National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Occult Primary (Cancer of Unknown Primary [CUP])

Version 2.2011

NCCN.org

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NCCN Guidelines™ Version 2.2011 Panel Members
Occult Primary

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Discussion

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† Medical Oncology
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§ Radiotherapy/Radiation Oncology
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¶ Surgery/Surgical Oncology
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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 2.2011 Updates Occult Primary

The 2.2011 version of the Occult Primary Guidelines represents the addition of the updated Discussion.

Updates in the 1.2011 version of the Occult Primary Guidelines from the 1.2010 version include:

OCC-1

- **Under initial evaluation, "urinalysis" was removed.**
- **Footnote b, "Based on clinical findings" was added to the page.**
- **Under workup, a new bullet was added, "Gene signature profiling for tissue of origin is not recommended for standard management at this time."**

OCC-3

- **Adenocarcinoma, "endoscopy" was removed from workup and footnote 'e' was added, "Symptom directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers." Also for OCC-4 through OCC-6 and OCC-11.**

OCC-4

- **Additional workup for peritoneal, "serum CA19-9 level if pancreatic or biliary tract primary suspected" was added. (Also for liver on OCC-5)**

OCC-6

- **Clinical presentation "multiple including skin" was clarified as "Multiple *sites of involvement*".**

OCC-8

- **Supraclavicular (unilateral or bilateral), the management was modified as "Treat per NCCN Head and Neck Cancer Guidelines for Occult Primary". Also for site specific squamous cell carcinoma on OCC-13.**

OCC-10

- **Footnote "Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin" was removed from the management of unilateral inguinal node.**

OCC-A 1 of 4

- **Footnote 1 was modified by adding, "Avoid a large series of immunohistochemistry markers. Communication with pathologist is essential to workup." Also for OCC-A 2 of 4 through OCC-A 4 of 4.**
- **Footnote 2, "Other pan-cytokeratin markers may be used" is new to the page.**

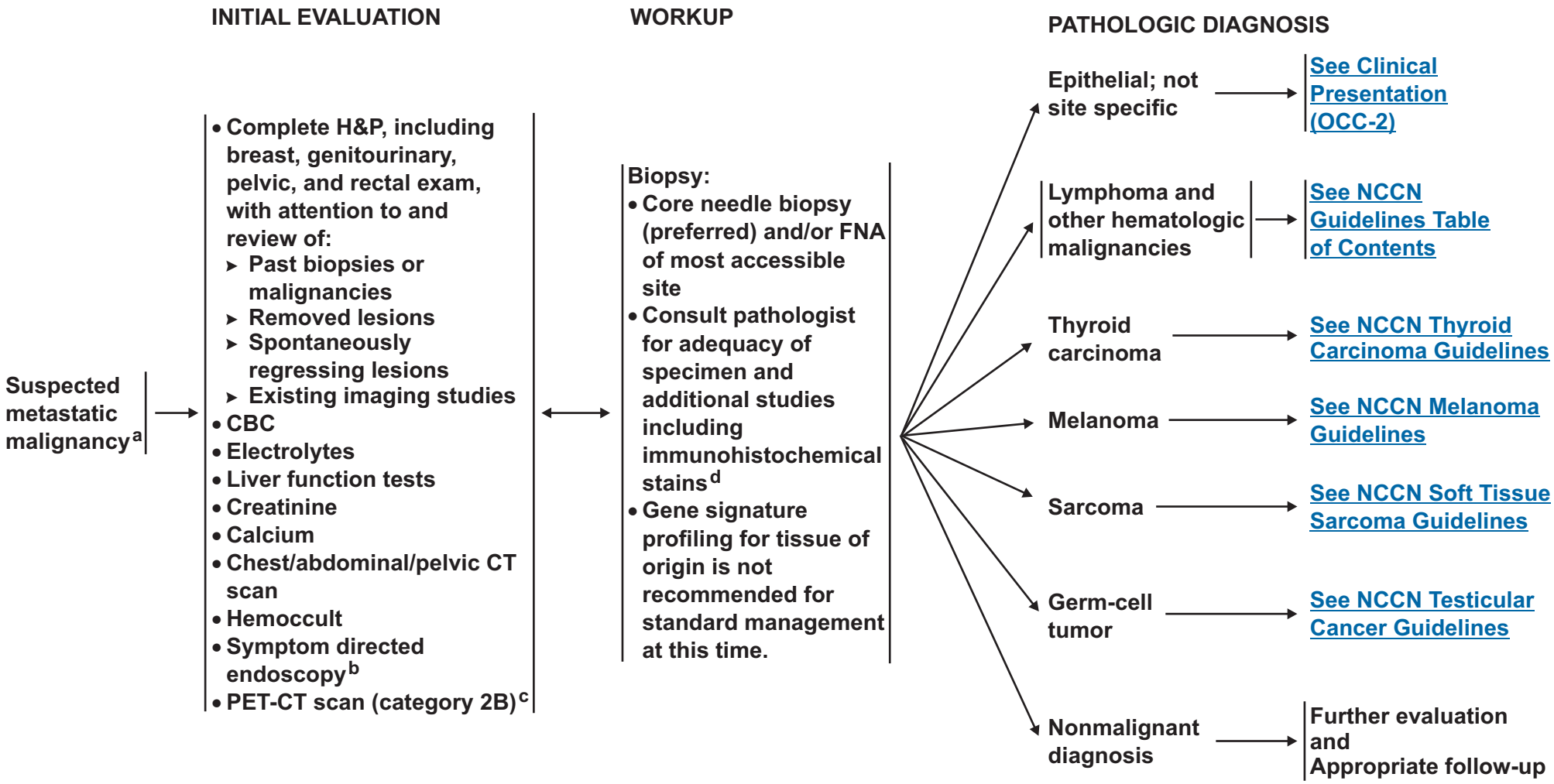
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[b] Based on clinical findings.

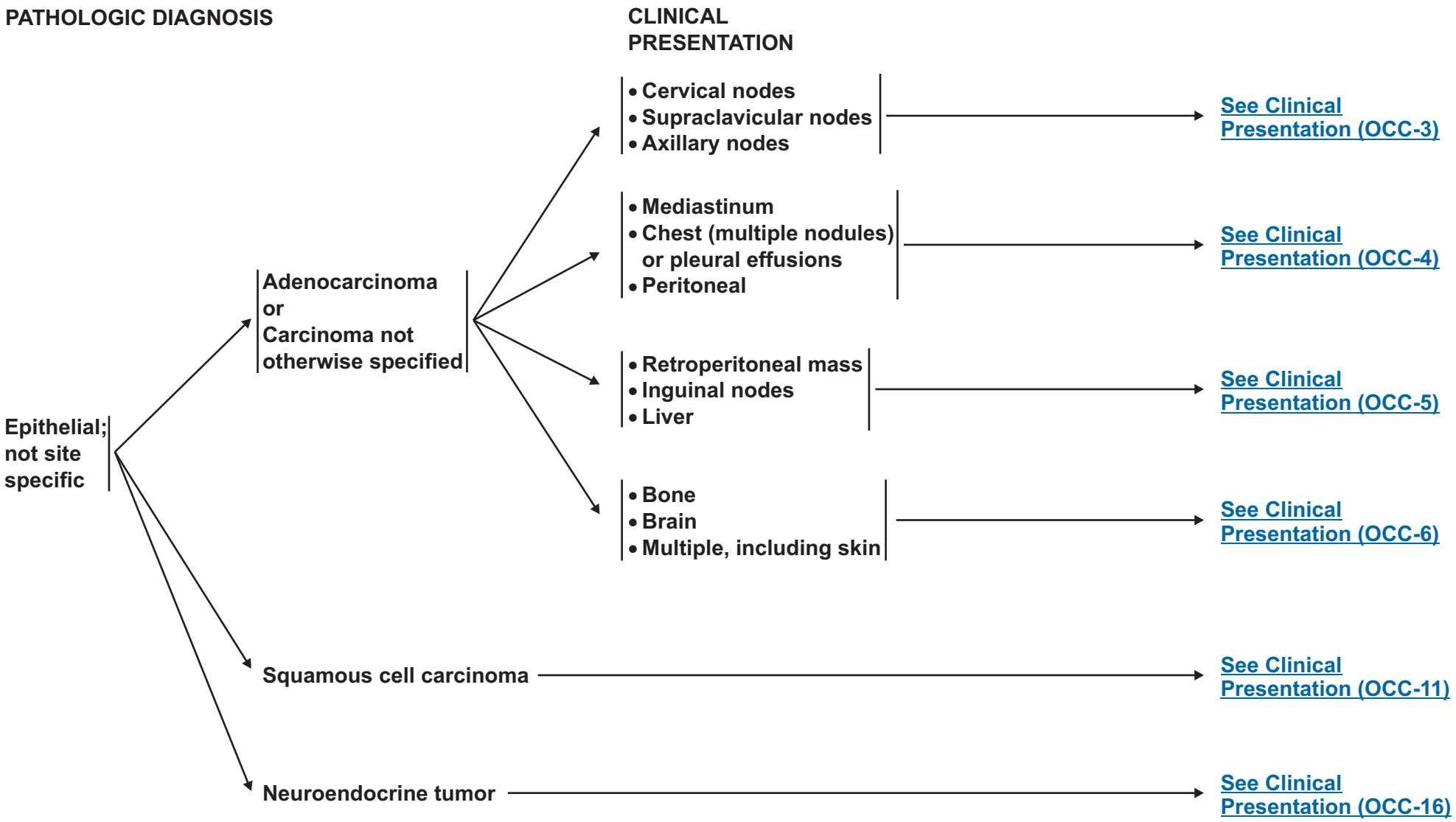
[c] Many patients are referred with PET-CT scans. Routine use is not recommended. PET-CT scans may be warranted in some situations, even in patients with unknown primary, especially when considering local/regional therapy.

