

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Occult Primary (Cancer of Unknown Primary [CUP])

Version 1.2012

NCCN.org

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NCCN Guidelines™ Version 1.2012 Panel Members

Occult Primary

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[Principles of Chemotherapy and Selected Chemotherapy Regimens For Occult Primaries \(OCC-B\)](#)

Clinical Trials: The 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](#)

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. ©2011.

Summary of changes in the 1.2012 version of the Occult Primary Guidelines from the 2.2011 version include:

- The discussion section was updated to reflect the changes in the algorithm ([MS-1](#)).

[OCC-2](#)

- The branch from Neuroendocrine to See Clinical Presentation (OCC-16) was changed to [See NCCN Neuroendocrine Tumor Guidelines](#).

[OCC-4](#)

Clinical Presentation

- *Ascites* was added to Peritoneal. (Also for [OCC-9](#))

[OCC-5](#)

- Alpha-fetoprotein was changed to category 2A from category 2B.

[OCC-7](#)

Management Based On Workup Findings

- Removed category 3 for NCCN Testicular Cancer Guidelines (fifth bullet at the bottom of the page).

[OCC-8](#)

Clinical Presentation

- After Mediastinum added; *Consider additional consultation with pathologist to determine if further analysis would be helpful.*

Management Based On Workup Findings

- Removed category 3 for NCCN Ovarian Cancer Guidelines and Non-Small Cell Lung Cancer Guidelines for the age range of 40 to <50.
- Footnote “i”: *PET/CT scan can be useful in the diagnosis of an occult primary mediastinal adenocarcinoma*, was removed.

[OCC-10](#)

Liver; Resectable:

- “Category 2B for omitting chemotherapy” was removed.

Neuroendocrine Tumors (OCC-16 thru OCC-19)

- Pages OCC-16, 17, 18 and 19 were removed from the algorithm. The user is directed to the [NCCN Neuroendocrine Tumor Guidelines](#) as per OCC-2.

[OCC-A 1 thru 4](#)

- Footnote “1”: (*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*). This footnote was moved to the top of the page as a subtitle under the title, [Immunohistochemistry Markers For Unknown Primary Cancers](#). In the text of the subtitle, “100%” was changed to *uniformly*.

[OCC-A 4 of 4](#)

- “Endometrial adeno CA” was changed to *Endometrioid adeno CA*.
- “p16+” was removed from Endometrioid adeno CA and added to *Endocervical adeno CA*.

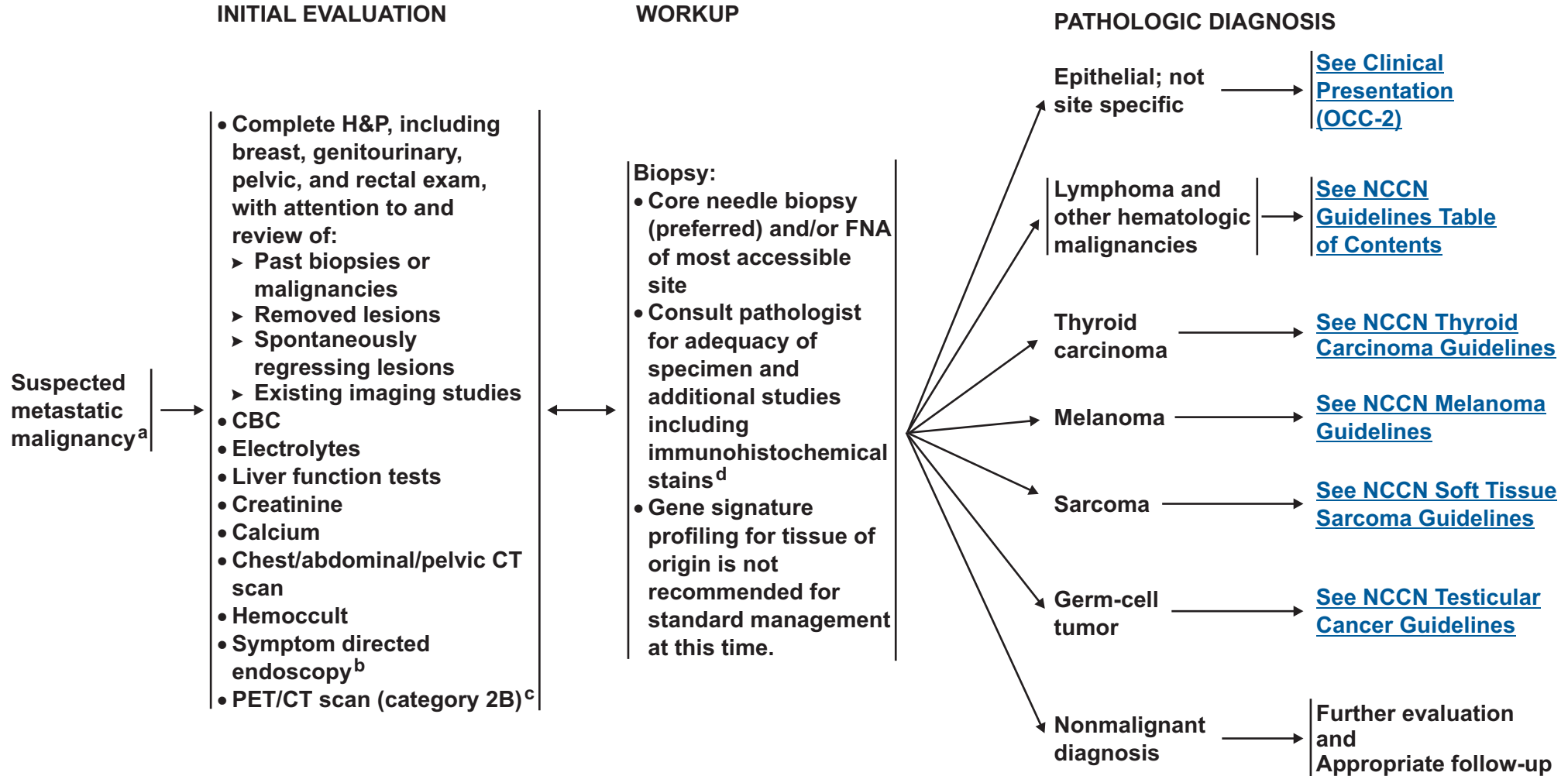
[OCC-B 1 of 2](#)

Principles of Chemotherapy

- (*list below and others*) was added parenthetically after regimen to the second bullet.

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^bBased on clinical findings.

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

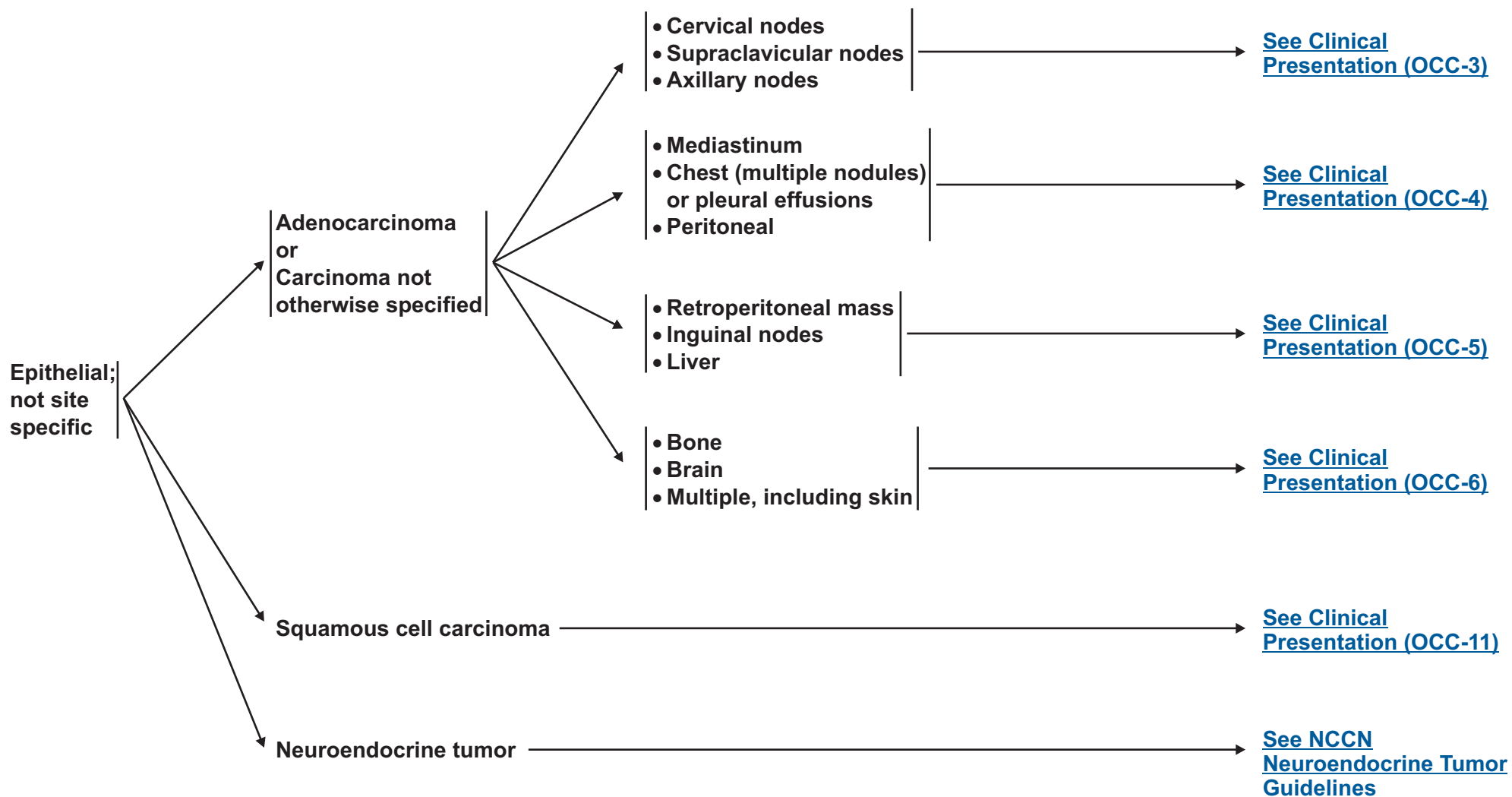
^d[See Immunohistochemistry Markers for Unknown Primary Cancers \(OCC-A\).](#)

