TEN YEARS A CUP CHARITY: is the unknown nearly known?

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cancer of unknown primary Jo's friends foundation

CUP FOUNDATION – *Jo's friends* was registered as a charity in May 2007. As with many small cancer charities, it was born of experience: the absence of knowledge, understanding, information and support available to those affected by a cancer diagnosis where the primary cancer site was hidden. The charity takes its name from Jo who died from CUP in her mid 40s in 2006.

Treatment for cancer then, and now in 2017, is based on identifying the primary site – the starting point of the cancer - because the genetic makeup of any scattered tumour retains many of the original characteristics wherever it spreads within the body.

Whilst the climate amongst the UK 'cancer community' of oncologists, scientists and cancer charities in 2007 might have been described best as 'nihilistic' in relation to CUP, there has been a 'sea change' in the last ten years. As a result of developments in cancer research, clinical organisation, improved management and treatment, there are grounds for cautious optimism in 2017.

"The future is already here – it's just not evenly distributed."

William Gibson - *The Economist,*
4 December 2003

We will explore the changes that have taken place and the reasons for optimism in due course but first it might be helpful to the general reader to have some background.

What is CUP?

By definition, a CUP patient presents with metastatic disease (cancer that has spread), which is evident as a suspected secondary cancer. If the primary site of a cancer is unknown it is difficult for doctors to design a treatment strategy along conventional, disease site-specific lines. About the only thing we know about CUP with any certainty is that the initial tumour spreads (metastasises) through the body's blood or lymphatic systems, when still small[1], in an atypical way – in other words it behaves unlike the common cancer cells or tumours of 'known' cancers. There are a number of hypotheses about the cloak of invisibility (see text box).

A CUP diagnosis is a challenge for the clinician and the pathologist as well as being a double agony for the patient *(you've got cancer but we can't tell what it is[2]).* The conventional strategies available to the oncologist with a site-specific cancer allow tried and tested treatment. But the cells visible to the pathologist from a CUP patient's biopsy – tissue taken from a metastatic site – are not differentiated in the way that they are for site-specific cancers. The cells, in this atypical cancer spread, have gone 'crazy' and 'fuzzy'.

Why is the primary unknown or hidden (occult or invisible)?

- **Fallen on stony ground.** The primary is successfully attacked by the immune system as it tries to get a toehold but it has already shed cells that migrate through the body to find secondary 'sanctuary' sites (where they can thrive and confuse, or hide, from the immune system and then seed and grow.)
- **The primary is minute.** Cancer spread (metastasis) occurs very early when the primary is too small to be picked-up by present day tests including ultrasound, CT scans, MRI and PET - and the primary itself subsequently remains dormant.
- **The primary regresses (shrinks) or disappears.** Cancer growth is diverted preferentially to the most aggressive seeding cells which act like parasites, leading to the primary being starved of nutrients or pushed out of the body (expunged) if, for example, it is hanging perilously to part of the digestive system after it has spread.

[1] Either too small to be picked-up by imaging or hidden in a mass of secondary cancer.
[2] This is a crude explanation. Coping with a CUP diagnosis can be influenced significantly by the way it is presented to the patient initially.

The size and shape of the problem in the UK

- CUP is the 11th commonest cancer in the UK (13th in men, 8th in women); a ratio of 1 male to 1.2 females. CUP represents about 3% of all cancer incidence.
- Nearly 30 people in the UK die each day from CUP (about 6% of all cancer deaths). CUP is the 5th highest cause of cancer death in the UK (after lung, bowel, breast and prostate cancers).
- 57% of patients diagnosed with CUP in the UK present as an emergency, compared with 23% for 'all cancers'
- 55% of CUP cases occur in those aged 75 and over.
- 21% of CUP patients are in the most deprived socio-economic group.
- Between 2003 and 2013 CUP incidence declined by 28% and mortality by 24%. (The previous decade saw a decline of 9% and 4% respectively).

Data sources: CRUK, NCIN now NCRAS. Incidence and mortality data are from 2014 (the latest available)

In 2017 the biology of CUP is no better understood than it was in 2007; or 1907 when the problem was first noted in a paper on 'Non Demonstrable Cancer' written by William Halstead in Annals of Surgery. However, we are now entering a 'molecular revolution' in cancer research. As research into metastatic cancer advances, and diagnostic techniques improve, it is likely that the mysteries of CUP will be revealed.