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

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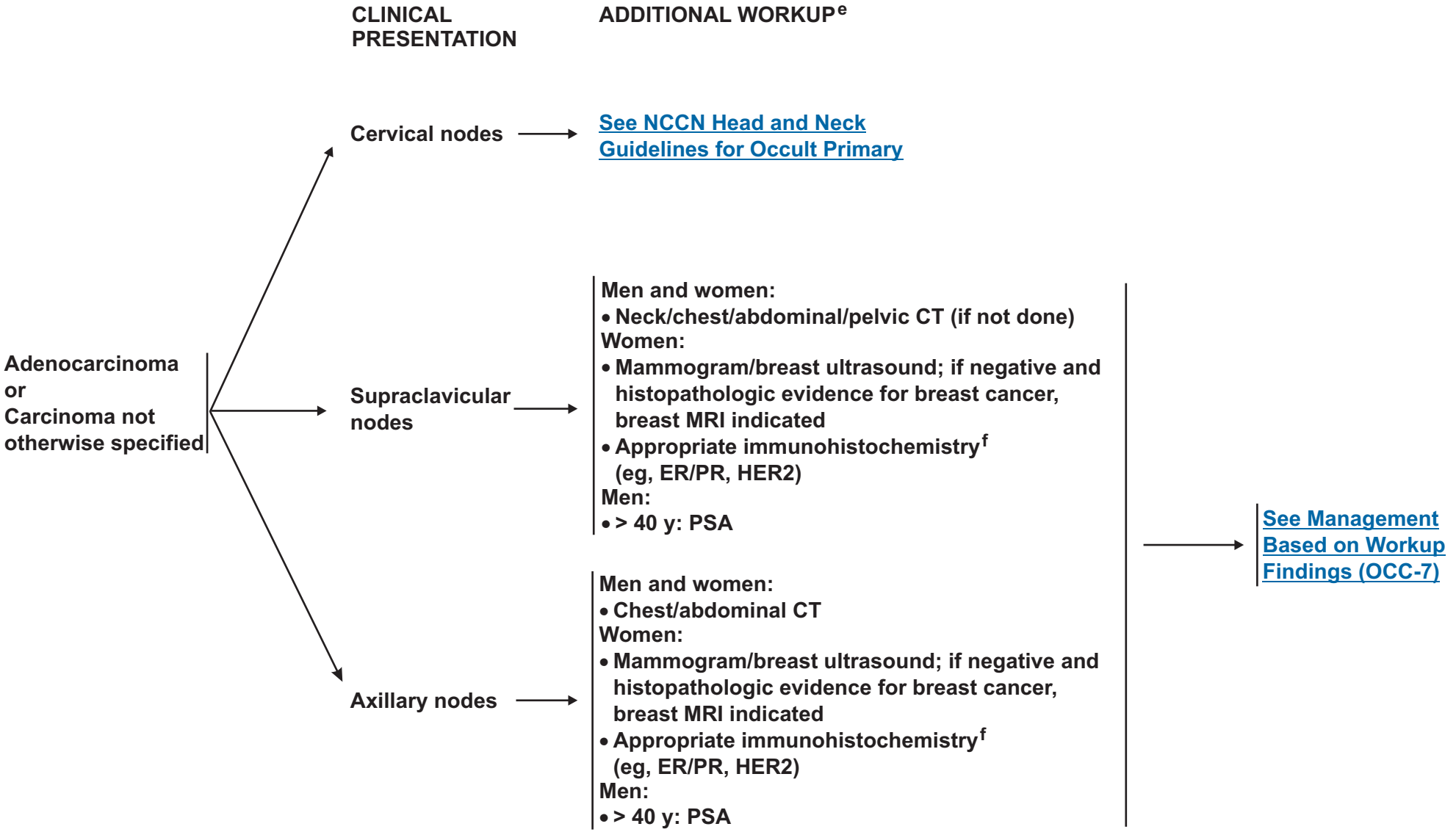
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[e]Symptom directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers.
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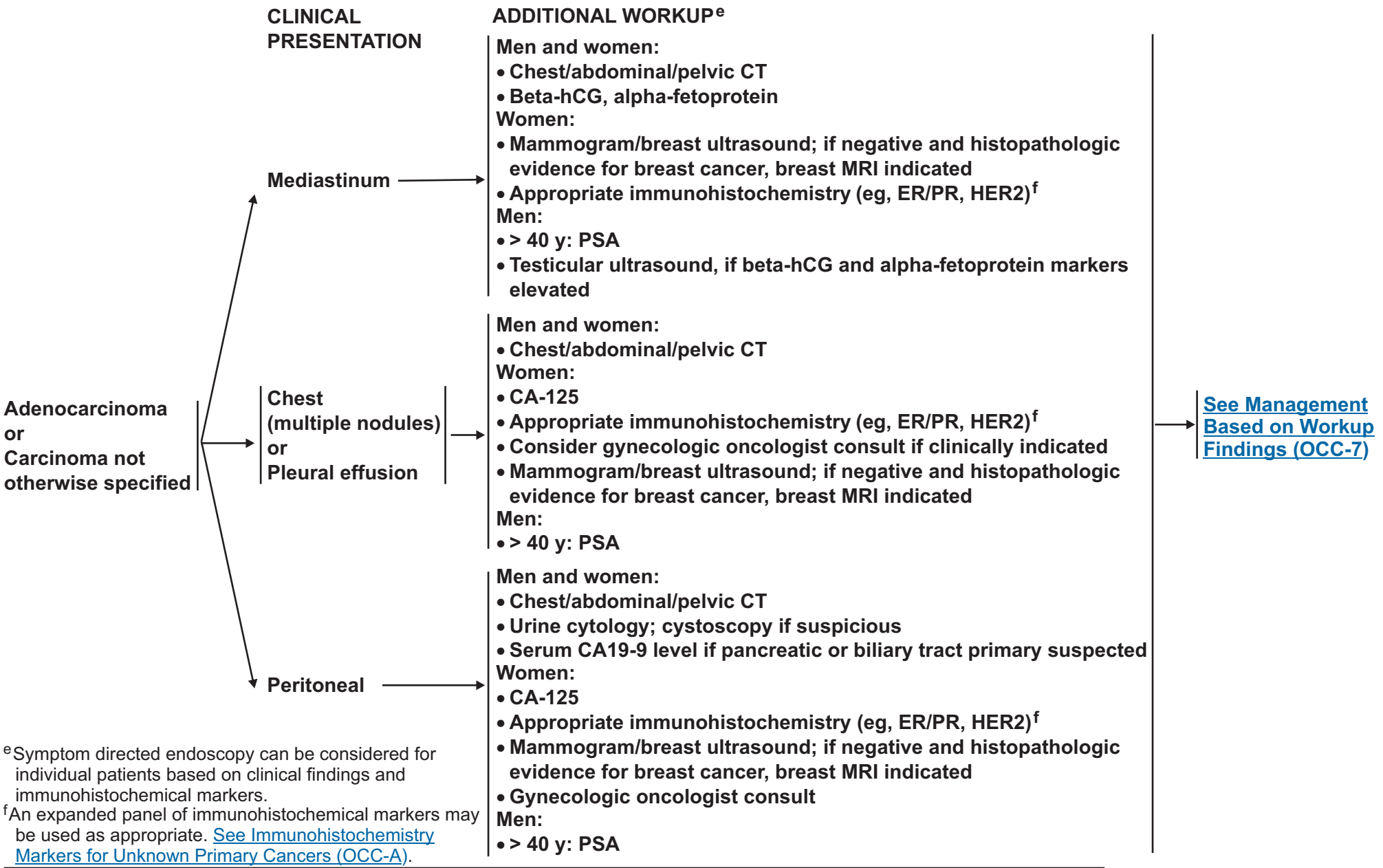
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CLINICAL PRESENTATION

ADDITIONAL WORKUP[e]

Adenocarcinoma or Carcinoma not otherwise specified

Retroperitoneal mass

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**

Inguinal nodes

Men and women:
- **Abdominal/pelvic CT**
- **Proctoscopy if clinically indicated**

Women:
- **CA-125**
- **Gynecologic oncologist consult**

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

Liver

Men and women:
- **Chest/abdominal/pelvic CT**
- **Colonoscopy**
- **Serum CA19-9 level if pancreatic or biliary tract primary suspected**
- **Alpha-fetoprotein (category 2B)**