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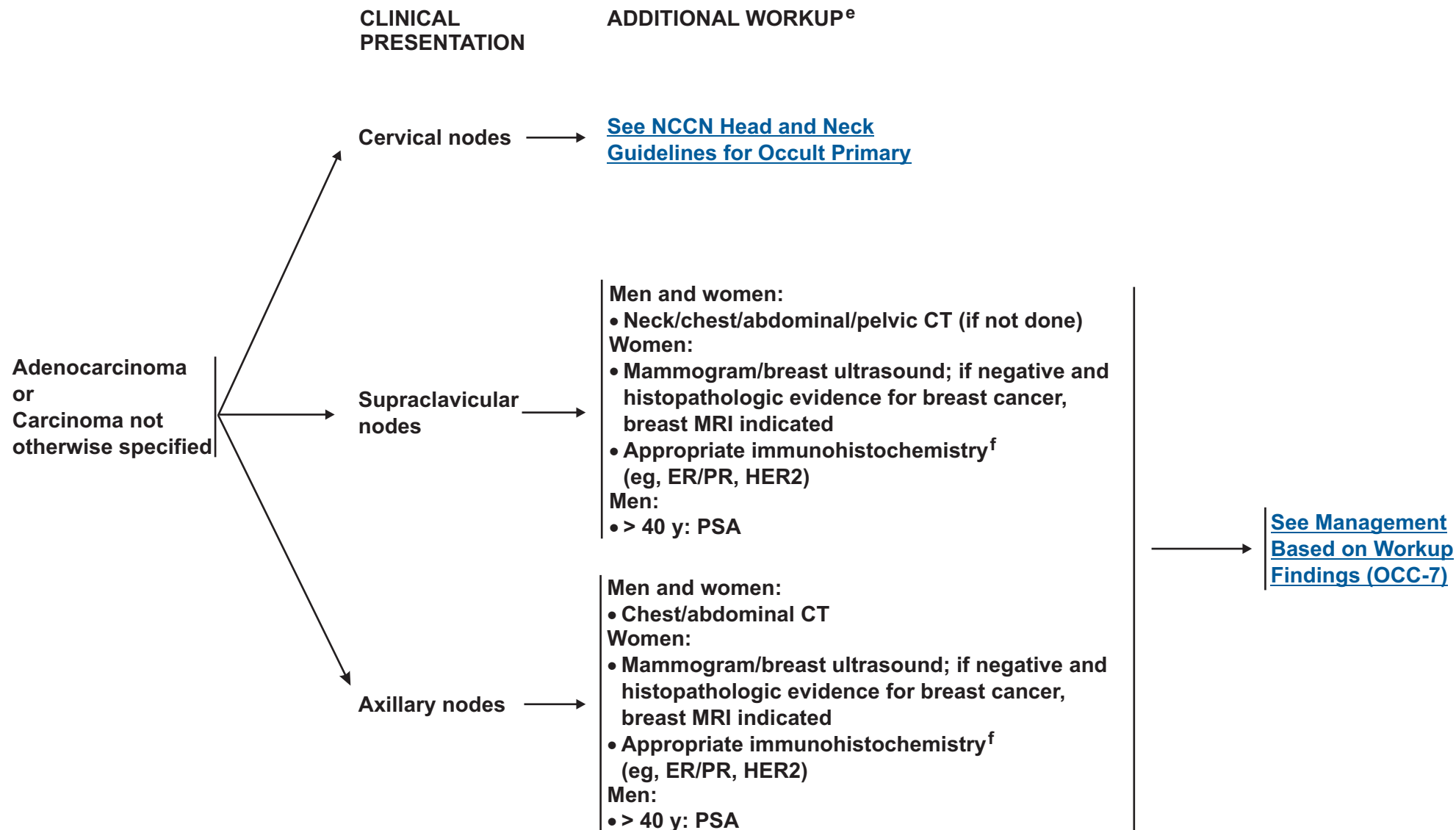
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PATHOLOGIC DIAGNOSIS

CLINICAL PRESENTATION



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

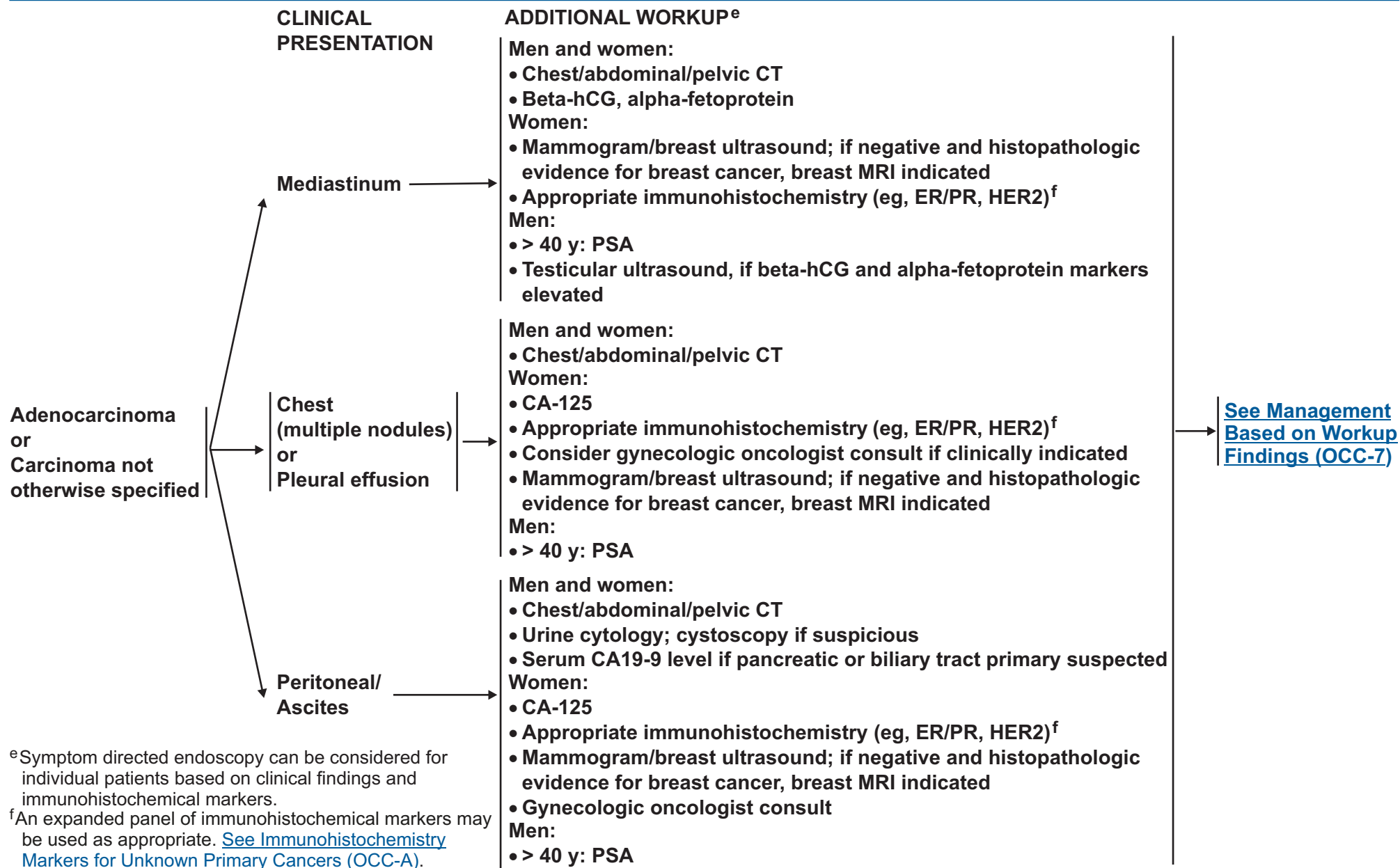
^fAn expanded panel of immunohistochemical markers may be used as appropriate. [See Immunohistochemistry Markers for Unknown Primary Cancers \(OCC-A\)](#).

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Occult Primary



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**CLINICAL
PRESENTATION**

ADDITIONAL WORKUP^e

Adenocarcinoma
or
Carcinoma not
otherwise specified

Retroperitoneal
mass

Inguinal
nodes

Liver

- Men and Women:**
- Chest/abdominal/pelvic CT
 - Urine cytology; consider cystoscopy if suspicious
- Women:**
- CA-125
 - Appropriate immunohistochemistry (eg, ER/PR, HER2)^f
 - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated
 - Gynecologic oncologist consult if clinically indicated
- Men:**
- > 40 y: PSA
 - < 65 y: Beta-hCG, alpha-fetoprotein, testicular ultrasound if markers elevated

- Men and women:**
- Abdominal/pelvic CT
 - Proctoscopy if clinically indicated
- Women:**
- CA-125
 - Gynecologic oncologist consult
- Men:**
- > 40 y: PSA

- Men and women:**
- Chest/abdominal/pelvic CT
 - Colonoscopy
 - Serum CA19-9 level if pancreatic or biliary tract primary suspected
 - Alpha-fetoprotein
- Women:**
- Appropriate immunohistochemistry (eg, ER/PR, HER2)^f
 - Mammogram/breast ultrasound; if negative and histopathologic evidence for breast cancer, breast MRI indicated

