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§ Radiotherapy/Radiation Oncology
♦ Internal Medicine
≠ Pathology
¶ Surgery/Surgical Oncology
‡ Hematology/Hematology oncology
* Writing committee member
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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of the Guidelines Updates

The changes in the 2.2007 version of the Occult Primary guidelines from the 1.2007 version is the addition of the updated manuscript representing the changes to the algorithm.

Summary of changes in the 1.2007 version of the Occult Primary Guidelines from the 1.2005 version include:

- Under initial evaluation, PET scan was changed from a category 3 to a category 2B recommendation (OCC-1).
- Footnote c, ‘See Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A)’ is new to the page (OCC-1).
- Under workup, women: The recommendation was modified for breast MRI and ultrasound and are indicated if the mammogram is negative and there is histopathologic evidence for breast cancer. (OCC-3, OCC-4).
- Under additional workup, men: <50 y was removed from consider testicular ultrasound (OCC-4).
- Under additional workup, men, < 65 y: Beta-hCG, alpha-fetoprotein: Testicular ultrasound is recommended if markers are elevated (OCC-5).
- Footnote d, ‘See Principles of Chemotherapy (OCC-B)’ is new to the algorithm.
- Under management based on workup findings for disseminated metastases: ‘Chemotherapy in symptomatic patients’ was changed to ‘Consider chemotherapy on individual basis’ (OCC-7, OCC-12, OCC-19).
- Under management based on workup findings for unilateral inguinal node: The management was changed to ‘Lymph node dissection, consider RT if ≥ 2 lymph nodes positive or extra-capsular extension, ± subsequent chemotherapy’ (OCC-10, OCC-15).
- The ‘Immunohistochemistry markers for unknown primary cancers’ page is new to the algorithm (OCC-A).
- The ‘Principles of chemotherapy’ page is new to the algorithm (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.
INITIAL EVALUATION

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

PATHOLOGIC DIAGNOSIS

- Epithelial; not site specific
  - See Clinical Presentation Epithelial (OCC-2)
- Lymphoma and other hematologic malignancies
  - See NCCN Guidelines Table of Contents
- Thyroid
  - See NCCN Thyroid Guidelines
- Melanoma
  - See NCCN Melanoma Guidelines
- Sarcoma
  - See NCCN Sarcoma Guidelines
- Germ-cell
  - See NCCN Testicular Cancer Guidelines
- Nonmalignant diagnosis
  - Further evaluation and Appropriate follow-up

Suspected metastatic malignancy

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Occult Primary

### Clinical Presentation

#### Adenocarcinoma or Carcinoma not otherwise specified

- **Cervical nodes**
  - **Supraclavicular nodes**
    - **Axillary nodes**

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### Additional Workup

**Men and women:**
- Neck/chest/abdominal/pelvic CT
- Consider symptom directed endoscopy

**Men:**
- > 40 y: PSA
  - Consider testicular ultrasound if age < 50 y

**Women:**
- Mammogram
  - Attention to ER/PR histochemistry; HER-2/neu

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**Men and women:**
- Chest and abdominal CT

**Women:**
- Mammogram; if negative and histopathologic evidence for breast cancer, breast MRI and ultrasound indicated
  - Attention to appropriate histochemistries (eg ER/PR, HER-2/neu)

**Men:**
- > 40 y: PSA

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CLINICAL PRESENTATION

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

ADDITIONAL WORKUP

Men and women:
- Chest/abdominal/pelvic CT
- Beta-hCG, alpha-fetoprotein

Women:
- Mammogram; if negative and histopathologic evidence for breast cancer, breast MRI and ultrasound indicated
- ER/PR histochemistry

Men:
- > 40 y: PSA
- Consider testicular ultrasound

Men and women:
- Chest/abdominal/pelvic CT

Women:
- CA-125, mammogram, ER/PR histochemistry, consider gyn/onc consult if clinically indicated
- Breast ultrasound; MRI if negative

Men:
- > 40 y: PSA

Men and women:
- Abdominal/pelvic CT
- Chest CT (category 2B)
- Urine cytology; cystoscopy if suspicious

Women:
- CA 125, mammogram, ER/PR histochemistry, gyn/onc consult

Men:
- > 40 y: PSA

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See Management Based on Workup Findings (OCC-7)
Occult Primary

**CLINICAL PRESENTATION**

- Retroperitoneal mass
- Adenocarcinoma or Carcinoma not otherwise specified
  - Inguinal nodes
  - Liver

**ADDITIONAL WORKUP**

**Men and Women:**
- Abdominal and pelvic CT
- Chest CT (category 2B)
- Urine cytology; consider cytoscopy if suspicious
- Symptom directed endoscopy

**Women:**
- CA-125, mammogram, ER/PR histochemistry, gyn/onc consult if clinically indicated
- > 40 y: PSA
- < 65 y: Beta-hCG, alpha-fetoprotein, testicular ultrasound if markers elevated

**Men:**
- PSA
- Alpha-fetoprotein, testicular ultrasound if markers elevated

**Men and women:**
- Abdominal and pelvic CT
- CA-125
- Gyn/onc consult

**Men:**
- > 40 y: PSA

**Men and women:**
- Abdominal and pelvic CT
- Chest CT (category 2B)
- Symptom directed endoscopy (category 2B)
- Colonoscopy
- Alpha-fetoprotein (category 2B)

