Cancer of Unknown Primary

Helen Rickards
Acute Oncology and Cancer of Unknown Primary CNS
July 2015
• Defining CUP
• Incidence
• Patient Pathways – getting a diagnosis
• Patient assessment
• The patient’s perspective
• Treatment
• Favourable / unfavourable sub sets
• Life expectancy
Definition

Umbrella term given to patients with a histologically confirmed metastatic cancer which, despite investigation, fails to detect a primary tumour.
Exclusions

- Any patients with metastatic disease and no identified primary but histology shows a non-epithelial malignancy e.g.
  - lymphoma or other haematological malignancy
  - melanoma
  - sarcoma
  - germ-cell tumour

These patients can be treated regardless of the primary site
Why can’t the primary be found? \(^{7,19}\)

- Not entirely clear but thought to be because either:
  1. Rapid growth and spread of secondary cancer(s) but the primary is too small to be visible on imaging
  2. The cancer has been growing in more than one area for some time – making it difficult to identify where it originated
  3. The primary may have disappeared even though there are secondaries and these are growing
Symptoms

• Dependent on location of secondaries:
  • Lung: persistent cough, dyspnoea, pleural effusion
  • Bone: pain or fracture
  • Liver: ascites, jaundice, nausea, poor appetite, abdo discomfort

General symptoms include:
• Unexplained weight loss
• Loss of appetite
• Fatigue
• Anaemia
Incidence

- Difficult to be absolute as most figures include MUO

- Approx 10,000 new diagnosis of CUP each year = 3% of all cancers / 10th commonest cancer $^{1,3,2,9}$

- Approx 11,000 deaths each year = 7% of all cancer deaths / 5th highest cause of cancer death $^{1,3}$

- Slightly higher female to male ratio (1.2 : 1)$^3$

- Nearly 40% were aged 80 or over $^3$
- 5% were under 50 $^3$
Incidence is falling –

40% fewer cases in since mid 1990’s \(^3\)

- Why is this?

- Not entirely clear! – but thought to be due to:

1. Improved diagnostic methods \(^3,14\)

2. Better information sources \(^3\)

3. Better registration practices - patients are more likely to be given an appropriate Site Specific code \(^3,14\)
How do we define CUP?

- Several terms are used during the diagnostic process:
  - MUO
  - Provisional CUP (pCUP)
  - Confirmed CUP (cCUP)

- All are patients presenting with metastatic disease with no obvious primary tumour
• For example:
• Patient presents at A&E with abdo pain
• CT shows liver metastases but no obvious primary
  = MUO

• Endoscopies reveal no additional information. Liver biopsy shows adeno carcinoma but could be from several possible primary sites
  = pCUP

• Discussion at MDT and further IHC is unable to establish definite primary
  = cCUP
In practice patients referred as CUP may include:

1. Patients where absolutely no work-up/assessment has been done

2. Patients who are too poorly to be investigated

3. Patients where investigations eventually identify the primary

4. A true Unknown Primary!
What are the difficulties of managing these patients?

- Patients have unique natural history which differs from patients with known primary cancers (e.g.):
  1. Early dissemination
  2. Clinical absence of primary tumour
  3. Unpredictability of metastatic pattern
  4. Aggressiveness of the disease itself
• Patients present with an advanced cancer (> 50% patients present with multiple site metastases)  

• More likely to present as an emergency (57% compared to 23% of all other cancers) 

• Importance of ensuring patients are appropriately investigated – avoiding under and (more likely) over-investigation
• Complexities of presentation makes developing diagnostic pathways difficult\textsuperscript{4}

• Historical “orphan” status:\textsuperscript{4}
  - lack of agreed definitions or understanding of disease process.
  - poorly structured – no MDT / CNS support – not seen as a speciality in its own right
• From patients perspective:

1. Lack of certainty / identity\(^4,9\)

2. Poor prognosis \(^4,6,12,14\)

3. Many are never fit enough for systemic treatment (60% - PS 3-4 on presentation\(^8\))
The patient’s perspective\textsuperscript{17, 18}

- Difficulty understanding diagnosis
  
  \textit{It’s confusion because you don’t know what to expect. I know there are loads and loads of cancers around and they know where most of them are, well why am I so different? Why are these unknown primaries?}

- Uncertainty regarding treatment
  
  “I thought, God, is it worse to find the primary or not find it.”