Chasing the primary

In 2017, the patient presenting with evidence of suspected metastatic cancer - without an obvious primary site on initial investigation - should be directed to an oncologist who is part of the hospital's CUP Multi-Disciplinary Team (MDT). The diagnostic and clinical skills of the MDT will be focused on identifying the 'Malignancy of Undefined primary Origin' (MUO) while providing support and symptomatic care.

The investigation will be directed at defining a primary site, if feasible, or otherwise distilling from the evidence that does exist a 'primary-site-like' description of the cancer which can aid selection of treatment[3]. It may be that the 'uncertain' presentation is non cancerous (for example, TB can sometimes be mistaken initially for CUP). It may be that the presentation is almost certainly a site-specific cancer and the patient is diverted to a site-specific team.

Various tests follow for the patient with a 'provisional CUP' diagnosis, who remains under the care of the CUP MDT, including a biopsy (the removal of a small sample of evident cancer tissue so that it can be examined) if not already undertaken. The pathologist will interrogate the tissue[4] to check first whether the cells are malignant and, if they are, to determine their broad cancer family type: carcinoma, melanoma, lymphoma, or sarcoma being the commonest.

The majority of CUP is 'carcinoma'[5]. If carcinoma, the subtype is then determined: e.g. adenocarcinoma or squamous. (There are also rarer unknown primaries such as germ cell and neuroendocrine). Sixty to seventy percent of CUP are adenocarcinoma. It is at this point that the problem for the pathologist starts. A panel of 'markers' is routinely applied to try and characterise the possible tissue of origin. A couple of simple 'stains' can allow certain primary sites to be included, or excluded, from the likely list of sources with considerable certainty[6]. Application of some specific stains (PSA is an example of a marker that most people have heard of in relation to prostate cancer) can sometimes rapidly add crucial clarity to the likely tissue of origin. But these tests are not uniformly helpful, and in many cases, the undifferentiated or 'fuzzy' nature of CUP tumour cells mean that confident pointers to a likely source are missing.

Possible outcomes from MUO investigation

Non malignant
Primary site identified
CUP – suitable for treatment
CUP – for symptomatic care alone

The pathologist and oncologist, and the other members of the MDT, will then work together to tease-out as many clues as possible. They look for

[3]We have taken the majority expert view that CUP is a hidden tumour without visible clinical signs. There is an alternative hypothesis that CUP forms a distinct biological entity with specific genetic and phenotypic characteristics.

[4]Liquid biopsies are in their infancy. It is possible to identify cancer cells in a blood sample but this is not yet of a sophistication to be able to help with a CUP diagnosis.

[5]We are focused primarily on Carcinoma of Unknown Primary – the very few cases that fall into other categories are covered by well-established management and treatment pathways.

[6]CUP is sometimes referred to as a 'diagnosis of exclusion' as the pathologist excludes methodically every possibility.

What does the patient presenting with an 'uncertain' cancer diagnosis need of the NHS?

- Rapid, expert-led, assessment and ***appropriate*** investigation with MDT review
- Cancer Nurse Specialist (CNS) and concurrent holistic support including Palliative Care ***early*** in the Pathway
- Not to be 'lost' as a too difficult cancer or to suffer 'MDT tennis'.

'primary-site-like' characteristics of the patient's presentation from the evidence that does exist to arrive at a best guess as to the likely nature of the hidden (occult) primary. Treatment can then be proposed along site-specific lines.

Those with a provisional CUP diagnosis being treated for a probable primary site, and those with confirmed CUP, are likely to be offered chemotherapy but the curative efficacy may be limited in both cases. One reason for this is that even if the oncologist is targeting the right area, advanced cancer continues to mutate and he or she is aiming at a constantly moving target.

Of course, any treatment is dependent on the 'performance status' (functional ability) of the patient and many elderly patients – and CUP is skewed towards older patients - with co-morbidities may not be fit for potentially punishing chemotherapy regimens.

