

DRAFT SUMMARY OF PROCEEDINGS - CUP FOUNDATION CONFERENCE 2012Health Warning

This document attempts to capture the conference proceedings through reportage but it is not a verbatim recording. It is intended as an information document to capture the essence of the presentations but remains in 'Draft' as it is not intended to be an 'academic' source document. Queries to john@cupfoundjo.org

PROGRESS IN THE SEARCH FOR IMPROVED DIAGNOSIS, MANAGEMENT AND TREATMENT

Royal College of Physicians. London. Friday 27 April

Chairman F Anthony Greco (USA)

Keynote speaker: Nicholas Pavlidis (Greece)

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OPENING STATEMENTS

TONY GRECO *Conference chairman:* In cancer research there is a group of patients who have been ignored over the years. But we can now identify them and help them. They have Cancer of Unknown Primary (CUP), and we can define that to a degree: 'a clinical pathologic syndrome that involves many groups'. What we want now is a one-world view to define this group.

PROFESSOR SIR MIKE RICHARDS *National Cancer Director:* We have started to transform cancer services in this country. Cancer is now a cultural and political priority. In England and Wales – there is strategy, guidance and funding in place now where 40 years ago there were none. 20 years ago we were fatalistic about high mortality rates. And then about 17 years ago there was a turning point, a cancer plan, and we are reaping the benefits. But CUP has lagged behind. Roughly 10,000 deaths per year in England and Wales matters – the numbers are too high and the patient experience is too poor. For too long CUP is likely to have been hidden under the title 'Other'. In 2008 the NHS through NICE initiated the development of a Guideline for the management and treatment of CUP, recognising their need for specialised attention: for cross-disciplinary care teams, improved diagnostics, better research and innovative applications. Two years later, the early stages of all these recommendations were in place and now peer-review measures are coming through. Further, CUP has a charity and, on 27 April 2012, a second world conference.

SESSION 1 - PATIENT PATHWAY

Presentation 1 : Key recommendations of the NICE Guideline and update on NCAT Peer Review Measures.

RICHARD OSBORNE *Consultant in Medical Oncology, Dorset Cancer Centre. Lead Clinician, CUP Guideline Development Group*

What can we learn from a successful UK model? Where have we got to?

1. Quicker recognition of MUO (malignancy of unknown primary origin). Referencing key recommendations from the NICE Guidelines for CUP, Richard noted that the key aim and improvement to date is the *speed* at which the cases of inpatients with MUO are reviewed. This is now taking place in many centres
2. Emergence of a new language: for e.g. the phrase MUO is now common parlance, and that is an achievement.
3. Patient pathways success: since 2010, 86% of Trusts in England now have patient pathways in place. CUP specialist nurses are being trained and clinical care for CUP is being improved as we 'surf on the wave of new acute oncology developments'.

Is it working?

However, this is not enough – there is a need now to establish specialist CUP clinics and encourage the take-up of CUP research amongst a greater numbers of oncologists. It is also important that this emerging community holds regular MDT (Multi-Disciplinary Team) meetings. Further data collection is now key but first CUP must be captured in all UK Cancer Registers. The Somerset Cancer Register which now cites CUP in its data is a good example of current best-practice.

The UK is good at getting patients in front of oncologists quickly but on the whole we target only the 5 to 6 big cancers efficiently. What is needed is fast-track care in an organised fashion - the same as for those with site-specific diseases.

So What Next?

1. Final draft of the CUP Measures are due shortly and will be published this year
2. The principle of 'rapid care' is enshrined in the new NICE guidelines. Nurses and doctors should be and are 'burning shoe leather' in hospital corridors to meet guidelines on rapid assessment and care of suspected CUP patients.
3. Initial iterations of the Guidelines have recommended that there be separate CUP MDTs, but another possibility, based on practicality, is that specialist CUP professionals should form part of an established site-specific oncology MDT in hospitals
4. But there is a tension which relates to Acute Oncology developments. There may be a natural tendency to 'bolt on' or 'bundle' CUP services with the acute oncology service. Perhaps this has its advantages, but there is a caveat: we've yet to see whether bundling CUP with acute oncology MDTs is the best way forward. There is a risk that MUO and CUP patients won't get focussed and ongoing attention beyond the first 6 hours normally allocated to acute cancer diagnostic and treatment pathways for patients with site-specific cancers.
5. The feelings relayed to the DH are that the 2010 Guidelines on creating specialist MDTs might have been a 'step too far'. This is mainly due to perceived problems with resources. Additionally, it could be argued that complex cases might benefit from the widest range of oncology input, rather than risk restriction to 'specialist' units.
6. The point is that MUO/CUP patients generally need a whole range of early interventions, and this differentiates them somewhat from site-specific cancer patients – i.e., early recognition of MUO/ CUP status, careful patient support and advice for patients and for their families, and involvement of radiologists, pathologists and oncologists with a knowledge of CUP traits to deliver the functions of an MUO MDT **prior** to actual therapy. We should not forget that MUO patients are different.

How to implement the changes?

Instead of specialist MDTs, the pragmatic path would be to use existing drivers – ie to ride this wave of development in acute oncology structures and treatments, but to ensure that consultants have CUP on their agenda in all MDT meetings, and that specialist diagnosis, care and treatment for CUP patients is differentiated. Best practice

will be to appoint specialist CUP coordinators to liaise with all MDTs, to share results with professionals and carers and to disseminate the experience within the community – as at this conference.

SUMMARY OF RISKS – we need to be aware of:

1. The need to have a distinct identity within acute oncology pathways
2. Risk of compromise by not having specialist MDTs but going for a high level management of CUP treatment pathways and maintaining best practice and momentum
3. Resistance from colleagues - CUP teams work differently and we must bring other oncologists along as this will involve them embracing new work
4. Recession makes all these changes more difficult to implement

Presentation 2: Developing a new pathway for CUP patients at Chesterfield Royal Hospital.