- Feeling lost and abandoned
  
  “Because there was nothing, I just stopped expecting anything.”
How can we optimise the management of these patients?

• Assessment is key
• Raise public and HCP’s awareness of CUP – (recognition of significance of symptoms, cupfoundjo)
• Onsite Oncology presence at General Hospitals
• Inter-network / national pathways to standardise investigation pathways
• Development of specialist knowledge / teams
• Clinical trials to improve knowledge base
Assessment / Investigation

• All patients require comprehensive assessment but investigations should only be performed if: $^{2,13}$

1. The results are likely to affect the treatment decision

2. The patient understands why they are being undertaken

3. The patient understands potential benefits and risks of investigations and treatment

and

4. The patient is prepared to accept treatment
Diagnostic phase

• Staging Objectives: ¹⁰

1. To identify full extent of disease and guide selection of optimal Bx site
2. To identify 1° site to assign appropriate therapy
3. To determine potentially favourable subsets of patients with highly treatable malignancies

• Symptom focused ²
• “High yield” ¹⁰,¹⁴
Diagnostic phase

• Comprehensive history inc: ²
  o Any symptoms/signs
  o Any FHx
  o Occupational/smoking history
  o Significant co-morbidity
  o Performance Status

• Clinical examination inc breast, nodal areas, skin genital, rectal and pelvic exam ²,10

• Basic bloods inc: FBC, U&E & creatinine, LFT’s, bone profile, LDH, urinalysis ²,5,12
Diagnostic phase

- CXR
- CT CAP
- Myeloma screen (isolated / multiple lytic bone mets)
- Symptom directed endoscopy

- Tumour markers
- Biopsy (IHC profile)
- Testicular U/S / Mamography
- PET

REFs – 2, 10, 12, 14
Tumour Markers

• Generally has no diagnostic value in identifying 1° except in specific circumstances ²,⁷

Do not measure except for:

1. **AFP & hCG** if presentation compatible with germ cell tumours - Mediastinal or retroperitoneal masses & in young men (<50)
2. **AFP** if presentation compatible with HCC
3. **PSA** if presentation compatible with prostate cancer
4. **CA125** in women with presentation compatible with ovarian cancer (including inguinal node, chest, pleural, peritoneal or retroperitoneal presentations)
Immuno-histochemistry

- Metastatic tumours are more difficult to classify than primary tumours using IHC \(^{11}\)

- IHC is limited when: \(^{11}\)
  1. No specific or few non-specific markers are positive
  2. Tissue samples are small, (common in CUP), are necrotic, or stain poorly
  3. IHC results conflict with morphology / clinical scenario
• Therefore:
  • Should be used selectively and in conjunction with the patient's presentation & imaging studies to guide management

• Remember:
  • **No IHC test is 100% specific**
    - E.g. PSA can be positive in salivary gland carcinoma
Overview of management

• Early identification of patients

• Early expert assessment/involvement by an appropriate oncologist

• Appropriate investigation
  - fitness for procedure
  - influence of information on patient management
  - Systematic / rational order
  - Minimise over-investigation
  - Know when to stop

• Rule out unusual primary tumours and non-malignant causes$^{5,14}$
Favourable sub-sets\textsuperscript{12}

- Accounts for 15 – 20% of patients
- 30 – 60% of which will experience long-term disease control
- Treated similarly to patients with equivalent known primary tumours with metastatic disease