If a treatment cannot offer cure – the focus should be on the quality of life of the individual, and the choice and risk/ benefits of the treatment need to be considered very carefully. One of our constant refrains as a charity is that palliative care should be made available early in the patient pathway and that patients' must be given the information that allows the active treatment versus best supportive care decision to be evaluated[7]. Continuing active treatment where the benefits are questionable should not be undertaken in order to avoid a difficult discussion about death and what may be seen by the doctor and the patient (and loved ones) as a failure.

WHAT HAS HAPPENED IN THE LAST 10 YEARS?

More has happened to benefit CUP patients in the last ten years than in any previous decade. But this may be unrecognisable to today's CUP patients who can, at times, still think they are in the Dark Ages, rather than the 21st century, if science fails to reveal the necessary detail of the disease, and the reasons for this are not adequately explained.

Management and treatment

- **The NICE Guideline.** The most important event for the management and treatment of patients in the last 10 years has been the development and introduction of the NICE Guideline for CUP (for England, Wales & N. Ireland[8]). This has moved NHS treatment for CUP from ad hocery to a rational, consistent, evidence-based approach. No longer is CUP a failure of diagnosis: it is a diagnosis in its own right. Whilst it is true that CUP is not a single disease, but rather a heterogeneous collection of cancer types with a wide variety of clinical presentations, the NICE Guideline effectively puts it on a par with site-specific cancers giving it standing as a cancer in its own right for management and treatment purposes.

The Guideline became extant in July 2010 after a 3-year development process (the author was on the guideline development group and the Peer Review development group). The publication of Peer Review Measures in 2012 gave teeth to the Guideline and in 2016 Trusts in England were subject to external reviewers to assess their compliance. CUP patients owe a significant debt to Dr Richard Osborne who, in 2004, started lobbying for a CUP Guideline and became the lead clinician for the Guideline's development. His perseverance was supported by Professor Sir Mike Richards, the National Cancer Director (now Chief Inspector of Hospitals) who was equally determined that CUP should lose its orphan status.

- **Reduction in nihilism and improvement in clinical expertise.** The nihilistic approach by many oncologists towards CUP, horribly evident to patients, has mostly evaporated in large part thanks to the Guideline, with support from Cancer Networks and motivated clinicians. Ten years ago there was frighteningly little knowledge about CUP amongst oncologists[9]. Now Trusts have local protocols based

[7] We have funded and are contributing to the development of a Patient Decision Aid to help patients understand the choices and decisions they face in the treatment pathway.

[8] The Peer Review Measures used to evaluate CUP MDTs apply only to England. It is frustrating and inefficient that the countries of the UK are unable to agree common practices.

[9] To be fair, this was as much a systemic failure as an individual, professional one. One oncologist consulted during the charity's 'proof of concept' in 2006/7 said of CUP: 'we are failing these patients'. Another - a very high profile figure – when asked about the merits of starting a CUP charity was unequivocal: 'you are wasting your time, it will never take off!'

on the NICE Guideline for oncologists to follow. Admittedly, some Trusts are more compliant than others but the situation overall is vastly improved. As a charity we receive the most heart-rending stories of patients who have faced what the NHS term, euphemistically, 'sub-optimal care'. We receive fewer now that the NICE Guideline has been rolled out.

Suffice it to say that in 2017 the patient benefits most from an oncologist who is knowledgeable , confident and experienced in managing CUP patients. CUP Cancer Nurse Specialists (CNSs) are now common and are highly valued by patients. There were none 10 years ago. They are part of the CUP MDT which takes responsibility for the patient presenting with a non specific cancer classified by the NICE Guideline as a Malignancy of Undefined primary Origin (MUO).

It was a brave and possibly career-limiting decision of doctor or scientist to show an interest in CUP ten years ago. Some hospital doctors were reluctant to admit their lack of knowledge and pressed-on to treatment that was, at best, ad hoc, rather than admit fallibility. Now that it is a recognised diagnosis it is seen more often as a challenging, but interesting, medical topic. Research shows the key dilemmas for clinicians to be: difficulty communicating uncertainty to patients, ambiguity (perhaps through lack of definitive protocols) in deciding optimal treatment plans, and the test or treat dilemma (when to discontinue chasing the primary).

