

Cancer of Unknown Primary

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October 2013

CUP/UKP/MUO

Patients who present with metastatic malignancy without an identified primary source.....



Important to distinguish between cancers where the 1⁰ will be identified after investigation and the true CUP

Background

- **9,778 new cases of CUP registered in England, 2006**
- **2.7% of total cancers in England, 2006**
 - 3-5% overall
- **F>M (54% V 46%)**
- **Median age at diagnosis is 65 years**
- **10% < 50 age group**
- **30% - multiple metastases at diagnosis**
- **Liver, bone (+ marrow), lung & LNs**
 - commonest metastatic sites
- **Often rapidly progressing**
 - 4th most common cause of cancer death
(NICE guidance July 2010)

Background

- It is a heterogeneous group of tumours which 1st present with metastases and not the primary.
- A work-up does not identify primary site at the time of diagnosis
- In 15-25% PM doesn't reveal the primary
- Occult primary is said to turn out to be colorectal, lung or pancreas in approx 60%

Background

- The term CUP in practice may cover:
 - Patients ‘referred’ where absolutely no work-up/assessment has been done;
 - Patients who are too poorly to be investigated
 - Patients where investigations eventually identify the primary
 - A true Unknown Primary!

Who to Investigate

Patients should only be investigated if:

- 1. the result is likely to affect treatment decision**
- 2. the patient understands why the investigations are being carried out, their risks and benefits**
- 3. they are prepared to accept the treatment.**

Decreasing in incidence

WHY?

Improved diagnosis

Change in cancer registry codes

Changes in clinical practice due to MDT working

- **CUP patients – don't come “packaged”**
- **Process is complex & labour intensive**
- **Median survival ranges from 4 to 11 months**
 - No change in survival between 1992 – 2006
 - Compare general cancer survival
- **1, 3 & 5-year survivals are 23%, 11% & 6% respectively**
- **Most do not benefit from chemo**

What do these patients need?

- A thorough history and examination
- Basic bloods esp U+E, LFTs, bone profile.
- Needs to include:
 - Any symptoms/signs
 - Any FHx
 - Occupational/smoking history
 - Significant comorbidity
 - Performance Status

What do these patients need?

- (Chest Xray)
- (CT abdo & pelvis (+/- chest))
- (U/S testes)
- (Mammogram)
- (FOB, urinalysis, myeloma screen)
- (Symptom directed Endoscopy).
- (Tumour Markers –AFP, HCG, PSA, CA125, CEA)
- (Biopsy)

Overview of management

- **Know when to investigate**
 - Patient fit for treatment
- **Maximise identification of treatable conditions**
- **Minimise over-investigation**
- **Early identification of patients**
- **Early expert assessment/involvement by an appropriate oncologist**
- **Relevant investigations in a rational order**
 - Initial investigations (high yield) e.g. CT scan
 - Secondary specialist investigations
 - L Gaspa et al (2002) yield of basic tests 62% and additional tests was 29%
- **Know when to stop investigations**

Tumour markers

Not recommended for diagnosis

Low sensitivity & specificity

Inappropriate requesting often leads to unnecessary, costly & potentially harmful investigations

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)

**Important factor to consider
initially is the**

CELL TYPE

epithelial V non-epithelial

Pathology

- **Heterogeneous collection of tumour types**
- Includes
 - Carcinomas
 - Poorly differentiated malignancies
- Sophisticated pathologic evaluation
 - Identify certain histologies
 - Allow appropriate therapy
- **Techniques**
 - Light microscopy
 - Immunohistochemical staining
 - Electron microscopy
 - Molecular genetics

Histological types in CUP

<u>Histological Subtype</u>	<u>Proportion of Cases</u>
Adenocarcinoma (Incl G1 & 2 differentiated Ca)	45-61%
Undifferentiated Carcinoma	24-39%
Squamous Cell Carcinoma	4-15%
Small cell Carcinoma (neuroendocrine carcinoma)	3-4%

