CANCER OF UNKNOWN PRIMARY
A Complex Disease

NICHOLAS PAVLIDIS, MD, PhD, FRCP (Edin)

PROFESSOR OF MEDICAL ONCOLOGY

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WHAT IS CANCER OF UNKNOWN PRIMARY (CUP)?

- Is a clinical disorder where patients present with histologically confirmed metastatic cancer for which standard diagnostic investigations failed to identify the primary site.
- Median age is 65 years, more common in men.
- It accounts for 3-5% of all human cancers.
- It is considered to be the 7th-8th most frequent malignant tumor.
CLINICAL CHARACTERISTICS AT PRESENTATION

- Early dissemination
- Clinical absence of primary
- Aggressiveness
- Unpredictable metastatic pattern i.e. hidden pancreatic cancer has higher incidence of bone or lung metastases
THE BIOLOGY OF CUP
Hypothesis A

CUP does not undergo type 1 progression (from a premalignant lesion to malignant)

but

Follows a type 2 progression (malignant at the onset of the disease without forming a primary site)

Frost P et al, Cancer Bull 1989, 41, 139-141
Hypothesis B

CUP follows the **parallel progression model** where metastases can arise early in the development of a malignancy...

**In contrast to**

the **linear progression model** where stepwise progression of accumulating genetic and epigenetic alterations accompanying cancer development

**Hypothesis C**

- The **migration ability of stem cells** can explain the existence of CUP.

- Stem cells (deregulated, premalignant or cancerous) migrate away from their natural tissues and **generate tumors in other locations**.
Summary of Data on Biology of CUP

• No trace of a «CUP biologic signature», distinct from metastases of known primaries

• CUP is characterized by intense chromosomal instability (accounting for the uncommon clinical presentation, chemoresistance and poor outcome)

Activated pathways in CUP:

• Angiogenesis with concurrent hypoxia
• AKT/S6RP axis with deficient apoptosis
• b-Catenin/Wnt axis
• MET axis
• EMT activity
Cancer of Unknown Primary Site:

One or more Diseases?
<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Well to moderately differentiated</td>
<td>50 %</td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>35 %</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10 %</td>
</tr>
<tr>
<td>Undifferentiated neoplasms</td>
<td></td>
</tr>
<tr>
<td>Not specified carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td></td>
</tr>
<tr>
<td>Melanomas</td>
<td></td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
</tr>
<tr>
<td>Embryonal malignancies</td>
<td></td>
</tr>
</tbody>
</table>
# CLINICOPATHOLOGICAL ENTITIES OF CUP

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>AdenoCa M or P diff</td>
</tr>
<tr>
<td></td>
<td>(mainly) and/or other organs</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Mediastinal – Retroperitoneal</td>
<td>U or P diff Ca</td>
</tr>
<tr>
<td>(midline distribution)</td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>AdenoCa W to P diff</td>
</tr>
<tr>
<td>Cervical</td>
<td>SCC Ca</td>
</tr>
<tr>
<td>Inguinal</td>
<td>U Ca, SCC, mixed SCC / adenoCa</td>
</tr>
</tbody>
</table>

*W = well,  M = moderately,  P = poorly,  U = undifferentiated*
### Peritoneal cavity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal adenocarcinomatosis</td>
<td>Papillary or serous adenoCa</td>
</tr>
<tr>
<td>in females</td>
<td>(± psammoma bodies)</td>
</tr>
<tr>
<td>Malignant ascites of other</td>
<td>Mucin adenoCa M or P diff</td>
</tr>
<tr>
<td>unknown origin</td>
<td>(± signet ring cells)</td>
</tr>
</tbody>
</table>

### Lungs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary metastases</td>
<td>AdenoCa various diff</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>AdenoCa M or P diff</td>
</tr>
</tbody>
</table>

*W = well,   M = moderately,   P = poorly,   U = undifferentiated*
### Bones
(solitary or multiple)  
AdenoCa of various diff

### Brain
(solitary of multiple)  
AdenoCa of various diff or squamous cell Ca

### Neuroendocrine tumors
P diff Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca

### Melanoma
U neoplasm with melanoma features.

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$W = \text{well}, \quad M = \text{moderately}, \quad P = \text{poorly}, \quad U = \text{undifferentiated}$
WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR?
HOW DO WE SEARCH FOR THE PRIMARY?

