Cancer Of Unknown Primary

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

Note: Consider Clinical Trials as treatment options for eligible patients.

EVALUATION

- History and physical including pelvic and/or rectal exam
- Hemoccult test
- CBC, LFTs, comprehensive metabolic profile, prostate specific antigen (PSA), other directed serum tumor markers
- CT chest, abdomen and pelvis
- Mammogram
- Endoscopy when indicated
- MRI brain
- Bone scan if symptomatic
- PET/CT (optional)
- Lifestyle risk assessment

Fine needle aspiration (FNA) or core biopsy (preferred) of most accessible lesion if not already performed, or if insufficient tissue is available for diagnosis and/or predictive/prognostic markers and/or molecular analysis

FINDINGS

- Metastatic cervical adenopathy
- Squamous cell carcinoma (5%)
- Metastatic inguinal adenopathy
- Disseminated, visceral metastases
- Undifferentiated carcinoma, neuroendocrine tumor/carcinoma, undifferentiated neoplasm (30% all included), see Page 2
- Adenocarcinoma, poorly differentiated carcinoma (65%), see Page 3

FURTHER WORK-UP

- Ultrasound
- FNA or core needle biopsy (preferred)
- CT head and neck
- Consider PET/CT
- Perineal exam, anoscopy if needed
- Pelvic examination in a woman
- PET/CT optional
- Cystoscopy/urologic evaluation if indicated
- Directed invasive tests as needed

TREATMENT

- Head and neck surgery: Tripe endoscopy
- Consider tonsillectomy
- Chemotherapy if good performance status
- If localized, lymph node dissection or local radiation therapy (or both in selected cases)
- Neoadjuvant chemotherapy in selected cases
- Chemotherapy if good performance status
- Radiation therapy as indicated

Refer to Head and Neck Service for further treatment recommendations

1 See MD Anderson approved biomarkers (click here)
2 See Physical Activity, Nutrition, and Tobacco Cessation Algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
3 The biopsied lesion may be the primary site
4 If suspecting head and neck, cervical, or anal malignancy, consider testing for HPV in situ hybridization
Cancer Of Unknown Primary

TREATMENT

For neuroendocrine carcinoma:
- Octreotide scan
- Bone scan and
- Neuroendocrine markers as indicated

Optreotide when indicated
- Systemic therapy
- Radiation therapy
- Surgery when indicated

Refer to Neuroendocrine Service when indicated

Low grade/intermediate

High grade

Chemotherapy with etoposide/cisplatin or irinotecan/cisplatin

Undifferentiated carcinoma, neuroendocrine tumor/carcinoma, undifferentiated neoplasm (30% all included)

Undifferentiated carcinoma, undifferentiated neoplasm

Serum and immunohistochemical markers to exclude extragonadal germ cell
- Chemotherapy in good performance status patients
- Surgery and radiation therapy if indicated

Note: Consider Clinical Trials as treatment options for eligible patients.
**FINDINGS**

- Adenocarcinoma, poorly differentiated carcinoma (65%)

**FURTHER WORK-UP**

- Immunohistochemical markers to help suggest most “likely” primary site (see Table 1)
- Estrogen receptor/progesterone receptor in women
- Alpha fetoprotein (αFP) and beta-human chorionic (βHCG) gonadotropin for poorly differentiated carcinoma to rule out germ cell (see Table 1, Figure 1)

**ADDITIONAL FINDINGS**

- Disseminated cancer, two or more sites involved
  - Women with peritoneal carcinoma (typically, serous papillary pathology) in the presence of normal ovaries: check cancer antigen-125
- Solitary site of metastasis
- Isolated axillary nodes in women
  - MRI breast if mammogram and ultrasound are negative

**TREATMENT**

- Chemotherapy if good performance status
  - If suggestive of primary peritoneal cancer, See Ovarian Cancer Algorithm. Palliative measures, as needed, for small bowel obstruction.
  - MRI negative: no surgery, consider radiation
  - Chemotherapy for breast cancer
  - MRI positive: breast surgery or radiation therapy and chemotherapy

---

1. Further work-up:
   - Gene expression profiling to identify the putative primary cancer profile (tissue of origin) is an emerging diagnostic test; currently experimental and studies are ongoing
   - Appropriate mutation analysis studies where indicated

