated interest for their potential to identify the tissue of origin of CUPs. These assays examine the presence of 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%). This assay is commercially available. This research group recently developed a second-generation microarray assessing the levels of 64 miRNAs to identify 42 tumor types. The assay was validated on a set of 509 blinded samples and showed a sensitivity of 85%. A follow-up study tested the 64 miRNA assay in blinded samples from 84 patients with CUPs. The assay results on predicted tissue of origin were in 70% agreement with the initial clinical presentation, in 89% agreement with the clinical diagnosis based upon patient management and outcome, and in 92% agreement with the final clinical diagnosis based on supplemental immunohistochemical staining.

Assessing the Clinical Benefit of Molecular Profiling

As noted above, several GEP tests are now commercially available and are being evaluated in prospective clinical studies in an attempt to determine if the information they provide translates into clinically meaningful benefit for patients. In one study, 32 patients whose tumors were classified as being of colorectal origin by 2 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 expected for patients with stage IV colorectal cancer. Results from a prospective, non-randomized phase II study of 289 patients with CUP 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. While median survival time of 12.5 months in the subset of patients that received GEP-directed treatment was better than the pre-defined historical cohort, similar results might be expected from empiric use of these regimens in a good PS group of patients with unknown primary cancer predominantly below the diaphragm. Thus, the clinical benefit that might be derived from the use of these molecular assays, if any, remains to be determined.

Recent reviews have compared the commercially available GEP tests. As noted, outcomes data are not currently available to recommend routine use of molecular profiling in the workup of occult primary tumors (category 2B). Likewise, no such data exist to endorse the automatic or indiscriminate use of IHC. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities on a case-by-case basis, with the best possible individualized patient outcome in mind.

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 (ie, epithelial occult primary [not site-specific]; thyroid, lymphoma, or other hematologic 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 (ie, 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 scans of the chest, abdomen, and pelvis are 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.

Diagnostic Imaging

Imaging can play an integral role in the multidisciplinary diagnostic evaluation of patients with CUP sites. In the past several years, PET scans and combination PET/CT scans have become 2 of the most frequently used imaging modalities in the management of patients with occult primary cancers. PET scans have been shown to be useful for the diagnosis, staging, and restaging of many malignancies, and might be warranted in some situations. PET scans have 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 scans 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 if 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 18F-fluorodeoxyglucose tracer in some neoplastic tissues. In these cases, the combination of a PET scan with either a 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
One 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. A second meta-analysis examined PET as a diagnostic tool for 246 patients with cervical nodal metastases of unknown primary tumors. The cumulative data showed a tumor detection rate of 44% and a sensitivity and specificity rate of 97% and 68%, respectively. The accuracy of PET and PET/CT in patients with occult primary tumors must be confirmed in larger clinical studies with long-term follow-up.

Although one study suggested that PET or PET/CT scans detected 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 scans for routine screening. However, PET/CT scans may be warranted in some situations, especially when considering local or regional therapy.

Workup

Patients with a suspected occult primary tumor 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 (eg, 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 (see Immunohistochemistry, above), large panels of immunohistochemical markers should be avoided. If CT scans of the neck, chest, abdomen, and pelvis were not performed previously, they are varyingly indicated depending on the clinical presentation.

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 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 tumor 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 for these patients. Appropriate testing for immunohistochemical markers is also recommended. MRI and/or ultrasound of the breast should be considered for a patient with a non-diagnostic mammogram and histopathologic evidence of breast cancer. MRI should also be considered when mammography is 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 by 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 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 of age. Thus, these guidelines suggest β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) measurements. 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 germ cell cancer and non-small cell lung cancer should be considered.

**Workup for Possible Ovarian Primary**

An occult non-germ cell 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.

**Workup for Possible Prostate Primary**

All men older than 40 years of age with an adenocarcinoma or carcinoma NOS, except those with metastases limited to the 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.

**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. A bone scan (if a 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 cystoscopy for suspicious findings. 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. Endoscopic evaluation is recommended for
patients presenting with malignancy in the liver, but is not routinely recommended in patients presenting with malignant ascites (ie, 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 may be as low as 1%. The use of AFP as a marker for hepatocellular carcinoma as part of the additional workup in adenocarcinoma or carcinoma NOS in the liver is also recommended.

**Workup for SCC**

SCC can be present in the nodes of the head and neck region, and in the supraclavicular, axillary, and inguinal nodes. CT scans of the abdomen and pelvis; perineal and lower extremity examination; gynecologic oncology consult; and anal endoscopy are recommended for patients with SCC with inguinal node involvement. A bone scan (if a PET/CT scan 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 website 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**

**Psychosocial Distress**

For many patients, the apparent uncertainties surrounding the diagnosis of CUP may result in significant psychosocial distress and increased difficulty in accepting treatment options. In fact, a recent study found that psychiatric manifestations, including anxiety and depression, were more common in patients with occult primary tumors than in those with known primaries. Empathetic discussion about the natural history of these types of cancers and their prognoses, and the provision of support and counseling by the primary oncology team and specialized services, may help alleviate this distress. Please see the NCCN Guidelines for Distress Management (available at www.NCCN.org).

