

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Occult Primary (Cancer of Unknown Primary [CUP])

Version 1.2018 — November 9, 2017

NCCN.org

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Occult Primary

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§ Radiation oncology/Radiotherapy
‡ Hematology/Hematology oncology
¶ Internal medicine
≠ Pathology
ϕ Diagnostic/Interventional radiology
* Discussion Section Writing Committee



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[Principles of Radiation Therapy \(OCC-C\)](#)

Clinical Trials: NCCN believes that the best management for any patient with cancer 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 indicated.

See [NCCN Categories of Evidence and Consensus](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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® (NCCN®) 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. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2017.



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NCCN Guidelines Version 1.2018 Updates

Occult Primary

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Updates in Version 1.2018 of the Guidelines for Occult Primary from Version 2.2017 include:

[MS-1](#)

- The discussion section has been updated to reflect the changes in the algorithm

[OCC-1](#)

Initial evaluation:

- Last bullet has been modified: "~~Symptom~~*Clinically directed endoscopy, as indicated*"

Workup:

- 1st bullet has been modified: "Core needle biopsy (preferred) and/or FNA *with cell block*"

[OCC-2](#)

- "*Localized*" has been added to "adenocarcinoma or carcinoma not otherwise specified" (Also for OCC-3, OCC-4, OCC-5, OCC-6)

Clinical presentation:

- 1st bullet has been modified: "*Predominant and isolated* cervical nodes" (Also for OCC-3)

[OCC-3](#)

Additional Workup:

- Supraclavicular nodes, Men and women: "*Endoscopy, if clinically indicated*" is new to the page.

[OCC-4](#)

Additional Workup:

- Peritoneal/Ascites: "Serum CA 19-9 level if pancreatic or biliary tract primary suspected" has been removed. (Also for OCC-5)

[OCC-5](#)

Additional workup:

- Retroperitoneal mass, Men, modified: "<65 y Beta-hCG, alpha-fetoprotein, testicular ultrasound ~~if markers elevated~~"

[OCC-9](#)

- 3rd column, pathway off Pleural effusion has been removed: "Consider local management"
- 3rd column, pathway off Peritoneal/Ascites has been modified: "Histology consistent with ovary, ~~negative for liver~~"

[OCC-11](#)

Additional Workup:

- Supraclavicular nodes, statement has been removed: "Chest/upper abdominal CT"

[OCC-A](#)

- *The Immunohistochemistry Markers section of the guidelines has been extensively modified.*

[OCC-C](#)

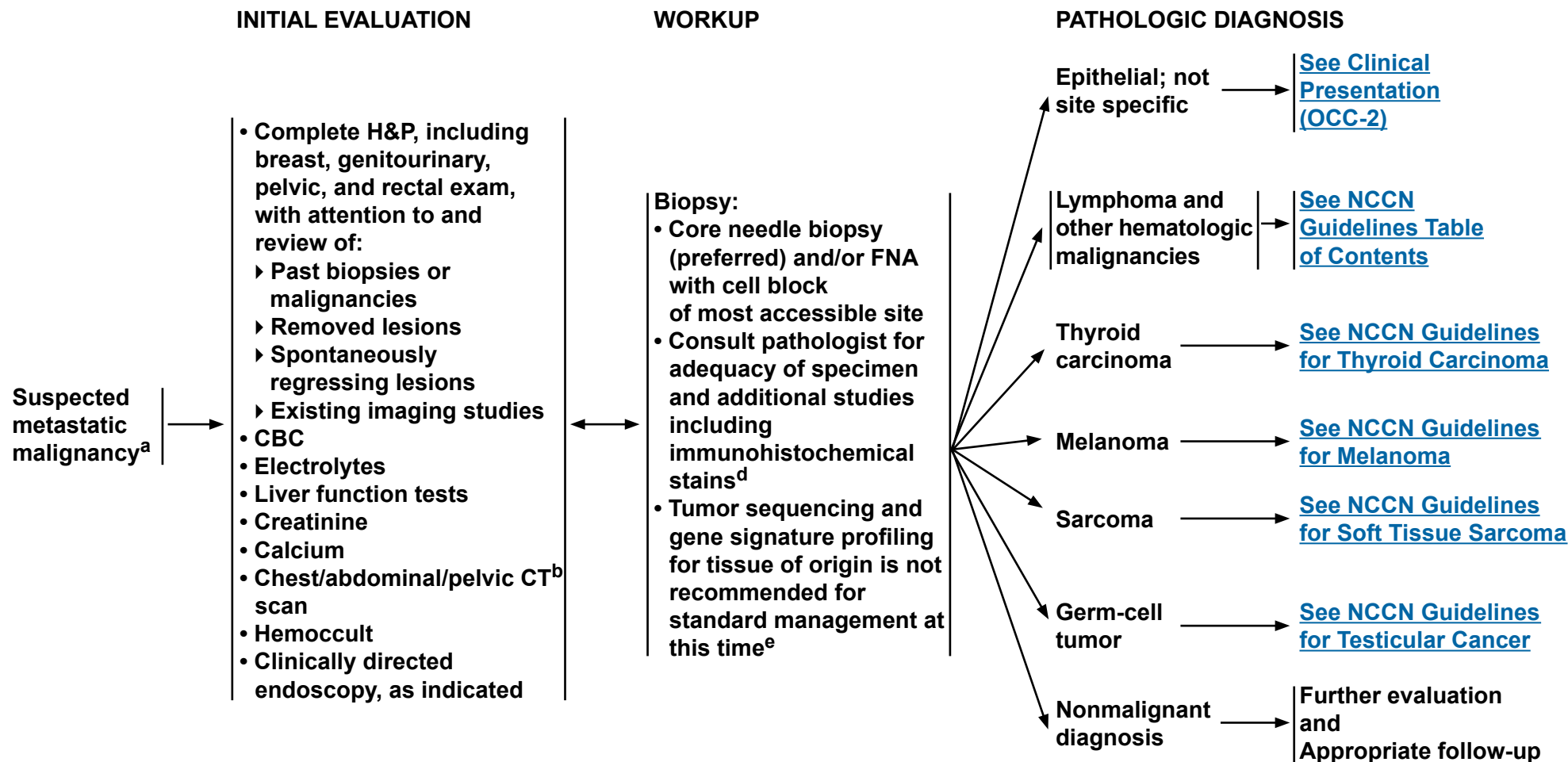
Principles of Radiation Therapy

- Palliative Therapy, 1st sub-bullet has been modified: Regimen: *A number of hypofractionation regimens could be considered, but typically 8 Gy in 1 fraction, 20 Gy in 4–5 fractions, or 30 Gy in 10 fractions are most frequently used.*



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^bCT/MRI imaging should be performed with IV contrast unless contraindicated.

^d[See Immunohistochemistry Markers for Unknown Primary Cancers \(OCC-A\).](#)

^eThere may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation.

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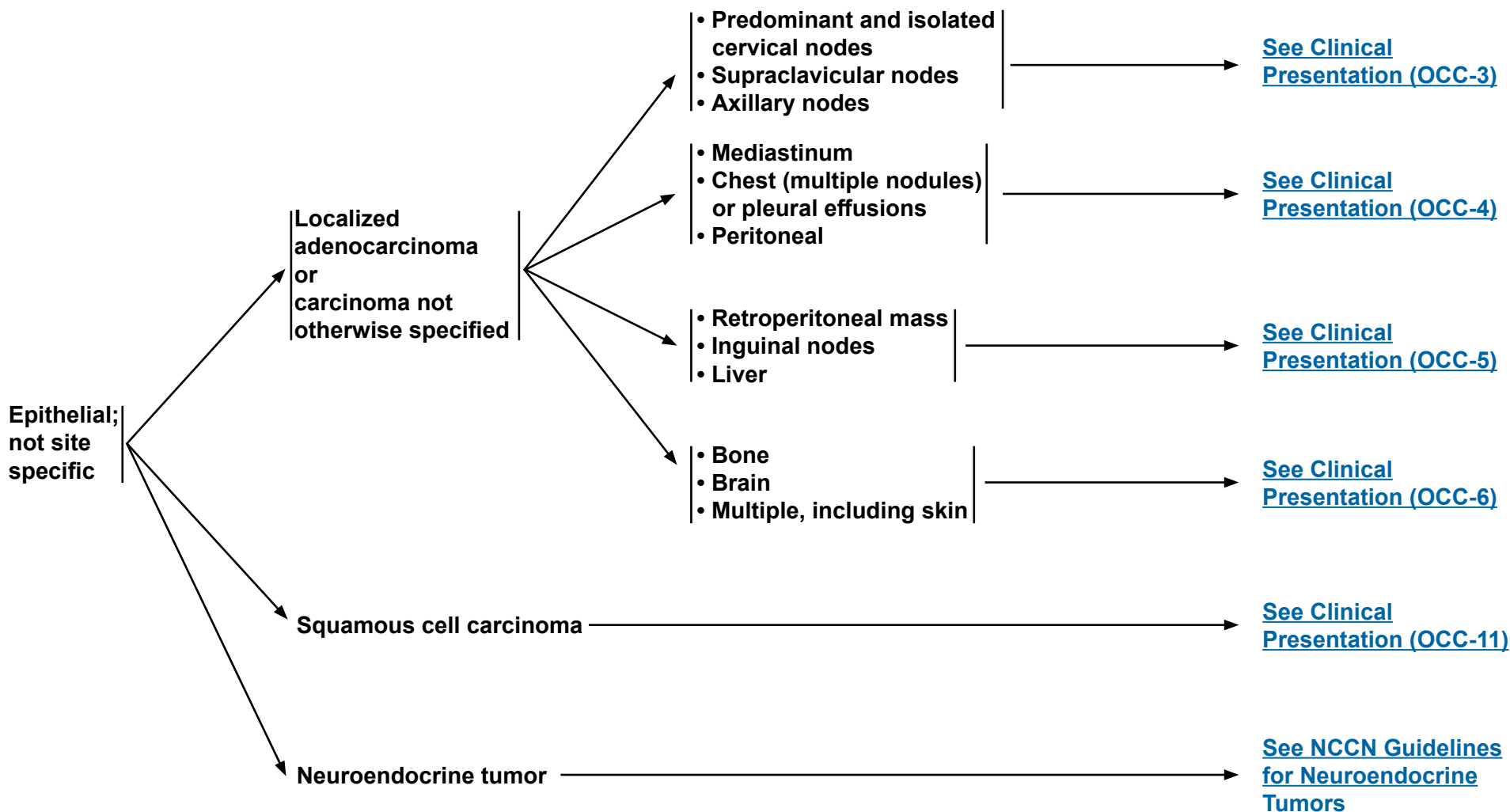