2. See MD Anderson approved biomarkers (click here)
**TABLE 1:** Commonly utilized immunoperoxidase stains to assist in the differential diagnosis of poorly differentiated neoplasms

<table>
<thead>
<tr>
<th>Likely primary site</th>
<th>Stain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Estrogen receptor (ER), gross cystic disease fluid fibrous protein-15 (GCDFP-15), mammaglobin, HER-2 neu, GATA-3</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>Thyroid transcription factor (TTF-1), surfactant protein A, napsin A</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>PSA, prostatic acid phosphatase (PAP), alpha-methylacyl CoA racemase/P504S (AMACR/P504S) protein</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Leukocyte common antigen (LCA), CD3, CD4, CD5, CD10, CD20, CD45, PAX5, Bcl-2, Bcl-6, cyclin D1</td>
</tr>
<tr>
<td>Mullerian/Ovarian</td>
<td>Estrogen receptor (ER), WT-1, PAX8</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Desmin(^1), factor VIII(^2), CD31, smooth muscle actin for leiomyosarcoma, MyoD1, myogenin for rhabdomyosarcoma</td>
</tr>
<tr>
<td>Neuroendocrine Tumor</td>
<td>Chromogranin, synaptophysin, CD56</td>
</tr>
<tr>
<td>Germ Cell Tumor</td>
<td>βHCG, αFP, OCT3/4, CKIT, SALL4, CD30 (embryonal)</td>
</tr>
<tr>
<td>Urothelial Malignancies</td>
<td>CK7, CK20, thrombomodulin, GATA-3</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>CK7, CK20, CDX-2, carcinoembryonic antigen (CEA), SATB2</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal cell carcinoma (RCC), CD10, PAX8</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>HepPar-1, CD10, glypican-3, arginase-1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>S100, HMB-45, tyrosinase and melan-A, SOX10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroglobulin, thyroid transcription factor (TTF-1), PAX8</td>
</tr>
</tbody>
</table>

\(^1\) Positive in desmoid tumors, rhabdomyosarcomas, and leiomyosarcomas  
\(^2\) Positive in angiosarcomas
Approach to cytokeratin (CK7 and CK20) markers used in cancer of unknown primary

**FIGURE 1**

CK7 and CK20

- **CK7 positive, CK20 positive**
  - Urothelial tumors
  - Ovarian mucinous adenocarcinoma
  - Pancreatic adenocarcinoma
  - Cholangiocarcinoma
  - Gastric carcinoma

- **CK7 positive, CK20 negative**
  - Lung adenocarcinoma
  - Breast carcinoma
  - Thyroid carcinoma
  - Endometrial carcinoma
  - Cervical carcinoma
  - Salivary gland carcinoma
  - Cholangiocarcinoma
  - Pancreatic carcinoma
  - Gastric carcinoma
  - Esophageal carcinoma

- **CK7 negative, CK20 positive**
  - Colorectal carcinoma
  - Merkel cell carcinoma
  - (dot-like pattern)

- **CK7 negative, CK20 negative**
  - Hepatocellular carcinoma
  - Renal cell carcinoma
  - Prostate carcinoma
  - Squamous cell and small cell lung carcinoma
  - Head and neck carcinoma
Cancer Of Unknown Primary

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

SUGGESTED READINGS


Continued on next page

Copyright 2018 The University of Texas MD Anderson Cancer Center

Department of Clinical Effectiveness V6
Approved by Executive Committee of the Medical Staff 01/30/2018
SUGGESTED READINGS - continued


DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Gastrointestinal Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Beth Chasen, MD (Nuclear Medicine)
Wendy Garcia, BS
Firoze Jameel, MSN, RN, OCN
Aurelio Matamoros, MD (Diagnostic Radiology-Body Imaging)
Kanwal Raghav, MD (GI Medical Oncology)
Asif Rashid, MD (Pathology, Anatomical)
Melissa Taggart, MD (Pathology, Anatomical)
Gauri Varadhachary, MD (GI Medical Oncology)†

†Core Development Team

* Clinical Effectiveness Development Team

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.