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)**

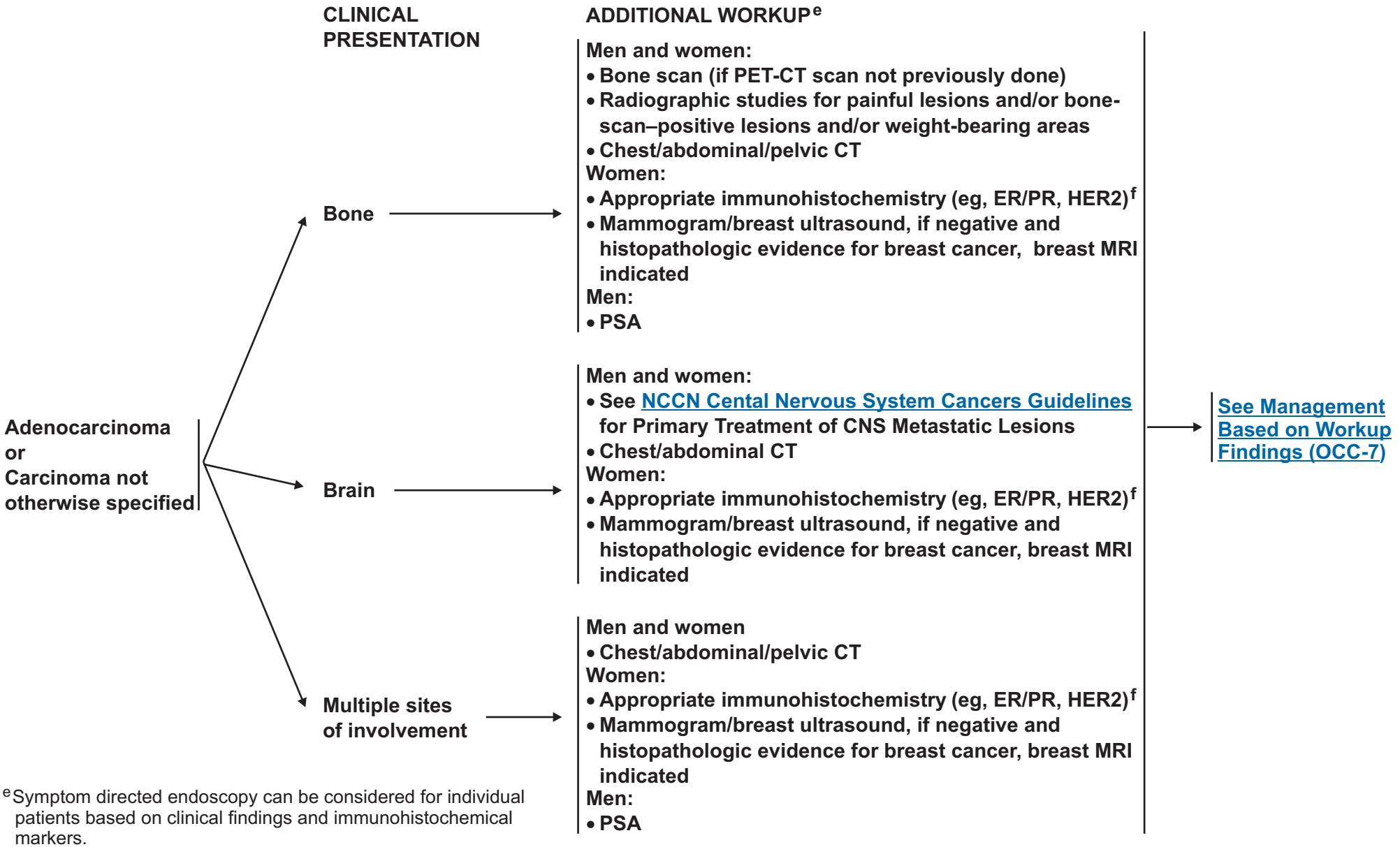
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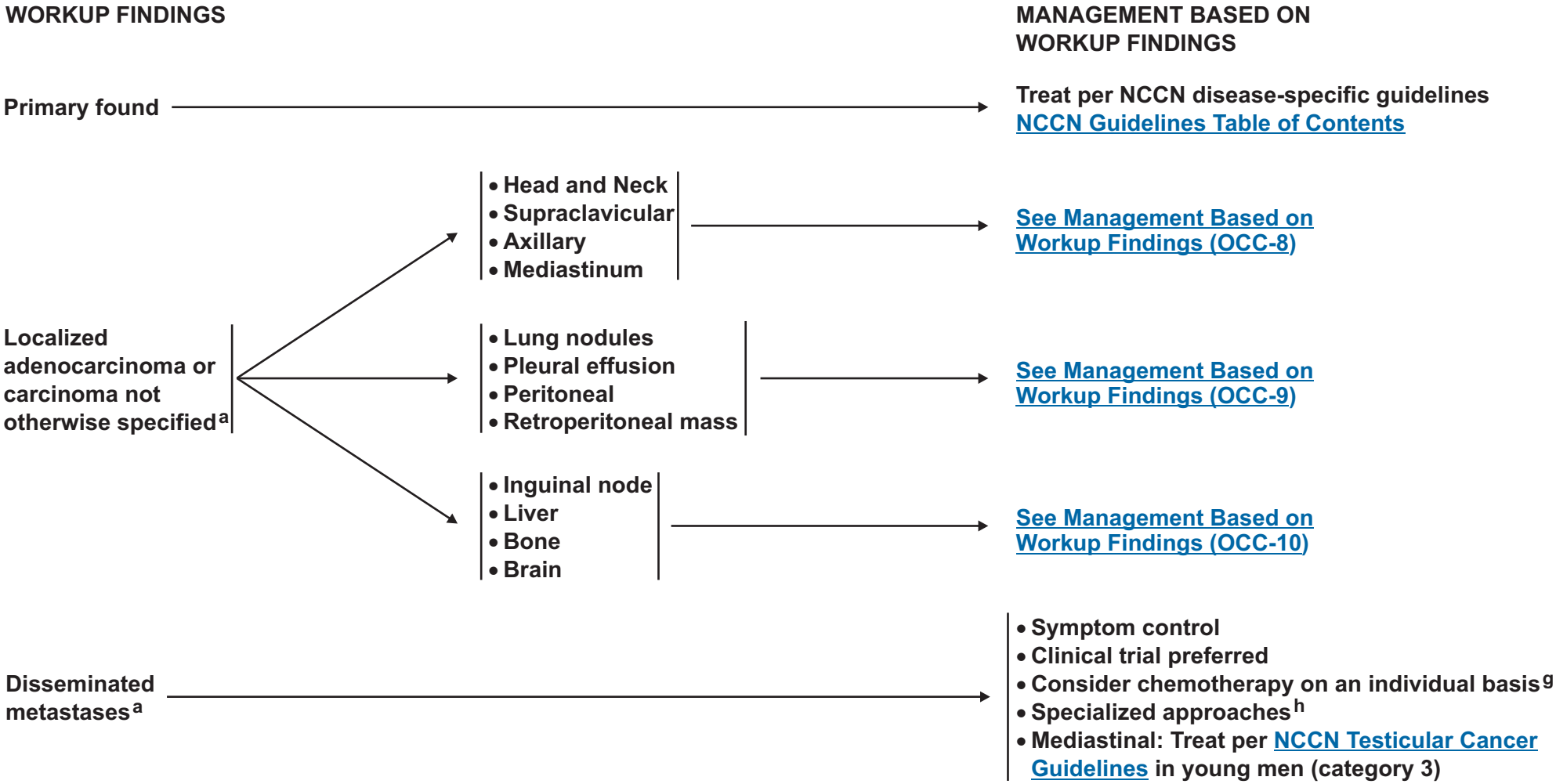
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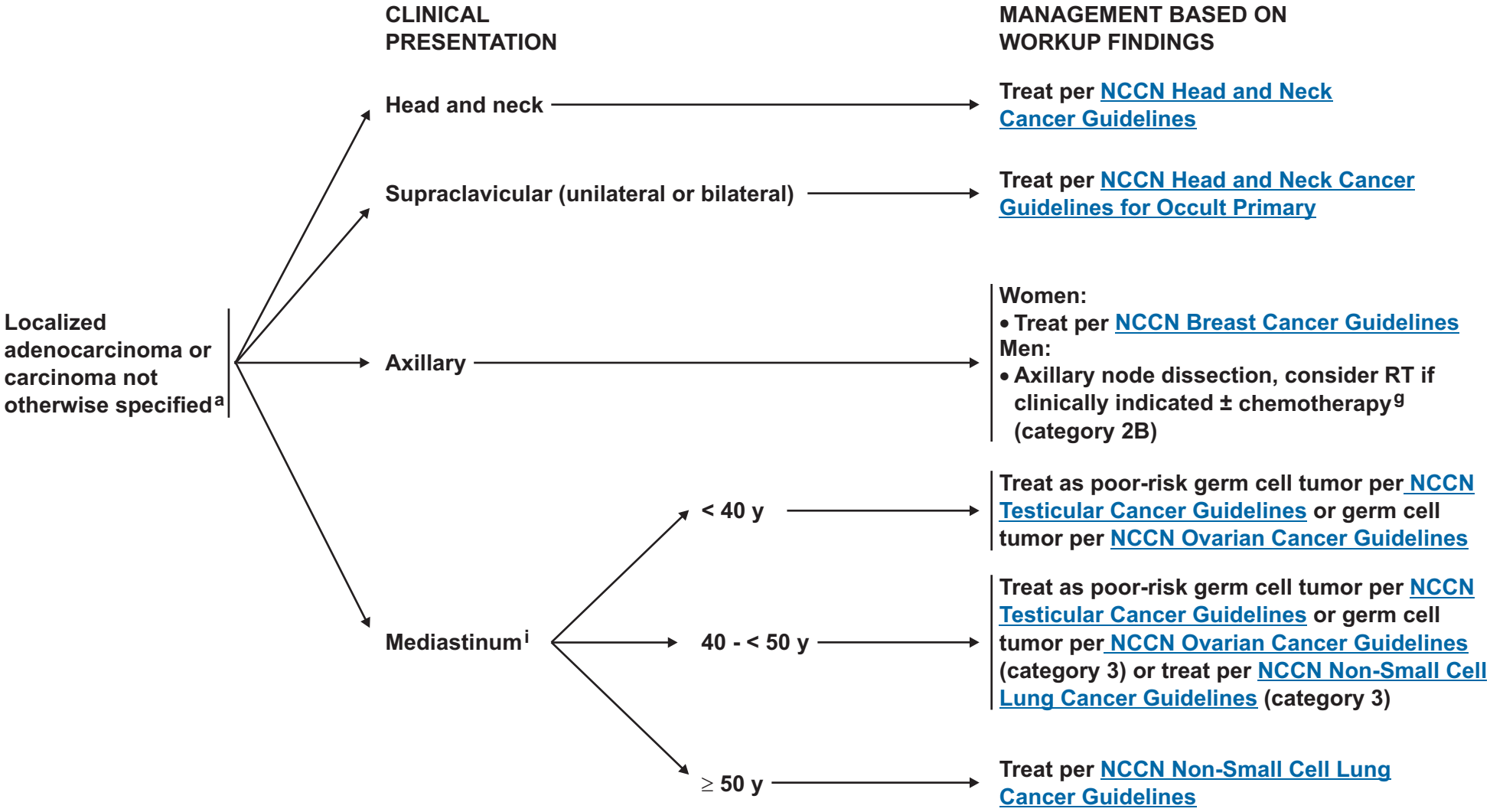
[h] For specialized approaches therapeutic in nature, see discussion (MS-7).

See Follow-up (OCC-20)

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

[i] PET-CT scan can be useful in the diagnosis of an occult primary mediastinal adenocarcinoma.

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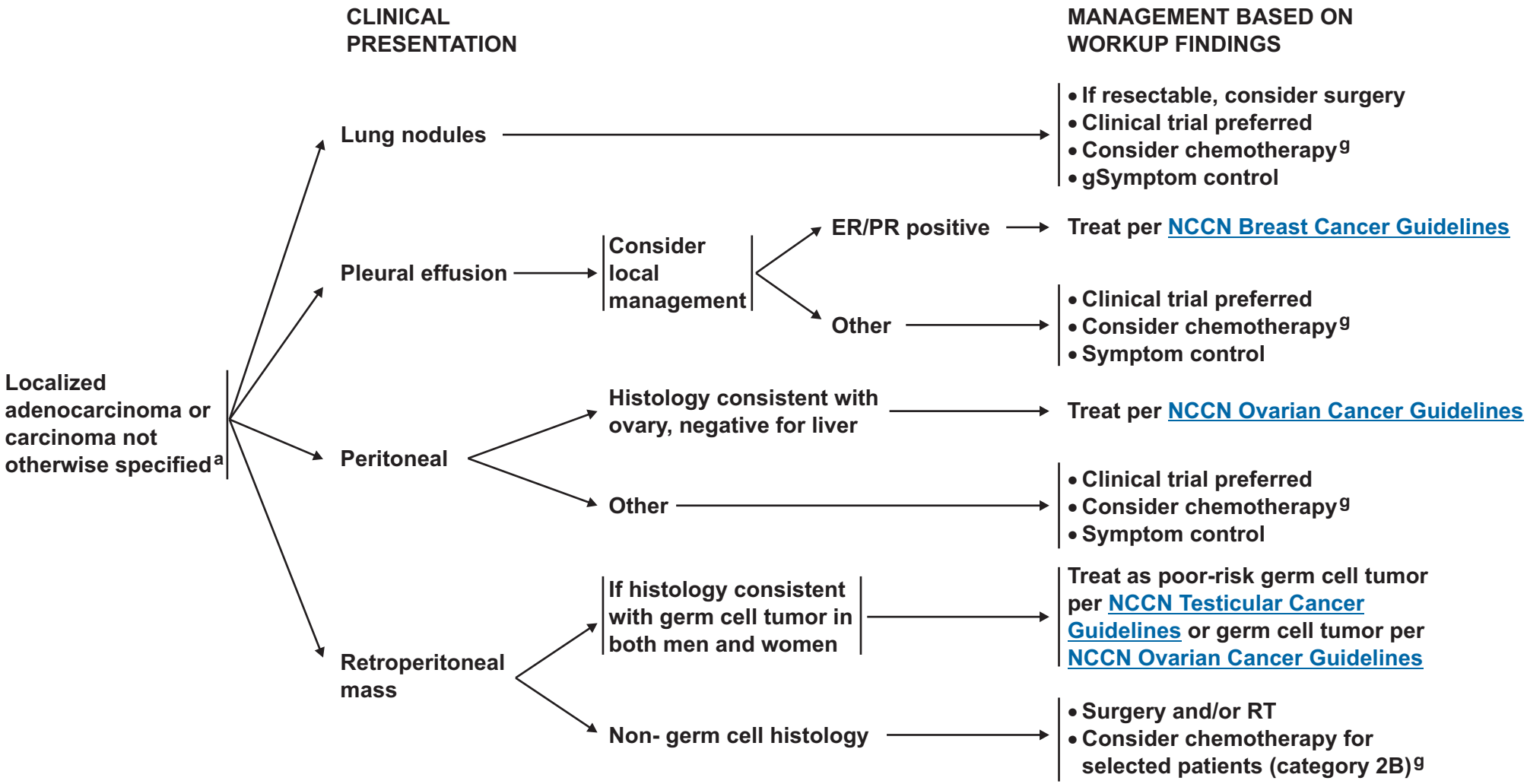
See Follow-up (OCC-20)

