National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Occult Primary (Cancer of Unknown Primary [CUP])

Version 2.2016

NCCN.org

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NCCN Guidelines Version 2.2016 Panel Members
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† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
‡ Hematology/Hematology oncology
Þ Internal medicine
≠ Pathology
ф Diagnostic/Interventional radiology
* Discussion Section Writing Committee

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

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

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

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2016 Updates Occult Primary

Updates in Version 2.2016 of the Guidelines for Occult Primary from Version 1.2016 include:

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2016 of the Guidelines for Occult Primary from Version 1.2015 include:

OCC-11

- **Under additional workup for Bone, 1st bullet has been modified: "Bone scan (if only ~~PET~~/*chest/abdomen/pelvis CT* ~~scan~~ previously done)."**

OCC-A

- **The Immunohistochemistry Markers section of the guidelines has been modified extensively.**
  - **For OCC-A (1 of 5): "Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnotic approach using immunohistochemistry. Adv Anat Pathol 2015;22(3):149-167" is a new reference replacing "Bahrami A, Truong L, Ro J. Undifferentiated tumor-True Identity by Immunohistochemistry. Arch Path Lab Med 2008;132:326-348."**

OCC-B (1 of 4)

- **On the Principles of Chemotherapy page, under Neuroendocrine tumors the first sentence has been modified: "For poorly differentiated (high grade or anaplastic) or small cell subtype ~~other than lung neuroendocrine tumors~~, see NCCN Guidelines for Small Cell Lung Cancer."**

OCC-B (2 of 4)

- **Two new chemotherapy regimens, *Irinotecan/Carboplatin* and *Irinotecan/Gemcitabine*, were added to Adenocarcinoma.**

OCC-C (1 of 1)

- ***Principles of Radiation Therapy* is a new section in the guidelines.**

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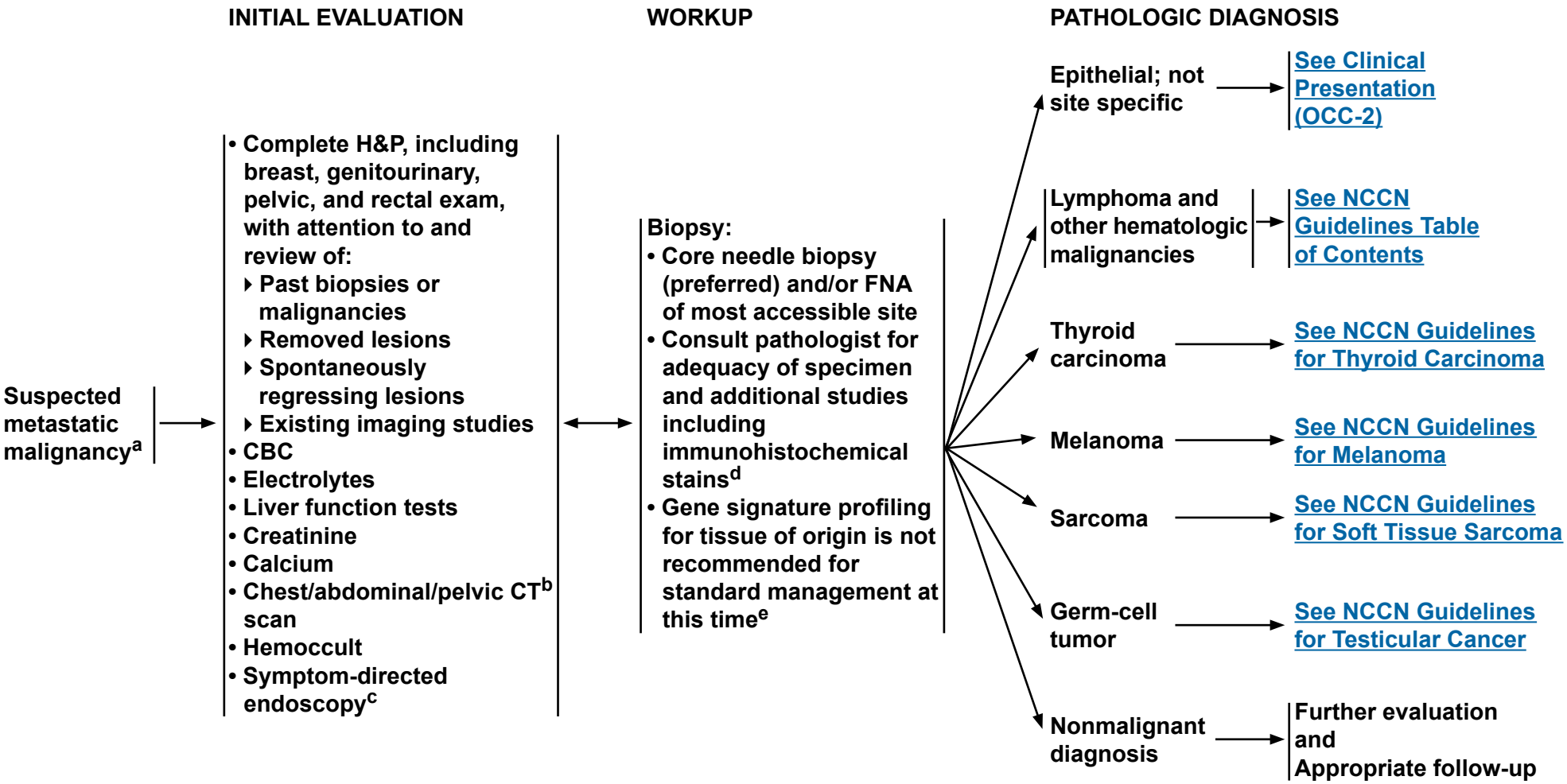

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[b]Routine use of PET/CT is not recommended. PET/CT scans may be warranted in some situations.
[c]Based on clinical findings.
[d]See Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A).
[e]There may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation.

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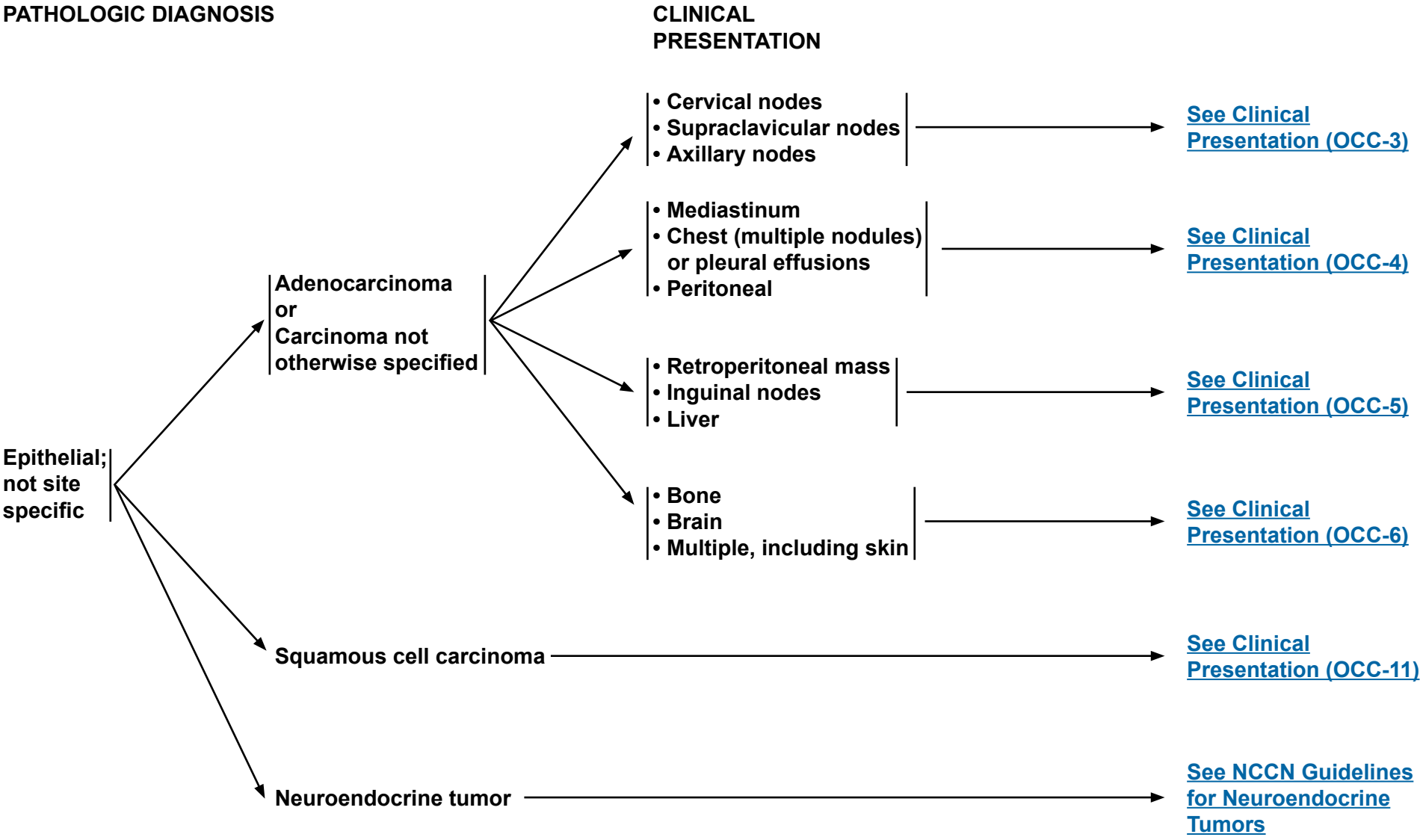

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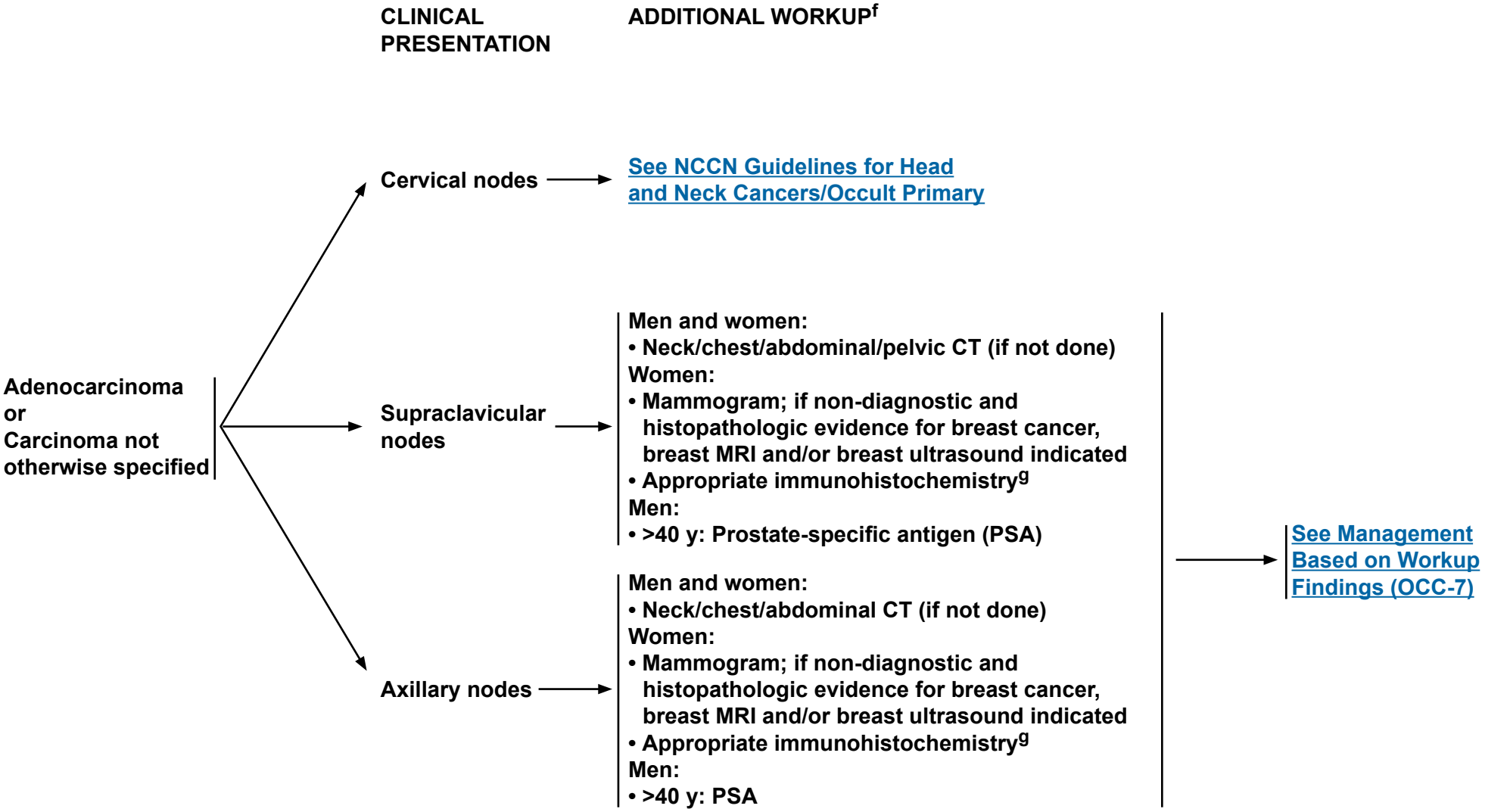