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Occult Primary

PATHOLOGIC DIAGNOSIS

CLINICAL PRESENTATION

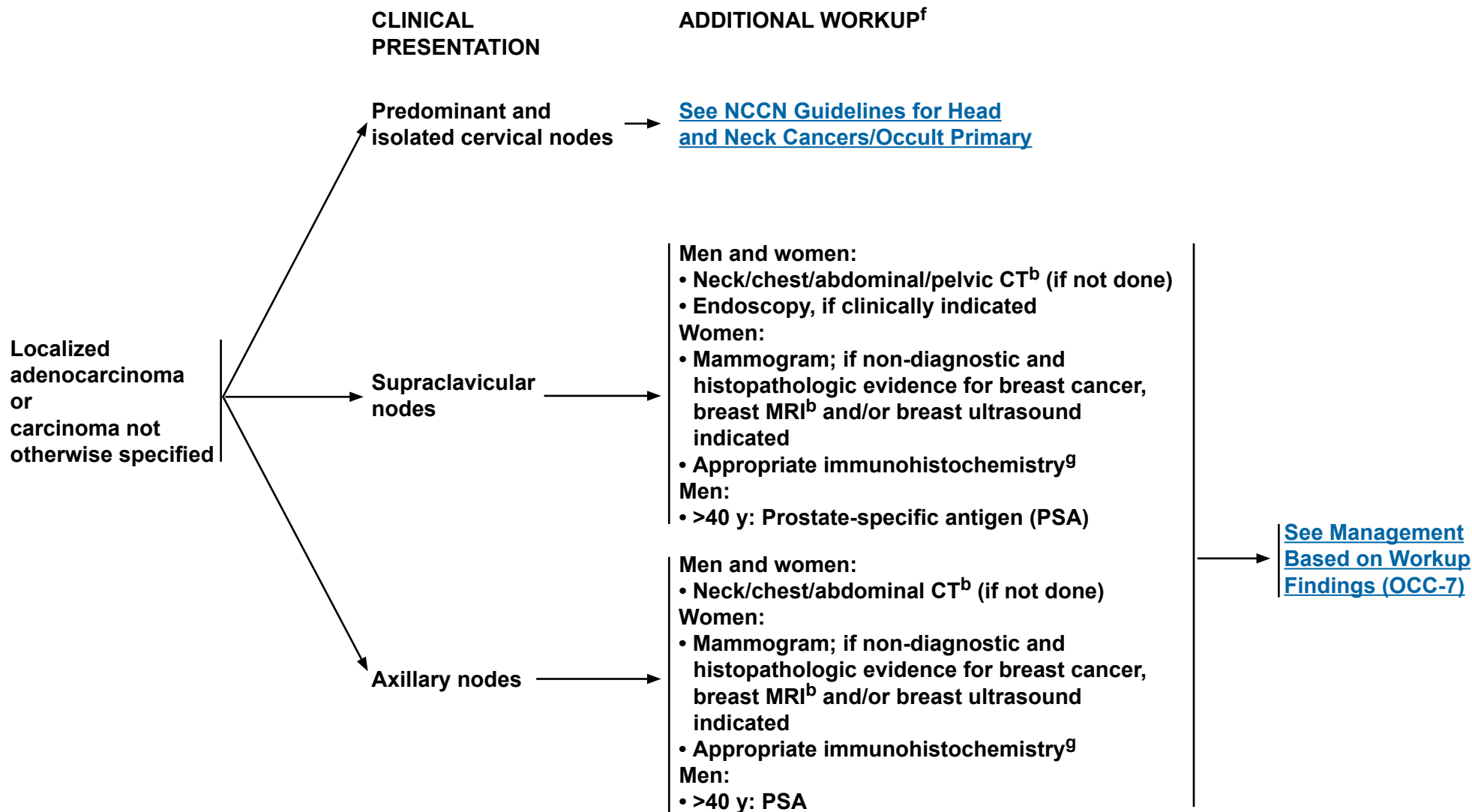


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^bCT/MRI imaging should be performed with IV contrast unless contraindicated.

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

^gAn expanded panel of immunohistochemical markers may be used as appropriate. [See Immunohistochemistry Markers for Unknown Primary Cancers \(OCC-A\).](#)

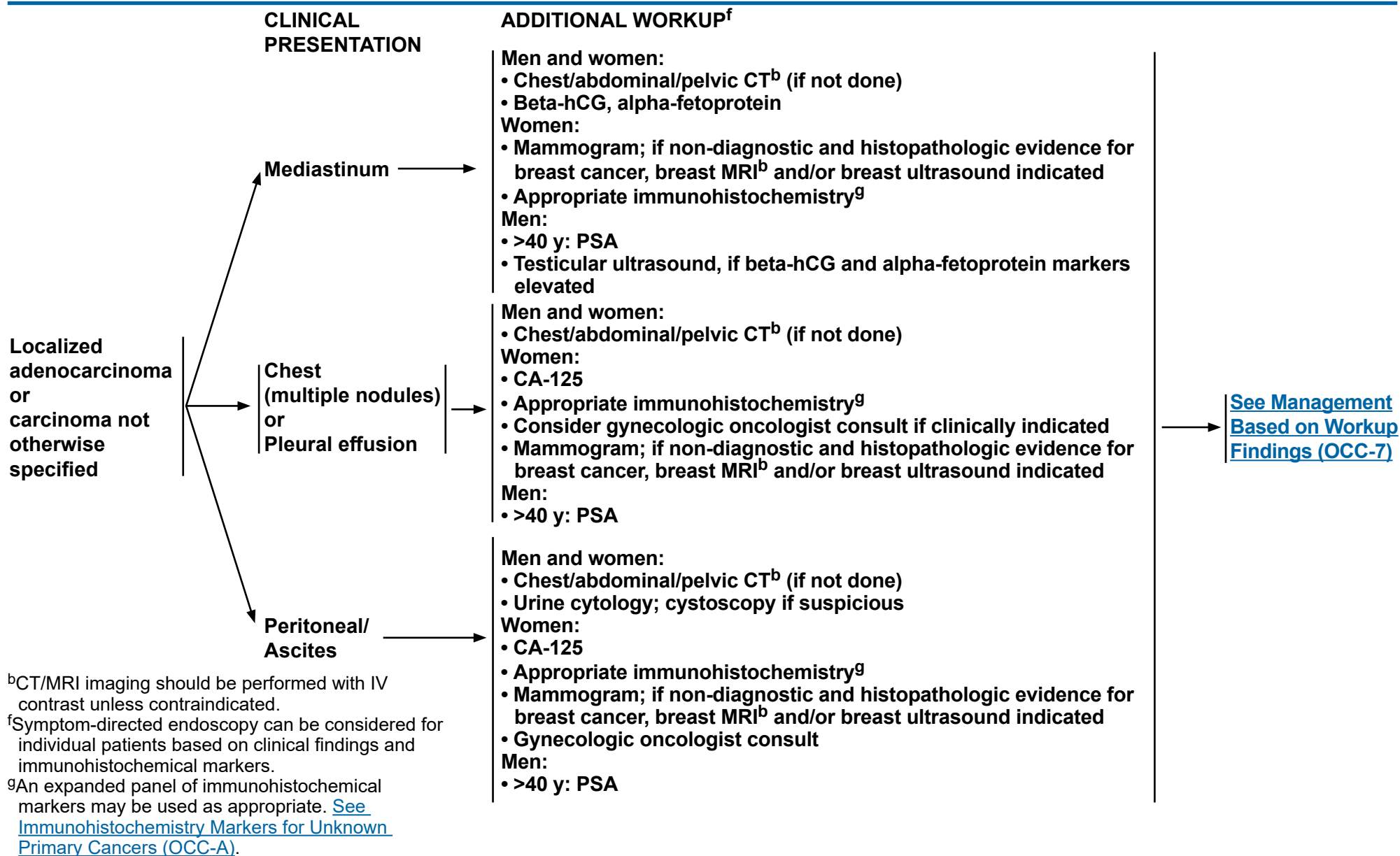
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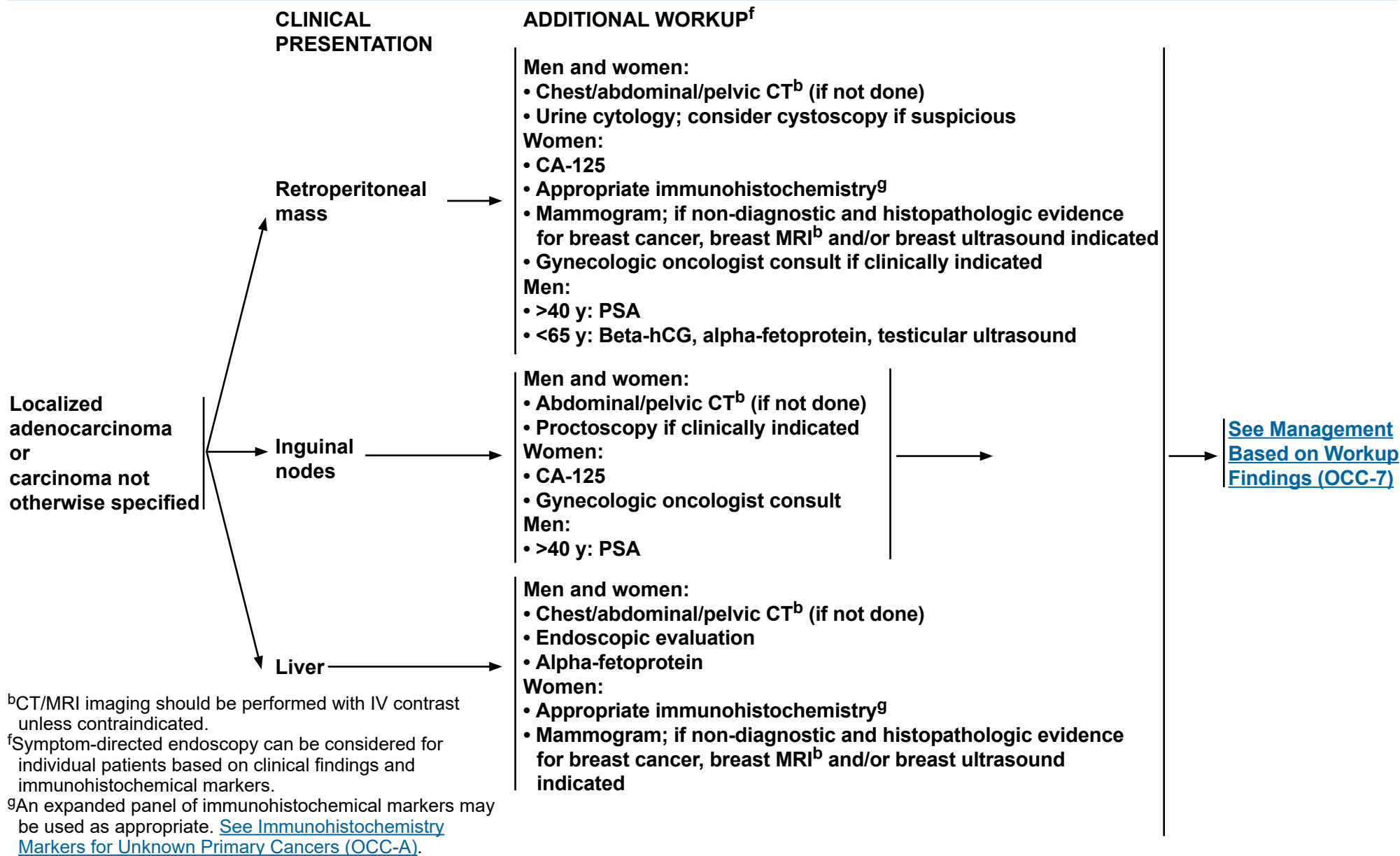
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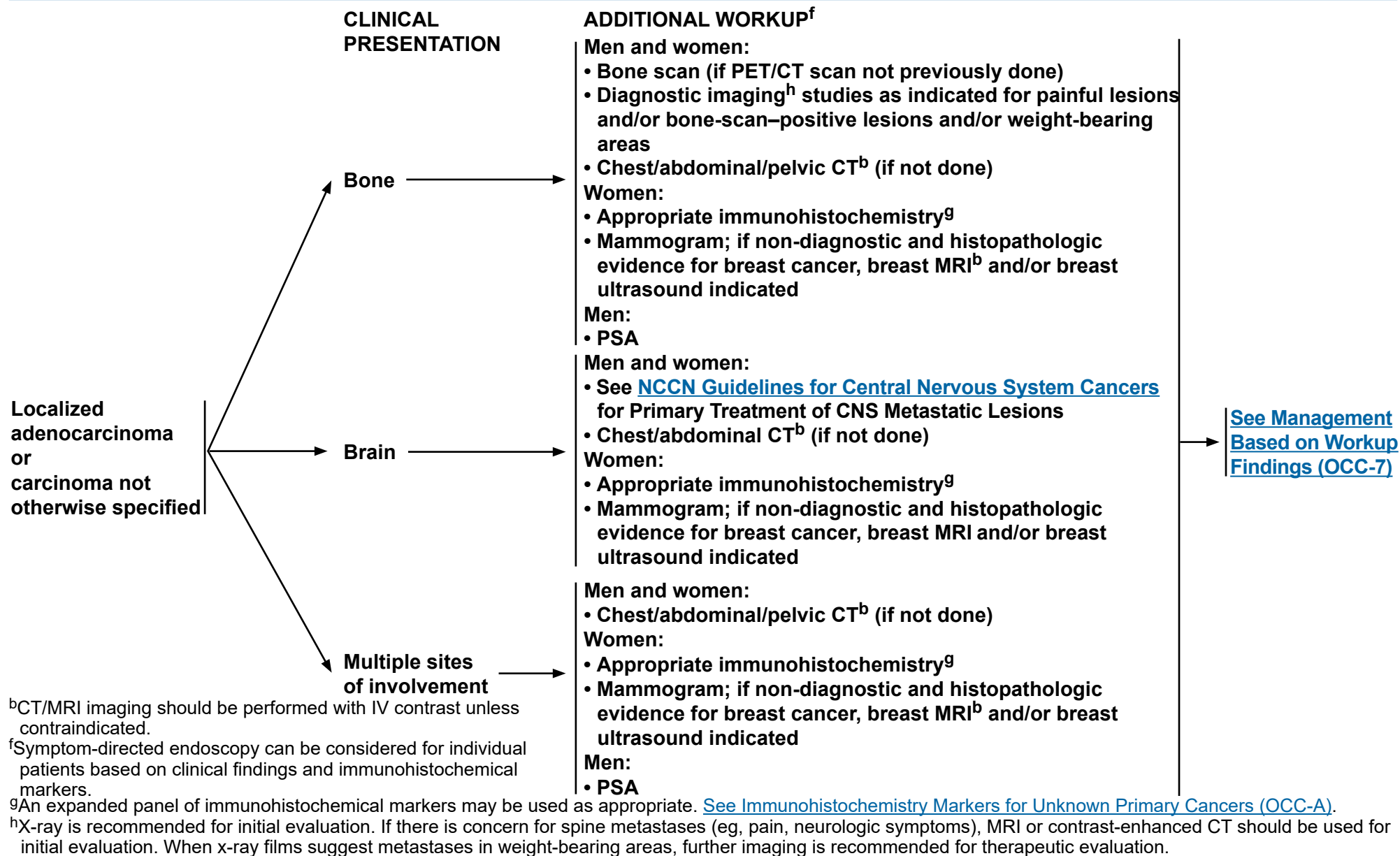
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Occult Primary