- **Molecular profiling.** Conventional means for classifying tumours depend on recognising particular features (physical appearance, expression of particular proteins recognised by immunohistochemical stains) which are determined by the genetic make-up of the tissue / cancer of origin. Molecular profiling adds another dimension by demonstrating patterns of gene expression which are to some extent tissue specific, therefore giving extra clues to the likely behaviour of a tumour when the origin is unknown. Molecular Profiling for CUP is not funded on a regular basis by the NHS and is generally only available to UK patients for a trial or if paid for privately or through health insurance (the cost is in the region of £2,000). Clinical experience, and refinement of molecular profiling assays has progressed significantly in the past 10 years. Its use often changes the direction of treatment for patients but there remains little formal evidence of a change of outcomes as a result of this approach (which allows the NHS to argue against funding it). Molecular profiling is not suitable for all patients and it can raise false hopes. On the other hand, even if it does not change the outcome for a patient, it can give comfort that a primary has been identified with considerable confidence[10]. The CUP patient faces unique psycho-social difficulties and not knowing the primary site is a significant stressor.

As a charity we would like to see these tests being made more widely available as part of the patient 'work-up' rather than as a last resort. There is more evidence of the value of molecular profiling in the USA. Dr Tony Greco's view is that the combination of IHC and molecular profiling can identify all but the most bizarre and inexplicable unknown primaries.

Research

Research is the key to solving the problem of CUP and improving patient experience in the shorter term. Given the significance of the high incidence and mortality rates, there is a chronic lack of research into CUP worldwide[11]. In relation to other cancers it has not been seen to be a topic of particular interest. Researching 'outliers' – in this case the least understood of all cancers – has the potential to reveal the most interesting results. In understanding CUP, the window into the behaviour of other highly metastatic cancers may be opened for mutual benefit.

What CUP patients face

- A lack of understanding about CUP; uncertainty regarding prognosis, possible recurrence and the primary's hereditary potential
- Higher levels of anxiety and depression, and worse physical, emotional, role and cognitive functioning in comparison with 'known' cancer patients
- Problems relating to health professionals co-ordination, accountability and timeliness of care because CUP is not as well understood as site specific cancers.

Clinical research. Pleasingly, research projects are growing and outline descriptions of ones from Greece, Italy, France, USA and Australia are shown on our website. In the UK the only significant clinical research has been CUP-ONE led by Dr Harpreet Wasan which has been running throughout the past 10 years. The trial has accrued over 600 patients and the results are expected towards the end of 2017.

[10] Logic suggests that the validity of the assays in identifying accurately the primary site might be ascertained post mortem. Post mortems are rare for cancer patients and evidence suggests that the primary may be visible in only some 70% of cases (supporting the hypothesis that the primary may disappear in some cases once it has sown its destructive seeds.)

[11] Drs Greco and Hainsworth in the USA are notable exceptions as long-standing CUP researchers.

The trial tested a particular chemotherapy combination and, more significantly, an expression profiling assay to determine how this might be best used in CUP for diagnosis and thus treatment choices.

The patient perspective. We have undertaken patient experience research often in conjunction with Southampton University. Much of the research was either started before the NICE Guideline, or before it started to achieve a national impact. However our impression is that, although the position in 2017 it not as bad as previously, there is considerable room for improvement. Combining research findings from Australia and Greece with those undertaken in the UK, in comparing CUP patients with site-specific cancer patients, it is clear that CUP patients, in comparison with those diagnosed with a known cancer, have a poor quality of life with higher levels of anxiety and depression, and worse physical, emotional, role and cognitive functioning.

The 100K Genomes Project. In December 2012 the British government announced the '100,000 Genomes Project' and on 5 July 2013 Genomics England - a company established by the Department of Health - was launched to deliver the project. Up to 100,000 patients with particularly complex diseases are having their whole genome - their personal DNA code –sequenced. CUP is one of the diseases to be studied from 2017[12]. CUP patients recruited to the 100k genome project will play a part much like conventional blood donors do today – providing specimens of their cancer as a service for medicine. It is not expected that individuals will benefit directly (although there may be instances where this happens). Scientists will use the data to define the changes in the tumour DNA, and try to identify factors that can be used to more accurately diagnose and understand CUP biology.