[f]Symptom-directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers.
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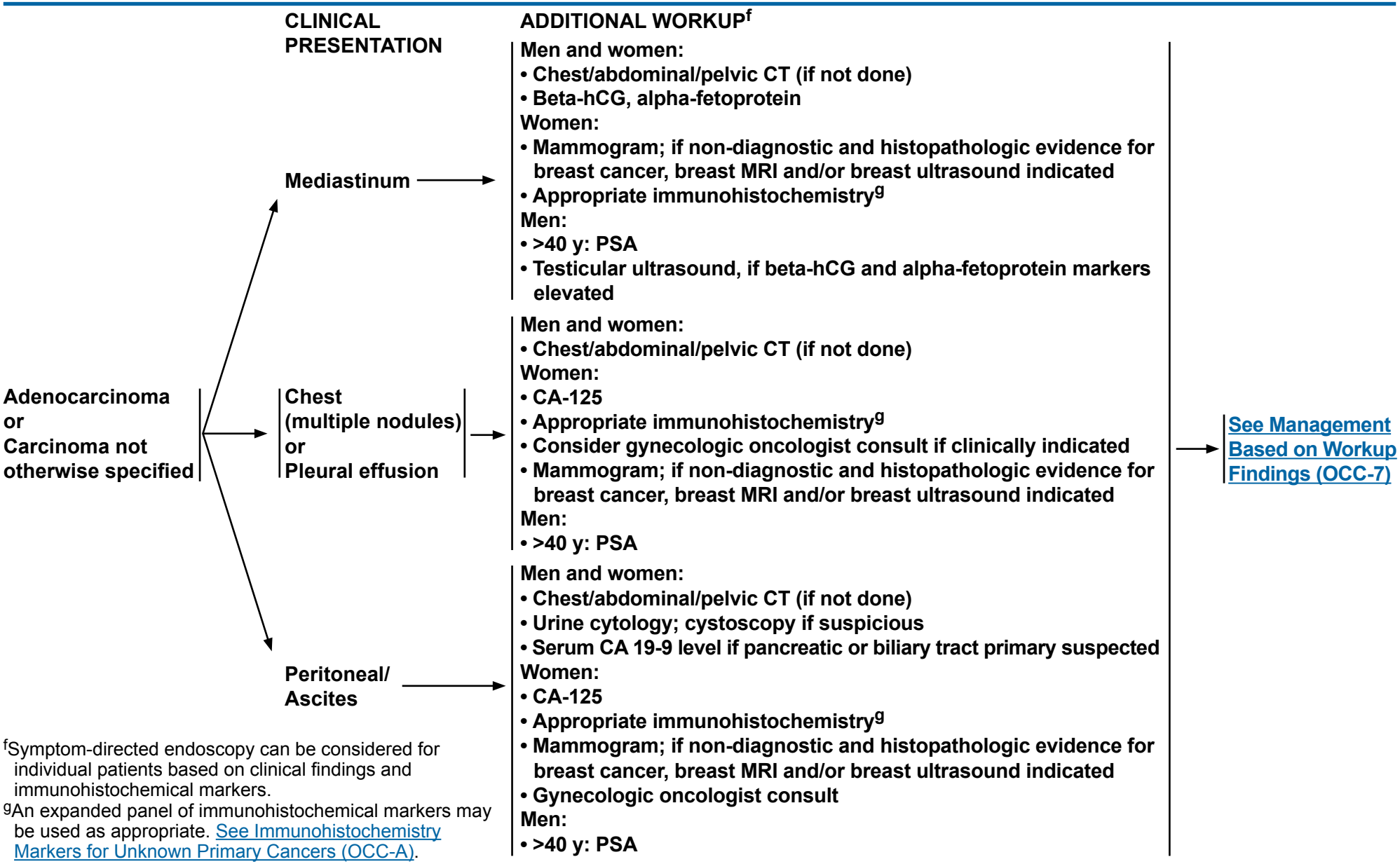

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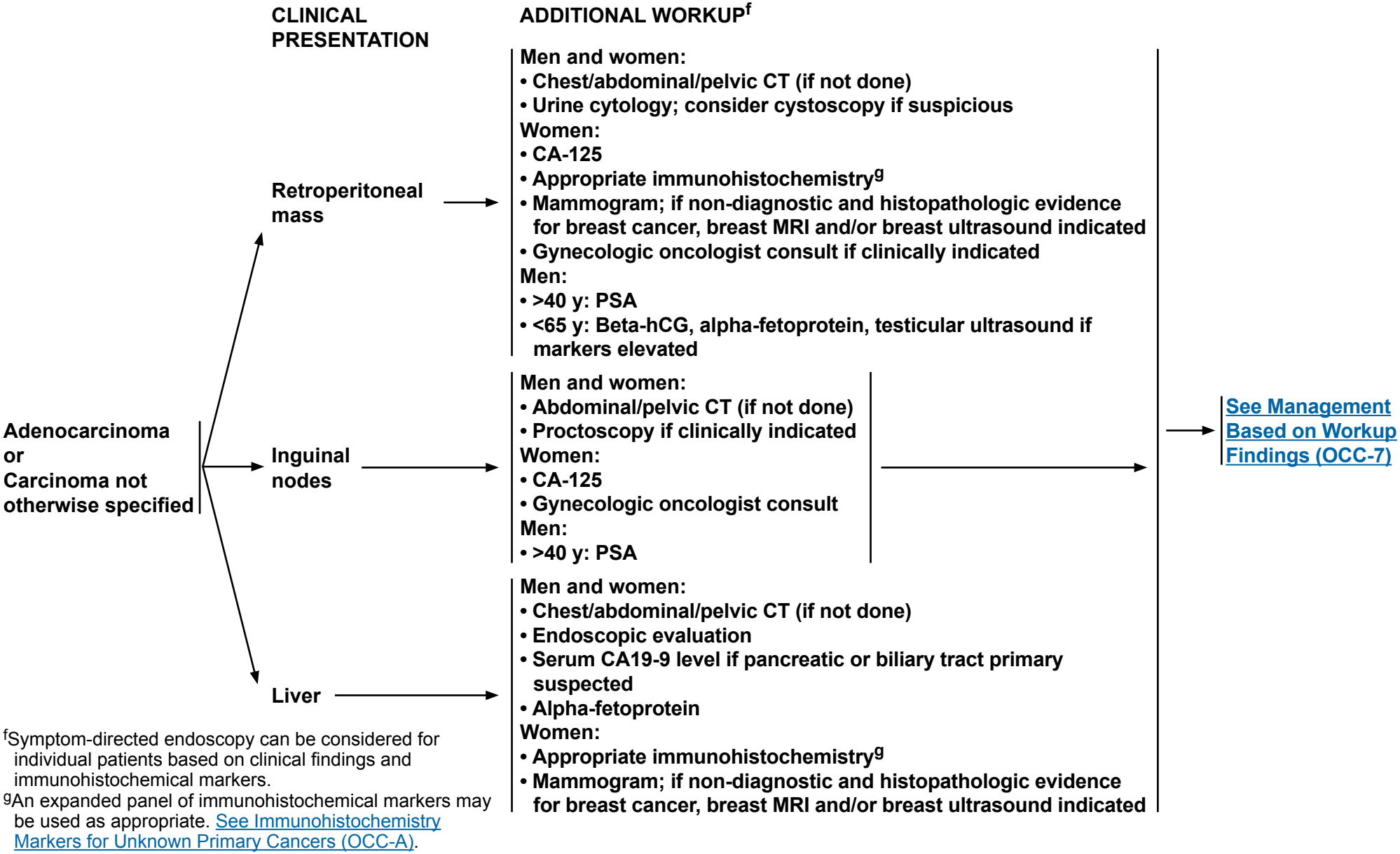

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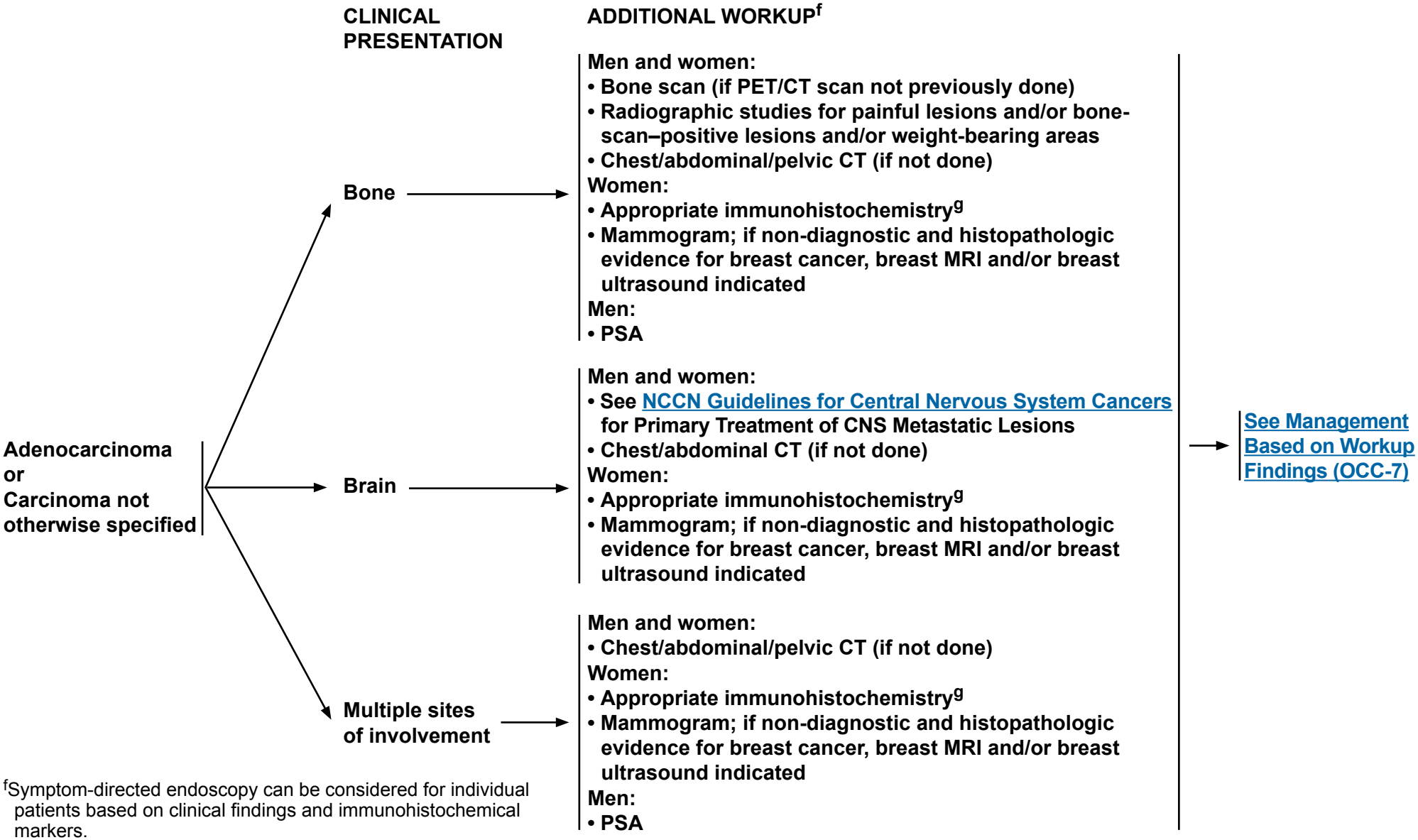