WORKUP FINDINGS

Primary found

MANAGEMENT BASED ON WORKUP FINDINGS

Treat per NCCN disease-specific guidelines
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Localized
adenocarcinoma
or carcinoma not
otherwise specified^a

- Head and neck
- Supraclavicular
- Axillary
- Mediastinum

[See Management Based on
Workup Findings \(OCC-8\)](#)

- Lung nodules
- Pleural effusion
- Peritoneal
- Retroperitoneal mass

[See Management Based on
Workup Findings \(OCC-9\)](#)

- Inguinal node
- Liver
- Bone
- Brain

[See Management Based on
Workup Findings \(OCC-10\)](#)

Disseminated
metastases^a

- Symptom control
- Clinical trial preferred
- Consider chemotherapy on an individual basisⁱ
- Specialized approaches^j

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ⁱ[See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries \(OCC-B\)](#).

^jFor specialized approaches that are therapeutic in nature, [see Discussion](#).

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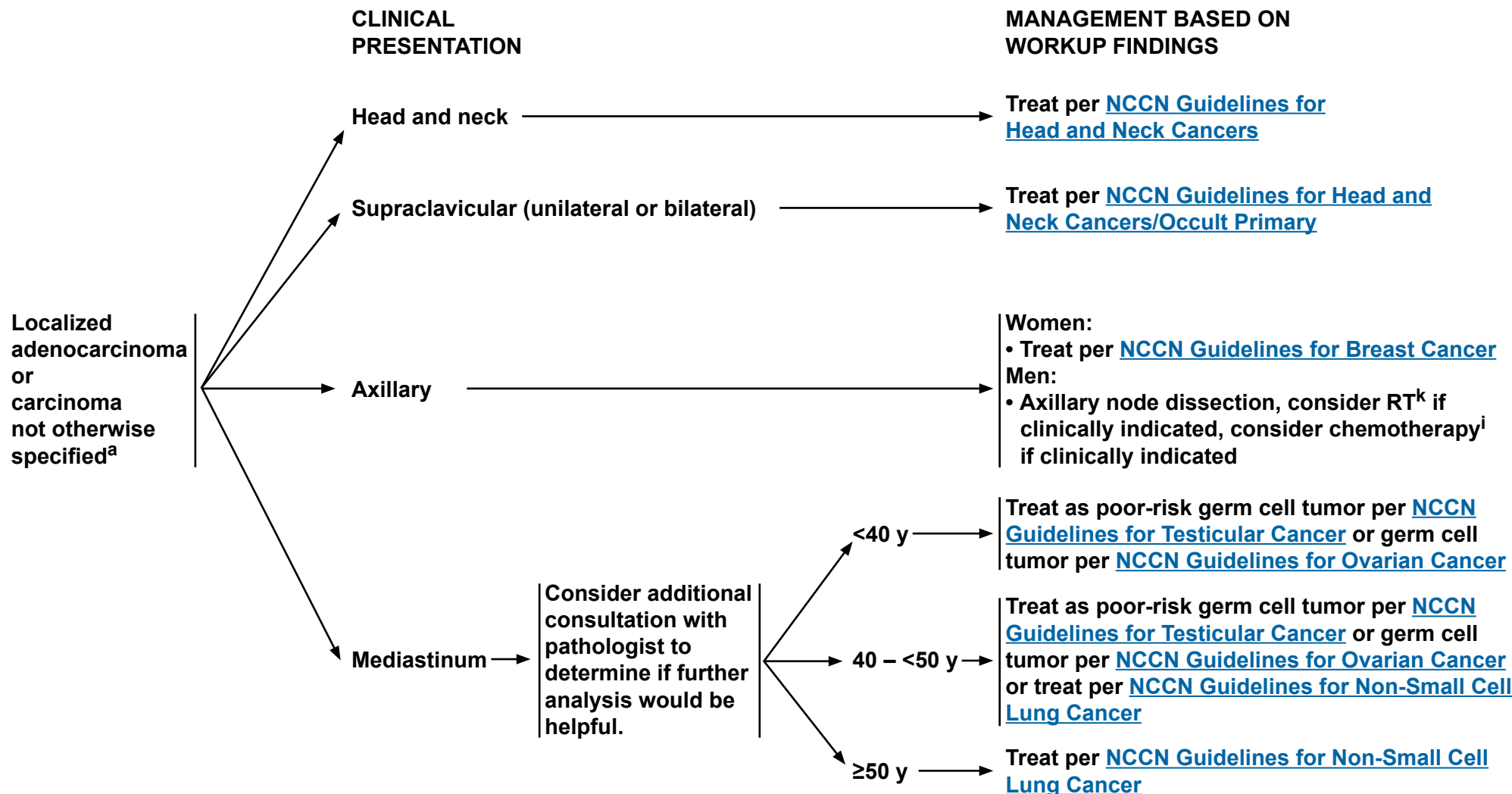
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[See Follow-up
\(OCC-16\)](#)



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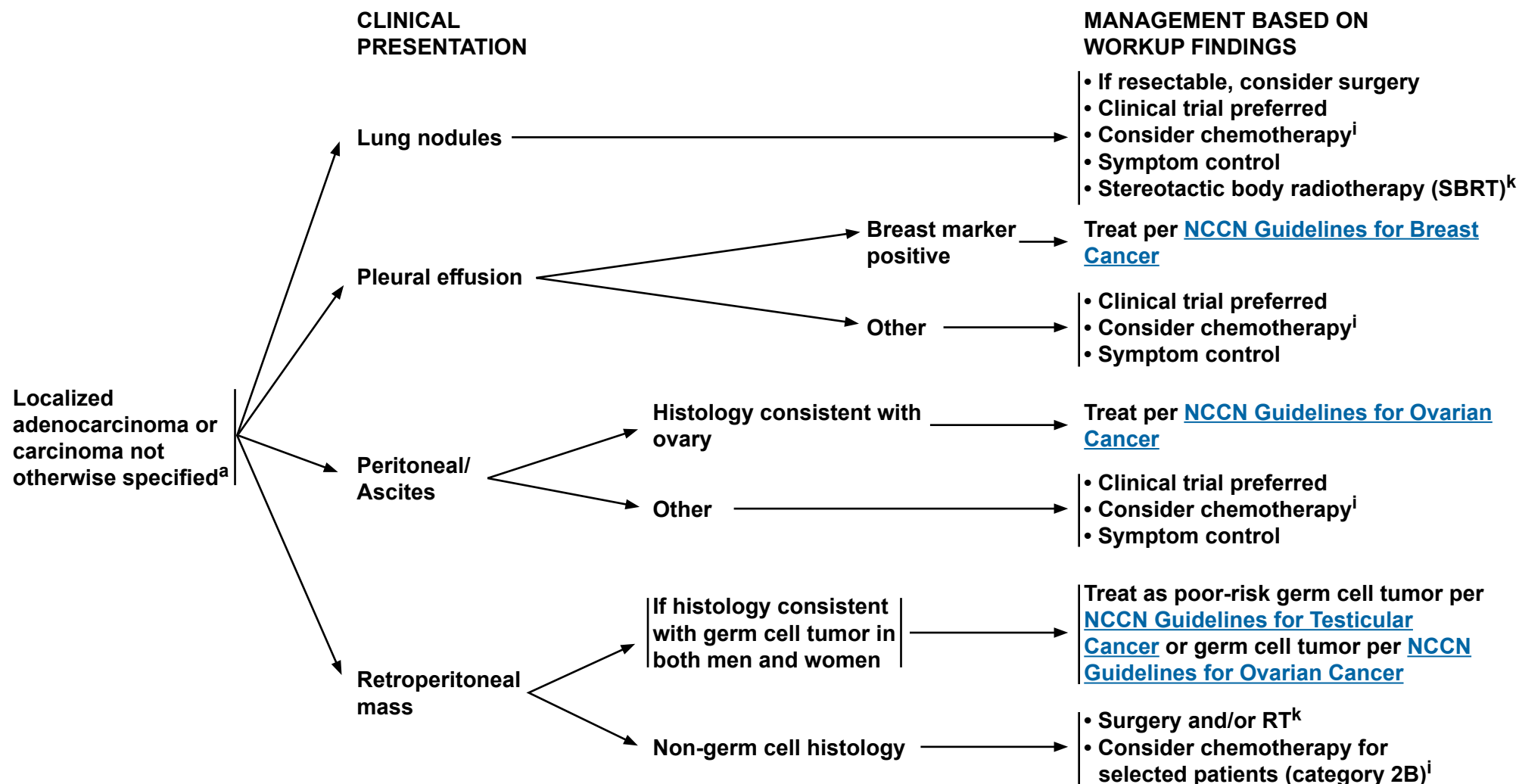
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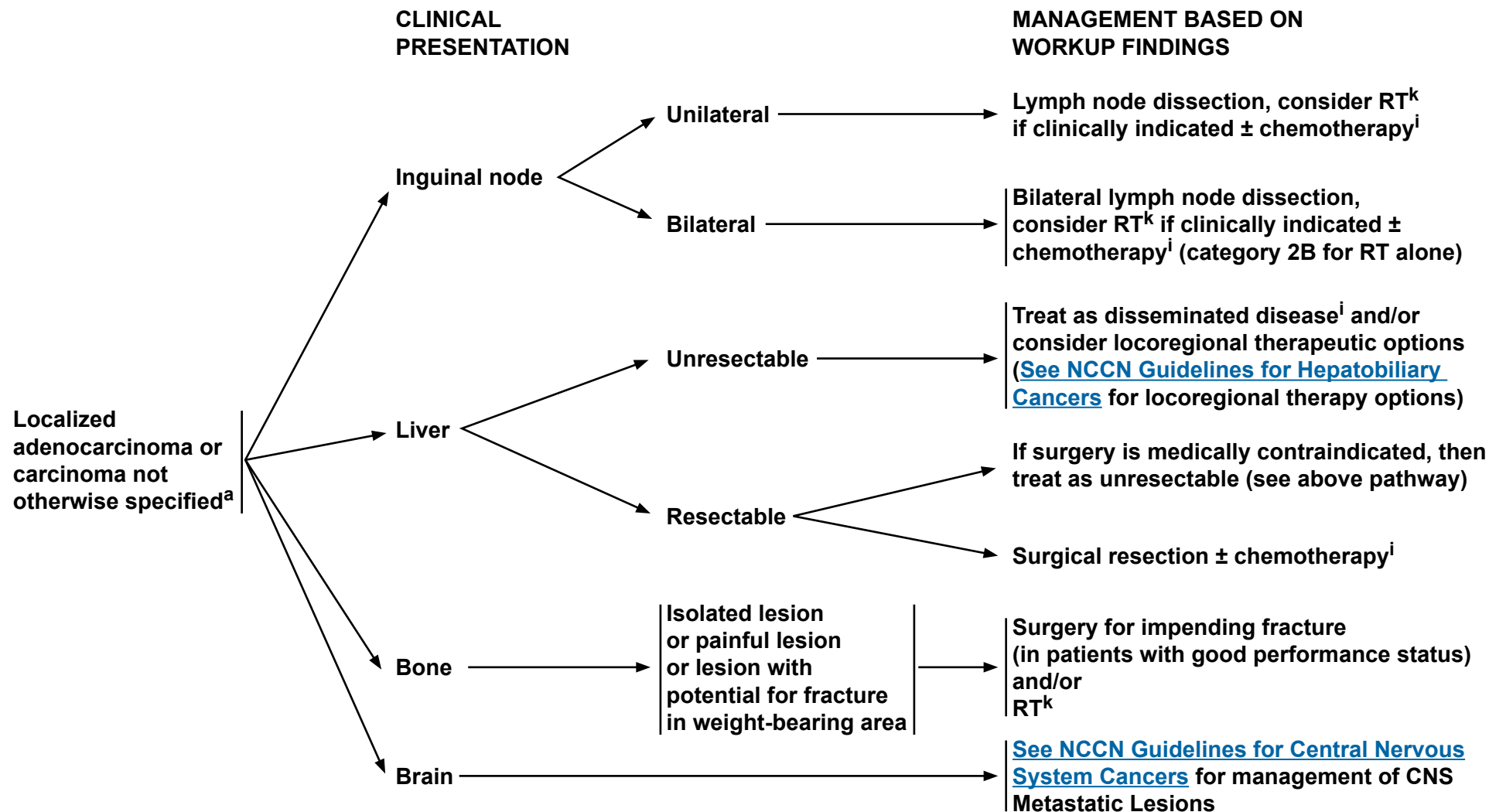
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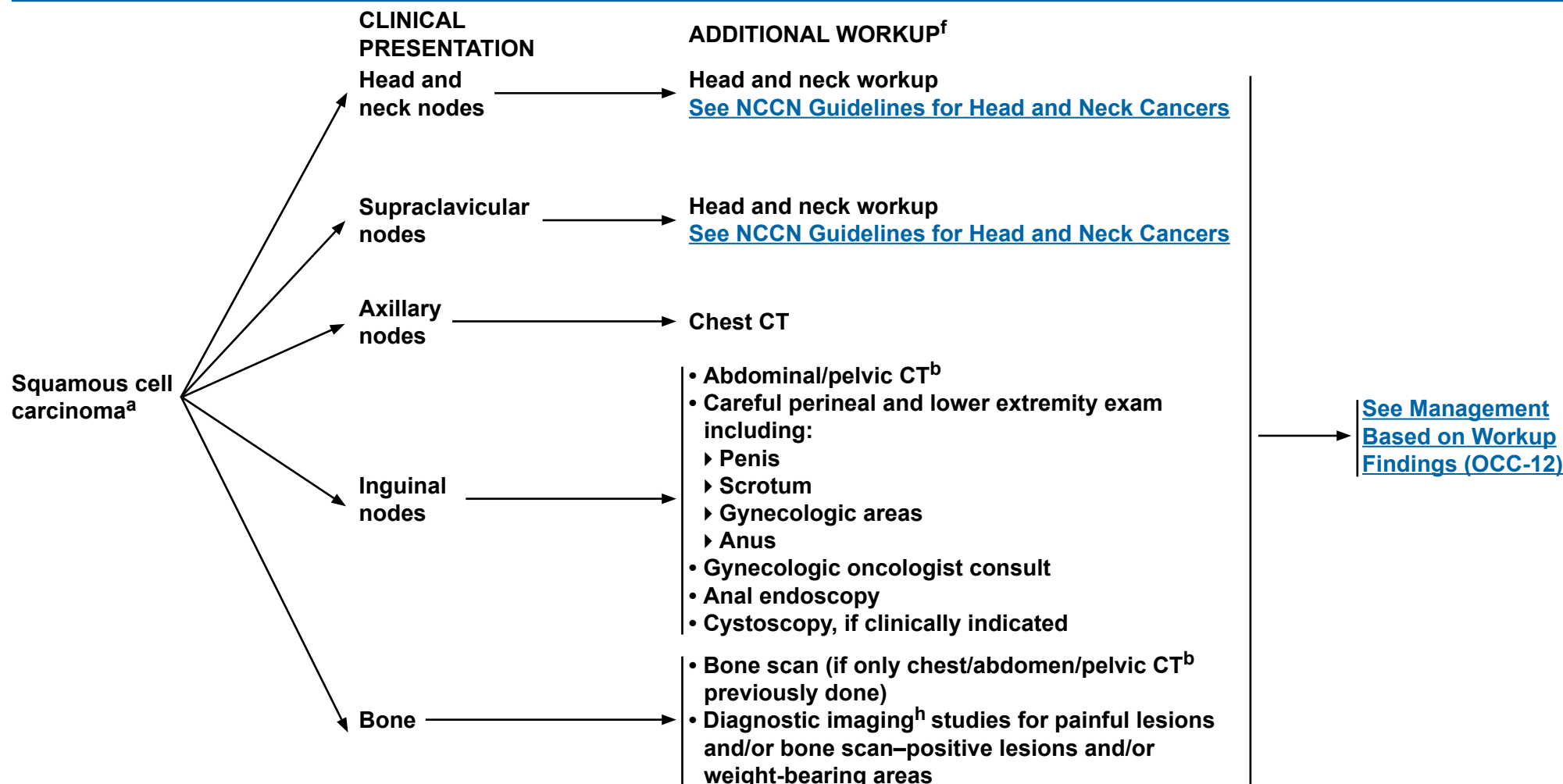
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^bCT/MRI imaging should be performed with IV contrast unless contraindicated.