- Clinical behaviour, biology, response to treatment and outcome - similar to metastatic tumours of known primary
1. Women with isolated axillary adenopathy
2. Women with papillary serous adenocarcinoma of the peritoneal cavity
3. Squamous cell carcinoma (SCC) involving cervical lymph nodes (2-5%)
4. Isolated inguinal adenopathy from SCC
5. Men with bone metastases, and IHC / serum PSA expression
6. Men with poorly differentiated carcinoma of midline distribution
7. Neuroendocrine tumours (Poor and well differentiated)
8. Single, small & potentially resectable metastatic site
Unfavourable sub-sets

Majority of patients (80-85%)

Less likely to have disease that is responsive to treatment

Two prognostic groups:
1. Good PS (0-1) and normal LDH – median life-expectancy = 1 year (<15%)
2. PS > 1 and raised LDH = median survival 4 months
Un-favourable sub-sets

1. Adenocarcinoma metastatic to the liver or other organs
2. Non-papillary malignant ascites
3. Multiple cerebral metastases
4. Multiple lung/pleural metastases
5. Multiple metastatic bone disease
6. Adrenal mets
7. Male
8. Adenocarcinoma (80-85%)
Treatment

- Radiotherapy
- Chemotherapy
- Surgery
- Bone strengthening agents
- Specialist Palliative Care
Prognosis\textsuperscript{5,6,12}

• Overall 1yr survival = 25%, 5yr 10%
• Poor prognosis group 1yr <15%, 5yr 5-10%
• Median overall survival = 6-10 months

• Importance of Specialist Palliative Care input:
  • Patients are presenting with advanced, symptomatic disease
  • Under ½ are fit enough to consider tumour directed treatment (inc RT) but less than 2/3 of these complete\textsuperscript{8}
Case Study One

- 65yr old female
- PMH: CABG, MVR, subdural bleed
- Presented abdo distention – assumed cardiac failure – Ascites 9L
- Additional symptoms: Nausea, Wt loss, diarrhoea, difficulty passing urine, fatigue
- CT: congestive hepatomegaly, gross ascites and peritoneal thickening, widespread lymphadenopathy and sclerotic skeletal mets
- Histopathology – no clear primary – suggested differentials inc Breast, Neuroendocrine, reproductive tract, UGI, Pancreas or Lung!
- Recent protracted IP stay – too unwell for chemo
• MRI – to rule out MSCC with neuro symptoms - neg
• Anti-emetics and PCT referral
• Paracentesis
• Commenced chemo 5 months after diagnosis as more symptomatic – 3 cycles Carboplatin
• Denosumab for bone mets

• On FU only and relatively well until 14 months from diagnosis – pleural effusion
• Survived more than 18 months after diagnosis
Case history Two

- 28yr old female – 3 children under 5
- 2-3 month Hx rapidly increasing symptoms – RUQ pain – targeted U/S no obvious abnormality - presumed gall stones / hernia
- CT multiple large liver mets only
- Liver Bx – poorly differentiated small cell – Ki 67 100%
- PET – malignant lymph nodes above and below diaphragm and bone mets, ??uterine / cervical primary
- 6 cycles Carbo-Etop – sustained response
- Monthly Denosumab
- Took family to Euro Disney! – still doing well
• In summary:

• Diverse group of cancers which do not follow predictable trajectories
• Patients present with symptoms of advanced disease
• Generally poor prognosis (with some exceptions)
• Lack of certainty / identity
• Investigation should be limited by the patients fitness to tolerate procedures and the results are likely to affect the treatment decision
• Importance of Specialist Palliative Care input
References