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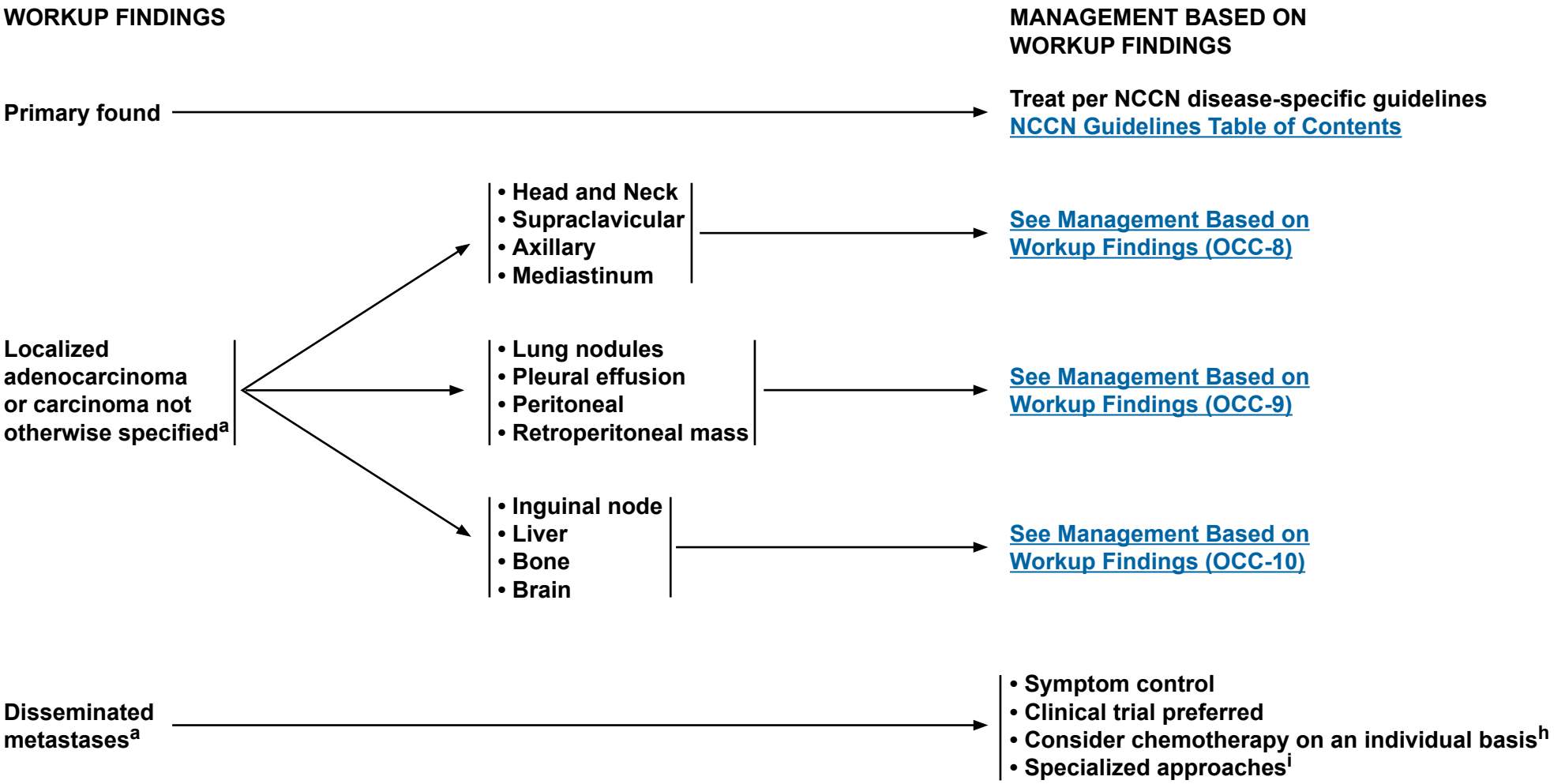

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[h]See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

[i]For specialized approaches that are therapeutic in nature, see Discussion (MS-18).

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See Follow-up (OCC-16)

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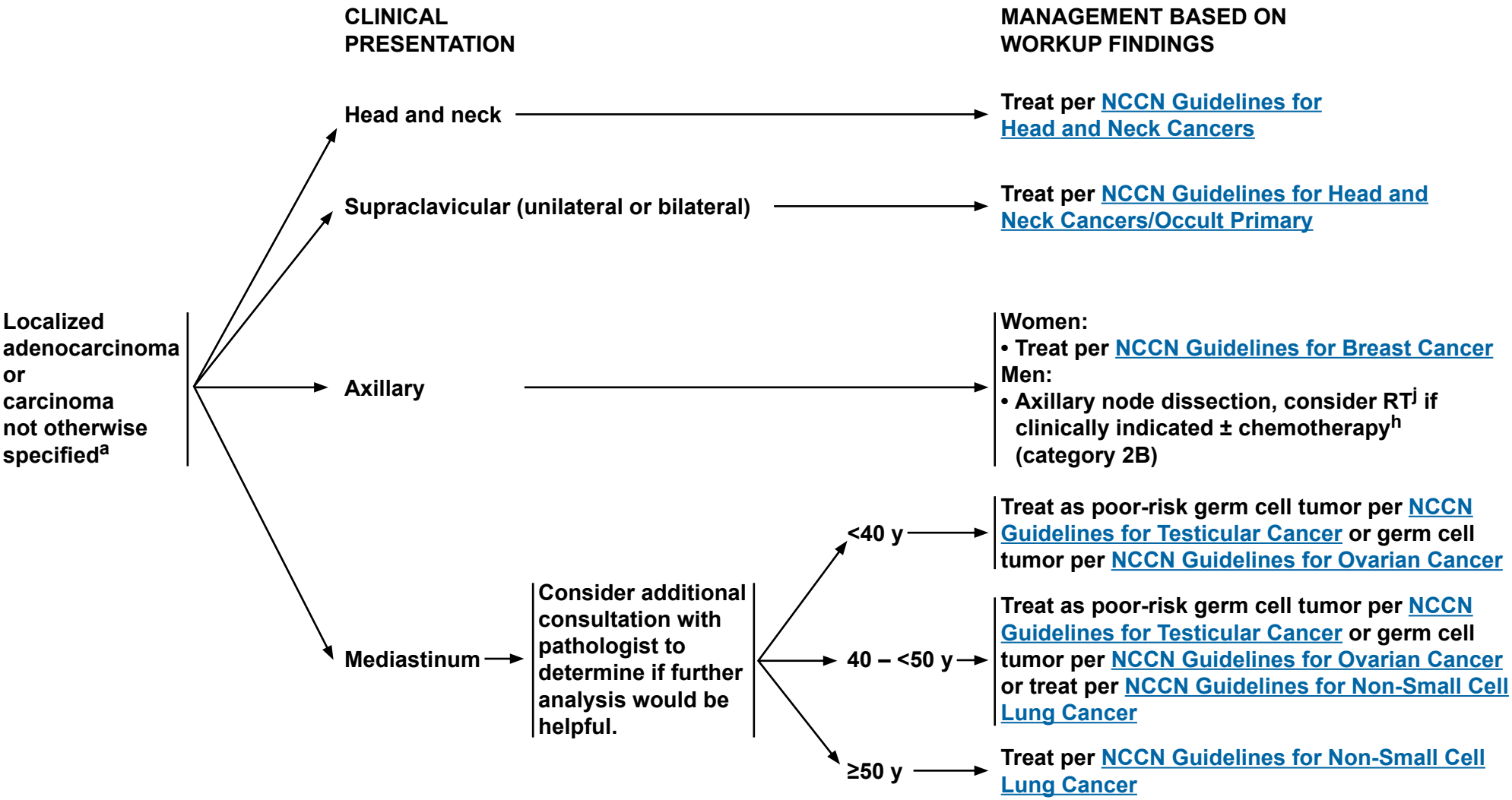

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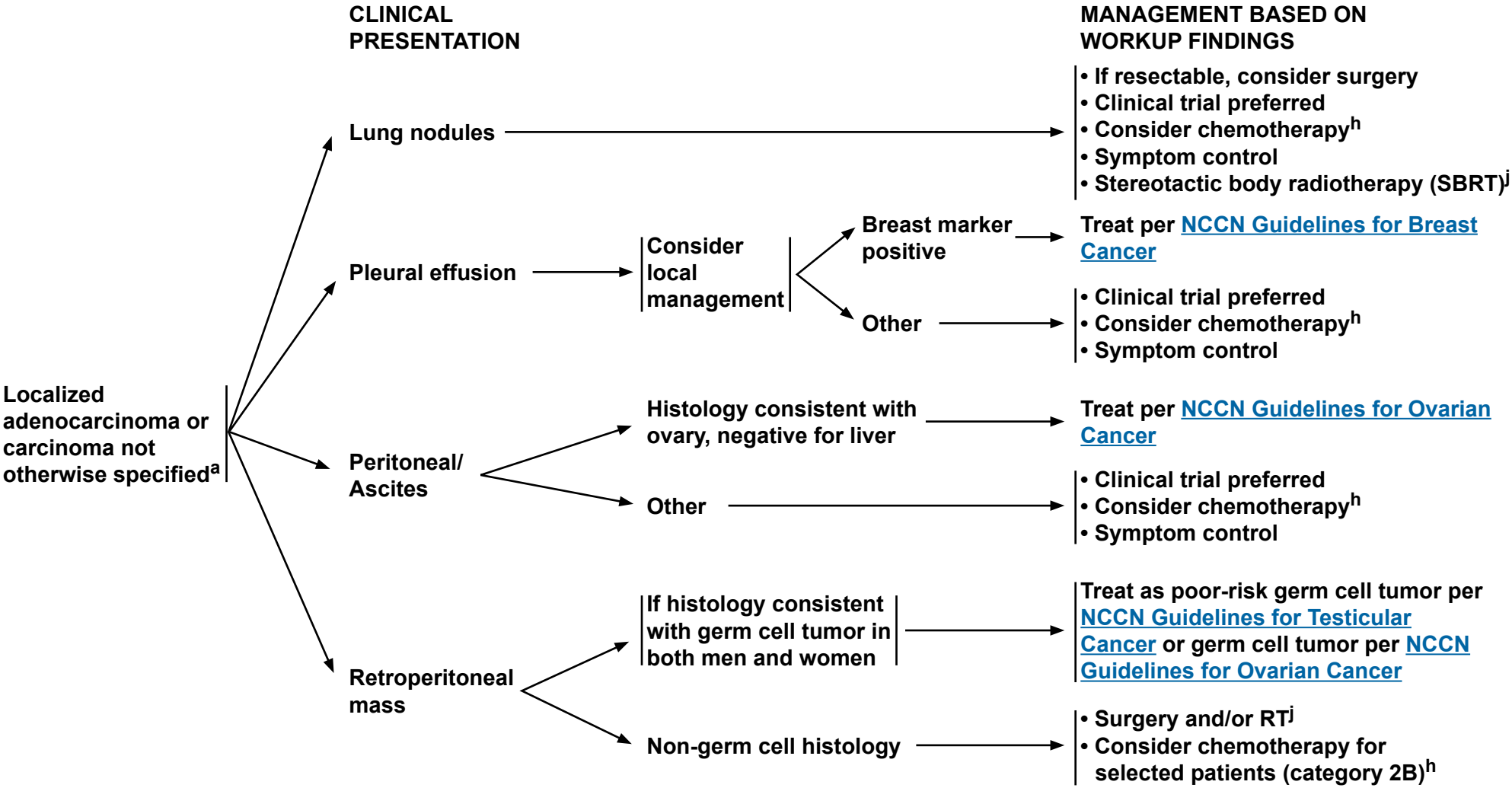