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

^hX-ray is recommended for initial evaluation. If there is concern for spine metastases (eg, pain, neurologic symptoms), MRI or contrast-enhanced CT should be used for initial evaluation. When x-ray films suggest metastases in weight-bearing areas, further imaging is recommended for therapeutic evaluation.

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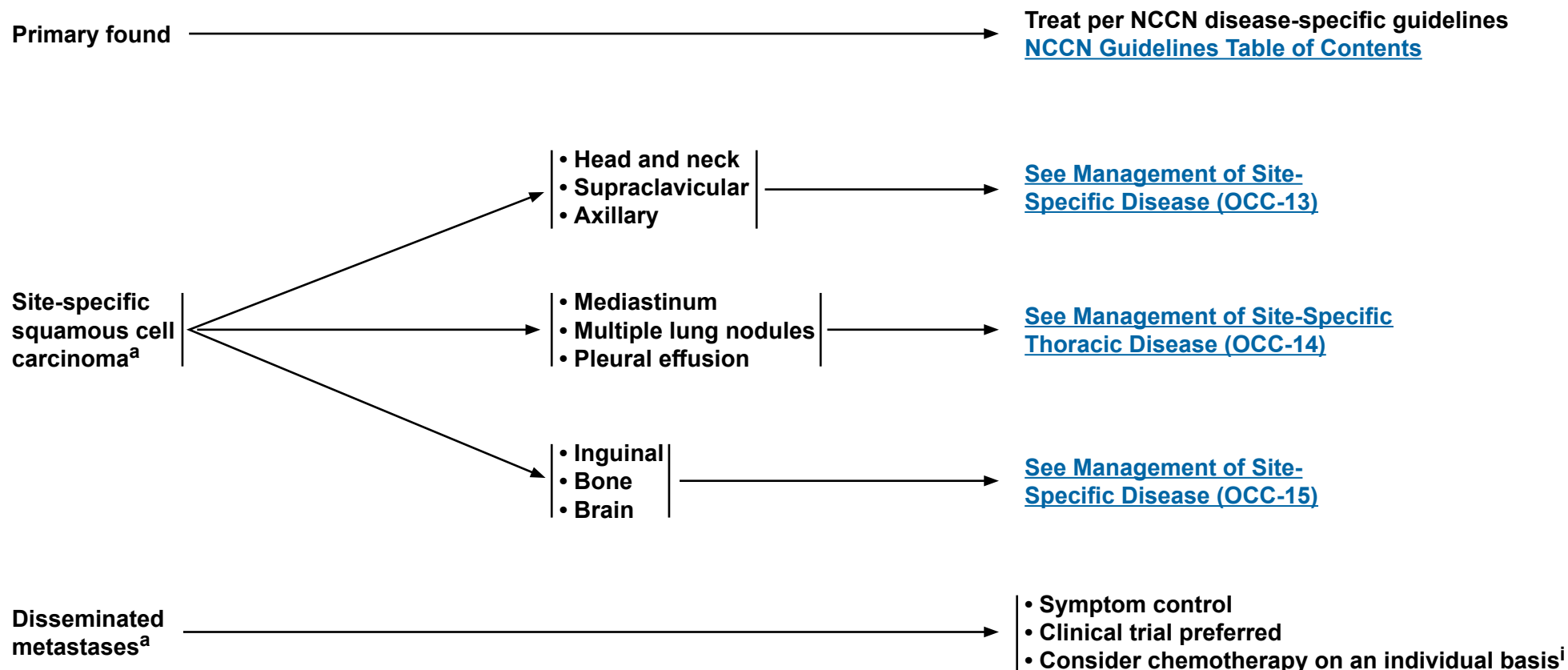


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WORKUP FINDINGS

MANAGEMENT BASED ON WORKUP FINDINGS



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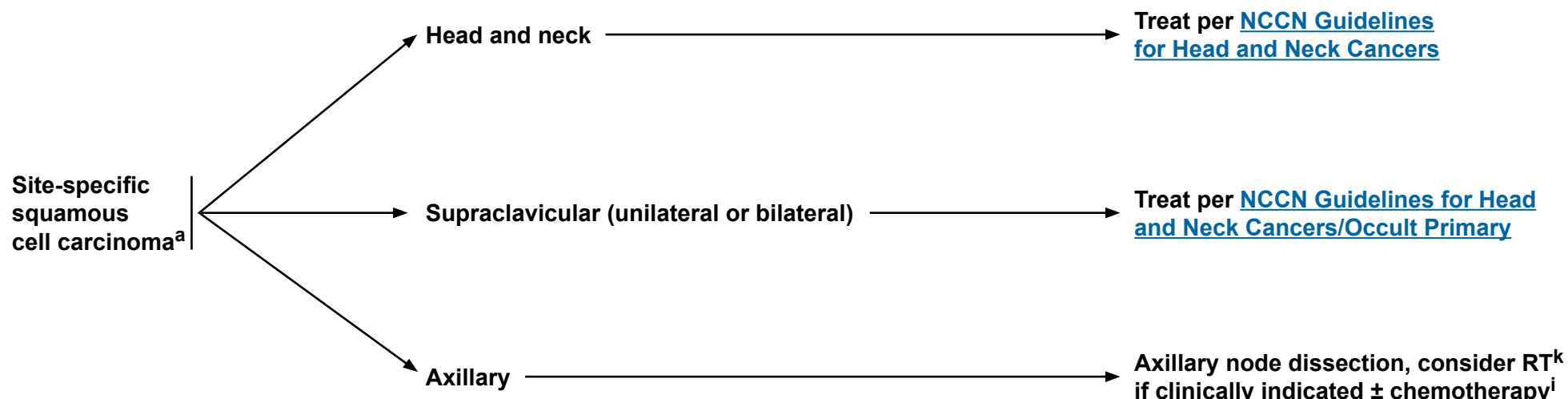


