National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Occult Primary
(Cancer of Unknown Primary [CUP])
NCCN Evidence Blocks™

Version 1.2020 — November 5, 2019

NCCN Evidence Blocks™

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Occult Primary
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

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Continue

ϕ Diagnostic/Interventional radiology
¤ Gastroenterology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Occult Primary
NCCN Evidence Blocks™

NCCN Occult Primary Panel Members
NCCN Evidence Blocks Definitions (EB-1)

Initial Evaluation (OCC-1)

Epithelial Occult Primaries (OCC-2)

Adenocarcinoma or Carcinoma Not Otherwise Specified (OCC-3)

Squamous Cell Carcinoma (OCC-11)

Follow-up for All Occult Primaries (OCC-16)

Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A)

Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B)

Principles of Radiation Therapy (OCC-C)

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

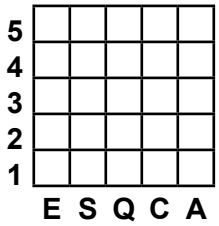
See NCCN Categories of Preference

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Occult Primary
NCCN Evidence Blocks™

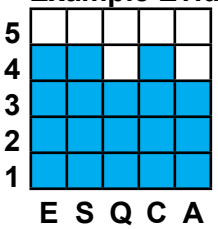
NCCN Guidelines Index
Table of Contents
Discussion

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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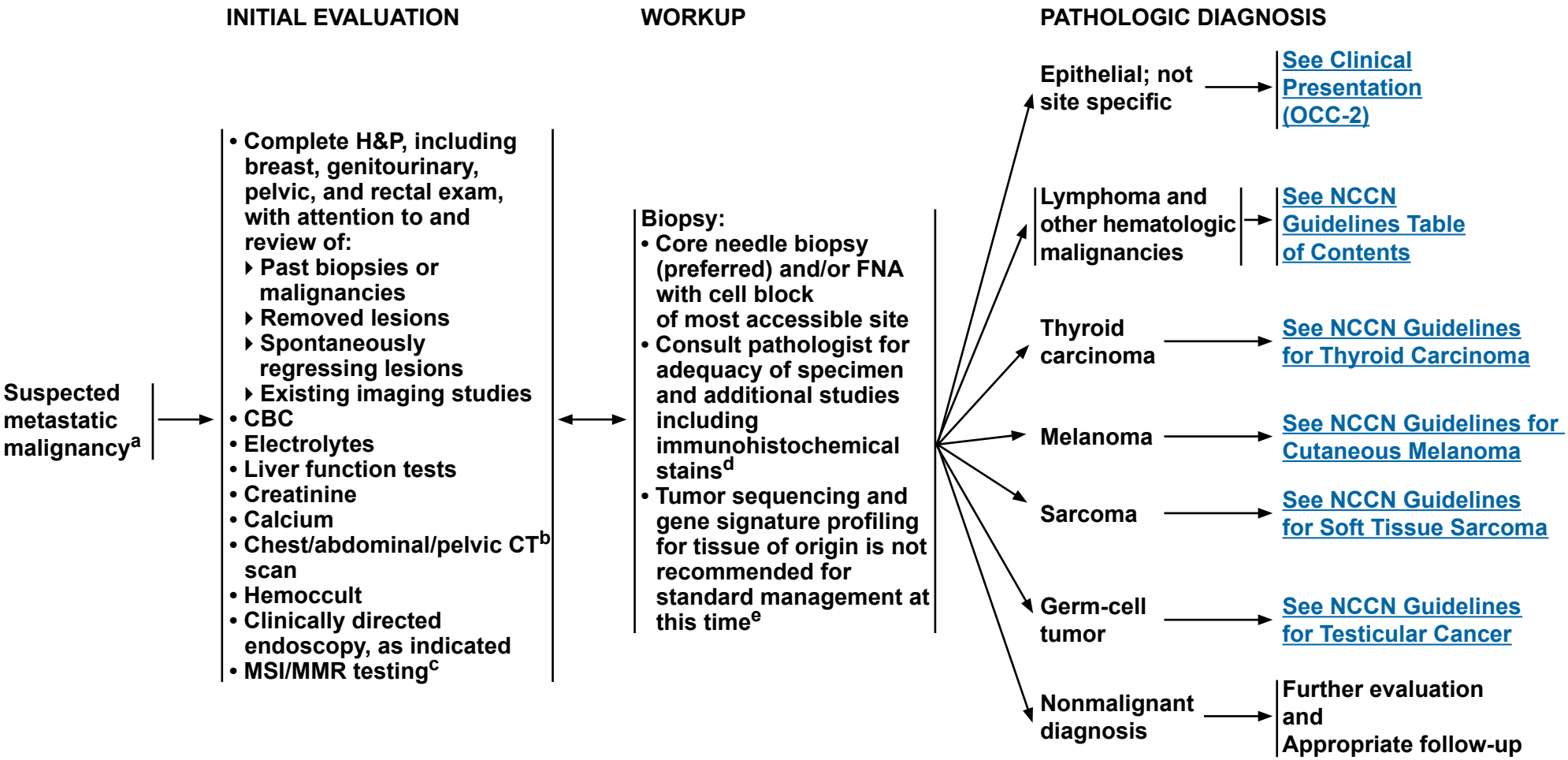
NCCN Guidelines Version 1.2020
Occult Primary
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
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 Guidelines for Distress Management.

[b]CT/MRI imaging should be performed with IV contrast unless contraindicated.

[c]The population of patients with MSI-high/MMR-deficient (MSI-H/dMMR) occult primary tumors is low. Use IHC for MMR or PCR for MSI, which are different assays measuring the same biological effect.

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

[e]There may be diagnostic benefit, though not necessarily clinical benefit. The use of gene signature profiling is a category 3 recommendation.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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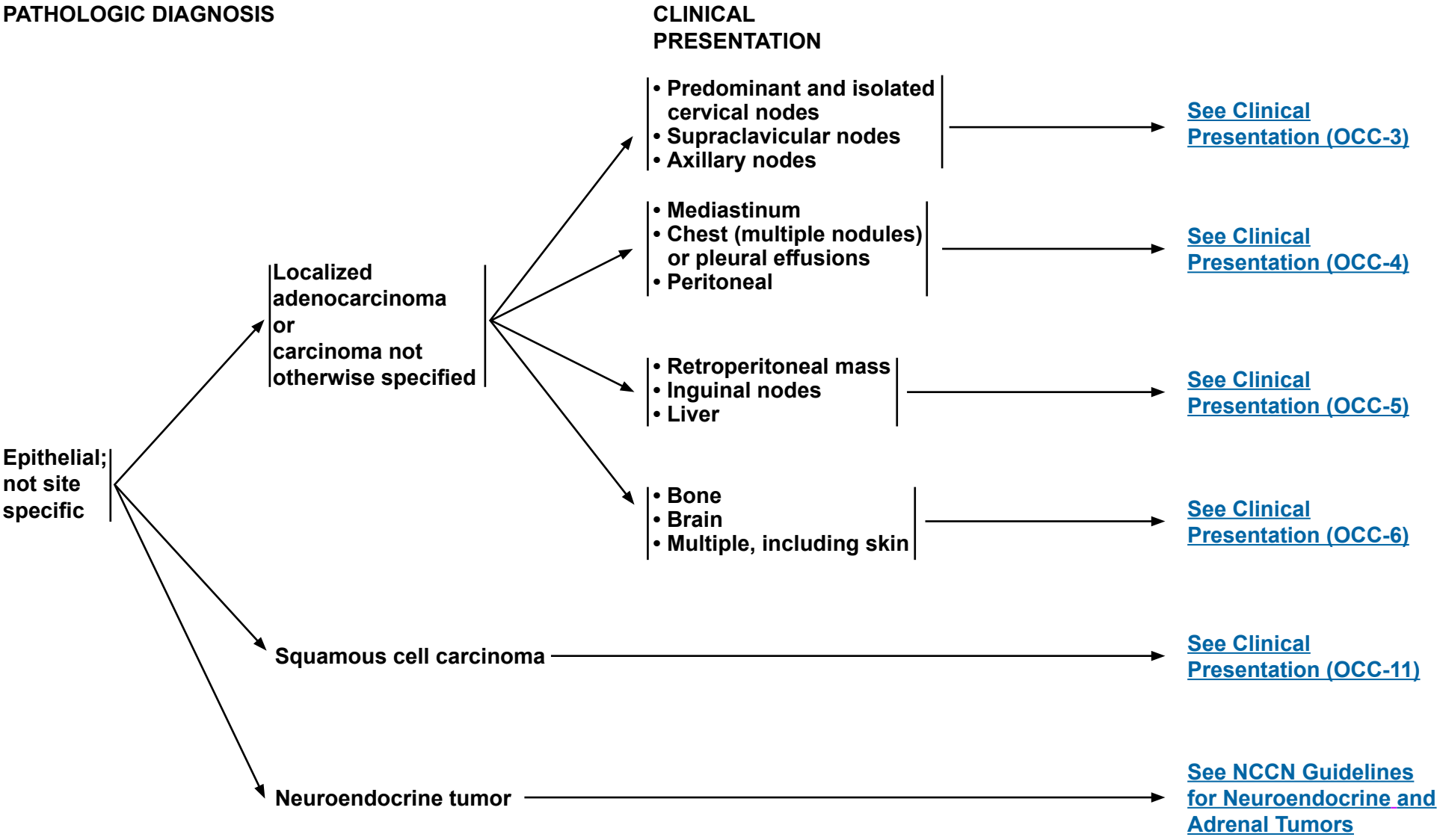

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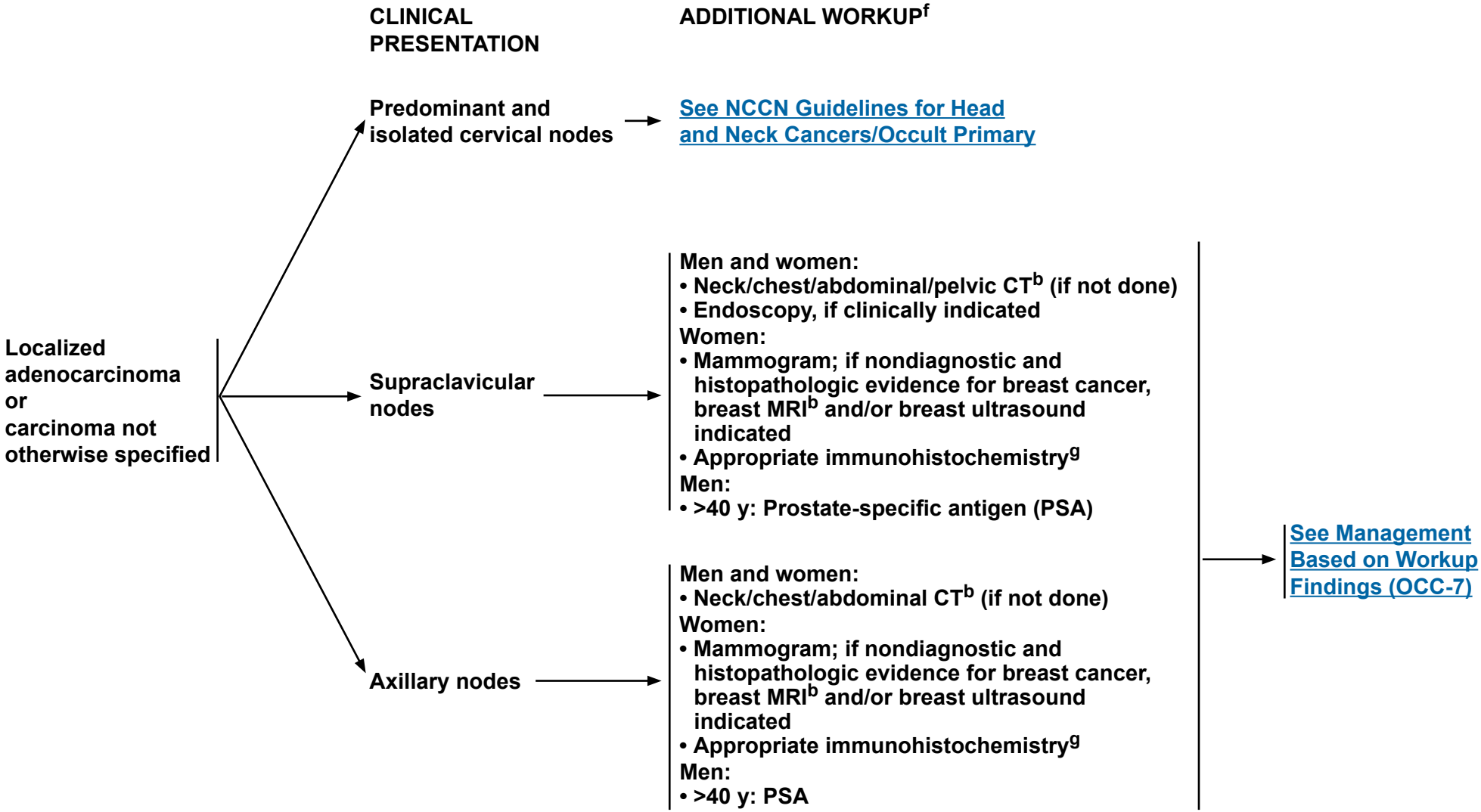

[b]CT/MRI imaging should be performed with IV contrast unless contraindicated.
[f]Symptom-directed endoscopy can be considered for individual patients based on clinical findings and immunohistochemical markers.
[g]An expanded panel of immunohistochemical markers may be used as appropriate. See Immunohistochemistry Markers for Unknown Primary Cancers (OCC-A).

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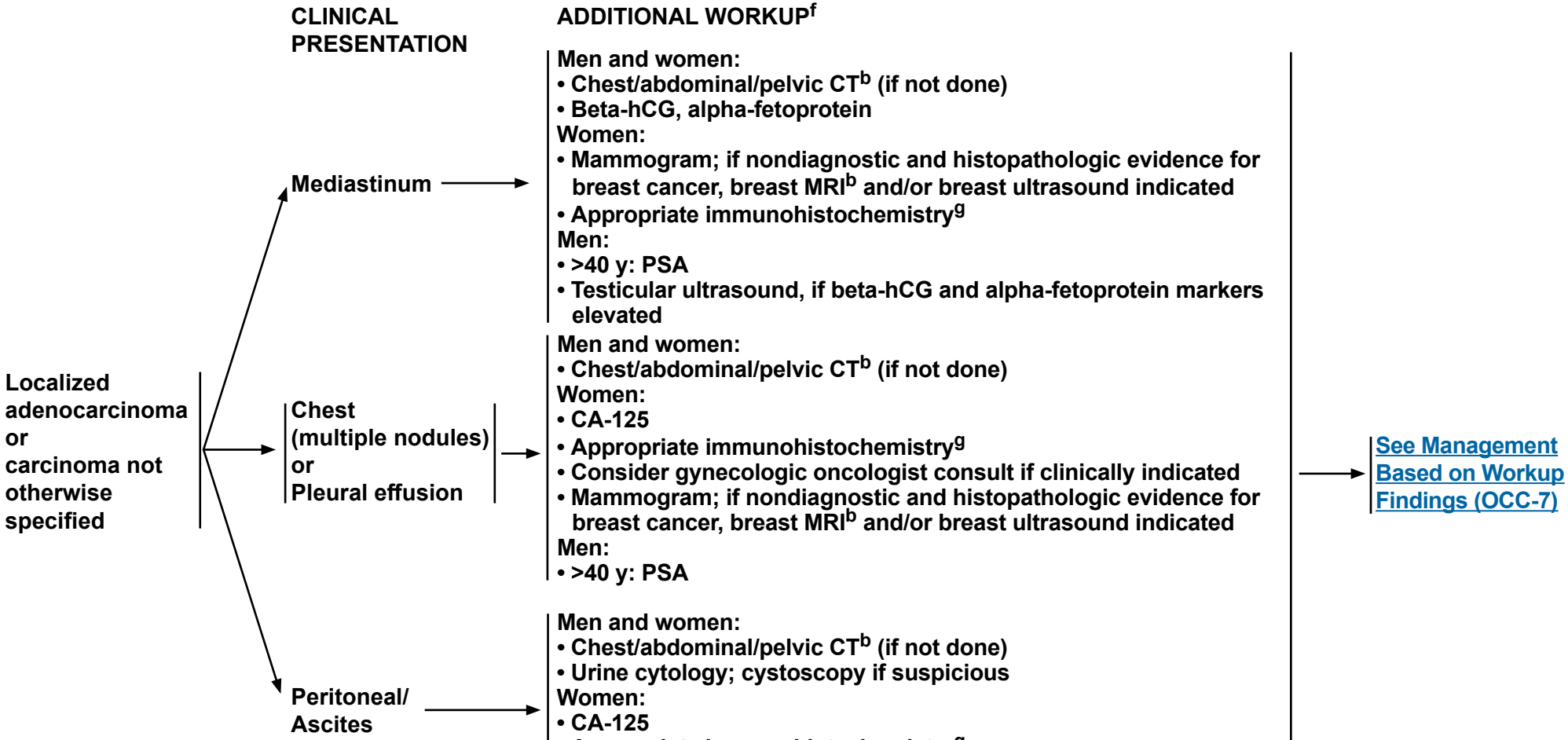