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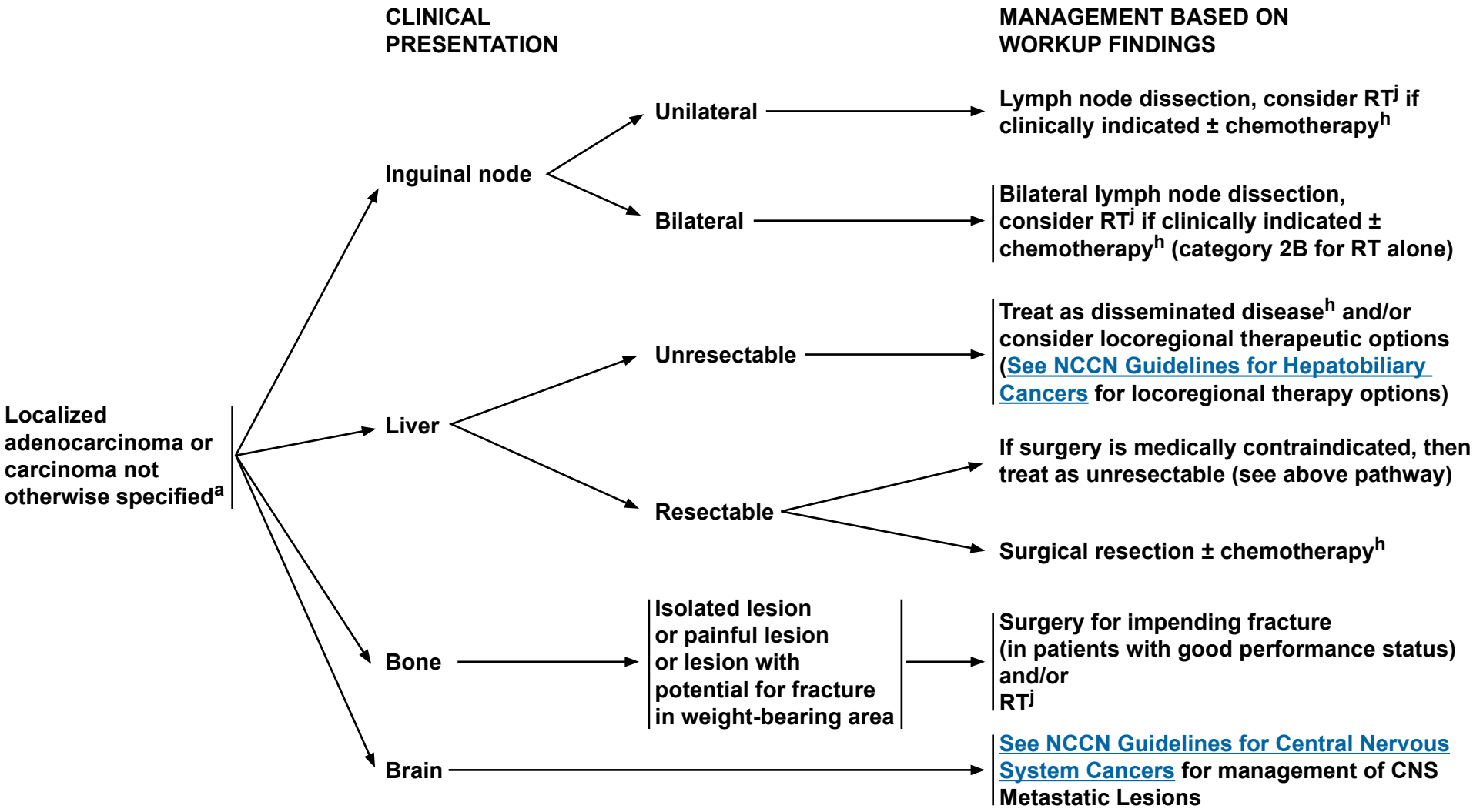

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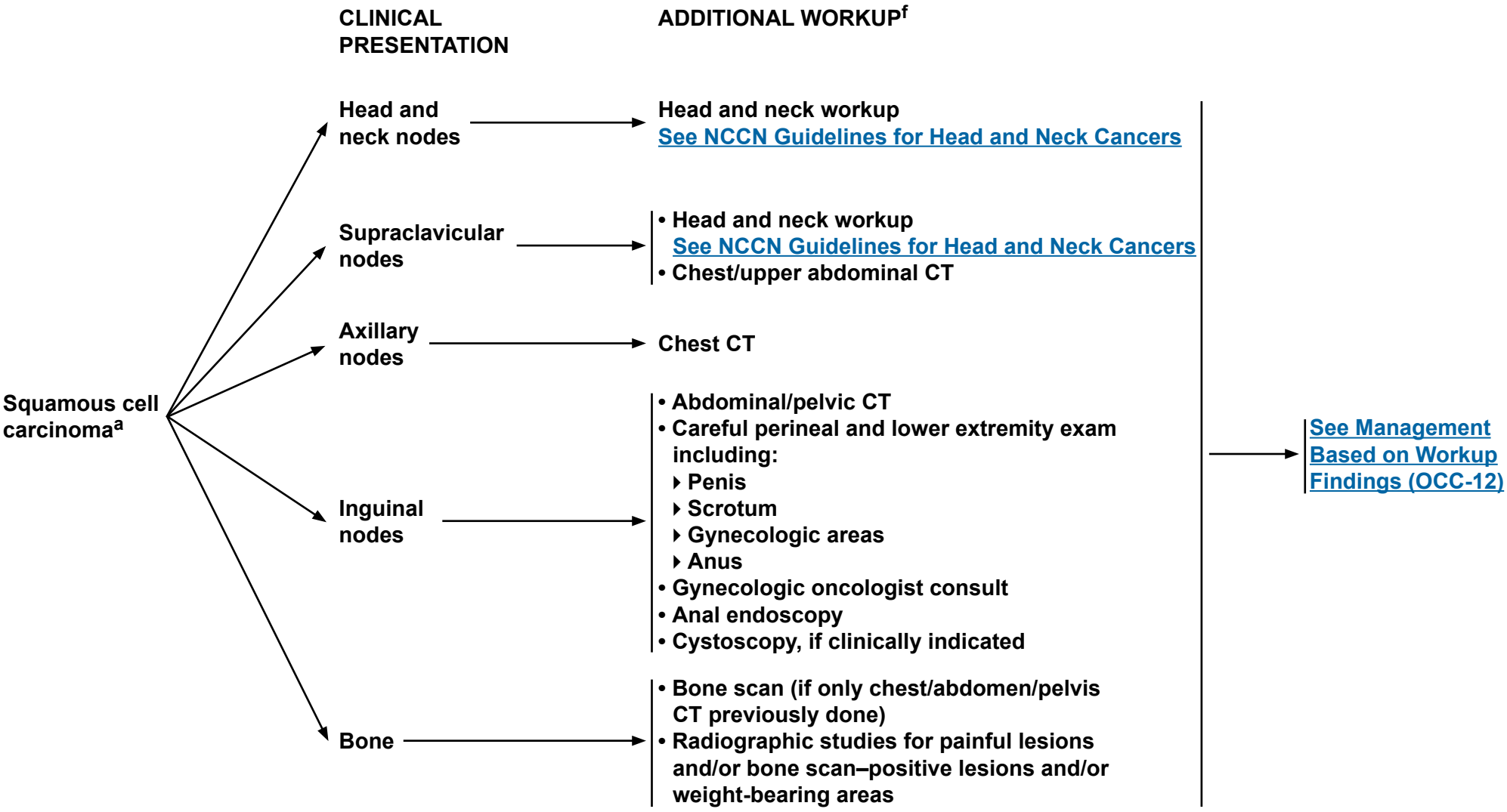

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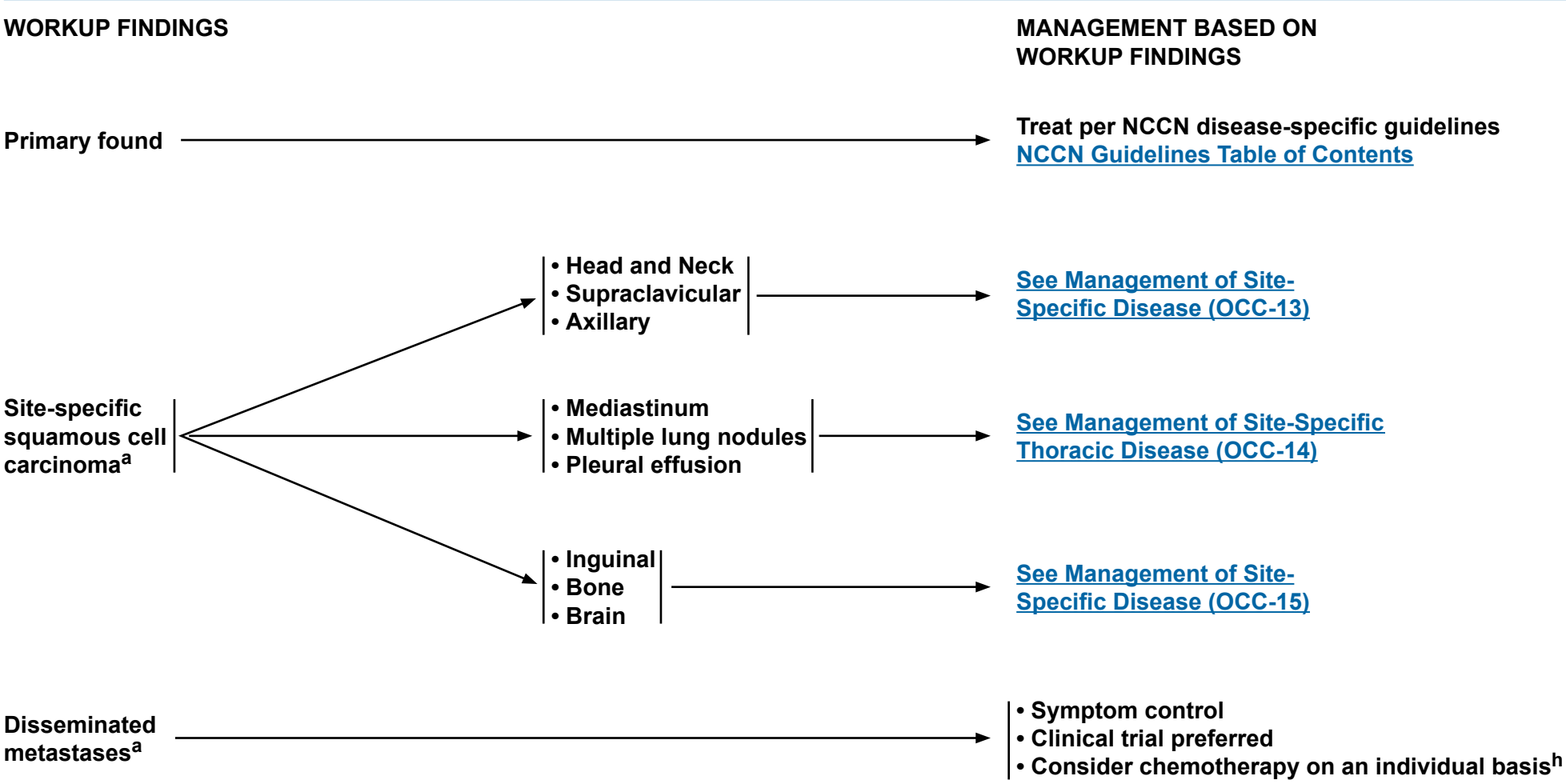