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CLINICAL PRESENTATION

MANAGEMENT BASED ON WORKUP FINDINGS



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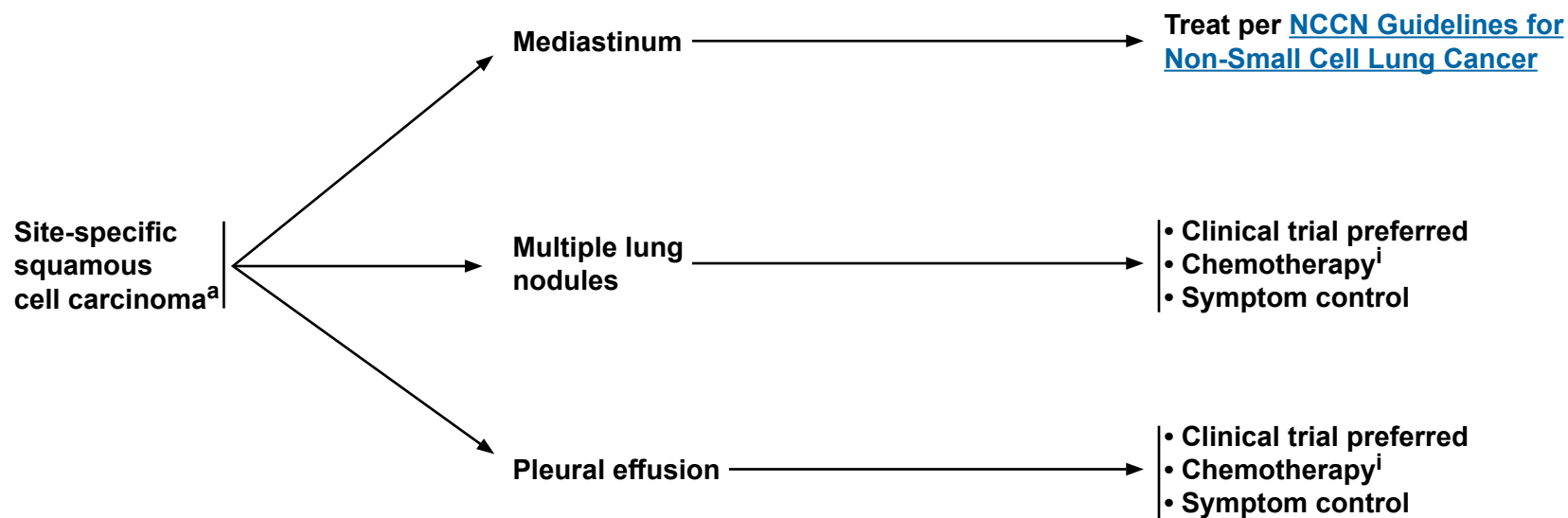


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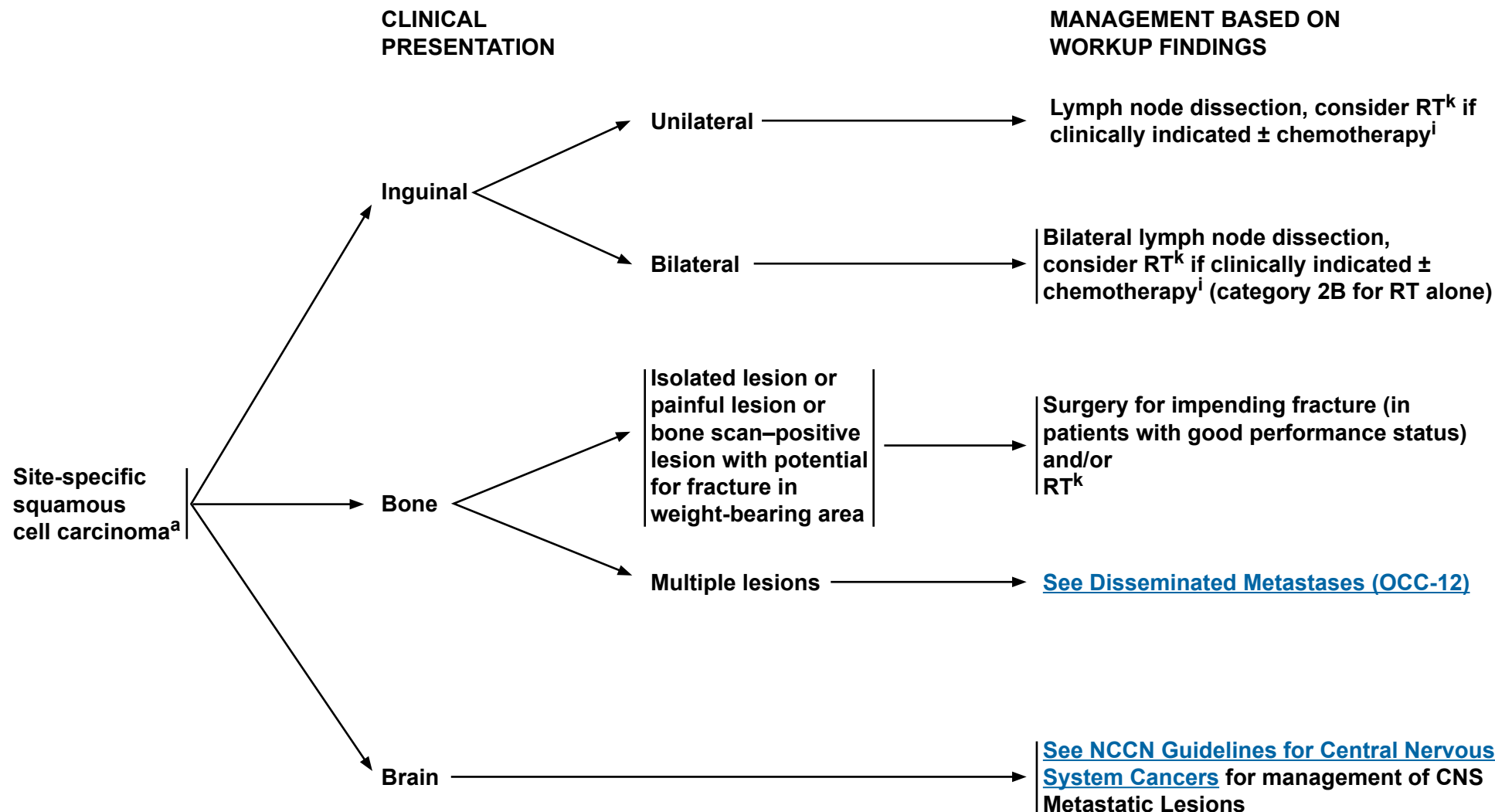
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FOLLOW-UP FOR ALL OCCULT PRIMARIES (NO ACTIVE TREATMENT)

- 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](#), [NCCN Guidelines for Distress Management](#), and [NCCN Guidelines for Survivorship](#).

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POTENTIAL 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 PATTERN¹

<u>Marker</u>	<u>Tumor</u>	<u>Staining Pattern</u>
Arginase-1	Hepatocellular	Nuclear/cytoplasmic
Calretinin	Mesothelioma, sex cord–stromal, adrenocortical	Nuclear/cytoplasmic
CDX2	Colorectal, other gastrointestinal, pancreaticobiliary tract	Nuclear
D2-40	Mesothelioma, lymphatic endothelial cell marker	Membranous
ER/PR	Breast, ovary, endometrium	Nuclear
GATA3	Breast, urinary bladder, salivary gland	Nuclear
GCDFP-15	Breast	Cytoplasmic
Glypican-3	Hepatocellular	Membranous/canalicular/cytoplasmic
HepPar-1	Hepatocellular	Cytoplasmic
Inhibin	Sex cord–stromal, adrenocortical	Cytoplasmic
Mammaglobin	Breast	Cytoplasmic
Melan-A	Adrenocortical, melanoma	Cytoplasmic
Napsin A	Lung	Cytoplasmic
NKX3-1	Prostate	Nuclear
PAP	Prostate	Cytoplasmic
PAX8	Thyroid, renal, ovary, endometrium, cervix	Nuclear
PSA	Prostate	Cytoplasmic
RCC marker	Renal	Membranous
SF-1	Adrenocortical, sex–cord stromal	Nuclear
SATB2	Colorectal, other gastrointestinal tract	Nuclear
Thyroglobulin	Thyroid	Cytoplasmic
TTF-1	Lung, thyroid	Nuclear
Uroplakin III	Urothelial	Membranous
Villin	Gastrointestinal (epithelia with brush border)	Apical
WT1	Ovarian serous, mesothelioma, Wilms	Nuclear

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

Bahrami A, Truong L, Ro J. Undifferentiated tumor: true identity by immunohistochemistry. Arch Pathol Lab Med 2008;132:326-348.

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POTENTIAL IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS

Undifferentiated Panel: For Determining Most Likely Cell Lineage²

Markers*	Most Likely Cell Lineage
Pan-keratin (AE1/AE3 & CAM5.2)	Carcinoma
CK5/6, p63/p40	Squamous cell carcinoma
S100, SOX10	Melanoma
LCA± CD20± CD3±	Lymphoma
OCT3/4± SALL4±	Germ cell tumor
WT1, calretinin, mesothelin, D2-40	Mesothelial tumor

***These markers are not uniformly specific or sensitive and can be present on other tumors.**

²Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol 2015;22(3):149-167.

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS²

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Adrenocortical carcinoma	CK7-/CK20-	SF-1 Melan A Inhibin	
Breast carcinoma	CK7+/CK20-	GATA3 GCDFP-15 (BRST2)± Mammaglobin±	ER/PR±
Endocervical adenocarcinoma	CK7+/CK20-	p16+ (strong diffuse staining) PAX8±	Vimentin- ER/PR± Human papillomavirus in situ hybridization
Endometrial adenocarcinoma	CK7+/CK20-	Vimentin PAX8	ER/PR± p16- (strong diffuse staining to distinguish from endocervical and uterine serous carcinoma)
Hepatocellular carcinoma	CK7±/CK20± usually CK7-/CK20-	Arginase-1 HepPar-1 Glypican-3 CD10 and polyclonal CEA± (peri-canalicular pattern)	MOC31- (to distinguish from intrahepatic cholangiocarcinoma) Albumin in situ hybridization - (also for intrahepatic cholangiocarcinoma)
Lower gastrointestinal carcinoma, including small intestinal, appendiceal, and colorectal	CK7±/CK20+	CDX2 Villin SATB2	

²Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol 2015;22(3):149-167.

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Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Lung adenocarcinoma	CK7+/CK20-	TTF1 NapsinA	
Mesothelioma	CK7±/CK20-	Calretinin WT1 CK5/6 D2-40 Mesothelin	p63- CEA- MOC31- BerEP4- TTF-1- (to distinguish from adenocarcinoma)
Neuroendocrine carcinoma, including small cell carcinoma	CK7±/CK20± ("dot-like" pattern in Merkel cell carcinoma)	Chromogranin Synaptophysin CD56	TTF1± CDX-2± Mitotic rate and/or Ki-67 (for grade)
Non-seminomatous germ cell tumor	CK7-/CK20-	SALL4 OCT3/4±	CD30 Glypican-3 PLAP (for further subtyping)
Ovarian mucinous carcinoma	CK7+/CK20±	PAX8± CDX2±	
Ovarian serous carcinoma	CK7+/CK20-	PAX8 WT1	p53 (diffuse) SATB2- CDX2-
Pancreaticobiliary carcinoma, including intrahepatic cholangiocarcinoma	CK7+/CK20±	CDX2± CK19	SMAD4 loss ± (pancreas, extrahepatic cholangiocarcinoma, and colorectal carcinomas) Albumin in-situ hybridization - (also for intrahepatic cholangiocarcinoma)
Prostate carcinoma	CK7-/CK20-	PSA PSAP NKX3-1 P501S (Prostein) ERG±	

²Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol 2015;22(3):149-167.

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

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS²

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Renal cell carcinoma	CK7±/CK20-	PAX2 PAX8 Carbonic anhydrase IX (CA9)± EMA± Vimentin± CD10± (membranous)	
Salivary gland carcinoma	CK7+/CK20-	CK5/6 p63	GATA3 AR
Squamous cell carcinoma	CK7-/CK20-	CK5/6 p63 or p40 34βE12	p16 (strong diffuse staining) and/or human papillomavirus in situ hybridization (HPV-associated carcinoma)
Thyroid carcinoma (follicular or papillary carcinomas)	CK7+/CK20-	TTF1 PAX8 CK19±	Thyroglobulin
Thyroid carcinoma (medullary carcinoma)	CK7+/CK20-	TTF1 PAX8 CK19±	Calcitonin, synaptophysin, chromogranin, and monoclonal CEA
Urothelial carcinoma	CK7+/CK20±	GATA3 p63 or p40 CK5/6± 34βE12 S100P Uroplakin II	
Upper gastrointestinal tract carcinoma, including esophagus and stomach	CK7+/CK20±	Polyclonal CEA CDX-2± Villin±	

²Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol 2015;22(3):149-167.

