Primary Unknown

Practice Guideline

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This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Primary Unknown
Practice Guideline

Background
• Primary Unknown (PUK) or Occult Primary malignancies are fairly common
• Extensive investigations to find the primary tumour do not often translate into significant changes in treatment outcome 1, 2
• The unknown nature of the tumour origin can cause distress for the patient
• Aim of treatment approach is to carefully assess for primary tumours that would have a specific treatment, and otherwise treat either with a broad-spectrum regimen or one tailored to the most likely origins (clinical picture, keeping in mind that patterns of metastatic spread are not always reliable).

Investigations
• Initial assessment should result in classification into one of five histological categories, some of which have typical clinical scenarios suggestive of a primary (see algorithm)
• Prognostic factors (median survival for metastatic disease is 6 – 9 months): For review see reference 3. Supportive care alone is an option to be considered for poor-performance status patients.
  • Good:
    - poorly differentiated carcinoma with midline distribution;
    - women with papillary adenocarcinoma of peritoneal cavity;
    - women with adenocarcinoma involving only axillary lymph nodes;
    - squamous cell carcinoma involving cervical lymph nodes;
    - isolated inguinal adenopathy (squamous carcinoma);
    - good PS
  • Adverse:
    - adenocarcinoma metastatic to the liver or other organs;
    - non-papillary malignant ascites (adenocarcinoma);
    - multiple cerebral metastases (adeno- or squamous carcinoma);
    - multiple lung/pleural metastases (adenocarcinoma);
    - multiple metastatic bone disease (adenocarcinoma).
    - Poor performance status
    - Male gender
    - High LDH
Initial Diagnostic Work-up and Classification

Suspected Metastatic Malignancy

- Complete H&P, including pelvic and rectal exam, with attention to and review of:
  - Past biopsies or malignancies
  - Removed lesions
  - Spontaneously regressing lesions
  - Existing imaging studies
- CBC
- Electrolytes
- Liver function tests
- Creatinine
- Calcium
- Urinalysis
- Chest x-ray
- Hemoccult
- LDH
- Consider CEA / CA-125 / CA19-9 / CA15-3 as baseline for monitoring therapy; not specific/sensitive for diagnosis

Biopsy:
- FNA (core needle biopsy optional)
- Most accessible site
- Consult pathologist for adequacy of specimen and additional studies including immunohistochemical stains

Adenocarcinoma (70%)
- During tissue Dx workup especially consider pancreas, biliary tract, lung, prostate (PSA), breast, colorectal as primaries

Squamous cell carcinoma
- (uncommon except for isolated neck mass)

Neuroendocrine malignancy
- (rare)

Poorly differentiated carcinoma (15-20%)

Poorly differentiated neoplasm (<5%)
# Specific Clinical Diagnostic Workup and Therapy by Type of Malignancy

**If single focus, in all cases also consider empiric resection ± radiation**

<table>
<thead>
<tr>
<th>Tissue Diagnosis</th>
<th>Additional Workup</th>
<th>Clinical Scenarios if Still No Primary Found</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroendocrine malignancy (rare)</strong></td>
<td>• Octreotide scan. ?MIBG scan. Serum Chromogranin, urinary 5HIAA. Ki67/MIB-1 index on tissue</td>
<td><strong>Aggressive tumour</strong> or Ki67 index &gt; 5-10%: etoposide/platinum. <strong>Idolent</strong>: Debulking/local treatment; octreotide, radioisotope therapy, interferon.</td>
</tr>
</tbody>
</table>
| **Squamous Cell Carcinoma** | • Site-directed examination and imaging;  
  • Head & Neck: triple endoscopy, CT chest H&N (can omit bronchoscopy if CT chest neg). Some advocate empiric ipsilateral diagnostic tonsillectomy. ?PET  
  • Supraclavicular or axillary area: CT chest and upper abdomen, symptom-directed endoscopy  
  • Mediastinal LN: CT chest, ?mediastinoscopy, bronchoscopy  
  • Inguinal area: examine GU system carefully. CT abd/pelvis | **If in lymph nodes**: dissection with rads if possible, otherwise chemorads. Chemotherapy should include platinum ± 5FU. Mediastinal, pulmonary: treat as NSCLC. |
| **Adenocarcinoma (70%)** | • Treat according to most likely site based on IHC, and limited search for primary based on location of malignancy:  
  • CT chest, abdomen, pelvis  
  • Consider mammogram  
  • Consider endoscopy and/or colonoscopy especially if liver, lung metastases, anemia  
  • Consider urine cytology and cystoscopy  
  • β HCG, AFP | **Women with peritoneal carcinomatosis**: treat as epithelial ovarian cancer  
**Women with axillary LN**: treat as stage II-IV breast cancer, including mastectomy or rads unless stage IV  
**Men with bony metastases**: consider treating as prostate cancer; assess type of lesions (sclerotic, etc.) and consider other bone-seeking tumours (thyroid, renal, lung)  
**Mediastinal mass or other midline pattern (thymoma, lymphoma, thyroid cancer excluded)**: treat as poor risk germ cell (esp. younger patients) or NSCLC (esp. smokers, older patients)  
**Single skin focus**: exclude eccrine cancer, treat with excision/radiation. Consider platinum-based adjuvant chemotherapy if poorly differentiated  
**Liver lesions only**: consider resection or ablation; treatment as upper GI/pancreatic, colorectal, lung or breast cancer depending on Hx and risk factors and prior workup  
Other, or no clear scenario: see page 6 ‘Treatment’. |
| **Poorly differentiated carcinoma (15-20%)** | As above, plus:  
  • Consider (esp. if midline/retroperitoneal distribution) chromosome analysis if available (i12p for germ cell tumours, t11;22 for neuroepithelioma, Ewing’s) and testicular/pelvic ultrasound | Other, or no clear scenario: see page 6 ‘Treatment’. |
| **Poorly differentiated neoplasm (<5%)** | As above, plus:  
  • IHC: LCA/CD45 positive likely lymphoma-like (~34-65%). Negative: melanoma, sarcoma –like (~15%), germ cell origin (~30%) | **Hematological origin likely**: treat as high-grade lymphoma. Otherwise: consider melanoma, sarcoma, poor risk germ cell. Therapy based on tissue/clinical workup. If unlikely any of these: see page 7 ‘Treatment’. |
Treatment