DAVID BROOKS *Macmillan Consultant in Palliative Medicine, Chesterfield Royal Hospital NHS Foundation Trust.*

DB noted 370,000 people in his hospital's catchment area. As a palliative care physician he was increasingly aware of being sent over-investigated and exhausted patients, who have been bounced between site-specific teams, suffered poor communication, and sent to him too late in the day for him to make a difference.

An example was the 'Headache lady' who was 70 yrs old, had multiple bone metastases, was not fit for anaesthetic or chemotherapy, had endured two and a half months of tests with nothing to show for it. She was admitted to the hospice with escalating symptoms. But it was always clear she had cancer and would have benefitted from palliative radiotherapy at the time of presentation. So an early look at her personal history, a sensible reckoning of the balance of her probabilities, a best-guess at the primary site and fast treatment of her cancer would have meant preventing escalation of her symptoms and relieved unnecessary suffering. Discussions and perhaps tests to work out a further treatment plan need not have delayed patient centred care. A patient focussed approach would have put the horse back before the cart and the lady back into some form of control.

Developing the CUP patient pathway – the Chesterfield experience:

In the early stages the local PCT was keen to back the development of a CUP patient pathway but had no money. It was going to be necessary to do the work anyway: gather support from colleagues, collect data, make a case for financial support and go back to the Trust at a later date with data and evidence for funding. In the meantime, there was part-funding available for evaluation from Macmillan Cancer Support. David also got support from colleagues in histopathology, oncology and palliative care, and was able to 'borrow' support from palliative care specialist nurses, and somehow pulled together

the over- worked cancer pathway teams to begin to build a CUP pathway into the system.

But how many were they talking about? The team collected 6 months worth of pre- and post- data for likely CUP patients and carers, including hospital data, bereavement questionnaires and demographics¹. An aspect of early CUP development work is that is it 'incredibly difficult to find these people' from the extant data. Their cases are poorly coded and it requires 'huge' resource-searching to identify the often small numbers of patients whose buried data might carry CUP signals.

In the end they found 88 patients (over the whole year), between the ages of 44 – 98 years old and on average in their 70s, slightly more females than males, and the vast majority performance status 3 & 4 – ie, they were very sick. In the final diagnosis 50% had their primary site identified (the majority having lung and colorectal cancer) the remaining 50% stayed as CUP. 26% of the patients did go on to have tumour-directed treatment, even so, in this cohort the median time from MUO referral to death was 43 days. But one upshot was that David did start to get people out of hospital with better support and more were enabled to die at home.

How to improve the diagnosis and the care for CUP patients? Lessons learnt from this study:

1. Early referral -getting to these patients early in the diagnostic process is key to making any improvements for CUP patients
2. Just doing such a study starts to change professional behaviour
3. Need focussed outpatients clinics - often better to treat CUP patients at home or as outpatients

Outcomes of the study:

1. Chesterfield has now got a Primary Investigation Outpatient Clinic up and running
2. They've established it on a 'choose and book' system so other clinicians can book directly into the clinic usually with less than a week's wait.
3. Set up radiology alert for CUP patients within first two weeks of being seen
4. 47% patients are now being seen within 5 working days

Many challenges remain:

1. Early referral of all CUP patients
2. Driving forward the referral through internal systems
3. Getting more CUP patients seen as outpatients

¹Hughes, Philippa. Bath, Peter. Farrington, Clare. Brooks,David. Noble, Bill. 2011. Evaluating the development of a pathway for patients presenting with metastatic cancer of unidentified primary origin.End of study report for Macmillan Cancer Support, University of Sheffield July.

4. Making positive choices about quality of end of life care - getting them home if necessary
5. Making clinical space for CUP patients
6. Being alert to the risk of these patients being seen in chemotherapy suites before knowing it that it is cancer
7. Junior doctors being educated so CUP becomes part of the future landscape of cancer care
8. Perhaps calling palliative care *Palliative and Supportive Care* so as to remove the 'end of life' stigma.

What to do next:

1. Recognise the key role palliative care can play in improving the experience and outcomes for CUP patients and bring palliative care practitioners in from the beginning of the patient pathway.

a) Get palliative care in early: need better recognition in-house and by all CUP patients that Palliative Care is not all about end of life care. Their holistic overview of a patients' history, personal experience and possible prognosis puts them in a good position to help the patient take control and make decisions best suited to them from early on in the care process.

b) Palliative care needs to put brakes on the treadmill of investigations CUP patients suffer if they aren't strictly appropriate or necessary. They are in the best position to flag up patients likely to benefit from treatment - in general, if patients are not fit enough for a biopsy as an outpatient they are not going to manage chemotherapy.

c) Get in-patients into out-patient services as often as possible – on the principle that home is better than hospital, and hospital stays are an infection risk!

d) Improve patient communication, focus on what is known, (for fit patients that they have cancer and the next step is likely to be chemotherapy and that the tests are designed to identify which chemo will be best for them.) Treat symptoms where possible. Where diagnosis is not established putting a clear best-guess plan into action, and keeping the patient informed of what their treatment pathway is.

e) Getting palliative care and end-of-life care into the home in time to support both patient and carers

The take home message is palliative care clinicians and CUP teams can do a lot right now – they don't have to wait. Develop your teams now, don't wait for MDTs, get on the phone, burn shoe leather, sort out problems, get radiologists and nurses and oncologists onsite, provide results to the MDT and Trust – get your data, prepare your argument and drive ahead of the system. It will then follow you.

Presentation 3: CUP epidemiology & health service utilisation in Australia.