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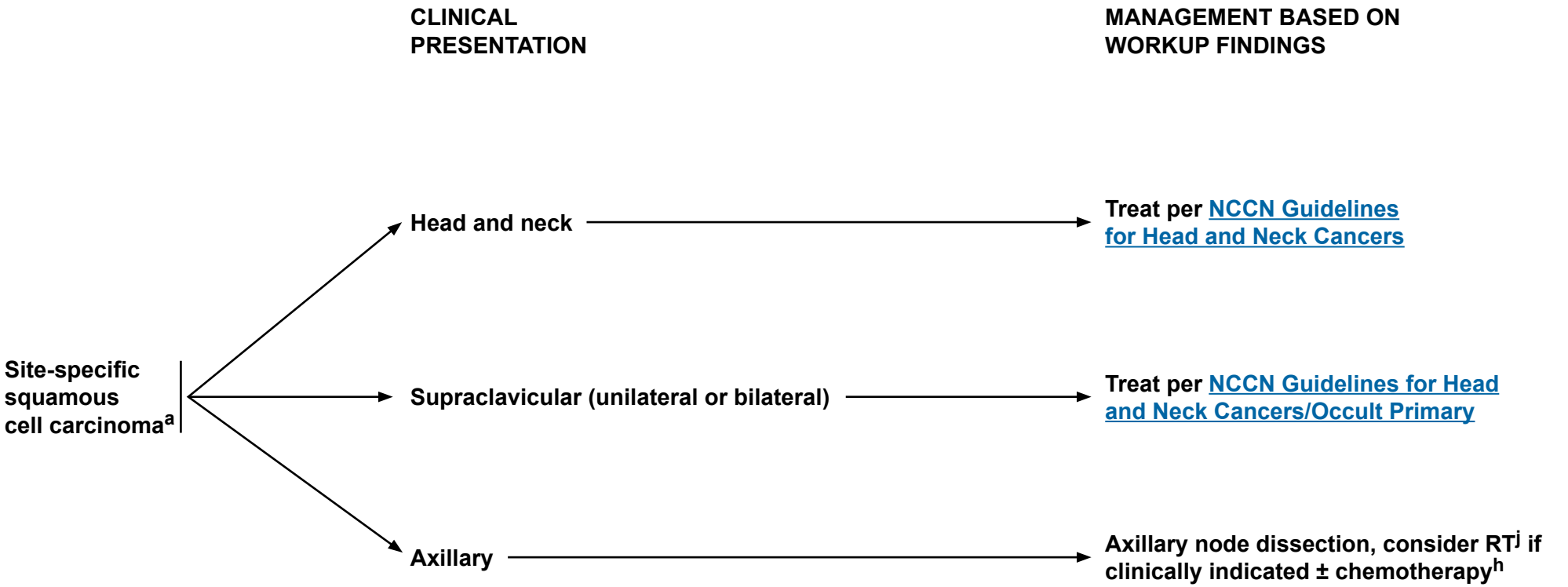

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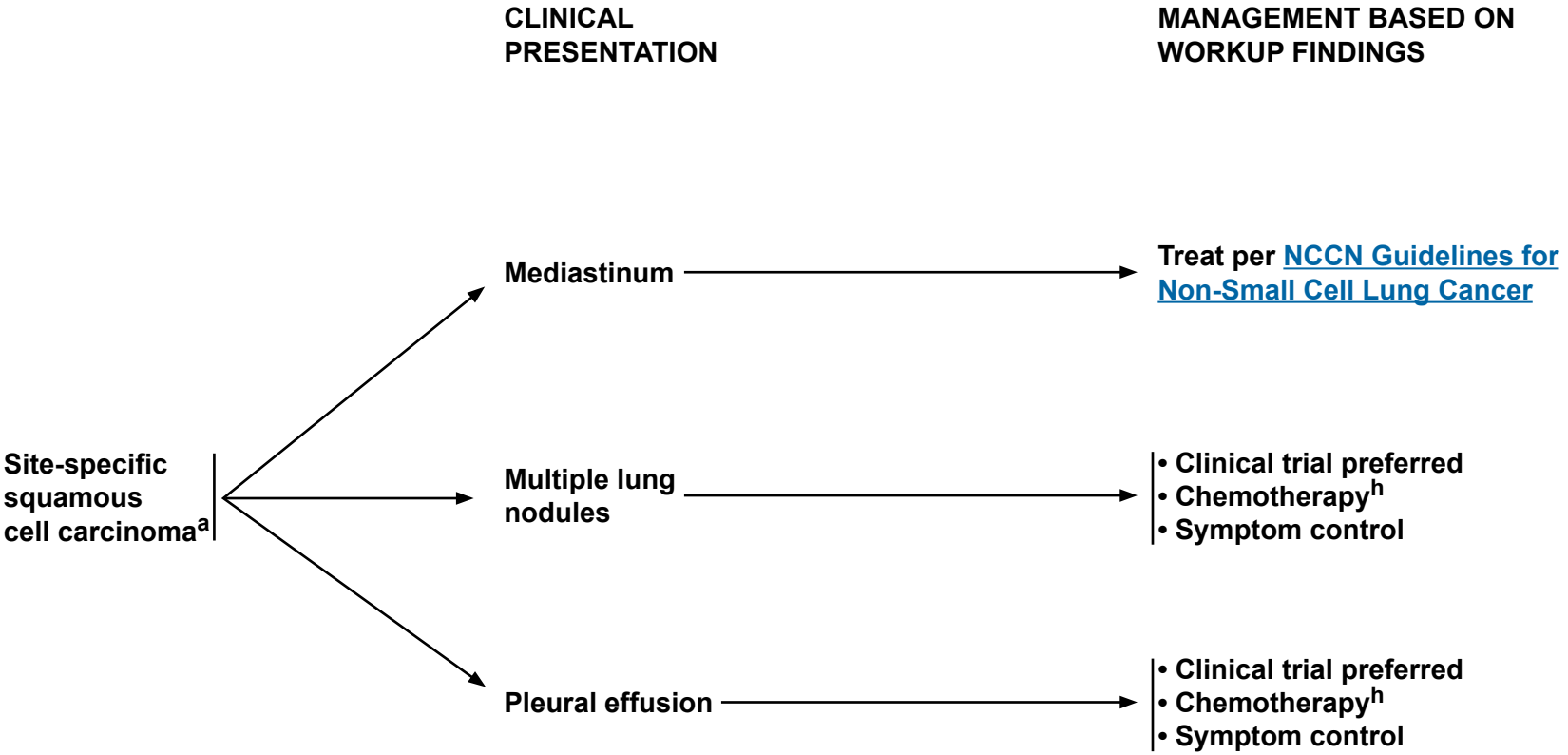

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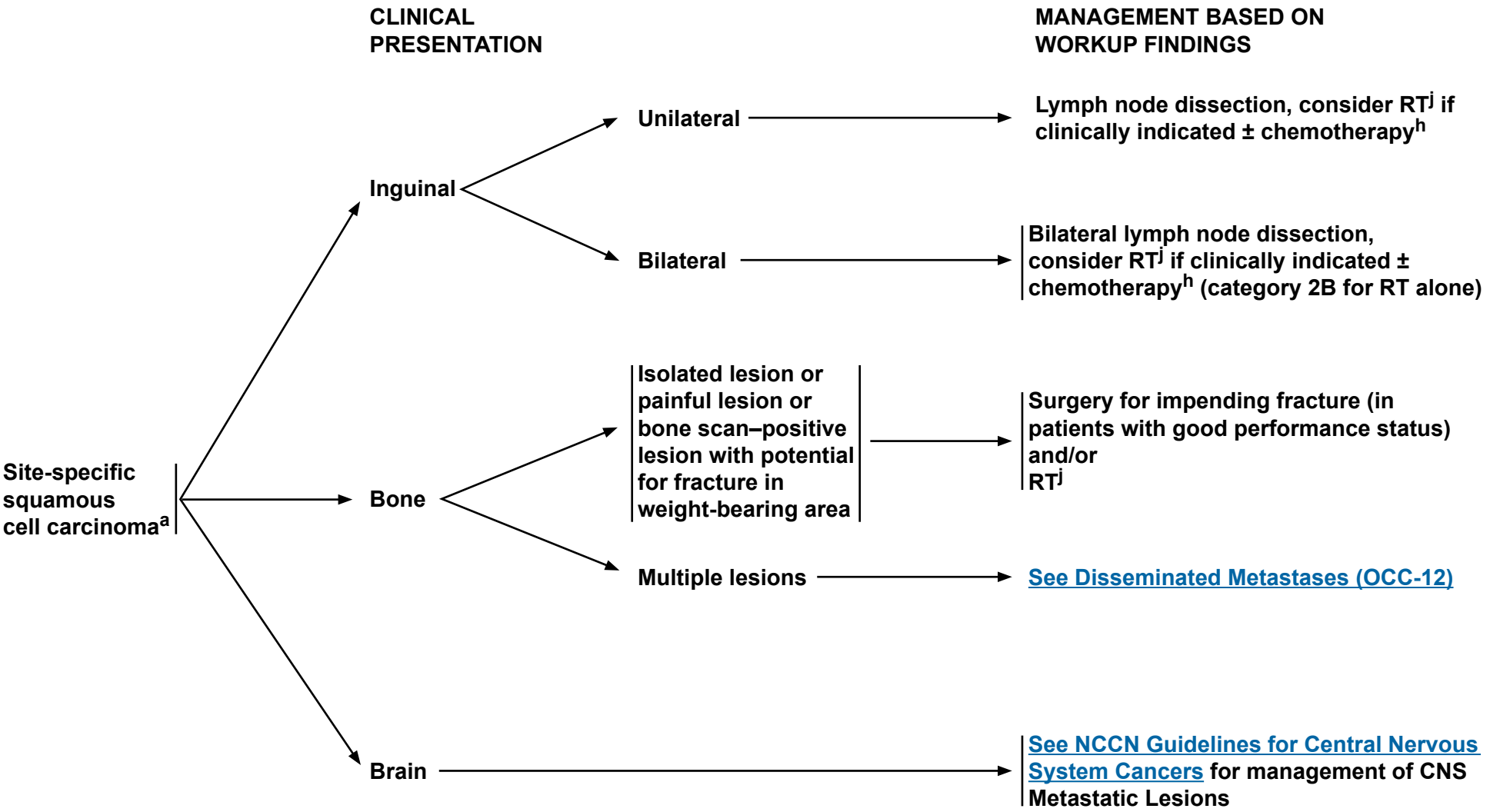

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FOLLOW-UP FOR ALL OCCULT PRIMARIES (NO ACTIVE TREATMENT)

- **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 and NCCN Guidelines for Distress Management.**

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS:

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

TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN[1]

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

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

Bahrami A, Truong L, Ro J. Undifferentiated tumor-True Identity by Immunohistochemistry. Arch Path Lab Med 2008; 132:326-348

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS
Undifferentiated Panel: For Determining Cell Lineage[2]

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

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

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[2]

Tumor site or type	Cytokeratin 7 (CK7) and cytokeratin 20 (CK20)	Other positive markers	Other useful markers
Adrenocortical carcinoma	CK-/CK20-	Calretinin Inhibin MelanA	Polyclonal CEA-
Breast carcinoma	CK7+/CK20-	GATA3 GCDFP-15 (BRST2)± Mammaglobin±	ER/PR±
Endocervical adenocarcinoma	CK7+/CK20-	Polyclonal CEA p16± (diffuse staining) PAX8±	Vimentin- ER/PR-
Endometroid adenocarcinoma	CK7+/CK20-	Vimentin PAX8 WT1 Mesothelin	Polyclonal CEA- p16- (no diffuse staining to distinguish from endocervical carcinoma)
Hepatocellular carcinoma	CK7-/CK20-	Arginase-1 HepPar-1 Glypican-3 CD10 and polyclonal CEA± (peri-canalicular pattern)	MOC31- (to distinguish from intrahepatic cholangiocarcinoma)
Lower gastrointestinal carcinoma, including small intestinal, appendiceal, and colorectal	CK7±/CK20+	Polyclonal CEA CDX2 Villin SATB2	

[2]Conner 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± Ki67 (for grading)
Non-seminomatous germ cell tumor	CK7-/CK20-	SAL4 OCT3/4	CD30 Glypican-3 PLAP (for further subtyping)
Ovarian mucinous carcinoma	CK7+/CK20±	PAX8± CDX2±	
Ovarian serous carcinoma	CK7+/CK20-	PAX8 WT1 Mesothelin	Polyclonal CEA-
Pancreaticobiliary carcinoma, including intrahepatic cholangiocarcinoma	CK7+/CK20+	Polyclonal CEA CDX2 CK19 CEAp CA19-9	SMAD4 loss ± (pancreas and extrahepatic cholangiocarcinoma)
Prostate carcinoma	CK7-/CK20-	PSA PSAP NKX3-1 P501S (Prostein) ERG±	

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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) RCC antigen	
Salivary gland carcinoma	CK7+/CK20-	CK5/6 p63	
Squamous cell carcinoma	CK7-/CK20-	CK5/6 p63 or p40 34βE12	p16 (diffuse staining) and/or human papilloma virus 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 S100 Uroplakin II	
Upper gastrointestinal tract carcinoma, including esophagus and stomach	CK7+/CK20±	Polyclonal CEA CDX-2± Villin±	

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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, Horton J, Davis TE, McFadden ET, Carbone PP. 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

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

SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

ADENOCARCINOMA

Paclitaxel and Carboplatin
Paclitaxel 200 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Repeat cycle every 3 weeks[1]

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 weeks[2]

Docetaxel and Carboplatin
Docetaxel 65 mg/m² IV Day 1
Carboplatin AUC 6 IV Day 1
Repeat cycle every 3 weeks[3]

Gemcitabine and Cisplatin
Gemcitabine 1250 mg/m² IV Days 1 and 8
Cisplatin 100 mg/m² IV Day 1
Repeat cycle every 3 weeks[4]

Gemcitabine and Docetaxel
Gemcitabine 1000 mg/m² IV Days 1 and 8
Docetaxel 75 mg/m² IV Day 8
Repeat cycle every 3 weeks[5]

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 weeks[6]

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 weeks [8]

Irinotecan and Carboplatin
Irinotecan 60 mg/m² IV Days 1, 8, and 15
Carboplatin AUC 5 IV Day 1
Repeat cycle every 4 weeks [9]

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 weeks [10]

See references on OCC-B 4 of 4

Note: All recommendations are category 2A unless otherwise indicated.
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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 weeks[1]

Cisplatin and Gemcitabine
Cisplatin 100 mg/m² IV Day 1
Gemcitabine 1250 mg/m² IV Days 1 and 8
Repeat cycle every 3 weeks[4]

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 weeks[12]

Paclitaxel and Cisplatin
Paclitaxel 175 mg/m² IV Day 1
Cisplatin 60 mg/m² IV Day 1
Repeat cycle every 3 weeks[14]

Docetaxel and Carboplatin
Docetaxel 75 mg/m² IV Day 1
Carboplatin AUC 5 IV Day 1
Repeat cycle every 3 weeks[15]

Docetaxel and Cisplatin
Docetaxel 60 mg/m² IV Day 1
Cisplatin 80 mg/m² IV Day 1
Repeat cycle every 3 weeks[11]

OR

Docetaxel and Cisplatin
Docetaxel 75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Repeat cycle every 3 weeks[8]

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 weeks[13]

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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

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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.