**Supportive Care**

In addition to psychosocial support, patients with active and incurable CUP often require symptom management and palliative care interventions. Given the natural history of this disease, end-of-life discussion should be initiated early in the clinical course. Hospice care should also be considered and utilized as appropriate. Please see the NCCN Guidelines for Palliative Care (available at www.NCCN.org).

**Treatment Based on Workup Findings**

Localized adenocarcinoma or carcinoma NOS is treated according to the most likely primary site.

**Adenocarcinoma**

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]). 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.\textsuperscript{101,102} 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 (Malignant Germ Cell Tumors pathway). For women with localized adenocarcinoma involving axillary nodes and those who are breast-marker positive and have pleural effusion, these guidelines recommend treatment according to the NCCN Guidelines for Breast Cancer. To view the most recent versions of these guidelines, visit the NCCN website 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 versions of these guidelines, visit the NCCN website 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 NOS with involvement of axillary nodes (category 2B). Surgery can be considered for resectable lung nodules, and chemotherapy can be considered with or without resection. Stereotactic body radiation therapy is also an option for patients with lung nodules. 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).\textsuperscript{103}

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 PS 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 PS 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 non-ovarian 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).
For patients with disseminated carcinoma of unknown primary, a clinical trial is preferred with the additional recommendations of symptom control, consideration of chemotherapy on an individual basis, and specialized approaches (see Specialized Approaches, below).

**SCC**
Patients with site-specific SCC with localized axillary or inguinal lymph node involvement 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 RT alone).\(^{103}\) 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 PS. 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.

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

**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-FU–based or cisplatin-based chemotherapeutic regimens.\(^{104-110}\) 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. However, 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 more recent years, various regimens have shown efficacy in the treatment of patients with occult primary tumors in phase II studies. However, a 2012 systematic review of chemotherapy trials in patients with occult primary tumors of unfavorable presentations concluded that no specific regimen can be recommended as standard of care.\(^{111}\) A systematic review and meta-analysis published in 2013 largely came to the same conclusions, with taxanes showing a possible slight advantage over platinum-based regimens.\(^{112}\) In general, chemotherapy shows limited efficacy and considerable toxicity in patients with occult primary tumors. Therefore, these guidelines recommend that chemotherapy for patients with disseminated disease be limited to
patients who are symptomatic with a PS of 1 to 2 or to patients who are asymptomatic 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.\(^{113,114}\)

Objective response rates reported in 2 studies from the early 1990s were 53% (van der Gaast et al\(^{114}\)) and 63% (Hainsworth et al\(^{113}\)) 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.\(^{113}\) In the other, patients with undifferentiated carcinomas had a better response rate than those with poorly differentiated adenocarcinomas (79% vs. 35%; \(P = .02\)).\(^{114}\)

In more 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.\(^{115-118}\) Schneider et al reported that the combination of carboplatin, gemcitabine, and capecitabine was active in occult primary tumors in patients with good PS.\(^{116}\) Median PFS 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.\(^{117}\) Similarly, gemcitabine plus oxaliplatin was assessed in patients with occult primary tumors in a phase II study.\(^{115}\) This well-tolerated combination gave a median overall survival (OS) of 12.8 months (95% CI, 8.5–18.5 months) and PFS of 3.1 months (95% CI, 1.7–6 months).

Recently, molecularly targeted agents have been tested for efficacy in treating patients with CUP. Hainsworth et al\(^{119,120}\) 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.\(^{119,120}\) In a phase II trial, the combination of bevacizumab and erlotinib induced partial responses in 10% of patients and stable disease in 61% of patients.\(^{119}\) 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 of paclitaxel and carboplatin with bevacizumab and erlotinib was active and well-tolerated as first-line therapy in patients with CUP.\(^{120}\) After a median follow-up of 19 months, the median PFS time and 2-year OS rates were 8 months (38% PFS at 1 year) and 27%, respectively.

The following regimens are included in the guidelines for treating adenocarcinoma of unknown primary, based on the results of phase II and/or III studies, as described. Regimens other than those listed below can also be considered.

**Paclitaxel and Carboplatin with or without Etoposide**

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.\(^{121-123}\) In the Hellenic Cooperative Oncology Group study, the combination of paclitaxel and carboplatin produced an overall response rate of 38.7% according to intention-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 one study, taxane-based chemotherapy (paclitaxel/carboplatin/etoposide; docetaxel/cisplatin; or docetaxel/carboplatin) 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. The median survival was 10 months.