By HISTOPATHOLOGY:
- Immunohistochemistry
- Advanced Molecular Technology

By IMAGING:
- Conventional Radiology
  - Ultrasonography
  - CT-scans
  - MRI
- PET-scans
- Mammography

By ENDOSCOPY:
- ENT panendoscopy
- Bronchoscopy
- Colonoscopy
- Proctoscopy
- Colposcopy
By Histopathology
**STEPS OF IMMUNOHISTOCHEMICAL DIAGNOSTIC APPROACH FOR CUP**

**STEP 1** (Detects broad type of cancer)

- **Carcinoma**: AE 1/3 pancytokeratin
- **Lymphoma**: Common leucocyte antigen (CLA)
- **Melanoma**: S100, HMB45
- **Sarcoma**: S100, Vimentin
STEP 2 (Detects subtype of carcinoma)

Adenocarcinoma
- CK 7/20, PSA

Germ cell tumour
- PLAP, OCT4, AFP, HCG

Hepatocellular Carcinoma
- Hepar 1, canalicular
- pCEA/CD10/CD13

Renal cell carcinoma
- RCC, CD10

Thyroid carcinoma
- TTF1, thyroglobulin

Neuroendocrine carcinoma
- Chromogranin, synaptophysin,
  PGP 9.5, CD56

Squamous carcinoma
- CK 5/6, p63
STEP 3 (Detects origin of an adenocarcinoma)

Prostate

PSA, PAP

Lung

TTF1

Breast

GCDFP-15, mammaglobulin, ER

Colon

CD X 2, CK 20

Pancreas/Biliary

CD X 2, CK 20, CK7

Ovary

ER, Ca 125, mesothelin
Cytokeratins (CKS)

Monoclonal antibodies against cytokeratin polypeptides CK7 and CK20
**CK7** + **CK20**

**CK7 + CK20 +**
- Urothelial tumors
- Ovarian mucinous adenocarcinoma
- Pancreatic adenocarcinoma
- Cholangiocarcinoma

**CK7 + CK20 -**
- Lung adenocarcinoma
- Breast carcinoma
- Thyroid carcinoma
- Endometrial carcinoma
- Cervical carcinoma
- Salivary gland carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma

**CK7 - CK20 +**
- Colorectal Carcinoma
- Merkel cell carcinoma

**CK7 - CK20 -**
- Hepatocellular carcinoma
- Renal cell carcinoma
- Prostate carcinoma
- Squamous cell & small cell lung carcinoma
- Head & neck carcinoma
MOLECULAR ANALYSIS
[Microarray Platforms]

> 80 - 90 % accuracy
# Gene expression profiling

## Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Platform</th>
<th>Tissue</th>
<th>No. of Tumor types</th>
<th>Number of genes</th>
<th>Accuracy in known tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veridex</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>6 and &quot;other&quot;</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>Pathwork Diagnostics Tissue of Origin test</td>
<td>cDNA microarray</td>
<td>Frozen/FFPE</td>
<td>15</td>
<td>1500</td>
<td>89</td>
</tr>
<tr>
<td>Rosetta Genomics MiReview met</td>
<td>RT-PCR miRNA</td>
<td>FFPE</td>
<td>22</td>
<td>48 miRNAs</td>
<td>86</td>
</tr>
<tr>
<td>bioTheranostics CancerType ID</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>39 (including subtypes)</td>
<td>92</td>
<td>86</td>
</tr>
</tbody>
</table>
ENDOSCOPY

✓ Should always be symptoms - or sings oriented investigational procedures

SERUM TUMOR MARKERS

✓ In general, routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance
WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY?
CUP

- Favourable or good prognosis subsets
- Unfavourable or poor prognosis subsets
DO WE HAVE EFFECTIVE DRUGS FOR CANCER OF UNKNOWN PRIMARY

OR

WE JUST HAVE RESPONSIVE SUBSETS OF PATIENTS?
THE FAVOURABLE SUBSETS
OR
GOOD PROGNOSIS SUBSETS
Favourable Subsets

1. Women with adenocarcinoma involving only axillary lymph nodes.
2. Women with papillary adenocarcinoma of peritoneal cavity.
3. Squamous cell carcinoma involving cervical lymph nodes
4. Poorly differentiated neuroendocrine carcinomas.
   Merkel cell carcinoma of unknown primary (localized disease)
5. Adenocarcinoma with a colon-profile (CK 20⁺, CK 7⁻, CDX 2⁺)
6. Men with blastic bone metastases and elevated PSA (adenocarcinoma).
7. Isolated inguinal adenopathy (squamous carcinoma).
8. Patients with a single, small, potentially resectable tumor.