PRINCIPLES OF RADIATION THERAPY

LOCALIZED DISEASE

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

ADJUVANT THERAPY

- **Consider adjuvant radiation therapy after lymph node dissection if the disease is limited to single nodal site with extranodal extension or inadequate nodal dissection with multiple positive nodes. 45 Gy with or without boost of 5–9 Gy/1.8–2.0 Gy fraction to nodal basin for isolated supraclavicular, or 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: 8 Gy in 1 fraction, 20 Gy in 4–5 fractions, 30 Gy in 10 fractions.**

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

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. Patients with occult primary tumors often present with general complaints, such as anorexia and weight loss. Early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors.[3] Life expectancy is generally very short. Patients with lymph node-confined metastases have a median survival of approximately 6 to 9 months, while patients with extranodal disease have a median survival of about 2 to 4 months.[4-9] Select patients with favorable subsets of occult primary tumors have median overall survival (OS) times in the range of 12 to 36 months.[5]

These guidelines provide recommendations for evaluation, workup, management, and follow-up of 2 pathologic diagnoses in patients with epithelial occult primary cancer:

- Adenocarcinoma, or carcinoma not otherwise specified (NOS)
- Squamous cell carcinoma (SCC)

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

The NCCN Guidelines for Occult Primary suggest diagnostic tests based on the location of disease and the patient's gender. For example, for SCC the guidelines focus on the most common sites of clinical presentation, namely the head and neck nodes, supraclavicular nodes, inguinal nodes, and bone. For adenocarcinoma, 12 different clinical presentations are addressed, with suggested diagnostic tests for each location. For each of the pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on recommendations in the NCCN Clinical Practice Guidelines for the cancer site corresponding to the primary tumor (see list of NCCN Guidelines for Treatment of Cancer by Site, available at www.NCCN.org).

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma and site-specific SCC. The panel endorses enrollment of patients in appropriate clinical trials when possible. In most patients, occult primary tumors are refractory to systemic treatments, and chemotherapy is only palliative and does not significantly improve long-term survival. In patients with disseminated disease in particular, the treatment goals are directed toward symptom control and providing the best quality of life possible. However, certain clinical presentations of these tumors are associated with a better prognosis.[10] Special pathologic studies can identify subsets of patients with tumor types that are more responsive to chemotherapy. Treatment options should be individualized for this selected group of patients to achieve optimal response and survival rates.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Occult Primary (Cancer of Unknown Primary), an electronic search of the PubMed database was performed to obtain key literature in cancers of unknown primary published between 06/01/2014 and 06/10/2015, 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 Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 235 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

Occult primary tumors occur roughly equally in men and women, with an average age at diagnosis of 60 years.[11,12] An estimated 31,430 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2014, accounting for approximately 2% of all cancers diagnosed in the United States.[13] However, deaths from cancer of unspecified primary site are estimated to be 44,680 in 2014. This discrepancy is believed to be from the lack of specificity in recording the underlying cause of death on death certificates. A recent analysis of the SEER database from 1973 to 2008 found that the percentage of cancers diagnosed as occult primary has been decreasing over time.[14] Unfortunately, no improvement in median survival was seen over this time period.

A recent analysis of the Swedish Family-Cancer Database revealed that occult primary tumors may have a genetic basis.[15] The analysis showed that 2.8% of occult primary cases were familial (ie, a parent and offspring were both diagnosed with occult primary cancer). In addition, occult primary tumors were associated with the occurrence of lung, kidney, and colorectal cancers in families, suggesting that these tumor types are often the primary sites of the disease.[15]

A primary tumor site is found in fewer than 30% of patients who present initially with an occult primary tumor. In 20% to 50% of patients, the primary tumor is not identified even after postmortem examination.[11,16,17]

Presentation and Prognosis

Multiple sites of involvement are observed in more than 50% of patients with occult primary tumors.[18] Common sites of involvement are the liver, lungs, bones, and lymph nodes.[19,20] Although certain patterns of metastases suggest possible primaries, occult primaries can metastasize to any site. Therefore, physicians should not rely on patterns of metastases to determine the primary site.

Patients with occult primary tumors may present with favorable or unfavorable prognostic signs and patterns of presentation.[3,21-24] A series of population-based analyses have been performed based on patient data from the Swedish Cancer Registry. Hemminki et al conducted an initial population-based survival analysis of >18,000 patients with occult primary tumors to elucidate 12-month survival rates and median survival times for each combination of histology and location.[6] The data revealed that patients with metastases limited to lymph nodes had better prognoses than those with extranodal disease (median survival of 8 months vs. 3 months).[6] In 2013, this group examined data from 9306 patients with occult primary tumors and extranodal metastases, examining survival rates based on the location of metastases. The

study suggested that location of metastasis may predict site-specific cancer deaths and provide insight into the location of primary tumors.[7]

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

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

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

Pathology

Occult primary tumors often have multiple chromosomal abnormalities and overexpression of several genes, including *EGFR*, *c-kit/PDGFR*, *Ras*, *BCL2*, *HER2*, and *p53*.[30-32] *BCL2* and *p53* are overexpressed in 40% and 53% of occult primary tumors, respectively.[33] The *BRD4-NUT* oncogene, resulting from the chromosomal translocation t(15;19), has been identified in children and young adults with carcinoma of midline structures and unclear primary sites.[1,34,35]

Occult primary cancers can be classified into 5 major subtypes after routine evaluation with light microscopy. The most frequently occurring subtype is well- or moderately differentiated adenocarcinoma (60%), followed by poorly differentiated adenocarcinoma or undifferentiated carcinoma (29%), SCC (5%), and poorly differentiated malignant neoplasm (5%).[1,20] Additionally, because of improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary have been recognized (1%).[36,37]

In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC).[38-41] In addition, gene expression profiling (GEP) assays have been developed to attempt to identify the tissue of origin in patients with occult primary cancers.[42-44] It is noteworthy that thus far the literature on this approach, as with the literature on IHC application in the workup of occult primary tumors, has focused far more on establishing a tissue of origin than on establishing whether such identification leads to better outcomes in patients. Thus, while there is diagnostic benefit of GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not recommend molecular profiling for the identification of tissue of origin as standard management in the diagnostic workup of patients with occult primary tumors (category 2B). Overall, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately. Both of these techniques are discussed in more detail below.

Immunohistochemistry

Communication between the treating oncologist and the pathologist is important to ensure adequate tissue sampling, ideally by means of a core biopsy. The use of IHC in occult primary tumors is based on the premise that concordance exists in the expression profiles of primary and metastatic cancers.[42,44] The predictive value of IHC panels improves with 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.

In patients with occult primary tumors, immunohistochemical studies are useful for the characterization of poorly differentiated or undifferentiated tumors and for cell-type determination and pathologic diagnosis.[38-41] 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.[45] Immunohistochemical studies should be used in conjunction with imaging studies to select the best possible treatment options for patients with occult primary tumors.

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, or melanoma). A second tier of IHC can be used to help suggest the putative primary site. 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. For a recent review of both new and historical markers that may aid in the diagnosis of cancer of unknown primary, see Connor and Hornick (2015).[46] See *Immunohistochemistry Markers for Unknown Primary Cancers* [OCC-A] in these guidelines for suggested IHC markers. However, a large series of IHC markers should be avoided.

Molecular Profiling

Over the past decade, studies have examined various molecular assays designed to identify the tissue of origin in occult primary tumors (recently reviewed by Varadhachary and Raber[44] and Hainsworth and Greco[47]). These assays are designed based on the assumption that metastatic tumors will have similar molecular profiles to that of the

Assays used in gene expression profiling utilize mRNA-, DNA-, or RNA-based platforms.[48-54]

When validated using samples from known tumor types, these assays have generally demonstrated an accuracy rate of 85% to 90%.[44,47] Because it is difficult to confirm site of origin in most cases of occult primary tumors, the accuracy of GEP assays in occult primary tumor samples are challenging to determine. Surrogate measures used include correlation with IHC findings, clinical presentation/ response to therapy, as well as appearance of latent disease at the primary tumor site. In approximately 70% to 75% of occult primary cases, a plausible primary site is predicted by GEP assay results.[44,47] Several studies suggest that GEP profiling is comparable or superior to the accuracy of IHC for poorly differentiated/undifferentiated carcinomas.[45,55]

In addition to DNA and messenger RNA (mRNA)–based assays, microRNA (miRNA)–based assays have also generated interest for their potential to identify tissue of origin. These assays examine the presence of miRNAs, which are noncoding RNAs that regulate gene expression and show high tissue specificity.[56-58]

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.[44,59-62] Data from ongoing studies evaluating effectiveness of novel targets against specific mutations will help define role this approach.

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 benefit for patients.[63] In one study, 32 patients whose tumors were classified as being of colorectal origin by 2 GEP assays (the 10-gene assay of Talantov et al[53] and the 92-gene assay of Ma et al[54]) showed a response to colorectal chemotherapy regimens as expected for patients with stage IV colorectal cancer.[64] Results from a prospective, non-randomized phase II study of 289 patients with occult primary tumors 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.[63] While median survival time of 12.5 months in the subset of patients that received GEP-directed treatment was better than the pre-defined historical cohort, similar results might be expected from empiric use of these regimens in a good PS group of patients with unknown primary cancer predominantly below the diaphragm. Thus, the clinical benefit that might be derived from the use of these molecular assays, if any, remains to be determined.

Recent reviews have compared the commercially available GEP tests.[44,47,65] As noted, outcomes data are not currently available to recommend routine use of molecular profiling in the workup of occult primary tumors (category 2B). Likewise, no such data exist to endorse the automatic or indiscriminate use of IHC. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities on a case-by-case basis, with the best possible individualized patient outcome in mind.[65]

Initial Evaluation

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

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

Diagnostic Imaging

Imaging can play an integral role in the multidisciplinary diagnostic evaluation of patients with occult primary sites.[66] In the past several years, PET scans and combination PET/CT scans have become 2 of the most frequently used imaging modalities in the management of patients with occult primary cancers. PET scans have been shown to be useful for the diagnosis, staging, and restaging of many malignancies,[67,68] and might be warranted in some situations. PET scans have shown intermediate specificity and high sensitivity in a few small studies, but larger studies are warranted to determine the clinical utility and role of PET scans in patients with occult primary tumors.[5,66,69,70] In a comprehensive review of 10 published studies, Seve et al concluded that PET is a valuable imaging modality for patients with occult primary tumors with a single site of metastasis if therapy with a curative intent is planned.[71]

One of the limitations of PET scans has been the limited accuracy of anatomic localization of functional abnormalities because of very little accumulation of 18F-fluorodeoxyglucose tracer in some neoplastic tissues. In these cases, the combination of a PET scan with either a CT scan or MRI can be more useful.[72,73] 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.[74-82]

One meta-analysis and systemic review on the use of PET/CT in patients with occult primaries found that primary tumors were detected in 37% of 433 patients from 11 studies, with pooled sensitivity and specificity both at 84%.[83] These results indicate that combined modality scanning could play an important role in the diagnosis of occult primary tumors. A second meta-analysis examined PET as a diagnostic tool for 246 patients with cervical nodal metastases of unknown primary tumors. The cumulative data showed a tumor detection rate of 44% and a sensitivity and specificity rate of 97% and 68%, respectively.[84] The accuracy of PET and PET/CT in patients with occult primary tumors must be confirmed in larger clinical studies with long-term follow-up.