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

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PRINCIPLES OF CHEMOTHERAPY

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

ECOG PERFORMANCE STATUS (PS)

Grade

- 0** Fully active, able to carry on all pre-disease performance without restriction
- 1** 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
- 2** Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3** Capable of only limited self care, confined to bed or chair more than 50% of waking hours
- 4** Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

Adapted from Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Neuroendocrine Tumors

For poorly differentiated (high-grade or anaplastic) or small cell subtype, [see NCCN Guidelines for Small Cell Lung Cancer](#)

For well-differentiated neuroendocrine tumors, [see NCCN Guidelines for Neuroendocrine Tumors](#) - Carcinoid Tumors

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Occult Primary

SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

ADENOCARCINOMA

Paclitaxel and Carboplatin

Paclitaxel 200 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Repeat cycle every 3 weeks¹

Paclitaxel, Carboplatin, and Etoposide

Paclitaxel 200 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Etoposide 50 mg/d PO alternating with 100 mg/d PO Days 1–10
Repeat cycle every 3 weeks²

Docetaxel and Carboplatin

Docetaxel 65 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Repeat cycle every 3 weeks³

Gemcitabine and Cisplatin

Gemcitabine 1250 mg/m² IV Days 1 and 8
Cisplatin 100 mg/m² IV Day 1
Repeat cycle every 3 weeks⁴

Gemcitabine and Docetaxel

Gemcitabine 1000 mg/m² IV Days 1 and 8
Docetaxel 75 mg/m² IV Day 8
Repeat cycle every 3 weeks⁵

CapeOX

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

mFOLFOX6

Oxaliplatin 85 mg/m² IV Day 1
Leucovorin 400 mg/m² IV Day 1
Fluorouracil 400 mg/m² IV bolus on Day 1, then
Fluorouracil 1200 mg/m²/d IV continuous infusion x 2 Days
(total 2400 mg/m² over 46–48 hours)
Repeat cycle every 2 weeks^{6,7}

Docetaxel and Cisplatin

Docetaxel 75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Repeat cycle every 3 weeks⁸

Irinotecan and Carboplatin

Irinotecan 60 mg/m² IV Days 1, 8, and 15
Carboplatin AUC 5 IV Day 1
Repeat cycle every 4 weeks⁹

Irinotecan and Gemcitabine

Irinotecan 100 mg/m² IV Days 1 and 8
Gemcitabine 1000 mg/m² IV Days 1 and 8
Repeat cycle every 3 weeks¹⁰

[See references on
OCC-B 4 of 4](#)

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SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

SQUAMOUS CELL

Paclitaxel and Carboplatin

Paclitaxel 200 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Repeat cycle every 3 weeks¹

Cisplatin and Gemcitabine

Cisplatin 100 mg/m² IV Day 1
Gemcitabine 1250 mg/m² IV Days 1 and 8
Repeat cycle every 3 weeks⁴

mFOLFOX6

Oxaliplatin 85 mg/m² IV Day 1
Leucovorin 400 mg/m² IV Day 1
Fluorouracil 400 mg/m² IV bolus on Day 1, then
Fluorouracil 1200 mg/m²/d IV continuous infusion x 2 Days
(total 2400 mg/m² over 46–48 hours)
Repeat every 2 weeks^{6,7}

Docetaxel, Cisplatin, and Fluorouracil

Docetaxel 75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Fluorouracil 750 mg/m²/d IV continuous infusion Days 1–5
Repeat cycle every 3 weeks¹²

Paclitaxel and Cisplatin

Paclitaxel 175 mg/m² IV Day 1
Cisplatin 60 mg/m² IV Day 1
Repeat cycle every 3 weeks¹⁴

Docetaxel and Carboplatin

Docetaxel 75 mg/m² IV Day 1
Carboplatin AUC 5 IV Day 1
Repeat cycle every 3 weeks¹⁵

Docetaxel and Cisplatin

Docetaxel 60 mg/m² IV Day 1
Cisplatin 80 mg/m² IV Day 1
Repeat cycle every 3 weeks¹¹

OR

Docetaxel and Cisplatin

Docetaxel 75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Repeat cycle every 3 weeks⁸

Cisplatin and Fluorouracil

Cisplatin 20 mg/m² IV Days 1–5
Fluorouracil 700 mg/m²/d IV continuous infusion Days 1–5
Repeat cycle every 4 weeks¹³

[See references on
OCC-B 4 of 4](#)

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

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



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PRINCIPLES OF RADIATION THERAPY

LOCALIZED DISEASE

- Consider definitive radiotherapy for patients with localized disease.
- Consider stereotactic ablative radiotherapy (SABR) for limited (1–3) metastases and pulmonary metastases (48–60 Gy/4–5 fractions).

ADJUVANT THERAPY

- Consider adjuvant radiation therapy after lymph node dissection if the disease is limited to a single nodal site with extranodal extension or inadequate nodal dissection with multiple positive nodes. 45 Gy is recommended with or without boost of 5–9 Gy/1.8–2.0 Gy fraction to nodal basin for isolated supraclavicular, axillary, or inguinal nodal metastasis.

PALLIATIVE THERAPY

- Consider palliative radiotherapy for symptomatic patients. Hypofractionated RT can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression.
 - ▶ Regimen: A number of hypofractionation regimens could be considered, but typically 8 Gy in 1 fraction, 20 Gy in 4–5 fractions, or 30 Gy in 10 fractions are most frequently used.

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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 indicated.

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Overview

Occult primary tumors, or cancers of unknown primary (CUPs), are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation.^{1,2} These heterogeneous tumors have a wide variety of clinical presentations and a poor prognosis in most patients. Early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors.³ Median survival is ~8 to 12 months and depends on several prognostic factors that are discussed below. Select patients with favorable subsets of CUP have median overall survival (OS) times in the range of 12 to 36 months.⁴

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, CUP is 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.⁵ 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 05/15/2016 and 05/15/2017, using the following search terms: occult primary OR cancer of 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.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized



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Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 93 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Epidemiology

CUP occurs roughly equally in men and women, with an average age at diagnosis of 60 years.^{6,7} An estimated 33,770 cases of CUP will be diagnosed in the United States in 2017, accounting for approximately 2% of all cancers diagnosed in the United States.⁸ However, deaths from these cancers are estimated to be 42,270 in 2017. This discrepancy is believed to arise from incongruity in the initial coding diagnosis and cause-of-death diagnosis, including the lack of specificity in recording the underlying cause of death on death certificates. An analysis of the SEER database from 1973 to 2008 found that the percentage of cancers diagnosed as occult primary has been decreasing over time.⁹ Unfortunately, no improvement in median survival was seen over this time period.

A study published in 2010 based on the analysis of the Swedish Family-Cancer Database revealed that CUP may have a genetic basis.¹⁰ 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, CUP was 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.¹⁰

A latent primary cancer may emerge during the natural course of the disease though it is uncommon. In 20% to 50% of patients, the primary tumor is not identified even after postmortem examination.^{6,11,12}

Presentation and Prognosis

Multiple sites of involvement are observed in more than 50% of patients with CUP.¹³ Common sites of involvement are the liver, lungs, bones, and lymph nodes.^{14,15} Although certain patterns of metastases suggest possible primary sites, CUP can metastasize to any site. Therefore, physicians should not rely on patterns of known metastases to determine the primary site.

Most patients with CUP 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.^{16,17} 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 cancers¹⁸); patients with isolated inguinal adenopathy (SCC); patients with poorly differentiated neuroendocrine (PDNE) carcinomas; men with



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blastic bone metastases and elevated prostate-specific antigen (PSA; adenocarcinoma); and patients with a single, small, and potentially resectable tumor.^{16,19,20} 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, few data exist to support this idea. In addition, results from a retrospective review of 179 patients with CUP suggested that patients with better PS, higher serum albumin, and lower serum lactate dehydrogenase (LDH) were more likely to benefit from chemotherapy.²¹

Pathology

CUP often has multiple chromosomal abnormalities and overexpression of several genes, including *EGFR*, *c-kit/PDGFR*, *Ras*, *BCL2*, *HER2*, and *p53*.²²⁻²⁴ *BCL2* and *p53* are overexpressed in 40% and 53% of occult primary tumors, respectively.²⁵ The *BRD4-NUT* oncogene, resulting from the chromosomal translocation t(15;19), has been identified in children and young adults with carcinoma of midline structures and unclear primary sites.^{1,26,27}

CUP 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%).^{1,15} Additionally, because of improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary have been recognized (1%).^{28,29}

In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC).³⁰⁻³³ In addition, gene expression profiling (GEP) assays have been developed to attempt to identify the tissue of origin in patients with occult primary cancers.³⁴⁻³⁶ Both methodologies offer a similar range of accuracy in tumor classification (approximately 75%).³⁷ Thus far, the literature on these approaches has focused far more on establishing a tissue of origin than on determining whether such identification leads to better outcomes in patients. Thus, while there is a diagnostic benefit to GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend cancer classifier assays (gene signature profiling) at this time for the identification of tissue of origin as standard management in the diagnostic workup of patients with CUP. Furthermore, 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

Communication between the treating oncologist and the pathologist is important to ensure adequate tissue sampling, ideally by means of a core needle biopsy and/or fine-needle aspiration (FNA) with cell block. The use of IHC in CUP is based on the premise that concordance exists in the expression profiles of primary and metastatic cancers.^{34,36} The predictive value of IHC panels improves with the recognition of patterns that are strongly indicative of specific tumors. However, the limitations of IHC testing include factors affecting tissue antigenicity, interobserver and intraobserver variability in interpretation, tissue heterogeneity, and inadequate biopsy sample. Nevertheless, with well-performed and interpreted IHC panels, pathologists can identify the putative site of origin of CUP in about 70% of the samples (validation to determine



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accuracy is a challenge given the unknown primary cancer designation).³⁷

In patients with CUP, IHC studies are useful for the characterization of poorly differentiated or undifferentiated tumors and for cell-type determination and pathologic diagnosis.³⁰⁻³³ However, exhaustive IHC studies (in excess of 10–12 stains) have not been shown to increase the diagnostic accuracy in identifying the putative primary sites.³⁸ IHC studies should be used in conjunction with imaging studies to select the best possible treatment options for patients with CUP.

To determine tissue of origin using IHC, a tiered approach is recommended. A first tier of IHC assays can be used to help determine tissue lineage using lineage-restricted markers (eg, carcinoma, sarcoma, lymphoma, melanoma). A second tier of IHC, using organ-specific markers, can be used to help suggest the putative primary site.³⁷ In select patients, it may be helpful to use a third tier of testing for tumor biomarkers that might inform treatment decisions, such as RAS, HER2, or ALK rearrangements. Combined with knowledge gained through imaging and clinical presentation, biomarker testing with clear therapeutic intent might be beneficial.

Informative new IHC markers continue to emerge and may aid in the diagnosis of CUP.³⁹ See *Immunohistochemistry Markers for Unknown Primary Cancers* in the algorithm for suggested IHC markers. However, testing a large series of IHC markers in individual patients should be avoided.

Molecular Profiling

Over the past decade, studies have examined various molecular assays designed to identify the tissue of origin in CUP (reviewed by Varadhachary and Raber³⁶ and Hainsworth and Greco⁴⁰). These assays are designed based on the assumption that metastatic tumors will have

similar molecular profiles to that of the primary tumor of origin. Assays used in GEP utilize messenger RNA (mRNA)—, DNA—, or microRNA (miRNA)—based platforms.⁴¹⁻⁴⁷ When validated using samples from known tumor types, these assays have generally demonstrated an accuracy rate of 85% to 90%.^{36,40} Because it is difficult to confirm the site of origin in most cases of CUP, the accuracy of GEP assays in occult primary tumor samples is challenging to determine. Surrogate measures used to determine accuracy include correlation with IHC findings, clinical presentation/response to therapy, as well as appearance of latent disease at the primary tumor site.^{36,40} Several studies suggest that GEP profiling is comparable or superior to the accuracy of IHC for poorly differentiated/undifferentiated carcinomas.^{38,48}

In addition to DNA— and mRNA—based assays, miRNA—based assays have also generated interest for their potential to identify tissue of origin. These assays examine the presence of specific miRNAs, which are noncoding RNAs that regulate gene expression and show high tissue specificity.⁴⁹⁻⁵¹

More recently, another active area of investigation has been next-generation sequencing (NGS) to characterize the genome of occult primary tumors. NGS has the potential to identify actionable biomarkers outside of tissue-specific markers, but this approach remains experimental.^{36,52-55} Data from ongoing studies evaluating effectiveness of novel targets against specific mutations will help define the role of this approach.

In a recent comprehensive GEP study of 200 CUP specimens, use of a hybrid-capture—based NGS assay enabled the identification of at least 1 potentially targetable genomic alteration in 85% of CUP specimens.⁵⁴ Mutations and/or amplifications of *ERBB2*, *EGFR*, and *BRAF* occurred more frequently in adenocarcinoma CUPs (10%, 8%, and 6%,



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respectively) than in non-adenocarcinoma CUPs (4%, 3%, and 4%, respectively). Additionally, clinically relevant alterations in the receptor tyrosine kinase (RTK)/Ras signaling pathway were found in 72% of adenocarcinoma CUPs but in only 39% of non-adenocarcinoma CUPs. Since the identification of clinically relevant genomic alterations has the potential to influence therapy options, use of comprehensive GEP may help identify novel treatment paradigms to address the limited treatment options and poor prognoses of patients with CUP.⁵⁴ Ongoing clinical trials will help define the impact.