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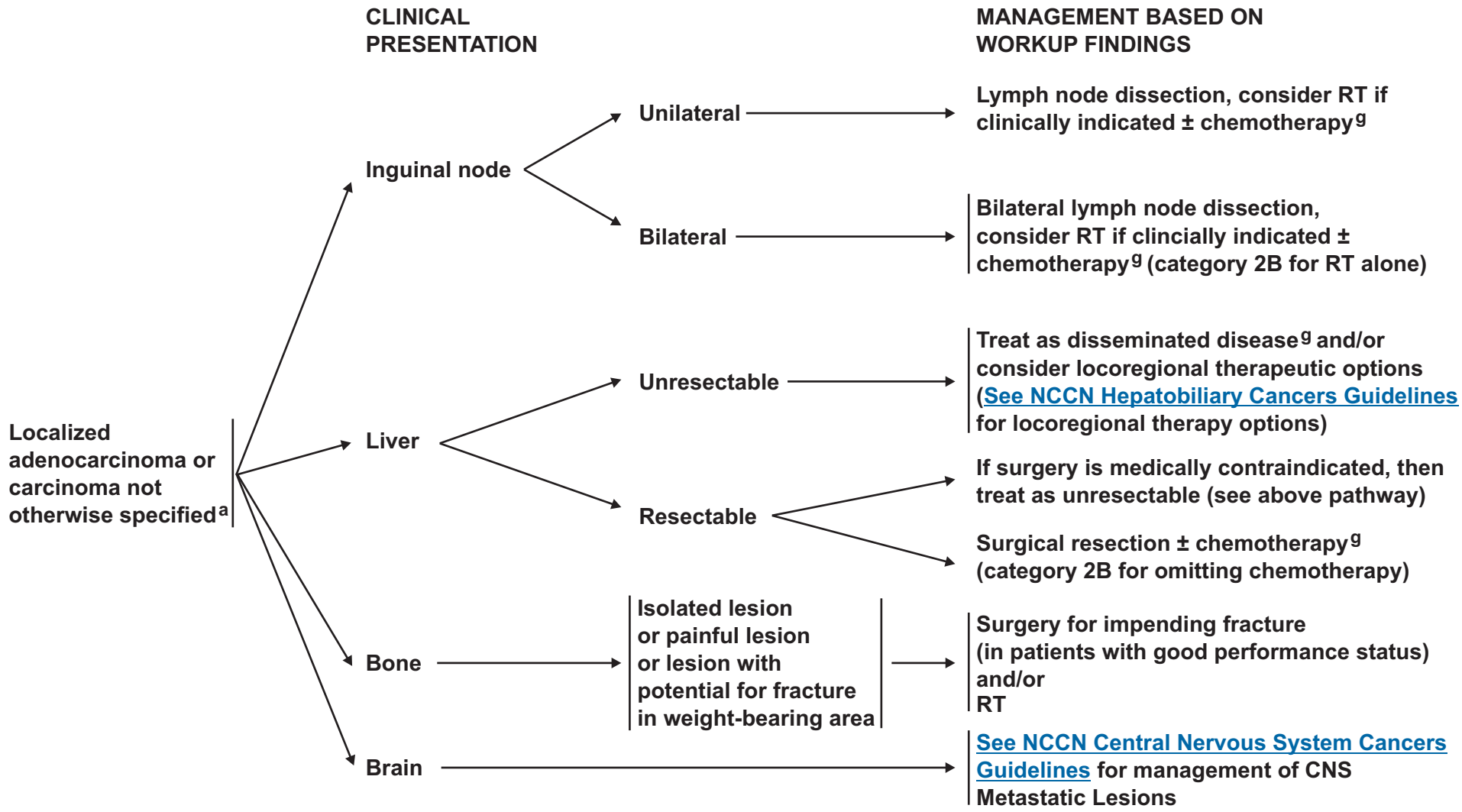
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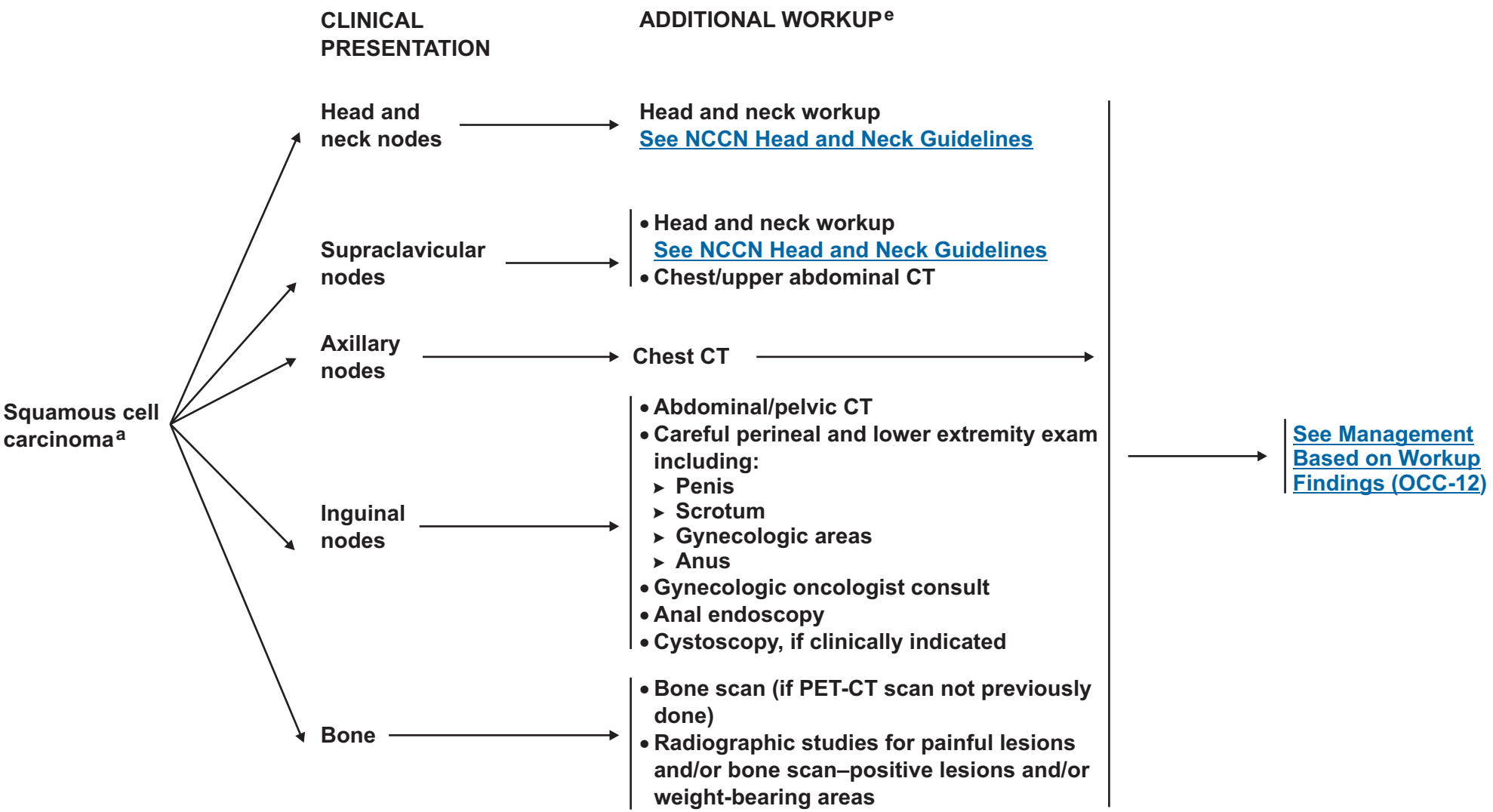
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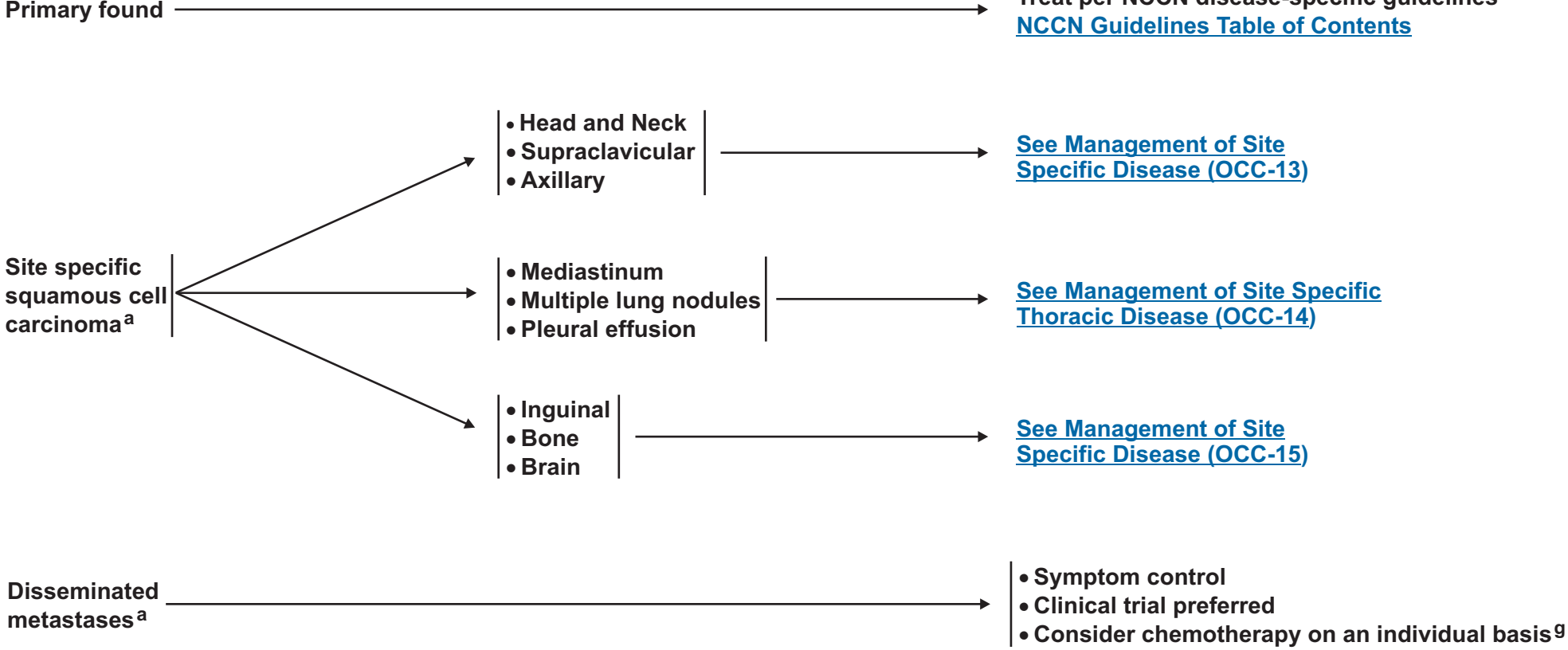
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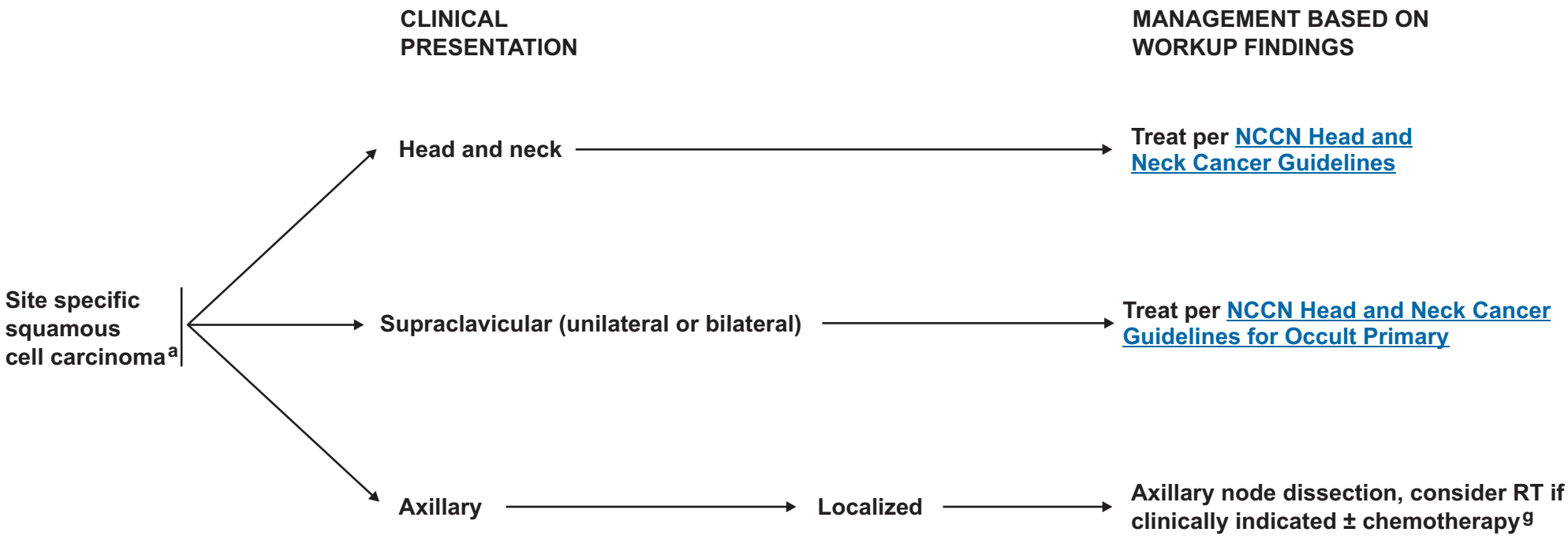
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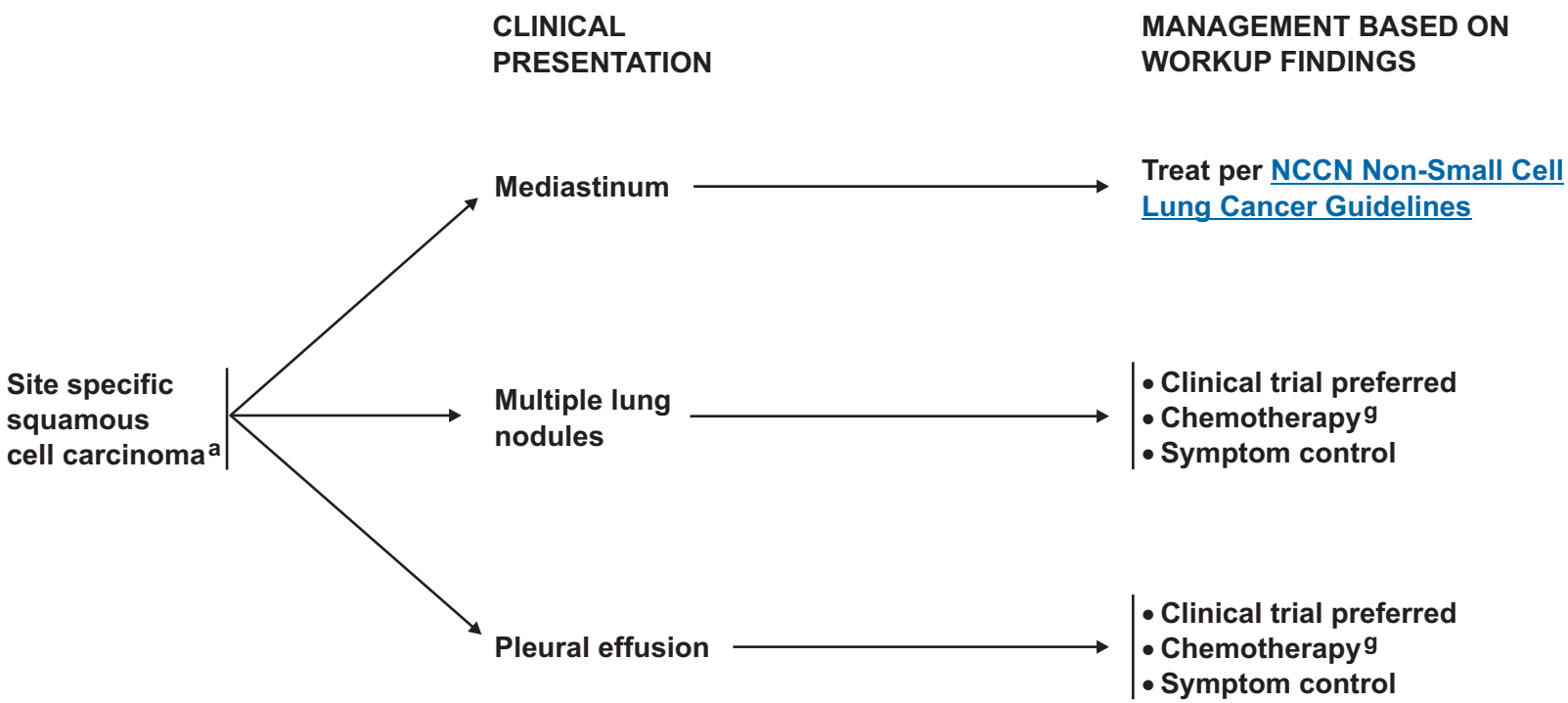
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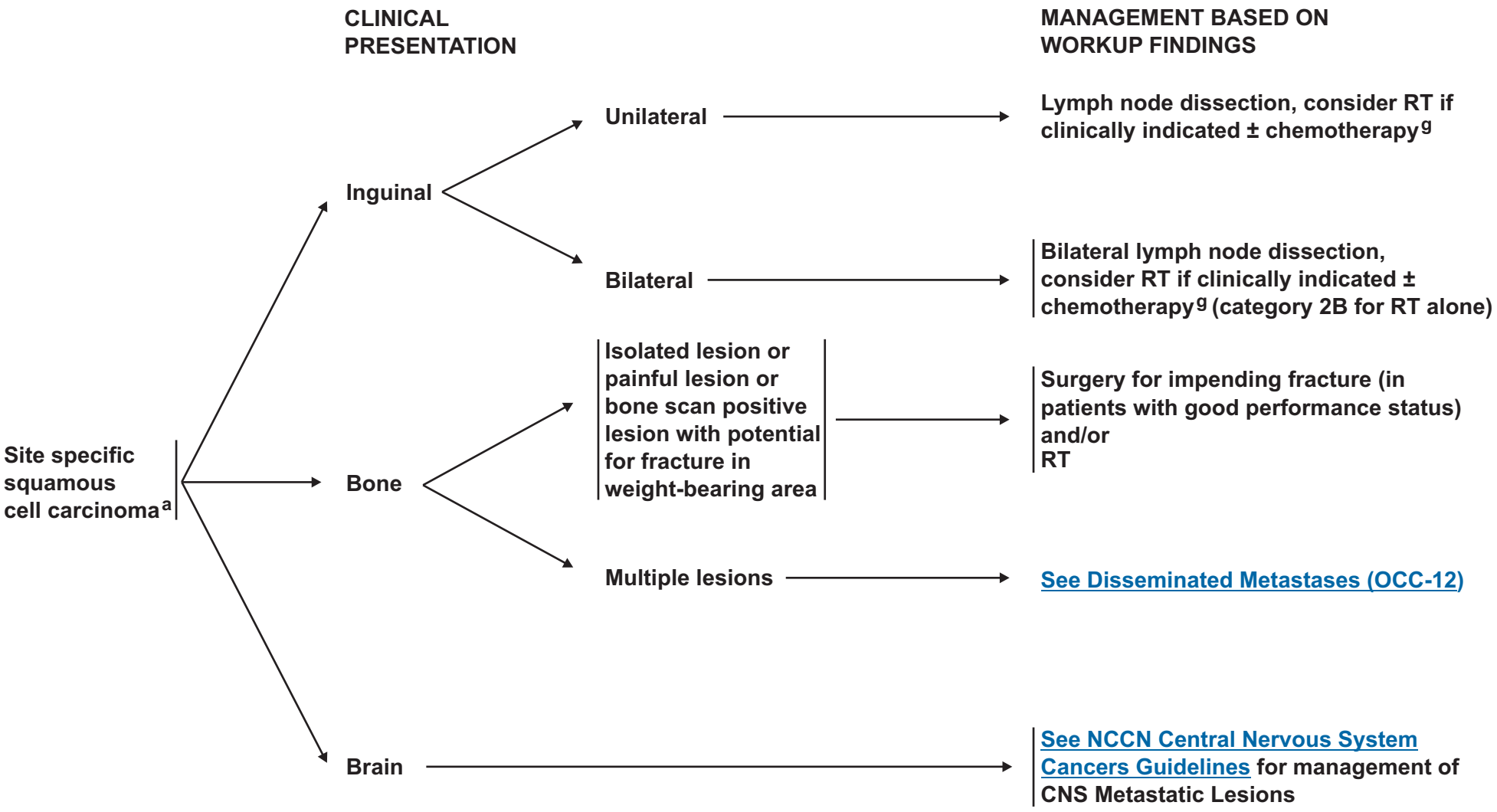
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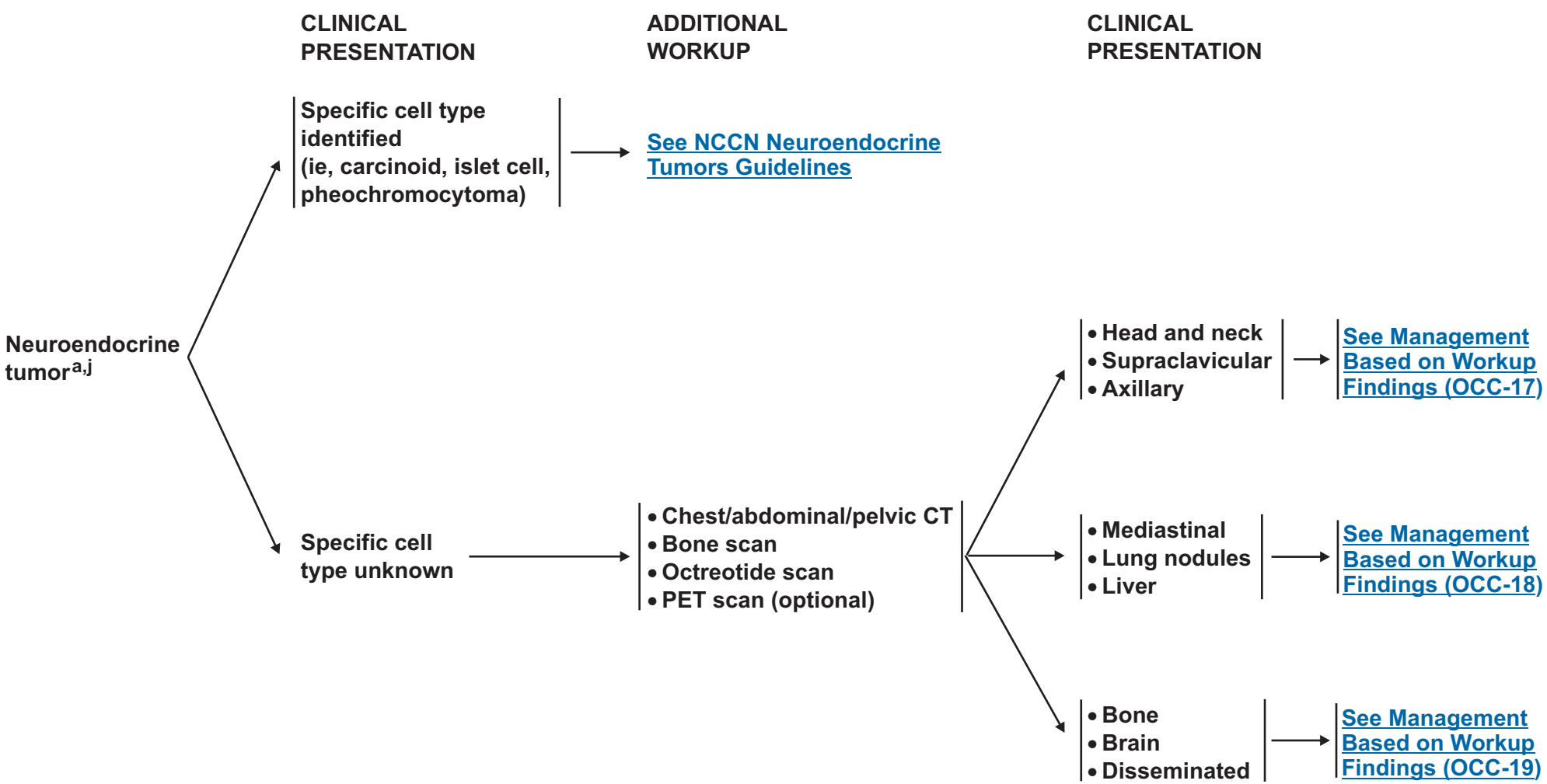
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[j] Consider 24-hour urine for 5-HIAA in well-differentiated neuroendocrine tumors (category 2B). See NCCN Neuroendocrine Tumors Guidelines.