Biomarkers pilot project. We have contributed £55,000 to Dr Wasan at Hammersmith Hospital for a molecular profiling pilot project that aims to uncover potential biomarkers (predictive and prognostic) for CUP. Next Generation Sequencing (NGS) is being performed on a subset of the samples as a pilot to help understand the disease and detect potentially 'drug-able' mutations. A successful pilot will enable further research.

Epidemiology - Defining CUP. Accurate measurements of a disease are critical for research funding, international comparison and patient management. Ten years ago CUP was known by a number of different and confusing descriptors. We have encouraged the single descriptor of 'Cancer of Unknown Primary' and a clear delineation of what international classification codes constitute CUP (ICD-10: C77-80). This allows international comparisons to be made to understand the burden of the disease in different countries. Before CUP was defined, in the NICE Guideline, it was easier to dismiss the condition on the basis of its heterogeneity. We can now make some interesting comparisons. For example, in the 20 years from 1993 to 2013 there was a decline in UK CUP incidence of 37% and a decline in mortality of 28%.

We can see that improvements to the CUP picture accelerated in the second of these decades: incidence declined by 28% and mortality by 24% (there was only a 4% decline in mortality between 1993-2003). We would expect the incidence of mortality to decline rapidly as the NICE Guideline improves the management and treatment of patients (there is a 3 year time lag in the availability of national statistics).

We initiated and have undertaken research, with partners, looking at international comparisons. Our study exposed the differences in registration and

Examples of our work

- **Information and support for CUP patients and their families.** Our website has some 1500 hits per month. Registered in England and Wales we have a worldwide reach as the only substantive charity focused on CUP.
- **Advocacy.** We are the 'go to' charity for pharma, government, researchers, and clinicians seeking information about CUP patients, diagnosis and treatment. As patient advocates we have been involved in the NICE Guideline and Peer Review Measures development as well as clinical research such as CUP–ONE.
- **Knowledge-sharing.** We have gathered world experts to attend our international conferences; held training events for oncologists; and participated in CUP MDT development days.
- **Raising awareness.** We have raised awareness of CUP amongst the UK medical profession and major cancer charities (CRUK and Macmillan). Our supporters raise public awareness through local fund-raising events.
- **Research funding.** We have funded patient experience research to understand better the needs of CUP patients as well as clinical research.

[12] We lobbied for the inclusion and the Cancer of Unknown Primary Clinical Interpretation Partnership (GECIP) domain has been formed with Dr Wasan as the clinical lead.

reporting practices for CUP in Australia, England, Wales, Scotland, N. Ireland, and the Republic of Ireland.

A note of caution. A number of CUP research proposals are presently in the pipeline at the conceptual stage but the research process for clinical trials in the UK is horribly slow. The NHS view a median of 15 years from the publication of results to widespread uptake as typical. From conception to approval, funding, research, and the publication of results is unlikely to be less than 5 years suggesting a 20 year period overall.

Spreading knowledge through conferences and workshops

It is through clinicians and scientists sharing knowledge and best practice that patients will benefit from research and improved management. In 2009, 2012 and 2015 we ran major international conferences in London bringing together clinicians and scientists to share the latest research. Up to that point, no other international conferences had been held devoted to CUP. We were fortunate to have the leading authority on CUP, Dr Tony Greco (USA), chair the conferences. We ran also, with the support of the European Society of Oncologists, an event in London chaired by Professor Nicholas Pavlidis for junior oncologists. Training for UK CUP MDTs has taken place in association with SBK Healthcare. We attend and present papers at many national conferences[13].

Raising awareness

Awareness of CUP (and the charity) amongst treating physicians has now reached high levels. Many oncologists and CUP CNSs pass on details of our website to patients. Awareness amongst other cancer charities has risen and this has been particularly important with major charities such as Cancer Research UK (CRUK) and Macmillan Cancer Support. CRUK are the major funding source of clinical trials[14]. We might speculate that it was our website that encouraged both these organisations to ramp-up their on-line information about CUP which was negligible 10 years ago. A number of organisations have taken extracts from our website but we view this as a compliment and have no objection if it is used for the benefit of CUP patients.

We have contributed a number of articles to medical journals about CUP and given interviews on radio (national and local) and TV both in the UK and in the USA. Our fundraisers are our principal public awareness-raisers. The many and varied activities they undertake lead to articles in the local press. On the whole, however, the general publics' awareness of CUP remains very limited. This adds to the distress of patients because it is frustrating to have to explain the unique nature of a CUP diagnosis to friends and acquaintances. Another avenue of awareness-raising has been amongst politicians and some of our supporters have helped us position Parliamentary Questions (PQs) to Health ministers.