Assessing the Clinical Benefit of Molecular Profiling

Several commercially available GEP tests have been evaluated in prospective clinical studies in an attempt to determine if the information they provide translates into clinically meaningful benefits for patients.⁵⁶ 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 al⁴⁶ and the 92-gene assay of Ma et al⁴⁷) showed a response to colorectal chemotherapy regimens as expected for patients with stage IV colorectal cancer.⁵⁷ 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.⁵⁶ While the median survival time of 12.5 months in the subset of patients who 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.^{36,40,58} As noted, outcomes data are not currently available to

recommend routine use of molecular profiling in the workup of CUP. 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.⁵⁸

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], lymphoma or other hematologic malignancy, melanoma, sarcoma, 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 contrast-enhanced chest/abdominal/pelvic CT scans are also recommended. Endoscopy can be included in the initial evaluation if clinically indicated. Other diagnostic studies should be based on the clinical presentation and subsequent histopathologic findings. 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.⁵⁹ In the past several years, PET scans



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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,^{60,61} and might be warranted in some situations for CUP. PET scans have shown intermediate specificity and high sensitivity in a few small studies, but larger studies are required to determine the clinical utility and role of PET scans in patients with CUP.^{4,59,62,63} In a comprehensive review of 10 published studies, Seve et al concluded that PET is a valuable imaging modality for patients with CUP with a single site of metastasis if therapy with a curative intent is planned.⁶⁴

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 (FDG) tracer in some neoplastic tissues. In these cases, the combination of a PET scan with either a CT scan or MRI can provide more useful information.^{65,66} Studies on the use of PET/CT scans for detecting occult primary tumors have reported that the combination of PET/CT identified the primary site in 25% to 75% of patients.⁶⁷⁻⁷⁵

One meta-analysis and systematic review on the use of PET/CT in patients with CUP found that primary tumors were detected in 37% of 433 patients from 11 studies, with pooled sensitivity and specificity both at 84%.⁷⁶ These results indicate that combined modality scanning could play an important role in the diagnosis of CUP. 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.⁷⁷ The accuracy of PET and PET/CT scans in patients with CUP 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%),⁷⁸ 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.

Recently, combined modality screening with PET/MRI has been evaluated in several studies for its diagnostic significance in CUP. In a preliminary comparison trial to evaluate the diagnostic potential of whole-body PET/MRI versus PET/CT, Ruhlmann et al found that both hybrid imaging techniques provide a comparable diagnostic ability for detection of the primary cancer site in patients with CUP.⁷⁹ Furthermore, due to the significantly lower dose of ionizing radiation (IR), PET/MRI may serve as an alternative to PET/CT, particularly for therapy monitoring and/or long-term surveillance.⁷⁹ In a prospective study by Sekine et al, 43 patients with suspected CUP were assessed with PET/CT and PET/MRI for the presence of a primary tumor, lymph node metastases, and distant metastases.⁸⁰ PET/MRI was found to be superior to PET/CT for primary tumor detection and comparable to PET/CT for the detection of lymph node and distant metastases. PET/CT also tended to misclassify physiologic uptake of FDG as malignancy compared with PET/MRI.⁸⁰

A relatively new technique, termed multiparametric MRI (MPMRI), allows for detailed visualization of tissues as well as their chemical makeup, enabling experienced radiologists to better separate cancerous tissue from benign tissue. In a retrospective study of 38 patients with CUP and cervical lymph node metastases, the accuracy of PET/CT and MPMRI in locating the primary cancer in the neck region



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was identical.⁸¹ Therefore, because of their lower IR dose levels and seemingly identical efficacy and accuracy, PET/MRI and MPMRI seem to be favorable over PET and/or CT scans in the workup of suspected occult malignancies. However, more robust data are required to support this assertion.

Workup

Patients with a suspected occult primary tumor will typically present to the oncologist after undergoing an initial core needle biopsy (preferred) and/or FNA with cell block. Accurate pathologic assessment of the biopsied material is of utmost importance. Therefore, the pathologist must be consulted to determine whether additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy).

Examination of the biopsy material by light microscopy is usually performed first. Other techniques include electron microscopy and flow cytometry. Although IHC stains can be informative (see *Immunohistochemistry* above), large panels of IHC markers should be avoided. As previously mentioned, the panel does not currently recommend tumor sequencing or gene signature profiling for the identification of the tissue of origin as standard practice. If contrast-enhanced CT scans of the neck, chest, abdomen, and pelvis were not performed previously, they are varyingly indicated depending on the clinical presentation of the patient.

This initial evaluation will identify a primary site in approximately 30% of patients presenting with CUP. 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, and 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 below. Additional studies can be important in determining whether the occult primary cancer is potentially curable, or in diagnosing a possibly 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 IHC markers is also recommended. Contrast-enhanced MRI and/or ultrasound of the breast should be considered for patients with a non-diagnostic mammogram and histopathologic evidence of breast cancer. Contrast-enhanced MRI should also be considered when mammography is not adequate to assess the extent of the disease, especially in women with dense breast tissue and/or positive axillary nodes, or to evaluate the chest wall.⁸² 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 select women by allowing for lumpectomy instead of mastectomy.⁸³⁻⁸⁵ In one report, the primary site was identified using MRI in approximately half of the women presenting with axillary metastases, irrespective of breast density.⁸⁶



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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 (or other putative primary sites) should be considered.

Workup for Possible Germ Cell Primary

Adenocarcinoma with positive mediastinal nodes suggests a possible primary germ cell tumor in patients younger than 40 years or those between 40 and 50 years of age, as does a retroperitoneal mass in men younger than 65 years of age. Thus, these guidelines recommend measurement of β -human chorionic gonadotropin (β -hCG) and α -fetoprotein (AFP) levels as well as testicular ultrasound for male patients in these age groups with occult primary adenocarcinoma having positive mediastinal nodes and/or a 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

Adenocarcinoma with positive mediastinal and/or inguinal nodes, with or without accompanying pleural effusion, peritoneal ascites, or retroperitoneal mass is suggestive of an occult non-germ cell ovarian primary tumor. Testing for the ovarian cancer marker CA-125 is recommended in these cases, as is consultation with a gynecologic oncologist, if clinically indicated.

Workup for Possible Prostate Primary

All men older than 40 years of age with an adenocarcinoma of unknown primary, except those with metastases limited to the liver or brain, should undergo testing for PSA levels. In addition, men presenting with bone metastases or multiple sites of involvement should have PSA levels assessed regardless of age.

Additional Workup for Localized Adenocarcinoma or Carcinoma Not Otherwise Specified

In patients with adenocarcinoma involving painful bone lesions, a bone scan (if a PET/CT scan was not previously performed) and diagnostic imaging studies are recommended. During diagnostic imaging, x-rays are recommended for the initial evaluation. If pain or other neurologic symptoms suggest spine metastases, an MRI or contrast-enhanced CT scan should be used for the initial evaluation. When x-ray films suggest metastases in weight-bearing areas, further imaging is recommended for therapeutic evaluation. Urine cytology is recommended for patients presenting with a retroperitoneal mass, followed by cystoscopy if findings are suspicious. 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.⁸⁷ Endoscopic evaluation is recommended for patients presenting with malignancy in the liver and is suggested for patients with positive supraclavicular nodes, if clinically indicated. However, endoscopy is not routinely recommended for patients presenting with malignant ascites (ie, peritoneal presentation). Since the differentiation between metastatic adenocarcinoma of the liver and primary hepatocellular carcinoma (HCC) is sometimes challenging, the use of AFP as a marker for HCC as part of the additional workup for CUP in the liver is recommended.⁸⁸ In the absence of a positive fecal occult blood test or other clinical factors suggesting a putative colon primary or concern for bowel



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involvement/obstruction from metastatic cancer or carcinomatosis, the diagnostic yield of colonoscopy is low and is therefore not recommended as standard practice in the workup process in the guidelines.⁸⁹

Workup for SCC

SCC can be present in the lymph nodes of the head and neck region, as well as in the supraclavicular, axillary, and inguinal nodes. Contrast-enhanced CT scans of the abdomen and pelvis; perineal and lower extremity examination; gynecologic oncology consult; and anal endoscopy are recommended for patients with SCC involving inguinal lymph nodes, unless contraindicated. A bone scan (if a chest/abdomen/pelvis contrast-enhanced CT scan was not previously performed) and diagnostic imaging studies are recommended for SCC involving painful or bone scan-positive bone lesions. Directives for diagnostic imaging in this context have been previously described under *Additional Workup for Localized Adenocarcinoma or Carcinoma Not Otherwise Specified* above.

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).

Workup for Neuroendocrine Tumors

Neuroendocrine tumors can metastasize to several sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal lymph 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).

Management

Psychosocial Distress

For many patients, the apparent uncertainties surrounding the diagnosis of unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. In fact, a study by Hyphantis et al found that psychiatric manifestations, including anxiety and depression, were more common in patients with CUP than in those with known primaries.⁹⁰ Empathetic discussion about the natural history of these types of cancers and their prognoses, and the provision of support and counseling by both the primary oncology team and specialized services, may help alleviate this distress. Please see the NCCN Guidelines for Distress Management for further information (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 discussions 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 and the NCCN Guidelines for Survivorship for more information (available at www.NCCN.org).

Treatment Based on Workup Findings

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



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Adenocarcinoma

Patients with localized adenocarcinoma involving supraclavicular nodes (unilateral or bilateral) or in the head and neck regions should be treated according to the Occult Primary pathway described in the NCCN Guidelines for Head and Neck Cancers. 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.^{91,92} 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). Women with localized adenocarcinoma involving axillary nodes and those who are breast-marker positive and have pleural effusion should be treated according to the NCCN Guidelines for Breast Cancer.

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 also 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.

Other locations of adenocarcinomas of unknown primary are not associated with a common primary site. Treatment recommendations in these cases are thus general and may involve local and systemic therapies. For example, axillary node dissection is recommended in men with localized adenocarcinoma involving the axillary nodes. Additionally, radiation therapy (RT) and chemotherapy can also be considered if clinically indicated. Surgery should be considered for resectable lung nodules. Chemotherapy, preferably as part of a clinical trial, or stereotactic body radiotherapy (SBRT) can be considered for oligometastatic lung nodules with or without resection. Lymph node dissection is recommended for inguinal nodal involvement; RT with or without chemotherapy can also be considered if clinically indicated. It should be noted that the use of RT alone in cases of bilateral inguinal node involvement is a category 2B recommendation.⁹³

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

For patients with good PS and bone lesions with potential for fracture in a weight-bearing area, surgery and/or RT are the recommended treatment options. In the case of patients with poor PS or those with isolated or painful bone lesions, RT 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. 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 RT is



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recommended, with chemotherapy considered for select patients (category 2B).

To view the most recent versions of these guidelines, visit the NCCN website at www.NCCN.org.

For patients with disseminated CUP, a clinical trial is preferred. Additional recommendations include symptom control, consideration of chemotherapy on an individual basis, and specialized approaches (see *Specialized Approaches* below).

SCC

In patients with site-specific SCC and localized axillary or inguinal lymph node involvement, lymph node dissection is recommended. RT can be considered if clinically indicated with or without chemotherapy (the use of RT alone in the case of bilateral inguinal node involvement is a category 2B recommendation).⁹³ 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 occult primary tumors described in the NCCN Guidelines for Head and Neck Cancers.

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 for impending fracture and/or RT are options for patients with an isolated bone lesion and good PS. In the case of patients with poor PS or those with painful bone lesions, RT is recommended. Patients with brain metastases should be treated according to the

recommendations for metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers.

To view the most recent versions of these guidelines, visit the NCCN website at www.NCCN.org.

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

Neuroendocrine Tumors

Treatment of neuroendocrine tumors should follow the Neuroendocrine Unknown Primary pathway of the NCCN Guidelines for Neuroendocrine Tumors (available at www.NCCN.org).