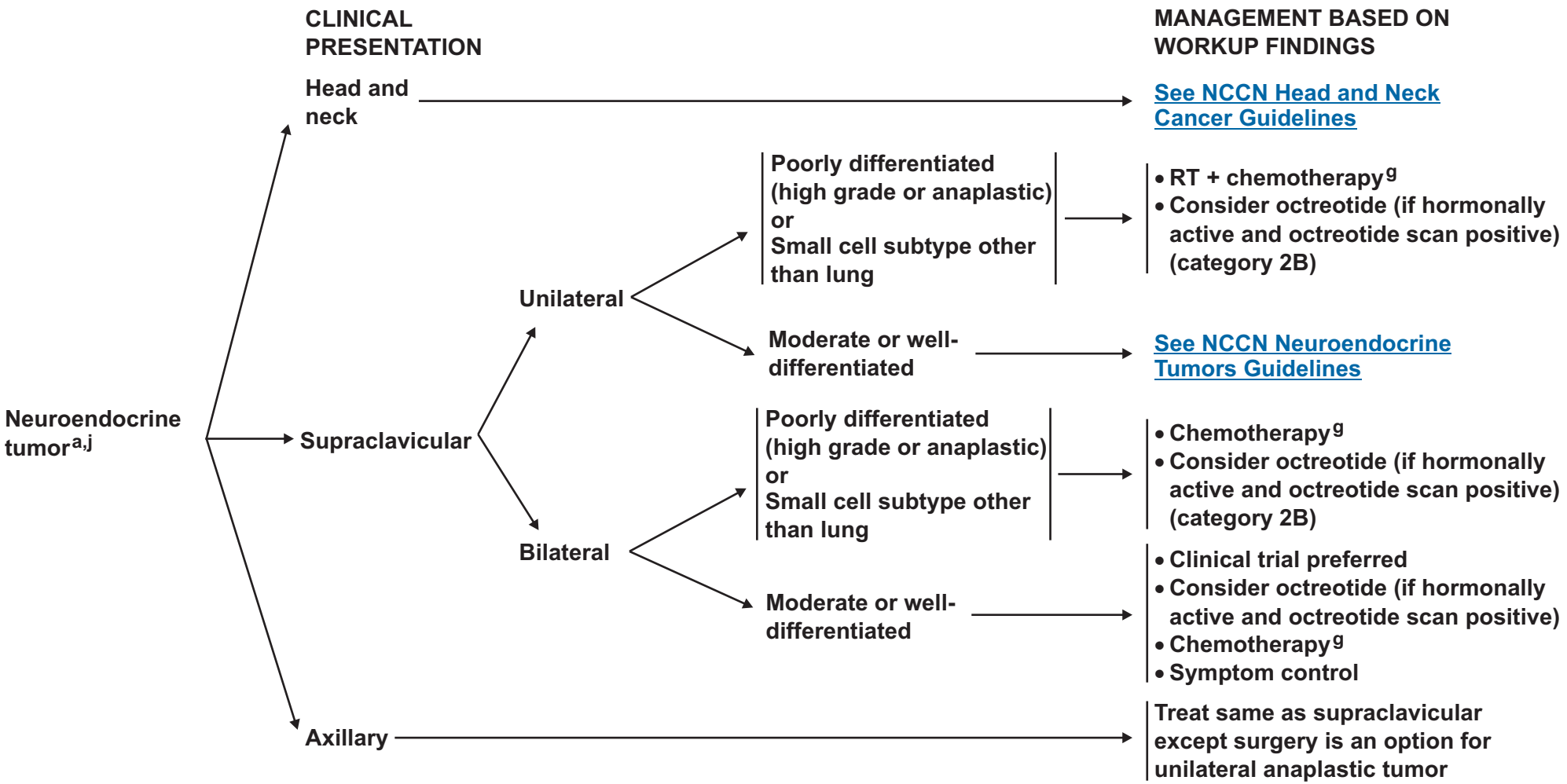
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NCCN Guidelines™ Version 2.2011
Occult Primary