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 OS, 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.

Carboplatin with Docetaxel
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 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 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 a PS of 0 to 2. Median time to progression was 5.5 months, whereas OS was 16.2 months. Survival was better in patients with favorable-risk disease (23 months vs. 5 months for those with visceral metastases). Predictors of superior outcome included good PS and low-volume disease.

Cisplatin and Docetaxel
Combination therapy with cisplatin and docetaxel was examined in a cohort of 29 patients with CUP. Approximately half of these patients (51.7%) had well- to moderately differentiated adenocarcinoma; patients with undifferentiated carcinoma (27.6%) and SCC histologies (13.8%) were also included. The objective response rate was 37.9%, and median PFS and OS were 6 and 16 months, respectively.

Cisplatin with Gemcitabine
The efficacy and toxicity of 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. The GEFCAPI 02 trial randomly assigned 52 patients to cisplatin with or without gemcitabine.\textsuperscript{132} Outcomes were similar between the arms, but trended better for the combination (1-year survival for the combination and cisplatin alone were 46% and 35%, respectively; \( P = .73 \)). Toxicity was significantly greater with the addition of gemcitabine.

\textbf{Oxaliplatin with Gemcitabine}  
A recent open-label, phase II study tested oxaliplatin and gemcitabine combination therapy in patients with occult primary tumors with a predominant histology of adenocarcinoma; the majority of the cohort presented with visceral metastases and had received no prior treatment.\textsuperscript{133} Median OS and PFS were 12.8 months and 3.1 months. The trial was terminated early due to a shift away from empiric therapy, but data from the initial 24 patients suggested good tolerability and efficacy on par with existing doublet regimens.

\textbf{Gemcitabine with Docetaxel}  
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.\textsuperscript{134} The overall response rate was 40%, with a median survival of 10 months.

\textbf{Capecitabine with Oxaliplatin and 5-FU/Leucovorin with Oxaliplatin}  
The combination of capecitabine and oxaliplatin (CapeOx) has been tested in phase II studies for first-line\textsuperscript{135} and second-line\textsuperscript{136} treatment of patients with carcinoma of unknown primary. This regimen gave response rates ranging from 12% to 19%, with disease-free survival of 2.3 to 3.7 months and OS of 3.9 to 9.7 months. This regimen appears to be active and well-tolerated and is an acceptable option for this patient population.

Although 5-FU/leucovorin/oxaliplatin (FOLFOX) has not been tested in patients with unknown primary tumors, FOLFOX has been shown to be equivalent to CapeOx in colorectal cancer.\textsuperscript{137-140} The panel therefore supports FOLFOX (mFOLFOX\textsuperscript{6}\textsuperscript{141,142}) as an acceptable treatment option for these patients.

\textbf{SCC}  
Platinum-based regimens have been used to treat disseminated SCC. Historically, the combination of cisplatin and 5-FU was the most frequently used regimen for patients with SCC of unknown primary.\textsuperscript{143,144} Overall, only a few small studies have assessed chemotherapy regimens in patients with SCC occult primaries, and the panel lists possible regimens based on evidence from studies of patients with SCC of known primary and small studies of patients with occult primary tumors. Regimens other than those listed can also be considered.

\textbf{Carboplatin with Paclitaxel}  
The combination of carboplatin and paclitaxel is used in non-small cell lung, gastric, and esophageal cancers.\textsuperscript{145-150} In the Hellenic Cooperative Oncology Group phase II study of patients with CUP (discussed above for adenocarcinoma), 3 patients had tumors of squamous cell histology.\textsuperscript{121} One of these patients had an objective response of 3 months duration after carboplatin/paclitaxel.

\textbf{Carboplatin with Docetaxel}  
The combination of carboplatin and docetaxel is used in head and neck and non-small cell lung cancers.\textsuperscript{151,152} The combination of carboplatin and docetaxel was assessed in a phase II trial of 47 patients with occult primary adenocarcinomas or poorly...
differentiated carcinomas, with a response rate of 32% and median OS of 16.2 months.  

Cisplatin with Paclitaxel
The combination of cisplatin and paclitaxel is used in head and neck cancer, non-small cell lung cancer, and esophageal cancer. In a randomized phase III trial of patients with advanced head and neck cancer, no significant differences were seen in patients treated with cisplatin/paclitaxel compared with patients treated with cisplatin/5-FU. This regimen has also been assessed in a phase II study of patients with unfavorable presentations of occult primary tumors. Three of the 31 patients had SCC. The regimen gave an overall response rate of 42%, and the median OS was 11 months (95% CI, 8.3–13.5).

Cisplatin with Docetaxel
The combination of cisplatin and docetaxel is used in non-small cell lung, esophageal, and gastric cancers. In a multi-center phase II trial of 34 evaluable patients with metastatic squamous cell esophageal cancer, cisplatin/docetaxel gave an objective tumor response rate of 33% in the ITT population. The median PFS and OS times were 5.0 months and 8.3 months, respectively.