Subset 1

Women with adenocarcinoma involving axillary nodes

- Mostly ductal adenocarcinoma (40% positive ER/PR)
- Mean age 52 years
- Should be managed as stage II breast cancers (axillary dissection, ipsilateral breast radiotherapy, adjuvant chemo/hormone therapy)
- 5-year survival: 72%
**Subset 2**

*Women with primary papillary adenocarcinoma peritoneal cavity*

- Similar presentation with advanced ovarian cancer.
- Median age 60 years
- Histopathology: serous or papillary adenocarcinoma
- Serum CA 125 is frequently increased
- Should be treated as stage III-IV ovarian cancer (cytoreduction, followed by platinum/taxanes)
- Responses: 80% (CR: 30-40%), Median survival: 36 months
Subset 3

Squamous cell carcinoma involving cervical nodes

• It constitutes 5% of all head-neck cancers

• Median age 60 years

• Sensitivity of PET-scan to detect the primary is 60%

• Treatment
  - $N_1$ or $N_{2a}$ disease without extracapsular extension: surgery alone
    
    \[ \text{locoregional control: 80 – 90\%, 5-yr survival: 65\%} \]
  
  - $\geq N_{2b}$ stage or with extracapsular extension: Postoperative chemoradiation
Subset 4

Poorly differentiated neuroendocrine carcinoma

- Frequently affects retroperitoneal, mediastinal, peripheral nodes less frequently liver or bones.
- Should be treated with platinum and/or taxane combinations
- Response: 55% (CR 20%), Survival: 15 months (10-15% long survivors)
Subset 5

Adenocarcinoma with a colon profile (CK20+, CK7-, CDX2+)

- Clinical presentation: abdominal nodes 51%, peritoneum 50%, liver 30%, ascites 27%
- Should be treated as advanced colorectal cancer with chemotherapy / targeting treatment
- Response: 50% (CR 15%, PR 35%)
  Median Survival: 21-37 months
OTHER FAVOURABLE SUBSETS

- Men with blastic bone metastases from an adenocarcinoma and elevated serum PSA treat as advanced prostate cancer

- Isolated inguinal adenopathy from squamous cell carcinoma
  local excision ± radiation

- Patients with a single, small, potentially resectable tumours
  local excision ± radiation
UNFAVOURABLE SUBSETS

1. Adenocarcinoma metastatic to the liver or other organs
2. Poorly differentiated carcinoma
3. Non-papillary malignant ascites (adenocarcinoma)
4. Multiple cerebral metastases (adeno or squamous Ca)
5. Multiple lung/pleural metastases (adenocarcinoma)
6. Multiple metastatic bone disease (adenocarcinoma)
7. Squamous – cell carcinoma of the abdominal cavity
THE UNFAVOURABLE OR POOR PROGNOSIS SUBSETS

• This group of CUP patients represents 80% of cases

• Usually treated with empirical chemotherapy (i.e. Platinum / Taxanes)

• Responses: 20%

• Median survival: 6-9 months
Prognostication in cancer of unknown primary (CUP): Development of a prognostic algorithm in 311 cases and review of the literature

Dimitrios Petrakis, George Pentheroudakis, Evangelos Voulgaris, Nicholas Pavlidis*
Fig. 1. Overall Survival by CUP Clinicopathologic Subgroups in univariate analysis.
DOES THE IDENTIFICATION OF PRIMARY SITE BY MOLECULAR PROFILING FOLLOWING SITE-SPECIFIC THERAPY IMPROVE PATIENTS’ OUTCOME?