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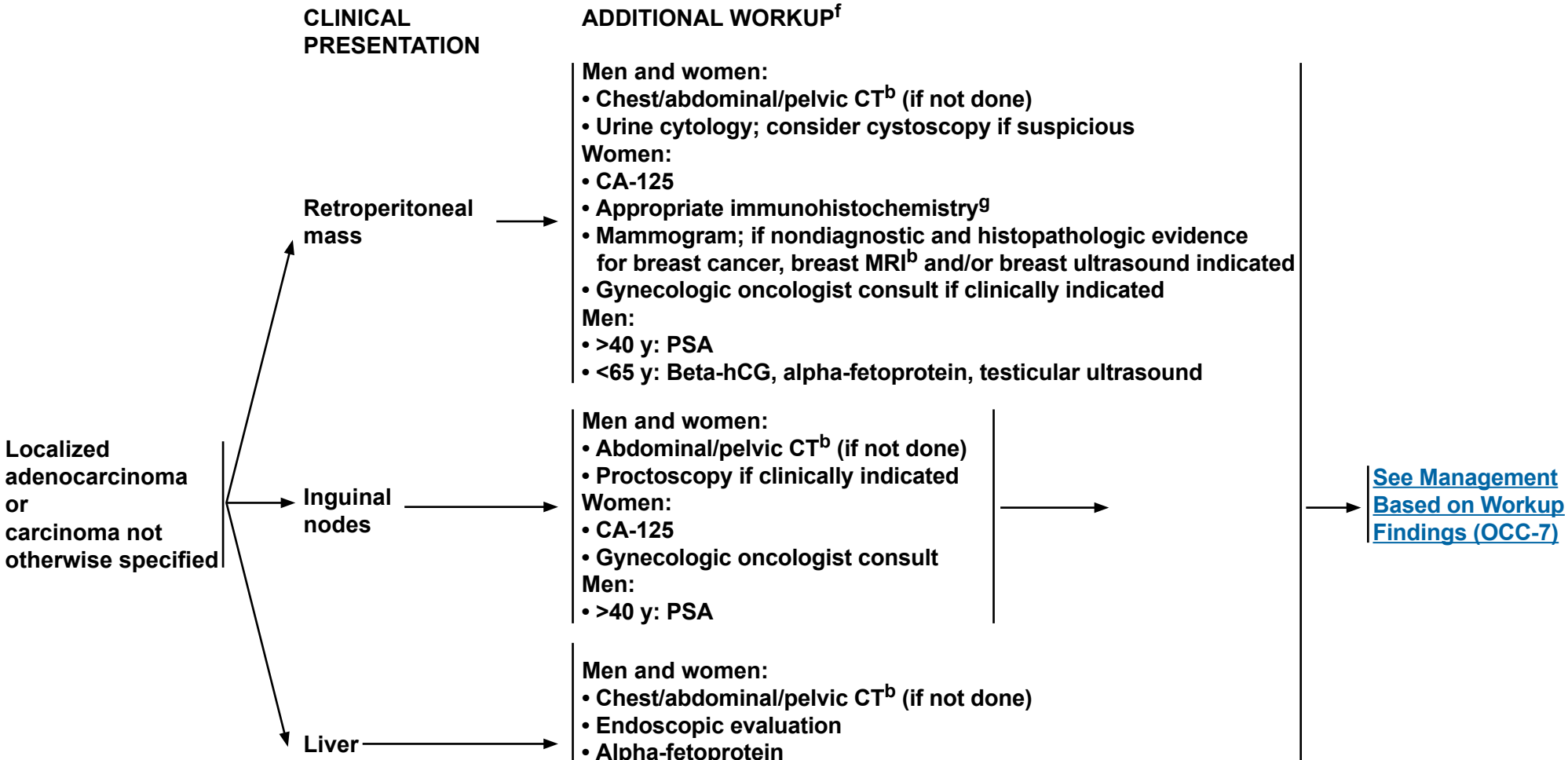

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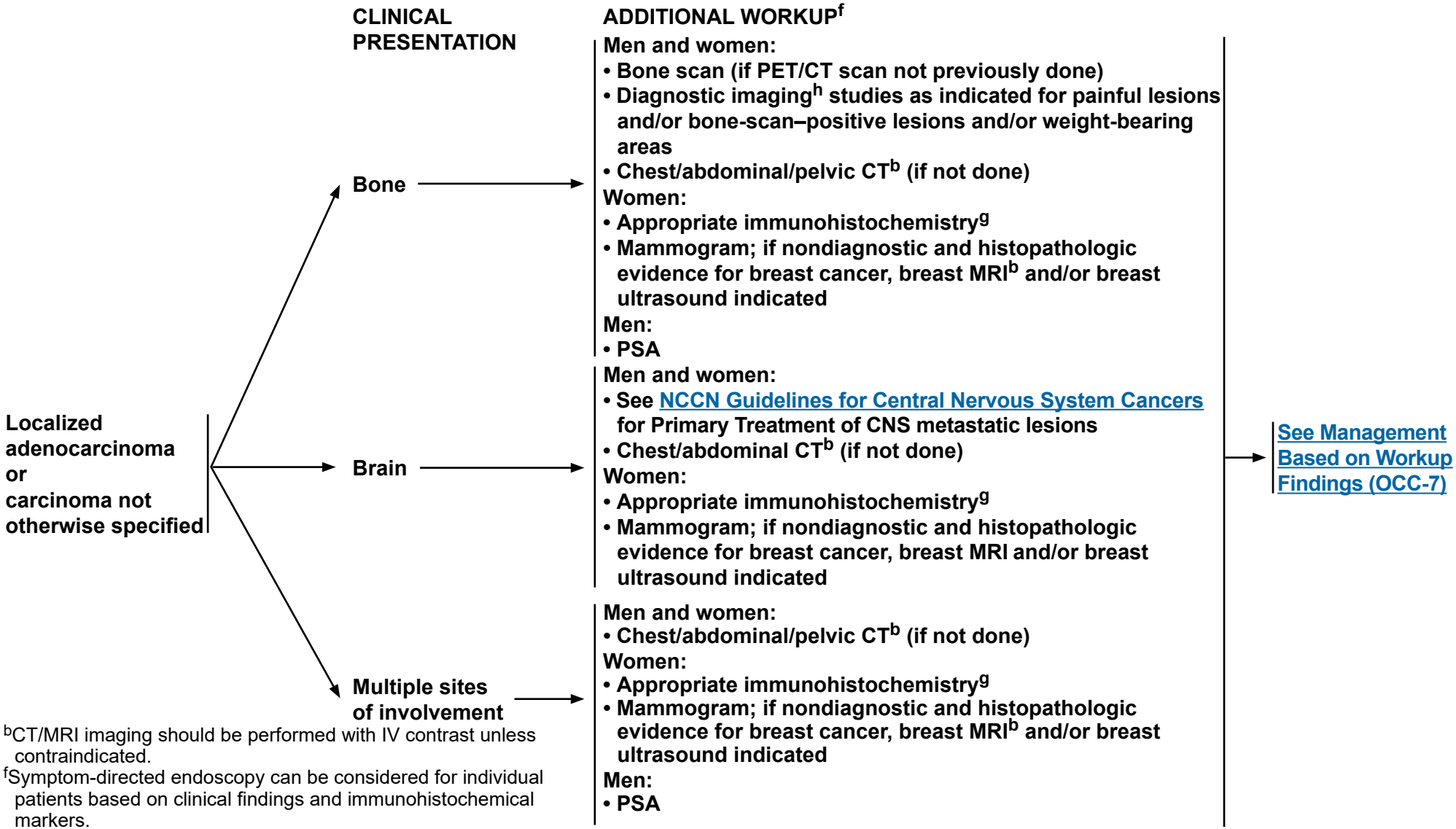

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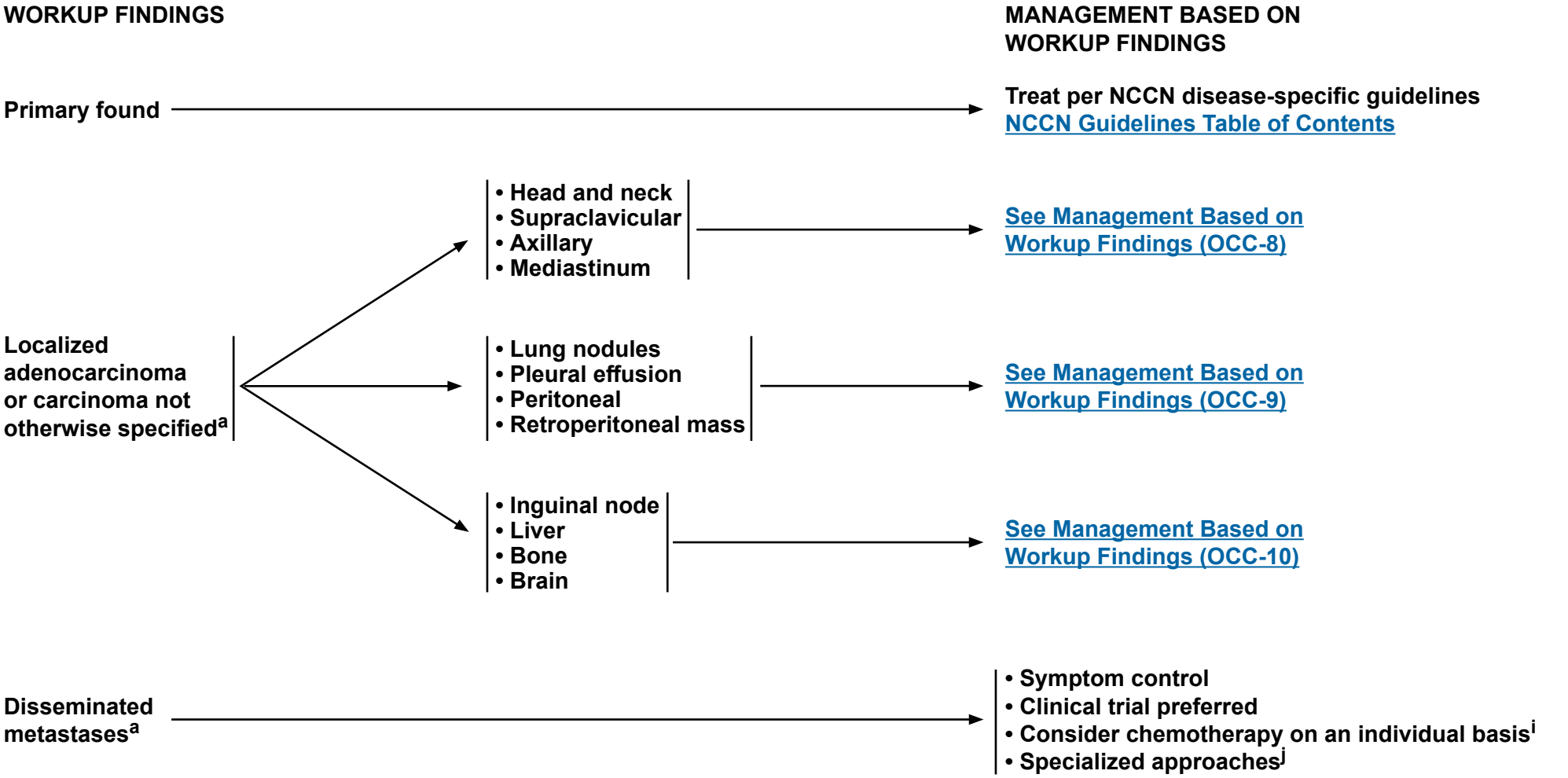

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[i]See Principles of Chemotherapy and Selected Chemotherapy Regimens for Occult Primaries (OCC-B).

[j]For specialized approaches that are therapeutic in nature, see Discussion.

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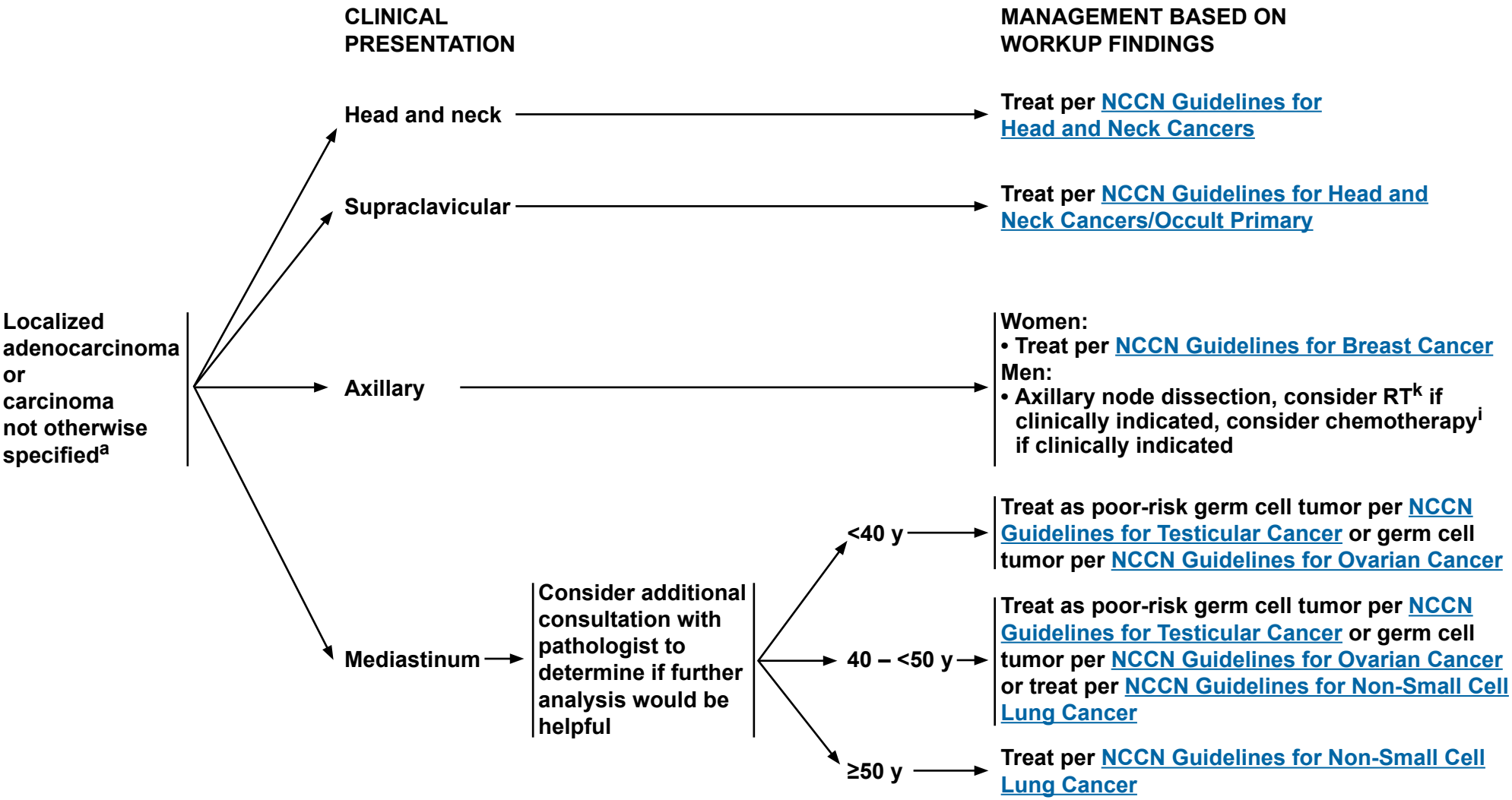
See Follow-up (OCC-16)



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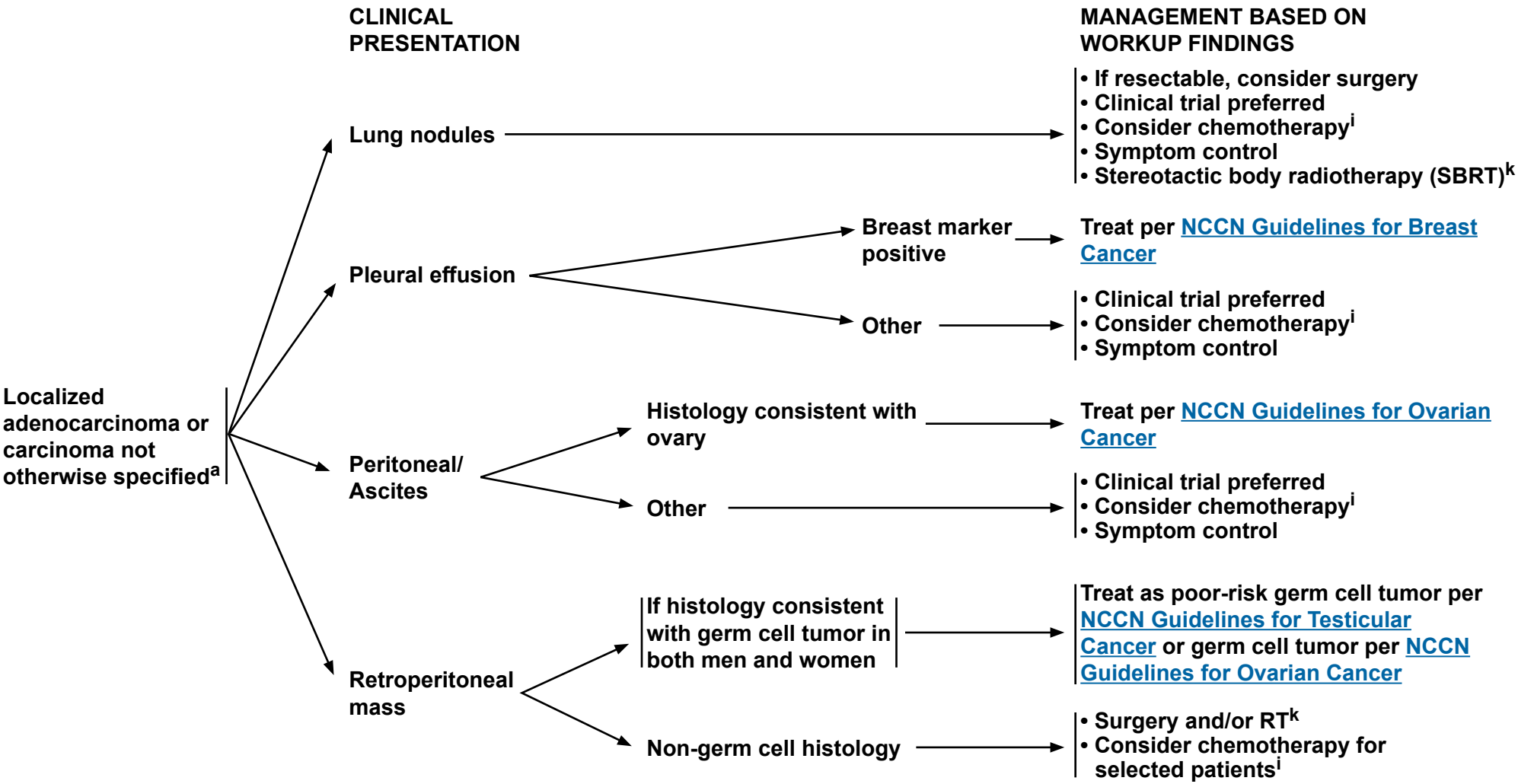