**Women:**
- Mammogram
- ER/PR histochemistry

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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**

- **Bone**
  - Adenocarcinoma or Carcinoma not otherwise specified
  - Brain
  - Multiple, including skin

**ADDITIONAL WORKUP**

- **Men and women:**
  - Bone scan
  - Radiographic studies for painful lesions and/or bone-scan–positive lesions and/or weight-bearing areas
  - Women:
    - Mammogram
    - ER/PR histochemistry
  - Men:
    - PSA if not already done

- **Men and women:**
  - See [NCCN CNS Cancers Guidelines](#) for Primary Treatment of CNS Metastatic Lesions
  - Chest and abdominal CT
  - Women:
    - Mammogram
    - ER/PR histochemistry

- **Women:**
  - Mammogram
  - ER/PR histochemistry

- **Men:**
  - PSA, if not already done

---

**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.
Primary found

Disseminated metastases\(^a\)

Localized adenocarcinoma or carcinoma not otherwise specified\(^a\)

\(^a\)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 Distress Management Guidelines.

\(^d\)See Principles of Chemotherapy (OCC-B).

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CLINICAL PRESENTATION

Localized adeno-carcinoma or carcinoma not otherwise specified

- Head and neck
  - Unilateral
  - Bilateral
- Supraclavicular
  - Unilateral
  - Bilateral
- Axillary
  - Women:
  - Treat per NCCN Breast Cancer Guidelines
  - Men:
  - Axillary node dissection, consider RT to axilla for gross extracapsular extension ± subsequent chemotherapy (category 2B)
- Mediastinum
  - < 40 y
  - 40 - < 50 y
  - ≥ 50 y
    - Treat as poor-risk germ cell tumor per NCCN Testicular Cancer Guidelines (See TEST-B)
  - ≤ 40 y
    - Treat as poor-risk germ cell tumor per NCCN Testicular Cancer Guidelines (category 3)
  - > 40 y
    - Treat as poor-risk germ cell tumor per NCCN Testicular Cancer Guidelines (category 3)

MANAGEMENT BASED ON WORKUP FINDINGS

- Treat per NCCN Head and Neck Cancer Guidelines
- RT ± subsequent chemotherapy (category 2B for chemotherapy)
- Treat per NCCN Non-Small Cell Lung Cancer Guidelines

Note: All recommendations are category 2A unless otherwise indicated.

See Follow-up (OCC-20)

See NCCN Distress Management Guidelines.

See Principles of Chemotherapy (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 by the primary oncology team and specialized services may help to alleviate this distress. See NCCN Distress Management Guidelines.

**See Principles of Chemotherapy (OCC-B).**

**See Follow-up (OCC-20)**
CLINICAL PRESENTATION

Localized adeno-carcinoma or carcinoma not otherwise specified

- Inguinal node
  - Unilateral
  - Bilateral
  - Unresectable
  - Resectable

- Liver
- Bone
- Brain

MANAGEMENT BASED ON WORKUP FINDINGS

- Lymph node dissection, consider RT if ≥2 lymph nodes positive or extracapsular extension, ± subsequent chemotherapy

- Bilateral lymph node dissection, consider RT if ≥2 lymph nodes positive or extracapsular extension ± subsequent chemotherapy (category 2B for omitting chemotherapy)

- Treat as disseminated disease and/or consider locoregional therapeutic options (See NCCN Hepatobiliary Cancers Guidelines)

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

- Surgical resection ± chemotherapy (category 2B for omitting chemotherapy)

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

See NCCN CNS Cancers Guidelines for management of CNS Metastatic Lesions

Note: All recommendations are category 2A unless otherwise indicated.

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See Follow-up (OCC-20)

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 Distress Management Guidelines.

Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin. See Principles of Chemotherapy (OCC-B).
**Occult Primary**

**CLINICAL PRESENTATION**

- Squamous cell carcinoma
  - Head and neck nodes
  - Supraclavicular nodes
  - Axillary nodes
  - Inguinal nodes
  - Bone

**ADDITIONAL WORKUP**

- Head and neck workup
  - See NCCN Head and Neck Guidelines
- Supraclavicular nodes
  - Chest CT
  - Abdominal and pelvic CT
  - Careful perineal and lower extremity exam including:
    - Penis
    - Scrotum
    - Gynecologic areas
    - Anus
  - Ob/gyn consult
  - Urine cytology; cystoscopy if suspicious
  - Bone scan
    - Radiographic studies for painful lesions and/or bone scan–positive lesions and/or weight-bearing areas

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**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.
Occult Primary

SQUAMOUS CELL CARCINOMA MANAGEMENT
BASED ON WORKUP FINDINGS

Primary found

Disseminated metastases\(^a\)

Site specific squamous cell carcinoma\(^a\)

- Head and Neck
- Supraclavicular
- Axillary

- Mediastinum
- Multiple lung nodules
- Pleural effusion

- Inguinal
- Bone
- Brain

Treat per NCCN disease-specific guidelines
NCCN Guidelines Table of Contents

- Symptom control
- Clinical trial preferred
- Consider chemotherapy on an individual basis\(^d\)

SeeManagement of Site Specific Disease (OCC-13)

See Management of Site Specific Thoracic Disease (OCC-14)

See Management of Site Specific Disease (OCC-15)

\(^a\)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 Distress Management Guidelines.