1. National Cancer intelligence Network Data Briefing – Routes to Diagnosis: Cancer of Unknown Primary 2014
2. NICE. Metastatic Malignant Disease of Unknown Primary. July 2010
11. Oien, KA. Dennis JL. 2012. Diagnostic work-up of carcinoma of unknown primary: from immunohistochemistry to molecular profiling Annals of Oncology 23 (Supplement 10)
12. Fizazi, K et al 2011 Cancers of unknown primary sites: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 22 (Supplement 6)
13. Network Guidelines for the Investigation and Management of Metastatic Malignant Disease of Unknown Primary. Yorkshire and The Humber Strategic Clinical Networks and Senate Cancer (West and North Yorkshire) 2014
### Histological type in CUP

<table>
<thead>
<tr>
<th>Histological Subtype</th>
<th>Proportion of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>45-61%</td>
</tr>
<tr>
<td>(Incl G1 &amp; 2 differentiated Ca)</td>
<td></td>
</tr>
<tr>
<td><strong>Undifferentiated Carcinoma</strong></td>
<td>24-39%</td>
</tr>
<tr>
<td><strong>Squamous Cell Carcinoma</strong></td>
<td>4-15%</td>
</tr>
<tr>
<td><strong>Small cell Carcinoma</strong> (neuroendocrine carcinoma)</td>
<td>3-4%</td>
</tr>
</tbody>
</table>

Souhami et al, Oxford Textbook of Oncology, 2nd Ed, 2002
Pathology

• Heterogeneous collection of tumour types
  • Includes
    o Carcinomas
    o Poorly differentiated malignancies
• Sophisticated pathologic evaluation
  o Identify certain histologies
  o Allow appropriate therapy

• Techniques
  o Light microscopy
  o Immunohistochemical staining
  o Electron microscopy
  o Molecular genetics
Immunohistochemistry

- Basic **haemotoxylin & eosin (H&E)** – high diagnostic rate
  - often insufficient to determine cell origin in adeno’s
- For CUP – panel of IHC is needed to exclude:
  - Melanoma
  - Lymphoma
  - Sarcoma
  - Germ Cell
- Expression of **cytokeratin 20 (CK20) & 7 (CK7)**
  - important in determining tissue of origin for adenocarcinomas
- **Thyroid Transcription Factor 1 (TTF-1)**
  - used to increase or reduce probability of bronchial carcinoma
- **Oestrogen receptor (ER)**
  - breast, esp in conjunction with CK20 & 7

- Must be guided by clinical features
Promising molecular targets and targeting compounds in CUP

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Therapeutic Mod</th>
<th>Developed agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bone Metastases
Bone mets from different primaries cause different radiological appearances

- **Blastic lesions**
  - prostate
  - Hodgkin's & NHL
  - thyroid
  - carcinoid
  - SCLC

- **Lytic lesions**
  - myeloma
  - melanoma
  - renal cell carcinoma
  - NSCLC

In CUP, bone appearances are of limited value in directing a search for a primary tumour
Immunohistochemistry

- **Epithelial origin**
  - cytokeratins
- **Melanoma**
  - S100
  - HMB45
- **Germ Cell Tumour**
  - AFP
  - βHCG
  - PLAP
- **Neuroendocrine**
  - chromogranin
  - Synaptophysin
  - CD56
- **Lymphoma**
  - CD45
  - CD20
  - CD10
  - CD3
- **Thyroid**
  - thyroglobulin
  - TTF1
- **Prostate**
  - PSA
- **Sarcoma**
  - AML
  - CD31
  - CD34
IHC markers in CUP's

- Cytokeratin 7  Cytokeratin K20

<table>
<thead>
<tr>
<th>CK7+ CK20+</th>
<th>CK7+ CK20-</th>
<th>CK7- CK20+</th>
<th>CK 7- CK20-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian mucinous adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary gland Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merkel cell Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate Carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell Lung SCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and Neck Ca</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CUP peer review measures – newly introduced

- Hospitals to develop CUP team
  - Named oncologist
  - CNS
  - Named palliative care consultant
- CUP assessment service
- Fast access clinic
- MDT
- Aim to improve patient experience, outcomes and reduce LoS