CLAIRE VAJDIC *Team Leader, Cancer Aetiology and Prevention Group, Prince of Wales Clinical School, University of New South Wales*

Australia, and New South Wales in particular, has been leading the way with the science of investigating CUP. Linking population data with community-based health data, three years ago they wrote a comprehensive CUP report to better describe its prevalence, patient profiles and the patient journey.

Defining CUP and understanding the incidence of 'confirmed CUP' is a knotty problem when national data from cancer registries don't carry sufficiently defined information - they only provide statistics for all three types of CUP bundled together (MUO, provisional CUP, and confirmed CUP). It is necessary to unpick the numbers and understand the incidence and risk factors for the different CUP sub-types. They don't yet, therefore, have an accurate picture of the incidence of Confirmed CUP.

What they do know is that among all CUP there is a higher incidence in Aboriginal peoples, rural populations, and areas of the country with the lowest levels of socioeconomic status. These findings confirm what has been established for some time, that CUP is partly due to poor access to health care. In Australia, CUP is listed among the top ten most common incident cancers, and it is the fifth most common cause of cancer-related death. However, the good news overall is that over the last 10 years CUP incidence rates have declined 30% in men and women and death from CUP has seen a 40% decline. While improved diagnostic methods partly inform these improvements, the challenge remains as to why CUP patients are presenting so late with the disease, giving medicine so little time to substantially improve outcomes.

To develop the evidence framework, what is needed now is:

1. Enhanced data
2. Better health service recognition of CUP
3. Improved health service data before and after CUP diagnosis
4. Comparisons of demographic data

Note: that while population-based observational research that utilises linked administrative health records has its strengths – there are no biases by hospital or clinic - it is nevertheless limited to information held in administrative data sets.

NSW story so far:

NSW have impressive access to Commonwealth and state-level data for specific cohorts and have collated 3.5 yrs of CUP patient information to 2007, through sourcing and linking Cancer Registry records, with billing records for health services such as GP visits, hospital admissions and more, and by requesting further information from the cancer registry during the period where privacy legislation prevented the registry from writing to doctors to confirm CUP cases.

Of the 574 incident CUP cases in a predominantly elderly cohort, the cancer registry audit reclassified 9 cases who didn't have cancer at all, and 155 who had primary-site cancers, leaving 410 (71%) as CUP. These findings alone have altered the way that CUP cases are registered now.

CUP cases

Of the 410 CUP cases, 20% had lymph node cancers, most commonly of the neck and underarm. Of the most commonly reported site of organs involved, the liver was the largest. From histopathology reports the most common (28%) cancer was adenocarcinoma, while 25% were squamous carcinomas. Tumour grade was not specified in a third of cases, but of those that were specified, the most common grade was poorly differentiated.

Conclusions:

1. Cancer registration methods influence the incidence of CUP
2. Integration of multi-data sources - medical records with population-based registries - allow improved classification of cancers in general and CUP in particular.
3. Confirmed CUP incidence is much lower than originally presented in the data before this review

What Next:

1. Update the study - Claire's group in NSW have the opportunity to repeat these investigations with another population-based cohort with a wider age group - from 45 yrs upwards – and to include baseline questionnaire data to examine demographic and behavioural risk factors for a CUP diagnosis
2. Set up a translational cancer research centre which will identify CUP patients early and systematically collect tumour and blood specimens from these patients.
3. Communicate and disseminate: (note: www.Actiononunknownprimary : website by patient Jane Barrett is a key patient resource).

SESSION 1 - EXPERT PANEL

Richard Osborne (Chair), Nicholas Pavlidis, David Brooks, Claire Vajdic, Tina Churchill (CNS Swindon)

Q1 - from lay member Cheshire cancer network. Can we update the patient's and carers' booklet with advice on when it is in the best interest of patient to go home. If ambulatory care is advised, then support at home is what is needed.

ACTION: Revision of Macmillan advice on provision of ambulatory care.

Q2 – this move to being a 'virtual patient' is highly innovative and will involve updated schemes of care.

A2.1 - Tony Greco:

- a) most patients are sick and not right for ambulatory medicine – there is a possible point of tension here about what is indeed in the patient’s best interest.
- b) Further, there is a separate problem which is that CUP is a negative definition and therefore more difficult to define!
- c) And confusion over cancer registrations happens all the time in all hospitals – it is a quality of data issue and this will lower the real incidence of CUP.

A2.2 - Richard Osborne: the Somerset Cancer Registry will be a force for good in providing high quality data – it provides a new and robust set of operational instructions for recording MUO and CUP. What we need now is joined-up thinking with the Cancer Registries to ensure the accurate input and recording of data.

ACTION: Revision of data collection methods recognising the need for correct registration of all patients in the first place.

Q3 - Richard Osborne then asked for thoughts on how to handle MDTs.

A.1 – don’t bolt on, make CUP stand alone

A.2 – but there is often not enough time in MDT meetings to cover CUP, especially if it is not in other members’ interests

A.3 - every hospital should have a specialist CUP MDT – even if it is bolted on. Peer review might be the stick by which we can enforce the development of MDT.

A.4 - David Brooks – at Chesterfield, CUP has a separate part in the meeting and other members do stay on for this section. The key is to get good info on the patients and their wishes beforehand and bring this to the meetings. Need to put the particular patient’s story at the centre of each consideration.

A.5 - Richard Osborne – one of the shortcomings of NICE is the time delay - what happened 3 yrs ago is only now starting to get enshrined in current practice. 3 years ago the idea of a fully-fledged CUP MDT was felt to be over-ambitious – it’s very difficult to get all the right people around the same table. The whole MDT process in a state of flux – RO thinks there are compromises in what the measures dictate but hopes intelligent people will drive and frame the groups in their regions.