\(^d\)See Principles of Chemotherapy (OCC-B).

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CLINICAL PRESENTATION

- Head and neck
  - Supraclavicular
    - Unilateral
    - Bilateral
  - Axillary
    - Localized

MANAGEMENT BASED ON WORKUP FINDINGS

- Treat per NCCN Head and Neck Cancer Guidelines
- RT
  - Consider either concurrent or subsequent chemotherapy (PS 0-2)\(^d,e\) (category 2B)
  - Clinical trial preferred
- Axillary node dissection, consider RT if ≥ 2 lymph nodes positive or extra-capsular extension, ± subsequent chemotherapy\(^d,f\)

\(^a\)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 Distress Management Guidelines.

\(^d\)See Principles of Chemotherapy (OCC-B).

\(^e\)ECOG Performance Status
- PS 0: Asymptomatic
- PS 1: Symptomatic, fully ambulatory
- PS 2: Symptomatic, in bed < 50% of day

\(^f\)Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin.

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.
Occult Primary

CLINICAL PRESENTATION

MANAGEMENT BASED ON WORKUP FINDINGS

Mediastinum

Treat per NCCN Non-Small Cell Lung Cancer Guidelines

- Symptom control
- Clinical trial preferred
- Chemotherapy (PS 0-2)

Site specific squamous cell carcinoma

Multiple lung nodules

- Symptom control
- Clinical trial preferred
- Chemotherapy (PS 0-2)

Pleural effusion

- Symptom control
- Clinical trial preferred
- Chemotherapy (PS 0-2)

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 Distress Management Guidelines.

See Principles of Chemotherapy (OCC-B).

ECOG Performance Status
PS 0: Asymptomatic
PS 1: Symptomatic, fully ambulatory
PS 2: Symptomatic, in bed < 50% of day

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin. See Principles of Chemotherapy (OCC-B).

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See Follow-up (OCC-20)

See Disseminated Metastases (OCC-12)

See NCCN CNS Cancers Guidelines for management of CNS Metastatic Lesions
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 Distress Management Guidelines.

Consider 24-hour urine and 5-HIAA in well-differentiated neuroendocrine tumors (category 2B). See NCCN Neuroendocrine Tumor Guidelines.
CLINICAL PRESENTATION

Head and neck

Neuroendocrine tumor

Supraclavicular

Unilateral

Small cell subtype or Anaplastic

Other

Small cell subtype or Anaplastic

Bilateral

Other

Axillary

MANAGEMENT BASED ON WORKUP FINDINGS

RT + chemotherapy\(^d\)

Surgery and/or RT

Chemotherapy

- Symptom control
- Clinical trial preferred
- Chemotherapy (PS 0-2)\(^d,e\)
- Consider octreotide (if hormonally active and octreotide scan positive)

Treat same as supraclavicular except surgery is an option for unilateral anaplastic tumor

\(^a\) 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 Distress Management Guidelines.

\(^d\) See Principles of Chemotherapy (OCC-B).

\(^e\) ECOG Performance Status

PS 0: Asymptomatic
PS 1: Symptomatic, fully ambulatory
PS 2: Symptomatic, in bed < 50% of day

\(^g\) Consider 24-hour urine and 5-HIAA in well-differentiated neuroendocrine tumors (category 2B). See NCCN Neuroendocrine Tumor Guidelines.

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CLINICAL PRESENTATION

Neuroendocrine tumor

- Mediastinal
- Lung nodules
  - Small cell subtype
  - Anaplastic
  - Other
- Liver
  - Well-differentiated
  - Anaplastic or fast-growing

MANAGEMENT BASED ON WORKUP FINDINGS

RT + sequential or concurrent chemotherapy (PS 0-2)\(^d,e\)

See NCCN Small Cell Lung Cancer Guidelines for Lung Neuroendocrine Tumors

Surgical resection

- Resectable
- Unresectable
  - Manage endocrinopathy, consider regional therapy; See NCCN Neuroendocrine Tumors Guidelines
  - Chemotherapy\(^d\) or Regional therapy (category 2B)

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CLINICAL PRESENTATION

- Small cell subtype or Anaplastic
  - Bone
    - Octreotide (if octreotide scan positive); RT ± chemotherapy for symptomatic patients
  - Other
    - Chemotherapy
    - Octreotide (if octreotide scan positive)
    - Symptom control
    - Clinical trial preferred
    - Consider chemotherapy on an individual basis

- Other
  - Treat per NCCN CNS Cancers Guidelines for CNS metastatic Lesions

Neuroendocrine tumor\(^a,g\)

- Bone
- Other

Disseminated

- Small cell subtype or Anaplastic
- Other

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 Distress Management Guidelines.

\(^d\)See Principles of Chemotherapy (OCC-B).

\(^g\)Consider 24-hour urine and 5-HIAA in well-differentiated neuroendocrine tumors (category 2B). See NCCN Neuroendocrine Tumor Guidelines.