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**

Immunohistochemistry

- **IHC markers help to define tumour lineage**
 - peroxidase-labeled antibodies are used against specific tumour antigens
- **Select appropriate set of antibodies**
 - cannot be replaced by using a universal battery of markers
- **No IHC test is 100% specific**
 - E.g. PSA can be positive in salivary gland carcinoma

IHC markers are for guidance to be used in conjunction with the patient's presentation & imaging studies to guide management

IHC markers in CUP's

Cytokeratin 7 Cytokeratin K20

CK7+ CK20+

Urothelial tumours
Ovarian mucinous adenoCa
Pancreatic adenoCa
Cholangiocarcinoma

CK7+ CK20-

Lung adenoCa
Breast Ca
Thyroid Ca
Endometrial Ca
Cervical Ca
Salivary gland Ca
Cholangiocarcinoma
Pancreatic carcinoma

CK7- CK20+

Colorectal Ca
Merkel cell Carcinoma

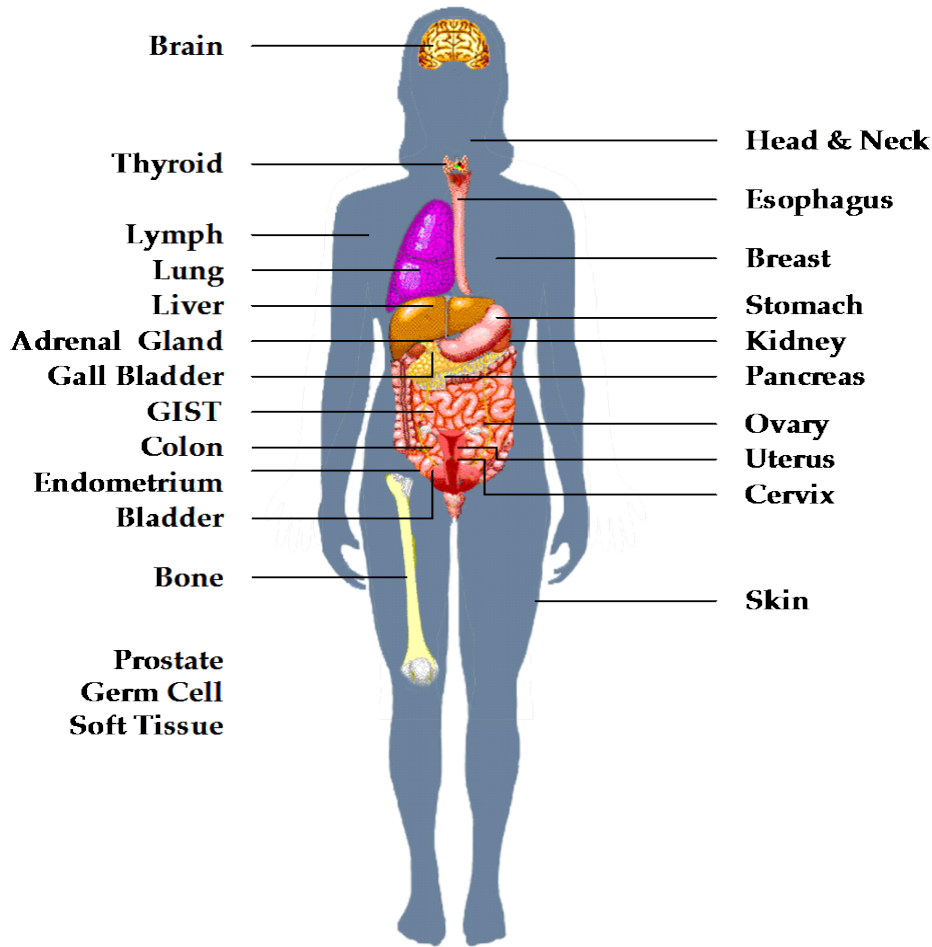
CK 7- CK20-

Hepatocellular Ca
Renal cell carcinoma
Prostate Carcinoma
Squamous cell Lung
SCLC
Head and Neck Ca