Q4 – a CUP oncologist: currently CUP is allocated to site-specific departments dependent on the CUP presentation. Is there a risk that marking out a CUP patient for different treatment might in fact slow down the rate at which they are treated?

A.1 – RO - this is the question: should we spread the patients out or lump them together? As long as a specialist CUP is allocated to them throughout, are the patients likely to mind which model is used?

Q5 – being stumped by CUP patients really makes you think - which is why CUP is so fascinating. Fudge local MDT arrangements if necessary, but what we do need is the collaboration of the specialists to get best outcome

A.1 - RO – yes, we do need specialist expertise. But one big question is how to get it. We don’t know who all the CUP specialists are and haven’t yet developed a robust network

ACTION: Build a nationwide network of CUP specialists – oncologists, specialists and nurses – needs to be developed. John Symons has started this but there is more work to be done.

Q6 – There are other key specialists who need to be brought in – such as the pathologists and histopathologists. How do we enthuse people outside specialist services who are nevertheless able to contribute?

- A.1 - teaching sessions for non-specialists
- raising awareness – literature and events
 - on local intranet
 - link with local palliative care teams

Q7 – weekly meetings will be too much for many groups, especially when there are very few CUP patients.

A.1 - MDT just stands for a team of people – remember they can also be talked to outside the room and beyond the table

Q8 – Why are there no GPs here? Need to:

- Push pathway out of hospital to GPs
- Get GPs here to this conference –
- And in future expect many more phone calls from GPs!

Q8 – The small numbers of CUP patients is crucial. CUP patients who are fit enough for trials or chemotherapy is in fact an incredibly small number: when does this go from being a local to a national service?

A.1 – this is an issue but it is nevertheless imperative that there are processes to feed this small number into clinical trials.

Richard Osborne – to recap the Actions Points:

1. Management of CUP – moving towards ambulatory care
2. Getting high quality data – for all the centres
3. Functioning of local MDT – centre on lithe teams; do we need meetings? – with the ambition to develop active and advanced MDTs on the horizon
4. Set up network of acute CUP oncology experience.

IMMEDIATE ACTION: RB – wants to set up specialist forum for palliative care group in this audience and start today, Friday 27th April.

Session 2 - PATIENT EXPERIENCE

Presentation 1. UK – recent research findings.

RICHARD WAGLAND, *Senior Research Fellow in Cancer Care, University of Southampton*

Study Title: Patient, family and health professional priorities for improving care and support in CUP. (Professor Julia Addington-Hall, Dr Richard Wagland, Dr Rebecca Foster, Professor Alison Richardson)

Study aim: To work with CUP patients, their family, and health professionals to determine priorities for improving the care and support offered to those living with or affected by CUP.

Method: The overall study comprised two phases; this presentation reported the findings of the focus groups that took place in Phase 2. Eleven Key themes/issues relating to the support needs of patients and their carers were derived from the Phase 1 case study data, in which 17 patients, 14 family members or friends, 13 health professionals were interviewed. Statements that operationalized the themes were then presented to five focus groups for discussion. A modified nominal group technique (NGT) was used to generate consensus, and prioritise between competing needs/demands. Following discussion of each of the themes, participants were asked to rate (0 'not important' to 10 'very important') each of the statements. Once statements had been rated, participants were then asked to choose the top 5 issues they thought were most important and to rank them 1 to 5 (1 being most important).

Figure 1: Full list of themes derived from Phase 1 data

- A.** A need for CUP and what it means to be explained
- B.** A need for a key person to co-ordinate the efforts of different HCPs
- C.** A need for a key person to give consistent information and support
- D.** A need for patients to understand the reasoning behind investigations and tests
- E.** A need to know everything appropriate has been done to find the primary cancer
- F.** A need for information to understand that more tests may not be the best thing
- G.** A need for early involvement of specialist palliative care services
- H.** A need to know that HCPs have not given up or abandoned patients and carers
- I.** A need for patients and carers to talk about causes of cancer
- J.** A need for patients and their carers to know their needs are recognised and addressed
- K.** A need to receive comprehensive written information about CUP

Results

Overall there was a high degree of consensus between the ways that separate statements were rated and ranked by participants. Although the order was different, the three themes that were *rated* highest amongst all participants were the same three that were *ranked* highest overall:

- The need for CUP and what it might mean to be explained
- The need for a key person to co-ordinate the efforts of different HCPs
- The need for a key person to give consistent information and support

These three support needs must therefore be seen as the most important support needs of patients with CUP and their carers.

Conclusion:

The study findings can be used to promote the importance of patient and family centred care in CUP, support the need for the CUP guidelines to be implemented, and help to identify the areas on which CUP teams and key workers should focus. The study also found that patients and families currently could not be sure of receiving this sort of care, even within Trusts with an interest in CUP.

Presentation 2 – Recent research findings – Australia.

PENELOPE SCHOFIELD, *Research Director, Department of Nursing and Supportive Care Research, Peter MacCallum Cancer Centre, Australia*

PS presented the results of two pilot studies designed to underpin a proposed national cohort study. No one has seen this data – this was ‘yesterday’s news’ (26th April).

The studies were presented against background evidence that CUP was perceived as complex, that being diagnosed ‘feels like a whirlpool’, patients feel a fear of something both new and inescapable, engendering a sense of ‘hopelessness’, and that they suffer an end without ‘closure’. There is clear professional recognition of the need to validate CUP as a known form of cancer.

Until now they have found no psycho-social research on CUP and limited clinical research. The aim of this study therefore is to understand un-met psycho-social and informational needs of people with CUP.