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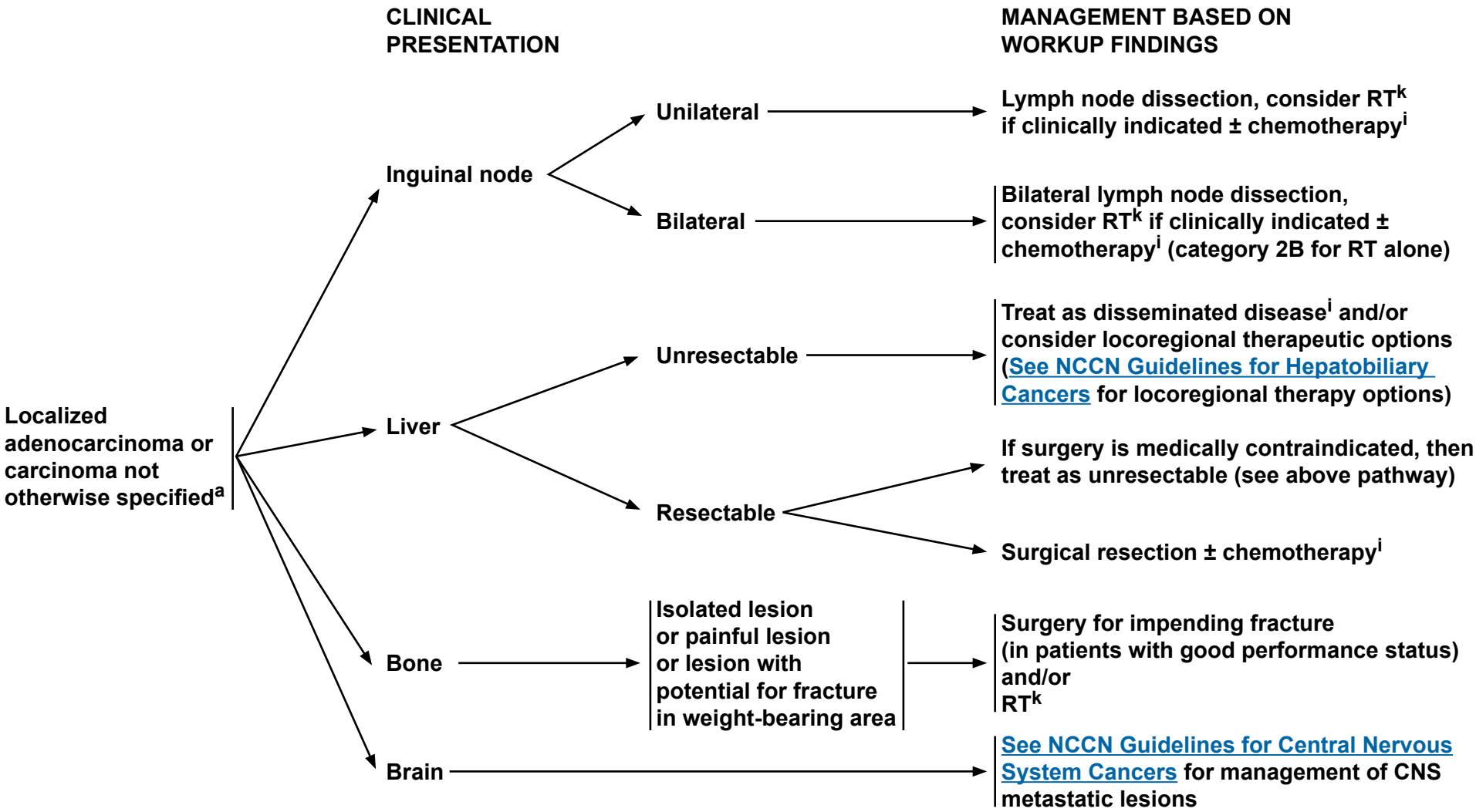

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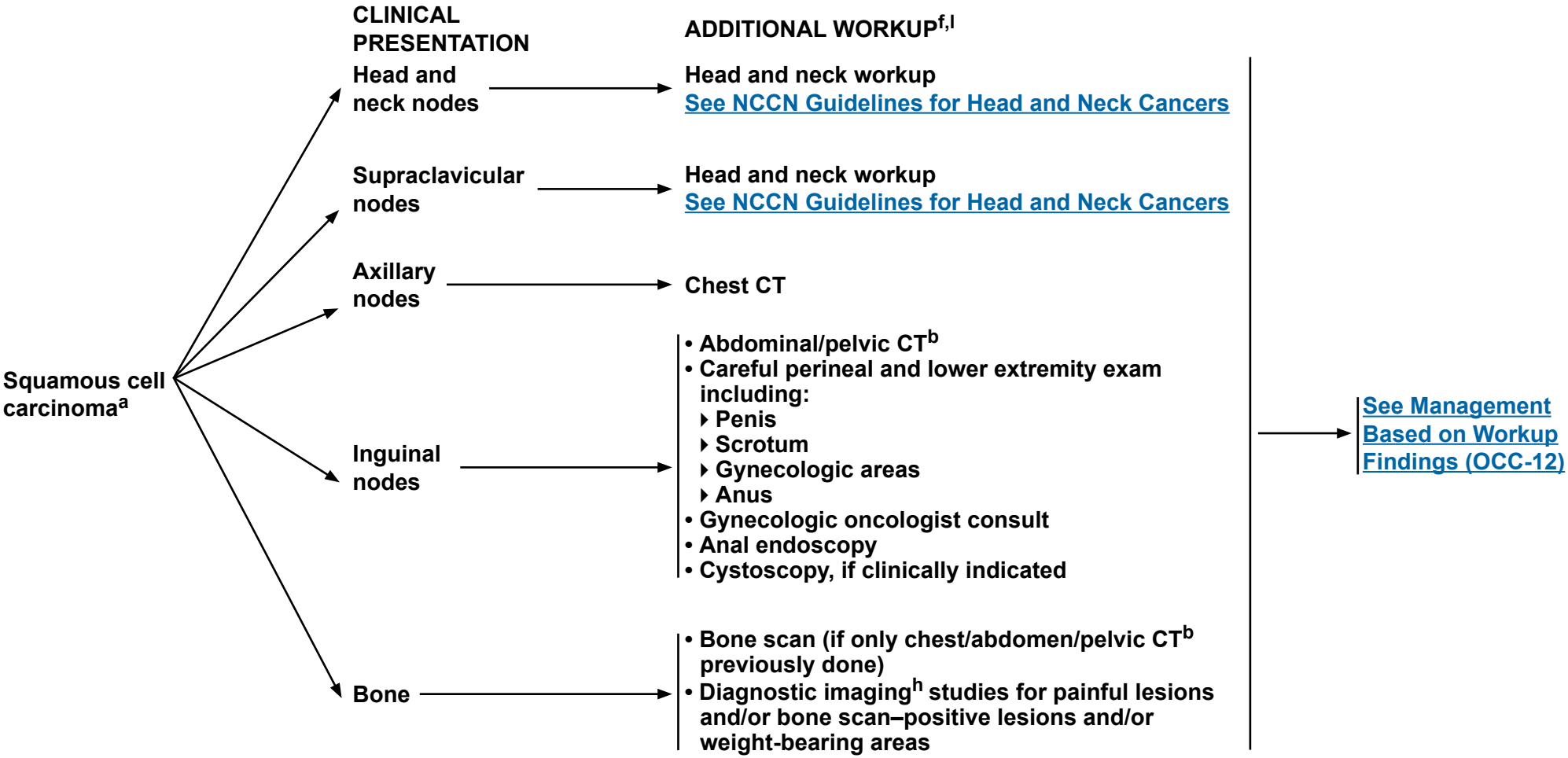

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[l]Check results of p16 immunohistochemistry/HPV in situ hybridization and EBV in situ hybridization; positive results can help localize primary site.

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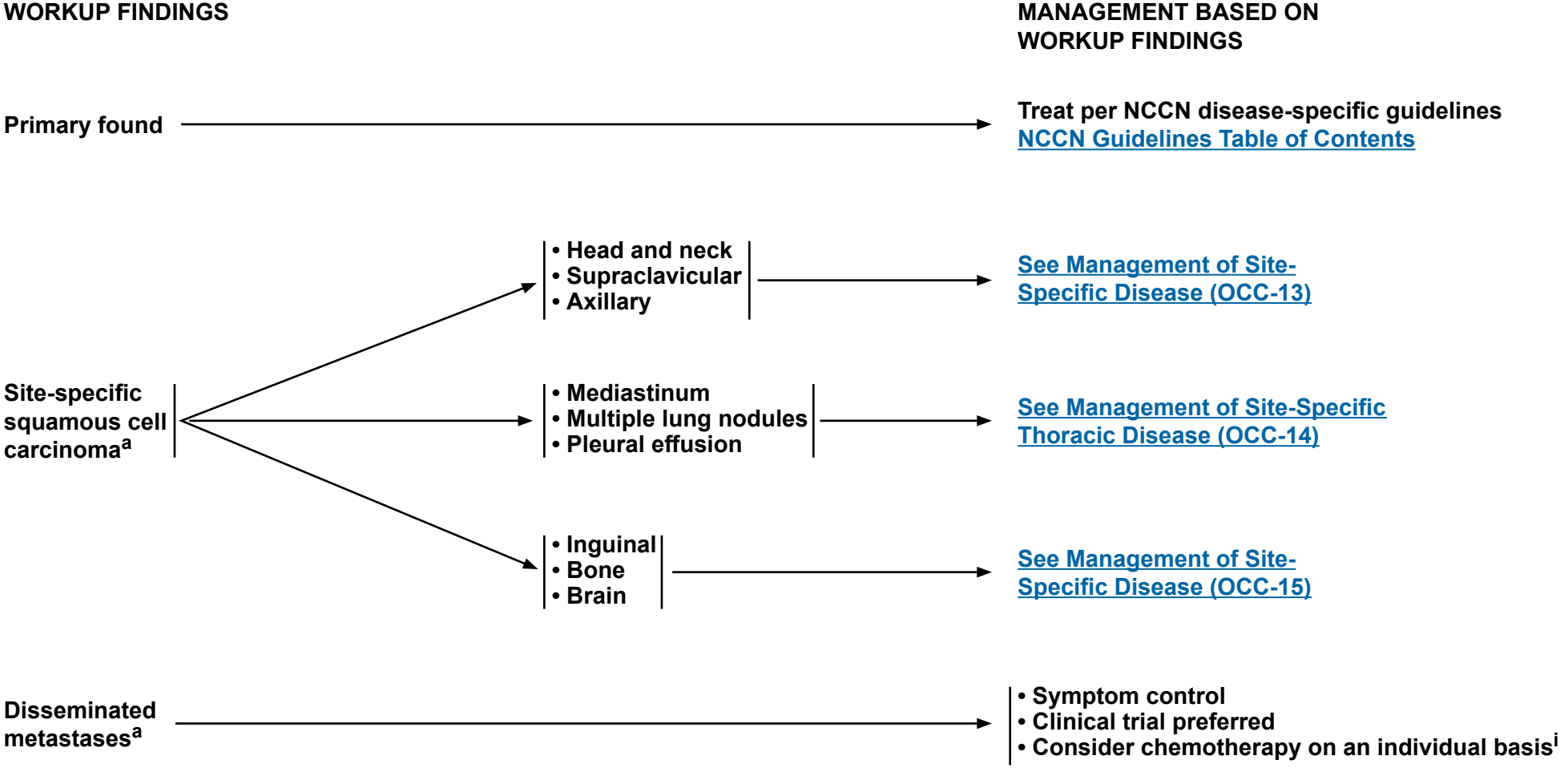
NCCN Guidelines Version 1.2020
Occult Primary
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion



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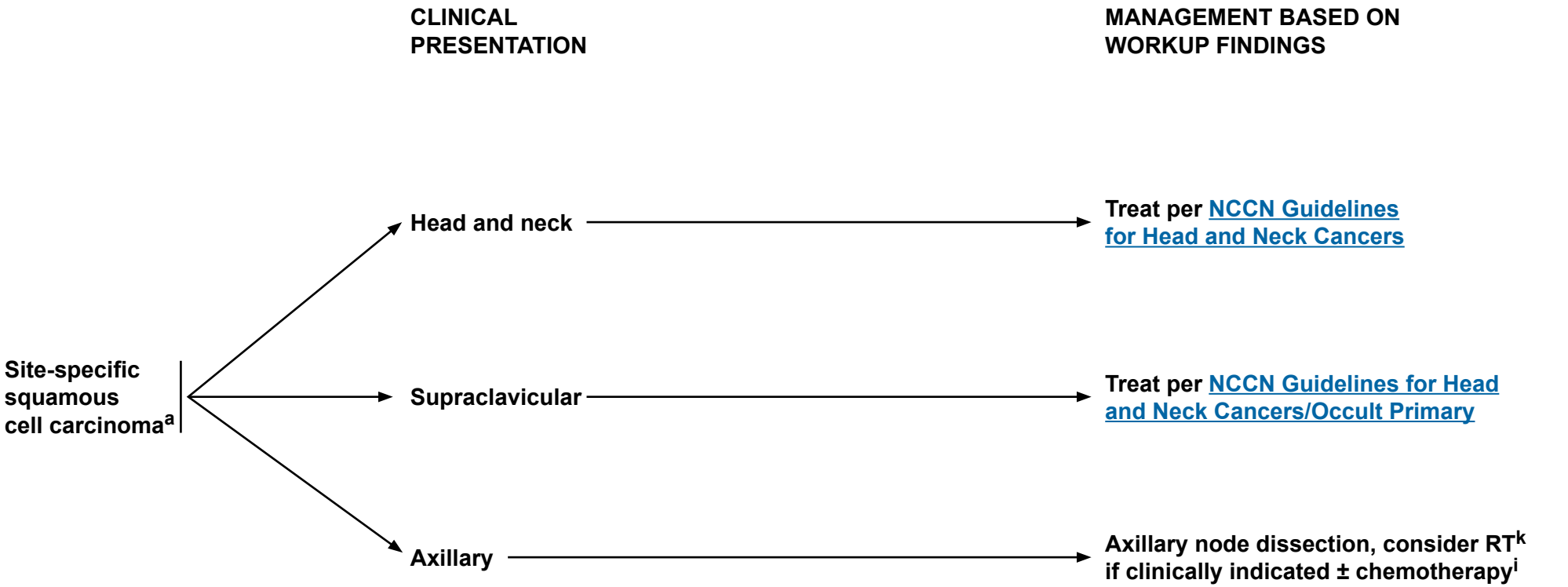

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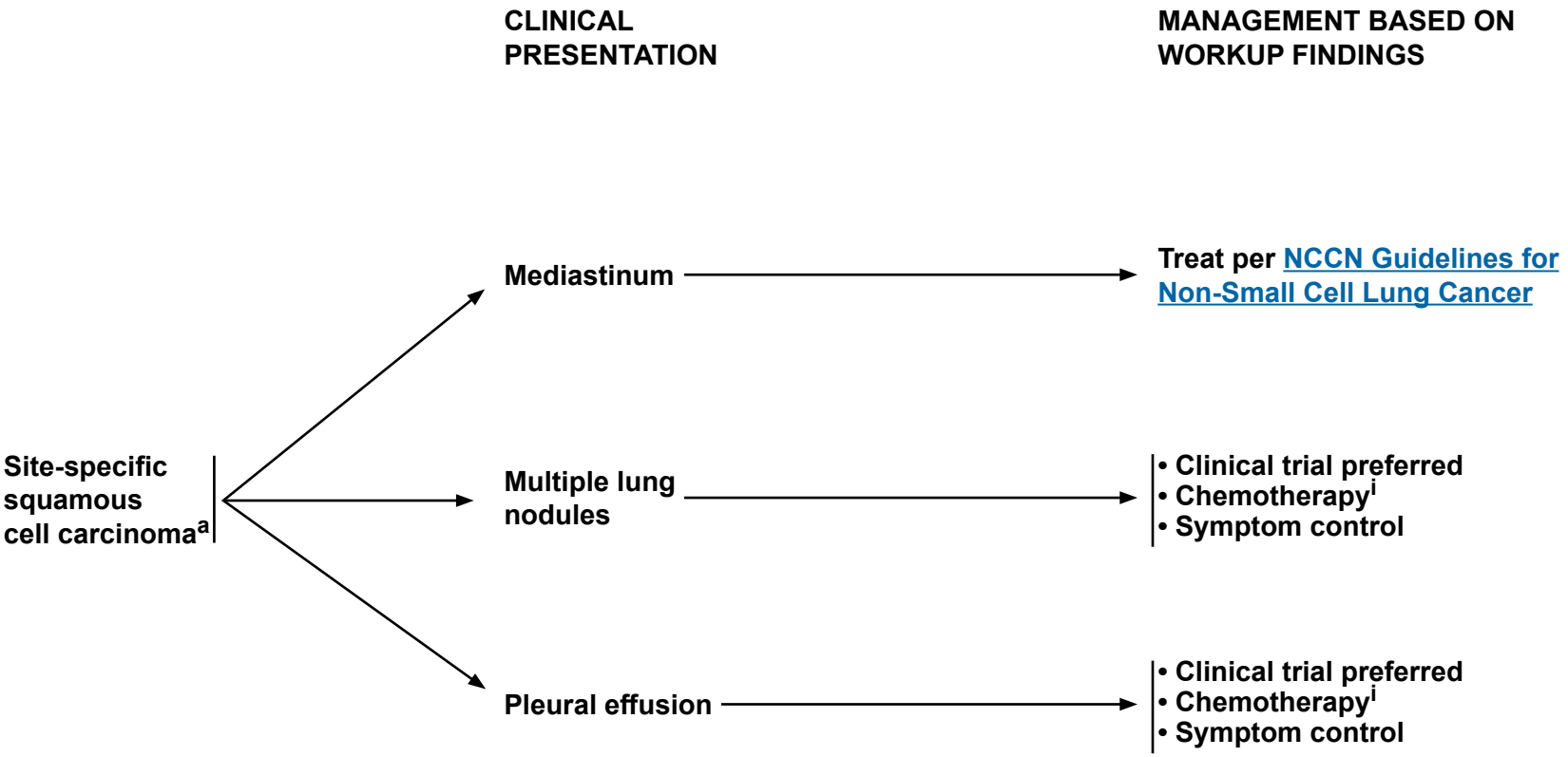