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

- H&P every 2-3 mo for first 18 mo, then every 3-4 mo for next 18 mo
- Diagnostic tests based on symptomatology
- Psychosocial support
<table>
<thead>
<tr>
<th>CK 7+ 20+</th>
<th>CK 7- 20+</th>
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<tbody>
<tr>
<td>Ovary mucinous 90%</td>
<td>Colorectal adenocarcinoma 80%</td>
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<td>Transitional cell 65%</td>
<td>Merkel cell 70%</td>
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<tr>
<td>Pancreas adenocarcinoma 65%</td>
<td>Gastric adenocarcinoma 35%</td>
</tr>
<tr>
<td>Cholangiocarcinoma 65%</td>
<td>Excluded tumors ≤ 5%</td>
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<td>Gastric adenocarcinoma 40%</td>
<td>Breast; Carcinoid; Cholangiocarcinoma</td>
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<tr>
<td>Excluded tumors ≤ 5%</td>
<td>Esophagus; Germ cell; Lung all types; Hepatocellular; Ovary; Pancreas adenocarcinoma; Renal adenocarcinoma; Transitional cell; Uterus</td>
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<td>CK 7- 20-</td>
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<td>Ovary non mucinous 100%</td>
<td>Adrenal 100%</td>
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<td>Cholangiocarcinoma 30%</td>
<td>Head/neck squamous 70%</td>
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<td>Excluded tumors ≤ 5%</td>
<td>Mesothelioma 35%</td>
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<td>Excluded tumors ≤ 5%</td>
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<td></td>
<td>Breast; Cholangiocarcinoma; Lung adenocarcinoma; Ovary; Pancreas adenocarcinoma</td>
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### PRINCIPLES OF CHEMOTHERAPY

- Consider chemotherapy in symptomatic patients PS 0-2 or asymptomatic patients with an aggressive cancer
- Base the chemotherapy regimen to be used on the histologic type of cancer

### SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

#### Adenocarcinoma

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dosage</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>Paclitaxel¹</td>
<td>200 mg/m²</td>
<td>3 h IV d 1</td>
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<tr>
<td>Carboplatin¹</td>
<td>AUC = 6</td>
<td>1, repeat cycle every 3 wks</td>
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<th>Chemotherapy</th>
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<td>Carboplatin²</td>
<td>AUC = 6</td>
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<tr>
<td>Etoposide²</td>
<td>50 mg/d PO alternating with 100 mg/d PO d 1-10, repeat cycle every 3 wks</td>
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<thead>
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<td>Docetaxel³</td>
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<td>Carboplatin³</td>
<td>AUC = 6</td>
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<td>1250 mg/m²</td>
<td>IV d 1 and 8</td>
</tr>
<tr>
<td>Cisplatin⁴</td>
<td>100 mg/m²</td>
<td>IV d 1, repeat cycle every 3 wks</td>
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<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dosage</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine⁵</td>
<td>1000 mg/m²</td>
<td>IV d 1 and 8</td>
</tr>
<tr>
<td>Docetaxel⁵</td>
<td>75 mg/m²</td>
<td>IV d 8, repeat cycle every 3 wks</td>
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#### Squamous Cell Carcinoma

<table>
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<tbody>
<tr>
<td>Paclitaxel⁶</td>
<td>175 mg/m²</td>
<td>3 h IV d 1</td>
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<td>Cisplatin⁶</td>
<td>100 mg/m²</td>
<td>IV d 2</td>
</tr>
<tr>
<td>5-FU⁶</td>
<td>500 mg/m²/d continuous infusion over 120 h, repeat cycle every 3 wks</td>
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<td>Docetaxel⁷</td>
<td>75 mg/m²</td>
<td>IV d 1</td>
</tr>
<tr>
<td>Cisplatin⁷</td>
<td>75 mg/m²</td>
<td>IV d 1</td>
</tr>
<tr>
<td>5-FU⁷</td>
<td>750 mg/m²/d continuous infusion d 1-5, repeat cycle every 3 wks</td>
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#### Neuroendocrine Tumors

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<th>Schedule</th>
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</thead>
<tbody>
<tr>
<td>Paclitaxel⁸</td>
<td>200 mg/m²</td>
<td>1 h IV d 1</td>
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<tr>
<td>Carboplatin⁸</td>
<td>AUC = 6</td>
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</tr>
<tr>
<td>Etoposide⁸</td>
<td>50 mg/d PO alternating with 100 mg/d PO d 1-10, repeat cycle every 3 wks</td>
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<tbody>
<tr>
<td>Cisplatin⁹</td>
<td>45 mg/m²</td>
<td>IV d 2 and 3</td>
</tr>
<tr>
<td>Etoposide⁹</td>
<td>100 mg/m²</td>
<td>IV d 1 and 3</td>
</tr>
<tr>
<td></td>
<td>repeat cycle every 4 wks</td>
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<td>Cisplatin¹⁰,¹¹</td>
<td>60-80 mg/m²</td>
<td>IV d 1</td>
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<tr>
<td>Etoposide¹⁰,¹¹</td>
<td>100-120 mg/m²</td>
<td>IV d 1 and 3, repeat cycle every 3-4 wks</td>
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</table>

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<thead>
<tr>
<th>Chemotherapy</th>
<th>Dosage</th>
<th>Schedule</th>
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</thead>
<tbody>
<tr>
<td>Carboplatin¹²</td>
<td>AUC = 5</td>
<td></td>
</tr>
<tr>
<td>Etoposide¹²</td>
<td>100 mg/m²</td>
<td>IV d 1, 2 and 3, repeat cycle every 4 wks</td>
</tr>
</tbody>
</table>