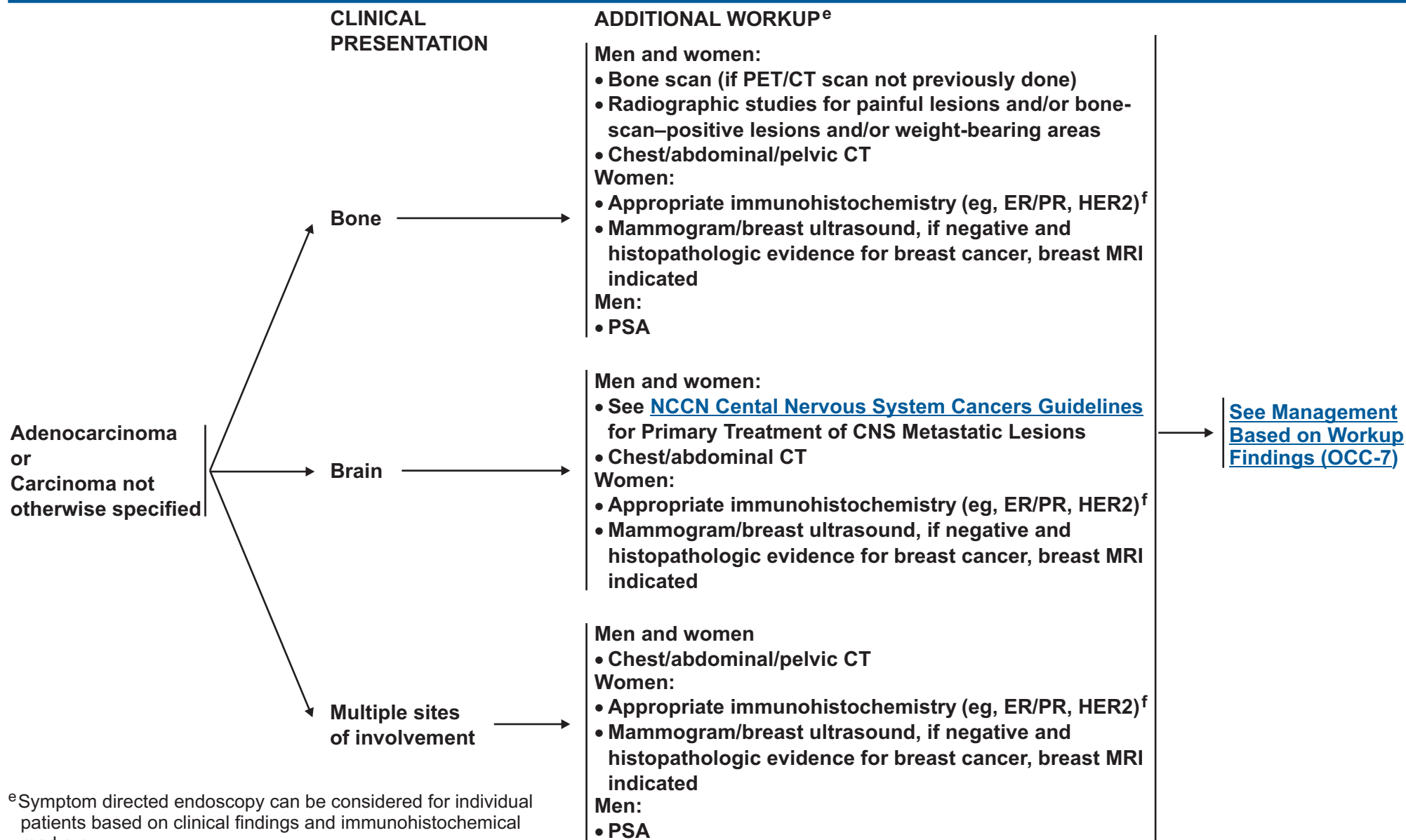
[See Management
Based on Workup
Findings \(OCC-7\)](#)

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

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WORKUP FINDINGS

MANAGEMENT BASED ON WORKUP FINDINGS

Primary found

Treat per NCCN disease-specific guidelines
[NCCN Guidelines Table of Contents](#)

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 basis^g
- Specialized approaches^h
- Mediastinal: Treat per [NCCN Testicular Cancer Guidelines](#) in young men

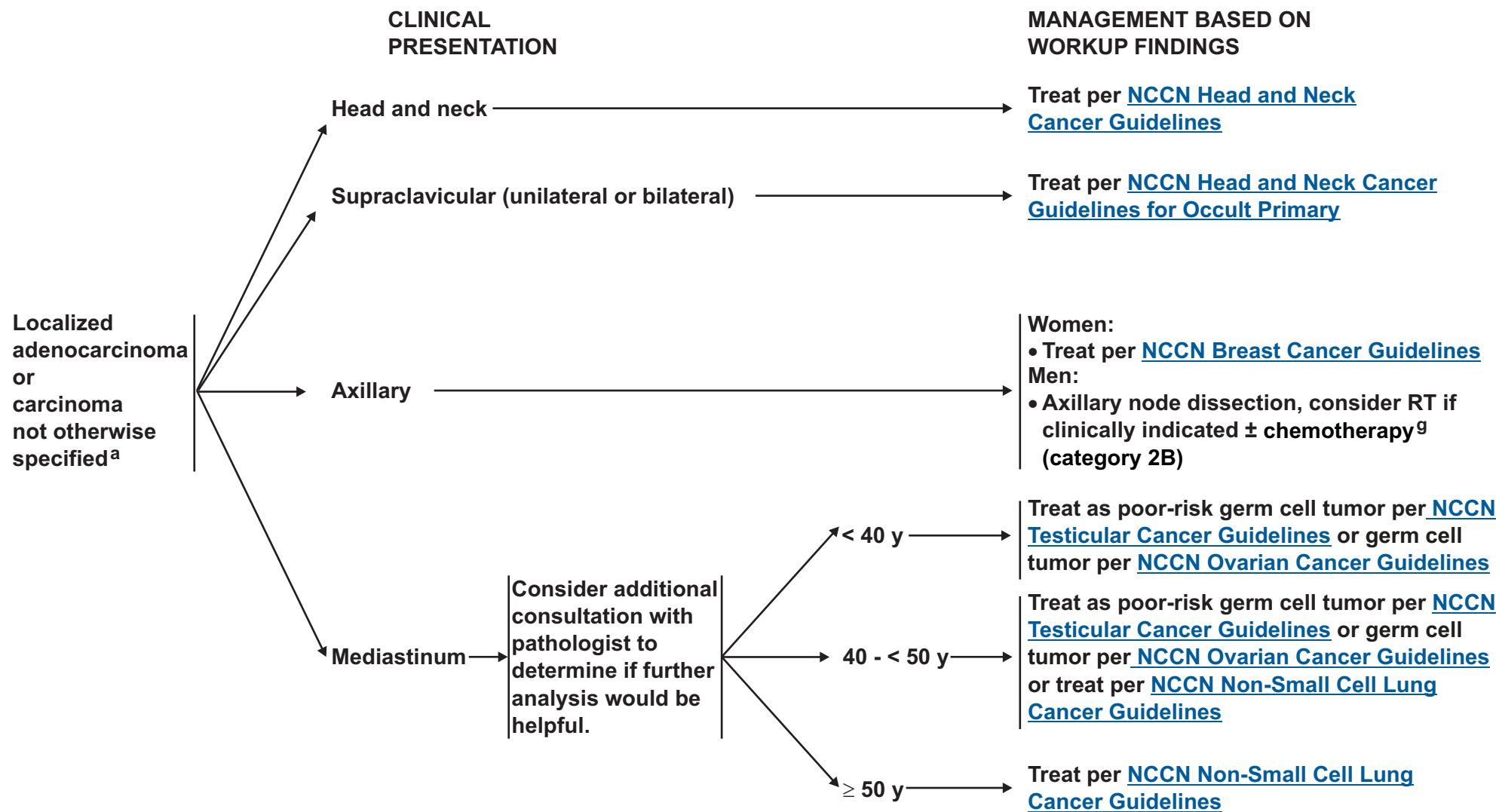
^aFor many patients the apparent uncertainties surrounding the diagnosis of an unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. Empathetic discussion about the natural history of these types of cancer and their prognosis,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

^g[See Principles of Chemotherapy \(OCC-B\).](#)

^hFor specialized approaches therapeutic in nature, [see discussion \(MS-8\).](#)

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

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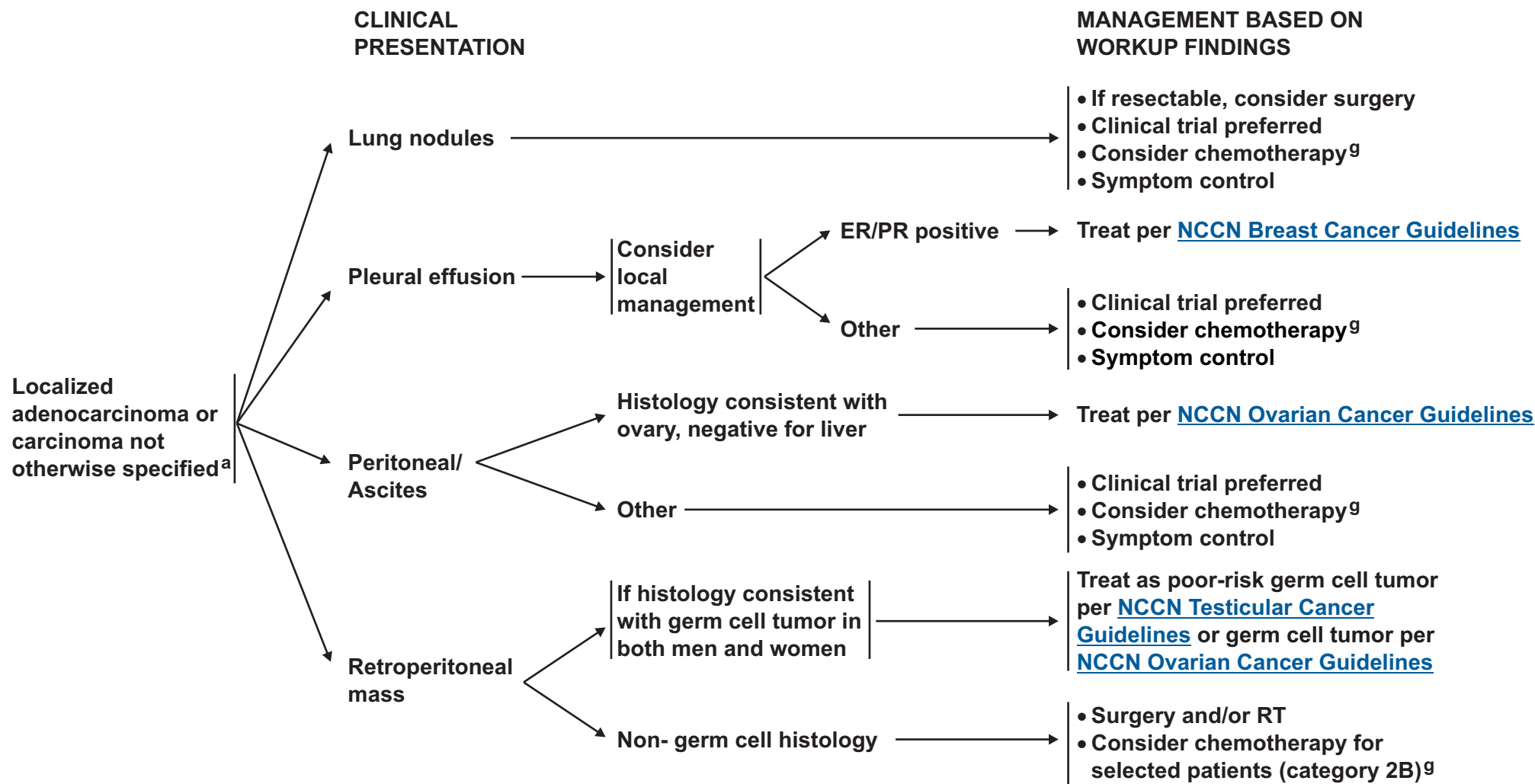


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[See Follow-up \(OCC-16\)](#)