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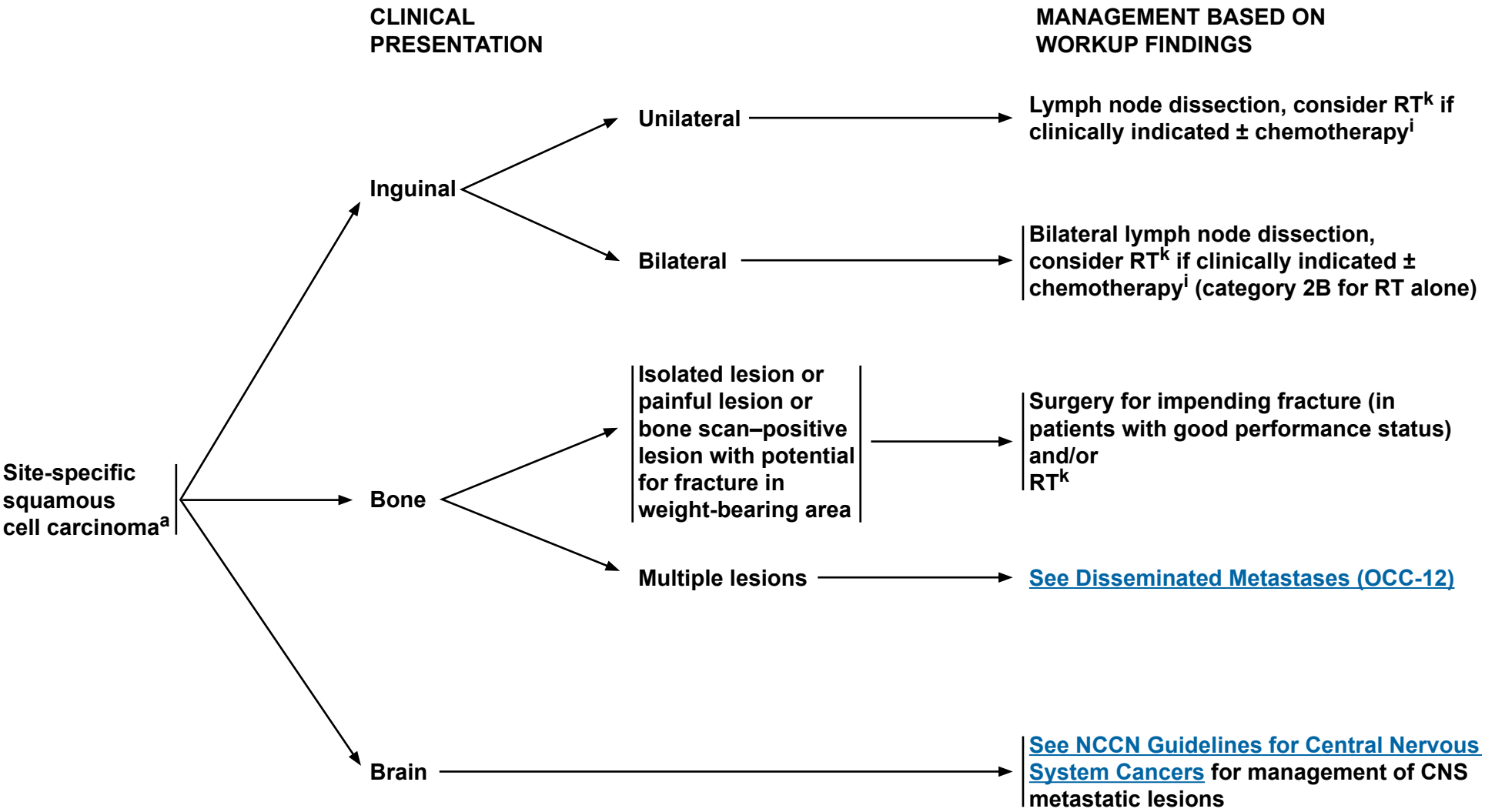

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FOLLOW-UP FOR ALL OCCULT PRIMARIES (NO ACTIVE TREATMENT)

- For patients with either active disease, or localized disease in remission, follow-up frequency should be determined by clinical need.
  - H&P
  - Diagnostic tests based on symptomatology

- For patients with active and incurable disease, psychosocial support, symptom management, end-of-life discussions, palliative care interventions, and hospice care should all be considered and utilized as appropriate.
- See NCCN Guidelines for Palliative Care, NCCN Guidelines for Distress Management, and NCCN Guidelines for Survivorship.

Back to Occult Primary Table of Contents

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POTENTIAL IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS

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

TUMOR-SPECIFIC MARKERS AND THEIR STAINING PATTERN[1,2]

Marker	Tumor	Staining Pattern
Arginase-1	Hepatocellular	Nuclear/cytoplasmic
Calretinin	Mesothelioma, sex cord–stromal, adrenocortical	Nuclear/cytoplasmic
CDX2	Colorectal, other gastrointestinal, pancreaticobiliary tract	Nuclear
D2-40	Mesothelioma, lymphatic endothelial cell marker	Membranous
EBV	Nasopharynx	Nuclear
ER/PR	Breast, ovary, endometrium	Nuclear
GATA3	Breast, urinary bladder, salivary gland	Nuclear
GCDFP-15	Breast	Cytoplasmic
Glypican-3	Hepatocellular	Cytoplasmic
HepPar-1	Hepatocellular	Cytoplasmic
HPV	Cervix, vulva, vagina, penis, anal, oropharynx	Nuclear (DNA ISH); nuclear/cytoplasmic (RNA ISH)
Inhibin	Sex cord–stromal, adrenocortical	Cytoplasmic
Mammaglobin	Breast	Cytoplasmic
Melan-A	Adrenocortical, melanoma	Nuclear
Napsin A	Lung	Cytoplasmic
NKX3-1	Prostate	Nuclear
P16	Cervix, vulva, vagina, penis, anal, oropharynx	Nuclear/cytoplasmic (if positive, perform HPV ISH)
PAP	Prostate	Membranous
PAX8	Thyroid, renal, ovary, endometrium, cervix, thymus	Nuclear
PSA	Prostate	Cytoplasmic
RCC marker	Renal	Membranous
SF-1	Adrenocorticol, sex–cord stromal	Nuclear
SATB2	Colorectal, other gastrointestinal tract	Nuclear
Thyroglobulin	Thyroid	Cytoplasmic
TTF-1	Lung, thyroid	Nuclear
Uroplakin III	Urothelial	Membranous
Villin	Gastrointestinal (epithelia with brush border)	Apical
WT1	Ovarian serous, mesothelioma, Wilms	Nuclear

[1]ER/PR, estrogen receptor/progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15; HepPar-1, hepatocyte paraffin 1; RCC, renal cell carcinoma; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; SF-1, steroidogenic factor-1; TTF-1, thyroid transcription factor 1. Reprinted from Bahrami A, Truong LD, Ro JY. Undifferentiated tumor: true identity by immunohistochemistry. Arch Pathol Lab Med 2008;132:326-348 with permission from Archives of Pathology & Laboratory Medicine. Copyright 2008 College of American Pathologists.

[2]Per physician discretion, TRK protein testing can be considered as part of broad immunohistochemistry testing (a positive test should then be confirmed with NGS): Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739; Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety for entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1, and Alka-372-001. ESMO Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation.

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

POTENTIAL IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS
Undifferentiated Panel: For Determining Most Likely Cell Lineage[3]

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

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

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

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

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

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

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

Tumor Site or Type	Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20)	Other Positive Markers	Other Useful Markers
Lung adenocarcinoma	CK7+/CK20-	TTF1 NapsinA	
Mesothelioma	CK7+/CK20-	Calretinin WT1 CK5/6 D2-40 Mesothelin	p63- CEA- MOC31- BerEP4- TTF-1- (to distinguish from pulmonary adenocarcinoma)
Neuroendocrine carcinoma, including small cell carcinoma	CK7±/CK20± ("dot-like" pattern in Merkel cell carcinoma)	Chromogranin Synaptophysin CD56	TTF1± CDX-2± Mitotic rate and/or Ki-67 (for grade)
Non-seminomatous germ cell tumor	CK7-/CK20-	SALL4 OCT3/4±	CD30 Glypican-3 PLAP (for further subtyping)
Ovarian mucinous carcinoma	CK7+/CK20±	PAX8± CDX2±	SATB2-
Ovarian serous carcinoma	CK7+/CK20-	PAX8 WT1	p53 (abnormal) p16 (diffuse, strong)
Pancreaticobiliary carcinoma, including intrahepatic cholangiocarcinoma	CK7+/CK20±	CDX2± CK19	SMAD4 loss ± (pancreas, extrahepatic cholangiocarcinoma, and colorectal carcinomas) Albumin in-situ hybridization - (also for intrahepatic cholangiocarcinoma)
Prostate carcinoma	CK7-/CK20-	PSA PSAP NKX3-1 P501S (Prostein) ERG±	

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

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COMMONLY USED IMMUNOHISTOCHEMISTRY MARKERS FOR UNKNOWN PRIMARY CANCERS[3]

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

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

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PRINCIPLES OF CHEMOTHERAPY

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

ECOG PERFORMANCE STATUS (PS)

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

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

Neuroendocrine Tumors

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

For well-differentiated neuroendocrine tumors, see NCCN Guidelines for Neuroendocrine Tumors - Carcinoid Tumors

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SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

ADENOCARCINOMA

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Paclitaxel and carboplatin[1] • Gemcitabine and cisplatin[2] • CapeOX[3] • mFOLFOX6[a,3,4,5] • FOLFIRI[6-10]	• Docetaxel and carboplatin[11] • Gemcitabine and docetaxel[12] • Docetaxel and cisplatin[13] • Irinotecan and carboplatin[14] • Capecitabine[a,15,16] • Fluorouracil[a,17-20]	• Paclitaxel, carboplatin, and etoposide[b,20] • Irinotecan and gemcitabine[c,21] • FOLFIRINOX[b,d,22] • Pembrolizumab[e,23-25]

For Squamous Cell see OCC-B 5 of 9

See Evidence Blocks on OCC-B (EB-1)

See references on OCC-B 8 of 9

[a]These regimens can be given with concurrent radiation.
[b]Only for patients with performance status ECOG 0–1.
[c]For patients ineligible to receive platinum-based chemotherapy.
[d]For patients with presumed GI primary site.
[e]Only for patients with MSI-H (or dMMR) tumors.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR OCCULT PRIMARY ADENOCARCINOMA

Preferred Regimens	
Paclitaxel and carboplatin	
Gemcitabine and cisplatin	
CapeOx	
mFOLFOX6	
mFOLFOX6 with concurrent RT	
FOLFIRI	

Other Recommended Regimens	
Docetaxel and carboplatin	
Gemcitabine and docetaxel	
Docetaxel and cisplatin	
Irinotecan and carboplatin	
Capecitabine	
Capecitabine with concurrent RT	
Fluorouracil	
Fluorouracil with concurrent RT	

Useful in Certain Circumstances	
Paclitaxel, carboplatin, and etoposide	
Irinotecan and gemcitabine	
FOLFIRINOX	
Pembrolizumab	

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SELECTED CHEMOTHERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES

ADENOCARCINOMA

Preferred Regimens

Paclitaxel and carboplatin
Paclitaxel 175–200 mg/m² IV Day 1
Carboplatin AUC 5–6 IV Day 1
Repeat every 3 weeks[1]

Gemcitabine and cisplatin
Gemcitabine 1000–1250 mg/m² IV Days 1 and 8
Cisplatin 75 mg/m² IV Day 1
Repeat every 3 weeks[2]

CapeOX
Oxaliplatin 130 mg/m² IV, Day 1
Capecitabine 850–1000 mg/m² PO twice daily Days 1–14
Repeat every 3 weeks[3]

mFOLFOX6
Oxaliplatin 85 mg/m² IV Day 1
Leucovorin* 400 mg/m² IV Day 1
Fluorouracil 400 mg/m² IV bolus on Day 1, then
Fluorouracil 1200 mg/m²/d IV
continuous infusion x 2 days
(total 2400 mg/m² over 46–48 hours)
Repeat every 2 weeks[3,4]

mFOLFOX6 with Radiation
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin* 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation[5]

Preferred Regimens (continued)

FOLFIRI
Irinotecan 180 mg/m² IV, Day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, Day 1
Fluorouracil 400 mg/m² IV bolus on Day 1, then 1200 mg/m²/d x 2 days
(total 2400 mg/m² over 46–48 hours)
continuous infusion
Repeat every 2 weeks[6-10]

Other Recommended Regimens

Docetaxel and carboplatin
Docetaxel 65 mg/m² IV Day 1
Carboplatin AUC 5–6 IV Day 1
Repeat every 3 weeks[11]

Gemcitabine and docetaxel
Gemcitabine 1000 mg/m² IV Days 1 and 8
Docetaxel 75 mg/m² IV Day 8
Repeat every 3 weeks[12]

Docetaxel and cisplatin
Docetaxel 60–75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Repeat every 3 weeks[13]

Irinotecan and carboplatin
Irinotecan 60 mg/m² IV Days 1, 8, and 15
Carboplatin AUC 5–6 IV Day 1
Repeat every 4 weeks[14]

Other Recommended Regimens (continued)

Capecitabine
Capecitabine 850–1250 mg/m²
PO twice daily, Days 1–14
Repeat every 3 weeks[15]

Capecitabine with radiation
Capecitabine 625–825 mg/m²
PO BID on Days 1–5 or 1–7
Weekly for 5 weeks with radiation[16]

Bolus or infusional fluorouracil/leucovorin*
Roswell Park regimen
Leucovorin* 500 mg/m² IV over 2 hours,
Days 1, 8, 15, 22, 29, and 36
Fluorouracil 500 mg/m² IV bolus 1 hour after start of leucovorin,* Days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks[17]

Simplified biweekly infusional Fluorouracil / Leucovorin* (sLV5FU2)
Leucovorin* 400 mg/m² IV over 2 hours on Day 1, followed by fluorouracil bolus 400 mg/m² and then 1200 mg/m²/d x 2 days
(total 2400 mg/m² over 46–48 hours)
continuous infusion
Repeat every 2 weeks[18]

Continued

See references on OCC-B 8 of 9

*Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availabilty, these regimens may be used with or without leucovorin.

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SELECTED CHEMOTHERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES
ADENOCARCINOMA

Other Recommended Regimens (continued)

Weekly
Leucovorin* 20 mg/m² IV over 2 hours on Day 1,
Fluorouracil 500 mg/m² IV,
bolus injection 1 hour after the start of leucovorin.
Repeat weekly[19]

Fluorouracil 2600 mg/m² by 24-hour infusion plus
leucovorin* 500 mg/m²
Repeat every week[19]

Fluorouracil with radiation
Fluorouracil 200–250 mg/m² IV continuous infusion
over 24 hours
daily on Days 1–5 or 1–7
Weekly for 5 weeks with radiation[20]

Useful in Certain Circumstances

Paclitaxel, carboplatin, and etoposide[b]
Paclitaxel 175–200 mg/m² IV Day 1
Carboplatin AUC 5–6 IV Day 1
Etoposide 50 mg/d PO alternating with
100 mg/d PO Days 1–10
Repeat every 3 weeks[21]

Irinotecan and gemcitabine[c]
Irinotecan 100 mg/m² IV Days 1 and 8
Gemcitabine 1000 mg/m² IV Days 1 and 8
Repeat every 3 weeks[22]

FOLFIRINOX[b,d]
Oxaliplatin 85 mg/m² IV on Day 1
Irinotecan 180 mg/m² IV Day 1
Leucovorin* 400 mg/m² on Day 1
Fluorouracil 400 mg/m² on Day 1
Fluorouracil 1200 mg/m² over 24 hours X 2 days
(total 2400 mg/m² over 46–48 hours) continuous
infusion starting on Day 1
Repeat every 2 weeks[23]

Pembrolizumab[e]
2 mg/kg IV on Day 1
Repeat every 3 weeks[24,25]
OR
200 mg IV Day 1
Repeat every 3 weeks[26]

*Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availabilty, these regimens may be used with or without leucovorin.
[b]Only for patients with performance status ECOG 0–1.
[c]For patients ineligible to receive platinum-based chemotherapy.
[d]For patients with presumed GI primary site.
[e]Only for patients with MSI-H (or dMMR) tumors.

See references on OCC-B 8 of 9

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SELECTED CHEMOTHERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES

SQUAMOUS CELL

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Paclitaxel and carboplatin[1] • mFOLFOX6[a,3,4,5]	• Gemcitabine and cisplatin[2] • Capecitabine[a,15,16] • Fluorouracil[a,17-20] • Paclitaxel and cisplatin[27] • Docetaxel and carboplatin[28] • Docetaxel and cisplatin[13,29] • Cisplatin and fluorouracil[a,30,31,32]	• Docetaxel, cisplatin, and fluorouracil[b,33]

[a]These regimens can be given with concurrent radiation.
[b]Only for patients with performance status ECOG 0–1.

See Evidence Blocks on OCC-B (EB-2)

See references on OCC-B 8 of 9

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVIDENCE BLOCKS FOR OCCULT PRIMARY SQUAMOUS CELL CARCINOMA

Preferred Regimens	
Paclitaxel and carboplatin	
mFOLFOX6	
mFOLFOX6 with concurrent RT	

Other Recommended Regimens	
Gemcitabine and cisplatin	
Capecitabine	
Capecitabine with concurrent RT	
Fluorouracil	
Fluorouracil with concurrent RT	
Paclitaxel and cisplatin	
Docetaxel and carboplatin	
Docetaxel and cisplatin	
Cisplatin and fluorouracil	
Cisplatin and fluorouracil with concurrent RT	

Useful in Certain Circumstances	
Docetaxel, cisplatin, and fluorouracil	

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SELECTED CHEMOTHERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES

SQUAMOUS CELL

Preferred Regimens

Paclitaxel and carboplatin
Paclitaxel 175–200 mg/m² IV Day 1
Carboplatin AUC 5–6 IV Day 1
Repeat cycle every 3 weeks[1]

mFOLFOX6
Oxaliplatin 85 mg/m² IV Day 1
Leucovorin* 400 mg/m² IV Day 1
Fluorouracil 400 mg/m² IV bolus on Day 1,
then Fluorouracil 1200 mg/m²/d IV
continuous infusion x 2 days
(total 2400 mg/m² over 46–48 hours)
Repeat every 2 weeks[3,4]

mFOLFOX6 with Radiation
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin* 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous
infusion over 24 hours daily on
Days 1 and 2
Cycled every 14 days for 3 cycles with
radiation[5]

Other Recommended Regimens

Gemcitabine and cisplatin
Cisplatin 75 mg/m² IV Day 1
Gemcitabine 1000–1250 mg/m² IV, Days 1 and 8
Repeat cycle every 3 weeks[2]

Capecitabine
Capecitabine 850–1250 mg/m²
PO twice daily, Days 1–14
Repeat every 3 weeks[15]

Capecitabine with radiation
Capecitabine 625–825 mg/m²
PO BID on Days 1–5 or 1–7
Weekly for 5 weeks[16]

Bolus or infusional fluorouracil/leucovorin*
Roswell Park regimen
Leucovorin* 500 mg/m² IV over 2 hours,
Days 1, 8, 15, 22, 29, and 36
Fluorouracil 500 mg/m² IV bolus 1 hour after start of
leucovorin*, Days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks[17]

**Simplified biweekly infusional Fluorouracil/
Leucovorin* (sLV5FU2)**
Leucovorin* 400 mg/m² IV over 2 hours on Day 1,
followed by Fluorouracil bolus 400 mg/m² and then
1200 mg/m²/d x 2 days
(total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks[18]

Other Recommended Regimens (continued)

Weekly
Leucovorin* 20 mg/m² IV over 2 hours on Day 1,
Fluorouracil 500 mg/m² IV bolus injection
1 hour after the start of leucovorin
Repeat weekly[19]

Fluorouracil 2600 mg/m² by 24-hour infusion
plus leucovorin* 500 mg/m²
Repeat every week[19]

Fluorouracil with radiation
Fluorouracil 200–250 mg/m² IV
continuous infusion over 24 hours
daily on Days 1–5 or 1–7
Weekly for 5 weeks with radiation[20]

Paclitaxel and cisplatin
Paclitaxel 175 mg/m² IV Day 1
Cisplatin 60 mg/m² IV Day 1
Repeat cycle every 3 weeks[27]

Docetaxel and carboplatin
Docetaxel 75 mg/m² IV Day 1
Carboplatin AUC 5–6 IV Day 1
Repeat cycle every 3 weeks[28]

Docetaxel and cisplatin
Docetaxel 60–75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Repeat cycle every 3 weeks[13,29]

Continued
See references on OCC-B 8 of 9

*Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availabilty, these regimens may be used with or without leucovorin.