WHAT IS THE EVIDENCE TODAY?
Conclusion

✓ The median survival time of 12.5 months for patients who received assay-directed site-specific therapy compares favorably with previous results using empiric CUP regimens.

✓ Molecular tumor profiling contributes to the management of patients with CUP and should be a part of their standard evaluation.
# SITE SPECIFIC TREATMENTS

<table>
<thead>
<tr>
<th>Predicted Tissue of Origin</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Taxane/bevacizumab</td>
</tr>
<tr>
<td>Colorectal</td>
<td>FOLFOX (or variant) + bevacizumab, or FOLFIRI (or variant) + bevacizumab</td>
</tr>
<tr>
<td>Lung cancer, non-small cell</td>
<td>Platinum-based doublet + bevacizumab</td>
</tr>
<tr>
<td>Ovary</td>
<td>Paclitaxel/carboplatin + bevacizumab</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Gemcitabine/erlotinib</td>
</tr>
<tr>
<td>Prostate</td>
<td>Androgen ablation therapy</td>
</tr>
<tr>
<td>Renal</td>
<td>Sunitinib or bevacizumab ± interferon</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>Standard first-line treatment per guidelines</td>
</tr>
</tbody>
</table>
OVERALL SURVIVAL: Assay-directed treatment vs. empiric treatment

PRESENTED BY: F. Anthony Greco, MD

Time (months)

Medean Survival (mo)

Assay-directed (N=194) 12.5

Empiric (N=29) 4.7

p = 0.02

Overall survival Probability

Overall survival Probability
I respectfully suggest, with regret, that their trial is insufficient to support this claim.

A trial in which patient with CUP are randomly assigned to best empiric therapy versus expression profile-directed therapy, or some similar design, remains needed.
## Ongoing Phase III Randomized Trials with the Use of Molecularly Assigned Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Design</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEFCAP 104</td>
<td>GEFCAPI, France</td>
<td>RCT Phase  III</td>
<td>cDDP + Gemcitabine vs Pathwork test – Based Therapy</td>
</tr>
<tr>
<td>CUP-ONE</td>
<td>CR UK</td>
<td>RCT Phase  III</td>
<td>ECX vs Molecularly Assigned Therapy</td>
</tr>
</tbody>
</table>
Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities (IHC and GEP) on a case–by–case basis, with the best possible individualized patient outcome in mind...
DOES GENE PROFILING (GP) DIAGNOSTIC TECHNOLOGY JUSTIFIES SPECIFIC DIRECT TREATMENT OR SURVIVAL BENEFIT IN CUP PATIENTS?
**SUPPORTERS**

**CUP doesn’t exist, since** 90% of small primaries can be found at autopsy or almost 90% can be identified by GP

**NON-SUPPORTERS**

**A primary that never grows** probably carries a unique i.e. distinct genetic signature, chromosomal instability, etc

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**BIOLOGY OF CUP**

**CHEMOTHERAPY OF CUP**

Data showed responses and survival benefit following specific direct treatment after GP

Existing information are deriving from non-randomized small studies and from one observational study

**TARGETED THERAPY OF CUP**

Targeted therapies are effective in some cases

Only a few anecdotal data exist. Biomarkers (EGFR, HER2, ALK) are not amplified or mutated.
Randomized prospective studies are urgently needed, especially between specific CUP subsets and relevant known primaries.

We succeeded to make THE UNKNOWN KNOWN.

(contin)
**STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT**

**DIAGNOSIS OF METASTATIC CARCINOMA** (by histopathology)

↓

**SEARCH FOR PRIMARY SITE**

**STEP I**

Clinical, immunohistochemistry, imaging, endoscopy studies

↓

**RULE-OUT POTENTIALLY TREATABLE OR CURABLE TUMORS**

(Immunohistochemistry or other studies)

i.e. Breast Cancer, Germ-cell Tumors, Lymphomas

↓

**STEP II**

**CHARACTERIZE THE SPECIFIC CLINICOPATHOLOGICAL ENTITY**

↓

**TREAT THE PATIENT**

↓

- **FAVOURABLE SUBSETS**
  [Similarly to relevant primaries with “Curative Intent”]

- **UNFAVOURABLE SUBSETS**
  [With empirical chemotherapy with “Palliative Intent” or with specific Rx following gene profiling]
Thank you