

**Overcoming the Unknown:
New Approaches to the Diagnosis and Treatment of Carcinomas of Unknown Primary.
London 15th October 2009**

**Why are we failing the CUP patient?
Richard Osborne**

I am delighted to be here on this important day, which I see as a jumping off point for both the UK, and hopefully, internationally, in revising our approach to the management of Cancer of Unknown Primary and making real headway in what has previously been a very sad backwater. I would like to congratulate John Symons on his ambition for this. If anyone can drive this forward I know that he will be in the driving seat.

The topic I was asked to talk about was: ‘Why are we still failing patients?’ and I was given 15 minutes to do this in. As I have alluded to, the whole panoply of failures which CUP patients suffer would take a very long time to itemise, and indeed, the NICE Guideline Development Group, which is looking at this, has spent two years doing exactly that. I am going to try to distil my views of where we are failing and make some suggestions as to the way forward that we might choose. Those will, of course, be picked up on by other speakers today.

I made a list of what I saw as the key areas where the management of CUP patients falls behind that of the management of cancer patients in general who have defined site for their disease:

- Lack of an agreed definition
- Lack of evidence base
- Lack of designated funding/resources
- Lack of ‘site-specific’ system for clinical care
 - Clinical specialists
 - ‘Site-specific team’ and structure
 - MDT, SSG, Keyworker
- Lack of support for patients and families
- Lack of biological understanding
- Therapeutic nihilism

Today I will concentrate on what I consider the three main areas:

1. There is a great deal of uncertainty about what we are talking about when talking about CUP and hence, if you do not know what you are talking about, you cannot focus on it.
2. The second point, speaking from the British perspective, is the recognition of the huge steps forward that have been made in the management of cancer now that we have a site-specific approach, rather than a generalist approach, which has come in over the past ten years. To try and establish a site-specific approach for CUP patients seems to me to be a very high priority.
3. Lack of biological understanding - everyone in this room knows that that is a short coming for this disease.

1. Definitions

To me, I think about CUP patients as being on various points in a journey, so there is not a single definition of CUP in my opinion. Clearly there are patients who present with an obvious primary tumour and those are well served by the existing systems we have, but you do get patients, a sizable number, who come through the door with metastatic malignancy which you can identify either on a clinical examination or imaging, but it is not obvious where their primary is. It is this group of people who are currently, I think, ill served by our systems. They bounce around the system because they don’t fall into a convenient site-specific definition, which means that they can be managed by a site-specific MDT.

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After a little while, and this varies from patient to patient, we will have performed quite a wide variety of tests and we will have failed to find a primary tumour and we will have concluded that these people can justifiably be called Cancer of Unknown Primary. We are excluding here patients with melanoma and lymphoma. These people with metastatic epithelial cancers have had quite a few tests, but we haven't identified where the primary tumour is. At this point we don't really know what to do with these patients. Should we stop at this point? Should we subject them to further exhaustive investigations? This is another area where patients are ill served, often by undertaking additional investigations which are unnecessary.

There is a role for careful examination of the situation after this middle point so that, if necessary, further tests can be done, but ultimately we do reach the final point where everybody would be satisfied that the label of CUP could be applied - when every relevant specialised test has been undertaken and the primary has not been discovered.

If we think about these time points in the course of a patient with CUP we can apply certain operational definitions:

- Malignancy of undetermined primary origin (MUO)
Metastatic malignancy identified on the basis of a limited number of tests, prior to comprehensive investigation.
- Provisional Carcinoma of Unknown Primary (pCUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology/cytology, with no primary detected despite an initial screen of investigations, prior to specialist review and possible further specialised investigations.
- Confirmed Carcinoma of Unknown Primary (cCUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of definitive histology, with no primary detected despite a selected screen of investigations, specialist review, and completion of further appropriate specialised tests.

If we can agree some formal definitions based on where people are in this pathway and what has been performed and then apply them to the pathway, what we have are three definitions for the CUP patient which reflect where they are on their diagnostic pathway:

1. MUO - Malignancy of undefined origin
2. pCUO - Provisional Cancer of Unknown Primary. Provisional because not every single test has been performed but it is a useful time point to stop and consider the best way of managing these patients.
3. cCUP – Confirmed CUP

These definitions are a proposal. I think that there is some merit in trying to fine tune them and agree them over as broad a consensus as we can.