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SELECTED CHEMOTHERAPY REGIMENS AND DOSING SCHEDULES FOR OCCULT PRIMARIES

SQUAMOUS CELL

Other Recommended Regimens (continued)

Cisplatin and fluorouracil
Cisplatin 20 mg/m² IV Days 1–5
Fluorouracil 700 mg/m²/d IV continuous infusion Days 1–5
Repeat cycle every 4 weeks[30]

Fluorouracil and cisplatin with radiation
Cisplatin 75–100 mg/m² IV on Days 1 and 29
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily
Days 1–4 and 29–32
35-day cycle with radiation[31]

Cisplatin 15 mg/m² IV daily on Days 1-5
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for 2 cycles with radiation[32]

Useful in Certain Circumstances

Docetaxel, cisplatin, and fluorouracil[b]
Docetaxel 75 mg/m² IV Day 1
Cisplatin 75 mg/m² IV Day 1
Fluorouracil 750 mg/m²/d IV continuous infusion Days 1–5
Repeat cycle every 3 weeks[33]

[b]Only for patients with performance status ECOG 0–1.

Continued
See references on
OCC-B 8 of 9

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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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]Gross-Goupil M, Fourcade A, Blot E, et al. Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: Results of the randomised GEFCAPI 02 trial. Eur J Cancer 2012;48(5):721-727.

[3]Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-2012.

[4]Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399.

[5]Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-314.

[6]Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a french intergroup study. J Clin Oncol 2014;32:3520-3526.

[7]Sebbagh S, Roux J, Dreyer C, et al. Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers. Acta Oncol 2016;55:1168-1174.

[8]Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. Cancer Chemother Pharmacol 2012;69:1641-1645.

[9]Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786.

[10]Hainsworth JD, Schnabel CA, Erlander MG, et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. Clin Colorectal Cancer 2012;11:112-118.

[11]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.

[12]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.

[13]Demirci U, Coskun U, Karaca H, et al. Docetaxel and cisplatin in first line treatment of patients with unknown primary cancer: a multicenter study of the Anatolian Society of Medical Oncology. Asian Pac J Cancer Prev 2014;15(4):1581-1584.

[14]Yonemori K, Ando M, Yunokawa M, et al. Irinotecan plus carboplatin for patients with carcinoma of unknown primary site. Br J Cancer 2009;100(1):50-55.

[15]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005; 352:2696-2704.

[16]Lee HS, Choi Y, Hur WJ, et al. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. World J Gastroenterol 2006;12:603-607.

[17]Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel protocol C-03. J Clin Oncol 1993;11:1879-1887.

[18]Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 1999 Sept;35(9):1334-1337.

[19]Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. J Clin Oncol 1996;14:2274-2279.

[20]Leong T, Joon DL, Willis D, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2011;79:690-695.

[21]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.

[22]Hainsworth JD, Spigel DR, Clark BL, et al. Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. Cancer J 2010;16(1):70-75.

[23]Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-1825.

[24]Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med 2015;372:2018-2028.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

REFERENCES FOR SELECTED CHEMOTHERAPY REGIMENS FOR OCCULT PRIMARIES

[25]Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520.

[26]Eggermont AM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789-1801.

[27]Park YH, Ryoo BY, Choi SJ, et al. A phase II study of paclitaxel plus cisplatin chemotherapy in an unfavourable group of patients with cancer of unknown primary site. Jpn J Clin Oncol 2004;34(11):681-685.

[28]Pentheroudakis G, Briasoulis E, Kalofonos HP, et al. Docetaxel and carboplatin combination chemotherapy as outpatient palliative therapy in carcinoma of unknown primary: a multicentre Hellenic Cooperative Oncology Group phase II study. Acta Oncol 2008;47(6):1148-1155.

[29]Mukai H, Katsumata N, Ando M, et al. Safety and efficacy of a combination of docetaxel and cisplatin in patients with unknown primary cancer. Am J Clin Oncol 2010;33(1):32-35.

[30]Kusaba H, Shibata Y, Arita S, et al. Infusional 5-fluorouracil and cisplatin as first-line chemotherapy in patients with carcinoma of unknown primary site. Med Oncol 2007;24(2):259-264.

[31]Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092.

[32]Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-1168.

[33]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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PRINCIPLES OF RADIATION THERAPY

General Principles

LOCALIZED DISEASE

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

ADJUVANT THERAPY

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

PALLIATIVE THERAPY

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

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

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 01/23/19

Table of Contents

Overview MS-2
Literature Search Criteria and Guidelines Update Methodology MS-2
Epidemiology MS-3
Presentation and Prognosis MS-3
Pathology MS-4
- Immunohistochemistry MS-4
- Molecular Profiling MS-5
  - Molecular Cancer Classifier Assays for Tissue of Origin MS-5
  - Mutational Testing with Next-Generation Sequencing MS-5
  - Assessing the Clinical Benefit of Molecular Profiling MS-5

Initial Evaluation MS-6
Diagnostic Imaging MS-6
Workup MS-8
- Workup for Possible Breast Primary MS-8
- Workup for Possible Germ Cell Primary MS-9
- Workup for Possible Ovarian Primary MS-9
- Workup for Possible Prostate Primary MS-9
- Additional Workup for Localized Adenocarcinoma or Carcinoma Not Otherwise Specified MS-9
- Workup for SCC MS-9
- Workup for Neuroendocrine Tumors MS-10

Management MS-10
- Psychosocial Distress MS-10
- Supportive Care MS-10
- Treatment Based on Workup Findings MS-10
  - Adenocarcinoma MS-10
  - SCC MS-11
  - Neuroendocrine Tumors MS-12
- Chemotherapy MS-12
  - Adenocarcinoma MS-12
  - SCC MS-15
  - Neuroendocrine Tumors MS-16
- Radiation Therapy MS-17
- Locoregional Therapeutic Options MS-17
- Specialized Approaches MS-17

Follow-up MS-17
References MS-18

Overview

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

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

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

Recommendations for neuroendocrine tumors of unknown primary origin can be found in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors.

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

The management portion of the algorithm focuses on treatment of disseminated or localized disease for adenocarcinoma and site-specific SCC. The panel endorses enrollment of patients in appropriate clinical trials when possible. In most patients, CUP is refractory to systemic treatments, and chemotherapy is only palliative and does not significantly improve long-term survival. In patients with disseminated disease in particular, the treatment goals are directed toward symptom control and providing the best quality of life possible. However, certain clinical presentations of these tumors are associated with a better prognosis.[5] Special pathologic studies can identify subsets of patients with tumor types that are more responsive to chemotherapy. Treatment options should be individualized for this selected group of patients to achieve optimal response and survival rates.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Occult Primary (Cancer of Unknown Primary [CUP]), an electronic search of the PubMed database was performed to obtain key literature using the following search terms: occult primary; cancer of unknown primary; cancer of unknown origin. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[6]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-

publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

Epidemiology

CUP occurs roughly equally in men and women, with an average age at diagnosis of 60 years.[2,7] CUP accounts for 3% to 5% of all tumors and is among the 10 most frequently diagnosed tumors in developed countries.[2] An estimated 31,480 cases of CUP will be diagnosed in the United States in 2019, accounting for approximately 2% of all U.S. cancers.[8] However, deaths from these cancers are estimated to reach 45,140 in 2019. This discrepancy is believed to reflect a lack of specificity in recording the underlying cause of death on death certificates and/or an undercount in the case estimate.[8] An analysis of the SEER database from 1973 to 2008 found that the percentage of cancers diagnosed as occult primary has been decreasing over time.[9] Unfortunately, no improvement in median survival was seen over this time period.

A study published in 2010 based on the analysis of the Swedish Family-Cancer Database revealed that CUP may have a genetic basis.[10] The analysis showed that 2.8% of occult primary cases were familial (ie, a parent and offspring were both diagnosed with occult primary cancer). In addition, CUP was associated with the occurrence of lung, kidney, and colorectal cancers in families, suggesting that these tumor types are often the primary sites of the disease.[10]

A latent primary cancer may emerge during the natural course of the disease, though it is uncommon. In 20% to 50% of patients, the primary tumor is not identified even after postmortem examination.[7,11,12]

Presentation and Prognosis

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

Eighty percent of patients with CUP have poor prognosis and median OS of only 6 months.[2] Unfavorable features include male gender; older age (≥65 years); poor performance status (PS); multiple comorbidities; pathologic diagnosis of adenocarcinoma with metastases involving multiple organs (eg, liver, lung, bone); nonpapillary malignant ascites (adenocarcinoma); peritoneal metastases; multiple cerebral metastases (adenocarcinoma or SCC); and adenocarcinoma with multiple lung/pleural or bone lesions.[2,15,16] For these patients, an empiric approach to therapy is recommended, although the likelihood of benefit is questionable.

The 20% of CUP patients with a more favorable prognosis include those with a single, small, and potentially resectable tumor; poorly differentiated carcinoma with midline nodal distribution; SCC involving cervical lymph nodes (constituting 2%–5% of all cases of occult primary cancers[17]); isolated inguinal adenopathy (SCC); poorly differentiated neuroendocrine (PDNE) carcinomas; women with papillary adenocarcinoma of the peritoneal cavity; women with adenocarcinoma involving only axillary lymph nodes; and men with blastic bone metastases and elevated prostate-specific antigen (PSA; adenocarcinoma).[2,15,18] For patients with favorable prognostic features, tailored approaches to treatment, such as locoregional treatments or specific chemotherapy regimens (eg, fluorouracil-based therapy for suspected colon primary or cisplatin-based therapy for possible germ cell tumor), are likely to provide clinical benefit and may prolong survival. In addition, results from a retrospective review

of 179 patients with CUP suggested that patients with better PS, higher serum albumin, and lower serum lactate dehydrogenase (LDH) were more likely to benefit from chemotherapy.[19]

Pathology

CUP often has multiple chromosomal abnormalities and overexpression of several genes, including *EGFR*, *c-kit/PDGFR*, *Ras*, *BCL2*, *HER2*, and *p53*.[20-22] *BCL2* and *p53* are overexpressed in 40% and 26%–53% of occult primary tumors, respectively.[23] The *BRD4-NUT* oncogene, resulting from the chromosomal translocation t(15;19), has been identified in children and young adults with carcinoma of midline structures and unclear primary sites.[1,24,25] Other chromosomal abnormalities frequently observed in CUP are activation of angiogenesis genes (50%–89% of CUP tumors), oncogene overexpression (10%–30%), epithelial-to-mesenchymal transition marker elevation (16%), and activation of hypoxia-related proteins (25%) and intracellular signaling molecules (20%–35%).[2]

CUP can be classified into 5 major subtypes after routine evaluation with light microscopy. The most frequently occurring subtype is well- or moderately differentiated adenocarcinoma (60%), followed by poorly differentiated adenocarcinoma or undifferentiated carcinoma (25%–30%), SCC (5%), and poorly differentiated or undifferentiated malignant neoplasm (5%).[1,2] Additionally, because of improved histopathologic diagnostic studies, neuroendocrine tumors of unknown primary have also been recognized (1%).[2]

In an attempt to identify the tissue of origin, biopsy specimens are often analyzed by immunohistochemistry (IHC).[26-29] In addition, gene expression profiling (GEP) assays have also been developed to attempt to identify the tissue of origin in patients with occult primary cancers.[30-32] Both methodologies offer a similar range of accuracy in tumor classification (approximately 75%).[33] Thus far, the literature on GEP has focused far more on establishing a tissue of origin than on determining whether such identification leads to better outcomes in patients. Thus, while there may be a diagnostic benefit to GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not currently recommend GEP for the identification of tissue of origin as standard management in the diagnostic workup of patients with CUP. Furthermore, the panel believes that neither IHC, a diagnostic tool in widespread use, nor GEP should be used indiscriminately. Both of these techniques are discussed in more detail below.

Immunohistochemistry

The use of IHC in CUP is based on the premise that concordance exists in the expression profiles of primary and metastatic cancers.[30,32] The predictive value of IHC panels improves with the recognition of patterns that are strongly indicative of specific tumors. However, limitations of IHC testing include factors affecting tissue antigenicity, interobserver and intraobserver variability in interpretation, tissue heterogeneity, and inadequate biopsy samples. Nevertheless, with well-performed and interpreted IHC panels, pathologists can identify the putative site of origin of CUP in about 75% of samples (validation to determine accuracy is a challenge given the unknown primary cancer designation).[33]

IHC studies are useful for the characterization of CUP tumors by providing information about tumor lineage, cell type, and pathologic diagnosis.[26-29] However, exhaustive IHC studies (in excess of 10–12 stains) have not been shown to increase the diagnostic accuracy in identifying the putative primary sites.[34] Therefore, testing a large series of IHC markers in individual patients should be avoided.

Communication between the treating oncologist and the pathologist is important to ensure adequate tissue sampling, ideally by means of a core needle biopsy or fine-needle aspiration (FNA) with cell block. To determine tissue of origin using IHC, a tiered approach is recommended in order to conserve the diagnostic material. A first tier of IHC assays can be used to

help determine tissue lineage using lineage-restricted markers (eg, carcinoma, sarcoma, lymphoma, melanoma). A second tier of IHC, using organ-specific markers, can be used to help suggest the putative primary site.[33] Per physician discretion, TRK protein testing can be considered as part of broad IHC testing.[35] A positive test should be confirmed with next-generation sequencing (NGS). In select patients, it may be helpful to use a third tier of testing for tumor biomarkers that might inform treatment decisions, such as mismatch repair (MMR), RAS, HER2, or ALK rearrangements. IHC studies should be used in conjunction with imaging studies to select the best possible treatment options for patients with CUP. Combined with knowledge gained through imaging and clinical presentation, biomarker testing with clear therapeutic intent may be beneficial.

Informative new IHC markers continue to emerge and may aid in the diagnosis of CUP.[36] See *Immunohistochemistry Markers for Unknown Primary Cancers* in the algorithm for suggested IHC markers.

Molecular Profiling

Molecular Cancer Classifier Assays for Tissue of Origin

Over the past decade, several studies have examined various molecular assays designed to identify the tissue of origin in CUP (reviewed by Varadhachary and Raber[32] and Hainsworth and Greco[37]). These assays are designed based on the assumption that metastatic tumors will have a similar molecular profile to that of the primary tumor. Assays used in GEP utilize messenger RNA (mRNA)-, DNA-, or microRNA (miRNA)-based platforms.[38-47] When validated using samples from known tumor types, these assays have generally demonstrated an accuracy rate of 85% to 90%.[32,37] However, because it is difficult to confirm the site of origin in most cases of CUP, the accuracy of GEP assays in occult primary tumor samples is challenging to determine. Surrogate measures used to determine accuracy include correlation with IHC findings, clinical presentation/response to therapy, as well as the appearance of latent disease at the primary tumor site.[32,37] Several studies suggest that the accuracy of GEP profiling is comparable or superior to the accuracy of IHC for poorly differentiated/undifferentiated carcinomas.[34,48]

Mutational Testing with Next-Generation Sequencing

Another active area of investigation has been the use of NGS to characterize the genome of occult primary tumors. NGS has the potential to identify potentially actionable biomarkers outside of tissue-specific markers, but the clinical benefit of targeted treatment in CUP based on molecular studies remains controversial.[2,32,49-52] In a recent comprehensive study of 200 CUP specimens, use of a hybrid-capture–based NGS assay enabled the identification of at least 1 potentially targetable genomic alteration in 85% of CUP specimens.[51] Mutations and/or amplifications of *ERBB2*, *EGFR*, and *BRAF* occurred more frequently in adenocarcinoma CUPs (10%, 8%, and 6%, respectively) than in non-adenocarcinoma CUPs (4%, 3%, and 4%, respectively). Additionally, clinically relevant alterations in the receptor tyrosine kinase (RTK)/Ras signaling pathway were found in 72% of adenocarcinoma CUPs but in only 39% of non-adenocarcinoma CUPs. Since the identification of clinically relevant genomic alterations has the potential to influence therapy options, use of comprehensive GEP may help identify novel treatment paradigms to address the limited treatment options and poor prognoses of patients with CUP.[51] However, more data from prospective trials are needed to evaluate the effectiveness of treating CUP patients according to molecular study results.

Assessing the Clinical Benefit of Molecular Profiling

Several commercially available GEP tests have been evaluated in prospective clinical studies in an attempt to determine if the information they provide translates into clinically meaningful benefits for patients.[53] In one study, 32 patients whose tumors were classified as being of colorectal

origin by 2 GEP assays (the 10-gene assay of Talantov et al[43] and the 92-gene assay of Ma et al[44]) showed a response to colorectal chemotherapy regimens as expected for patients with stage IV colorectal cancer.[54] Results from a prospective, non-randomized, phase II study of 289 patients with CUP in which treatments were based on the identification of primary sites by the 92-gene assay showed that clinical features and response to treatment were generally consistent with assay results.[53] While the median survival time of 12.5 months in the subset of patients who received GEP-directed treatment was better than the predefined historical cohort, similar results might be expected from empiric use of these regimens in a good PS group of patients with unknown primary cancer predominantly below the diaphragm. Thus, the clinical benefit that might be derived from the use of these molecular assays, if any, remains to be determined. Comparisons between commercially available GEP tests have also been published.[32,37,55]

As noted, outcomes data are not currently available to recommend routine use of molecular profiling in the workup of CUP. Likewise, no such data exist to endorse the automatic or indiscriminate use of IHC. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities on a case-by-case basis, with the best possible individualized patient outcome in mind.[55]

Initial Evaluation

Patients with a suspected metastatic malignancy should undergo an initial evaluation, including a complete history and physical examination (including breast, genitourinary, pelvic, and rectal examinations) with a detailed review of past biopsies or malignancies, removed lesions, spontaneously regressing lesions, and existing imaging studies. Routine laboratory tests (ie, CBC, electrolytes, liver function tests, calcium), occult blood stool testing, and contrast-enhanced chest/abdominal/ pelvic CT scans are also recommended. Endoscopy can be included in the initial evaluation if clinically indicated. At this point, a specific pathologic diagnosis may be made (ie, epithelial occult primary [not site-specific], lymphoma or other hematologic malignancy, melanoma, sarcoma, germ cell tumor). Other diagnostic studies should be based on clinical presentation and subsequent histopathologic findings. Furthermore, it is important to determine if the initially identified malignancy is localized or disseminated, because the treatment for localized and disseminated disease may be different. Microsatellite instability (MSI)/MMR testing is also indicated for patients with CUP; however, it should be noted that the population of patients with MSI-high/MMR-deficient (MSI-H/dMMR) occult primary tumors is generally low.

