John Symons

Director

CUP Foundation - Jo’s friends
30 people in the UK die each day from CUP. CUP is the 5th highest cause of cancer death in the UK.

CRUK 2012 data

57% of patients diagnosed with CUP in the UK (9% of all cancer cases) present as an emergency.

50% of UK CUP patients are aged 50-80 (45% aged 80 and over). Ratio of 1 male to 1.2 females. 21% from the most deprived socio-economic group.

NCIN 2006-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>UK new cases</th>
<th>UK deaths</th>
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<tbody>
<tr>
<td>1996</td>
<td>15,838</td>
<td>15,024</td>
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<td>1998</td>
<td>14,972</td>
<td>15,259</td>
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<td>2000</td>
<td>14,013</td>
<td>14,559</td>
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<td>2002</td>
<td>13,428</td>
<td>14,058</td>
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<td>2004</td>
<td>12,640</td>
<td>13,288</td>
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<td>2006</td>
<td>11,566</td>
<td>12,267</td>
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<td>2008</td>
<td>10,752</td>
<td>11,228</td>
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<tr>
<td>2010</td>
<td>9,585</td>
<td>10,472</td>
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<tr>
<td>2012</td>
<td>9,620</td>
<td>10,625</td>
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ICD 10 C77-80

10th highest number of new cancer cases in the UK are CUP.

CRUK 2012 data

40% drop in UK incidence over last 16 years

30% drop in UK mortality over last 16 years

NCIN/CRUK data

144 CUP teams peer reviewed in 2013/14

PHE - Quality Surveillance Team

CUP Foundation
Network Compliance

- **30%** Lead clinician and core team in place; **8 Immediate risks;**
- **41 Serious concerns** (from no functional MDT to lack of: cover, robust pathways, good practice)
- **100%** compliant: Maidstone Hospital;
- **4%** compliant: S** & **Hospitals
- **23%** Patients experience exercise;
- **60%** Patient written info.

PHE - Quality Surveillance Team - formerly Peer Review Programme
A challenging diagnosis for oncologists

I’d like to subject you to dozens of tests—come to vague conclusions—try lots of drugs that won’t work and have horrid side effects and leave you feeling worse than you did before you came to see me...

Thank-you, Doctor

A ‘double agony’ for patients and families
Digest of CUP patient experience research including NCPES *(2010, 2011-12 & 2013)*

- Multiple investigations
- Uncertainty/ CUP not diagnosed
- Pathway guidance failures
  - ‘MDT tennis’, Delays & Disruption
- Lack of communication & Poor patient information
- Poor accountability
- Poor understanding of CUP/
  Poor explanation of causality
- Healthcare professionals not knowing, not communicating, not able to treat (issue of trust)
- Impact on family & friends
- Difficulty of explaining CUP to others
- CNSs highly valued
1500BC Record of cauterisation to destroy tumours, *the fire drill*, in Egypt. Distinction made between benign and malignant disease

1700s Cancer hospital established in France

1899 Radiation first used for cancer treatment

1907 **William Halstead paper on ‘non demonstrable cancer’ in Annals of Surgery**

1926 Nobel prize for discovering the cause of cancer (a worm!)

1940s Chemo first used

1953 **Crick & Watson publish on DNA structure**

1970s CUP definition & associated autopsy data

1980s - Australian Guideline
  - Recognition of Prognostic factors & favourable clinicopathologic subsets

1990s Era of CUP empiric chemotherapy

2005s Improved, evolving immunohistochemistry and use of molecular profiling

2010s - ESMO (2011) and NICE (2010) Guidelines
  - ‘CUP One’ recruitment in the UK (2010 – 2014)
  - Data accumulating to support accurate cancer type diagnosis, site specific therapy with potential of improved outcome for large number of CUP patients

2020 95% of ‘CUP’ patients in developed countries treated with specific therapies based on a confident determination of tissue of origin.
Dr. F. Anthony Greco
Co-Founder, Sarah Cannon Research Institute
&
Chairman CUP 2015
Recognized for decades; where is the primary tumor?

Very few clinical investigators had any interest in the study and understanding of CUP.

Essentially no new insights until late 1970’s except autopsy studies revealed very small clinically undetectable primary sites in most patients (75%).

Empiric chemotherapy

• 1970’s ➔ Present
CUP History

- Recognition of treatable/favorable subsets of patients within the heterogeneous CUP group
  - Late 1970’s – Present

- Diagnosis of anatomical primary tumor site or tissue of origin NOT possible. Medical imaging and endoscopies find some small primaries (Not CUP).
  - Decades ago – 2007
Improving Diagnosis and Patient Management

- Development and improving immunohistochemistry
  - 1970’s → Present

- Development and improving gene expression profiling
  - 2007 → Present

- Diagnosis of the cancer type or tissue of origin now possible in the majority of patients

- Site-specific therapy based on diagnosis of the cancer type in CUP improves the outcome for many patients
Introductory Remarks

- **CUP** – Not one cancer, but one constant feature – anatomical primary site not detected.

- **Autopsy Data** – About 75% of CUP patients have very small primary tumor sites found and these are the source of metastasis
Primary Sites Determined at Autopsy in 884 Patients with Unknown Primary Cancer

Autopsy-found primaries, 644 of 884 (73%)

Lung 27%
Pancreas 24%
Liver/Bile duct 8%
Kidney/Adrenal 8%
Bowel 7%
Genital System 7%
Stomach 6%
Bladder 0.5%
Breast 0.5%
Other 10%
Introductory Remarks

- Does the size of the known primary cancer site change the therapeutic plan?

- Lung – 1.1 cm spiculated lesion in right lung apex with large mediastinal mass, bone and adrenal metastasis

- Breast – 0.7 cm lesion found by breast MRI with metastasis to liver and bone
Introductory Remarks

- CUP – Most have clinically undetectable very small primary cancers but give rise to detectable metastasis

- Cancer type in CUP defined by immunohistochemistry and molecular assay of a metastatic site in about 95%+ of patients

- These diagnostic tests not universally applied to CUP—Why?

- The aim of “make the unknown, known” has been accomplished.