Providing information and support

Providing information and support to patients and their families is at the heart of our work. Registered in England and Wales we have a worldwide reach as the only substantive charity focused on CUP. Our website averages 1,500 hits per month from all over the world. We reach the widest audience through the internet and we receive also many individual requests by eMail. We produced a hard copy booklet in conjunction with Cancer Backup – a charity which has now been absorbed by Macmillan Cancer Support. The booklet 'Understanding Cancer of Unknown Primary' is distributed by Macmillan and we are invited to contribute to every update.

WHERE ARE WE NOW AND WHAT OF THE FUTURE?

Science fiction writer and essayist William Gibson was not, but could have been, writing about CUP with his contention that: "The future is already here – it's just not evenly distributed". At our 2015 international conference, Dr Tony Greco of The Sarah Cannon Cancer Center in the USA, who was chairing the conference, took our charity strapline of 'making the unknown, known' and stated that the unknown is now usually known.

The future for CUP patients – and it is partly here, if not evenly distributed - lies in understanding the molecular nature of the tumour. Two ways of approaching this are apparent: using gene expression profiling of the CUP tumour to aid diagnosis which gives a better idea of its potential primary site for more rational chemotherapy selection; and using molecular analysis techniques to identify 'actionable mutations' of the cancer, for targeted treatments where the primary site is of little relevance.

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[13] As illustrations of how CUP and the charity has become recognised the charity's Director was invited to chair the opening plenary session of one of the UK's largest cancer conferences and on another occasion spoke to a training session of the Royal College of Physicians on the subject of CUP diagnosis and patient experience.

[14] CUP trial applications route through the HB subgroup of the Upper GI Clinical Studies Group of the National Cancer Research Institute (NCRI)

Gene expression based profiling

Does molecular profiling of the tumour lead to a better outcome (increased life expectancy) than (empiric) chemotherapy? Molecular targeting for CUP is resisted by many pathologists and oncologists because of the lack of 'standard' evidence and, of course, by the NHS; the NHS on cost/benefit grounds. Dr Greco's view is that he can identify the primary (in the sense of defining clinically useful 'primary-like' features to guide therapy) 95% of the time with a combination of immunohistochemistry and gene expression profiling:

"*In my view the first step in CUP evaluation is to determine the type of cancer they harbor. With IHC and molecular cancer classifier assays … this is now possible in about 95% of CUP patients. If they have a responsive cancer type then these specific treatments should be given and in essence the puzzle for that patient is solved*[15]."

This does not mean that 95% of UK NHS CUP patients will have the primary site of their 'unknown' cancer identified. Sadly, UK treatment lags far, far behind that of leading centres in the USA. It is important to recognise also that an accurate identification of the putative primary site does not mean a 'cure'. It means that treatment can be targeted better; but because the disease will have mutated already it may only slow progression and thereby extend life.

In 2017 is it really necessary to continue to chase the primary site? Is it really necessary to use cytotoxic chemotherapy drugs that have an impact on good, as well as cancerous, cells? When we started writing about CUP ten years ago we used the military metaphor in describing chemotherapy as a 'thousand bomber raid' (with its inevitable collateral damage) in comparison to the equivalent of a surgical strike of a precision-guided missile (targeting mutations or genetic changes in cancer cells). Precision strikes are now becoming a reality.

Immunotherapy

The talk about cancer in recent years often involves the terms 'precision medicine', 'stratification' and 'targeted' treatment. Precision medicine involves the identification of 'actionable mutations' - genetic mutations that are potentially responsive to targeted therapy with immunotherapy drugs. The basis of precision medicine is that each tumour will have a different cocktail of genomic mutations identified by Next Generation Sequencing (NGS).
Cancer immunotherapy attempts to stimulate, or unblock, the immune system to destroy tumours in a similar way that the immune system tackles other invasions[16]. Immunotherapy drugs boost the body's pre-existing anti-tumour immune response (by awakening paralysed T-cells). Patients are likely to be stratified on the basis of the immune-related molecular signature of their cancer to predict for outcome and benefit in relation to particular drugs.