NCCN Guidelines Index
Occult Primary TOC
Discussion



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

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

[j] Consider 24-hour urine for 5-HIAA in well-differentiated neuroendocrine tumors (category 2B). See NCCN Neuroendocrine Tumors Guidelines.

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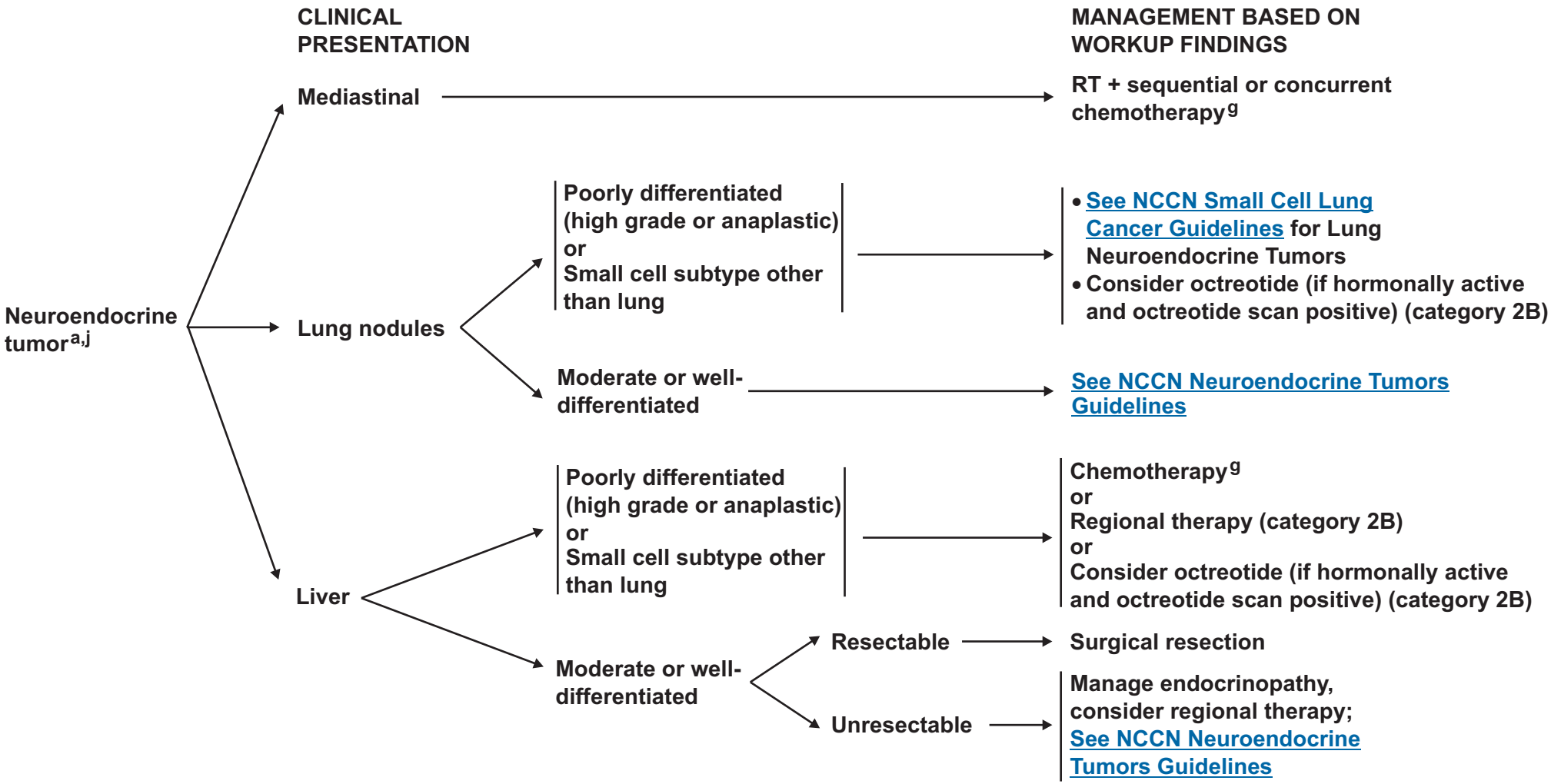
See Follow-up (OCC-20)

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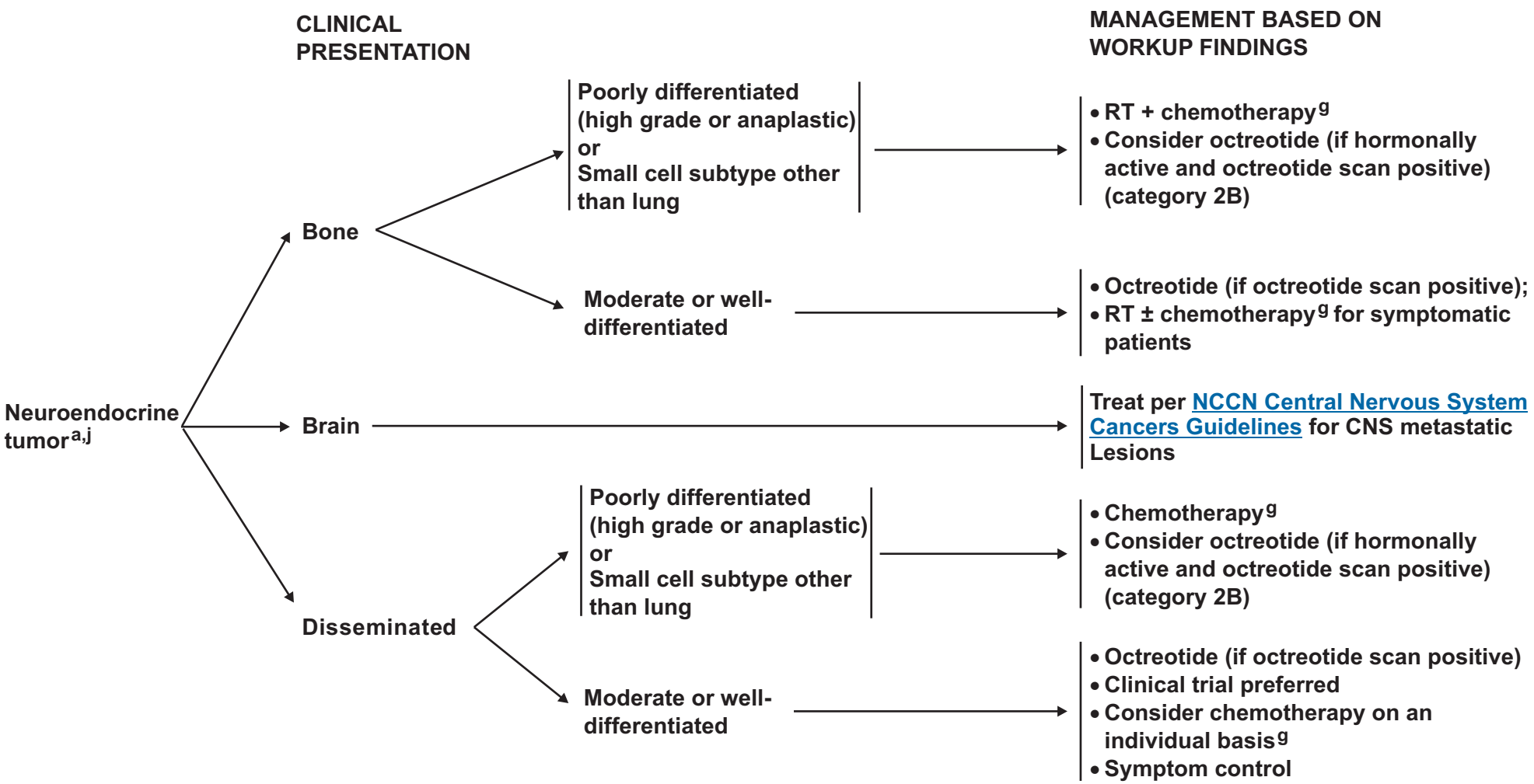
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FOLLOW-UP FOR ALL OCCULT PRIMARIES (NO ACTIVE TREATMENT)

- **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[1]

KEY SCREENING ANTIBODIES FOR UNDIFFERENTIATED MALIGNANCY

	CAM5.2[2]	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).

[1] Immunohistochemistry markers for unknown primary cancers are provided as a resource to assist in localizing a primary but are not 100% specific or sensitive. Avoid a large series of immunohistochemistry markers. Communication with the pathologist is essential to workup.

[2] Other pan-cytokeratin markers may be used.