PILOT STUDY 1 – PATIENT DATA:

Using qualitative phone interviews and quantitative surveys, with patients and care-givers, they recruited patients with pancreatic cancers via cancer council, help line, websites and clinical referral and they received over 100 expressions of interest. Using an opt-in recruitment approach, from this database they got 15 expressions of interest

and a final response rate of 10 over a similar time frame. This indicates that this will be a challenging group to do research with.

Their findings match with the Southampton data, key themes being a difficulty understanding the treatment, general lack of knowledge, uncertainty over how to make decisions and feeling lost in and abandoned by the 'system'.

PILOT STUDY 2 – PROFESSIONAL DATA:

They also conducted an electronic data survey with professionals, mostly medical oncologists in public hospitals in capital cities.

From this data the findings are:

1. CUP diagnosis - the majority were prepared to provide a final diagnosis of 'CUP', but many said 'it depends'.
2. Primary-site diagnosis – they were sometimes prepared to make a 'best guess' on the primary site, and most didn't believe there was a single cup entity.
3. Perhaps tellingly, 'most oncologists' would provide a diagnosis based on the likely primary location of the cancer in order to obtain government funding for drugs
4. Majority say there are no treatment protocols for CUP – Australia seems to be behind the UK in that regard
5. Nor is there a consistent classification system to diagnose CUP in Australia. There are various uses of language to explain CUP, often discussing a 'poor prognosis', but *very few referred to it as a recognised cancer entity.*

NEXT STAGE - SUPER Study: Psycho-social sub-study

This is the next stage in psycho-social research and will be conducted in the coming year, aiming for 120 cases per group, and will include a patient questionnaire on 'hopelessness', as this appears to be a unique emotional aspect of this group.

First and foremost this study will provide a longitudinal description of the educational, information and communication needs of this group.

Subsequent stages of research will involve developing and testing interventions for this group and assess what is acceptable and sustainable in this age of serious economic downturn. We need to be smart about using new technologies to optimise outcomes while minimising clinical time.

There are acknowledged difficulties in this sort of research, not least the difficulty for patients to identify with a CUP label or their poor prognosis and the short time-span for research. But it can be done, and we have to meet this challenge.

Session 2 - EXPERT PANEL –

David Brooks (chair), Richard Wagland, Penelope Schofield, Nicola James (Macmillan Nurse Consultant, Chesterfield Royal Hospital), and Julia Barton (widow of a deceased CUP patient).

Expert panel

Julia's husband's story: it took 6 months to diagnose his cancer followed by 6 months of treatment, including radio and chemotherapy and palliative care. During that time they were never made aware of 'CUP' – he was classed as a head and neck patient.

Q.1 – for Julia Barton: would he have had chemotherapy twice if he'd known he had CUP?

A.1 – Julia Barton: 'no'. He did more with the family without treatment in the last 5-6 weeks than at any time during his illness before then. He spent a total of 60 days in hospital. Instead they would have liked more qualitative time with him.

A.2 - this highlights the importance of patient needs - about how patients make decisions when they've got the diagnosis of CUP. Research shows that while older patients might opt out of treatment, younger patients are more likely to choose to proceed with treatment. Everyone must get enough information to make this choice.

Q2 – it is important to recognise that some patients with CUP have a good prognosis even when we don't find the primary.

A.1 - RB – This is why palliative care should come in early – they are very interested in identifying those that are wrongly referred to them and sometimes they can steer treatment with success.

A.2 - Tony Greco – while these are very small studies, the conclusions are intuitively obvious. A bigger study would provide the same conclusions - and those conclusions are right. Do we need bigger studies? TG also queried the extent to which the psychological needs of CUP patients differed from generic needs of cancer patients

A.3 - RW argued that we do need these studies to validate the intuitive evidence that CUP patients have a unique set of needs. It would be wrong to base service guidelines upon evidence that was only intuitive and not scientifically validated.

A4 PS emphasised some of the specific areas in which CUP patients and their families need specialist care and attention:

- they have a greater sense of hopelessness and uncertainty than other cancer patients
- they suffer poorer communication with their oncologists
- they need different support materials

and to recognise the speed of the cancer. Many describe it as being 'Hit by a train'.

Q3 – how do we communicate information about CUP to general medical wards, and get round the problem that most doctors on wards aren't familiar with CUP themselves, and that their uncertainty is transmitted to families.

A.1– there is a need to empower junior doctors to recognise how well or unwell patients are and get them straight to palliative care - short-circuiting specialist oncologists who are already over stretched by inappropriate referrals with people they shouldn't be seeing

Q4 – AUTOPSIES – How do we talk to CUP families about the importance of autopsies both as a research tool and as possible closure for relatives?

A.1 – JB- her family didn't want it. They had had enough and wanted to move on. PS also found family resistance, and noted that the management of autopsies requires that highly skilled support nurses be available to the families.

A.2 - T Greco – autopsies are now very rare. We'd be lucky to get 1 out of 600 patients. Something has changed culturally and it's important to talk about that.

A.3 - Post Shipman and the Alder Hay body-parts scandals we have restrictive legislation round autopsies so it is difficult to request hospital post-mortems. Often PMs confirmed CUP and didn't find a primary - but in a group where a tissue diagnosis hasn't been obtained an autopsy would be important.

Q5 – Histopathologists and radiotherapists do need to be in the MDT, and in person, not on a remote connection via video conferencing. But to get these onto the MDT requires a business case.

A.1 - RO - agreed with this point, and suggested the need for some 'horse trading'. ie while NICE Guidelines dropped the recommendation for specialist MDTs , professionals should trade instead the need for histopathologists and radiotherapists in specialist CUP meetings.

Q6 – a necessary outcome for today is to establish a list of UK CUP oncologists and make it accessible on line – this isn't an advertisement, but would meet a basic need to know that you are seeing a specialist or to get a second opinion.