Although one study suggested that PET or PET/CT scans detected more primary sites (24%– 40%) than conventional imaging techniques (20%–27%),[85] their exact role remains undefined because of the lack of prospective clinical trials comparing PET/CT scans with conventional imaging modalities. Therefore, the panel does not recommend using PET/CT scans for routine screening. However, PET/CT scans may be warranted in some situations, especially when considering local or regional therapy.

Workup

Patients with a suspected occult primary tumor will typically present to the oncologist after undergoing an initial core needle biopsy (preferred) and/or fine-needle aspiration. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy). Light microscopic examination of the biopsy material is usually performed first. Other techniques include electron microscopy and flow cytometry. Although immunohistochemical stains can be informative (see *Immunohistochemistry*, above), large panels of immunohistochemical markers should be avoided. If CT scans of the neck, chest, abdomen, and pelvis were not performed previously, they are varyingly indicated depending on the clinical presentation.

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

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

Workup for Possible Breast Primary

Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. These guidelines suggest the use of a mammogram for these patients. Appropriate testing for immunohistochemical markers is also recommended. MRI and/or ultrasound of the breast should be considered for a patient with a non-diagnostic mammogram and histopathologic evidence of breast cancer. MRI should also be considered when mammography is not adequate to assess the extent of the disease, especially in women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor, or to evaluate the chest wall.[86] Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in selected women by allowing for lumpectomy instead of mastectomy.[87-89] In one report, the primary site was identified using MRI in approximately half of the women presenting with axillary metastases, irrespective of breast density.[90]

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

Workup for Possible Germ Cell Primary

Involvement of mediastinal nodes in patients with adenocarcinoma suggests a possible germ cell tumor, as does a retroperitoneal mass in men younger than 65 years of age. Thus, these guidelines suggest β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) measurements. Testicular ultrasound should also be considered if β-hCG and AFP levels are elevated in a man with a mediastinal or retroperitoneal mass.

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

Workup for Possible Ovarian Primary

An occult non-germ cell ovarian primary tumor is suspected for mediastinal, inguinal, chest, peritoneal, or retroperitoneal malignancies. Testing for the ovarian cancer marker CA-125 is recommended in these cases, as is a gynecologic oncologic consultation, if clinically indicated.

Workup for Possible Prostate Primary

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

Additional Workup for Adenocarcinoma or Carcinoma Not Otherwise Specified

In patients with peritoneal disease or liver involvement, serum CA 19-9 level can be considered if pancreatic or biliary tract primary is suspected. A bone scan (if a PET/CT scan was not previously performed) and radiographic studies are recommended for adenocarcinoma involving painful or bone scan-positive bone lesions. Urine cytology is recommended for patients presenting with a retroperitoneal mass, followed by cystoscopy for suspicious findings. In patients with inguinal lymph node involvement, the guidelines include proctoscopy for men and women, if clinically indicated, to assess for rectal or anal cancer.[91] Endoscopic evaluation is recommended for patients presenting with malignancy in the liver, but is not routinely recommended in patients presenting with malignant ascites (ie, peritoneal presentation). In the absence of a positive fecal occult blood test or other clinical factors suggesting a tumor in the colon, the diagnostic yield of colonoscopy may be as low as 1%.[92] The use of AFP as a marker for hepatocellular carcinoma as part of the additional workup in adenocarcinoma or carcinoma NOS in the liver is also recommended.

Workup for SCC

SCC can be present in the nodes of the head and neck region, and in the supraclavicular, axillary, and inguinal nodes. CT scans of the abdomen and pelvis; perineal and lower extremity examination; gynecologic oncology consult; and anal endoscopy are recommended for patients with SCC with inguinal node involvement. A bone scan (if a chest/abdomen/pelvis CT scan was not previously performed) and radiographic studies are recommended for SCC involving painful or bone scan-positive bone lesions.

The workup recommendations for Occult Primary in the NCCN Guidelines for Head and Neck Cancers should be followed for unknown primary lesions in the head and neck and supraclavicular nodes (to view the most recent version of these guidelines, visit the NCCN website at www.NCCN.org [OCC-1]).

Workup for Neuroendocrine Tumors

Neuroendocrine tumors can metastasize to several sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal nodes, liver, bone, brain, and skin. The workup recommendations for Neuroendocrine Unknown Primary in the NCCN Guidelines for Neuroendocrine Tumors should be followed (available at www.NCCN.org [NUP-1]).

Management

Psychosocial Distress

For many patients, the apparent uncertainties surrounding the diagnosis of occult primary tumors may result in significant psychosocial distress and increased difficulty in accepting treatment options. In fact, a recent study found that psychiatric manifestations, including anxiety and depression, were more common in patients with occult primary tumors than in those with known primaries.[93] Empathetic discussion about the natural history of these types of cancers and their prognoses, and the provision of support and counseling by the primary oncology team and specialized services, may help alleviate this distress. Please see the NCCN Guidelines for Distress Management (available at www.NCCN.org).

Supportive Care

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

Treatment Based on Workup Findings

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

Adenocarcinoma

Patients with localized adenocarcinoma involving supraclavicular nodes (unilateral or bilateral) or in the head and neck should be treated according to the Occult Primary pathway described in the NCCN Guidelines for Head and Neck Cancers (available at www.NCCN.org [OCC-1]). Those presenting with localized adenocarcinoma with a peritoneal mass or ascites consistent with ovarian histology should be treated according to the NCCN Guidelines for Ovarian Cancer.[94,95] Localized adenocarcinoma with a retroperitoneal mass consistent with germ cell histology should be treated according to the NCCN Guidelines for Testicular Cancer or NCCN Guidelines for Ovarian Cancer (Malignant Germ Cell Tumors pathway). For women with localized adenocarcinoma involving axillary nodes and those who are breast-marker positive and have pleural effusion, these guidelines recommend treatment according to the NCCN Guidelines for Breast Cancer. To view the most recent versions of these guidelines, visit the NCCN website at www.NCCN.org.

Localized adenocarcinoma occurring in the mediastinum most likely derives from either a germ cell tumor or a non-small cell lung tumor. Additional consultation with a pathologist should be considered to determine if further analysis would help determine the origin of the

primary tumor. In the absence of additional diagnostic information, the recommended treatment depends on the age of the patient at diagnosis. Patients younger than 40 years and those between 40 and 50 years of age should be treated for poor-risk germ cell tumors according to the NCCN Guidelines for Testicular Cancer or the NCCN Guidelines for Ovarian Cancer. Alternatively, patients aged 40 to 50 years could be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer. Patients aged 50 years or older should be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer. To view the most recent versions of these guidelines, visit the NCCN website at www.NCCN.org.

Other locations of unknown primary adenocarcinomas are not associated with a common primary site. Treatment recommendations in these cases are thus general and involve local and systemic therapies. For example, axillary node dissection and radiation therapy to axilla for gross extracapsular extension with or without chemotherapy is recommended for men with localized adenocarcinoma or carcinoma NOS with involvement of axillary nodes (category 2B). Surgery can be considered for resectable lung nodules, and chemotherapy can be considered with or without resection. Stereotactic body radiation therapy is also an option for patients with lung nodules. Lymph node dissection is recommended for inguinal nodal involvement; radiation therapy with or without chemotherapy can also be considered if clinically indicated (category 2B recommendation for the use of radiation therapy alone in the case of bilateral inguinal node involvement).[96]

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

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

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

SCC

Patients with site-specific SCC with localized axillary or inguinal lymph node involvement may benefit from lymph node dissection with or without subsequent chemotherapy. Radiation therapy can be considered if clinically indicated (category 2B recommendation in the case of bilateral inguinal node involvement for the use of RT alone).[96] Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin.

Patients with unilateral and bilateral involvement of the supraclavicular lymph nodes or with SCC involvement in the head and neck should be

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

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

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

Neuroendocrine Tumors

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

Chemotherapy

Many chemotherapeutic regimens have been evaluated in patients with occult primary tumors in an attempt to prolong survival and provide relief of symptoms when present. Studies conducted in the 1980s used 5-FU–based or cisplatin-based chemotherapeutic regimens.[97-103] Most of the patients in these studies had adenocarcinoma, with only 5% to 10% having poorly differentiated carcinoma. Overall response rates to these regimens were 20% to 35%, with median survival times of 5 to10 months. However, some of the studies reported longer median survival duration. These older regimens are not used as standard treatment for adenocarcinoma, because complete response is rarely observed.

In more recent years, various regimens have shown efficacy in the treatment of patients with occult primary tumors in phase II studies. However, a 2012 systematic review of chemotherapy trials in patients with occult primary tumors of unfavorable presentations concluded that no specific regimen can be recommended as standard of care.[104] A systematic review and meta-analysis published in 2013 largely came to the same conclusions, with taxanes showing a possible slight advantage over platinum-based regimens.[105] In general, chemotherapy shows limited efficacy and considerable toxicity in patients with occult primary tumors. Therefore, these guidelines recommend that chemotherapy for patients with disseminated disease be limited to patients who are symptomatic with a PS of 1 to 2 or to patients who are asymptomatic with a PS of 0 and aggressive cancer. The choice of the regimen should be based on the histologic type of cancer. Regimens in addition to those listed in the guidelines can be considered.

Adenocarcinoma

Poorly differentiated carcinomas and adenocarcinomas or undifferentiated 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.[106,107] Objective response rates reported in 2 studies from the early 1990s were 53% (van der Gaast et al[107]) and 63% (Hainsworth et al[106]) with complete response rates of 12% and 26%, respectively. In one study, patients who had tumors with extragonadal germ cell features showed a high response rate.[106] In the other, patients with undifferentiated carcinomas had a better response rate than those with poorly differentiated adenocarcinomas (79% vs. 35%; P = .02).[107]

In more recent years, newer regimens containing taxanes and/or gemcitabine have shown efficacy in phase II studies in the treatment of patients with occult primary tumors.[108-111] Schneider et al reported that the combination of carboplatin, gemcitabine, and capecitabine was active in occult primary tumors in patients with good PS.[109] Median PFS was 6.2 months, and 1- and 2-year survival rates were 35.6% and 14.2%, respectively. In another phase II study conducted by the Minnie Pearl Cancer Research Network, the combination of carboplatin, gemcitabine, and paclitaxel followed by weekly paclitaxel was active and tolerable for patients with occult primary tumors and poor prognostic features.[110] Similarly, gemcitabine plus oxaliplatin was assessed in patients with occult primary tumors in a phase II study.[108] This well-tolerated combination gave a median overall survival (OS) of 12.8 months (95% CI, 8.5–18.5 months) and PFS of 3.1 months (95% CI, 1.7–6 months).

Recently, molecularly targeted agents have been tested for efficacy in treating patients with occult primary tumors. Hainsworth et al[112,113119,120] reported that the combination of bevacizumab and erlotinib (alone or combined with paclitaxel and carboplatin) had substantial activity as first- or second-line therapy in patients with occult primary tumors.[119,120] In a phase II trial, the combination of bevacizumab and erlotinib induced partial responses in 10% of patients and stable disease in 61% of patients.[112] Median survival was 7.4 months (1-year survival, 33%), which, in retrospective comparison, was superior to that observed by the same group with gemcitabine alone and gemcitabine and irinotecan (3 and 4.5 months, respectively). In a recent multicenter phase II study, the combination of paclitaxel and carboplatin with bevacizumab and erlotinib was active and well-tolerated as first-line therapy in patients with occult primary tumors.[113] After a median follow-up of 19 months, the median PFS time and 2-year OS rates were 8 months (38% PFS at 1 year) and 27%, respectively.

