Cancer of Unknown Primary
Clinical Case Discussion

A/Prof Linda Mileshkin
Department of Medical Oncology
Peter MacCallum Cancer Centre
Melbourne, Australia
Disclosures

No conflicts of interest to disclose
Cancer of Unknown Primary

Metastatic cancer for which the primary site of origin remains unknown despite extensive pathological and clinical investigation.

Represent 3-5% of all new cancer diagnoses
One of the 10 most frequent cancer diagnosis world-wide (Pavlidis et al 2003)

Sources of unknown primary tumours:

Lung; 31%
Liver/Bile Duct; 9%
Genital system; 8%

CUP subsets

- Well or moderately differentiated adenocarcinomas (50%)
- Undifferentiated or poorly differentiated adenocarcinomas or carcinomas (30%)
- Squamous cell carcinomas (15%)
- Undifferentiated neoplasm (5%)

- Good prognosis or favourable subsets within these groups
  - Relies on a good quality biopsy and careful histopathological assessment
Basic IHC work-up

Primary markers

- **CK7-/CK20+**
  - Colorectal and Merkel cell carcinoma

- **CK7+/CK20-**
  - Lung, breast, thyroid, endometrial, cervical, ovarian

- **CK7+/CK20+**
  - Urothelial, pancreatic and cholangiocarcinoma

- **CK7-/CK20-**
  - Hepatocellular, renal cell, prostate, squamous cell

Additional markers

- CEA and CDX-2
- TTF-1, ER, PR, GCDFP-15, PAX8
- Urothelin, CK19
- Hep Par-1 and PSA
## ESMO Diagnosis and staging guidelines

<table>
<thead>
<tr>
<th>Assessment suggested</th>
<th>Target patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorough History and Examination</td>
<td>ALL</td>
</tr>
<tr>
<td>Basic blood and biochemistry analysis</td>
<td>ALL</td>
</tr>
<tr>
<td>CT Chest/Abdomen/Pelvis</td>
<td>ALL</td>
</tr>
<tr>
<td>Mammogram</td>
<td>ALL FEMALES</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>Females with axillary adenocarcinoma</td>
</tr>
<tr>
<td>αFP AND βHCG</td>
<td>Patients with midline metastatic disease</td>
</tr>
<tr>
<td>Serum PSA</td>
<td>Males with adenocarcinoma bone mets</td>
</tr>
<tr>
<td>CT/PET</td>
<td>H+N SCC or single CUP metastasis</td>
</tr>
<tr>
<td>Endoscopies</td>
<td>Sign/Symptom/Laboratory oriented</td>
</tr>
<tr>
<td>Octreoscan/Chromogranin A</td>
<td>Patients with Neuroendocrine CUP</td>
</tr>
<tr>
<td>Additional diagnostic tests</td>
<td>Sign/Symptom/Laboratory oriented</td>
</tr>
</tbody>
</table>
Role of PET/CT in CUP

- ESMO guidelines recommend use in squamous cell carcinoma in cervical nodes or single-site CUP
- “Limited role” in other cases so not mandatory

  However

- Literature suggests
  - Ability to detect a primary in about 1/3 cases (after CT)
  - Can find additional sites of disease
  - Can change management
  - (68)Ga-DOTATATE PET may change Rx in neuroendocrine CUP

- Disadvantages
  - Cost / Lack of reimbursement
  - False positives
Utility of FDG PET/CT in 121 patients seen in PeterMac CUP clinic

93 PET/CT scans were performed

54% of the scans were helpful in terms of identifying a primary site (n=31) or the best site to biopsy (n=19)

Changed management in 46% of patients

- Change in Rx intent
- Change in Rx given
- Confirmation of benign disease
- Targeted site for new biopsy

Tan L, Medical Oncology Group of Australia ASM 2105
### Table 3. Therapy for patients with favourable-risk cancers of unknown primary site (CUPs)