Broad-spectrum chemotherapy if unable to determine likely primary or clinical scenario

• Etoposide/Platinum (especially if germ cell origin possible)
  • Cisplatin 25mg/m² + Etoposide 100mg/m² d1,2,3,q21d.
  • Carboplatin AUC2 + Etoposide 100mg/m² d1,2,3,q21d.
• Epirubicin 60 mg/m² + Carboplatin AUC5 q21d, + 5FU 200mg/m² infusion (or Capecitabine 2000mg/m² daily x14/q21d)
• Epirubicin 60 mg/m² + Cisplatin 50 mg/m² q21d, + 5FU 200mg/m² infusion (or Capecitabine 2000mg/m² daily x14/q21d)
• Epirubicin/Oxaliplatin/5FU (or capecitabine) (especially if possibly GI source)
• Carboplatin/Paclitaxel + oral etoposide (“Nashville” regimen, Greco / Hainsworth)
• Irinotecan/Gemcitabine (not funded)
• Cisplatin/Irinotecan (not funded)
• Fluorouracil/Doxorubicin/Methotrexate (adenocarcinoma) – older regimen but non-platinum containing
References


Table 3
Toxicity by Worst WHO Grade per Patient (n = 32)

<table>
<thead>
<tr>
<th>Toxicity</th>
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<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>5</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Leukopenia</td>
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<td>0</td>
<td>5</td>
<td>2</td>
<td>1</td>
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<td>Thrombocytopenia</td>
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<td>2</td>
<td>0</td>
<td>1</td>
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<tr>
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<td>11</td>
<td>8</td>
<td>10</td>
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<tr>
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<td>9</td>
<td>3</td>
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<td>0</td>
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<tr>
<td>Nausea</td>
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<td>9</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Neurotoxicity</td>
<td>23</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Renal</td>
<td>29</td>
<td>3</td>
<td>0</td>
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<td>0</td>
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</tbody>
</table>

*aBlood counts measured at time of chemotherapy administration (not nadir counts). No cases of heart failure. No cases of clinical ototoxicity. One patient developed skin toxicity (generalized ichthyosis).

Fig. 1. Survival curve for all patients treated with ECF (standard or modified) between June 1994 and June 1998. Survival was measured from the time of chemotherapy commencement. A total of 36 patients were treated; 35 of whom have died. The median survival was 9 mos.
**Treatment 2nd Line**

Limited evidence of benefits, ongoing studies e.g.:

- Gemcitabine in the second-line therapy of patients with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. Hainsworth JD; Burris HA 3rd; Calvert SW; Willcutt NT; Scullin DC Jr; Bramham J; Greco FA *Cancer Invest* 2001;19(4):335-9.

- 90% received platinum/taxane as 1st line
- 8% PR, 25% SD, TTP 5mos, well tolerated
References

1. NCCN Practice Guidelines in Oncology – v.1.2005 – occult primary
2. UpToDate reviews on Cancer of Unknown Primary (CUP), J. Hainsworth and F. Greco, accessed Nov 28 2006
4. Some guidelines suggest breast MRI (NCCN)
Authors, Contact Information

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