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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 references on page 2 of 2 OCC-B
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.
Overview

Occult primary tumors or cancers of unknown primary (CUP) are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation. These tumors account for 5-10% of all diagnosed cancers.\(^1\)\(^2\) They are manifested by a wide variety of clinical presentations and have a poor prognosis in most patients. Even after postmortem examination, the primary tumor is not identified in 20-50% patients.\(^3\)\(^4\)\(^5\) An estimated 32,100 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2007.\(^6\)

Occult primary tumors often have chromosomal abnormalities in the short arm of chromosome 1 and chromosome 12.\(^7\)\(^8\) Bcl-2 and p53 genes are over expressed in 40% and 53% of unknown primary tumors respectively.\(^9\) Clinical absence of primary tumor, early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors. Life expectancy is very short with a median survival of about 6-9 months.\(^10\) Multiple sites of involvement are observed in more than 50% of patients with occult primary tumors. While it is true that certain patterns of metastases suggest possible primaries, occult primaries can metastasize to any site. Therefore, one should not rely on patterns of metastases to determine the primary site. The common sites of involvement are the liver, lungs, bones, and lymph nodes.\(^11\) Patients with cancer of unknown primary site demonstrate common characteristics and present with general complaints such as anorexia, weigh loss, etc.

In a majority of patients, occult primary tumors are refractory to systemic treatments and chemotherapy is only palliative and does not significantly improve long term survival. However, certain clinical presentations of these tumors are associated with better prognosis.\(^12\) Special pathologic studies can identify these subsets of patients with tumor types that are more responsive to chemotherapy. Treatment options should be individualized for this selected group of patients to achieve improved response and survival rates.

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

Epidemiology

Occult primary tumors occur equally in men and women, usually in the sixth decade of life. A primary tumor site is found in fewer than 30% of patients who present initially with an occult primary tumor. At
presentation, half of patients with an occult primary tumor have multiple sites of involvement such as lymph nodes, lung, bone, liver, pleura, and the brain. Patients with occult primary tumors may present with favorable or unfavorable sets of prognostic signs. Favorable prognostic factors include poorly differentiated carcinoma with midline distribution, women with papillary adenocarcinoma of peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, squamous cell carcinoma involving cervical lymph nodes, isolated inguinal adenopathy (squamous carcinoma), etc. Unfavorable features include male gender, pathologic diagnosis of adenocarcinoma with multiple metastases involving liver, lung/pleural or bone metastases, non-papillary malignant ascites (adenocarcinoma), multiple cerebral metastases (adenocarcinoma or squamous cell carcinoma).

Introduction to the Guidelines

The 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 [i.e. epithelial occult primary (not site specific), thyroid, lymphoma and other hematological malignancies, melanoma, sarcoma, or germ-cell tumor]. The NCCN Occult Primary Guidelines focus on three pathologic diagnoses in those patients with epithelial occult primary cancer:

- Adenocarcinoma, or carcinoma not otherwise specified
- Squamous cell carcinoma
- Neuroendocrine tumors

Patients with other specific diagnosis will be treated according to the appropriate NCCN guidelines for treatment of cancer. NCCN Testicular Cancer Guidelines and NCCN Ovarian Cancer Guidelines discuss the treatment for germ cell tumors.

The next step in the guidelines is to determine the primary tumor site, and whether the disease is localized or disseminated. The guidelines suggest diagnostic tests based on the location of disease and the patient's gender, where appropriate. For example, for squamous cell carcinoma 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, 13 different clinical presentations are addressed, with suggested diagnostic tests for each location.

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma, site-specific squamous cell carcinoma, and neuroendocrine tumors. The panel endorses enrollment of patients in appropriate clinical trials when possible. For each of the three pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on the NCCN Cancer treatment guidelines corresponding to the primary.

Pathologic Evaluation

Patients with a suspected occult primary will typically present to the oncologist after undergoing an initial biopsy, frequently by fine needle aspiration. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether additional biopsy material is necessary (e.g. core needle, incisional or excisional biopsy). Light microscopic examination of the biopsy material is usually done first. Based on the initial assessment, several histologic subtypes can be distinguished. The most frequently occurring subtype is well or moderately differentiated adenocarcinoma (60%) followed by poorly differentiated adenocarcinoma or undifferentiated carcinoma (30%), squamous cell carcinoma (5%), and poorly differentiated malignant neoplasm (5%). Additionally, due to improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary site have been
recognized.\textsuperscript{19,20} Other techniques besides light microscopic examination include electron microscopy and flow cytometry.

Immunohistochemical (IHC) studies are useful for the characterization of poorly differentiated or undifferentiated tumors. IHC studies should be used in conjunction with other imaging studies to select the best possible treatment option for patients with occult primary tumors.