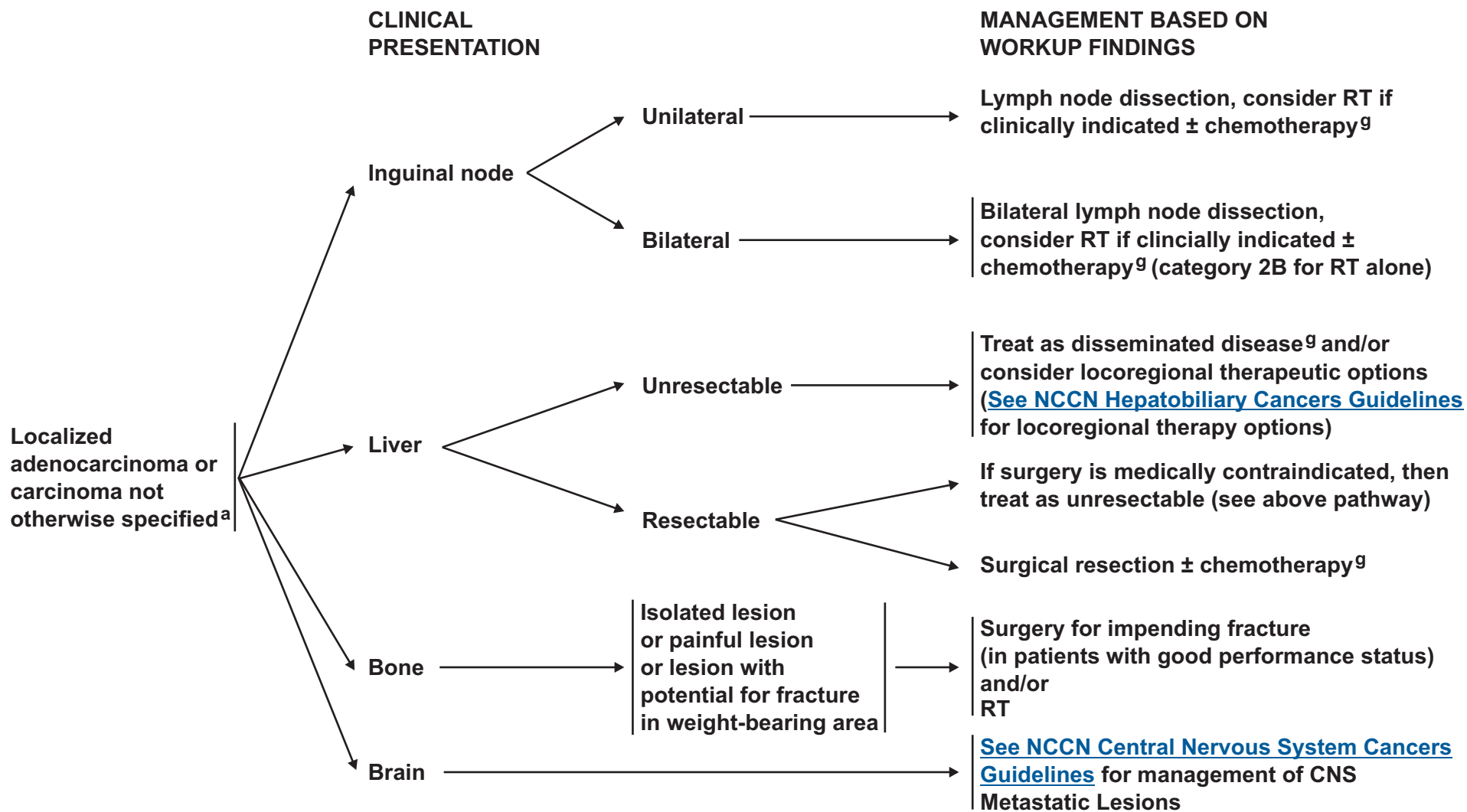


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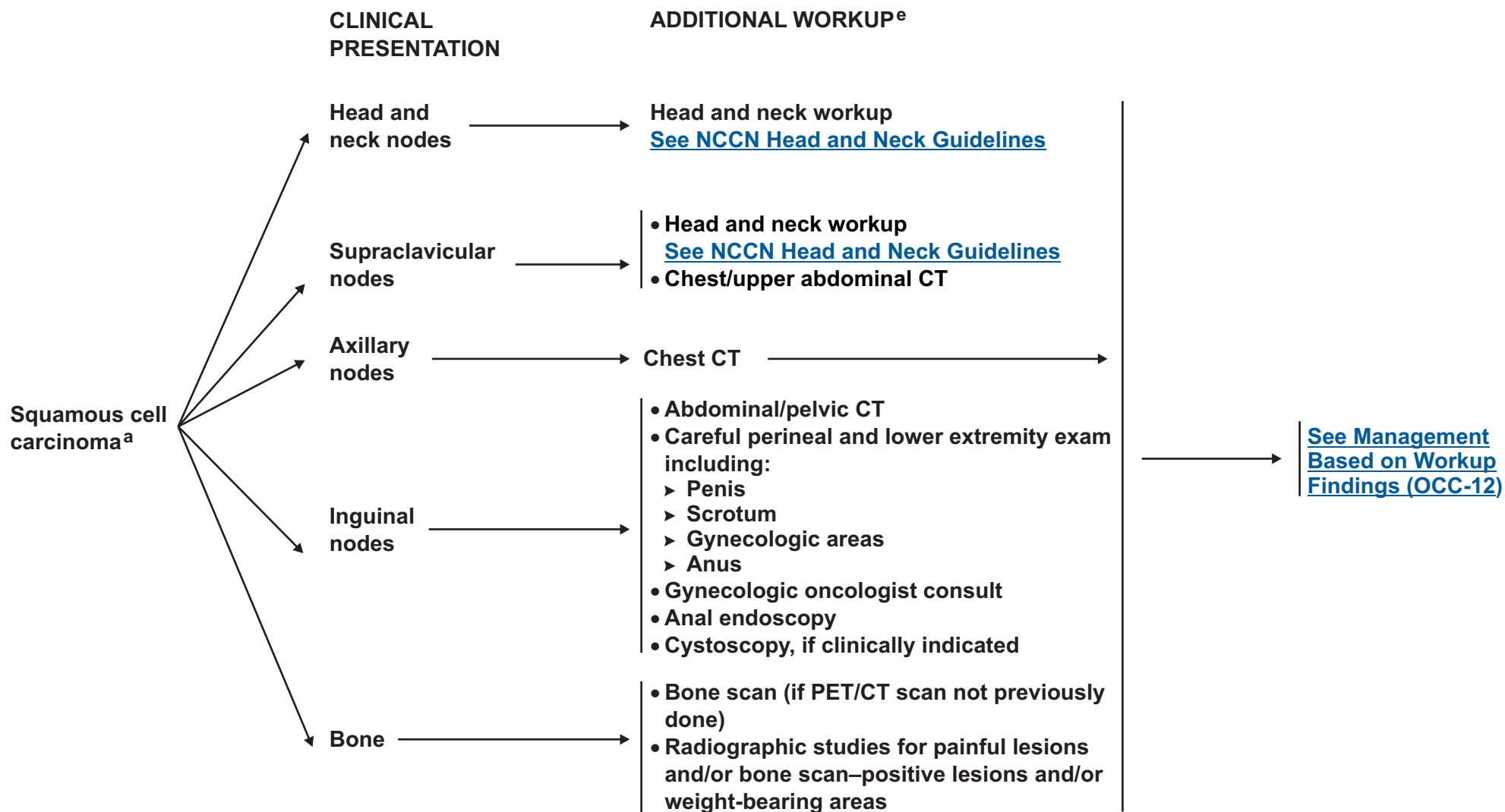
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WORKUP FINDINGS

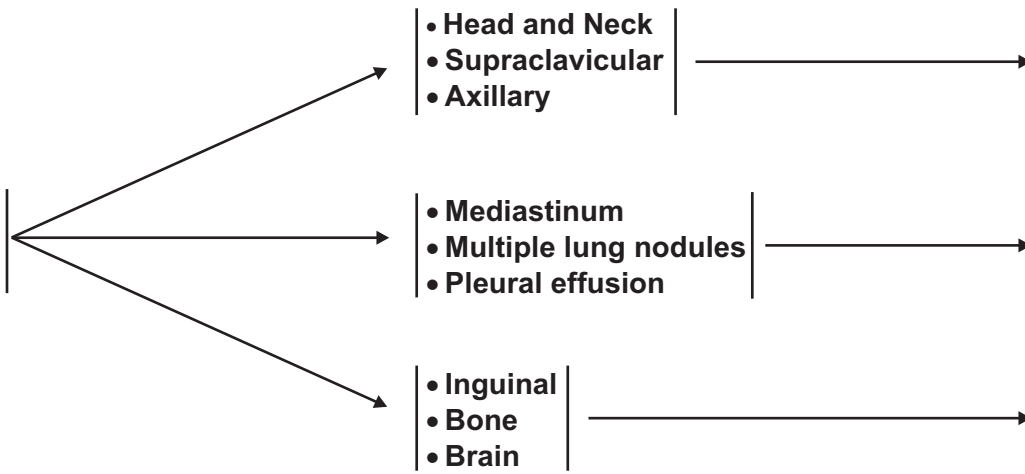
**MANAGEMENT BASED ON
WORKUP FINDINGS**

Primary found



Treat per NCCN disease-specific guidelines
[NCCN Guidelines Table of Contents](#)

Site specific
squamous cell
carcinoma^a



[See Management of Site Specific Disease \(OCC-13\)](#)

[See Management of Site Specific Thoracic Disease \(OCC-14\)](#)

[See Management of Site Specific Disease \(OCC-15\)](#)