Diagnostic Imaging

Imaging can play an integral role in the multidisciplinary diagnostic evaluation of patients with CUP.[56] CT is the most frequently used imaging modality in the management of patients with occult primary cancers. PET scan has been shown to be useful for the diagnosis, staging, and restaging of many malignancies,[57,58] and might be warranted in some situations for CUP. PET scan has shown intermediate specificity and high sensitivity in a few small studies, but larger randomized studies are required to determine the clinical utility of PET in patients with CUP.[4,56,59] In a comprehensive review of 10 published studies, Seve et al concluded that PET is a valuable imaging modality for patients with CUP with a single site of metastasis if therapy with a curative intent is planned.[60] Cumulative data from a meta-analysis examining PET as a diagnostic tool in 246 patients with cervical nodal metastases of unknown primary tumors demonstrated a tumor detection rate of 44% and a sensitivity and specificity rate of 97% and 68%, respectively.[61]

One of the limitations of PET has been the limited accuracy of anatomic localization of functional abnormalities because of very little accumulation

of 18F-fluorodeoxyglucose (FDG) tracer in some neoplastic tissues. In these cases, the combination of PET with either CT or MRI can provide more useful information.[62,63] Several studies have reported that the combination of PET/CT identified the primary site in 25% to 75% of CUP patients.[64-72] A meta-analysis and systematic review on the use of PET/CT in patients with CUP found that primary tumors were detected in 37% of 433 patients from 11 studies, with pooled sensitivity and specificity both at 84%.[73] In a prospective study of 56 CUP patients, the sensitivity and accuracy of PET/CT for the detection of primary tumors were significantly higher than the sensitivity and accuracy of CT/MRI (69% and 77% vs. 41% and 48%, respectively; $P < .04$).[74] PET/CT has also been shown to improve the accuracy of staging CUP by detecting more metastases than CT alone.[75] These results indicate that combined modality scanning could play an important role in the diagnosis of CUP. Although one study suggested that PET/CT detected more primary sites (24%–40%) than conventional CT (20%–27%),[76] the exact role of PET/CT remains undefined because of the lack of large prospective clinical trials comparing PET/CT with conventional imaging modalities. Therefore, the panel does not recommend using PET/CT for routine screening at this time. However, PET/CT may be warranted in some situations, especially when considering local or regional therapy.

Recently, combined modality screening with PET/MRI has been evaluated in several studies for its diagnostic significance in CUP. In a preliminary comparison trial to evaluate the diagnostic potential of whole-body PET/MRI versus PET/CT, Ruhlmann et al found that both hybrid imaging techniques provide a comparable diagnostic ability for detection of the primary cancer site in patients with CUP.[77] Furthermore, due to the significantly lower dose of ionizing radiation (IR), PET/MRI may serve as an alternative to PET/CT, particularly for therapy monitoring and long-term surveillance.[77] In a prospective study by Sekine et al, 43 patients with suspected CUP were assessed with PET/CT and PET/MRI for the presence of a primary tumor, lymph node metastases, and distant metastases.[78] PET/MRI was found to be superior to PET/CT for primary tumor detection (sensitivity/specificity, 85%/97% vs. 69%/73%; $P = .02$) and comparable to PET/CT for the detection of lymph node metastases (93%/100% vs. 93%/93%; $P = .157$) and distant metastases (100%/97% vs. 82%/100%; $P = .564$). PET/CT also tended to misclassify physiologic uptake of FDG as malignancy compared with PET/MRI.[78]

Recently, advances in MRI technology have enabled the emergence of more sensitive and accurate techniques. Multiparametric MRI (MPMRI), which consists of 3 separate imaging parameters (T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging), allows for detailed visualization of tissues as well as their chemical makeup, enabling experienced radiologists to better separate cancerous tissue from benign tissue. In a retrospective study of 38 patients with CUP and cervical lymph node metastases, the accuracy of PET/CT and MPMRI in locating the primary tumor in the neck region was identical, with MPMRI having the added advantage of sparing patients the exposure to IR.[79] T1-weighted high-resolution isotropic volume examination (THRIVE) is a 3D ultrafast spoiled gradient MRI sequence that provides more detailed anatomic information and improved spatial resolution with reduced artifacts when compared to traditional 2D spin-echo MRI. In a retrospective study of 73 patients with CUP and cervical lymph node metastases, 3D-THRIVE MRI enabled the identification of the primary tumor in 72.9% of patients compared to 49.2% and 36.4%, respectively, for spin-echo MRI and contrast-enhanced CT.[80] The diagnostic accuracy of 3D-THRIVE MRI (71.2%) was found to be higher than the accuracies of spin-echo MRI (53.4%) and CT (46.4%; $P = .001$). Therefore, because of their lower IR dose levels and either identical or improved efficacy and accuracy, PET/MRI, MPMRI, and 3D-THRIVE MRI may be favorable over PET/CT scans in the workup of suspected occult malignancies. However,

more robust data from randomized prospective trials that include treatment outcome and patient survival data are required to support this assertion.

Workup

Patients with a suspected occult primary tumor will typically present to an oncologist after undergoing an initial core needle biopsy (preferred) and/or FNA with cell block. Accurate pathologic assessment of the biopsied material is of utmost importance. Therefore, a pathologist must be consulted to determine whether additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy). Examination of the biopsy material by light microscopy is usually performed first. Other techniques include electron microscopy and flow cytometry. Although IHC stains can be informative (see *Immunohistochemistry* above), large panels of IHC markers should be avoided. As previously mentioned, the panel does not currently recommend tumor sequencing or gene signature profiling for the identification of the tissue of origin as standard practice. If contrast-enhanced CT scans of the neck, chest, abdomen, and pelvis were not performed previously, they are varyingly indicated depending on the clinical presentation of the patient.

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

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

Workup for Possible Breast Primary

Adenocarcinoma with positive axillary and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. These guidelines suggest the use of a mammogram for these patients. Appropriate testing for IHC markers is also recommended. Contrast-enhanced MRI and/or ultrasound of the breast should be considered for patients with a non-diagnostic mammogram and histopathologic evidence of breast cancer. Contrast-enhanced MRI should also be considered when mammography is not adequate to assess the extent of the disease, especially in women with dense breast tissue and/or positive axillary nodes, or to evaluate the chest wall.[81] Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in select women by allowing for lumpectomy instead of mastectomy.[82,83] In one report, the primary site was identified using MRI in approximately half of the women presenting with axillary metastases, irrespective of breast density.[84]

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

Workup for Possible Germ Cell Primary

Adenocarcinoma with positive mediastinal nodes suggests a possible primary testicular germ cell tumor in men <50 years of age, as does a retroperitoneal mass in men <65 years of age. Thus, these guidelines recommend measurement of the serum tumor markers β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) in these patients. Testicular ultrasound is indicated for male patients found to have elevated levels of serum β-hCG and AFP.

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

Workup for Possible Ovarian Primary

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

Workup for Possible Prostate Primary

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

Additional Workup for Localized Adenocarcinoma or Carcinoma Not Otherwise Specified

In patients with adenocarcinoma involving painful bone lesions, a bone scan (if a PET/CT scan was not previously performed) and diagnostic imaging studies are recommended. X-rays are recommended for the initial evaluation. If pain or other neurologic symptoms suggest spine metastases, an MRI or contrast-enhanced CT scan should be used for the initial evaluation. When X-ray films suggest metastases in weight-bearing areas, further imaging is recommended for therapeutic evaluation. Urine cytology is recommended for patients presenting with a retroperitoneal mass or ascites, followed by cystoscopy if findings are suspicious. In patients with inguinal lymph node involvement, the guidelines include proctoscopy for men and women, if clinically indicated, to assess for rectal or anal cancer.[85] Endoscopic evaluation is recommended for patients presenting with malignancy in the liver and is suggested for patients with positive supraclavicular nodes, if clinically indicated. However, endoscopy is not routinely recommended for patients presenting with malignant ascites (ie, peritoneal presentation). Since the differentiation between metastatic adenocarcinoma of the liver and primary hepatocellular carcinoma (HCC) is sometimes challenging, the use of AFP as a marker for HCC as part of the additional workup for CUP in the liver is recommended.[86] In the absence of a positive fecal occult blood test or other clinical factors suggesting a putative colon primary or concern for bowel involvement/obstruction from metastatic cancer or carcinomatosis, the diagnostic yield of colonoscopy is low and is therefore not recommended as standard practice in the workup process in the guidelines.[87]

Workup for SCC

SCC can be present in the lymph nodes of the head and neck region, as well as in the supraclavicular, axillary, and inguinal nodes. Contrast-

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

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

Workup for Neuroendocrine Tumors

Neuroendocrine tumors can metastasize to several sites, including the head and neck, supraclavicular lymph nodes, lung, inguinal lymph nodes, liver, bone, brain, and skin. The workup recommendations for Neuroendocrine Unknown Primary in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors should be followed.

Management

Psychosocial Distress

For many patients, the apparent uncertainties surrounding the diagnosis of unknown primary cancer may result in significant psychosocial distress and increased difficulty in accepting treatment options. In fact, a study by Hyphantis et al found that psychiatric manifestations, including anxiety and depression, were more common in patients with CUP than in those with known primary cancers.[88] Empathetic discussion about the natural history of these types of cancers and their prognoses, and the provision of support and counseling by both the primary oncology team and specialized services, may help alleviate this distress. Please see the NCCN Guidelines for Distress Management for further information.

Supportive Care

In addition to psychosocial support, patients with active and incurable CUP often require symptom management and palliative care interventions. Given the natural history of this disease, end-of-life discussions should be initiated early in the clinical course. Hospice care should also be considered and utilized as appropriate. Please see the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Survivorship for more information.

Treatment Based on Workup Findings

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

Adenocarcinoma

Patients with localized adenocarcinoma or carcinoma NOS involving supraclavicular nodes (unilateral or bilateral) or the head and neck regions should be treated according to the Occult Primary pathway described in the NCCN Guidelines for Head and Neck Cancers. Those presenting with localized adenocarcinoma with a peritoneal mass or ascites consistent with ovarian histology should be treated according to the NCCN Guidelines for Ovarian Cancer. Localized adenocarcinoma with a retroperitoneal mass consistent with germ cell histology should be treated according to the NCCN Guidelines for Testicular Cancer or NCCN Guidelines for Ovarian Cancer (Malignant Germ Cell Tumors pathway). Women with localized adenocarcinoma involving axillary nodes as well as those who are breast-marker positive and have pleural effusion should be treated according to the NCCN Guidelines for Breast Cancer.

Localized adenocarcinoma occurring in the mediastinum most likely derives from either a germ cell tumor or a non-small cell lung tumor. Additional consultation with a pathologist should be considered to determine if further analysis would help determine the origin of the primary tumor. In the absence of additional diagnostic information, the recommended treatment depends on the age of the patient at diagnosis. Patients <40 years and those between 40 and 50 years of age should be treated for poor-risk germ cell tumors according to the NCCN Guidelines for Testicular Cancer or the NCCN Guidelines for Ovarian Cancer. Alternatively, patients aged 40 to 50 years could also be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer. Patients aged 50 years or older should be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer.

Other locations of adenocarcinomas of unknown primary are not associated with a common primary site. Treatment recommendations in these cases are thus general and may involve local and systemic therapies. For example, axillary node dissection is recommended in men with localized adenocarcinoma involving the axillary nodes. Additionally, radiation therapy (RT) and chemotherapy can also be considered if clinically indicated. Surgery should be considered for resectable lung nodules. Chemotherapy, preferably as part of a clinical trial, or stereotactic body RT (SBRT) can be considered for oligometastatic lung nodules with or without resection. Lymph node dissection is recommended for inguinal nodal involvement; RT with or without chemotherapy can also be considered if clinically indicated. It should be noted that the use of RT alone in cases of bilateral inguinal node involvement is a category 2B recommendation.[89]

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

For patients with good PS and bone lesions with potential for fracture in weight-bearing areas, surgery and RT are the recommended treatment options. In the case of patients with poor PS, RT without surgery is recommended. Patients with brain metastases should be managed according to the recommendations for treating metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers. Chemotherapy (preferably within a clinical trial) can be considered for patients presenting with breast marker-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 chemotherapy considered only for select patients.

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

SCC

In patients with site-specific SCC and localized axillary or inguinal lymph node involvement, lymph node dissection is recommended. RT can be considered if clinically indicated with or without chemotherapy (the use of RT alone in the case of bilateral inguinal node involvement is a category 2B recommendation).[89] Chemotherapy is not recommended if the tumor has a high likelihood of cutaneous origin.

Patients with unilateral and bilateral involvement of the supraclavicular lymph nodes or with SCC involvement in the head and neck should be treated according to the recommendations for occult primary tumors described in the NCCN Guidelines for Head and Neck Cancers. Patients with site-specific SCC in the mediastinum should be treated according to the NCCN Guidelines for Non-Small Cell Lung Cancer. Participation in a

clinical trial is the preferred treatment option for patients with multiple lung nodules or pleural effusion. Alternatively, chemotherapy can also be considered for this group of patients.

Surgery for impending fracture and RT are options for patients with an isolated or painful bone lesion and good PS. In the case of patients with poor PS, RT alone is recommended. Patients with brain metastases should be treated according to the recommendations for metastatic lesions in the NCCN Guidelines for Central Nervous System Cancers.

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

Neuroendocrine Tumors

Treatment of neuroendocrine tumors should follow the Neuroendocrine Unknown Primary pathway of the NCCN Guidelines for Neuroendocrine Tumors.

Chemotherapy

Many chemotherapeutic regimens have been evaluated in patients with CUP in an attempt to prolong survival and provide symptom relief. Various regimens have shown efficacy in the treatment of patients with CUP in phase II studies. However, a 2012 systematic review of chemotherapy trials in patients with CUP of unfavorable presentations concluded that no specific regimen can be recommended as standard of care.[90] Historically, response rates (RRs) of around 20% and median OS of 6 months have been observed in CUP patients treated with taxane- or platinum-based regimens.[2,91] A systematic review and meta-analysis published in 2013 largely came to the same conclusion, with taxanes showing a possible slight advantage over platinum-based regimens.[92] In general, chemotherapy shows limited efficacy and considerable toxicity in patients with CUP. Therefore, these guidelines recommend that chemotherapy for patients with disseminated disease be limited to patients who are symptomatic with a PS of 1-2 or to patients who are asymptomatic with aggressive cancer and a PS of 0. The choice of regimen should be based on the histologic type of cancer. Regimens in addition to those listed in the guidelines can be considered.

Adenocarcinoma

Poorly differentiated or undifferentiated occult primary tumors respond differently from well- to moderately differentiated occult primary tumors. Tumors in the former group seem to be highly responsive to cisplatin-based combination chemotherapy.[93,94] Objective RRs reported in 2 studies from the early 1990s were 53% (van der Gaast et al[94]) and 63% (Hainsworth et al[93]) with complete RRs of 12% and 26%, respectively, with cisplatin-based regimens. In one study, patients who had tumors with extragonadal germ cell features showed an especially high RR.[93] In the other, patients with undifferentiated carcinomas had a better RR than those with poorly differentiated carcinomas (79% vs. 35%; $P = .02$).[94] Taxane-based chemotherapy has also been 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, and a median survival of 10 months.[95]

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

Paclitaxel and Carboplatin with or without Etoposide

In phase II studies, the combination of paclitaxel and carboplatin with or without etoposide was found to be effective for the treatment of adenocarcinoma of unknown primary.[95-100] In the Hellenic Cooperative Oncology Group study, the combination of paclitaxel and carboplatin

produced an overall RR (ORR) of 38.7% according to intention-to-treat (ITT) analysis; no difference was seen in the RRs for adenocarcinomas versus undifferentiated carcinomas.[96] In a randomized prospective phase II study conducted by the German CUP Study Group, paclitaxel and carboplatin showed better clinical activity than gemcitabine and vinorelbine.[100] The median OS, 1-year survival rate, and RR were 11.0 months, 38%, and 23.8%, respectively, for patients treated with paclitaxel and carboplatin, compared with 7.0 months, 29%, and 20%, respectively, for those treated with gemcitabine and vinorelbine.

A phase III randomized study found paclitaxel, carboplatin, and etoposide to be effective in the first-line treatment of patients with CUP.[99] The RR was 18% among 93 patients; median progression-free survival (PFS) and OS were 3.3 months and 7.4 months, respectively, and the 2-year survival rate was 15%. In a phase II trial, long-term follow-up of patients treated with paclitaxel, carboplatin, and oral etoposide showed 1-, 2-, and 3-year survival rates of 48%, 20%, and 14%, respectively.[97] Sequential treatment with paclitaxel/carboplatin/ etoposide and gemcitabine/ irinotecan was also found to be active in patients with CUP.[98] However, survival was similar to that observed in previous phase II trials and the overall toxicity was found to be greater than that observed with other regimens. Therefore, this sequential treatment regimen is not recommended.

Docetaxel and Carboplatin

Greco et al reported that docetaxel in combination with either cisplatin or carboplatin was active in patients with adenocarcinoma and poorly differentiated carcinoma of unknown primary.[101] Major response to therapy was observed in 26% of patients receiving docetaxel and cisplatin, with a median survival of 8 months and a 1-year survival rate of 42%. In patients receiving docetaxel and carboplatin, the corresponding RR was 22%, with a median survival of 8 months and a 1-year survival rate of 29%. Docetaxel in combination with carboplatin was better tolerated than docetaxel with cisplatin in this study.[101]

In a report on the Hellenic Cooperative Oncology Group phase II study, a 1-hour treatment with docetaxel and carboplatin every 3 weeks was found to be as safe and effective as a palliative treatment for patients with adenocarcinoma or poorly differentiated carcinoma of unknown primary with a PS of 0 to 2.[102] Median time to progression was 5.5 months, whereas OS was 16.2 months. Survival was better in patients with favorable-risk disease (23 months vs. 5 months for those with visceral metastases). Predictors of superior outcome included good PS and low-volume disease.