Low molecular weight cytokeratins (CK7 and CK20) are the two most common immunostains used in cancer of unknown primary site.\textsuperscript{21,22} CK7 is mainly found in tumors of the lung, ovary, endometrium and breast. CK-20 is usually expressed in gastrointestinal, urothelial and merkell cell carcinomas. CK7-positive/CK20-negative/narrows the diagnosis to lung, breast, thyroid, biliary, pancreatic, ovarian or endometrial carcinomas. CK7-negative/CK20-positive are indicative of colorectal carcinoma and merkell cell carcinoma. Immunohistochemical markers for unknown primary cancers are listed in detail in OCC-A.

In addition to the above-mentioned cytokeratins, some of the other IHC markers that are used to distinguish occult primary tumors include thyroid transcription factor (TTF-1), gross cystic disease fibrous protein (GCDFP) and uroplakin III (UROIII).\textsuperscript{22} The use of TTF-1 marker further distinguishes lung primary tumors from other CK7-positive tumors. TTF-1 staining is positive in lung and thyroid carcinomas. UROIII, high molecular weight cytokeratins, thrombomodulin and CK20 are the typical markers favoring the diagnosis of urothelial carcinoma.

**Initial Evaluation**

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

Many patients with unknown primary tumor are referred with PET scans. It was shown that PET scan is the useful method for the diagnosis, staging, and restaging of many malignancies and it might be warranted in some situations (e.g., presence of supraclavicular nodes).\textsuperscript{23} PET scan has intermediate specificity and high sensitivity but further larger studies are warranted to determine the clinical utility and role of PET scan in patients with unknown primary tumor.\textsuperscript{24,25} One of the limitations of PET scan has been the limited accuracy of anatomic localization of functional abnormalities due to very little accumulation of FDG tracer in some neoplastic tissues. In such cases, combination of PET scan with either CT scan or MRI can be more useful.\textsuperscript{26} Recent studies on the use of PET/CT scans for the detection of occult primary tumors, have reported that the combination of PET/CT identified the primary site in 33-35\% of patients.\textsuperscript{27,28} In another study reported by Nanni et al, PET/CT detected occult primary tumor in 57\% of cases, which is a higher detection rate than that reported in earlier studies.\textsuperscript{29} These results indicate that combined modality scanning could play an important role in the diagnosis cancer of the unknown primary site. However, these results need to be confirmed in larger clinical studies with long-term follow-up.

Additional evaluation will identify a primary site in about 30\% of patients presenting with occult metastases. These patients should be treated according to the appropriate NCCN Cancer Treatment guidelines. Additional studies are of utmost importance in determining whether the occult primary cancer is potentially curable or in diagnosing a possible
treatable disease associated with long-term survival. Lymphoma, primary breast, ovarian, thyroid, prostate, and germ-cell tumors must be diagnosed or ruled out since effective therapy is available for these cancers. There is a great deal of controversy regarding whether an exhaustive, time-consuming, costly evaluation should be conducted to search for the primary beyond these initial tests, as opposed to a more directed evaluation based on the complete history and physical examination, clinical presentation, histopathologic diagnosis, and metastatic sites of involvement. Suggested diagnostic tests for each pathologic subtype, location, and gender (where appropriate) are indicated in the guidelines.

Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Breast MRI has been shown to be useful for stage II or IV patients with occult primary breast cancer. In a recent report, the primary site was identified in about half of the women presenting with axillary metastases, irrespective of the breast density.\(^\text{30}\) Thus, the guidelines suggest the use of a mammogram, breast MRI and ultrasound in this group of patients and attention to appropriate histochemistries, such as ER/PR and HER-2/neu if the mammogram is negative. Elevated ER/PR levels provide strong evidence for the breast cancer diagnosis.\(^\text{31}\) Adenocarcinoma involving mediastinal nodes suggests a possible germ-cell tumor. Thus, beta-hCG and alpha-fetoprotein measurements are suggested by the guidelines. Abdominal and pelvic CT scans are now recommended for both men and women for chest, peritoneal and retroperitoneal adenocarcinoma. Testicular ultrasound should also be considered. Chest CT scans (category 2B) for adenocarcinoma found in the peritoneum, retroperitoneum, and liver are also performed at some NCCN member institutions. Bone scan and radiographic studies are recommended for adenocarcinoma and squamous cell carcinoma involving painful or bone-scan positive bone lesions.

Testicular ultrasound is suggested in men under the age of 50 with an adenocarcinoma involving the supraclavicular nodes. All men over age 40 with an adenocarcinoma or carcinoma not otherwise specified should have a prostate specific antigen (PSA) test.\(^\text{2}\) In women with retroperitoneal disease, recommended tests include CA-125, abdominal and pelvic computerized tomographic scans, mammogram, and ER/PR histochemistry. For men with retroperitoneal disease, recommended tests include beta-hCG, alpha-fetoprotein, and testicular ultrasound. As part of the additional workup for women with inguinal lymph node involvement, a CA-125 should be obtained as well as a gynecologic oncology consultation, if clinically indicated.\(^\text{22}\)

Squamous cell carcinoma can be present in the nodes of the head and neck region, supraclavicular, axillary and inguinal nodes. Abdominal and pelvic CT scans, peritoneal and lower extremity exam and urine cytology are recommended for squamous cell carcinoma with inguinal nodes involvement.

Neuroendocrine tumors can metastasize to a number of sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal nodes, liver, bone, brain, and skin. An octreotide scan is frequently useful in identifying the primary site or additional sites of involvement of neuroendocrine tumors. The panel also advises that symptom-directed endoscopy be considered for tumors found in supraclavicular nodes.