Disseminated
metastases^a



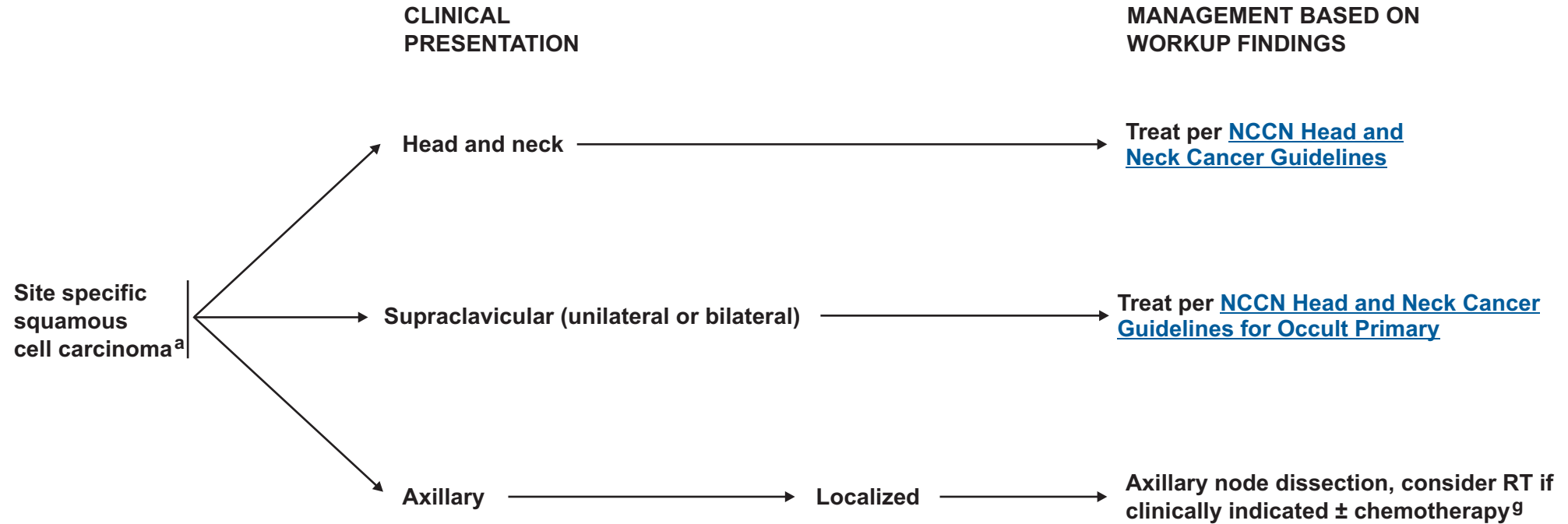
• Symptom control
• Clinical trial preferred
• Consider chemotherapy on an individual basis⁹

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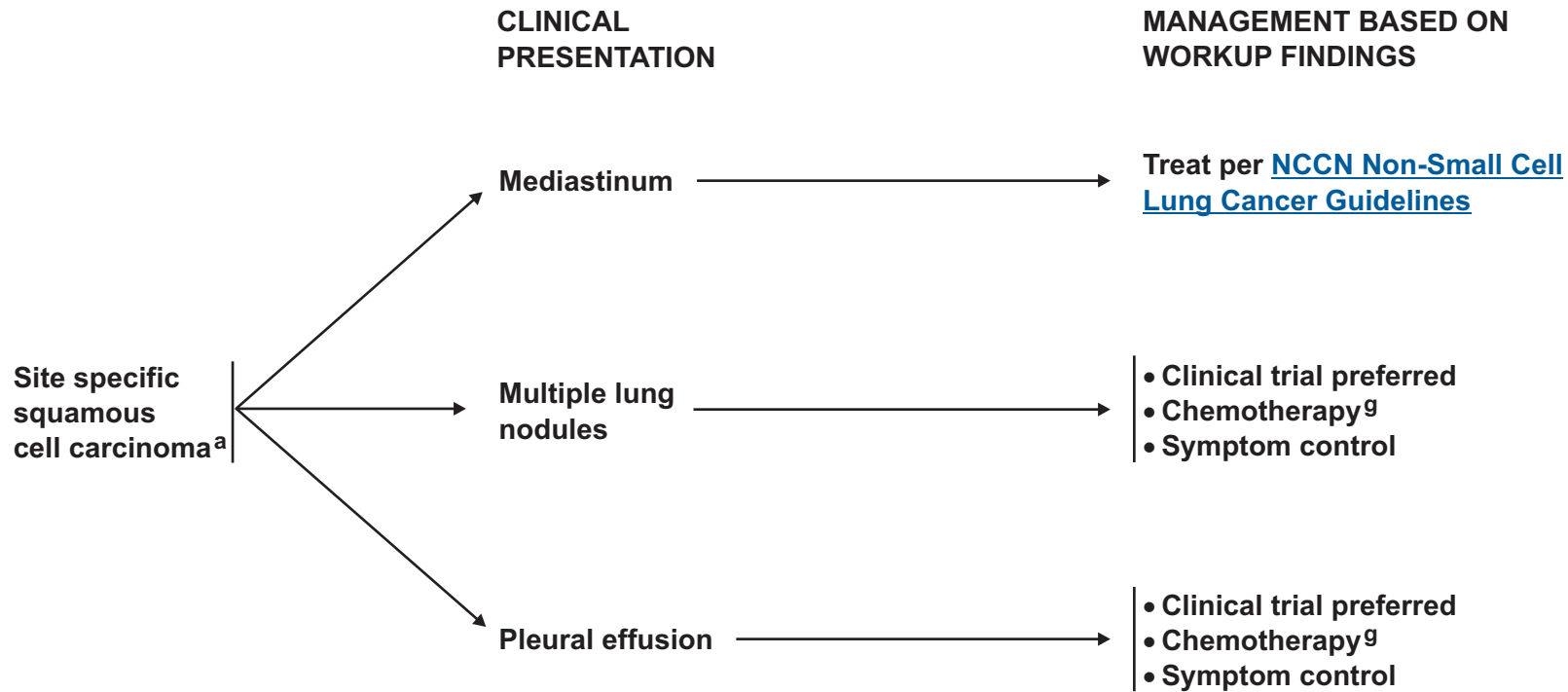


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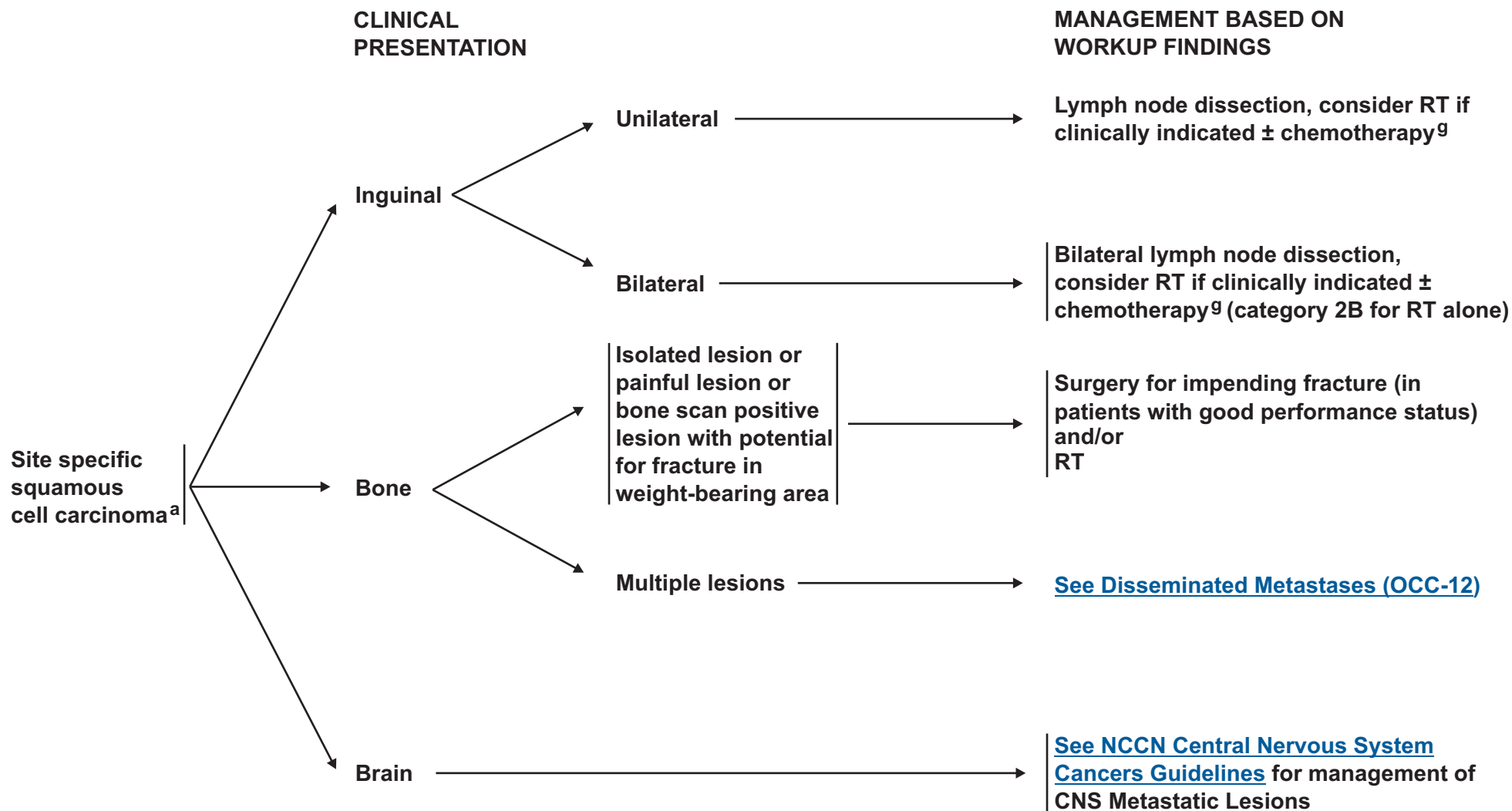


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**FOLLOW-UP FOR ALL OCCULT PRIMARIES
(NO ACTIVE TREATMENT)**

- **H&P every 3-6 mo for first 3 y, then as indicated**
- **Diagnostic tests based on symptomatology**
- **Psychosocial support**

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS:

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

KEY SCREENING ANTIBODIES FOR UNDIFFERENTIATED MALIGNANCY

	CAM5.2 ¹	Epithelial Membrane Antigen (EMA)	S-100	Leukocyte Common Antigen (LCA)	Placenta-Like Alkaline Phosphatase (PLAP)
Carcinoma	POS	POS	NEG/POS	NEG	NEG/POS
Melanoma	NEG	NEG	POS	NEG	NEG
Lymphoma/ Leukemia	NEG	NEG	NEG	POS	NEG
Nonseminoma Germ Cell Neoplasm	POS	NEG	NEG	NEG	POS
Germ Cell Seminoma	NEG	NEG	NEG	NEG	POS

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

¹Other pan-cytokeratin markers may be used.