Gemcitabine and Cisplatin

The efficacy and toxicity of cisplatin with either gemcitabine or irinotecan were evaluated in a randomized phase II study conducted by the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01).[103] Well-differentiated adenocarcinoma was the most common histology, with one-fourth of patients having a single metastatic site. Objective RRs were 55% for the gemcitabine and cisplatin arm and 38% for the irinotecan and cisplatin arm. Median survival rates were 8 and 6 months, respectively, and both combination regimens were associated with significant toxicities. The GEFCAPI 02 trial randomly assigned 52 patients to cisplatin with or without gemcitabine.[104] Outcomes were similar between the arms, but trended better for the combination (1-year survival for the combination and cisplatin alone were 46% and 35%, respectively; $P = .73$). However, toxicity was significantly greater with the addition of gemcitabine.

Gemcitabine and Docetaxel

A non-cisplatin–based regimen containing gemcitabine and docetaxel was found to be active and well-tolerated as first-line therapy in patients with CUP.[105] Of 35 patients, 1 complete response and 13 partial responses

were observed, with an ORR of 40%. The median time to disease progression was 2 months and the median OS was 10 months.

Fluorouracil/Leucovorin with Irinotecan (FOLFIRI)

The combination of fluorouracil, leucovorin, and irinotecan (FOLFIRI) is commonly used in the first- and second-line treatment of gastrointestinal cancers.[106-110] The landmark phase III French Intergroup trial, which compared first-line treatment with FOLFIRI to epirubicin, cisplatin, and fluorouracil (ECF) in patients with advanced or metastatic gastric adenocarcinoma, showed that the median time to treatment failure was significantly longer with FOLFIRI than with ECF (5.1 months vs. 4.2 months; $P = .008$).[107] However, this did not translate into significant differences in median PFS (5.3 months vs. 5.8 months; $P = .96$) or median OS (9.5 months vs. 9.7 months; $P = .95$). Importantly, FOLFIRI was associated with a more favorable toxicity profile than ECF (overall rate of grade 3–4 toxicity, 69% vs. 84%; $P < .001$). Second-line therapy with FOLFIRI has also been shown to be active and well-tolerated in patients with metastatic gastric cancer, recurrent/advanced biliary tract cancer, and locally advanced/ metastatic pancreatic cancer.[108,110]

A retrospective study identified 32 CUP patients predicted to have a colorectal site of origin by molecular profiling who were treated with colorectal cancer regimens, including FOLFIRI.[54] Results showed significantly improved overall response rates in patients treated with site-specific regimens such as FOLFIRI compared to empirical regimens used to treat CUP (50% vs. 17%; $P = .0257$). Since a colorectal primary site is among the most common primary sites in CUP[111,112], the panel feels that FOLFIRI is an acceptable option for first- or second-line therapy in patients with CUP.

Capecitabine with Oxaliplatin (CapeOx) and Fluorouracil/Leucovorin with Oxaliplatin (mFOLFOX6)

The combination of capecitabine and oxaliplatin (CapeOx) has been tested in phase II studies for first-line[113] and second-line[114] treatment of patients with CUP. This regimen gave RRs ranging from 12% to 19%, with disease-free survival of 2.5 to 3.7 months and OS of 7.5 to 9.7 months. CapeOx is active and well-tolerated and is an acceptable option for this patient population.

Although fluorouracil/leucovorin/oxaliplatin (FOLFOX) has not been tested in patients with CUP, FOLFOX has been shown to be equivalent to CapeOx in colorectal cancer.[115-118] The panel therefore supports FOLFOX (mFOLFOX6 regimen[119,120]) as an acceptable treatment option for these patients.

Docetaxel and Cisplatin

Combination therapy with docetaxel and cisplatin was examined in a cohort of 29 patients with CUP.[121] Approximately half of these patients (51.7%) had well- to moderately differentiated adenocarcinoma; patients with undifferentiated carcinoma (27.6%) and SCC histologies (13.8%) were also included. The objective RR was 37.9%, and median PFS and OS were 6 and 16 months, respectively.

Irinotecan and Carboplatin

The combination regimen of irinotecan and carboplatin was evaluated in a phase II study of 45 patients with CUP who were chemotherapy-naïve. The regimen was associated with an ORR of 41.9%; median PFS was 4.8 months and OS was 12.2 months. However, this regimen was also associated with significant toxicities, including grade 3 or greater leukopenia (21%), neutropenia (33%), anemia (25%), and thrombocytopenia (20%).[122]

Irinotecan and Gemcitabine

In a phase III randomized study comparing paclitaxel/carboplatin/etoposide to irinotecan/gemcitabine, both regimens performed similarly. The RR for irinotecan/gemcitabine was 18% with a 2-year survival rate of 18%. Among the 105 patients receiving irinotecan/gemcitabine, median PFS and OS were 5.3 months and 8.5 months, respectively.[99]

SCC

Platinum-based regimens have typically been used to treat disseminated SCC. Historically, the combination of cisplatin and fluorouracil has been the most frequently used regimen for patients with SCC of unknown primary.[123,124] Overall, only a few small studies have assessed chemotherapy regimens in patients with SCC occult primaries. Therefore, the panel lists possible regimens based on evidence from studies of patients with SCC of known primaries and small studies of patients with SCC of occult primaries. Regimens other than those listed can also be considered.

Paclitaxel and Carboplatin

The combination of paclitaxel and carboplatin is commonly used in non-small cell lung, gastric, and esophageal cancers.[125-130] In the Hellenic Cooperative Oncology Group phase II study of combined paclitaxel and carboplatin in patients with CUP (discussed above for adenocarcinoma), 3 patients had tumors of SCC histology.[96] These patients had an RR of 30% and a median response duration of 3 months.

Cisplatin and Gemcitabine

The combination of cisplatin and gemcitabine is commonly used in non-small cell lung cancer and bladder cancer.[127,128,131-134] The GEFCAPI 02 trial compared cisplatin to cisplatin plus gemcitabine in 52 patients with CUP.[104] Although the trial was terminated early due to poor accrual, there was a trend towards better OS with the addition of gemcitabine (11 months vs. 8 months, with overlapping confidence intervals [CIs]).

mFOLFOX6

FOLFOX is used to treat SCC of the esophagus and stomach.[135,136] The panel lists mFOLFOX6 as a possible regimen for occult primary SCC, based on the evidence discussed above for adenocarcinoma.[119,120]

Docetaxel, Cisplatin, and Fluorouracil

The combination of docetaxel, cisplatin, and fluorouracil is used in gastric, esophageal, and head and neck cancers.[137-140] In a randomized phase III trial of 501 patients with advanced SCC of the head and neck, patients received cisplatin and fluorouracil with or without docetaxel followed by chemoradiation.[138] The ORRs after induction chemotherapy were 72% and 64% in the 3-drug and 2-drug arms, respectively.

Paclitaxel and Cisplatin

The combination of paclitaxel and cisplatin is used in esophageal, head and neck, and non-small cell lung cancers.[128,141-144] In a randomized phase III trial of patients with advanced head and neck cancer, no significant differences were seen in patients treated with paclitaxel and cisplatin compared with patients treated with cisplatin and fluorouracil.[143] This regimen has also been assessed in a phase II study of patients with unfavorable presentations of CUP.[145] Three of the 37 patients had SCC. The regimen gave an ORR of 42%, and the median OS was 11 months (95% CI, 8.3–13.5).

Docetaxel and Carboplatin

The combination of docetaxel and carboplatin is used in head and neck and non-small cell lung cancers.[146,147] The combination of docetaxel and carboplatin was assessed in a phase II trial of 47 patients with occult

primary adenocarcinomas or poorly differentiated carcinomas, with an RR of 32% and median OS of 16.2 months.[102]

Docetaxel and Cisplatin

The combination of docetaxel and cisplatin is used in non-small cell lung, esophageal, and gastric cancers.[128,146,148-150] In a multicenter phase II trial of 34 evaluable patients with metastatic esophageal SCC, docetaxel and cisplatin gave an objective tumor RR of 33% in the ITT population. The median PFS and OS times were 5.0 months and 8.3 months, respectively.[149] The safety and efficacy of this regimen has also been assessed in 45 patients with CUP.[151] The reported ORR was 65.1%, and the median OS was 11.8 months. Two patients had tumors of SCC histology, and both had a partial response to the docetaxel/cisplatin regimen. Combination therapy with docetaxel and cisplatin was also examined in a cohort of 29 patients with CUP, 4 of whom had tumors with SCC histology.[121] The ORR was 37.9%, and median PFS and OS were 6 months and 16 months, respectively.

Cisplatin and Fluorouracil

This historic regimen has been used in the treatment of metastatic anal, head and neck, esophageal, and gastric cancers.[143,152-156] It has also been tested in patients with SCC of unknown primary.[123,124] Kusaba et al reviewed the experience of treating patients with CUP with this regimen, and reported an RR of 54.5% and a median OS of 10 months.[157]

Neuroendocrine Tumors

Neuroendocrine CUPs are uncommon, and their clinical behavior is dependent on the tumor grade and level of differentiation.[158] Neuroendocrine tumors, regardless of grade, represent a favorable prognostic subset of CUP that are responsive to combination chemotherapy, making long-term survival a possibility in a minority of patients.[158]

Hainsworth et al evaluated the efficacy of paclitaxel/carboplatin/ etoposide in metastatic PDNE carcinomas in patients who had received no prior treatment.[159] Of these patients, 62% had PDNE CUP. Major responses were observed in 53% of patients, with a median survival of 14.5 months and 2- and 3-year survival rates of 33% and 24%, respectively. The results of this trial showed that PDNE carcinomas are chemosensitive, with a high ORR to combination chemotherapy.

PDNE tumors can also be treated following small cell lung cancer regimens. In a randomized phase III trial (JCOG 9702), the combination of carboplatin plus etoposide was equally as effective as cisplatin plus etoposide in elderly patients with small cell lung cancer or those with poor-risk disease who were not previously treated.[160] No significant differences were seen in RR (73% for both regimens) and median OS (10.6 months for carboplatin/etoposide vs. 9.9 months for cisplatin/etoposide).

In another study, the combination of cisplatin and etoposide produced significant responses in patients with poorly differentiated, rapidly progressing neuroendocrine tumors (carcinoids and pancreatic neuroendocrine tumors of known primaries) when used as a second- or third-line treatment.[161] In 2 small series of patients, temozolomide, as a single agent or in combination with thalidomide, was also found to be effective in the treatment of advanced or metastatic neuroendocrine tumors.[162,163]

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

Radiation Therapy

RT is a treatment option for a variety of localized tumors, particularly as follow-up treatment after lymph node dissection. Adjuvant RT may be appropriate if the disease is limited to a single nodal site with extra-nodal extension, or in the case of inadequate nodal dissection with multiple positive nodes. Definitive RT can be considered for select patients with localized disease. RT alone may also be considered for bone lesions, a retroperitoneal mass with a non-germ cell histology, or supraclavicular nodal involvement in site-specific SCC. In the palliative setting, hypofractionated RT can be considered for symptomatic patients with uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.

A study by Janssen et al examined individualized intensity-modulated RT (IMRT) with risk-adapted planning treatment volumes in 28 patients with CUP and cervical nodal metastases.[164] The majority of patients (71%) received concomitant systemic therapy. In this cohort, 3-year OS, mucosal control, neck control, and distant metastasis-free survival rates were 76%, 100%, 93%, and 88%, respectively. No patient experienced a locoregional recurrence and no grade 2 or higher adverse events were observed. Another retrospective study evaluated the utility of IMRT in 260 patients with CUP metastatic to the neck. The 5-year OS, regional control, and distant metastases-free survival rates were 84%, 91%, and 94%, respectively.[165] However, 7% of patients were diagnosed with chronic radiation-associated dysphagia. A third retrospective study assessed RT in 68 patients with metastatic head and neck SCC of unknown primary.[166] These patients underwent oropharynx-targeted RT to spare the mucosal surfaces of the nasopharynx, hypopharynx, and larynx; 40% of patients received IMRT and 56% of patients received concurrent chemoradiation, resulting in an actuarial locoregional control rate of 95.5% and a median time to locoregional recurrence of 18 months. RT-associated toxicities included grade 1 xerostomia, dysphagia, neck stiffness, and trismus. The results of these studies are promising; however, large randomized prospective trials are needed to further assess the efficacy and safety of IMRT-based treatment approaches for CUP.

Locoregional Therapeutic Options

In patients with unresectable localized liver lesions (either adenocarcinoma or neuroendocrine), locoregional therapeutic options may be considered, where indicated, based on tumor size, pathology, and clinical presentation. Recommendations for locoregional treatment options are described in the NCCN Guidelines for Hepatobiliary Cancers.

Specialized Approaches

Specialized approaches are suggested for all patients with disseminated metastases. The term emphasizes the importance of an individualized approach. Specialized approaches may include palliative care options (such as thoracentesis and paracentesis), targeted therapies, and/or novel approaches to RT.

Follow-up

For patients with either active disease or localized disease in remission, follow-up frequency should be determined by clinical need. Follow-up consists of a history and physical examination, with diagnostic tests for patients who are symptomatic.

For patients with active and incurable disease, psychosocial support, symptom management, end-of-life discussions, palliative care interventions, and hospice care should all be considered and used as appropriate (see *Psychosocial Distress* and *Supportive Care*, above). Please also see the NCCN Guidelines for Distress Management and the NCCN Guidelines for Palliative Care.

References

1. Greco FA, Hainsworth JD. Cancer of Unknown Primary Site. In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology (ed 10th). Philadelphia: Lippincott Williams & Wilkins; 2014:1720-1737.

2. Losa F, Soler G, Casado A, et al. SEOM clinical guideline on unknown primary cancer (2017). Clin Transl Oncol 2018;20:89-96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29230692.

3. Pavlidis N. Cancer of unknown primary: biological and clinical characteristics. Ann Oncol 2003;14 Suppl 3:iii11-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12821533.

4. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet 2012;379:1428-1435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22414598.

5. Hainsworth JD, Lawrence M. Weiss LM. Carcinoma of an unknown primary site In: Pazdur R, Wagman LD, Camphausen C, Hoskins WJ, eds. Cancer Management: A Multidisciplinary Approach (ed 12): CMPMedica LLC; 2009.

6. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

7. Bugat R, Bataillard A, Lesimple T, et al. Summary of the standards, options and recommendations for the management of patients with carcinoma of unknown primary site (2002). Br J Cancer 2003;89 Suppl 1:S59-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12915904.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019. Available at: https://onlinelibrary.wiley.com/doi/abs/10.3322/caac.21551.

9. Urban D, Rao A, Bressel M, et al. Cancer of unknown primary: a population-based analysis of temporal change and socioeconomic disparities. Br J Cancer 2013;109:1318-1324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23860528.

10. Hemminki K, Ji J, Sundquist J, Shu X. Familial risks in cancer of unknown primary: tracking the primary sites. J Clin Oncol 2011;29:435-440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189391.

11. Blaszyk H, Hartmann A, Bjornsson J. Cancer of unknown primary: clinicopathologic correlations. APMIS 2003;111:1089-1094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14678017.

12. Hillen HF. Unknown primary tumours. Postgrad Med J 2000;76:690-693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11060142.

13. Buttar A, Lambert L, Liebmann J, Pieters R. Cancers of Unknown Primary. In: Pieters R, Liebmann J, eds. Cancer Concepts: A Guidebook for the Non-Oncologist. Worcester, MA: University of Massachusetts Medical School; 2015.

14. Chorost MI, Lee MC, Yeoh CB, et al. Unknown primary. J Surg Oncol 2004;87:191-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15334635.

15. Culine S. Prognostic factors in unknown primary cancer. Semin Oncol 2009;36:60-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179189.

16. Thomassen I, Verhoeven RH, van Gestel YR, et al. Population-based incidence, treatment and survival of patients with peritoneal metastases of unknown origin. Eur J Cancer 2014;50:50-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24011935.

17. Jereczek-Fossa BA, Jassem J, Orecchia R. Cervical lymph node metastases of squamous cell carcinoma from an unknown primary. Cancer Treat Rev 2004;30:153-164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15023433.

18. Hainsworth JD, Fizazi K. Treatment for patients with unknown primary cancer and favorable prognostic factors. Semin Oncol 2009;36:44-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179187.

19. Chen KW, Liu CJ, Lu HJ, et al. Evaluation of prognostic factors and the role of chemotherapy in unfavorable carcinoma of unknown primary site: a 10-year cohort study. BMC Res Notes 2012;5:70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22280526.

20. van de Wouw AJ, Jansen RLH, Speel EJM, Hillen HFP. The unknown biology of the unknown primary tumour: a literature review. Ann Oncol 2003;14:191-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12562643.

21. Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). Crit Rev Oncol Hematol 2005;54:243-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15890271.

22. Kamposioras K, Pentheroudakis G, Pavlidis N. Exploring the biology of cancer of unknown primary: breakthroughs and drawbacks. Eur J Clin Invest 2013;43:491-500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23480555.

23. Varadhachary GR. Carcinoma of unknown primary origin. Gastrointest Cancer Res 2007;1:229-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19262901.

24. Stelow EB, French CA. Carcinomas of the upper aerodigestive tract with rearrangement of the nuclear protein of the testis (NUT) gene (NUT midline carcinomas). Adv Anat Pathol 2009;16:92-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19550370.

25. French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 2004;22:4135-4139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15483023.

26. Dabbs DJ. Diagnostic Immunohistochemistry (ed 3). Philadelphia: Saunders Elsevier; 2010.

27. Oien KA. Pathologic evaluation of unknown primary cancer. Semin Oncol 2009;36:8-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179185.

28. Varadhachary GR, Greco FA. Overview of patient management and future directions in unknown primary carcinoma. Semin Oncol 2009;36:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179191.

29. Wick MR. Immunohistochemical approaches to the diagnosis of undifferentiated malignant tumors. Ann Diagn Pathol 2008;12:72-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18164421.

30. Bender RA, Erlander MG. Molecular classification of unknown primary cancer. Semin Oncol 2009;36:38-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179186.

31. Monzon FA, Koen TJ. Diagnosis of metastatic neoplasms: molecular approaches for identification of tissue of origin. Arch Pathol Lab Med 2010;134:216-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20121609.

32. Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med 2014;371:757-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25140961.

33. Kandalaft PL, Gown AM. Practical applications in immunohistochemistry: carcinomas of unknown primary site. Arch Pathol Lab Med 2016;140:508-523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26457625.

34. Handorf CR, Kulkarni A, Grenert JP, et al. A multicenter study directly comparing the diagnostic accuracy of gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. Am J Surg Pathol 2013;37:1067-1075. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23648464.

35. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29466156.

36. Conner JR, Hornick JL. Metastatic carcinoma of unknown primary: diagnostic approach using immunohistochemistry. Adv Anat Pathol

2015;22:149-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25844674.

37. Hainsworth JD, Greco FA. Gene expression profiling in patients with carcinoma of unknown primary site: from translational research to standard of care. Virchows Arch 2014;464:393-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24487792.