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[1]

TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN*

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

*** 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[1]

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%	Excluded tumors	≤ 5%
Gastric adeno	40%	Breast; Carcinoid lung; Cholangio; Esoph squam; Germ cell; Lung all types; Hepatocellular; Ovary; Pancreas adeno; Renal adeno; Transitional cell; Uterus endometrioid	
Excluded tumors	≤ 5%		
Carcinoid; Germ cell; Esoph squam; Head/neck squam; Hepatocellular; Lung small cell & squam; Ovary-non mucinous; Renal adeno			
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%
Excluded tumors	≤ 5%	Excluded tumors	≤ 5%
Colorectal adeno; ovary mucinous; seminoma; yolk sac tumor (YST)		Breast; Cholangio; Lung adeno; Ovary; Pancreas adeno	

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

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IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS- ANALYSIS OF UNDIFFERENTIATED CARCINOMAS[1]

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

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

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.

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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 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
Palitaxel[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

See references on OCC-B 2 of 2

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.

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REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

[1] Briasoulis 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.

[2] Greco 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.

[3] Greco 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.

[4] Culine 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.

[5] Pouessel 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.

[6] Hitt R, López-Pousa A, Martínez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005; 23:8636-8645.

[7] Pointreau 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.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

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 are manifested by a wide variety of clinical presentations and have a poor prognosis in most patients. Patients with occult primary tumors demonstrate common characteristics and present with general complaints such as anorexia, weight loss, etc. Clinical absence of primary tumor, early dissemination, aggressiveness, and unpredictability of metastatic pattern are characteristic of these tumors. Life expectancy is very short with a median survival of about 6-9 months.[3]

In a majority of patients, occult primary tumors are refractory to systemic treatments and chemotherapy is only palliative and does not significantly improve long term survival. However, certain clinical presentations of these tumors are associated with better prognosis.[4] 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 equally in men and women, usually in the sixth decade of life. An estimated 30,680 cases of cancer of unspecified primary sites will be diagnosed in the United States in 2010, accounting for about 2% of all the cancers diagnosed in the United States.[5] However, deaths due to cancer of the unspecified primary site are estimated to be 44,030. This discrepancy is believed to be due to the lack of specificity in recording underlying cause of death on death certificates. Occult primary cancers represent the eighth and fifth most frequently diagnosed cancer in males and females respectively. In females, it is more common than non-Hodgkin's lymphoma. 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.[6-8]

Pathology

Occult primary tumors often have multiple chromosomal abnormalities and overexpression of several genes including *Ras, BCL2, HER-2 and p53*.[9, 10] *BCL-2* and *p53* genes are over expressed in 40% and 53% of occult primary tumors respectively.[11] *BRD4-NUT* oncogene resulting from the chromosomal translocation, t(15;19) has been identified in

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children and young adults with carcinoma of midline structures and unclear primary sites.[1,12,13]

Occult primary cancers can be classified in to four 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 (30%), squamous cell carcinoma (SCC; 5%), and poorly differentiated malignant neoplasm (5%).[14] Additionally, due to improved histopathologic diagnostic studies, neuroendocrine tumors of CUP have been recognized.[15,16] Multiple sites of involvement are observed in more than 50% of patients with occult primary tumors. The common sites of involvement are the liver, lungs, bones, and lymph nodes.[14,17] 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.[18-21] Favorable prognostic factors include poorly differentiated carcinoma with midline distribution, women with papillary adenocarcinoma of peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, 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 single, small and potentially resectable tumor. [22, 23] Cervical lymph node metastases of SCC constitute about 2-5% of all patients with occult primary cancers.[24]

Unfavorable features include male gender, pathologic diagnosis of adenocarcinoma with multiple metastases involving other organs (liver, lung, or bone), non-papillary malignant ascites (adenocarcinoma), multiple cerebral metastases (adenocarcinoma or SCC), adenocarcinoma with multiple lung/pleural or multiple bone disease.[25]

Immunohistochemistry

Immunohistochemical studies are useful for the characterization of poorly differentiated or undifferentiated tumors.[26, 27] In patients with occult primary tumors, immunohistochemical markers are useful for cell differentiation and pathologic diagnosis.[28] Immunohistochemical studies should be used in conjunction with other imaging studies to select the best possible treatment option 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 (CD45) is expressed virtually in all hematolymphoid malignancies and is highly specific for non-Hodgkin's lymphoma. Placental alkaline phosphatase (PLAP) is mainly found in seminomas but also expressed in some nonseminoma germ cell tumors, genitourinary, gastrointestinal, and pulmonary carcinomas. Carcinoembryonic antigen (CEA; monoclonal) can be useful for the differential diagnosis of gastrointestinal adenocarcinomas, endocervical and some lung tumors from other sites of origin.

Cytokeratins are useful for cell line differentiation 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.[29-31] CK7 is mainly found in tumors of the lung, ovary, endometrium and breast. CK20 is usually expressed in gastrointestinal, urothelial and Merkel cell carcinomas. CK7 positive/CK20 negative narrows the diagnosis to lung, breast, thyroid, biliary, pancreatic, ovarian or endometrial carcinomas. CK7

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negative/CK20 positive are indicative of colorectal carcinoma and Merkel cell carcinoma. CK7/CK20 phenotype is also useful for differentiating between prostate (CK7 negative/CK20 negative) and urothelial (CK7 positive/CK20 positive) carcinoma. CK5 and CK6 can be useful for the differential diagnosis of poorly differentiated metastatic SCC. [32] Majority of poorly differentiated SCCs (84%) show CK5/6 positivity whereas only 21% of non-SCCs are positive for CK5/6.[32] In addition to poorly differentiated SCC, urothelial carcinomas (35%) and all mesotheliomas express CK5 and CK6.[32]

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 fibrous protein-15 (GCDFP-15), uroplakin III and WT-1 as reviewed by Bahrami et al.[33] The use of TTF-1 marker further distinguishes lung primary tumors from other CK7-positive tumors. TTF-1 staining is positive in most of the lung and thyroid carcinomas. 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, they both are not 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%. Uroplakin III is expressed in about 60% and 50% in 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.[33] P63, a p53-homologue nuclear transcription factor could also be useful to identify carcinomas with squamous cell, urothelial and myoepithelial differentiation. Most poorly differentiated SCCs (86%) show immunoreactivity for p63 and only 14% of non-SCCs are positive for p63.[32] Malignant mesotheliomas are consistently negative for p63 and p63 is expressed in about 70% of urothelial carcinomas.[32]

Gene Expression Profiling

Gene expression profiling (GEP) is an emerging diagnostic tool to identify tissue of origin. Recently, several GEP assays have been developed to identify the tissue of origin in patients with occult primary cancers.[34, 35] Talantov et al have developed a molecular assay to evaluate the expression of 10-specific gene markers using RT-PCR which is designed to detect tumors originating from lung, breast, colon, ovary, pancreas, and prostate.[36] 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 in 104 patients with CUP.[37] The tissue of origin was identified in 61% of patients and it was compatible with clinicopathological features. In a recent study, patients with unknown primary cancer with a colon cancer tissue of origin as identified by molecular profiling showed concordance with their IHC profile for colon cancer (CK20 and CDX-2 positive and CK7 negative), better response and survival to colon cancer specific regimens.[38]

Some tests are commercially available and are being evaluated in prospective clinical studies.[39-42] Ma et al have developed a 92 gene-based real time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) assay to identify the site of origin for metastatic tumors, especially in patients with CUP.[39] In a retrospective, multicenter study, this assay identified primary sites in 75% of patients after the initial diagnosis of CUP.[43] Monzon et al have developed a microarray based 1,550 gene expression test,[40, 41] which had 88% sensitivity and 99% specificity in the diagnosis of uncertain primary tumors.[44]

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Preliminary data from the prospective studies have provided some data regarding the accuracy of some of the commercially available tests in the identification of primary sites in CUP.[45, 46] However, at the present time, the panel feels that there is not sufficient data to confirm whether this approach can be used in choosing treatment options which would improve the prognosis of patients with occult primary cancers. Hence, the panel does not recommend GEP as part of routine evaluation.

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-flourouracil-based or cisplatin-based chemotherapeutic regimens.[47-53] Most of the patients in these studies had adenocarcinoma and only 5-10% had poorly differentiated carcinoma. Overall response rates to these regimens were 20-35%, with median survival times of 5-8 months, although some of the studies reported longer median survival duration. Older regimens are not used as standard treatment since complete response is rarely observed. In recent years, newer regimens containing paclitaxel and gemcitabine have shown efficacy in phase II studies in the treatment of patients with occult primary tumors.[54-60]

Taxane-based chemotherapy was associated with long-term survival in a minority of patients with CUP. The median survival was 10 months with 1-, 2-, 3-, and 4-year survival rates of 42%, 22%, 17%, and 17%, respectively.[60] Recently, Hainsworth et al reported that the combination of bevacizumab and erlotinib (alone or combined with paclitaxel and carboplatin) had substantial activity as first-line therapy in patients with occult primary tumors.[56, 57] In a phase II trail, the combination of bevacizumab and erlotinib induced partial responses in 10% of patients and 61% had stable disease.[56] Median survival was 7.4 months (1-year survival, 33%), which in retrospective comparison was superior to that observed with gemcitabine 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.[57] After a median follow-up of 19 months, the median progression-free survival (PFS) and 2-year OS rate were 8 months (38% PFS at one year) and 27%, respectively.

Schneider et al reported that the combination of carboplatin, gemcitabine and capecitabine was active in occult primary tumors with liver metastases in patients with good performance status.[54] 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 gemcitabine, carboplatin and paclitaxel followed by weekly paclitaxel was active and tolerable for occult primary tumors in patients with poor prognostic features.[55]

The NCCN Guidelines recommend that chemotherapy for patients with disseminated disease should be limited to symptomatic patients with a performance status of 1-2 or asymptomatic patients with aggressive cancer. The choice of the regimen should be based on the histologic type of cancer.

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

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cisplatin-based combination chemotherapy. [61, 62] 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. In both studies patients had tumors with extragonadal germ cell features.

In phase II studies, paclitaxel and carboplatin with or without etoposide was found to be effective for the treatment of adenocarcinoma of occult primary tumors. [59, 63, 64] In the Hellenic Cooperative Oncology Group Study, combination of paclitaxel and carboplatin produced an overall response rate of 38.7% by intent-to-treat analysis; there was no difference in the response rates for adenocarcinomas and undifferentiated carcinomas.[63] In another phase II trial, long-term follow-up of patients treated with the triple drug combination (paclitaxel, carboplatin and oral etoposide) showed 1-year, 2-year and 3-year survival rates of 48%, 20% and 14% respectively. [64] In a recent phase III randomized study, the triple drug regimen had comparable efficacy with gemcitabine and irinotecan in the first-line treatment of patients with CUP.[65] In a randomized phase study conducted by the German CUP study group, paclitaxel and carboplatin combination demonstrated better clinical activity than gemcitabine and vinorelbine combination.[66] 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.[67] Overall toxicity of sequential treatment was found to be greater than that observed with other regimens and survival was also similar to that observed in previous phase II trials.

Greco et al have reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated adenocarcinoma.[68] Major response to therapy was observed in 26% of patients receiving docetaxel and cisplatin with a median survival of eight months and one year survival of 42%. In patients receiving docetaxel and carboplatin the corresponding response rate was 22% with a median survival of eight months and one year survival of 29%. Docetaxel in combination with carboplatin was better tolerated.

In a recent report of the Hellenic Cooperative Oncology Group phase II study, one hour docetaxel and carboplatin combination was found to be safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated CUP with performance status of 0-2.[69] Median time to progression (TTP) and overall survival (OS) were 5.5 and 16.2 months respectively. Survival was better in favorable risk patients (23 months vs. 5 months for those with visceral metastases). Good performance status and low volume disease predicted for superior outcome.