It should also be noted which diagnostic tests are not routinely recommended. For example, Colonoscopy is not routinely recommended in patients presenting with malignant ascites (i.e., peritoneal presentation). In the absence of a positive fecal occult blood test or other clinical factors suggesting a tumor in the colon, the diagnostic yield of colonoscopy is less than 5%. The use of alpha-fetoprotein, chest CT, and symptom directed endoscopy as part of the additional workup in adenocarcinoma or carcinoma not otherwise specified in the liver is a category 2B recommendation (OCC-5).
Management Based on Workup Findings

Localized adenocarcinoma or carcinoma not otherwise specified is treated according to the most likely primary site. The recommended treatment for localized adenocarcinoma occurring in the mediastinum depends on the age of the patient at the time of diagnosis (OCC-8). Patients under 40 yrs should be treated for poor-risk germ-cell tumor using the NCCN Testicular Cancer Guidelines. Patients aged 40-50 yrs should be treated for poor-risk germ-cell tumor using the NCCN Testicular Cancer Guidelines (category 3) or as a non-small cell lung cancer utilizing the NCCN Non-Small Cell Lung Cancer Guidelines (category 3). Patients 50 yrs or older are treated according to the NCCN Non-Small Cell Lung Cancer Guidelines. The guidelines recommend treatment according to the NCCN Breast Cancer Guidelines for localized adenocarcinoma involving axillary nodes or pleural effusion in hormone receptor positive women (OCC-8 and OCC-9). Axillary node dissection and radiation therapy to axilla for gross extracapsular extension with or without chemotherapy is recommended for men with localized adenocarcinoma or not otherwise specified adenocarcinoma with involvement of axillary nodes (category 2B). Those presenting with localized adenocarcinoma with a peritoneal mass consistent with ovarian histology are treated as per NCCN Ovarian Cancer Guidelines. Localized adenocarcinoma with a retroperitoneal mass consistent with germ cell histology should be treated as per NCCN Testicular Cancer Guidelines or NCCN Ovarian Cancer Guidelines (OCC-9). Lymph node dissection followed by radiation therapy, with or without subsequent chemotherapy, is recommended for axillary or inguinal nodal involvement, if two or more lymph nodes are positive (OCC-9 and OCC-10).

In patients with disseminated disease for all of the above pathologic diagnoses, the treatment goals are directed toward symptom control and providing the best quality of life possible.

Chemotherapy

Poorly differentiated carcinomas and adenocarcinomas or undifferentiated carcinomas of unknown primary respond differently from well- to moderately-differentiated carcinoma of unknown primaries. Tumors in the former group appear to be highly responsive to cisplatin-based combination chemotherapy. Response rates reported in two studies were 53% (van der Gaast et al) and 63% (Hainsworth et al) with complete response rates of 12% and 26%, respectively. The tumors of these patients had extragonadal germ-cell features.

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 utilized 5-flourouracil-based or cisplatin-based chemotherapeutic regimens. Most of the patients in these studies had adenocarcinoma and only 5-10% had poorly differentiated carcinoma. Overall response rates to these regimens were 20-35%, with median
survival times of 5-8 months, although some of the studies reported longer median survival duration. Older regimens are not used as standard treatment since complete response is rarely observed. In recent years, newer regimens containing taxanes, gemcitabine and topoisomerase inhibitors have shown efficacy in phase II studies in the treatment of cancer of the unknown primary.

NCCN guidelines recommend that chemotherapy for patients with disseminated disease should be limited to symptomatic patients with a performance status (PS) 0-2 or asymptomatic patients with aggressive cancer. The choice of the regimen should be based on the histologic type of cancer. Selected chemotherapy regimens for occult primary tumors are listed in OCC-B.

**Adenocarcinoma**

In two separate phase II studies, paclitaxel and carboplatin with or without etoposide was found to be effective for the treatment of adenocarcinoma of unknown primary.\(^{46,47}\) In the Hellenic Cooperative Oncology Group Study, combination of paclitaxel and carboplatin produced an overall response rate of 38.7\% by intent-to-treat analysis; there was no difference in the response rates for adenocarcinomas and undifferentiated carcinomas.\(^{46}\) In another phase II trial, long-term follow-up of patients treated with the triple drug combination (paclitaxel, carboplatin and oral etoposide) showed 1-year, 2-year and 3-year survival rates of 48\%, 20\% and 14\% respectively.\(^{47}\)

Sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan was also found to be active in patients with carcinoma of the unknown primary.\(^{48}\) Overall toxicity of sequential treatment was found to be greater than that observed with other regimens and survival was also similar to that observed in previous phase II trials. Survival was also similar to regimens tested in other phase II trials.

Greco et al have reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated adenocarcinoma.\(^{49}\) Docetaxel in combination with carboplatin was better tolerated.

Efficacy and toxicity of combination regimens including cisplatin with either gemcitabine (GC) or irinotecan (IC) was evaluated in a phase II study conducted by French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01).\(^{50}\) Well differentiated adenocarcinoma was the most common histology with one fourth of patients having single metastatic site. Objective response rates were 55\% for GC arm and 38\% for IC arm. With a median follow-up of 22 months, median survival rates were 8 and 6 months respectively for GC and IC arms. However, toxicity was associated with both regimens.