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TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN*

<u>Marker</u>	<u>Tumor</u>	<u>Staining Pattern</u>
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

* 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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CYTOKERATIN/KERATIN DISTRIBUTION

CK 7+ 20+		CK 7- 20+	
Ovary mucinous	90%	Colorectal adeno	80%
Transitional cell	65%	Merkel cell	70%
Pancreas adeno	65%	Gastric adeno	35%
Cholangio	65%	<u>Excluded tumors</u>	≤ 5%
Gastric adeno	40%	Breast; Carcinoid lung; Cholangio;	
<u>Excluded tumors</u>	≤ 5%	Esoph squam; Germ cell; Lung all	
Carcinoid; Germ cell; Esoph squam;		types; Hepatocellular; Ovary;	
Head/neck squam; Hepatocellular;		Pancreas adeno; Renal adeno;	
Lung small cell & squam; Ovary-non		Transitional cell; Uterus	
mucinous; Renal adeno		endometrioid	
CK 7+ 20-		CK 7- 20-	
Ovary non mucinous	100%	Adrenal	100%
Thyroid (all three types)	100%	Seminoma & YST	95%
Breast	90%	Prostate	85%
Lung adeno	90%	Hepatocellular	80%
Uterus endometrioid	85%	Renal adeno	80%
Embryonal	80%	Carcinoid GI & lung	80%
Mesothelioma	65%	Lung small cell & squam	75%
Transitional cell	35%	Esoph squam	70%
Pancreas adeno	30%	Head/neck squam	70%
Cholangio	30%	Mesothelioma	35%
<u>Excluded tumors</u>	≤ 5%	<u>Excluded tumors</u>	≤ 5%
Colorectal adeno; ovary mucinous;		Breast; Cholangio; Lung adeno;	
seminoma; yolk sac tumor (YST)		Ovary; Pancreas adeno	

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

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Carcinomatous tumors → Broad spectrum CK's+, S100-, HMB45-, C45-



CK7+/CK20 +	CK7+/CK20 -		CK7-/CK20 +	CK7- /CK20 -		
<p>Urothelial CA uroplakin + thrombomodulin + p63 + CK5/6 (~1/2+)</p> <p>Pancreatic adeno CA (~2/3) CEA + CA19-9 + MUC5-AC + MUC-2 - CDX2 +/- DPC4-</p> <p>Ovarian mucinous CA MUC5-AC + MUC-2 - CDX2 +/-</p> <p>AdenoCA of bladder thrombomodulin + CDX2 +/-</p> <p>Gastric adeno CA (subset) CDX2 +/-</p> <p>CholangioCA (minor subset) CDX2 +/-</p>	<p>Breast CA ER/PR + GCDFP + mammoglobin + CEA +</p> <p>Endometrioid adeno CA vimentin + ER/PR + CEA -</p> <p>Endocervical adeno CA CEA + vimentin - p16 + ER/PR -</p> <p>Ovarian serous CA WT1 + ER/PR + mesothelin + CEA -</p> <p>Lung adeno CA TTF-1 + CEA + CK5/6 - p63 -</p>	<p>Cholangio CA CEA+ CK19 + MOC31+ CA19-9 + CDX2 +/- HepPar1-</p> <p>Lung SmCC (majority) TTF-1 + NE markers* + p63 -</p> <p>Mesothelioma (~2/3) calretinin + WT1 + CK5/6 + thrombomodulin + D2-40 + mesothelin + p63 - CEA - MOC31 - Ber-EP4 - TTF-1 -</p>	<p>Thyroid CA TTF-1 +^ψ thyroglobulin +^ψ CEA - (expect medullary CA)</p> <p>SCC of cervix p16 +</p> <p>Salivary gland tumor</p> <p>Urothelial CA (subset)</p> <p>Pancreatic adeno CA (subset) CDX2 +/- DPC4-</p> <p>Gastric adeno CA CDX2 +/-</p>	<p>Colorectal adeno CA CDX2 + CEA + MUC-2 + MUC5-AC -</p> <p>Merkel cell CA NE markers* +</p> <p>Gastric adeno CA (subset) CDX2 +/-</p>	<p>Prostate adenoCA PSA + PAP + CEA - uroplakin - thrombomodulin - p63 - CK5/6 -</p> <p>SCC p63 + CK5/6 + thrombomodulin +</p> <p>RCC vimentin + RCC marker + CD10 + CEA -</p> <p>HCC HepPar1 + pCEA +^ξ CD10 +^ξ MOC31 - CK19 -</p>	<p>Adenocortical CA inhibin + calretinin + melanA + vimentin + CEA -</p> <p>Nonseminoma GCTs [¶] PLAP + EMA - Yolk sac tumor: AFP + Embryonal CA: OCT3/4 + CD30 +</p> <p>Mesothelioma (~1/3)</p> <p>Lung SmCC (minor subset)</p> <p>Gastric adeno CA (subset) CDX2 +/-</p>

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

Bahrami A, Truong L, Ro J. Undifferentiated tumor-True Identity by Immunohistochemistry. Arch Path Lab Med 2008; 132:326-348. Adapted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2008. College of American Pathologists. Varadhachary G, Abbruzzese J, Lenzi, R. Diagnostic Strategies for Unknown Primary Cancer. Cancer 2004;100:1776-1785.

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

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

PRINCIPLES OF CHEMOTHERAPY

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

SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

Adenocarcinoma	
Paclitaxel ¹	200 mg/m ² /3 h IV d 1
Carboplatin ¹	AUC = 6 d 1, repeat cycle every 3 wks
Paclitaxel ²	200 mg/m ² /1 h IV d 1
Carboplatin ²	AUC = 6
Etoposide ²	50 mg/d PO alternating with 100 mg/d PO d 1-10, repeat cycle every 3 wks
Docetaxel ³	65 mg/m ² IV d 1
Carboplatin ³	AUC = 6 d 1, repeat cycle every 3 wks
Gemcitabine ⁴	1250 mg/m ² IV d 1 and 8
Cisplatin ⁴	100 mg/m ² IV d 1, repeat cycle every 3 wks
Gemcitabine ⁵	1000 mg/m ² IV d 1 and 8
Docetaxel ⁵	75 mg/m ² IV d 8, repeat cycle every 3 wks

Squamous Cell Carcinoma	
Paclitaxel ⁶	175 mg/m ² /3 h IV d 1
Cisplatin ⁶	100 mg/m ² IV d 2
5-FU ⁶	500 mg/m ² /d continuous infusion over 120 h, repeat cycle every 3 wks
Docetaxel ⁷	75 mg/m ² IV d 1
Cisplatin ⁷	75 mg/m ² IV d 1
5-FU ⁷	750 mg/m ² /d continuous infusion d 1-5, repeat cycle every 3 wks

Neuroendocrine Tumors
For poorly differentiated (high grade or anaplastic) or small cell subtype other than lung neuroendocrine tumors, see NCCN Small Cell Lung Cancer Guidelines
For moderate and well-differentiated neuroendocrine tumors, see NCCN Neuroendocrine Tumors Guidelines-Carcinoid Tumors

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hrs
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

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.

[See references on OCC-B 2 of 2](#)

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REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

- ¹Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary carcinoma: A phase II Hellenic Cooperative Oncology Group Study. J Clin Oncol 2000;18:3101-3107.**
- ²Greco F, Burris, H, Erland J, et al. Carcinoma of unknown primary site: Long term follow-up after treatment with paclitaxel, carboplatin, and etoposide. Cancer 2000;89:2655-2660.**
- ³Greco F, Erland J, Morrissey H, et al. Carcinoma of unknown primary site: Phase II trials with docetaxel plus cisplatin or carboplatin. Ann Oncol 2000;11:211-215.**
- ⁴Culine S, Lortholary A, Voigt J, et al. Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: Results of a randomized phase II study trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). J Clin Oncol 2003;21:3479-3482.**
- ⁵Pouessel D, Culine S, Becht C, et al. Gemcitabine and docetaxel as front-line chemotherapy in patients with carcinoma of an unknown primary site. Cancer. 2004;100(6):1257-1261.**
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- ⁷Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst. 2009;101(7):498-506.**

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.

Overview

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

In a majority of patients, occult primary tumors are refractory to systemic treatments, and chemotherapy is only palliative and does not significantly improve long-term survival. However, certain clinical

presentations of these tumors are associated with a better prognosis.⁵ Special pathologic studies can identify these subsets of patients with tumor types that are more responsive to chemotherapy. Treatment options should be individualized for this selected group of patients to achieve improved response and survival rates.

Epidemiology

Occult primary tumors occur roughly equally in men and women, with an average age at diagnosis of 60.^{6,7} An estimated 30,500 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2011, accounting for about 2% of all the cancers diagnosed in the United States.⁷ However, deaths due to cancer of unspecified primary site are estimated to be 44,260 in 2011. This discrepancy is believed to be due to the lack of specificity in recording underlying cause of death on death certificates.

A recent analysis of the Swedish Family-Cancer Database revealed that occult primary tumors may have a genetic basis.⁸ 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 cancer in families, suggesting that these tumor types are often the primary site of the disease.⁸

A primary tumor site is found in fewer than 30% of patients who present initially with an occult primary tumor. In 20-50% of patients, the primary tumor is not identified even after postmortem examination.^{6,9,10}

Pathology

Occult primary tumors often have multiple chromosomal abnormalities and overexpression of several genes including *Ras*, *BCL2*, *HER-2*, and *p53*.^{11,12} *BCL-2* and *p53* genes are over-expressed in 40% and 53% of



occult primary tumors, respectively.¹³ *BRD4-NUT* oncogene resulting from the chromosomal translocation, t(15;19) has been identified in children and young adults with carcinoma of midline structures and unclear primary sites.^{1, 14, 15}

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

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

Patients with occult primary tumors may present with favorable or unfavorable sets of prognostic signs.^{3, 21-23} Favorable prognostic factors include poorly differentiated carcinoma with midline distribution, women with papillary adenocarcinoma of the peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, SCC involving cervical lymph nodes, isolated inguinal adenopathy (SCC), poorly differentiated neuroendocrine carcinomas, men with blastic bone metastases and elevated PSA (adenocarcinoma), and patients with a single small and potentially resectable tumor.^{22, 24, 25} Cervical lymph

node metastases of SCC constitute about 2-5% of all patients with occult primary cancers.²⁶

Unfavorable features include male gender, pathologic diagnosis of adenocarcinoma with multiple metastases involving multiple organs (liver, lung, or bone), non-papillary malignant ascites (adenocarcinoma), multiple cerebral metastases (adenocarcinoma or SCC), adenocarcinoma with multiple lung/pleural or multiple bone lesions.²²

Immunohistochemistry

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

Carcinomas are usually positive for anti-cytokeratin antibody CAM5.2 and epithelial membrane antigen (EMA). S-100 is usually expressed in melanoma, clear cell sarcoma, glioma, and malignant peripheral nerve sheath tumors. Leucocyte common antigen (LCA or CD45) is expressed in virtually all hematolymphoid malignancies and is highly specific for non-Hodgkin's lymphoma. Placental alkaline phosphatase (PLAP) is mainly found in seminomas but is also expressed in some nonseminoma germ cell tumors, genitourinary, gastrointestinal, and pulmonary carcinomas. Carcinoembryonic antigen (CEA) can be useful

for the differential diagnosis of gastrointestinal adenocarcinomas, endocervical cancer, and some lung tumors from other sites of origin.³¹

Cytokeratins are useful for cell-type determination in primary and metastatic carcinomas. Low-molecular-weight cytokeratins (CK7 and CK20) are the two most common immunostains used in occult primary tumors to define subsets of carcinomas.³²⁻³⁴ CK7 is mainly found in tumors of the lung, ovary, endometrium, thyroid, and breast. CK20 is usually expressed in gastrointestinal, urothelial, and Merkel cell carcinomas. CK7-positive/CK20-negative staining narrows the diagnosis to lung, breast, thyroid, pancreatic, ovarian, endometrioid, gastric, urothelial, or endocervical carcinomas. CK7-negative/CK20-positive cells are indicative of colorectal carcinoma, gastric carcinoma, or Merkel cell carcinoma. CK7/CK20 phenotype is also useful for differentiating between prostate (CK7-negative/CK20-negative) and urothelial (CK7-positive/CK20-positive or negative) carcinoma.