Immunotherapy treatment has led to remarkable clinical responses in patients with many different types of cancer, including melanomas, non–small-cell lung cancer, renal cell carcinoma, bladder cancer, and Hodgkin's lymphoma. The cancer patients where immunotherapy seems to have worked most effectively is when the cancer is 'hyper-mutated'. Dr Richard Osborne of our advisory board puts it like this:

"..essentially the more mutations the better – since this renders tumours more immunogenic and hence more likely to be recognised by a revitalised immune system after immunotherapy. The question is whether there is anything about CUP that puts the majority of patients into that potentially responsive group. Given the nature of the disease, one would hope this was the case. This can be assessed very easily based on an immunohistochemistry test looking at 'mismatch repair (MMR)'".

Looking for actionable mutations is still molecularly -driven treatment but it is not targeted at identifying the primary per se.

CONCLUSION

Cancer, as we have known it, is changing rapidly because scientists are beginning to understand cancer at the deeper, molecular level and developing better therapies as a result. As the population ages there are more and more people in the UK living with cancer. Through scientific advances, treatment has never been better for site-specific cancers; for metastatic cancer with an obvious, treatable, primary, there is already the increasing potential for significant life extension and good quality of life.

CUP patients are not in such a good position, as yet. But for those presenting to the MUO/ CUP team with an uncertain cancer in a hospital in England, Wales and N. Ireland, in 2017, the patients prospects of recognition, support and optimal management have never been better[17]. This is due largely to the

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[15] eMail discussion with the author of 9 Apr 2017

[16] Interestingly, cancer immunotherapy is thought to have its conceptual origins in late 19th century and early 20th century cases of spontaneous regression of sarcomas.

[17] Although the NICE Guideline does not cover Scotland, similar protocols have been developed. We show on our website (Research > Management & Treatment Guidelines), for example, the protocol used by the Edinburgh Cancer Centre.

implementation of the NICE Guideline on CUP that requires Trusts to operate a CUP Multi Disciplinary Team (MDT). Experience and expertise in CUP is growing amongst oncologists and the nihilistic approach of ten years ago has changed with a clearly managed pathway.

Diagnosis is the critical element. For the patient who is fit for treatment, this is currently undertaken primarily by obtaining the best clues through immunohistochemistry (IHC). A combination of IHC and molecular profiling to determine the primary-like behaviour of the cancer is likely to offer more clues for effective treatment.

Dr Greco's view is that about 95% of Cancers of Unknown Primary can be much managed better in this way. There will be some patients prepared to pay for molecular profiling and this should be explained and facilitated by treating oncologists where it is appropriate. Identifying the primary origin does not mean a cure – it means that the cancer is no longer CUP.

But it remains a metastatic cancer and hence not amenable to the standard curative treatments such as surgery and radiotherapy directed at localised disease; and some patients will be more responsive to treatment than others at that stage. Given that CUP is primarily a disease of older people, and that the outcomes are historically poor, palliative care and information allowing informed decisions about treatment remain important factors.

Moving forward, we need two things: an understanding of the biology of CUP – why the elusive primary behaves as it does and its overall characteristics (if there are homogenous characteristics) and/or a drug, or drug combinations, that tackle effectively the cancers of a CUP patient without needing to chase the primary or necessarily understand its biology.

Molecular science is fast-moving and the research on 'actionable mutations' may prove a promising avenue. Immunotherapy drugs that target accurately identified genetic mutations make the primary site largely irrelevant. Research is needed and we have committed £100,000 to help initiate an immunotherapy trial at Hammersmith Hospital.

It would seem that in trials in some cancers the more genetic mutations the patient has, the better, as this renders tumours more immunogenic and hence more likely to be recognised by a revitalised immune system after immunotherapy. Without trials it is impossible to know whether there is anything about CUP that puts the majority of patients into that potentially responsive group. Could this be something that, even if we do not understand why, reverses significantly the cancer for CUP patients?

Notwithstanding our underlying thesis that "the future is already here just not evenly distributed", *making the unknown, known* remains as relevant a role in 2017 as it was ten years ago when the charity was founded. The challenges and opportunities have now changed.

cancer of unknown primary foundation

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