Efficacy and toxicity of combination regimens including cisplatin with either gemcitabine or irinotecan was evaluated in a phase II study conducted by French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01).[70] Well differentiated adenocarcinoma was the most common histology with one fourth of patients having single metastatic site. Objective response rates were 55% for gemcitabine and cisplatin arm and 38% for irinotecan and cisplatin arm. With a median follow-up of 22 months, median survival rates were 8 and 6 months respectively for these two combination regimens. However, toxicity was associated with both regimens.

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Finally, a non-cisplatin-based regimen containing gemcitabine and docetaxel was found to be well tolerated and active in patients with occult primary tumors.[71] 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. 5-flourouracil and cisplatin is the most frequently used combination regimen. In a phase III study, 5-flourouracil and cisplatin (CF) was compared with the combination of paclitaxel, cisplatin and 5-fluorouracil (PCF).[72] Induction chemotherapy with PCF had better tolerance and produced higher complete response rate (33% vs.14%) than CF regimen.

In another randomized phase III trial induction chemotherapy with docetaxel, cisplatin and 5-flourouracil (TPF) was compared with cisplatin and 5-fluorouracil (PF). TPF regimen produced significantly superior overall response rate (80% vs. 59%) compared with PF regimen.[73]

Neuroendocrine Tumors

Neuroendocrine carcinomas of unknown primary site are uncommon and their clinical behavior is dependent on the tumor grade and differentiation.[74] 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.[15]

Hainsworth et al have evaluated the efficacy of combination regimen containing paclitaxel, carboplatin and etoposide in metastatic poorly differentiated neuroendocrine (PDNE) carcinomas in patients who had received no prior treatment.[75] Sixty two percent of the patients had PDNE carcinoma of unknown primary site. Patients with known primary sites were also eligible for the study. Major responses were observed in 53% of the patients, proving that PDNE carcinomas are chemosensitive. The median, 2-year and 3-year survival for the entire group were 14.5 months, 33% and 24% respectively. The 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.

The combination of cisplatin and etoposide produced significant responses in patients with poorly differentiated rapidly progressing neuroendocrine tumors, when used as a second or third-line treatment.[76]

In a randomized phase III trial (JCOG 9702), the combination of carboplatin plus etoposide was equally efficient to cisplatin and etoposide in elderly or poor risk patients with extensive disease small-cell lung cancer.[77] 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 a small series of patients, temozolomide, as a single agent or in combination with thalidomide was found to effective for the treatment advanced or metastatic neuroendocrine tumors.[78, 79]

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.

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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.[80]

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
- Neuroendocrine tumors

Patients with other specific diagnosis will be treated according to the appropriate NCCN Guidelines for Treatment of Cancer by Site. 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, 13 different clinical presentations are addressed, with suggested diagnostic tests for each location.

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma, site specific SCC, and neuroendocrine tumors. The panel endorses enrollment of patients in appropriate clinical trials when possible. For each of the three pathologic diagnoses, if a primary tumor is subsequently found, treatment should be based on the NCCN 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 [i.e. epithelial occult primary (not site specific), thyroid, lymphoma and other hematological malignancies, 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, and spontaneously regressing lesions; existing imaging studies; routine laboratory studies (complete blood count, electrolytes, liver function tests, creatinine, calcium, urinalysis); computed tomography (CT) scan of chest, abdomen and pelvic; occult blood stool testing; and symptom directed endoscopy.

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Other diagnostic studies should be based on the clinical presentation and subsequent histopathologic findings. It is also important to determine if the initially identified malignancy is localized or disseminated, as the treatment for localized and disseminated disease may be different.

PET scan has been shown to be a useful method for the diagnosis, staging, and restaging of many malignancies and it might be warranted in some situations (e.g. presence of supraclavicular nodes).[81] PET scan has intermediate specificity and high sensitivity but further larger studies are warranted to determine the clinical utility and role of PET scan in patients with occult primary tumors.[82, 83] In a recent review, Seve et al concluded that PET is a valuable imaging modality for patients with occult primary tumors with single site of metastasis and when therapy with a curative intent is planned.[84]

One of the limitations of PET scan has been the limited accuracy of anatomic localization of functional abnormalities due to very little accumulation of ^{18}F-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.[85] Recent studies on the use of PET-CT scans for the detection of occult primary tumors, have reported that the combination of PET-CT identified the primary site in 33-35% of patients.[86,87] In another study reported by Nanni et al, PET-CT detected occult primary tumor in 57% of cases, which is a higher detection rate than that reported in earlier studies.[88] 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.

In the past 5 years, positron emission tomography (PET) scans and/or a combination of PET-CT scan has become one of the most frequent imaging modalities in the management of patients with occult primary cancers. Although PET or PET-CT scans detect more sites of metastases (24-40%) compared to conventional imaging techniques (20-27%), its exact role remains undefined due to the lack of prospective clinical trials comparing PET-CT scans with conventional imaging modalities.[89]

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). Large panels of immunohistochemical markers should be avoided. The guidelines recommend that communication with the pathologist is essential for initial workup. Light microscopic examination of the biopsy material is usually done first. Other techniques besides light microscopic examination include electron microscopy and flow cytometry.

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

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by Site. Additional studies are of utmost importance in determining whether the occult primary cancer is potentially curable or in diagnosing a possible treatable disease associated with long-term survival. Lymphoma, primary breast, ovarian, thyroid, prostate, and germ-cell tumors must be diagnosed or ruled out since effective therapy is available for these cancers.

There is a great deal of controversy regarding whether an exhaustive, time consuming, costly evaluation should be conducted to search for the primary beyond these initial tests, as opposed to a more directed evaluation based on the complete history and physical examination, clinical presentation, histopathologic diagnosis, and metastatic sites of involvement. Suggested diagnostic tests for each pathologic subtype, location, and gender (where appropriate) are indicated in the guidelines and are discussed below.

Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in selected women.[90,91] In a recent report, the primary site was identified in about half of the women presenting with axillary metastases, irrespective of the breast density.[92]

The guidelines suggest the use of a mammogram and breast ultrasound for patients presenting with adenocarcinoma with positive supraclavicular axillary and mediastinal nodes. Appropriate testing for immunohistochemical markers, such as ER/PR and HER2 is also recommended. 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 occult primary breast tumor or to evaluate the chest wall.[93]

Elevated ER/PR levels provide strong evidence for the breast cancer diagnosis.[94] Involvement of mediastinal nodes in patients with adenocarcinoma suggests a possible germ cell tumor. Thus, beta-human chorionic gonadotropin (beta-hCG) and alpha fetoprotein (AFP) measurements are suggested by the guidelines. CT scans of abdomen and pelvic are now recommended for both men and women for mediastinal, chest, peritoneal and retroperitoneal adenocarcinoma. Testicular ultrasound should also be considered if beta-hCG and AFP levels are elevated for mediastinal and retroperitoneal mass. Chest CT scans for adenocarcinoma found in the peritoneum, retroperitoneum, and liver are also performed at some NCCN member institutions. Bone scan (if PET-CT scan is not previously done) and radiographic studies are recommended for adenocarcinoma and SCC involving painful or bone scan positive bone lesions.

All men over age 40 with an adenocarcinoma or carcinoma not otherwise specified should have a prostate specific antigen (PSA) test. In patients with peritoneal disease or liver involvement, serum CA 19-9 level can be considered of pancreatic or biliary tract primary is suspected. In women with retroperitoneal disease, recommended tests include CA-125, CT scans of abdomen and pelvic, mammogram, and ER/PR immunohistochemistry. For men with retroperitoneal disease, recommended tests include beta-hCG, AFP, and testicular ultrasound. In patients with inguinal lymph node involvement, the guidelines have included testing for CA-125 as well as a gynecologic oncologist consultation for women and proctoscopy for men and women, if clinically indicated.[31]

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

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

Neuroendocrine tumors can metastasize to a number of sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal nodes, liver, bone, brain, and skin. An octreotide scan is frequently useful in identifying the primary site or additional sites of involvement of neuroendocrine tumors.

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

Management Based on Workup Findings

Adenocarcinoma

Localized adenocarcinoma or carcinoma not otherwise specified is treated according to the most likely primary site. The recommended treatment for localized adenocarcinoma occurring in the mediastinum depends on the age of the patient at the time of diagnosis. Patients under 40 years as well those between 40-50 years should be treated for poor risk germ cell tumor using the NCCN Guidelines for Testicular Cancer or the NCCN Guidelines for Ovarian Cancer. Alternatively, patients aged 40-50 years could also be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer (category 3). Patients 50 years or older are treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer.

Patients with localized adenocarcinoma involving supraclavicular nodes (unilateral or bilateral) should be treated according to the occult primary tumors described in NCCN Guidelines for Head and Neck Cancers. The guidelines recommend treatment according to the NCCN Guidelines for Breast Cancer for localized adenocarcinoma involving axillary nodes or pleural effusion in hormone receptor positive women. 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.

Those presenting with localized adenocarcinoma with a peritoneal mass consistent with ovarian histology are treated as per the NCCN Guidelines for Ovarian Cancer.[95, 96] 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. Lymph node dissection with or without subsequent chemotherapy, is recommended for inguinal nodal involvement. RT can be considered if clinically indicated.[97] 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.

Surgery for impending fracture and/or RT is an option for patients with good performance status with isolated bone lesion. Patients with brain

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metastases should be managed according to the NCCN Guidelines for Central Nervous System Cancers.

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.

- 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.[97, 98] 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 should be treated according to the treatment of occult primary tumors described in the NCCN Guidelines for Head and Neck cancers. Participation in a clinical trial is the preferred treatment option for patients with multiple lung nodules or pleural effusion. Alternatively, chemotherapy can also be considered for this group of patients.

Surgery for impending fracture and/or RT is an option for patients with good performance status with isolated bone lesion. Patients with brain metastases should be managed according to the NCCN Guidelines for Central Nervous System Cancers. Based on the results of clinical studies, the guidelines have included the combination of cisplatin and 5-fluorouracil with either paclitaxel or docetaxel for the treatment of SCC of unknown primary.

Neuroendocrine Tumors

Neuroendocrine tumors with specific cell type identified are managed according to the NCCN Guidelines for Neuroendocrine Tumors. Tumors with unknown specific cell type are treated depending on whether the tumor is poorly differentiated (high-grade or anaplastic) or small cell subtype other than lung or moderate to well-differentiated following work-up findings. Poorly differentiated (high-grade or anaplastic) or small cell sub-type tumors are treated in a manner similar to small-cell lung carcinoma as per the NCCN Guidelines for Small Cell Lung Cancer. Moderate or well differentiated tumors are treated according to the NCCN Guidelines for Neuroendocrine Tumors.

Patients with unilateral supraclavicular or axillary nodal involvement can be treated with chemoradiation therapy whereas chemotherapy alone is an option for bilateral involvement. Regional therapy may be appropriate for moderate and well-differentiated unresectable neuroendocrine tumors in the liver. Resectable moderate and well-differentiated neuroendocrine tumors in the liver are treated with surgery. For poorly differentiated (high-grade or anaplastic) or small cell sub-type tumors in liver, options include chemotherapy or regional therapy (category 2B).

Neuroendocrine tumors frequently express somatostatin receptors (SSTRs). Radiolabeled somatostatin analogues have been used in the diagnosis and treatment of unresectable or disseminated neuroendocrine tumors. [111]Indium-diethylene-triaminepentaacetic acid (DTPA) octreotide (pentetreotide) is one such radiolabeled somatostatin analog that has been used to visualize and eradicate SSTR expressing tumors.[99]

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Octreotide is the treatment option for hormonally active and octreotide scan positive poorly differentiated (high-grade or anaplastic) or small cell subtype and moderate or well-differentiated neuroendocrine tumors with supraclavicular or axillary nodal involvement, lung nodules, liver lesions and neuroendocrine tumors with disseminated or bone metastases.[100] Close monitoring is recommended for patients on octreotide therapy to avoid severe side effects such as bone marrow depression etc.

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, their prognosis, 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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