CK5 and CK6 can be useful for the differential diagnosis of poorly differentiated metastatic SCC.³⁵ The majority of poorly differentiated SCCs (84%) show CK5/6 positivity, whereas only 21% of non-SCCs are positive for CK5/6.³⁵ In addition to poorly differentiated SCC, urothelial carcinomas (35%) and all mesotheliomas express CK5 and CK6.³⁵

In addition to the above-mentioned cytokeratins, some of the other IHC markers that are used to distinguish occult primary tumors include thyroid transcription factor (TTF-1), thyroglobulin, gross cystic disease fluid protein-15 (GCDFP-15), uroplakin III, and WT1 as reviewed by Bahrami et al.³¹ The use of TTF-1 staining further distinguishes lung primary tumors from other CK7-positive tumors, as most lung and thyroid carcinomas are positive for TTF-1. Thyroglobulin is a very specific marker for thyroid carcinoma (papillary and follicular).

GCDFP-15 and uroplakin III are highly specific markers for breast and urothelial cancer, respectively; however, neither is very sensitive for the deduction of breast and urothelial carcinomas. In a study involving 690 neoplasms, GCDFP-15 was able to identify breast carcinomas with a sensitivity of 74% and a specificity of 95%.³⁶ Uroplakin III is expressed in about 60% and 50% of primary and metastatic urothelial carcinomas, respectively. WT1 is a sensitive marker for epithelioid mesothelioma, and it is also positive in almost all cases of ovarian serous carcinoma including high-grade forms.³¹ The p53 homologue nuclear transcription factor p63 can also be useful to identify carcinomas with squamous cell, urothelial, and myoepithelial differentiation. Most poorly differentiated SCCs (86%) show immunoreactivity for p63, while only 14% of non-SCCs are positive for p63.³⁵ Malignant mesotheliomas are consistently negative for p63, whereas p63 is expressed in about 70-95% of urothelial carcinomas.^{31, 35}

Molecular Profiling

Molecular profiling is an emerging diagnostic tool to help identify tissue of origin. Recently, several gene expression profiling (GEP) assays have been developed to identify the tissue of origin in patients with occult primary cancers.^{37, 38} Talantov et al have developed a molecular assay that is designed to detect tumors originating from lung, breast, colon, ovary, pancreas, and prostate by evaluating the expression of 10 specific genes using real time quantitative reverse transcription-polymerase chain reaction (qRT-PCR).³⁹ This assay identified the tissue of origin of metastatic carcinomas in 204 of 260 tested samples with an overall accuracy of 78%. Varadachary et al have assessed the feasibility of this assay retrospectively in 104 patients with CUP.⁴⁰ The tissue of origin was identified in 61% of patients, and the results were compatible with clinicopathological features and response to therapy in most cases. Similarly, Ma et al

have developed a 92-gene-based qRT-PCR assay to identify the site of origin for metastatic tumors, especially in patients with CUP.⁴¹ In a retrospective, multicenter study, this assay identified primary sites in 75% of patients after the initial diagnosis of CUP.⁴²

These GEP tests are now commercially available and are being evaluated in prospective clinical studies. Preliminary data from a prospective study in which treatments were based on the identification of primary sites by the 92-gene assay demonstrated that clinical features and response to treatment were generally consistent with assay results.⁴³ Similarly, 32 patients whose tumors were classified as being of colorectal origin by both of these GEP assays (the 10-gene assay of Talantov et al and the 92-gene assay of Ma et al) demonstrated a response to colorectal chemotherapy regimens as expected for stage IV colorectal patients.⁴⁴

Using a microarray approach, Monzon et al have developed a 1,550-GEP test,^{45, 46} which had 88% sensitivity and 99% specificity in the diagnosis of uncertain primary tumors in a blinded multicenter validation study.⁴⁷ This test is also commercially available.

Another form of molecule profiling has recently generated some interest for its potential to identify the tissue of origin of cancers of unknown primary. This assay is based on the presence of microRNAs (miRNAs), which are non-coding RNAs that regulate gene expression and show high tissue specificity.⁴⁸⁻⁵⁰ Using a panel of 48 miRNAs, blinded sets of samples were identified with an accuracy of 85-89%.^{48, 49} When this assay was prospectively studied in patients with occult primary tumors, the tissue of origin diagnosed was consistent with clinical and/or pathological features of the disease in 62 of 74 patients (84%).⁵⁰

At the present time, the panel feels that there is not sufficient data to confirm whether molecular profiling can be used in choosing treatment options that would improve the prognosis of patients with occult primary cancers. Hence, the panel does not recommend molecular profiling as part of routine evaluation.

Psychosocial Distress

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

Treatment Options

Chemotherapy

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

In recent years, newer regimens containing taxanes and/or gemcitabine have shown efficacy in phase II studies in the treatment of patients with occult primary tumors.⁵⁸⁻⁶² In one study, taxane-based chemotherapy was associated with long-term survival in some patients with CUP, with 1-, 2-, 3-, and 4-year survival rates of 42%, 22%, 17%, and 17%, respectively.⁶² The median survival was 10 months. Schneider et al reported that the combination of carboplatin, gemcitabine, and capecitabine was active in occult primary tumors in patients with good performance status.⁵⁸ Median PFS was 6.2 months; 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.⁵⁹

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

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

Adenocarcinoma

Poorly differentiated carcinomas and adenocarcinomas or undifferentiated carcinomas of unknown primary respond differently from well- to moderately-differentiated carcinomas of unknown primary. Tumors in the former group appear to be highly responsive to cisplatin-based combination chemotherapy.^{65, 66} Objective response rates reported in two studies were 53% (van der Gaast et al) and 63% (Hainsworth et al) with complete response rates of 12% and 26%, respectively.^{65, 66} In one study, patients who had tumors with extragonadal germ cell features demonstrated a high response rate.⁶⁵ In the other, patients with undifferentiated carcinomas had a better response rate than those with poorly differentiated adenocarcinomas (79% vs. 35%; $P = 0.02$).⁶⁶

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.^{61, 67, 68} In the Hellenic Cooperative Oncology Group study, combination of paclitaxel and carboplatin produced an overall response rate of 38.7% by intent-to-treat (ITT) analysis; there was no difference in the response rates for adenocarcinomas and undifferentiated carcinomas.⁶⁷ 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-year, 2-year, and 3-year survival rates of 48%, 20%, and 14%, respectively.⁶⁸ In a recent phase III randomized study, the triple drug regimen had efficacy comparable to gemcitabine and irinotecan in the first-line treatment of patients with CUP.⁶⁹ In a randomized prospective phase II study conducted by the German CUP Study Group, the paclitaxel and carboplatin combination demonstrated better clinical activity than the gemcitabine and vinorelbine combination.⁷⁰ The median overall survival, 1-year survival rate, and response rate were 11.0 months, 38%, and 23.8%, respectively for patients treated with paclitaxel and carboplatin, compared to 7.0 months, 29%, and 20%, respectively for those who received gemcitabine and vinorelbine. Sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan was also found to be active in patients with occult primary tumors.⁷¹ While survival was similar to that observed in previous phase II trials, overall toxicity of sequential treatment was found to be greater than that observed with other regimens.

Greco et al reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated adenocarcinoma.⁷² 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.⁷²

In a recent report of the Hellenic Cooperative Oncology Group phase II study, a 1-hour treatment with docetaxel and carboplatin every 3 weeks was found to be safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated carcinoma with performance status of 0-2.⁷³ Median time to progression was 5.5

months, while overall survival was 16.2 months. Survival was better in favorable-risk patients (23 months vs. 5 months for those with visceral metastases). Predictors of superior outcome included good performance status and low volume disease.

Efficacy and toxicity of combination regimens including cisplatin with either gemcitabine or irinotecan were evaluated in a randomized phase II study conducted by the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01).⁷⁴ 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 two combination regimens, which were both associated with significant toxicities.

Finally, a non-cisplatin-based regimen containing gemcitabine and docetaxel was found to be well tolerated and active as first-line therapy in patients with occult primary tumors.⁷⁵ The overall response rate was 40%, with a median survival of 10 months.

Squamous Cell Carcinoma

Platinum-based regimens are used to treat disseminated SCC. Historically, the combination of cisplatin and 5-fluorouracil was the most frequently used regimen for patients with squamous cell carcinoma of unknown primary.^{76, 77} In more recent years, however, studies have shown that the addition of paclitaxel or docetaxel to such a regimen is beneficial to patients with squamous cell carcinoma. In a randomized phase III study, cisplatin and 5-fluorouracil was compared with the combination of paclitaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer.⁷⁸ Induction chemotherapy with paclitaxel, cisplatin, and 5-fluorouracil produced a higher complete



response rate (33% vs.14%) and was better tolerated than the cisplatin and 5-flourouracil regimen.

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

Neuroendocrine Tumors

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

Hainsworth et al evaluated the efficacy of a combination regimen containing paclitaxel, carboplatin, and etoposide in metastatic poorly-differentiated neuroendocrine (PDNE) carcinomas in patients who had received no prior treatment.⁸¹ Sixty-two percent of the patients had PDNE carcinoma of unknown primary site; patients with known primary sites were also eligible for the study. Major responses were observed in 53% of the patients and the median survival was 14.5 months.

Two-year and 3-year survival rates were 33%, and 24%, respectively. The results of this trial showed that PDNE carcinomas are chemosensitive, with a high overall response rate to combination chemotherapy and a minority of complete responses.

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

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

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

Radiation Therapy

Radiation therapy (RT) is a treatment option for a variety of localized tumors, particularly as follow-up treatment after lymph node dissection for the involvement of axillary or inguinal nodes if more than two nodes are involved or extracapsular extension is present. 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 squamous cell cancer.