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

Paclitaxel and Carboplatin with or without Etoposide

In phase II studies, the combination of paclitaxel and carboplatin with or without etoposide was found to be effective for the treatment of adenocarcinoma of occult primary tumors.[114-116] In the Hellenic Cooperative Oncology Group study, the combination of paclitaxel and carboplatin produced an overall response rate of 38.7% according to intention-to-treat (ITT) analysis; no difference was seen in the response rates for adenocarcinomas and undifferentiated carcinomas.[114] 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.[115]

In one study, taxane-based chemotherapy (paclitaxel/carboplatin/etoposide; docetaxel/cisplatin; or docetaxel/carboplatin) was associated with long-term survival in some patients with occult primary tumors, with 1-, 2-, 3-, and 4-year survival rates of 42%, 22%, 17%, and 17%, respectively.[117] The median survival was 10 months.

In a recent phase III randomized study, the triple drug regimen had comparable efficacy to gemcitabine and irinotecan in the first-line treatment of patients with occult primary tumors.[118] Response rate 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 paclitaxel and carboplatin combination showed better clinical activity than the gemcitabine and vinorelbine combination.[119] The median OS, 1-year survival rate, and response rate were 11.0 months, 38%, and 23.8%, respectively, for patients treated with paclitaxel and carboplatin, compared with 7.0 months, 29%, and 20%, respectively, for those treated with gemcitabine and vinorelbine. Sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan was also found to be active in patients with occult primary tumors.[120] Although survival was similar to that observed in previous phase II trials, the overall toxicity of sequential treatment was found to be greater than that observed with other regimens.

Carboplatin with Docetaxel

Greco et al reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated adenocarcinoma.[121] Major response to therapy was observed in 26% of patients receiving docetaxel and cisplatin, with a median survival of 8 months and 1-year survival of 42%. In patients receiving docetaxel and carboplatin, the corresponding response rate was 22%, with a median survival of 8 months and 1-year survival of 29%. Docetaxel in combination with carboplatin was better tolerated than docetaxel with cisplatin in this study.[121]

In a report of the Hellenic Cooperative Oncology Group phase II study, a 1-hour treatment with docetaxel and carboplatin every 3 weeks was found to be safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated carcinoma with a PS of 0 to 2.[122] 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.

Carboplatin with Irinotecan

The combination regimen of carboplatin plus irinotecan was evaluated in a phase II study of 45 patients with occult primary tumors 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 grade 3 or greater leukopenia (21%), neutropenia (33%), anemia (25%) and thrombocytopenia (20%). [123]

Cisplatin with Docetaxel

Combination therapy with cisplatin and docetaxel was examined in a cohort of 29 patients with occult primary tumors.[124] Approximately half of these patients (51.7%) had well- to moderately differentiated adenocarcinoma; patients with undifferentiated carcinoma (27.6%) and SCC histologies (13.8%) were also included. The objective response rate was 37.9%, and median PFS and OS were 6 and 16 months, respectively.

Cisplatin with Gemcitabine

The efficacy and toxicity of cisplatin with either gemcitabine or irinotecan were evaluated in a randomized phase II study conducted by the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01).[125] Well-differentiated adenocarcinoma was the most common histology, with one-fourth of patients having a single metastatic site. Objective response rates were 55% for the gemcitabine and cisplatin arm and 38% for the irinotecan and cisplatin arm. Median survival rates were 8 and 6 months, respectively, for these 2 combination regimens, which were both associated with significant toxicities. The GEFCAPI 02 trial randomly assigned 52 patients to

cisplatin with or without gemcitabine.[126] 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.

Irinotecan with Gemcitabine

In a phase III randomized study comparing paclitaxel/carboplatin/etoposide to irinotecan/gemcitabine, both regimens performed similarly. Response rate 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.[118]

Oxaliplatin with Gemcitabine

A recent open-label, phase II study tested oxaliplatin and gemcitabine combination therapy in patients with occult primary tumors with a predominant histology of adenocarcinoma; the majority of the cohort presented with visceral metastases and had received no prior treatment.[127] Median OS and PFS were 12.8 months and 3.1 months. The trial was terminated early due to a shift away from empiric therapy, but data from the initial 24 patients suggested good tolerability and efficacy on par with existing doublet regimens.

Gemcitabine with Docetaxel

A non-cisplatin–based regimen containing gemcitabine and docetaxel was found to be well-tolerated and active as first-line therapy in patients with occult primary tumors.[128] The overall response rate was 40%, with a median survival of 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-line[129] and second-line[130] treatment of patients with carcinoma of unknown primary. This regimen gave response rates ranging from 12% to 19%, with disease-free survival of 2.3 to 3.7 months and OS of 3.9 to 9.7 months. This regimen appears to be active and well-tolerated and is an acceptable option for this patient population.

Although 5-FU/leucovorin/oxaliplatin (FOLFOX) has not been tested in patients with unknown primary tumors, FOLFOX has been shown to be equivalent to CapeOx in colorectal cancer.[131-134] The panel therefore supports FOLFOX (mFOLFOX6[135,136]) as an acceptable treatment option for these patients.

SCC

Platinum-based regimens have been used to treat disseminated SCC. Historically, the combination of cisplatin and 5-FU was the most frequently used regimen for patients with SCC of unknown primary.[137,138]

Overall, only a few small studies have assessed chemotherapy regimens in patients with SCC occult primaries, and the panel lists possible regimens based on evidence from studies of patients with SCC of known primary and small studies of patients with occult primary tumors. Regimens other than those listed can also be considered.

Carboplatin with Paclitaxel

The combination of carboplatin and paclitaxel is used in non-small cell lung, gastric, and esophageal cancers.[139-144]

In the Hellenic Cooperative Oncology Group phase II study of patients with occult primary tumors (discussed above for adenocarcinoma), 3 patients had tumors of squamous cell histology.[114] One of these patients had an objective response of 3 months duration after carboplatin/paclitaxel.

Carboplatin with Docetaxel

The combination of carboplatin and docetaxel is used in head and neck and non-small cell lung cancers.[145,146]

The combination of carboplatin and docetaxel was assessed in a phase II trial of 47 patients with occult primary adenocarcinomas or poorly differentiated carcinomas, with a response rate of 32% and median OS of 16.2 months.[122]

Cisplatin with Paclitaxel

The combination of cisplatin and paclitaxel is used in head and neck cancer, non-small cell lung cancer, and esophageal cancer.[143,147-150] In a randomized phase III trial of patients with advanced head and neck cancer, no significant differences were seen in patients treated with cisplatin/paclitaxel compared with patients treated with cisplatin/5-FU.[149]

This regimen has also been assessed in a phase II study of patients with unfavorable presentations of occult primary tumors.[151] Three of the 31 patients had SCC. The regimen gave an overall response rate of 42%, and the median OS was 11 months (95% CI, 8.3–13.5).

Cisplatin with Docetaxel

The combination of cisplatin and docetaxel is used in non-small cell lung, esophageal, and gastric cancers.[143,145,152-154] In a multi-center phase II trial of 34 evaluable patients with metastatic squamous cell esophageal cancer, cisplatin/docetaxel gave an objective tumor response rate of 33% in the ITT population. The median PFS and OS times were 5.0 months and 8.3 months, respectively.[153]

The safety and efficacy of this regimen has also been assessed in 45 patients with occult primary tumors.[155] The reported overall response rate was 65.1%, and the median OS was 11.8 months. Two patients had tumors of SCC histology, and both had a partial response to the cisplatin/docetaxel regimen.

Combination therapy with cisplatin and docetaxel was also examined in a cohort of 29 patients with occult primary tumors, 4 of whom had tumors with squamous cell histology.[124] The objective response rate was 37.9%, and median PFS and OS were 6 months and 16 months, respectively.

Cisplatin with 5-FU

This historic regimen has been tested in patients with SCC of unknown primary.[137,138] It is also used in the treatment of metastatic anal, head and neck, esophageal, and gastric cancers.[149,156-160]

More recently, Kusaba et al reviewed their experiences of treating patients with occult primary tumors with this regimen.[161] They reported a response rate of 54.5% and a median OS of 10 months.

Cisplatin with Docetaxel and 5-FU

The combination of cisplatin, docetaxel, and 5-FU is used in head and neck cancer, gastric cancer, and esophageal cancer.[162-165] 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.[163] The overall response rates after induction chemotherapy were 72% and 64% in the 3-drug and 2-drug arms, respectively.

Cisplatin with Gemcitabine

The combination of cisplatin and gemcitabine is used in non-small cell lung cancer.[142,143,166-168]

The GEFCAPI 02 trial compared cisplatin to cisplatin plus gemcitabine in 52 patients with occult primary tumors.[126] Although the trial was

terminated early due to poor accrual, there was a trend towards better OS with the addition of gemcitabine (11 months vs. 8 months, with overlapping confidence intervals [CIs]).

mFOLFOX6

The panel lists mFOLFOX6 as a possible regimen for occult primary SCC, based on the evidence discussed above for adenocarcinoma.[135,136] FOLFOX is used in SCC of the esophagus and stomach.[169,170]

Neuroendocrine Tumors

Neuroendocrine carcinomas of unknown primary site are uncommon, and their clinical behavior is dependent on the tumor grade and differentiation.[171] Neuroendocrine tumors, regardless of grade, represent a favorable prognostic subset of occult primary tumors that are responsive to combination chemotherapy, and long-term survival is possible in a minority of patients.[36]

Hainsworth et al evaluated the efficacy of a combination regimen containing paclitaxel, carboplatin, and etoposide in metastatic PDNE carcinomas in patients who had received no prior treatment.[172] Of these patients, 62% had PDNE carcinoma of unknown primary site; patients with known primary sites were also eligible for the study. Major responses were observed in 53% of the patients, and the median survival was 14.5 months; 2- and 3-year survival rates were 33% and 24%, respectively. The results of this trial showed that PDNE carcinomas are chemosensitive, with a high overall response rate to combination chemotherapy and a minority of complete responses.

PDNE tumors can also be treated following small cell lung cancer regimens. In a randomized phase III trial (JCOG 9702), the combination of carboplatin plus etoposide was equally as efficient as cisplatin plus etoposide in elderly patients or those with poor-risk disease with extensive small cell lung cancer who were not previously treated.[173] No significant differences were seen in response rate (73% for both regimens) and median OS (10.6 months for carboplatin and etoposide vs. 9.9 months for cisplatin and etoposide).

In one study, the combination of cisplatin and etoposide produced significant responses in patients with poorly differentiated, rapidly progressing neuroendocrine tumors (carcinoids and pancreatic neuroendocrine tumors of known primaries) when used as a second- or third-line treatment.[174] 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.[175,176]

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

Radiation Therapy

Radiation therapy is a treatment option for a variety of localized tumors, particularly as follow-up treatment after lymph node dissection. Adjuvant radiation therapy 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 radiation therapy can be considered for select patients with localized disease. Stereotactic ablative radiation therapy may be appropriate for patients with limited pulmonary metastases. Radiation therapy alone may also be considered for bone lesions, a retroperitoneal mass with a non-germ cell histology, or supraclavicular nodal involvement in site-specific SCC.

In the palliative setting, radiation therapy can be considered for symptomatic patients with uncontrolled pain, for impending pathological fracture, or impending spinal cord compression.

One study examined individualized intensity-modulated radiation therapy (IMRT) with risk-adapted planning treatment volumes in 28 patients with cervical nodal metastases of unknown primary tumors.[177] The majority of patients (71%) received concomitant systemic therapy. In this cohort, 3-year OS, mucosal control, neck control, and distant metastasis-free survival rates were 76%, 100%, 93%, and 88 %, respectively. Additional controlled studies are needed to further assess the efficacy of individualized IMRT-based treatment approaches.

A recent retrospective study assessed radiation therapy in 68 patients with metastatic SCC of the head and neck of unknown primary tumor site.[178] These patients underwent oropharynx-targeted RT to spare the mucosal surfaces of the nasopharynx, hypopharynx, and larynx; 40% of patients received IMRT and 56% of patients received concurrent chemoradiation, resulting in an actuarial locoregional control rate of 95.5% and a median time to locoregional recurrence of 18 months.

Locoregional Therapeutic Options

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

Specialized Approaches

Specialized approaches are suggested as a treatment option in all patients with disseminated metastases. The term emphasizes the importance of an individual approach. Specialized approaches may include palliative treatment options, such as thoracentesis and paracentesis; novel forms of drug delivery; targeted therapies, such as radioimmunotherapy; and novel forms of radiation therapy, such as intraoperative radiation therapy, IMRT, image-guided radiation therapy, or proton therapy.[179]

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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