Chemotherapy

Many chemotherapeutic regimens have been evaluated in patients with CUP 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.⁹⁴⁻¹⁰⁰ Most of the patients in these studies had adenocarcinoma, with only 5% to 10% having poorly differentiated carcinoma. Overall response rates (ORRs) 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 no longer 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 CUP in phase II studies. However, a 2012 systematic review of chemotherapy trials in patients with CUP of unfavorable presentations concluded that no specific regimen can be recommended as standard of care.¹⁰¹ A systematic review and meta-



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analysis published in 2013 largely came to the same conclusion, with taxanes showing a possible slight advantage over platinum-based regimens.¹⁰² In general, chemotherapy shows limited efficacy and considerable toxicity in patients with CUP. 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 aggressive cancer and a PS of 0. The choice of 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 or undifferentiated occult primary tumors respond differently from well- to moderately differentiated occult primary tumors. Tumors in the former group seem to be highly responsive to cisplatin-based combination chemotherapy.^{103,104} Objective response rates (RRs) reported in 2 studies from the early 1990s were 53% (van der Gaast et al¹⁰⁴) and 63% (Hainsworth et al¹⁰³) with complete RRs of 12% and 26%, respectively. In one study, patients who had tumors with extragonadal germ cell features showed a high RR.¹⁰³ In the other, patients with undifferentiated carcinomas had a better RR than those with poorly differentiated carcinomas (79% vs. 35%; $P = .02$).¹⁰⁴

In more recent years, newer regimens containing taxanes and/or gemcitabine have shown efficacy in phase II studies for the treatment of patients with CUP.¹⁰⁵⁻¹⁰⁸ Schneider et al reported that the combination of carboplatin, gemcitabine, and capecitabine was active in CUP in patients with good PS.¹⁰⁶ Median progression-free survival (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 CUP and poor prognostic features.¹⁰⁷ Gemcitabine plus oxaliplatin was also assessed in patients with CUP in a phase II study.¹⁰⁵ This well-tolerated combination gave a median OS of 12.8 months (95% CI, 8.5–18.5 months) and PFS of 3.1 months (95% CI, 1.7–6 months).

In subsequent studies, molecularly targeted agents have been tested for efficacy in treating patients with CUP. Hainsworth et al^{109,110} 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 CUP. 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.¹⁰⁹ Median survival was 7.4 months (1-year survival, 33%), which was superior to that observed by the same group with gemcitabine alone and gemcitabine plus irinotecan (3 and 4.5 months, respectively). In a 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.¹¹⁰ After a median follow-up of 19 months, the median PFS time and 2-year OS rates were 8 months 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 phase III studies, as described below. Regimens other than those listed 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 unknown primary.¹¹¹⁻¹¹³ In the Hellenic Cooperative Oncology Group study, the combination of paclitaxel and carboplatin



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produced an ORR of 38.7% according to intention-to-treat (ITT) analysis; no difference was seen in the RRs for adenocarcinomas versus undifferentiated carcinomas.¹¹¹ 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.¹¹²

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.¹¹⁴ The median survival time was 10 months.

A phase III randomized study found that the triple drug regimen of paclitaxel, carboplatin, and etoposide had comparable efficacy to gemcitabine and irinotecan in the first-line treatment of patients with CUP.¹¹⁵ The RR for paclitaxel/carboplatin/etoposide was 18% among 93 patients; median PFS and OS were 3.3 months and 7.4 months, respectively, and the 2-year survival rate was 15%. In a randomized prospective phase II study conducted by the German CUP Study Group, the double drug regimen of paclitaxel and carboplatin showed better clinical activity than the gemcitabine and vinorelbine combination.¹¹⁶ The median OS, 1-year survival rate, and RR 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 CUP.¹¹⁷ However, survival was similar to that observed in previous phase II trials and the overall toxicity was found to be greater than that observed with other regimens. Therefore, this sequential treatment regimen is not recommended.

Docetaxel and Carboplatin

Greco et al reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated carcinoma of unknown primary.¹¹⁸ Major response to therapy was observed in 26% of patients receiving docetaxel and cisplatin, with a median survival of 8 months and a 1-year survival rate of 42%. In patients receiving docetaxel and carboplatin, the corresponding RR was 22%, with a median survival of 8 months and a 1-year survival rate of 29%. Docetaxel in combination with carboplatin was better tolerated than docetaxel with cisplatin in this study.¹¹⁸

In a report on the Hellenic Cooperative Oncology Group phase II study, a 1-hour treatment with docetaxel and carboplatin every 3 weeks was found to be as safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated carcinoma of unknown primary with a PS of 0 to 2.¹¹⁹ 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.

Gemcitabine and Cisplatin

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).¹²⁰ Well-differentiated adenocarcinoma was the most common histology, with one-fourth of patients having a single metastatic site. Objective RRs 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, and both combination regimens were associated with significant toxicities. The GEFCAPI 02 trial randomly



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assigned 52 patients to cisplatin with or without gemcitabine.¹²¹ 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.

Gemcitabine and Docetaxel

A non-cisplatin-based regimen containing gemcitabine and docetaxel was found to be active and well-tolerated as first-line therapy in patients with CUP.¹²² Of 35 patients, 1 complete response and 13 partial responses were observed, with an ORR of 40%. The median time to disease progression was 2 months and the median OS was 10 months.

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-line¹²³ and second-line¹²⁴ treatment of patients with CUP. This regimen gave RRs ranging from 12% to 19%, with disease-free survival of 2.5 to 3.7 months and OS of 7.5 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 CUP, FOLFOX has been shown to be equivalent to CapeOx in colorectal cancer.¹²⁵⁻¹²⁸ The panel therefore supports FOLFOX (mFOLFOX6^{129,130}) as an acceptable treatment option for these patients.

Docetaxel and Cisplatin

Combination therapy with docetaxel and cisplatin was examined in a cohort of 29 patients with CUP.¹³¹ 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 RR was 37.9%, and median PFS and OS were 6 and 16 months, respectively.

Irinotecan and Carboplatin

The combination regimen of irinotecan and carboplatin was evaluated in a phase II study of 45 patients with CUP who were chemotherapy-naïve. The regimen was associated with an ORR of 41.9%; median PFS was 4.8 months and OS was 12.2 months. The regimen was considered active by the authors and was associated with significant toxicities, including grade 3 or greater leukopenia (21%), neutropenia (33%), anemia (25%), and thrombocytopenia (20%).¹³²

Irinotecan and Gemcitabine

In a phase III randomized study comparing paclitaxel/carboplatin/etoposide to irinotecan/gemcitabine, both regimens performed similarly. The RR for irinotecan/gemcitabine was 18% with a 2-year survival rate of 18%. Among the 105 patients receiving irinotecan/gemcitabine, median PFS and OS were 5.3 months and 8.5 months, respectively.¹¹⁵

SCC

Platinum-based regimens have typically been used to treat disseminated SCC. Historically, the combination of cisplatin and 5-FU has been the most frequently used regimen for patients with SCC of unknown primary.^{133,134}

Overall, only a few small studies have assessed chemotherapy regimens in patients with SCC occult primaries. Therefore, the panel lists possible regimens based on evidence from studies of patients with



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SCC of known primaries and small studies of patients with SCC occult primaries. Regimens other than those listed can also be considered.

Paclitaxel and Carboplatin

The combination of paclitaxel and carboplatin is commonly used in non-small cell lung, gastric, and esophageal cancers.¹³⁵⁻¹⁴⁰

In the Hellenic Cooperative Oncology Group phase II study of combined paclitaxel and carboplatin in patients with CUP (discussed above for adenocarcinoma), 3 patients had tumors of SCC histology.¹¹¹ These patients had an RR of 30% and a median response duration of 3 months.

Cisplatin and Gemcitabine

The combination of cisplatin and gemcitabine is used in non-small cell lung cancer.^{137,138,141-143}

The GEFCAPI 02 trial compared cisplatin to cisplatin plus gemcitabine in 52 patients with CUP.¹²¹ 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

FOLFOX is used to treat SCC of the esophagus and stomach.^{144,145} The panel lists mFOLFOX6 as a possible regimen for occult primary SCC, based on the evidence discussed above for adenocarcinoma.^{129,130}

Docetaxel, Cisplatin, and 5-FU

The combination of docetaxel, cisplatin, and 5-FU is used in gastric, esophageal, and head and neck cancers.¹⁴⁶⁻¹⁴⁹ 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.¹⁴⁷ The ORRs after induction chemotherapy were 72% and 64% in the 3-drug and 2-drug arms, respectively.

Paclitaxel and Cisplatin

The combination of paclitaxel and cisplatin is used in esophageal, head and neck, and non-small cell lung cancers.^{138,150-153} In a randomized phase III trial of patients with advanced head and neck cancer, no significant differences were seen in patients treated with paclitaxel/cisplatin compared with patients treated with cisplatin/5-FU.¹⁵²

This regimen has also been assessed in a phase II study of patients with unfavorable presentations of CUP.¹⁵⁴ Three of the 37 patients had SCC. The regimen gave an ORR of 42%, and the median OS was 11 months (95% CI, 8.3–13.5).

Docetaxel and Carboplatin

The combination of docetaxel and carboplatin is used in head and neck and non-small cell lung cancers.^{155,156}

The combination of docetaxel and carboplatin was assessed in a phase II trial of 47 patients with occult primary adenocarcinomas or poorly differentiated carcinomas, with an RR of 32% and median OS of 16.2 months.¹¹⁹

Docetaxel and Cisplatin

The combination of docetaxel and cisplatin is used in non-small cell lung, esophageal, and gastric cancers.^{138,155,157-159} In a multicenter phase II trial of 34 evaluable patients with metastatic esophageal SCC, docetaxel/cisplatin gave an objective tumor RR of 33% in the ITT population. The median PFS and OS times were 5.0 months and 8.3 months, respectively.¹⁵⁸



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The safety and efficacy of this regimen has also been assessed in 45 patients with CUP.¹⁶⁰ The reported ORR 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 docetaxel/cisplatin regimen.

Combination therapy with docetaxel and cisplatin was also examined in a cohort of 29 patients with CUP, 4 of whom had tumors with squamous cell histology.¹³¹ The ORR was 37.9%, and median PFS and OS were 6 months and 16 months, respectively.

Cisplatin and 5-FU

This historic regimen has been used in the treatment of metastatic anal, head and neck, esophageal, and gastric cancers.^{152,161-165} It has also been tested in patients with SCC of unknown primary.^{133,134}

Kusaba et al reviewed their experiences of treating patients with CUP with this regimen, and reported an RR of 54.5% and a median OS of 10 months.¹⁶⁶

Neuroendocrine Tumors

Neuroendocrine CUPs are uncommon, and their clinical behavior is dependent on the tumor grade and level of differentiation.¹⁶⁷

Neuroendocrine tumors, regardless of grade, represent a favorable prognostic subset of CUP that are responsive to combination chemotherapy, making long-term survival a possibility in a minority of patients.²⁸

Hainsworth et al evaluated the efficacy of paclitaxel/carboplatin/etoposide in metastatic PDNE carcinomas in patients who had received no prior treatment.¹⁶⁸ Of these patients, 62% had PDNE CUP. Major responses were observed in 53% of patients, with a median survival time of 14.5 months and 2- and 3-year survival rates of 33% and 24%, respectively. The results of this trial showed that

PDNE carcinomas are chemosensitive, with a high ORR to combination chemotherapy.

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.¹⁶⁹ No significant differences were seen in RR (73% for both regimens) and median OS (10.6 months for carboplatin/etoposide vs. 9.9 months for cisplatin/etoposide).

In another 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.¹⁷⁰ 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.^{171,172}

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

RT is a treatment option for a variety of localized tumors, particularly as follow-up treatment after lymph node dissection. Adjuvant RT after lymph node dissection may be appropriate if the disease is limited to a single nodal site with extra-nodal extension, or in the case of inadequate nodal dissection with multiple positive nodes. Definitive RT



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can be considered for select patients with localized disease. RT 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. In the palliative setting, hypofractionated RT can be considered for symptomatic patients with uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.

One study examined individualized intensity-modulated RT (IMRT) with risk-adapted planning treatment volumes in 28 patients with CUP and cervical nodal metastases.¹⁷³ 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 retrospective study assessed RT in 68 patients with metastatic head and neck SCC of unknown primary.¹⁷⁴ 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. Where indicated, based on tumor size, pathology, and clinical presentation, select locoregional options can be considered.

Specialized Approaches

Specialized approaches are suggested as a treatment option in all patients with disseminated metastases. The term emphasizes the importance of an individualized approach. Specialized approaches may include palliative treatment options, such as thoracentesis and paracentesis, targeted therapies, and novel approaches to RT.

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).



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