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 RT such as intra-operative radiation therapy (IORT), intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT), or proton therapy.⁸⁶

NCCN Recommendations

The NCCN Guidelines focus on three pathologic diagnoses in those patients with epithelial occult primary cancer:

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

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

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma and site-specific SCC. The panel endorses enrollment of patients in appropriate clinical trials when possible. For each of the 3 pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on the NCCN Guidelines for Treatment of Cancer by Site corresponding to the

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

Initial Evaluation

The NCCN 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 hematological malignancy, melanoma, sarcoma, or germ cell tumor).

Initial evaluation of a patient with a suspected metastatic malignancy should include a complete history and physical examination, including breast, genitourinary, pelvic, and rectal examination, with attention to and review of past biopsies or malignancies, removed lesions, spontaneously regressing lesions, and existing imaging studies; routine laboratory studies (complete blood count, 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. Computed tomography (CT) scan of the chest, abdomen, and pelvis is also recommended; it is important to determine if the initially identified malignancy is localized or disseminated, as the treatment for localized and disseminated disease may be different.

In the past several years, positron emission tomography (PET) scans and a combination PET/CT scan have become two of the most frequently used imaging modalities in the management of patients with occult primary cancers. PET scan has been shown to be a useful method for the diagnosis, staging, and restaging of many malignancies,^{87, 88} and it might be warranted in some situations (eg, presence of supraclavicular nodes). PET scan has shown intermediate

specificity and high sensitivity in a few small studies, but larger studies are warranted to determine the clinical utility and role of PET scan in patients with occult primary tumors.^{89, 90} In a comprehensive review of 10 published studies, Seve et al concluded that PET is a valuable imaging modality for patients with occult primary tumors with a single site of metastasis and when therapy with a curative intent is planned.⁹¹

One of the limitations of PET scans has been the limited accuracy of anatomic localization of functional abnormalities due to very little accumulation of ¹⁸F-fluorodeoxyglucose tracer in some neoplastic tissues. In such cases, combination of PET scan with either CT scan or magnetic resonance imaging (MRI) can be more useful.^{92, 93} Studies on the use of PET/CT scans for the detection of occult primary tumors have reported that the combination of PET/CT identified the primary site in 25-57% of patients.⁹⁴⁻⁹⁷ A recent meta-analysis and systemic review on the use of PET/CT in patients with occult primaries found that primary tumors were detected in 37% of 433 patients from 11 studies, with pooled sensitivity and specificity both at 84%.⁹⁸ These results indicate that combined modality scanning could play an important role in the diagnosis of occult primary tumors. However, these results need to be confirmed in larger clinical studies with long-term follow-up.

Although PET or PET/CT scans detect more primary sites (24-40%) compared to conventional imaging techniques (20-27%),⁹⁹ its exact role remains undefined due to the lack of prospective clinical trials comparing PET/CT scans with conventional imaging modalities. Therefore, the panel does not recommend the use of PET/CT scan for routine screening. However, PET/CT scans may be warranted in some situations, especially when considering local or regional therapy. In the guidelines, PET/CT scan is included for initial evaluation with a category 2B recommendation.

Workup

Patients with a suspected occult primary will typically present to the oncologist after undergoing an initial biopsy: 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 done first. Other techniques besides light microscopic examination include electron microscopy and flow cytometry. While immunohistochemical stains can be informative, large panels of immunohistochemical markers should be avoided.

This initial evaluation will identify a primary site in about 30% of patients presenting with occult metastases. These patients should be treated according to the appropriate NCCN Guidelines for Treatment of Cancer by Site.

For the remaining patients, there is a great deal of controversy regarding whether an exhaustive, time consuming, costly evaluation should be conducted to search for the primary beyond these initial tests, as opposed to a more directed evaluation based on the complete history and physical examination, clinical presentation, histopathologic diagnosis, and metastatic sites of involvement. Suggested diagnostic tests for each pathologic subtype, location, and gender (where appropriate) are indicated in the guidelines and are discussed below. 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. The guidelines suggest the use of a mammogram and breast ultrasound for such patients. Appropriate testing for immunohistochemical markers, such as ER/PR and HER2 is also recommended. Elevated ER/PR levels provide strong evidence for a breast cancer diagnosis.¹⁰⁰ MRI of the breast should be considered for a patient with histopathological evidence of breast cancer only when mammography and ultrasound are not adequate to assess the extent of the disease especially in the case of women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor or to evaluate the chest wall.¹⁰¹ 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.^{102, 103} In one report, the primary site was identified using MRI in about half of the women presenting with axillary metastases, irrespective of the breast density.¹⁰⁴

For a woman with involvement of the mediastinum whose workup does not indicate primary breast cancer, additional consultation with a pathologist to determine if further analysis would be helpful in differentiating 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 a man younger than 65 years. Thus, beta-human chorionic gonadotropin (beta-hCG) and alpha-fetoprotein (AFP) measurements

are suggested by the guidelines. CT scans of the chest, abdomen, and pelvis are recommended for both men and women for mediastinal and retroperitoneal adenocarcinoma. Testicular ultrasound should also be considered if beta-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 if further analysis would be helpful in differentiating between testicular or ovarian cancer and non-small cell lung cancer should be considered.

Workup for possible prostate primary

All men over age 40 with an adenocarcinoma or carcinoma not otherwise specified should have a prostate specific antigen (PSA) test, with the exception of those with metastases limited to liver or brain. In addition, men presenting with bone metastases or multiple sites of involvement should have PSA levels assessed regardless of age.

Workup for possible ovarian primary

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

Additional workup for adenocarcinoma or carcinoma not otherwise specified

In patients with peritoneal disease or liver involvement, serum CA 19-9 level can be considered if pancreatic or biliary tract primary is suspected. In patients with inguinal lymph node involvement, the guidelines include proctoscopy for men and women, if clinically



indicated, to assess for rectal or anal cancer.³⁴ Bone scan (if PET/CT scan was not previously done) 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.

Colonoscopy is recommended for patients presenting with malignancy in the liver, but is not routinely recommended in patients presenting with malignant ascites (i.e., peritoneal presentation). In the absence of a positive fecal occult blood test or other clinical factors suggesting a tumor in the colon, the diagnostic yield of colonoscopy is less than 5%. The use of AFP as a marker for hepatocellular carcinoma as part of the additional workup in adenocarcinoma or carcinoma not otherwise specified in the liver has been changed from a category 2B to a category 2A recommendation in the 2012 guidelines.

Workup for squamous cell carcinomas

SCC can be present in the nodes of the head and neck region, supraclavicular, axillary, and inguinal nodes. CT scans of the abdomen and pelvis; perineal and lower extremity exam; gynecologic oncologic consult; and anal endoscopy are recommended for SCC with inguinal nodes involvement. For adenocarcinoma in the bone, bone scan (if PET/CT scan was not previously done) and radiographic studies are recommended for SCC involving painful or bone scan-positive bone lesions.

The workup recommendations for “Occult Primary” in the NCCN Head and Neck Guidelines should be followed for unknown primary lesions in the head and neck and supraclavicular nodes.

Workup for neuroendocrine tumors

Neuroendocrine tumors can metastasize to a number of sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal nodes, liver, bone, brain, and skin. Please see the section on “Neuroendocrine Unknown Primary” in the NCCN Neuroendocrine Tumors Guidelines for workup recommendations.

Management Based on Workup Findings

Adenocarcinoma

Localized adenocarcinoma or carcinoma not otherwise specified is treated according to the most likely primary site. For example, patients with localized adenocarcinoma involving supraclavicular nodes (unilateral or bilateral) or in the head and neck should be treated according to the “Occult Primary” pathway described in the NCCN Guidelines for Head and Neck Cancers. On the other hand, those presenting with localized adenocarcinoma with a peritoneal mass or ascites consistent with ovarian histology are treated as per the NCCN Guidelines for Ovarian Cancer.^{105, 106} Localized adenocarcinoma with a retroperitoneal mass consistent with germ cell histology should be treated as per the NCCN Guidelines for Testicular Cancer or NCCN Guidelines for Ovarian Cancer. For women with localized adenocarcinoma involving axillary nodes and for hormone-receptor-positive women with pleural effusion, the guidelines recommend treatment according to the NCCN Guidelines for Breast Cancer.

Localized adenocarcinoma occurring in the mediastinum most likely derives either from 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 be helpful in determining the origin of the primary tumor. In the absence of additional diagnostic information, the recommended treatment depends on the age of the patient at the time of diagnosis. Patients under 40 years as well those



between 40-50 years should be treated for poor-risk germ cell tumors using the NCCN Guidelines for Testicular Cancer or the NCCN Guidelines for Ovarian Cancer. Alternatively, patients aged 40-50 years could be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer. Patients 50 years or older are treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer.

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 RT to axilla for gross extracapsular extension with or without chemotherapy is recommended for men with localized adenocarcinoma or not otherwise specified adenocarcinoma with involvement of axillary nodes (category 2B). Surgery can be considered for resectable lung nodules, and chemotherapy can be considered with or without resection. Lymph node dissection is recommended for inguinal nodal involvement; RT with or without chemotherapy can also be considered if clinically indicated (category 2B recommendation for the use of RT alone in the case of bilateral inguinal node involvement).¹⁰⁷

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, the guidelines recommend chemotherapy and/or locoregional treatment options as described in the NCCN Guidelines for Hepatobiliary Cancers.

For patients with good performance status and bone lesions with potential for fracture in a weight-bearing area, surgery and/or RT are options. In the case of poor-performance status patients or for patients with isolated or painful bone lesions, RT is recommended. Patients with brain metastases should be managed according to the NCCN

Guidelines for Central Nervous System Cancers recommendations for metastatic lesions. 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 recommended, with consideration of chemotherapy in selected patients (category 2B).

Young men with disseminated metastases should be treated as per the NCCN Testicular Cancer Guidelines. For all other 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,” above).

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

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

Squamous cell carcinoma

Patients with site-specific SCC with localized axillary or inguinal involvement of lymph nodes may benefit from lymph node dissection with or without subsequent chemotherapy. RT can be considered if clinically indicated (category 2B recommendation in the case of bilateral inguinal node involvement for the use of RT alone).¹⁰⁷ 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 treatment of “Occult Primary” tumors described in the NCCN Guidelines for Head and Neck cancers. Patients with site-specific SCC in the mediastinum should be treated as per the NCCN Non-Small Cell Lung Cancer guidelines. 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 RT for impending fracture are options for a patient with an isolated bone lesion and good performance status. Patients with brain metastases should be managed according to the recommendations for metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers.

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

The following regimens are included in the guidelines for the treatment of squamous cell carcinoma of unknown primary, based on randomized phase III studies.^{78, 79} Regimens other than those listed here can also be considered.

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

Neuroendocrine Tumors

Neuroendocrine tumors are managed according to the NCCN Guidelines for Neuroendocrine Tumors, following the “Neuroendocrine Unknown Primary” pathway.

Follow-Up

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

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

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