Immunohistochemistry

- **Epithelial origin**
 - cytokeratins
- **Melanoma**
 - S100
 - HMB45
- **Germ Cell Tumour**
 - AFP
 - bHCG
 - PLAP
- **Neuroendocrine**
 - chromogranin
 - Synaptophysin
 - CD56
- **Lymphoma**
 - CD45
 - CD20
 - CD10
 - CD3
- **Thyroid**
 - thyroglobulin
 - TTF1
- **Prostate**
 - PSA
- **Sarcoma**
 - AML
 - CD31
 - CD34

Why Gene Expression Profiling Can Classify Cancers Types



- **Cancers from different origins are derived from cells from different developmental processes**
- **Gene expression is distinct between different developmentally-derived cell types**

Promising molecular targets and targeting compounds in CUP

Molecule	Therapeutic Mod	Developed agents
Ras	Farnesyl-transferase inh	Tipifarnib, lonafarnib
HER2	Antibodies, TKI's	Trastuzumab, lapatinib
EGFR	Antibodies, TKI's	Cetuximab, gefitinib, erlotinib
C-KIT	TKI's	Imatinib, sunitinib
PDGFR	TKI's	Imatinib, sunitinib
BCL2	Antisense oligonucleotides	Oblimersen G3139
P53	Gene Rx, degradation inh	ONYX015, INGN201, MI63
VEGF	Antibodies	Bevacizumab
VEGFR	TKI's	ZD6474, sorafenib, sunitinib

FAVOURABLE SUBSETS

- 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**
- 4. Isolated inguinal adenopathy from SCC**
- 5. Men with bone metastases, elevated serum PSA, or PSA positive on tumor staining**
- 6. Men with poorly differentiated carcinoma of midline distribution**
- 7. Poorly differentiated neuroendocrine carcinoma**
- 8. Single, small & potentially resectable metastatic site**

UNFAVOURABLE SUB-SETS

- 1. Adenocarcinoma metastatic to the liver or other organs**
- 2. Non-papillary malignant ascites (adeno)**
- 3. Multiple cerebral metastases (adeno or squamous carcinoma)**
- 4. Multiple lung/pleural metastases (adeno)**
- 5. Multiple metastatic bone disease (adeno)**

Prognostic factors

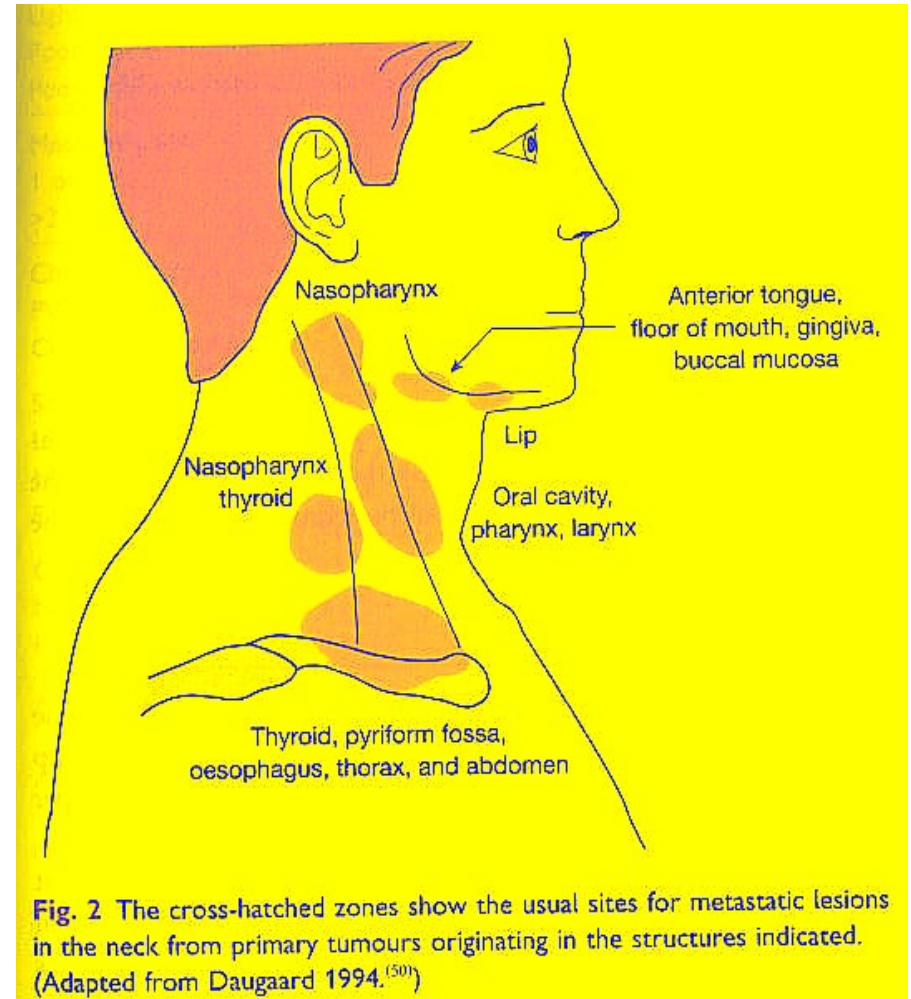
- **Majority have a limited life expectancy**
 - weeks to months
- **Subsets with better prognosis**
 - Some achieve survival rates of years
- **Groups that have responded well to empirical chemo**
 - with the advent of IHC some tumours have been found to be extragonadal GCTs and Lymphomas
- **Other CUP groups with better than average prognosis**
 - women with axillary LAN (adenoCa)
 - patients with cervical LAN (SCC)