A1– ACTION - there is a further need to bring the forum for palliative care (APM hosting this) and this list of oncologists together.

Q7 – there a danger with a CUP diagnosis that patient access to specialised drugs might in fact fall.

Q9 – T.Greco – could be a dichotomy between setting up ambitious CUP treatment structures in the UK and then finding that CUP recedes and having to disband it. Instead we should moving towards a model where patients are diagnosed with colon-*like* or breast-*like* cancer, using increasingly accurate new diagnostic tools, where we are finding the treatment works, and so CUP recedes.

Q10 - RD – Doctors need to know the minds of their patients – we can often understand more through reading a patient blog that through any questionnaires. After conducting a 'holistic needs assessment' by a specialist nurse – we should aspire to do this better.
CUP isn't on the medical student curriculum but should be

Q11 - GPs should be at this conference – it is difficult for them because it's rare but patients needs are huge in this situation and GPs are in a perfect position to engage push for early interventions. Then again, GPs are equally frustrated – direct access to acute oncology clinics might be a solution.

Q12 - TG: Many of these issues can be solved by a different use of language: We can always say '*You do have primary site, but at present our technology isn't refined enough to find it*'. Most patients will accept that as an answer.

SESSION 3 – SCIENTIFIC RESEARCH

Presentation 1. Report on the UK NCRI CUP-ONE TRIAL:

HARPREET WASAN *Consultant & Reader in (Medical) Oncology, Hammersmith Hospital. Chief Investigator, CUP-One Trial*

Key question: will the Cup patient pathway eventually be applicable to most metastatic disease?

Up to Oct 2004, when the UK NCRI initiated the development of a national clinical trial in CUP, it was extremely difficult to define CUP to clinical trial standards (this classification problem is still being discussed in 2012). Our aims were to a focus on improving outcomes, as well as understand the utility of modern diagnostic tests.

In most metastatic cancers, including CUP, the survival is under a year but in some, such as breast, colon and prostate cancers survival rates are improving and crossing over the 18 month to 2yr mark – could these be linked to CUP patients in that a subset identified that do better? In addition, as researchers, we don't normally don't look at patients who are not benefitting from treatments - those at bottom of the curve who do badly - but this was where we felt the focus the CUP-ONE trial research could help in the future. The CUP-ONE trial was set up in two parts :

1. Translational part of the trial

looks at modern molecular diagnostics which may link some CUPs to better or worse subsets. Three approaches are being tested We want to try and establish some sort of 'gold standard' test that quickly gives us a profile of the tumour and clues as to its origin.

2. Clinical trial

offers a standard chemotherapy treatment and will help– ie finding biological and clinical correlates – and getting answers about who and who not to treat in the future. The CUP-ONE trial is ongoing in the UK and now has over 150 patients (April 2012). Many patients aren't fit for chemotherapy.

We are already getting clues from the trial as to how to set up CUP MDTs more effectively as the pattern of spread of the cancer is being tracked and will have the largest such prospective cohort in the world that will give us clues to why this disease is so nasty and aggressive.

Where next:

HW is interested in where the rest of cancer research is going and whether the primary site or origin of a cancer is really going to matter in future as things are changing so fast?

His personal view is “possibly not”. With new profiling techniques we might come to understand and map the inter-relatedness of a variety of cancer and cancer-sub types and find ourselves as we are now treating already some breast and gastric cancers, for instance, with the same modern targeted drugs.

National Cancer Research Network (NCRN) framework now needs to plan a ‘next generation’ study, so we find out whether to treat cancers ‘like’ the site of origin or go with full molecular analysis and targeted treatments.

Presentation 2. Molecular biology - Reporting on the work of David Bowtell and Richard Tothill’s work on expanding the role of molecular profile diagnoses

PENELOPE SCHOFIELD – *Peter MacCallum Institute Melbourne*

CUP-ONE is important because we need novel therapeutic approaches. The key questions are

1. Can we better classify CUP?
2. Is the biology different and if so, can we exploit that?

Gene expression therapy works because tumours remember where they came from in terms of their genetic expression Bowtell and Tothill have developed a new assay test which classifies CUP samples in to likely site of origin by comparing the genetic profile of the CUP tumour with genetic expression database of known tumours. This new test is likely to be released in the middle of the year in Australia after undergoing further validation testing. The second stream of research currently being conducted at Peter MacCallum Cancer Centre is molecular profiling of over 100 CUP tumours. Specifically, they will screen the 40-50 genes for which targeted agents currently exist to determine the frequency of actionable mutations and explore another ~750 genes that are potential drivers of CUP biology.

But different sources of information may imply convergent or divergent approaches to treatment, which points to the question of how will we design clinical trials in the future? In the SUPER project they will have access to a broad recruitment base in order

to get highly defined CUP groups, which makes it an interesting project to watch for future success.

Conclusion

CUP presents a unique clinical opportunity to develop molecular-guided approaches as first-line therapy. These are exciting times in which we are going to see rapid changes in the next 5-10 years in how disease is tackled. It is important to bring experts in the field together – and this is happening largely thanks to John Symons.

Presentation 3. USA – Research update

TONY GRECO, *Director, The Sarah Cannon Cancer Center*

Introduction: TONY GRECO has been working with and researching CUP since 1976. His papers are a source material for researchers and his practice is a guide to best practice throughout world. In particular, his work on molecular profiling points the way forward for treatment of CUP.

TG: “This is an evolving area, and it’s evolving quickly. Using molecular techniques combined with histopathology we can in fact reliably know what most of these cancers are. We are no longer in the dark for most CUP patients. Not everyone will swallow that. But data talks.”