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2. Lack of system of clinical care

There is a lack of a system of clinical care for patients with CUP. If you have got breast cancer, lung cancer, bowel cancer or any other organ defined cancer, you have got your specialist nurse, specialist oncologist, MDT, the whole panoply of multidisciplinary and site-specific group working which now works so well in this country. If you have CUP, however, none of this applies broadly speaking. I think that this is another area in which we really must make headway by actually regarding CUP as a site-specific diagnosis so that a site-specific system of care can be put in place for patients.

I think that we are failing these patients at the moment because we are not providing the same care e.g:

- No specialist Oncologist
- No specialist nurse
- No multi-disciplinary team
- No MDT management approach
- No rapid systematic investigation
- No site-specific protocols
- No site-specific audit
- No site-specific research
- No cancer measures
- No site-specific information + support
- No accurate epidemiology

3 Biological understanding

I do not think that we can say that we understand everything about organ specific cancer but I think that we would all agree that biological understanding of CUP is even further behind. Having said that, this is one area in which I am very optimistic.

This is one area in which I think the investigations being performed in CUP patients actually do lead, in some instances, to site-specific cancers. I am thinking here of gene expression based profiling. CUP is clearly the best test bed for a lot of the work that needs to be done with gene expression based profiling. I think that this is the one area where we can really say that useful work has been done so far, and furthermore, this is probably going to be the cutting edge of making CUP a high profile disease in the future.

At the present we are in a dire situation with regard to, say, clinical work. Last week was the 2009 NCRI Conference, which went on for four days with more than a thousand abstracts and only two studies undertaken, and reported at that meeting, which dealt with some fairly tangential aspects of the clinical management of CUP. If you look at the NCRI portfolio of trials, which runs to many hundreds, there are no NCRI trials in this country relating to this disease.

As I have indicated Gene expression based molecular profiling is going to play a large part in helping patients with this disease, and helping our understanding of it and, from that, helping us to develop new therapeutic strategies.

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For me there are a couple of other priorities relating to biological understanding:

- I am a believer in serendipity, and learning from odd cases and I think that identification of long term survivors of CUP and careful analysis of the clinical features, and more importantly, what was done for those patients to result in their being long-term survivors, seems to be an important place where we could learn more about the disease. Some form of registry of these cases, and possibly even tissue banking, so that subsequent analysis could be performed on these sub-groups would do very well.
- Probably top of my list of priorities would be for there to be a national organisation to promote research of a broad range in CUP.

How can we help patients with Cancer of Unknown Primary?

I hope that we will come out of today with some form of CUP manifesto. This has been in the dark ages for decades, despite the work of some luminaries. I think that if we can come out of this meeting with:

- Some agreed definitions
- A recognition and agreement that some form of site-specific system for CUP patients is needed alongside the organ specific MDTs that we have for other diseases would be a step forward
- If we can energise the work to broaden the research base, both from a clinical and a molecular point of view, that would be worthwhile.

I would like to see the following in the future, as a way of taking us from the current position, where we are failing CUP patients, to actually helping them:

- I think that putting down a marker for a definition of CUP would be very helpful. Every so often we find editorials in the BMJ, The Lancet and other journals which review the state of the art. Often they say ‘This is what you should be doing in the future’, but some form of major editorial putting down a marker for what CUP is, going forward is needed. This might be written in a way which took account of molecular definitions as well as the clinical definitions which I have described.
- We have got a NICE Guideline Development Group which is trying to define a system of care for CUP patients and we hope that next year the NICE Guideline will be reported or released and that will result in the development of a site-specific system of clinical care for patients.
- We need to lobby for there to be a Clinical Studies Group in the UK at the NCRI, along with the other twenty three clinical studies groups which are site-specific or other topic-specific, so that CUP gets a fair crack of the whip when it comes to research funding and other aspects.

That is my prescription for what I would like to see in the future but I also hope that I have laid a foundation for the subsequent speakers to fill in some of the points that I have highlighted as deficiencies in CUP care.