SCF LN

- **Rarely H&N primaries**
- Commonly from sites below the clavicles
 - oesophagus, lung, breast, GI, prostate
- **Usually adenocarcinoma**
 - (R) SCF – breast & lung primaries
 - (L) SCF – intra-abdominal malignancies
 - spread via thoracic duct

Metastatic Cervical LNs

- Cervical node metastases of **squamous cell carcinoma** from occult primary constitute about 2-5% of all patients with CUP
- **Mets in upper & mid neck**
 - attributed to H&N cancers
- **Lower neck (SCF)**
 - associated with 1^o below the clavicles e.g. lung or GI tract




TREATMENT

FAVORABLE SUBSETS

Squamous cell carcinoma of the cervical lymph nodes

- Despite aggressive diagnostic approach, the primary site is not found in the majority of patients
- Ipsilateral tonsillectomy is often performed since the primary can be found in 10 to 25% of cases - **Small tumors may originate in the deep crypts and not be detected by superficial biopsy**
- Treat as **locally advanced head and neck cancer**
Low stage (N1) – Surgery → RT or RT alone
High stage (N2-N3) - Chemoradiotherapy

Inguinal LN

- **Rare presentation of CUP**
- **May arise from**
 - Skin malignancy of leg or lower trunk**
 - Occult melanoma**
 - Perineal & pelvic malignancy**
- **Histology may direct investigations**
 - mixed squamous/adenoCa – signifies a ‘cloacogenic’ primary that may be occult
 - examination of anorectal region
 - gynaecological exam
 - cystoscopy
- **Regional RT can  prolonged responses (esp. if SCC)**
 - If LN mets only site & occult melanoma excluded

TREATMENT

FAVORABLE SUBSETS

Isolated inguinal squamous cell carcinoma

- Tumour is usually located in the genital or anorectal area
- Patients without an identifiable primary tumour may benefit from inguinal lymphadenectomy, +/- adjuvant RT
- Role for chemotherapy in the adjuvant setting is not well defined

Surgery ± RT, ? chemotherapy

TREATMENT

FAVORABLE SUBSETS

Men with bone metastases, elevated serum PSA, or PSA positive on tumor staining

Prostate cancer is the most likely diagnosis

1. Elderly men with adenocarcinoma of unknown primary & predominantly blastic bone metastases
2. Patients with increased PSA or positive PSA staining on the biopsy specimen despite atypical presentation

Hormonal therapy

TREATMENT

FAVORABLE SUBSETS

Women with isolated axillary adenopathy

- Lymph nodes should be tested for ER, PR & HER-2
- In cases of negative mammogram, the primary may be seen on MRI or after mastectomy
- Prognosis is similar to lymph node positive breast cancer
- Mobile lymph nodes (**N1**) - **Treat as stage IIA breast cancer**
- Fixed lymph nodes (**N2**) - **Treated as stage IIIA breast cancer**