CUP cases are 2-5% of all advanced cancers, with 70-85,000 cases per annum in the US and fifth of that in UK. It’s not rare. These patients DO have primary sites – they are just too small to find with current technology. Today we can’t do enough autopsies, but when we could, we can see the primaries in the old autopsies – they are just very small, sometimes 2-3mm. But the point is, we don’t need to find the anatomic site of the primary to further define the tissue of origin and properly manage the patient.

The ‘shot-gun therapy’ approach to CUP will end soon. We have evolved more promising diagnostics:

1. Immunohistochemical (IHC) staining
2. Gene expression profiling of human tumours – there are three commercially available tests which are upwards of 90% accurate.

Gene Expression Profiling

For funding and pragmatic reasons Greco’s team studied bioTheranostic’s CancerTYPE ID RT-PCR assay. This method helps determine the origin of tumours by looking at the collective expression of genes - not looking at single markers - and compares it to a reference database of tumours of known origin.

With regard to selecting effective gene expression profiling techniques, there are key questions to ask:

- 1) How accurate do they have to be to be meaningful? More than 50% accurate and the answers start being useful.
- 2) Can we use this information to complement standard histopathology to improve the diagnosis?
- 3) Will CUP patients with a colorectal molecular profile diagnosis treated for colorectal do as well as a standard patient treated for colorectal cancer?

As we can no longer use autopsies as a gold standard we must turn to other methods.

1. Direct method - Latent primaries: occasionally the primary is found late (months or years after the initial diagnosis) and we can use them as the 'gold standard'.
2. Indirect methods – correlate with clinical features and diagnostic histopathology. This becomes the substantiating evidence for the primary diagnosis and leads to similar treatment outcomes.

He has used the RT_PCR molecular profiling assay on 171 tissue biopsy specimens from 171 patients between 2008-2010. Of the 24 patients found to have latent primaries the assay was **79% accurate**. Of the 171 patients, the findings for 52 patients correlated with the single IHC diagnoses of the pathologists 77% of time. That is strong evidence that the assay is accurate. In colorectal cancers the correlation was 93%, in breast it was 100%.

Still, two thirds of the patients had no single primary site highly suggested by immunohistochemistry. However, when pathologists were asked to estimate their first and second most likely primary site based on IHC, the molecular assay was in agreement with one in about 50%

Iterative System of Profiling

In other words, this iterative system of profiling and cross-checking against IHC and clinical features is effective, followed by treatment for the likely or known primary sites. Bear in mind, we are looking for accuracy of the diagnosis by the molecular assay, so we chose a subset amenable for treatment: for instance, of 26 CUP patients with colorectal defined metastases by the molecular assay, 21 were suitable for treatment. And in spite of the fact that none of them had documented primary site colorectal cancer – their colonoscopies were negative - their treatment results were strikingly similar to those with known colorectal cancer.

Conclusion

1. Gene profiling can be accurate *enough*
2. A single diagnosis from a pathologist using IHC is *good enough* to guide an iterative process towards effective treatment
3. *So use molecular assay in patients where the tissue of origin is uncertain based on IHC – it complements the pathology*

The immediate future is going to be better for diagnosing CUP patients. Pancreatic and biliary cancers are more difficult as we can't treat them well even when we know what they are. But we don't need to keep asking whether this approach works – it clearly does. As treatment improves for several currently less responsive tumor types their precise diagnosis will be more important.

Presentation: *Keynote: The biology of CUP: have we made any progress towards understanding the disease and in targeting strategic molecular pathways?*

NICHOLAS PAVLIDIS, *Director of the Medical Oncology Department, University of Ioannina, Greece.*

The Biology of CUP –

A hypothesis from recent Swedish data suggests that CUP frequently matched known cancers in the family – in other words, CUP may be modified cancers rather than new cancers.

We have made some progress in understanding the disease using genetic markers.

Pavlidis presented data from his own and other studies correlating genetic markers, denoted by the over-expression of certain proteins, with survival rates in CUP patients. Again, the MET protein, associated with a poor prognosis, appears to be a genetic marker commonly associated with CUP.

Conclusion: Molecular profiling using microarray tests is the way forward for diagnosing CUP patients. In 95% cases we can find the primary tumour. For those patients well enough for therapy who have symptoms which look like known cancers, we treat them that way. But the questions then are: *What exactly is working when we treat these CUP patients? Do we have effective drugs? Or do we just have responsive subsets of patients?*

Drugs combinations can work, while some patients will benefit from specific treatments. We do need randomised studies, to find novel agents, and develop pharmacogenomics, which may be part of the future.

We can look out for certain proteins which are switched on and off in CUP patients. Some are aberrant, others active, some are over-expressed – and all of them can be tracked.

However, for those patients with unfavourable subsets it is different and it is less likely we have effective targeted treatments for them. CUP-ONE is one of the four ongoing trials for this subset worldwide.

Future treatment and research:

1. Certain drugs which use antibodies and pathway inhibitors will be likely candidates for future therapeutic development, as will pharmacogenomics.

2. Future research will be dependent on better collaboration and the development of internal electronic CUP registries and a tissue bank of the CUP cell lines
3. And we need an international CUP task force looking for CUP signatures and comparing microarrays.

Session 3 - EXPERT PANEL

Harpreet Wasan (Chair), Nicholas Pavlidis, Tony Greco, Richard Osborne, Penelope Schofield.

Q1 - Are there many specific drug treatments beyond those for colon-like or breast-like treatments?

A.1 - TG – yes, but we don't have many specific drugs even for known cancers. The point is, CUP patients are different and we don't understand the difference yet.

Q3- Need we care about the cell origin or can we just treat it according to its molecular profile?