<table>
<thead>
<tr>
<th>CUP subtype</th>
<th>Proposed treatment</th>
<th>Potential equivalent tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated neuroendocrine carcinomas of an unknown primary</td>
<td>Platinum + etoposide combination chemotherapy</td>
<td>Poorly differentiated neuroendocrine carcinomas with a known primary</td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine tumour of unknown primary</td>
<td>Somatostatin analogues, streptozocin+5-FU, sunitinib, everolimus</td>
<td>Well-differentiated neuroendocrine tumour of a known primary site</td>
</tr>
<tr>
<td>Peritoneal adenocarcinomatosis of a serous papillary histological type in females</td>
<td>Optimal surgical debulking followed by platinum-taxane-based chemotherapy</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Isolated axillary nodal metastases in females</td>
<td>Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy</td>
<td>Breast cancer (found in 50%–70% when breast MRI is performed)</td>
</tr>
<tr>
<td>Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes</td>
<td>Neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation</td>
<td>Head and neck squamous cell cancer</td>
</tr>
<tr>
<td>CUP with a colorectal IHC (CK20+ CDX2+ CK7−) or molecular profile</td>
<td>Systemic treatment used for colorectal cancer</td>
<td>Metastatic colorectal cancer</td>
</tr>
<tr>
<td>Single metastatic deposit from unknown primary</td>
<td>Resection and/or RT ± systemic therapy</td>
<td>Single metastasis</td>
</tr>
<tr>
<td>Men with blastic bone metastases or IHC/serum PSA expression</td>
<td>Androgen deprivation therapy ± RT</td>
<td>Prostate cancer</td>
</tr>
</tbody>
</table>

5-FU, 5-fluouracil; MRI, magnetic resonance imaging; IHC, immunohistochemistry; PSA, prostate-specific antigen; RT, radiotherapy; CK, cytokeratin.
Our case

• An abdominal ultrasound followed by guided core-needle biopsy reveals multiple hypoechoic areas in both lobes, consistent with metastases.

• Tru-cut needle biopsy yields presence of poorly differentiated adenocarcinoma.
What we often get to work with

Biopsy report

Macroscopic description

“The specimen consists of one core of tissue measuring 6mm in length and less than 1mm in diameter”

Reported to show poorly differentiated adenocarcinoma

Immunohistochemically the population is positive with CK20, EMA and CDX2. The population is negative with CK7, PSA, TTF1, PAX8 and GATA3. This pattern suggests a large bowel or appendiceal primary, while not excluding pancreatic duct.
Immunohistochemistry: Expression Heterogeneity and Potential for Sampling Error

Biopsy Core 1

Biopsy Core 2

18g needle = 800 µm
Patient with a carcinoma of unknown primary (CUP)

Strong suspicion of a primary cancer with potential specific treatment eg IHC, molec test
- bone mets from prostate cancer
- breast, ovary, renal, colorectal, lung

Consider site-specific treatment

Ensure adequate exclusion of a non-CUP neoplasm:
- non-epithelial cancer
- extra-gonadal germ cell tumour

Recognize a specific subset of CUP
- Women with adenoCa in axillary node
- SCC in cervical node
- Neuroendocrine CUP
- CUP of a single location
- Poorly differentiated carcinoma of midline

Specific treatment

Non-specific subset of CUP

PS ≤ 1
Normal LDH
- Favorable prognosis:
  Median survival = 12 months
- Consider 2-drug chemotherapy

PS ≥ 2 and/or elevated LDH
- Poor prognosis:
  Median survival = 4 months
- Chemotherapy or best supportive care
Patients and clinicians prefer to make a site-specific diagnosis!

- On-line survey responses from 86 Australian medical oncologists
- 27% stated that they would prefer to provide a best guess of the primary site of the cancer rather than diagnose CUP as a specific diagnostic entity
- 83% of respondents stated that they would label CUP cases with a specific primary in an effort to obtain access to government funded drugs only available for certain cancer types

Karapetis et al, manuscript in preparation 2015
Molecular approaches to improving the clinical management of CUP

Detection of likely site of origin

Mutational profiling for actionable mutations
Site of origin gene-expression classification

Molecular Classification of Human Carcinomas by Use of Gene Expression Signatures

Andrew L. Su, John B. Welch, Lisa M. Sapinoso, Suzanne G. Kern, Peter Dimitroff, Hilmar Lapp, Peter G. Schultz, Steven M. Powell, Christopher A. Modrich, Henry F. Frierson, Jr., and Garrett M. Hampton

Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037 (A.F.S., B.G.S.); Genomics Institute of the Novartis Research Foundation, San Diego, California 92121 (P.B., L.M.S., S.G.K., P.G.S., P.G., H.P.H., H.F.F., G.M.H.); and Departments of Medicine (G.F.S.P.) and Pathology (L.M.S., H.P.H.), University of Virginia Health System, Charlottesville, Virginia 22908

Su et al 2001

Multiclass cancer diagnosis using tumor gene expression signatures


Ramaswamy et al 2001

An Expression-Based Site of Origin Diagnostic Method Designed for Clinical Application to Cancer of Unknown Origin

Richard W. Tothill*, Adam Kowalczyk,† Danny Rischin,‡ Alex Bousioutas,§ Izhak Haviv,¶ Ryan K. van Laar,∥ Paul M. Waring,‡ Adam Zalcberg,‡ Robyn Ward,‡ Andrew V. Biankin,‡ Robert L. Sutherland,§ Susan M. Henshall,§ Kwan Fong,§ Jonathan R. Pollack,* David D.L. Bowtell,‡ and Andrew J. Holloway‡

Tothill et al 2005

eg. CUPGuide from Healthscope pathology
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

John D. Hainworth, Mark S. Rubin, David R. Spigel, Ralph V. Boccia, Samuel Ruby, Raven Quinn, and F. Anthony Creco

**A**

- **Overall Survival (probability)**
  - **More responsive (n = 115)**: Median Survival (months) = 13.4
  - **Less responsive (n = 79)**: Median Survival (months) = 7.6

- **Time (months)**: 0, 6, 12, 18, 24, 30, 36, 42

- **Overall Survival (probability)**
  - **≥80% probability (n = 95)**
  - **<80% probability (n = 99)**

**B**

- **Overall Survival (probability)**
  - **Median Survival (months)**: 12.5
  - **Median Survival (months)**: 10.8

- **Time (months)**: 0, 6, 12, 18, 24, 30, 36, 42

**Flowchart**

- Patients enrolled (N = 289)
  - Insufficient tissue for assay (n = 37)
    - Off study
  - Successful assay (n = 252)
    - Candidate for treatment (n = 223)
      - Received empiric CUP therapy (n = 29)
      - Received site-specific therapy based on assay results (n = 194)
        - Received site-specific therapy for more responsive tumor types (n = 115)
        - Received site-specific therapy for less responsive tumor types (n = 79)
Comprehensive Genomic Profiling of Carcinoma of Unknown Primary Site
New Routes to Targeted Therapies

Jeffrey S. Ross, MD; Kai Wang, MD, PhD; Laurie Gay, PhD; Geoff A. Otto, PhD; Emily White, BS; Kiel Iwanik, BS; Gary Paliner, MD; Roman Yelensky, PhD; Doron M. Lipson, PhD; Julianne Chmielecki, PhD; Rachel L. Erlich, PhD; Andrew N. Rankin, PhD; Siraj M. Ali, MD, PhD; Julia A. Elvin, MD, PhD; Deborah Morosini, MD; Vincent A. Miller, MD; Philip J. Stephens, PhD

Original Investigation

Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: Analysis of 1806 cases

Zoran Gatalica1, Sherri Z. Millis1, Semir Vranic2, Ryan Bender1, Gargi D. Basu1, Andreas Voss1, Daniel D. Von Hoff3

1 Carls Life Sciences, Phoenix, United States of America
2 Department of Pathology, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina
3 Translational Genomic Research Institute and Virginia G Piper Cancer Center, Phoenix, United States of America
Clinical decision making:
Site of origin CUP test versus mutation profile – or both?

- Which result makes most sense clinically
- Likely efficacy of anatomically-based therapy
- Likely efficacy of targeted agent
- Practical availability of targeted agent for a given patient
- Ability to combine or sequence therapies

URGENT NEED FOR TRIALS TO DETERMINE IF IMPACTS ON PATIENT OUTCOMES!

LETTER

doi:10.1038/nature10868

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prabhakad*, Chong Sun*, Sidong Huang*, Federica Di Nicolantonio,† Ramon Salazar†, Davide Zecchin†, Roderick L. Beijersbergen†, Alberto Bardelli‡,§ & René Bernards†

Context matters!