Finally, a non-cisplatin-based regimen containing gemcitabine and docetaxel was found to be well tolerated and active in carcinomas of unknown primary site.\(^{51}\) The overall response rate was 40\% with a median survival of 10 months.

The guidelines have included the following regimens for the treatment of adenocarcinoma of unknown primary, based on the results of the above mentioned phase II studies (OCC-B).

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

**Squamous Cell Carcinoma**

Platinum-based regimens are used to treat disseminated squamous cell carcinoma. 5-flourouracil and cisplatin is the most frequently used combination regimen. In a phase III study, 5-flourouracil and cisplatin (CF) was compared with the combination of paclitaxel, cisplatin and
5-fluorouracil (PCF).\textsuperscript{52} Induction chemotherapy with PCF had better tolerance and produced higher complete response rate (33\% vs. 14\%) than CF regimen. In another randomized phase III trial induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) was compared with cisplatin and 5-fluorouracil. Preliminary results showed that TPF regimen produced significantly superior overall response rate (82.8\% vs. 60.8\%) compared to cisplatin and 5-fluorouracil.\textsuperscript{53}

Based on these results, the guidelines have included the combination of cisplatin and 5-fluorouracil with either paclitaxel or docetaxel for the treatment of squamous cell carcinoma of unknown primary (OCC-B).

**Neuroendocrine Tumors**

Neuroendocrine occult primary tumors are treated depending on whether the tumor is aggressive (anaplastic or small cell subtype) or indolent (classified as “other”). Anaplastic lung tumors are treated in a manner similar to small-cell lung carcinoma as per the NCCN Small Cell Lung Cancer Guidelines. Regional therapy (hepatic artery infusion, chemoembolization, etc.) may be appropriate for well-differentiated unresectable neuroendocrine tumors in the liver. Resectable well-differentiated neuroendocrine tumors in the liver are treated with surgery. For anaplastic or fast growing tumors in liver, options include chemotherapy or regional radiation therapy (category 2B).

Hainsworth et al have evaluated the efficacy of combination regimen containing paclitaxel, carboplatin and etoposide in advanced poorly differentiated neuroendocrine (PDNE) carcinomas.\textsuperscript{54} Sixty two percent of the patients 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, proving that PDNE carcinomas are chemosensitive. The median, 2-year and 3-year survival for the entire group were 14.5 months, 33\% and 24\% respectively. The combination of cisplatin and etoposide produced significant responses in patients with poorly differentiated rapidly progressing neuroendocrine tumors, when used as a second or third-line treatment.\textsuperscript{55}

The guidelines have included carboplatin and paclitaxel, which is active in SCLC,\textsuperscript{56} paclitaxel/carboplatin /etoposide, cisplatin and etoposide for the treatment of neuroendocrine tumors of unknown primary (OCC-B).

Neuroendocrine tumors frequently express somatostatin receptors (SSTRs). Octreotide is a synthetic analogue of somatostatin and has a longer half-life than somatostatin. Radiolabelled somatostatin analogues have been used in the diagnosis and treatment of unresectable or disseminated neuroendocrine tumors.\textsuperscript{111} Indium-diethylene-triaminepentaacetic acid (DTPA) octreotide (pentetreotide) is one such radiolabelled somatostatin analog that has been used to visualize and eradicate SSTR expressing tumors.\textsuperscript{57} Octreotide is the treatment option for disseminated neuroendocrine tumors or unresectable neuroendocrine tumors in the bone, which are hormonally active and octreotide scan positive, excluding small cell or anaplastic types.\textsuperscript{58} Close monitoring is recommended for patients on octreotide therapy to avoid severe side effects such as bone marrow depression etc (OCC-19).

**Radiation Therapy**

Radiation therapy (RT) 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 two 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 squamous cell cancer.
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 novel forms of drug or RT delivery, such as intraperitoneal RT. These individualized approaches may also include various types of local palliative treatments, such as thoracentesis or paracentesis.

Locoregional Therapeutic Options

In patients with unresectable localized liver lesions (either adenocarcinoma or neuroendocrine), locoregional therapeutic options may be considered. These therapies include hepatic artery infusion, chemoembolization, hepatic cryosurgery, radiofrequency ablation of hepatic lesions, or percutaneous ethanol injections. These treatment options are also addressed in the NCCN Hepatobiliary Cancers Guidelines and the NCCN Neuroendocrine Tumors Guidelines.

Follow-Up

For all occult primary tumors under no active treatment, follow-up consists of a history and physical every 2 to 3 months for the first 18 months, then every 3 to 4 months for the following 18 months. Diagnostics tests should be performed based on symptomatology. Psychological support should be ongoing (OCC-20).

Disclosures for the NCCN Occult Primary Guideline Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Bristol-Myers Squibb, Genentech, Inc., GlaxoSmithKline, ImClone Systems, Inc., Lily, Merck & Co., Inc., MGI Pharma Inc., Novartis, OSI Pharmaceuticals, Pfizer, Inc., Roche, Sanofi-Aventis, Schering-Plough and Wyeth. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

Recommended Reading


References


57. van der Hiel B, Stokkel MP, Chiti A et al. Effective treatment of bone metastases from a neuroendocrine tumour of the pancreas with high