The safety and efficacy of this regimen has also been assessed in 45 patients with occult primary tumors. The reported overall response rate was 65.1%, and the median OS was 11.8 months. Two patients had tumors of SCC histology, and both had a partial response to the cisplatin/docetaxel regimen.

Combination therapy with cisplatin and docetaxel was also examined in a cohort of 29 patients with occult primary tumors, 4 of whom had tumors with squamous cell histology. The objective response rate was 37.9%, and median PFS and OS were 6 months and 16 months, respectively.

Cisplatin with 5-FU
This historic regimen has been tested in patients with SCC of unknown primary. It is also used in the treatment of metastatic anal, head and neck, esophageal, and gastric cancers. More recently, Kusaba et al reviewed their experiences of treating patients with occult primary tumors with this regimen. They reported a response rate of 54.5% and a median OS of 10 months.

Cisplatin with Docetaxel and 5-FU
The combination of cisplatin, docetaxel, and 5-FU is used in head and neck cancer, gastric cancer, and esophageal cancer. In a randomized phase III trial of 501 patients with advanced SCC of the head and neck, patients received cisplatin and 5-FU with or without docetaxel followed by chemoradiation. The overall response rates after induction chemotherapy were 72% and 64% in the 3-drug and 2-drug arms, respectively.

Cisplatin with Gemcitabine
The combination of cisplatin and gemcitabine is used in non-small cell lung cancer. The GEFCAPI 02 trial compared cisplatin to cisplatin plus gemcitabine in 52 patients with occult primary tumors. Although the trial was terminated early due to poor accrual, there was a trend towards better OS with the addition of gemcitabine (11 months vs. 8 months, with overlapping confidence intervals [CIs]).
mFOLFOX6
The panel lists mFOLFOX6 as a possible regimen for occult primary SCC, based on the evidence discussed above for adenocarcinoma.\textsuperscript{141,142} FOLFOX is used in SCC of the esophagus and stomach.\textsuperscript{175,176}

Neuroendocrine Tumors
Neuroendocrine carcinomas of unknown primary site are uncommon, and their clinical behavior is dependent on the tumor grade and differentiation.\textsuperscript{177} 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{36}

Hainsworth et al evaluated the efficacy of a combination regimen containing paclitaxel, carboplatin, and etoposide in metastatic PDNE carcinomas in patients who had received no prior treatment.\textsuperscript{178} 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.

PDNE tumors can also be treated following small cell lung cancer regimens. In a randomized phase III trial (JCOG 9702), the combination of carboplatin plus etoposide was equally as efficient as cisplatin plus etoposide in elderly patients or those with poor-risk disease with extensive small cell lung cancer who were not previously treated.\textsuperscript{179} No significant differences were seen in response rate (73% for both regimens) and median OS (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{180} 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{181,182}

The panel recommends that poorly differentiated (high-grade or anaplastic) or small cell subtypes other than lung neuroendocrine tumors be treated following the NCCN Guidelines for Small Cell Lung Cancer. Well-differentiated neuroendocrine tumors should be treated as carcinoid tumors in the NCCN Guidelines for Neuroendocrine Tumors.

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.

One study examined individualized intensity-modulated radiation therapy (IMRT) with risk-adapted planning treatment volumes in 28 patients with cervical nodal metastases of unknown primary tumors.\textsuperscript{183} The majority of patients (71%) received concomitant systemic therapy. In this cohort, 3-year OS, mucosal control, neck control, and distant
metastasis-free survival rates were 76%, 100%, 93%, and 88%, respectively. Additional controlled studies are needed to further assess the efficacy of individualized IMRT-based treatment approaches.

A recent retrospective study assessed radiation therapy in 68 patients with metastatic SCC of the head and neck of unknown primary tumor site. These patients underwent oropharynx-targeted RT to spare the mucosal surfaces of the nasopharynx, hypopharynx, and larynx; 40% of patients received IMRT and 56% of patients received concurrent chemoradiation, resulting in an actuarial locoregional control rate of 95.5% and a median time to locoregional recurrence of 18 months.

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, IMRT, image-guided radiation therapy, or proton therapy.

Follow-up
For patients with either active disease or localized disease in remission, follow-up frequency should be determined by clinical need. Follow-up consists of a history and physical, with diagnostic tests for patients who are symptomatic.

For patients with active and incurable disease, psychosocial support, symptom management, end-of-life discussions, palliative care interventions, and hospice care should all be considered and used as appropriate (see Psychosocial Distress and Supportive Care, above). Please also see the NCCN Guidelines for Distress Management and the NCCN Guidelines for Palliative Care (available at www.NCCN.org).
References


Occult Primary


