Cancer of Unknown Primary Origin: Challenges, Experience and the Future.

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Challenges of CUP as a Diagnosis

- Inexact diagnosis
- Lacks organisational structure
- Problem facing 2% all cancer inpatients at any one time
- Patients often experience long hospital stays and undergo multiple invasive tests
- Uncertainty of diagnosis is difficult for patients
- Prognosis often poor (3-11 months)
CUP: 4th Leading Cause of Death from Cancer

New Cancer Diagnosis

- All Other Cancers: 95%
- CUP: 5%

Deaths from Cancer (Women)

- All Other Cancers: 92%
- CUP: 8%

New CUP Diagnosis By Age**

- Age > 65: 75%
- Age < 65: 25%

Deaths from Cancer (Men)

- All Other Cancers: 94%
- CUP: 6%
Moving Forward with CUP since 2010

Definitions

• National Institute of Clinical Excellence (NICE) guidelines published July 2010

Patient Support and Empowerment

• Macmillan published patient information booklet

Awareness

• 2 National Conferences since 2010

Research

• 1 National Clinical Trial (CUP ONE)
Malignancy of Unknown Origin (MUO)

- CT scan (Chest, Abdomen, Pelvis)
- Core Biopsy (x 2: 3% failure rate)

Fit for further investigation

- Provisional Cancer of Unknown Primary (pCUP)

Specialist Review

- Unfavourable Subset (80%)
- Favourable Subset (20%)

Confirmed Cancer of Unknown Primary (cCUP)

Malignancy of Unknown Origin (MUO)

Primary site identified

67% 33%
RUH CUP Service Evaluation

2010 - 2012
Malignancy of Unknown Origin (MUO)

Fit for further investigation

Unfit for further investigation

Provisional Cancer of Unknown Primary (pCUP)

Specialist Review

Primary site identified

Confirmed Cancer of Unknown Primary (cCUP)

Median age 75 (range 37-96)

117

100

44*

17

56*
Source of Referral to CUP Service

- 56% Inpatient
- 25% Unknown
- 19% GP
Primary Treatment following cCUP Diagnosis

- Best Supportive Care: 58%
- Chemotherapy: 9%
- Favourable Subset (20%)
- Other: 22%
Challenge of CUP for the NHS

- 75% patients are admitted as an acute admission
- Accounts for 2% all cancer inpatients at any time
- Number of admissions/patient = 3 (range 1-12)
- 35% admitted for > 10 days
- 25% for >14 days
- 6% > 1 month
- Median survival 3.5 months (range 4 – 471 days)
- 65% patients die in the acute hospital setting
The Future
IHC for diagnosis of CUP patient

Immunohistochemistry in undifferentiated neoplasms

- Hematoxylin/eosin morphology
  - Undifferentiated neoplasm
    - CD45RO
      - Lymphoma
    - S100, MTF, MELAN-A, HMB45
      - Melanoma
    - AE1/3 CAM5.2
      - Carcinoma
    - Vimentin
      - Sarcoma

- CK7+CK20+
  - Lung
    - Small cell, non-small cell
      - TTF1+, CEA+
      - Transitional cell
        - Uroplakin+ P63+ Thrombomodulin+
      - Ovary mucinous
        - WT-1+ (S)
  - CK7+CK20-
    - Breast
      - GCDFP15+ ER+ PR+
    - Squamous
      - CK5+ P63+
  - CK7-CK20-
    - Prostate
      - PSA+
  - CK7-CK20+
    - Merkel cell
      - Chromog+ Synaptophysin+
    - Colorectal
      - CDX2+ LE/villin+

- Endometrioid
  - Vimentin+, ER
  - Ovary serous
    - WT-1+, BerEp4+
  - Ovary mucinous
    - WT-1+ (S)

- Endocrine
  - Chromog+
    - Synaptophysin+
  - Neuroendocrine
    - Sg8/SerEp4 MOC-31

- Germ cell
  - EMA (-)
  - PLAP+
  - α-fetoprotein+ (endodermal sinus)
  - HCG+ (chorio)
  - COX20+
  - OCT4+ (embryonal)

- Thyroid
  - TTF 1+
  - CEA (-)

- Seminoma
  - Keratin (-)
  - OCT4+
Gene Expression Profiles

Biopsy with complete IHC

30-40% primary diagnosis

60-70% cCUP

Clinical Trials (CUP ONE)

Gene Profiling

Malignant tissues retain some of the primary gene expression profile

Cost of unnecessary investigations and treatment

50% change in clinical management

NO change in clinical management
1300 known cancer samples and 509 blinded samples

- 84% specificity
- 92% concordance with clinical data

64 RNA microarrays

(49 cancer types – covered 95% of CUP diagnosis)

- Metastasis correlates with primary tumor (not bone)
- 25% cases – treatable cancers (Breast 9%, CRC14%)
- 3% male breast cancer (0.26% general population)
- 17% HPB origin (3.6% general population)
Conclusions

- Common diagnosis with increasing incidence
- Faster diagnostic pathway
- Genomics to provide personalised medicine
  - Recognise and treat the favourable subtypes early to improve survival
  - Recognise and manage the unfavourable subtypes early to improve quality of life
Conclusions

Common diagnosis with increasing incidence

Faster diagnostic pathway

Comprehensive Holistic Assessment

Top 10 concerns in patients with CUP are very different from other cancer patients**

46% incidence if depression in patients with CUP*

“Chemotherapy feels like a shotgun approach.” “Genomics focuses on my cancer, feels optimistic.”

Recognise and treat the favourable subtypes early to improve survival and minimise distress

Recognise and manage the unfavourable subtypes early to improve quality of life and minimise distress

*Hyphantis + Pavlidis Psychoncology 2013  **SUPER trial -Peter Mac Cancer Centre
Thanks to the RUH CUP Team

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All members of the CUP Specialist MDM
Questions