38. Monzon FA, Dumur CI. Diagnosis of uncertain primary tumors with the Pathwork tissue-of-origin test. Expert Rev Mol Diagn 2010;10:17-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20014919.

39. Monzon FA, Lyons-Weiler M, Buturovic LJ, et al. Multicenter validation of a 1,550-gene expression profile for identification of tumor tissue of origin. J Clin Oncol 2009;27:2503-2508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19332734.

40. Pillai R, Deeter R, Rigl CT, et al. Validation and reproducibility of a microarray-based gene expression test for tumor identification in formalin-fixed, paraffin-embedded specimens. J Mol Diagn 2011;13:48-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21227394.

41. Tothill RW, Shi F, Paiman L, et al. Development and validation of a gene expression tumour classifier for cancer of unknown primary. Pathology 2015;47:7-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25485653.

42. Meiri E, Mueller WC, Rosenwald S, et al. A second-generation microRNA-based assay for diagnosing tumor tissue origin. Oncologist 2012;17:801-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22618571.

43. Talantov D, Baden J, Jatkoe T, et al. A quantitative reverse transcriptase-polymerase chain reaction assay to identify metastatic carcinoma tissue of origin. J Mol Diagn 2006;8:320-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16825504.

44. Ma X-J, Patel R, Wang X, et al. Molecular classification of human cancers using a 92-gene real-time quantitative polymerase chain reaction assay. Arch Pathol Lab Med 2006;130:465-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16594740.

45. Rosenfeld N, Aharonov R, Meiri E, et al. MicroRNAs accurately identify cancer tissue origin. Nat Biotechnol 2008;26:462-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18362881.

46. Rosenwald S, Gilad S, Benjamin S, et al. Validation of a microRNA-based qRT-PCR test for accurate identification of tumor tissue origin. Mod Pathol 2010;23:814-823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20348879.

47. Varadhachary GR, Spector Y, Abbruzzese JL, et al. Prospective gene signature study using microRNA to identify the tissue of origin in patients with carcinoma of unknown primary (CUP). Clin Cancer Res 2011;17:4063-4070. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21531815.

48. Weiss LM, Chu P, Schroeder BE, et al. Blinded comparator study of immunohistochemical analysis versus a 92-gene cancer classifier in the diagnosis of the primary site in metastatic tumors. J Mol Diagn 2013;15:263-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23287002.

49. Economopoulou P, Mountzios G, Pavlidis N, Pentheroudakis G. Cancer of unknown primary origin in the genomic era: elucidating the dark box of cancer. Cancer Treat Rev 2015;41:598-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26033502.

50. Tothill RW, Li J, Mileshkin L, et al. Massively-parallel sequencing assists the diagnosis and guided treatment of cancers of unknown primary. J Pathol 2013;231:413-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24037760.

51. Ross JS, Wang K, Gay L, et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. JAMA Oncol 2015;1:40-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26182302.

52. Gatalica Z, Millis SZ, Vranic S, et al. Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: analysis of 1806 cases. Oncotarget 2014;5:12440-12447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25415047.

53. Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. J Clin Oncol 2013;31:217-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23032625.

54. Hainsworth JD, Schnabel CA, Erlander MG, et al. A retrospective study of treatment outcomes in patients with carcinoma of unknown primary site and a colorectal cancer molecular profile. Clin Colorectal Cancer 2012;11:112-118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22000811.

55. Handorf CR. Gene expression analysis and immunohistochemistry in evaluation of cancer of unknown primary: time for a patient-centered approach. J Natl Compr Canc Netw 2011;9:1415-1420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22157559.

56. Kim KW, Krajewski KM, Jagannathan JP, et al. Cancer of unknown primary sites: what radiologists need to know and what oncologists want to know. AJR Am J Roentgenol 2013;200:484-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23436835.

57. Chen K, Chen X. Positron emission tomography imaging of cancer biology: current status and future prospects. Semin Oncol 2011;38:70-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21362517.

58. Demir H, Berk F, Raderer M, et al. The role of nuclear medicine in the diagnosis of cancer of unknown origin. Q J Nucl Med Mol Imaging 2004;48:164-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15243411.

59. Delgado-Bolton RC, Fernandez-Perez C, Gonzalez-Mate A, Carreras JL. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. J Nucl Med 2003;44:1301-1314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902422.

60. Seve P, Billotey C, Broussolle C, et al. The role of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site. Cancer 2007;109:292-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17167760.

61. Zhu L, Wang N. 18F-fluorodeoxyglucose positron emission tomography-computed tomography as a diagnostic tool in patients with cervical nodal metastases of unknown primary site: a meta-analysis. Surg Oncol 2013;22:190-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23849685.

62. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw 2009;7 Suppl 2:1-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19555588.

63. Townsend DW, Carney JPJ, Yap JT, Hall NC. PET/CT today and tomorrow. J Nucl Med 2004;45 Suppl 1:14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14736831.

64. Breuer N, Behrendt FF, Heinzel A, et al. Prognostic relevance of 18F-FDG PET/CT in carcinoma of unknown primary. Clin Nucl Med 2013;39:131-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24368527.

65. Gutzeit A, Antoch G, Kuhl H, et al. Unknown primary tumors: detection with dual-modality PET/CT--initial experience. Radiology 2005;234:227-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15564390.

66. Hu M, Zhao W, Zhang PL, et al. Clinical applications of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of unknown primary. Chin Med J (Engl) 2011;124:1010-1014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21542959.

67. Imperiale A, Rust E, Gabriel S, et al. 18F-Fluorodihydroxyphenylalanine PET/CT in patients with neuroendocrine tumors of unknown origin: relation to tumor origin and differentiation. J

Nucl Med 2013;55:367-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24343986.

68. Nanni C, Rubello D, Castellucci P, et al. Role of 18F-FDG PET-CT imaging for the detection of an unknown primary tumour: preliminary results in 21 patients. Eur J Nucl Med Mol Imaging 2005;32:589-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15726356.

69. Pelosi E, Pennone M, Deandreis D, et al. Role of whole body positron emission tomography/computed tomography scan with 18F-fluorodeoxyglucose in patients with biopsy proven tumor metastases from unknown primary site. Q J Nucl Med Mol Imaging 2006;50:15-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16557200.

70. Prowse SJ, Shaw R, Ganeshan D, et al. The added value of 18F-fluorodeoxyglucose positron emission tomography computed tomography in patients with neck lymph node metastases from an unknown primary malignancy. J Laryngol Otol 2013;127:780-787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23919968.

71. Tamam MO, Mulazimoglu M, Guveli TK, et al. Prediction of survival and evaluation of diagnostic accuracy whole body 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography in the detection carcinoma of unknown primary origin. Eur Rev Med Pharmacol Sci 2012;16:2120-2130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23280029.

72. Wang G, Wu Y, Zhang W, et al. Clinical value of whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with carcinoma of unknown primary. J Med Imaging Radiat Oncol 2013;57:65-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23374557.

73. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. Eur Radiol 2009;19:731-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18925401.

74. Lee JR, Kim JS, Roh JL, et al. Detection of occult primary tumors in patients with cervical metastases of unknown primary tumors: comparison of (18)F FDG PET/CT with contrast-enhanced CT or CT/MR imaging-prospective study. Radiology 2015;274:764-771. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25405771.

75. Wolpert F, Weller M, Berghoff AS, et al. Diagnostic value of (18)F-fluordesoxyglucose positron emission tomography for patients with brain metastasis from unknown primary site. Eur J Cancer 2018;96:64-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29677642.

76. Ambrosini V, Nanni C, Rubello D, et al. 18F-FDG PET/CT in the assessment of carcinoma of unknown primary origin. Radiol Med 2006;111:1146-1155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17171520.

77. Ruhlmann V, Ruhlmann M, Bellendorf A, et al. Hybrid imaging for detection of carcinoma of unknown primary: a preliminary comparison trial of whole-body PET/MRI versus PET/CT. Eur J Radiol 2016;85:1941-1947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27776644.

78. Sekine T, Barbosa FG, Sah BR, et al. PET/MR outperforms PET/CT in suspected occult tumors. Clin Nucl Med 2017;42:88-95. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27922861.

79. Godeny M, Lengyel Z, Polony G, et al. Impact of 3T multiparametric MRI and FDG-PET-CT in the evaluation of occult primary cancer with cervical node metastasis. Cancer Imaging 2016;16:38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27814768.

80. Yoo MG, Kim J, Bae S, et al. Detection of clinically occult primary tumours in patients with cervical metastases of unknown primary tumours: comparison of three-dimensional THRIVE MRI, two-dimensional spin-echo MRI, and contrast-enhanced CT. Clin Radiol 2018;73:410 e419-410 e415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29195660.

81. Bleicher RJ, Morrow M. MRI and breast cancer: role in detection, diagnosis, and staging. Oncology (Williston Park) 2007;21:1521-1528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18077995.

82. McMahon K, Medoro L, Kennedy D. Breast magnetic resonance imaging: an essential role in malignant axillary lymphadenopathy of unknown origin. Australas Radiol 2005;49:382-389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16174176.

83. Olson JA, Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol 2000;7:411-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10894136.

84. Buchanan CL, Morris EA, Dorn PL, et al. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol 2005;12:1045-1053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16244803.

85. Varadhachary GR, Abbruzzese JL, Lenzi R. Diagnostic strategies for unknown primary cancer. Cancer 2004;100:1776-1785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15112256.

86. Swaid F, Downs D, Rosemurgy AS. A practical approach to liver metastasis from unknown primary cancer: what surgeons need to know. Cancer Genet 2016;209:559-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27601260.

87. Saliminejad M, Bemanian S, Ho A, et al. The yield and cost of colonoscopy in patients with metastatic cancer of unknown primary. Aliment Pharmacol Ther 2013;38:628-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23869398.

88. Hyphantis T, Papadimitriou I, Petrakis D, et al. Psychiatric manifestations, personality traits and health-related quality of life in cancer of unknown primary site. Psychooncology 2013;22:2009-2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23359412.

89. Guarischi A, Keane TJ, Elhakim T. Metastatic inguinal nodes from an unknown primary neoplasm. A review of 56 cases. Cancer 1987;59:572-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3791166.

90. Amela EY, Lauridant-Philippin G, Cousin S, et al. Management of "unfavourable" carcinoma of unknown primary site: synthesis of recent literature. Crit Rev Oncol Hematol 2012;84:213-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22503530.

91. Pentheroudakis G, Stoyianni A, Pavlidis N. Cancer of unknown primary patients with midline nodal distribution: midway between poor and favourable prognosis? Cancer Treat Rev 2011;37:120-126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20673701.

92. Lee J, Hahn S, Kim DW, et al. Evaluation of survival benefits by platinums and taxanes for an unfavourable subset of carcinoma of unknown primary: a systematic review and meta-analysis. Br J Cancer 2013;108:39-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23175147.

93. Hainsworth JD, Johnson DH, Greco FA. Cisplatin-based combination chemotherapy in the treatment of poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary site: results of a 12-year experience. J Clin Oncol 1992;10:912-922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1375284.

94. van der Gaast A, Verweij J, Henzen-Logmans SC, et al. Carcinoma of unknown primary: identification of a treatable subset? Ann Oncol 1990;1:119-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1706613.

95. Greco FA, Gray J, Burris HA, et al. Taxane-based chemotherapy for patients with carcinoma of unknown primary site. Cancer J 2001;7:203-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11419028.

96. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10963638.

97. Greco FA, Burris HA, Erland JB, et al. Carcinoma of unknown primary site. Cancer 2000;89:2655-2660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11135228.

98. Greco FA, Rodriguez GI, Shaffer DW, et al. Carcinoma of unknown primary site: sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan: a Minnie Pearl Cancer Research Network phase II trial. Oncologist 2004;9:644-652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15561808.

99. Hainsworth JD, Spigel DR, Clark BL, et al. Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. Cancer J 2010;16:70-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20164695.

100. Huebner G, Link H, Kohne CH, et al. Paclitaxel and carboplatin vs gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: a randomised prospective phase II trial. Br J Cancer 2009;100:44-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19066607.

101. Greco FA, Erland JB, Morrissey LH, et al. Carcinoma of unknown primary site: phase II trials with docetaxel plus cisplatin or carboplatin. Ann Oncol 2000;11:211-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10761758.

102. Pentheroudakis G, Briasoulis E, Kalofonos HP, et al. Docetaxel and carboplatin combination chemotherapy as outpatient palliative therapy in carcinoma of unknown primary: a multicentre Hellenic Cooperative Oncology Group phase II study. Acta Oncol 2008;47:1148-1155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18607872.

103. Culine S, Lortholary A, Voigt J-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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12972523.

104. Gross-Goupil M, Fourcade A, Blot E, et al. Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: results of the randomised GEFCAPI 02 trial. Eur J Cancer 2012;48:721-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22317952.

105. 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;100:1257-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15022294.

106. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17947725.

107. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014;32:3520-3526. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25287828.

108. Sebbagh S, Roux J, Dreyer C, et al. Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers. Acta Oncol 2016;55:1168-1174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27333436.

109. Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. Cancer Chemother Pharmacol 2012;69:1641-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22576338.

110. Maugeri-Sacca M, Pizzuti L, Sergi D, et al. FOLFIRI as a second-line therapy in patients with docetaxel-pretreated gastric cancer: a historical cohort. J Exp Clin Cancer Res 2013;32:67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24330513.

111. Varadhachary GR, Raber MN, Matamoros A, Abbruzzese JL. Carcinoma of unknown primary with a colon-cancer profile-changing paradigm and emerging definitions. Lancet Oncol 2008;9:596-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18510991.

112. Varadhachary GR, Talantov D, Raber MN, et al. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. J Clin Oncol 2008;26:4442-4448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18802157.

113. Schuette K, Folprecht G, Kretzschmar A, et al. Phase II trial of capecitabine and oxaliplatin in patients with adeno- and undifferentiated carcinoma of unknown primary. Onkologie 2009;32:162-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19372710.

114. Hainsworth JD, Spigel DR, Burris HA, 3rd, et al. Oxaliplatin and capecitabine in the treatment of patients with recurrent or refractory carcinoma of unknown primary site: a phase 2 trial of the Sarah Cannon Oncology Research Consortium. Cancer 2010;116:2448-2454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20209610.

115. Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011;105:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21673685.

116. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012;13:1225-1233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23168362.

117. Ducreux M, Bennouna J, Hebbar M, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer 2011;128:682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20473862.

118. Rothenberg ML, Cox JV, Butts C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol 2008;19:1720-1726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18550577.

119. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18421053.

120. Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.

121. Demirci U, Coskun U, Karaca H, et al. Docetaxel and cisplatin in first line treatment of patients with unknown primary cancer: a multicenter study of the Anatolian Society of Medical Oncology. Asian Pac J Cancer Prev 2014;15:1581-1584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24641371.

122. Yonemori K, Ando M, Yunokawa M, et al. Irinotecan plus carboplatin for patients with carcinoma of unknown primary site. Br J Cancer 2009;100:50-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19088717.

123. Jeremic B, Zivic DJ, Matovic M, Marinkovic J. Cisplatin and 5-fluorouracil as induction chemotherapy followed by radiation therapy in metastatic squamous cell carcinoma of an unknown primary tumor localized to the neck. A phase II study. J Chemother 1993;5:262-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8229155.

124. Khansur T, Allred C, Little D, Anand V. Cisplatin and 5-fluorouracil for metastatic squamous cell carcinoma from unknown primary. Cancer Invest 1995;13:263-266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7743377.

125. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005;23:5883-5891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16087941.

126. Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol 2003;26:37-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12576922.

127. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17079694.

128. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11784875.

129. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22646630.

130. van Meerten E, Muller K, Tilanus HW, et al. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. Br J Cancer 2006;94:1389-1394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16670722.

131. Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2000;18:122-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10623702.

132. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-3551. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506025.

133. Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113:2471-2477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18823036.

134. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068-3077. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11001674.

135. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18349393.

136. Conroy T, Yataghene Y, Etienne PL, et al. Phase II randomised trial of chemoradiotherapy with FOLFOX4 or cisplatin plus fluorouracil in oesophageal cancer. Br J Cancer 2010;103:1349-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20940718.

137. 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;101:498-506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19318632.

138. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-1715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17960013.

139. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17075117.

140. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-1704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17960012.

141. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10653877.

142. Garden AS, Harris J, Vokes EE, et al. Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol 2004;22:2856-2864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15254053.

143. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an Intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:3562-3567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15908667.

144. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000;6:316-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11079171.

145. Park YH, Ryoo BY, Choi SJ, et al. A phase II study of paclitaxel plus cisplatin chemotherapy in an unfavourable group of patients with cancer of unknown primary site. Jpn J Clin Oncol 2004;34:681-685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613558.

146. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837811.

147. Samlowski WE, Moon J, Kuebler JP, et al. Evaluation of the combination of docetaxel/carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group Phase II study. Cancer Invest 2007;25:182-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17530488.

148. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005;23:5660-5667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110025.

149. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010;66:31-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19763571.

150. Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007;25:3217-3223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664469.

151. Mukai H, Katsumata N, Ando M, Watanabe T. Safety and efficacy of a combination of docetaxel and cisplatin in patients with unknown primary cancer. Am J Clin Oncol 2010;33:32-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786850.

152. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer

(ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20728210.

153. Faivre C, Rougier P, Ducreux M, et al. 5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer 1999;86:861-865. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10572237.

154. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009;20:666-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19153121.

155. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009;20:1667-1673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19549707.

156. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-1127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18784101.

157. Kusaba H, Shibata Y, Arita S, et al. Infusional 5-fluorouracil and cisplatin as first-line chemotherapy in patients with carcinoma of unknown primary site. Med Oncol 2007;24:259-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17848753.

158. Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. Semin Oncol 2009;36:52-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179188.

159. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol 2006;24:3548-3554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16877720.

160. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 2007;97:162-169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17579629.

161. Fjällskog M-LH, Granberg DPK, Welin SLV, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. Cancer 2001;92:1101-1107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11571721.

162. Ekeblad S, Sundin A, Janson ET, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res 2007;13:2986-2991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17505000.

163. Kulke MH, Stuart K, Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 2006;24:401-406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421420.

164. Janssen S, Glanzmann C, Huber G, Studer G. Individualized IMRT treatment approach for cervical lymph node metastases of unknown primary. Strahlenther Onkol 2014;190:386-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24638240.

165. Kamal M, Mohamed ASR, Fuller CD, et al. Outcomes of patients diagnosed with carcinoma metastatic to the neck from an unknown primary source and treated with intensity-modulated radiation therapy. Cancer 2018;124:1415-1427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29338089.

166. Mourad WF, Hu KS, Shasha D, et al. Initial experience with oropharynx-targeted radiation therapy for metastatic squamous cell carcinoma of unknown primary of the head and neck. Anticancer Res

2014;34:243-248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24403470.