MRM + AND → chemotherapy ± hormonal therapy/RT
Neoadjuvant chemotherapy for N2 disease

TREATMENT

FAVORABLE SUBSETS

Women with papillary serous adenocarcinoma of the peritoneal cavity

- Germinal epithelium of the ovary & peritoneal mesothelium share the same embryological origin
- More common in women with BRCA-1 mutation and may also be seen after prophylactic oophorectomy
- Outcomes are similar to ovarian cancer at equivalent stage
- Patients should be treated as **stage III ovarian carcinoma**

Surgical debulking followed by chemotherapy

TREATMENT

FAVORABLE SUBSETS

Poorly differentiated neuroendocrine carcinoma

- IHC usually stains positive for chromogranin or NSE
- Patients frequently present with diffuse metastases to the liver or bones

Platinum-based chemotherapy (platinum + etoposide)

TREATMENT

FAVORABLE SUBSETS

Men with poorly differentiated carcinoma of midline distribution

- Young males with tumours of predominant midline distribution (mediastinum & retroperitoneum) should be treated as **extragonadal germ cell tumors**

Cisplatin-based chemotherapy (BEP)

TREATMENT

FAVOURABLE SUBSETS

Single metastatic site

- Although other metastatic sites may become evident within a short period, some patients may achieve a prolonged disease-free interval with local therapies such as surgery or radiotherapy
- Adjuvant chemotherapy may also be considered

Surgery or RT

Bone Metastases



Bone Metastases

- **Between 6 - 27 % patients present with bone symptoms due to mets**
 - Souhami et al 2002
- **In CUP patients**
 - **w/o skeletal symptoms**
 - bone scan + ve in 50 %
 - **with symptoms**
 - bone scan + ve in 90 %

Bone mets from different primaries cause different radiological appearances

- **Blastic lesions**

- prostate
- Hodgkin's & NHL
- thyroid
- carcinoid
- SCLC

- **Lytic lesions**

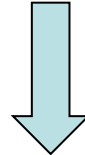
- myeloma
- melanoma
- renal cell carcinoma
- NSCLC

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

**Always consider suitable
clinical trials**

Current Clinical Practice

Diagnosis of metastatic cancer

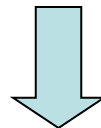


Search for primary site

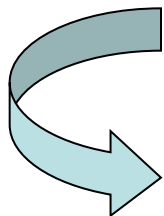
Rule out non-carcinoma hx - Lymphoma, melanoma, sarcoma



Identify favourable subgroups

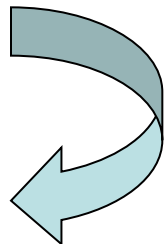


Good PS ← Unfavourable subgroup → Poor PS



- Clinical trial
- Platinum-taxane chemotherapy

Best Supp Care





BSC

Germ cell

UNSURE

Melanoma

Grade 4 ca

SCC level II

Axillary adeno

Who should be involved with
the care of CUP patients?

Who gets involved with a potential CUP?

- ?All Clinicians
- Need to be able to assess for any potential primary and refer then to appropriate team.
- When primary not obvious, early advice from Oncology
 - Direct which tests
 - Direct appropriateness of Investigations
- Large Input expected from Palliative Care
 - Majority of cases are too poorly for Treatment and need palliation

What about dealing with patients who require admission?

- Whoever is on call at that time?
- ?Admit patient under an appropriate team eg named General Medicine firm, named General surgery team, named orthopaedics team? ie Each area would have a responsible team!
- Should they be admitted directly under an Oncologist?
- Should they be admitted directly under Palliative Care?

If they do not need admission, which clinic should they be booked into?

- -In Chesterfield there is a CUP clinic lead by Palliative Care consultant.
- Should this be the standard?
- Should there be a team in each hospital designated to look after patients who have a potential malignancy?
- Should it be an Oncologist running this clinic?
- Should clinic be dependent on most prominent sign?

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

Thank you

www.cupfoundjo.org