A.1 – TG – the story is more complex than we think, so it is never this simple. Our next efforts will be to study these targeted drugs – but not as first-line therapy. They might be used in some cancers but not for others. Currently our knowledge about these drugs is only from their use and performance in a clinical trial setting. And then there is the issue of who pays. Medicare in the US won't pay for personal treatments, so some patients pay out of their own pocket. The UK won't pay for these drugs either, so the pharma don't get the data. Cost is going to be a major issue going forward.

Q4 – RO - Are the high responders going to teach us something genetically – relating to chemo -sensitivity for instance? Perhaps not in CUP patients, but in the rest of oncology and with our improving tools?

A.1 - Yes – for example, maybe it's the host immunology that's preventing the spread of tumours.

TG – we need to move on in researching cancer. Cancer is a cellular genetic disease, we know that now. Trials are already moving to mutation testing. Once you select them down, they start to look like the known cancers - though there is still a genetic difference in CUP which we don't understand. The cancer landscape is like a jigsaw puzzle as big as football field. There are literally millions of pieces to decipher, interacting, changing and branching, evolving in the same tumour and within the metastases. But at least we have the tools now to take this forward.

APPENDICES

Appendix 1. Programme – see also slides

Welcome & Introduction

Tony Greco, *Conference Chairman*

Sir Mike Richards, *National Cancer Director*

MANAGING THE PATIENT PATHWAY

Key recommendations of the NICE Guideline and update on NCAT Peer Review Measures.

Richard Osborne, *Consultant in Medical Oncology, Dorset Cancer Centre. Lead Clinician, CUP Guideline Development Group*

Developing a new pathway for CUP patients at Chesterfield Royal Hospital – **David Brooks**, *Macmillan Consultant in Palliative Medicine & Member of the NICE Guideline Development Group*

CUP epidemiology & health service utilisation in Australia - **Claire Vajdic**, *Team Leader, Cancer Aetiology and Prevention Group, Prince of Wales Clinical School, University of New South Wales*
Expert panel and audience discussion. *Implementing the Guideline/ Measures and improving the patient pathway*

PATIENT EXPERIENCE

Recent research findings:

UK – **Richard Wagland** for **Julia Addington Hall**, *Professor of End of Life Care, University of Southampton*

Australia - **Penelope Schofield**, *Research Director, Department of Nursing and Supportive Care Research, Peter MacCallum Cancer Centre, Australia*

Expert panel and audience discussion. *Understanding the patient and carer needs. How can the experience be improved?*

SCIENTIFIC RESEARCH

UK - Preliminary findings from the CUP One Trial and putative CUP research projects. **Harpreet Wasan**, *Principal Investigator, CUP-One Trial*

Australia – Update on Peter MacCallum Cancer Centre studies on CUP and putative projects. **Penelope Schofield**, *Peter MacCallum Cancer Centre*

USA - Update of the Sarah Cannon Research Institute Studies and the Expanding Role of Molecular Profile Diagnoses. **Tony Greco**, *Director, The Sarah Cannon Cancer Center Department, University of Ioannina, Greece*

Expert panel & audience discussion. *Does CUP have a specific genetic signature? Are specific CUP genetic signatures other than local tumour growth and metastasis control pathways expected? Do CUP patients with specific molecular profile tissue of origin diagnoses treated with site specific treatments have similar outcomes to patients with known metastatic carcinomas? Will therapeutic targeting of specific pathways in CUP be any different compared to other known advanced cancers? What are the research priorities moving forward?*

Appendix 2 – Call to arms by John Symons, Director CUP Foundation

Although Cancer of Unknown Primary (CUP) in the UK is the 4th highest killer after Lung, Colorectal and Breast cancers, it remains a largely unrecognised public health problem.² Despite recent initiatives, knowledge of its true nature, and understanding of its impact on patients and carers, remains woeful.

But progress is being made. With its new definitions of the spectrum of the condition, the 2010 NICE Clinical Guideline for England and Wales has given clinicians an adequate lexicon for discussion and understanding. CUP patients are now being managed in the same “site-specific” fashion as other cancers, with teams and infrastructure which were previously lacking. A formerly neglected group of patients should now be receiving evidence-based investigation and treatment appropriate to their condition. Proof of the benefits reported at this conference show the advantages for a hospital that has established a dedicated CUP pathway:

- The patient is considered without delay by specialist palliative care and an oncologist with a special interest in CUP
- The length of time patients stay in hospital is reduced
- Tests are less likely to be duplicated
- An improved pathway puts the focus on the patient, with patients reporting better experience of care

The introduction of Peer Review Measures by NCAT in 2012 will give “teeth” to the Guideline and raise standards nationally. Introducing new measures is challenging and clinical expertise needs to be developed; but the increasing number of specialist nurses and oncologists identifying themselves with an interest in CUP is most encouraging. **CUP patients tell us that they want to be treated by a specialist, not a generalist, and supported by nursing staff who understand this very difficult diagnosis.** An important facet of this meeting is the opportunity for enthusiastic clinicians to interact, exchange best practice and formulate research proposals.

We need research: research that translates into improved diagnosis and treatment for this diverse group of patients; research that provides evidence that particular diagnostic techniques enable targeted treatments and a change of outcome for patients.

CUP is an international problem.³ This conference provides an opportunity to learn from patients, researchers and practitioners in different fields from different parts of the world.

Thank you for coming today and I would like to thank our speakers and sponsors who have made this event possible. With your help, we will continue to work actively to help *make the unknown known*.

² Cancer Research UK statistics, published Apr 2011, show UK CUP incidence at 10,951 persons and mortality at 11,250 whilst recognising that the disease is under-reported.

³ A study of WHO’s data on CUP (IARC, Vol ix) using ICD10 CODES C26, C39, C76-80 shows CUP incidence worldwide ranging from 2-10%.